REVIEW OF OPTIMAL RADIOTHERAPY UTILISATION RATES

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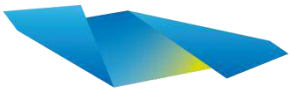

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EXECUTIVE SUMMARY

A study into optimal radiotherapy utilisation for all cancers in Australia was conducted by the Collaboration for Cancer Outcomes Research and Evaluation (CCORE) from April 2001 to June 2003. Since the public dissemination of the results of the study in 2003, the radiotherapy benchmarks identified in the study have been used as the basis for planning future radiotherapy services both nationally and internationally. The current study aimed to review the evidence to determine a contemporary position in regard to the optimal proportion of new cancers that would benefit from radiotherapy as part of their treatment plan.

Objectives

The objectives of the study were as follows:

- To review and update all the indications for first treatment radiotherapy in the existing CCORE model of optimal radiotherapy utilisation.
- To update the epidemiological data in the model using the latest available Australian national, state or cancer registry data where applicable
- To calculate customised estimates of the overall rate of optimal radiotherapy utilisation for each of the States and Territories
- To incorporate indications for concurrent chemoradiotherapy into the updated model of optimal radiotherapy utilisation, where possible
- To incorporate indications for brachytherapy into the updated model of optimal radiotherapy utilisation, where possible
- To determine the overall sensitivity around the benchmark optimal utilisation rate.
- To assess the effect of factors that may affect actual utilisation by incorporating patient preference data into the breast cancer and prostate cancer models where available
- To describe the trends in radiotherapy indications over time
- To discuss changes in technology that may affect radiotherapy treatment in the future

Methodology

The methodology was primarily based on the existing model of optimal radiotherapy utilisation that was constructed by our group seven years ago. An indication for radiotherapy is defined as a clinical situation for which radiotherapy is recommended as *the treatment of choice* on the basis of evidence that radiotherapy has a superior clinical outcome compared to alternative treatment modalities (including no treatment) and where the patient is suitable to undergo radiotherapy based on an assessment of performance status indicators and the presence or absence of co-morbidities. The superiority of radiotherapy over other treatment options could be based on survival, local control or toxicity profiles. Palliative indications were also included when they were the treatment of choice for a clinical problem.

The indications for radiotherapy for each cancer site were derived from evidence-based treatment guidelines issued by major national and international organizations. We gave the highest priority to Australian evidence-based clinical-practice guidelines issued by national institutions such as the National Health and Medical Research Council (NHMRC).

The 2003 model of optimal radiotherapy utilisation was reviewed and updated with reference to indications for radiotherapy and epidemiological data. The guidelines were reviewed to check whether the indications for radiotherapy have changed, whether there were any new indications for radiotherapy, or whether any existing indications for radiotherapy were no longer valid due to other treatment options like chemotherapy delivering equivalent or superior outcomes. Patient choice was considered for breast and prostate cancers where there are a number of alternative treatments with equivalent outcomes. Indications for most other cancer sites are more clear-cut and choice was not examined for these sites.

We only considered cancers that are notified to cancer registries. Non-melanomatous skin cancers and benign conditions were excluded because population-based data are not available on the number of cases that occur each year. Our previous work suggests that non-notifiable conditions comprise 10% of the caseload of Australian radiation oncology departments.

We constructed models of optimal utilisation for all notifiable cancer sites with an incidence greater than 1% of all cancers. For epidemiological data, preference was given to Australian population-based data. If this was not available we used the highest quality data in the international literature. Australian data on cancer stage was available for breast and prostate cancers. Other stage data were obtained mostly from the Surveillance, Epidemiology and End Results (SEER) data base produced by the US National Cancer Institute because Australian staging data were not available.

From the evidence on the efficacy of radiotherapy and the epidemiological data on the occurrence of indications for radiotherapy, the proportions of patients in whom radiotherapy would be recommended were calculated. The overall recommended radiotherapy utilisation rate was determined by summing these proportions.

Univariate and multivariate sensitivity analyses were performed and overall optimal radiotherapy utilisation rates were estimated for each State and Territory. Optimal brachytherapy utilisation models were incorporated into the model where appropriate.

Results

We estimated that optimal radiotherapy, chemoradiotherapy and brachytherapy utilisation rates were 48.3%, 8.9% and 3.3%, respectively. The chemoradiotherapy rate is a subset of the overall rate for external beam radiotherapy. Brachytherapy could be given alone or with radiotherapy or chemoradiotherapy. The optimal radiotherapy utilisation rate has decreased from the original estimate

of 52.3% because of changing proportions of patients with indication and reduction in indications for some cancer types. Our previous work suggests that 84% of all indications were for cure or prolongation of survival and 16% were palliative for the relief of symptoms.

Optimal radiotherapy utilisation rates were calculated for each State and Territory based on the most recent data available from their central cancer registry. Utilisation rates ranged from 46.6% in Queensland to 50.8% in the Northern Territory. The variability is due to the slightly different distributions of cancer sites. Northern Territory had higher proportions of Head and Neck, oesophagus and lung cancers and Tasmania has higher proportion of prostate cancers than the other jurisdictions.

We also examined the optimum number of attendances or fractions for each radiotherapy indication based on the guideline recommendation. When two regimens were of equal strength the lower number of fractions was used in the model. Overall the average cancer diagnosis with an indication for radiotherapy should receive an average of 18 fractions per treatment course for the first course of radiotherapy.

A number of new technologies may be incorporated into radiotherapy practice over the next decade. These are broadly classifiable into those technologies that improve the delivery of external beam radiotherapy such as stereotactic body radiotherapy, and those that may provide an alternative to radiotherapy such as hadron therapy and intra-operative partial breast irradiation. Some technology such as image guided radiotherapy may increase the proportion of liver and lung cancer cases with an indication for radiotherapy. Hypofractionation and stereotactic body radiation may reduce the number of attendances but may not affect the proportion of cases with an indication for radiotherapy. Partial breast irradiation may reduce the proportion of early breast cancers with an indication for radiotherapy.

Factors that affect actual radiotherapy utilisation can be grouped into health system, patient and provider factors. Health system factors include distance from a treatment centre, treatment centre characteristics, and waiting times. Patient factors include socio-demographic factors, age, co-morbidity, cultural beliefs, and life expectancy. Provider factors include referral practices and provider awareness of the benefits of radiotherapy.

Conclusion

The evidence based guidelines suggest that in Australia, radiotherapy (alone or with chemotherapy or brachytherapy) is the treatment of choice for 48.3% of notifiable cancers. Chemo-radiation is indicated in 8.9% of new cancer diagnoses (alone or with brachytherapy), and brachytherapy (alone or with external beam radiotherapy or chemoradiotherapy) is indicated in 3.3% of new cancer cases. These estimates exclude cancers that are not notified to cancer registries such as non-melanomatous skin cancers, benign conditions and retreatment of previously diagnosed cancers that have already received radiotherapy at an earlier date.

METHODOLOGY

The methodology for this study is based on the methodology used for the existing model of optimal radiotherapy utilisation that was constructed by our group seven years ago. Since our initial study, our methodology has been positively assessed by eminent authors in the field as the best methodology for calculating an optimal utilisation rate (1) and our methods have been widely published throughout the peer-reviewed literature, not only for radiotherapy (2-14), but also for chemotherapy (15-20), endocrine therapy (21) and genetics (22) and has been used by others to estimate radiotherapy resource needs in a number of different countries (1;23).

Study Population

The population is all cancer cases registered by Central Cancer Registries in Australia in the most recent year available. This cohort includes only malignancies notifiable to the Australian state-based cancer registries (therefore includes ductal carcinoma in situ of the breast but excludes non-melanomatous skin cancer, carcinoma in situ of the cervix and benign tumours). All cancers with an incidence of 1% or greater were examined with the remaining cancers being classified as "other cancers". The incidence of rare cancers is difficult to estimate because of the small numbers involved.

1. Defining evidence for the efficacy of radiotherapy

In this study, an indication for radiotherapy is defined as a clinical situation for which radiotherapy is recommended as *the treatment of choice* on the basis of evidence that radiotherapy has a superior clinical outcome compared to alternative treatment modalities (including no treatment) and where the patient is suitable to undergo radiotherapy based on an assessment of performance status indicators and the presence or absence of co-morbidities. The superiority of radiotherapy over other treatment options could be based on survival, local control or toxicity profiles.

The indications for radiotherapy for each cancer site were derived from evidence-based treatment guidelines issued by major national and international organizations. We gave the highest priority to Australian evidence-based clinical-practice guidelines issued by national institutions such as the National Health and Medical Research Council (NHMRC). The study cut-off date for inclusion of guidelines in the previous radiotherapy utilisation study was June 2003. In this review, we searched for the latest versions of the evidence-based guidelines cited in the previous study and any new guidelines that have been released since then. The guidelines were reviewed to check whether the indications for radiotherapy have changed, whether there were any new indications for radiotherapy, or whether any existing indications for radiotherapy were no longer valid due to other treatment options like chemotherapy delivering equivalent or superior outcomes. We assessed the quality of

evidence for radiotherapy based on the NHRMC hierarchy of levels of evidence (24) (see Table 1). If there was any change in the quality of evidence for radiotherapy since the last study, it was noted and reported in a table of changes. Since brachytherapy was not included in the original radiotherapy utilisation study, guidelines published prior to July 2003 may have been cited for brachytherapy if more recent guidelines are not available.

Table 1. Levels of evidence for indications for Radiotherapy

Level	Description
I	Systematic review of all relevant randomised studies
II	At least one properly conducted randomised trial
III	Well-designed controlled trials without randomisation. These include trials with "pseudo-randomisation" where a flawed randomisation method occurred (e.g. alternate allocation of treatments) or comparative studies with either comparative or historical controls.
IV	Case series

National Health and Medical Council (NHMRC) (24)

2. Indications for radiotherapy and radiotherapy utilisation trees

Patient and tumour-related attributes that were used to define specific radiotherapy indications included:

- histology,
- clinical stage,
- surgical clearance of the tumour margin,
- patient fitness or performance status,
- presence or absence of symptoms, and
- outcome of previous treatments.

Any indications for radiotherapy identified in clinical practice guidelines or other literature were included in the analysis. We recognise that some indications were supported by high-level evidence while others were not. Sensitivity analyses were performed when uncertainties existed (see below) to estimate the magnitude of potential variation in the estimate of radiotherapy utilisation. In the original study, for each type of cancer, a radiotherapy utilisation tree was developed in which each branch point represented an attribute of an indication for radiotherapy. For each branch a proportion of patients with that attribute (such as the stage of the tumour, or whether or not surgery was clear of the tumour margins) was quantified. All the indications for external beam radiotherapy in the original CCORE model of optimal radiotherapy utilisation were reviewed and updated in the optimal utilisation tree based on the latest guideline recommendations.

TreeAge software version 3.5™ was used to construct the original radiotherapy utilisation trees. This software has been extensively used for decision analyses in health and in economic assessments of the cost effectiveness of various treatments (25). This particular software was chosen because it depicts indications for a particular treatment modality in a diagrammatic form, and the software provides a convenient way to perform multiplication of various factors and the summation of the results; the software provides tools to perform statistical analyses such as sensitivity analyses of variability and can assist future researchers to easily adapt the tree parameters should indications for the treatment modality or epidemiological data distributions change over time. To update the utilisation trees, we used TreeAge Pro™ software, which is an updated version of the software used in the original radiotherapy utilisation study.

Each branch of the tree ends in a "pay-off" of either 'radiotherapy' or 'no radiotherapy' as the final outcome. The pay-off for radiotherapy being given is allocated a value of '1' and no radiotherapy given a value of '0'. In some circumstances, the indication for radiotherapy occurs in the initial stages of management. In other circumstances, radiotherapy may be delayed (for instance, in patients who develop a local recurrence, and who have not previously required radiotherapy). As the purpose of our project was to determine the proportion of all cancer patients who have at least one indication for radiotherapy at some time in the course of their illness, patients requiring radiotherapy were counted only once, even if they have multiple indications at different stages in their illness. Each terminal branch of the tree shows whether or not radiotherapy was recommended for a particular type of cancer in individuals with particular attributes.

3. Epidemiology of cancer types, tumour sites and stages

In the original study, searches for information on the proportions of patients that have the different attributes associated with each cancer type and each tumour site were performed. A hierarchy of data quality was derived from Tyldesley et al (26) (Table 2). Australian data were given the highest rating and used wherever possible. The highest level data came from well-known National or State surveys or databases. However, not all branches had Australian data available. Where national or state data did not exist, other epidemiological data were identified by searching large citation databases (eg. Medline, Pubmed, Cochrane), manual bibliographic searches and examination of review articles. In this review, the epidemiological data in the utilisation tree were reviewed to see if more recent data were available. This pertains particularly to the early branches in the tree which contain national or state level data on cancer incidence rates and stages. In the revised tree, we updated data on i) incidence of cancers based on the latest available AIHW data ii) any available new population-based data on stage proportions and iii) data for any new indications for radiotherapy. If there is a change in the hierarchical quality of the epidemiological data, this was noted and reported in a table of changes.

Table 2. Hierarchy of epidemiological data

Quality of Source	Source Type
α	Australian National Epidemiological data
β	Australian State Cancer Registry
γ	Epidemiological databases from other large international groups (e.g. SEER)
δ	Results from reports of a random sample from a population
ε	Comprehensive multi-institutional database
ζ	Comprehensive single-institutional database
θ	Multi-institutional reports on selected groups (e.g. multi-institutional clinical trials)
λ	Single-institutional reports on selected groups of cases
μ	Expert opinion

Taken from Delaney et al (3)

4. **Estimation of the optimal proportion of cancer patients who should receive radiotherapy**

From the evidence on the efficacy of radiotherapy and the epidemiological data on the occurrence of indications for radiotherapy, the proportions of patients in whom radiotherapy would be recommended were calculated. The overall recommended radiotherapy utilisation rate was determined by summing these proportions. If there was any change in the optimal radiotherapy utilisation rate for any cancer site, based on either a change in indication or change in epidemiological data, this was noted.

5. **Estimate overall optimal radiotherapy utilisation rates for each State and Territory in Australia**

The most recent publicly available data from Central Cancer Registries were used to estimate overall optimal radiotherapy utilisation rates for each State and Territory.

6. Incorporation of brachytherapy into the optimal radiotherapy utilisation model

We have recently developed optimal brachytherapy utilisation trees and data for the major cancer sites in which brachytherapy is indicated (cancers of the prostate, cervix, uterus and vagina).

Incorporation of brachytherapy models into the radiotherapy utilisation tree involved alteration of the branches in the existing tree together with changes to associated epidemiological data. Estimates are provided for brachytherapy alone and in combination with external beam radiotherapy.

7. Sensitivity analysis

Sensitivity analyses were undertaken in the original study to assess changes in the recommended radiotherapy utilisation rate that would result from

(a) Different estimates of the proportions of patients with particular attributes, or

(b) Different probabilities of benefit from treatment, which could be suggested by different data sources or

(c) Different recommendations for the use of radiotherapy where there was conflict in radiotherapy recommendations between treatment guidelines.

TreeAge software can be used for one-way sensitivity analyses and multivariate Monte Carlo simulation techniques. The univariate and multivariate sensitivity analyses were updated using current indications and epidemiological evidence to test the robustness of the model. This is more useful than standard statistical techniques because it allows transparent assessment of the different assumptions in the model. One-way sensitivity analyses allow a single uncertain variable to be modelled to assess the effect that the uncertainty had on the final optimal radiotherapy utilisation. Monte Carlo simulations allowed for assessments of multiple uncertain data for their effect on the radiotherapy utilisation rate. Monte Carlo simulations are based upon the random sampling of variables from discrete and continuous distributions during individual trials. Sensitivity analysis for radiotherapy, chemo-radiotherapy and brachytherapy is given for each cancer site where relevant. Univariate and Monte Carlo was used for the sensitivity analysis of the whole decision tree.

8. Combined radiotherapy and chemotherapy

The indications for radiotherapy were reviewed to identify those indications where radiotherapy was recommended in conjunction with concurrent chemotherapy. These combined chemotherapy and radiotherapy indications were listed as an additional payoff in the overall utilisation tree, so that the proportion of all patients who have a combined chemotherapy and radiotherapy indication could be identified and reported.

9. Patient choice

One of the important factors influencing actual utilisation rates of radiotherapy is patient choice. We reviewed the available literature on patient choice and incorporated the data into the model where relevant. The effect of patient choice on the utilisation rate was assessed.

10. Identification of the factors that affect actual utilisation and optimal utilisation

We conducted a literature review using large citation databases (eg. Medline, Pubmed, Cochrane library) and cross-references from published literature, to identify the factors that affect radiotherapy utilisation in actual practice. Secondary manual searches of bibliographies were performed to follow up on additional references identified in the guidelines or in retrieved papers.

The factors that affect optimal utilisation were identified in the individual branches in the optimal radiotherapy utilisation tree. The factors in the proximal branches (incidence and stage distribution) had the greatest effect on the optimal rate. The controversial areas of practice (where further clinical trials are needed) that can have an effect on the overall optimal radiotherapy utilisation rate were identified.

11. Trends in radiotherapy indications

We examined the chronology of radiotherapy indications to estimate time trends in the proportion of cancer cases with an indication for radiotherapy as treatment of choice.

12. Changes in technology that may affect radiotherapy treatment in the future

With the rapid advance in technology, new radiotherapy techniques have been developed such as intensity-modulated radiation therapy, image guided radiation therapy, gating, intra-operative radiotherapy and tomography. These techniques allow more precise radiotherapy delivery with the aims to improve the tumour control probability and reduce toxicity. We reviewed the available literature on the use of new radiotherapy techniques and estimated how they may lead to changes to radiotherapy indications.

13. Summary of PhD project findings

A summary of the findings of the PhD project undertaken by Dr. Karen Wong, "*Estimate of the optimal number of fractions per patient and per treatment course"* is provided.

14. External peer review

Draft reports tabulating all the changes in radiotherapy indications and epidemiological data for each cancer site were sent for review in electronic form to the relevant NSW Oncology Group and Victorian Co-operative Oncology Group for distribution to their members. These groups are composed of key clinical experts (surgeons, medical oncologists, haematologists, radiation oncologists) who specialise in that particular cancer site. Drafts were sent in electronic form to the Faculty of Radiation Oncology, Medical Oncology group of Australia and Royal Australasian College of Surgeons for distribution to site-specific interest groups within their organisations.

The reviewers' comments and the actions taken in response to those comments were recorded.

References

1. Bentzen SM, Heeren G, Cottier B, Slotman B, Glimelius B, et al. Towards evidence-based guidelines for radiotherapy infrastructure and staffing needs in Europe: the ESTRO QUARTS project. *Radiotherapy and Oncology* 2005;75:355-65.

2. Delaney G, Barton B, Jacob S. Estimation of an optimal radiotherapy utilization rate for breast cancer: A review of the evidence. *Cancer* 2003;98:1977-86.

3. Delaney G, Barton M, Jacob S, Jalaludin B. A model for decision making for the use of radiotherapy in lung cancer. *Lancet Oncol* 2003;4:120-8.

4. Delaney G, Jacob S, Featherstone C, Barton MB. The role of radiotherapy in cancer treatment. Estimating optimal utilization from a review of evidence-based clinical guidelines. *Cancer* 2005;104:1129-37.

5. Delaney G, Barton M, Jacob S. Estimation of an optimal radiotherapy utilization rate for gastrointestinal cancer: A review of the evidence. *Cancer* 2004;101:657-70.

6. Delaney G, Jacob S, Barton M. Estimating the optimal external beam radiotherapy utilization rate for genitourinary malignancies. *Cancer* 2005;103:462-73.

7. Delaney G, Jacob S, Barton M. Estimation of an optimal external beam radiotherapy utilization rate for head and neck carcinoma. *Cancer* 2005;103:2216-27.

8. Delaney G, Barton M, Jacob S. Estimation of an optimal radiotherapy utilization rate for melanoma. A review of the evidence. *Cancer* 2004;100:1293-301.

9. Delaney G, Jacob S, Barton M. Estimation of an optimal radiotherapy utilization rate for gynecologic cancer: Part I - malignancies of the cervix, ovary, vagina and vulva. *Cancer* 2004;101:671-81.

10. Delaney G, Jacob S, Barton M. Estimation of an optimal radiotherapy utilization rate for gynecologic cancer: Part II - carcinoma of the endometrium. *Cancer* 2004;101:682-92.

11. Delaney G, Jacob S, Barton M. Estimating the optimal radiotherapy utilization for cancer of the central nervous system, thyroid cancer, and cancer of unknown primary origin from evidence-based clinical guidelines. *Cancer* 2006;106:453-65.

12. Featherstone C, Delaney G, Jacob S, Barton M. Estimating the optimal utilization rates of radiotherapy for hematologic malignancies from a review of the evidence: Part I - Lymphoma. *Cancer* 2005;103:383-92.

13. Featherstone C, Delaney G, Jacob S, Barton M. Estimating the optimal utilization rates of radiotherapy for hematologic malignancies from a review of the evidence: Part II - leukemia and myeloma. *Cancer* 2005;103:393-401.

14. Jacob S, Wong K, Delaney G, Adams P, Barton M. Estimation of an optimal utilisation rate for palliative radiotherapy in newly diagnosed cancer patients. *Clinical Oncology* 2010;22:56-64.

15. Jacob S, Ng W, Asghari R, Delaney G, Barton M. Estimation of an optimal chemotherapy utilisation rate for colon cancer: an evidence-based benchmark for cancer care. *Eur J Cancer* 2009;45:2503-9.

16. Jacob S, Hovey E, Ng W, Vinod S, Delaney G, Barton M. Estimation of an optimal chemotherapy utilisation rate for lung cancer: an evidence-based benchmark for cancer care. *Lung Cancer* 2010;69:307-14.

17. Ng W, Jacob S, Delaney G, Barton M. Estimation of an optimal chemotherapy utilisation rate for head and neck carcinoma: setting an evidence-based benchmark for best-quality cancer care. *Eur J Cancer* 2009;45:2150-9.

18. Ng W, Delaney GP, Jacob S, Barton MB. Estimation of an optimal chemotherapy utilisation rate for breast cancer: setting an evidence-based benchmark for the best-quality cancer care. *Eur J Cancer* 2010;46:703-12.

19. Jacob S, Ng W, Delaney GP, Barton MB. Estimation of an optimal chemotherapy utilisation rate for primary malignant brain tumours: an evidence-based benchmark for cancer care. *Clinical Oncology* 2011;23:48-54.

20. Jacob S, Ng W, Asghari R, Delaney GP, Barton MB. Chemotherapy in rectal cancer: variation in utilization and development of an evidence-based benchmark rate of optimal chemotherapy utilization. *Clin Colorectal Cancer* 2011;10:102-7.

21. Fong A, Ng W, Barton MB, Delaney G. Estimation of an evidence-based benchmark for the optimal endocrine therapy utilization rate in breast cancer. *The Breast* 2010;19:345-9.

22. Featherstone C, Colley A, Tucker K, Kirk J, Barton MB. Estimating the referral rate for cancer genetic assessment from a systematic review of the evidence. *Br J Cancer* 2007;96:391-8.

23. Erridge SC, Featherstone C, Chalmers R, Campbell J, et al. What will be the radiotherapy machine capacity required for optimal delivery of radiotherapy in Scotland in 2015? *Eur J Cancer* 2007;43:1802-9.

24. National Health and Medical Research Council. Guide to the development, implementation and evaluation of clinical practice guidelines. Appendix B, 56. 1998.
Ref Type: Report

25. Hunink M, Glasziou PP. Decision making in health and medicine. Integrating evidence and values. Cambridge: Cambridge University Press, 2001.

26. Tyldesley S, Boyd C, Shulze K, Walker H, Mackillop WJ. Estimating the need for radiotherapy for lung cancer: an evidence-based, epidemiologic approach. *Int J Radiat Oncol Biol Phys* 2001;49:973-85.

BLADDER CANCER

Evidence-based treatment guidelines for urinary bladder cancer were reviewed. Bladder cancer management guidelines published by major national and international organisations since the completion of the previous radiotherapy utilisation study in July 2003 have been reviewed.

Updated Guidelines

The following new or updated guidelines were identified and reviewed:

- National Comprehensive Cancer Network (NCCN). Clinical practice guidelines in oncology: Bladder cancer, Version 2.2012 (1)
- National Cancer Institute (NCI). Bladder Cancer Treatment (PDQ®), 2012 (2)
- Royal Australasian College of Physicians (FRACP) guideline, 2011 (3)
- SIGN guideline on management of transitional cell carcinoma of the bladder, 2005 (4)
- National Institute for Health and Clinical Excellence (NICE). Improving outcomes in urological cancers, 2002 (5)
- European Association of Urology (EAU) guideline on muscle-invasive and metastatic bladder cancer, 2011 (6)
- Moffit Centre, Florida guideline on bladder preservation in muscle-invasive bladder cancer, 2004 (7)

Indications for radiotherapy

All the indications for external beam radiotherapy in the original CCORE model of optimal radiotherapy utilisation for bladder cancer have been reviewed and updated based on the latest guideline recommendations (Table 1). *There are some modifications to the indications previously reported on medically inoperable bladder cancers (Table 1 and Figure 1); all other previous radiotherapy (RT) indications remain supported by current evidence-based guidelines.*

Level of evidence

According to the methods applied for the previous radiotherapy utilisation model, the indications of radiotherapy for bladder have been derived from evidence-based treatment guidelines issued by major national and international organisations. The guidelines reviewed are those published after the previous radiotherapy utilisation study was completed (July 2003) up to 2011.

Based on guidelines review, all indications of radiotherapy for bladder cancer remain supported by level I-III evidence similar to those reported in the earlier model. Fourteen outcomes in the model have radiotherapy indications and of them 11 outcomes are supported by level I-II evidence comprising 34% population with bladder cancer (Table 1 and Figure 1).

Epidemiology of cancer stages

The epidemiological data in the bladder cancer utilisation tree have been reviewed to examine whether more recent data are available through extensive electronic search using the key words 'bladder cancer stage', 'epidemiology bladder cancer', 'incidence', 'local control', 'radiotherapy treatment', 'recurrence', 'survival', 'treatment outcome' in various combinations. Table 2 provides an updated list of data used and assessment of the hierarchical quality of that data (Table 2). Since the completion of the previous radiotherapy utilisation project the national data on cancer statistics published by AIHW have been updated to 2008 (8). In 2008, urinary bladder cancer accounted for 2.0% of all cancers in Australia.

Estimation of the optimal radiotherapy utilisation

From the evidence on the efficacy of radiotherapy and the most recent epidemiological data on the occurrence of indications for radiotherapy, the proportion of bladder cancer patients in whom radiotherapy would be recommended is 47% (Table 1 and Figure 1) compared with the original estimate of 58%. The change is due to changes in epidemiological data for bladder cancer in different stages. A considerable proportion of medically inoperable bladder cancer patients may not be offered radical therapy because of their age, co-morbidity or poor performance status (9). Overall, 35% of bladder cancer patients in Australia in 2008 were aged 80 years and over and would be unlikely to tolerate any radical treatment (8).

Estimation of the optimal combined radiotherapy and chemotherapy utilisation

The indications of radiotherapy for bladder cancer were reviewed to identify those indications where radiotherapy is recommended in conjunction with concurrent chemotherapy as the first treatment. According to the best available practice evidence there is only one indication for combined chemotherapy and radiotherapy, medically inoperable locally advanced (stage II-III) bladder cancer fit for radical treatment for which concurrent chemoradiation (CRT) was beneficial over radiotherapy alone as the first indicated treatment. Concurrent CRT benefit was noted for local control only, no change was noted for distant metastasis control or overall survival (10). Our model predicted that 9% of bladder cancer patients unsuitable for surgery would benefit from addition of CRT over RT alone (Table 3).

Sensitivity analysis

Univariate sensitivity analysis has been undertaken to assess changes in the recommended bladder cancer radiotherapy utilisation rate that would result from different estimates of the proportions of patients with particular attributes as mentioned in Table 2 (Figure 3). The variability in the estimate of optimal radiotherapy utilisation due to these uncertainties ranged from 39% to 53% as shown in the Tornado diagram (Figure 3).

Table 1: Bladder Cancer. Indications for radiotherapy - Levels and sources of evidence

Original RTU study				Updates 2011					
Outcome No. in Tree	Clinical Scenario	Level of evidence	Proportion of all bladder cancer	Change of Indication	Guideline updated	Current level of evidence	Change to proportion of all bladder cancer		References
							Yes/ No	Updated value	
1	Bladder cancer, Stage I, local recurrence or progression, age <75 yrs, local recurrence after cystectomy	III	<0.01	No	Yes	III	Yes	0.01	NCCN (1), NCI PDQ (2), FRACP (3), SIGN (4), NICE (5)
2	Stage I, local recurrence or progression, age <75 yrs, no local recurrence, distant recurrence, brain metastases	II	<0.01	No	Yes	II	No	<0.01	NCCN (1), NCI PDQ (2), SIGN (4), NICE (5), EAU (6)

Original RTU study				Updates 2011					
Outcome No. in Tree	Clinical Scenario	Level of evidence	Proportion of all bladder cancer	Change of Indication	Guideline updated	Current level of evidence	Change to proportion of all bladder cancer		References
							Yes/ No	Updated value	
3	Stage I, local recurrence or progression, <75yrs, distant recurrence, painful bone metastases	I	<0.01	No	Yes	I	No	<0.01	NCCN (1), NCI PDQ (2), SIGN (4), NICE (5), EAU (6)
6	Stage I, local recurrence or progression, >=75 yrs	III	0.07	No	Yes	III	Yes	0.08	NCCN (1), NCI PDQ (2), FRACP (3)
7	Stage I, no local recurrence, distant recurrence, brain metastases	II	<0.01	No	Yes	II	Yes	0.02	NCCN (1), NCI PDQ (2), SIGN (4), NICE (5), EAU (6)
8	Stage I, no local recurrence, distant recurrence, painful bone metastases	I	0.01	No	Yes	I	Yes	0.05	NCCN (1), NCI PDQ (2), SIGN (4), NICE (5), EAU

Original RTU study				Updates 2011					
Outcome No. in Tree	Clinical Scenario	Level of evidence	Proportion of all bladder cancer	Change of Indication	Guideline updated	Current level of evidence	Change to proportion of all bladder cancer		References
							Yes/ No	Updated value	
11	Stages II-III, operable, locoregional recurrence	III	<0.01	No	Yes	III	Yes	0.04	NCCN (1), NCI PDQ (2), SIGN (4), NICE (5)
12	Stages II-III, operable, no locoregional recurrence, distant recurrence, brain metastases	II	<0.01	No	Yes	II	No	0.01	NCCN (1), NCI PDQ (2), SIGN (4), NICE (5), EAU (6)
13	Stages II-III, operable, no locoregional recurrence, distant recurrence, painful bone metastases	I	<0.01	No	Yes	I	Yes	0.03	NCCN (1), NCI PDQ (2), SIGN (4), NICE (5), EAU (6)

Original RTU study				Updates 2011					
Outcome No. in Tree	Clinical Scenario	Level of evidence	Proportion of all bladder cancer	Change of Indication	Guideline updated	Current level of evidence	Change to proportion of all bladder cancer		References
							Yes/ No	Updated value	
16	Stages II-III, medically inoperable, fit for radical treatment	Revised indication	N/A	N/A	Yes	II	N/A	0.09	NCCN (1), NCI PDQ (2), FRACP (3), SIGN (4), NICE (5), EAU (6), Moffit Centre (7)
17	Stages II-III, medically inoperable, not fit for radical treatment, symptomatic with palliative RT indication	Revised indication	N/A	N/A	Yes	II	N/A	0.04	NCCN (1), NCI PDQ (2), SIGN (4), NICE (5), EAU (6)
19	Stage IV, symptomatic	II	0.07	No	Yes	II	Yes	0.05	NCCN (1), NCI PDQ (2), SIGN (4), NICE (5), EAU (6)

Original RTU study				Updates 2011					
Outcome No. in Tree	Clinical Scenario	Level of evidence	Proportion of all bladder cancer	Change of Indication	Guideline updated	Current level of evidence	Change to proportion of all bladder cancer		References
							Yes/ No	Updated value	
20	Stage IV, not symptomatic, brain metastases	II	0.01	No	Yes	II	No	0.01	NCCN (1), NCI PDQ (2), SIGN (4), NICE (5), EAU (6)
21	Stage IV, not symptomatic, painful bone metastases	I	0.03	No	Yes	I	Yes	0.04	NCCN (1), NCI PDQ (2), SIGN (4), NICE (5), EAU (6)
Proportion of all bladder cancer patients in whom radiotherapy is recommended			0.58	**Updated proportion of all bladder cancer patients in whom radiotherapy is recommended**				**0.47**	

Table 2: Bladder Cancer; The incidence of attributes used to define indications for radiotherapy

Original RTU study				Updates 2011			
Population or sub-population of interest	**Attribute**	**Proportion of population with the attribute**	**Quality of Information**	**Change in proportion of population with attribute Yes/ No**	**Altered Proportion**	**Updated quality of information**	**Updated Reference**
All registry cancers	Bladder cancer	0.03	α	Yes	0.02	α	AIHW 2011 (8)
Bladder cancer	Stage I	0.46	β	Yes	0.51	γ	SEER 2011 (11)
Stage I	Local recurrence/ progression after conservative treatment	0.32	ε	No	0.32	ε	Larsson P 2003 (12)
Stage I, local recurrence	Age< 75 years to undergo cystectomy	0.53	β	No	N/A	N/A	South Australian Hospital Registry 2000 (13)
Stage I, local recurrence, age <75 yrs treated with radical cystectomy	Local recurrence after cystectomy	0.04	ζ	Yes	0.15	γ	Visser et al 2005 (14)

Original RTU study				Updates 2011			
Population or sub-population of interest	**Attribute**	**Proportion of population with the attribute**	**Quality of Information**	**Change in proportion of population with attribute Yes/ No**	**Altered Proportion**	**Updated quality of information**	**Updated Reference**
Stage I, local recurrence, <75 yrs treated with radical cystectomy, no repeat local recurrence	Distant recurrence	0.09	θ	No	N/A	N/A	Herr et al 1995 (15)
Stage I, local recurrence, <75 yrs, cystectomy, no repeat local recurrence, distant recurrence	Brain metastases	0.01 0.12	ζ ζ	No	N/A	N/A	Slaton et al 1999 (16) Sternberg et al 1989 (17)
Stage I, local recurrence, <75 yrs, cystectomy, distant recurrence, no brain metastases	Painful bone metastases	0.43 0.17	ζ ζ	No	N/A	N/A	Slaton et al 1999 (16) Sengelov et al 1996 (18)

Original RTU study				Updates 2011			
Population or sub-population of interest	**Attribute**	**Proportion of population with the attribute**	**Quality of Information**	**Change in proportion of population with attribute Yes/ No**	**Altered Proportion**	**Updated quality of information**	**Updated Reference**
Stage I, no local recurrence	Distant recurrence	0.05	ζ	No	N/A	N/A	Slaton et al 1999 (16)
Stage I, no local recurrence, distant recurrence	Brain metastases	0.01 0.12	ζ ζ	No	N/A	N/A	Slaton et al 1999 (16) Sternberg et al 1989 (17)
Stage I, no local recurrence, distant recurrence, no brain metastases	Painful bone metastases	0.43 0.17	ζ ζ	No	N/A	N/A	Slaton et al 1999 (16) Sengelov et al 1996 (18)
Bladder Cancer	Stages II-III	0.38	β	Yes	0.34	γ	SEER 2011 (11)
Stages II-III	Medically operable	0.0 0.47	μ β	Yes	0.30 0.60	γ γ	Visser et al 2005 (14) Scrimger et al 2001 (9)
Stages II-III, operable	Locoregional recurrence	0.08	ζ	Yes	0.19	γ	Visser et al 2005 (14)
Stages II-III, operable, no local recurrence	Distant recurrence	0.31	ζ	Yes	0.40	ζ	Louie-Johnsun et al 2007 (19)

Original RTU study				Updates 2011			
Population or sub-population of interest	**Attribute**	**Proportion of population with the attribute**	**Quality of Information**	**Change in proportion of population with attribute Yes/ No**	**Altered Proportion**	**Updated quality of information**	**Updated Reference**
Stages II-III, operable, no local recurrence, distant recurrence	Brain metastases	0.01 0.12	ζ ζ	No	N/A	N/A	Slaton et al 1999 (16) Sternberg et al 1989 (17)
Stages II-III, operable, no local recurrence, distant recurrence, no brain metastases	Painful bone metastases	0.43 0.17	ζ ζ	No	N/A	N/A	Slaton et al 1999 (16) Sengelov et al 1996 (18)
Stages II-III, medically inoperable	Fit for radical treatment	Revised indication	N/A	N/A	0.65	α	AIHW 2011 (8)
Stages II-III, medically inoperable, not fit for radical treatment	Symptomatic with palliative RT indication	Revised indication	N/A	N/A	0.88	θ	Duchesne et al 2000 (20)
Stage IV	Symptomatic primary tumour	0.43	ζ	Yes	0.36	θ	Duchesne et al 2000 (20)

Original RTU study				Updates 2011			
Population or sub-population of interest	**Attribute**	**Proportion of population with the attribute**	**Quality of Information**	**Change in proportion of population with attribute Yes/ No**	**Altered Proportion**	**Updated quality of information**	**Updated Reference**
Stage IV, no symptomatic primary	Brain metastases	0.01 0.12	ζ ζ	No	N/A	N/A	Slaton et al 1999 (16) Sternberg et al 1989 (17)
Stage IV, no symptomatic primary, no brain metastases	Painful bone metastases	0.43 0.18	ζ ζ	No	N/A	N/A	Slaton et al 1999 (16) Sengelov et al 1996 (18)

Table 3: Bladder Cancer. Indications for concurrent chemoradiotherapy (CRT) - Levels and sources of evidence

Outcome No. in Tree	Clinical Scenario	Level of Evidence	References	Proportion of all bladder cancer patients
16	Stage II-III bladder cancer, medically inoperable, fit for radical treatment	III	NCCN (1), NCI PDQ (2), FRACP (3), Moffit Centre (7)	0.09
The total proportion of all patients with bladder cancer in whom concurrent chemoradiotherapy (CRT) is recommended				0.09(9%)

Figure 1. Bladder Cancer Radiotherapy Utilization Tree

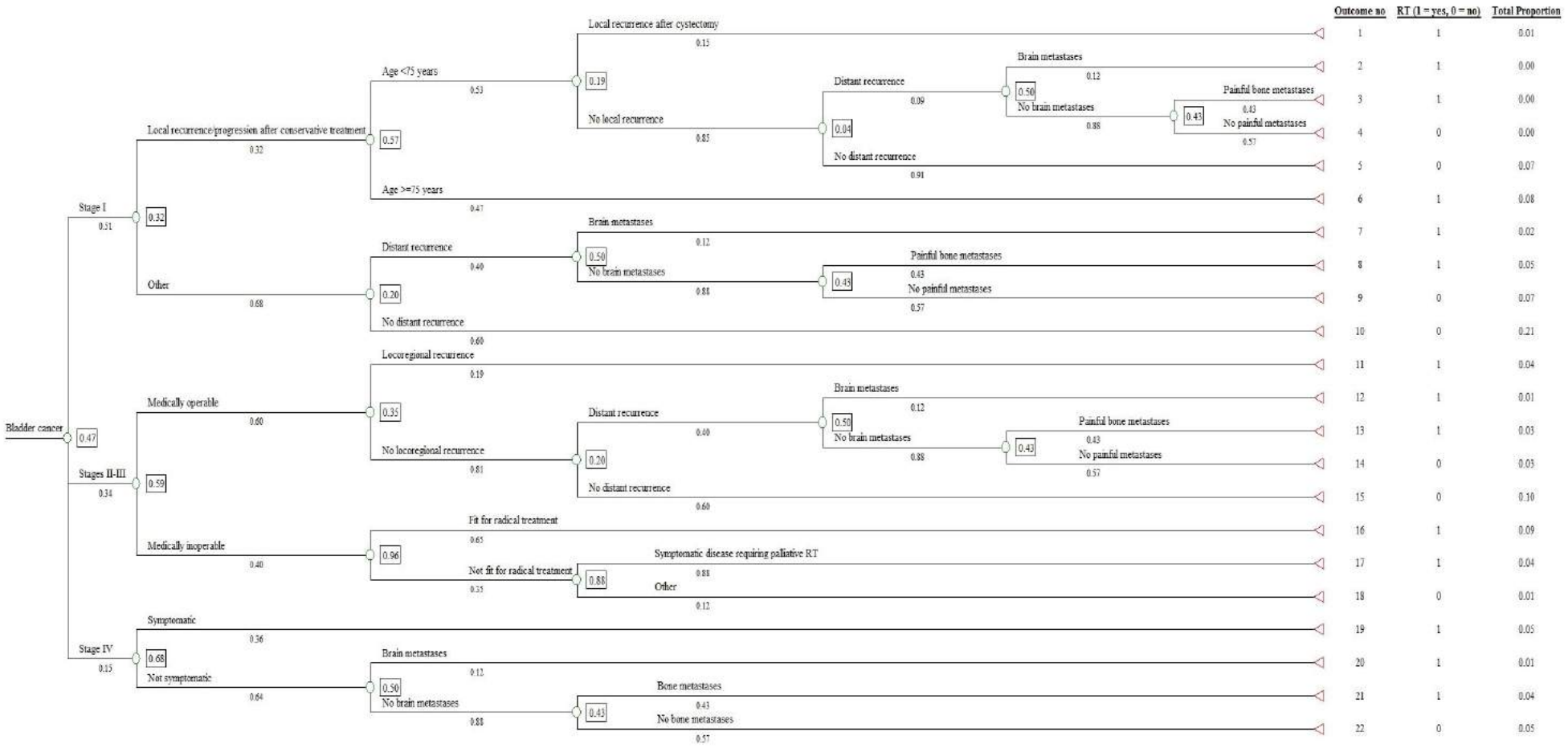


Figure 2. Bladder Cancer Concurrent ChemoRadiotherapy (CRT) Utilization Tree

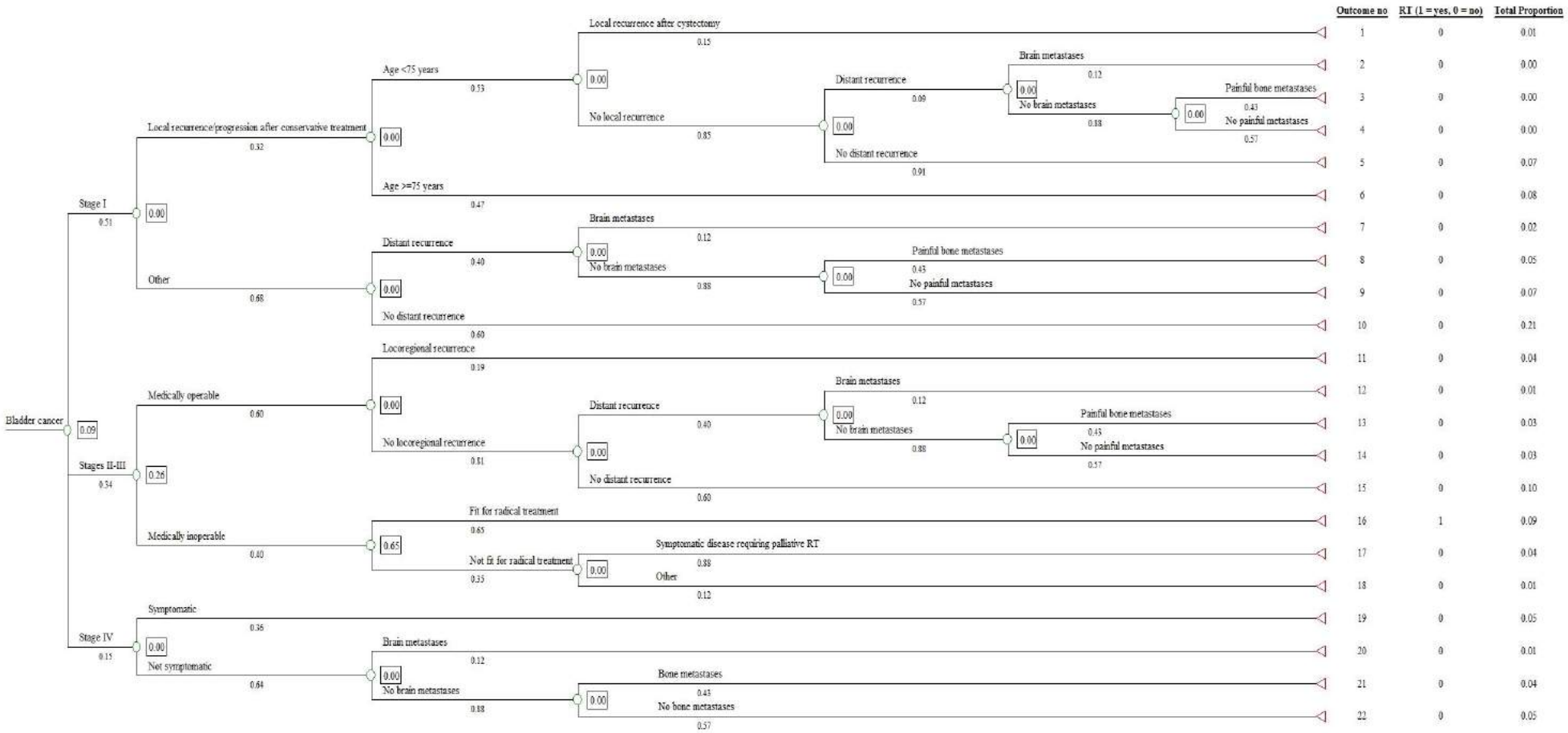
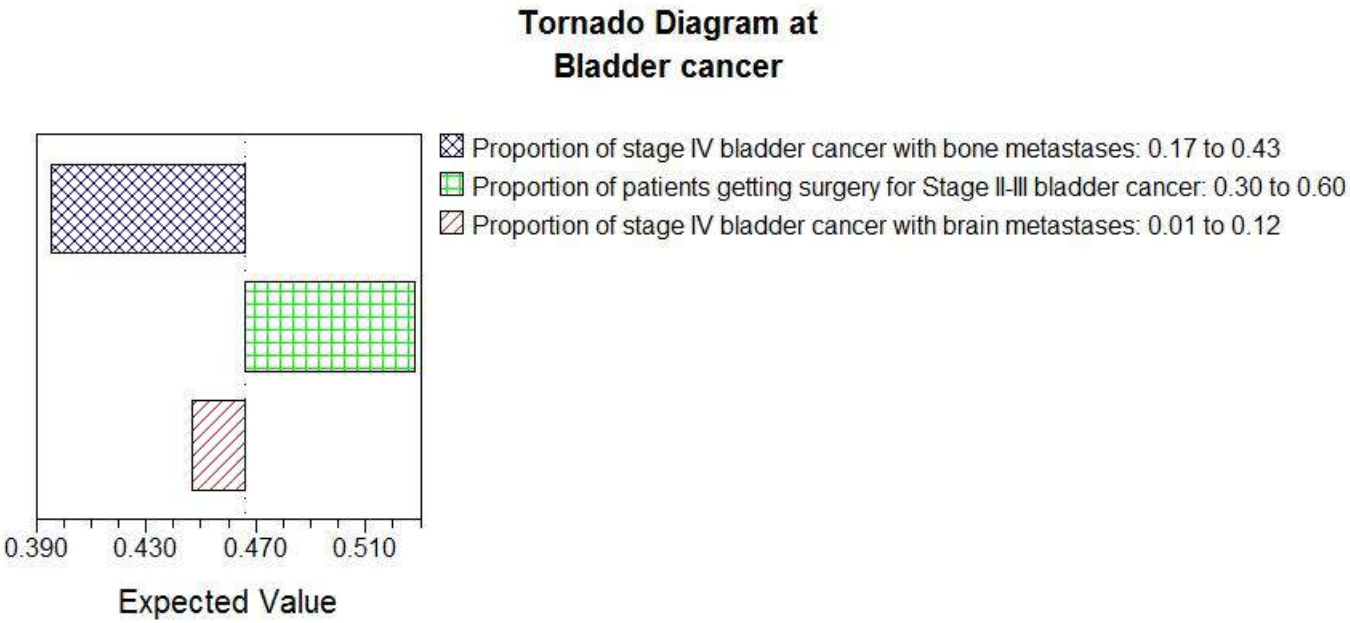


Figure 3. Tornado diagram for univariate sensitivity analyses



References

1. National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology: Bladder cancer.Version 2.2012. 2011.

2. National Cancer Institute (NCI). Bladder cancer treatment (PDQ). 2012.

3. Arianayagam R, Arianayagam M, Rashid P. Bladder cancer current management. Australian Family Physician 2011;40(4):209-13.

4. Scottish Intercollegiate Guidelines Network (SIGN). Management of transitional cell carcinoma of the bladder. A national clinical guideline. Edinburgh: SIGN, Royal College of Physicians; 2005.

5. National Institute for Health and Clinical Excellence (NICE). Guidence on cancer services: Improving outcomes in urological cancers . London: NICE; 2002.

6. Stenzl A, Cowan NC, Santis ME, et al. Treatment of muscle-invasive and metastatic bladder cancer: Update of the EAU Guidelines. European Urology 2011;59:1009-18.

7. Torres-Roca JF. Bladder preservation protocols in the treatment of muscle-invasive bladder cancer. Moffitt Cancer Center & Research Institute, Tampa, Florida; 2004.

8. Australian Institute of Health and Welfare (AIHW). Australian Cancer Incidence and Mortality (ACIM) books. Available from http://www aihw gov au/acim-books/ 2012 [cited 2012 Apr 16];

9. Scrimger RA, Murtha AD, Parliament MB, et al. Muscle-invasive transitional cell carcinoma of the urinary bladder: a population-based study of patterns of care and prognostic factors. Int J Radiat Oncol Biol Phys 2001 Sep 1;51(1):23-30.

10. Coppin CM, Gospodarowicz MK, James K, Tannock IF, Zee B, Carson J, et al. Improved local control of invasive bladder cancer by concurrent cisplatin and preoperative or definitive radiation. The National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol 1996 Nov;14(11):2901-7.

11. Surveillance Research Program, National Cancer Institute SEER*Stat software (seer.cancer.gov/seerstat). Version 7.0.5. [computer program]. Bethesda, MD: National Cancer Institute (NCI); 2011.

12. Larsson P, Wijkstrom H, Thorstenson A, Adolfsson J, Norming U, Wiklund P, et al. A population-based study of 538 patients with newly detected urinary bladder neoplasms followed during 5 years. Scand J Urol Nephrol 2003;37(3):195-201.

13. SA Cancer Registry. 2000 Cancer Report - Epidemiology of Cancer in South Australia 1977-1999. http://www health sa gov au/pehs/cancer-report2000 htm 2000 [cited 2007 Nov 26];

14. Visser O, Nieuwenhuijzen JA, Horenblas S. Local recurrence after cystectomy and survival of patients with bladder cancer: a population based study in Greater Amsterdam. J Urol 2005 Jul;174(1):97-102.

15. Herr HW, Schwalb DM, Zhang ZF, et al. Intravesical Bacillus Calmette-Guerin therapy prevents tumor progression and death from superficial bladder cancer: ten-year follow-up of a prospective randomized trial. J Clin Oncol 1995;13:1404-8.

16. Slaton JW, Swanson DA, Grossman HB, Dinney CPN. A stage specific approach to tumor surveillance after radical cystectomy for transitional cell carcinoma of the bladder. J Urol 1999;162(3-I):710-4.

17. Sternberg CN, Yagoda A, Scher HI, Watson RC, et al. Methotrexate, Vinblastine, Doxorubicin and Cisplatin for advanced transitional cell carcinoma of the urothelium. Cancer 1989;64:2448-58.

18. Sengelov L, Kamby C, von der Maase H. Pattern of metastses in relation to characteristics of primary tumor and treatment in patients with disseminated urothelial carcinoma. J Urol 1996;155:111-4.

19. Louie-Johnsun MW, Braslis KG, Murphy DL, Neerhut GJ, Grills RJ. Radical cystectomy for primary bladder malignancy: a 10 year review. ANZ J Surg 2007 Apr;77(4):265-9.

20. Duchesne GM, Bolger JJ, Griffiths GO, et al. A randomized trial of hypofractionated schedules of palliative radiotherapy in the management of bladder carcinoma: results of medical research council trial BA09. Int J Radiat Oncol Biol Phys 2000 May 1;47(2):379-88.

BRAIN CANCER

The brain tumours included in this study are primary malignant brain tumours arising from neuro-epithelial tissue in the brain. Metastatic brain tumours are discussed in the section on the relevant primary cancer.

Updated Guidelines

The following new guidelines were identified since the original RTU study:

1. Australian Cancer Network Guidelines published in 2009 (1)
2. NICE guidelines published in 2006 (2)
3. ESMO guidelines published in 2010 (3)
4. European (EFNS-EANO)guidelines on low-grade gliomas published in 2010 (4)

The following guidelines have been updated:

1. NCI-PDQ (adult brain tumors) updated on 07/08/2010 (5)
2. NCCN guidelines updated in 2011 (6)
3. NCI-PDQ (childhood astrocytomas treatment) updated on 20/05/2011 (7)
4. NCI-PDQ (childhood central nervous system embryonal tumors) updated on 19/05/2011 (8)

Changes to Radiotherapy Indications

All the indications for external beam radiotherapy in the original CCORE model of optimal radiotherapy utilisation for brain cancer have been reviewed and updated in the optimal utilisation tree based on the latest guideline recommendations (see Figure 1 and Table 1). The following indications for radiotherapy have changed since 2002 (when the original optimal radiotherapy utilisation report was published).

Low-grade astrocytoma

The ACN guidelines state that “Consensus opinion is that for the majority of low grade astrocytoma (LGA) patients, an initial policy of observation post-surgery is appropriate, with treatment being deferred until there is clear radiological or symptomatic progression” (1).

The ACN guidelines also state that “the policy of initial observation is not appropriate for patients with high-risk features who demonstrate early progression and poor median survival”. The proportion of patients who have high-risk features is very low [patients with LGA constitute only 1.6% of all brain cancers; 26% of all patients with LGA have high-risk features (9)]. The data available on progression rates of LGA from the EORTC trial refers to all patients with LGA and is not confined to low-risk

patients, hence the low risk/high risk groups are not separated out in the tree (in any case the number of patients involved would be extremely small). In the optimal radiotherapy utilisation tree, radiotherapy is recommended for all LGAs on progression.

Oligodendroglioma

The Australian ACN guidelines recommend radiotherapy as standard treatment for high-grade oligodendrogliomas (1). In low-grade tumours, the ACN guidelines state that observation is acceptable in patients with gross technical resection, and good prognostic features (age < 40 yrs, low grade, 1p-,19q-), "thus allowing patients to avoid the risk of long-term radiotherapy toxicities until disease progression".

In the optimal radiotherapy utilisation tree, radiotherapy is recommended for all patients with oligodendroglioma since it will be recommended either as part of the initial treatment (following resection) or at progression. The behaviour of low-grade oligodendrogliomas is such that all will eventually undergo progression; El Hateer et al conducted a retrospective review of low-grade oligodendrogliomas in which the 5, 10 and 15-year progression-free survival rates were 46, 7.7 and 0% respectively (10).

Pilocytic Astrocytoma

The ACN guidelines, NCCN guidelines and NICE guidelines do not include guidance for management of paediatric brain tumours. Only the NCI PDQ guidelines discuss the management of paediatric brain tumours (7).

NCI PDQ: "Surgical resection is the primary treatment for childhood low-grade astrocytoma and surgical feasibility is determined by tumor location. Radiation therapy is usually reserved until progressive disease is documented, and its use may be further delayed through the use of chemotherapy, a strategy that is commonly employed in young children. Patients with low-grade astrocytomas who relapse after being treated with surgery alone should be considered for another surgical resection. If this is not feasible, local radiation therapy is the usual treatment."

Burkhard et al (11) in a population-based study of 55 patients with pilocytic astrocytoma reported that only 13% of patients received radiotherapy and concluded that "because of the benign biological behaviour of pilocytic astrocytomas and advances in microneurosurgery, the survival rates for patients with these tumours are excellent, regardless of postoperative radiotherapy". The authors go on to state that in their opinion "postsurgery adjuvant therapy is unnecessary." Due-Tonnessen et al conducted a retrospective study of 110 consecutive patients with cerebellar astrocytoma and found that spontaneous regression of residual tumour is more frequent than growth of residual tumour (12). Only 5 patients (5%) in their series received radiotherapy and they state that "at present we avoid RT

in patients with benign cerebellar astrocytomas". Benesch et al reported that 9% of patients with pilocytic astrocytoma in their series received radiotherapy (13).

The role of adjuvant radiotherapy in pilocytic astrocytomas is not clear since tumour recurrence following surgery may be treated by watchful waiting, second surgery, chemotherapy or radiotherapy. Recent publications have reported that they tend to avoid radiotherapy in this group due to the long-term side-effects in children (11-13) . In the optimal radiotherapy utilisation tree, radiotherapy is recommended for 13% of patients with pilocytic astrocytoma, based on the actual radiotherapy rate reported by Burkhard et al which is population-based and includes all pilocytic astrocytomas regardless of their site (the other two series include only cerebellar tumours).

Ependymoma

The ACN, NICE and ESMO guidelines do not review the management of intracranial ependymoma. The NCCN guidelines state that "the survival benefits of RT following surgical recovery have been established for anaplastic ependymomas and suboptimally resected tumours. The value of RT is more controversial for differentiated ependymomas, with data demonstrating improved survival mainly for subtotally resected tumors" (6).

The NCI PDQ guidelines state that grade II ependymal tumours can be "treated by surgery alone if the tumor is totally resectable; surgery followed by radiation therapy to known or suspected residual tumor". These guidelines also state that anaplastic ependymoma should be treated by surgery plus radiation therapy" (5).

Astrocytoma NOS and other Astrocytomas

Astrocytoma Not Otherwise Specified (NOS) is a non-specific histological diagnosis that is not included in the WHO histological classification of brain tumours; hence none of the guidelines discuss the management of patients with this diagnosis. The incidence of astrocytoma NOS and glioma NOS has been decreasing over time, probably due to improvements in diagnosis and histological classification (14;15).

However all available epidemiological databases of brain tumours, including the recent 2011 data used in the updated tree, include a proportion of cases with NOS diagnoses. In the optimal utilisation tree, we have made the assumption that most cases of astrocytoma NOS are low-grade astrocytomas, (since it would be comparatively easier to make a histological diagnosis of high grade astrocytoma). Therefore 77% of this group of tumours are recommended to receive radiotherapy (this is the estimated optimal radiotherapy utilisation rate for low-grade astrocytic tumours).

Level of evidence

Out of nine outcome branches in the model that have an indication for radiotherapy (Figure 1), 5 branches are supported by level I-II evidence. The updated model predicts that 70% of the whole brain cancer population have an indication for radiotherapy based on level I-II evidence of benefit.

Changes in Epidemiological Data

Incidence of Brain Cancer:

Since the publication of the previous radiotherapy utilisation project, the Australian national cancer incidence data published by the Australian Institute of Health and Welfare (AIHW) has been updated, with the most recent data available being 2007 data. The latest ACIM (Australian Cancer Incidence and Mortality) book published by AIHW in 2010 states that in 2007, brain cancer accounted for 1.4% of all cancer in Australia (16). In the original model of radiotherapy utilisation, brain cancer accounted for 2% of all cancers in Australia based on AIHW data for the year 1998.

Incidence by Histological Type

The Central Brain Tumor Registry of the United States (CBTRUS) contains the largest aggregation of population–based data on the incidence of all primary brain and CNS tumors in the United States. The CBTRUS report published in February 2011 contains data on primary brain tumours diagnosed in the United States in the years 2004-2007(17). This report contains data collected from the National Program of Cancer Registries (NPCR) and states belonging to the National Cancer Institutes' Surveillance, Epidemiology and End Results (SEER) program as its data sources. Data from forty-eight population-based cancer registries were included. Since this is the largest and most recent population-based database of brain tumours available, these data were used in the optimal radiotherapy utilisation tree.

'Mixed' gliomas and "gliomas malignant NOS" together constitute around 10% of all gliomas in the CBTRUS database. These groups have been included under the overall 'Astrocytoma' branch in the optimal utilisation tree, since the treatment of these tumours is similar to the treatment recommended for astrocytomas. The branch "Astrocytoma NOS and other astrocytomas" in the optimal radiotherapy utilisation tree is composed of the groups 'Astrocytoma, NOS' and 'unique astrocytoma variants' from the CBTRUS database.

Proportion of low-grade astrocytomas that undergo progression

In 1986 the EORTC Radiotherapy and Brain Tumor groups initiated a prospective trial to compare early radiotherapy with delayed radiotherapy in low-grade gliomas (astrocytoma and oligodendroglioma) in adults. The long term results after a median follow-up of 7.8 years were reported in 2005 by van den Bent et al (18); 96 out of 124 patients (77%) in the control arm (deferred

radiotherapy until the time of progression) progressed. This data has been used in the updated radiotherapy utilisation tree.

Histological grading of ependymomas

Metellus et al (19) reported on the results of a multicentric French study of 152 adult patients with intracranial ependymomas; 109 patients (72%) were diagnosed with WHO grade II and 43 patients (28%) with grade III tumours.

Other authors have reported on smaller series of patients with ependymoma which were not used in the tree due to the smaller numbers involved (20;21). Rodriguez et al (22) reported on 2408 cases from the SEER database but data on intracranial tumors could not be separated from data on spinal tumors and hence these data were not used in the tree.

Extent of surgery of low-grade ependymomas

Metellus et al (19) reported on the results of a multicentric French study of 152 adult patients with intracranial ependymomas; of the 109 patients who were diagnosed with WHO grade II, 64 (59%) had total resection of the tumour while 45 (41%) had incomplete tumour resection.

Estimation of Optimal Radiotherapy Utilisation

From the evidence on the efficacy of radiotherapy and the most recent epidemiological data on the occurrence of indications for radiotherapy, the proportions of brain cancer patients in whom radiotherapy would be recommended is 80% (Table 1 and Figure 1). The original optimal radiotherapy utilisation rate derived in 2003 was 92%. The main reason for the decrease in the utilisation rate is due to the epidemiological re-distribution of the histological types of brain cancer, based on the most recently available population-based data. Some indications for radiotherapy have also changed as described above.

Concurrent Chemoradiotherapy in Brain Cancer

The indications for radiotherapy for brain cancer were reviewed to identify those indications where radiotherapy is recommended in conjunction with concurrent chemotherapy as the 1st treatment. These combined chemotherapy and radiotherapy indications (chemoradiation) are listed as an additional payoff in the overall utilisation tree (Table 3 and Figure 2).

According to the best available practice evidence the optimal proportion of brain cancer patients for whom chemoradiation is beneficial is 53%. All patients with newly diagnosed glioblastoma multiforme who are considered fit for radical therapy are recommended to have surgical resection followed by

radiotherapy with concurrent temozolomide and post-radiation adjuvant temozolomide. This is recommended by all the guidelines based on the evidence of Stupp et al, who demonstrated in a randomised trial of 573 patients with glioblastoma multiforme that daily temozolomide administered with postoperative RT followed by adjuvant temozolomide resulted in significantly better median survival and 2-year survival when compared with radiotherapy alone (23).

Figure 1. Revised Brain Cancer Optimal Radiotherapy Utilisation Tree

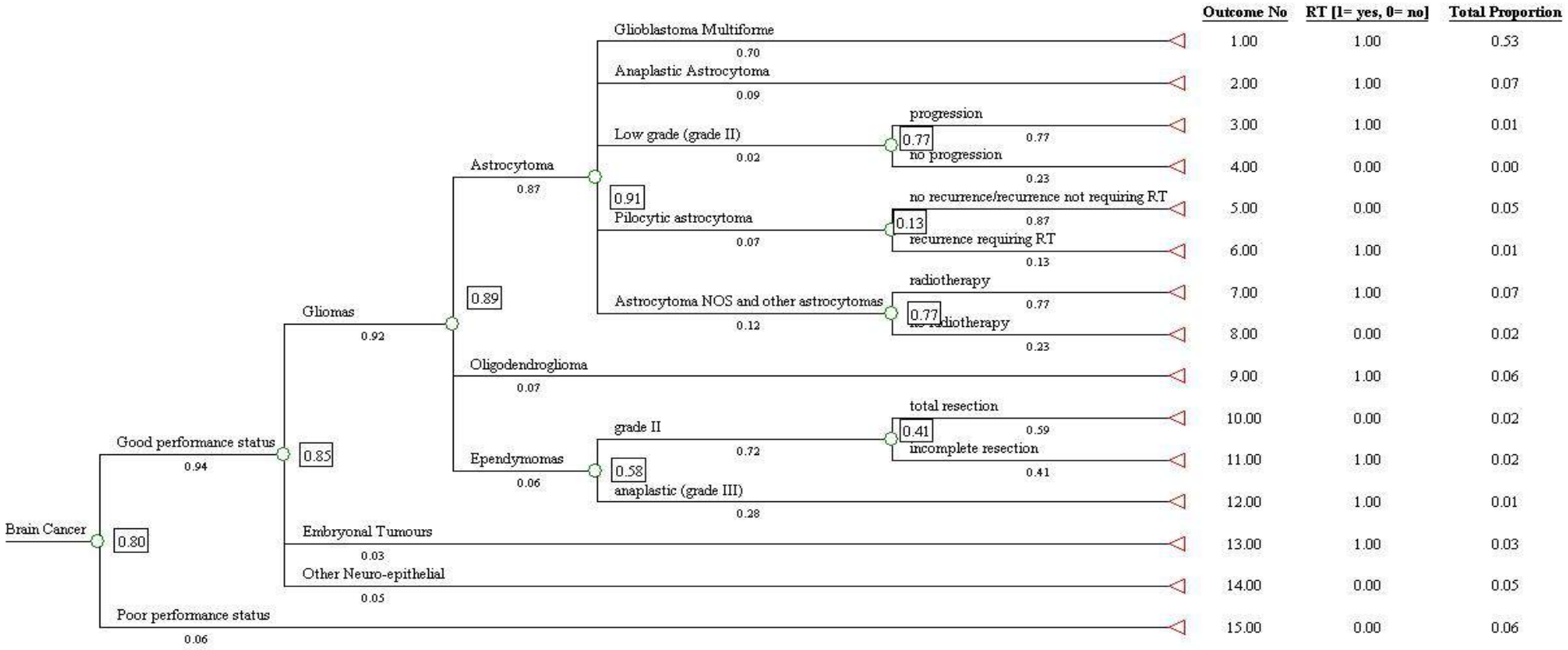


Table 1: Brain Cancer. Indications for radiotherapy - Levels and sources of evidence

Updates 2011							
Outcome No. in Tree	Clinical Scenario	Change of Indication	Guideline updated	Current level of evidence	Change to proportion of all brain cancer		References
					Yes/ No	Updated value	
1	Brain Cancer, good PS, Glioblastoma Multiforme	No	Yes	I	Yes	0.53	ACN guidelines (1), NCI PDQ (5), NCCN (6), ESMO (3), NICE (2)
2	Brain Cancer, good PS, Anaplastic Astrocytoma	No	Yes	I	Yes	0.07	ACN guidelines (1), NCI PDQ (5), NCCN (6), ESMO (3), NICE (2)
3	Brain Cancer, good PS, Low-grade Astrocytoma, progression	Yes	Yes	II	Yes	0.01	ACN guidelines (1), NCI PDQ (5), NCCN (6), NICE (2)
6	Brain Cancer, good PS, Pilocytic Astrocytoma, recurrence requiring RT	Yes	Yes	III	Yes	0.01	NCI PDQ (Childhood Astrocytomas) (7)
7	Brain Cancer, good PS, Astrocytoma NOS and other astrocytomas	Yes	N/A	N/A	Yes	0.07	Treatment of Astrocytoma “NOS” is not described in any guidelines.

Updates 2011							
Outcome No. in Tree	Clinical Scenario	Change of Indication	Guideline updated	Current level of evidence	Change to proportion of all brain cancer		References
					Yes/ No	Updated value	
9	Brain Cancer, good PS, Oligodendroglioma	Yes	Yes	II	Yes	0.06	ACN guidelines (1), NCI PDQ (5), NCCN (6), NICE (2)
11	Brain Cancer, good PS, Ependymoma, grade II, incomplete resection	Yes	Yes	IV	Yes	0.02	NCI PDQ (5), NCCN (6),
12	Brain Cancer, good PS, Ependymoma, anaplastic	Yes	Yes	III	Yes	0.01	NCI PDQ (5), NCCN (6),
13	Brain Cancer, good PS, Embryonal tumours	No	Yes	II	Yes	0.03	NCI PDQ (CNS Embryonal Tumors) (8)
Updated proportion of all patients with brain cancer in whom radiotherapy is recommended						**0.80 (80%)**	
Original proportion of all patients with brain cancer in whom radiotherapy is recommended (2003 study)						0.92 (92%)	

Abbreviations: PS – performance status, ACN – Australian Cancer Network, ESMO - European Society for Medical Oncology, NCCN – National Comprehensive Cancer Network (USA), NCI PDQ – National Cancer Institute Physicians Data Query (USA), RT - radiotherapy

Levels of Evidence for Indications for Radiotherapy: Level I – evidence obtained from a systematic review of all relevant randomised controlled trials; Level II – evidence obtained from at least one properly-designed randomised controlled trial; Level III – evidence obtained from well-designed controlled trials without randomisation -these include trials with 'pseudo-randomisation' where a flawed randomisation method was used (eg. alternate allocation of treatments) or comparative studies with either comparative or historical controls; Level IV – evidence obtained from case series . Taken from the National Health and Medical Research Council (NHMRC) hierarchy of levels of evidence (24)

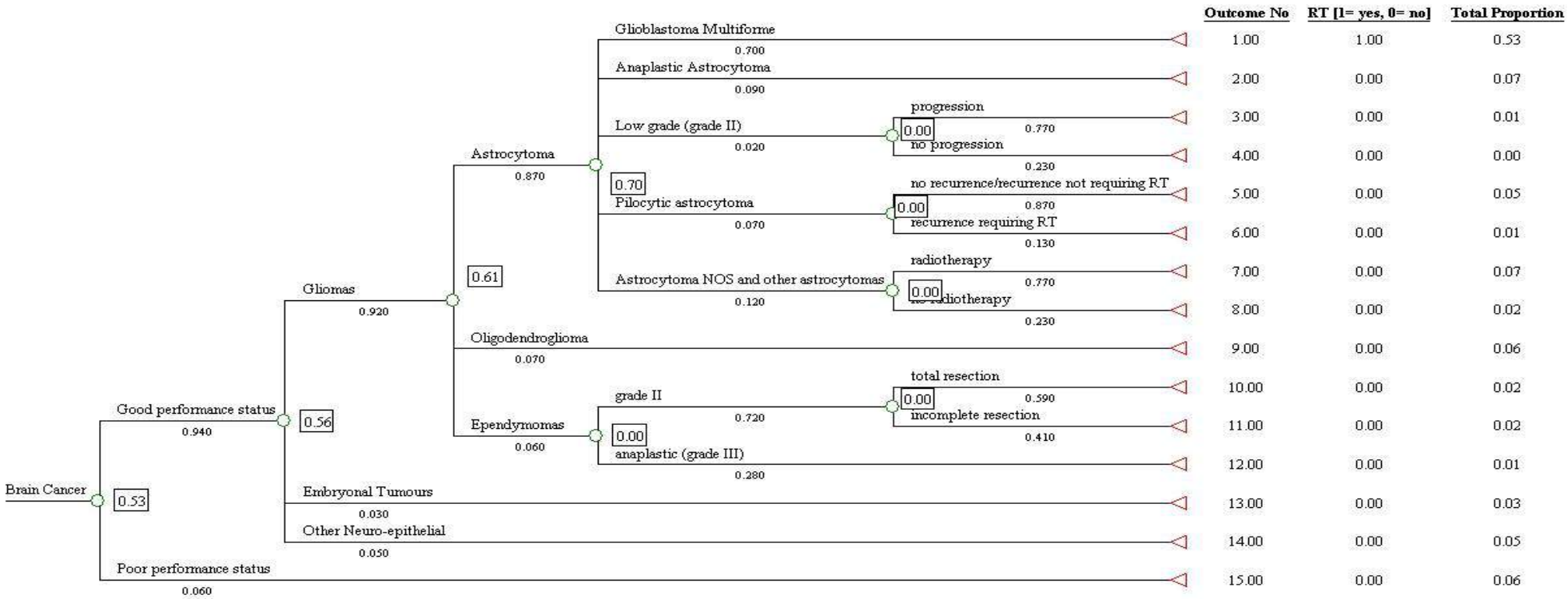
Table 2: Brain Cancer. The incidence of attributes used to define indications for radiotherapy

Population or subpopulation of interest	Attribute	Proportion of populations with this attribute	Quality of information	References
All registry Cancers	Brain Cancer	0.014 (1.4%)	α	AIHW 2007 (16)
Brain Cancer	Good Performance Status (PS)	0.94	ϵ	SA Hospital Registry (25)
Brain Cancer, good PS	Gliomas	0.92	γ	CBTRUS (17)
Brain Cancer, good PS, Gliomas	Astrocytoma	0.87	γ	CBTRUS (17)
Brain Cancer, good PS, Gliomas, Astrocytoma	Glioblastoma	0.70	γ	CBTRUS (17)
Brain Cancer, good PS, Gliomas, Astrocytoma	Anaplastic Astrocytoma	0.09	γ	CBTRUS (17)
Brain Cancer, good PS, Gliomas, Astrocytoma	Low grade (grade II) astrocytoma	0.02	γ	CBTRUS (17)
Brain Cancer, good PS, Gliomas, Astrocytoma, low grade astrocytoma (grade II)	Progression	0.77	ϵ	van den Bent et al (18)
Brain Cancer, good PS, Gliomas,	Pilocytic astrocytoma	0.07	γ	CBTRUS (17)

Population or subpopulation of interest	Attribute	Proportion of populations with this attribute	Quality of information	References
Astrocytoma				
Brain Cancer, good PS, Gliomas, Astrocytoma	Astrocytoma NOS and Other astrocytomas	0.12	γ	CBTRUS (17)
Brain Cancer, good PS, Gliomas, Astrocytoma NOS and Other astrocytomas	Radiotherapy indicated	0.77		Based on radiotherapy utilisation rate derived for LGA
Brain Cancer, good PS, Gliomas	Oligodendroglioma	0.07	γ	CBTRUS (17)
Brain Cancer, good PS, Gliomas	Ependymoma	0.06	γ	CBTRUS (17)
Brain Cancer, good PS, Gliomas, Ependymoma	Grade II	0.72	ϵ	Metellus et al (19)
Brain Cancer, good PS, Gliomas, Ependymoma, Grade II	Total resection	0.59	ϵ	Metellus et al (19)
Brain Cancer, good PS	Embryonal tumours	0.03	γ	CBTRUS (17)
Brain Cancer, good PS	Other Neuro-epithelial tumours	0.05	γ	CBTRUS (17)

NOTE: The indications for radiotherapy from the original 2002 RTU utilisation tree for brain cancer have not been included in Table 1 and the original epidemiological data have not been included in Table 2. The updated radiotherapy utilisation tree (2011) has been significantly altered from the original tree (2002) and therefore it is not possible to compare the indications, outcome numbers and epidemiological data from the two trees in one table.

Figure 2. Brain Cancer. Optimal Utilisation Tree for Concurrent Chemo-Radiation.



Outcome No	RT [1= yes, 0= no]	Total Proportion
1.00	1.00	0.53
2.00	0.00	0.07
3.00	0.00	0.01
4.00	0.00	0.00
5.00	0.00	0.05
6.00	0.00	0.01
7.00	0.00	0.07
8.00	0.00	0.02
9.00	0.00	0.06
10.00	0.00	0.02
11.00	0.00	0.02
12.00	0.00	0.01
13.00	0.00	0.03
14.00	0.00	0.05
15.00	0.00	0.06

Table 3: Brain Cancer. Indications for Concurrent Chemo-Radiation - levels and sources of evidence

Outcome no. in tree	Clinical scenario	Level of evidence	References	Proportion of all brain cancer patients
1	Brain Cancer, good PS, Glioblastoma multiforme	I	ACN guidelines (1), NCI PDQ (5), NCCN (6), ESMO (3), NICE (2)	0.53
The total proportion of all patients with brain cancer in whom Concurrent Chemo-Radiation is recommended				**0.53 (53%)**

References

1. Cancer Council Australia, Australian Cancer Network, and Clinical Oncological Society of Australia. Australian Cancer Network Adult Brain Tumour Guidelines Working Party. Clinical Practice Guidelines for the management of Adult Gliomas: Astrocytomas and Oligodendrogliomas. 2009. Sydney, Australia, Cancer Council Australia.
   Ref Type: Serial (Book,Monograph)

2. National Institute for Clinical Excellence. Improving Outcomes for people with brain and other CNS tumours. The Evidence Review.
   http://www.nice.org.uk/nicemedia/live/10905/28965/28965.pdf . 2006. 27-7-2011.
   Ref Type: Electronic Citation

3. Stupp R, Tonn JC, Brada M, Pentheroudakis G. High-grade malignant glioma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2010;21:v190-v193.

4. Soffietti R, Baumert BG, Bello L, et al. Guidelines on management of low-grade gliomas: report of an EFNS-EANO task force. *European Journal of Neurology* 2010;17:1124-33.

5. National Cancer Institute. PDQ Cancer Information Summaries: Treatment of Adult Brain Tumors. http://www.cancer.gov/cancertopics/pdq/treatment/adultbrain/healthprofessional/ . 2010.27-7-2011.
   Ref Type: Electronic Citation

6. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Central Nervous System Cancers. V.2.2011.
   http://www.nccn.org/professionals/physician_gls/PDF/cns.pdf . 31-1-2011. 27-7-2011.
   Ref Type: Electronic Citation

7. National Cancer Institute. PDQ Childhood Astrocytomas Treatment.
   http://www.cancer.gov/cancertopics/pdq/treatment/child-astrocytomas/HealthProfessional . 2011. 22-8-2011.
   Ref Type: Electronic Citation

8. National Cancer Institute. Childhood Central Nervous System Embryonal Tumors treatment (PDQ).
   http://www.cancer.gov/cancertopics/pdq/treatment/childCNSembryonal/healthprofessional . 2011.9-8-2011.
   Ref Type: Electronic Citation

9. Pignatti F, van den Bent M, Curran D, Debruyne C, et al. Prognostic factors for survival in adult patients with cerebral low-grade glioma. *J Clin Oncol* 2002;20:2076-84.

10. El-Hateer H, Souhami L, Rogerge D, et al. Low-grade oligodendroglioma: an indolent but incurable disease? *Journal Neurosurg* 2009;111:265-71.

11. Burkhard C, Di Patre P, Schuler D, Schuler G, et al. A population-based study of the incidence and survival rates in patients with pilocytic astrocytoma. *J Neurosurg* 2003;98:1170-4.

12. Due-Tonnessen BJ, Helseth E, Scheie D, et al. Long-term outcome after resection of benign cerebellar astrocytomas in children and young adults (0-19 years): report of 110 consecutive cases. *Pediatr Neurosurg* 2002;37:71-80.

13. Benesch M, Eder HG, Sovinz P, Raith J, et al. Residual or recurrent cerebellar low-grade glioma in children after tumor resection: is re-treatment needed? A single center experience from 1983 to 2003. *Pediatric Neurosurgery* 2006;42:159-64.

14. Hoffman S, Propp JM, McCarthy BJ. Temporal trends in incidence of primary brain tumors in the United States, 1985 - 1999. *Neuro-Oncology* 2006;8:27-37.

15. Jukich PJ, McCarthy BJ, Surawicz TS, Freels S, Davis FG. Trends in incidence of primary brain tumors in the United States, 1985-1994. *Neuro-Oncology* 2001;3:141-51.

16. Australian Institute of Health and Welfare (AIHW). Australian Cancer Incidence and Mortality (ACIM).Books.http://www.aihw.gov.au/acim-books/.2010.10-8-2011.
Ref Type: Electronic Citation

17. Central Brain Tumor Registry of the United States (CBTRUS). CBTRUS Statistical Report: Primary Brain and Central Nervous System Tumors diagnosed in the United States in 2004-2007.www.cbtrus.org.2011.
Ref Type: Electronic Citation

18. van den Bent MJ, Afra D, de Witte O, Ben Hassel M, Schraub S, et al. Long-term efficacy of early versus delayed radiotherapy for low-grade astrocytoma and oligodendroglioma in adults: the EORTC 22845 randomised trial. *Lancet* 2005;366:985-90.

19. Metellus P, Barrie M, Figarella-Branger D, Chinot O, et al. Multicentric French study on adult intracranial ependymomas: prognostic factors analysis and therapeutic considerations from a cohort of 152 patients. *Brain* 2007;130:1338-49.

20. Metellus P, Figarella-Branger D, Guyotat J, Barrie M, et al. Supra-tentorial ependymomas: prognostic factors and outcome analysis in a retrospective series of 46 adult patients. *Cancer* 2008;113:175-85.

21. Kawabata Y, Takahashi JA, Arakawa Y, Hashimoto N. Long-term outcome in patients harboring intracranial ependymoma. *J Neurosurg* 2005;103:31-7.

22. Rodriguez D, Cheung MC, Housri N, et al. Outcomes of malignant CNS ependymomas: an examination of 2408 cases through the Surveillance, Epidemiology and End Results (SEER) database (1973-2005). *Journal Surg Res* 2009;156:340-51.

23. Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med* 2005;352:987-96.

24. National Health and Medical Research Council. Guide to the development, implementation and evaluation of clinical practice guidelines. Appendix B, 56. 1998.
Ref Type: Report

25. SA Cancer Registry. Epidemiology of Cancer in South Australia. September 2000(Cancer Series No 22). 2000. Adelaide, South Australian Cancer Registry.
Ref Type: Serial (Book,Monograph)

BREAST CANCER

Evidence-based treatment guidelines for breast cancer management issued by major national and international organisations reviewed for the model are those published after the previous radiotherapy utilisation study was completed (July 2003) up to the most recent ones published in 2011.

Updated Guidelines

The following new or updated guidelines were identified and reviewed since the original RTU study:

- National Health &Medical Research Council (NHMRC). Clinical practice guidelines for the management of early breast cancer. Second edition, 2001 (1)
- National Health and Medical Research Council (NHMRC). Clinical practice guidelines for the management of advanced breast cancer, 2001 (2)
- National Comprehensive Cancer Network (NCCN). Clinical practice guidelines in oncology: Breast cancer, Version 2.2011 (3)
- National Cancer Institute (NCI). Breast Cancer Treatment (PDQ®), 2011 (4)
- BC Cancer Agency. Cancer Management Guidelines: Breast, 2011 (5)
- National Institute for Health and Clinical Excellence (NICE). Early and locally advanced breast cancer: Diagnosis and treatment. NICE clinical guideline no. 80, 2009 (6)
- Association of Breast Surgery at BASO. Surgical guidelines for the management of breast cancer, 2009 (7)
- Scottish Intercollegiate Guidelines Network (SIGN). Management of breast cancer in women: A national clinical guideline, 2005 (8)
- Recht A et al. Postmastectomy radiotherapy: clinical practice guidelines of the American Society of Clinical Oncology (ASCO), 2001 (9)
- Cancer Care Ontario (CCO). Breast irradiation in women with early stage invasive breast cancer following breast conserving surgery, 2010 (10)
- Shenkier et al. BC Cancer Agency (BCCA) Clinical practice guidelines for the care and treatment of breast cancer: Treatment for women with stage III or locally advanced breast cancer, 2004 (11)

Indications for radiotherapy

All the indications for external beam radiotherapy in the original CCORE model of optimal radiotherapy utilisation for breast cancer have been reviewed and updated in the optimal utilisation tree based on the latest guideline recommendations (Table 1).

The model has been updated as follows:

1. *The indications for DCIS have been omitted from the updated model as the in-situ tumours are not notifiable disease in the cancer registry and so should not be included as treatment indications for invasive breast cancer*

All of the other previous indications remain supported by current guidelines.

Level of evidence

According to the methods applied for the previous radiotherapy utilisation model the indications of radiotherapy for breast cancer have been derived from evidence-based treatment guidelines issued by major national and international organisations. The guidelines reviewed are those published after the previous radiotherapy utilisation study was completed (July 2003) up to December 2010. Highest priority has been given to Australian evidence-based clinical-practice guidelines (eg. NHMRC endorsed clinical practice guidelines).

Based on guidelines review, all indications of radiotherapy for breast cancer remain *supported by level I-III evidence* similar to those reported in the earlier model. Notably, for a number of indications the evidence has been upgraded to level II from level III. Out of twelve outcome branches in the model that have an indication of radiotherapy (Figure 1) 58% (7 branches) are supported by level I-II evidence; proportion of indications supported by Level I evidence has increased in the current model from 25% (3 indications) in the earlier model to 42% (5 indications) in the new model. The updated model predicts 74% breast cancer population with an indication of radiotherapy have level I or II evidence of benefit if treated according to evidence-based guidelines.

Evidence of radiotherapy benefit for early stage post-mastectomy local recurrence or those with mention of performance status are limited; hence, these indications are supported by level III evidence.

Epidemiology of cancer stages

The epidemiological data in the breast cancer utilisation tree have been reviewed to see if more recent data are available through extensive electronic search using the key words ‘Australia’, ‘epidemiology breast cancer’, ‘incidence’, ‘breast cancer stage‘, ‘radiotherapy treatment’, ‘recurrence’, ‘survival’ ‘treatment outcome’ in various combinations. This has been applied particularly to the early branches in the tree for which national or State level data on cancer incidence rates and stages are available. If there is a change in the hierarchical quality of the epidemiological data, this has also been noted (Table 2).

Since the completion of the previous radiotherapy utilisation project the national data on cancer statistics published by AIHW have been updated to more recent years till 2008 (12) and a number of publications from Australian State based registry data have been available (19-21). In 2008, Breast cancer accounted for 12.2% of all cancers in Australia. The epidemiological evidence for several outcome branches in the current model has been upgraded accordingly to be more representative of the Australian population.

Estimation of the optimal radiotherapy utilisation

From the evidence on the efficacy of radiotherapy and the most recent epidemiological data on the occurrence of indications for radiotherapy, the proportion of breast cancer patients in whom radiotherapy would be recommended is 87% (Table 1 and Figure 1) compared with the original estimate of 83%. The increase is due to omission of DCIS indications from the model and addition of a radiotherapy indication for invasive breast carcinoma.

Estimation of the optimal combined radiotherapy and chemotherapy utilisation

The indications of radiotherapy for breast cancer were reviewed to identify those indications where radiotherapy is recommended in conjunction with concurrent chemotherapy as the first treatment. According to the best available practice evidence there are no indications identified for which concurrent chemoradiation is beneficial over radiotherapy alone as the first indicated treatment.

Sensitivity analysis

Univariate sensitivity analysis has been undertaken to assess changes in the recommended breast cancer radiotherapy utilisation rate that would result from different estimates of the proportions of patients with particular attributes as mentioned in Table 2 (Figure 2). Also the sensitivity analyses tested the effect of including or excluding the recommendation for radiotherapy for T1-2 N0-1 M0 post-mastectomy 1-3 node positive nodes; this addresses the issue of conflict in radiotherapy recommendations between treatment guidelines for the above branch. There still exists a level of uncertainty whether radiotherapy should be recommended for post mastectomy ‘1-3’ node positive patients because the recommendation is based on sub-group analysis. The variability in the estimate of optimal radiotherapy utilisation due to these uncertainties was 3% and the expected value ranged from 87% to 90% as shown in the Tornado diagram (Figure 2).

Table 1: Breast Cancer. Indications for radiotherapy - Levels and sources of evidence

Updated RTU model 2012						
Outcome No. in Tree	Clinical Scenario	Guideline updated	Current level of evidence	Change to proportion of all breast cancer		References
				Yes/ No	Updated value	
1	T1-2 N0-1 M0, BCS	Yes	I	No	0.71	NHMRC (1), NCCN (3), NCI (4), BCCA (5) , CCO (10), NICE (6), UK Association of breast surgeons (7), New Zealand Guidelines Group (13)
2	T1-2 N0-1 M0 mastectomy, negative nodes, local recurrence	Yes	III	No	0.01	NHMRC (2), NCCN (3)
3	T1-2 N0-1 M0, mastectomy, negative nodes, distant relapse with painful bone metastases	Yes	I	Yes	< 0.01	NHMRC (2), NCCN (3), NICE (6)
4,6	T1-2 N0-1 M0, distant relapse with symptomatic brain metastases	Yes	II	No	< 0.01	NHMRC (2)

Updated RTU model 2012						
Outcome No. in Tree	**Clinical Scenario**	**Guideline updated**	**Current level of evidence**	**Change to proportion of all breast cancer**		**References**
				Yes/ No	**Updated value**	
10	T1-2 N0-1 M0, mastectomy, > 3 positive lymph nodes	Yes	I	Yes	0.02	NHMRC (1), NCCN (3), NCI (4), BCCA (5), NICE (6), UK Association of breast surgeons (7), New Zealand Guidelines Group (13), ASCO (9)
11	T3-4 Any N M0, good/fair PS or Any T N2-3 M0, good/fair PS	Yes	III	Yes	0.12	NCCN (3), Shenkier et al 2004 (11) ASCO guideline 2001 (9)
13	Any T Any N M1, no bone metastases, brain metastases	Yes	II	No	< 0.01	NHMRC (2)
15	Any T Any N M1, painful bone metastases	Yes	I	No	0.01	NHMRC (2), NCCN (3), NICE (6)
16	Any T Any N M1, painless bone metastases, brain metastases	Yes	II	No	< 0.01	NHMRC (2)
Proportion of all breast cancer patients in whom radiotherapy is recommended					**0.87 (87%)**	

Table 2: Breast Cancer; The incidence of attributes used to define indications for radiotherapy

Population or sub-population of interest	Attribute	Proportion	Updated Quality of Information	Updated Reference
All registry cancers	Breast cancer	0.12	α	AIHW 2010 (12)
All breast cancer	T1-2 N0-1 M0	0.83	β	National Breast and Ovarian Cancer Centre (NBOCC) 2010 (14)
All breast cancer	T3-4 Any N M0, or Any T N2-3 M0	0.13	β	NBOCC 2010 (14)
All breast cancer	Any T Any N M1	0.04	β	NBOCC 2010 (14)
T1-2 N0-1 M0	Breast-conserving surgery	0.86	γ	Morrow et al 2009 (15)
T1-2N0-1M0 mastectomy	0 lymph nodes	0.67	β	Delaney et al 2008 (16)
T1-2 N0-1 M0, mastectomy, 0 lymph nodes	Local recurrence	0.06	ζ	Jagsi et al 2005 (17)
T1-2 N0-1M0 mastectomy, no local recurrence	Distant recurrence	0.12	ζ	Wilking et al 1992 (18)

Population or sub-population of interest	Attribute	Proportion	Updated Quality of Information	Updated Reference
T1-2 N0-1 M0 mastectomy, no local recurrence, distant recurrence Or Any T Any N M1	Bone metastases	0.42 0.71 0.69 0.57	ζ	Pivot et al 2000 (19) Solomayer et al 2000 (20) Coleman et al 1987 (21) Leone et al 1988 (22)
All bone metastases	Painful bone metastases	0.95 0.80	ζ	Pivot et al 2000 (19) Solomayer et al 2000 (20)
T1-2 N0-1M0 mastectomy, 0-3 lymph nodes, no local recurrence, distant recurrence, no symptomatic bone metastases or Any T Any N M1, no symptomatic bone metastases	Brain metastases	0.12	ζ	Pivot et al 2000 (19)
T1-2 N0-1M0 mastectomy	4+ positive lymph nodes	0.16	λ	Chua et al 2002 (23)
T3-4 Any N M0, or Any T N2-3 M0	Good/Fair PS	0.91	ε	South Australian Cancer Registry Report 2000 (24)
Non-symptomatic bone metastases +/- visceral metastases	Symptomatic brain metastases	0.12	ζ	Pivot et al 2000 (19)

Figure 1. Breast Cancer Radiotherapy Utilization Tree

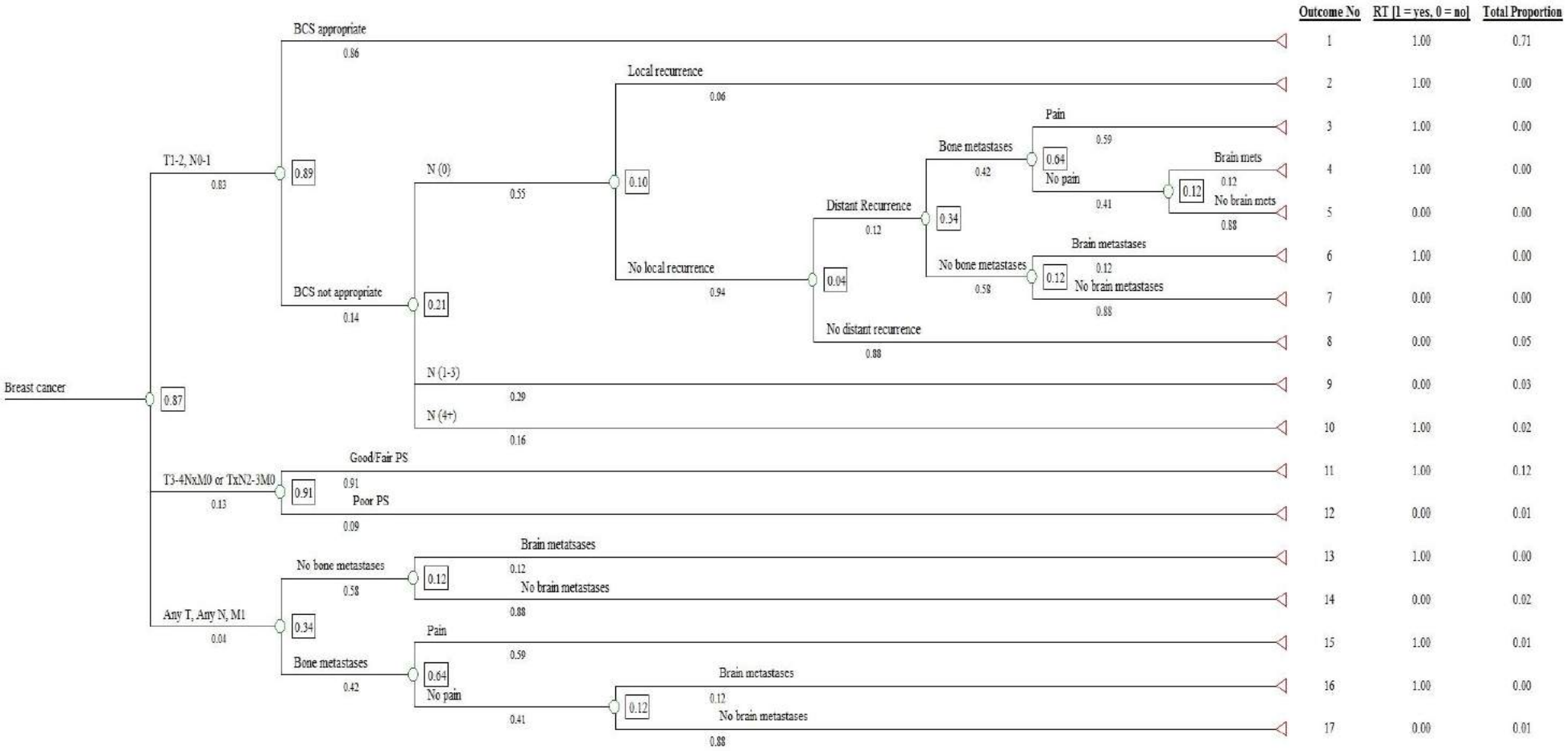
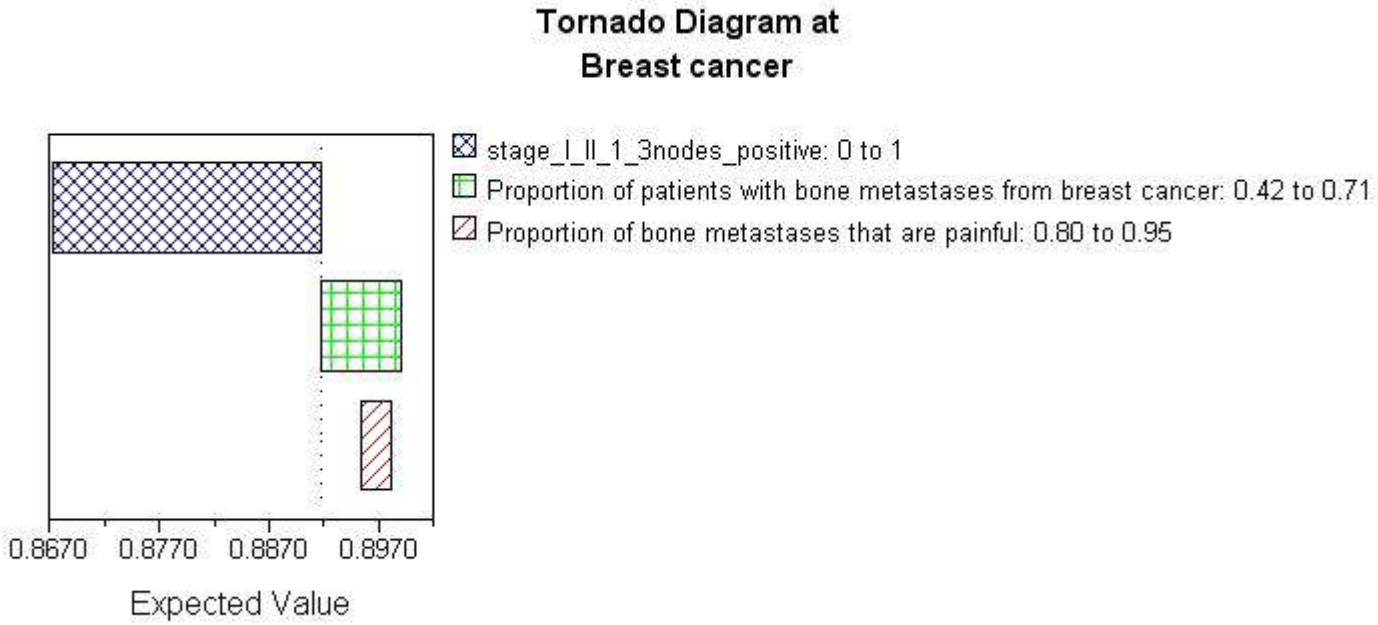


Figure 2. Tornado diagram for univariate sensitivity analyses



References

1. National Health &Medical Research Council (NHMRC). Clinical practice guidelines for the management of early breast cancer. Second edition. Canberra: NHMRC; 2001.

2. National Health and Medical Research Council (NHMRC). Clinical practice guidelines for the management of advanced breast cancer. Canberra: NHMRC; 2001.

3. National Comprehensive Cancer Network (NCCN). Clinical practice guidelines in oncology: Breast cancer. Version 2.2011. 2011.

4. National Cancer Institute (NCI). Breast Cancer Treatment (PDQ®). Available from : http://www cancer gov/cancertopics/pdq/treatment/breast/healthprofessional 2011 [cited 2011 Sep 6];

5. BC Cancer Agency. Cancer Management Guidelines: Breast. Available from: http://www bccancer bc ca/HPI/CancerManagementGuidelines/default htm 2011 [cited 2011 Sep 7];

6. National Institute for Health and Clinical Excellence (NICE). Early and locally advanced breast cancer: Diagnosis and treatment. NICE clinical guideline no. 80. London: National Institute for Health and Clinical Excellence; 2009.

7. Association of Breast Surgery at BASO. Surgical guidelines for the management of breast cancer. Eur J Surg Oncol 2009;35 Suppl 1:1-22.

8. Scottish Intercollegiate Guidelines Network (SIGN). Management of breast cancer in women: A national clinical guideline. Available from: www sign ac uk 2005 [cited 2011 Aug 16];

9. Recht A, Edge SB, Solin LJ, Robinson DS, Estabrook A, Fine RE, et al. Postmastectomy radiotherapy: clinical practice guidelines of the American Society of Clinical Oncology. J Clin Oncol 2001 Mar 1;19(5):1539-69.

10. Cancer Care Ontario. Breast irradiation in women with early stage invasive breast cancer following breast conserving surgery. Practice Guideline Report #1-2. Toronto ON: Cancer Care Ontario; 2010.

11. Shenkier T, Weir L, Levine M, Olivotto I, Whelan T, Reyno L. BC Cancer Agency. Clinical practice guidelines for the care and treatment of breast cancer: Treatment for women with stage III or locally advanced breast cancer. CMAJ 2004 Mar 16;170(6):983-94.

12. Australian Institute of Health and Welfare (AIHW). Australian Cancer Incidence and Mortality (ACIM) books. Available from: http://www aihw gov au/acim-books/ 2011 [cited 2011 Aug 16];

13. New Zealand Guidelines Group (NZGG). Management of early breast cancer. Wellington: New Zealand Ministry of Health; 2009.

14. National Breast and Ovarian Cancer Centre. Breast cancer staging and treatment: Data linkage report. Surry Hills NSW: National Breast and Ovarian Cancer Centre; 2010.

15. Morrow M, Jagsi R, Alderman AK, Griggs JJ, Hawley ST, Hamilton AS, et al. Surgeon recommendations and receipt of mastectomy for treatment of breast cancer. JAMA 2009 Oct 14;302(14):1551-6.

16. Delaney G, Shafiq J, Chappell G, Barton M. Establishing treatment benchmarks for mammography-screened breast cancer population based on a review of evidence-based clinicalguidelines.Cancer.2008.May.1;112(9):1912-22.

17. Jagsi R, Raad RA, Goldberg S, Sullivan T, Michaelson J, Powell SN, et al. Locoregional recurrence rates and prognostic factors for failure in node-negative patients treated with mastectomy: implications for postmastectomy radiation. Int J Radiat Oncol Biol Phys 2005 Jul 15;62(4):1035-9.

18. Wilking N, Rutqvist LE, Carstensen J, Mattsson A, Skoog L. Prognostic significance of axillary nodal status in primary breast cancer in relation to the number of resected nodes. Acta Oncol 1992;31(1):29-35.

19. Pivot X, Asmar L, Hortobagyi GN, et al. A retrospective study of first indicators of breast cancer recurrence. Oncology 2000;58:185-90.

20. Solomayer EF, Diel IJ, Meyberg GC, Gollan C, Bastert G. Metastatic breast cancer: clinical course, prognosis and therapy related to the first site of metastasis. Breast Cancer Res Treat 2000;59:271-8.

21. Coleman RE, Rubens RD. The clinical course of bone metastases from breast cancer. Br J Cancer 1987;55:61-6.

22. Leone BA, Romero A, Rabinovich MG, Vallejo CT, et al. Stage IV Breast Cancer: Clinical course and survival of patients with osseous versus extraosseous metastases at initial diagnosis. Am J Clin Oncol (CCT) 1988;11(6):618-22.

23. Chua B, Ung O, Taylor R, Boyages J. Is there a role for axillary dissection for patients with operable breast cancer in this era of conservatism? ANZ J Surg 2002 Nov;72(11):786-92.

24. South Australian Cancer Registry. 2000 Cancer Report - Epidemiology of Cancer in South Australia 1977-1999. Available from: http://www health sa gov au/pehs/cancer-report2000 htm 2000 [cited 2007 Nov 26];

CERVICAL CANCER

In the original EBRT and BT utilisation models the indications for EBRT and BT for cervical cancer were derived from evidence-based treatment guidelines issued by major national and international organisations until December 2004. The current updated model includes guidelines published until February 2012.

Updated Guidelines

The following clinical practice guidelines for the management of cervical cancer have not been updated:

- (SGOG) The Sydney Gynaecologic Oncology Group, Royal Prince Alfred and Liverpool Hospitals: Clinical Practice and Management Policies (1)

The following new or updated clinical practice guidelines for the management of cervical cancer were identified:

- (FIGO) Federation Internationale de Gynecologie et d'Obstetrique: Staging classifications and clinical practice guidelines for gynaecologic cancers (2)
- (PDQ) CancerNet PDQ Cancer Information Summaries: Treatment of Cervical Cancer (3)
- (NCCN) National Comprehensive Cancer Network: Clinical Practice Guidelines in Oncology - v1.2012 - Cervical Cancer (4)
- (SICN) Scottish Intercollegiate Network: Management of cervical cancer: A national clinical guideline (5)
- (NSW) NSW Gynaecological Oncology Group Best Practice Guideline, 2009 (6)
- (CCO) Cancer Care Ontario: Primary Treatment for Locally Advanced Cervical Cancer (7)
- (BCCA) British Columbia Cancer Agency: Cancer Management Guidelines >> Gynecology >> 4. Cervix (8)
- (YCN) Yorkshire Cancer Network Guidelines for the Management of Gynaecological Cancers (9)
- (ESMO) Cervical cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up (10)
- (ABS) American Brachytherapy Society Cervical Cancer Brachytherapy Task Group (11)
- (ACR) ACR Appropriateness Criteria on Advanced Cervical Cancer Expert Panel on Radiation Oncology – Gynecology (12)

Indications for radiotherapy

All the indications for EBRT and for BT in the original CCORE models of optimal RT and BT utilisation for cervical cancer were reviewed based on the latest guideline recommendations (Figures 1 and 2 and Tables 1 and 2*).* For EBRT, the original model did not include indications for RT for a small

percentage of patients with stage IA disease, either because of medical inoperability, local recurrence after surgery, or lymph node positivity. These indications were included in the later BT utilization tree and are here incorporated into the combined model.

Changes to Epidemiological Data

The epidemiological data in the cervical cancer utilization trees have been reviewed to identify whether more recent data are available through extensive electronic searches. This has been applied to the early branches in the trees for which national or state level data on cancer incidence rates and stages are available. No changes to the hierarchical quality of the epidemiological data were identified, but there were changes in the magnitude of the indications based on up-dated SEER stage data (13) (Table 3).

Incidence of Cervical Cancer:

Since the publication of the previous radiotherapy utilisation project, the Australian national cancer incidence data published by the Australian Institute of Health and Welfare (AIHW) has been updated, with the most recent data available being 2007 data. In 2007, cervical cancer accounted for 17% of gynaecological cancers, and 0.7% of all cancer in Australia (14).

Stage proportions for Cervical Cancer

The SEER database (13) provided the most recent population level data for cervical cancer stage distribution, and these 2004-07 data were substituted for the previous 1973-1995 data (Table 3).

Estimation of the Optimal External Beam Radiotherapy Utilisation Rate in Cervical Cancer

Based on the evidence of the efficacy of radiotherapy and the most recent epidemiological data on the occurrence of indications for EBRT, EBRT is recommended in 71% of all cervical cancer patients in Australia (Table 1 and Figure 1). The previous optimal EBRT rate for cervical cancer derived in 2003 was 58%. The increase in the revised optimal utilisation rate is predominantly due to two factors: incorporation of indications for EBRT for stage I disease, and changes in the stage incidence of cervical cancer.

Estimation of the Optimal Brachytherapy Utilisation Rate in Cervical Cancer

Based on the evidence of the efficacy of radiotherapy and the most recent epidemiological data on the occurrence of indications for BT, BT is recommended in 53% of all cervical cancer patients in Australia (Table 2 and Figure 2). The previous optimal BT rate for cervical cancer derived in 2004 was 49%. The small increase in the revised optimal utilisation rate is due to changes in the epidemiological data, rather than any changes in the indications for BT.

Estimation of the Optimal Concurrent Chemoradiotherapy Utilisation Rate in Cervical Cancer

The indications for radiotherapy for cervical cancer were reviewed to identify the indications where radiotherapy is recommended in conjunction with concurrent chemotherapy (CRT) as the first treatment. Based on this model, 51% of all cervical cancer patients should receive concurrent radiotherapy with chemotherapy (Figure 3 and Table 4). It is acknowledged that some of these patients will not be fit to receive concurrent chemotherapy and this is dealt with by sensitivity analysis of the combined utilisation tree.

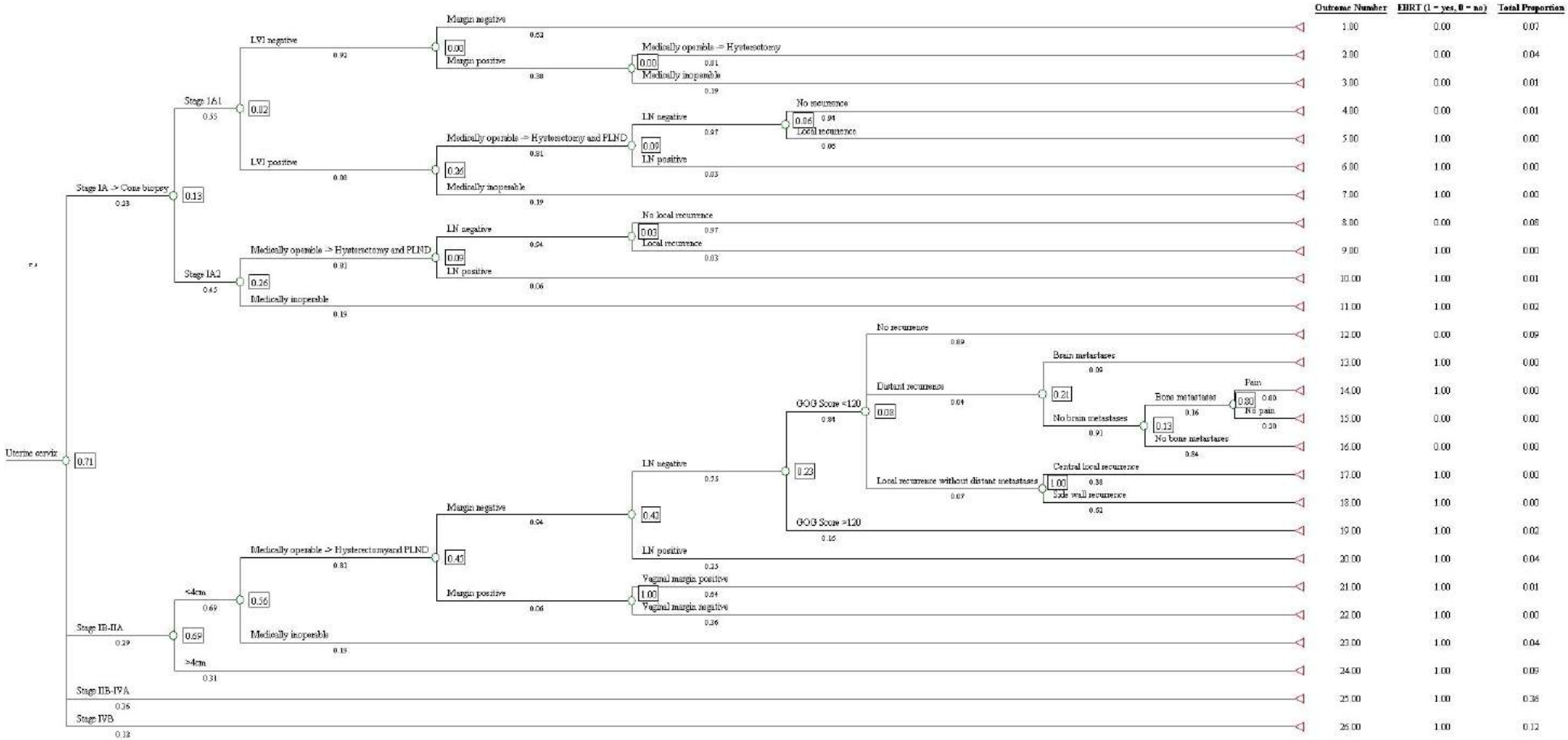
Level of evidence

The levels of evidence supporting the indications for EBRT and BT are unchanged. Level I-II evidence supports the indications for 8% of the total 71% EBRT optimal utilisation; 0% of the total 53% BT optimal utilisation; and 50% of the total 51% concurrent CRT optimal utilisation

Sensitivity Analyses

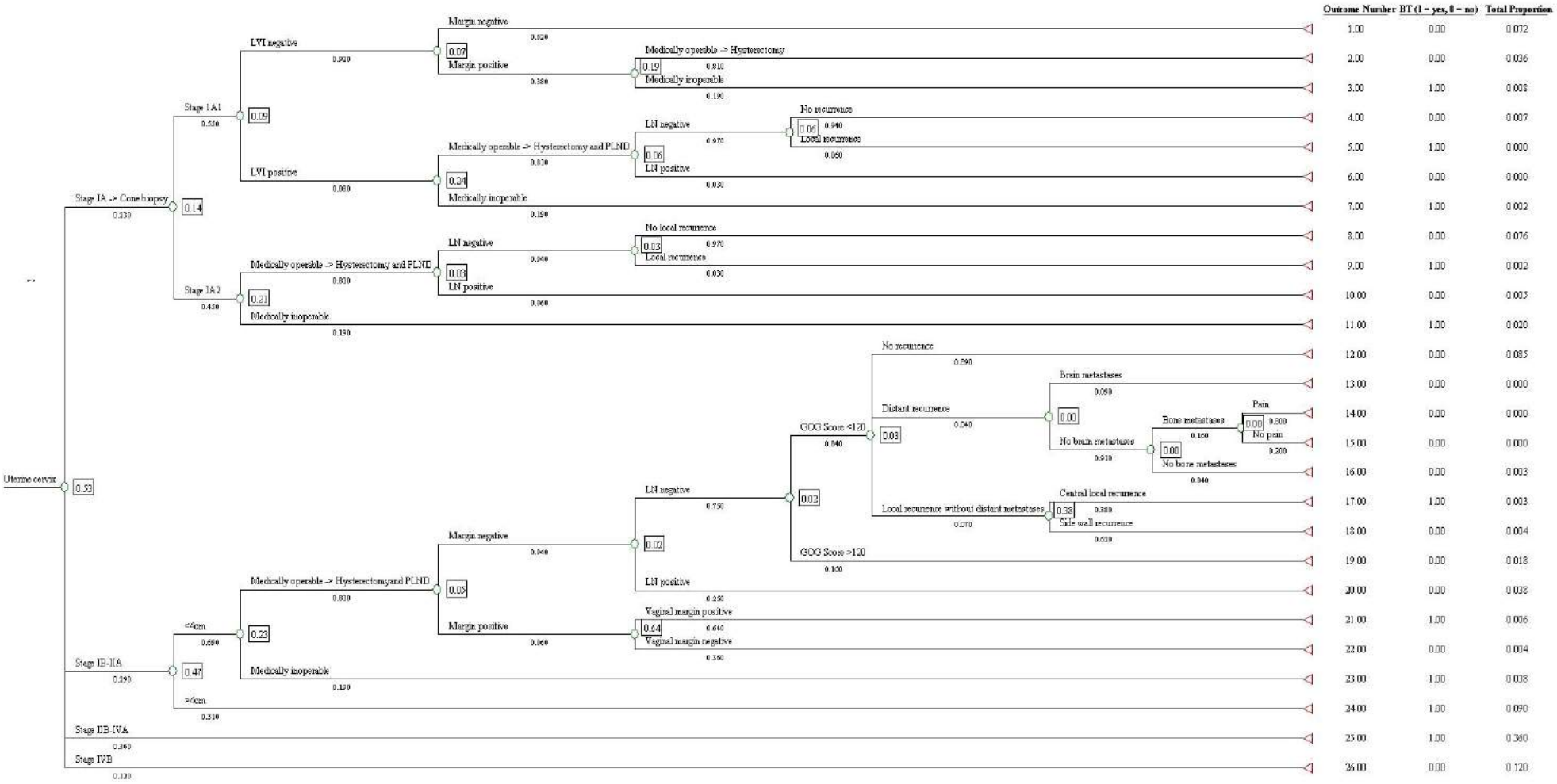
Univariate sensitivity analyses were undertaken (Figures 4-6) to assess any changes in the optimal utilisation rate for EBRT, BT and CRT that would result from different estimates of the proportions of patients with particular attributes as mentioned in Table 3. The variability in the estimate of optimal EBRT utilisation due to these uncertainties was 3% and the expected value ranged from 68% to 71% as shown in the Tornado diagram (Figure 4). The variability in the estimate of optimal BT utilisation due to these uncertainties was 56% and the expected value ranged from 48% to 53% as shown in the Tornado diagram (Figure 5). The variability in the estimate of optimal CRT utilisation due to these uncertainties was 1% and the expected value ranged from 51% to 52% as shown in the Tornado diagram (Figure 6).

Figure 1. Revised Optimal External Beam Radiotherapy Utilisation Tree for Cervical Cancer



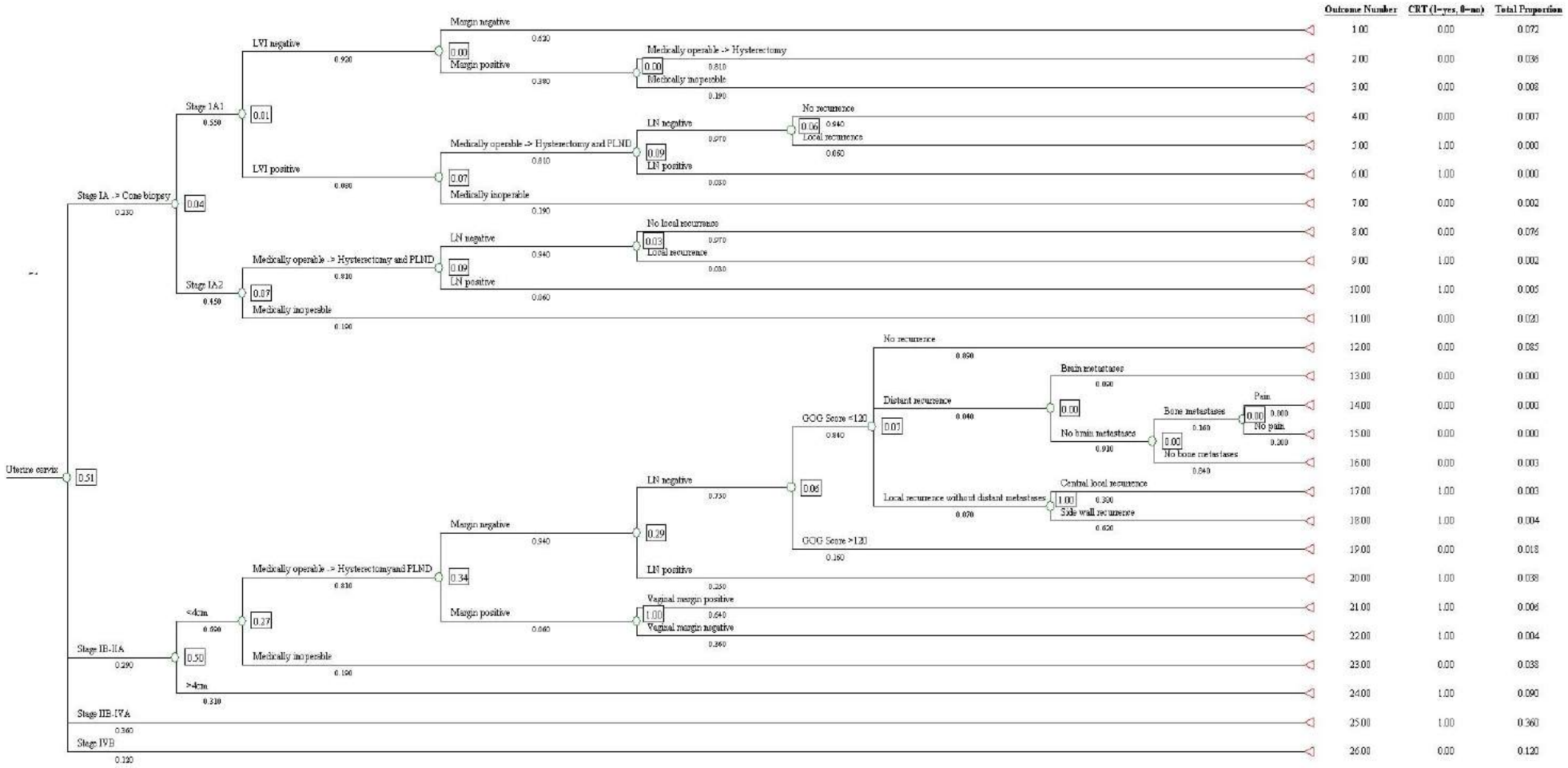
LVI, Lymphatic Vascular Space Invasion; PLND, Pelvic Lymph Node Dissection; LN, Lymph Node; GOG, Gynecology Oncology Group; EBRT, External Beam Radiotherapy

Figure 2. Revised Optimal Brachytherapy Utilisation Tree for Cervical Cancer



LVI, Lymphatic Vascular Space Invasion; PLND, Pelvic Lymph Node Dissection; LN, Lymph Node; GOG, Gynecology Oncology Group; BT, Brachytherapy

Figure 3. Cervical Cancer. Optimal Utilisation Tree for Concurrent Chemoradiation



LVI, Lymphatic Vascular Space Invasion; PLND, Pelvic Lymph Node Dissection; LN, Lymph Node; GOG, Gynecology Oncology Group; CRT, Concurrent Chemoradiation

Table 1: Cervical Cancer. Indications for External Beam Radiotherapy - Levels and sources of evidence

Original RTU study					Updates 2012					
Outcome Nos. in Updated Tree	Clinical Scenario	Treatment Indicated	Level of Evidence	Proportion of all Cervical Cancer	Change of Indication	Guideline updated	Current level of evidence	Change to proportion of all cervical cancer		References
								Yes/ No	Updated value	
5	Stage IA1 (Cone biopsy); LVI positive; Medically operable (Hyst and PLND); LN negative; Local recurrence	No	n/a	n/a	Yes: EBRT and BT	Yes	IV	n/a	<0.01	FIGO (2), PDQ (3), NCCN (4), NSW (6), SGOG (1), ESMO (10)
6	Stage IA1 (Cone biopsy); LVI positive; Medically operable (Hyst and PLND); LN positive	No	n/a	n/a	Yes: EBRT	Yes	II	n/a	<0.01	FIGO (2), PDQ (3), NCCN (4), SICN (5), NSW (6), CCO (7), YCN (9), SGOG (1), ESMO (10)

7	Stage IA1 (Cone biopsy); LVI positive; Medically inoperable	No	n/a	n/a	Yes: EBRT and BT	Yes	IV	n/a	<0.01	PDQ (3), NCCN (4), BCCA (8), ABS (11)
9	Stage IA2 (Cone biopsy); Medically operable (Hyst and PLND); LN negative; Local recurrence	No	n/a	n/a	Yes: EBRT and BT	Yes	IV	n/a	<0.01	FIGO (2), PDQ (3), NCCN (4), NSW (6), SGOG (1), ESMO (10)
10	Stage IA2 (Cone biopsy); Medically operable (Hyst and PLND); LN positive	No	n/a	n/a	Yes: EBRT	Yes	II	n/a	0.01	FIGO (2), PDQ (3), NCCN (4), SICN (5), NSW (6), CCO (7), YCN (9), SGOG (1), ESMO (10)
11	Stage IA2 (Cone biopsy); Medically inoperable	No	n/a	n/a	Yes: EBRT and BT	Yes	IV	n/a	0.02	PDQ (3), NCCN (4), BCCA (8), ABS (11)

13	Stage IB-IIA; <4cm; Medically operable (Hyst and PLND); Margin negative; LN negative; GOG score<120; Distant recurrence; Brain metastases	EBRT	II	<0.01	No: EBRT	Yes	II	No	<0.01	FIGO (2), PDQ (3)
14	Stage IB-IIA; <4cm; Medically operable (Hyst and PLND); Margin negative; LN negative; GOG score<120; Distant recurrence; No brain metastases; Bone metastases; Pain	EBRT	I	<0.01	No: EBRT	Yes	I	No	<0.01	FIGO (2), PDQ (3)

17	Stage IB-IIA; <4cm; Medically operable (Hyst and PLND); Margin negative; LN negative; GOG score<120; Local recurrence (nil distant metastases); Central local recurrence	EBRT and BT	IV	Outcome 17 and 18 total 0.01	No: EBRT and BT	Yes	IV	No	<0.01	FIGO (2), PDQ (3), NCCN (4), NSW (6), SGOG (1), ESMO (10)
18	Stage IB-IIA; <4cm; Medically operable (Hyst and PLND); Margin negative; LN negative; GOG score<120; Local recurrence (nil distant metastases); Side wall recurrence	EBRT	IV	Outcome 17 and 18 total 0.01	No: EBRT	Yes	IV	No	<0.01	FIGO (2), PDQ (3), NCCN (4), NSW (6), SGOG (1), ESMO (10)
19	Stage IB-IIA; <4cm; Medically operable (Hyst and PLND); Margin negative; LN negative; GOG score>120	EBRT	II*	0.03	No: EBRT	Yes	II	Yes	0.02	FIGO (2), PDQ (3), NCCN (4), SICN (5), NSW (6), SGOG (1)

20	Stage IB-IIA; <4cm; Medically operable (Hyst and PLND); Margin negative; LN positive	EBRT	II	0.06	No: EBRT	Yes	II	Yes	0.04	FIGO (2), PDQ (3), NCCN (4), SICN (5), NSW (6), CCO (7), YCN (9), SGOG (1), ESMO (10)
21	Stage IB-IIA; <4cm; Medically operable (Hyst and PLND); Margin positive; Vaginal margin positive	EBRT and BT	II*	Outcome 17 and 18 total 0.01	No: EBRT and BT	Yes	II	No	0.01	FIGO (2), PDQ (3), NCCN (4), CCO (7), YCN (9), SGOG (1), ESMO (10)
22	Stage IB-IIA; <4cm; Medically operable (Hyst and PLND); Margin positive; Vaginal margin negative	EBRT	II*	Outcome 17 and 18 total 0.01	No: EBRT	Yes	II	No	<0.01	FIGO (2), PDQ (3), NCCN (4), CCO (7), YCN (9), SGOG (1), ESMO (10)
23	Stage IB-IIA; <4cm; Medically inoperable	EBRT and BT	IV	0.02	No: EBRT and BT	Yes	III	Yes	0.04	PDQ (3), NCCN (4), NSW (6), BCCA (8), YCN (9), SGOG (1), ABS (11)

24	Stage IB-IIA; >4cm	EBRT and BT	II, III	0.10	No: EBRT and BT	Yes	II, III	Yes	0.09	FIGO (2), PDQ (3), NCCN (4), SICN (5), NSW (6), CCO (7), BCCA (8), YCN (9), SGOG (1), ESMO (10), ABS (11), ACR (12)
25	Stage IIB-IVA	EBRT and BT	IV	0.26	No: EBRT and BT	Yes	IV	Yes	0.36	FIGO (2), PDQ (3), NCCN (4), SICN (5), NSW (6), CCO (7), BCCA (8), YCN (9), SGOG (1), ESMO (10), ABS (11), ACR (12)
26	Stage IVB	EBRT	IV	0.09	No: EBRT	Yes	IV	Yes	0.12	FIGO (2), PDQ (3), YCN (9), SGOG (1)
Proportion of all cervical cancer patients in whom EBRT was recommended				0.58 (58%)	**Updated Proportion of all cervical cancer patients in whom EBRT is recommended**				**0.71 (71%)**	

*Level of evidence in original RTU study erroneously reported to be III rather than II Abbreviations: RTU, Radiotherapy Utilisation; LVI, Lymphatic Vascular Space Invasion; Hyst, Hysterectomy; PLND, Pelvic Lymph Node Dissection; LN, Lymph Node; GOG, Gynecology Oncology Group; RT, Radiotherapy; EBRT, External Beam Radiotherapy; BT, Brachytherapy; PDQ, CancerNet PDQ Cancer Information Summaries: Treatment of Cervical Cancer; NCCN, National Comprehensive Cancer Network: Clinical Practice Guidelines in Oncology - v1.2012 - Cervical Cancer; NSW, New South Wales Gynaecological Oncology Study Group: Gynaecological Oncology Clinical Practice Guidelines; SGOG, The Sydney Gynaecologic Oncology Group, Royal Prince Alfred and Liverpool Hospitals: Clinical Practice and Management Policies; ESMO, Cervical cancer: European Society for Medical Oncology Clinical Practice Guidelines for diagnosis, treatment and follow-up; FIGO, Federation Internationale de Gynecologie et d'Obstetrique staging classifications and clinical practice guidelines in the management of gynaecologic cancers; CCO, Cancer Care Ontario: Primary Treatment for Locally Advanced Cervical Cancer; YCN, Yorkshire Cancer Network Guidelines for the Management of Gynaecological Cancers; BCCA, British Columbia Cancer Agency: Cancer Management Guidelines >> Gynecology >> 4. Cervix; ABS, American Brachytherapy Society Cervical Cancer Brachytherapy Task Group; SICN, Scottish Intercollegiate Network: Management of cervical cancer: A national clinical guideline; ACR, American College of Radiology Appropriateness Criteria on Advanced Cervical Cancer Expert Panel on Radiation Oncology – Gynecology;

Table 2: Cervical Cancer. Indications for Brachytherapy - Levels and sources of evidence

Original BTU study					Updates 2012					
Outcome Nos. in Updated Tree	Clinical Scenario	Treatment Indicated	Level of Evidence	Proportion of all Cervical Cancer	Change of Indication	Guideline updated	Current level of evidence	Change to proportion of all cervical cancer		References
								Yes/ No	Updated value	
3	Stage IA1 (Cone biopsy); LVI negative; Margin positive; Medically inoperable	BT	IV	0.01	No: BT	Yes	IV	Yes	<0.01	PDQ (3), NCCN (4), ABS (11)
5	Stage IA1 (Cone biopsy); LVI positive; Medically operable (Hyst and PLND); LN negative; Local recurrence	EBRT and BT	IV	<0.01	No: EBRT and BT	Yes	IV	No	<0.01	FIGO (2), PDQ (3), NCCN (4), NSW (6), SGOG (1), ESMO (10)
7	Stage IA1 (Cone biopsy); LVI positive; Medically inoperable	EBRT and BT	IV	<0.01	No: EBRT and BT	Yes	IV	No	<0.01	PDQ (3), NCCN (4), BCCA (8), ABS (11)

9	Stage IA2 (Cone biopsy); Medically operable (Hyst and PLND); LN negative; Local recurrence	EBRT and BT	IV	<0.01	No: EBRT and BT	Yes	IV	No	<0.01	FIGO (2), PDQ (3), NCCN (4), NSW (6), SGOG (1), ESMO (10)
11	Stage IA2 (Cone biopsy); Medically inoperable	EBRT and BT	IV	0.02	No: EBRT and BT	Yes	IV	No	0.02	PDQ (3), NCCN (4), BCCA (8), ABS (11)
17	Stage IB-IIA; <4cm; Medically operable (Hyst and PLND); Margin negative; LN negative; GOG score<120; Local recurrence (nil distant metastases); Central local recurrence	EBRT and BT	IV	<0.01	No: EBRT and BT	Yes	IV	No	<0.01	FIGO (2), PDQ (3), NCCN (4), NSW (6), SGOG (1), ESMO (10)
21	Stage IB-IIA; <4cm; Medically operable (Hyst and PLND); Margin positive; Vaginal margin positive	EBRT and BT	IV	<0.01	No: EBRT and BT	Yes	IV	Yes	0.01	PDQ (3), NCCN (4), YCN(9), SGOG (1), ESMO (10)

23	Stage IB-IIA; <4cm; Medically inoperable	EBRT and BT	IV	0.06	No: EBRT and BT	Yes	IV	Yes	0.04	PDQ (3), NCCN (4), NSW (6), BCCA (8), YCN (9), SGOG (1), ABS (11)
24	Stage IB-IIA; >4cm	EBRT and BT	II, III	0.13	No: EBRT and BT	Yes	II, III	Yes	0.09	FIGO (2), PDQ (3), NCCN (4), SICN (5), NSW (6), BCCA (8), YCN (9), SGOG (1), ESMO (10), ABS (11), ACR (12)
25	Stage IIB-IVA	EBRT and BT	IV	0.25	No: EBRT and BT	Yes	IV	Yes	0.36	FIGO (2), PDQ (3), NCCN (4), SICN (5), NSW (6), CCO (7), BCCA (8), YCN (9), SGOG (1), ESMO (10), ABS (11), ACR (12)
Proportion of all cervical cancer patients in whom BT was recommended				0.49 (49%)	**Updated Proportion of all cervical cancer patients in whom BT is recommended**				**0.53 (53%)**	

Abbreviations: BTU, Brachytherapy Utilisation; LVI, Lymphatic Vascular Space Invasion; Hyst, Hysterectomy; PLND, Pelvic Lymph Node Dissection; LN, Lymph Node; GOG, Gynecology Oncology Group; RT, Radiotherapy; EBRT, External Beam Radiotherapy; BT, Brachytherapy; PDQ, CancerNet PDQ Cancer Information Summaries: Treatment of Cervical Cancer; NCCN, National Comprehensive Cancer Network: Clinical Practice Guidelines in Oncology - v1.2012 - Cervical Cancer; ABS, American Brachytherapy Society Cervical Cancer Brachytherapy Task Group; NSW, New South Wales Gynaecological Oncology Study Group: Gynaecological Oncology Clinical Practice Guidelines; SGOG, The Sydney Gynaecologic Oncology Group, Royal Prince Alfred and Liverpool Hospitals: Clinical Practice and Management Policies; ESMO, Cervical cancer: European Society for Medical Oncology Clinical Practice Guidelines for diagnosis, treatment and follow-up; BCCA, British Columbia Cancer Agency: Cancer Management Guidelines >> Gynecology >> 4. Cervix; FIGO, Federation Internationale de Gynecologie et d'Obstetrique staging classifications and clinical practice guidelines in the management of gynaecologic cancers; YCN, Yorkshire Cancer Network Guidelines for the Management of Gynaecological Cancers; SICN, Scottish Intercollegiate Network: Management of cervical cancer: A national clinical guideline; ACR, American College of Radiology Appropriateness Criteria on Advanced Cervical Cancer Expert Panel on Radiation Oncology – Gynecology; CCO, Cancer Care Ontario: Primary Treatment for Locally Advanced Cervical Cancer

Table 3: Cervical Cancer. The incidence of attributes used to define indications for radiotherapy

Original RTU/BTU studies				Updates 2012				
Population or sub-population of interest	Attribute	Proportion of population with the attribute	Quality of Information	Change in proportion of population with attribute Yes/ No	Updated Proportion	Updated Quality of Information	Updated Reference	Comments
All registry cancers	Gynaecological cancer	0.05 (RTU) 0.05 (BTU)	α α	Yes	0.039	α	AIHW 2011 (14)	-
All gynaecological cancer	Cervical cancer	0.23 (RTU) 0.19 (BTU)	α α	Yes	0.17	α	AIHW 2011 (14)	-
All Cervical cancer	Stage IA	0.30 (RTU) 0.26 (BTU)	γ γ	Yes	0.23	γ	SEER 2004-2007 (13)	-
Stage IA	Stage IA1	0.55 (BTU)	γ	No	0.55	No	n/a	
Stage IA1, (Conization)	LVI negative	0.92 (BTU)	ε	No	0.92	No	n/a	
Stage IA1; (Conization); LVI negative	Margin positive	0.38 (BTU)	ζ	No	0.38	No	n/a	
Stage IA1, (Conization); LVI negative; Margin positive	Medically operable (Hyst)	0.81 (BTU)	β	No	0.81	No	n/a	

Original RTU/BTU studies				Updates 2012				
Population or sub-population of interest	Attribute	Proportion of population with the attribute	Quality of Information	Change in proportion of population with attribute Yes/ No	Updated Proportion	Updated Quality of Information	Updated Reference	Comments
Stage IA1, (Conization); LVI positive	Medically operable (Hyst and PLND)	0.81 (BTU)	β	No	0.81	No	n/a	
Stage IA1, (Conization); LVI positive; Medically operable, (Hyst and PLND	LN negative	0.97 (BTU)	ε	No	0.97	No	n/a	
Stage IA1, (Conization); LVI positive; Medically operable, (Hyst and PLND); LN negative	Local recurrence	0.06 (BTU)	ε	No	0.06	No	n/a	
All cervical cancer	Stage IB/IIA	0.35 (RTU) 0.43 (BTU)	γ γ	Yes	0.29	γ	SEER 2004-2007 (13)	-
Stage IB/IIA	"Non-bulky" disease	0.69 (RTU) 0.69 (BTU)	ζ ζ	No	0.69	No	n/a	
Stage IB/IIA; "Non-bulky" disease	Operable(Hysterectomy and PLND)	0.95 (RTU) 0.81 (BTU)	ζ β	No	0.81	No	n/a	

Original RTU/BTU studies				Updates 2012				
Population or sub-population of interest	Attribute	Proportion of population with the attribute	Quality of Information	Change in proportion of population with attribute Yes/ No	Updated Proportion	Updated Quality of Information	Updated Reference	Comments
Stage IB/IIA; “Non-bulky” disease; Medically operable, (Hyst and PLND)	Margin negative	0.94 (RTU) 0.94 (RTU)	θ θ	No	0.94	No	n/a	
Stage IB/IIA; “Non-bulky” disease; Medically operable; (Hyst and PLND); Margin negative	LN negative	0.75 (RTU) 0.75 (BTU)	θ θ	No	0.75	No	n/a	
Stage IB/IIA; “Non-bulky” disease; Medically operable, (Hyst and PLND); Margin negative; LN negative	“Low risk” for recurrence (GOG score <120)	0.84 (RTU) 0.84 (BTU)	ε ε	No	0.84	No	n/a	
Stage IB/IIA, “Non-bulky” disease, Medically operable, (Hyst and PLND); Margin negative; LN negative; “Low risk”	Distant relapse	0.05 (RTU)	θ	Yes	0.04	No	Delgado et al (15), Samlal et al (16)	Corrected calculation of relapse rates

Original RTU/BTU studies				Updates 2012				
Population or sub-population of interest	Attribute	Proportion of population with the attribute	Quality of Information	Change in proportion of population with attribute Yes/ No	Updated Proportion	Updated Quality of Information	Updated Reference	Comments
Stage IB/IIA, “Non-bulky” disease, Medically operable, (Hyst and PLND); Margin negative; LN negative; “Low risk” for recurrence (GOG score <120); Distant Recurrence	Brain Metastases	0.09 (RTU)	ζ	No	0.09	No	n/a	
Stage IB/IIA, “Non-bulky” disease, Medically operable, (Hyst and PLND); Margin negative; LN negative; “Low risk” for recurrence (GOG score <120); Distant recurrence; No Brain Metastases	Bone Metastases	0.16 (RTU)	ζ	No	0.16	No	n/a	
Stage IB/IIA, “Non-bulky” disease, Medically operable,	Painful Pain Metastases	0.80 (RTU)	ζ	No	0.80	No	n/a	

Original RTU/BTU studies				Updates 2012				
Population or sub-population of interest	Attribute	Proportion of population with the attribute	Quality of Information	Change in proportion of population with attribute Yes/ No	Updated Proportion	Updated Quality of Information	Updated Reference	Comments
(Hyst and PLND); Margin negative; LN negative; “Low risk” for recurrence (GOG score <120); Distant recurrence; No Brain Metastases; Bone Metastases								
Stage IB/IIA, “Non-bulky” disease, Medically operable, (Hyst and PLND); Margin negative; LN negative; “Low risk” for recurrence (GOG score <120)	Local relapse	0.11 (RTU) 0.07 (BTU)	θ θ	Yes	0.07	No	Same Refs: Delgado et al (15), Samlal et al (16)	Corrected calculation of local and distant relapse rates

Original RTU/BTU studies				Updates 2012				
Population or sub-population of interest	Attribute	Proportion of population with the attribute	Quality of Information	Change in proportion of population with attribute Yes/ No	Updated Proportion	Updated Quality of Information	Updated Reference	Comments
Stage IB/IIA; "Non-bulky" disease; Medically operable, (Hyst and PLND); Margin negative; LN negative; "Low risk" for recurrence; Local recurrence	Central local relapse	0.38 (BTU)	ζ	No	0.38	No	n/a	
Stage IB/IIA; "Non-bulky" disease; Medically operable, (Hyst and PLND); Margin + ve	Vaginal margin positive	0.64 (BTU)	ζ	No	0.64	No	n/a	
All cervical cancer	Stage IIB-IV A	0.26 (RTU) 0.25 (BTU)	γ γ	Yes	0.36	γ	SEER 2004-2007 (13)	
All cervical cancer	Stage IVB	0.09 (RTU) 0.06 (BTU)	γ γ	Yes	0.12	γ	SEER 2004-2007 (13)	

Abbreviations: LVI, Lymphatic Vascular Space Invasion; Hyst, Hysterectomy; PLND, Pelvic Lymph Node Dissection; LN, Lymph Node; GOG, Gynecology Oncology Group; RTU, Radiotherapy Utilization; BTU, Brachytherapy Utilization

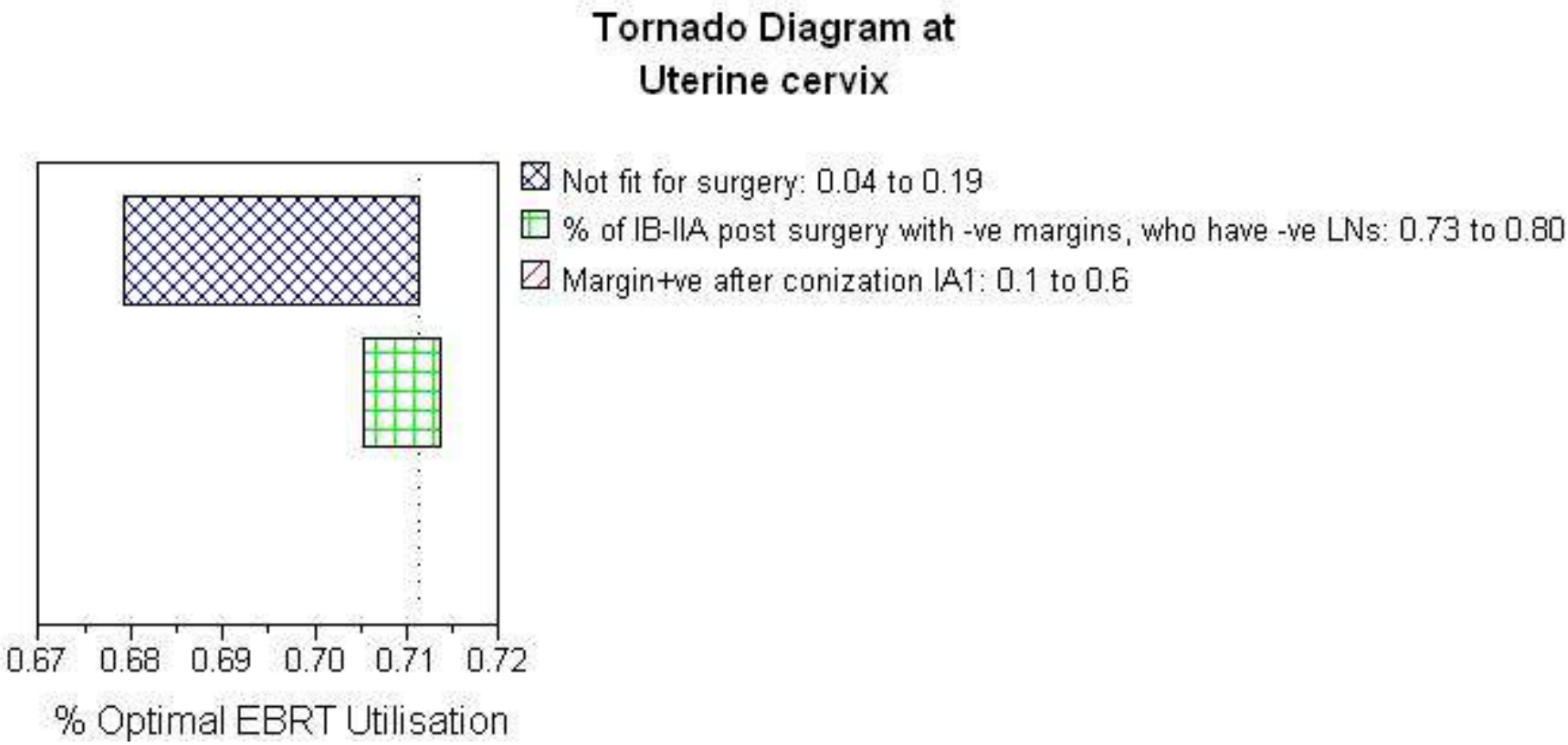
Table 4: Cervical Cancer. Indications for concurrent chemoradiotherapy - levels and sources of evidence

Outcome Numbers in Tree	Clinical Scenario	Level of evidence	References	Proportion of all Cervical Cancer Patients
5	Stage IA1 (Cone biopsy); LVI positive; Medically operable (Hyst and PLND); LN negative; Local recurrence	IV	FIGO (2), PDQ (3), NCCN (4), NSW (6)	<0.01
6	Stage IA1 (Cone biopsy); LVI positive; Medically operable (Hyst and PLND); LN positive	II	FIGO (2), PDQ (3), NCCN (4), SICN (5), NSW (6), CCO (7), YCN (9), SGOG (1), ESMO (10)	<0.01
9	Stage IA2 (Cone biopsy); Medically operable (Hyst and PLND); LN negative; Local recurrence	IV	FIGO (2), PDQ (3), NCCN (4), NSW (6)	<0.01
10	Stage IA2 (Cone biopsy); Medically operable (Hyst and PLND); LN positive	II	FIGO (2), PDQ (3), NCCN (4), SICN (5), NSW (6), CCO (7), YCN (9), SGOG (1), ESMO (10)	<0.01
17	Stage IB-IIA; <4cm; Medically operable (Hyst and PLND); Margin negative; LN negative; GOG score<120; Local recurrence (nil distant metastases); Central local recurrence	IV	FIGO (2), PDQ (3), NCCN (4), NSW (6)	<0.01
18	Stage IB-IIA; <4cm; Medically operable (Hyst and PLND); Margin negative; LN negative; GOG score<120; Local recurrence (nil distant metastases); Side wall recurrence	IV	FIGO (2), PDQ (3), NCCN (4), NSW (6)	<0.01

20	Stage IB-IIA; <4cm; Medically operable (Hyst and PLND); Margin negative; LN positive	II	FIGO (2), PDQ (3), NCCN (4), SICN (5), NSW (6), CCO (7), YCN (9), SGOG (1), ESMO (10)	0.04
21	Stage IB-IIA; <4cm; Medically operable (Hyst and PLND); Margin positive; Vaginal margin positive	II	FIGO (2), PDQ (3), NCCN (4), CCO (7), SGOG (1), ESMO (10)	0.01
22	Stage IB-IIA; <4cm; Medically operable (Hyst and PLND); Margin positive; Vaginal margin negative	II	FIGO (2), PDQ (3), NCCN (4), CCO (7), SGOG (1), ESMO (10)	<0.01
24	Stage IB-IIA; >4cm	I	FIGO (2), PDQ (3), NCCN (4), SICN (5), NSW (6), CCO (7), BCCA (8), YCN (9), SGOG (1), ESMO (10), ABS (11), ACR (12)	0.09
25	Stage IIB-IVA	I	FIGO (2), PDQ (3), NCCN (4), SICN (5), NSW (6), CCO (7), BCCA (8), YCN (9), SGOG (1), ESMO (10), ABS (11), ACR (12)	0.36
Proportion of all cervical cancer patients in whom concurrent chemoradiation is recommended				**0.51 (51%)**

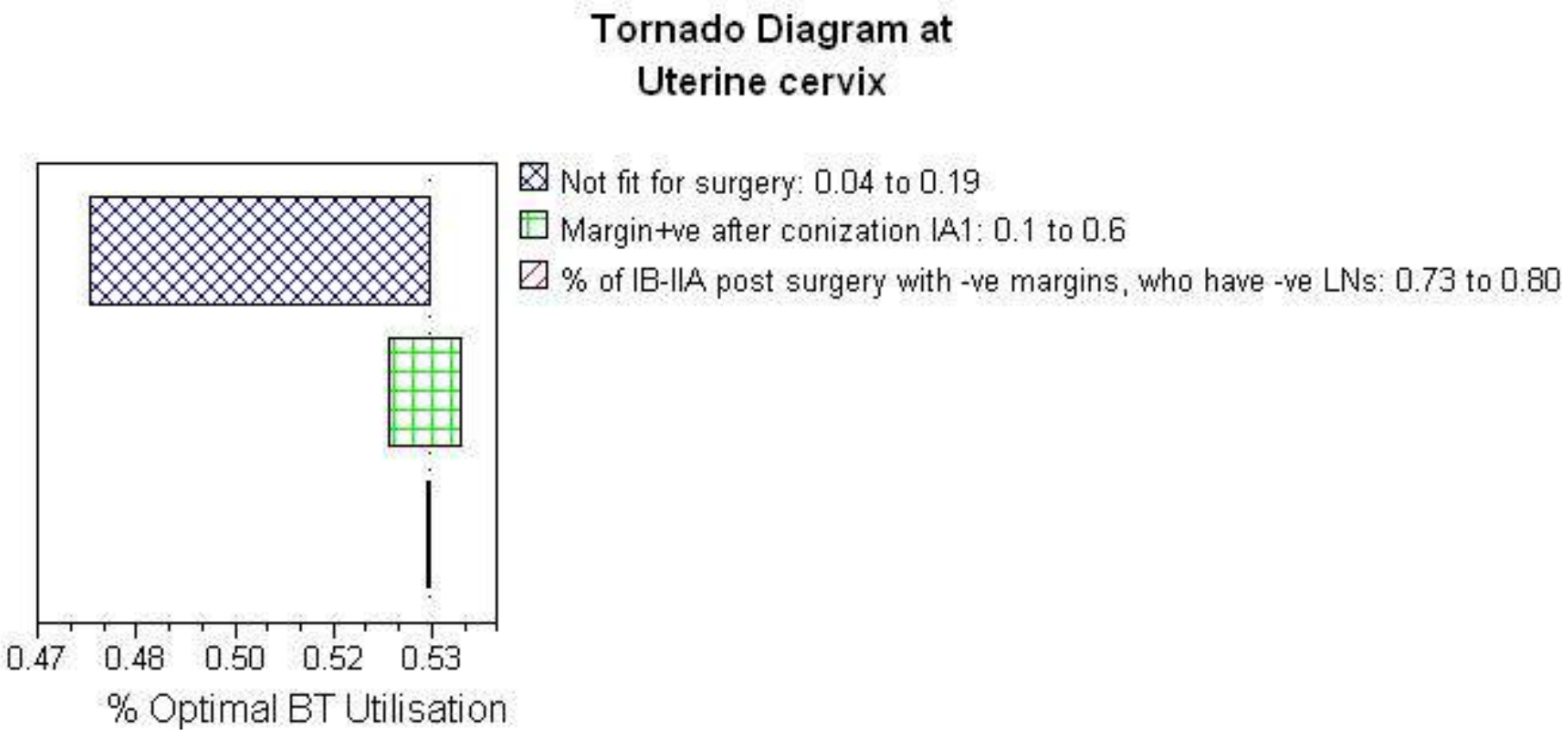
Abbreviations: LVI, Lymphatic Vascular Space Invasion; Hyst, Hysterectomy; PLND, Pelvic Lymph Node Dissection; LN, Lymph Node; GOG, Gynecology Oncology Group; FIGO, Federation Internationale de Gynecologie et d'Obstetrique staging classifications and clinical practice guidelines in the management of gynaecologic cancers; PDQ, CancerNet PDQ Cancer Information Summaries: Treatment of Cervical Cancer; NCCN, National Comprehensive Cancer Network: Clinical Practice Guidelines in Oncology - v1.2012 - Cervical Cancer; NSW, New South Wales Gynaecological Oncology Study Group: Gynaecological Oncology Clinical Practice Guidelines; SICN, Scottish Intercollegiate Network: Management of cervical cancer: A national clinical guideline; CCO, Cancer Care Ontario: Primary Treatment for Locally Advanced Cervical Cancer; YCN, Yorkshire Cancer Network Guidelines for the Management of Gynaecological Cancers; SGOG, The Sydney Gynaecologic Oncology Group, Royal Prince Alfred and Liverpool Hospitals: Clinical Practice and Management Policies; ESMO, Cervical cancer: European Society for Medical Oncology Clinical Practice Guidelines for diagnosis, treatment and follow-up; BCCA, British Columbia Cancer Agency: Cancer Management Guidelines >> Gynecology >> 4. Cervix; ABS, American Brachytherapy Society Cervical Cancer Brachytherapy Task Group; ACR, American College of Radiology Appropriateness Criteria on Advanced Cervical Cancer Expert Panel on Radiation Oncology – Gynecology;

Figure 4. Cervical Cancer External Beam Radiotherapy. Tornado Diagram for Univariate Sensitivity Analysis



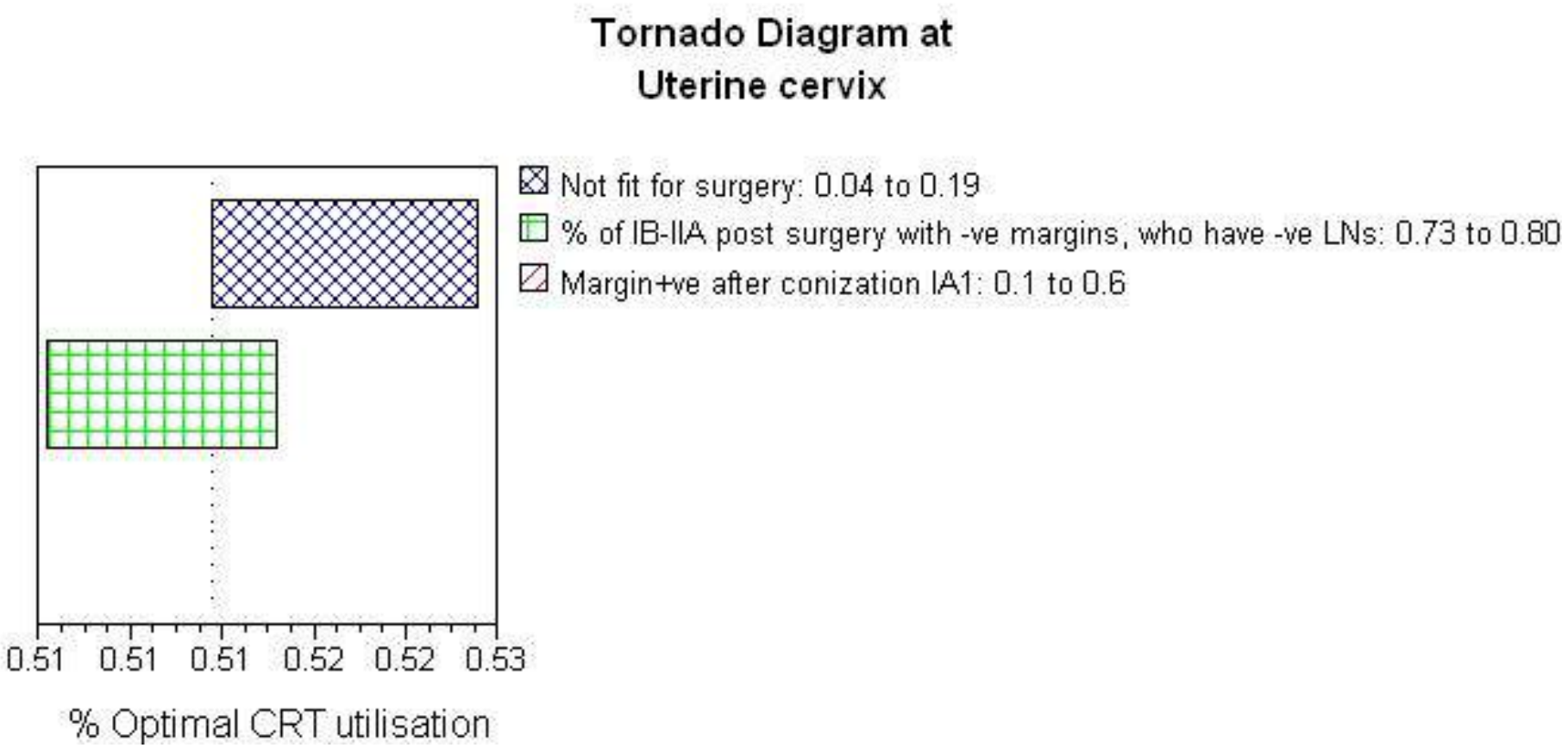
LN, Lymph nodes; EBRT, External Beam Radiotherapy

Figure 5. Cervical Cancer Brachytherapy. Tornado Diagram for Univariate Sensitivity Analysis



LN, Lymph nodes; BT, Brachytherapy

Figure 6. Cervical Cancer Concurrent Chemo-Radiation. Tornado Diagram for Univariate Sensitivity Analysis



LN, Lymph nodes; CRT, Concurrent Chemoradiotherapy

References

1. Sydney Gynaecologic Oncology Group, Royal Prince Alfred and Liverpool Hospitals Sydney. Clinical Practice and Management Policies. Johnathan Carter. 1-6-2004. Sydney, Johnathan Carter.
   Ref Type: Serial (Book,Monograph)

2. FIGO Committee on Gynecologic Oncology. Staging classifications and clinical practice guidelines for gynaecologic cancers. www.figo.org . 2006. 12-9-2012.
   Ref Type: Electronic Citation

3. National Cancer Institute. National Cancer Institute: PDQ® Cervical Cancer Treatment. http://cancer.gov/cancertopics/pdq/treatment/cervical/HealthProfessiona . 22-8-2011. 8-2-2012.
   Ref Type: Electronic Citation

4. National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology - v1.2012 - Cervical Cancer. http://www.nccn.org/professionals/physician_gls/pdf/cervical.pdf . 2012. 8-2-2012.
   Ref Type: Electronic Citation

5. Scottish Intercollegiate Guidelines Network. Management of cervical cancer: A national clinical guideline. http://www.sign.ac.uk/ . 2008. 27-3-2012.
   Ref Type: Electronic Citation

6. Greater Metropolitan Clinical Taskforce (GMCT). Best clinical practice: Gynaecological cancer guidelines 2009. 2009. Sydney, NSW Depatment of Health. 2009.
   Ref Type: Serial (Book,Monograph)

7. Cancer Care Ontario. Primary Treatment for Locally Advanced Cervical Cancer. https://www.cancercare.on.ca/ . 2004. 8-2-2012.
   Ref Type: Electronic Citation

8. BC Cancer Agency. Cancer Management Guidelines >> Gynecology >> 4. Cervix. http://www.bccancer.bc.ca/HPI/CancerManagementGuidelines/Gynecology/UterineCervix . 2008. 28-3-2012.
   Ref Type: Electronic Citation

9. Yorkshire Cancer Network Gynaecology NSSG. Guidelines for the Management of Gynaecological Cancers. http://www.ycn.nhs.uk/ . 2011. 19-10-2011.
   Ref Type: Electronic Citation

10. European Society of Medical Oncology. Cervical cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2010;21:v37-v40.

11. Viswanathan AN and Thomadsen B. American Brachytherapy Society Cervical Cancer Brachytherapy Task Group. http://www.americanbrachytherapy.org/guidelines/cervical_cancer_taskgroup.pdf . 2011. 8-2-2012.
    Ref Type: Electronic Citation

12. American College of Radiology. ACR Appropriateness Criteria on Advanced Cervical Cancer Expert Panel on Radiation Oncology - Gynecology. *Int J Radiat Oncol Biol Phys* 2011;81:609-14.

13. National Cancer Institute (Cancer Statistics Branch). SEER*Stat 6.6.2 Surveillance, Epidemiology and End Results Cancer Incidence Public-Use Database, 1973-2007. 2010. Bethesda, US Department of Health and Human Services.
Ref Type: Data File

14. Australian Institute of Health and Welfare (AIHW). Australian Cancer Incidence and Mortality (ACIM) books. http://www.aihw.gov.au/acim-books/ . 2007. 8-3-2012.
Ref Type: Electronic Citation

15. Delgado G, Bundy B, Zaino RJ, Sevin BU, Creasman WT, Major F. Prospective surgical-pathological study of disease-free interval in patients with Stage IB squamous cell carcinoma of the cervix: a Gynecologic Oncology Group study. *Gynecol Oncol* 1990;38:352-7.

16. Samlal RA, van der Velden J, Ten Kate FJ, Schilthuis MS, et al. Surgical pathologic factors that predict recurrence in stage IB and IIA cervical carcinoma patients with negative pelvic lymph nodes. *Cancer* 1997;80:1234-40.

COLON CANCER

In the original radiotherapy utilisation model the indications for radiotherapy for colon cancer were derived from evidence-based treatment guidelines issued by major national and international organisations. The guidelines reviewed are those published after the previous radiotherapy utilisation study was completed (July 2003) up to August 2011.

Updated Guidelines

The following new or updated guidelines were identified since the original RTU study:

- National Health and Medical Council (NHMRC) Guidelines for the Prevention, Early Detection and Management of Colorectal Cancer. 2005 (1)
- National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines on Colon Cancer (Version 3, 2011) (2)
- National Cancer Institute (NCI PDQ) guideline on colon cancer (2011) (3)
- National Institute for Clinical Excellence (NICE) guidelines. Improving outcomes in Colorectal cancers. 2004 (4)
- BC Cancer Agency Cancer Management Guidelines Colon (2005) (5)
- Scottish Intercollegiate Guidelines Network (SIGN). Management of Colorectal Cancer (2003). (6)
- Association of Coloproctology of Great Britain and Ireland. Guidelines for the management of colorectal cancer (2007). (7)

Indications for radiotherapy

All the indications for external beam radiotherapy in the original CCORE model of optimal radiotherapy utilisation for colon cancer were reviewed and updated in the optimal utilisation tree based on the latest guideline recommendations (Figure 1 and Table 1). No new indications for radiotherapy are recommended. The indication for adjuvant radiotherapy in T4 colon cancer has been removed from the optimal utilisation model (see below).

Adjuvant radiotherapy in colon cancer

Among all the above updated guidelines, only the NCCN guidelines recommend that “conformal external beam radiation should be routinely used for T4 non-metastatic disease”. The other guidelines do not mention a role for adjuvant radiotherapy in colon cancer. The previous evidence in favour of radiotherapy in this clinical situation in the original optimal utilisation model was based on a non-randomised retrospective study by Willett et al which suggested that postoperative adjuvant radiation therapy improved local control in patients who had tumour adherence to surrounding structures (8). A subsequent randomised trial (the Intergroup 0130 trial) published in 2004 did not meet its accrual

objective; however it is one of the largest studies of adjuvant radiotherapy in colon cancer to date and it found that patients who received chemotherapy or chemo-RT had similar overall survival and disease-free survival, but toxicity was higher among chemo-RT patients (9). A patterns of care study of external beam radiotherapy in colon cancer published in 2010 found that RT use in colon cancer has declined markedly since the late 1980s and the authors noted that the role for RT in colon cancer is not clearly defined (10).

Since the majority of the guidelines do not recommend adjuvant radiotherapy in colon cancer and in view of the findings from the above Intergroup trial (9), radiotherapy is no longer recommended for T4 colon cancer in the optimal radiotherapy utilisation model.

Level of evidence

The main indications for radiotherapy in colon cancer are in the treatment of bone and brain metastases; these indications are supported by level I-II evidence. There is only one other indication for radiotherapy in colon cancer which is supported by level IV evidence (palliative radiotherapy in patients with metastatic disease and primary that is non-resectable due to fixation to other organs) but this indication affects such a small proportion of patients that it has no effect on the optimal utilisation rate. The updated model predicts that 4% of the entire colon cancer population have an indication for radiotherapy that is based on level I-II evidence of benefit.

Changes to Epidemiological Data

The epidemiological data in the colon cancer utilisation tree were reviewed to identify more recent data if available through extensive electronic searches using the key words ‘colon cancer’, ‘radiotherapy’, ‘epidemiology colon cancer’, ‘incidence’, ‘colon cancer stage‘ ‘T4’, ‘metastases’, ‘brain metastases’, ‘bone metastases’, ‘skeletal metastases’ in various combinations . This applied particularly to the early branches in the tree for which national level data on cancer incidence rates and stages were available. Any changes in the hierarchical quality of the epidemiological data have been noted (Table 2).

<u>Incidence of Colon Cancer</u>:

Since the publication of the previous radiotherapy utilisation project, the Australian national cancer incidence data published by AIHW has been updated, with the most recent data available being 2007 data. The latest AIHW ACIM book published in 2010 states that in 2007, bowel cancer accounted for 13.1% of all cancer in Australia. We contacted AIHW and received a breakdown of bowel cancer incidence by site: Colon (ICD-10 code C18) accounted for 8.58 % of all cancers, Rectosigmoid junction (ICD-10 code C19) accounted for 1.07% of all cancers and Rectum (ICD-10 code C20) accounted for 3.48% of all cancers in Australia in the year 2007 (11). Since the management of

cancers arising in the rectosigmoid junction is similar to that of colon cancer, we have taken the incidence of colon cancer to be 9.6% of all cancers in Australia in 2007.

Non-metastatic Colon Cancer

Data on the stage at presentation of patients with colorectal cancer were obtained from the Australian National Colorectal Cancer Care Survey of Australian Clinical Practice in the year 2000 (12). All newly reported individuals diagnosed with colorectal cancer and notified to each Australian Cancer Registry over the three-month period between 1 February 2000 and 30 April 2000 were included in this survey. Among all colon cancer patients with known stage at presentation, 80% presented with non-metastatic disease.

Proportion of patients withT4 colon cancer

Extraction of data from the SEER Stat Database of 17 registries across the United States for the years 2004-2007 shows that there were 70,466 cases of non-metastatic (M0) colon cancer; of these 10.9% (7739 patients) had T4 disease (13). This data has been used in the optimal utilisation tree.

The proportion of patients presenting with T4 disease shows a decreasing trend over time.
In the original RTU study, the only available data on the proportion of patients with Stage T4NxM0 tumours were from hospital series and varied from 7% to 25% (14;15). Gunderson et al reported in 2009 that SEER data from 1992 to 2004 showed that 13.7% of non-metastatic cases of colon cancer had T4 disease (16). The latest available SEER data for the years 2004-2007 (used in the revised tree) shows that 10.9% of patients had T4 disease (13).

Estimation of the Optimal Radiotherapy Utilisation Rate

Based on the most recent evidence and epidemiological data, radiotherapy is recommended in 4% of all colon cancer patients in Australia (Table 1 and Figure 1). The previous optimal radiotherapy rate for colon cancer derived in 2003 was 14%. The decrease in the optimal utilisation rate is due to radiotherapy no longer being recommended for patients with colon cancer who have T4 disease at presentation.

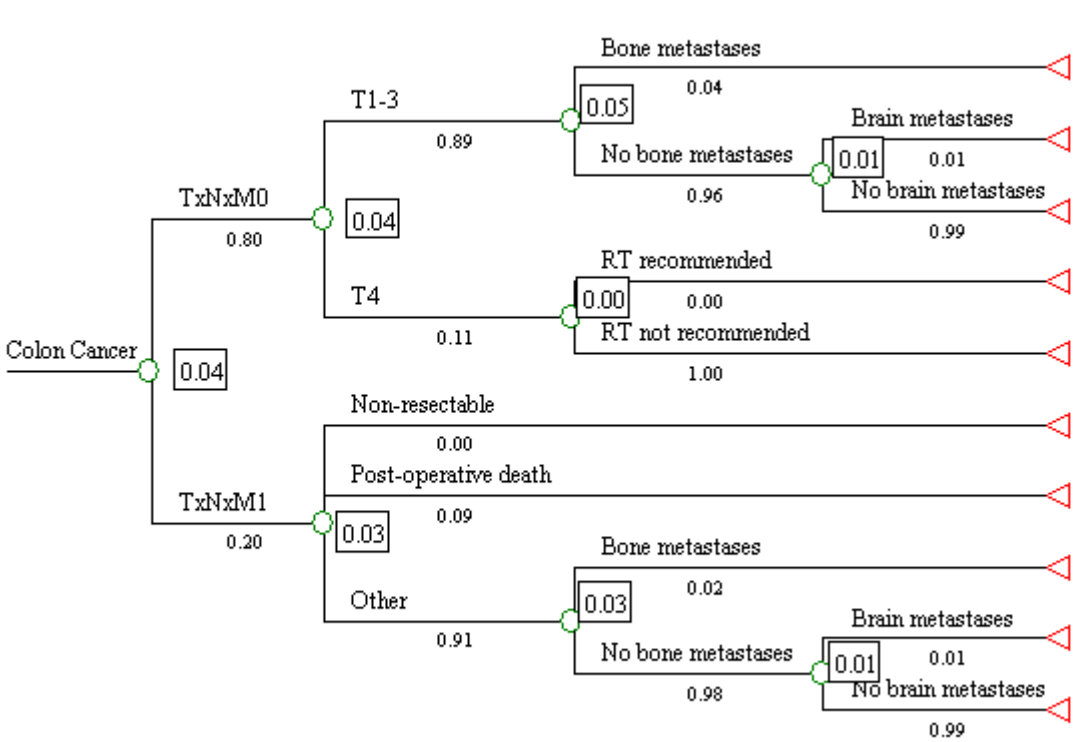
Concurrent Chemoradiotherapy in Colon Cancer

There are no indications for radiotherapy in conjunction with concurrent chemotherapy as the first treatment in colon cancer. The NCCN guidelines recommend chemoradiation for non-metastatic T4 colon cancer but this is not recommended by any of the other guidelines and is therefore not incorporated into the optimal radiotherapy utilisation tree.

Sensitivity analysis

A univariate sensitivity analysis was undertaken to assess the changes in the recommended radiotherapy utilisation rate that would result from different estimates of the proportions of patients with particular attributes. There is some uncertainty regarding whether or not radiotherapy is indicated in patients with T4 disease, with one guideline (NCCN) recommending radiotherapy in this situation whereas none of the other guidelines make this recommendation. Hence the proportion of patients with T4 colon cancer that may benefit from radiotherapy was varied between 0% and 5.5% (i.e no T4 patients get radiotherapy through to 50% of T4 patients get radiotherapy) in the sensitivity analysis. As in the original utilisation tree, the sensitivity analysis also varied the proportion of symptomatic patients presenting in Stage TXNXM1 with unresectable tumours requiring radiotherapy from 0-11%. The results of the sensitivity analysis are depicted in the tornado diagram in Figure 2. The variation in the estimate of the proportion of colon cancer patients for whom radiotherapy may be indicated ranges from 4.0 to 6.2% as shown in Figure 2.

Figure 1. Revised Optimal Radiotherapy Utilisation Tree for Colon Cancer



Outcome No	RT [1=yes, 0=no]	Total Proportion
1.00	1.00	0.03
2.00	1.00	0.01
3.00	0.00	0.68
4.00	1.00	
5.00	0.00	0.09
6.00	1.00	
7.00	0.00	0.02
8.00	1.00	0.00
9.00	1.00	0.00
10.00	0.00	0.18

Table 1: Colon Cancer. Indications for radiotherapy - Levels and sources of evidence

Original RTU study				Updates 2011					
Outcome No. in Tree	Clinical Scenario	Level of evidence	Proportion of all Colon cancer	Change of Indication	Guideline updated	Current level of evidence	Change to proportion of all Colon cancer		References
							Yes/ No	Updated value	
1	Stage T1-3, any N, M0 bone metastases	I	0.03	No	Yes	I	No	0.03	NICE guidelines (4)
2	Stage T1-3, any N, M0 No bone metastases Brain metastases	II	0.01	No	N/A	II	No	0.01	The management of brain metastases is not discussed in any of the guidelines.
6	Stage any T, any N, M1 non-resectable due to fixation to other organs	IV	<0.01	No	No	IV	No	<0.01	Willett et al (8)
8	Stage any T, any N, M1 Bone metastases	I	<0.01	No	Yes	I	No	<0.01	NICE guidelines (4)
9	Stage any T, any N, M1 No bone metastases Brain metastases	II	<0.01	No	N/A	II	No	<0.01	The management of brain metastases is not discussed in any of the guidelines.

Original RTU study				Updates 2011					
Outcome No. in Tree	Clinical Scenario	Level of evidence	Proportion of all Colon cancer	Change of Indication	Guideline updated	Current level of evidence	Change to proportion of all Colon cancer		References
							Yes/ No	Updated value	
Proportion of all Colon cancer patients in whom Radiotherapy is recommended			0.14 (14%)	**Updated Proportion of all Colon cancer patients in whom Radiotherapy is recommended**				**0.04 (4%)**	

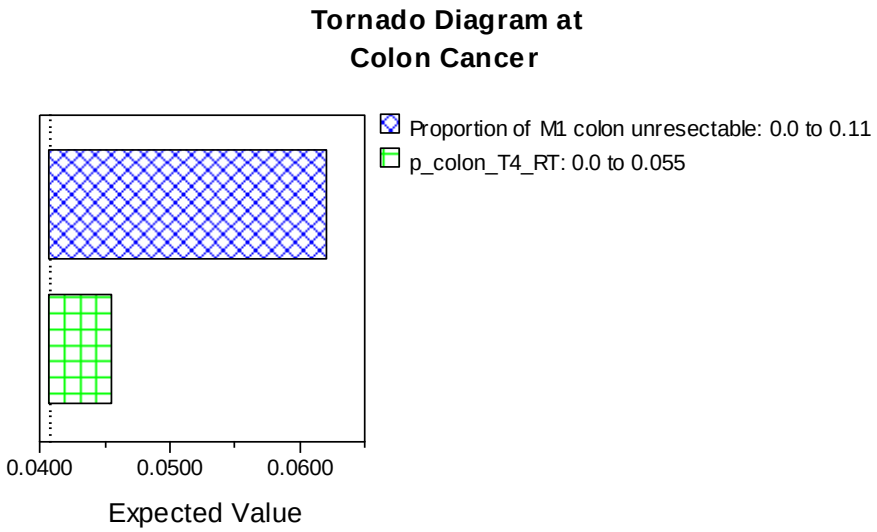
Abbreviations: RTU – Radiotherapy Utilisation, NICE - National Institute for Clinical Excellence, NHMRC – National Health and Medical Research Council, NCCN – National Comprehensive Cancer Network

Table 2: Colon Cancer: The incidence of attributes used to define indications for radiotherapy

Original RTU study				Updates 2011				
Population or sub-population of interest	**Attribute**	**Proportion of population with the attribute**	**Quality of Information**	**Change in proportion of population with attribute Yes/ No**	**Updated Proportion**	**Updated Quality of Information**	**Updated Reference**	**Comments**
All registry cancers	Colon cancer	0.09	α	Yes	0.096	α	AIHW 2011 (11)	Based on AIHW 2007 data (personal communication from AIHW)
All Colon Cancers	Any T, any N, M0	0.80	γ	No	0.80	α	National colorectal cancer survey (12)	The data has been updated but the proportion remains the same.
Colon Cancer, Any T, any N, M0	T 4, any N, M0	0.07 – 0.25	ζ	Yes	0.11	γ	SEER (13)	Based on SEER 2004-2007 data
Stage T 1-3, any N, M0	Bone metastases	0.04	ζ	No	N/A	N/A	Bonnheim et al (17)	

Original RTU study				Updates 2011				
Population or sub-population of interest	**Attribute**	**Proportion of population with the attribute**	**Quality of Information**	**Change in proportion of population with attribute Yes/ No**	**Updated Proportion**	**Updated Quality of Information**	**Updated Reference**	**Comments**
Stage T 1-3, any N, M0 and no bone metastases	Brain metastases	0.01	ζ	No	N/A	N/A	Hammoud et al (18)	
Stage any T, any N, M1	Unresectable due to fixation to other organs	0.22	ζ	No	N/A	N/A	Willett et al (14)	
Stage any T, any N, M1	Post-operative death	0.09	ζ	No	N/A	N/A	Willett et al (14)	
Stage any T, any N, M1	Bone metastases	0.02	ζ	No	N/A	N/A	Russell et al (15)	
Stage any T, any N, M1, no bone metastases	Brain metastases	0.01	ζ	No	N/A	N/A	Russell et al (15)	

Figure 2. Colon Cancer. Tornado Diagram for Univariate Sensitivity Analysis



References

1. Australian Cancer Network Colorectal Cancer Guidelines Revision Committee. Clinical Practice Guidelines for the prevention, early detection and management of colorectal cancer. http://www.nhmrc.health.gov.au . 2005. Sydney, The Cancer Council Australia and Australian CancerNetwork.
   Ref Type: Report

2. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Colon Cancer. Version 3.2011. http://www.nccn.org/professionals/physician_gls/PDF/colon.pdf . 2011.15-8-2011.
   Ref Type: Electronic Citation

3. National Cancer Institute. Colon Cancer Treatment (PDQ). http://www.cancer.gov/cancertopics/pdq/treatment/colon/HealthProfessional . 2011. 5-9-2011.
   Ref Type: Electronic Citation

4. National Institute for Clinical Excellence (NICE). Improving Outcomes in Colorectal Cancers. www.nice.org.uk.2004.
   Ref Type: Electronic Citation

5. BC Cancer Agency. Cancer Management Guidelines for Cancer of the Colon. http://www.bccancer.bc.ca/HPI/CancerManagementGuidelines/Gastrointestinal/05.Colon/Management/default.htm.2005.15-10-2008.
   Ref Type: Electronic Citation

6. Scottish Intercollegiate Guidelines Network. Management of colorectal cancer. A national clinicalguideline.www.sign.ac.uk.2003.6-11-2006.
   Ref Type: Electronic Citation

7. Association of Coloproctology of Great Britain and Ireland. Guidelines for the management of colorectal cancer. http://www.acpgbi.org.uk/assets/documents/COLO_guides.pdf . 2007. 20-9-2011.
   Ref Type: Electronic Citation

8. Willett CG, Tepper JE, Kaufman DS, Shellito PC. Adjuvant postoperative radiation therapy for colonic carcinoma. *Semin Radiat Oncol* 1993;3:64-7.

9. Martenson JA, Willett CG, Sargent DJ, et al. Phase III study of adjuvant chemotherapy and radiation therapy compared with chemotherapy alone in the surgical adjuvant treatment of colon cancer: results of Intergroup Protocol 0130. *J Clin Oncol* 2004;22:3277-83.

10. Dunn EF, Kozak KR, Moody JS. External beam radiotherapy for colon cancer: patterns of care. *Int J Radiat Oncol Biol Phys* 2010;76:1420-4.

11. Australian Institute of Health and Welfare (AIHW). Australian Cancer Database. 2011.
    Ref Type: Personal Communication

12. Clinical Governance Unit. The National Colorectal Cancer Care Survey. Australian clinical practice in 2000. 1-124. 2002. Melbourne, National Cancer Control Initiative.
    Ref Type: Report

13. National Cancer Institute and Surveillance, Epidemilogy and End Results SEER Program. Surveillance, Epidemiology and End Results (SEER) Program SEER*Stat Database: Incidence - SEER 17 Regs Research Data, Nov 2009 Sub (1973-2007 varying) - Linked to county attributes-TotalUS.,1969-2007.Counties.2010.
    Ref Type: Data File

14. Willett CG, Tepper JE, Cohen AM, Orlow E, Welch CE. Failure patterns following curative resection of colonic carcinoma. *Ann Surg* 1984;200:685-90.

15. Russell AH, Tong D, Dawson LE, Wisbeck W. Adenocarcinoma of the proximal colon. Sites of initial dissemination and patterns of recurrence following surgery alone. *Cancer* 1984;53:360-7.

16. Gunderson L, Jessup JM, Sargent DJ, Greene FJ, Stewart AK. Revised TN categorization for colon cancer based on National Survival Outcomes Data. *J Clin Oncol* 2010;28:264-71.

17. Bonnheim DC, Petrelli NJ, Herrera L, Walsh D, Mittelman A. Osseous metastases from colorectal carcinoma. *Am J Surg* 1986;151:457-9.

18. Hammoud MA, McCutcheon IE, Elsouki R, Schoppa D, Patt YZ. Colorectal carcinoma and brain metastasis: distribution, treatment and survival. *Ann Surg Oncol* 1996;3:453-63.

GALLBLADDER CANCER

Evidence-based treatment guidelines for gallbladder cancer management issued by major international, national and provincial organisations reviewed for the model are those published after the previous radiotherapy utilisation study was completed (July 2003) up to the most recent ones published in 2012.

Updated guidelines

The following new or updated guidelines were identified and reviewed since the original RTU study:

- NCCN clinical practice guidelines on gallbladder cancer, version 2, 2012 (1)
- NCI gallbladder cancer treatment PDQ, 2012 (2)
- BC Cancer Agency gastrointestinal cancer management guidelines (Gallbladder), 2012 (3)

Indications for radiotherapy

The only indication for external beam radiotherapy in the original CCORE model of optimal radiotherapy utilisation for gallbladder cancer was for patients of good performance status with unresectable localised disease. Based on the latest guidelines, both radiotherapy and chemotherapy are recommended treatment options for these patients, with the chemotherapy recommendation being based on a recently published randomised controlled study which showed a survival benefit with combination chemotherapy of gemcitabine and cisplatin compared to gemcitabine alone in patients with locally advanced or metastatic gallbladder cancer, cholangiocarcinoma or ampullary cancer (4). The optimal utilisation tree has been updated to reflect the current guideline recommendations, with the branch of patients of good performance status with unresectable localised disease being divided into two branches: patients recommended to have radiotherapy (0.5) and patients recommended to have chemotherapy (0.5) (Table 1, Figure 1). The proportion of 0.5 has been chosen arbitrarily as there are no published studies which compare chemotherapy with radiotherapy in these patients, and hence there is no evidence for superiority of either treatment approach.

There are no new indications for radiotherapy according to the latest guidelines.

Level of evidence

According to the methods applied for the previous radiotherapy utilisation model the indication for radiotherapy for gallbladder cancer has been derived from evidence-based treatment guidelines issued by major international, national and provincial organisations.

Based on guidelines review, the indication of radiotherapy for gallbladder cancer is supported by level IV evidence, unchanged from the original model.

Epidemiology of cancer stages

The epidemiological data in the gallbladder cancer utilisation tree have been reviewed to see if more recent data are available through extensive electronic search using the key words 'Australia', 'epidemiology gallbladder cancer', 'incidence', 'gallbladder cancer stage', 'radiotherapy treatment', 'distant metastases', 'survival', 'treatment outcome' in various combinations. This has been applied particularly to the early branches in the tree for which national or state level data on cancer incidence rates and stages are available. If there is a change in the hierarchical quality of the epidemiological data, this has also been noted (Table 2).

Since the completion of the previous radiotherapy utilisation project the national data on cancer statistics published by AIHW have been updated to more recent years till 2008 (5). There has been no change in the incidence of gallbladder cancer in Australia. The proportion of patients with metastatic disease has been updated according to recent SEER data (6).

Estimation of the optimal radiotherapy utilisation

From the evidence on the efficacy of radiotherapy and the most recent epidemiological data on the occurrence of the indication for radiotherapy, the proportion of gallbladder cancer patients in whom radiotherapy would be recommended is 17% (Table 1 and Figure 1) compared with the original estimate of 13%.

Estimation of the optimal combined radiotherapy and chemotherapy utilisation

For patients with unresectable localised disease, the NCCN guidelines (1) recommend radiotherapy in conjunction with concurrent chemotherapy (Table 3 and Figure 2). The optimal proportion of gallbladder cancer patients for whom concurrent chemoradiotherapy is recommended is 17%.

Sensitivity analysis

Univariate sensitivity analysis has been undertaken to assess changes in the recommended gallbladder cancer radiotherapy utilisation rate that would result from different estimates of the proportions of patients with particular attributes as mentioned in Table 2 (Figures 3 and 4). As the guidelines recommend both chemotherapy and chemoradiotherapy as treatment options for patients of good performance status with unresectable localised disease, sensitivity analysis was performed to assess the impact of varying the proportion of patients receiving chemoradiotherapy from 0% to 100% on the overall optimal radiotherapy utilisation rate for gallbladder cancer. The variability in the estimate of optimal radiotherapy utilisation due to these uncertainties ranged from 0% to 33% as shown in the Tornado diagram (Figure 3). The optimal chemoradiotherapy utilisation rate also ranged from 0% to 33% (Figure 4).

Table 1: Gallbladder Cancer. Indications for radiotherapy - Levels and sources of evidence

Original RTU study				Updates 2012					
Outcome No. in Tree	Clinical Scenario	Level of evidence	Proportion of all gallbladder cancer	Change of Indication	Guideline updated	Current level of evidence	Change to proportion of all gallbladder cancer		References
							Yes/ No	Updated value	
2	Gallbladder cancer, no metastatic disease, good performance status, unresectable	IV	0.13	No	Yes	IV	Yes	0.17	NCCN (1), NCI (2), BCCA (3)
Proportion of all gallbladder cancer patients in whom radiotherapy is recommended			0.13 (13%)	**Updated proportion of all gallbladder cancer patients in whom radiotherapy is recommended**				**0.17 (17%)**	

Table 2: Gallbladder Cancer. The incidence of attributes used to define indications for radiotherapy

Original RTU study				Updates 2012				
Population or sub-population of interest	Attribute	Proportion of population with the attribute	Quality of Information	Change in proportion of population with attribute Yes/ No	Altered Proportion	Updated Quality of Information	Updated Reference	Comments
All registry cancers	Gallbladder cancer	0.01	α	No	0.01	α	AIHW 2012 (5)	Data have been updated but the proportion remains unchanged
Gallbladder cancer	Metastatic disease	0.62 0.50	ζ ζ	Yes	0.38 0.39 0.47 0.37 0.55	γ γ γ ζ ζ	SEER 2011 (6) Kiran et al 2007 (7) Kayahara et al 2007 (8) Duffy et al 2008 (9) Chan et al 2008 (10)	SEER data used as most recent and highest level of epidemiological data
Gallbladder cancer, no metastatic disease	Good PS	0.97	ε	No	N/A	N/A	Cubertafond et al 1994 (11)	

Original RTU study				Updates 2012				
Population or sub-population of interest	Attribute	Proportion of population with the attribute	Quality of Information	Change in proportion of population with attribute Yes/ No	Altered Proportion	Updated Quality of Information	Updated Reference	Comments
Gallbladder cancer, no metastatic disease, good PS	Resectable	0.58 0.97 0.43	ζ ζ ζ	Yes	0.45 0.59	ζ ζ	Duffy et al 2008 (9) Chan et al 2008 (10)	Data from Duffy et al used as larger sample size

Table 3: Gallbladder Cancer. Indications for concurrent chemoradiotherapy - Levels and sources of evidence

Outcome No. in Tree	Clinical Scenario	Level of Evidence	References	Proportion of all gallbladder cancer patients
2	Gallbladder cancer, no metastatic disease, good performance status, unresectable	IV	NCCN guidelines (1)	0.17
The total proportion of all patients with gallbladder cancer in whom concurrent chemoradiotherapy is recommended				**0.17 (17%)**

Figure 1. Gallbladder cancer radiotherapy utilisation tree

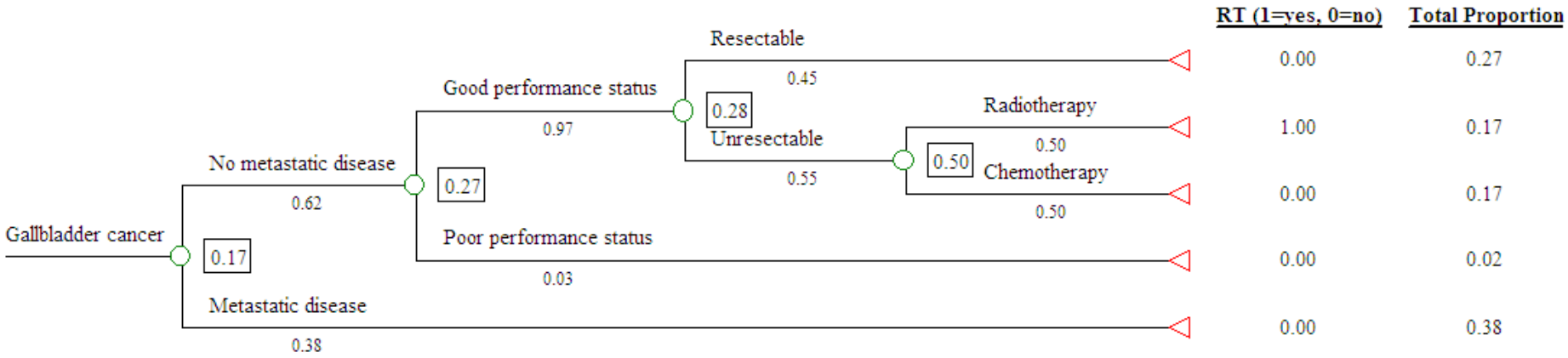


Figure 2. Gallbladder cancer concurrent chemoradiotherapy utilisation tree

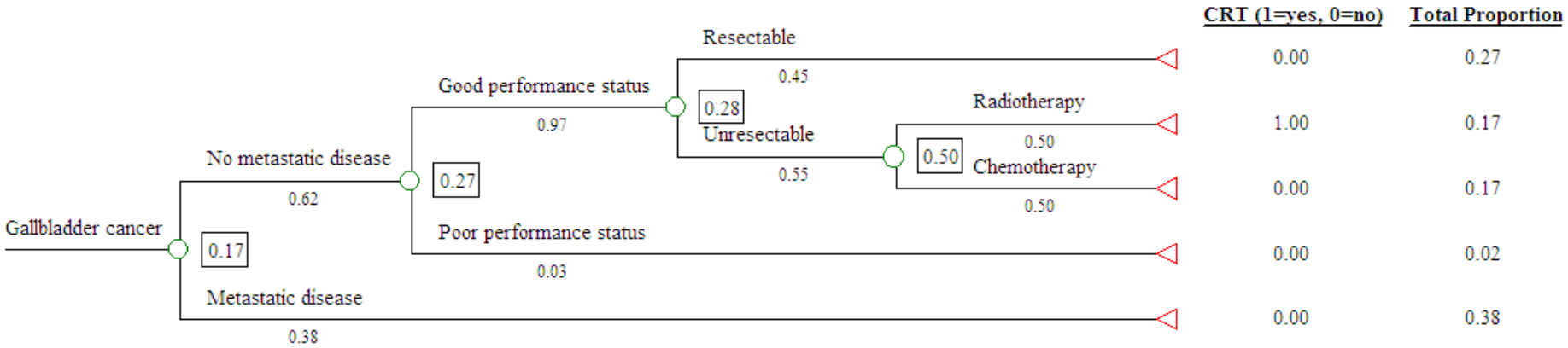


Figure 3. Tornado diagram: univariate sensitivity analyses for radiotherapy utilisation

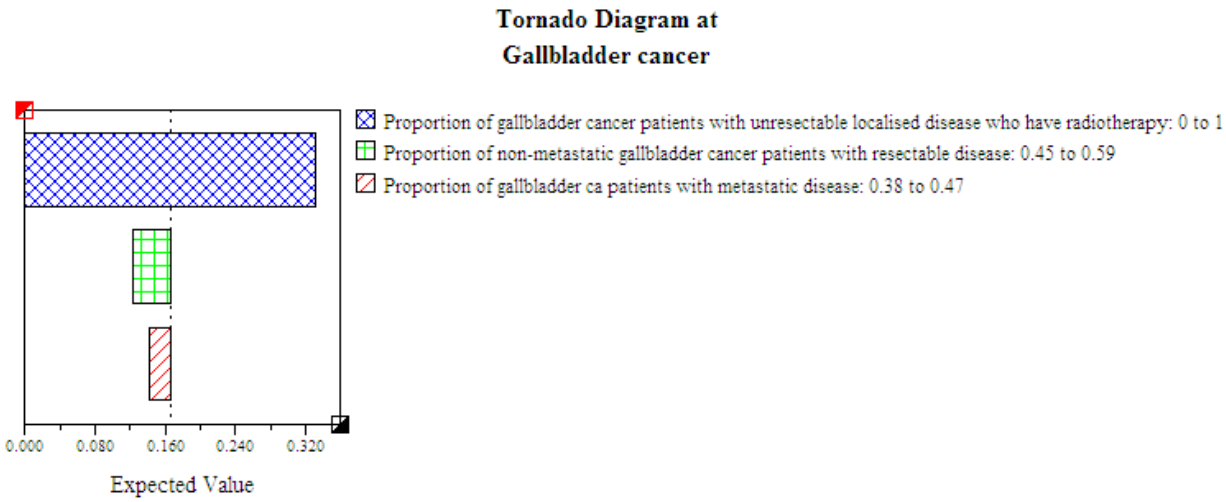
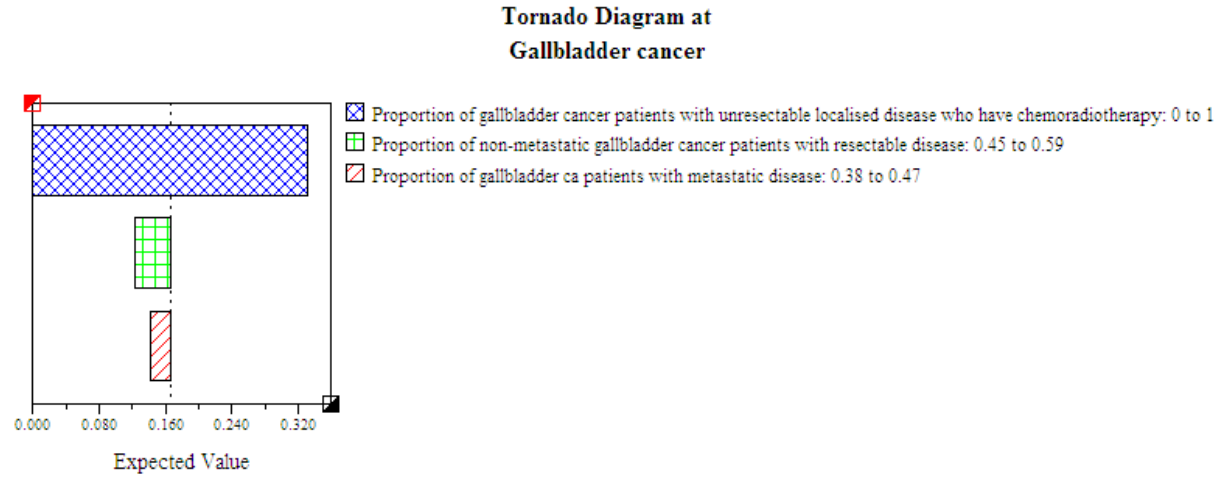


Figure 4. Tornado diagram: univariate sensitivity analyses for chemoradiotherapy utilisation



References

1. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Hepatobiliary Cancers Version 2.2012: www.nccn.org; 2012. Accessed 28/8/2012.

2. National Cancer Institute. PDQ Summary: Gallbladder Cancer Treatment: www.cancer.gov; 2012. Accessed 14/9/2012.

3. British Columbia Cancer Agency. Cancer Management Guidelines: Gastrointestinal Cancer (Gallbladder): www.bccancer.bc.ca; 2012. Accessed 14/9/2012.

4. Valle J, Wasan H, Palmer DH*, et al.* Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. *N Engl J Med* 2010;362:1273-1281.

5. Australian Institute of Health and Welfare (AIHW). Australian Cancer Incidence and Mortality (ACIM) books. : www.aihw.gov.au/acim-books/; 2012. Accessed 29/08/2012.

6. Surveillance Research Program, National Cancer Institute SEER*Stat software (seer.cancer.gov/seerstat). Version 7.0.5. [computer program]. Bethesda, MD: National Cancer Institute (NCI); 2011.

7. Kiran RP, Pokala N, Dudrick SJ. Incidence pattern and survival for gallbladder cancer over three decades--an analysis of 10301 patients. *Ann Surg Oncol* 2007;14:827-832.
8. Kayahara M, Nagakawa T. Recent trends of gallbladder cancer in Japan: an analysis of 4,770 patients. *Cancer* 2007;110:572-580.

9. Duffy A, Capanu M, Abou-Alfa GK*, et al.* Gallbladder cancer (GBC): 10-year experience at Memorial Sloan-Kettering Cancer Centre (MSKCC). *J Surg Oncol* 2008;98:485-489.

10. Chan SY, Poon RT, Lo CM*, et al.* Management of carcinoma of the gallbladder: a single-institution experience in 16 years. *J Surg Oncol* 2008;97:156-164.

11. Cubertafond P, Gainant A, Cucchiaro G. Surgical treatment of 724 carcinomas of the gallbladder. Results of the French Surgical Association Survey. *Ann Surg* 1994;219:275-280.

HEAD & NECK CANCER

Evidence-based guidelines issued by major national and international organisations for the treatment of head and neck cancer were reviewed. The guidelines reviewed were those published from July 2003 (when the previous radiotherapy utilisation study was completed) to April 2012.

Updated Guidelines

The following new or updated clinical practice guidelines for the management of head and neck cancer were identified:

- National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines on Head and Neck Cancers (Version.2.2011) (1)
- Scottish Intercollegiate Guideline Network (SIGN) guidelines 2006 (2)
- Cancer Care Ontario guideline (2009) (3)
- National Cancer Institute (NCI PDQ) guidelines on head and neck cancer (2012) (4-11)
- European Society of Medical Oncology (ESMO) and European Society for Therapeutic Radiology and Oncology (ESTRO) guidelines (2010) (12;13)
- Spanish guidelines (2010) (14)
- BC (British Columbia) Cancer Agency guidelines (2003) (15)
- Danish national guidelines for oral squamous carcinoma (2006) (16)
- Guidelines on management of skin cancer (17;18)
- State of the Art Oncology in Europe (START) guidelines (19)
- United Kingdom ENT guidelines (20)
- American Society of Clinical Oncology (ASCO) guidelines (21)

Indications for radiotherapy

All the indications for external beam radiotherapy in the original CCORE model of optimal radiotherapy utilisation for head and neck cancer were reviewed based on the latest guideline recommendations (Figure 1 and Table 1).

Lip Cancer

In the original model of optimal radiotherapy utilisation in lip cancer, radiotherapy was recommended for all locoregional recurrences following surgery or in cases where the lip cancer was not cosmetically excisable. The updated guidelines recommend that in addition to the above indications, adjuvant radiotherapy is indicated in patients with adverse risk features after surgery if re-excision with acceptable cosmetic and functional outcomes is not feasible or adequate to address the risk of recurrence (1;17). These adverse features are positive margins (</=1mm), perineural invasion, or

lymphovascular invasion for clinical stage I/II cancers. Most lip cancer presents at stage I/II. For the rare advanced case managed primarily with surgery, indications for adjuvant radiation also included multiple positive nodes and extracapsular nodal spread.

Oral Cavity Cancer

In the original model of optimal radiotherapy utilisation, radiotherapy was recommended for all patients who presented with stage III or IV oral cavity cancer. The tree has been amended to take into account the roles of surgery followed by adjuvant radiotherapy and/or concurrent chemoradiation in the treatment of oral cavity cancer. The two scenarios for chemoradiation use in oral cavity cancer were for radical radiotherapy for advanced cancers, and for adjuvant radiation for patients with positive resection margins (<=1 mm) or extracapsular extension (ECE) (Table 1).

Indications for radiotherapy alone were for radical treatment of stage I-II oral cancers, and for all other indications for adjuvant radiation. In the revised model, adjuvant radiotherapy is recommended for adverse pathology (pN2-3, advanced T-category, lymphatic, vascular or perineural invasion, level IV/V node positive) based on guideline recommendations (1-3;13;14). The guidelines generally agreed that adjuvant radiation should be at minimum *considered* for resected pathologic stage III-IV disease with close margins (1-3;13;14), although both the SIGN and Cancer Care Ontario (CCO) guidelines acknowledged the lack of randomized trial evidence supporting adjuvant radiation use. In the revised model, adjuvant radiation is not indicated for patients with T1-2 N1 cancers without established risk factors, based on guideline recommendations (3;8;15;16).

Radiotherapy was generally considered an acceptable option for radical treatment in all stages, although guidelines indicated that surgery was the recommended or preferred option for initial management, wherever possible. When radical radiotherapy was recommended, radiotherapy alone was consistently recommended for stage I-II oral cavity cancers and radical chemoradiation was recommended for stage III-IV oral cavity (1-3;13;14). Given the toxicity of combining concurrent chemotherapy with radical radiotherapy for head and neck cancer, the Cancer Care Ontario (CCO) guideline most strongly recommends its use in those under the age of 70 and the medically fit (2).

Cancer of the Larynx

The indications for radiotherapy in laryngeal cancer have not changed; however chemoradiation is now standard in the treatment of head and neck cancer. The optimal radiotherapy utilisation tree for laryngeal cancer has been modified by adding more branches in order to separate the proportion of patients in whom radiation is recommended in conjunction with concurrent chemotherapy. In laryngeal cancer concurrent chemotherapy is recommended in two situations: i) in locally advanced (stage III-IVB) cancer with *radical* radiotherapy in patients with sufficiently good performance status and ii)

following laryngectomy or laryngeal preserving surgery as *adjuvant* treatment with radiotherapy in patients with positive margins or extra-capsular extension (ECE) (1-4;13).

The changes to the optimal utilisation tree can be summarised as follows:
In the original model, all patients with supra-glottic cancer who were not suitable for laryngeal conserving surgery and all patients with stage III or IV glottic and sub-glottic cancer were recommended to have radiotherapy. In the revised model, patients with locally advanced resectable laryngeal cancer (stage III-IVB) can be treated by either total laryngectomy with or without postoperative radiotherapy or by radical radiotherapy with concurrent chemotherapy, reserving surgery for salvage. The choice of approach will be dependent on the patient's desire for organ preservation, presence of invasion through thyroid cartilage and general performance status (2;3). Given the toxicity of combining concurrent chemotherapy with radical radiotherapy for head and neck cancer, the Cancer Care Ontario (CCO) guideline most strongly recommends its use in those under the age of 70 and the medically fit (3). The NCCN guidelines state that there is a group of patients undergoing laryngectomy (T1-3,N0 or N1) who do not require adjuvant radiation or adjuvant chemoradiation as long as no adverse histological features are present such as positive margins or extra-capsular lymph node extension (1).

For larynx cancer, indications for radiotherapy alone were for radical treatment of stage I-II larynx cancers [radiotherapy and larynx preservation surgery are equally effective (1)], and for all adjuvant radiation not involving ECE or positive margins. The guidelines generally agreed that adjuvant radiation alone should be offered for resected pathologic stage III-IV disease with close margins (1;3;13)]. Other recommended pathological features where adjuvant radiotherapy alone can be considered are pathologic N2-3 category, pathologic T3-4 category, lymphovascular invasion and perineural invasion.

Cancer of the Oropharynx

In the original model of optimal utilisation, radiotherapy was indicated in all patients with oropharyngeal cancer. One of the aims of this review is to estimate a separate optimal utilisation rate for concurrent chemoradiotherapy (CRT); therefore a new optimal utilisation model for oropharyngeal cancer was developed. In the new model as for other head and neck mucosal sites, standard indications for radiotherapy were radical radiotherapy for stage I-II disease, radical CRT for advanced disease (stage III-IVB), and adjuvant radiotherapy or CRT depending on surgical findings.

Recent data has identified a rapidly increasing proportion of oropharyngeal cancers associated with infection with carcinogenic sub-types of human papillomavirus (HPV) (22;23). At the same time, there has been a fall in incidence rates of tobacco and alcohol-related head and neck cancers, including the oropharynx (22;24;25). Although guidelines recommend the same treatment algorithm be applied for HPV-positive and HPV-negative patients, it was necessary to separate HPV-positive and HPV-

negative oropharynx cancers in the revised model as the prevalence of prognostic features differ and the benefit of adding concurrent chemotherapy to radical radiation is better defined for HPV-negative cancers than for HPV-positive cancers.

Salivary Gland Cancer

There is substantial variation in natural history and histology among salivary gland tumors; however most patients with salivary gland cancer are recommended to have surgery plus or minus adjuvant radiation (1;20). As there have been no trials and the guidelines do not recommend it, there is no role for concurrent chemoradiation in the model.

Adjuvant Radiation for Salivary Gland Cancer

According to the guidelines the indications for adjuvant radiation are high grade cancer, adenoid cystic cancer, advanced-stage disease (T3-4 or node-positive), presence of close or positive resection margins, tumor spillage/capsule rupture and/or perineural invasion (1;10;15).

Recurrent Salivary Gland Cancer

A small group of patients with small, low-grade salivary cancer will recur. Recommended treatment for this group was generally surgery plus adjuvant radiotherapy if resectable (1). For inoperable or unresectable recurrent disease treated with curative intent, radical radiation was recommended by most guidelines (1;10;19).

Inoperable and/or Unresectable Salivary Gland Cancer

For inoperable and/or unresectable cancers, radical radiation therapy was recommended where curative intent treatment was possible (1;10). In the optimal radiotherapy utilisation tree, all patients with stages III or IV disease and/or all high-grade tumours are recommended to receive radiotherapy; this group would be likely to include inoperable or unresectable tumours requiring radical radiation, operable and resectable tumours requiring adjuvant radiation and those requiring palliative radiation .

Cancer of the Hypopharynx

In the original model of optimal radiotherapy utilisation, radiotherapy was recommended for all patients with hypopharyngeal cancer. This is still the case, since radiotherapy can be recommended as radical treatment, as postoperative adjuvant treatment following surgery or in conjunction with concurrent chemotherapy. It was necessary to revise the model in order to separate the indications for concurrent chemoradiotherapy from other indications for radiotherapy. Since the incidence of hypopharyngeal cancer is small as a proportion of all head and neck cancers, to simplify the tree a sensitivity analysis was conducted to estimate the optimal proportion of patients without distant metastatic disease in whom CRT (either post-operative adjuvant CRT for extracapsular extension and/or positive margins or definitive CRT) is recommended.

Paranasal Sinus and Nasal Cavity Cancer

In the original model of optimal radiotherapy utilisation, radiotherapy was recommended for all patients with paranasal sinus and nasal cavity cancer. This is still the case, since radiotherapy can be recommended as radical treatment, as postoperative adjuvant treatment following surgery or in conjunction with concurrent chemotherapy. It was necessary to revise the model in order to separate the indications for concurrent CRT from other indications for radiotherapy. According to the guidelines, concurrent CRT is indicated as adjuvant treatment for extracapsular extension and/or positive margins and for intracranial extension (1;6;15;20). Radical CRT is indicated for advanced stage disease for patients with adequate performance status (Stages III-IVB).

Nasopharyngeal Cancer

In the original model of optimal radiotherapy utilisation, radiotherapy was recommended for all patients. There is no change in the updated model. The majority of patients will have an indication for chemoradiation (1). For the purposes of the model, all patients among the small group of head and neck cancer patients who have nasopharyngeal cancer were considered to have an indication for chemoradiation.

Occult Primary Head & Neck Cancer

There are no changes to the model of optimal radiotherapy utilisation for occult primary head and neck cancer. Since the incidence of occult primary cancer is small as a proportion of all head and neck cancers, to simplify the tree a sensitivity analysis was conducted to estimate the optimal proportion of patients in whom chemoradiotherapy (either post-operative adjuvant CRT for extracapsular extension and/or positive margins or definitive CRT) is recommended.

Levels of evidence

The updated model predicts that 18% of the whole head and neck cancer population have an indication for radiotherapy based on level I-II evidence of benefit. The remainder of the indications of radiotherapy in head and neck cancer are based on level III or IV evidence.

Changes to Epidemiological Data

The epidemiological data in the head and neck cancer radiotherapy utilisation tree have been updated with more recent data where available; this has been applied particularly to the early branches in the tree for which national or state level data on cancer incidence rates and stages are available. Additional epidemiological data has been identified for the new branches that have been added to the model. Any changes to the hierarchical quality of the epidemiological data have been noted in Table 2.

Incidence of Head and Neck Cancer:

Since the publication of the previous radiotherapy utilisation project, the Australian national cancer incidence data published by the Australian Institute of Health and Welfare (AIHW) has been updated, with the most recent data available being 2008 data. The latest Australian Cancer Incidence and Mortality (ACIM) book published by AIHW in 2011 reports that in 2008, Head and Neck cancer accounted for 3.3% of all cancer in Australia; this is slightly less than the rate of 4% in the original model which was based on AIHW 1998 data (26). However the proportion of oropharyngeal cancer in Australia has increased from 8% of all head and neck cancers in the previous model to 17% in 2008. This is in line with reported increases in the incidence of HPV related oropharyngeal cancer in the United States (22).

Lip Cancer

As the literature reported a wide range of proportions of incomplete excision, a sensitivity analysis was performed with values for the proportion of lip cancers that are cosmetically excisable ranging from 0.81-0.99% (27-29). Data from a number of sources were used to estimate the prevalence of adverse features (19% in the model, based on summing the following rates) among cosmetically excised lip cancer patients. Hjortdal et al reported a 12% rate of ≤1 mm margins in a series of surgically excised lip cancers (30). The proportion of cases with perineural invasion and/or lymphovascular invasion among cosmetically excised lip cancer was estimated as 6% from a large series from de Visscher et al (31). It was estimated that 1% of patients managed with surgery had clinically involved lymph nodes based on data from Peter MacCallum Cancer Centre and a population-based report from the Netherlands on lip cancer (27;28). As there was wide variation among estimates of positive margin rates for lip cancer in the literature (32-34), a sensitivity analysis was performed .

Oral Cavity Cancer

Based on an analysis of SEER data for the years 2004-2007, the population-based stage distribution for oral cancer was 48% stage I-II, 45% stage III-IVB and 7% stage IVC and palliative. Patients managed without documented surgery or radiotherapy were assumed to have been palliatively managed. Analysis of SEER data showed that 79% of patients with stage III-IVB oral cancer were managed with radical surgery, and 21% with radical radiotherapy. Among those treated with radical radiotherapy, 41% were aged 70 years or older (29).

Given that such a large proportion of advanced oral cancer were managed with primary surgery, and that contemporary guidelines strongly favoured radical surgery over radical radiation wherever possible, we modified the original estimated range of early-stage oral cancer that were managed with primary surgery (76%-90% instead of 0%-90%). The low range for surgery use was based on an

Australian series by Farhadieh et al (35). This was the lowest rate in the two large series we identified on this topic (35;36).

Among stage III-IVB patients managed with radical surgery, we estimated that 8% or less would need no further treatment. This was based on an original SEER analysis indicating that 16.6% of surgically managed stage III-IVB oral cancers were T1-2N1 (radiotherapy not indicated unless other risk features present), combined with data from Shim et al and Brannan et al suggesting that probably around half of these cases would have an indication for radiotherapy such as close/positive margins or extracapsular spread (37;38). Given disagreement among guidelines on the use of radiotherapy in T1-2N1 patients, we performed a sensitivity analysis, varying the proportion of patients without an indication for adjuvant radiotherapy between 0-8%.

Based on Brown et al's surgical series of 462 oral cancer patients managed in Liverpool, U.K., 50% of resected stage III-IVB oral cancer patients had an indication for adjuvant chemoradiation (39). This proportion was in keeping with estimates from other large series (40;41).

Laryngeal Cancer

Data supplied to us by the AIHW shows that in 2008, there were 491 laryngeal cancers diagnosed in Australia; 151 (31%) of these were supraglottic cancers. Historically, the most common mode of larynx preservation surgery for supraglottic larynx cancer was supraglottic laryngectomy; however in recent years, there has been increased utilisation of conservative laser surgery to manage supraglottic and glottic laryngeal cancer (42). Data from SEER (2005-2007) shows that 15% of supraglottic larynx cancer were managed with voice-preserving surgery (29). An audit from the U.K. found that 23% of early laryngeal cancer was managed with laser surgery (43). To evaluate the effect of this data variation on the optimal utilisation rate, the proportion of patients with stage I/II supraglottic and glottic laryneal cancer managed with conservative surgery was varied from 0 – 23% in the sensitivity analysis.

Due to the high propensity for nodal metastasis of supraglottic larynx cancer, a high proportion of patients managed with voice-conserving surgery will still require post-operative radiation. In a large series from M.D. Anderson Cancer Center, 83% of patients managed with supraglottic laryngectomy and neck dissection had indications for post-operative radiation (44). Radiotherapy indications were multiple nodes, extracapsular spread, lymphatic or perineural invasion, locally advanced primary, and/or positive microscopic margins.

Indications for adjuvant chemoradiation are positive resection margins or extracapsular spread (45). To estimate the incidence of indications for chemoradiation after laryngeal conserving surgery for supraglottic larynx cancer, we used data from Chun et al describing the incidence of pathologic node involvement and margin involvement after supraglottic partial laryngectomy (46). In this series, 12/48 had positive resection margins and an additional 21/48 had pathologically involved lymph nodes,

meaning that 33/48 had an indication for adjuvant radiation. We estimated that half of the 21 patients with pathologically involved lymph nodes would have extracapsular spread. This was based on Snyderman et al's supraglottic larynx surgical series (47). Thus 70% of patients with an indication for radiotherapy after voice preserving surgery for supraglottic cancer had an indication for chemoradiation.

We used data from SEER to describe the stage groupings of supraglottic cancer patients who were not managed with larynx conserving surgery. 26% of patients were stage I-II and 57% were stage III-IVB (29). Stage IVC patients were grouped with patients who were palliatively managed (17% of all patients). In a similar fashion, we estimated that for glottic larynx cancer patients, 73% were stage I-II, 20% stage III-IVB and 7% stage IVC and/or palliative management (29).

A small proportion of patients with supraglottic larynx cancer may be managed with laryngectomy instead of radical radiotherapy. This was estimated as 5% for stage I/II and 12% for stage III/IVB patients based on population-based data on patterns of care in Ontario, Canada (48). For glottic larynx cancer, we estimated a 19% laryngectomy rate for stage III-IVB patients based on population-based patterns of practice by T-category from Ontario, and stage data from SEER (29;49). The most common reason for laryngectomy is locally advanced larynx cancer with tumour invasion through the thyroid cartilage (49).

No single source reported on the rate of both extracapsular extension and margin status for patients managed with *total* laryngectomy for stage III-IV supraglottic cancer. Two sources of data were thus utilized. Among Snyderman et al's surgical series, 53% of patients with pathologic node positive supraglottic larynx cancer cases had extracapsular spread (47). Data from Bradford et al suggest that few patients with stage III-IV supraglottic larynx cancer will have positive margins as their only indication for adjuvant chemoradiation after total laryngectomy (probably 2-5%) (50). We thus estimated a 57% rate for CRT indications.

The proportion of patients needing adjuvant chemoradiation following laryngectomy for stage III-IV *glottic* larynx cancer was estimated as 40% based on Hirabayashi et al's surgical series (51). This hospital-based series provided information on the rate of pathologic extracapsular extension in patients based on T-category and N-category. As positive margins are uncommon following a laryngectomy for glottic cancer, the proportion of patients requiring adjuvant chemoradiation for glottic cancer was based solely on rates of extracapsular extension.

Oropharyngeal Cancer

There were no identified population-based estimates of prevalence or incidence of HPV-positive oropharyngeal cancer in Australia. The best Australian data identified came from a multi-institutional series that reported a rise in HPV-positive oropharyngeal cancers from 19% in 1987-1990 to 66% in

2005-2006 (23). This HPV-positive rate of 66% was in keeping with contemporary population-based estimates from Sweden and the United States (22;52). As it was unknown whether the prevalence of HPV-positive tumours in Australia may have increased since 2005-2006, a sensitivity analysis was performed with the upper limit for the prevalence of HPV-related tumors set at 80%, based on linear extrapolation of Hong et al's data (23) . This extrapolated value was used only in sensitivity analysis, as it was equally plausible that the peak rate of HPV-related cancers has been reached in Australia.

The guidelines did not clearly or consistently specify whether radical surgery or radical radiation was preferable for either early-staged or advanced resectable oropharyngeal cancers since there is a lack of evidence to guide selection of surgery versus radiation. Given the lack of population-based data, patient preference data and clinical trial data to guide the estimate of the optimal proportion of patients that should receive radical radiotherapy over surgery, patterns of practice data were used for the model recognising that these may not reflect optimal practice. Population-based data from the SEER database were used to measure temporal trends in the use of surgery and radiation (29). Data from 1985-1989 was used to estimate the use of surgery versus radical radiation in HPV-negative patients, and 2005-2007 SEER data for HPV-positive patients. These periods were chosen as Chaturvedi et al estimated that the population-based prevalence of HPV-positive oropharynx cancers in the United States was 16% in the 1980's and over 70% in the 2000's (22).

Notably, it was found that between these two time periods, there was almost no change in the use of surgery over radiation: 42% were treated with radical radiation in 1985-1989 compared to 44% receiving radiation alone for 2005-2007. These rates were constant in the intervening years. As it was unknown if these rates truly reflected optimal practice, a sensitivity analysis was performed. Using a number of large series, including two that were population based, it was estimated that the optimal proportion of patients receiving radical radiotherapy, regardless of HPV status, lay between 24-84% (23;43;53-55).

Radical Radiation versus Radical Chemoradiation for HPV+ and HPV- oropharynx cancer

Data on the optimal proportion of patients receiving radiotherapy alone vs chemoradiation according to HPV status were derived form a large case series from Princess Margaret Hospital (PMH) in Toronto, Canada. O'Sullivan et al reported on a large group of oropharyngeal cancer patients according to HPV status (56). The patients in this group included all patients who presented to the PMH (patients were not excluded on the basis of comorbidity or performance status) and hence constituted a representative mix of patient age and comorbidity that would plausibly be seen in the Australian population of oropharynx cancer patients. We estimated the proportion of patients with a radical *chemoradiation* indication as the proportion of patients in this series with stage III-IV disease below the age of 70 without medical contraindications to concurrent chemotherapy.

The estimate for HPV negative patients was based on the same method. In addition to data from O'Sullivan et al, this involved use of separate reports from PMH on the use of XRT and CRT in

advanced head and neck cancer, as well as data on the age distribution of tongue cancer patients from the Australian Institute of Health and Welfare (AIHW) (26;57-59). These additional sources were needed as the O'Sullivan series did not fully describe patient and treatment characteristics for the HPV negative cohort treated with chemoradiation.

Notably, the proportion of advanced oropharynx cancer patients (stage III-IV) estimated to be appropriately treated by radical radiation instead of chemoradiation according to HPV status was almost identical to the patterns of practice described in a large case series from Australia, largely representing patients from Royal Prince Alfred Hospital, Sydney (60). PMH data was used in preference as unlike the Australian series, the reasons for choice of treatment were explicitly described in this source, and the PMH series included stage I-II patient data.

Adjuvant treatment of HPV-positive and HPV-negative oropharynx cancer

The stage distribution of resected HPV positive oropharyngeal cancer was based on 2004-2007 SEER data (29) . During this time, evidence suggests that most oropharyngeal cancers would have been HPV positive (22;61;62). Details on pathologic risk features (positive margins, extracapsular extension) according to T and N category were derived from Walvekar et al and Haughey et al (61;63).

For resected HPV negative oropharyngeal cancer, the stage distribution was based on an Australian surgical series from RPA (64). Patients in this series were seen between 1987-1997. Data from Hong et al suggest that the prevalence of HPV-positive oropharyngeal cancer was about 20% in this patient cohort (23). Details on pathologic risk features according to T and N category were derived from Walvekar et al, Li et al and Zelefsky et al (63;65;66).

Salivary Gland Cancer

The stage distribution and histological grading of salivary gland cancers was based on analysis of 2004-2007 SEER data (29). The SEER data were used since no published studies could be identified that reported on grading by stage for salivary gland cancer. Out of a total of 3820 patients diagnosed with malignant salivary gland tumours in the SEER registry, 519 patients (13.6%) were in stages I or II and the tumours were histologically classified as low-grade. The remaining 3301 patients were either in stages III or IV, or had histologically high grade tumours. All squamous cell carcinomas, salivary ductal carcinomas and adenoid cystic carcinomas were considered high-risk and/or high-grade histologies requiring adjuvant radiation. All acinic cell carcinomas were considered low-grade. Grade II/intermediate grade was grouped with high-grade, in keeping with guidelines (1;19).

For low-grade stage I and II cancers, the proportion of patients with adjuvant radiotherapy indications was based solely on the presence of positive or close margins. Ghosh-Laskar et al described the

prevalence of positive or close margins for mucoepidermoid cancers of the parotid according to tumour grade (67). Most low-grade tumours were T1 or T2.

Locoregional recurrence in stage I-II low-grade tumours with negative margins

The prevalence of locoregional recurrence was estimated based on a large surgery- alone series from Chen et al (68). For patients with low-grade tumours treated with surgery alone, 17% of patients developed a locoregional recurrence. Though data was not available on margin status or stage for these patients, univariate data on stage and margin status for the whole study group suggest this was a reasonable estimate (67;68). Low-grade tumours are often small, and hence most often resected with clear margins (67).

Hypopharyngeal Cancer

The proportion of patients with hypopharyngeal cancers who presented with distant metastatic disease was based on analysis of 2004-2007 SEER data since no published population-based Australian data were identified (29). Out of a total of 1490 patients diagnosed with squamous cell carcinoma of the hypopharynx during the above period, 130 patients were stage IVC (distant metastases at presentation), and a further 170 patients presenting in stages I-IVB had no treatment (regarded for our purposes as not suitable for radical treatment but eligible for palliative treatment).

We attempted to identify recent data on the proportion of hypopharyngeal cancer patients who are treated with concurrent CRT. Older studies were identified (including one national population-based study on treatment of hypopharyngeal cancer), but these data were not used since it is likely that the rates of CRT have risen in recent years (69-71). A recent study on 70 patients with hypopharyngeal cancer treated at a single-institution reported that 57 patients (81%) received either postoperative or definitive CRT (72). A sensitivity analysis was conducted on the effect on the overall CRT rate of recommending concurrent CRT in 50-81% of patients with hypopharyngeal cancer who presented without distant metastases.

Paranasal Sinus and Nasal Cavity Cancer

The proportion of patients with paranasal and nasal cavity cancer who had metastatic disease were extracted from SEER. The proportion of patients with advanced stage and/or inoperable disease was calculated from a report on a Finnish population-based series (73). The guidelines are in favour of surgery for all operable, non-metastatic cases, but there was some disagreement with minority recommendation of radiation for T1-4a ethmoid cancer, T1-4a nasal cavity cancer and T4a maxillary cancer. Therefore sensitivity analysis was conducted with the proportion of patients receiving radical radiation varied from 0-62% (based on SEER data broken down by site and stage, up to 62% of T1-4a operable, non-metastatic patients may be treated with radical radiation).

Estimation of the Optimal Radiotherapy Utilisation Rate

Based on the most recent evidence on the efficacy of radiotherapy and on epidemiological data on the occurrence of indications for radiotherapy, the proportion of all Head & Neck cancer patients in whom radiotherapy would be recommended is 74% (Table 1 and Figure 1). The original optimal radiotherapy utilisation rate derived in 2003 for Head & Neck cancer was also 74%.

Concurrent Chemoradiotherapy in Head & Neck Cancer

According to the current guidelines concurrent chemoradiotherapy is indicated as adjuvant therapy in a proportion of advanced operable head and neck cancers and as primary therapy where the tumours are inoperable and addition of chemotherapy is proved superior to RT alone. Our model predicted 26% optimal CRT utilisation for all head and neck cancers (Table 3 and Figure 2).

Sensitivity Analysis

Univariate sensitivity analysis was undertaken (Figure 3 and 4) to assess any changes in the optimal radiotherapy utilisation rate that would result from uncertainty in treatment recommendations or in different estimates of the proportions of patients with particular attributes. The expected value in the estimate of optimal *radiotherapy* utilisation due to these uncertainties ranged from 71% to 77% as shown in the Tornado diagrams (Figure 3); the optimal CRT utilisation ranged from 25% to 26% (Figure 4).

Table 1: Head & Neck Cancer. Indications for radiotherapy - Levels and sources of evidence

Original RTU study				Updates 2012					
Outcome Nos. in Updated Tree	Clinical Scenario	Level of evidence	Proportion of all H&N cancer	Change of Indication	Guideline updated	Current level of evidence	Change to proportion of all H&N cancer		References
							Yes/ No	Updated value	
LIP CANCER									
1	Lip cancer, cosmetically excisable, no adverse features, locoregional recurrence	IV	0.02	No	Yes	IV	No	0.02	NCCN (1), NCI PDQ (8)
3	Lip cancer, cosmetically excisable, adverse features	N/A (new indication)		Yes	Yes	III	Yes	0.04	NCCN (1),CCA/ACN (17)
4	Lip cancer, not cosmetically excisable	III	0.02	No	Yes	III	Yes	0.04	NCCN (1), NCI PDQ (8)
ORAL CAVITY CANCER									
5	Oral Cavity, Stages I-II, surgery, adverse pathology	IV	0.02	No	Yes	IV	No	0.02	NCCN (1), CCO (3), ESTRO (13), SIGN(2) SEOM (14), BCCA(15), UK ENT (20)
6	Oral Cavity, Stages I-II, surgery, no adverse	IV	0.01	No	Yes	IV	Yes	0.02	NCI PDQ (8, NCCN (1), BCCA(15)

Original RTU study				Updates 2012					
Outcome Nos. in Updated Tree	Clinical Scenario	Level of evidence	Proportion of all H&N cancer	Change of Indication	Guideline updated	Current level of evidence	Change to proportion of all H&N cancer		References
							Yes/ No	Updated value	
	pathology, locoregional recurrence								
8	Oral Cavity, Stages I-II, radical radiotherapy	III	0.01	No	Yes	III	No	0.01	NCCN (1), CCO (3), ESTRO (13), SIGN(2) SEOM (14), BCCA(15), UK ENT (20)
9	Oral Cavity, Stages III-IVB, surgery, adverse pathology (adjuvant RT)	N/A (new indication)		Yes	Yes	III	Yes	0.04	NCCN (1), CCO (3), ESTRO (13), SIGN(2) SEOM (14), BCCA(15), UK ENT (20)
10	Oral Cavity, Stages III-IVB, surgery, ECE or positive margins (CRT)	N/A (new indication)		Yes	Yes	I	Yes	0.04	NCCN (1), CCO (3), ESTRO (13), SIGN(2) SEOM (14), BCCA(15), UK ENT (20)
12	Oral Cavity, Stages III-IVB, <70 yrs old (CRT)	N/A (amended indication)		No	Yes	I	Yes	0.01	NCCN (1), CCO (3), ESTRO (13), SIGN(2) SEOM (14), BCCA(15), UK ENT (20)
13	Oral Cavity, Stages III-IVB, > 70 yrs old,	N/A (new indication)		Yes	Yes	IV	Yes	0.01	NCCN (1), CCO (3), ESTRO (13), SIGN(2)

Original RTU study				Updates 2012					
Outcome Nos. in Updated Tree	Clinical Scenario	Level of evidence	Proportion of all H&N cancer	Change of Indication	Guideline updated	Current level of evidence	Change to proportion of all H&N cancer		References
							Yes/ No	Updated value	
	(radical radio-therapy)								SEOM (14), BCCA(15), UK ENT (20)
14	Oral Cavity, Stage IVC and palliative	N/A (amended indication)		No	Yes	IV	Yes	0.02	NCCN (1), NCI PDQ (8)
LARYNGEAL CANCER									
16	Supraglottic, larynx preserving surgery, adverse features, (adjuvant RT)	IV	<0.01	No	Yes	III	No	<0.01	NCCN (1), CCO (3), ESTRO (13), SIGN(2) SEOM (14), BCCA(15), UK ENT (20)
17	Supraglottic, larynx preserving surgery, ECE and/or margin + (CRT)	N/A (new indication)		Yes	Yes	I	Yes	<0.01	NCCN (1), CCO (3), ESTRO (13), SIGN(2) SEOM (14), BCCA(15), UK ENT (20)
18	Supraglottic, Stage I-II, radical RT	N/A (amended indication)		No	Yes	IV	Yes	0.01	NCCN (1), CCO (3), ESTRO (13), SIGN(2) SEOM (14), BCCA(15), UK ENT (20), NCI PDQ (8), ASCO (21)

Original RTU study				Updates 2012					
Outcome Nos. in Updated Tree	Clinical Scenario	Level of evidence	Proportion of all H&N cancer	Change of Indication	Guideline updated	Current level of evidence	Change to proportion of all H&N cancer		References
							Yes/ No	Updated value	
20	Supraglottic, Stage III-IVB, radical radiotherapy, <70 yrs (plus CRT)	N/A (new indication)		Yes	Yes	I	Yes	0.01	NCCN (1), CCO (3), ESTRO (13), SIGN(2) SEOM (14), BCCA(15), UK ENT (20)
21	Supraglottic, Stage III-IVB, radical radiotherapy, >70 yrs	N/A (amended indication)		No	Yes	IV	Yes	0.01	NCCN (1), CCO (3), ESTRO (13), SIGN(2) SEOM (14), BCCA(15), UK ENT (20), NCI PDQ (8), ASCO (21)
22	Supraglottic, Stage III-IVB, laryngectomy, adverse pathology (adjuvant RT)	N/A (new indication)		Yes	Yes	III	Yes	<0.01	NCCN (1), CCO (3), ESTRO (13), SIGN(2) SEOM (14), BCCA(15), UK ENT (20)
23	Supraglottic, Stage III-IVB, laryngectomy, ECE or positive margins (CRT)	N/A (new indication)		Yes	Yes	I	Yes	<0.01	NCCN (1), CCO (3), ESTRO (13), SIGN(2) SEOM (14), BCCA(15), UK ENT (20)
25	Supraglottic, Stage IVC and palliative	N/A (amended indication)		No	Yes	IV	Yes	0.01	NCCN (1), NCI PDQ (8)

Original RTU study				Updates 2012					
Outcome Nos. in Updated Tree	Clinical Scenario	Level of evidence	Proportion of all H&N cancer	Change of Indication	Guideline updated	Current level of evidence	Change to proportion of all H&N cancer		References
							Yes/ No	Updated value	
26	Glottic and subglottic, Stages I-II, radiotherapy	III	0.07	No	Yes	III	No	0.07	NCCN (1), CCO (3), ESTRO (13), SIGN(2) SEOM (14), BCCA(15), UK ENT (20), NCI PDQ (8), ASCO (21)
28	Glottic and subglottic, Stages III-IVB, radiotherapy, <70 yrs (plus CRT)	N/A (new indication)		Yes	Yes	I	Yes	0.01	NCCN (1), CCO (3), ESTRO (13), SIGN(2) SEOM (14), BCCA(15), UK ENT (20)
29	Glottic and subglottic, Stages III-IVB, radiotherapy, >70 yrs	N/A (amended indication)		No	Yes	IV	Yes	0.01	NCCN (1), CCO (3), ESTRO (13), SIGN(2) SEOM (14), BCCA(15), UK ENT (20), NCI PDQ (8), ASCO (21)
30	Glottic and subglottic, Stages III-IVB, laryngectomy, adverse pathology (adjuvant RT)	N/A (new indication)		Yes	Yes	III	Yes	<0.01	NCCN (1), CCO (3), ESTRO (13), SIGN(2) SEOM (14), BCCA(15), UK ENT (20)

Original RTU study				Updates 2012					
Outcome Nos. in Updated Tree	Clinical Scenario	Level of evidence	Proportion of all H&N cancer	Change of Indication	Guideline updated	Current level of evidence	Change to proportion of all H&N cancer		References
							Yes/ No	Updated value	
31	Glottic and subglottic, Stages III-IVB, laryngectomy, ECE or positive margins (CRT)	N/A (new indication)		Yes	Yes	I	Yes	<0.01	NCCN (1), CCO (3), ESTRO (13), SIGN(2) SEOM (14), BCCA(15), UK ENT (20)
33	Glottic and subglottic, Stage IVC and palliative	N/A (amended indication)		No	Yes	IV	Yes	0.01	NCCN (1), NCI PDQ (8)
OROPHARYNGEAL CANCER									
34	Oropharyngeal cancer, HPV+, surgery, indications for adjuvant RT	N/A (new indication)		Yes	Yes	III	Yes	0.01	NCCN (1), CCO (3), ESTRO (13), SIGN(2) SEOM (14), BCCA(15), UK ENT (20)
35	Oropharyngeal cancer, HPV+, surgery, indications for adjuvant CRT	N/A (new indication)		Yes	Yes	I	Yes	0.03	NCCN (1), CCO (3), ESTRO (13), SIGN(2) SEOM (14), BCCA(15), UK ENT (20)
37	Oropharyngeal cancer, HPV+, radical radiation	N/A (new indication)		Yes	Yes	IV	Yes	0.01	NCCN (1), CCO (3), ESTRO (13), SIGN(2) SEOM (14), BCCA(15), UK ENT (20)

Original RTU study				Updates 2012					
Outcome Nos. in Updated Tree	Clinical Scenario	Level of evidence	Proportion of all H&N cancer	Change of Indication	Guideline updated	Current level of evidence	Change to proportion of all H&N cancer		References
							Yes/ No	Updated value	
38	Oropharyngeal cancer, HPV+, radical CRT	N/A (new indication)		Yes	Yes	I	Yes	0.03	NCCN (1), CCO (3), ESTRO (13), SIGN(2) SEOM (14), BCCA(15), UK ENT (20)
39	Oropharyngeal cancer, HPV+, palliative radiation	N/A (new indication)		Yes	Yes	IV	Yes	<0.01	NCCN (1), NCI PDQ (8)
40	Oropharyngeal cancer, HPV negative, surgery, adjuvant RT indicated	N/A (new indication)		Yes	Yes	III	Yes	0.01	NCCN (1), CCO (3), ESTRO (13), SIGN(2) SEOM (14), BCCA(15), UK ENT (20)
41	Oropharyngeal cancer, HPV negative, surgery, adjuvant CRT indicated	N/A (new indication)		Yes	Yes	I	Yes	0.01	NCCN (1), CCO (3), ESTRO (13), SIGN(2) SEOM (14), BCCA(15), UK ENT (20)
43	Oropharyngeal cancer, HPV negative, radical radiation	N/A (new indication)		Yes	Yes	IV	Yes	0.01	NCCN (1), CCO (3), ESTRO (13), SIGN(2) SEOM (14), BCCA(15), UK ENT (20)

Original RTU study				Updates 2012					
Outcome Nos. in Updated Tree	Clinical Scenario	Level of evidence	Proportion of all H&N cancer	Change of Indication	Guideline updated	Current level of evidence	Change to proportion of all H&N cancer		References
							Yes/ No	Updated value	
44	Oropharyngeal cancer, HPV negative, radical CRT indicated	N/A (new indication)		Yes	Yes	I	Yes	0.01	NCCN (1), CCO (3), ESTRO (13), SIGN(2) SEOM (14), BCCA(15), UK ENT (20)
45	Oropharyngeal cancer, HPV negative, palliative radiation	N/A (new indication)		Yes	Yes	IV	Yes	<0.01	NCCN (1), NCI PDQ (8)
SALIVARY GLAND CANCER									
46	Salivary gland cancer, Stages I or II, low grade, close margins following resection	N/A (new indication)		Yes	Yes	III	Yes	<0.01	NCCN (1), BCCA(15), UK ENT (20), NCI PDQ (8), START (19), SSO (74)
47	Salivary gland cancer, Stages I or II, low	IV	<0.01	No	Yes	IV	No	<0.01	NCCN (1), UK ENT (20), NCI PDQ (8),

Original RTU study				Updates 2012					
Outcome Nos. in Updated Tree	Clinical Scenario	Level of evidence	Proportion of all H&N cancer	Change of Indication	Guideline updated	Current level of evidence	Change to proportion of all H&N cancer		References
							Yes/ No	Updated value	
	grade, resection with clear margins, locoregional recurrence								START (19),
49	Salivary gland cancer, Stages III or IV and/or all high-grade	IV	<0.01	No	Yes	IV	Yes	0.06	NCCN (1), UK ENT (20), NCI PDQ (8), START (19),
HYPOPHARYNGEAL CANCER									
50-52	Radiotherapy is recommended in all patients with hypopharyngeal cancer	III	0.05	No	Yes	III	Yes	0.03	NCCN (1), SIGN (2), CCO (3), NCI PDQ (11)
PARANASAL SINUS AND NASAL CAVITY CANCER									
53-59	Radiotherapy is recommended in all patients with paranasal sinus cancer	III	0.05	No	Yes	III	No	0.05	NCCN (1), NCI PDQ (5), UK ENT (20), BCCA(15)

Original RTU study				Updates 2012					
Outcome Nos. in Updated Tree	Clinical Scenario	Level of evidence	Proportion of all H&N cancer	Change of Indication	Guideline updated	Current level of evidence	Change to proportion of all H&N cancer		References
							Yes/ No	Updated value	
NASOPHARYNGEAL CANCER									
60	Radiotherapy (either CRT or radical) is recommended in all patients with nasopharyngeal cancer	III	0.04	No	Yes	I/III	Yes	0.03	NCCN (1), SIGN (2), CCO (3), NCI PDQ (6)
OCCULT PRIMARY HEAD & NECK CANCER									
61	Unknown primary, N1-2a, local or regional recurrence, RT alone indicated	IV	<0.01	No	Yes	IV	No	<0.01	NCCN (1), UK ENT (20), BCCA(15)
62	Unknown primary, N1-2a, local or regional recurrence, CRT indicated	N/A (new indication)		Yes	Yes	I	No	<0.01	NCCN (1), UK ENT (20), BCCA(15)

Original RTU study				Updates 2012					
Outcome Nos. in Updated Tree	**Clinical Scenario**	**Level of evidence**	**Proportion of all H&N cancer**	**Change of Indication**	**Guideline updated**	**Current level of evidence**	**Change to proportion of all H&N cancer**		**References**
							Yes/ No	**Updated value**	
64	Unknown primary, N2b-N3	IV	0.02	No	Yes	IV	No	0.02	NCCN (1), UK ENT (20), BCCA(15)
Proportion of all Head & Neck cancer patients in whom radiotherapy is recommended			0.74 (74%)	**Updated Proportion of all Head & Neck cancer patients in whom radiotherapy is recommended**				**0.74 (74%)**	

Table 2: Head & Neck Cancer. The incidence of attributes used to define indications for radiotherapy

Original RTU study				Updates 2012				
Population or sub-population of interest	**Attribute**	**Proportion of population with the attribute**	**Quality of Information**	**Change in proportion of population with attribute Yes/ No**	**Updated Proportion**	**Updated Quality of Information**	**Updated Reference**	**Comments**
All registry cancers	Head & Neck cancer	0.04	α	Yes	0.025	α	AIHW 2011 (26)	Based on AIHW 2008 data
LIP CANCER								
All Head & Neck Cancers	Lip cancers	0.22	α	Yes	0.23	α	AIHW 2011 (26)	Based on AIHW 2008 data
Lip cancer	Cosmetically excisable	0.89	ζ	Yes	0.81	λ	McCombe et al (27)	Sensitivity analysis from 0.81-0.99%
Lip cancer, cosmetically excisable	Adverse features	N/A due to modifications to model		Yes	0.19	λ	Hjortdal et al (30), de Visscher et al (31), McCombe et al (27)	Sensitivity analysis from 0.07-0.34%
Lip cancer, cosmetically excisable, no adverse features	Locoregional recurrence	0.10	ζ	No	0.10	λ	Rowe et al (75)	
ORAL CAVITY CANCER								
All Head & Neck Cancers	Oral Cavity Cancers	0.28	α	Yes	0.24	α	AIHW 2011 (26)	Based on AIHW 2008 data
Oral Cavity Cancers	Stage I-II	0.45	β	Yes	0.48	γ	SEER (29)	Based on analysis of 2004-2007 data

Original RTU study				Updates 2012				
Population or sub-population of interest	**Attribute**	**Proportion of population with the attribute**	**Quality of Information**	**Change in proportion of population with attribute Yes/ No**	**Updated Proportion**	**Updated Quality of Information**	**Updated Reference**	**Comments**
Oral cavity cancers, Stages I – II	Surgery	0.90	β	Yes	0.76	λ	Farhadieh et al (35)	Sensitivity analysis conducted between original and new values (0.76 -0.90)
Oral cavity cancers, Stages I – II, surgery	Adverse pathology	0.20	ζ	No	0.20	ζ	Jones (76)	
Oral cavity cancers, Stages I – II, surgery, no adverse pathology	Locoregional recurrence	0.19	ζ	No	0.19	ζ	Wolfensberger et al (77)	
Oral Cavity Cancer	Stage III-IVB	N/A due to modifications to model		Yes	0.45	γ	SEER (29)	Based on analysis of 2004-2007 data
Oral Cavity Cancer, Stage III-IVB	Surgery	N/A due to modifications to model		Yes	0.79	γ	SEER (29)	Based on analysis of 2004-2007 data
Oral Cavity Cancer, Stage III-IVB, Surgery	ECE and/or positive margins	N/A due to modifications to model		Yes	0.50	ζ	Brown et al (39)	
Oral Cavity Cancer, Stage III-IVB, Surgery	No adverse pathology	N/A due to modifications to model		Yes	0.08	γ λ θ	SEER (29) Shim et al (38) Brannan et al (37)	Sensitivity analysis from 0 – 8%.
Oral Cavity Cancer, Stage III-IVB, radical Radiotherapy	<70 yrs old	N/A due to modifications to model		Yes	0.59	γ	SEER (29)	

Original RTU study				Updates 2012				
Population or sub-population of interest	**Attribute**	**Proportion of population with the attribute**	**Quality of Information**	**Change in proportion of population with attribute Yes/ No**	**Updated Proportion**	**Updated Quality of Information**	**Updated Reference**	**Comments**
LARYNGEAL CANCER								
All Head & Neck Cancers	Larynx Cancers	0.20	α	Yes	0.16	α	AIHW 2011 (26)	Based on AIHW 2008 data
Laryngeal Cancer	Supraglottic	0.28	ζ	Yes	0.31	α	AIHW 2011 (26)	Based on AIHW 2008 data
Supraglottic Laryngeal Cancer	Suitable for conservative surgery	0	ζ	Yes	0.15	γ	SEER (29)	Sensitivity analysis from 0 - 23%
Supraglottic Laryngeal Cancer, conservative surgery	Adverse features	N/A due to modifications to model		Yes	0.83	ζ	Lee et al (44)	
Supraglottic Laryngeal Cancer, conservative surgery, adverse features	ECE and/or positive margins	N/A due to modifications to model		Yes	0.70	λ	Chun et al (46) Snyderman et al (47)	
Supraglottic laryngeal cancer, Radiation or Laryngectomy	Stage I-II	N/A due to modifications to model		Yes	0.26	γ	SEER (29)	
Supraglottic laryngeal cancer, no conservative surgery, Stage I-II	Laryngectomy	N/A due to modifications to model		Yes	0.05	γ	Groome et al (48)	
Supraglottic laryngeal cancer, Radiation or Laryngectomy	Stage III-IVB	N/A due to modifications to model		Yes	0.57	γ	SEER (29)	

Original RTU study				Updates 2012				
Population or sub-population of interest	**Attribute**	**Proportion of population with the attribute**	**Quality of Information**	**Change in proportion of population with attribute Yes/ No**	**Updated Proportion**	**Updated Quality of Information**	**Updated Reference**	**Comments**
Supraglottic laryngeal cancer, no conservative surgery, Stage III-IVB	Laryngectomy	N/A due to modifications to model		Yes	0.12	γ	Groome et al (48)	
Supraglottic laryngeal cancer, no conservative surgery, Stage III-IVB, Radiotherapy	< 70 yrs old	N/A due to modifications to model		Yes	0.60	α	AIHW 2011 (26)	
Supraglottic laryngeal cancer, no conservative surgery, Stage III-IVB, Laryngectomy	ECE and/or positive margins	N/A due to modifications to model		Yes	0.57	λ	Snyderman et al (47) Bradford et al (50)	
Supraglottic laryngeal cancer, no conservative surgery, Stage III-IVB, Laryngectomy	No XRT indication	N/A due to modifications to model		Yes	0.10	γ	SEER (29)	
Supraglottic laryngeal cancer, Radiation or Laryngectomy	Stage IVC and palliative	N/A due to modifications to model		Yes	0.26	γ	SEER (29)	
Glottic and Subglottic laryngeal cancer	Stages I-II	0.51	β	Yes	0.73	γ	SEER (29)	
Glottic and Subglottic, Stages I-II	Laser/conservative surgery appropriate	0	Z	Yes	0.10	γ	SEER (29)	Sensitivity analysis from 0 - 23%

Original RTU study				Updates 2012				
Population or sub-population of interest	**Attribute**	**Proportion of population with the attribute**	**Quality of Information**	**Change in proportion of population with attribute Yes/ No**	**Updated Proportion**	**Updated Quality of Information**	**Updated Reference**	**Comments**
Glottic and Subglottic laryngeal cancer	Stages III-IVB	N/A due to modifications to model		Yes	0.20	γ	SEER (29)	
Glottic and Subglottic, Stages III-IVB	Laryngectomy	N/A due to modifications to model		Yes	0.19		Groome et al (48) SEER (29)	
Glottic and Subglottic, Stages III-IVB, Radical Radiotherapy	<70 yrs old	N/A due to modifications to model		Yes	0.60	α	AIHW 2011 (26)	
Glottic and Subglottic, Stages III-IVB, Laryngectomy	Extracapsular extension	N/A due to modifications to model		Yes	0.40	λ	Hirabayashi et al (51)	
Glottic and Subglottic, Stages III-IVB, Laryngectomy	No XRT indication	N/A due to modifications to model		Yes	0.11	γ	SEER (29)	
Glottic and Subglottic laryngeal cancer	Stages IVC and palliative	N/A due to modifications to model		Yes	0.07	γ	SEER (29)	
OROPHARYNGEAL CANCER								
All Head & Neck Cancers	Oropharyngeal Cancers	0.08	α	Yes	0.17	α	AIHW 2011 (26)	Based on AIHW 2008 data
Oropharyngeal cancers	HPV positive	N/A due to modifications to model		Yes	0.66	θ	Hong et al (23)	Sensitivity analysis 66-80%
Oropharyngeal cancer, HPV+	Surgery	N/A due to modifications to model		Yes	0.54	γ	SEER (29)	

Original RTU study				Updates 2012				
Population or sub-population of interest	**Attribute**	**Proportion of population with the attribute**	**Quality of Information**	**Change in proportion of population with attribute Yes/ No**	**Updated Proportion**	**Updated Quality of Information**	**Updated Reference**	**Comments**
Oropharyngeal cancer, HPV+, surgery	Adjuvant RT	N/A due to modifications to model		Yes	0.19	γ	SEER (29)	
Oropharyngeal cancer, HPV+, surgery	Adjuvant CRT	N/A due to modifications to model		Yes	0.45	ε ζ	Haughey et al (61) Walvekar et al (63)	
Oropharyngeal cancer, HPV+	Radical Radiation	N/A due to modifications to model		Yes	0.43	γ	SEER (29)	
Oropharyngeal cancer, HPV+, Radical radiation	Radical radiation only (no CRT)	N/A due to modifications to model		Yes	0.31	ζ	O'Sullivan et al (56)	
Oropharyngeal cancer, HPV+	Palliative radiation	N/A due to modifications to model		Yes	0.03	ζ	Straetmans et al (55)	
Oropharyngeal cancer, HPV negative	Surgery	N/A due to modifications to model		Yes	0.53	γ	SEER (29)	
Oropharyngeal cancer, HPV negative, surgery	Adjuvant RT	N/A due to modifications to model		Yes	0.31	ζ	McMahon et al (64)	
Oropharyngeal cancer, HPV negative, surgery	Adjuvant CRT	N/A due to modifications to model		Yes	0.35	ζ λ λ	Walvekar et al (63) Li et al (65) Zelefsky et al (66)	

Original RTU study				Updates 2012				
Population or sub-population of interest	**Attribute**	**Proportion of population with the attribute**	**Quality of Information**	**Change in proportion of population with attribute Yes/ No**	**Updated Proportion**	**Updated Quality of Information**	**Updated Reference**	**Comments**
Oropharyngeal cancer, HPV negative	Radical Radiation	N/A due to modifications to model		Yes	0.41	γ	SEER (29)	
Oropharyngeal cancer, HPV negative, Radical Radiation	Radical radiation only (no CRT)	N/A due to modifications to model		Yes	0.56	ζ ζ ζ γ	O'Sullivan et al (56) Huang et al (58;59) O'Sullivan (57) AIHW (26)	
Oropharyngeal cancer, HPV negative	Palliative radiation	N/A due to modifications to model		Yes	0.06	ζ	Straetmans et al (55)	
SALIVARY GLAND CANCER								
All Head & Neck Cancers	Salivary Gland Cancers	0.06	α	Yes	0.07	α	AIHW 2011 (26)	Based on AIHW 2008 data
Salivary cancers	Stage I-II, Low grade	N/A due to modifications to model		Yes	0.14	γ	SEER (29)	
Salivary cancers, Stage I-II, Low grade	Close or positive margins	N/A due to modifications to model		Yes	0.21	λ	Ghosh-Laskar et al (67)	

Original RTU study				Updates 2012				
Population or sub-population of interest	**Attribute**	**Proportion of population with the attribute**	**Quality of Information**	**Change in proportion of population with attribute Yes/ No**	**Updated Proportion**	**Updated Quality of Information**	**Updated Reference**	**Comments**
Salivary cancers, Stage I-II, Low grade, clear margins	Loco-regional recurrence	N/A due to modifications to model		Yes	0.17	λ	Chen et al (68)	
HYPOPHARYNGEAL CANCER								
All Head & Neck Cancers	Hypopharynx Cancers	0.06	α	Yes	0.03	α	AIHW 2011 (26)	Based on AIHW 2008 data
Hypopharyngeal cancers	No distant metastases at presentation	N/A due to modifications to model		Yes	0.80	γ	SEER (29)	
Hypopharyngeal cancers, no distant metastases	CRT recommended	N/A due to modifications to model		Yes	0.81	λ	Paximadis et al (72)	Sensitivity analysis from 0.50-0.81
PARANASAL SINUS AND NASAL CAVITY CANCER								
All Head & Neck Cancers	Paranasal sinus and nasal cavity Cancers	0.05	α	No	0.05	α	AIHW 2011 (26)	Based on AIHW 2008 data
Paranasal sinus and nasal cavity cancers	T1-4a N0-3 M0, Operable	N/A due to modifications to model		Yes	0.70	γ	SEER (29)	
Paranasal sinus and nasal cavity cancers, T1-4a N0-3 M0, Operable	Radical Radiation	N/A due to modifications to model		Yes	0.62	γ	SEER (29)	Sensitivity analysis from 0-62%, default value set at 0.

Original RTU study				Updates 2012				
Population or sub-population of interest	**Attribute**	**Proportion of population with the attribute**	**Quality of Information**	**Change in proportion of population with attribute Yes/ No**	**Updated Proportion**	**Updated Quality of Information**	**Updated Reference**	**Comments**
Paranasal sinus and nasal cavity cancers, T1-4a N0-3 M0, Operable, Radical Radiation	CRT indicated	N/A due to modifications to model		Yes	0.28	γ ζ	SEER (29) Huang et al (59)	
Paranasal sinus and nasal cavity cancers, T1-4a N0-3 M0, Operable, Radical Surgery	CRT indicated	N/A due to modifications to model		Yes	0.43	λ	Wiegner et al (78)	
Paranasal sinus and nasal cavity cancers	T4bN0-3M0 and/or inoperable	N/A due to modifications to model		Yes	0.19	γ	Koivunen et al (73)	
Paranasal sinus and nasal cavity cancers, T4bN0-3M0 and/or inoperable	Unfit for concurrent CRT	N/A due to modifications to model		Yes	0.31	ζ	Huang et al (59)	
Paranasal sinus and nasal cavity cancers	Metastatic and/or palliative at presentation	N/A due to modifications to model		Yes	0.11	γ	SEER (29)	
NASOPHARYNGEAL CANCER								
All Head & Neck Cancers	Nasopharynx cancer	0.04	α	Yes	0.03	α	AIHW 2011 (26)	Based on AIHW 2008 data

Original RTU study				Updates 2012				
Population or sub-population of interest	**Attribute**	**Proportion of population with the attribute**	**Quality of Information**	**Change in proportion of population with attribute Yes/ No**	**Updated Proportion**	**Updated Quality of Information**	**Updated Reference**	**Comments**
OCCULT PRIMARY HEAD & NECK CANCER								
All Head & Neck Cancers	Occult primary head & Neck cancers	0.02	ζ	No	0.02	ζ	Sinnathamby et al (79)	
Occult primary (Head and Neck)	N1-2a	0.22	ζ	No	0.22	ζ	Sinnathamby et al (79)	
Occult primary (Head and Neck), N1-2a	Local or regional recurrence	0.54	ζ	No	0.54	ζ	Grau et al (80)	

Table 3: Head & Neck Cancer. Indications for concurrent chemoradiotherapy - levels and sources of evidence

Outcome no. in tree	Clinical scenario	Level of evidence	References	Proportion of all H & N cancer patients
10	Oral Cavity, Stages III-IVB, surgery, ECE or positive margins (CRT)	I	NCCN (1), CCO (3), ESTRO (13), SIGN(2) SEOM (14), BCCA(15), UK ENT (20)	0.04
12	Oral Cavity, Stages III-IVB, <70 yrs old (CRT)	I	NCCN (1), CCO (3), ESTRO (13), SIGN(2) SEOM (14), BCCA(15), UK ENT (20)	0.01
17	Supraglottic, larynx preserving surgery, ECE and/or margin + (CRT)	I	NCCN (1), CCO (3), ESTRO (13), SIGN(2) SEOM (14), BCCA(15), UK ENT (20)	<0.01
20	Supraglottic, Stage III-IVB, radical radiotherapy, <70 yrs (plus CRT)	I	NCCN (1), CCO (3), ESTRO (13), SIGN(2) SEOM (14), BCCA(15), UK ENT (20)	0.01
23	Supraglottic, Stage III-IVB, laryngectomy, ECE or positive margins (CRT)	I	NCCN (1), CCO (3), ESTRO (13), SIGN(2) SEOM (14), BCCA(15), UK ENT (20)	<0.01
28	Glottic and subglottic, Stages III-IVB, radiotherapy, <70 yrs (plus CRT)	I	NCCN (1), CCO (3), ESTRO (13), SIGN(2) SEOM (14), BCCA(15), UK ENT (20)	0.01

Outcome no. in tree	Clinical scenario	Level of evidence	References	Proportion of all H & N cancer patients
31	Glottic and subglottic, Stages III-IVB, laryngectomy, ECE or positive margins (CRT)	I	NCCN (1), CCO (3), ESTRO (13), SIGN(2) SEOM (14), BCCA(15), UK ENT (20)	<0.01
35	Oropharyngeal cancer, HPV+, surgery, indications for adjuvant CRT	I	NCCN (1), CCO (3), ESTRO (13), SIGN(2) SEOM (14), BCCA(15), UK ENT (20)	0.03
38	Oropharyngeal cancer, HPV+, radical CRT	I	NCCN (1), CCO (3), ESTRO (13), SIGN(2) SEOM (14), BCCA(15), UK ENT (20)	0.03
41	Oropharyngeal cancer, HPV negative, surgery, adjuvant CRT indicated	I	NCCN (1), CCO (3), ESTRO (13), SIGN(2) SEOM (14), BCCA(15), UK ENT (20)	0.01
44	Oropharyngeal cancer, HPV negative, radical CRT indicated	I	NCCN (1), CCO (3), ESTRO (13), SIGN(2) SEOM (14), BCCA(15), UK ENT (20)	0.01
50	Hypopharyngeal cancer, no distant metastasis, CRT indicatted	I	NCCN (1), SIGN (2), CCO (3), NCI PDQ (11)	0.02
54, 56	Paranasal sinus and nasal cavity	I	NCCN (1), NCI PDQ (5), UK ENT	0.02

Outcome no. in tree	Clinical scenario	Level of evidence	References	Proportion of all H & N cancer patients
	cancer, operable, radical radiation/surgery, CRT indicated		(20), BCCA(15)	
58	Paranasal sinus and nasal cavity cancer, advanced/inoperable, CRT indicated	I	NCCN (1), NCI PDQ (5), UK ENT (20), BCCA(15)	0.01
60	Nasopharyngeal cancer	I	NCCN (1), SIGN (2), CCO (3), NCI PDQ (6)	0.03
62	Unknown primary, N1-2a, local or regional recurrence, CRT indicated	I	NCCN (1), UK ENT (20), BCCA(15)	<0.01
64	Unknown primary, N2b-N3	I	NCCN (1), UK ENT (20), BCCA(15)	0.02
The total proportion of all patients with Head & Neck cancer in whom concurrent chemoradiotherapy is recommended				**0.26 (26%)**

Figure 1. Head and Neck cancer radiotherapy utilisation tree

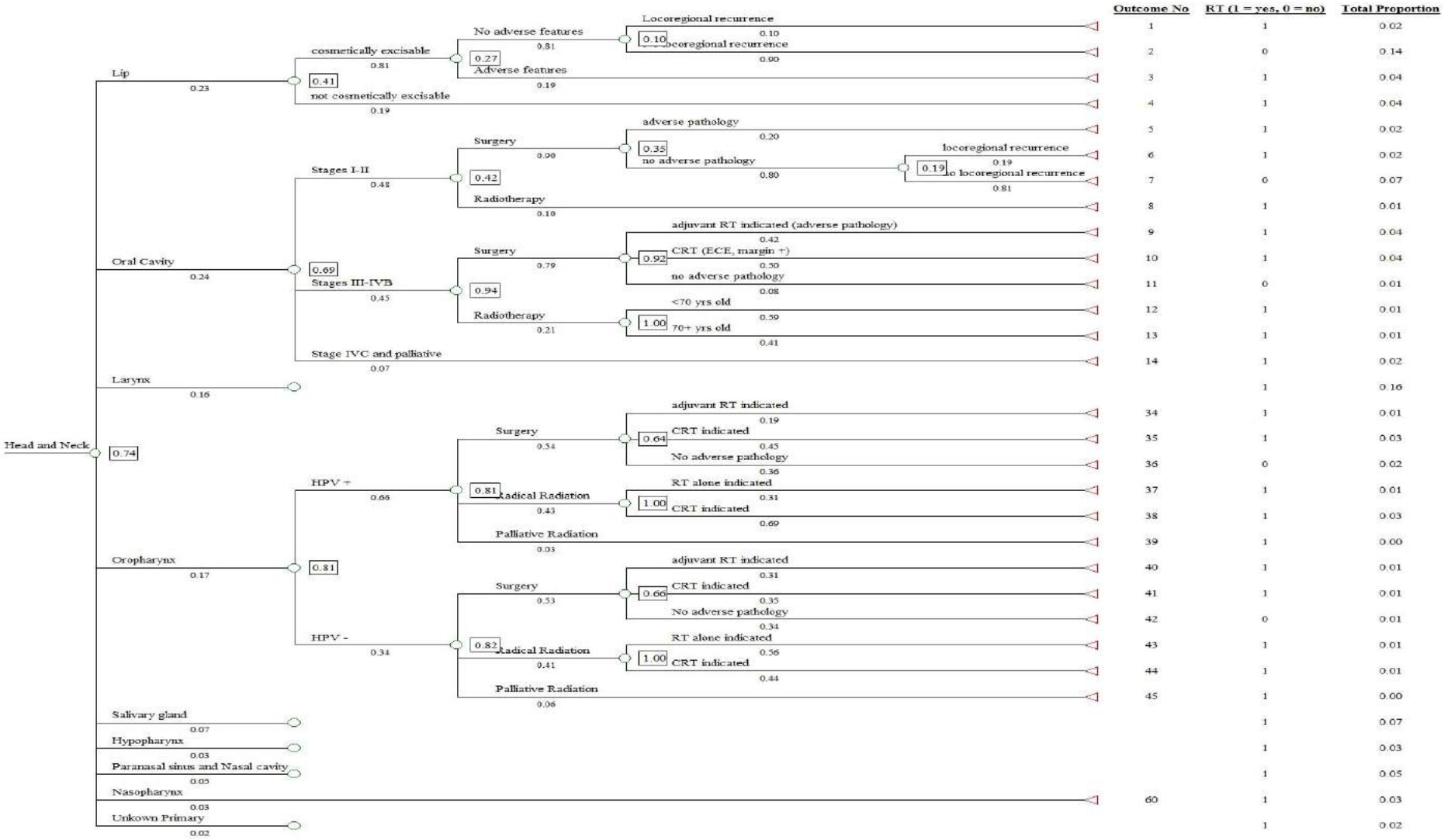


Figure 1. Head and Neck cancer radiotherapy utilisation tree (contd.)

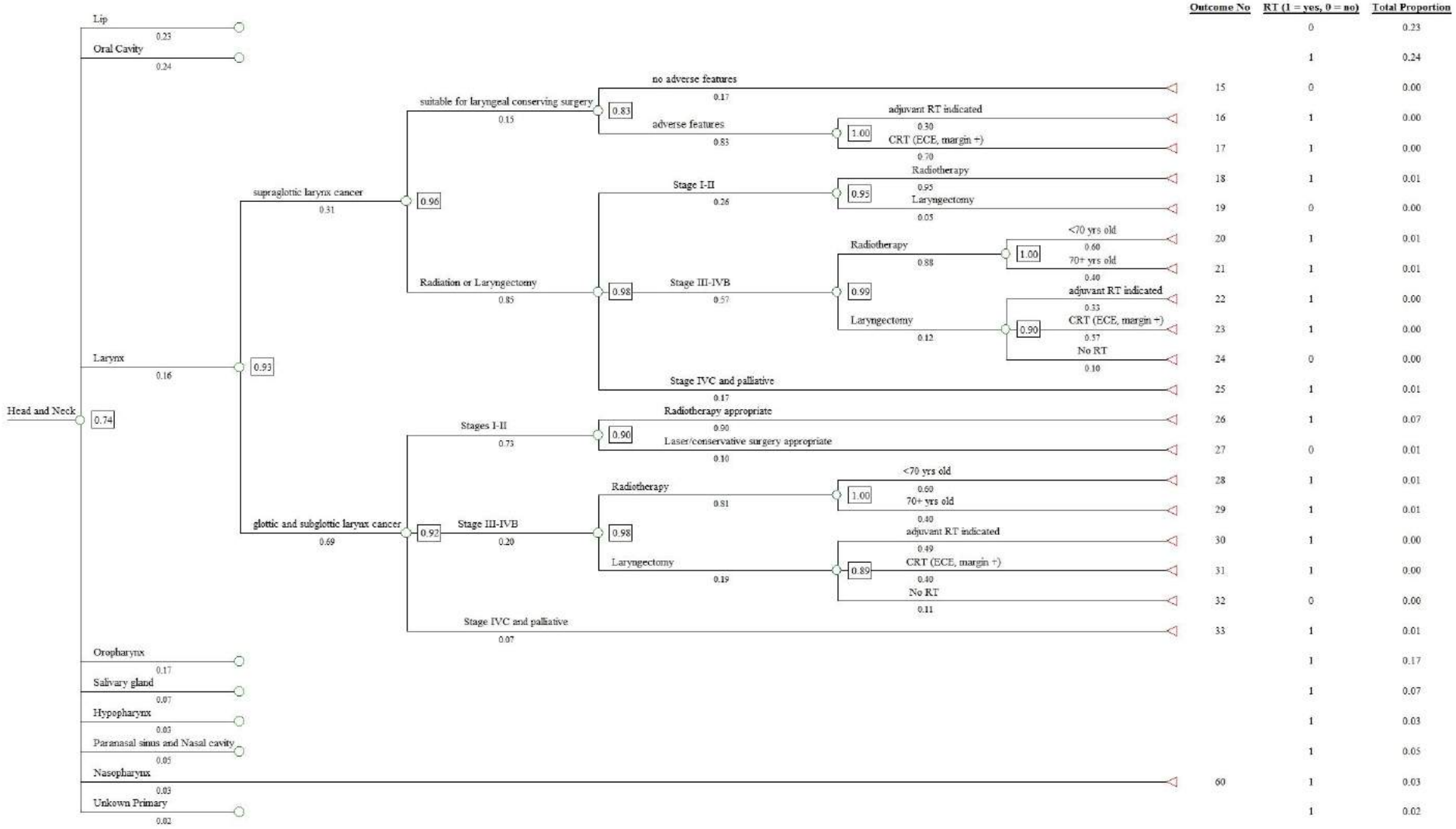


Figure 1. Head and Neck cancer radiotherapy utilisation tree (contd.)

Figure 2. Head and Neck cancer concurrent chemoradiotherapy utilisation tree

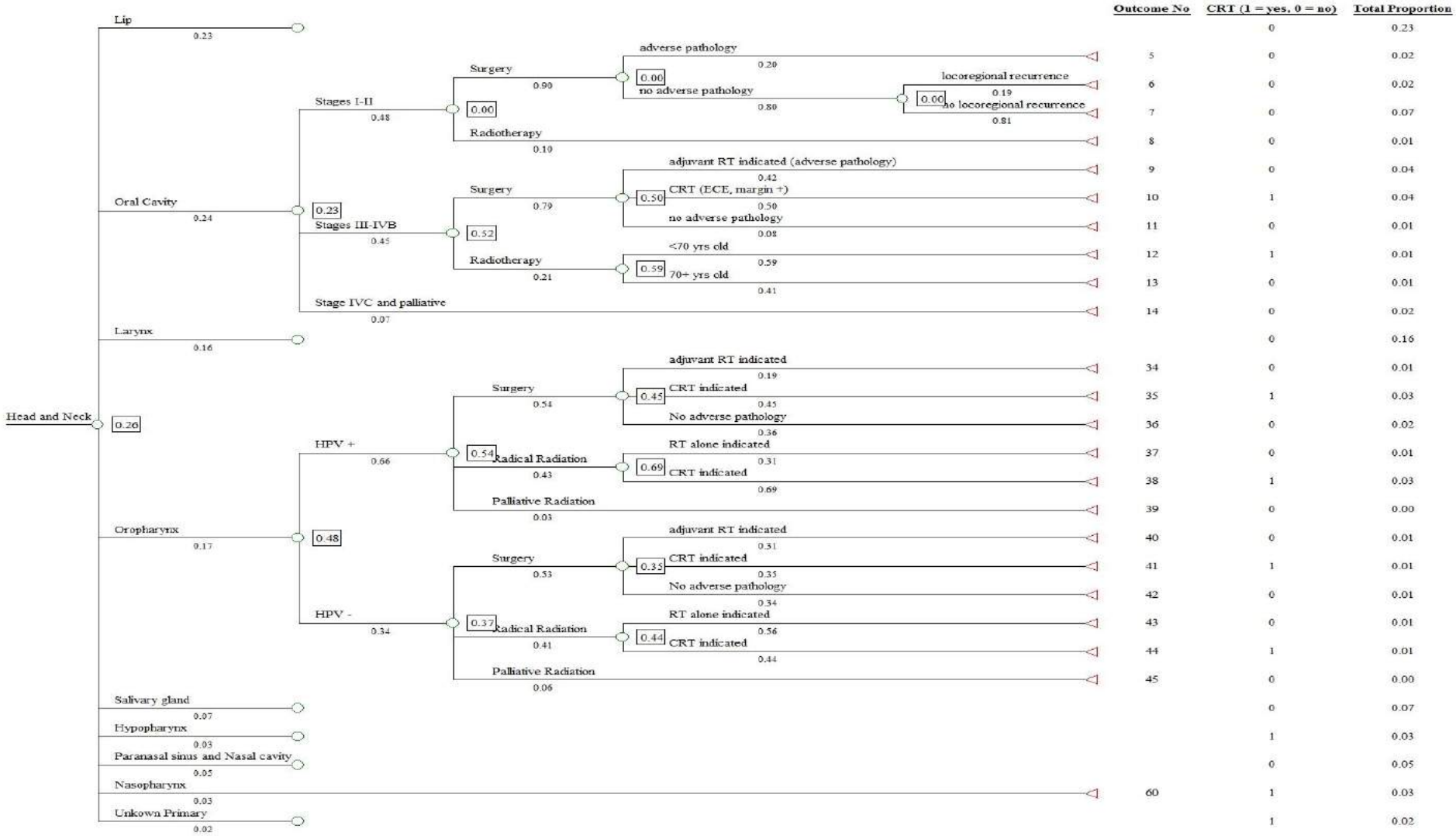


Figure 2. Head and Neck cancer concurrent chemoradiotherapy utilisation tree (contd.)

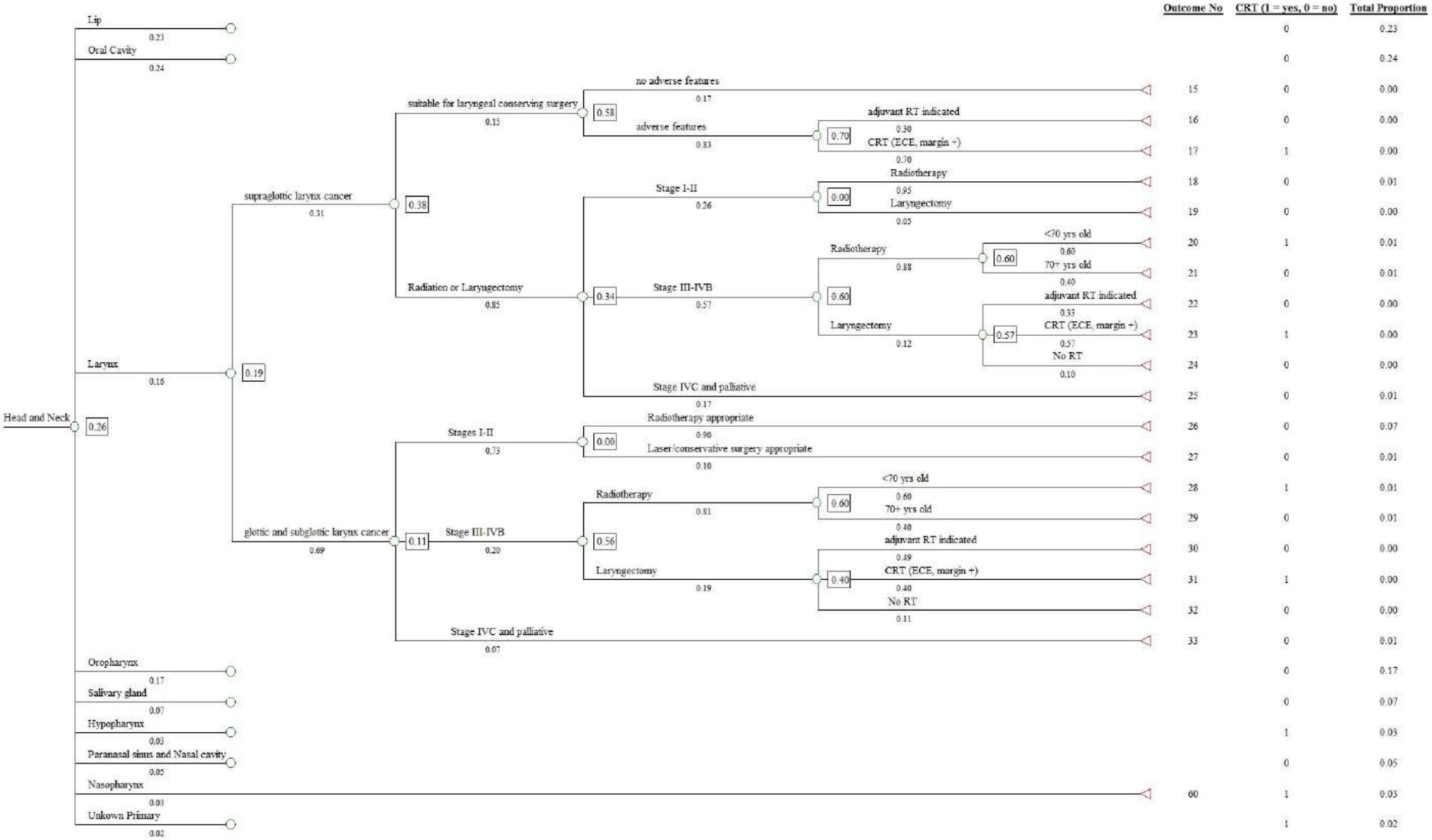
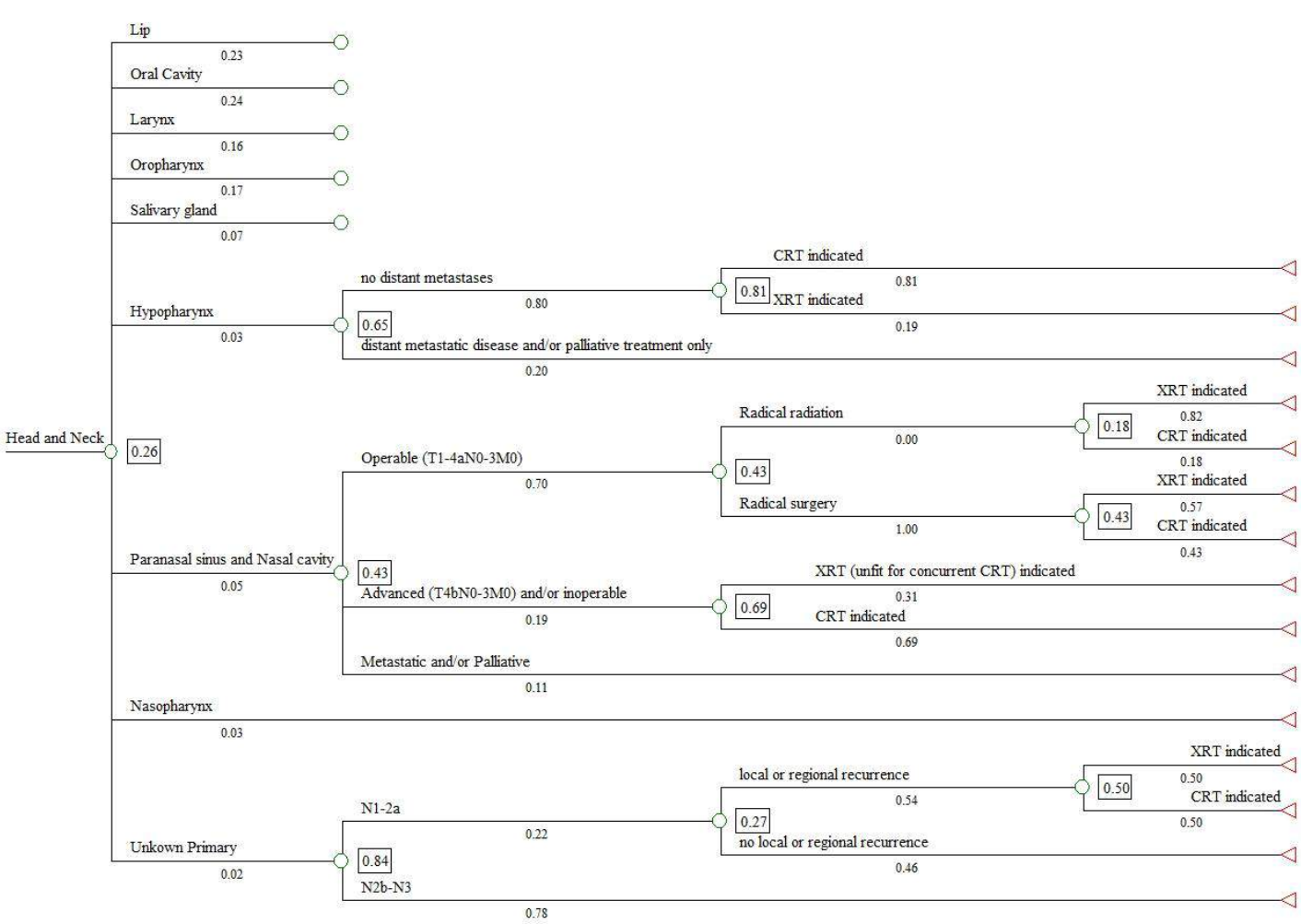


Figure 2. Head and Neck cancer concurrent chemoradiotherapy utilisation tree (contd.)



Outcome No	CRT (1 = yes, 0 = no)	Total Proportion
	0	0.23
	0	0.24
	0	0.16
	0	0.17
	0	0.07
50	1	0.02
51	0	0.00
52	0	0.01
53	0	
54	1	
55	0	0.02
56	1	0.02
57	0	0.00
58	1	0.01
59	0	0.01
60	1	0.03
61	0	0.00
62	1	0.00
63	0	0.00
64	1	0.02

Figure 3. Tornado diagram: univariate sensitivity analyses for RT utilisation

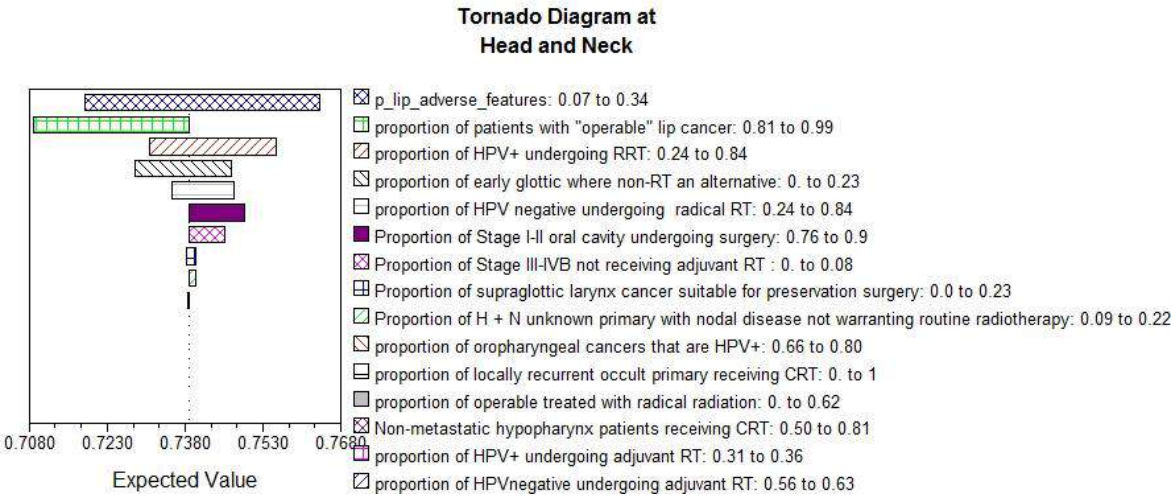
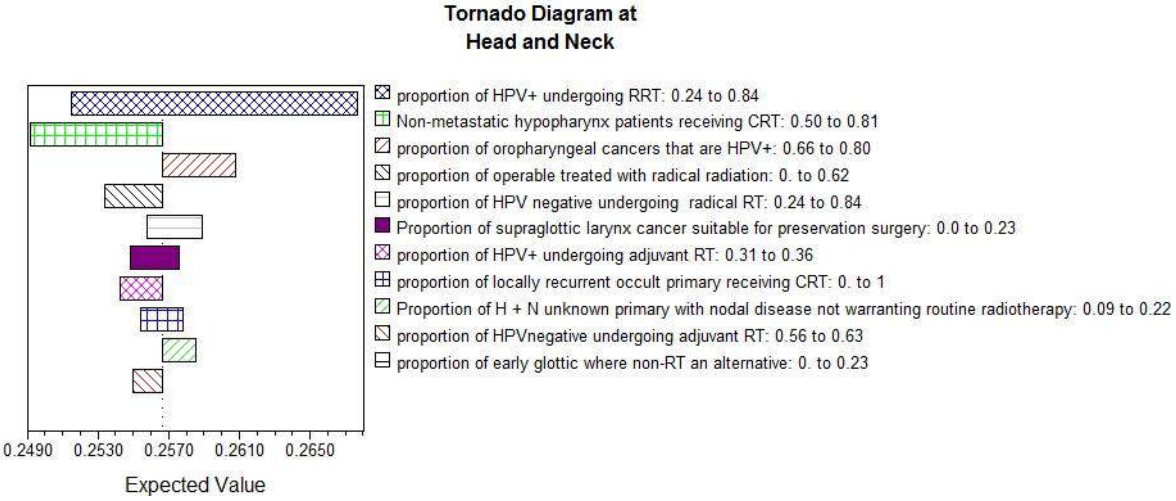


Figure 4. Tornado diagram: univariate sensitivity analyses for CRT utilisation



References

1. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology - Head and Neck Cancers - V.2.2011. http://www.nccn.org/professionals/physician_gls/pdf/head-and-neck.pdf . 30-3-2011. 2-4-2012.
   Ref Type: Electronic Citation

2. Scottish Intercollegiate Guidelines Network (SIGN). Diagnosis and management of head and neck cancer. www.sign.ac.uk . 2006. 2-4-2012.
   Ref Type: Electronic Citation

3. Cancer Care Ontario (CCO) program in evidence-based care (PEBC). The management of head and neck cancer in Ontario: organizational and clinical practice guideline recommendations. https://www.cancercare.on.ca/common/pages/UserFile.aspx?fileId=58590 . 2009. 28-5-2012.
   Ref Type: Electronic Citation

4. National Cancer Institute. PDQ Laryngeal Cancer Treatment. http://www.cancer.gov/cancertopics/pdq/treatment/laryngeal/HealthProfessional . 2012. 28-5-2012.
   Ref Type: Electronic Citation

5. National Cancer Institute. PDQ Paranasal sinus and Nasal Cavity Cancer Treatment. http://www.cancer.gov/cancertopics/pdq/treatment/paranasalsinus/HealthProfessional . 2012. 28-5-2012.
   Ref Type: Electronic Citation

6. National Cancer Institute. PDQ Nasopharyngeal cancer treatment. http://www.cancer.gov/cancertopics/pdq/treatment/nasopharyngeal/HealthProfessional . 2012. 28-5-2012.
   Ref Type: Electronic Citation

7. National Cancer Institute. PDQ Metastatic squamous neck cancer with occult primary treatment. http://www.cancer.gov/cancertopics/pdq/treatment/metastatic-squamous-neck/HealthProfessional . 2012. 28-5-2012.
   Ref Type: Electronic Citation

8. National Cancer Institute. PDQ Lip and Oral Cavity cancer Treatment. http://www.cancer.gov/cancertopics/pdq/treatment/lip-and-oral-cavity/HealthProfessional . 2012. 28-5-2012.
   Ref Type: Electronic Citation

9. National Cancer Institute. PDQ Oropharyngeal cancer treatment. http://www.cancer.gov/cancertopics/pdq/treatment/oropharyngeal/HealthProfessional . 2012. 28-5-2012.
   Ref Type: Electronic Citation

10. National Cancer Institute. Salivary gland cancer treatment. http://www.cancer.gov/cancertopics/pdq/treatment/salivarygland/HealthProfessional . 2012. 28-5-2012.
    Ref Type: Electronic Citation

11. National Cancer Institute. PDQ Hypopharyngeal cancer treatment. http://www.cancer.gov/cancertopics/pdq/treatment/hypopharyngeal/HealthProfessional . 2012. 28-5-2012.
    Ref Type: Electronic Citation

12. Chan ATC, Gregoire V, Lefebvre JL, Licitra L, Felip E. Nasopharyngeal cancer: EHNS-ESMO-ESTRO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2010;21:v187-v189.

13. Gregoire V, Lefebvre JL, Licitra L, Felip E. Squamous cell carcinoma of the head and neck: EHNS-ESMO-ESTRO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann.Oncol* 2010;21:v184-v186.

14. Nin RM, Borgonon MP, Hernandez JJ, Casado DI. SEOM clinical guidelines for the treatment of head and neck cancer. *Clin Trans Oncol* 2010;12:742-8.

15. BC Cancer Agency. Cancer Management Guidelines for Head and Neck. http://www.bccancer.bc.ca/HPI/CancerManagementGuidelines/HeadnNeck/Management/default.htm . 2003. 21-6-2012.
Ref Type: Electronic Citation

16. Bilde A, et al. The Danish national guidelines for treatment of oral squamous cell carcinoma. *Acta Oncol* 2006;45:294-9.

17. Cancer Council Australia and Australian Cancer Network. Basal cell carcinoma, squamous cell carcinoma and related lesions - a guide to clinical management in Australia. 2008. Sydney, Cancer Council Australia.
Ref Type: Report

18. Motley R, Kersey P, Lawrence C. Multiprofessional guidelines for the management of the patient with primary cutaneous squamous cell carcinoma. *Br J Dermatology* 2002;146:18-25.

19. Guzzo M, Locati L, and Prott FJ. Major and minor salivary gland tumours. State of the Art Oncology in Europe (START). http://www.startoncology.net/site/index.php?option=com_content&view=article&id=95%3Amajor-and-minor-salivary-gland-tumours&catid=48%3Ahead-and-neck-cancers-cat&Itemid=53&lang=en . 2012. 19-4-2012.
Ref Type: Electronic Citation

20. Roland NJ, Paleri VE. Head and Neck Cancer: Multidisciplinary Management Guidelines, 4th Edition ed. 2011.

21. Pfister DG, et al. American Society of Clinical Oncology clinical practice guideline for the use of larynx-preservation strategies in the treatment of laryngeal cancer. *J Clin Oncol* 2006;24:3693-704.

22. Chaturvedi AK, Engels EA, Pfeiffer RM, Hernandez BY, et al. Human papillomavirus and rising oropharyngeal cancer incidence in the United States. *J Clin Oncol* 2011;29:4294-301.

23. Hong AM, et al. Squamous cell carcinoma of the oropharynx in Australian males induced by human papillomavirus vaccine targets. *Vaccine* 2010;28:3269-72.

24. Carvalho AL, et al. Trends in incidence and prognosis for head and neck cancer in the United States: a site-specific analysis of the SEER database. *Int J Cancer* 2005;114:806-16.

25. Sturgis EM, Cinciripini PM. Trends in head and neck cancer incidence in relation to smoking prevalence: an emerging epidemic of human papillomavirus-associated cancers. *Cancer* 2007;110:1429-35.

26. Australian Institute of Health and Welfare (AIHW). Australian Cancer Incidence and Mortality (ACIM) books. AIHW . 2011. 16-8-2011.
Ref Type: Electronic Citation

27. McCombe D, et al. Squamous cell carcinoma of the lip: a retrospective review of the Peter MacCallum Cancer Institute experience 1979-88. *Aust NZ J Surg* 2000;70:358-61.

28. de Visscher JG, et al. Epidemiology of cancer of the lip in the Netherlands. *Oral Oncol* 1998;34:421-6.

29. National Cancer Institute and Surveillance, Epidemilogy and End Results SEER Program. Surveillance, Epidemiology and End Results (SEER) Program SEER*Stat Database: Incidence - SEER 17 Regs Research Data, Nov 2009 Sub (1973-2007 varying) - Linked to county attributes- Total US., 1969-2007 Counties. 2010.
Ref Type: Data File

30. Hjortdal O, Naess A, Berner A. Squamous cell carcinomas of the lower lip. *J Craniomaxillofac Surg* 1995;23:34-7.

31. de Visscher JG, et al. Surgical treatment of squamous cell carcinoma of the lower lip: evaluation of long-term results and prognostic factors - a retrospective analysis of 184 patients. *J Oral Maxillofac Surg* 1998;56:814-20.

32. Talbot S, Hitchcock B. Incomplete primary excision of cutaneous basal and squamous cell carcinomas in the Bay of Plenty. *N Z Med J* 2004;117:U848.

33. de Visscher JG. Surgical margins for resection of squamous cell carcinoma of the lower lip. *Int J Oral Maxillofac Surg* 2002;31:154-7.

34. Veness MJ, et al. Squamous cell carcinoma of the lip. Patterns of relapse and outcome: reporting the Westmead Hospital experience, 1980-1997. *Australas Radiol* 2001;45:195-9.

35. Farhadieh RD, et al. Radiotherapy is not associated with an increased rate of second primary tumours in oral squamous carcinoma: a study of 370 patients. *Oral Oncol* 2009;45:941-5.

36. Robertson AG, et al. Treatment of oral cancer: the need for defined protocols and specialist centres. Variation in the treatment of oral cancer. *Clin Oncol (R Coll Radiol)* 2001;13:409-15.

37. Brannan AG, Johnstone PA, Cooper J. Extracapsular tumor extension in cervical lymph nodes: reconciling the literature and SEER data. *Head Neck* 2011;33:525-8.

38. Shim SJ, et al. Clinical Outcomes for T1-2N0-1 oral and tongue cancer patients who underwent surgery with and without postoperative radiotherapy. *Radiother Oncol* 2010;5:43.

39. Brown JS, et al. A comparison of outcomes for patients with oral squamous cell carcinoma at intermediate risk of recurrence treated by surgery alone or with post-operative radiotherapy. *Oral Oncol* 2007;43:764-73.

40. Chan AK, et al. Postoperative IMRT following surgery for oral cavity squamous cell carcinoma: patterns of failure. *Int J Radiat Oncol Biol Phys* 2011;81:S105.

41. Sutton DN, et al. The prognostic implications of the surgical margin in oral squamous cell carcinoma. *Int J Oral Maxillofac Surg* 2003;32:30-4.

42. Silver CE, et al. Current trends in initial management of laryngeal cancer: the declining use of open surgery. *Eur Arch OtoRhino Laryngol* 2009;266:1333-52.

43. NHS Information Centre. National Head & Neck Cancer Audit 2010. Key findings for England and Wales for the audit November 2009 to October 2010. 2011. Leeds.
Ref Type: Report

44. Lee NK, Goepfert H, Wendt CD. Supraglottic laryngectomy for intermediate-stage cancer: U.T.M.D. Anderson Cancer Center experience with combined therapy. *Laryngoscope* 1990;100:831-6.

45. Bernier J, et al. Defining risk levels in locally advanced head and neck cancers: a comparative analysis of concurrent postoperative radiation plus chemotherapy trials of the EORTC (#22931) and RTOG (#9501). *Head & Neck* 2005;27:843-50.

46. Chun JY, et al. The oncologic safety and functional preservation of supraglottic partial laryngectomy. *Am J Otolaryngol* 2010;31:246-51.

47. Snyderman NL, et al. Extracapsular spread of carcinoma in cervical lymph nodes. Impact upon survival in patients with carcinoma of the supraglottic larynx. *Cancer* 1985;56:1597-9.

48. Groome PA, et al. Management and outcome differences in supraglottic cancer between Ontario, Canada and the Surveillance, Epidemiology and End Results areas of the United States. *J Clin Oncol* 2003;21:496-505.

49. Groome PA, et al. Glottic cancer in Ontario, Canada and the SEER areas of the United States. Do different management philosophies produce different outcome profiles? *J Clin Epidemiol* 2001;54:301-15.

50. Bradford CR, et al. Prognostic importance of surgical margins in advanced laryngeal squamous carcinoma. *Head & Neck* 1996;18:11-6.

51. Hirabayashi H, et al. Extracapsular spread of squamous cell carcinoma in neck lymph nodes: prognostic factor of laryngeal cancer. *Laryngoscope* 1991;101:502-6.

52. Hammarstedt L, et al. Human papillomavirus as a risk factor for the increase in incidence of tonsillar cancer. *Int J Cancer* 2006;119:2620-3.

53. Junor E, et al. Benefit of chemotherapy as part of treatment for HPV DNA-positive but p16-negative squamous cell carcinoma of the oropharynx. *Br J Cancer* 2012;106:358-65.

54. Ukpo OC, et al. High-risk human papillomavirus E6/E7 mRNA detection by a novel in situ hybridization assay strongly correlates with p16 expression and patient outcomes in oropharyngeal squamous cell carcinoma. *Am J Surg Pathol* 2011;35:1343-50.

55. Straetmans JM, et al. Human papillomavirus reduces the prognostic value of nodal involvement in tonsillar squamous cell carcinomas. *Laryngoscope* 2009;119:1951-7.

56. O'Sullivan B, et al. Outcomes of HPV-related oropharyngeal cancer patients treated by radiotherapy alone using altered fractionation. *Radiother Oncol* 2012;103:49-56.

57. O'Sullivan B. How should we manage patients with locoregionally advanced head and neck cancer who are not suitable for chemoradiotherapy? *Radiother Oncol* 2011;99:S24.

58. Huang SH, et al. Patterns of care in elderly head and neck cancer radiation oncology patients: a single center cohort study. *Int J Radiat Oncol Biol Phys* 2011;79:46-51.

59. Huang S, et al. Outcome of radiotherapy alone for locoregionally advanced head and neck cancer patients unfit for chemotherapy. *Eur J Cancer* 2011;47:S546.

60. Hong AM, et al. Human papillomavirus predicts outcome in oropharyngeal cancer in patients treated primarily with surgery or radiation therapy. *Br J Cancer* 2010;103:1510-7.

61. Haughey BH, et al. Transoral laser microsurgery as primary treatment for advanced stage oropharyngeal cancer: a United States multicenter study. *Head Neck* 2011;33:1683-94.

62. Chenevert J, Chiosea S. Incidence of human papillomavirus in oropharyngeal squamous cell carcinomas: now and 50 years ago. *Hum Pathol* 2012;43:17-22.

63. Walvekar RR. Role of surgery in limited (T1-2, N0-1) cancers of the oropharynx. *Laryngoscope* 2008;118:2129-34.

64. McMahon J, et al. Influence of condition of surgical margins on local recurrence and disease-specific survival in oral and oropharyngeal cancer. *Br J Oral Maxillofac Surg* 2003;41:224-31.

65. Li XM, et al. Cervical lymph node metastatic patterns of squamous carcinomas in the upper aerodigestive tract. *J Laryngol Otol* 1996;110:937-41.

66. Zelefsky MJ, Harrison LB, Armstrong JG. Long-term treatment results of postoperative radiation therapy for advanced stage oropharyngeal carcinoma. *Cancer* 1992;70:2388-95.

67. Ghosh-Laskar S, et al. Mucoepidermoid carcinoma of the parotid gland: factors affecting outcome. *Head Neck* 2011;33:497-503.

68. Chen AM, et al. Local-regional recurrence after surgery without postoperative irradiation for carcinomas of the major salivary glands: implications for adjuvant therapy. *Int J Radiat Oncol Biol Phys* 2007;67:982-7.

69. Sewnaik A, HoorwegJJ, Knegt PP, et al. Treatment of hypopharyngeal carcinoma: analysis of nationwide study in the Netherlands over a 10-year period. *Clin Otolaryngol* 2005;30:52-7.

70. Hoffman HT, Karnell LH, Shah JP, et al. Hypopharyngeal cancer patient care evaluation. *Laryngoscope* 1997;107:1005-17.

71. Chang MF, Wang H, Kang C, et al. Treatment results for hypopharyngeal cancer by different treatment strategies and its secondary primary - an experience in Taiwan. *Radiation Oncology* 2010;5:91-8.

72. Paximadis P, Yoo G, Lin H, et al. Concurrent chemoradiotherapy improves survival in patients with hypopharyngeal cancer. *Int J Radiat Oncol Biol Phys* 2012;82:1515-21.

73. Koivunen P, et al. A national series of 244 sinonasal cancers in Finland in 1990-2004. *Eur Arch Otorhinolaryngol* 2012;269:615-21.

74. Society of Surgical Oncology Practice Guidelines. Parotid gland cancer surgical practice guidelines. *Oncology* 1997;11:1219-23.

75. Rowe DE, Carroll RJ, Day CL. Prognostic factors for local recurrence, metastasis, and survival rates in squamous cell carcinoma of the skin, ear and lip. Implications for treatment modality selection. *J Am Acad Dermatol* 1992;26:976-90.

76. Jones KR, Lodge-Rigal D, Reddick RL, et al. Prognostic factors in the recurrence of stage I and II squamous cell cancer of the oral cavity. *Arch Otolaryngol Head Neck Surg* 1992;118:483-5.

77. Wolfensberger M, Zbaren P, Dulguerov P, Muller W, et al. Surgical treatment of early oral carcinoma - results of a prospectively controlled multicenter study. *Head & Neck* 2001;23:525-30.

78. Wiegner EA, et al. Intensity-modulated radiotherapy for tumors of the nasal cavity and paranasal sinuses: clinical outcomes and patterns of failure. *Int J Radiat Oncol Biol Phys* 2012;83:243-51.

79. Sinnathamby K, Peters LJ, Laidlaw C, Hughes PG. The occult Head and Neck primary: to treat or not to treat? *Clin Oncol (R Coll Radiol)* 1997;9:322-9.

80. Grau C, Johansen LV, Jakobsen J, Geertsen P, Andersen E, Jensen BB. Cervical lymph node metastases from unknown primary tumours Results from a national survey by the Danish Society for Head and Neck Oncology. *Radiotherapy and Oncology* 2000;55:121-9.

KIDNEY CANCER

In the original radiotherapy utilisation model the indications for radiotherapy for kidney cancer were derived from evidence-based treatment guidelines issued by major national and international organisations. The guidelines reviewed are those published after the previous radiotherapy utilisation study was completed (July 2003) up to February 2012.

Updated Guidelines

All the guidelines have been updated since the publication of the original radiotherapy utilisation study. The following updated national level clinical practice guidelines for the management of kidney cancer were identified:

- National Cancer Institute (NCI PDQ) guideline on kidney cancer (2012) (1)
- BC Cancer Agency guidelines on management of kidney cancer (2008) (2)
- NCCN Clinical practice guidelines on kidney cancer (3)

The following new clinical practice guidelines for the management of kidney cancer were identified:

- EAU guidelines on Renal Cell Carcinoma: the 2010 update (4)
- Renal cell carcinoma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up (2010) (5)
- Management of kidney cancer: Canadian kidney cancer forum consensus update (2009) (6)

Indications for radiotherapy and changes to the optimal utilisation model

External beam radiotherapy (EBRT) has a limited role in the treatment of kidney cancer and is mainly used for the palliation of symptoms of metastatic disease or local symptoms. It is possible that the increased uptake of new treatments such as targeted therapy may further reduce the role of EBRT in the future.

The indications for external beam radiotherapy in the original CCORE model of optimal radiotherapy utilisation for kidney cancer have been reviewed and updated in the optimal utilisation tree based on the latest guideline recommendations (see Figure 1 and Table 1).

None of the updated guidelines recommend external beam radiotherapy for local recurrence after nephrectomy for non-metastatic renal cancer (the NCCN guidelines state that “adjuvant radiation therapy after nephrectomy has not shown benefit, even in patients with nodal involvement or incomplete resection”) and therefore this indication has been removed from the revised model.

Levels of evidence

The levels of evidence supporting the indications for radiotherapy in kidney cancer are unchanged. The only indications that are based on level I or II evidence of benefit are the indications for palliative radiotherapy in the management of brain and bone metastases. The updated model predicts that 13%

of the whole kidney cancer population have an indication for radiotherapy based on level I-II evidence of benefit.

Changes to Epidemiological Data

The epidemiological data for the revised kidney cancer tree were identified through extensive electronic searches using the key words 'kidney cancer', 'radiotherapy', 'epidemiology kidney cancer', 'incidence', 'patterns of care', 'patterns of treatment', 'metastases', 'follow up', 'outcomes', 'unresectable' in various combinations. This has been applied particularly to the early branches in the tree. The epidemiological data together with their sources and hierarchical level are documented in Table 2.

Since the publication of the previous radiotherapy utilisation project, the Australian national cancer incidence data published by the Australian Institute of Health and Welfare (AIHW) have been updated, with the most recent data available being 2008 data. The latest ACIM (Australian Cancer Incidence and Mortality) book published by AIHW in 2011 reports that in 2008, kidney cancer accounted for 2.3% of all cancer in Australia (7).

Stage data were extracted from the SEER database for the years 2004-2008 (chosen because this is the most recent period available and also AJCC stage data are only available for the years 2004 onwards) (8). The data showed that out of 50,050 patients diagnosed with known stage kidney cancer in the SEER registry in the above period, 40,723 patients (81.3 %) had non-metastatic disease. The SEER registry also contains information on "reason no cancer-directed surgery" and this shows that 94.3% of patients diagnosed with non-metastatic kidney cancer either had or were recommended to have cancer surgery. The SEER stage and fitness for surgery data were used in the optimal utilisation tree since these data are recent and are population-based.

Aben et al reported on 328 patients diagnosed with metastatic kidney cancer between 1999 and 2005 from a population-based cancer registry in the Netherlands (9). The distribution of bone and brain metastases reported by Aben et al were used in the revised model since they were more recent, from a larger series and of higher quality than the data in the original model.

Woodward et all reported on skeletal complications in renal cancer patients with bone metastases (10). In their series, 199 out of 254 patients with bone metastases (78%) received radiotherapy to bone, most commonly for bone pain.

The BC Cancer Agency Cancer Management Guidelines (2) mention a role for EBRT in the treatment of symptomatic primary ("to control bleeding and pain from the primary tumour") in Stage IV disease. A population-based study of patients diagnosed with metastatic kidney cancer in the Netherlands by Aben et al found that 38% of patients underwent nephrectomy and 31.7% received radiotherapy, but they did not specify the site of radiotherapy and it can be assumed that the majority of radiotherapy treatments were directed towards metastases (9). Despite extensive searches, no data could be found

to indicate the proportion of patients presenting with Stage IV disease who require radiotherapy to treat a symptomatic primary. Wersall et al reported on the results of 53 patients with metastatic renal cell carcinoma who were treated with stereotactic radiotherapy; 3 patients (6%) had treatment to the primary tumour (11). While this data is not ideal since it is derived from a highly selected group of patients and is based on actual treatment data, it may be more realistic than the data used in the original model and this value of 6% was used as the upper limit in the sensitivity analysis. In the original model due to the lack of available data it was assumed that all metastatic kidney cancer patients who presented with haematuria at diagnosis (20% of patients since this is a common presenting symptom of renal cancer) had a symptomatic primary tumour that could potentially be treated with either surgery or radiotherapy and sensitivity analysis was conducted using 20% as the upper level.

Estimation of the Optimal Radiotherapy Utilisation Rate

Based on the most recent evidence on the efficacy of radiotherapy and on epidemiological data on the occurrence of indications for radiotherapy, the proportion of all kidney cancer patients in whom radiotherapy would be recommended is 15% (Table 1 and Figure 1). The original optimal radiotherapy utilisation rate derived in 2003 for kidney cancer was 28%. The reduction in the optimal utilisation rate can be mainly attributed to changes in the stage distribution of kidney cancer, with the proportion of patients with stage IV disease at diagnosis falling from 31% in the 2003 model to 19% in the current model (the main indications for radiotherapy in kidney cancer are in the treatment of symptomatic metastases). One indication for radiotherapy (for local recurrence after nephrectomy) has also been removed from the revised model, further reducing the revised radiotherapy utilisation rate.

Concurrent Chemoradiotherapy in Kidney Cancer

The indications for radiotherapy for kidney cancer were reviewed to identify the indications where radiotherapy is recommended in conjunction with concurrent chemotherapy as the first treatment. The guidelines currently do not recommend concurrent chemo-radiotherapy in kidney cancer.

Sensitivity Analysis

Univariate sensitivity analysis was undertaken (Figure 2) to assess any changes in the optimal radiotherapy utilisation rate that would result from uncertainty in treatment recommendations or in different estimates of the proportions of patients with particular attributes. Sensitivity analysis was conducted on the proportion of patients who develop distant metastases post-nephrectomy, since the reported values varied significantly, and on the proportion of patients presenting in Stage IV who receive radiotherapy for a symptomatic primary. The expected value in the estimate of optimal radiotherapy utilisation due to these uncertainties ranged from 13% to 21.6% as shown in the Tornado diagram (Figure 2).

Figure 1. Revised Optimal Radiotherapy Utilisation Tree for Kidney Cancer

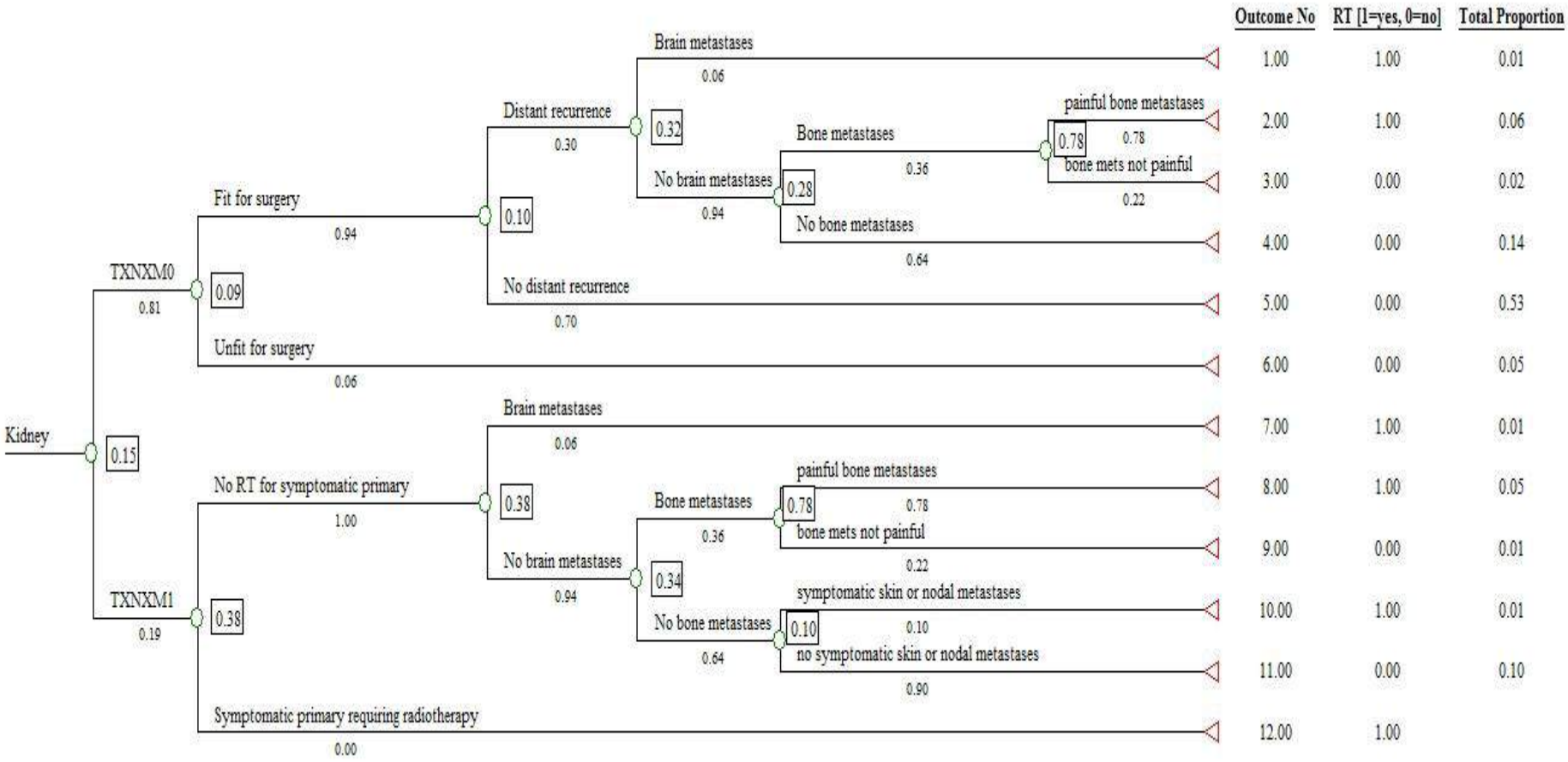


Figure 2. Kidney Cancer - Tornado Diagram for Univariate Sensitivity Analysis

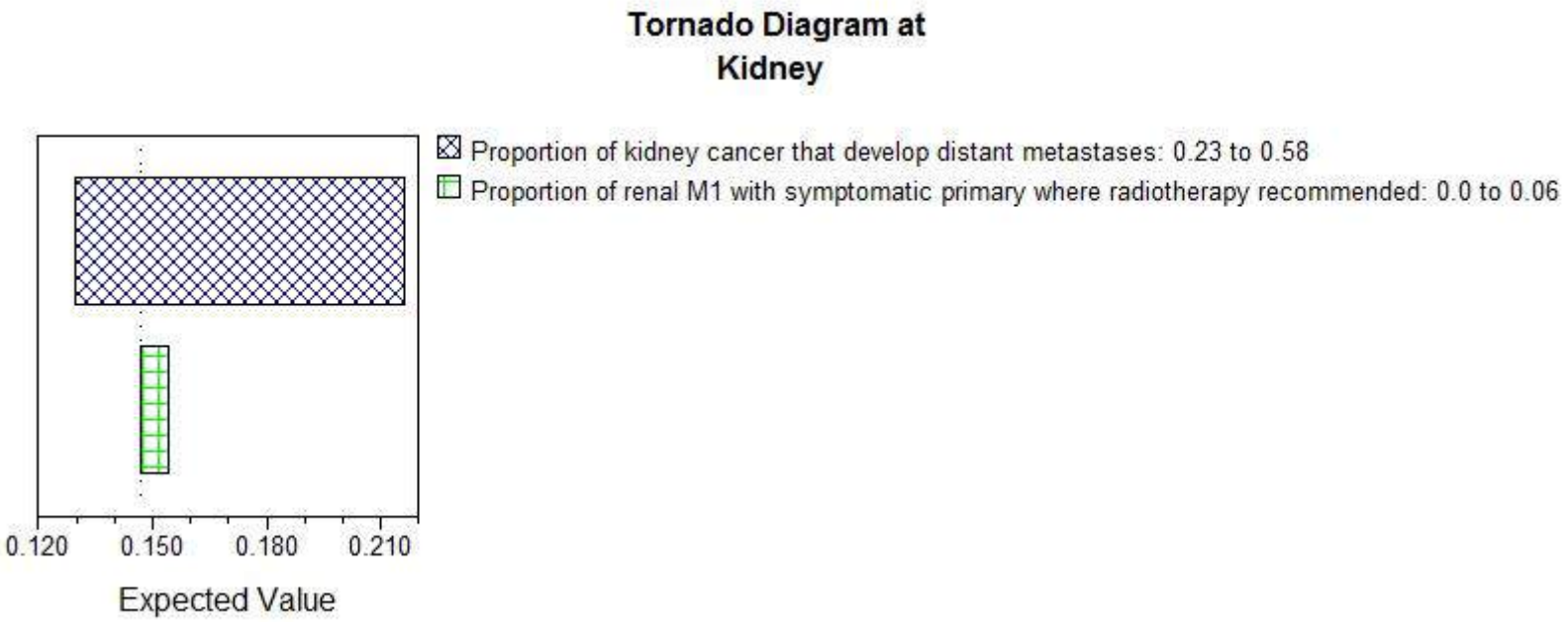


Table 1: Kidney Cancer. Indications for radiotherapy - Levels and sources of evidence

Original RTU study				Updates 2012					
Outcome Nos. in Updated Tree	Clinical Scenario	Level of evidence	Proportion of all kidney cancer	Change of Indication	Guideline updated	Current level of evidence	Change to proportion of all kidney cancer		References
							Yes/ No	Updated value	
1	Stage TxNxM0, fit for surgery, distant recurrence with brain metastases	II	0.02	No	Yes	II	Yes	0.01	NCI PDQ (1), BCCA (2), NCCN (3), EAU (4)
2	Stage TxNxM0, fit for surgery, distant recurrence with no brain metastases and painful bone metastases	I	0.07	No	Yes	I	Yes	0.06	NCI PDQ (1), BCCA (2), NCCN (3), EAU (4)
7	Stage TxNxM1, no symptomatic primary, brain metastases	II	0.03	No	Yes	II	Yes	0.01	NCI PDQ (1), BCCA (2), NCCN (3), EAU (4)

Original RTU study				Updates 2012					
Outcome Nos. in Updated Tree	**Clinical Scenario**	**Level of evidence**	**Proportion of all kidney cancer**	**Change of Indication**	**Guideline updated**	**Current level of evidence**	**Change to proportion of all kidney cancer**		**References**
							Yes/ No	**Updated value**	
8	Stage TxNxM1, no symptomatic primary, no brain metastases, painful bone metastases	I	0.11	No	Yes	I	Yes	0.05	NCI PDQ (1), BCCA (2), NCCN (3), EAU (4)
10	Stage TxNxM1, no symptomatic primary, no brain metastases, no painful bone metastases, symptomatic skin or nodal metastases	IV	0.02	No	Yes	IV	Yes	0.01	NCI PDQ (1)
12	Stage TxNxM1, symptomatic primary	III	0	No	Yes	III	No	0	NCI PDQ (1)
Proportion of all kidney cancer patients in whom radiotherapy is recommended			0.28 (28%)	**Updated Proportion of all kidney cancer patients in whom radiotherapy is recommended**				**0.15 (15%)**	

Abbreviations: NCI PDQ – National Cancer Institute Physician Data Query, BCCA – British Columbia Cancer Agency, NCCN – National Comprehensive Cancer Network, EAU – European Association of Urolog

Table 2: Kidney Cancer. The incidence of attributes used to define indications for radiotherapy

Original RTU study				Updates 2012				
Population or sub-population of interest	**Attribute**	**Proportion of population with the attribute**	**Quality of Information**	**Change in proportion of population with attribute Yes/ No**	**Updated Proportion**	**Updated Quality of Information**	**Updated Reference**	**Comments**
All registry cancers	Kidney cancer	0.03	α	Yes	0.023	α	AIHW 2011 (7)	Based on AIHW 2008 data
All kidney cancer	TxNxM0	0.69	β	Yes	0.81	γ	SEER (8)	Based on 2004-2008 SEER data
TxNxM0	Fit for surgery	0.98	β	Yes	0.94	γ	SEER (8)	Based on 2004-2008 SEER data
TxNxM0, fit for surgery	Local recurrence	0.04	ε	No	0.04	ε	Campbell (12)	
TxNxM0, fit for surgery, no local recurrence	Distant recurrence	0.30	ζ	No	0.30	ζ	Ljungberg (13)	Sensitivity analysis (0.23-0.58)
Metastatic kidney cancer	Brain metastases	0.10	δ	Yes	0.06	γ	Aben et al (9)	

Original RTU study				Updates 2012				
Population or sub-population of interest	**Attribute**	**Proportion of population with the attribute**	**Quality of Information**	**Change in proportion of population with attribute Yes/ No**	**Updated Proportion**	**Updated Quality of Information**	**Updated Reference**	**Comments**
Metastatic kidney cancer, no brain metastases	Bone metastases	0.39	ζ	Yes	0.36	γ	Aben et al (9)	
Metastatic kidney cancer, bone metastases	Painful bone metastases	N/A (new branch in tree)		Yes	0.78	ζ	Woodward et al (10)	
TxNxM1, no symptomatic primary, no brain or bone metastases	Symptomatic skin or nodal metastases	0.10	ζ	No	0.10	ζ	Ljungberg (13)	
TxNxM1	Symptomatic primary	0.20 (sensitivity analysis)	ζ	Yes	0.06 (sensitivity analysis)	λ	Wersall et al (11)	Sensitivity analysis (0-0.06)

References

1. National Cancer Institute. PDQ Renal Cell Cancer Treatment. http://www.cancer.gov/cancertopics/pdq/treatment/renalcell/HealthProfessional . 6-1-2012. Bethesda, MD:National Cancer Institute. 28-2-2012.
Ref Type: Electronic Citation

2. BC Cancer Agency. Cancer Management Guidelines: Kidney Cancer. http://www.bccancer.bc.ca . 2008. 20-2-2012.
Ref Type: Electronic Citation

3. National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology Kidney Cancer V.2.2012. http://www.nccn.org/professionals/physician_gls/pdf/kidney.pdf . 2012.
Ref Type: Electronic Citation

4. Ljungberg B, Cowan NC, Hanbury DC, Hora M, Kuczyk MA, et al. EAU Guidelines on Renal Cell Carcinoma: the 2010 update. *European Urology* 2010;58:398-406.

5. Escudier B, Kataja V, ESMO Guidelines Working Group. Renal Cell Carcinoma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Annals of Oncology* 2010;21:v137-v139.

6. Canadian Kidney Cancer Forum. Management of kidney cancer: Canadian Kidney Cancer Forum Consensus Update. *Canadian Urological Association Journal* 2009;3:200-4.

7. Australian Institute of Health and Welfare (AIHW). Australian Cancer Incidence and Mortality (ACIM) books. AIHW . 2011. 16-8-2011.
Ref Type: Electronic Citation

8. National Cancer Institute and Surveillance, Epidemilogy and End Results SEER Program. Surveillance, Epidemiology and End Results (SEER) Program SEER*Stat Database: Incidence - SEER 17 Regs Research Data, Nov 2009 Sub (1973-2007 varying) - Linked to county attributes- Total US., 1969-2007 Counties. 2010.
Ref Type: Data File

9. Aben KKH, Heskamp S, Janssen-Heijnen ML, et al. Better survival in patients with metastasised kidney cancer after nephrectomy: a population-based study in the Netherlands. *Eur J Cancer* 2011;47:2023-32.

10. Woodward E, Jagdev S, McParland L, et al. Skeletal complications and survival in renal cancer patients with bone metastases. *Bone* 2011;48:160-6.

11. Wersall PJ, Blomgren H, Lax I, et al. Extracranial stereotactic radiotherapy for primary and metastatic renal cell carcinoma. *Radiotherapy and Oncology* 2005;77:88-95.

12. Campbell SC, Novick AC. Management of local recurrence following radical nephrectomy or partial nephrectomy. *Urol Clin North Am* 1994;21:593-9.

13. Ljungberg B, Alamdari FI, Rasmuson T, Roos G. Follow-up guidelines for nonmetastatic renal cell carcinoma based on the occurrence of metastases after radical nephrectomy. *BJU International* 1999;84:405-11.

LEUKAEMIA

We reviewed evidence-based treatment guidelines for Lymphoid and Myeloid leukaemia. Childhood and adult acute lymphoblastic leukaemia (ALL), chronic lymphocytic leukaemia (CLL), acute myeloid leukaemia (AML) and chronic myeloid leukaemia (CML) management guidelines published by major national and international organisations since the completion of previous radiotherapy utilisation study in July 2003 have been reviewed.

Updated Guidelines

The following new or updated guidelines were identified and reviewed:

- NCCN clinical practice guidelines for acute lymphoblastic leukaemia, Version 1, 2012 (1)
- NCI PDQ on childhood acute lymphoblastic leukaemia, 2012 (2)
- NCI PDQ on adult acute lymphoblastic leukaemia, 2012 (3)
- Polish Adult Leukaemia Group guideline on prophylactic treatment of central nervous system (4)
- NICE guideline on haematological cancers, 2003 (5)
- German Registry for Stem Cell Transplantation guideline, 2006 (6)
- British Society of Haematology guideline on chronic lymphocytic leukaemia, 2004 (7)
- NCI PDQ on chronic lymphocytic leukaemia (8)
- NCCN clinical practice guidelines for acute myeloid leukaemia, Version 2, 2011 (9)
- NCI PDQ on childhood acute myeloid leukaemia, 2012 (10)
- NCI PDQ on adult acute myeloid leukaemia, 2012 (11)
- British Society for Haematology guideline on adult acute myeloid leukaemia, 2006 (12)
- NCI PDQ on chronic myelogenous leukaemia (13)

Indications for radiotherapy

All the indications for external beam radiotherapy in the original CCORE model of optimal radiotherapy utilisation for leukaemia have been reviewed and updated in the optimal utilisation tree based on the latest guideline recommendations (Table 1 and Figure 1). As the model has been revised substantially, the tree is newly designed and **NOT** an update of the previous one.

According to the latest clinical practice guidelines, radiotherapy is recommended for leukaemia with central nervous system (CNS) involvement and as conditioning treatment, commonly known as Total Body Irradiation (TBI), prior to hematopoietic cell transplantation (HCT) in suitable patients diagnosed with lymphoid and myeloid leukaemia.

The model has been updated as follows:

1. *Based on radiotherapy recommendation for leukaemia, clinical scenarios have been modified in the model.*
2. *Radiotherapy is now only indicated in some cases of acute childhood leukaemia where central nervous system (CNS) involvement is present at diagnosis; routine prophylactic cranial irradiation is no longer recommended because of its long term effect on growth and neurological impairment and use of intrathecal chemotherapy as a substitute (2;10).*
3. *Radiotherapy is still a major treatment option for adult CNS leukaemia at diagnosis or relapse (1;3;9;11)*
4. *Prophylactic cranial irradiation is recommended as a CNS prophylaxis for a tiny proportion of patients with adult ALL but the use is restricted to only the group resistant to intrathecal treatment (1;4); this indication is not included in our model because of lack of epidemiological evidence.*
5. *TBI continues to be a key part of the conditioning regimen in acute lymphoid and myeloid leukaemia at complete remission or relapse after remission (6) in younger patients <60 years of age.*
6. *TBI is usually combined with high dose chemotherapy to maximise the conditioning effect and is not generally recommended for elderly patients aged >65 years with acute lymphocytic leukaemia (ALL) and aged >60 years with acute myeloid leukaemia (AML) (1;9) who generally are not suitable candidates for HCT because of their poor physical condition and comorbidities.*
7. *There is no radiotherapy treatment recommendation for chronic lymphocytic leukaemia (CLL) as this disease is generally not curable, occurs in an elderly population, and often progresses slowly and hence, most often treated in a conservative fashion with watchful observation (7;8).*
8. *Occasionally, involved field radiotherapy is used for CLL with large nodal mass or with splenic involvement (8) but the proportion of CLL patients who are recommended with this option was hard to estimate because of lack of suitable epidemiological data. Hence, this indication is not included in our model.*
9. *There is no recommendation for TBI in patients with chronic myeloid leukaemia (CML) as these patients usually are not eligible for HCT approach because of age, comorbid conditions, lack of suitable donors as well as the risk of substantial morbidity and mortality resulting from HCT (13).*

Level of evidence

According to the methods applied for the previous radiotherapy utilisation model, the indications of radiotherapy for leukaemia have been derived from evidence-based treatment guidelines issued by major national and international organisations. The guidelines reviewed are those published after the previous radiotherapy utilisation study was completed (July 2003) up to 2011.

In the Lymphoid Leukaemia model, 5 of 14 outcomes have an indication of radiotherapy (Figure 1) and all are supported by level III evidence representing half (2%) of the population with leukaemia that require RT (Table I).

In the Myeloid Leukaemia model, 3 of 9 outcomes have an indication of radiotherapy (Figure 1); all of the indications are supported by level III evidence representing 2% population with leukaemia requiring RT (Table 1).

Epidemiology of cancer stages

The epidemiological data in the Leukaemia utilisation tree have been reviewed to see if more recent data are available through extensive electronic search using the key words 'acute leukaemia', 'Australia', 'epidemiology', 'incidence', 'myeloid leukaemia', 'lymphoid/lymphoblastic/lymphocytic leukaemia', 'radiotherapy treatment', 'recurrence', 'relapse', 'remission', 'survival', 'total body irradiation (TBI), 'treatment outcome' in various combinations. Since the completion of the previous radiotherapy utilisation project the national data on cancer statistics published by AIHW have been updated to 2008 (14). In 2008, leukaemia accounted for 2% of all cancers in Australia (14). The detailed epidemiological evidence for the current model has been adopted according to the literature published in the recent years (Table 2).

Estimation of the optimal radiotherapy utilisation

From the evidence on the efficacy of radiotherapy and the most recent epidemiological data on the occurrence of indications for radiotherapy, the proportion of leukaemia patients in whom radiotherapy would be recommended is 4% (Table 1 and Figure 1); the proportion remain unchanged as compared with the original estimate of 4%.

The optimal radiotherapy utilisation rates for different subtypes of leukaemia (Figure 1) are as follows

- For childhood ALL 15%
- For adult ALL 25%
- For childhood AML 2% and
- For adult AML 4%

The radiotherapy utilisation model has been revised as follows

1) Update of epidemiological data for all indications with most up-to-date data from AIHW (14), and various recently published multinational studies, some of them from Australia (15;16).
2) Indication for CNS leukaemia has been revised both for ALL and AML
3) TBI indication prior to bone marrow transplantation in eligible patients remain unchanged both for ALL and AML

Estimation of the optimal combined radiotherapy and chemotherapy utilisation

The indications of radiotherapy for leukaemia were reviewed to identify those indications where radiotherapy is recommended in conjunction with concurrent chemotherapy as the first treatment. According to the best available practice evidence there are no indications identified for which concurrent chemoradiation is beneficial as the first indicated treatment.

Sensitivity analysis

Univariate sensitivity analysis has been undertaken to assess changes in the recommended leukaemia radiotherapy utilisation rate that would result from different estimates of the proportions of patients with particular attributes as mentioned in Table 2. Epidemiological data for relapse of childhood ALL has been adopted from review of multicentre clinical trials in USA and Europe where the results varied (12%-46%) because of variable selection criteria of the trials (17) (table 2) but preference for our model has been given to the patterns of care study (15) that included data from Australia. Similarly, for epidemiological data of AML with complete remission and relapse, numerous clinical trials data exist with variable results, thus we have recorded the range (43%-70%) of proportions published in high quality systematic reviews with individual patient data (18;19). The variability in the estimate of optimal radiotherapy utilisation due to these uncertainties was 1% and the expected value ranged from 3.4% to 4.7% as shown in the Tornado diagram (Figure 2).

Table 1: Leukaemia. Indications for radiotherapy - Levels and sources of evidence

Outcome No. in Tree	Clinical Scenario	Guideline updated	Level of evidence	Proportion of all leukaemia patients	References
1	ALL, Children <15 years, CNS involvement at diagnosis	Yes	III	<0.01	NCCN (1) , NCI (2)
2	ALL, Children <15 years, CNS/testicular relapse	Yes	III	0.01	NCCN (1), NCI (2)
3	ALL, Children <15 years, bone marrow relapse, bone marrow relapse, HLA compatible donor	Yes	III	<0.01	NCCN (1), NCI (2), German guidelines (6), NICE (5)
7	ALL, adults, <65 years, CNS involvement at diagnosis or relapse	Yes	III	<0.01	NCCN (1), NCI (3)
8	ALL, adults, <65 years, no CNS involvement, complete remission, relapse, HLA compatible donor	Yes	III	<0.01	NCCN (1), NCI (3)
10	ALL, adults, <65 years, no CNS involvement, complete remission, no relapse, HLA compatible donor	Yes	III	0.01	NCCN (1), NCI (3), DRST (6), NICE (5)
15	AML, children <15 years, CNS involvement at diagnosis	Yes	III	<0.01	NCCN (9), NCI (10)
17	AML, adults, <65 years, CNS involvement at diagnosis or relapse	Yes	III	<0.01	NCCN (9), NCI (11)

Outcome No. in Tree	Clinical Scenario	Guideline updated	Level of evidence	Proportion of all leukaemia patients	References
18	AML, adults, no CNS involvement, <60 years, complete remission, relapse, HLA compatible donor	Yes	III	0.01	NCCN (9), NCI (11), DRST (6), British Society of Haematology (12)
Updated proportion of all leukaemia patients in whom radiotherapy is recommended				**0.039 (4%)**	
Original proportion of all leukaemia patients in whom Radiotherapy is recommended				0.042 (4%)	

Table 2: Leukaemia; The incidence of attributes used to define indications for radiotherapy

Population or subpopulation of interest	Attribute	Proportion of population with the attribute	Quality of Information	References	Comments
All Cancers	Leukaemia	0.02	α	**AIHW 2008 (14)**	
All leukaemia	Lymphoid leukaemia Myeloid leukaemia	0.54 0.46	α	AIHW 2008 (14)	
Lymphoid leukaemia	Acute lymphoblastic leukaemia (ALL) Chronic lymphocytic leukaemia	0.23 0.77	α	AIHW 2008 (14)	
Acute lymphoblastic leukaemia (ALL)	Children <15 years	0.53	α	AIHW 2008 (14)	
ALL, Children <15 years	CNS involvement at diagnosis	0.03 (range 0.03-0.07)	θ	Pui and Howard 2008 (17)	CNS involvement at presentation in multiple trials of U.S. and Canadian clinical trial cooperative group (CCG), range included in sensitivity analysis

Population or subpopulation of interest	Attribute	Proportion of population with the attribute	Quality of Information	References	Comments
ALL, Children <15 years	Any relapse	0.23 (range 0.12-0.46)	λ θ	Forward et al 2010 (15) Pui and Howard 2008 (17)	Australian patterns of care study on childhood ALL (Forward et al) selected for the model, range from CCG included in sensitivity analysis
ALL, Children <15 years, relapse	Bone marrow relapse	0.53	ε	Van den Berg et al 2011 (20)	Dutch multi-institutional study
ALL, Children <15 years, bone marrow relapse	Early relapse	0.63	ε	Van den Berg et al 2011 (20)	
ALL, Children <15 years, bone marrow relapse, early relapse	HLA compatible donor	0.23	ε	Van den Berg et al 2011 (20)	
ALL, adults 15+ years	<65 years	0.81	β	AIHW 2008 (14)	
ALL, adults, <65 years	CNS involvement at diagnosis or relapse	0.10	θ	Reman et al 2008 (21)	French Multi- institutional study
ALL, adults, <65 years, no CNS involvement	Complete remission	0.91	θ	Fielding et al 2007 (22)	

Population or subpopulation of interest	Attribute	Proportion of population with the attribute	Quality of Information	References	Comments
ALL, adults, <65 years, no CNS involvement, complete remission	Relapse	0.44	θ	Fielding et al 2007 (22)	
ALL, adults, <65 years, no CNS involvement, complete remission, relapse	HLA compatible donor	0.20	θ	Fielding et al 2007 (22)	
ALL, adults, <65 years, no CNS involvement, , complete remission	HLA compatible donor	0.30	θ	Goldstone et al 2008 (23)	
Myeloid leukaemia	Acute myeloid leukaemia (AML) Chronic myeloid leukaemia	0.66 0.34	α	AIHW 2008 (14)	
AML	Children <15 years	0.05	α	AIHW 2008 (14)	
AML, children <15 years	CNS involvement at diagnosis	0.02	θ	Pui and Howard 2008 (17)	

Population or subpopulation of interest	Attribute	Proportion of population with the attribute	Quality of Information	References	Comments
AML, adults 15+ years	<60 years	0.34	α	AIHW 2008 (14)	
AML, adults, <60 years	CNS involvement at diagnosis or relapse	0.03	λ	Shihadeh et al 2012 (24)	Large retrospective study from The University of Texas MD Anderson Cancer Centre
AML, adults, <60 years, no CNS involvement	Complete remission (CR)	0.67 0.50 - 0.70	 θ	Shihadeh et al 2012 (24) Kimby et al 2001 (19)	Large single centre data that fitted well with the clinical scenario of CR without CNS involvement Swedish multi-centre review study
AML, adults, no CNS involvement, <60 years, complete remission	Relapse	0.60 0.43	θ θ	Buyse et al 2011 (18) Breems et al 2005 (25)	Individual patient data meta-analysis from trials in Europe and USA European Haematology Cooperative group trials review
AML, adults, no CNS involvement, <60 years, complete remission, relapse	HLA compatible donor	0.24	θ	Nivision-Smith et al 2011 (16)	Australia/New Zealand study with data from Australasian Bone Marrow Transplant Recipient Registry (ABMTRR)

Figure 1. Leukaemia Radiotherapy Utilization Tree

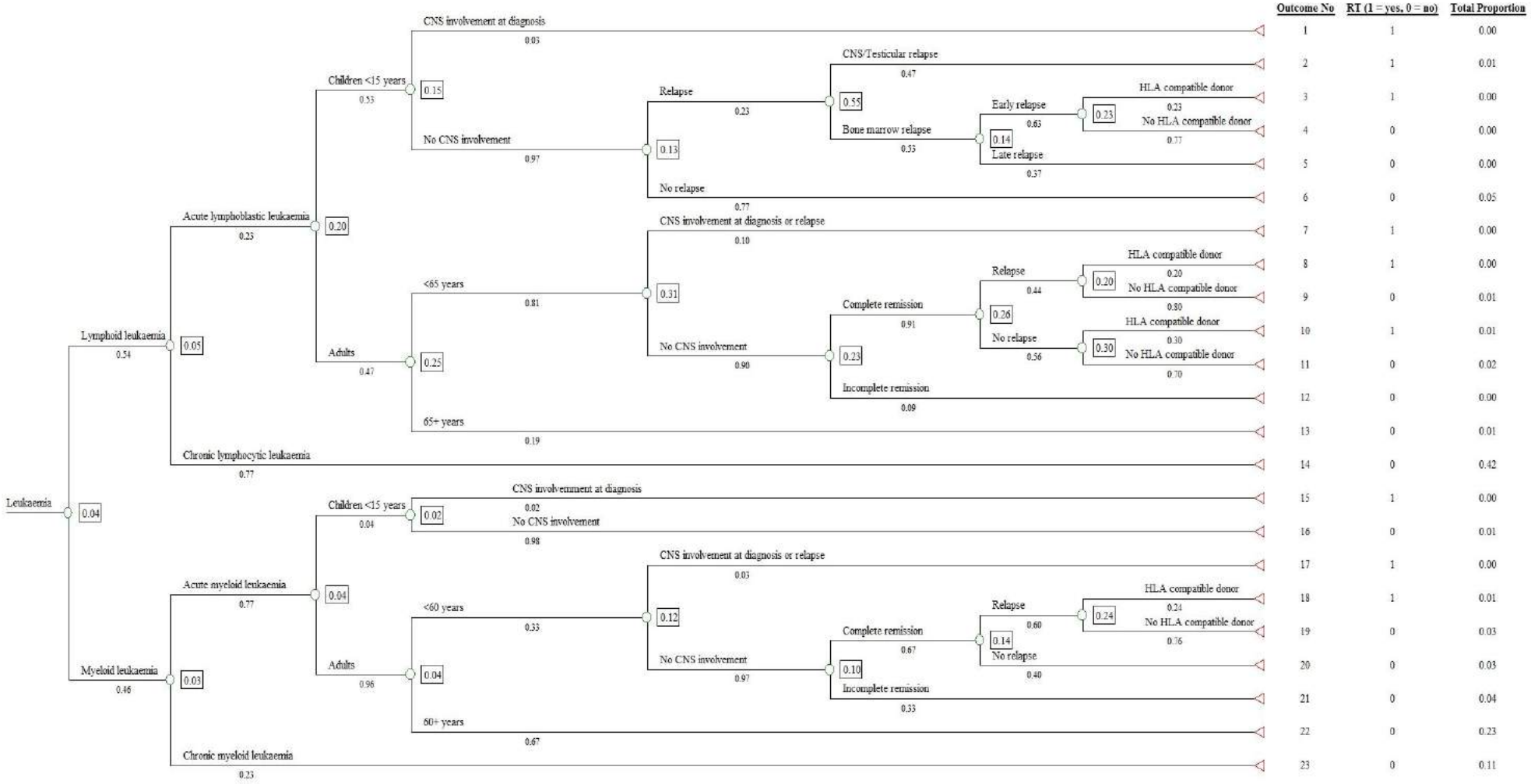
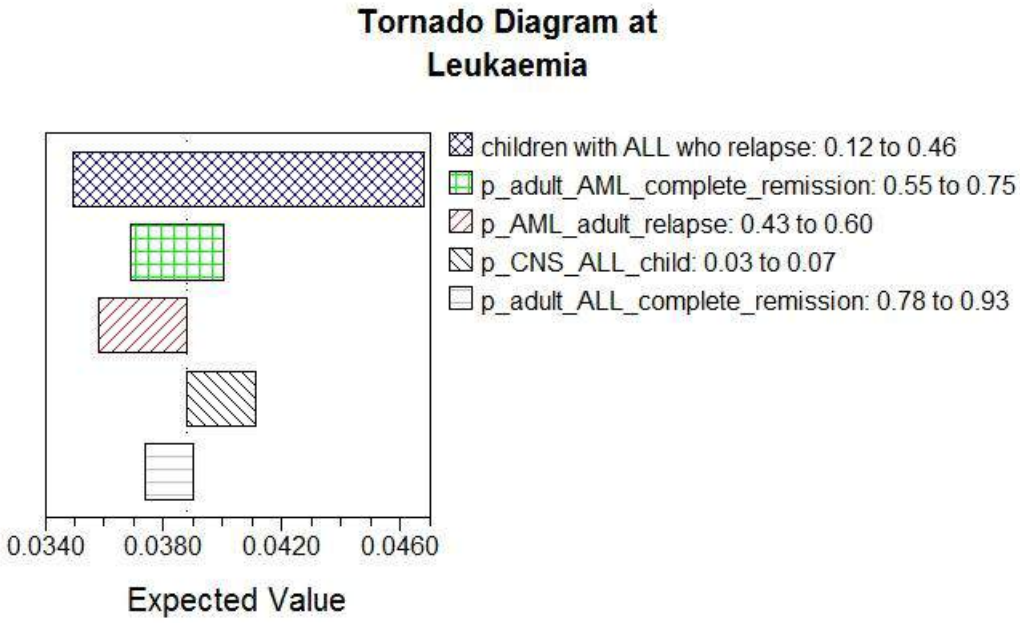


Figure 2. Tornado diagram for univariate sensitivity analyses



References

1. National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology: Acute Lymphoblastic Leukemia. Version 1.2012. 2012.

2. National Cancer Institute (NCI). Childhood Acute Lymphoblastic Leukemia Treatment (PDQ®). Available from: http://www cancer gov/cancertopics/pdq/treatment/childALL/HealthProfessional 2012 [cited 2012 Mar 15];

3. National Cancer Institute (NCI). Adult Acute Lymphoblastic Leukemia Treatment (PDQ®). Available from: http://www cancer gov/cancertopics/pdq/treatment/adultALL/HealthProfessional 2012 [cited 2012 Mar 15];

4. Giebel S, Krawczyk-Kulis M, mczyk-Cioch M, Czyz A, Lech-Maranda E, Piatkowska-Jakubas B, et al. Prophylaxis and therapy of central nervous system involvement in adult acute lymphoblastic leukemia: recommendations of the Polish Adult Leukemia Group. Pol Arch Med Wewn 2008 Jun;118(6):356-61.

5. National Institute for Clinical Excellence (NICE). Improving Outcomes in Haematological Cancers. Haematological cancers service guidance. London; 2003.

6. Heinzelmann F, Ottinger H, Muller CH, Allgaier S, Faul C, Bamberg M, et al. Total-body irradiation--role and indications: results from the German Registry for Stem Cell Transplantation (DRST). Strahlenther Onkol 2006 Apr;182(4):222-30.

7. British Society for Haematology. Guidelines on the diagnosis and management of chronic lymphocytic leukaemia. British Journal of Haematology 2004;125:294-317.

8. National Cancer Institute (NCI). Chronic Lymphocytic Leukemia Treatment (PDQ®). Available from: http://www cancer gov/cancertopics/pdq/treatment/CLL/healthprofessional 2012 [cited 2012 Mar 15];

9. National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology: Acute Myloid Leukemia.Version 2.2011. 2011.

10. National Cancer Institute (NCI). Childhood Acute Myeloid Leukemia/Other Myeloid Malignancies Treatment (PDQ®). Available from: http://www cancer gov/cancertopics/pdq/treatment/childAML/HealthProfessional 2012 [cited 2012 Mar 15];

11. National Cancer Institute (NCI). Adult Acute Myeloid Leukemia Treatment (PDQ®). Available from: http://www cancer gov/cancertopics/pdq/treatment/adultAML/healthprofessional 2012 [cited 12 A.D. Mar 15];

12. British Committee for Standards in Haematology. Guidelines on the management of acute myeloid leukaemia in adults. British Journal of Haematology 2012;135:450-74.

13. National Cancer Institute (NCI). Chronic Myelogenous Leukemia Treatment (PDQ®). Available from: http://www cancer gov/cancertopics/pdq/treatment/CML/HealthProfessional 2012 [cited 2012 Mar 15];

14. Australian Institute of Health and Welfare (AIHW). Australian Cancer Incidence and Mortality (ACIM) books. Available from: http://www aihw gov au/acim-books/ 2011 [cited 2011 Aug 16];

15. Forward H, Zheng GC, Cole CH. Twenty-five years of treatment for childhood acute lymphoblastic leukaemia in Western Australia: how do we compare? Med J Aust 2010 Nov 15;193(10):585-9.

16. Nivison-Smith I, Dodds AJ, Dunckley H, Ma DD, Moore JJ, Simpson JM, et al. Increased activity and improved outcome in unrelated donor haemopoietic cell transplants for acute myeloid leukaemia in Australia, 1992-2005. Intern Med J 2011 Jan;41(1a):27-34.

17. Pui CH, Howard SC. Current management and challenges of malignant disease in the CNS in paediatric leukaemia. Lancet Oncol 2008 Mar;9(3):257-68.

18. Buyse M, Squifflet P, Lange BJ, Alonzo TA, Larson RA, Kolitz JE, et al. Individual patient data meta-analysis of randomized trials evaluating IL-2 monotherapy as remission maintenance therapy in acute myeloid leukemia. Blood 2011 Jun 30;117(26):7007-13.

19. Kimby E, Nygren P, Glimelius B. A systematic overview of chemotherapy effects in acute myeloid leukaemia. Acta Oncol 2001;40(2-3):231-52.

20. van den BH, de Groot-Kruseman HA, men-Korbijn CM, de Bont ES, Schouten-van Meeteren AY, Hoogerbrugge PM. Outcome after first relapse in children with acute lymphoblastic leukemia: a report based on the Dutch Childhood Oncology Group (DCOG) relapse all 98 protocol. Pediatr Blood Cancer 2011 Aug;57(2):210-6.

21. Reman O, Pigneux A, Huguet F, Vey N, Delannoy A, Fegueux N, et al. Central nervous system involvement in adult acute lymphoblastic leukemia at diagnosis and/or at first relapse: results from the GET-LALA group. Leuk Res 2008 Nov;32(11):1741-50.

22. Fielding AK, Richards SM, Chopra R, Lazarus HM, Litzow MR, Buck G, et al. Outcome of 609 adults after relapse of acute lymphoblastic leukemia (ALL); an MRC UKALL12/ECOG 2993 study. Blood 2007 Feb 1;109(3):944-50.

23. Goldstone AH, Richards SM, Lazarus HM, Tallman MS, Buck G, Fielding AK, et al. In adults with standard-risk acute lymphoblastic leukemia, the greatest benefit is achieved from a matched sibling allogeneic transplantation in first complete remission, and an autologous transplantation is less effective than conventional consolidation/maintenance chemotherapy in all patients: final results of the International ALL Trial (MRC UKALL XII/ECOG E2993). Blood 2008 Feb 15;111(4):1827-33.

24. Shihadeh F, Reed V, Faderl S, Medeiros LJ, Mazloom A, Hadziahmetovic M, et al. Cytogenetic profile of patients with acute myeloid leukemia and central nervous system disease. Cancer 2012 Jan 1;118(1):112-7.

25. Breems DA, Van Putten WL, Huijgens PC, Ossenkoppele GJ, Verhoef GE, Verdonck LF, et al. Prognostic index for adult patients with acute myeloid leukemia in first relapse. J Clin Oncol 2005 Mar 20;23(9):1969-78.

LIVER CANCER

Evidence-based treatment guidelines for liver cancer management issued by major international, national and provincial organisations reviewed for the model are those published after the previous radiotherapy utilisation study was completed (July 2003) up to the most recent ones published in 2012.

Updated Guidelines

The following new or updated guidelines were identified and reviewed since the original RTU study:

- NCCN clinical practice guidelines on hepatobiliary cancers (version 2.2012) (1)
- NCI PDQ guidelines on adult primary liver cancer (2012) (2)
- BC Cancer Agency gastrointestinal cancer management guidelines (liver) (2012) (3)
- ESMO clinical practice guidelines on hepatocellular carcinoma (2010) (4)

Indications for Radiotherapy

There were no indications for external beam radiotherapy in the original CCORE model of optimal radiotherapy utilisation for liver cancer according to evidence-based clinical guidelines available at the time.

The current NCCN guidelines (1) state that there is growing evidence supporting the usefulness of conformal or stereotactic body radiation therapy for patients with unresectable liver cancer, and that prospective clinical trials evaluating the role of stereotactic body radiation therapy are encouraged. The guidelines recommend that radiotherapy can be considered as an alternative to ablation or embolisation techniques or when these therapies have failed in patients with unresectable disease and those with local disease only who are not operable due to performance status or comorbidity. This recommendation has been classified as a category 2B recommendation (based on lower level evidence, with non-uniform NCCN consensus). The NCI guidelines (2) mention that surgery, chemotherapy and radiotherapy may be combined in clinical trials for patients with a dominant hepatic mass and multifocal involvement with small amounts of tumour. The BC Cancer Agency guidelines (3) state that radiotherapy is generally not used to treat hepatocellular carcinoma, and that conformal radiotherapy is being evaluated. The ESMO guidelines (4) state that management of patients with invasion of the portal vein or inferior vena cava is debatable, and that conformal radiotherapy is one of the investigational but clinically applicable options for selected patients.

According to the current clinical guidelines, the role of radiotherapy remains not well established. Therefore there are no indications for external beam radiotherapy in the updated model of optimal radiotherapy utilisation for liver cancer.

Changes to Epidemiological Data

Since the completion of the previous radiotherapy utilisation project the national data on cancer statistics published by AIHW have been updated to more recent years till 2008 (5). In 2008, liver cancer accounted for 1.2% of all cancers in Australia.

References

1. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Hepatobiliary Cancers Version 2.2012: www.nccn.org; 2012. Accessed 28/8/2012.

2. National Cancer Institute. PDQ Summary: Adult Primary Liver Cancer Treatment: www.cancer.gov; 2012. Accessed 28/8/2012.

3. British Columbia Cancer Agency. Cancer Management Guidelines: Gastrointestinal Cancer (Liver): www.bccancer.bc.ca; 2012. Accessed 28/08/2012.

4. Jelic S, Sotiropoulos GC. Hepatocellular carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2010;21 Suppl 5:v59-64.

5. Australian Institute of Health and Welfare (AIHW). Australian Cancer Incidence and Mortality (ACIM) books. : www.aihw.gov.au/acim-books/; 2012. Accessed 29/08/2012.

LUNG CANCER

In the original radiotherapy utilisation model the indications for radiotherapy for lung cancer were derived from evidence-based treatment guidelines issued by major national and international organisations. The guidelines reviewed for the updated model are those published after the previous radiotherapy utilisation study was completed (July 2003) up to the most recent ones published in 2011.

Updated Guidelines

The following new or updated guidelines were identified and reviewed since the original RTU study:

- National Health and Medical Research Council (NHMRC). Clinical practice guidelines for the prevention, diagnosis and management of lung cancer, 2004 (1)
- National Comprehensive Cancer Network (NCCN). Clinical practice guidelines in oncology: Small cell lung cancer. Version 2.2011 (2)
- National Comprehensive Cancer Network (NCCN). Clinical practice guidelines in oncology: Non-Small cell lung cancer. Version 3.2011 (3)
- National Institute for Health and Clinical Excellence (NICE). The diagnosis and treatment of lung cancer. NICE clinical guideline 121, 2011 (4)
- British Columbia cancer Agency (BCCA). Cancer management guidelines, 2010 (5)
- Scottish Intercollegiate Guidelines Network (SIGN). Management of patients with lung cancer: A national clinical guideline, 2005 (6)
- Lim E, et al. Guidelines on the radical management of patients with lung cancer. A joint initiative by the British Thoracic Society and the Society for Cardiothoracic Surgery in Great Britain and Ireland, 2010 (7)
- Treatment of non-small cell lung cancer stage I and stage II: ACCP evidence-based clinical practice guidelines (2nd edition), 2007 (8)
- Management of unresected stage Ill non-small cell lung cancer: A clinical practice guideline. Evidence-based Series #7-3 (Version 2.2005): Section 1. A Quality Initiative of the Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO), 2006 (9)
- Small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up, 2010 (10)
- Early stage and locally advanced (non-metastatic) non-small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up, 2010 (11)

Indications for radiotherapy

All the indications for external beam radiotherapy in the original CCORE model of optimal radiotherapy utilisation for lung cancer have been reviewed and updated in the optimal utilisation tree based on the latest guideline recommendations (Table 1). *There were no changes to the indications*

previously noted. All of the previous indications remain supported by current guidelines and no new indications are recommended.

Level of evidence

Based on recent guidelines review, the level of evidence for a number of clinical outcomes in the model has been upgraded to level II from level III-IV reported in the previous model. For example, there is now stronger level of evidence of radiotherapy recommendation for stage I-II NSCLC with positive surgical margins or no surgery as reported in USA National Comprehensive Cancer Network (NCCN) and other well respected clinical practice guidelines; these changes have been recorded in Table 1. Out of twenty two outcome branches in the model that have an indication of radiotherapy (Figure 1) 86% (19 branches) are now supported by level I-II evidence compared to 55% reported in the earlier model; the current model predicts that 70% of lung cancer population have level I or II evidence of benefit from radiotherapy if treated according to evidence-based guidelines; in other words, if the proportion of lung cancer population with an indication of radiotherapy is considered to be 100% than for 91% the recommendation is supported by Level I-II evidence. The small proportions of indications supported by lower level of evidence are those for the treatment of positive margins or symptomatic local or distant recurrence with poor performance status.

Epidemiology of cancer stages

The epidemiological data in the lung cancer utilisation tree have been reviewed to see if more recent data are available through extensive electronic search using the key words 'Australia', 'epidemiology lung cancer', 'incidence', 'lung cancer stage', 'radiotherapy treatment', 'recurrence', 'treatment outcome' in various combinations. This has been applied particularly to the early branches in the tree for which national or state level data on cancer incidence rates and stages are available. If there is a change in the hierarchical quality of the epidemiological data, this has also been noted (Table 2)

Since the completion of the previous radiotherapy utilisation project the national data on cancer statistics published by AIHW have been updated to more recent years till 2007 (12) and a number of population based 'patterns of care studies' for Australian lung cancer population have been published (13-16). As more national and State level recent population data are now available the epidemiological evidence for several outcome branches in the current model has been upgraded to be more representative of the Australian population.

Estimation of the optimal radiotherapy utilisation

From the evidence on the efficacy of radiotherapy and the most recent epidemiological data on the occurrence of indications for radiotherapy, the proportion of lung cancer patients in whom radiotherapy would be recommended is 77% (Table 1 and Figure 1) compared with the original estimate of 76%.

Estimation of the optimal combined radiotherapy and chemotherapy utilisation

The indications of radiotherapy for lung cancer were reviewed to identify those indications where radiotherapy is recommended in conjunction with concurrent chemotherapy as the first treatment. These combined chemotherapy and radiotherapy indications (CRT) are listed as an additional payoff in the overall utilisation tree (Table 3 and Figure 2). This identified that the optimal proportion of lung cancer patients for whom CRT is beneficial is 26% and 51% of lung cancer population would benefit from radiotherapy alone as their first indicated treatment.

Sensitivity analysis

Univariate sensitivity analysis has been undertaken to assess changes in the recommended lung cancer radiotherapy utilisation rate that would result from different estimates of the proportions of patients with particular attributes as mentioned in Table 2 (Figure 3). The variability in the estimate of optimal radiotherapy utilisation due to these uncertainties was minimal that ranged from 76.4% to 77.4% as shown in the Tornado diagram (Figure 3).

Table 1: Lung Cancer. Indications for radiotherapy - Levels and sources of evidence

Original RTU study				Updates 2011					
Outcome no. in Tree	Clinical scenario	Level of evidence	Proportion of all lung cancer	Change of indication	Guideline updated	Current level of evidence	Change to proportion of all lung cancer		References
							Yes/ No	Updated value	
1	Small-cell lung cancer, limited stage, good PS	I	0.07	No	Yes	I	Yes	0.04	NHMRC (1), NCCN SCLC (2), NICE (4), BCCA (5)
3	Small-cell lung cancer, extensive, good PS, symptomatic local disease	III	0.05	No	Yes	II	Yes	0.03	NHMRC (1), NCCN (2), SIGN (6)
4	Small-cell lung cancer, extensive, good PS, no local symptoms, brain metastases	II	0.01	No	Yes	II	No	0.01	NHMRC (1), NCCN (2), BCCA (5)
5	Small-cell lung cancer, extensive, good PS, no local symptoms, bone metastases	I	0.01	No	Yes	I	No	0.01	NHMRC (1), NICE (4), BCCA (5), SIGN guideline 2005 (6)
8	NSCLC, Stage I-II, Good PS, surgery, positive margins	IV	<0.01	No	Yes	III	Yes	0.01	NCCN (3), BCCA (5), BTS (7), SIGN (6)

Original RTU study				Updates 2011					
Outcome no. in Tree	Clinical scenario	Level of evidence	Proportion of all lung cancer	Change of indication	Guideline updated	Current level of evidence	Change to proportion of all lung cancer		References
							Yes/ No	Updated value	
9	NSCLC, Stage I-II, Good PS, surgery, negative margins, symptomatic local relapse	III	0.04	No	Yes	II	Yes	0.02	NHMRC (1), NCCN NSCLC (3)
11	NSCLC, Stage I-II, Good PS, surgery, negative margins, no local relapse, brain metastases	II	0.01	No	Yes	II	No	0.01	NHMRC (1), NCCN NSCLC (3), NICE (4), SIGN (6)
12	NSCLC, Stage I-II, Good PS, surgery, negative margins, no local relapse, no brain metastases, painful bone metastases	I	<0.01	No	Yes	I	Yes	0.01	NHMRC (1), NICE (4), BCCA (5), SIGN (6)
15	NSCLC, Stage I-II, Good PS, no surgery.	III	0.08	No	Yes	II	Yes	0.10	NHMRC (1), NCCN NSCLC (3), NICE (4), BCCA (5), ACCP (8), SIGN (6)

Original RTU study				Updates 2011					
Outcome no. in Tree	Clinical scenario	Level of evidence	Proportion of all lung cancer	Change of indication	Guideline updated	Current level of evidence	Change to proportion of all lung cancer		References
							Yes/ No	Updated value	
16	NSCLC, Stage I-II, Poor PS, no surgery, symptomatic local or distant relapse requiring RT	III	<0.01	No	Yes	III	Yes	**0.01**	NCCN (3), BTS (7), SIGN (6)
18	NSCLC, Stage IIIA, Good PS, surgery, N0 or N1, positive margins	IV	<0.01	No	Yes	III	No	<0.01	NCCN (3), BCCA (5), BTS (7), SIGN (6)
19	NSCLC, Stage III A, Good PS, surgery, N0 or N1, negative margins, symptomatic local relapse	III	0.01	No	Yes	II	No	**0.01**	NHMRC (1), NCCN (3)
20	NSCLC, Stage IIIA, Good PS, surgery, N0 or N1, negative margins, no local relapse, distant relapse, brain metastases	II	<0.01	No	Yes	II	No	<0.01	NHMRC (1), NCCN (3), NICE (4), SIGN (6)

Original RTU study				Updates 2011					
Outcome no. in Tree	Clinical scenario	Level of evidence	Proportion of all lung cancer	Change of indication	Guideline updated	Current level of evidence	Change to proportion of all lung cancer		References
							Yes/ No	Updated value	
21	NSCLC, Stage IIIA, Good PS, surgery, N0 or N1, negative margins, no local relapse, distant relapse, no brain metastases, painful bone metastases	I	<0.01	No	Yes	I	No	<0.01	NHMRC (1), NICE (4), BCCA (5), SIGN (6)
25	NSCLC, Stage IIIA, Good PS, surgery, N2 disease	II	0.01	No	Yes	II	No	**0.01**	NCCN (3), BCCA (5)
26	NSCLC, Stage IIIA, Good PS, no surgery	II	0.10	No	Yes	II	Yes	**0.09**	NHMRC (1), NCCN (3), CCO (9), SIGN (6)
27	NSCLC, Stage III A, Poor PS, no surgery, local or distant symptoms requiring RT	III	<0.01	No	Yes	II	No	<0.01	CCO (9)
29	NSCLC, Stage IIIB, good PS	II	0.13	No	Yes	**II**	Yes	**0.12**	NCCN (3), SIGN (6)

Original RTU study				Updates 2011					
Outcome no. in Tree	Clinical scenario	Level of evidence	Proportion of all lung cancer	Change of indication	Guideline updated	Current level of evidence	Change to proportion of all lung cancer		References
							Yes/ No	Updated value	
30	NSCLC, Stage IIIB, poor PS, local symptoms	III	0.02	No	Yes	II	Yes	**0.01**	CCO (9), SIGN (6)
32	NSCLC, Stage IV, symptomatic local disease	III	0.19	No	Yes	II	Yes	**0.25**	NHMRC (1), NCCN (3), SIGN (6)
33	NSCLC, Stage IV, no local symptoms, brain metastases	II	0.02	No	Yes	II	No	**0.02**	NHMRC (1), NCCN (3), NICE (4), SIGN (6)
34	NSCLC, Stage IV, no local symptoms, no brain metastases, painful bone metastases	I	0.01	No	Yes	I	No	**0.01**	NHMRC (1), NICE (4), BCCA (5), SIGN (6)
Proportion of all lung cancer patients in whom radiotherapy is recommended			0.76 (76%)	**Updated proportion of all lung cancer patients in whom radiotherapy is recommended**				**0.77 (77%)**	

Table 2: Lung Cancer; The incidence of attributes used to define indications for radiotherapy

Original RTU study				Updates 2011				
Population or sub-population of interest	Attribute	Proportion of population with the attribute	Quality of information	Change in proportion of population with attribute Yes/ No	Altered proportion	Updated quality of information	Updated reference	Comments
All registry cancers	Lung cancer	0.1	α	Yes	0.09	α	AIHW 2010 (12)	Updated to 2007 data
All lung cancers	Small cell	0.16	β	Yes	0.15	α	NHMRC evidence based guidelines for GPs 2005 (17)	2003 national Australian data
Small cell (SC)	Limited stage	0.43	γ	Yes	0.30	β	Vinod et al 2008 (14)	NSWCCR 2001-2002
Small cell (SC) Limited stage	Good PS (ECOG 0-2)	0.94	ε	Yes	0.87	β	Vinod et al 2008 (14)	NSWCCR 2001-2002
Small cell (SC) extensive	Good PS	0.80	ε	Yes	0.62	β	Vinod et al 2008 (14)	NSWCCR 2001-2002
SC extensive, good PS	Symptomatic local disease	0.61/0.43	θ	Yes	0.52	ε	Boxer et al 2011 (18)	

Original RTU study				Updates 2011				
Population or sub-population of interest	**Attribute**	**Proportion of population with the attribute**	**Quality of information**	**Change in proportion of population with attribute Yes/ No**	**Altered proportion**	**Updated quality of information**	**Updated reference**	**Comments**
SC, extensive, good PS, no local symptoms	Brain metastases	0.49 0.27	ζ ζ	Yes	0.26 0.16	ζ θ	Seute et al 2004 (19) Bremnes et al 2003 (20)	
SC, extensive, good PS, no local symptoms, no brain metastases	Bone metastases	0.26	θ	Yes	0.34	θ	Bremnes et al 2003 (20)	
NSCLC	Stage I-II	0.33	ε	Yes	0.31	β	Vinod et al 2008 (14)	NSWCCR 2001-2002
NSCLC, Stage I-II	Good PS	0.90	ε	Yes	0.82	β	Vinod et al 2008 (14)	NSWCCR 2001-2002
NSCLC, Stage I-II, Good PS	Surgery	0.68	γ	Yes	0.52	β	Vinod et al 2008 (14)	NSWCCR 2001-2002
NSCLC, Stage I-II, Good PS, Surgery	Positive margins	0.02 0.005	ζ	Yes	0.05	ε	Wind et al 2007 (21)	

Original RTU study				Updates 2011				
Population or sub-population of interest	**Attribute**	**Proportion of population with the attribute**	**Quality of information**	**Change in proportion of population with attribute Yes/ No**	**Altered proportion**	**Updated quality of information**	**Updated reference**	**Comments**
NSCLC, Stage I-II, Good PS, Surgery, negative margins	Symptomatic local relapse	0.23 0.24	λ λ	No	N/A	N/A	Van Houtte et al 1980 (22) Kelsey et al 2009 (23) Verlotto et al 2009 (24)	
NSCLC, Stage I-II, Good PS, Surgery, negative margins, no local relapse	Distant relapse	0.27 0.32	λ λ	Yes	0.34 0.16	ζ ζ	Kelsey et al 2009 (23) Verlotto et al 2009 (24)	
NSCLC, Stage I-II, Good PS, Surgery, negative margins, no local relapse, distant relapse	Brain metastases	0.30	θ	Yes	0.24	γ	Barnholtz-Sloan et al 2004 (25)	SEER data
NSCLC, Stage I-II, Good PS, Surgery, negative margins, no local relapse, distant relapse, no brain metastases	Bone metastases	0.19	ε	Yes	0.36	ε	Coleman 2001 (26)	

Original RTU study				Updates 2011				
Population or sub-population of interest	**Attribute**	**Proportion of population with the attribute**	**Quality of information**	**Change in proportion of population with attribute Yes/ No**	**Altered proportion**	**Updated quality of information**	**Updated reference**	**Comments**
NSCLC, Stage I-II, Good PS, Surgery, negative margins, no local relapse, distant relapse, no brain metastases, bone metastases	Painful bone metastases	0.80	ζ	No	N/A	N/A	Estimated	
NSCLC, Stage I-II, Poor PS	Symptomatic local or distant disease requiring RT	0.12	ε	Yes	0.19	ζ	Reinfuss et al 2011 (27)	Recent comprehensive single institution data with large sample (n=1250)
NSCLC	Stage IIIA	0.16	ε	Yes	0.15	ε	Boxer et al 2011 (18)	SSWAHS Clinical Cancer Registry data 2005-2008

Original RTU study				Updates 2011				
Population or sub-population of interest	**Attribute**	**Proportion of population with the attribute**	**Quality of information**	**Change in proportion of population with attribute Yes/ No**	**Altered proportion**	**Updated quality of information**	**Updated reference**	**Comments**
NSCLC, Stage IIIA	Good PS	0.94	ε	Yes	0.91	ε	Boxer et al 2011 (18)	SSWAHS Clinical Cancer Registry data 2005-2008
NSCLC, Stage III A, Good PS	Surgery	0.22 0.25	γ ε	Yes	0.17	β	Hall et al 2004 (15)	WA Cancer registry linked data
NSCLC, Stage III A, Good PS, surgery	>N1	0.32	ζ	No	N/A	N/A	Mayer et al 1997 (28) Datzenberg et al 1999 (29) Feng et al 2000 (30)	
NSCLC, Stage III A, Good PS, surgery, N0 or N1	Positive margins	0.02	ζ	Yes	0.01 0.01	ζ	Massard et al 2000 (31) Lequalglie et al 2003 (32)	
NSCLC, Stage III A, Good PS, surgery, N0 or N1, negative margins	Local relapse	0.44 0.24 0.31	θ	Yes	0.38 0.09	θ	Jeremic et al review 2002 (33)	

Original RTU study				Updates 2011				
Population or sub-population of interest	**Attribute**	**Proportion of population with the attribute**	**Quality of information**	**Change in proportion of population with attribute Yes/ No**	**Altered proportion**	**Updated quality of information**	**Updated reference**	**Comments**
NSCLC, Stage III A, Good PS, surgery, N0 or N1, negative margins, no local symptoms	Distant relapse	0.37 0.32 0.42 0.59 0.45	θ	No	N/A	N/A	Van Houtte et al 1980 (22) Feng et al 2000 (30) Stephens et al 1996 (34) Mayer et al 1997 (28)	
NSCLC, Stage III A, Good PS, surgery, N0 or N1, negative margins, no local symptoms, distant relapse	Brain metastases	0.30	θ	Yes	0.24	γ	Barnholtz-Sloan et al 2004 (25)	SEER data
NSCLC, Stage III A, Good PS, surgery, N0 or N1, negative margins, distant relapse no brain metastases	Bone metastases	0.19	ε	Yes	0.36	ε	Coleman 2006 (26)	

Original RTU study				Updates 2011				
Population or sub-population of interest	**Attribute**	**Proportion of population with the attribute**	**Quality of information**	**Change in proportion of population with attribute Yes/ No**	**Altered proportion**	**Updated quality of information**	**Updated reference**	**Comments**
NSCLC, Stage III A, Good PS, surgery, N0 or N1, negative margins, no local symptoms, distant relapse, no brain metastases, bone metastases	Painful bone metastases	0.80	ζ	No	N/A	N/A	Estimated	
NSCLC, Stage IIIA, poor PS	Local or distant symptoms requiring RT	0.12	ε	Yes	0.19	ζ	Reinfuss et al 2011 (27)	Recent comprehensive single institution data with large sample (n=1250)
NSCLC	Stage IIIB	0.19	ε	Yes	0.17	ε	Boxer et al 2011 (18)	

Original RTU study				Updates 2011				
Population or sub-population of interest	**Attribute**	**Proportion of population with the attribute**	**Quality of information**	**Change in proportion of population with attribute Yes/ No**	**Altered proportion**	**Updated quality of information**	**Updated reference**	**Comments**
NSCLC, Stage IIIB	Good PS	0.84	ε	No	0.84	ε	Boxer et al 2011 (18)	SSWAHS Clinical Cancer Registry data 2005-2008;
NSCLC, Stage IIIB, poor PS	Local or distant symptoms requiring RT	0.71 0.56 0.69	λ	Yes	0.65	ε	Boxer et al 2011 (18)	SSWAHS Clinical Cancer Registry data 2005-2008
NSCLC	Stage IV	0.32	ε	Yes	0.37	β	Vinod et al 2008 (14)	NSWCR 2001-2002
NSCLC, Stage IV	Local symptoms	0.71 0.56 0.69	λ	Yes	0.79	ε	Boxer et al 2011 (18)	SSWAHS Clinical Cancer Registry data 2005-2008

Original RTU study				Updates 2011				
Population or sub-population of interest	**Attribute**	**Proportion of population with the attribute**	**Quality of information**	**Change in proportion of population with attribute Yes/ No**	**Altered proportion**	**Updated quality of information**	**Updated reference**	**Comments**
NSCLC, Stage IV, no local symptoms	Brain metastases	0.30	θ	Yes	0.28	γ	Barnholtz-Sloan et al 2004 (25)	SEER data
NSCLC, Stage IV, no local symptoms, no brain metastases	Bone metastases	0.19	ε	Yes	0.36	ε	Coleman 2001 (26)	
NSCLC, Stage IV, no local symptoms, no brain metastases, bone metastases	Painful bone metastases	0.80	ζ	No	N/A	N/A	Estimated	

Table 3: Lung Cancer. Indications for concurrent chemoradiotherapy (CRT) - Levels and sources of evidence

Outcome No. in Tree	Clinical Scenario	Level of Evidence	References	Proportion of all lung cancer patients
1	Small-cell lung cancer, limited stage, good PS	I	NCCN (2) , NICE (4), BCCA (5), ESMO (10), CCO (9), ACCP (8)	0.04
18	NSCLC, Stage IIIA, Good PS, surgery, N1, positive margins	III	NCCN (3), BCCA (5)	<0.01
25	NSCLC, Stage IIIA, Good PS, surgery, N2 disease	III	NCCN (3), BCCA (5)	0.01
26	NSCLC, Stage IIIA, Good PS, no surgery	I	NHMRC (I), NCCN (3), NICE (4), BTS (7), CCO (9), SIGN (6), ESMO 2010 (11)	0.09
29	NSCLC, Stage IIIB, good PS	I	NHMRC (I), NCCN (3), NICE (4), CCO (9), ESMO (11)	0.12
The total proportion of all patients with lung cancer in whom concurrent chemoradiotherapy (CRT) is recommended				**0.26 (26%)**

Figure 1. Lung Cancer Radiotherapy (RT) Utilisation Tree

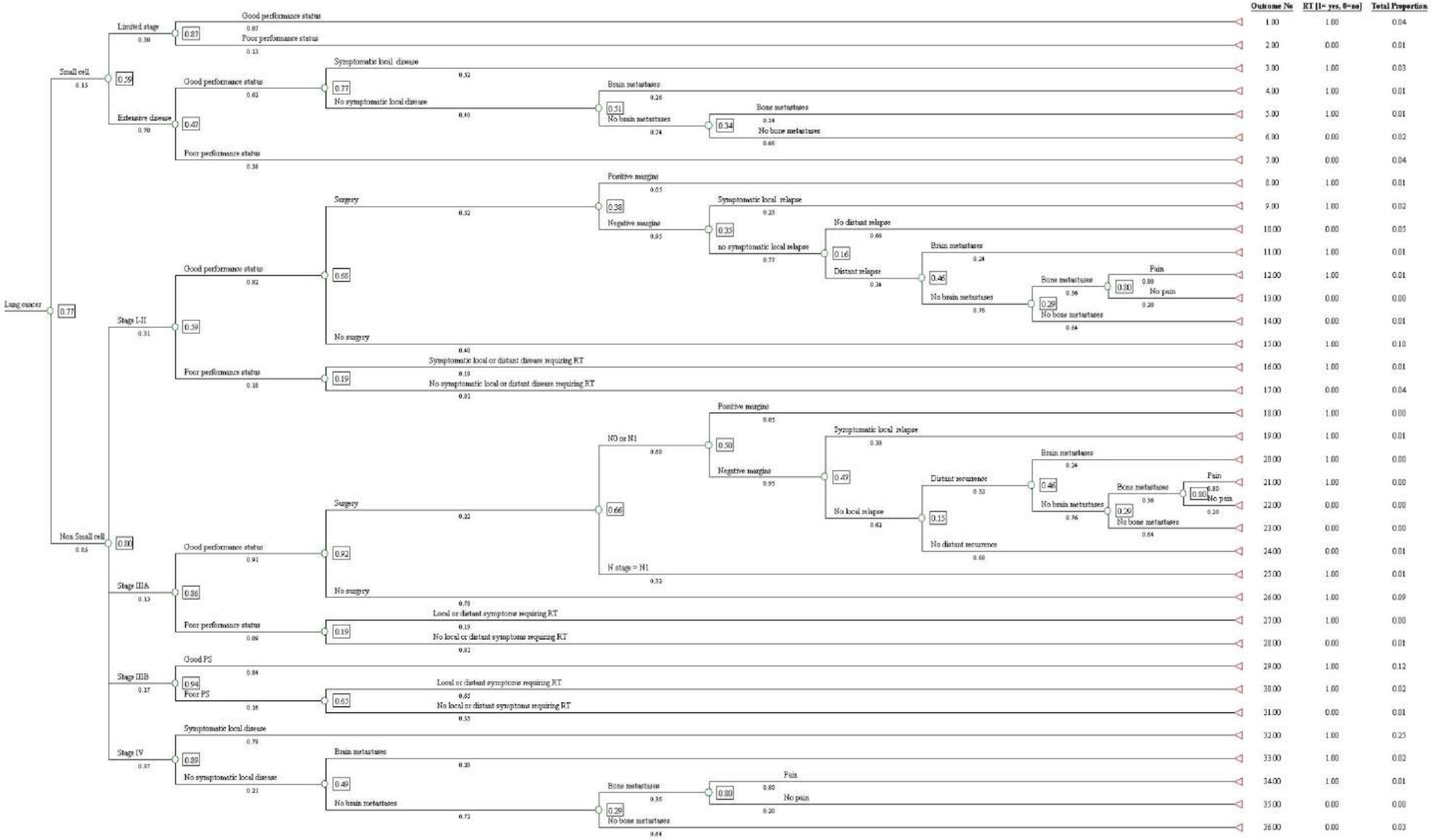


Figure 2. Lung Cancer Concurrent Chemoradiotherapy (CRT) Utilisation Tree

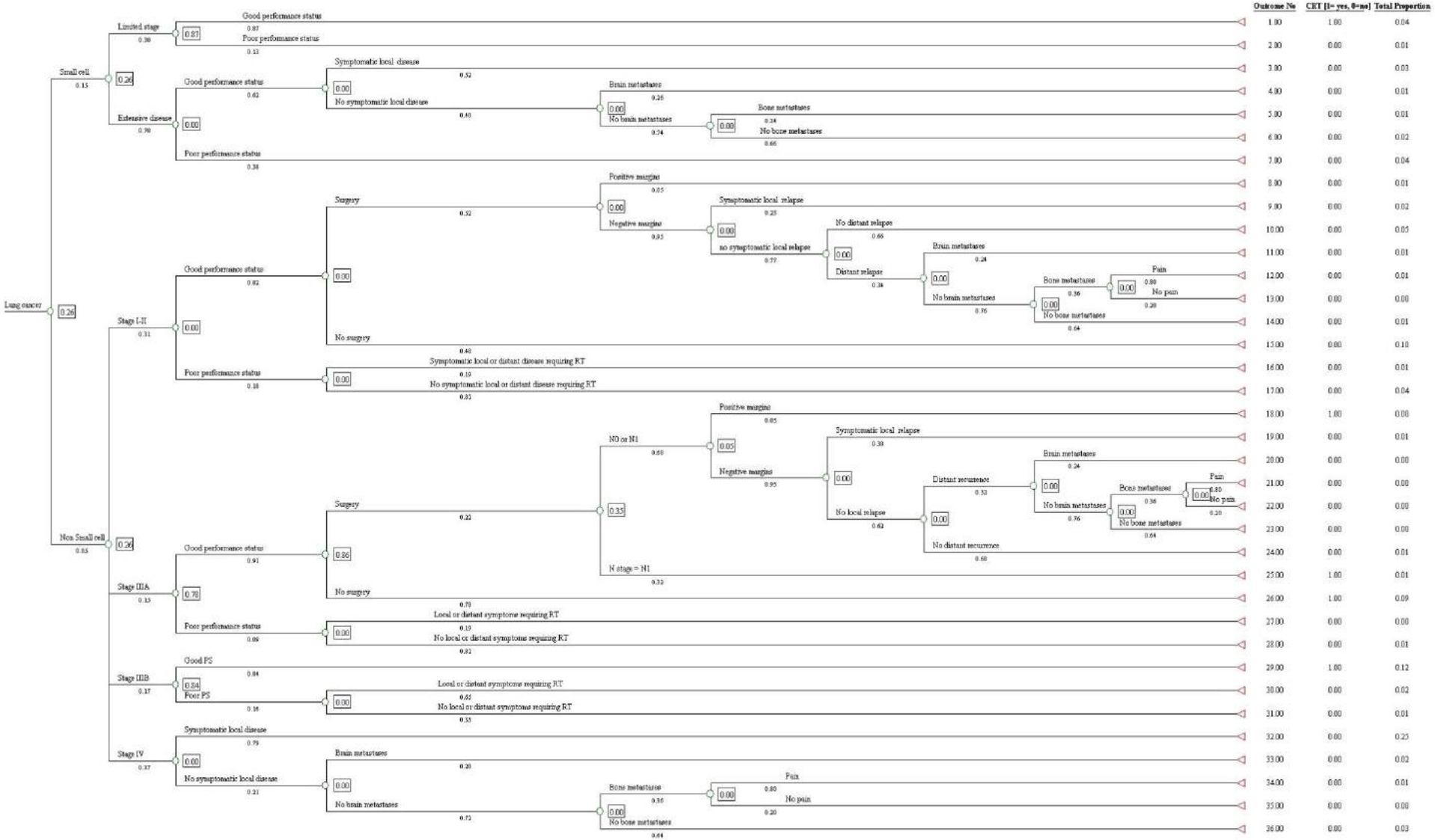
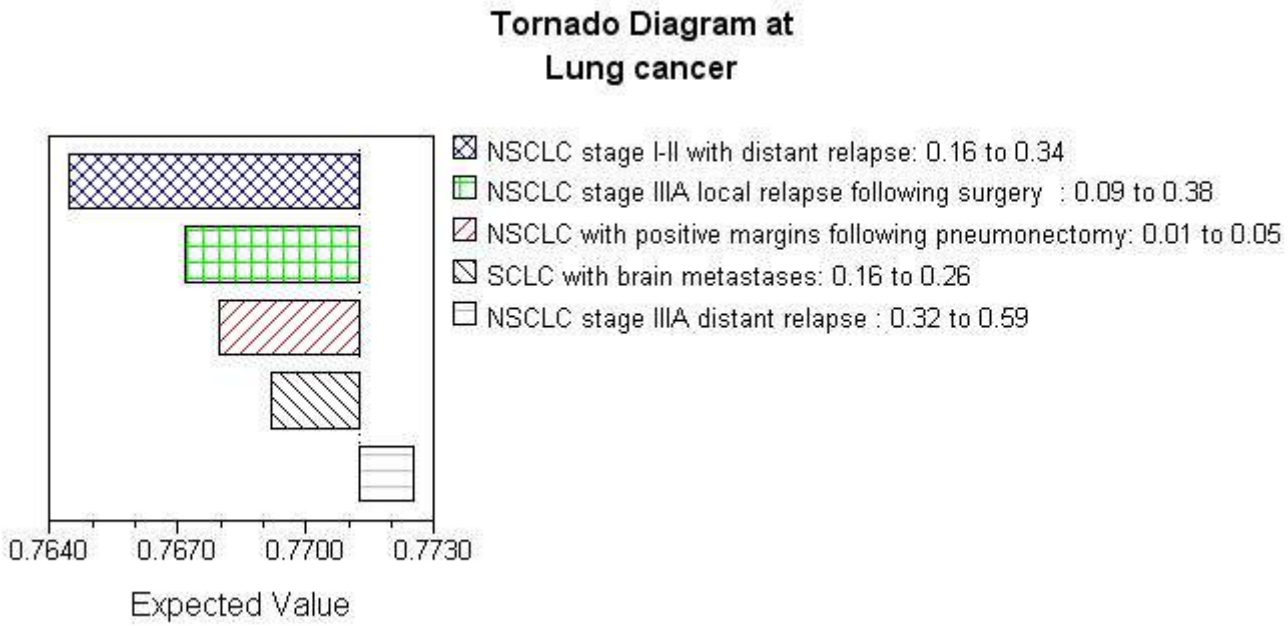


Figure 3. Tornado diagram for univariate sensitivity analyses



References

1. National Health and Medical Research Council (NHMRC). Clinical practice guidelines for the prevention, diagnosis and management of lung cancer. Sydney: Cancer Council Australia; 2004.

2. National Comprehensive Cancer Network (NCCN). Clinical practice guidelines in oncology: Small cell lung cancer. Version 2.2011. 2011.

3. National Comprehensive Cancer Network (NCCN). Clinical practice guidelines in oncology: Non-Small cell lung cancer. Version 3.2011. 2011.

4. (4) National Institute for Health and Clinical Excellence (NICE). The diagnosis and treatment of lung cancer**.** NICE clinical guideline 121. London: NICE; 2011.

5. British Columbia cancer Agency (BCCA). Cancer management guidelines. BC Cancer Agency (BCCA) 2010 [cited 2011 Jul 26];Available from: URL: http://www.bccancer.bc.ca/HPI/CancerManagementGuidelines/default.htm

6. Scottish Intercollegiate Guidelines Network (SIGN). Management of patients with lung cancer. A national clinical guideline. Edinburgh: SIGN, Royal College of Physicians; 2005.

7. Lim E, Baldwin D, Beckles M, Duffy J, Entwisle J, Faivre-Finn C, et al. Guidelines on the radical management of patients with lung cancer. A joint initiative by the British Thoracic Society and the Society for Cardiothoracic Surgery in Great Britain and Ireland. Thorax 2010 Oct;65 Suppl 3:iii1-27.

8. Scott WJ, Howington J, Feigenberg S, Movsas B, Pisters K. Treatment of non-small cell lung cancer stage I and stage II: ACCP evidence-based clinical practice guidelines (2nd edition). Chest 2007 Sep;132(3 Suppl):234S-42S.

9. Okawara G, Mackay JA, Evans WK, Ung YC. Management of unresected stage Ill non-small cell lung cancer: A clinical practice guideline. Evidence-based Series #7-3 (Version 2.2005): Section 1. A Quality Initiative of the Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO). Cancer Care Ontario (CCO); 2005.

10. Sorensen M, Pijls-Johannesma M, Felip E. Small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2010 May;21 Suppl 5:v120-v125.

11. Crino L, Weder W, van MJ, Felip E. Early stage and locally advanced (non-metastatic) non-small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2010 May;21 Suppl 5:v103-v115.

12. Australian Institute of Health and Welfare (AIHW). Australian Cancer Incidence and Mortality (ACIM) books. Available from: http://www aihw gov au/acim-books/ 2011 [cited 2011 Aug 16];

13. Vinod SK, Hui AC, Esmaili N, Hensley MJ, Barton MB. Comparison of patterns of care in lung cancer in three area health services in New South Wales, Australia. Intern Med J 2004;34:677-83.

14. Vinod SK, O'Connell DL, Simonella L, Delaney GP, et al. Gaps in optimal care for lung cancer. J Thorac Oncol 2008;3:871-9.

15. Hall SE, Holman CD, Sheiner H. The influence of socio-economic and locational disadvantage on patterns of surgical care for lung cancer in Western Australia 1982-2001. Aust Health Rev 2004;27(2):68-79.

16. Simonella L, O'Connell DL, Vinod SK, Delaney GP, Boyer M, Esmaili N, et al. No improvement in lung cancer care: the management of lung cancer in 1996 and 2002 in New South Wales. Intern Med J 2009 Jul;39(7):453-8.

17. National Health and Medical Research Council (NHMRC). Assessment and Management of Lung Cancer. Evidence based guidelines: A Guide for General Practitioners. The Australian Lung Foundation 2005 [cited 2011 Aug 25];Available from: URL: http://www.lungfoundation.com.au/professional-resources/guidelines/assessment-and-management-of-lung-cancer

18. Boxer MM, Vinod SK, Shafiq J, Duggan KJ. Do multidisciplinary team meetings make a difference in the management of lung cancer? Cancer 2011 Apr 26;[Epub ahead of print].

19. Seute T, Leffers P, ten Velde GP, Twijnstra A. Neurologic disorders in 432 consecutive patients with small cell lung carcinoma. Cancer 2004 Feb 15;100(4):801-6.

20. Bremnes RM, Sundstrom S, Aasebo U, Kaasa S, Hatlevoll R, Aamdal S. The value of prognostic factors in small cell lung cancer: results from a randomised multicenter study with minimum 5 year follow-up. Lung Cancer 2003 Mar;39(3):303-13.

21. Wind J, Smit EJ, Senan S, Eerenberg JP. Residual disease at the bronchial stump after curative resection for lung cancer. Eur J Cardiothorac Surg 2007 Jul;32(1):29-34.

22. Van Houtte P, Rocmans P, Smets P, Goffin J, et al. Postoperative radiation therapy in lung cancer: a controlled trial after resection of curative design. Int J Radiat Oncol Biol Phys 1980;6:983-6.

23. Kelsey CR, Marks LB, Hollis D, Hubbs JL, Ready NE, D'Amico TA, et al. Local recurrence after surgery for early stage lung cancer: an 11-year experience with 975 patients. Cancer 2009 Nov 15;115(22):5218-27.

24. Varlotto JM, Recht A, Flickinger JC, Medford-Davis LN, Dyer AM, Decamp MM. Factors associated with local and distant recurrence and survival in patients with resected nonsmall cell lung cancer. Cancer 2009 Mar 1;115(5):1059-69.

25. Barnholtz-Sloan JS, Sloan AE, Davis FG, Vigneau FD, Lai P, Sawaya RE. Incidence proportions of brain metastases in patients diagnosed (1973 to 2001) in the Metropolitan Detroit Cancer Surveillance System. J Clin Oncol 2004 Jul 15;22(14):2865-72.

26. Coleman RE. Metastatic bone disease: clinical features, pathophysiology and treatment strategies. Cancer Treat Rev 2001 Jun;27(3):165-76.

27. Reinfuss M, Mucha-Malecka A, Walasek T, Blecharz P, Jakubowicz J, Skotnicki P, et al. Palliative thoracic radiotherapy in non-small cell lung cancer. An analysis of 1250 patients. Palliation of symptoms, tolerance and toxicity. Lung Cancer 2011 Mar;71(3):344-9.

28. Mayer R, Smolle-Juettner FM, Szolar D, Stuecklschweiger GF, et al. Postoperative radiotherapy in radically resected non-small cell lung cancer. Chest 1997;112(4):954-9.

29. Dautzenberg B, Arriagada R, Chammard AB, Jarema A, Mezzetti M, Mattson K, et al. A controlled study of postoperative radiotherapy for patients with completely resected nonsmall cell lung carcinoma. Cancer 1999 Jul 15;86(2):265-73.

30. Feng QF, Wang M, Wang LJ, Yang ZY, Zhang YG, Zhang DW, et al. A study of postoperative radiotherapy in patients with non-small-cell lung cancer: a randomized trial. Int J Radiat Oncol Biol Phys 2000 Jul 1;47(4):925-9.

31. Massard G, Doddoli C, Gasser B, Ducrocq X, Kessler R, Schumacher C, et al. Prognostic implications of a positive bronchial resection margin. Eur J Cardiothorac Surg 2000 May;17(5):557-65.

32. Lequaglie C, Conti B, Brega Massone PP, Giudice G. Unsuspected residual disease at the resection margin after surgery for lung cancer: fate of patients after long-term follow-up. Eur J Cardiothorac Surg 2003 Feb;23(2):229-32.

33. Jeremic B, Bamberg M. External beam radiation therapy for bronchial stump recurrence of non-small-cell lung cancer after complete resection. Radiother Oncol 2002 Sep;64(3):251-7.

34. Stephens RJ, Girling DJ, Bleehen NM, Moghissi K, et al. The role of post-operative radiotherapy in non-small cell lung cancer: a multicentre randomised trial in patients with pathologically staged T1-2, N1-2, M0 disease. Medical Research Council Lung Cancer Working Party. Br J Cancer 1996;74(4):632-9.

LYMPHOMA

We reviewed evidence-based treatment guidelines for Hodgkin Lymphoma (HL) and Non-Hodgkin Lymphoma (NHL) management issued by major national and international that were published after the previous radiotherapy utilisation study was completed (July 2003) up to the most recent ones published in 2011.

Updated Guidelines

The following new or updated guidelines were identified and reviewed since the original RTU study:

- NHMRC management guideline on lymphoma, 2005 (1)
- NCCN clinical practice guidelines for Hodgkin lymphoma, Version 3, 2011 (2)
- NCI PDQ on Adult Hodgkin lymphoma, 2011 (3)
- Italian Society of Haematology guideline on Hodgkin Lymphoma, 2009 (4)
- NICE guideline on haematological cancers, 2003 (5)
- ESMO guideline for Hodgkin lymphoma, 2011 (6)
- NCCN clinical practice guidelines for non-Hodgkin lymphoma (NHL), Version 4, 2011 (7)
- ESMO recommendation on gastric MALT lymphoma, 2009 (8)
- NCI PDQ on Adult non-Hodgkin lymphoma, 2011 (9)
- Alberta Health Service guideline on lymphoma, 2011 (10)
- Spanish clinical practice guideline for treatment of follicular lymphoma, 2011 (11)
- NCI PDQ on primary CNS lymphoma, 2011 (12)

Indications for radiotherapy

All the indications for external beam radiotherapy in the original CCORE model of optimal radiotherapy utilisation for Lymphoma have been reviewed and updated in the optimal utilisation tree based on the latest guideline recommendations (Table 1 and Figure 1).

The model has been updated as follows:

10. *Based on radiotherapy recommendation for 'bulky (>5cm)' Hodgkin and non-Hodgkin lymphoma, clinical scenarios have been modified in the model*
11. *New indication of radiotherapy use in primary CNS lymphoma has been added*
12. *A new clinical outcome for radiotherapy use in Mycosis Fungoides (Thick plaque or solitary lesion) has been added*

All of the other previous indications remain supported by current guidelines.

Level of evidence

According to the methods applied for the previous radiotherapy utilisation model, the indications of radiotherapy for lymphoma have been derived from evidence-based treatment guidelines issued by

major national and international organisations. The guidelines reviewed are those published after the previous radiotherapy utilisation study was completed (July 2003) up to 2011. Highest priority has been given to Australian evidence-based clinical-practice guidelines (eg. NHMRC endorsed clinical practice guidelines).

Based on guidelines review, indications of radiotherapy for lymphoma remain supported by level I-IV evidence. Notably, new indications of radiotherapy have been added to the model and some indications have been modified. For some of the indications, the level of evidence for adjuvant radiotherapy use is now stronger and upgraded from level IV to level III; for one indication (Stage I-IIA Hodgkin lymphoma) the level is upgraded from level IV to level I.

In the Hodgkin lymphoma model, 6 of 9 outcomes have an indication of radiotherapy (Figure 1) and 2 indications with curative intent supported by level I-II evidence representing one third of (33%) population with Hodgkin lymphoma that require radiotherapy (Table I).

In the non-Hodgkin lymphoma model, 18 of 36 outcomes have an indication of radiotherapy (Figure 1); one indication (early stage aggressive NHL) is supported by level II evidence (6% population with NHL requiring RT) and the remaining ones are supported by level III evidence (Table 1).

Epidemiology of cancer stages

The epidemiological data in the Lymphoma utilisation tree have been reviewed to see if more recent data are available through extensive electronic search using the key words 'Australia', 'epidemiology', 'Hodgkin lymphoma', 'incidence', 'lymphoma stage', 'Non-Hodgkin lymphoma', 'radiotherapy treatment', 'recurrence', 'survival' 'treatment outcome' in various combinations. This has been applied particularly to the early branches in the tree for which national or State level data on cancer incidence rates and stages are available. If there is a change in the hierarchical quality of the epidemiological data, this has also been noted (Table 2).

Since the completion of the previous radiotherapy utilisation project the national data on cancer statistics published by AIHW have been updated to 2007 (13). The epidemiological evidence for several indications in the current model has been upgraded according to the literature published in the recent years; for some indications in the model epidemiological data have been updated from most recent higher quality US population based data from SEER (14).

Estimation of the optimal radiotherapy utilisation

From the evidence on the efficacy of radiotherapy and the most recent epidemiological data on the occurrence of indications for radiotherapy, the proportion of Lymphoma patients in whom radiotherapy would be recommended is 73% (Table 1 and Figure 1) compared with the original estimate of 65%. According to our model, 90% of population of **Hodgkin Lymphoma** (Figure 2) and 71% of **NHL** population (Figures 3-5) would have beneficial effect from radiotherapy treatment.

The optimal radiotherapy utilisation rates for different subtypes of NHL lymphoma are as follows

- Low grade NHL 61% (Figure 3)
- Aggressive NHL (previously known as intermediate grade) 79% (Figure 4) and
- High grade 58% and miscellaneous 73-83% (Mycosis Fungoides 83% and primary CNS lymphoma 73%) (Figure 5)

The change in overall utilisation rate is due to

1) Modification of radiotherapy indications for lymphoma especially for those with 'bulky' > 5cm disease; unlike the previous model, age has not been included as an outcome for bulky disease as there is now stronger evidence for adjuvant radiotherapy use, where low dose small field radiotherapy is tolerated with minimal toxicity even in patients older than 70 years (4;15).
2) Addition of new indications of RT for younger patients with primary CNS lymphoma and thick plaque or solitary Mycosis Fungoides.
3) Update of epidemiological data for lymphoma for some branches, especially for the earlier branches in the model with most up-to-date data from SEER.

Estimation of the optimal combined radiotherapy and chemotherapy utilisation

The indications of radiotherapy for lymphoma were reviewed to identify those indications where radiotherapy is recommended in conjunction with concurrent chemotherapy as the first treatment. According to the best available practice evidence there are **no indications identified for which concurrent chemoradiation** is beneficial as the first indicated treatment.

Sensitivity analysis

Univariate sensitivity analysis has been undertaken to assess changes in the recommended lymphoma radiotherapy utilisation rate that would result from different estimates of the proportions of patients with particular attributes as mentioned in Table 2 (Figure 6). The epidemiological data on proportions of patients with gastric MALT lymphoma that had complete response to Helicobacter Pylori treatment ranged from 56 to 81%; also the proportion of patients with low grade stage III-IV NHL who would have complete response to initial CT or second line CT after relapse varied. Due to these uncertainties, the estimate of optimal radiotherapy utilisation ranged from 70.9% to 74.9% as shown in the Tornado diagram (Figure 6).

Table 1: Lymphoma. Indications for radiotherapy - Levels and sources of evidence

Original RTU study				Updates 2011					
Outcome No. in Tree	Clinical Scenario	Level of evidence	Proportion of all lymphoma	Change of Indication	Guideline updated	Current level of evidence	Change to proportion of all lymphoma		References
							Yes/ No	Updated value	
1	Hodgkin lymphoma, Stage I-IIA	III	0.05	No	Yes	I	Yes	0.08	NHMRC (1), NCCN (2), NCI (3), Italian Society of Haematology (4), NICE (5)
2	Hodgkin lymphoma, Stage IIB-IV, bulky Disease	Indication updated according to new clinical practice guidelines			Yes	II	N/A	0.02	NHMRC (1), NICE (5)
4	Hodgkin lymphoma, Stage IIB-IV, non-bulky disease, complete response to chemotherapy, relapse, suitable for	Indication updated according to new clinical practice guidelines			Yes	IV	N/A	<0.01	NHMRC (1), NCCN (2), Italian Society of Haematology (4)

Original RTU study				Updates 2011					
Outcome No. in Tree	Clinical Scenario	Level of evidence	Proportion of all lymphoma	Change of Indication	Guideline updated	Current level of evidence	Change to proportion of all lymphoma		References
							Yes/ No	Updated value	
	HDCT/transplant, residual mass								
6	Hodgkin lymphoma, Stage IIB-IV, non-bulky disease, complete response to chemotherapy, relapse, not suitable for HDCT/transplant	Indication updated according to new clinical practice guidelines			Yes	IV	N/A	<0.01	NHMRC (1), NCCN (2), ESMO (6)
7	Hodgkin lymphoma, Stage IIB-IV, non-bulky disease, progressive /stable disease with chemotherapy, residual	Indication updated according to new clinical practice guidelines			Yes	III	No	<0.01	NHMRC (1), NCCN (2)

Original RTU study				Updates 2011					
Outcome No. in Tree	Clinical Scenario	Level of evidence	Proportion of all lymphoma	Change of Indication	Guideline updated	Current level of evidence	Change to proportion of all lymphoma		References
							Yes/ No	Updated value	
	disease after HDCT								
9	Non-Hodgkin's lymphoma (NHL), low grade, MALT, gastric, stage I-II, complete response to helicobacter eradication, relapse	III	<0.01	No	Yes	III	No	**<0.01**	NHMRC (1), NCCN (7), ESMO (8)
11	NHL, low grade, MALT, gastric, stage I-II, helicobacter negative or incomplete response to helicobacter eradication	Clinical scenario modified according to new clinical practice guidelines			Yes	III	N/A	<0.01	NHMRC (1), NCCN (7), ESMO (8)

Original RTU study				Updates 2011					
Outcome No. in Tree	Clinical Scenario	Level of evidence	Proportion of all lymphoma	Change of Indication	Guideline updated	Current level of evidence	Change to proportion of all lymphoma		References
							Yes/ No	Updated value	
13	NHL, low grade, MALT lymphoma, not gastric, stage I-II	IV	0.03	No	Yes	III	No	0.02	NHMRC (1), NCCN (7), NCI (9), Alberta Health Service (10)
15	NHL, low grade, non-MALT lymphoma, stage I-II	III	0.08	No	Yes	III	Yes	0.09	NHMRC (1), NCCN (7)
17	NHL, low grade, non-MALT lymphoma, stage III-IV, require treatment at presentation, complete response to chemotherapy, relapse, partial/no response second line CT	IV	0.02	No	Yes	III	No	0.03	NCCN (7), NCI (9), Spanish guidelines on follicular lymphoma (11)

Original RTU study				Updates 2011					
Outcome No. in Tree	Clinical Scenario	Level of evidence	Proportion of all lymphoma	Change of Indication	Guideline updated	Current level of evidence	Change to proportion of all lymphoma		References
							Yes/ No	Updated value	
20	NHL, low grade, non-MALT lymphoma, stage III-IV, require treatment at presentation, incomplete response to initial chemotherapy, partial/no response second line CT	III	0.02	No	Yes	III	No	0.02	NCCN (7), NCI (9), Spanish guidelines on follicular lymphoma (11)
22	NHL, low grade, non-MALT, stage III-IV, suitable for initial surveillance, require treatment for nodal disease, complete response to initial chemotherapy, relapse, partial/no response second line CT	III	0.01	No	Yes	III	No	0.01	NCCN (7), NCI (9), Spanish guidelines on follicular lymphoma (11)

Original RTU study				Updates 2011					
Outcome No. in Tree	Clinical Scenario	Level of evidence	Proportion of all lymphoma	Change of Indication	Guideline updated	Current level of evidence	Change to proportion of all lymphoma		References
							Yes/ No	Updated value	
25	NHL, low grade, non-MALT, stage III-IV, suitable for initial surveillance, require treatment for nodal disease, incomplete response to initial chemotherapy, partial/no response second line CT	III	<0.01	No	Yes	**III**	Yes	0.01	NCCN (7), NCI (9), Spanish guideline on follicular lymphoma (11)
28	NHL, intermediate grade (aggressive), stage I-II	II	0.3	No	Yes	II	Yes	0.26	NHMRC (1), NCCN (7), Alberta Health Service (10)
29	NHL, intermediate grade, stage III-IV, bulky disease	Clinical scenario modified according to new clinical practice guidelines			Yes	III	N/A	0.06	NHMRC (1), NCCN (7)
31	NHL, aggressive, stage III-IV, complete response to chemotherapy, non-bulky disease, complete	Clinical scenario modified according to new clinical practice guidelines			Yes	III	N/A	0.01	NHMRC (1), NCCN (7), NCI (9)

Original RTU study				Updates 2011					
Outcome No. in Tree	Clinical Scenario	Level of evidence	Proportion of all lymphoma	Change of Indication	Guideline updated	Current level of evidence	Change to proportion of all lymphoma		References
							Yes/ No	Updated value	
	response to CHOP therapy, relapse, non-response/ineligible for second line CT								
34	NHL , Intermediate grade, stage III-IV, incomplete response to chemotherapy, non-response/ineligible for second line CT	Clinical scenario modified according to new clinical practice guidelines			Yes	III	N/A	0.06	NHMRC (1), NCCN (7)
35	NHL, high grade, lymphoblastic lymphoma adult, prophylactic cranial irradiation	III	0.01	No	Yes	III	No	0.03	NHMRC (1)
38	NHL, mycosis fungoides, stage I-II, thick plaque/solitary lesion	New indication added to the model based on updated clinical practice guidelines			N/A	III	N/A	<0.01	NHMRC (1)

Original RTU study				Updates 2011					
Outcome No. in Tree	Clinical Scenario	Level of evidence	Proportion of all lymphoma	Change of Indication	Guideline updated	Current level of evidence	Change to proportion of all lymphoma		References
							Yes/ No	Updated value	
39	NHL, mycosis fungoides, stage I-II, complete response to PUVA/topical agents, relapse	IV	<0.01	No	Yes	III	No	<0.01	NHMRC (1)
41	NHL, mycosis fungoides, stage I-II, incomplete response to PUVA/topical agents	IV	<0.01	No	Yes	III	No	<0.01	NHMRC (1)
42	NHL, mycosis fungoides, stage III-IV	IV	<0.01	No	Yes	III	Yes	0.01	NHMRC (1)
43	NHL. Primary CNS lymphoma, <60 years	New indication added to the model based on updated clinical practice guidelines			N/A	III	N/A	0.01	NHMRC (1), NCI (12)
Proportion of all Lymphoma patients in whom Radiotherapy is recommended		0.65 (65%)		**Updated Proportion of all Lymphoma patients in whom Radiotherapy is recommended**				**0.73 (73%)**	

Table 2: Lymphoma; The incidence of attributes used to define indications for radiotherapy

Original RTU study				Updates 2011				
Population or sub-population of interest	**Attribute**	**Proportion of population with the attribute**	**Quality of Information**	**Change in proportion of population with attribute Yes/ No**	**Altered Proportion**	**Updated Quality of Information**	**Updated Reference**	**Comments**
All registry cancers	All lymphoma	0.04	α	No	N/A	α	AIHW 2007 (13)	
Lymphoma	Hodgkin lymphoma	0.10	α	Yes	0.12	α	AIHW 2007 (13)	
Hodgkin lymphoma	Stage I-IIA	Indication updated according to new clinical practice guidelines			0.70	δ	Gobbi et al 2004 (16)	
Hodgkin lymphoma, Stage IIB-IV	Bulky Disease	Indication updated according to new clinical practice guidelines			0.42	θ	Aleman et al 2003 (17)	Multi-centre data from Europe
Hodgkin lymphoma, Stage IIB-IV, non-bulky disease	Complete response to chemotherapy	Indication updated according to new clinical practice guidelines			**0.62**	**θ**	Aleman et al 2003 (17)	

Original RTU study				Updates 2011				
Population or sub-population of interest	**Attribute**	**Proportion of population with the attribute**	**Quality of Information**	**Change in proportion of population with attribute Yes/ No**	**Altered Proportion**	**Updated Quality of Information**	**Updated Reference**	**Comments**
Hodgkin lymphoma, Stage IIB-IV, non-bulky disease, complete response to chemotherapy	Relapse	Indication updated according to new clinical practice guidelines			0.15	θ	Aleman et al 2003 (17)	
Hodgkin lymphoma, Stage IIB-IV, non-bulky disease, complete response to chemotherapy, relapse	Suitable for high dose chemotherapy (HDCT)/ transplant	0.32	θ	No	N/A	N/A	Amini et al 2002 (18)	
Hodgkin lymphoma, Stage IIB-IV, non-bulky disease, complete response to chemotherapy,	Residual disease	0.23	θ	No	N/A	N/A	Linch et al 1993 (19)	

Original RTU study				Updates 2011				
Population or sub-population of interest	**Attribute**	**Proportion of population with the attribute**	**Quality of Information**	**Change in proportion of population with attribute Yes/ No**	**Altered Proportion**	**Updated Quality of Information**	**Updated Reference**	**Comments**
relapse, HDCT/ transplant								
Hodgkin lymphoma, Stage IIB-IV, non-bulky disease	Partial response to chemotherapy	Indication updated according to new clinical practice guidelines			0.30	θ	Aleman et al 2003 (17)	
Hodgkin lymphoma, Stage IIB-IV, non-bulky disease, progressive /stable disease with chemotherapy	Residual disease after HDCT	0.23	θ	No	N/A	N/A	Linch et al 1993 (19)	

Original RTU study				Updates 2011				
Population or sub-population of interest	Attribute	Proportion of population with the attribute	Quality of Information	Change in proportion of population with attribute Yes/ No	Altered Proportion	Updated Quality of Information	Updated Reference	Comments
Lymphoma	Non-Hodgkin lymphoma (NHL)	0.90	α	Yes	0.88	α	AIHW 2007 (13)	
NHL by grade	Low Intermediate High	0.32 0.61 0.05	γ	Yes	0.36 0.56 0.05	γ	SEER 2011 (14)	SEER data 2001-2008
NHL, low grade	Malt lymphoma	0.21	ζ	Yes	0.10	γ	SEER 2011 (14)	SEER data 2001-2008
NHL, low grade, MALT	Gastric	0.16	γ	Yes	0.14	γ	SEER 2011 (14)	SEER data 2001-2008
NHL, low grade, MALT, gastric	Stage I-II	0.88	ζ	Yes	0.87	ζ	Thieblemont 2005 (20)	Epidemiolgical data updated; change in proportion was minimal

Original RTU study				Updates 2011				
Population or sub-population of interest	Attribute	Proportion of population with the attribute	Quality of Information	Change in proportion of population with attribute Yes/ No	Altered Proportion	Updated Quality of Information	Updated Reference	Comments
NHL, low grade, MALT, gastric, stage I-II	Complete response to helicobacter pylori (HP) eradication	0.81 0.56 0.89 0.81	θ θ λ λ	No	N/A	N/A	Stolte et al 2002 (21) Ruskone-Formestraux et al 2001(22) Fischbach 2000 (23) Thiede et al 2000 (24)	
NHL, low grade, MALT, gastric, stage I-II, complete response to HP eradication	Relapse	0.10	θ	Yes	0.09	θ	Nakamura et al 2011 (25)	Epidemiolgical data updated; change in proportion was minimal
NHL, low grade, MALT, non-gastric	Stage I-II	0.65	ζ	No	N/A	ζ	Thieblemont 2005 (20)	
NHL, low grade, non-MALT lymphoma	Stage I-II	0.33	ε	No	N/A	N/A	International Non-Hodgkin's Lymphoma Project 1997 (26)	

Original RTU study				Updates 2011				
Population or sub-population of interest	Attribute	Proportion of population with the attribute	Quality of Information	Change in proportion of population with attribute Yes/ No	Altered Proportion	Updated Quality of Information	Updated Reference	Comments
NHL, low grade, non-MALT, stage III-IV	Requires treatment at presentation	0.61	λ	Yes	0.51	θ	Ardeshna et al 2003 (27)	
NHL, low grade, non-MALT, stage III-IV , require treatment at presentation	Complete response to chemotherapy (CT)	0.38 0.65 0.66	ε ε θ	No	N/A	N/A	Maartense et al (28) Federico et al (29) Peterson et al (30)	
NHL, low grade, non-MALT, stage III-IV, require treatment at presentation, complete response to CT	Relapse	0.65	ζ	No	N/A	N/A	Johnstone et al (31)	

Original RTU study				Updates 2011				
Population or sub-population of interest	**Attribute**	**Proportion of population with the attribute**	**Quality of Information**	**Change in proportion of population with attribute Yes/ No**	**Altered Proportion**	**Updated Quality of Information**	**Updated Reference**	**Comments**
NHL, low grade, non-MALT lymphoma, stage III-IV, require treatment at presentation, complete response to CT, relapse	Complete response to second line CT	0.41	λ	Yes	0.30 0.41	θ λ	Van Oers et al 2010 (32) Montoto et al (33)	
NHL, Low Grade Stage III-IV suitable for surveillance at presentation	Requires treatment	0.61	λ	Yes	0.73	θ	Ardeshna et al 2003 (27)	
NHL, Low Grade Stage III-IV suitable for surveillance at presentation, requires treatment	Nodal disease	0.72	λ	No	N/A	N/A	Portlock et al (34)	

Original RTU study				Updates 2011				
Population or sub-population of interest	**Attribute**	**Proportion of population with the attribute**	**Quality of Information**	**Change in proportion of population with attribute Yes/ No**	**Altered Proportion**	**Updated Quality of Information**	**Updated Reference**	**Comments**
NHL, Low Grade Stage III-IV suitable for surveillance at presentation, requires treatment, nodal disease	Complete response	0.38 0.65 0.66	ε ε θ	No	N/A	N/A	Maartense et al (28) Federico et al (29) Peterson et al (30)	
NHL, Low Grade Stage III-IV suitable for surveillance at presentation, requires treatment, nodal disease, complete response	Relapse	0.65	ζ	No	N/A	N/A	Johnstone et al. (31)	

Original RTU study				Updates 2011				
Population or sub-population of interest	**Attribute**	**Proportion of population with the attribute**	**Quality of Information**	**Change in proportion of population with attribute Yes/ No**	**Altered Proportion**	**Updated Quality of Information**	**Updated Reference**	**Comments**
NHL, Low Grade Stage III-IV suitable for surveillance at presentation, requires treatment, nodal disease, complete response, relapse	Complete response to second line CT	0.41	λ	Yes	0.30 0.41	θ λ	Van Oers et al 2010 (32) Montoto et al (33)	
NHL, Low Grade Stage III-IV suitable for surveillance at presentation, requires treatment, nodal disease, incomplete response	Complete response to second line CT	0.41	λ	Yes	0.30 0.41	θ λ	Van Oers et al 2010 (32) Montoto et al. (33)	

Original RTU study				Updates 2011				
Population or sub-population of interest	**Attribute**	**Proportion of population with the attribute**	**Quality of Information**	**Change in proportion of population with attribute Yes/ No**	**Altered Proportion**	**Updated Quality of Information**	**Updated Reference**	**Comments**
NHL, intermediate grade (aggressive)	Stage I-II	0.54	θ	Yes	0.52	γ	Shenkier et al 2001 (35)	BCCA lymphoma database
NHL, aggressive, stage III-IV	Bulky disease	Indication updated according to new clinical practice guidelines			0.25	γ	Sehn et al 2005 (36)	BCCA lymphoma database
NHL, aggressive, stage III-IV, non-bulky disease	Complete response to CHOP therapy	Indication updated according to new clinical practice guidelines			0.53	γ	Sehn et al 2005 (36)	BCCA lymphoma database
NHL, aggressive, stage III-IV, non-bulky disease, complete response to CHOP therapy	Relapse	Indication updated according to new clinical practice guidelines			0.20	γ	Savage et al 2005 (37)	BCCA lymphoma database
stage III-IV, CT response, non-bulky disease, CHOP therapy, relapse	Complete response to second line CT	Indication updated according to new clinical practice guidelines			0.30 0.41	θ λ	Van Oers et al 2010 (32) Montoto et al (33)	

Original RTU study				Updates 2011				
Population or sub-population of interest	**Attribute**	**Proportion of population with the attribute**	**Quality of Information**	**Change in proportion of population with attribute Yes/ No**	**Altered Proportion**	**Updated Quality of Information**	**Updated Reference**	**Comments**
NHL, aggressive, stage III-IV, complete response to chemotherapy, non-bulky disease, incomplete response to CHOP therapy	Complete response to second line CT	Indication updated according to new clinical practice guidelines			0.30 0.41	θ λ	Van Oers et al 2010 (32) Montoto et al (33)	
NHL, high grade	lymphoblastic lymphoma adult	0.77	γ	Yes	0.75	γ	SEER 2011 (14)	SEER data 2001-2008
NHL	Mycosis fungoides	0.02	γ	No	N/A	γ	SEER 2011 (14)	SEER data 2001-2008
NHL, mycosis fungoides, stage I-II	Thick plaque/solitary lesion	New indication	N/A	N/A	0.05	λ	Ysebaert et al 2004 (38)	
NHL, mycosis fungoides, I-II PUVA/topical	Relapse	0.66	λ	No	N/A	N/A	Herrmann et al 1995 (39)	

Original RTU study				Updates 2011				
Population or sub-population of interest	Attribute	Proportion of population with the attribute	Quality of Information	Change in proportion of population with attribute Yes/ No	Altered Proportion	Updated Quality of Information	Updated Reference	Comments
NHL, mycosis fungoides, stage I-II	Incomplete response to PUVA/topical agents	0.58	λ	No	N/A	N/A	Herrmann et al 1995 (39)	
NHL, mycosis fungoides	Stage III-IV	0.35	ε	No	N/A	N/A	Green et al 1981 (40)	
NHL	Primary CNS lymphoma	New indication	N/A	N/A	0.01	γ	SEER 2011 (14)	SEER data 2001-2008
NHL, primary CNS lymphoma	<60 years	New indication	N/A	N/A	0.55	γ	SEER 2011 (14)	SEER data 2001-2008

Figure 1. Lymphoma Radiotherapy Utilization Tree

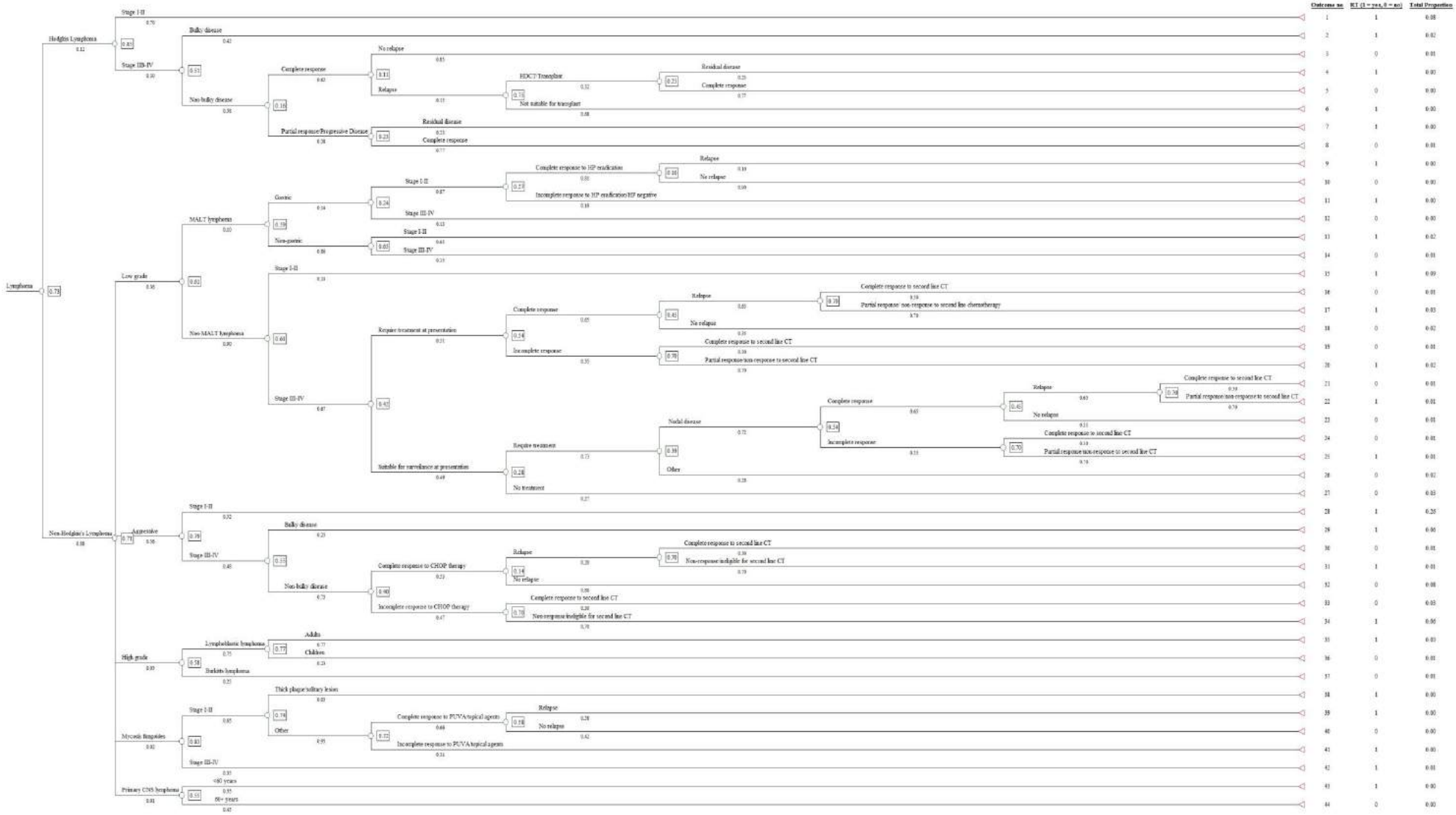
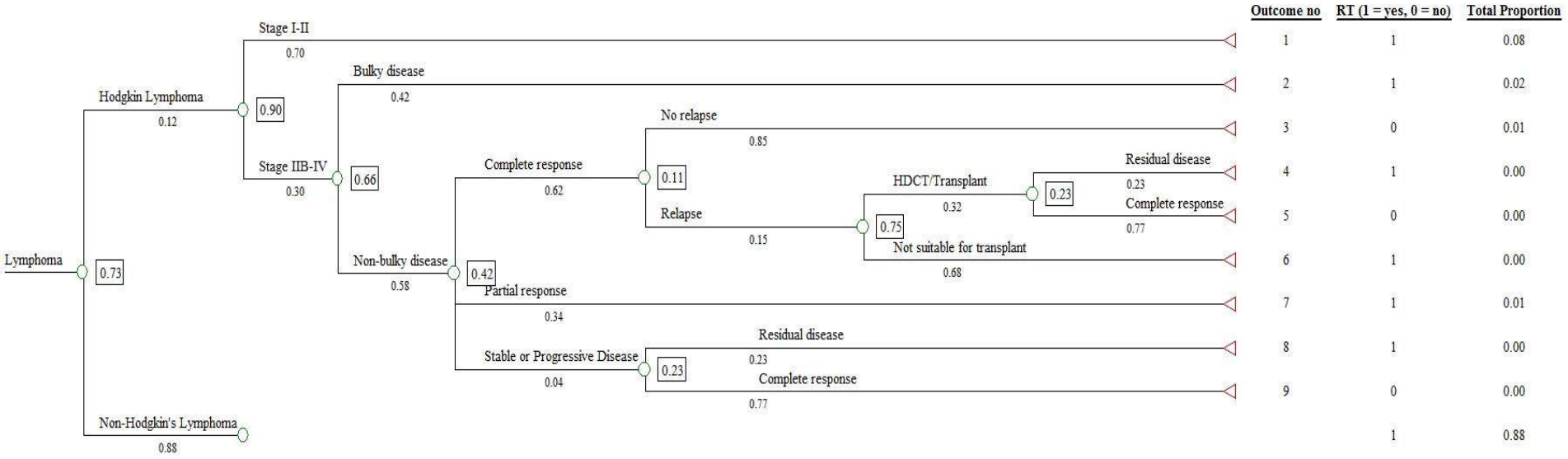


Figure 2. Hodgkin Lymphoma Radiotherapy Utilization Tree



Outcome no	RT (1 = yes, 0 = no)	Total Proportion
1	1	0.08
2	1	0.02
3	0	0.01
4	1	0.00
5	0	0.00
6	1	0.00
7	1	0.01
8	1	0.00
9	0	0.00
	1	0.88

Figure 3. Non-Hodgkin Lymphoma Radiotherapy Utilization Tree (Low grade)

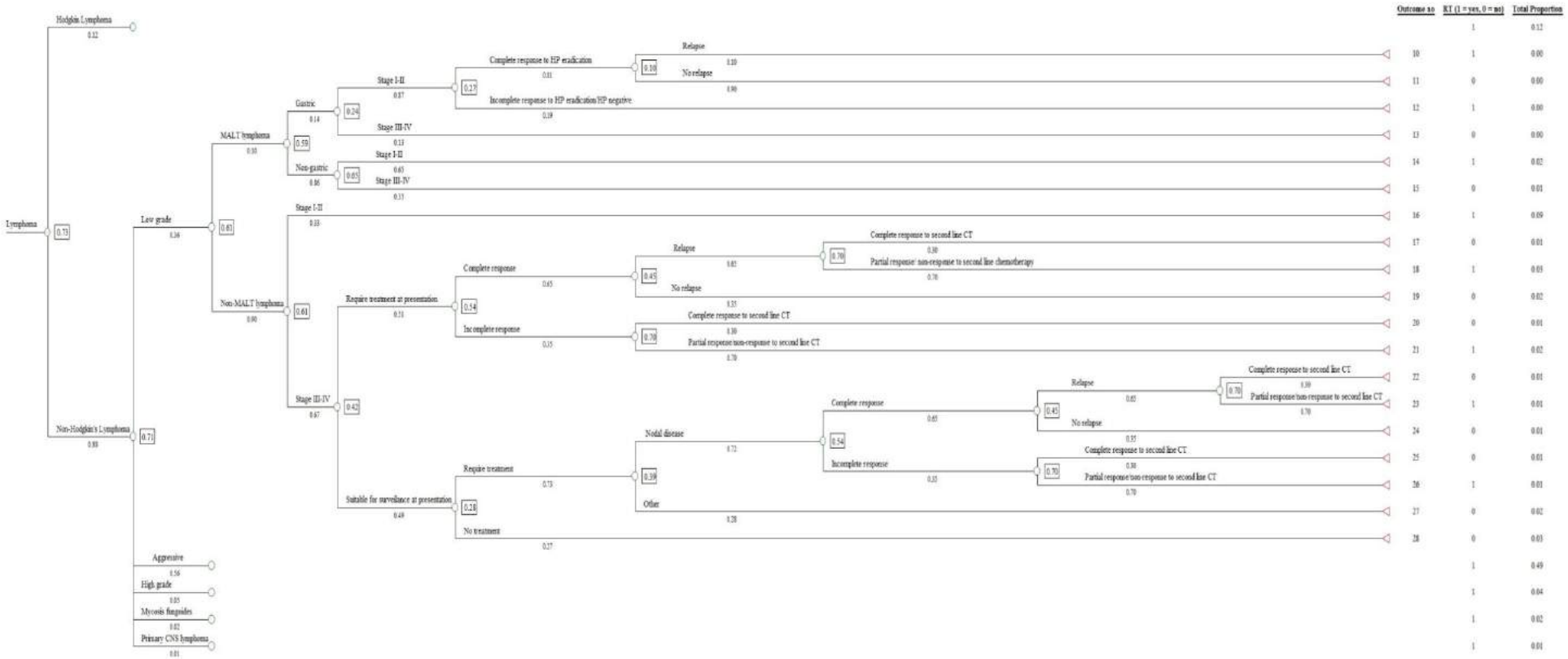
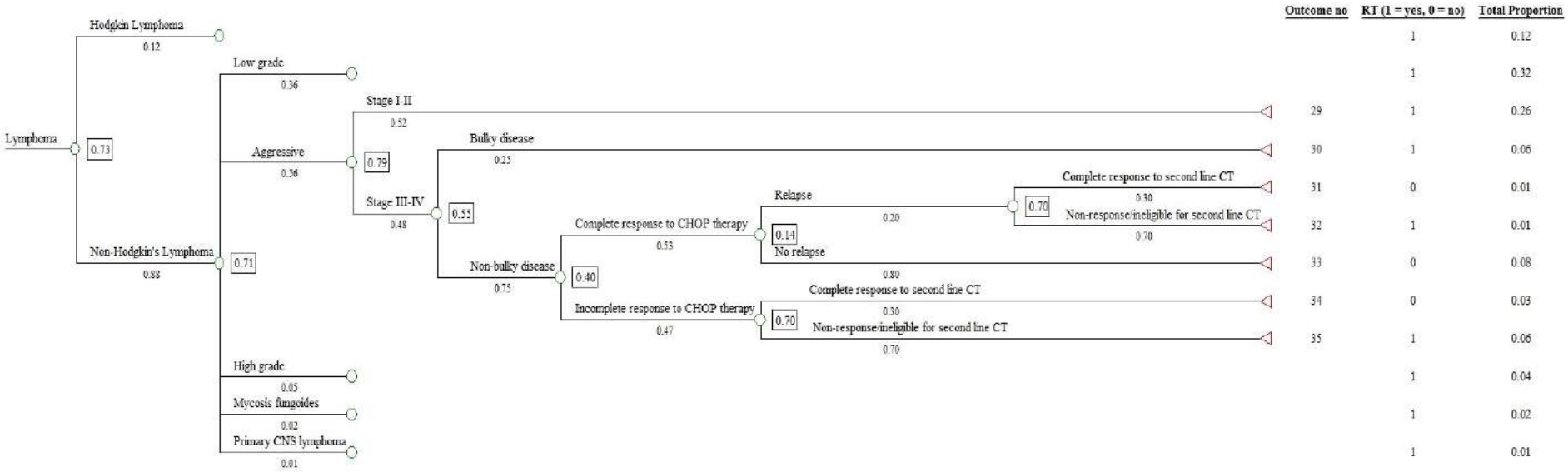
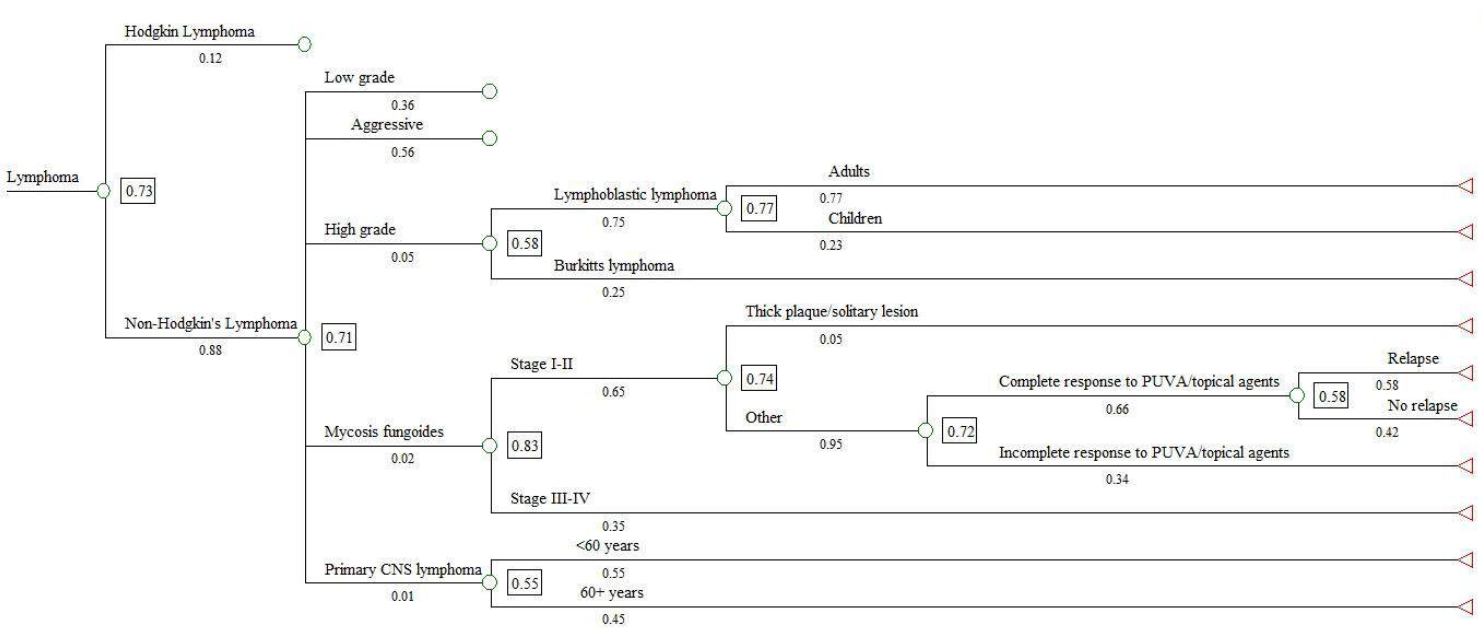


Figure 4. Non-Hodgkin Lymphoma Radiotherapy Utilization Tree (Aggressive)



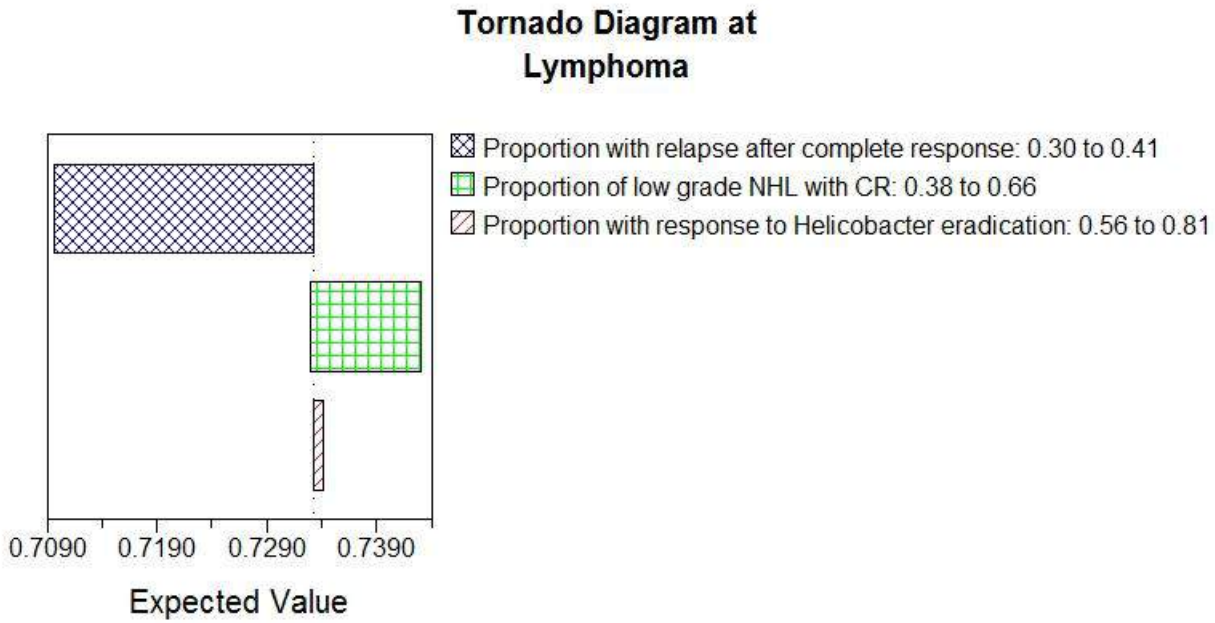
Outcome no	RT (1 = yes, 0 = no)	Total Proportion
	1	0.12
	1	0.32
29	1	0.26
30	1	0.06
31	0	0.01
32	1	0.01
33	0	0.08
34	0	0.03
35	1	0.06
	1	0.04
	1	0.02
	1	0.01

Figure 5. Non-Hodgkin Lymphoma Radiotherapy Utilization Tree (High grade and others)



Outcome no	RT (1 = yes, 0 = no)	Total Proportion
	1	0.12
	1	0.32
	1	0.49
35	1	0.03
36	0	0.01
37	0	0.01
38	1	0.00
39	1	0.00
40	0	0.00
41	1	0.00
42	1	0.01
43	1	0.00
44	0	0.00

Figure 6. Tornado diagram for univariate sensitivity analyses



References

1. Australian Cancer Network Diagnosis and Management of Lymphoma Guidelines Working Party. Guidelines for the diagnosis and management of Lymphoma. Sydney: The Cancer Council Australia and Australian Cancer Network on behalf of NHMRC; 2005.

2. National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology: Hodgkin Lymphoma.Version 3.2011. 2011.

3. National Cancer Institute (NCI). Hodgkin Lymphoma Treatment (PDQ®). Available from http://www cancer gov/cancertopics/pdq/treatment/adulthodgkins/HealthProfessional 2011 [cited 2012 Feb 15];

4. Brusamolino E, Bacigalupo A, Barosi G, et al. Classical Hodgkin's lymphoma in adults: guidelines of the Italian Society of Hematology, the Italian Society of Experimental Hematology, and the Italian Group for Bone Marrow Transplantation on initial work-up, anagement, and follow-up. Haematologica 2009;94:550-65.

5. National Institute for Clinical Excellence (NICE). Improving Outcomes in Haematological Cancers. Haematological cancers service guidance. London; 2003.

6. Eichenauer DA, Engert A, Dreyling M, On behalf of the ESMO Guidelines Working Group. Hodgkin's lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology 2011;22(Supplement 6):vi55-vi58.

7. National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology: Non-Hodgkin Lymphoma.Version 4.2011. 2011.

8. Zucca E, Dreyling M, On behalf of the ESMO Guidelines Working Group. Gastric marginal zone lymphoma of MALT type: ESMO Clinical Recommendations for diagnosis, treatment and follow-up. Annals of Oncology 2009;20(Supplement 4):iv113-iv114.

9. National Cancer Institute (NCI). Adult Non-Hodgkin Lymphoma Treatment (PDQ®). Available from: http://www cancer gov/cancertopics/pdq/treatment/adult-non-hodgkins/HealthProfessional 2012

10. Alberta Health Service. Clinical practice guideline: Lymphoma. Available from: www albertahealthservices ca 2011 [cited 2012 Feb 1];

11. López-Guillermo A, Caballero D, Canales C, et al. Clinical practice guidelines for first-line/after-relapse treatment of patients with follicular lymphoma. Leukemia & Lymphoma 2011;52(Suppl. 3):1-14.

12. National Cancer Institute (NCI). Primary CNS Lymphoma Treatment (PDQ®). Available from: http://www cancer gov/cancertopics/pdq/treatment/primary-CNS-lymphoma/HealthProfessional 2011 [cited 2012 Feb 1];

13. Australian Institute of Health and Welfare (AIHW). Australian Cancer Incidence and Mortality (ACIM) books. Available from: http://www aihw gov au/acim-books/ 2011 [cited 2011 Aug 16];

14. Surveillance Research Program, National Cancer Institute SEER*Stat software (seer.cancer.gov/seerstat). Version 7.0.5. [computer program]. Bethesda, MD: National Cancer Institute (NCI); 2011.

15. Shikama N, Oguchi M, Isobe K, et al. A long-term follow-up study of prospective 80%-dose CHOP followed by involved-field radiotherapy in elderly lymphoma patients. Jpn J Clin Oncol 2011;41(6):764-9.

16. Gobbi PG, Broglia C, Di Giulio G, et al. The clinical value of tumor burden at diagnosis in Hodgkin lymphoma. Cancer 2004;101(8):1824-34.

17. Aleman BMP, Raemaekers JMM, Tirelli U, et al. Involved-field radiotherapy for advanced Hodgkin's lymphoma. N Engl J Med 2003;348(24):2396-406.

18. Amini RM, Glimelius B, Gustavsson A, et al. A population based study of the outcome for patients with first relapse of Hodgkin's lymphoma. Eur J of Haem 2002;68:225-32.

19. Linch D, Winfield D, Goldstone AH. Dose intensification with autologous bone-marrow transplantation in relapse and resistant Hodgkin's disease: results of a BNLI randomised trial. Lancet 1993;341:1051-4.

20. Thieblemont C. Clinical presentation and management of marginal zone lymphomas. Hematology Am Soc Hematol Educ Program 2005;307-13.

21. Stolte M, Bayerdorffer E, Morgner A, et al. Helicobacter and gastric MALT lymphoma. Gut 2002;50:19-24.

22. Ruskone-Fourmestraux A, Lavergne A, Aergerter PH, et al. Predictive factors for regression of gastric MALT lymphoma after anti-Helicobacter pylori treatment. Gut 2001;48:297-303.

23. Fischbach W, Dragosics B, Kolve-Goebeler ME, et al. Primary gastric B-cell lymphoma: results of a prospective multicentre study. Gastroenterology 2000;119:1191-202.

24. Thiede C, Wundisch T, Neubauer B. Eradication of Helicobacter pylori and stability of emissions in low-grade gastric B-cell lymphomas of the mucosa-associated lymphoid tissue: results of an ongoing multicenter trial. Cancer Research 2000;156:125-33.

25. Nakamura S, Sugiyama T, Matsumoto T, Iijima K, Ono S, Tajika M, et al. Long-term clinical outcome of gastric MALT lymphoma after eradication of Helicobacter pylori: a multicentre cohort follow-up study of 420 patients in Japan. Gut 2011 Sep 2.

26. The Non-Hodgkin's Lymphoma Classification Project. A clinical evaluation of the International Lymphoma Study Group classification of Non-Hodgkin's lymphoma. Blood 1997;89(11):3909-18.

27. Ardeshna KM, Smith P, Norton A, et al. Long-term effect of a watch and wait policy versus immediate systemic treatment for asymptomatic advanced-stage non-Hodgkin lymphoma: a randomised controlled trial. The Lancet 2003;362:516-22.

28. Maartense E, Hermans J, Kluin-Nelemans JC, et al. Elderly patients with non-Hodgkin's lymphoma: population based results in the Netherlands. Annals of Oncology 1998;9:1219-27.

29. Federico M, Vitolo U, Zinazani PL, et al. Prognosis of follicular lymphoma: a predictive model based on a retrospective analysis of 987 cases. Blood 2000;95:783.

30. Peterson BA, Petroni GR, Frizzera G, et al. Prolonged single agent versus combination chemotherapy in indolent follicular lymphomas: a study of the cancer and leukaemia group B. Peterson BA. J Clin Oncol 2003;21:5-15.

31. Johnstone PWM, Rohatiner AZS, Whelan JS, et al. Patterns of survival in patients with recurrent follicular lymphoma: a 20-year study from a single centre. J Clin Oncol 1995;13:140-7.

32. van Oers MHJ, Glabbeke MV, Giurgea L, et al. Rituximab maintenance treatment of relapsed/resistant follicular non-Hodgkin's lymphoma: Long-term outcome of the EORTC 20981 phase III randomized intergroup study. J Clin Oncol 2010;28(17):2853-8.

33. Montoto S, Lopez-Guillermo A, Ferrer A, et al. Survival after progression in patients with follicular lymphoma: analysis of prognostic factors. Annals of Oncology 2002;13:523-30.

34. Portlock CS, Rosenberg SA. No initial therapy for Stage III and IV non-Hodgkin's lymphoma of favourable histologic types. Annals of Internal Medicine 1979;90:10-3.

35. Shenkier TN, Voss N, Fairey R, et al. Brief chemotherapy and involved-region irradiation for limited-stage diffuse large-cell lymphoma: An 18-Year experience from the British Columbia Cancer Agency. J Clin Oncol 2001;20(1):197-204.

36. Sehn LH, Donaldson J, Chhanabhai M, et al. Introduction of combined CHOP plus Rituximab therapy dramatically improved outcome of diffuse large B-Cell lymphoma in British Columbia. J Clin Oncol 2005;23(22):5027-33.

37. Savage KJ, Al-Rajhi N, Voss N, et al. Favorable outcome of primary mediastinal large B-cell lymphoma in a single institution: The British Columbia experience. Annals of Oncology 2006;17(1):123-30.

38. Ysebaert L, Truc G, Dalac S, Lambert D, Petrella T, Barillot I, et al. Ultimate results of radiation therapy for T1-T2 mycosis fungoides (including reirradiation). Int J Radiat Oncol Biol Phys 2004 Mar 15;58(4):1128-34.

39. Herrmann JJ, Roenigk HH, Hurria A, et al. Treatment of Mycosis Fungoides with photochemotherapy (PUVA): Long-term follow-up. JAAD 1995;33:234-42.

40. Green SB, Byar DP, Lamberg SI. Prognostic variables in mycosis fungoides. Cancer 1981 Jun 1;47(11):2671-7.

MELANOMA

Evidence-based treatment guidelines for melanoma management issued by major national and international organisations reviewed for the model are those published after the previous radiotherapy utilisation study was completed (July 2003) up to the most recent ones published in 2011.

Updated Guidelines

The following new or updated guidelines were identified and reviewed since the original RTU study:

- Clinical practice guidelines for the management of melanoma in Australia and New Zealand, 2008 (1)
- National Cancer Institute (NCI) intraocular melanoma treatment PDQ, 2011 (2)
- German guidelines on surgical treatment and radiotherapy of melanoma, 2008 (3)
- Alberta Health Services clinical practice guideline for melanoma, 2011 (4)
- NCCN clinical practice guidelines for melanoma, Version 4, 2011 (5)
- START guideline for melanoma, 2004 (6)
- Moffitt Cancer Centre and Research Institute (Florida, USA) radiation therapy guideline for melanoma, 2011 (7)

Indications for radiotherapy

All the indications for external beam radiotherapy in the original CCORE model of optimal radiotherapy utilisation for melanoma have been reviewed and updated in the optimal utilisation tree based on the latest guideline recommendations (Table 1).

The model has been updated as follows:

13. *Based on new level II evidence of loco-regional control benefit of radiotherapy for node positive melanomas of both head and neck and non-head and neck sites, clinical scenarios have been revised; radiotherapy is now indicated for multiple node positive melanomas and for single node positive melanomas with extra nodal spread or nodal diameter of >4cm for all sites*
14. *Based on radiotherapy recommendation for surgically inoperable invasive melanoma in situ including Lentigo Maligna Melanoma (LMM) in elderly patients, a new clinical outcome has been added to the model*

All of the other previous indications remain supported by current guidelines.

Level of evidence

According to the methods applied for the previous radiotherapy utilisation model, the indications of radiotherapy for melanoma have been derived from evidence-based treatment guidelines issued by major national and international organisations. The guidelines reviewed are those published after the

previous radiotherapy utilisation study was completed (July 2003) up to December 2010. Highest priority has been given to Australian evidence-based clinical-practice guidelines (eg. NHMRC endorsed clinical practice guidelines).

Based on guidelines review, all indications of radiotherapy for melanoma remain supported by level II-IV evidence similar to those reported in the earlier model. Notably, three new RT indications have been added for node positive melanoma with level II evidence due to reporting of the results of a new clinical trial (8). Twelve outcomes in the model have an indication of radiotherapy (Figure 1) and of them 3 (25%) is supported by level II evidence; all the remaining indications are supported by level III-IV evidence. The updated model predicts that for 83% of the melanoma population with an indication of radiotherapy, the evidence of benefit is supported by level II-III literature.

Epidemiology of cancer stages

The epidemiological data in the melanoma utilisation tree have been reviewed to see if more recent data are available through extensive electronic search using the key words 'Australia', 'epidemiology melanoma', 'incidence', 'melanoma stage', 'radiotherapy treatment', 'recurrence', 'survival' 'treatment outcome' in various combinations. This has been applied particularly to the early branches in the tree for which national or State level data on cancer incidence rates and stages are available. If there is a change in the hierarchical quality of the epidemiological data, this has also been noted (Table 2).

Since the completion of the previous radiotherapy utilisation project the national data on cancer statistics published by AIHW have been updated to 2007 (9) and a number of publications of national and State data on melanoma have been available (8;10-14). The epidemiological evidence for several indications in the current model has been upgraded accordingly to be more representative of the Australian population.

NHMRC endorsed latest clinical practice guideline for melanoma described that at least 5% of population with melanoma are diagnosed with Lentigo Maligna or Lentigo Maligna Melanoma (LMM) that require active treatment with surgery or radiotherapy where surgical margins are inadequate or surgery is not possible (1); hence, a new clinical scenario with indication of radiotherapy for inoperable melanoma in situ has been added to the model.

In the current model, stage I-III cutaneous melanomas have been further categorised into stage I and stage II-III; most up-to-date stage-based data obtained from large population based databases are higher than described in the previous model. A large multi-centre epidemiological study (N=17600) (11) done to validate the American Joint Committee on Cancer (AJCC) staging of melanoma that included data from Australian melanoma database reported a higher proportion of stage IV melanoma compared to that reported in the previous model (7% vs 1%). Because of these changes in casemix, the proportion of stage I-III cutaneous melanoma has been revised from 99% to 85%.

Estimation of the optimal radiotherapy utilisation

From the evidence on the efficacy of radiotherapy and the most recent epidemiological data on the occurrence of indications for radiotherapy, the proportion of melanoma patients in whom radiotherapy would be recommended is 21% (Table 1 and Figure 1) compared with the original estimate of 23%.

The change in overall utilisation rate is due to changes in the epidemiological data for the model. Although new indications of radiotherapy have been added to the model there are substantial changes in the clinical scenarios with updated epidemiological data added to the model.

Estimation of the optimal brachytherapy utilisation for ocular melanoma

According to the most updated treatment guidelines (1-2) plaque brachytherapy is preferred over surgery in treatment of ocular melanoma (melanoma of choroid, conjunctiva) because of better tumour control and lower ocular morbidity. Hence, a brachytherapy utilisation model for melanoma has been developed and the optimal utilization rate estimate is 2%.

Estimation of the optimal combined radiotherapy and chemotherapy utilisation

The indications of radiotherapy for melanoma were reviewed to identify those indications where radiotherapy is recommended in conjunction with concurrent chemotherapy as the first treatment. According to the best available practice evidence there are **no indications identified for which concurrent chemoradiation** is beneficial over radiotherapy alone as the first indicated treatment.

Sensitivity analysis

Univariate sensitivity analysis has been undertaken to assess changes in the recommended melanoma radiotherapy utilisation rate that would result from different estimates of the proportions of patients with particular attributes as mentioned in Table 2; also radiotherapy indications for single node positive melanomas with ENS or large nodal size are based on data from a single randomized controlled trial. The variability in the estimate of optimal radiotherapy utilisation due to these uncertainties was 3% and the expected value ranged from 18% to 21% as shown in the Tornado diagram (Figure 2).

Table 1: Melanoma. Indications for radiotherapy - Levels and sources of evidence

Original RTU study				Updates 2011					
Outcome No. in Tree	Clinical Scenario	Level of evidence	Proportion of all melanoma	Change of Indication	Guideline updated	Current level of evidence	Change to proportion of all melanoma		References
							Yes/ No	Updated value	
1	Non-Head and neck Mucosal melanoma	IV	0.01	No	Yes	IV	No	0.01	Australian Cancer Council (1)
2	Ocular melanoma	Indication for brachytherapy			Yes	N/A	N/A	N/A	Australian Cancer Council (1), NCI (2)
4	Cutaneous, Melanoma in-situ, Lentigo Melinga Melanoma (LMM), inoperable/inadequate margin	New indication branch added to the model based on updated clinical practice guidelines		N/A	Yes	IV	N/A	0.01	Australian Cancer Council (1), German guidelines (3), Alberta Health Service (4)
5	Cutaneous, Stage I-III, desmoplastic	III	0.02	No	Yes	III	No	0.02	Australian Cancer Council (1), NCCN (5), START (6)
7	Cutaneous, non-desmoplastic, stage I, nodal/brain/bone recurrence	Modified clinical scenario		No	Yes	III	No	0.01	Australian Cancer Council (1), Alberta Health Service (4), NCCN (5), START (6), Moffitt Cancer Centre (7)

Original RTU study				Updates 2011					
Outcome No. in Tree	Clinical Scenario	Level of evidence	Proportion of all melanoma	Change of Indication	Guideline updated	Current level of evidence	Change to proportion of all melanoma		References
							Yes/ No	Updated value	
8	Cutaneous, non-desmoplastic, stage II-III, node positive, single node, node size <4cm, no extranodal spread, nodal/brain/bone recurrence	Modified clinical scenario		N/A	Yes	II	N/A	<0.01	Australian Cancer Council (1), Alberta Health Service (4), NCCN (5), START (6), Moffitt Cancer Centre (7)
10	Cutaneous, non-desmoplastic, stage II-III, node positive, single node, node size <4cm, extra-nodal spread	Modified the clinical scenario based on new level II evidence of adjuvant RT use for node positive melanoma		No	Yes	III	Yes	0.01	Australian Cancer Council (1), NCCN (5), START (6)
11	Cutaneous, non-desmoplastic, stage II-III, node positive, single node, node size >4cm	Modified the clinical scenario based on new level II evidence of adjuvant RT use for node positive melanoma		N/A	Yes	II	N/A	0.02	Australian Cancer Council (1), NCCN (5), START (6)

Original RTU study				Updates 2011					
Outcome No. in Tree	Clinical Scenario	Level of evidence	Proportion of all melanoma	Change of Indication	Guideline updated	Current level of evidence	Change to proportion of all melanoma		References
							Yes/ No	Updated value	
12	Cutaneous, non-desmoplastic, stage II-III, node positive, multiple nodes	Modified the clinical scenario based on new level II evidence of adjuvant RT use for node positive melanoma		N/A	Yes	II	N/A	0.05	Australian Cancer Council (1), NCCN (5), START (6)
14	Cutaneous, non-desmoplastic, stage II-III, node negative, head and neck, pT1-3, nodal/brain/bone recurrence	Modified clinical scenario		N/A	Yes	III	No	< 0.01	Australian Cancer Council (1), Alberta Health Service (4), NCCN (5), START (6), Moffitt Cancer Centre 2008 (7)
16	Cutaneous, non-desmoplastic, stage II-III, node negative, head and neck, pT4	Modified clinical scenario		N/A	Yes	III	No	0.01	Australian Cancer Council (1), NCCN (5), START (6)

Original RTU study				Updates 2011					
Outcome No. in Tree	Clinical Scenario	Level of evidence	Proportion of all melanoma	Change of Indication	Guideline updated	Current level of evidence	Change to proportion of all melanoma		References
							Yes/ No	Updated value	
18	Cutaneous, non-desmoplastic, stage II-III, node negative, non-head and neck, nodal/brain/bone recurrence	Modified clinical scenario		N/A	Yes	III	No	0.04	Australian Cancer Council (1), Alberta Health Service (4), NCCN (5), START (6), Moffitt Cancer Centre 2008 (7)
19	Cutaneous, Stage IV, symptomatic brain/bone/ node metastases	III	< 0.01	No	Yes	III	Yes	0.03	Australian Cancer Council (1), NCCN (5), START (6)
Proportion of all melanoma patients in whom radiotherapy is recommended			0.23 (23%)	**Updated proportion of all melanoma patients in whom radiotherapy is recommended**				**0.21 (21%)**	

Table 2: Melanoma; The incidence of attributes used to define indications for radiotherapy

Original RTU study				Updates 2011				
Population or sub-population of interest	Attribute	Proportion of population with the attribute	Quality of Information	Change in proportion of population with attribute Yes/ No	Altered Proportion	Updated Quality of Information	Updated Reference	Comments
All registry cancers	Melanoma	0.11	α	Yes	0.10	α	AIHW 2007 (9)	
Melanoma	Non-Head and neck Mucosal	0.01	ε	No	N/A	ε	Australia and New Zealand melanoma guideline 2008 (1)	Multiple hospital sources reported in the guideline
Melanoma	Ocular	0.02	ε	No	N/A	β	Vajdic et al 2003 (10)	NSW Cancer Registry data
Melanoma	Cutaneous	0.97	α	No	N/A	α	AIHW 2007 (9)	
Cutaneous melanoma, Invasive melanoma in-situ/ Lentigo maligna melanoma (LMM)	No surgery/ Inadequate margin	New indication	N/A	N/A	0.07	ζ	Farshad et al 2001 (15)	

Original RTU study				Updates 2011				
Population or sub-population of interest	**Attribute**	**Proportion of population with the attribute**	**Quality of Information**	**Change in proportion of population with attribute Yes/ No**	**Altered Proportion**	**Updated Quality of Information**	**Updated Reference**	**Comments**
Cutaneous melanoma	Stage I - III	0.99	ζ	Yes	0.85	ε	Balch et al 2001 (11)	Comprehensive multi-institutional database including Australian institutions
Cutaneous melanoma, Stage I - III	Non-desmoplastic	0.98	ε	No	N/A	N/A	SA Australian Registry (16)	
Cutaneous melanoma, non-desmoplastic	Stage I	Revised clinical scenario	N/A	N/A	0.56	β	Sydney Health Projects Group Report 2005 (12)	NSW Cancer Registry data
Cutaneous melanoma, non-desmoplastic, stage I	Nodal/brain/ bone recurrence	Revised indication	N/A	N/A	0.02	ζ	McKinnon et al 2005 (17)	

Original RTU study				Updates 2011				
Population or sub-population of interest	**Attribute**	**Proportion of population with the attribute**	**Quality of Information**	**Change in proportion of population with attribute Yes/ No**	**Altered Proportion**	**Updated Quality of Information**	**Updated Reference**	**Comments**
Cutaneous melanoma, non-desmoplastic, stage II-III	Node positive	Revised clinical scenario	N/A	N/A	0.24	ε	Balch et al 2001 (11)	Comprehensive multi-institutional database including Australian institutions
Cutaneous melanoma, non-desmoplastic, stage II-III, node positive	Single node	Revised clinical scenario	N/A	N/A	0.45	ε	Balch et al 2001 (11)	
Cutaneous melanoma, non-desmoplastic, stage II-III, node positive, single node, node size <=4cm, no extra-nodal spread	Nodal/brain/ bone recurrence	Revised clinical scenario	N/A	N/A	0.25	ζ	Murali et al 2011 (14)	Surgical patterns of care study from data held by Melanoma Institute Australia (MIA)

Original RTU study				Updates 2011				
Population or sub-population of interest	**Attribute**	**Proportion of population with the attribute**	**Quality of Information**	**Change in proportion of population with attribute Yes/ No**	**Altered Proportion**	**Updated Quality of Information**	**Updated Reference**	**Comments**
Cutaneous melanoma, non-desmoplastic, stage II-III, node positive, single node, node size <=4cm	Extra-nodal spread (ENS)	New indication	N/A	N/A	0.50	ε	Burmeister et al 2010 (8)	Proportion with attribute based on TROG clinical trial on the adjuvant RT use for melanoma with positive nodes
Cutaneous melanoma, non-desmoplastic, stage II-III, node positive, single node	Node size >4cm	New indication	N/A	N/A	0.39	ε	Burmeister et al 2010 (8)	
Cutaneous melanoma, non-desmoplastic, stage II-III, node positive	Multiple nodes involved	Revised indication	N/A	N/A	0.55 (1+ positive nodes)	ε	Balch et al 2001 (11)	

Original RTU study				Updates 2011				
Population or sub-population of interest	**Attribute**	**Proportion of population with the attribute**	**Quality of Information**	**Change in proportion of population with attribute Yes/ No**	**Altered Proportion**	**Updated Quality of Information**	**Updated Reference**	**Comments**
Cutaneous melanoma, non-desmoplastic, stage II-III, node negative	Head and neck melanoma	Revised clinical scenario	N/A	N/A	0.21	γ	SEER 2011 (18)	
Cutaneous melanoma, non-desmoplastic, stage II-III, node negative, head and neck	PT1-3	0.84	ζ	No	N/A	ζ	O'Brien et al 1991 (19)	
Cutaneous melanoma, non-desmoplastic, stage II-III, node negative, head and neck, pT1-3	Nodal or systemic recurrence	0.08	ζ	No	N/A	ζ	O'Brien et al 1991 (19)	

Original RTU study				Updates 2011				
Population or sub-population of interest	**Attribute**	**Proportion of population with the attribute**	**Quality of Information**	**Change in proportion of population with attribute Yes/ No**	**Altered Proportion**	**Updated Quality of Information**	**Updated Reference**	**Comments**
Cutaneous melanoma, non-desmoplastic, stage II-III, node negative, head and neck, pT1-3, nodal or systemic recurrence	Nodal/brain/ bone recurrence	0.51 0.21	ζ	Yes	0.50	β	Green et al 1996 (13)	State Cancer registry data from NSW, Victoria and Queensland
Cutaneous melanoma, non-desmoplastic, stage II-III, node negative, head and neck	PT4	0.84	ζ	No	N/A	ζ	O'Brien et al 1991 (19)	

Original RTU study				Updates 2011				
Population or sub-population of interest	**Attribute**	**Proportion of population with the attribute**	**Quality of Information**	**Change in proportion of population with attribute Yes/ No**	**Altered Proportion**	**Updated Quality of Information**	**Updated Reference**	**Comments**
Cutaneous melanoma, non-desmoplastic, stage II-III, node negative, non - head and neck	Nodal/brain/ bone recurrence	Revised clinical scenario	N/A	N/A	0.20	ε	Cohn-Cedermark et al 2000 (20)	
Cutaneous melanoma	Stage IV	0.01	N/A	Yes	0.07	ε	Balch et al 2001 (11)	Comprehensive multi-institutional database including Australian institutions
Cutaneous melanoma, Stage IV	Symptomatic brain/bone/ node metastases	0.51 0.21	ζ	Yes	0.50	β	Green et al 1996 (13)	State Cancer registry data from NSW, Victoria and Queensland

Table 3: Melanoma. Indications for brachytherapy - Levels and sources of evidence

Outcome No. in Tree	Clinical Scenario	Level of Evidence	References	Proportion of all lung cancer patients
2	Ocular melanoma	II	Australian cancer Council (1), NCI (2)	0.02
The total proportion of all patients with melanoma in whom brachytherapy is recommended				**0.02 (2%)**

Figure 1. Melanoma Radiotherapy Utilization Tree

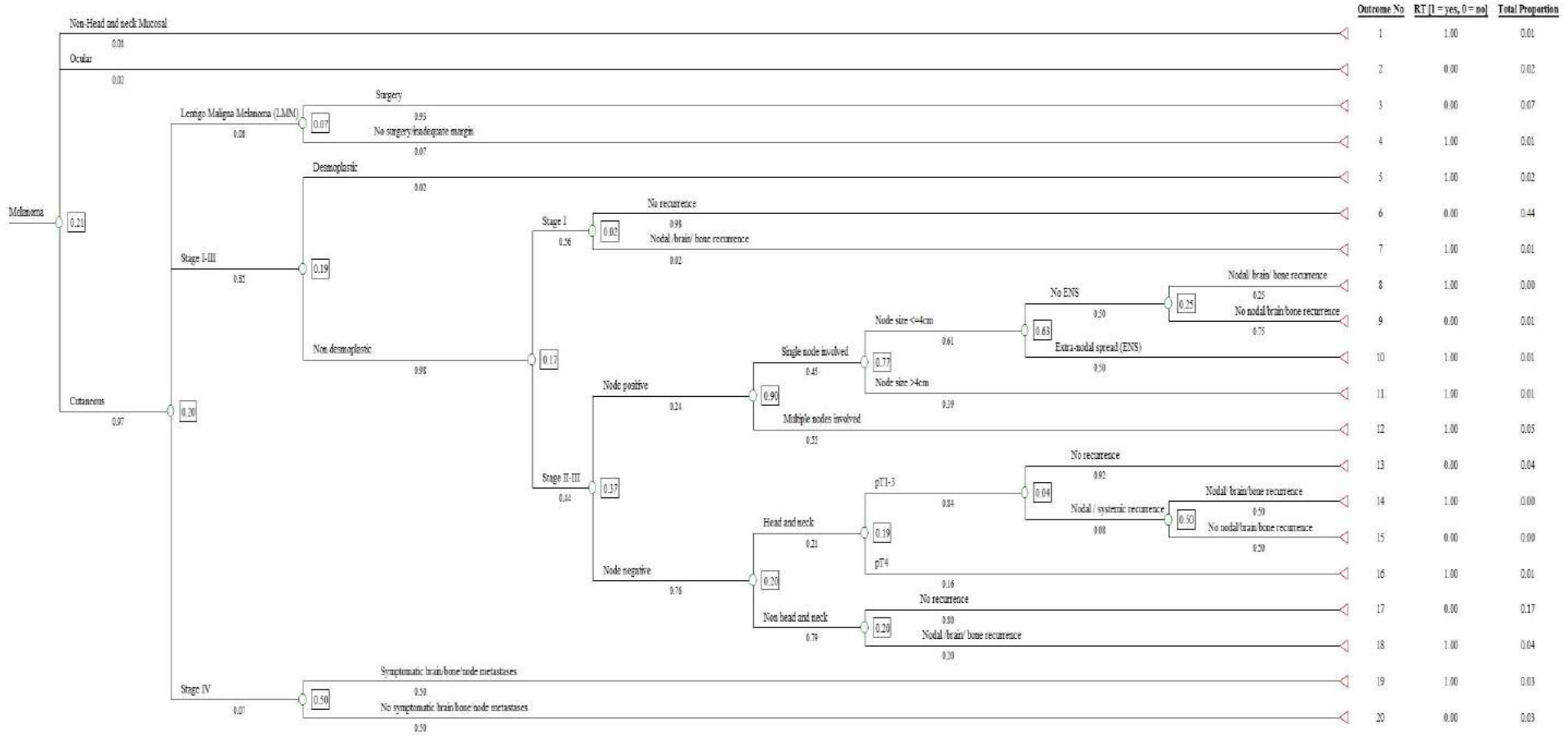
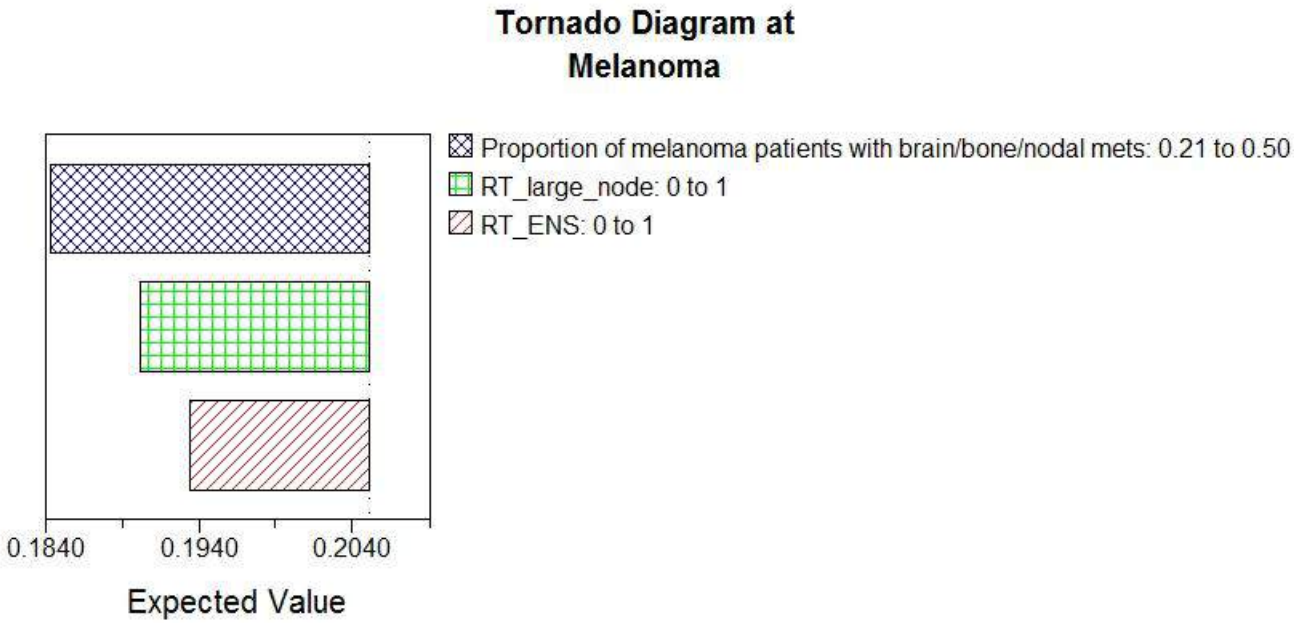


Figure 2. Tornado diagram for univariate sensitivity analyses



References

1. Australian Cancer Network Melanoma Guidelines Revision Working Party, on behalf of NHMRC. Clinical Practice Guidelines for the Management of Melanoma in Australia and New Zealand. Cancer Council Australia and Australian Cancer Network, Sydney and New Zealand Guidelines Group, Wellington; 2008.

2. National Cancer Institute (NCI). Intraocular melanoma treatment (PDQ). 2011.

3. Garbe C, Hauschild A, Volkenandt M, et al. Evidence and interdisciplinary consensus-based German guidelines: surgical treatment and radiotherapy of melanoma. Melanoma Research 2008;18:61-7.

4. Alberta Health Services. Adjuvant radiation in malignant melanoma. Clinical practice guideline CU-003. 2011.

5. National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology: Melanoma.Version 4.2011. 2011.

6. Organisation of European Cancer Institutes. State of the Art (START) oncology in Europe: Melanoma. Available from: http://www startoncology net/site/index php?option=com_content&view=article&id=122%3Amelanoma&catid=53%3Amelanoma-cat&Itemid=53&lang=en 2004

7. Berk LB. Radiation therapy as primary and adjuvant treatment for local and regional melanoma. Moffitt Cancer Center & Research Institute, Tampa, Florida; 2008.

8. Burmeister B, Henderson M, Thompson J, et al. Adjuvant radiotherapy improves regional (lymph node field) control in melanoma patients after lymphadenectomy: results of an intergroup randomised trial (TROG 02.01, ANZMTG 01.02). Int J Rad Oncol Biol Phys 2010;75(S3).

9. Australian Institute of Health and Welfare (AIHW). Australian Cancer Incidence and Mortality (ACIM) books. Available from http://www aihw gov au/acim-books/ 2011 [cited 2011 Aug 16];

10. Vajdic CM, Kricker A, Giblin M, et al. Incidence of ocular melanoma in Australia from 1990 to 1998. Int J Cancer 2003;105:117-22.

11. Balch CM, Soong SJ, Gershenwald JE, Thompson JF, Reintgen DS, Cascinelli N, et al. Prognostic factors analysis of 17,600 melanoma patients: validation of the American Joint Committee on Cancer melanoma staging system. J Clin Oncol 2001 Aug 15;19(16):3622-34.

12. Holt P, Frommer M. The epidemiology of melanoma in NSW. Sydney Health Projects Group, School of Public Health, University of Sydney; 2005.

13. Green A, McCredie M, Giles G, Jackman L. Occurrence of melanomas on the upper and lower limbs in Eastern Australia. Melanoma Res 1996 Oct;6(5):387-94.

14. Murali R, Desilva C, Thompson JF, Scolyer RA. Factors predicting recurrence and survival in sentinel lymph node-positive melanoma patients. Ann Surg 2011 Jun;253(6):1155-64.

15. Farshad A, Burg G, Panizzon R, Dummer R. A retrospective study of 150 patients with lentigo maligna and lentigo maligna melanoma and the efficacy of radiotherapy using Grenz or soft X-rays. Br J Dermatol 2002 Jun;146(6):1042-6.

16. SA Cancer Registry. Epidemiology of Cancer in South Australia 1997-1999. Adelaide: South Australian Cancer Registry; 2000. Report No.: September 2000.

17. McKinnon JG, Starritt EC, Scolyer RA, McCarthy WH, Thompson JF. Histopathologic excision margin affects local recurrence rate: analysis of 2681 patients with melanomas < or =2 mm thick. Ann Surg 2005 Feb;241(2):326-33.

18. Surveillance Research Program, National Cancer Institute SEER*Stat software (seer.cancer.gov/seerstat). Version 7.0.5. [computer program]. Bethesda, MD: National Cancer Institute (NCI); 2011.

19. O'Brien CJ, Coates AS, Petersen-Schaefer K, Shannon K, et al. Experience with 998 cutaneous melanomas of the head and neck over 30 years. Am J Surg 1991;162:310-3.

20. Cohn-Cedermark G, Rutqvist LE, Andersson R, Breivald M, Ingvar C, Johansson H, et al. Long term results of a randomized study by the Swedish Melanoma Study Group on 2-cm versus 5-cm resection margins for patients with cutaneous melanoma with a tumor thickness of 0.8-2.0 mm. Cancer 2000 Oct 1;89(7):1495-501.

MYELOMA

Evidence-based treatment guidelines for myeloma management issued by major national and international organisations reviewed for the model are those published after the previous radiotherapy utilisation study was completed (July 2003) up to the most recent ones published in 2012.

Updated Guidelines

The following new or updated guidelines were identified and reviewed since the original RTU study:

- NCCN clinical practice guidelines for multiple myeloma, Version 1, 2012 (1)
- British committee for standards in haematology (BCSH) guidelines on diagnosis and management of solitary plasmacytoma (2)
- British committee for standards in haematology and UK Myeloma Forum guidelines on diagnosis and management of multiple myeloma, 2010 (3)
- National Cancer Institute (NCI) plasma cell neoplasm (including multiple myeloma) treatment PDQ, 2011 (4)
- International myeloma foundation management guideline, 2002 (5)
- Mayo clinic consensus guidelines on management of symptomatic multiple myeloma, 2009 (6)

Indications for radiotherapy

All the indications for external beam radiotherapy in the original CCORE model of optimal radiotherapy utilisation for myeloma have been reviewed and updated in the optimal utilisation tree based on the latest guideline recommendations (Table 1). All of the radiotherapy indications in the model are for palliative intent; a new indication of solitary plasmacytoma has been added where radiotherapy is recommended as the primary treatment.

The model has been updated as follows:

15. *Based on radiotherapy recommendation for solitary plasmacytoma, a new clinical outcome has been added to the model*
16. *New palliative indication for radiotherapy use in spinal cord compression (SCC) for myeloma has been added as new population based incidence of SCC (5%) in myeloma has been published (7)*

All of the other previous indications remain supported by current guidelines.

Level of evidence

According to the methods applied for the previous radiotherapy utilisation model, the indications of radiotherapy for myeloma have been derived from evidence-based treatment guidelines issued by major national and international organisations. The guidelines reviewed are those published after the previous radiotherapy utilisation study was completed (July 2003) up to December 2010. Highest

priority has been given to Australian evidence-based clinical-practice guidelines (eg. NHMRC endorsed clinical practice guidelines).

Based on guidelines review, all indications of radiotherapy for myeloma remain supported by level III-IV evidence similar to those reported in the earlier model. Notably, new indications of radiotherapy have been added to the model; one for definitive treatment of solitary plasmacytoma and other two for palliative treatment of spinal cord compression (level II evidence) as described in the guidelines.

Seven of 14 outcomes in the model have an indication of radiotherapy (Figure 1) and one of them has curative intent. Two of the palliative intent radiotherapy indications (29%) are supported by level II evidence; all the remaining indications are supported by level III evidence. The updated model predicts that for 86% of the myeloma population with an indication for radiotherapy, the evidence of benefit is supported by level II-III literature.

Epidemiology of cancer stages

The epidemiological data in the myeloma utilisation tree have been reviewed to see if more recent data are available through extensive electronic search using the key words 'Australia', 'epidemiology myeloma', 'incidence', 'myeloma stage', 'radiotherapy treatment', 'recurrence', 'survival' 'treatment outcome' in various combinations. This has been applied particularly to the early branches in the tree for which national or State level data on cancer incidence rates and stages are available. If there is a change in the hierarchical quality of the epidemiological data, this has also been noted (Table 2).

Since the completion of the previous radiotherapy utilisation project the national data on cancer statistics published by AIHW have been updated to 2007 (8). The epidemiological evidence for several indications in the current model has been upgraded according to the literature published in the recent years (7;9-12).

Estimation of the optimal radiotherapy utilisation

From the evidence on the efficacy of radiotherapy and the most recent epidemiological data on the occurrence of indications for radiotherapy, the proportion of myeloma patients in whom radiotherapy would be recommended is 45% (Table 1 and Figure 1) compared with the original estimate of 38%. The change in overall utilisation rate is due to addition of new radiotherapy indications for myeloma and changes in the epidemiological data for some branches in the model.

Estimation of the optimal combined radiotherapy and chemotherapy utilisation

The indications of radiotherapy for myeloma were reviewed to identify those indications where radiotherapy is recommended in conjunction with concurrent chemotherapy as the first treatment. According to the best available practice evidence there are **no indications identified for which concurrent chemoradiation** is beneficial over radiotherapy alone as the first indicated treatment.

Sensitivity analysis

Univariate sensitivity analysis has been undertaken to assess changes in the recommended myeloma radiotherapy utilisation rate that would result from different estimates of the proportions of patients with particular attributes as mentioned in Table 2 (Figure 2). Proportions of patients with bone pain varied in the literature due to variability in the description of pain and mentioned sites. Due to this uncertainty, the estimate of optimal radiotherapy utilisation ranged from 17% to 47% as shown in the Tornado diagram (Figure 2).

Table 1: Myeloma. Indications for radiotherapy - Levels and sources of evidence

Original RTU study				Updates 2011					
Outcome No. in Tree	Clinical Scenario	Level of evidence	Proportion of all myeloma	Change of Indication	Guideline updated	Current level of evidence	Change to proportion of all myeloma		References
							Yes/ No	Updated value	
1	Solitary plasmacytoma	New indication branch added to the model based on updated clinical practice guidelines			N/A	III	N/A	0.04	NCCN (1), BCSH (2)
2	Multiple myeloma, symptomatic, age < 60 years, relapse after initial therapy, palliative treatment for bone pain	III	0.03	No	Yes	III	No	0.04	NCCN (1), BCSH (3), NCI (4), International Myeloma Foundation (5)
6	Multiple myeloma, symptomatic, age < 60 years, unable to tolerate initial therapy, palliative treatment for bone pain	III	0.02	No	Yes	III	No	0.01	NCCN (1), BCSH (3), NCI (4), International Myeloma Foundation (5)

Original RTU study				Updates 2011					
Outcome No. in Tree	Clinical Scenario	Level of evidence	Proportion of all myeloma	Change of Indication	Guideline updated	Current level of evidence	Change to proportion of all myeloma		References
							Yes/ No	Updated value	
8	Multiple myeloma, symptomatic, age < 60 years, no initial therapy, palliative treatment for bone pain	III	0.01	No	Yes	III	No	0.01	NCCN (1), BCSH (3), NCI (4), International Myeloma Foundation (5)
10	Multiple myeloma, symptomatic, age < 60 years, no initial therapy, palliative treatment for spinal cord compression	New indication			N/A	II	N/A	<0.01	NCCN guideline on myeloma (1), BCSH (3), Mayo Clinic (6)
11	Multiple myeloma, symptomatic, Age >60 years, palliative treatment for bone pain	III	0.32	No	Yes	III	Yes	0.31	NCCN (1), BCSH (3), NCI (4), International Myeloma Foundation (5)

Original RTU study				Updates 2011					
Outcome No. in Tree	Clinical Scenario	Level of evidence	Proportion of all myeloma	Change of Indication	Guideline updated	Current level of evidence	Change to proportion of all myeloma		References
							Yes/ No	Updated value	
13	Multiple myeloma, symptomatic, Age >60 years, palliative treatment for spinal cord compression	New indication			N/A	II	N/A	0.04	NCCN (1), BCSH (3), Mayo Clinic (6)
Proportion of all myeloma patients in whom radiotherapy is recommended			0.38 (38%)	**Updated proportion of all myeloma patients in whom radiotherapy is recommended**				**0.45 (45%)**	

Table 2: Myeloma; The incidence of attributes used to define indications for radiotherapy

Original RTU study				Updates 2011				
Population or sub-population of interest	**Attribute**	**Proportion of population with the attribute**	**Quality of Information**	**Change in proportion of population with attribute Yes/ No**	**Altered Proportion**	**Updated Quality of Information**	**Updated Reference**	**Comments**
All registry cancers	Myeloma	0.01	α	Yes	0.01	α	AIHW 2007 (8)	
Myeloma	Solitary plasmacytoma	New outcome	N/A	N/A	0.04	γ	Dores et al 2009 (10)	SEER data
Myeloma	Symptomatic	0.97	λ	No	N/A	N/A	Dimopoulos et al 1992 (13)	
Myeloma, symptomatic	Age <60 years	0.22	γ	No	0.22	α	AIHW 2007 (8)	
Myeloma, symptomatic, age < 60 years	Suitable for bone marrow transplant	0.86	ε	Yes	0.91	ε	Lenhoff et al 2006 (11)	
Myeloma, symptomatic, age < 60 years, suitable for bone marrow transplant	Able to complete transplant	0.78	ε	Yes	0.89	ε	Lenhoff et al 2006 (11)	

Original RTU study				Updates 2011				
Population or sub-population of interest	**Attribute**	**Proportion of population with the attribute**	**Quality of Information**	**Change in proportion of population with attribute Yes/ No**	**Altered Proportion**	**Updated Quality of Information**	**Updated Reference**	**Comments**
Myeloma, symptomatic, age < 60 years, suitable for transplant, able to complete transplant	Proportion who relapse	0.62	θ	Yes	0.68	θ	Spencer et al 2009 (12)	Clinical trial with Australia and New Zealand patient population
Myeloma, symptomatic, age < 60 years, suitable for transplant, able to complete transplant, relapse	Suitable for salvage treatment	0.89	θ	Yes	0.79	ε	Alegre et al 2002 (9)	Spanish myeloma registry data
Myeloma, symptomatic, age < 60 years, suitable for transplant, able to complete transplant, relapse, suitable for salvage treatment	Bone pain after bisphosphonates	0.42	θ	No	N/A	θ	Cochrane review 2010 (14)	Proportion updated from Cochrane review published in 2010

Original RTU study				Updates 2011				
Population or sub-population of interest	**Attribute**	**Proportion of population with the attribute**	**Quality of Information**	**Change in proportion of population with attribute Yes/ No**	**Altered Proportion**	**Updated Quality of Information**	**Updated Reference**	**Comments**
Myeloma, symptomatic, age < 60 years, suitable for transplant, unable to complete transplant	Bone pain after bisphosphonates	0.42	θ	No	N/A	θ	Cochrane review 2010 (14)	Proportion updated from Cochrane review published in 2010
Myeloma, symptomatic, age < 60 years, unsuitable for bone marrow transplant	Uncontrollable bone pain	0.42	θ	No	N/A	θ	Cochrane review 2010 (14)	Proportion updated from Cochrane review published in 2010
Myeloma, symptomatic, age < 60 years, unsuitable for bone marrow transplant	Spinal cord compression (SCC)	New outcome	N/A	N/A	0.06	γ	Loblow et al 2003 (7)	Population based SCC incidence in Canada
Myeloma, symptomatic, age 60+ year	Uncontrollable bone pain	0.42	θ	No	N/A	θ	Cochrane review 2010 (14)	Proportion updated from Cochrane review published in 2010

Original RTU study				Updates 2011				
Population or sub-population of interest	Attribute	Proportion of population with the attribute	Quality of Information	Change in proportion of population with attribute Yes/ No	Altered Proportion	Updated Quality of Information	Updated Reference	Comments
Myeloma, symptomatic, age 60+ year	Spinal cord compression (SCC)	New outcome	N/A	N/A	0.06	γ	Loblow et al 2003 (7)	Population based SCC incidence in Canada

Figure 1. Myeloma Radiotherapy Utilization Tree

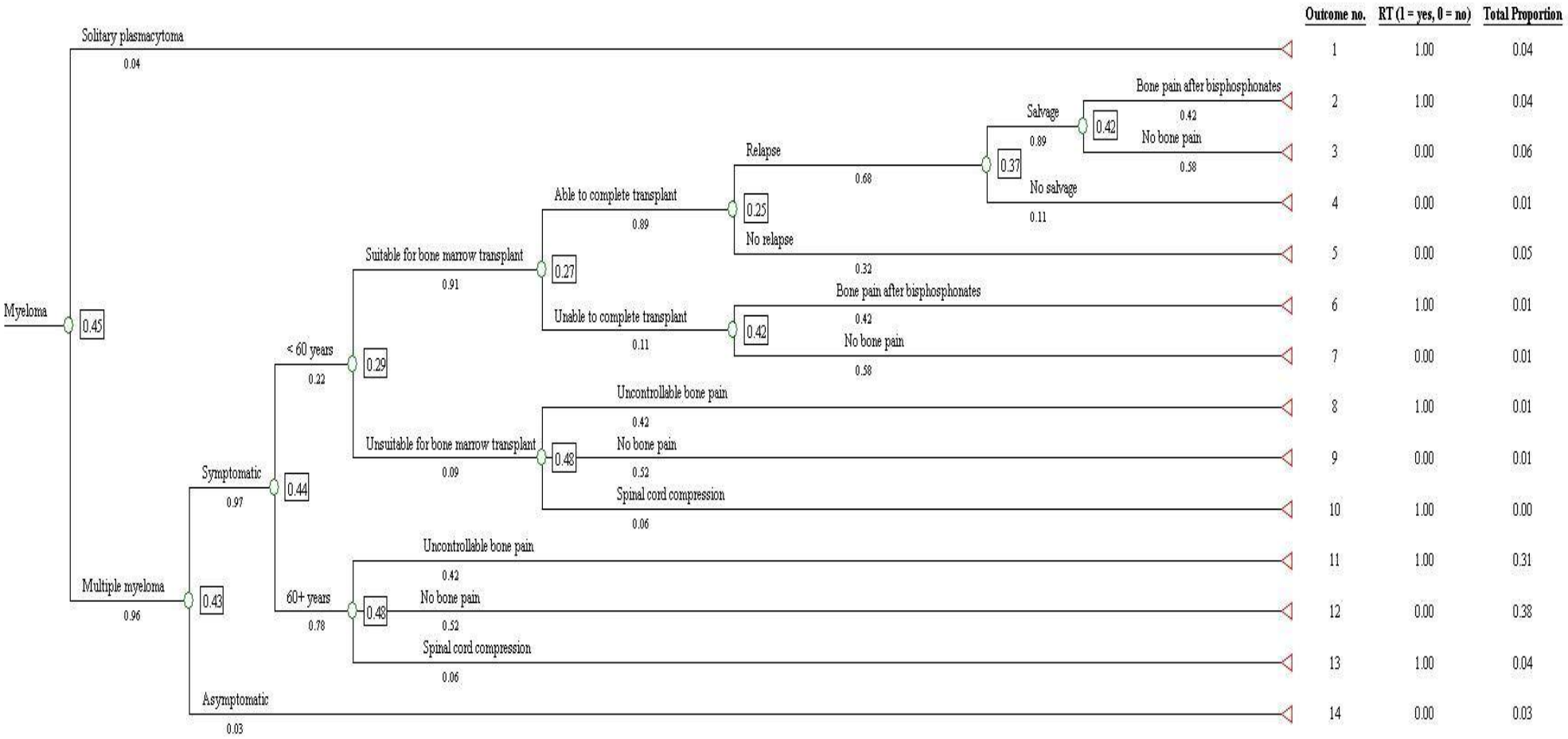
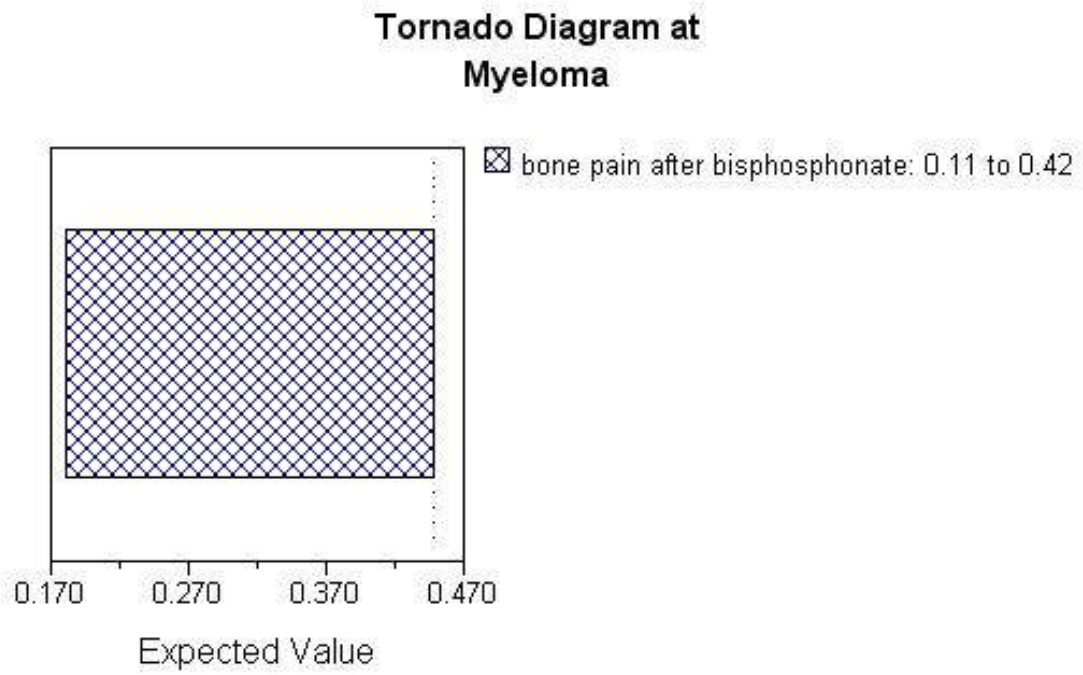


Figure 2. Tornado diagram for univariate sensitivity analyses



References

1. National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology: Multiple Myeloma.Version 1.2012. 2011.

2. Hughes M, Soutar R, Lucraft H, Owen R, Bird J. Guidelines on the diagnosis and management of solitary plasmacytoma of bone, extramedullary plasmacytoma and multiple solitary plasmacytomas: 2009 update. London (UK): British Committee for Standards in Haematology; 2009.

3. British Committee for Standards in Haematology in conjunction with the UK Myeloma Forum (UKMF). Guidelines on the diagnosis and management of multiple myeloma. 2010.

4. National Cancer Institute (NCI). Plasma cells neoplasm (including multiple myeloma) treatment (PDQ). 2011.

5. International Myeloma Foundation. Myeloma management guidelines. Available from: myeloma org/pdfs/MyelomaManagementGuidelines pdf 2002 [cited 2011 Dec 6];

6. Kumar SK, Mikhael JR, Buadi FK, Dingli D, et al. Management of newly diagnosed symptomatic multiple myeloma: updated Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART) consensus guidelines. Mayo Clin Proc 2009 Dec;84(12):1095-110.

7. Loblaw DA, Laperriere NJ, Mackillop WJ. A population-based study of malignant spinal cord compression in Ontario. Clinical Oncology 2003;15:211-7.

8. Australian Institute of Health and Welfare (AIHW). Australian Cancer Incidence and Mortality (ACIM) books. Available from http://www aihw gov au/acim-books/ 2011 [cited 2011 Aug 16].

9. Alegre A, Granda A, Martinez-Chamorro C, et al. Different patterns of relapse after autologous peripheral blood stem cell transplantation in multiple myeloma: clinical results of 280 cases from the Spanish Registry. Haematologica 2002 Jun;87(6):609-14.

10. Dores GM, Landgren O, McGlynn KA, et al. Plasmacytoma of bone, extramedullary plasmacytoma, and multiple myeloma: incidence and survival in the United States, 1992-2004. Br J Haematol 2009 Jan;144(1):86-94.

11. Lenhoff S, Hjorth M, Westin J, et al. Impact of age on survival after intensive therapy for multiple myeloma: a population-based study by the Nordic Myeloma Study Group. Br J Haematol 2006 May;133(4):389-96.

12. Spencer A, Prince HM, Roberts AW, et al. Consolidation therapy with low-dose thalidomide and prednisolone prolongs the survival of multiple myeloma patients undergoing a single autologous stem-cell transplantation procedure. J Clin Oncol 2009 Apr 10;27(11):1788-93.

13. Dimopoulos MA, Moulopoulos A, Smith T, et al. Risk of disease progression in asymptomatic multiple myeloma. American Journal of Medicine 1993;94:57-61.

14. Mhaskar R, Redzepovic J, Wheatley K, et al. Bisphosphonates in multiple myeloma (Review). Cochrane Database of Systematic Reviews 2010;3.

OESOPHAGEAL CANCER

Evidence-based treatment guidelines for oesophageal cancer published by major national and international organisations since the completion of the previous radiotherapy utilisation study in July 2003 have been identified and reviewed.

Updated Guidelines

The following new or updated guidelines were reviewed:

- National Comprehensive Cancer Network (NCCN). Clinical practice guidelines in oncology: Oesophageal cancer, Version 1.2012 (1)
- National Cancer Institute (NCI). Oesophageal Cancer Treatment (PDQ®), 2012 (2)
- Cancer Care Ontario guidelines for resectable and unresectable oesophageal cancers, 2011 (3;4)
- Saskatchewan Cancer Agency (Canada) oesophageal cancer guidelines, 2011 (5)
- European Society for Medical Oncology (ESMO) guidelines, 2010 (6)
- Clinical guidelines for management of oesophageal cancer in India, 2010 (7)
- SIGN guidelines for management of gastric and oesophageal cancer, 2006 (8)
- British Society of Gastroenterology (GE) guidelines for management of oesophageal and gastric cancer, 2002 (9)

Indications for radiotherapy

All the indications for external beam radiotherapy in the original CCORE model of optimal radiotherapy utilisation for oesophageal cancer have been reviewed and updated based on the latest guideline recommendations (Table 1).

There were some changes to the indications previously reported, mainly, because of newer evidence of benefit of concurrent chemoradiation for specific clinical scenarios; radiotherapy along with chemotherapy concurrently applied as a preoperative therapy for suitable patients showed better survival and locoregional control compared with surgery only option (10-12); all of the other previous radiotherapy (RT) indications remain supported by current evidence-based guidelines.

Level of evidence

According to the methods applied for the previous utilisation model, the indications of RT for oesophageal cancer have been derived from evidence-based treatment guidelines issued by major national and international organisations.

Based on guidelines review, the level of evidence for some clinical scenarios in the model has been upgraded; for postoperative oesophageal cancer without clear margins (R1 or R2) and for

locoregional recurrence after surgery the evidence level have been revised to level III from level IV reported in the previous model because of stronger evidence of RT benefit (1;5;9). Also, there is now newer evidence of radiotherapy advantage for symptomatic stage IV oesophageal cancer, especially, the palliative RT advantage for dysphagia (6;8); hence, this level of evidence is upgraded from level IV to level II. These changes have been recorded in Table 1. Ten outcomes in the model have radiotherapy indications and of them 8 outcomes are supported by level I-II evidence comprising 69% population with oesophageal cancer (Table 1 and Figure 1).

Epidemiology of cancer stages

The epidemiological data in the oesophageal cancer utilisation tree have been reviewed to examine whether more recent data are available through extensive electronic search using the key words 'epidemiology oesophageal cancer', 'oesophageal cancer stage', 'incidence', 'local control', 'radiotherapy treatment', 'recurrence', 'survival', 'treatment outcome' in various combinations. Table 2 provides an updated list of data used and assessment of the hierarchical quality of that data. Since the completion of the previous radiotherapy utilisation project the national data on cancer statistics published by AIHW have been updated to 2008 (13). In 2008, oesophageal cancer accounted for 1.2% of all cancers in Australia.

Estimation of the optimal radiotherapy utilisation

From the evidence on the efficacy of RT and the most recent epidemiological data, the proportion of oesophageal cancer patients in whom RT would be recommended is 71% (Table 1 and Figure 1) compared with the original estimate of 80%. The change is due to update of RT indications and changes in epidemiological data for oesophageal cancer in different stages.

Estimation of the optimal combined radiotherapy and chemotherapy utilisation

The indications of RT for oesophageal cancer were reviewed to identify those indications where the therapy is recommended in conjunction with concurrent chemotherapy. According to the best available evidence there are two indications for combined therapy; they are 1) as a preoperative therapy of certain resectable oesophageal cancers and 2) for inoperable locally advanced (stage II-III) oesophageal cancers if patients are suitable for concurrent chemoradiotherapy (CRT).

Neoadjuvant concurrent CRT has been recommended in several cancer management guidelines (1;3;6;7) as the therapy downstages tumours and facilitates complete resection, especially, in patients with bulky disease with borderline operability where the chances of a clear resection are less likely; published meta-analyses of randomised trials also showed better survival and locoregional control over surgery alone (10-12). Hence, this therapy is included in our model as a new outcome branch.

Guidelines also suggested that concurrent CRT is superior to RT alone for patients with localized oesophageal cancer but with significant toxicities and thus should be recommended to patients who are in good general condition and the risk benefit has been thoroughly discussed with the patients

(4;5). Based on these recommendations, the outcome indication of definitive non-surgical treatment in our model has been revised and the indication with epidemiological data on patients with poor general condition (mainly elderly patients) that are unlikely to tolerate concurrent CRT was included (Outcome 9). Our model predicted that 33% of oesophageal cancer patients would benefit from addition of CRT to their treatment (Table 3 and Figure 2).

Sensitivity analysis

Univariate sensitivity analysis has been undertaken to assess changes in the recommended oesophageal cancer RT utilisation rate that would result from different estimates of the proportions of patients with particular attributes as mentioned in Table 2 (Figure 3). Also, the sensitivity analysis tested the effect of including or excluding the RT recommendation as a preoperative therapy. The epidemiological data on the proportion of patients that have complete surgical resection with clear margins (53%-80%), recur after surgery (40%-50%) and the proportion that have locoregional recurrence (21%-68%) have been variable as the study results varied depending on site of tumour, stage as well as variability in surgical techniques in the patient population (14-17). In addition, the studies that reported the proportions with painful bone metastasis (16% to 33%) have also varied (18-20) (Table 2). The variability in the estimate of optimal radiotherapy utilisation due to these uncertainties was 15% and the expected value ranged from 57% to 72% as shown in the Tornado diagram (Figure 3).

Table 1: Oesophageal Cancer. Indications for radiotherapy - Levels and sources of evidence

Original RTU study				Updates 2012					
Outcome No. in Tree	Clinical Scenario	Level of evidence	Proportion of all oesophageal cancer	Change of Indication	Guideline updated	Current level of evidence	Change to proportion of all oesophageal cancer		References
							Yes/ No	Updated value	
2	Stage II-III, surgery, preoperative therapy	New outcome branch			Yes	I	N/A	0.13	NCCN (1), NCI PDQ (2), Sask Cancer Agency (5), ESMO (6), Indian guidelines (7), SIGN (8)
3	Stage II-III, surgery, no preoperative therapy, resection with clear margins, locoregional recurrence	IV	0.06	No	Yes	III	Yes	0.01	NCCN (1), NCI PDQ (2), Sask Cancer Agency (5), ESMO (6), Indian guidelines (7), SIGN (8)
4	Stage II-III, surgery, no preoperative therapy, resection with clear margins, brain metastases	II	<0.01	No	Yes	II	No	<0.01	NCCN (1), NCI PDQ (2), Sask Cancer Agency (5), ESMO (6), Indian guidelines (7), SIGN (8)

Original RTU study				Updates 2012					
Outcome No. in Tree	Clinical Scenario	Level of evidence	Proportion of all oesophageal cancer	Change of Indication	Guideline updated	Current level of evidence	Change to proportion of all oesophageal cancer		References
							Yes/ No	Updated value	
5	Stage II-III, surgery, no preoperative therapy, resection with clear margins, distant recurrence, no brain metastases, painful bone metastases	I	0.01	No	Yes	I	No		NCCN (1), NCI PDQ (2), Sask Cancer Agency (5), ESMO (6), Indian guidelines (7), SIGN (8)
8	Stage II-III, surgery, no preoperative therapy, resection, no clear margins	IV	0.06	No	Yes	III	Yes	0.01	NCCN (1), NCI PDQ (2), ESMO (6), Indian guidelines (7), SIGN (8)
9	Stage II-III, no surgery, fit for concurrent chemo-radiotherapy	Modified outcome branch			Yes	II	N/A	0.20	NCCN (1), NCI PDQ (2), CCO (4), Sask Cancer Agency (5), ESMO (6), Indian guidelines (7), SIGN (8) , British GE Society (9)

Original RTU study				Updates 2012					
Outcome No. in Tree	Clinical Scenario	Level of evidence	Proportion of all oesophageal cancer	Change of Indication	Guideline updated	Current level of evidence	Change to proportion of all oesophageal cancer		References
							Yes/ No	Updated value	
10	Stage II-III, no surgery, not fit for concurrent chemo-radiotherapy	Modified outcome branch			Yes	II	N/A	0.04	NCCN (1), NCI PDQ (2), CCO (4), Sask Cancer Agency (5), ESMO (6), Indian guidelines (7), SIGN (8), British GE Society (9)
11	Stage IV, symptomatic locoregional disease	IV	0.24	No	Yes	II	Yes	0.28	NCCN (1), NCI PDQ (2), Sask Cancer Agency (5), ESMO (6), Indian guidelines (7), British GE Society (9)
12	Stage IV, no symptomatic locoregional disease, brain metastases	II	0.01	No	Yes	II	No	0.01	NCCN (1), NCI PDQ (2), Sask Cancer Agency (5), ESMO (6), Indian guidelines (7), SIGN (8)

Original RTU study				Updates 2012					
Outcome No. in Tree	Clinical Scenario	Level of evidence	Proportion of all oesophageal cancer	Change of Indication	Guideline updated	Current level of evidence	Change to proportion of all oesophageal cancer		References
							Yes/ No	Updated value	
13	Stage IV, no symptomatic locoregional disease, no brain metastases, painful bone metastases	I	0.02	No	Yes	I	Yes	0.03	NCCN (1), NCI PDQ (2), Sask Cancer Agency (5), ESMO (6), Indian guidelines (7), SIGN (8)
Proportion of all oesophageal cancer patients in whom radiotherapy is recommended			0.80 (80%)	**Updated proportion of all oesophageal cancer patients in whom radiotherapy is recommended**				**0.71 (71%)**	

Table 2: Oesophageal Cancer. The incidence of attributes used to define indications for radiotherapy

Original RTU study				Updates 2011			
Population or sub-population of interest	**Attribute**	**Proportion of population with the attribute**	**Quality of Information**	**Change in proportion of population with attribute Yes/ No**	**Altered Proportion**	Updated quality of information	**Updated Reference**
All registry cancers	Oesophageal cancer	0.01	α	No	0.01	α	AIHW 2011 (13)
Oesophageal cancer	Stage II-III	Modified outcome branch			0.62	γ	SEER 2011 (21)
Stage II-III	Surgery	Modified outcome branch			0.43	γ	SEER 2011 (21)
Stage II-III, surgery	Preoperative therapy required	New outcome branch			0.76	ε	Meredith et al 2010 (22)
Stage II-III, surgery, no preoperative therapy	Resection with clear margins	0.80	δ	No	0.80 0.53-0.80	δ ζ	Pye et al 2001 (23) Khan et al 2010 (14)
Stage II-III, surgery, no preoperative, clear margins	Recurrence	Modified outcome branch			0.50 0.40	ζ ζ	Marriete et al 2004 (16) Hofstetter et al 2002 (17)

Original RTU study				Updates 2011			
Population or sub-population of interest	**Attribute**	**Proportion of population with the attribute**	**Quality of Information**	**Change in proportion of population with attribute Yes/ No**	**Altered Proportion**	Updated quality of information	**Updated Reference**
Stage II-III, surgery, no preoperative therapy, resection with clear margins, recurrence	Locoregional recurrence	0.27	ζ		0.33 0.21-0.68	ζ ζ	Marriete et al 2003 (24) Lee et al 2004 (15)
Stage II-III, surgery, no preoperative therapy, resection with clear margins, distant recurrence	Brain metastases	0.10	ζ	No	N/A	N/A	Dresner and Griffin 2000 (18)
Stage II-III, surgery, no preoperative therapy, clear margins, distant recurrence, no brain metastases	Painful bone metastases	0.33 0.16	ζ ζ	No	N/A	N/A	Dresner and Griffin 2000 (18) Law et al 1996 (20)

Original RTU study				Updates 2011			
Population or sub-population of interest	**Attribute**	**Proportion of population with the attribute**	**Quality of Information**	**Change in proportion of population with attribute Yes/ No**	**Altered Proportion**	Updated quality of information	**Updated Reference**
Stage II-III, no surgery	Fit for concurrent chemo-radiotherapy	Modified outcome branch			0.84	θ	Smith et al 2009 (25)
Stage IV	Symptomatic local disease	0.75	ζ	Yes	0.74	δ	Smithers et al 2010 (26)
Stage IV, no symptomatic primary	Brain metastases	0.10	ζ	No	N/A	N/A	Dresner and Griffin 2000 (18)
Stage IV, no symptomatic primary, no brain metastases	Painful bone metastases	0.33 0.16	ζ ζ	No	N/A	N/A	Dresner and Griffin 2000 (18) Law et al 1996 (20)

Table 3: Oesophageal Cancer. Indications for concurrent chemoradiotherapy (CRT) - Levels and sources of evidence

Outcome No. in Tree	Clinical Scenario	Level of Evidence	References	Proportion of all oesophageal cancer patients
2	Oesophageal cancer, Stage II-III, surgery, preoperative therapy	I	NCCN (1), NCI PDQ (2), Sask Cancer Agency (5), ESMO (6), Indian guidelines (7), SIGN (8), British Society of GE (9)	0.13
9	Stage II-III, no surgery, fit for concurrent chemo-radiotherapy	II	NCCN (1), NCI PDQ (2), Sask Cancer Agency (5), ESMO (6), Indian guidelines (7), SIGN (8), British Society of GE (9)	0.20
The total proportion of all patients with oesophageal cancer in whom concurrent chemoradiotherapy (CRT) is recommended				**0.33 (33%)**

Figure 1. Oesophageal Cancer Radiotherapy Utilization Tree

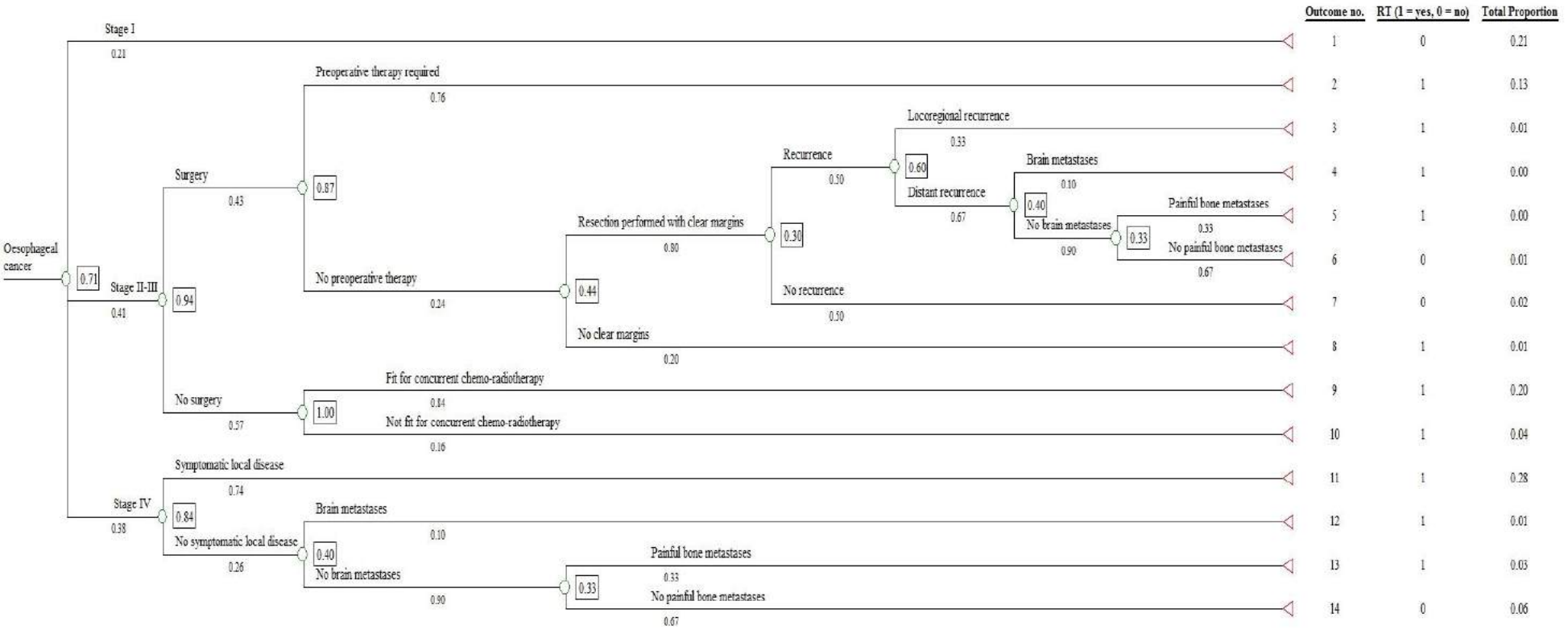


Figure 2. Oesophageal Cancer Concurrent ChemoRadiotherapy (CRT) Utilization Tree

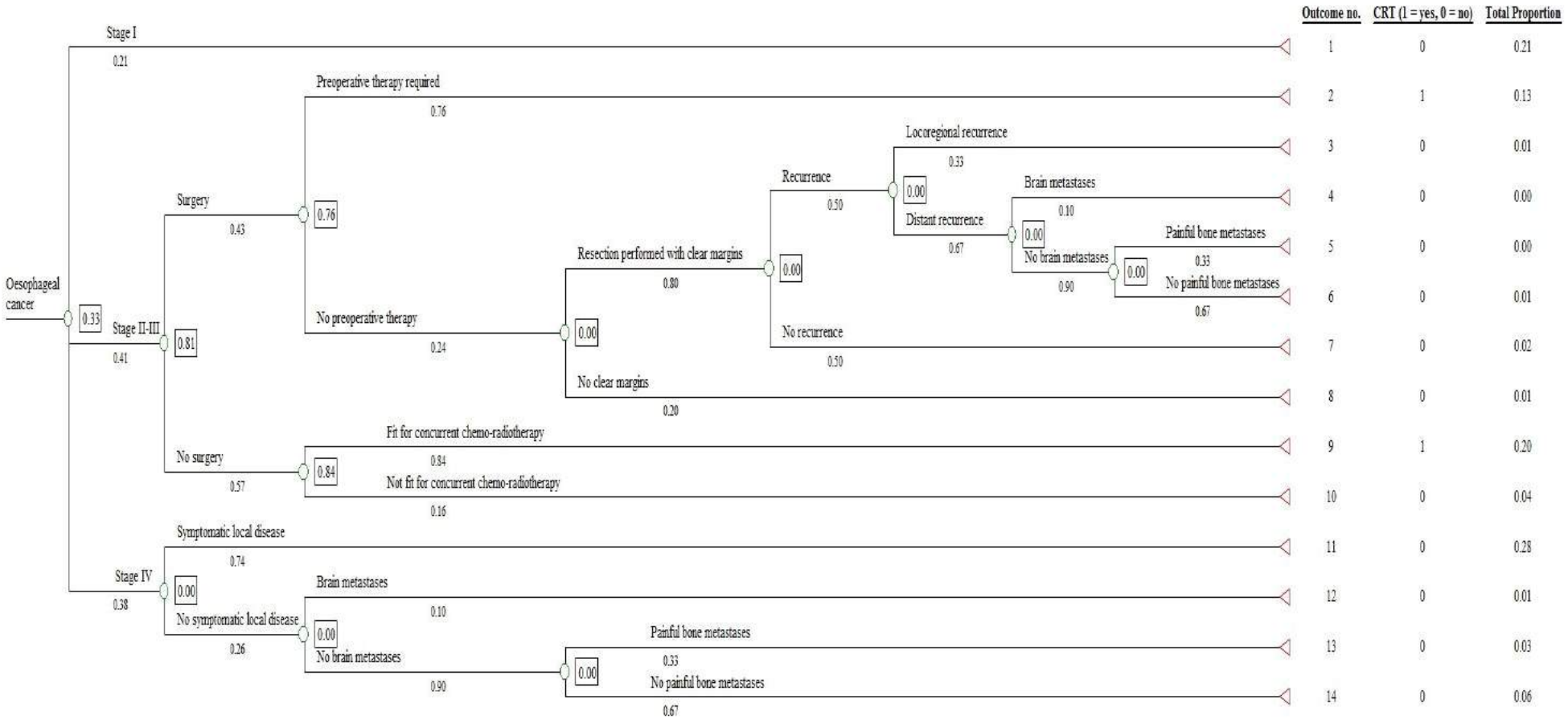
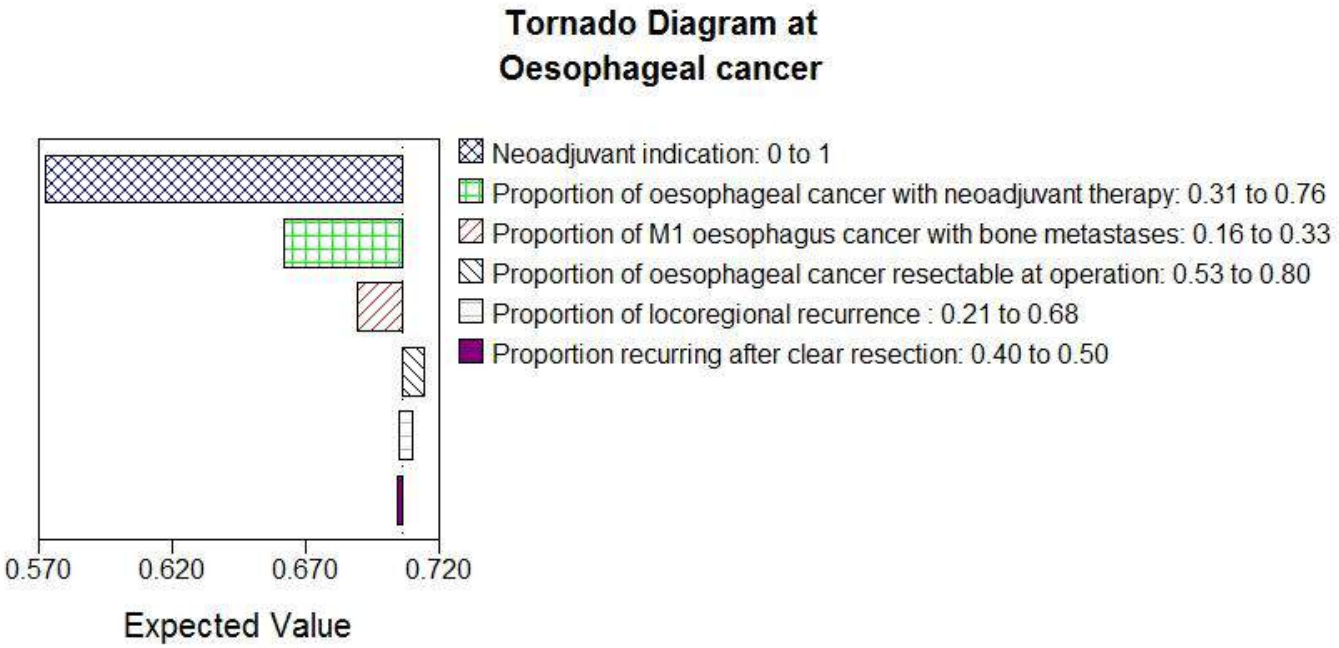


Figure 3. Tornado diagram for univariate sensitivity analyses



References

1. National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology: Esophageal and esophagogastric junction cancer.Version 1.2012. 2012.

2. National Cancer Institute (NCI). Esophageal cancer treatment (PDQ). 2012.

3. Malthaner RA, Wong RK, Spithoff K, et al, Gastrointestinal Cancer Disease Site Group. Preoperative or postoperative therapy for resectable esophageal cancer: guideline recommendations. Toronto: Cancer Care Ontario (CCO); 2008.

4. Members of the Gastrointestinal Cancer Disease Site Group, Wong R, Tey R, reviewers. Combined modality radiotherapy and chemotherapy in the non-surgical management of localized carcinoma of the esophagus. Program in Evidence-based Care Evidence-Based Series No.: 2-12 Version 2. Toronto: Cancer Care Ontario (CCO); 2011.

5. Saskatchewan Cancer Agency. Provincial Esophageal Cancer and Gastro-esophageal junction Cancer Treatment Guidelines. 2011.

6. Stahl M., Budach W, Meyer HJ, Cervantes A, On behalf of the ESMO Guidelines Working Group. Esophageal cancer: ESMO clinical recommendations for diagnosis, treatment and follow-up. Ann Oncol 2010;21 Suppl 5:v46-v49.

7. World Health Organisation (WHO) Country Office for India. Clinical guidelines for management of esophageal cancer in India . 2010.

8. Scottish Intercollegiate Guidelines Network (SIGN). Management of oesophageal and gastric cancer. Edinburgh: SIGN, Royal College of Physicians; 2006.

9. Allum WH, Griffin SM, Watson A, Colin-Jones D, on behalf of the British Society of Gastroenterology. Guidelines for the management of oesophageal and gastric cancer. Gut 2002 Jun;50 Suppl 5:v1-23.

10. Sjoquist K, Burmeister B, Smithers BM, Zalcberg J, Simes RJ, Barbour A, et al. Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal carcinoma: an updated meta-analysis. Lancet Oncol 2011;12(7):681-92.

11. Fiorica F, Di Bona D, Schepis F, et al. Preoperative chemoradiotherapy for oesophageal cancer: a systematic review and meta-analysis. Gut 2004 Jul;53(7):925-30.

12. Urschel JD, Vasan H. A meta-analysis of randomized controlled trials that compared neoadjuvant chemoradiation and surgery to surgery alone for resectable esophageal cancer. Am J Surg 2003 Jun;185(6):538-43.

13. Australian Institute of Health and Welfare (AIHW). Australian Cancer Incidence and Mortality (ACIM) books. Available from http://www aihw gov au/acim-books/ 2012 [cited 2012 Apr 16];

14. Khan OA, Cruttenden-Wood D, Toh SK. Is an involved circumferential resection margin following oesphagectomy for cancer an important prognostic indicator? Interact Cardiovasc Thorac Surg 2010 Nov;11(5):645-8.

15. Lee SJ, Lee KS, Yim YJ, et al. Recurrence of squamous cell carcinoma of the oesophagus after curative surgery: rates and patterns on imaging studies correlated with tumour location and pathological stage. Clin Radiol 2005 May;60(5):547-54.

16. Mariette C, Taillier G, Van Seuningen I, Triboulet JP. Factors affecting postoperative course and survival after en bloc resection for esophageal carcinoma. Ann Thorac Surg 2004 Oct;78(4):1177-83.

17. Hofstetter W, Swisher SG, Correa AM, et al. Treatment outcomes of resected esophageal cancer. Ann Surg 2002 Sep;236(3):376-84.

18. Dresner SM, Griffin SM. Pattern of recurrence following radical oesophagectomy with two-field lymphadenectomy. Br J Surg 2000;87:1426-33.

19. Fok M, McShane J, Law SYK, Wong J. Prospective randomised study on radiotherapy and surgery in the treatment of oesophageal carcinoma. Asian J Surgery 1994;17(3):223-9.

20. Law SYK, Fok M, Wong J. Pattern of recurrence after oesophageal resection for cancer: clinical implications. Br J Surg 1996;83:107-11.

21. Surveillance Research Program, National Cancer Institute SEER*Stat software (seer.cancer.gov/seerstat). Version 7.0.5. [computer program]. Bethesda, MD: National Cancer Institute (NCI); 2011.

22. Meredith KL, Weber JM, Turaga KK, et al. Pathologic response after neoadjuvant therapy is the major determinant of survival in patients with esophageal cancer. Ann Surg Oncol 2010 Apr;17(4):1159-67.

23. Pye JK, Crumplin MKH, Charles J, Kerwat R, et al. One-year survey of carcinoma of the oesophagus and stomach in Wales. Br J Surg 2001;88:278-85.

24. Mariette C, Balon JM, Piessen G, et al. Pattern of recurrence following complete resection of esophageal carcinoma and factors predictive of recurrent disease. Cancer 2003 Apr 1;97(7):1616-23.

25. Smith GL, Smith BD, Buchholz TA, et al. Patterns of care and locoregional treatment outcomes in older esophageal cancer patients: The SEER-Medicare Cohort. Int J Radiat Oncol Biol Phys 2009 Jun 1;74(2):482-9.

26. Smithers BM, Fahey PP, Corish T, et al. Symptoms, investigations and management of patients with cancer of the oesophagus and gastro-oesophageal junction in Australia. Med J Aust 2010 Nov 15;193(10):572-7.

OVARIAN CANCER

Evidence-based treatment guidelines for ovarian cancer were reviewed. Ovarian management guidelines published by major national and international organisations since the completion of the previous radiotherapy utilisation study in July 2003 have been reviewed.

Updated Guidelines

The following new or updated guidelines were identified and reviewed:

- NHMRC endorsed guidelines on management of ovarian cancer, 2004 (1)
- NSW Gynaecological Oncology Group best practice guidelines, 2009 (2)
- National Comprehensive Cancer Network (NCCN). Clinical practice guidelines in oncology: Ovarian cancer, Version 3.2012 (3)
- National Cancer Institute (NCI). Ovarian Cancer Treatment (PDQ®), 2012 (4)
- Yorkshire Cancer Network gynaecological cancer management guidelines (5)
- Alberta Health Service palliative radiotherapy guidelines, 2010 (6)
- BC Cancer Agency ovarian cancer management guidelines, 2007 (7)
- SIGN guidelines on management of ovarian cancer, 2007 (8)
- International Federation of Gynaecology and Obstetrics (FIGO) guidelines on gynaecological cancers, 2006 (9)
- Cancer Care Ontario (CCO) guidelines on ovarian cancer, 2004 (10)

Indications for radiotherapy

All the indications for external beam radiotherapy in the original CCORE model of optimal radiotherapy utilisation for ovarian cancer have been reviewed and updated based on the latest guideline recommendations (Table 1). *There was no change to the indications previously reported; the radiotherapy (RT) indications in the model remain supported by the current guidelines.*

RT use in ovarian cancer is mostly limited to palliative treatment of brain metastasis and symptom control for some groups of patients with advanced stage disease (1;2); a randomised controlled trial in Sweden reported better progression free survival for a group of FIGO stage III ovarian cancer patients with complete surgical and pathologic remission who were offered whole abdomen radiotherapy (WART) compared with the groups with chemotherapy or no treatment option, but the toxicity for the radiotherapy group was higher (11). NHMRC guidelines for ovarian cancer published in 2004 and BC Cancer Agency ovarian cancer guidelines (1;7) recommended WART for selective stage III patients; but more recent NSW gynaecological oncology guidelines (2) state that WART is appropriate for a highly selective group of ovarian cancer patients with very small <1cm pelvic disease with no upper abdominal extension. Since WART is not a therapy recommended in high level international guidelines (3;4;8) and it has been very hard to find epidemiological data on the above-mentioned

indication, our updated model includes indications of RT only for palliative treatment of stage IV ovarian cancer similar to that of the previous model.

Level of evidence

The indications of radiotherapy for ovarian have been derived from evidence-based treatment guidelines issued by major national and international organisations. The guidelines reviewed are those published after the previous radiotherapy utilisation study completed in July 2003 up to March 2012.

There is only one outcome in the model that has a radiotherapy indication: that is palliative radiotherapy for stage IV patients with brain, bone or distant lymph node metastases. This indication is supported by level II evidence as reported in the earlier model (Table 1 and Figure 1).

Epidemiology of cancer stages

The epidemiological data in the ovarian cancer utilisation tree have been reviewed to see if more recent data are available through extensive electronic search using the key words 'epidemiology ovarian cancer', 'incidence', 'local control', 'ovarian cancer stage', 'radiotherapy treatment', 'recurrence', 'survival', 'treatment outcome' in various combinations. Table 2 provides an updated list of data used and assessment of the hierarchical quality of that data. Since the completion of the previous radiotherapy utilisation project the national data on cancer statistics published by AIHW have been updated to 2008 (12). In 2008, ovarian cancer accounted for 1.1% of all cancers in Australia.

The epidemiological data on the palliative radiotherapy indication for brain, bone or distant lymph node metastasis (12%-18%) were updated from retrospective single institution studies from UK (13) and USA (14-15) (Table 2). The proportion used for the model (12%) was based on similar metastatic site distribution in the studies from Royal Marsden Hospital, London (13) and Harvard Medical School, Boston (15); the model effect of the data variability was tested though sensitivity analysis.

Estimation of the optimal radiotherapy utilisation

From the evidence on the efficacy of radiotherapy and the most recent epidemiological data on the occurrence of indications for radiotherapy, the proportion of ovarian cancer patients in whom radiotherapy would be recommended is 3.6% (4%) (Table 1 and Figure 1); the rate remains similar to that of the original estimate of 4.2%. The slight change in proportion is due to changes in epidemiological data.

Estimation of the optimal combined radiotherapy and chemotherapy utilisation

Concurrent chemoradiation is not recommended for treatment of ovarian cancer.

Sensitivity analysis

The epidemiological data on proportion of advanced stage ovarian cancer patients that have an indication of RT were updated from single institution studies in UK and USA (13-15) that reported 12%-18% proportion of ovarian cancer patients had brain, bone or distant lymph node metastasis; the sensitivity analysis with this data range showed the estimate of radiotherapy utilization varied from 3.6% to 5.5% (Figure 2).

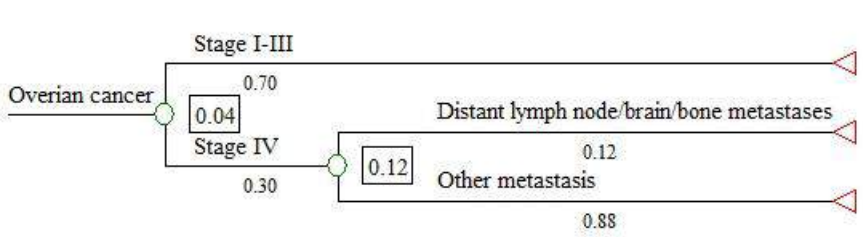
Table 1: Ovarian Cancer. Indications for radiotherapy - Levels and sources of evidence

Original RTU study				Updates 2012					
Outcome No. in Tree	Clinical Scenario	Level of evidence	Proportion of all ovarian cancer	Change of Indication	Guideline updated	Current level of evidence	Change to proportion of all ovarian cancer		References
							Yes/ No	Updated value	
1	Ovarian cancer, Stage IV, brain, bone or distant lymph node metastases	II	0.042	No	Yes	II	Yes	0.036	NHMRC (1), NSW GO group (2), YCN (5), Alberta Health Service (6), BCCA (7), SIGN (8), FIGO (9), CCO (10)
Proportion of all ovarian cancer patients in whom radiotherapy is recommended			0.042 (4%)	**Updated proportion of all ovarian cancer patients in whom radiotherapy is recommended**				**0.036 (4%)**	

Table 2: Ovarian Cancer; The incidence of attributes used to define indications for radiotherapy

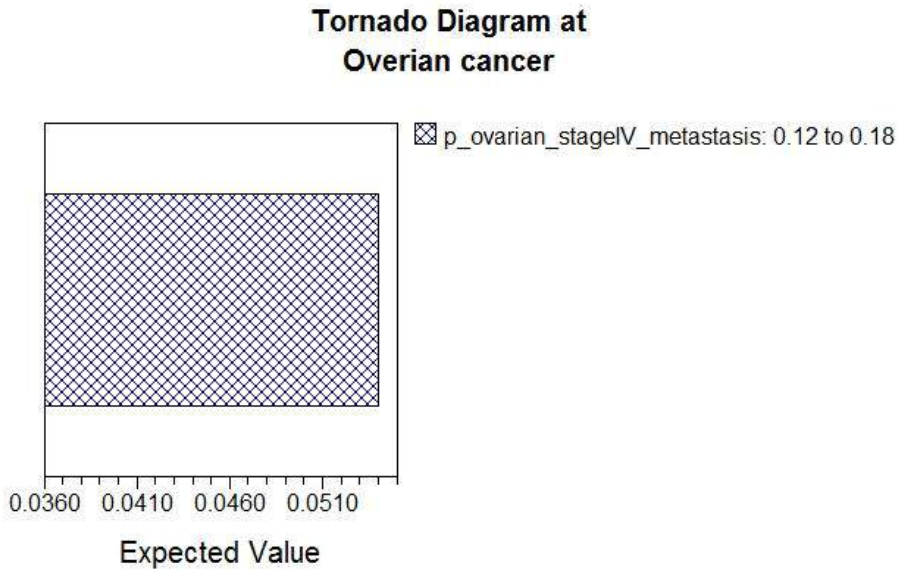
Original RTU study				Updates 2012			
Population or sub-population of interest	**Attribute**	**Proportion of population with the attribute**	**Quality of Information**	**Change in proportion of population with attribute Yes/ No**	**Altered Proportion**	**Updated quality of information**	**Updated Reference**
All registry cancers	Ovarian cancer	0.01	α	No	0.01	α	AIHW 2011 (12)
Ovarian cancer	Stage IV	0.38	ζ	Yes	0.30	γ	SEER 2011 (16)
Ovarian cancer, Stage IV	Distant lymph node, brain and bone metastasis that require palliative RT	0.11	ζ	Yes	0.12 0.18 0.12	ζ ζ ζ	Bonnefoi et al 1999 (13) Tinger et al 2001 (14) Rauh-Hain et al 2012 (15)

Figure 1. Ovarian Cancer Radiotherapy Utilization Tree



Outcome no	RT (1 = yes, 0 = no)	Total Proportion
1	0	0.70
2	1	0.04
3	0	0.26

Figure 2. Tornado diagram for univariate sensitivity analysis



References

1. Australian Cancer Network and National Breast Cancer Centre. Clinical practice guidelines for the management of women with epithelial ovarian cancer. Sydney: NHMRC; 2004.

2. Greater Metropolital Clinical Taskforce (GMCT). Best clnical practice: Gynaecological cancer guidelines 2009. Sydney: NSW Depatment of Health; 2009.

3. National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology: Ovarian cancer.Version 3.2012. 2012.

4. National Cancer Institute (NCI). Ovarian cancer treatment (PDQ). Available at: http://www cancer gov/cancertopics/pdq/treatment/ovarianepithelial/HealthProfessional 2012 [cited 2012 May 22];

5. Yorkshire Cancer Network (YCN). YCN Gynaecology Netwrok Group guidelines for the management of gynaecological cancers. Available at: http://www ycn nhs uk/html/downloads/ycn-gynae-guidelinesclinical-aug2011 pdf 2011 [cited 2012 May 15];

6. Alberta Health Services CC. Palliative radiotherapy. Edmonton, Alberta; 2010.

7. BC Cancer Agency. Cancer management guidelines. Gynaecology - Ovarian cancer management. Available at: http://www bccancer bc ca/HPI/CancerManagementGuidelines/Gynecology/OvaryEpithelial/Management htm 2007 [cited 2012 May 9];

8. Scottish Intercollegiate Guidelines Network (SIGN). Epithelial ovarian cancer. A national clinical guideline. Edinburgh: SIGN, Royal College of Physicians; 2007.

9. FIGO Committee on Gynecologic Oncology. FIGO staging classifications and clinical practice guidelines in the management of gynecologic cancers. 2006 Oct.

10. Cancer Care Ontario. Adjuvant care for stage I ovarian cancer. Practice Guideline Report #4-13. Toronto ON: Cancer Care Ontario; 2004.

11. Sorbe B. Consolidation treatment of advanced ovarian carcinoma with radiotherapy after induction chemotherapy. Int J Gynecol Cancer 2003 Nov;13 Suppl 2:192-5.

12. Australian Institute of Health and Welfare (AIHW). Australian Cancer Incidence and Mortality (ACIM) books. Available from: http://www aihw gov au/acim-books/ 2011 [cited 2011 Aug 16];

13. Bonnefoi H, A'Hern RP, Fisher C, Macfarlane V, Barton D, Blake P, et al. Natural history of stage IV epithelial ovarian cancer. J Clin Oncol 1999 Mar;17(3):767-75.

14. Tinger A, Waldron T, Peluso N, Katin MJ, Dosoretz DE, Blitzer PH, et al. Effective palliative radiation therapy in advanced and recurrent ovarian carcinoma. Int J Radiat Oncol Biol Phys 2001 Dec 1;51(5):1256-63.

15. Rauh-Hain JA, Winograd D, Growdon WB, Schorge JO, Goodman AK, Boruta DM, et al. Prognostic determinants in patients with uterine and ovarian clear carcinoma. Gynecol Oncol 2012 May;125(2):376-80.

16. Surveillance Research Program, National Cancer Institute SEER*Stat software (seer.cancer.gov/seerstat). Version 7.0.5. [computer program]. Bethesda, MD: National Cancer Institute (NCI); 2011.

PANCREATIC CANCER

Evidence-based treatment guidelines for pancreatic cancer published by major national and international organisations since the completion of the previous radiotherapy utilisation study in July 2003 have been identified and reviewed.

Updated Guidelines

The following new or updated guidelines were reviewed:

- National Comprehensive Cancer Network (NCCN). Clinical practice guidelines in oncology: Pancreatic cancer, Version 1.2012 (1)
- National Cancer Institute (NCI). Pancreatic Cancer Treatment (PDQ®), 2012 (2)
- Cancer Care Ontario guidelines for locally advanced pancreatic cancers, 2011 (3)
- European Society for Medical Oncology (ESMO) guidelines, 2010 (4)
- British Society of Gastroenterology (GE) guidelines for management of pancreatic cancer, 2005 (5)

Indications for radiotherapy

All the indications for external beam radiotherapy (RT) in the original CCORE model of optimal radiotherapy utilisation for pancreatic cancer have been reviewed and updated based on the latest guideline recommendations (Table 1 and Figure 1). *As the model has been revised substantially, the tree is newly designed and NOT comparable to the previous one.*

Level of evidence

According to the methods applied for the previous utilisation model, the indications of RT for pancreatic cancer have been derived from evidence-based treatment guidelines issued by major national and international organisations. Five outcomes in the model have RT indications and three of them are supported by level II evidence comprising 35% of population with pancreatic cancer (Table 1 and Figure 1).

Epidemiology of cancer stages

The published recent epidemiological data on pancreatic cancer have been identified through extensive electronic search using the key words ‘epidemiology pancreatic cancer’, ‘pancreatic cancer stage‘, ‘incidence’, ‘local control’, ‘radiotherapy treatment’, ‘survival’, ‘treatment outcome’ in various combinations. Table 2 provides an updated list of data used and assessment of the hierarchical quality of that data. According to the updated national data on cancer statistics published by AIHW, pancreatic cancer accounted for 2.1% of all cancers in Australia in 2008 (6).

For epidemiological data of most of the clinical scenarios in the model SEER data have been used (7). The proportion of early stage pancreatic cancer patients that receive adjuvant RT varied between studies (Table 2)(8;9). For our model the proportion estimate (60%) of the most recently studied Corsini et al study (8) been used.

Estimation of the optimal radiotherapy utilisation

From the evidence on the efficacy of RT and the most recent epidemiological data, the proportion of pancreatic cancer patients in whom RT would be recommended is 49% (Table 1 and Figure 1) compared with the original estimate of 57%. The change is due to the revised epidemiological data for the newly designed model.

Estimation of the optimal combined radiotherapy and chemotherapy utilisation

The indications of RT for pancreatic cancer were reviewed to identify those indications where the therapy is recommended in conjunction with concurrent chemotherapy. According to the best available evidence there are three indications for combined therapy; they are 1) as adjuvant therapy for resectable pancreatic cancers 2) for inoperable stage I-II pancreatic cancers and 3) for locally advanced (stage III) pancreatic cancers if patients are suitable for concurrent chemoradiotherapy (CRT). Our model predicted that 35% of pancreatic cancer patients would benefit from addition of CRT to their treatment (Table 3 and Figure 2).

Although, there is level II evidence of concurrent CRT benefit for inoperable locally advanced pancreatic cancers (10-12), the therapy is not recommended for a large proportion of advanced pancreatic cancer patients because of their poor general condition from the disease and/or advanced age thus making them unsuitable for the aggressive therapy (3). Since epidemiological data on pancreatic cancer patients with poor general condition are scarce, the data on stage III pancreatic cancer patients aged <75 years from SEER database (7) been used in our model to represent the proportion of patients that would most likely be suitable for concurrent CRT therapy.

Sensitivity analysis

There is uncertainty about the recommendations that pancreatic cancer patients who undergo resection should receive RT as adjuvant therapy; also there are arguments in favour of 'chemotherapy only' option for inoperable locally advanced cancers (4); these variations were modelled in the sensitivity analysis varying the proportion of patients with resected pancreatic cancer who should be treated with adjuvant RT (outcome one), early stage inoperable or locally advanced cancers (outcomes 3 and 4) from 0 to 100%, resulting in (Figure 3) variation in optimal RT utilization between 40% and 53%.

Chemotherapy alone with gemcitabine has been considered an acceptable alternative to concurrent CRT for inoperable pancreatic cancers (1-3); also in our model an age proxy was used to estimate the proportion of patients with poor performance status that are not suitable of concurrent therapy based on recommendations from the international guidelines (3). Sensitivity analysis was carried out to assess the effect of uncertainty for these factors varying the proportions of patients from 0 to 100% that showed a variability of 13% for the CRT utilisation (26% to 39%) (Figure 4).

Table 1: Pancreatic Cancer. Indications for radiotherapy - Levels and sources of evidence

Outcome No. in Tree	Clinical Scenario	Guideline updated	Level of evidence	Proportion of all pancreatic cancer patients	References
1	Pancreatic cancer, Stage I-II, operable, adjuvant therapy	Yes	II	0.06	NCCN (1), NCI PDQ (2), CCO (3), , ESMO (4), British GE Society (5)
3	Pancreatic cancer, Stage I-II, inoperable	Yes	II	0.22	NCCN (1), NCI PDQ (2), CCO (3), ESMO (4), British GE Society (5),
4	Pancreatic cancer, stage III, fit for concurrent CRT	Yes	II	0.07	NCCN (1), NCI PDQ (2), CCO (3), ESMO (4), British GE Society (5),
5	Pancreatic cancer, stage III, not fit for concurrent CRT, symptomatic disease needing palliative RT	Yes	III	0.01	NCI PDQ (2)
6	Pancreatic cancer, stage IV, symptomatic disease needing palliative RT	Yes	III	0.13	NCI PDQ (2)
Updated proportion of all pancreatic cancer patients in whom radiotherapy is recommended				**0.49 (49%)**	
Original proportion of all pancreatic cancer patients in whom radiotherapy was recommended				0.57 (57%)	

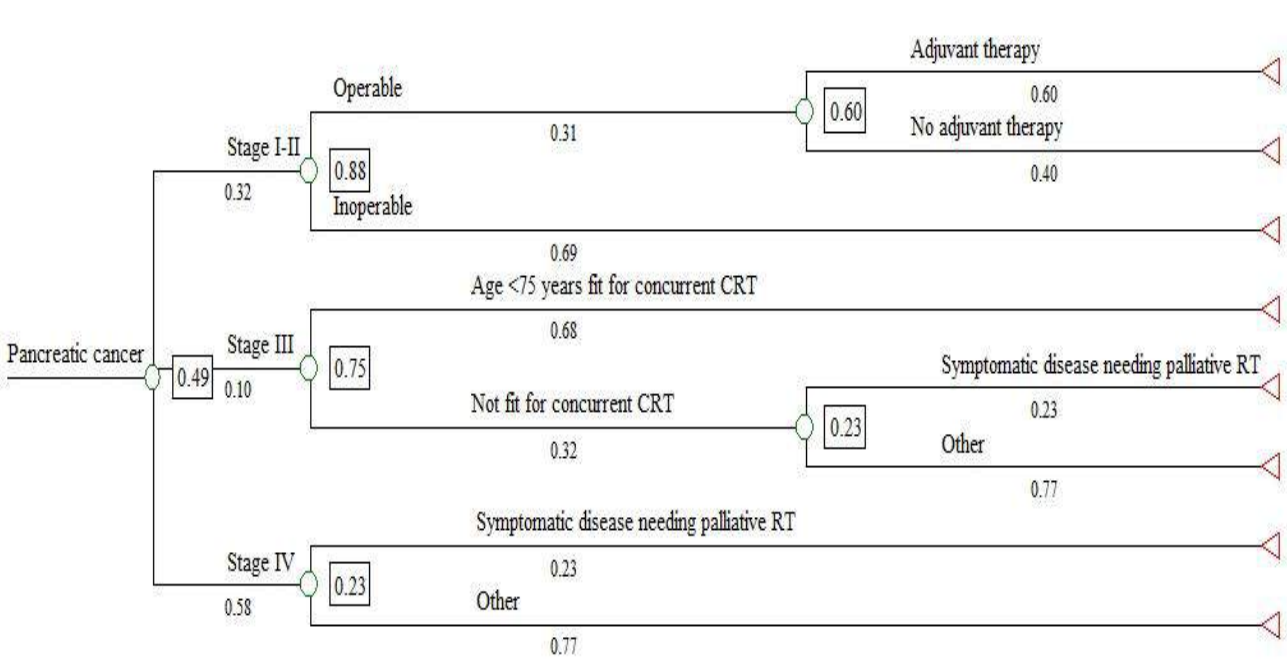
Table 2: Pancreatic Cancer. The incidence of attributes used to define indications for radiotherapy

Population or subpopulation of interest	Attribute	Proportion of population with the attribute	Quality of Information	References
All registry cancers	Pancreatic cancer	0.02	α	AIHW 2008 (6)
Pancreatic cancer	Stage I-II	0.32	γ	SEER 2011 (7)
Stage I-II	Operable	0.31	γ	SEER 2011 (7)
Stage I-II, operable	Adjuvant therapy	0.60 0.44	ζ ζ	Corsini et al 2008 (8) Herman et al 2008 (9)
Pancreatic cancer	Stage III	0.10	γ	SEER 2011 (7)
Stage III	<75 years not fit for concurrent CRT	0.68	γ	SEER 2011 (7)
Stage III, not fit for concurrent CRT	Symptomatic disease requiring palliative RT	0.23	ζ	Morganti et al 2003 (13)
Stage IV	Symptomatic disease requiring palliative RT	0.23	ζ	Morganti et al 2003 (13)

Table 3: Pancreatic Cancer. Indications for concurrent chemoradiotherapy (CRT) - Levels and sources of evidence

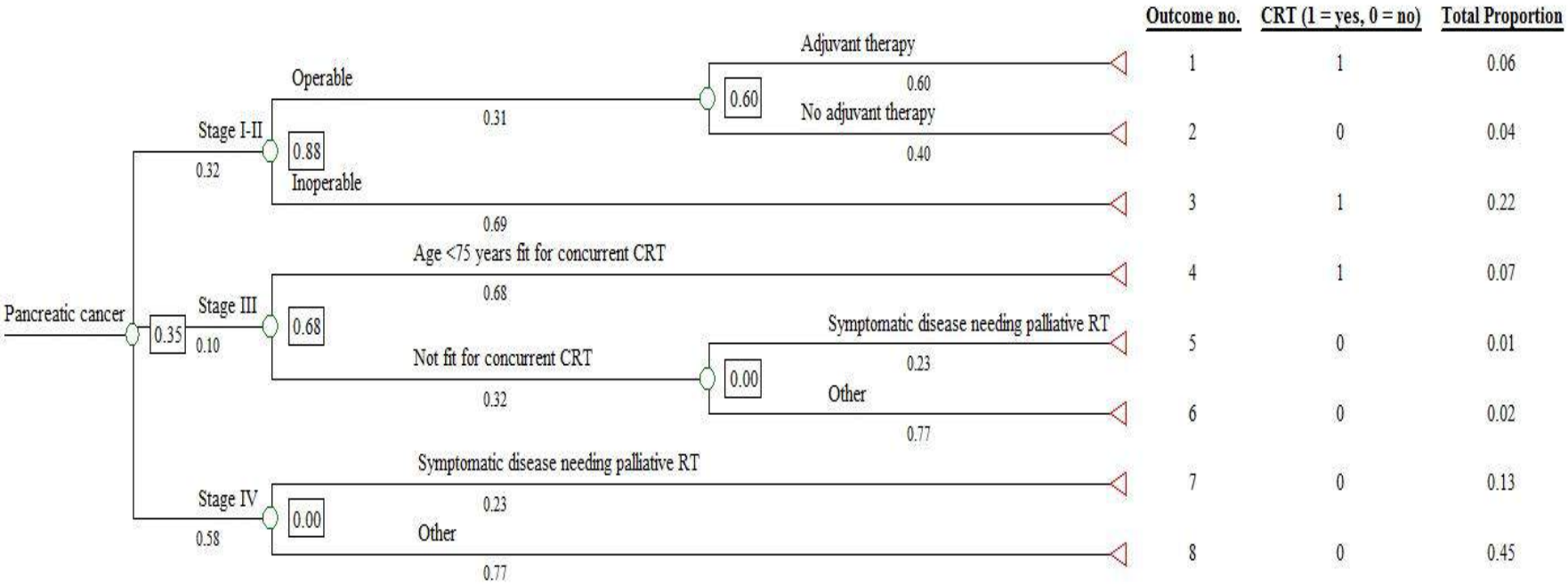
Outcome No. in Tree	Clinical Scenario	Level of Evidence	References	Proportion of all pancreatic cancer patients
1	Pancreatic cancer, Stage I-II, operable, adjuvant therapy	II	NCCN (1), NCI PDQ (2), CCO (3), ESMO (4), British GE Society (5)	0.06
3	Pancreatic cancer, Stage I-II, inoperable	II	NCCN (1), NCI PDQ (2), CCO (3), ESMO (4), British GE Society (5)	0.22
4	Pancreatic cancer, stage III, fit for concurrent CRT	II	NCCN (1), NCI PDQ (2), CCO (3), ESMO (4), British GE Society (5)	0.07
The total proportion of all patients with pancreatic cancer in whom concurrent chemoradiotherapy (CRT) is recommended				**0.35 (35%)**

Figure 1. Pancreatic Cancer Radiotherapy (RT) Utilization Tree



Outcome no.	RT (1 = yes, 0 = no)	Total Proportion
1	1	0.06
2	0	0.04
3	1	0.22
4	1	0.07
5	1	0.01
6	0	0.02
7	1	0.13
8	0	0.45

Figure 2. Pancreatic Cancer Concurrent ChemoRadiotherapy (CRT) Utilization Tree



Outcome no.	CRT (1 = yes, 0 = no)	Total Proportion
1	1	0.06
2	0	0.04
3	1	0.22
4	1	0.07
5	0	0.01
6	0	0.02
7	0	0.13
8	0	0.45

Figure 3. Tornado diagram: univariate sensitivity analyses for RT utilisation

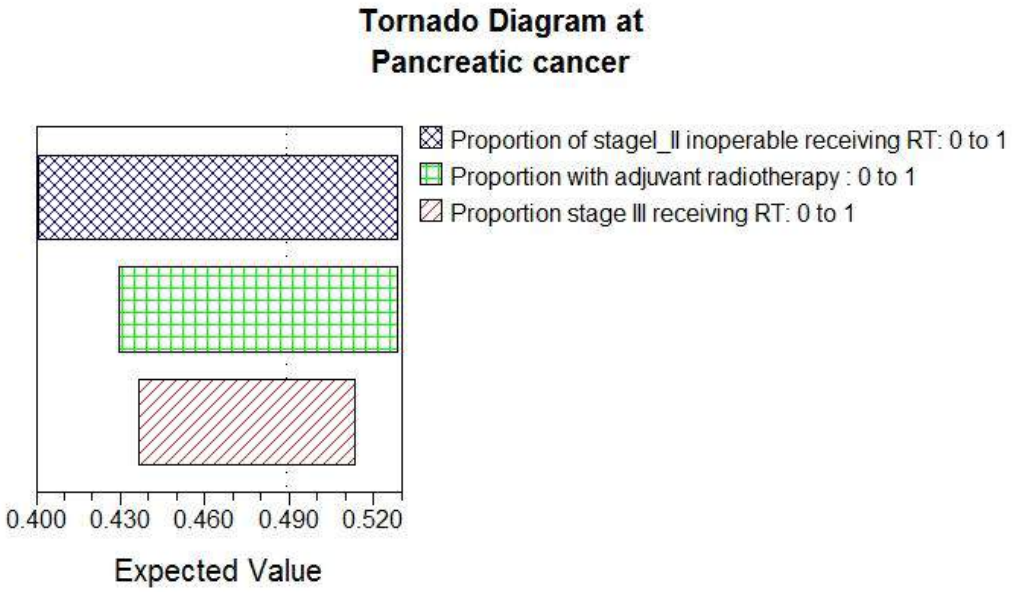
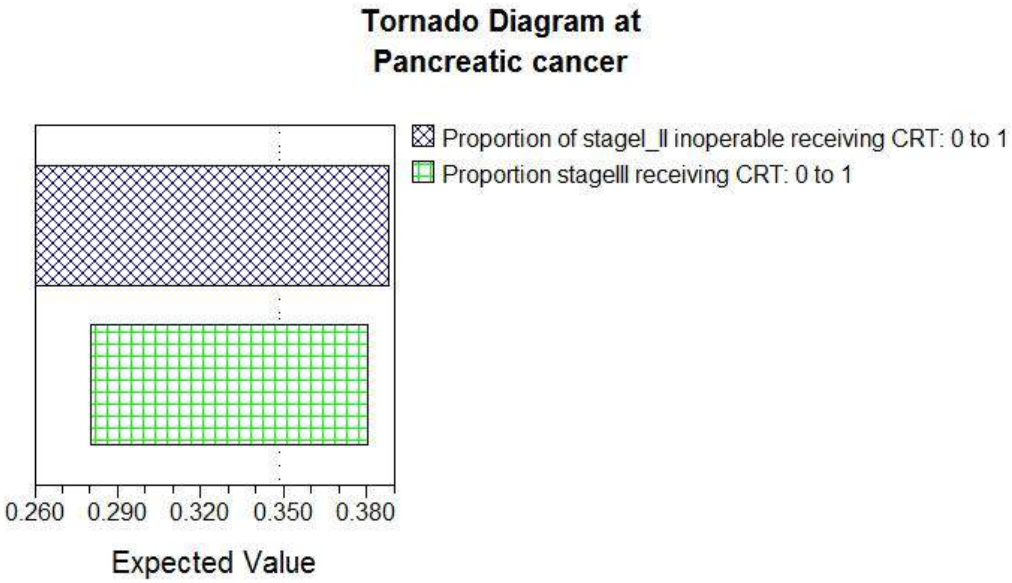


Figure 4. Tornado diagram: univariate sensitivity analysis for CRT utilisation



References

1. National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology: Pancreatic Adenocarcinoma.Version 2.2012. 2012.

2. National Cancer Institute (NCI). Pancreatic cancer treatment (PDQ). 2012.

3. Members of the Gastrointestinal Cancer Disease Site Group, Earle C, Tey R, reviewers. The treatment of locally advanced pancreatic cancer. Program in Evidence-based Care Evidence-Based Series No.: 2-7 Version 2. Toronto: Cancer Care Ontario (CCO); 2011.

4. Cascinu S, Falconi M, Valentini V, Jelic S. Pancreatic cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2010 May;21 Suppl 5:v55-v58.

5. Guidelines for the management of patients with pancreatic cancer periampullary and ampullary carcinomas. On behalf of British Society of Gastroenterology, Pancreatic Society of Great Britain and Ireland, Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland, Royal College of Pathologists, Special Interest Group for Gastro-Intestinal Radiology. Gut 2005 Jun;54 Suppl 5:v1-16.

6. Australian Institute of Health and Welfare (AIHW). Australian Cancer Incidence and Mortality (ACIM) books. Available from http://www aihw gov au/acim-books/ 2012 [cited 2012 Apr 16];

7. Surveillance Research Program, National Cancer Institute SEER*Stat software (seer.cancer.gov/seerstat). Version 7.0.5. [computer program]. Bethesda, MD: National Cancer Institute (NCI); 2011.

8. Corsini MM, Miller RC, Haddock MG, et al. Adjuvant radiotherapy and chemotherapy for pancreatic carcinoma: the Mayo Clinic experience (1975-2005). J Clin Oncol 2008 Jul 20;26(21):3511-6.

9. Herman JM, Swartz MJ, Hsu CC, et al. Analysis of fluorouracil-based adjuvant chemotherapy and radiation after pancreaticoduodenectomy for ductal adenocarcinoma of the pancreas: results of a large, prospectively collected database at the Johns Hopkins Hospital. J Clin Oncol 2008 Jul 20;26(21):3503-10.

10. Loehrer PJ Sr., Feng Y, Cardenes H, et al. Gemcitabine alone versus gemcitabine plus radiotherapy in patients with locally advanced pancreatic cancer: an Eastern Cooperative Oncology Group trial. J Clin Oncol 2011 Nov 1;29(31):4105-12.

11. Moertel CG, Frytak S, Hahn RG, et al. Therapy of locally unresectable pancreatic carcinoma: a randomized comparison of high dose (6000 rads) radiation alone, moderate dose radiation (4000 rads + 5-fluorouracil), and high dose radiation + 5-fluorouracil: The Gastrointestinal Tumor Study Group. Cancer 1981 Oct 15;48(8):1705-10.

12. Treatment of locally unresectable carcinoma of the pancreas: comparison of combined-modality therapy (chemotherapy plus radiotherapy) to chemotherapy alone. Gastrointestinal Tumor Study Group. J Natl Cancer Inst 1988 Jul 20;80(10):751-5.

13. Morganti AG, Trodella L, Valentini V, et al. Pain relief with short-term irradiation in locally advanced carcinoma of the pancreas. J Palliat Care 2003;19(4):258-62.

PROSTATE CANCER

The original EBRT utilisation models were derived from evidence-based treatment guidelines issued by major national and international organisations until August 2003 (1). The subsequent BT model was based on evidence-based guidelines published until 2004 (2), and the later prostate seed BT report used guidelines published through to December 2008 (3). The current updated model includes guidelines published until July 2012.

Updated Guidelines

The following clinical practice guidelines for the management of prostate cancer were identified. Guidelines updated since the previous models are asterisked.

Multinational:

- ESTRO/EAU/EORTC: Recommendations on permanent seed implantation for localized prostate cancer (4)
- GEC/ESTRO-EAU: Recommendations on temporary brachytherapy using stepping sources for localised prostate cancer (5)

Australian National:

- NHMRC: National Health and Medical Research Council. Clinical Practice Guidelines: Evidence-based information and recommendations for the management of localised prostate cancer (6)
- * ACN: Australian Cancer Network Clinical Practice Guidelines for the Management of Locally Advanced and Metastatic Prostate Cancer (7)

Other National:

- * PDQ: National Cancer Institute PDQ Statement on Prostate Cancer Treatment (8)
- * NCCN: National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology: Prostate Cancer (9)
- NICE: Prostate cancer: diagnosis and treatment (10)

Australian State:

- None identified

Other State/Provincial:

- CCO-CRT: Cancer Care Ontario: The Use of Conformal Radiotherapy and the Selection of Radiation Dose in T1 or T2 Prostate Cancer (11)
- * CCO-AdjRT: Cancer Care Ontario: Adjuvant radiotherapy following radical prostatectomy for pathologic T3 or margin-positive prostate cancer (12)

- * BCCA: British Columbia Cancer Agency: Cancer Management Guidelines – Prostate Cancer (13)

Australian Single Disciplinary:

- * FROGG-AdjRT: Post-prostatectomy radiation therapy: Consensus guideline of the Australian and New Zealand Radiation Oncology Genito-Urinary Group (14)
- * FROGG-DefRT: Australian and New Zealand Faculty of Radiation Oncology Genito-Urinary Group: 2010 consensus guideline for definitive external beam radiotherapy for prostate cancer (15)

Other Single Disciplinary:

- * EAU: European Association of Urology: EAU Guidelines on Prostate Cancer (16)
- AUA: American Urological Association. Guideline for the Management of Clinically Localized Prostate Cancer: 2007 Update (17)
- * ACR-ASTRO-BT: American College of Radiology - American Society for Therapeutic Radiology and Oncology Practice Guideline for Transperineal Permanent Brachytherapy of Prostate Cancer (18)
- * ACR-BT: American College of Radiology Appropriateness Criteria - Permanent Source Brachytherapy for Prostate Cancer (19)
- * ACR-LAPC: American College of Radiology Appropriateness Criteria - Locally Advanced (High Risk) Prostate Cancer (20)
- * ACR-TP: American College of Radiology Appropriateness Criteria - Treatment Planning for Clinically Localized Prostate Cancer (21)
- * ACR-EBRT: American College of Radiology Appropriateness Criteria - Definitive External Beam Irradiation in Stage T1 and T2 Prostate Cancer (22)
- *ACR-AdjRT: American College of Radiology Appropriateness Criteria – Postradical Prostatectomy Irradiation in Prostate Cancer (23)
- * ABS-SBT: American Brachytherapy Society consensus guidelines for transrectal ultrasound-guided permanent prostate brachytherapy (24)
- * ABS-HDRBT: American Brachytherapy Society Prostate High-Dose Rate Task Group (25)

The following previously used clinical practice guidelines for the management of prostate cancer have been removed from the internet in order to be updated, have been superseded, or are otherwise no longer available:

- COIN: The Royal College of Radiologists (Clinical Oncology Information Network) / British Association of Urological Surgeons: Guidelines on the Management of Prostate Cancer (26)
- FNCLCC/AFU: French National Federation of Cancer Centres and the French Urology Association: Summary of the Standards, Options and Recommendations for the management of patients with non-metastatic prostate cancer (27)
- CCO-BT: Cancer Care Ontario: The Use of Brachytherapy in T1 or T2 Prostate Cancer (28)

- ANZ-3D-CRT: Australian and New Zealand 3D Conformal Radiotherapy Consensus Guidelines for Prostate Cancer (29)

Indications for radiotherapy

All the indications for EBRT and for BT in the original CCORE models of optimal RT and BT utilisation for prostate cancer were reviewed based on the latest guideline recommendations (Figures 1 and 2 and Tables 1 and 2). A number of changes to the tree design have occurred as a result of changes in evidence and guideline recommendations.

Changes to Epidemiological Data

The epidemiological data in the prostate cancer utilization trees have been reviewed to identify whether more recent data are available through extensive electronic searches. These have been applied to the early branches in the trees for which national or state level data on cancer incidence rates and stages are available. No changes to the hierarchical quality of the epidemiological data were identified, but there were changes in the magnitude of the RTU indications based on up-dated SEER stage data (30) (Table 3).

Incidence of Prostate Cancer:

Since the publication of the previous radiotherapy utilisation project, the Australian national cancer incidence data published by the Australian Institute of Health and Welfare (AIHW) has been updated, with the most recent data available being 2008 data. In 2008, prostate cancer accounted for 18% of all cancer in Australia (31) (Table 3).

Stage proportions for Prostate Cancer

The SEER database (30) provided the most recent population level data for stage distribution of prostate cancer, and these 2004-07 data were substituted for the previous 1973-1995 data used for the RTU tree and the 1997-2001 data used for the BTU tree (Table 3).

Notes on Optimal RTU/BTU Decision Tree for Prostate Cancer

One of the issues that makes constructing an evidence-based decision tree in prostate cancer problematic is that there is a relative lack of modern randomised trials comparing treatments. As a result there are multiple treatment options for patients with non-metastatic cancer and uniform agreement between guidelines regarding treatment indications was frequently not the case. This leaves the recommendations open for several treatment options, whereas for most other tumour sites, treatment recommendations are often more definitive. The methods used to overcome this limitation are detailed below.

Options for treatment of localised prostate cancer include:

- Active Surveillance (AS).
- Radical prostatectomy (RP) with or without post-operative radiotherapy (RT).
- External beam radiotherapy (EBRT) with or without dose escalation, either by EBRT or by brachytherapy (BT) boost.
- Brachytherapy Monotherapy, BT(m).

Risk Categorization

In the previous RTU model, prostate cancer stage was used as the basis for RT indications, without taking into account Gleason Score (GS) or PSA, as population based data for these factors were not available. These data were later incorporated into the BTU models (2) (3) and have been incorporated into this update. T stage, GS and PSA are combined to create Low, Intermediate and High Risk Disease categories, based on the original and widely accepted proposal by D'Amico et al (32). Low Risk Disease is defined as T1-2a and GS </=6 and PSA <10; Intermediate Risk Disease is T2b/c and/or GS 7 and/or PSA 10-20 and not High Risk; High Risk Disease is T3-4 or GS 8-10 or PSA >20. This categorization is used by most guidelines: ESTRO/EAU/EORTC (4), GEC/ESTRO-EAU (5), NCCN (9), NICE (10), FROGG-DefRT (15), EAU (16); although some used slightly different definitions: BCCA includes T2b in Low Risk (13) and AUA and ACR-EBRT include T2c in High Risk (17) (22). The New South Wales Prostate Cancer Care and Outcomes Study (NSW PCCOS) was used to provide population based Australian (NSW) data to categorize patients according to prostate cancer group (33).

Low Risk Disease:

There is no evidence for the superiority of any one treatment approach for Low Risk (LR) Disease and AS, RP, EBRT and BT(m) are recommended as treatment options for fit enough patients by guidelines (4) (9) (10) (13) (15) (16) (17) (18) (19) (22) (24).

Intermediate risk disease

There is no evidence for the superiority of any one treatment approach for Intermediate Risk (IR) Disease and RP and EBRT with dose escalation with EBRT or with BT boost are recommended as treatment options for fit enough patients by guidelines (4) (5) (9) (10) (11) (13) (15) (16) (17) (18) (19) (22) (24). An area of controversy is the suitability of BT(m) for these patients, based on conflicting level III data. Some guidelines recommend against (or less strongly than for other recommended treatments) BT(m) for these patients - ESTRO/EAU/EORTC (4), NCCN (9), NICE (10), EAU (16), ACR-ASTRO-BT (18), ACR-BT (19). Others consider it a treatment option for selected patients - BCCA (13), AUA (17), ABS-SBT (24). As discussed in the previous Seed BT report (3), the utilization tree has followed the guideline hierarchy and does not gives BT(m) as an indication for IR disease. Sensitivity analysis (below) is performed to assess the effect of including BT(m) as an option for patients with Good IR disease (IR with GS 7 and/or Stage T2b/c but not PSA 10-20, as per Australian Medicare Benefits Schedule).

High risk disease

For High Risk (HR) Disease, treatment options include EBRT (7) (8) (9) (10) (13) (15) (16) (17) (20) (22), with dose escalation with EBRT or with BT boost (5) (7) (9) (10) (13) (19) (22) (24). The GEC/ESTRO-EAU guidelines limit BT boost to patients likely to be curable and with disease encompassable by BT, excluding those with PSA >50 or T4 disease (5). RP may an option for some patients if clear margins are likely (9) (10) (13) (16) (17), although the Australian guidelines state that there is "insufficient evidence to support the use of surgery" (7). Of the guidelines that support surgery, none specify appropriate candidates apart from requiring life expectancy greater than 10 years, fitness for surgery, and likely clear margins – chances of which diminish with increasing GS, PSA and T stage (34). The previous EAU guidelines explicitly stated that RP is only an option if PSA<20 and GS≤8 and T≤3a and these limits are used for the decision tree (35).

Life Expectancy

The guidelines recommend that radical treatment should be reserved for patients likely to live long enough to benefit (4) (6) (9) (13) (16) (18) (24) and recommend that there is a life-expectancy of at least five to ten years before radical treatment is considered**.** Patients with a shorter life expectancy have been shown to be unlikely to benefit from radical treatment of their prostate cancer (36) (37) (38). Data from the Australian Bureau of Statistics (39) and the Australian Institute of Health and Welfare (40) were used in the previous BTU models (2) (3) to estimate that 67% of newly diagnosed prostate cancer patients are unlikely to die within 5-10 years from their co-morbidities and are therefore potentially candidates for curative treatment. It is this figure that is used in constructing the current model with respect to appropriateness for curative treatment for patients with LR and IR disease. Patients with HR disease are more likely to become symptomatic, even if with a limited lifespan, and treatment is recommended if fit enough (7) (9) (16) (17). As in the original RTU model, data from the US POCS reported by Harlan et al (41) are used, showing that 11% of patients with localised prostate cancer are of poor performance status, and therefore unlikely to be fit for radical treatment.

Physical Contra-indications to Brachytherapy

As discussed in the previous BT utilization models, a proportion of patients with localised prostate cancer will not be suitable candidates for BT due to an unacceptable risk of significant morbidity from this treatment. Physical contraindications (CI) to SBT listed in the guidelines include prior TURP (4) (9) (13) (18) (19) (24); very large prostate volume (4) (9) (13) (16) (18) (24); and significant lower urinary obstructive symptoms (LUTS) (4) (9) (16) (18) (19) (24); these are also listed as CI to temporary HDR BT (5) (9) (25). Data from the NSW Prostate Cancer Care and Outcomes Study was previously used to determine the proportions of patients with Low Risk, Intermediate and High Risk disease with these physical CI (33). The three CI were mapped as separate branches on the previous BTU models (2) (3), but are here rolled together into one branch to clarify presentation.

Patient Preference

Where evidence is lacking for a benefit from one particular treatment option over another, the treatment choice lies with the patient. In order to model patient choice, patient choice studies or patterns of care studies may be used. A disadvantage of both approaches is that they contain biases; patients use a wide variety of sources of information to arrive at a preference, with the patient's physician having greatest influence (42). It has been demonstrated that different professional groups have little agreement regarding the optimal treatment choice (43). A specific disadvantage of using patterns of care studies is that there is a wide variation in treatments administered between countries (41) (44) and even within countries (45) (46), reflecting the fact that patterns of care studies reveal what treatment is being administered and perhaps what is more accessible, not necessarily the optimal treatment that should be administered. Patterns of care studies are biased by such issues as geographical access to treatments, and to medical practitioners and by varying costs to patients of different treatments.

For the purposes of this utilization tree, patient choice studies, despite the above-listed limitations, were used to determine the proportion of patients choosing between equivalent treatment options, with sensitivity analyses performed to assess the effect on the model of varying the patient preference. Patient choice studies used or considered in previous optimal utilisation models for prostate cancer (1) (2) (3) (47) have disadvantages that include: not all treatment options being offered (48) (49) (50) (51), hypothetical scenarios being offered to well men without prostate cancer (48) (49), small sample size (49) (50), or inadequate pre-choice counselling without consultation with both a radiation oncologist and a urologist (48) (49) (50) (52) (53). The only well conducted patient choice study that systematically presented all treatment options to patients with localised prostate cancer (AS, RP, EBRT or BT) was performed by the UK North-West Uro-Oncology Group (54). All deficiencies listed in the patient choice studies above were addressed. All patients discussed all management options with a urologist, a radiation oncologist, and a specialist nurse, were given comprehensive information leaflets, and then were offered a second appointment to further discuss matters. Of 768 patients, 40% chose to undergo RP, 31% EBRT, 21% BT, and 8% AS. These data were therefore used for all branches on the decision tree where equivalent treatment options were applicable.

Estimation of the Optimal External Beam Radiotherapy Utilisation Rate in the Treatment of Prostate Cancer

Based on the evidence of the efficacy of radiotherapy and the most recent epidemiological data on the occurrence of indications for EBRT, EBRT is recommended in 58% of all patients with prostate cancer in Australia (Table 1 and Figure 1). The previous optimal EBRT rate for prostate cancer derived in 2003 was 60%. As discussed above, the major changes to the Utilisation Tree were: the incorporation of prostate cancer disease risk group based on Stage, PSA and GS, rather than basing the tree on Stage only; use of updated SEER stage data; and use of an updated and improved patient preference study.

Estimation of the Optimal Brachytherapy Utilisation Rate

Based on the evidence of the efficacy of BT and the most recent epidemiological data on the occurrence of indications for BT, BT is recommended in 9.8% of all patients with prostate cancer in Australia (Table 2 and Figure 2). The previous optimal BTU rate for prostate cancer derived in 2009, accounting for BT monotherapy and BT boost, was 11.9%. The previous model used patient disease risk grouping, and there has been little change in the proportion of patients presenting with metastatic disease. The small decrease in the revised optimal BT utilisation rate is due predominantly to an updated and larger patient preference study.

Estimation of the Optimal Concurrent Chemoradiotherapy Utilisation Rate

The indications for radiotherapy for prostate cancer were reviewed to identify the indications where radiotherapy is recommended in conjunction with concurrent chemotherapy (CRT) as the first treatment. None of the guidelines supported concurrent CRT for prostate cancer**.** Since none of the guidelines specifically recommend concurrent CRT, it has not been implemented into the optimal utilisation tree.

Level of evidence

The levels of evidence supporting the indications for EBRT and BT are essentially unchanged, except that there are now multiple RCTs supporting adjuvant EBRT for margin positivity post RP (55) (56) (57). Level I-II evidence supports the indications for 17% (absolute) of the total 58% EBRT optimal utilisation and partially supports 7.5% (absolute) of the total 9.8% BT optimal utilisation.

Sensitivity Analyses

Univariate sensitivity analyses were undertaken (Figures 3 and 4) to assess any changes in the optimal utilisation rate that would result from different estimates of the proportions of patients with particular attributes as mentioned in Table 3. Areas of uncertainty were:

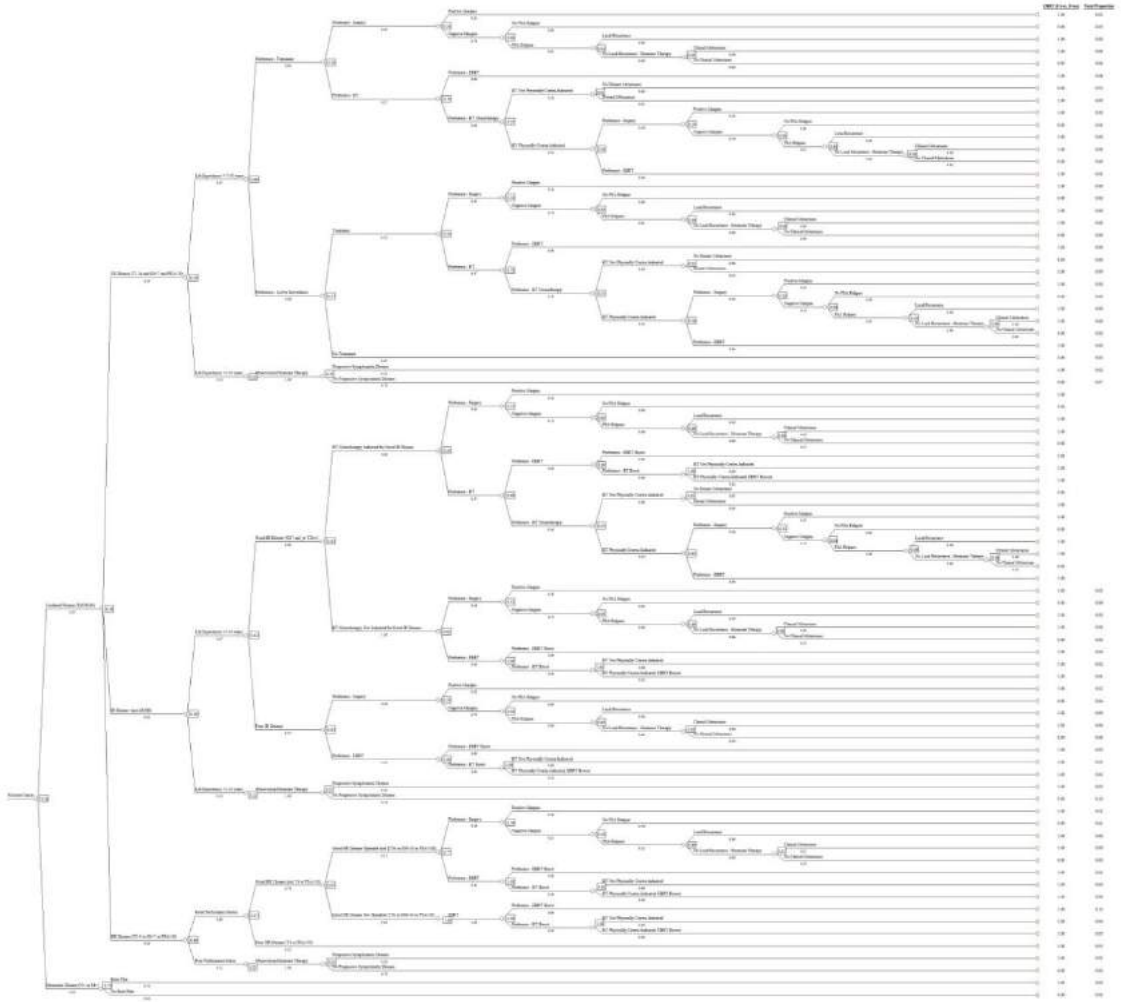
1. Proportions of eligible patients who would choose RP, EBRT or BT. These options are dichotomised in the Utilisation Trees as the TreeAge software only allows two branches to be tested with sensitivity analysis with any one test. Baseline preferences are drawn from the study conducted by the UK North-West Uro-Oncology Group, for reasons discussed above (54). A higher surgical preference model is tested by increasing the proportion of patients choosing RP over other options to 75%; a higher RT preference model is tested by increasing the proportion of patients choosing RT over other options to 75%; higher EBRT preference is tested by increasing the proportion of patients choosing EBRT over other options to 75%; and higher BT preference is tested by increasing the proportion of patients choosing BT over other options to 75%. It is acknowledged that these proportions are arbitrary. They are based on the similar 70:20 ratio used in the previous EBRT model (1), aiming to test the effect of using an extreme patient preference estimate on the final model. The true preference is likely to be well within this range.

2. Proportions of patients with physical contra-indications to BT, as discussed above. Proportions were varied as per the previous BTU models (2) (3), using data from NSW PCCOS (33): depending on whether moderate or severe LUTS or severe LUTS only are considered CI to BT. For LR disease, 42% of patients have physical CI to BT, this proportion may vary from 33% to 62%. For IR disease, 32% of patients have CI, this proportion may vary from 20% to 52%. For HR disease, 40% of patients have CI, this proportion may vary from 29% to 61%.

3. Whether or not patients with Good IR Disease (IR Disease due to GS 7 and/or Stage T2b/c) are potentially suitable for BT(m). As discussed above, the default for the tree was set at 0%, but sensitivity analysis was performed to increase this to 100% to model the two diametrically opposed views presented in the guidelines.

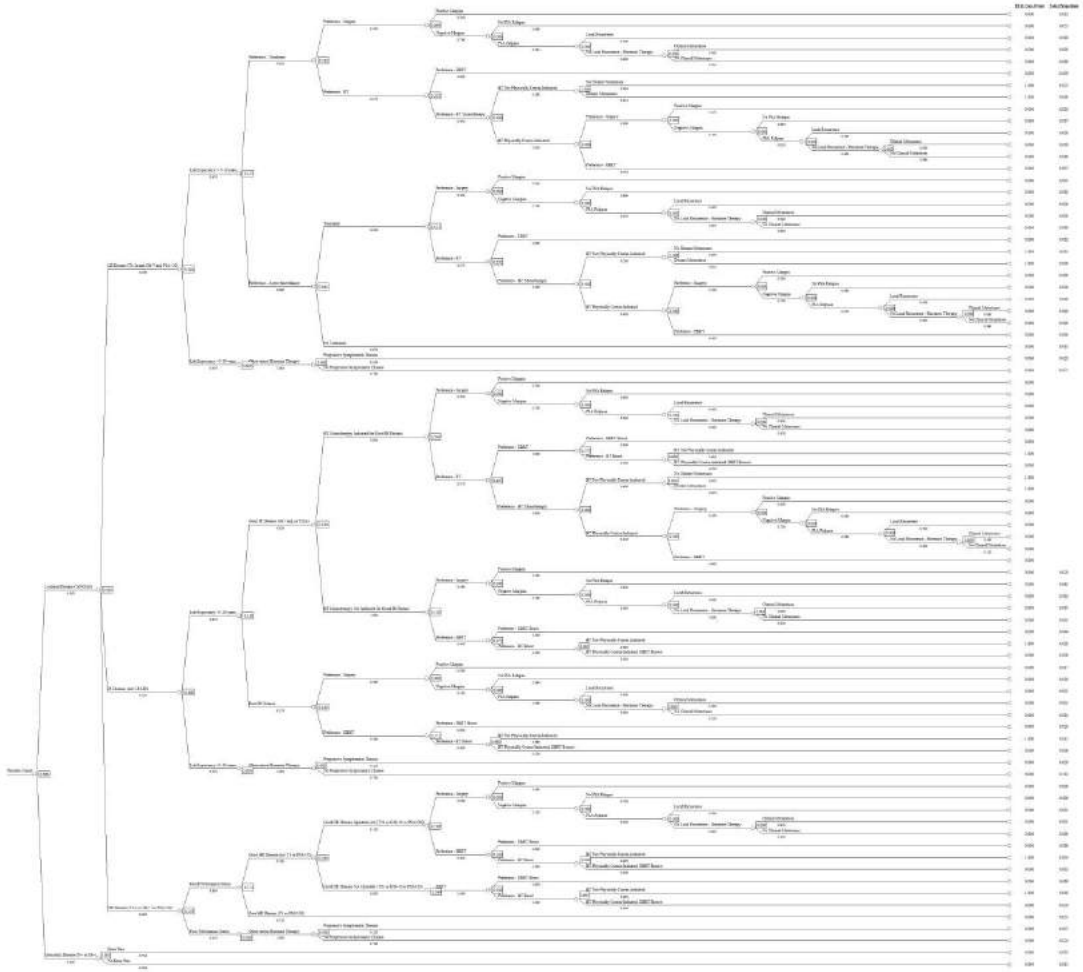
Optimal EBRT utilisation was 58%, and the range in the estimate due to these uncertainties was 55% - 65%, as shown in the Tornado Diagram (Figure 3). Optimal BT utilisation was 9.8%, and the range in the estimate due to these uncertainties was 6.1% - 18.3%, as shown in the Tornado Diagram (Figure 4). The greatest contributors to the variability were uncertainty in patient preference.

Figure 1. Revised Optimal External Beam Radiotherapy Utilisation Tree for Prostate Cancer



LVI, Lymphatic Vascular Space Invasion; RT, Radiotherapy; EBRT, External Beam Radiotherapy; BT, Brachytherapy

Figure 2. Revised Optimal Brachytherapy Utilisation Tree for Prostate Cancer



LVI, Lymphatic Vascular Space Invasion; RT, Radiotherapy; EBRT, External Beam Radiotherapy; BT, Brachytherapy

Table 1: Prostate Cancer. Indications for External Beam Radiotherapy - Levels and sources of evidence

Outcome Nos. in Updated Tree	Clinical Scenario	Original RTU study*			Updates 2012					
		Treatment Indicated	Level of Evidence for EBRT	Proportion of all Prostate Cancer	Treatment Indicated	Guideline updated	Current level of evidence for EBRT	Change to proportion of all Prostate Cancer		References
								Yes/No	Updated value	
1	Localised Disease LR Disease Life Expectancy >5-10yrs Pref: Treatment Pref: Surgery Positive Margins	RT	IV	n/a	(RP and) EBRT	Yes	I	Yes	0.02	ACN (7), NCCN (9) CCO-AdjRT (12), BCCA (13), FROGG-AdjRT (14), EAU(16), ACR-AdjRT (23)

3	Localised Disease LR Disease Life Expectancy >5-10yrs Pref: Treatment Pref: Surgery Negative Margins PSA Relapse Local Recurrence	RT	IV	n/a	(RP then) EBRT	Yes	IV	Yes	<0.01	NHMRC (6); ACN (7), PDQ (8); NCCN (9), NICE (10)
4	Localised Disease LR Disease Life Expectancy >5-10yrs Pref: Treatment Pref: Surgery Negative Margins PSA Relapse No Local Recurrence (HRx) Clinical Metastases	RT	I	n/a	(RP then) EBRT	Yes	I	Yes	<0.01	NHMRC (6); ACN (7), PDQ (8), NCCN (9), NICE (10)

6	Localised Disease LR Disease Life Expectancy >5-10yrs Pref: Treatment Pref: RT Pref: EBRT	RT	III**	n/a	EBRT	Yes	III	Yes	0.06	NCCN (9), NICE (10); BCCA (13), FROGG-DefRT (15), EAU (16), AUA (17), ACR-EBRT (22)
8	Localised Disease LR Disease Life Expectancy >5-10yrs Pref: Treatment Pref: RT Pref: BT(m) BT not Physically CI Distant Metastases	RT	I	n/a	(BT then) EBRT	Yes	I	Yes	<0.01	NHMRC (6); ACN (7), PDQ (8), NCCN (9), NICE (10)

9	Localised Disease LR Disease Life Expectancy >5-10yrs Pref:Treatment Pref: RT Pref: BT(m) BT Physically CI Pref: Surgery Positive Margins	RT	IV	n/a	(RP and) EBRT	Yes	I	Yes	<0.01	ACN (7), NCCN (9) CCO-AdjRT (12), BCCA (13), FROGG-AdjRT (14), EAU(16), ACR-AdjRT (23)
11	Localised Disease LR Disease Life Expectancy >5-10yrs Pref: Treatment Pref: RT Pref: BT(m) BT Physically CI Pref: Surgery Negative Margins PSA Relapse Local Recurrence	RT	IV	n/a	(RP then) EBRT	Yes	IV	Yes	<0.01	NHMRC (6); ACN (7), PDQ (8); NCCN (9), NICE (10)

12	Localised Disease LR Disease Life Expectancy >5-10yrs Pref: Treatment Pref: RT Pref: BT(m) BT Physically CI Pref: Surgery Negative Margins PSA Relapse No Local Recurrence (HRx) Clinical Metastases	RT	I	n/a	(RP then) EBRT	Yes	I	Yes	<0.01	NHMRC (6); ACN (7), PDQ (8), NCCN (9), NICE (10)
14	Localised Disease LR Disease Life Expectancy >5-10yrs Pref: Treatment Pref: RT Pref: BT(m) BT Physically CI Pref: EBRT	RT	III**	n/a	EBRT	Yes	III	Yes	0.01	NCCN (9), NICE (10); BCCA (13), FROGG-DefRT (15), EAU (16), AUA (17), ACR-EBRT (22)

15	Localised Disease LR Disease Life Expectancy >5-10yrs Pref: AS Treatment Pref: Surgery Positive Margins	RT	IV	n/a	(RP and) EBRT	Yes	I	Yes	<0.01	ACN (7), NCCN (9) CCO-AdjRT (12), BCCA (13), FROGG-AdjRT (14), EAU (16), ACR-AdjRT (23)
17	Localised Disease LR Disease Life Expectancy >5-10yrs Pref: AS Treatment Pref: Surgery Negative Margins PSA Relapse Local Recurrence	RT	IV	n/a	(RP then) EBRT	Yes	IV	Yes	<0.01	NHMRC (6); ACN (7), PDQ (8); NCCN (9), NICE (10)

18	Localised Disease LR Disease Life Expectancy >5-10yrs Pref: AS Treatment Pref: Surgery Negative Margins PSA Relapse No Local Recurrence (HRx) Clinical Metastases	RT	I	n/a	(RP then) EBRT	Yes	I	Yes	<0.01	NHMRC (6); ACN (7), PDQ (8), NCCN (9), NICE (10)
20	Localised Disease LR Disease Life Expectancy >5-10yrs Pref: AS Treatment Pref: RT Pref: EBRT	RT	III**	n/a	EBRT	Yes	III	Yes	<0.01	NCCN (9), NICE (10); BCCA (13), FROGG-DefRT (15), EAU(16), AUA (17), ACR-EBRT (22)

22	Localised Disease LR Disease Life Expectancy >5-10yrs Pref: AS Treatment Pref: RT Pref: BT(m) BT not Physically CI Distant Metastases	RT	I	n/a	(BT then) EBRT	Yes	I	Yes	<0.01	NHMRC (6); ACN (7), PDQ (8), NCCN (9), NICE (10)
23	Localised Disease LR Disease Life Expectancy >5-10yrs Pref: AS Treatment Pref: RT Pref: BT(m) BT Physically CI Pref: Surgery Positive Margins	RT	IV	n/a	(RP and) EBRT	Yes	I	Yes	<0.01	ACN (7), NCCN (9) CCO-AdjRT (12), BCCA (13), FROGG-AdjRT (14), EAU(16), ACR-AdjRT (23)

25	Localised Disease LR Disease Life Expectancy >5-10yrs Pref: AS Treatment Pref: RT Pref: BT(m) BT Physically CI Pref: Surgery Negative Margins PSA Relapse Local Recurrence	RT	IV	n/a	(RP then) EBRT	Yes	IV	Yes	<0.01	NHMRC (6); ACN (7), PDQ (8); NCCN (9), NICE (10)

26	Localised Disease LR Disease Life Expectancy >5-10yrs Pref: AS Treatment Pref: RT Pref: BT(m) BT Physically CI Pref: Surgery Negative Margins PSA Relapse No Local Recurrence (HRx) Clinical Metastases	RT	I	n/a	(RP then) EBRT	Yes	I	Yes	<0.01	NHMRC (6); ACN (7), PDQ (8), NCCN (9), NICE (10)
28	Localised Disease LR Disease Life Expectancy >5-10yrs Pref: AS Treatment Pref: RT Pref: BT(m) BT Physically CI Pref: EBRT	RT	III**	n/a	EBRT	Yes	III	Yes	<0.01	NCCN (9), NICE (10); BCCA (13), FROGG-DefRT (15), EAU(16), AUA (17), ACR-EBRT (22)

30	Localised Disease LR Disease Life Expectancy <5-10yrs Observation/HRx Symptomatic Disease	RT	I	n/a	EBRT	Yes	I	Yes	0.02	PDQ (8), NCCN (9)
32	Localised Disease IR Disease Life Expectancy >5-10yrs Good IR Disease BT(m) Indicated for GIR Pref: Surgery Positive Margins	RT	IV	n/a	(RP and) EBRT	Yes	I	Yes	0.00	ACN (7), NCCN (9) CCO-AdjRT (12), BCCA (13), FROGG-AdjRT (14), EAU(16), ACR-AdjRT (23)

34	Localised Disease IR Disease Life Expectancy >5-10yrs Good IR Disease BT(m) Indicated for GIR Pref: Surgery Negative Margins PSA Relapse Local Recurrence	RT	IV	n/a	(RP then) EBRT	Yes	IV	Yes	0.00	NHMRC (6); ACN (7), PDQ (8); NCCN (9), NICE (10)
35	Localised Disease IR Disease Life Expectancy >5-10yrs Good IR Disease BT(m) Indicated for GIR Pref: Surgery Negative Margins PSA Relapse No Local Recurrence (HRx) Clinical Metastases	RT	I	n/a	(RP then) EBRT	Yes	I	Yes	0.00	NHMRC (6); ACN (7), PDQ (8), NCCN (9), NICE (10)

37	Localised Disease IR Disease Life Expectancy >5-10yrs Good IR Disease BT(m) Indicated for GIR Pref: RT Pref: EBRT Pref: EBRT Boost	RT	III**	n/a	EBRT (and BT)	Yes	III	Yes	0.00	NCCN (9), NICE (10), CCO-CRT (11), BCCA (13), FROGG-DefRT (15), EAU(16), AUA (17), ACR-EBRT (22)
38	Localised Disease IR Disease Life Expectancy >5-10yrs Good IR Disease BT(m) Indicated for GIR Pref: RT Pref: EBRT Pref: BT Boost BT Not Physically CI	RT	III**	n/a	EBRT (and BT)	Yes	III	Yes	0.00	NCCN (9), NICE (10), CCO-CRT (11), BCCA (13), FROGG-DefRT (15), EAU(16), AUA (17), ACR-EBRT (22)

39	Localised Disease IR Disease Life Expectancy >5-10yrs Good IR Disease BT(m) Indicated for GIR Pref: RT Pref: EBRT Pref: BT Boost BT Physically CI	RT	III**	n/a	EBRT	Yes	III	Yes	0.00	NCCN (9), NICE (10), CCO-CRT (11), BCCA (13), FROGG-DefRT (15), EAU(16), AUA (17), ACR-EBRT (22)
41	Localised Disease IR Disease Life Expectancy >5-10yrs Good IR Disease BT(m) Indicated for GIR Pref: RT Pref: BT(m) BT Not Physically CI Distant Metastases	RT	I	n/a	(BT then) EBRT	Yes	I	Yes	0.00	NHMRC (6); ACN (7), PDQ (8), NCCN (9), NICE (10)

42	Localised Disease IR Disease Life Expectancy >5-10yrs Good IR Disease BT(m) Indicated for GIR Pref: RT Pref: BT(m) BT Physically CI Pref: Surgery Positive Margins	RT	IV	n/a	(RP and) EBRT	Yes	I	Yes	0.00	ACN (7), NCCN (9) CCO-AdjRT (12), BCCA (13), FROGG-AdjRT (14), EAU(16), ACR-AdjRT (23)

44	Localised Disease IR Disease Life Expectancy >5-10yrs Good IR Disease BT(m) Indicated for GIR Pref: RT Pref: BT(m) BT Physically CI Pref: Surgery Negative Margins PSA Relapse Local Recurrence	RT	IV	n/a	(RP then) EBRT	Yes	IV	Yes	0.00	NHMRC (6); ACN (7), PDQ (8); NCCN (9), NICE (10)

45	Localised Disease IR Disease Life Expectancy >5-10yrs Good IR Disease BT(m) Indicated for GIR Pref: RT Pref: BT(m) BT Physically CI Pref: Surgery Negative Margins PSA Relapse No Local Recurrence (HRx) Clinical Metastases	RT	I	n/a	(RP then) EBRT	Yes	I	Yes	0.00	NHMRC (6); ACN (7), PDQ (8), NCCN (9), NICE (10)

47	Localised Disease IR Disease Life Expectancy >5-10yrs Good IR Disease BT(m) Indicated for GIR Pref: RT Pref: BT(m) BT Physically CI Pref: EBRT	RT	III**	n/a	EBRT	Yes	III	Yes	0.00	NCCN (9), NICE (10), CCO-CRT (11), BCCA (13), FROGG-DefRT (15), EAU (35), AUA (17), ACR-EBRT (22)
48	Localised Disease IR Disease Life Expectancy >5-10yrs Good IR Disease BT(m) Not Indicated GIR Pref: Surgery Positive Margins	RT	IV	n/a	(RP and) EBRT	Yes	I	Yes	0.03	ACN (7), NCCN (9) CCO-AdjRT (12), BCCA (13), FROGG-AdjRT (14), EAU(16), ACR-AdjRT (23)

50	Localised Disease IR Disease Life Expectancy >5-10yrs Good IR Disease BT(m) Not Indicated GIR Pref: Surgery Negative Margins PSA Relapse Local Recurrence	RT	IV	n/a	(RP then) EBRT	Yes	IV	Yes	<0.01	NHMRC (6); ACN (7), PDQ (8); NCCN (9), NICE (10)
51	Localised Disease IR Disease Life Expectancy >5-10yrs Good IR Disease BT(m) Not Indicated GIR Pref: Surgery Negative Margins PSA Relapse No Local Recurrence (HRx) Clinical Metastases	RT	I	n/a	(RP then) EBRT	Yes	I	Yes	<0.01	NHMRC (6); ACN (7), PDQ (8), NCCN (9), NICE (10)

53	Localised Disease IR Disease Life Expectancy >5-10yrs Good IR Disease BT(m) Not Indicated GIR Pref: EBRT Pref: EBRT Boost	RT	III**	n/a	EBRT	Yes	III	Yes	0.04	NCCN (9), NICE (10), CCO-CRT (11), BCCA (13), FROGG-DefRT (15), EAU(16), AUA (17), ACR-EBRT (22)
54	Localised Disease IR Disease Life Expectancy >5-10yrs Good IR Disease BT(m) Not Indicated GIR Pref: EBRT Pref: BT Boost BT Not Physically CI	RT	III**	n/a	EBRT (and BT)	Yes	III	Yes	0.02	NCCN (9), NICE (10), CCO-CRT (11), BCCA (13), FROGG-DefRT (15), EAU(16), AUA (17), ACR-EBRT (22)

55	Localised Disease IR Disease Life Expectancy >5-10yrs Good IR Disease BT(m) Not Indicated GIR Pref: EBRT Pref: BT Boost BT Physically CI	RT	III**	n/a	EBRT	Yes	III	Yes	0.01	NCCN (9), NICE (10), CCO-CRT (11), BCCA (13), FROGG-DefRT (15), EAU(16), AUA (17), ACR-EBRT (22)
56	Localised Disease IR Disease Life Expectancy >5-10yrs Poor IR Disease Pref: Surgery Positive Margins	RT	IV	n/a	(RP and) EBRT	Yes	I	Yes	0.02	ACN (7), NCCN (9) CCO-AdjRT (12), BCCA (13), FROGG-AdjRT (14), EAU(16), ACR-AdjRT (23)

58	Localised Disease IR Disease Life Expectancy >5-10yrs Poor IR Disease Pref: Surgery Negative Margins PSA Relapse Local Recurrence	RT	IV	n/a	(RP then) EBRT	Yes	IV	Yes	<0.01	NHMRC (6); ACN (7), PDQ (8); NCCN (9), NICE (10)
59	Localised Disease IR Disease Life Expectancy >5-10yrs Poor IR Disease Pref: Surgery Negative Margins PSA Relapse No Local Recurrence (HRx) Clinical Metastases	RT	I	n/a	(RP then) EBRT	Yes	I	Yes	<0.01	NHMRC (6); ACN (7), PDQ (8), NCCN (9), NICE (10)

61	Localised Disease IR Disease Life Expectancy >5-10yrs Poor IR Disease Pref: EBRT Pref: EBRT Boost	RT	III**	n/a	EBRT	Yes	III	Yes	0.03	NCCN (9), NICE (10), CCO-CRT (11), BCCA (13), FROGG-DefRT (15), EAU(16), AUA (17), ACR-EBRT (22)
62	Localised Disease IR Disease Life Expectancy >5-10yrs Poor IR Disease Pref: EBRT Pref: BT Boost BT Not Physically CI	RT	III**	n/a	EBRT (and BT)	Yes	III	Yes	0.01	NCCN (9), NICE (10), CCO-CRT (11), BCCA (13), FROGG-DefRT (15), EAU(16), AUA (17), ACR-EBRT (22)
63	Localised Disease IR Disease Life Expectancy >5-10yrs Poor IR Disease Pref: EBRT Pref: BT Boost BT Physically CI	RT	III**	n/a	EBRT	Yes	III	Yes	0.01	NCCN (9), NICE (10), CCO-CRT (11), BCCA (13), FROGG-DefRT (15), EAU(16), AUA (17), ACR-EBRT (22)

64	Localised Disease IR Disease Life Expectancy <5-10yrs Observation/HRx Symptomatic Disease	RT	I	n/a	EBRT	Yes	I	Yes	0.03	PDQ (8) NCCN (9)
66	Localised Disease HR Disease Good Performance Status Good HR Disease Good HR Operable Pref: Surgery Positive Margins	RT	IV	n/a	(RP and) EBRT	Yes	I	Yes	0.01	ACN (7), NCCN (9) CCO-AdjRT (12), BCCA (13), FROGG-AdjRT (14), EAU(16), ACR-AdjRT (23)

68	Localised Disease HR Disease Good Performance Status Good HR Disease Good HR Operable Pref: Surgery Negative Margins PSA Relapse Local Recurrence	RT	IV	n/a	(RP then) EBRT	Yes	IV	Yes	<0.01	NHMRC (6); ACN (7), PDQ (8); NCCN (9), NICE (10)
69	Localised Disease HR Disease Good Performance Status Good HR Disease Good HR Operable Pref: Surgery Negative Margins PSA Relapse No Local Recurrence (HRx) Clinical Metastases	RT	I	n/a	(RP then) EBRT	Yes	I	Yes	<0.01	NHMRC (6); ACN (7), PDQ (8), NCCN (9), NICE (10)

71	Localised Disease HR Disease Good Performance Status Good HR Disease Good HR Operable Pref: EBRT Pref: EBRT Boost	RT	III	n/a	EBRT	Yes	III	Yes	0.01	ACN (7), NCCN (9), NICE (10), BCCA (13), FROGG-DefRT (15), EAU(16), AUA (17), ACR-EBRT (22), ACR-LAPC (20)
72	Localised Disease HR Disease Good Performance Status Good HR Disease Good HR Operable Pref: EBRT Pref: BT Boost BT Not Physically CI	RT	III	n/a	EBRT (and BT)	Yes	III	Yes	<0.01	ACN (7), NCCN (9), NICE (10), BCCA (13), FROGG-DefRT (15), EAU(16), AUA (17), ACR-EBRT (22), ACR-LAPC (20)

73	Localised Disease HR Disease Good Performance Status Good HR Disease Good HR Operable Pref: EBRT Pref: BT Boost Pref: BT Boost BT Physically CI	RT	III	n/a	EBRT	Yes	III	Yes	<0.01	ACN (7), NCCN (9), NICE (10), BCCA (13), FROGG-DefRT (15), EAU(16), AUA (17), ACR-EBRT (22), ACR-LAPC (20)
74	Localised Disease HR Disease Good Performance Status Good HR Disease Good HR Not Operable EBRT Pref: EBRT Boost	RT	III	n/a	EBRT	Yes	III	Yes	0.10	ACN (7), NCCN (9), NICE (10), BCCA (13), FROGG-DefRT (15), EAU(16), AUA (17), ACR-EBRT (22), ACR-LAPC (20)

75	Localised Disease HR Disease Good Performance Status Good HR Disease Good HR Not Operable EBRT Pref: BT Boost BT Not Physically CI	RT	III	n/a	EBRT (and BT)	Yes	III	Yes	0.04	ACN (7), NCCN (9), NICE (10), BCCA (13), FROGG-DefRT (15), EAU(16), AUA (17), ACR-EBRT (22), ACR-LAPC (20)
76	Localised Disease HR Disease Good Performance Status Good HR Disease Good HR Not Operable EBRT Pref: BT Boost BT Physically CI	RT	III	n/a	EBRT	Yes	III	Yes	0.03	ACN (7), NCCN (9), NICE (10), BCCA (13), FROGG-DefRT (15), EAU (16;35), AUA (17), ACR-EBRT (22), ACR-LAPC (20)

77	Localised Disease HR Disease Good Performance Status Poor HR Disease	RT	III	n/a	EBRT	Yes	III	Yes	0.05	ACN (7), NCCN (9), NICE (10), BCCA (13), FROGG-DefRT (15), EAU (16;35), AUA (17), ACR-EBRT (22), ACR-LAPC (20)
78	Localised Disease HR Disease Poor Performance Status Observation/HRx Symptomatic Disease	RT	I	n/a	EBRT	Yes	I	Yes	0.01	PDQ (8) NCCN (9)
80	Metastatic Disease Bone Pain	RT	I	n/a	(RP then) EBRT	Yes	I	Yes	0.03	NHMRC (6); ACN (7), PDQ (8), NCCN (9), NICE (10)
Proportion of all patients with prostate cancer in whom EBRT was recommended				0.60 (60%)	**Updated Proportion of all patients with prostate cancer in whom EBRT is recommended**				**0.58 (58%)**	

*Note that in the original RTU study, prostate cancer risk categories were not included, thereby limiting comparability between previous and current models.
**Level of evidence in original RTU study erroneously reported to be IV rather than III
Abbreviations: Nos, Numbers; RTU, Radiotherapy Utilisation; LR, Low Risk; Pref, Preference; RT, Radiotherapy; RP, Radical Prostatectomy; EBRT, External Beam Radiotherapy; BT, Brachytherapy; BT(m), Brachytherapy Monotherapy; Local Rec, Local Recurrence; DM, Distant Metastases; HRx, Hormone Therapy; CI, Contra-Indications; AS, Active Surveillance; IR, Intermediate Risk; HR, High Risk

Table 2: Prostate Cancer. Indications for Brachytherapy - Levels and sources of evidence

Outcome Nos. in Updated Tree	Clinical Scenario	Original BTU studies			Updates 2012					References
		Treatment Indicated	Level of Evidence for BT	Proportion of all Prostate Cancer	Treatment Indicated	Guideline updated	Current level of evidence for BT	Change to proportion of all Prostate Cancer		
								Yes/ No	Updated value	
7	Localised Disease LR Disease Life Expectancy >5-10yrs Pref: Treatment Pref: RT Pref: BT(m) BT not Physically CI No Distant Metastases	BT	III	0.031	BT	Yes	III	Yes	0.022	ESTRO/EAU/EORTC (4), NCCN (9), NICE (10), BCCA (13), EAU (16), AUA (17), ACR-ASTRO-BT (18), ACR-BT (19), ABS-SBT (24)

8	Localised Disease LR Disease Life Expectancy >5-10yrs Pref: Treatment Pref: RT Pref: BT(m) BT not Physically CI Distant Metastases	BT	III		BT (then EBRT)	Yes	III	Yes	<0.001	ESTRO/EAU/EORTC (4), NCCN (9), NICE (10), BCCA (13), EAU(16), AUA (17), ACR-ASTRO-BT (18), ACR-BT (19), ABS-SBT (24)
21	Localised Disease LR Disease Life Expectancy >5-10yrs Pref: AS Treatment Pref: RT Pref: BT(m) BT not Physically CI No Distant Metastases	BT	IV	<0.001	BT	Yes	IV	Yes	0.001	NCCN (9), NICE (10), BCCA (13), EAU (16), AUA (17)

22	Localised Disease LR Disease Life Expectancy >5-10yrs Pref: AS Treatment Pref: RT Pref: BT(m) BT not Physically CI Distant Metastases	BT	IV	<0.001	BT (then EBRT)	Yes	IV	Yes	<0.001	NCCN (9), NICE (10), BCCA (13), EAU (16), AUA (17)
38	Localised Disease IR Disease Life Expectancy >5-10yrs Good IR Disease BT(m) Indicated for GIR Pref: RT Pref: EBRT Pref: BT Boost BT Not Physically CI	EBRT and BT	II, III	Outcome 40 + 57 = 0.000	(EBRT and) BT	Yes	II, III	Yes	0.000	GEC/ESTRO-EAU (5), NCCN (9), ACR-BT (19), ACR-EBRT (22), ABS-SBT (24)

40	Localised Disease IR Disease Life Expectancy >5-10yrs Good IR Disease BT(m) Indicated for GIR Pref: RT Pref: BT(m) BT Not Physically CI No Distant Metastases	BT	III	0.000	BT	Yes	III	Yes	0.000	ESTRO/EAU/EORTC (4), , BCCA (13), AUA (17), ABS-SBT (24)
41	Localised Disease IR Disease Life Expectancy >5-10yrs Good IR Disease BT(m) Indicated for GIR Pref: RT Pref: BT(m) BT Not Physically CI Distant Metastases	BT	III		BT (then EBRT)	Yes	III	Yes	0.000	ESTRO/EAU/EORTC (4), BCCA (13), AUA (17), ABS-SBT (24)

54	Localised Disease IR Disease Life Expectancy >5-10yrs Good IR Disease BT(m) Not Indicated GIR Pref: EBRT Pref: BT Boost BT Not Physically CI	EBRT and BT	II, III	Outcome 40 + 57 = 0.023	(EBRT and) BT	Yes	II, III	Yes	0.020	GEC/ESTRO-EAU (5), NCCN (9), ACR-BT (19), ACR-EBRT (22), ABS-SBT (24)
62	Localised Disease IR Disease Life Expectancy >5-10yrs Poor IR Disease Pref: EBRT Pref: BT Boost BT Not Physically CI	EBRT and BT	II, III	0.019	(EBRT and) BT	Yes	II, III	Yes	0.012	GEC/ESTRO-EAU (5), NCCN (9), ACR-BT (19), ACR-EBRT (22), ABS-SBT (24)

72	Localised Disease HR Disease Good Performance Status Good HR Disease Good HR Operable Pref: EBRT Pref: BT Boost BT Not Physically CI	EBRT and BT	II, III	0.004	(EBRT and) BT	Yes	II, III	Yes	0.003	GEC/ESTRO-EAU (5), ACN (7), NCCN (9), NICE (10), BCCA (13), ACR-BT (19), ACR-EBRT (22), ABS-SBT (24)
75	Localised Disease HR Disease Good Performance Status Good HR Disease Good HR Not Operable EBRT Pref: BT Boost BT Not Physically CI	EBRT and BT	II, III	0.042	(EBRT and) BT	Yes	II, III	Yes	0.040	GEC/ESTRO-EAU (5), ACN (7), NCCN (9), NICE (10), BCCA (13), ACR-BT (19), ACR-EBRT (22), ABS-SBT (24)
Proportion of all patients with prostate cancer in whom BT was recommended				0.119 (11.9%)	**Updated Proportion of all patients with prostate cancer in whom BT is recommended**				**0.098 (9.8%)**	

Abbreviations: Nos, Numbers; BTU, Brachytherapy Utilisation; BT, Brachytherapy; BT(m), Brachytherapy Monotherapy; LR, Low Risk; Pref, Preference; RT, Radiotherapy; CI, Contra-Indications; HRx, Hormone Therapy; EBRT, External Beam Radiotherapy; AS, Active Surveillance;IR, Intermediate Risk; GIR, Good Intermediate Risk; HR, High Risk

Table 3: Prostate Cancer. The incidence of attributes used to define indications for radiotherapy and brachytherapy

Population or sub-population of interest	Attribute	Original RTU/BTU studies*		Updates 2012			
		Proportion of population with the attribute	Quality of Information	Change in proportion of population with attribute	Updated Proportion	Updated Quality of Information	Updated Reference
All registry cancers	Prostate cancer	0.12 (RTU) 0.175 (BTU)	α	Yes	0.18	α	AIHW 2011 (31)
Prostate cancer	Localised Disease	0.84 (RTU) 0.95 (BTU)	α γ	Yes	0.95	γ	SEER 2004-2007 (30)
Localized disease	Low risk disease	0.29 (BTU)	β	No	0.29	n/a	n/a
Localized disease; LR disease	Life expectancy from co-morbidities >5-10yrs	0.67 (BTU)	α	No	0.67	n/a	n/a
Localized disease; LR disease; Life expectancy >5-10yrs	Pref Treatment	n/a	n/a	Yes	0.92	θ	Anandadas et al (54)
	Active Surveillance				0.08		
Localized disease; LR disease; Life expectancy >5-10yrs; Pref Treatment	Pref Surgery	n/a	n/a	Yes	0.43 **	θ	Anandadas et al (54)
	Pref RT				0.57 **		

Population or sub-population of interest	Attribute	Original RTU/BTU studies*		Updates 2012			
		Proportion of population with the attribute	Quality of Information	Change in proportion of population with attribute	Updated Proportion	Updated Quality of Information	Updated Reference
Localized disease; LR disease; Life expectancy >5-10yrs; Pref Treatment; Pref Surgery	Positive Margins	0.22 (RTU)	γ	Yes	0.24	γ	CaPSURE (58)
Localized disease; LR disease; Life expectancy >5-10yrs; Pref Treatment; Pref Surgery; Negative Margins	PSA Relapse	n/a	n/a	Yes	0.01	λ	Alkhateeb et al (59)
Localized disease; LR disease; Life expectancy >5-10yrs; Pref Treatment; Pref Surgery; Negative Margins; PSA Relapse	Local Recurrence	n/a	n/a	Yes	0.40	γ	CaPSURE (60)
Localized disease; LR disease; Life expectancy >5-10yrs; Pref Treatment; Pref Surgery; Negative Margins; PSA Relapse; No Local Recurrence (HRx)	Clinical Metastases	n/a	n/a	Yes	0.06	λ	Antonarakis et al (61)

Population or sub-population of interest	Attribute	Original RTU/BTU studies*		Updates 2012			
		Proportion of population with the attribute	Quality of Information	Change in proportion of population with attribute	Updated Proportion	Updated Quality of Information	Updated Reference
Localized disease; LR disease; Life expectancy >5-10yrs; Pref Treatment: Pref RT	Pref EBRT	n/a	n/a	Yes	0.60 **	θ	Anandadas et al (54)
	Pref BT(m)				0.40 **		
Localized disease; LR disease; Life expectancy >5-10yrs; Pref Treatment; Pref RT; Pref BT(m)	BT Not Physically CI	0.58 (BTU)	β ζ	No	0.58 **	No	n/a
Localized disease; LR disease; Life expectancy >5-10yrs; Pref Treatment; Pref RT; Pref BT(m); BT Not Physically CI	Distant Metastases	n/a	n/a	Yes	0.01	ζ ζ	Forsythe et al (62) Taira et al (63)
Localized disease; LR disease; Life expectancy >5-10yrs; Pref Treatment; Pref RT; Pref BT(m); BT Physically CI	Pref Surgery	0.69 (RTU)	γ	Yes	0.56 **	θ	Anandadas et al (54)
	Pref EBRT	0.31 (RTU)			0.44 **		

Population or sub-population of interest	Attribute	Original RTU/BTU studies*		Updates 2012			
		Proportion of population with the attribute	Quality of Information	Change in proportion of population with attribute	Updated Proportion	Updated Quality of Information	Updated Reference
Localized disease; LR disease; Life expectancy >5-10yrs; Pref Treatment; Pref RT; Pref BT(m); BT Physically CI; Pref Surgery	Positive Margins	0.22 (RTU)	γ	Yes	0.24	γ	CaPSURE (58)
Localized disease; LR disease; Life expectancy >5-10yrs; Pref Treatment; Pref RT; Pref BT(m); BT Physically CI; Pref Surgery; Negative Margins	PSA Relapse	n/a	n/a	Yes	0.01	λ	Alkhateeb et al (59)
Localized disease; LR disease; Life expectancy >5-10yrs; Pref Treatment; Pref RT; Pref BT(m); BT Physically CI; Pref Surgery; Negative Margins; PSA Relapse	Local Recurrence	n/a	n/a	Yes	0.40	γ	CaPSURE (60)

Population or sub-population of interest	Attribute	Original RTU/BTU studies*		Updates 2012			
		Proportion of population with the attribute	Quality of Information	Change in proportion of population with attribute	Updated Proportion	Updated Quality of Information	Updated Reference
Localized disease; LR disease; Life expectancy >5-10yrs; Pref Treatment; Pref RT; Pref BT(m); BT Physically CI; Pref Surgery; Negative Margins; PSA Relapse; No Local Recurrence (HRx)	Clinical Metastases	n/a	n/a	Yes	0.06	λ	Antonarakis et al (61)
Localized disease; LR disease; Life expectancy >5-10yrs; Active Surveillance	Treatment	0.33 (BTU)	ε	No	0.33	No	n/a
Localized disease; LR disease; Life expectancy >5-10yrs; AS; Treatment	Pref Surgery	n/a	n/a	Yes	0.43 **	θ	Anandadas et al (54)
	Pref RT				0.57 **		
Localized disease; LR disease; Life expectancy >5-10yrs; AS; Treatment; Pref Surgery	Positive Margins	0.22 (RTU)	γ	Yes	0.24	γ	CaPSURE (58)

Population or sub-population of interest	Attribute	Original RTU/BTU studies*		Updates 2012			
		Proportion of population with the attribute	Quality of Information	Change in proportion of population with attribute	Updated Proportion	Updated Quality of Information	Updated Reference
Localized disease; LR disease; Life expectancy >5-10yrs; AS; Treatment; Pref Surgery; Negative Margins	PSA Relapse	n/a	n/a	Yes	0.01	λ	Alkhateeb et al (59)
Localized disease; LR disease; Life expectancy >5-10yrs; AS; Treatment; Pref Surgery; Negative Margins; PSA Relapse	Local Recurrence	n/a	n/a	Yes	0.40	γ	CaPSURE (60)
Localized disease; LR disease; Life expectancy >5-10yrs; AS; Treatment; Pref Surgery; Negative Margins; PSA Relapse; No Local Recurrence (HRx)	Clinical Metastases	n/a	n/a	Yes	0.06	λ	Antonarakis et al (61)
Localized disease; LR disease; Life expectancy >5-10yrs; AS; Treatment; Pref RT	Pref EBRT	n/a	n/a	Yes	0.60 **	θ	Anandadas et al (54)
	Pref BT(m)				**0.40 ** **		

Population or sub-population of interest	Attribute	Original RTU/BTU studies*		Updates 2012			
		Proportion of population with the attribute	Quality of Information	Change in proportion of population with attribute	Updated Proportion	Updated Quality of Information	Updated Reference
Localized disease; LR disease; Life expectancy >5-10yrs; AS; Treatment; Pref RT; Pref BT(m)	BT Not Physically CI	0.58 (BTU)	β ζ	No	0.58 **	No	n/a
Localized disease; LR disease; Life expectancy >5-10yrs; AS; Treatment; Pref RT; Pref BT(m); BT Not Physically CI	Distant Metastases	n/a	n/a	Yes	0.01	ζ ζ	Forsythe et al (62) Taira et al (63)
Localized disease; LR disease; Life expectancy >5-10yrs; AS; Treatment; Pref RT; Pref BT(m); BT Physically CI	Pref Surgery	0.69 (RTU)	γ	Yes	0.56 **	θ	Anandadas et al (54)
	Pref EBRT	0.31 (RTU)			0.44 **		
Localized disease; LR disease; Life expectancy >5-10yrs; AS; Treatment; Pref RT; Pref BT(m); BT Physically CI; Pref Surgery	Positive Margins	0.22 (RTU)	γ	Yes	0.24	γ	CaPSURE (58)

Population or sub-population of interest	Attribute	Original RTU/BTU studies*		Updates 2012			
		Proportion of population with the attribute	Quality of Information	Change in proportion of population with attribute	Updated Proportion	Updated Quality of Information	Updated Reference
Localized disease; LR disease; Life expectancy >5-10yrs; AS; Treatment; Pref RT; Pref BT(m); BT Physically CI; Pref Surgery; Negative Margins	PSA Relapse	n/a	n/a	Yes	0.01	λ	Alkhateeb et al (59)
Localized disease; LR disease; Life expectancy >5-10yrs; AS; Treatment; Pref RT; Pref BT(m); BT Physically CI; Pref Surgery; Negative Margins; PSA Relapse	Local Recurrence	n/a	n/a	Yes	0.40	γ	CaPSURE (60)
Localized disease; LR disease; Life expectancy >5-10yrs; AS; Treatment; Pref RT; Pref BT(m); BT Physically CI; Pref Surgery; Negative Margins; PSA Relapse; No Local Recurrence (HRx)	Clinical Metastases	n/a	n/a	Yes	0.06	λ	Antonarakis et al (61)

Population or sub-population of interest	Attribute	Original RTU/BTU studies*		Updates 2012			
		Proportion of population with the attribute	Quality of Information	Change in proportion of population with attribute	Updated Proportion	Updated Quality of Information	Updated Reference
Localized disease; LR disease; Life expectancy <5-10yrs; Observation/Hormone Therapy	Symptomatic Disease	0.10 (RTU)	ζ	Yes	0.22	γ	CaPSURE (64)
Localized disease	Intermediate Risk disease	0.42 (BTU)	β	No	0.42	n/a	n/a
Localized disease; IR disease	Life expectancy from co-morbidities >5-10yrs	0.67 (BTU)	α	No	0.67	n/a	n/a
Localized disease; IR disease; Life expectancy >5-10yrs	Good Intermediate Risk disease	0.63 (BTU)	β	No	0.63	n/a	n/a
Localized disease; IR disease; Life expectancy >5-10yrs; GIR disease	BT(m) Indicated for GIR disease	0.00 (BTU)	n/a	n/a	0.00 **	n/a	n/a

Population or sub-population of interest	Attribute	Original RTU/BTU studies*		Updates 2012			
		Proportion of population with the attribute	Quality of Information	Change in proportion of population with attribute	Updated Proportion	Updated Quality of Information	Updated Reference
Localized disease; IR disease; Life expectancy >5-10yrs; GIR disease; BT(m) Indicated for GIR disease	Pref Surgery	n/a	n/a	Yes	0.43 **	θ	Anandadas et al (54)
	Pref RT				0.57 **		
Localized disease; IR disease; Life expectancy >5-10yrs; GIR disease; BT(m) Indicated for GIR disease; Pref Surgery	Positive Margins	0.35 (RTU)	γ	Yes	0.30	γ	CaPSURE (58)
Localized disease; IR disease; Life expectancy >5-10yrs; GIR disease; BT(m) Indicated for GIR disease; Pref Surgery; Negative Margins	PSA Relapse	n/a	n/a	Yes	0.06	λ	Alkhateeb et al (59)
Localized disease; IR disease; Life expectancy >5-10yrs; GIR disease; BT(m) Indicated for GIR disease; Pref Surgery; Negative Margins; PSA Relapse	Local Recurrence	n/a	n/a	Yes	0.40	γ	CaPSURE (60)

Population or sub-population of interest	Attribute	Original RTU/BTU studies*		Updates 2012			
		Proportion of population with the attribute	Quality of Information	Change in proportion of population with attribute	Updated Proportion	Updated Quality of Information	Updated Reference
Localized disease; IR disease; Life expectancy >5-10yrs; GIR disease; BT(m) Indicated for GIR disease; Pref Surgery; Negative Margins; PSA Relapse; No Local Recurrence (HRx)	Clinical Metastases	n/a	n/a	Yes	0.48	λ	Antonarakis et al (61)
Localized disease; IR disease; Life expectancy >5-10yrs; GIR disease; BT(m) Indicated for GIR disease; Pref RT	Pref EBRT	n/a	n/a	Yes	0.60 **	θ	Anandadas et al (54)
	Pref BT(m)				0.40 **		
Localized disease; IR disease; Life expectancy >5-10yrs; GIR disease; BT(m) Indicated for GIR disease; Pref RT; Pref EBRT	Pref EBRT Boost	0.44 (BTU)	θ	Yes	0.60 **	θ	Anandadas et al (54)
	Pref BT Boost	0.56 (BTU)			0.40 **		

Population or sub-population of interest	Attribute	Original RTU/BTU studies*		Updates 2012			
		Proportion of population with the attribute	Quality of Information	Change in proportion of population with attribute	Updated Proportion	Updated Quality of Information	Updated Reference
Localized disease; IR disease; Life expectancy >5-10yrs; GIR disease; BT(m) Indicated for GIR disease; Pref RT; Pref EBRT; Pref BT Boost	BT Not Physically CI	0.68 (BTU)	β ζ	No	0.68 **	No	n/a
Localized disease; IR disease; Life expectancy >5-10yrs; GIR disease; BT(m) Indicated for GIR disease; Pref RT; Pref BT(m)	BT Not Physically CI	0.68 (BTU)	β ζ	No	0.68 **	No	n/a
Localized disease; IR disease; Life expectancy >5-10yrs; GIR disease; BT(m) Indicated for GIR disease; Pref RT; Pref BT(m); BT Not Physically CI	Distant Metastases	n/a	n/a	Yes	0.05	ζ ζ	Forsythe et al (62) Taira et al (63)
Localized disease; IR disease; Life expectancy >5-10yrs; GIR disease; BT(m) Indicated for GIR disease; Pref RT; Pref BT(m); BT Physically CI	Pref Surgery	0.65 (RTU) 0.50 (BTU)	γ (RTU) θ (BTU)	Yes	0.56 **	θ	Anandadas et al (54)
	Pref EBRT	0.35 (RTU) 0.50 (BTU)			0.44 **		

Population or sub-population of interest	Attribute	Original RTU/BTU studies*		Updates 2012			
		Proportion of population with the attribute	Quality of Information	Change in proportion of population with attribute	Updated Proportion	Updated Quality of Information	Updated Reference
Localized disease; IR disease; Life expectancy >5-10yrs; GIR disease; BT(m) Indicated for GIR disease; Pref RT; Pref BT(m); BT Physically CI; Pref Surgery	Positive Margins	0.35 (RTU)	γ	Yes	0.30	γ	CaPSURE (58)
Localized disease; IR disease; Life expectancy >5-10yrs; GIR disease; BT(m) Indicated for GIR disease; Pref RT; Pref BT(m); BT Physically CI; Pref Surgery; Negative Margins	PSA Relapse	n/a	n/a	Yes	0.06	λ	Alkhateeb et al (59)
Localized disease; IR disease; Life expectancy >5-10yrs; GIR disease; BT(m) Indicated for GIR disease; Pref RT; Pref BT(m); BT Physically CI; Pref Surgery; Negative Margins; PSA Relapse	Local Recurrence	n/a	n/a	Yes	0.40	γ	CaPSURE (60)

Population or sub-population of interest	Attribute	Original RTU/BTU studies*		Updates 2012			
		Proportion of population with the attribute	Quality of Information	Change in proportion of population with attribute	Updated Proportion	Updated Quality of Information	Updated Reference
Localized disease; IR disease; Life expectancy >5-10yrs; GIR disease; BT(m) Indicated for GIR disease; Pref RT; Pref BT(m); BT Physically CI; Pref Surgery; Negative Margins; PSA Relapse; No Local Recurrence (HRx)	Clinical Metastases	n/a	n/a	Yes	0.48	λ	Antonarakis et al (61)
Localized disease; IR disease; Life expectancy >5-10yrs; GIR disease; BT(m) CI for GIR disease	Pref Surgery	0.65 (RTU) 0.50 (BTU)	γ (RTU) θ (BTU)	Yes	0.56 **	θ	Anandadas et al (54)
	Pref EBRT	0.35 (RTU) 0.50 (BTU)			0.44 **		
Localized disease; IR disease; Life expectancy >5-10yrs; GIR disease; BT(m) CI for GIR disease; Pref Surgery	Positive Margins	0.35 (RTU)	γ	Yes	0.30	γ	CaPSURE (58)

Population or sub-population of interest	Attribute	Original RTU/BTU studies*		Updates 2012			
		Proportion of population with the attribute	Quality of Information	Change in proportion of population with attribute	Updated Proportion	Updated Quality of Information	Updated Reference
Localized disease; IR disease; Life expectancy >5-10yrs; GIR disease; BT(m) CI for GIR disease; Pref Surgery; Negative Margins	PSA Relapse	n/a	n/a	Yes	0.06	λ	Alkhateeb et al (59)
Localized disease; IR disease; Life expectancy >5-10yrs; GIR disease; BT(m) CI for GIR disease; Pref Surgery; Negative Margins; PSA Relapse	Local Recurrence	n/a	n/a	Yes	0.40	γ	CaPSURE (60)
Localized disease; IR disease; Life expectancy >5-10yrs; GIR disease; BT(m) CI for GIR disease; Pref Surgery; Negative Margins; PSA Relapse; No Local Recurrence (HRx)	Clinical Metastases	n/a	n/a	Yes	0.48	λ	Antonarakis et al (61)

Population or sub-population of interest	Attribute	Original RTU/BTU studies*		Updates 2012			
		Proportion of population with the attribute	Quality of Information	Change in proportion of population with attribute	Updated Proportion	Updated Quality of Information	Updated Reference
Localized disease; IR disease; Life expectancy >5-10yrs; GIR disease; BT(m) CI for GIR disease; Pref EBRT	Pref EBRT Boost	0.44 (BTU)	θ	Yes	0.60 **	θ	Anandadas et al (54)
	Pref BT Boost	0.56 (BTU)			0.40 **		
Localized disease; IR disease; Life expectancy >5-10yrs; GIR disease; BT(m) CI for GIR disease; Pref EBRT; Pref BT Boost	BT Not Physically CI	0.68 (BTU)	β ζ	No	0.68 **	No	n/a
Localized disease; IR disease; Life expectancy >5-10yrs	Poor Intermediate Risk Disease	0.37 (BTU)	β	No	0.37	n/a	n/a
Localized disease; IR disease; Life expectancy >5-10yrs; PIR disease	Pref Surgery	0.65 (RTU) 0.50 (BTU)	γ (RTU) θ (BTU)	Yes	0.56 **	θ	Anandadas et al (54)
	Pref EBRT	0.35 (RTU) 0.50 (BTU)			0.44 **		

Population or sub-population of interest	Attribute	Original RTU/BTU studies*		Updates 2012			
		Proportion of population with the attribute	Quality of Information	Change in proportion of population with attribute	Updated Proportion	Updated Quality of Information	Updated Reference
Localized disease; IR disease; Life expectancy >5-10yrs; PIR disease; Pref Surgery	Positive Margins	0.35 (RTU)	γ	Yes	0.30	γ	CaPSURE (58)
Localized disease; IR disease; Life expectancy >5-10yrs; PIR disease; Pref Surgery; Negative Margins	PSA Relapse	n/a	n/a	Yes	0.06	λ	Alkhateeb et al (59)
Localized disease; IR disease; Life expectancy >5-10yrs; PIR disease; Pref Surgery; Negative Margins; PSA Relapse	Local Recurrence	n/a	n/a	Yes	0.40	γ	CaPSURE (60)
Localized disease; IR disease; Life expectancy >5-10yrs; PIR disease; Pref Surgery; Negative Margins; PSA Relapse; No Local Recurrence (HRx)	Clinical Metastases	n/a	n/a	Yes	0.48	λ	Antonarakis et al (61)

Population or sub-population of interest	Attribute	Original RTU/BTU studies*		Updates 2012			
		Proportion of population with the attribute	Quality of Information	Change in proportion of population with attribute	Updated Proportion	Updated Quality of Information	Updated Reference
Localized disease; IR disease; Life expectancy >5-10yrs; PIR disease; Pref EBRT	Pref EBRT Boost	0.44 (BTU)	θ	Yes	0.60 **	θ	Anandadas et al (54)
	Pref BT Boost	0.56 (BTU)			0.40 **		
Localized disease; IR disease; Life expectancy >5-10yrs; PIR disease; Pref EBRT; Pref BT Boost	BT Not Physically CI	0.68 (BTU)	β ζ	No	0.68 **	No	n/a
Localized disease; IR disease; Life expectancy <5-10yrs; Observation/Hormone Therapy	Symptomatic Disease	0.12 (RTU)	ζ	Yes	0.22	γ	CaPSURE (64)
Localized disease	High Risk disease	0.29 (BTU)	β	No	0.29	n/a	n/a
Localized disease; HR disease	Good Performance Status	0.89 (RTU)	γ	No	0.89	n/a	n/a
Localized disease; HR disease; Good PS	Good High Risk Disease	0.79 (BTU)	β	No	0.79	n/a	n/a

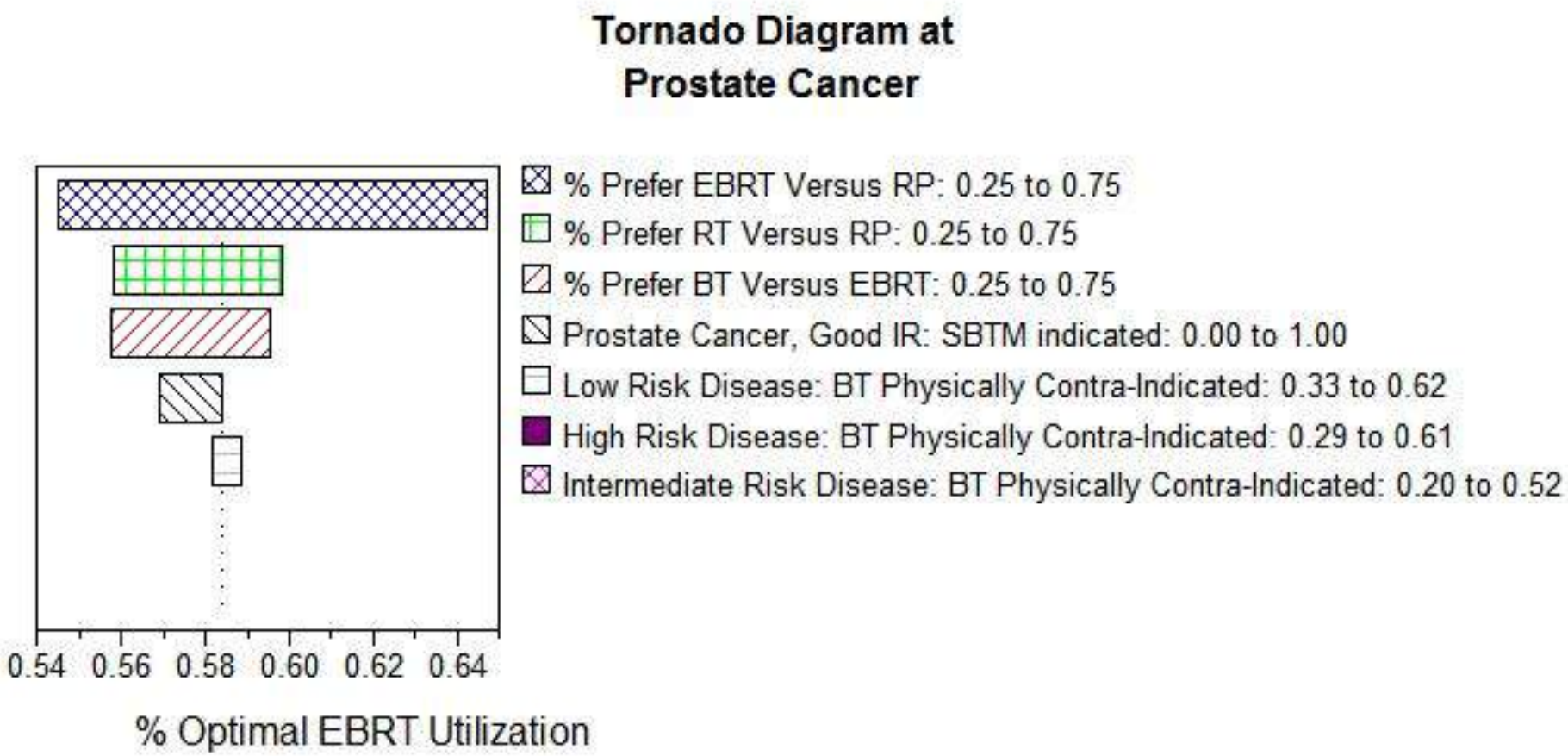
Population or sub-population of interest	Attribute	Original RTU/BTU studies*		Updates 2012			
		Proportion of population with the attribute	Quality of Information	Change in proportion of population with attribute	Updated Proportion	Updated Quality of Information	Updated Reference
Localized disease; HR disease; Good PS; Good HR Disease	Operable	0.15 (BTU)	β	No	0.15	n/a	n/a
Localized disease; HR disease; Good PS; Good HR Disease; Operable	Pref Surgery	0.50 (BTU)	θ	Yes	0.56 **	θ	Anandadas et al (54)
	Pref EBRT	0.50 (BTU)			0.44 **		
Localized disease; HR disease; Good PS; Good HR Disease; Operable; Pref Surgery	Positive Margins	n/a	n/a	Yes	0.49 **	λ	Xylinas et al (65)
Localized disease; HR disease; Good PS; Good HR Disease; Operable; Pref Surgery; Negative Margins	PSA Relapse	n/a	n/a	Yes	0.22	λ	Alkhateeb et al (59)
Localized disease; HR disease; Good PS; Good HR Disease; Operable; Pref Surgery; Negative Margins; PSA Relapse	Local Recurrence	n/a	n/a	Yes	0.40	γ	CaPSURE (60)

Population or sub-population of interest	Attribute	Original RTU/BTU studies*		Updates 2012			
		Proportion of population with the attribute	Quality of Information	Change in proportion of population with attribute	Updated Proportion	Updated Quality of Information	Updated Reference
Localized disease; HR disease; Good PS; Good HR Disease; Operable; Pref Surgery; Negative Margins; PSA Relapse; No Local Recurrence (HRx)	Clinical Metastases	n/a	n/a	Yes	0.81	λ	Antonarakis et al (61)
Localized disease; HR disease; Good PS; Good HR Disease; Operable; Pref EBRT	Pref EBRT Boost	0.44 (BTU)	θ	Yes	0.60 **	θ	Anandadas et al (54)
	Pref BT Boost	0.56 (BTU)			0.40 **		
Localized disease; HR disease; Good PS; Good HR Disease; Operable; Pref EBRT; Pref BT Boost	BT Not Physically CI	0.60 (BTU)	β ζ	No	0.60 **	No	n/a
Localized disease; HR disease; Good PS; Good HR Disease; Not Operable - EBRT	Pref EBRT Boost	0.44 (BTU)	θ	Yes	0.60 **	θ	Anandadas et al (54)
	Pref BT Boost	0.56 (BTU)			0.40 **		
Localized disease; HR disease; Good PS; Good HR Disease; Not Operable – EBRT; Pref BT Boost	BT Not Physically CI	0.60 (BTU)	β ζ	No	0.60 **	No	n/a

Population or sub-population of interest	Attribute	Original RTU/BTU studies*		Updates 2012			
		Proportion of population with the attribute	Quality of Information	Change in proportion of population with attribute	Updated Proportion	Updated Quality of Information	Updated Reference
Localized disease; HR disease; Good PS	Poor High Risk Disease	0.21 (BTU)	β	No	0.21	n/a	n/a
Localized disease; HR disease; Poor PS; Observation/Hormone Therapy	Symptomatic Disease	0.12 (RTU)	ζ	Yes	0.22	γ	CaPSURE (64)
Prostate Cancer	Nodal or Haematogenous Metastases	0.84 (RTU) 0.95 (BTU)	α γ	Yes	0.05	γ	SEER 2004-2007 (30)
Prostate Cancer; Nodal or Haematogenous Metastases	Bone Pain	0.70	θ	No	0.70	No	n/a

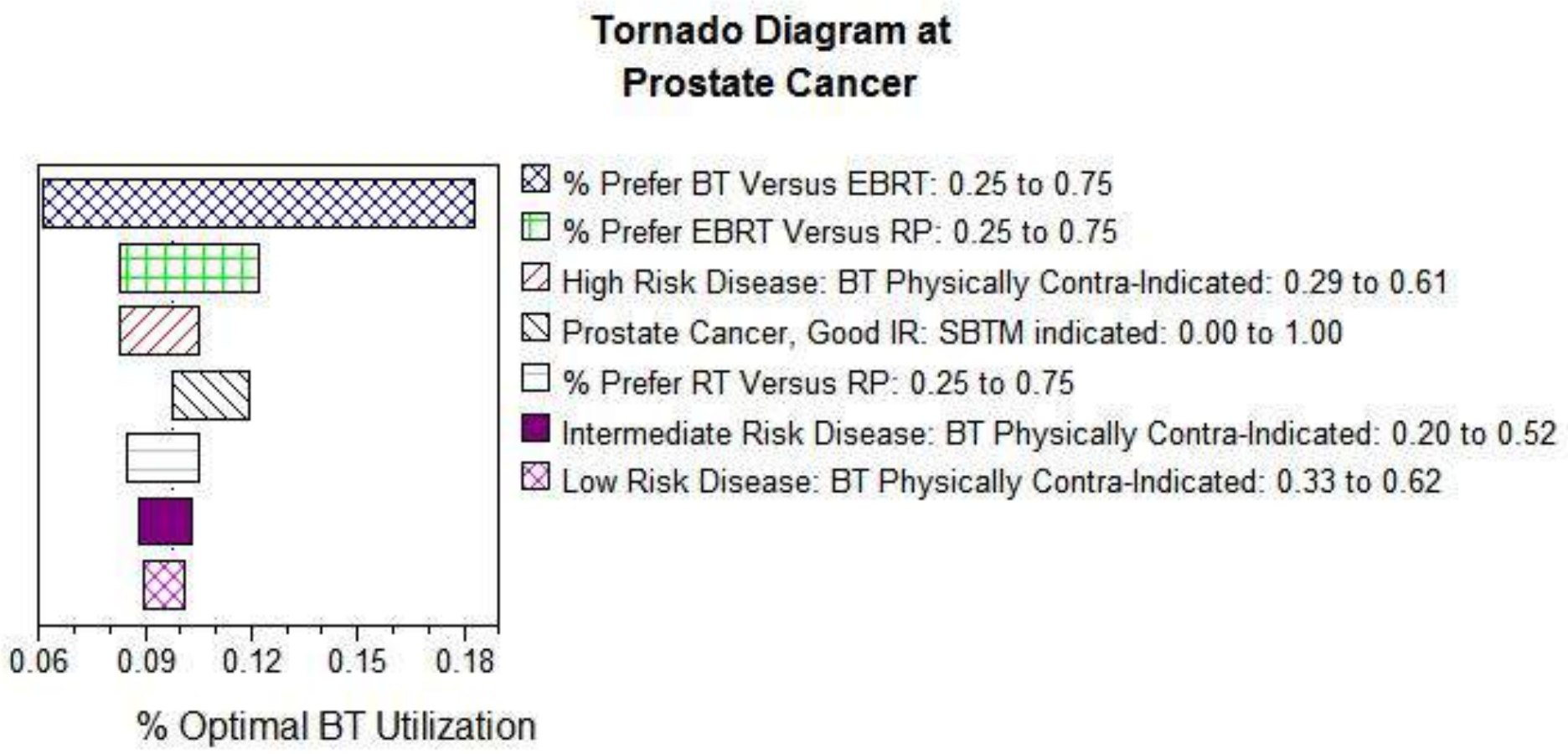
* Note that in the original RTU study, prostate cancer risk categories were not included, thereby limiting comparability between previous and current models.
** Sensitivity Analysis performed
Abbreviations: RTU, Radiotherapy Utilization; BTU, Brachytherapy Utilization; AIHW, Australian Institute of Health and Welfare; SEER, Surveillance, Epidemiology, End Results Database; LR Disease, Low Risk Disease; yrs, years; Pref, Preference; RT, Radiotherapy; HRx, Hormone Therapy; EBRT, External Beam Radiotherapy; BT(m), Brachytherapy Monotherapy; CI, Contra-Indications; AS, Active Surveillance; IR Disease, Intermediate Risk Disease; GIR Disease, Good Intermediate Risk Disease; PIR Disease, Poor Intermediate Risk Disease; HR Disease, High Risk Disease

Figure 3. Prostate Cancer. External Beam Radiotherapy. Tornado Diagram for Univariate Sensitivity Analysis



EBRT, External Beam Radiotherapy; RP, Radical Prostatectomy; BT, Brachytherapy; IR, Intermediate Risk Disease; SBTM, Brachytherapy Monotherapy

Figure 4. Prostate Cancer. Brachytherapy. Tornado Diagram for Univariate Sensitivity Analysis



EBRT, External Beam Radiotherapy; RP, Radical Prostatectomy; BT, Brachytherapy; IR, Intermediate Risk Disease; SBTM, Brachytherapy Monotherapy

References

1. Delaney GP, Jacob S, Featherstone C, and Barton MB. Radiotherapy in cancer care: estimating optimal utilisation from a review of evidence-based clinical guidelines. www.ncci.org.au . 2003.
   Ref Type: Electronic Citation

2. Thompson SR, Delaney G, and Barton MB. Estimating the optimal utilization of brachytherapy for the treatment of cancer. 2004. Submitted to NSW Department of Health.
   Ref Type: Report

3. Thompson SR and Barton M. Optimal utilization of permanent seed brachytherapy for the treatment of prostate cancer. 2009. Submitted to NSW Department of Health.
   Ref Type: Report

4. Ash D, Flynn A, Battermann J, de Reijke T, Lavagnini P, Blank L. ESTRO/EAU/EORTC recommendations on permanent seed implantation for localized prostate cancer. *Radiotherapy and Oncology* 2000;57:315-21.

5. Kovacs G, Potter R, Loch T, Hammer J, Kolkman-Deurloo I, de la Rosette J et al. GEC/ESTRO-EAU recommendations on temporary brachytherapy using stepping sources for localised prostate cancer. *Radiotherapy and Oncology* 2005;74:137-48.

6. National Health and Medical Research Council. Clinical Practice Guidelines: Evidence-based information and recommendations for the management of localised prostate cancer. http://www.nhmrc.gov.au . 2002. 10-2-2004.
   Ref Type: Electronic Citation

7. Australian Cancer Network Management of Metastatic Prostate Cancer Working Party. Clinical Practice Guidelines for the Management of Locally Advanced and Metastatic Prostate Cancer. 2010. Sydney, Australia, Cancer Council Australia and Australian Cancer Network.
   Ref Type: Report

8. National Cancer Institute. PDQ® Prostate Cancer Treatment. http://cancer.gov/cancertopics/pdq/treatment/prostate/HealthProfessional . 20-1-2012. 25-7-2012.
   Ref Type: Electronic Citation

9. National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology - v3.2012 - Prostate Cancer. http://www.nccn.org/professionals/physician_gls/PDF/prostate.pdf . 2012. 25-7-2012.
   Ref Type: Electronic Citation

10. National Collaborating Centre for Cancer. Prostate cancer: diagnosis and treatment. http://www.nice.org.uk/nicemedia/pdf/CG58FullGuideline.pdf . 2008. 3-12-2008.
    Ref Type: Electronic Citation

11. Cancer Care Ontario Practice Guideline Initiative. The Use of Conformal Radiotherapy and the Selection of Radiation Dose in T1 or T2 Prostate Cancer. www.cancercare.on.ca . 2002. 10-2-2004.
    Ref Type: Electronic Citation

12. Cancer Care Ontario Practice Guideline Initiative. Adjuvant radiotherapy following radical prostatectomy for pathologic T3 or margin-positive prostate cancer. https://www.cancercare.on.ca/ . 2010. 25-7-2012.
    Ref Type: Electronic Citation

13. BC Cancer Agency. Cancer Management Guidelines >> Genitourinary >> Prostate. http://www.bccancer.bc.ca/HPI/CancerManagementGuidelines/Genitourinary/Prostate/Management/default.htm . 2009. 25-7-2012.
Ref Type: Electronic Citation

14. Sidhom MA, Kneebone AB, Lehman M, et al. Post-prostatectomy radiation therapy: Consensus guideline of the Australian and New Zealand Radiation Oncology Genito-Urinary Group. *Radiother Oncol* 2008;88:10-9.

15. Hayden AJ, Martin JM, Kneebone AB, et al. Australian and New Zealand Faculty of Radiation Oncology Genito-Urinary Group: 2010 consensus guideline for definitive external beam radiotherapy for prostate cancer. *Journal of Medical Imaging and Radiaition Oncology* 2010;54:513-25.

16. European Association of Urology. Guidelines on Prostate Cancer. http://www.uroweb.org/guidelines/online-guidelines/ . 2012. 25-7-2012.
Ref Type: Electronic Citation

17. American Urological Association. Guideline for the Management of Clinically Localized Prostate Cancer: 2007 Update. http://www.auanet.org/content/guidelines-and-quality-care/clinical-guidelines/main-reports/proscan07/content.pdf . 2007. 3-12-2008.
Ref Type: Electronic Citation

18. American College of Radiology and American Society for Therapeutic Radiology and Oncology. ACR-ASTRO Practice Guideline for Transperineal Permanent Brachytherapy of Prostate Cancer. http://www.americanbrachytherapy.org/guidelines/ . 2010. 9-8-2012.
Ref Type: Electronic Citation

19. American College of Radiology. American College of Radiology Appropriateness Criteria - Permanent Source Brachytherapy for Prostate Cancer. http://www.acr.org/~/media/ACR/Documents/AppCriteria/Oncology/PermanentSourceBrachytherapyForProstateCancer.pdf . 2010. 9-8-2012.
Ref Type: Electronic Citation

20. American College of Radiology. American College of Radiology: Appropriateness Criteria - Locally Advanced (High Risk) Prostate Cancer. http://www.acr.org/~/media/ACR/Documents/AppCriteria/Oncology/LocallyAdvancedHighRiskProstateCancer.pdf . 2011. 9-8-2012.
Ref Type: Electronic Citation

21. American College of Radiology. American College of Radiology Appropriateness Criteria - Treatment Planning for Clinically Localized Prostate Cancer. http://www.acr.org/~/media/ACR/Documents/AppCriteria/Oncology/ExternalBeamRadiationTherapyTreatmentPlanningForClinicallyLocalizedProstateCancer.pdf . 2011. 9-8-2012.
Ref Type: Electronic Citation

22. American College of Radiology. American College of Radiology Appropriateness Criteria - Definitive External Beam Irradiation in Stage T1 and T2 Prostate Cancer. http://www.acr.org/~/media/ACR/Documents/AppCriteria/Oncology/DefinitiveExternalBeamIrradiationInStageT1AndT2ProstateCancer.pdf . 2010. 9-8-2012.
Ref Type: Electronic Citation

23. American College of Radiology. American College of Radiology Appropriateness Criteria - Postradical Prostatectomy Irradiation in Prostate Cancer. http://www.acr.org/~/media/ACR/Documents/AppCriteria/Oncology/PostradicalProstatectomyIrradiationInProstateCancer.pdf . 2010. 9-8-2012.
Ref Type: Electronic Citation

24. Davis BJ, Horwitz EM, Lee WR, et al. American Brachytherapy Society consensus guidelines for transrectal ultrasound-guided permanent prostate brachytherapy. *Brachytherapy* 2012;11:6-19.

25. Hsu IC, Yamada Y, Vigneault E, and Pouliot J. American Brachytherapy Society Prostate High-Dose Rate Task Group. http://www.americanbrachytherapy.org/guidelines/HDRTaskGroup.pdf . 2008. 9-8-2012.
Ref Type: Electronic Citation

26. Royal College of Radiologists COIN (Clinical Oncology Information Network) and British Association of Urological surgeons. Guidelines on the Management of Prostate Cancer. http://www.rcr.ac.uk/prostate.html . 2001. 10-2-2004.
Ref Type: Electronic Citation

27. Villers A, Pommier P, Bataillard A, et al. Summary of the Standards, Options and Recommendations for the management of patients with nonmetastatic prostate cancer (2001). *Br J Cancer* 2003;89:S50-S58.

28. Cancer Care Ontario Practice Guideline Initiative. The Use of Brachytherapy in T1 or T2 Prostate Cancer. www.cancercare.on.ca . 2001. 10-2-2004.
Ref Type: Electronic Citation

29. Skala M, Berry M, Duchesne G, et al. Australian and New Zealand 3D Conformal Radiotherapy Consensus Guidelines for Prostate Cancer. *Australas Radiol* 2004;48:493-501.

30. National Cancer Institute (Cancer Statistics Branch). SEER*Stat 6.6.2 Surveillance, Epidemiology and End Results Cancer Incidence Public-Use Database, 1973-2007. 2010. Bethesda, US Department of Health and Human Services.
Ref Type: Data File

31. Australian Institute of Health and Welfare (AIHW). Australian Cancer Incidence and Mortality (ACIM) books. http://www.aihw.gov.au/acim-books/ . 2008. 8-3-2012.
Ref Type: Electronic Citation

32. D'Amico AV, Whittington R, Malkowicz SB, et al. Biochemical Outcome After Radical Prostatectomy, External Beam Radiation Therapy, or Interstitial Radiation Therapy for Clinically Localized Prostate Cancer. *JAMA* 1998;280:969-74.

33. Cancer Council NSW. New South Wales Prostate Cancer Care and Outcomes Study. 2004.
Ref Type: Personal Communication

34. Partin AW.Kattan MW.Subong EN.Walsh PC.Wojno KJ.Oesterling JE.Scardino PT.Pearson JD. Combination of prostate-specific antigen, clinical stage, and Gleason score to predict pathological stage of localized prostate cancer. A multi-institutional update. *JAMA* 1997;277:1445-51.

35. European Association of Urology. Guidelines on Prostate Cancer. http://www.uroweb.org/fileadmin/user_upload/Guidelines/07_Prostate_Cancer_2007.pdf . 2007. 3-12-2008.
Ref Type: Electronic Citation

36. Chodak GW, Thisted RA, Gerber GS, et al. Results of conservatively managed clinically localized prostate cancer. *New Engl J Med* 1994;330:242-8.

37. Albertsen PC, Fryback DG, Storer BE, Kolon TF, Fine J. Long-term Survival Among Men With Conservatively Treated Localized Prostate Cancer. *JAMA* 1995;274:626-31.

38. Bill-Axelson A, Holmberg L, Ruutu M, Haggman M, Andersson S, Bratell S et al. Radical Prostatectomy versus Watchful Waiting in Early Prostate Cancer. *New Engl J Med* 2005;352:1977-84.

39. Australian Bureau of Statistics. Australian Historical Population Statistics. www.abs.gov.au . 2004. 8-6-2004.
Ref Type: Electronic Citation

40. Australian Institute of Health and Welfare (AIHW). Cancer incidence data: Cancer age-standardised database (2000). http://www.aihw.gov.au/cancer/datacubes/index.cfm . 2004. 25-5-2004.
Ref Type: Electronic Citation

41. Harlan LC, Potosky A, Gilliland FD, Hoffman R, Albertsen PC, et al. Factors associated with initial therapy for clinically localized prostate cancer: prostate cancer outcomes study. *J Natl Cancer Inst* 2001;93:1864-71.

42. Patel HR, Mirsadraee S, Emberton M. The patient's dilemma: prostate cancer treatment choices. *J Urol* 2003;169:828-33.

43. Feldman-Stewart D, Brundage MD, Hayter C, Groome PA, et al. What prostate cancer patients should know: variation in professionals' opinions. *Radiother Oncol* 1998;49:111-23.

44. Spapen SJJC, Damhuis RAM, Kirkels WJ. Trends in the curative treatment of localized prostate cancer after the introduction of prostate-specific antigen: data from the Rotterdam Cancer Registry. *BJU International* 2000;85:474-80.

45. Harlan LC, Brawley O, Pommerenke F, Wali P, Kramer B. Geographic, age and racial variation in the treatment of local/regional carcinoma of the prostate. *J Clin Oncol* 1995;13:93-100.

46. Mettlin CJ, Murphy GP, Cunningham MP, Menck HR. The National Cancer Data Base Report on Race, Age, and Region Variations in Prostate Cancer Treatment. *Cancer* 1997;80:1261-6.

47. Foroudi F, Tyldesley S, Barbera L, Huang J, Mackillop WJ. Evidence-based estimate of appropriate radiotherapy utilization rate for prostate cancer. *Int J Radiat Oncol Biol Phys* 2003;55:51-63.

48. Mazur DJ, Merz JF. How older patients' treatment preferences are influenced by disclosures about therapeutic uncertainty: surgery versus expectant management for localized prostate cancer. *J Am Geriatr Soc* 1996;44:934-7.

49. Feldman-Stewart D, Brundage MD, Van Manen L. A decision aid for men with early stage prostate cancer: theoretical basis and a test by surrogate patients. *Health Expectations* 2001;4:221-34.

50. O'Rourke ME. Narrowing the options: the process of deciding on prostate cancer treatment. *Cancer Investigation* 1999;17:349-59.

51. The North-West Uro-Oncology Group. A preliminary report on a patient preference study to compare treatment options in early prostate cancer. *BJU International* 2002;90:253-6.

52. Diefenbach MA, Dorsey J, Uzzo RG, et al. Decision-Making Strategies for Patients With Localized Prostate Cancer. *Sem in Urol Oncol* 2002;20:55-62.

53. Sommers BD, Beard CJ, D'Amico AV, et al. Predictors of Patient Preferences and Treatment Choices for Localized Prostate Cancer. *Cancer* 2008;113:2058-67.

54. Anandadas CN, Clarke NW, Davidson SE, et al. Early prostate cancer - which treatment do men prefer and why? *BJU International* 2010;107:1762-8.

55. Bolla M, van Poppel H, Tombal B, et al. 10-year results of adjuvant radiotherapy after radical prostatectomy in pT3N0 prostate cancer (EORTC 22911). *Int J Radiat Oncol Biol Phys* 2010;78:S29.

56. Wiegel T, Bottke D, Steiner U, et al. Phase III postoperative adjuvant radiotherapy after radical prostatectomy compared with radical prostatectomy alone in pT3 prostate cancer with post-operative undetectable prostate-specific antigen: ARO 96-02/AUO AP 09/95. *J Clin Oncol* 2009;27:2924-30.

57. Thompson IM, Tangen CM, Paradelo J, et al. Adjuvant radiotherapy for pathological T3N0M0 prostate cancer significantly reduces risk of metastases and improves survival: long-term followup of a randomized clinical trial. *J Urol* 2009;181:956-62.

58. Hong YM, Hu JC, Pacliorek AT, Knight SJ, Carroll PR. Impact of radical prostatectomy positive surgical margins on fear of cancer recurrence: results fromCaPSURE. *Urologic Oncology* 2010;28:268-73.

59. Alkhateeb S, Alibhai S, Fleshner N, et al. Impact of positive surgical margins after radical prostatectomy differs by disease risk group. *J Urol* 2010;183:145-50.

60. Agarwal PK, Sadetsky N, Konety BR, Resnick MI, Carroll PR. Treatment failure after primary and salvage therapy for prostate cancer: likelihood, patterns of care, and outcomes. *Cancer* 2008;112:307-14.

61. Antonarakis ES, Feng Z, Trock BJ, et al. The natural history of metastatic progression with prostate-specific antigen recurrence after radical prostatectomy: long-term follow-up. *BJU International* 2011;109:32-9.

62. Forsythe K, Burri R, Stone N, Stock RG. Predictors of metastatic disease after prostate brachytherapy. *Int J Radiat Oncol Biol Phys* 2012;83:645-52.

63. Taira AV, Merrick GS, Galbreath RW, et al. Distant metastases following permanent interstitial brachytherapy for patients with clinically localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2012;82:e225-e232.

64. Kawakami J, Cowan JE, Elkin EP, et al. Androgen-deprivation therapy as primary treatment for localized prostate cancer: data from Cancer of the Prostate Strategic Urologic Research Endouvor. *Cancer* 2006;106:1708-14.

65. Xylinas E, Dache A, Roupret M. Is radical prostatectomy a viable therapeutic option in clinically locally advanced (cT3) prostate cancer? *BJU International* 2010;106:1596-600.

RECTAL CANCER

In the original radiotherapy utilisation model the indications for radiotherapy for rectal cancer were derived from evidence-based treatment guidelines issued by major national and international organisations. The guidelines reviewed are those published after the previous radiotherapy utilisation study was completed (July 2003) up to August 2011.

Updated Guidelines

All the guidelines including the Australian NHMRC guidelines have been updated since the publication of the original radiotherapy utilisation study. The following updated national level clinical practice guidelines for the management of rectal cancer were identified:

- National Health and Medical Research Council (NHMRC) Guidelines for the Prevention, Early Detection and Management of Colorectal Cancer. 2005 (1)
- National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines on Rectal Cancer (Version 1, 2012) (2)
- National Cancer Institute (NCI PDQ) guideline on rectal cancer (2010) (3)
- National Institute for Clinical Excellence (NICE) guidelines. Improving outcomes in Colorectal cancers. 2004 (4)
- BC Cancer Agency Cancer Management Guidelines Rectum (2005) (5)
- Scottish Intercollegiate Guidelines Network (SIGN). Management of Colorectal Cancer (2003). (6)
- Association of Coloproctology of Great Britain and Ireland. Guidelines for the management of colorectal cancer (2007). (7)
- Cancer Care Ontario guidelines on preoperative or postoperative therapy for stage II or III rectal cancer (2008) (8)
- The RCR radiotherapy dose-fractionation guidelines (2006) (9)
- Dutch national guidelines rectal cancer (2008) (10)
- Cochrane Collaboration Review. Preoperative chemoradiation versus radiation alone for stage II and III resectable rectal cancer (2009) (11)

Indications for radiotherapy

All the indications for external beam radiotherapy in the original CCORE model of optimal radiotherapy utilisation for rectal cancer were reviewed based on the latest guideline recommendations (Figure 1 and Table 1). There are no changes in the indications for radiotherapy in rectal cancer, based on updated guideline recommendations. Some extra terminal branches have been added to the optimal radiotherapy utilisation tree; however these branches were added solely for

the purpose of calculating an optimal utilisation rate for concurrent chemo-radiotherapy and have no effect on the optimal radiotherapy utilisation rate.

Level of evidence

The level of evidence in favour of radiotherapy for Stages II and III rectal cancer has been upgraded from Level II to Level I based on the publication of fresh evidence (12). The levels of evidence supporting the other indications for radiotherapy are unchanged. Out of thirteen outcome branches in the model that have an indication for radiotherapy (Figure 1), 5 branches are supported by level I-II evidence. The updated model predicts that 52% of the whole rectal cancer population have an indication for radiotherapy based on level I-II evidence of benefit.

Changes to Epidemiological Data

The epidemiological data in the rectal cancer utilisation tree have been reviewed to see if more recent data are available through extensive electronic searches using the key words 'rectal cancer', 'radiotherapy', 'epidemiology rectal cancer', 'incidence', 'rectal cancer stage', 'resection rates', 'metastases', 'brain metastases', 'bone metastases', 'skeletal metastases' in various combinations . This has been applied particularly to the early branches in the tree for which national or state level data on cancer incidence rates and stages are available. Any changes to the hierarchical quality of the epidemiological data have been noted (Table 2).

Incidence of Rectal Cancer:

Since the publication of the previous radiotherapy utilisation project, the Australian national cancer incidence data published by the Australian Institute of Health and Welfare (AIHW) has been updated, with the most recent data available being 2008 data. The latest Australian Cancer Incidence and Mortality (ACIM) book published by AIHW in 2011 states that in 2008, bowel cancer accounted for 12.7% of all cancer in Australia (13). The AIHW provided us with a breakdown of bowel cancer incidence by site: cancers arising in the Rectum (ICD-10 code C20) accounted for 4.2% of all cancers in Australia in the year 2008 (14).

Stage proportions for rectal cancer

Recent population-based data on stage for all patients with rectal cancer in the Netherlands Cancer Registry is available for the years 2004-2006 (15). However, the stage proportions for stages I – IV are similar to the Australian national stage data for the year 2000 used in our original model; moreover the Dutch data is not broken up into T1N0M0 and T2N0M0. Therefore no changes have been made to the stage data in the optimal utilisation tree.

There are no other changes to the epidemiological data in the optimal radiotherapy utilisation tree for rectal cancer.

Clinically unresectable rectal cancer

The proportion of patients with clinically unresectable rectal cancer was sourced from the Australian National Colorectal Cancer Care Survey (16). Of the 130 patients who received adjuvant radiotherapy for rectal cancer, 32 (25%) received pre-operative radiotherapy for initially unresectable rectal cancer. We have made the assumption that all patients receiving adjuvant radiotherapy had stage II or III rectal cancer. It is possible that the proportion of patients with unresectable cancer may be slightly over-estimated if in fact some patients with stage IV rectal cancer had also received adjuvant radiotherapy

Estimation of the Optimal Radiotherapy Utilisation Rate

Based on the evidence of the efficacy of radiotherapy and the most recent epidemiological data on the occurrence of indications for radiotherapy, radiotherapy is recommended in 60% of all rectal cancer patients in Australia (Table 1 and Figure 1). The previous optimal radiotherapy rate for rectal cancer derived in 2003 was 65%. The decrease in the revised optimal utilisation rate is due to the correction of mistakes in the original utilisation tree (some of which were published as an errata in Cancer) (17) and not due to any changes either in radiotherapy indications or in epidemiological data.

Concurrent Chemoradiotherapy in Rectal Cancer

The indications for radiotherapy for rectal cancer were reviewed to identify the indications where radiotherapy is recommended in conjunction with concurrent chemotherapy as the first treatment.
There are three radiotherapy options for the management of stages II and III rectal cancer: (i) short-course pre-operative radiotherapy (no concurrent chemotherapy), (ii) pre-operative radiotherapy combined with concurrent chemotherapy or (iii) post-operative radiotherapy with concurrent chemotherapy. The US and Canadian guidelines recommend pre-operative radiotherapy with concurrent chemotherapy (2;3;8) whereas the British and Dutch guidelines recommend pre-operative short-course radiotherapy for resectable disease (4;9;10). The Australian NHMRC guidelines mention the various treatment options but do not recommend any single option.

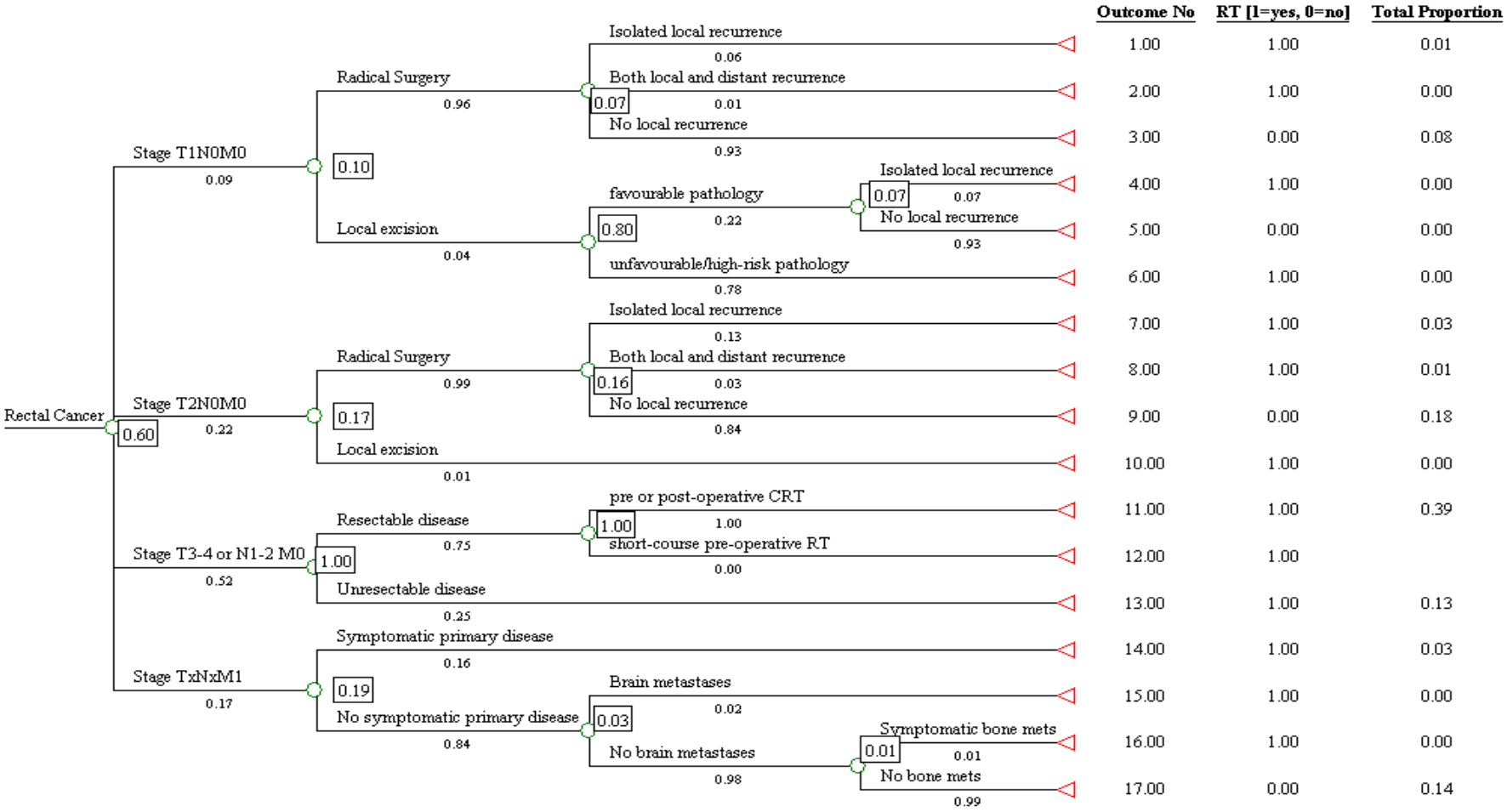
In the model of optimal utilisation for concurrent chemoradiotherapy, all patients with unresectable stages II or III rectal cancer are recommended to receive concurrent chemoradiotherapy. In patients with resectable disease, as the base case scenario all patients are again recommended to receive concurrent chemoradiotherapy. Based on this model, 55% of all rectal cancer patients should receive concurrent radiotherapy with chemotherapy (Figure 2 and Table 3). The effect on the optimal utilisation rate of recommending short-course pre-operative radiotherapy (with no concurrent chemotherapy) for resectable disease was tested in the sensitivity analysis.

Sensitivity analysis

Sensitivity analysis was not required for the optimal radiotherapy utilisation tree as there was no uncertainty either in the indications for radiotherapy in rectal cancer or in the incidence data (the uncertainty involves the optimal schedule of radiotherapy to be recommended but not whether or not radiotherapy is indicated).

In the concurrent chemoradiotherapy tree, in the absence of universal guideline agreement regarding whether or not concurrent chemoradiotherapy is indicated for stages II and III rectal cancer, a univariate sensitivity analysis was undertaken. The proportion of patients with resectable disease receiving concurrent chemoradiotherapy was varied from 0% to 100% of all patients with resectable disease in the sensitivity analysis, to take into account the effect on the utilisation rate of patients who receive short-course pre-operative radiotherapy with no concurrent chemotherapy. The results of the sensitivity analysis are depicted in the tornado diagram in Figure 3 and show that the proportion of rectal cancer patients in whom concurrent chemoradiotherapy is indicated can vary from 16 to 55% (Figure 3).

Figure 1. Revised Optimal Radiotherapy Utilisation Tree for Rectal Cancer



Outcome No	RT [1=yes, 0=no]	Total Proportion
1.00	1.00	0.01
2.00	1.00	0.00
3.00	0.00	0.08
4.00	1.00	0.00
5.00	0.00	0.00
6.00	1.00	0.00
7.00	1.00	0.03
8.00	1.00	0.01
9.00	0.00	0.18
10.00	1.00	0.00
11.00	1.00	0.39
12.00	1.00	
13.00	1.00	0.13
14.00	1.00	0.03
15.00	1.00	0.00
16.00	1.00	0.00
17.00	0.00	0.14

Table 1: Rectal Cancer. Indications for radiotherapy - Levels and sources of evidence

Original RTU study				Updates 2011					
Outcome Nos. in Updated Tree	Clinical Scenario	Level of evidence	Proportion of all rectal cancer	Change of Indication	Guideline updated	Current level of evidence	Change to proportion of all rectal cancer		References
							Yes/ No	Updated value	
1 and 2	Stage T1N0M0, radical surgery, local recurrence	III	<0.01	No	Yes	III	No.	0.01	NCCN (2), NHMRC (1), NCI PDQ (3), SIGN (6)
4	Stage T1N0M0, local excision, favourable pathology, local recurrence	III	<0.01	No	Yes	III	No.	<0.01	NCCN (2), NHMRC (1), NCI PDQ (3), SIGN (6)
6	Stage T1N0M0, local excision, unfavourable pathology	III	0.01	No	Yes	III	Yes.	<0.01	Russell et al (18)
7 and 8	Stage T2N0M0, radical surgery, local recurrence	III	0.02	No	Yes	III	Yes	0.04	NCCN (2), NHMRC (1), NCI PDQ (3), SIGN (6)
10	Stage T2N0M0, local excision	III	0.06	No	N/A	N/A	Yes.	<0.01	This indication is not specifically mentioned in the guidelines

Original RTU study				Updates 2011					
Outcome Nos. in Updated Tree	Clinical Scenario	Level of evidence	Proportion of all rectal cancer	Change of Indication	Guideline updated	Current level of evidence	Change to proportion of all rectal cancer		References
							Yes/ No	Updated value	
11, 12 and 13	Stage T3-4N0M0 and Stage TxN1-2M0	II	0.52	No	Yes	I	No.	0.52	NCCN (2), NHMRC (1), NCI PDQ (3), CCOPEBC (8), NICE (4)
14	Stage TxNxM1, symptomatic primary disease	III	0.03	No	Yes	III	No	0.03	SIGN (6)
15	Stage TxNxM1, brain metastases	II	<0.01	No	N/A	II	No	<0.01	The management is not discussed in any of the guidelines
16	Stage TxNxM1, no brain metastases, symptomatic bone metastases	I	0.01	No	N/A	I	No	<0.01	NICE (4)
Proportion of all rectal cancer patients in whom Radiotherapy is recommended			0.65 (65%)	**Updated Proportion of all rectal cancer patients in whom Radiotherapy is recommended**				**0.60 (60%)**	

Abbreviations: RTU – Radiotherapy Utilisation, NICE - National Institute for Clinical Excellence, NHMRC – National Health and Medical Research Council, NCCN – National Comprehensive Cancer Network, SIGN – Scottish Intercollegiate Guidelines Network, CCOPEBC – Cancer Care Ontario Program in Evidence-based Care

Notes: Values for proportion of patients with T1N0M0 and T2N0M0 who underwent either radical surgery or local excision were correctly entered in the original tables but wrongly entered in the original tree. Hence the changes in proportions are due to the mistakes being picked up and not due to any change in indications or epidemiological data.

Table 2: Rectal Cancer. The incidence of attributes used to define indications for radiotherapy

Original RTU study				Updates 2011				
Population or sub-population of interest	**Attribute**	**Proportion of population with the attribute**	**Quality of Information**	**Change in proportion of population with attribute Yes/ No**	**Updated Proportion**	**Updated Quality of Information**	**Updated Reference**	**Comments**
All registry cancers	Rectal cancer	0.05	α	Yes	0.03	α	AIHW 2011 (14)	Based on AIHW 2007 data (personal communication from AIHW)
All rectal cancer	Stage T1N0M0	0.09	α	No	N/A	N/A	N/A	
All rectal cancer	Stage T2N0M0	0.22	α	No	N/A	N/A	N/A	
All rectal cancer	Stage T3-4N0M0	0.26	α	No	N/A	N/A	N/A	
All rectal cancer	Stage TxN1-2M0	0.26	α	No	N/A	N/A	N/A	
All rectal cancer	Stage TxNxM1	0.17	α	No	N/A	N/A	N/A	

Original RTU study				Updates 2011				
Population or sub-population of interest	**Attribute**	**Proportion of population with the attribute**	**Quality of Information**	**Change in proportion of population with attribute Yes/ No**	**Updated Proportion**	**Updated Quality of Information**	**Updated Reference**	**Comments**
Stage T1N0M0	Radical surgery	0.96	α	No	N/A	N/A	N/A	Corrected mistaken value (0.67) in original tree
Stage T1N0M0, radical surgery	Isolated local recurrence	N/A	N/A	Yes	0.06	ζ	Bethune (19)	New branch added in order to estimate concurrent CRT
Stage T1N0M0, radical surgery	Both local and distant recurrence	N/A	N/A	Yes	0.01	ζ	Bethune (19)	New branch added in order to estimate concurrent CRT
Stage T1N0M0, local excision	favourable pathology	0.22	ε	No	N/A	N/A	N/A	Corrected mistaken value (0.52) in original tree
Stage T1N0M0, local excision, favourable pathology	Local relapse	0.01	ε	Yes	0.07	ε	Russell et al (18)	Corrected mistaken value (0.01) in original table
Stage T2N0M0	Radical surgery	0.99	α	No	N/A	N/A	N/A	Corrected value (0.72) in original tree

Original RTU study				Updates 2011				
Population or sub-population of interest	**Attribute**	**Proportion of population with the attribute**	**Quality of Information**	**Change in proportion of population with attribute Yes/ No**	**Updated Proportion**	**Updated Quality of Information**	**Updated Reference**	**Comments**
Stage T2N0M0 Radical surgery	Isolated local recurrence	N/A	N/A	Yes	0.13	ζ	Bethune (19)	New branch added in order to estimate concurrent CRT
Stage T2N0M0 Radical surgery	Both local and distant recurrence	N/A	N/A	Yes	0.03	ζ	Bethune (19)	New branch added in order to estimate concurrent CRT
Stage T3-4 or N1-2, M0	Resectable	N/A	N/A	Yes	0.75	α	National CRC survey (16)	New branch added in order to estimate concurrent CRT
Stage TxNxM1	Symptomatic local disease	0.16	δ	No	N/A	N/A	N/A	
Stage TxNxM1	Symptomatic brain metastases	0.02	ζ	No	N/A	N/A	N/A	
Stage TxNxM1, no symptomatic brain metastases	Symptomatic bone metastases	0.01	ζ	No	N/A	N/A	N/A	

Figure 2. Rectal Cancer. Optimal Utilisation Tree for Concurrent Chemo-Radiation

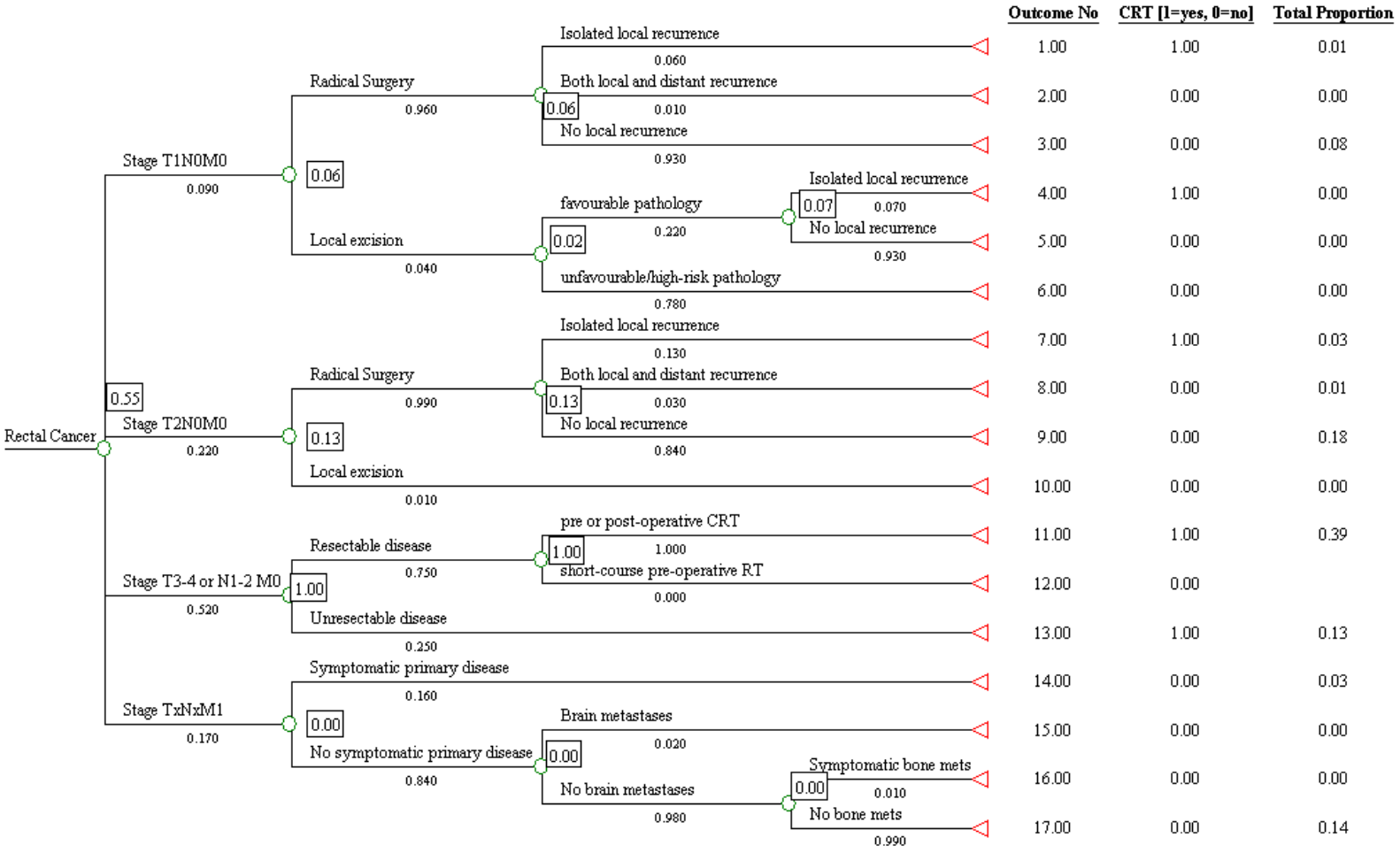
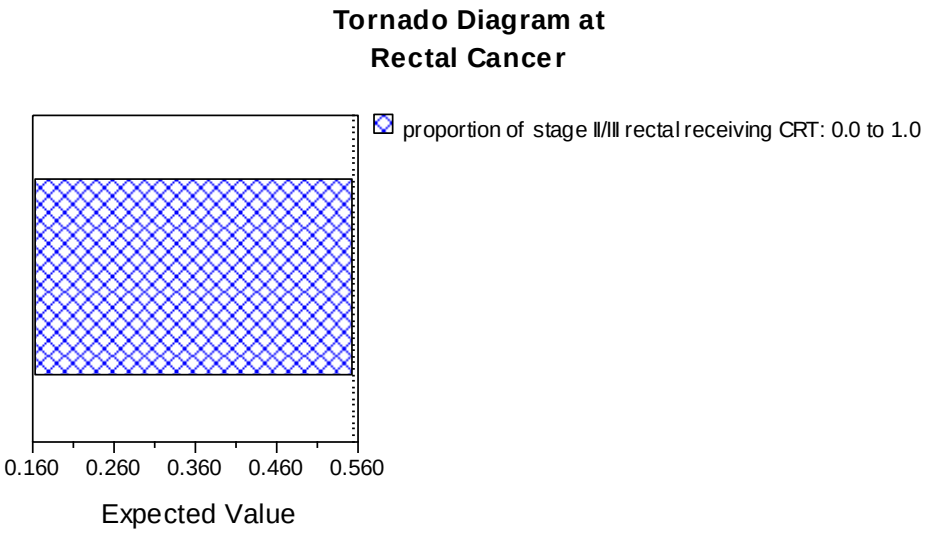


Table 3: Rectal Cancer. Indications for concurrent chemoradiotherapy - levels and sources of evidence

Outcome no. in tree	Clinical scenario	Level of evidence	References	Proportion of all Rectal cancer patients
1	T1N0M0, radical surgery, isolated local recurrence	IV	NCCN (2), NCI PDQ (3),	0.01
4	T1N0M0, local excision, favourable pathology, isolated local recurrence	IV	NCCN (2), NCI PDQ (3),	<0.01
7	T2N0M0, radical surgery, isolated local recurrence	IV	NCCN (2), NCI PDQ (3),	0.03
11	T3-4 or N1-2, M0, resectable disease, pre or post-operative CRT	I	NCCN (2), NCI PDQ (3), CCOPEBC (8),	0.39
13	T3-4 or N1-2, M0, unresectable disease	I	NCCN (2), NCI PDQ (3), CCOPEBC (8), RCR guidelines (9), Dutch guidelines (10)	0.13
The total proportion of all patients with Rectal cancer in whom concurrent chemoradiotherapy is recommended				**0.55 (55%)**

Figure 3. Rectal Cancer. Tornado Diagram for Univariate Sensitivity Analysis



References

1. Australian Cancer Network Colorectal Cancer Guidelines Revision Committee. Clinical Practice Guidelines for the prevention, early detection and management of colorectal cancer. http://www.nhmrc.health.gov.au . 2005. Sydney, The Cancer Council Australia and Australian Cancer Network.
   Ref Type: Report

2. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology - Rectal Cancer. V.1.2012. http://www.nccn.org/professionals/physician_gls/PDF/rectal.pdf . 2008. 21-9-2011.
   Ref Type: Electronic Citation

3. National Cancer Institute. PDQ Cancer Information Summaries: Treatment of Rectal Cancer. http://www.cancer.gov/cancertopics/pdq/treatment/rectal/healthprofessional/ . 25-3-2010. 21-9-2011.
   Ref Type: Electronic Citation

4. National Institute for Clinical Excellence (NICE). Improving Outcomes in Colorectal Cancers. www.nice.org.uk . 2004.
   Ref Type: Electronic Citation

5. BC Cancer Agency. Cancer Management Guidelines: Cancer of the Rectum. www.bccancer.bc.ca . 2005. 15-10-2008.
   Ref Type: Electronic Citation

6. Scottish Intercollegiate Guidelines Network. Management of colorectal cancer. A national clinical guideline. www.sign.ac.uk . 2003. 6-11-2006.
   Ref Type: Electronic Citation

7. Association of Coloproctology of Great Britain and Ireland. Guidelines for the management of colorectal cancer. http://www.acpgbi.org.uk/assets/documents/COLO_guides.pdf . 2007. 20-9-2011.
   Ref Type: Electronic Citation

8. Cancer Care Ontario Program in Evidence-Based Care. Preoperative or postoperative therapy for the management of patients with Stage II or III Rectal Cancer. https://www.cancercare.on.ca/common/pages/UserFile.aspx?fileId=14008 . 15-7-2008. 21-9-2011.
   Ref Type: Electronic Citation

9. Royal College of Radiologists. Radiotherapy Dose-Fractionation. http://www.rcr.ac.uk/docs/oncology/pdf/Dose-Fractionation_Final.pdf . 2006. 10-10-2011.
   Ref Type: Electronic Citation

10. National Working Group on Gastrointestinal Cancers. Dutch National Guideline rectal cancer. http://www.oncoline.nl/index.php?pagina=/richtlijn/item/pagina.php&richtlijn_id=615 . 2008. 19-10-2011.
    Ref Type: Electronic Citation

11. Ceelen WP, Van Nieuwenhove Y, and Fierens K. Preoperative chemoradiation versus radiation alone for stage II and III resectable rectal cancer. The Cochrane Collaboration. Cochrane Database Syst Rev CD006041. 2009. John Wiley & Sons Ltd.
    Ref Type: Report

12. Latkauskas T, Paskauskas S, Dambrauskas Z, et al. Preoperative chemoradiation vs radiation alone for stage II and III resectable rectal cancer: a meta-analysis. *Colorectal Disease* 2010;12:1075-83.

13. Australian Institute of Health and Welfare (AIHW). Australian Cancer Incidence and Mortality (ACIM) Books. http://www.aihw.gov.au/acim-books/ . 2010. 10-8-2011.
    Ref Type: Electronic Citation

14. Australian Institute of Health and Welfare (AIHW). Australian Cancer Database. 2012.
Ref Type: Personal Communication

15. Elferink MAG, van Steenbergen LN, Krijnen P, et al. Marked improvements in survival of patients with rectal cancer in the Netherlands following changes in therapy, 1989 - 2006. *Eur J Cancer* 2010;46:1421-9.

16. Clinical Governance Unit. The National Colorectal Cancer Care Survey. Australian clinical practice in 2000. 1-124. 2002. Melbourne, National Cancer Control Initiative.
Ref Type: Report

17. Delaney G, Barton MB, Jacob S. Erratum: Delaney G, Barton M, Jacob S. Estimation of an optimal radiotherapy utilization rate for gastrointestinal carcinoma: a review of the evidence. *Cancer*. 2004; 101(4):657-60. *Cancer* 2006;107:660.

18. Russell AH, Harris J, Rosenberg PJ, Sause WT, Fisher BJ, et al. Anal sphincter conservation for patients with adenocarcinoma of the distal rectum: long-term results of radiation therapy oncology group protocol 89-02. *Int J Radiat Oncol Biol Phys* 2000;46:313-22.

19. Bethune WA. Carcinoma of the rectum: 508 patients with failure analysis and implication for adjuvant therapy. *Canadian Association of Radiologists Journal* 1987;38:209-14.

STOMACH CANCER

Evidence-based guidelines issued by major national and international organisations for the treatment of gastric cancer were reviewed. The guidelines reviewed were those published from July 2003 (when the previous radiotherapy utilisation study was completed) to April 2012.

Updated Guidelines

The following updated national level clinical practice guidelines for the management of gastric cancer were identified:

- National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines on Gastric Cancer (Version 2, 2011) (1)
- National Cancer Institute (NCI PDQ) guideline on gastric cancer (2012) (2)

The following new guidelines for the management of gastric cancer were identified:

- Cancer Care Ontario guideline on Neoadjuvant or adjuvant therapy for resectable gastric cancer (2011) (3)
- Guidelines of the Upper GI surgeons of Great Britain and Ireland, the British Society of Gastroenterology and the British Association of Surgical Oncology (2011) (4)
- Scottish Intercollegiate Guidelines Network (SIGN). Management of Oesophageal and Gastric Cancer (2006) (5)
- ESMO clinical practice guidelines (2010) (6)
- Japanese gastric cancer treatment guidelines (2011) (7)
- BC Cancer Agency Cancer Management Guidelines Stomach (2005) (8)
- Chinese Ministry of Health guidelines for diagnosis and treatment of gastric cancer (2011) (9)
- Indian ICMR guidelines for management of stomach cancer (2010) (10)

Indications for radiotherapy

All the indications for external beam radiotherapy in the original CCORE model of optimal radiotherapy utilisation for stomach cancer were reviewed based on the latest guideline recommendations (Figure 1 and Table 1). One additional indication for radiotherapy has been added to the model of optimal utilisation based on updated guideline recommendations (1;2;6), i.e. in the revised model radiotherapy is recommended to palliate bleeding, obstruction or pain caused by a symptomatic primary tumour in patients who present with metastatic disease.

There is controversy between guidelines regarding whether or not post-operative adjuvant radiotherapy with concurrent chemotherapy is recommended for resectable gastric cancer. The American NCCN and NCI guidelines, Chinese and Indian guidelines recommend post-operative

adjuvant chemo-radiotherapy for resectable node-positive and muscle-invasive (stage IB and above) gastric cancer (1;2;9;9;10). The Japanese and European guidelines recommend chemotherapy but not chemo-radiotherapy in this situation (6;7). The Cancer Care Ontario guidelines recommend either postoperative chemo-radiotherapy or perioperative chemotherapy (3). The SIGN guidelines do not recommend neoadjuvant or adjuvant chemotherapy or radiotherapy outside of a clinical trial (5). A British surgical guideline states that adjuvant chemo-radiotherapy "should be considered in patients at high risk of recurrence who have not received neoadjuvant therapy" (4).

In an attempt to resolve the above uncertainty regarding optimal treatment, the Trans-Tasman Radiation Oncology Group (TROG) is currently recruiting patients for a randomised phase II/III trial of preoperative chemoradiotherapy versus preoperative chemotherapy for resectable gastric cancer (TOPGEAR) (11). In the absence of any current evidence that either treatment approach is superior, in this review we have assigned equal importance to both the treatment options. In the revised model, post-operative adjuvant chemo-radiotherapy is indicated for half of all patients with resectable stage IB and above, and pre-operative chemotherapy (without radiotherapy) is recommended for the remaining half of the patients. This constitutes a change from the original model in which radiotherapy (in conjunction with chemotherapy) was recommended for all patients with resectable Stage IB and above disease.

Level of evidence

The recommendations for palliative radiotherapy in the treatment of bone or brain metastases and for post-operative adjuvant chemo-radiotherapy for resectable gastric cancer are based on Level I –II evidence, accounting for 21% of all patients with gastric cancer. An additional 6% of the whole gastric cancer population have an indication for radiotherapy based on level III evidence (palliative radiotherapy for a symptomatic primary).

Changes to Epidemiological Data

The epidemiological data in the stomach cancer radiotherapy utilisation tree have been reviewed to see if more recent data are available through extensive electronic searches using the key words 'stomach cancer', 'radiotherapy', 'palliative radiotherapy', 'epidemiology stomach cancer', 'incidence', 'stomach cancer stage', 'resection rates', 'bleeding', 'metastases', 'brain metastases', 'bone metastases', 'skeletal metastases' in various combinations . This has been applied particularly to the early branches in the tree for which national or state level data on cancer incidence rates and stages are available. Any changes to the hierarchical quality of the epidemiological data have been noted (Table 2).

Incidence of Gastric Cancer:

Since the publication of the previous radiotherapy utilisation project, the Australian national cancer incidence data published by the Australian Institute of Health and Welfare (AIHW) has been updated, with the most recent data available being 2008 data. The latest Australian Cancer Incidence and Mortality (ACIM) book published by AIHW in 2011 states that in 2008, stomach cancer accounted for 1.8% of all cancer in Australia (12). This rate is much lower than the incidence in East Asian countries such as China and Japan where gastric cancer is a leading cause of cancer deaths (13).

Stage proportions for stomach cancer

The reported stage proportions of gastric cancer vary internationally due to the impact of screening in some Asian countries, different staging systems used (AJCC or Japanese classifications) and changes to staging categories. The most widely used staging system used is the TNM classification of the American Joint Committee on Cancer (AJCC) (14). In the latest 7th edition of the AJCC staging of gastric cancer (published in 2010), only M1 (distant metastatic) disease is included under Stage IV. In the AJCC 6th edition staging manual, Stage IV gastric cancer includes involvement of intra-abdominal lymph nodes as well as distant metastases. Thus the reported stage proportions of Stage IV gastric cancer can vary significantly depending on the staging criteria and edition of AJCC staging used.

In the original 2003 optimal utilisation model for gastric cancer, the proportion of gastric cancer patients presenting with metastatic disease varied from 17-29%; sensitivity analysis was conducted due to the above variation in epidemiological data between published sources (15;16).

Stage data extracted from the SEER database for the years 2004-2008 using the AJCC 6th edition stage grouping showed that out of a total of 22,274 patients diagnosed with known stage gastric cancer in the SEER registries in the above period, 10,348 (46.5%) were diagnosed with Stage IV disease (17). A population-based study of gastric cancer in the Netherlands between 1990 and 2007 reported that 48.5% of patients presented with Stage IV cancer; the staging system used was not specified (18).

The SEER database for the years 2004-2007 was re-analysed to determine the proportion of all gastric cancer patients that presented with distant metastases (17). This showed that out of 13,929 patients with gastric adenocarcinoma with adequate information available, 5588 patients (40.1%) presented with distant metastases. This data has been used in the tree in preference to reported Stage proportions based on AJCC 6th edition staging, since this is the only data that specifically demarcates the proportion of patients presenting with distant metastases.

Fitness for Surgery

The SEER registry also contains information on “reason no cancer-directed surgery” and this shows that 18.6% of patients diagnosed with non-metastatic gastric cancer were not recommended to have cancer surgery.

The SEER stage and fitness for surgery data were used in the optimal utilisation tree since these data are more recent than the data used in the original model and are population-based.

Bone or Brain Metastases for Stage IA

Metastases to bone or brain are rare in gastric cancer, and even more so in early gastric cancer. In the original 2003 model of optimal radiotherapy utilisation for gastric cancer, the proportion of patients with stage T1N0M0 who developed distant relapse following surgery could not be identified since there was no published data. There are recent published reports on the outcomes of laparoscopic gastrectomy for early gastric cancer. Lee et al reported on 601 patients who underwent laparoscopic gastrectomy (LG) in Osaka, Japan (in their center, LG is indicated for all patients up to preoperative stage T2N1) (19). There were 478 patients who presented in stage IA; of these only 2 developed recurrences - one locoregional and the other a distant recurrence to bone. Fujiwara et al reported that 3 out of 83 patients with stage IA treated with LG developed recurrences, 1 locoregional and 2 distant (none to bone or brain) (20). Thus the rates of bone and brain metastases in stage IA are unchanged from the original model where they were assumed to be zero (data from the larger series of Lee et al is used in the optimal radiotherapy utilisation tree).

Incidence of metastases to bone or brain in metastatic gastric cancer

As noted in the original study, since metastases to bone or brain are rare, it is difficult to identify data for these branches in the utilisation tree. A comparison of two chemotherapy regimens in the treatment of metastatic gastric cancer reported that in their series of 70 patients with metastatic gastric cancer, 2 patients had bone metastases and no patients had brain metastases (21). This data has been used in the utilisation tree since no other data could be identified.

Incidence of symptomatic primary requiring palliative radiotherapy

An extensive review of the literature revealed several recent retrospective case series on the palliative treatment of advanced gastric cancer with radiotherapy (22-25). All of the published papers described the patients in their case series and details of radiotherapy treatment given but none mentioned the incidence of patients receiving palliative radiotherapy as a proportion of all gastric cancer or as a proportion of all patients with metastatic disease. Extensive searches were conducted to determine the incidence of symptoms such as bleeding and obstruction in advanced gastric cancer, but no data were identified for these parameters either. Data from the SEER database for the years 2004-2007 showed that 15.6% of patients presenting with metastatic gastric cancer received radiotherapy. The site of radiotherapy treatment is not known, but since metastases to brain and bone are rare in gastric cancer, it has been assumed that most of these patients would have received palliative radiotherapy for their primary cancer. We acknowledge that using actual utilisation data in the model is a limitation; however the actual utilisation data has been used in the revised model of optimal utilisation only because no other data could be identified.

Estimation of the Optimal Radiotherapy Utilisation Rate

Based on the best available evidence and the most recent epidemiological data, radiotherapy is recommended in 27% of all gastric cancer patients in Australia (Table 1 and Figure 1) in the revised optimal radiotherapy utilisation model. Since this utilisation rate is based on a controversial indication for radiotherapy, sensitivity analysis has been conducted (see below).

The previous optimal radiotherapy rate for gastric cancer derived in 2003 was 68% (varying in sensitivity analysis between 58 and 68% due to variation in epidemiological data on stage proportions).

Concurrent Chemoradiotherapy in Gastric Cancer

The indications for radiotherapy for gastric cancer were reviewed to identify indications where radiotherapy is recommended in conjunction with concurrent chemotherapy as the first treatment. Concurrent chemotherapy is recommended along with post-operative adjuvant radiotherapy for resectable gastric cancer above Stage IA by some guidelines, but this recommendation is controversial (as discussed under the heading 'Indications for radiotherapy'). In the model of optimal utilisation for concurrent chemoradiotherapy, 20% of all gastric cancer patients should receive concurrent radiotherapy with chemotherapy (Figure 2 and Table 3). Since this utilisation rate is based on a controversial indication for concurrent chemo-radiotherapy, sensitivity analysis has been conducted (see below).

Sensitivity analysis

Sensitivity analysis was conducted due to the guideline uncertainty regarding whether post-operative adjuvant radiotherapy with concurrent chemotherapy is recommended for resectable Stage IB and above gastric cancer. In the sensitivity analysis, the proportion of eligible patients receiving post-operative adjuvant radiotherapy with concurrent chemotherapy was varied from zero (no eligible patients receive this treatment) to one (all eligible patients receive concurrent chemo-RT). In the sensitivity analysis, the optimal radiotherapy utilisation rate varied from 7.4% to 47.1% (Figure 3) and the optimal concurrent chemoradiotherapy rate varied from 0-40% (Figure 4) depending on whether this indication was included in the model.

Figure 1. Revised Optimal Radiotherapy Utilisation Tree for Gastric Cancer

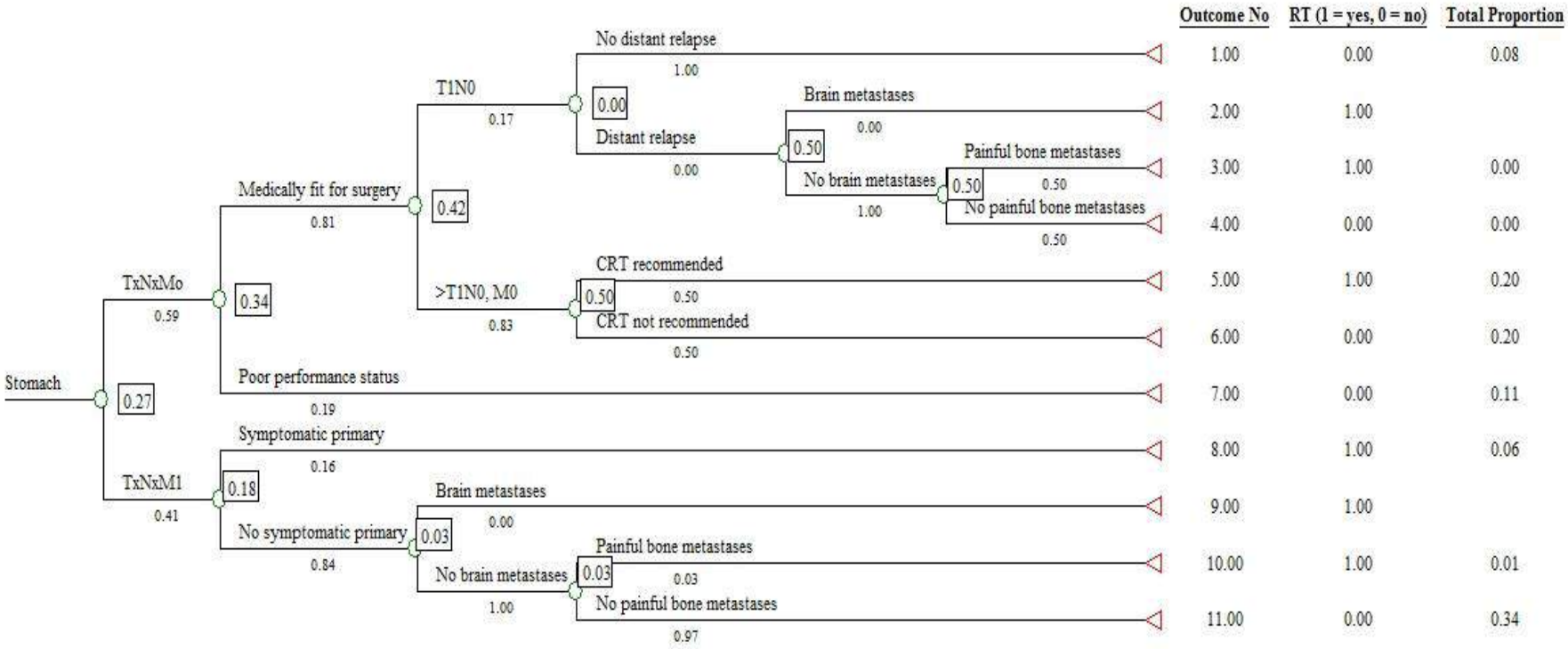


Table 1: Gastric Cancer. Indications for radiotherapy - Levels and sources of evidence

Original RTU study				Updates 2011					
Outcome Nos. in Updated Tree	Clinical Scenario	Level of evidence	Proportion of all gastric cancer	Change of Indication	Guideline updated	Current level of evidence	Change to proportion of all gastric cancer		References
							Yes/ No	Updated value	
2	Stage TxNxM0 TxNxM0, medically fit for surgery, T1N0, distant relapse, brain metastases	II	<0.01	No	Yes	II	No	<0.01	The treatment of brain or bone metastases are not specifically mentioned in any of the guidelines since they are rare in gastric cancer.
3	Stage TxNxM0 TxNxM0, Medically fit for surgery, T1N0, distant relapse, no brain metastases, painful bone metastases	I	<0.01	No	Yes	I	No	<0.01	
5	TxNxM0, medically fit for surgery, Stage IB and above	II	0.68	No	Yes	II	Yes	0.20	NCCN (1),NCI PDQ (2), Chinese (9), ICMR (10)
8	TxNxM1,symptomatic primary requiring RT	N/A	N/A	Yes	Yes	III	Yes	0.06	NCCN (1),NCI PDQ (2), ESMO (6)
9	TxNxM1, no symptomatic primary, brain metastases	II	<0.01	No	Yes	II	No	<0.01	The treatment of brain or bone metastases are not specifically

Original RTU study				Updates 2011					
Outcome Nos. in Updated Tree	Clinical Scenario	Level of evidence	Proportion of all gastric cancer	Change of Indication	Guideline updated	Current level of evidence	Change to proportion of all gastric cancer		References
							Yes/ No	Updated value	
10	TxNxM1, no symptomatic primary, no brain metastases, painful bone metastases	I	<0.01	No	Yes	I	No	0.01	mentioned in any of the guidelines since they are rare in gastric cancer.
Proportion of all gastric cancer patients in whom Radiotherapy is recommended				0.68 (68%)	**Updated Proportion of all gastric cancer patients in whom Radiotherapy is recommended**			**0.27 (27%)**	

Table 2: Gastric Cancer. The incidence of attributes used to define indications for radiotherapy

Original RTU study				Updates 2011				
Population or sub-population of interest	**Attribute**	**Proportion of population with the attribute**	**Quality of Information**	**Change in proportion of population with attribute Yes/ No**	**Updated Proportion**	**Updated Quality of Information**	**Updated Reference**	**Comments**
All registry cancers	Gastric cancer	0.02	α	No	0.018	α	AIHW 2011 (12)	Based on AIHW 2008 data
Gastric cancer	Stage TxNxM0	0.71 - 0.83	γ	Yes	0.59	γ	SEER (17)	Based on SEER 2004-2007 data
Stage TxNxM0	Medically fit for surgery	0.87	γ	Yes	0.81	γ	SEER (17)	Based on SEER 2004-2008 data
Stage TxNxM0, Medically fit for surgery	T1N0M0 (Stage IA)	0.06 – 0.20	γ	Yes	0.17	γ	SEER (17)	Based on SEER 2004-2008 data
Stage TxNxM0, Medically fit for surgery, T1N0M0	Distant relapse	0.05	ζ	Yes	0.004	ζ	Lee et al (19)	
Stage TxNxM0, Medically fit for surgery, T1N0M0, distant relapse	Brain metastases	0	No data identified	No	0	ζ	Lee et al (19)	I

Original RTU study				Updates 2011				
Population or sub-population of interest	**Attribute**	**Proportion of population with the attribute**	**Quality of Information**	**Change in proportion of population with attribute Yes/ No**	**Updated Proportion**	**Updated Quality of Information**	**Updated Reference**	**Comments**
Stage TxNxM0, Medically fit for surgery, T1N0M0, distant relapse, no brain metastases	Painful bone metastases	0	No data identified	Yes	0.5	ζ	Lee et al (19)	
Stage TxNxM1	Symptomatic primary	N/A (new branch)	N/A (new branch)	Yes	0.156	γ	SEER (17)	Based on SEER 2004-2008 data
Stage TxNxM1	Brain metastases	0	No data identified	No	0	λ	Kos et al (21)	
Stage TxNxM1, no brain metastases	Bone metastases	0	No data identified	Yes	0.03	λ	Kos et al (21)	

Figure 2. Gastric Cancer. Optimal Utilisation Tree for Concurrent Chemo-Radiation

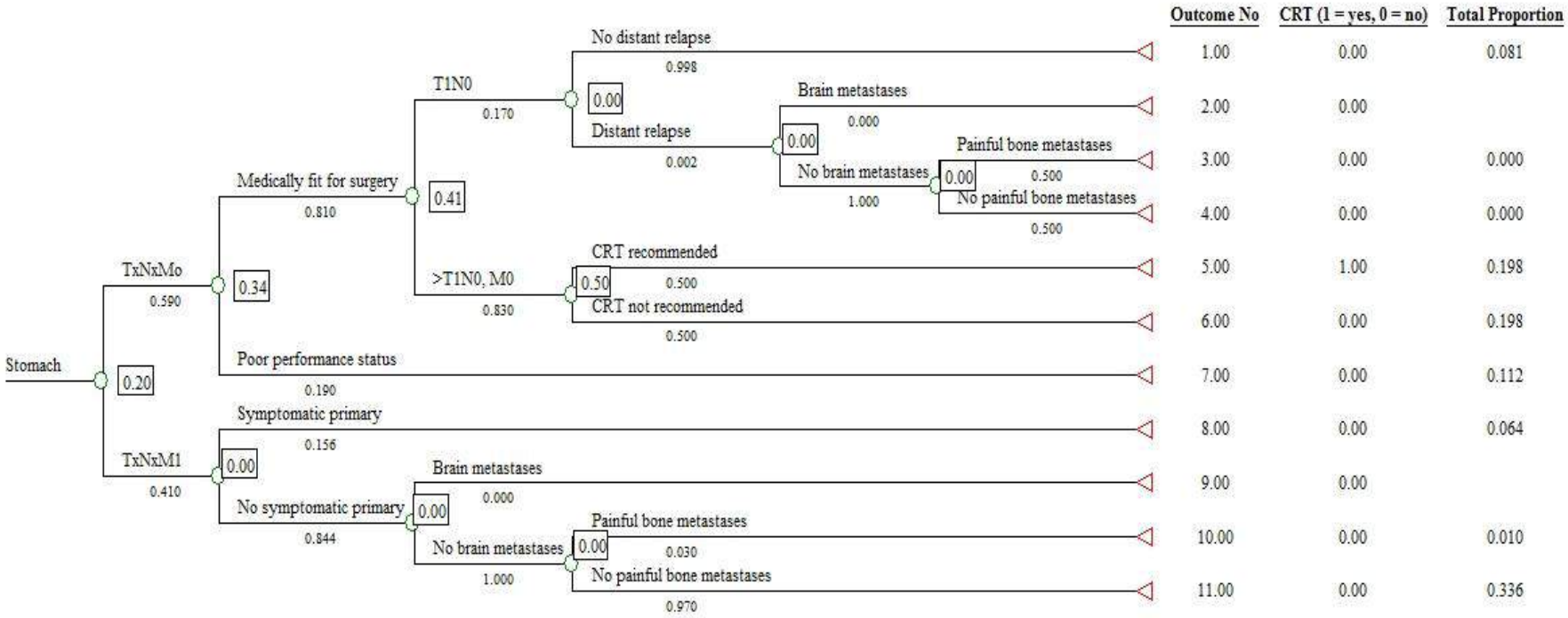


Table 3: Gastric Cancer. Indications for concurrent chemoradiotherapy - levels and sources of evidence

Outcome no. in tree	Clinical scenario	Level of evidence	References	Proportion of all Gastric cancer patients
5	TxNxM0, medically fit for surgery, all Stage IB and above	II	NCCN (1),NCI PDQ (2), Chinese (9), ICMR (10)	0.20
The total proportion of all patients with Gastric cancer in whom concurrent chemoradiotherapy is recommended				**0.20 (20%)**

Abbreviations: RTU – Radiotherapy Utilisation Rate, NCCN – National Comprehensive Cancer Network, NCI PDQ – National Cancer Institute Physicians Data Query, ICMR – Indian Council of Medical Research

Figure 3. Gastric Cancer. Radiotherapy Utilisation -Tornado Diagram for Univariate Sensitivity Analysis

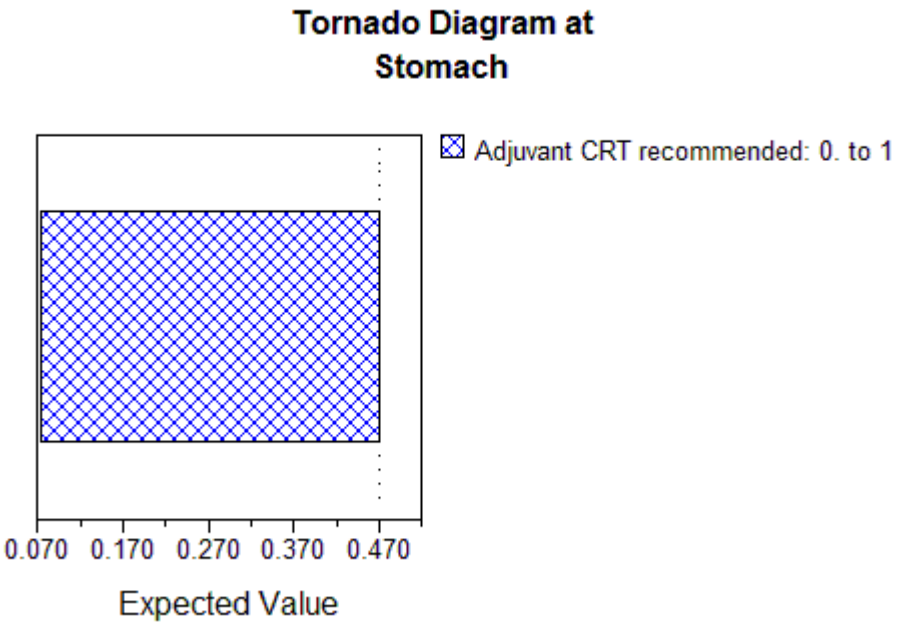
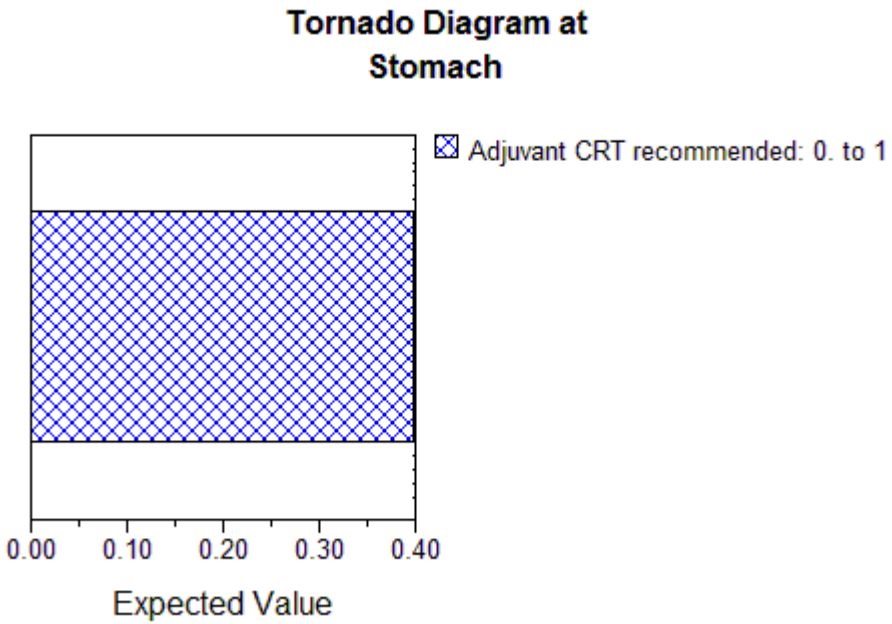


Figure 4. Gastric Cancer. Concurrent ChemoRadiotherapy Utilisation -Tornado Diagram for Univariate Sensitivity Analysis



References

1. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Gastric Cancer V.2.2011. http://www.nccn.org/professionals/physician_gls/pdf/gastric.pdf . 13-5-2011. 2-4-2012.
   Ref Type: Electronic Citation

2. National Cancer Institute. PDQ Gastric Cancer Treatment. http://www.cancer.gov/cancertopics/pdq/treatment/gastric/HealthProfessional . 6-1-2012. 3-4-2012.
   Ref Type: Electronic Citation

3. Cancer Care Ontario (CCO) program in evidence-based care (PEBC). Neoadjuvant or adjuvant therapy for resectable gastric cancer. https://www.cancercare.on.ca/common/pages/UserFile.aspx?fileId=13972 . 2011. 3-4-2012.
   Ref Type: Electronic Citation

4. Allum WH, Blazeby JM, Griffin SM, et al. Guidelines for the management of oesophageal and gastric cancer. *Gut* 2011;60:1449-72.

5. Scottish Intercollegiate Guidelines Network. Management of oesophageal and gastric cancer. A national clinical guideline. http://www.sign.ac.uk/pdf/sign87.pdf . 2006. 3-4-2012.
   Ref Type: Electronic Citation

6. Okines A, Verheij M, Allum W, et al. Gastric cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Annals of Oncology* 2010;21:v50-v54.

7. Japanese gastric cancer association. Japanese gastric cancer treatment guidelines 2010 (v 3). http://cancerdundee.files.wordpress.com/2011/05/japanese-guidelines.pdf . 2011. 3-4-2012.
   Ref Type: Electronic Citation

8. BC Cancer Agency. Cancer Management Guidelines. Stomach. http://www.bccancer.bc.ca/HPI/CancerManagementGuidelines/Gastrointestinal/02.Stomach/Management/default.htm . 2005. 3-4-2012.
   Ref Type: Electronic Citation

9. Gastric Cancer Diagnosis and Treatment Expert Panel of the Chinese Ministry of Health. Chinese guidelines for diagnosis and treatment of gastric cancer (2011 edition). http://www.amepc.org/tgc/article/view/549/549 . 2012. 10-4-2012.
   Ref Type: Electronic Citation

10. Indian Council of Medical Research. Guidelines for management of stomach cancer. http://icmr.nic.in/guide/cancer/SCMG.pdf . 2010. 3-4-2012.
    Ref Type: Electronic Citation

11. Trans Tasman Radiation Oncology Group (TROG). A randomised phase II/III trial of preoperative chemoradiotherapy versus preoperative chemotherapy for resectable gastric cancer (TOPGEAR). http://www.trog.com.au/Default.aspx?tabid=71#Gastro . 2012. 22-5-2012.
    Ref Type: Electronic Citation

12. Australian Institute of Health and Welfare (AIHW). Australian Cancer Incidence and Mortality (ACIM) books. AIHW . 2011. 16-8-2011.
    Ref Type: Electronic Citation

13. Lin Y, Ueda J, Kikuchi S, et al. Comparative epidemiology of gastric cancer between Japan and China. *World J Gastroenterol* 2011;17:4421-8.

14. American Joint Committee on Cancer. AJCC Cancer Staging Manual 7th Edition. New York: Springer, 2010.

15. Hundahl SA, Menck HR, Mansour EG, Winchester DP. The National Cancer Data Base Report on Gastric Carcinoma. *Cancer* 1997;80:2333-41.

16. Siewert JR, Bottcher K, Stein HJ, Roder JD, German Gastric Carcinoma Study Group. Relevant prognostic factors in gastric cancer. Ten-year results of the German gastric cancer study. *Ann Surg* 1998;228:449-61.

17. National Cancer Institute and Surveillance, Epidemilogy and End Results SEER Program. Surveillance, Epidemiology and End Results (SEER) Program SEER*Stat Database: Incidence - SEER 17 Regs Research Data, Nov 2009 Sub (1973-2007 varying) - Linked to county attributes-Total US., 1969-2007 Counties. 2010.
Ref Type: Data File

18. Dassen AE, Lemmens VEPP, van de Poll-Franse LV, Creemers GJ, et al. Trends in incidence, treatment and survival of gastric adenocarcinoma between 1990 and 2007: a population-based study in the Netherlands. *Eur J Cancer* 2010;46:1101-10.

19. Lee S, Nomura E, Bouras G, et al. Long-term oncologic outcomes from laparoscopic gastrectomy for gastric cancer: a single-center experience of 601 consecutive resections. *J Am Coll Surg* 2010;211:33-40.

20. Fujiwara M, Kodera Y, Misawa K, et al. Longterm outcomes of early-stage gastric carcinoma patients treated with laparoscopy-assisted surgery. *J Am Coll Surg* 2008;206:138-43.

21. Kos F, Uncu D, Oezdemir N, et al. Comparison of Cisplatin-5-Fluorouracil-Folinic Acid versus Modified Docetaxel-Cisplatin-5-Fluorouracil regimens in the first-line treatment of metastatic gastric cancer. *Chemotherapy* 2011;57:230-5.

22. Tey J, Back MF, Shakespeare TP, et al. The role of palliative radiation therapy in symptomatic locally advanced gastric cancer. *Int J Radiat Oncol Biol Phys* 2007;67:385-8.

23. Asakura H, Hashimoto T, Harada H, Mizumoto M, et al. Palliative radiotherapy for bleeding from advanced gastric cancer: is a schedule of 30 Gy in 10 fractions adequate? *J Cancer Res Clin Oncol* 2011;137:125-30.

24. Hashimoto K, Mayahara H, Takashima A, et al. Palliative radiation therapy for hemorrhage of unresectable gastric cancer: a single institute experience. *J Cancer Res Clin Oncol* 2009.

25. Lee JA, Lim DH, Park W, Ahn YC, Huh SJ. Radiation therapy for gastric cancer bleeding. *Tumori* 2009;95:726-30.

TESTICULAR CANCER

Evidence-based treatment guidelines for testicular cancer management issued by major international, national and provincial organisations reviewed for the model are those published after the previous radiotherapy utilisation study was completed (July 2003) up to the most recent ones published in 2011.

Updated Guidelines

The following new or updated guidelines were identified and reviewed since the original RTU study:

- The Société Internationale d'Urologie (SIU) and International Consultation on Urological Diseases (ICUD) consensus guidelines on management of stage I-II seminoma, 2011 (1)
- NCCN clinical practice guidelines on testicular cancer, version 1, 2011 (2)
- NCI testicular cancer treatment PDQ, 2011 (3)
- BC Cancer Agency genitourinary cancer management guidelines (Testis), 2005 (4)
- Canadian consensus guidelines for the management of testicular germ cell cancer, 2010 (5)
- Cancer Care Ontario guidelines on management of stage I seminoma, 2010 (6)
- Cancer Care Nova Scotia guidelines for the management of adult testicular cancer, 2005 (7)
- Scottish Intercollegiate Guidelines Network (SIGN) guidelines on management of adult testicular germ cell tumours, 2011 (8)
- European Association of Urology (EAU) guidelines on testicular cancer, 2011 (9)
- European Society of Medical Oncology (ESMO) clinical practice guidelines for diagnosis, treatment and follow-up of testicular seminoma, 2010 (10)
- ESMO clinical practice guidelines for diagnosis, treatment and follow-up of testicular non-seminoma, 2010 (11)
- European Germ Cell Cancer Consensus Group (EGCCCG) consensus report on diagnosis and treatment of germ cell cancer: Part I, 2008 (12)
- EGCCCG consensus report on diagnosis and treatment of germ cell cancer: Part II, 2008 (13)
- EGCCCG consensus report on diagnosis and treatment of germ cell cancer, 2004 (14)

Indications for radiotherapy

All the indications for external beam radiotherapy in the original CCORE model of optimal radiotherapy utilisation for testicular cancer have been reviewed and updated in the optimal utilisation tree based on the latest guideline recommendations (Table 1). Changes to the indications for radiotherapy are as follows:

i. Adjuvant treatment in stage I seminoma.

In the original optimal radiotherapy utilisation model, patients with stage I seminoma were recommended to have adjuvant radiotherapy or to undergo observation after surgery, based on recommendations of guidelines available at the time. Updated guidelines recommend adjuvant chemotherapy as an additional option after surgery based on evidence showing no difference in relapse-free survival in patients receiving adjuvant chemotherapy or adjuvant radiotherapy (15). All guidelines continue to recommend adjuvant radiotherapy and observation as treatment options, except the updated EAU guidelines (9) which no longer recommend adjuvant radiotherapy based on published data on long-term toxicity (16-17).

A new outcome branch with indication of adjuvant chemotherapy has been added to the model. In this model, 11% of patients are recommended to undergo observation, based on the Victorian Patterns of Care study (18) in which 11% of patients with stage I seminoma chose observation over radiotherapy post-orchidectomy. This study was conducted at the time when only radiotherapy and observation were recommended treatment options after surgery. In this model, the rest of the patients (89%) are recommended to have chemotherapy in view of the long-term toxicity of radiotherapy. Since the majority of guidelines still recommend adjuvant radiotherapy as a treatment option post-orchidectomy, the alternative view that patients should be given radiotherapy instead of chemotherapy has been factored into the model by changing the proportion of patients having radiotherapy from 0% to 44.5% in the sensitivity analysis (i.e. of the 89% of patients who choose to have active treatment post-orchidectomy, half of the patients would have chemotherapy and the other half would have radiotherapy). This proportion has been chosen arbitrarily as adjuvant chemotherapy and adjuvant radiotherapy have been shown to result in equivalent relapse-free survival in these patients.

ii. Cranial radiotherapy in testicular cancer patients with brain metastases at diagnosis

In the original optimal radiotherapy utilisation model, patients with brain metastases at diagnosis were recommended to have cranial radiotherapy. The EAU guidelines (9) state that chemotherapy is the initial treatment, and some data support the use of consolidation radiotherapy, even in the case of a total response after chemotherapy. The NCCN guidelines (2) recommend chemotherapy and radiotherapy, with or without surgery, for patients with brain metastases from non-seminomatous germ cell tumours. The Canadian consensus guidelines (5) and the EGCCCG guidelines (13) indicate that the optimal sequence of chemotherapy, radiotherapy and surgery is not known and that the role of cranial radiotherapy is not well defined. In this model, patients with brain metastases at diagnosis are recommended to have radiotherapy. In view of the uncertainty of the benefit of radiotherapy as discussed in the clinical guidelines, the alternative view that patients should not be treated with radiotherapy has been factored into the model by changing the proportion of patients

having radiotherapy from 100% to 0% in the sensitivity analysis (i.e. no patients would have radiotherapy).

All of the other previous indications remain supported by current guidelines.

Level of evidence

According to the methods applied for the previous radiotherapy utilisation model the indications for radiotherapy for testicular cancer have been derived from evidence-based treatment guidelines issued by major international, national and provincial organisations.

Based on guidelines review, all indications of radiotherapy for testicular cancer are supported by level I-IV evidence similar to those reported in the earlier model. Notably, for one indication the evidence has been upgraded to level II from level III.

Out of 17 outcome branches in the model that have an indication of radiotherapy (Figures 1b and 1c) 65% (11 branches) are supported by level I-II evidence. The updated model predicts that 0.4% of the whole testicular cancer population have an indication for radiotherapy based on level I-II evidence of benefit and 6% of the testicular cancer population with an indication for radiotherapy have level I or II evidence of benefit if treated according to evidence-based guidelines.

Epidemiology of cancer stages

The epidemiological data in the testicular cancer utilisation tree have been reviewed to see if more recent data are available through extensive electronic search using the key words ‘Australia’, ‘epidemiology testicular cancer’, ‘incidence’, ‘testicular cancer stage‘, ‘radiotherapy treatment’, ‘recurrence’, ‘distant metastases’, ‘survival’, ‘treatment outcome’ in various combinations. This has been applied particularly to the early branches in the tree for which national or state level data on cancer incidence rates and stages are available. If there is a change in the hierarchical quality of the epidemiological data, this has also been noted (Table 2).

Since the completion of the previous radiotherapy utilisation project the national data on cancer statistics published by AIHW have been updated to more recent years till 2007 (19). There has been no change in the incidence of testicular cancer in Australia. More recent population-based data on stage for all patients with testicular cancer in the US SEER database for the year 1999 (20) and in the Icelandic Cancer Registry for the years 1955-2002 (21) are available. However, the stage proportions are similar to the Australian state data for the years 1988-1993 used in our original model, therefore no changes have been made to the stage data in the optimal utilisation tree.

Several staging systems have been used for testicular cancer at different institutions. Most systems have in common the division into three stages, with stage I being tumour limited to the testis, stage II metastases to subdiaphragmatic lymph nodes and stage III involvement of supradiaphragmatic lymph

nodes or extralymphatic metastases. The previous testicular cancer utilisation tree was based on the 4-stage system, where stage III disease was subdivided into stage III (supradiaphragmatic lymph node metastases) and stage IV (extralymphatic spread). A major change in the updated testicular cancer utilisation tree is the use of the 3-stage system, which is the most commonly used staging system in Australia, resulting in deletion and addition of outcome branches (Table 2).

Estimation of the optimal radiotherapy utilisation

From the evidence on the efficacy of radiotherapy and the most recent epidemiological data on the occurrence of indications for radiotherapy, the proportion of testicular cancer patients in whom radiotherapy would be recommended is 7% (Table 1 and Figures 1a, 1b and 1c) compared with the original estimate of 49%.

Estimation of the optimal combined radiotherapy and chemotherapy utilisation

The indications of radiotherapy for testicular cancer were reviewed to identify those indications where radiotherapy is recommended in conjunction with concurrent chemotherapy as the first treatment. According to the best available evidence there are no indications identified for which concurrent chemoradiation is beneficial over radiotherapy alone as the first indicated treatment.

Sensitivity analysis

Univariate sensitivity analysis has been undertaken to assess changes in the recommended testicular cancer radiotherapy utilisation rate that would result from different estimates of the proportions of patients with particular attributes as mentioned in Table 2 (Figure 2). Also the sensitivity analyses tested the effect of including or excluding the recommendation for radiotherapy for testicular cancer patients with brain metastases at diagnosis; this addresses the issue of conflict in radiotherapy recommendations between treatment guidelines for these patients.

The main uncertainty in the management of testicular cancer relates to adjuvant treatment after radical orchidectomy for stage I seminoma. To model this uncertainty and the impact on the overall optimal radiotherapy utilisation rate for testicular cancer, two scenarios were used in the updated model. In both scenarios, 11% of patients were designated having observation. In the first scenario, all patients who did not undergo observation were recommended having chemotherapy (89% of stage I seminoma patients). In the second scenario, half of the patients who did not undergo observation were recommended having chemotherapy (44.5% of stage I seminoma patients) and the other half (44.5%) were recommended having radiotherapy.

The variability in the estimate of optimal radiotherapy utilisation due to these uncertainties ranged from 7% to 28% as shown in the Tornado diagram (Figure 2). This large variation was due to the uncertainty of adjuvant treatment after radical orchidectomy for stage I seminoma.

Table 1: Testicular Cancer. Indications for radiotherapy - Levels and sources of evidence

Original RTU study				Updates 2011					
Outcome No. in Tree	Clinical Scenario	Level of evidence	Proportion of all testicular cancer	Change of Indication	Guideline updated	Current level of evidence	Change to proportion of all testicular cancer		References
							Yes/ No	Updated value	
1	Seminoma, stage I, radiotherapy	III	0.41	Yes	Yes	II	Yes	0	SIU/ICUD (1), NCCN (2), NCI (3), Canadian consensus guidelines (5), BCCA (4), Cancer Care Nova Scotia (7), SIGN (8), ESMO (10), EGCCCG (12)
2	Seminoma, stage I, observation, nodal recurrence	IV	0.01	No	Yes	IV	No	0.01	BCCA (4), Cancer Care Nova Scotia (7), EGCCCG (12)
3	Seminoma, stage I, observation, no nodal recurrence, distant recurrence, brain metastases	II	<0.01	No	Yes	II	No	<0.01	SIGN (8)

Original RTU study				Updates 2011					
Outcome No. in Tree	Clinical Scenario	Level of evidence	Proportion of all testicular cancer	Change of Indication	Guideline updated	Current level of evidence	Change to proportion of all testicular cancer		References
							Yes/ No	Updated value	
4	Seminoma, stage I, observation, no nodal recurrence, distant recurrence, no brain metastases, bone metastases	I	<0.01	No	Yes	I	No	<0.01	McQuay et al 1997 (22), Wu et al 2003 (23)
7	Seminoma, stage II, non-bulky disease (stage IIA/IIB)	III	0.07	No	Yes	III	Yes	0.05	SIU/ICUD (1), NCCN (2), NCI (3), BCCA (4), Cancer Care Nova Scotia (7), SIGN (8), EAU (9), ESMO (10), EGCCCG (12)
8	Seminoma, stage II, bulky disease, residual disease post-chemotherapy	IV	< 0.01	No	Yes	IV	No	< 0.01	NCCN (2)

Original RTU study				Updates 2011					
Outcome No. in Tree	Clinical Scenario	Level of evidence	Proportion of all testicular cancer	Change of Indication	Guideline updated	Current level of evidence	Change to proportion of all testicular cancer		References
							Yes/ No	Updated value	
9	Seminoma, stage II, bulky disease, no residual disease post-chemotherapy, recurrent disease, brain metastases	II	<0.01	No	Yes	II	No	<0.01	SIGN (8)
10	Seminoma, stage II, bulky disease, no residual disease post-chemotherapy, recurrent disease, no brain metastases, bone metastases	I	<0.01	No	Yes	I	No	<0.01	McQuay et al 1997 (22), Wu et al 2003 (23)

Original RTU study				Updates 2011					
Outcome No. in Tree	Clinical Scenario	Level of evidence	Proportion of all testicular cancer	Change of Indication	Guideline updated	Current level of evidence	Change to proportion of all testicular cancer		References
							Yes/ No	Updated value	
14	Seminoma, stage III, brain metastases at diagnosis	New outcome branch added to the model as the original model used the 4-stage staging system			N/A	III	N/A	<0.01	Canadian consensus guidelines (5), EAU (9), EGCCCG (13)
16	Seminoma, stage III, no brain metastases at diagnosis, residual disease post-chemotherapy	New outcome branch added to the model as the original model used the 4-stage staging system			N/A	IV	N/A	< 0.01	NCCN (2)
17	Seminoma, stage III, no brain metastases at diagnosis, no residual disease post-chemotherapy, recurrent disease, brain metastases	New outcome branch added to the model as the original model used the 4-stage staging system			N/A	II	N/A	<0.01	SIGN (8)

Original RTU study				Updates 2011					
Outcome No. in Tree	Clinical Scenario	Level of evidence	Proportion of all testicular cancer	Change of Indication	Guideline updated	Current level of evidence	Change to proportion of all testicular cancer		References
							Yes/ No	Updated value	
18	Seminoma, stage III, no brain metastases at diagnosis, no residual disease post-chemotherapy, recurrent disease, bone metastases	New outcome branch added to the model as the original model used the 4-stage staging system			N/A	I	N/A	<0.01	McQuay et al 1997 (22), Wu et al 2003 (23)
21	NSGCT and non-germ cell tumour, stage I, recurrent disease, brain metastases	New outcome branch added to the model as the original model used the 4-stage staging system			N/A	II	N/A	<0.01	SIGN (8)
22	NSGCT and non-germ cell tumour, stage I, recurrent disease, no brain metastases, bone metastases	New outcome branch added to the model as the original model used the 4-stage staging system			N/A	I	N/A	<0.01	McQuay et al 1997 (22), Wu et al 2003 (23)

Original RTU study				Updates 2011					
Outcome No. in Tree	Clinical Scenario	Level of evidence	Proportion of all testicular cancer	Change of Indication	Guideline updated	Current level of evidence	Change to proportion of all testicular cancer		References
							Yes/ No	Updated value	
25	NSGCT and non-germ cell tumour, stage II-III, brain metastases at diagnosis	New outcome branch added to the model as the original model used the 4-stage staging system			N/A	III	N/A	<0.01	NCCN (2), Canadian consensus guidelines (5), EGCCCG (13)
27	NSGCT and non-germ cell tumour, stage II-III, no brain metastases at diagnosis, recurrent disease, brain metastases	New outcome branch added to the model as the original model used the 4-stage staging system			N/A	II	N/A	<0.01	SIGN (8)
28	NSGCT and non-germ cell tumour, stage II-III, no brain metastases at diagnosis, recurrent disease, no brain metastases, bone metastases	New outcome branch added to the model as the original model used the 4-stage staging system			N/A	I	N/A	<0.01	McQuay et al 1997 (22), Wu et al 2003 (23)
Proportion of all testicular cancer patients in whom radiotherapy is recommended			0.49 (49%)	**Updated proportion of all testicular cancer patients in whom radiotherapy is recommended**				**0.07 (7%)**	

Table 2: Testicular Cancer. The incidence of attributes used to define indications for radiotherapy

Original RTU study				Updates 2011				
Population or sub-population of interest	**Attribute**	**Proportion of population with the attribute**	**Quality of Information**	**Change in proportion of population with attribute Yes/ No**	**Altered Proportion**	**Updated Quality of Information**	**Updated Reference**	**Comments**
All registry cancers	Testicular cancer	0.01	α	No	N/A	N/A	AIHW 2010 (24)	Updated 2007 data showed no change in incidence
Testicular cancer	Seminoma	0.56 0.54	β γ	No	N/A	β γ γ	Toner et al 2001 (18) Osswald et al 2009 (20) Agnarsson et al 2006 (21)	SEER and Icelandic Cancer Registry showed similar data
Seminoma	Stage I	0.83	β	No	N/A	β γ γ	Toner et al 2001 (18) Osswald et al 2009 (20) Agnarsson et al 2006 (21)	SEER and Icelandic Cancer Registry showed similar data

Original RTU study				Updates 2011				
Population or sub-population of interest	**Attribute**	**Proportion of population with the attribute**	**Quality of Information**	**Change in proportion of population with attribute Yes/ No**	**Altered Proportion**	**Updated Quality of Information**	**Updated Reference**	**Comments**
Seminoma, stage I	Radiotherapy	0.89	β	No	N/A	N/A	Toner et al 2001 (18)	
Seminoma, stage I, observation	Nodal recurrence	0.19 0.14	ε ζ	No	N/A	ε	Warde et al 2002 (25)	Pooled data from 4 centres showed same recurrence rate of 0.19
Seminoma, stage I, observation, no nodal recurrence	Distant recurrence	0.08	ζ	No	N/A	N/A	Duchesne et al 1997 (26)	
Seminoma, stage I, observation, no nodal recurrence, distant recurrence	Brain metastases	0.01	ε	No	N/A	N/A	International Germ Cell Cancer Collaborative Group 1997 (27)	
Seminoma, stage I, observation, distant recurrence, no brain met	Bone metastases	0.05	ε	No	N/A	N/A	International Germ Cell Cancer Collaborative Group 1997 (27)	

Original RTU study				Updates 2011				
Population or sub-population of interest	**Attribute**	**Proportion of population with the attribute**	**Quality of Information**	**Change in proportion of population with attribute Yes/ No**	**Altered Proportion**	**Updated Quality of Information**	**Updated Reference**	**Comments**
Seminoma	Stage II	0.14	β	No	N/A	β γ γ	Toner et al 2001 (18) Osswald et al 2009 (20) Agnarsson et al 2006 (21)	SEER and Icelandic Cancer Registry showed similar data
Seminoma, stage II	Bulky disease	0.16	ζ	Yes	0.31	ζ	Chung et al 2004 (28)	
Seminoma, stage II, bulky disease	Residual disease post-chemotherapy	0.07	θ	No	N/A	N/A	Duchesne et al 1997 (26)	
Seminoma, stage II, bulky disease, no residual disease post-chemotherapy	Recurrence	0.0	ζ	Yes	0.04	ζ	Chung et al 2004 (28)	

Original RTU study				Updates 2011				
Population or sub-population of interest	**Attribute**	**Proportion of population with the attribute**	**Quality of Information**	**Change in proportion of population with attribute Yes/ No**	**Altered Proportion**	**Updated Quality of Information**	**Updated Reference**	**Comments**
Seminoma, stage II, bulky disease, no residual disease post-chemotherapy, distant recurrence	Brain metastases	0.01	ε	No	N/A	N/A	International Germ Cell Cancer Collaborative Group 1997 (27)	
Seminoma, stage II, bulky disease, no residual disease post-chemotherapy, distant recurrence, no brain metastases	Bone metastases	0.05	ε	No	N/A	N/A	International Germ Cell Cancer Collaborative Group 1997 (27)	
Seminoma	Stage III	0.03	β	No	N/A	β γ γ	Toner 2001 (18) Osswald et al 2009 (20) Agnarsson et al 2006 (21)	SEER and Icelandic Cancer Registry showed similar data

Original RTU study				Updates 2011				
Population or sub-population of interest	**Attribute**	**Proportion of population with the attribute**	**Quality of Information**	**Change in proportion of population with attribute Yes/ No**	**Altered Proportion**	**Updated Quality of Information**	**Updated Reference**	**Comments**
Seminoma, stage III	Brain metastases at diagnosis	New outcome	N/A	N/A	0.01	ε	International Germ Cell Cancer Collaborative Group 1997 (27)	
Seminoma, stage III, no brain metastases at diagnosis	Residual disease post-chemotherapy	New outcome	N/A	N/A	0.15	ζ	Logothetis et al 1987 (29)	
Seminoma, stage III, no brain metastases at diagnosis, no residual disease post-chemotherapy	Recurrent disease	New outcome	N/A	N/A	0.05	λ	Pizzocaro et al 1986 (30) Schmoll et al 1993 (31) Howard et al 2005 (32)	

Original RTU study				Updates 2011				
Population or sub-population of interest	**Attribute**	**Proportion of population with the attribute**	**Quality of Information**	**Change in proportion of population with attribute Yes/ No**	**Altered Proportion**	**Updated Quality of Information**	**Updated Reference**	**Comments**
Seminoma, stage III, no brain metastases at diagnosis, no residual disease post-chemotherapy, recurrent disease	Brain metastases	New outcome	N/A	N/A	0.01	ε	International Germ Cell Cancer Collaborative Group 1997 (27)	
Seminoma, stage III, no brain metastases at diagnosis, no residual disease post-chemotherapy, recurrent disease, no brain metastases	Bone metastases	New outcome	N/A	N/A	0.05	ε	International Germ Cell Cancer Collaborative Group 1997 (27)	

Original RTU study				Updates 2011				
Population or sub-population of interest	**Attribute**	**Proportion of population with the attribute**	**Quality of Information**	**Change in proportion of population with attribute Yes/ No**	**Altered Proportion**	**Updated Quality of Information**	**Updated Reference**	**Comments**
Testicular cancer	Non-seminomatous germ cell and non-germ cell tumours	0.44	β	**No**	**N/A**	**β** γ γ	Toner et al 2001 (18) Osswald et al 2009 (20) Agnarsson 2006 (21)	SEER and Icelandic Cancer Registry showed similar data
Non-seminatous germ cell and non-germ cell tumours	Stage I	New outcome	N/A	N/A	0.58	β γ γ	Toner et al 2001 (18) Osswald et al 2009 (20) Agnarsson et al 2006 (21)	
Non-seminatous germ cell and non-germ cell tumours, stages I	Recurrent disease	New outcome	N/A	N/A	0.14	**γ**	Germa-Lluch et al 2002 (33)	

Original RTU study				Updates 2011				
Population or sub-population of interest	**Attribute**	**Proportion of population with the attribute**	**Quality of Information**	**Change in proportion of population with attribute Yes/ No**	**Altered Proportion**	**Updated Quality of Information**	**Updated Reference**	**Comments**
Non-seminatous germ cell and non-germ cell tumours, stages I, recurrent disease	Brain metastases	New outcome	N/A	N/A	0.08	ζ	Motzer et al 1991 (34)	
Non-seminatous germ cell and non-germ cell tumours, stages I, recurrent disease, no brain metastases	Bone metastases	New outcome	N/A	N/A	0.01	ε	International Germ Cell Cancer Collaborative Group 1997 (27)	
Non-seminatous germ cell and non-germ cell tumours	Stage II-III	New outcome	N/A	N/A	0.42	β γ γ	Toner et al 2001 (18) Osswald et al 2009 (20) Agnarsson et al 2006 (21)	

Original RTU study				Updates 2011				
Population or sub-population of interest	**Attribute**	**Proportion of population with the attribute**	**Quality of Information**	**Change in proportion of population with attribute Yes/ No**	**Altered Proportion**	**Updated Quality of Information**	**Updated Reference**	**Comments**
Non-seminatous germ cell and non-germ cell tumours, stage II-III	Brain metastases at diagnosis	New outcome	N/A	N/A	0.01	ε	International Germ Cell Cancer Collaborative Group 1997 (27)	
Non-seminatous germ cell and non-germ cell tumours, stage II-III, no brain metastases at diagnosis	Recurrent disease	New outcome	N/A	N/A	0.09	ζ	Ehrlich et al 2010 (35)	
Non-seminatous germ cell and non-germ cell tumours, stage II-III, no brain metastases at diagnosis, recurrent disease	Brain metastases	New outcome	N/A	N/A	0.08	ζ	Motzer et al 1991 (34)	

Original RTU study				Updates 2011				
Population or sub-population of interest	**Attribute**	**Proportion of population with the attribute**	**Quality of Information**	**Change in proportion of population with attribute Yes/ No**	**Altered Proportion**	**Updated Quality of Information**	**Updated Reference**	**Comments**
Non-seminatous germ cell and non-germ cell tumours, stage II-III, no brain metastases at diagnosis, recurrent disease, no brain metastases	Bone metastases	New outcome	N/A	N/A	0.01	ε	International Germ Cell Cancer Collaborative Group 1997 (27)	

Figure 1a. Testicular cancer radiotherapy utilisation tree

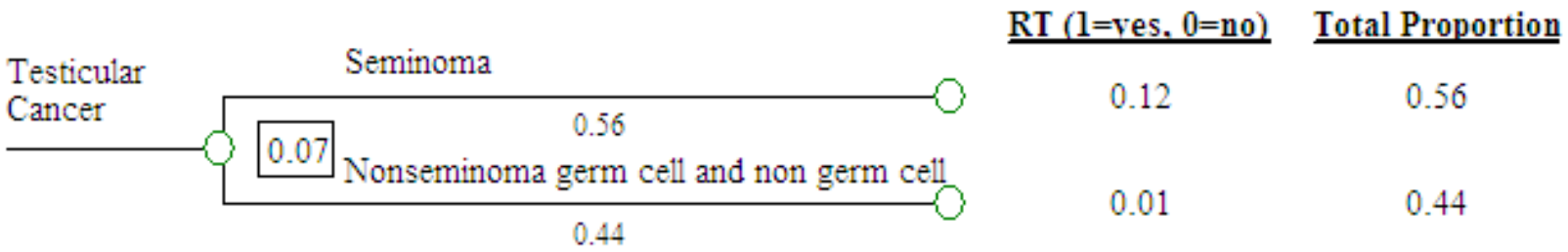


Figure 1b. Seminoma radiotherapy utilisation tree

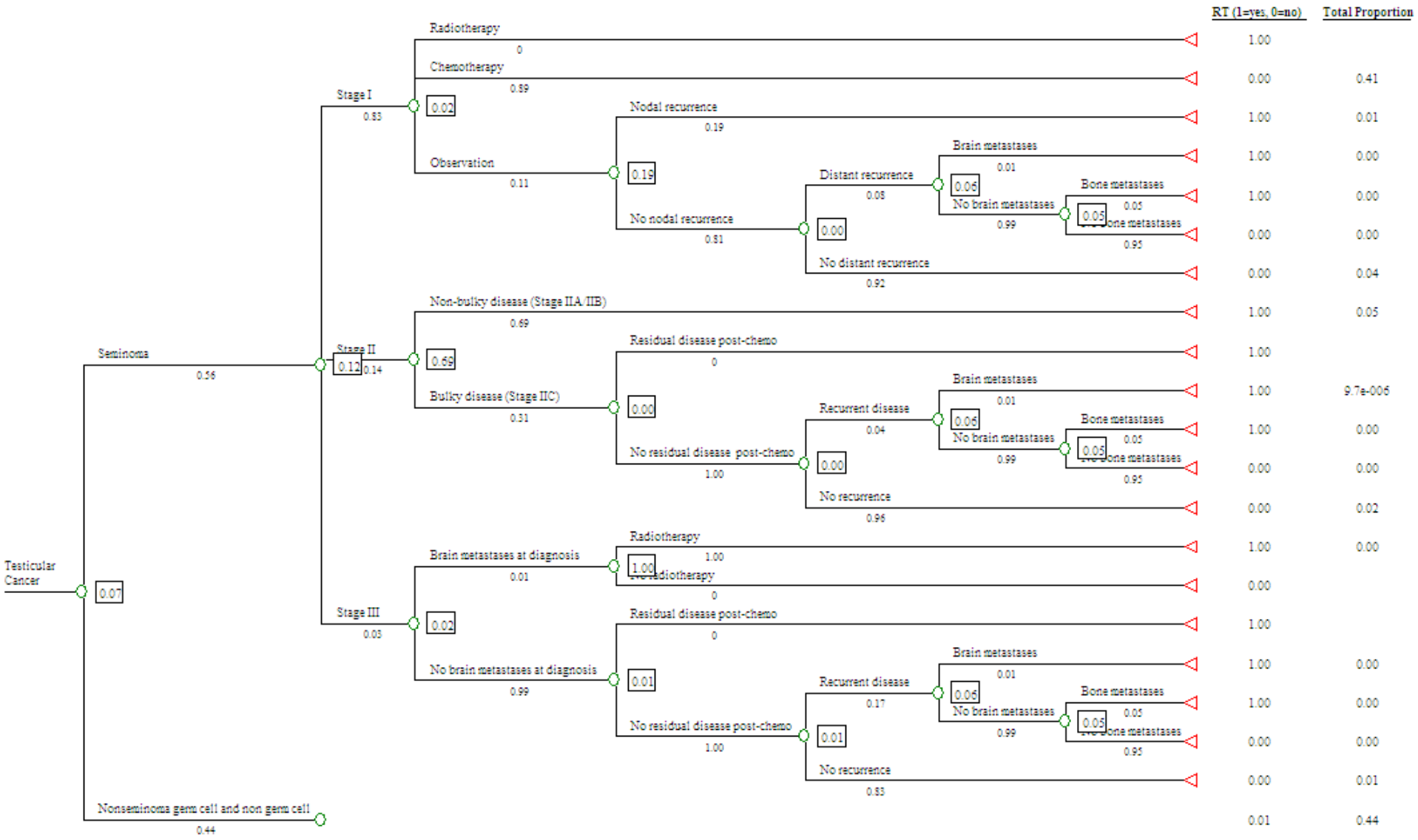


Figure 1c. Non-seminomatous germ-cell and non-germ cell tumours radiotherapy utilisation tree

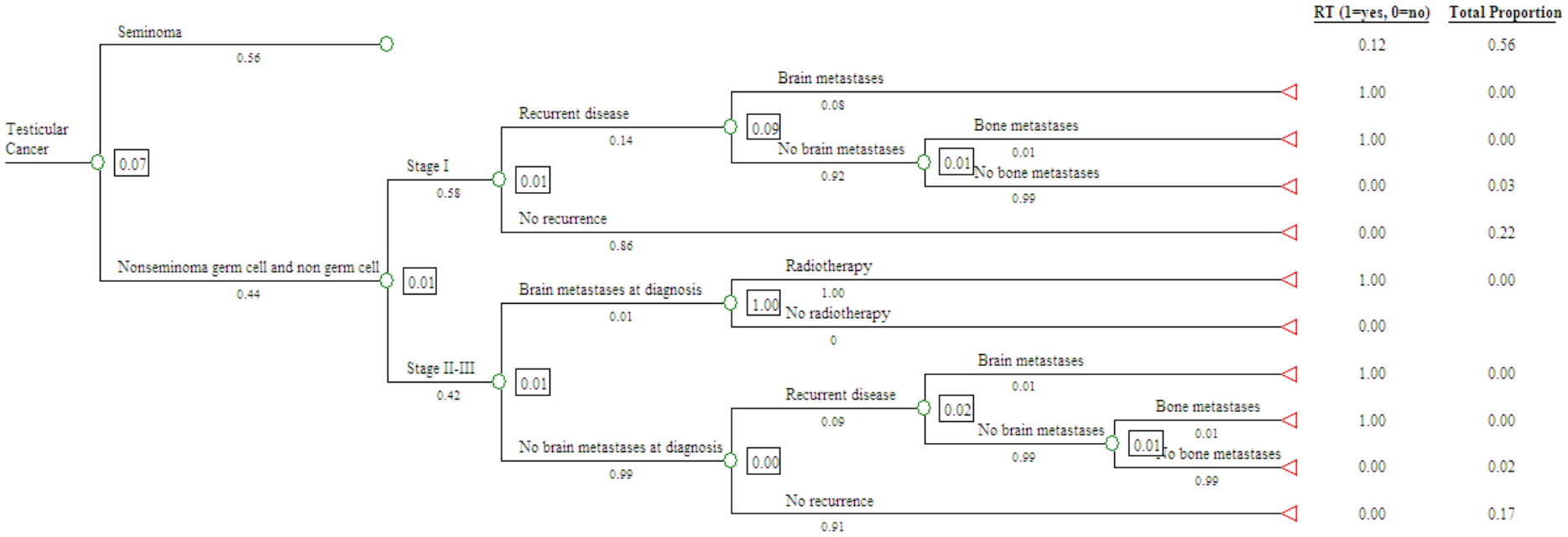
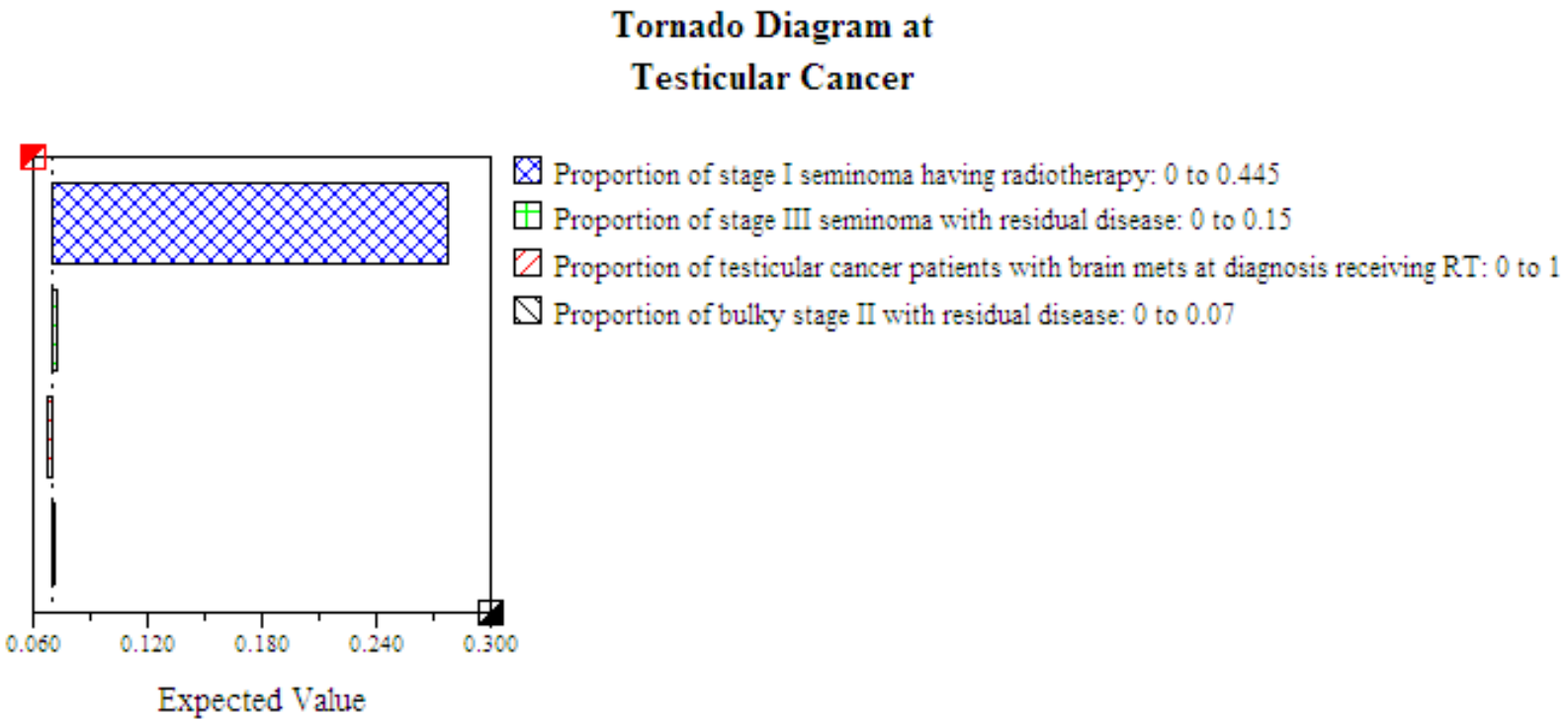


Figure 2. Tornado diagram for univariate sensitivity analyses



References

1. Warde P, Huddart R, Bolton D*, et al.* Management of localized seminoma, stage I-II: SIU/ICUD Consensus Meeting on Germ Cell Tumors (GCT), Shanghai 2009. *Urology* 2011;78:S435-443.

2. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Testicular Cancer Version 1.2011: www.nccn.org; 2011. Accessed 08/10/2011.

3. National Cancer Institute. PDQ Summary: Testicular Cancer Treatment: www.cancer.gov; 2011. Accessed 08/10/2011.

4. British Columbia Cancer Agency. Cancer Management Guidelines: Genitourinary Cancer (Testis): www.bccancer.bc.ca; 2005. Accessed 10/8/2011.

5. Wood L, Kollmannsberger C, Jewett M*, et al.* Canadian consensus guidelines for the management of testicular germ cell cancer. *Can Urol Assoc J* 2010;4:e19-38.

6. Chung P, Mayhew LA, Warde P*, et al.* Management of stage I seminomatous testicular cancer: a systematic review. *Clin Oncol (R Coll Radiol)* 2010;22:6-16.

7. Cancer Care Nova Scotia. Guidelines for the management of adult testicular cancer: www.cancercare.ns.ca; 2005. Accessed 10/8/2011.

8. Scottish Intercollegiate Guidelines Network. Management of adult testicular germ cell tumours. A national clinical guideline (report no.124): http://www.sign.ac.uk/pdf/sign124.pdf; 2011. Accessed 7/12/2011.

9. European Association of Urology. Guidelines on testicular cancer: www.uroweb.org; 2011. Accessed 31/10/2012.

10. Schmoll HJ, Jordan K, Huddart R*, et al.* Testicular seminoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2010;21 Suppl 5:v140-146.

11. Schmoll HJ, Jordan K, Huddart R*, et al.* Testicular non-seminoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2010;21 Suppl 5:v147-154.

12. Krege S, Beyer J, Souchon R*, et al.* European consensus conference on diagnosis and treatment of germ cell cancer: a report of the second meeting of the European Germ Cell Cancer Consensus group (EGCCCG): part I. *Eur Urol* 2008;53:478-496.

13. Krege S, Beyer J, Souchon R*, et al.* European consensus conference on diagnosis and treatment of germ cell cancer: a report of the second meeting of the European Germ Cell Cancer Consensus Group (EGCCCG): part II. *Eur Urol* 2008;53:497-513.

14. Schmoll HJ, Souchon R, Krege S*, et al.* European consensus on diagnosis and treatment of germ cell cancer: a report of the European Germ Cell Cancer Consensus Group (EGCCCG). *Ann Oncol* 2004;15:1377-1399.

15. Oliver RT, Mason MD, Mead GM*, et al.* Radiotherapy versus single-dose carboplatin in adjuvant treatment of stage I seminoma: a randomised trial. *Lancet* 2005;366:293-300.

16. Robinson D, Moller H, Horwich A. Mortality and incidence of second cancers following treatment for testicular cancer. *Br J Cancer* 2007;96:529-533.
17. van den Belt-Dusebout AW, de Wit R, Gietema JA*, et al.* Treatment-specific risks of second malignancies and cardiovascular disease in 5-year survivors of testicular cancer. *J Clin Oncol* 2007;25:4370-4378.

18. Toner GC, Neerhut GJ, Schwarz MA*, et al.* The management of testicular cancer in Victoria, 1988-1993. Urology Study Committee of the Victorian Co-operative Oncology Group. *Med J Aust* 2001;174:328-331.

19. Australian Institute of Health and Welfare (AIHW). Australian Cancer Incidence and Mortality (ACIM) books. : www.aihw.gov.au/acim-books/; 2011. Accessed 26/11/2011.

20. Osswald M, Harlan LC, Penson D*, et al.* Treatment of a population based sample of men diagnosed with testicular cancer in the United States. *Urol Oncol* 2009;27:604-610.

21. Agnarsson BA, Gudbjartsson T, Einarsson GV*, et al.* Testicular germ cell tumours in Iceland: a nationwide clinicopathological study. *APMIS* 2006;114:779-783.

22. McQuay HJ, Carroll D, Moore RA. Radiotherapy for painful bone metastases: a systematic review. *Clin Oncol (R Coll Radiol)* 1997;9:150-154.

23. Wu JS, Wong R, Johnston M*, et al.* Meta-analysis of dose-fractionation radiotherapy trials for the palliation of painful bone metastases. *Int J Radiat Oncol Biol Phys* 2003;55:594-605.

24. Australian Institute of Health and Welfare (AIHW). Australian Cancer Incidence and Mortality (ACIM) books. : www.aihw.gov.au/acim-books/; 2010. Accessed 26/11/2011.

25. Warde P, Specht L, Horwich A*, et al.* Prognostic factors for relapse in stage I seminoma managed by surveillance: a pooled analysis. *J Clin Oncol* 2002;20:4448-4452.

26. Duchesne GM, Stenning SP, Aass N*, et al.* Radiotherapy after chemotherapy for metastatic seminoma--a diminishing role. MRC Testicular Tumour Working Party. *Eur J Cancer* 1997;33:829-835.

27. International Germ Cell Consensus Classification: a prognostic factor-based staging system for metastatic germ cell cancers. International Germ Cell Cancer Collaborative Group. *J Clin Oncol* 1997;15:594-603.

28. Chung PW, Gospodarowicz MK, Panzarella T*, et al.* Stage II testicular seminoma: patterns of recurrence and outcome of treatment. *Eur Urol* 2004;45:754-759; discussion 759-760.

29. Logothetis CJ, Samuels ML, Ogden SL*, et al.* Cyclophosphamide and sequential cisplatin for advanced seminoma: long-term followup in 52 patients. *J Urol* 1987;138:789-794.

30. Pizzocaro G, Salvioni R, Piva L*, et al.* Cisplatin combination chemotherapy in advanced seminoma. *Cancer* 1986;58:1625-1629.

31. Schmoll HJ, Harstrick A, Bokemeyer C*, et al.* Single-agent carboplatinum for advanced seminoma. A phase II study. *Cancer* 1993;72:237-243.

32. Howard GC, Conkey DS, Peoples S*, et al.* The management and outcome of patients with germ-cell tumours treated in the Edinburgh Cancer Centre between 1988 and 2002. *Clin Oncol (R Coll Radiol)* 2005;17:435-440.
33. Germa-Lluch JR, Garcia del Muro X, Maroto P*, et al.* Clinical pattern and therapeutic results achieved in 1490 patients with germ-cell tumours of the testis: the experience of the Spanish Germ-Cell Cancer Group (GG). *Eur Urol* 2002;42:553-562; discussion 562-553.

34. Motzer RJ, Geller NL, Tan CC*, et al.* Salvage chemotherapy for patients with germ cell tumors. The Memorial Sloan-Kettering Cancer Center experience (1979-1989). *Cancer* 1991;67:1305-1310.

35. Ehrlich Y, Brames MJ, Beck SD*, et al.* Long-term follow-up of Cisplatin combination chemotherapy in patients with disseminated nonseminomatous germ cell tumors: is a postchemotherapy retroperitoneal lymph node dissection needed after complete remission? *J Clin Oncol* 2010;28:531-536.

THYROID CANCER

The original optimal radiotherapy utilisation study was limited to the use of external beam radiotherapy in thyroid cancer and the use of radioactive iodine was not included; the same approach has been adopted in this review.

In the original radiotherapy utilisation model, the indications for radiotherapy for thyroid cancer were derived from evidence-based treatment guidelines issued by major national and international organisations. The guidelines reviewed are those published after the previous radiotherapy utilisation study was completed (July 2003).

Updated Guidelines

The following new or updated guidelines were identified since the original RTU study:

- Revised American Thyroid Association (ATA) Guidelines for patients with Differentiated Thyroid Cancer (2009) (1)
- British Thyroid Association (BTA), Royal College of Physicians Guidelines (2007) (2)
- European Thyroid Association guidelines (2006) (3)
- European Society of Medical Oncology (ESMO) guidelines (2010) (4)
- National Comprehensive Cancer Network (NCCN) guidelines (2011) (5)
- National Cancer Institute PDQ Thyroid Cancer Treatment (2012) (6)
- Medullary Thyroid Cancer: Management Guidelines of the American Thyroid Association (7)

Indications for radiotherapy and changes to the optimal utilisation model

The indications for external beam radiotherapy in the original CCORE model of optimal radiotherapy utilisation for thyroid cancer have been reviewed and updated in the optimal utilisation tree based on the latest guideline recommendations (see Figure 1 and Table 1). Some changes have been made to the optimal radiotherapy utilisation model for thyroid cancer as described below.

Differentiated thyroid cancer: In the revised model of optimal radiotherapy utilisation, EBRT is recommended for unresectable disease, for gross residual disease following surgery when radioactive iodine (RAI) would likely be ineffective, for neck recurrences not amenable to treatment with RAI or surgery and for bone and brain metastases. The original model of optimal radiotherapy utilisation recommended EBRT for bone and brain metastases and for 'persistent' neck recurrences; however the data used in the original tree for 'persistent' neck recurrences in fact referred to all neck recurrences. Neck recurrences from differentiated thyroid cancer are initially amenable to treatment with radioactive iodine or surgery (8) and EBRT would be indicated only as a final option after repeated treatment with radioactive iodine or surgery.

Medullary thyroid cancer: In medullary thyroid cancer, the original model of optimal radiotherapy utilisation recommended EBRT for patients with locally advanced disease, bone and brain metastases. However, the ATA and BTA guidelines recommend that locally advanced disease should be managed surgically with total thyroidectomy and neck dissection (central +/- lateral dissection depending on extent of lymph node involvement). In the revised utilisation model, EBRT is recommended for patients who undergo a gross incomplete resection and for brain and bone metastases, but not for locally advanced disease. It is possible that patients with locally advanced disease may later develop bone or brain metastases and this is not accounted for in the tree; this group would constitute a very small proportion of all patients with thyroid cancer and is therefore unlikely to have much effect on the optimal radiotherapy utilisation rate.

Levels of evidence

The levels of evidence supporting the indications for radiotherapy in thyroid cancer are unchanged, with the evidence still derived from retrospective studies. There is no high-level evidence for a benefit from treatment of differentiated thyroid carcinoma with adjuvant EBRT since no prospective randomised trials have been completed (a European trial closed due to failure to accrue patients) (9;10). The only indications for radiotherapy in thyroid cancer that are supported by level I-II evidence are treatment of bone and brain metastases (accounting for 6 out of 14 outcome branches in the model that have an indication of radiotherapy). The updated model predicts that 4% of the entire thyroid cancer population have an indication for radiotherapy and that 25% of these (ie 1% of the total) have an indication based on level I-II evidence of benefit.

Changes to Epidemiological Data

The epidemiological data for the revised thyroid cancer tree were identified through extensive electronic searches using the key words ‘thyroid cancer’, ‘external beam radiotherapy’, ‘epidemiology thyroid cancer’, ‘incidence’, ‘patterns of care’, ‘patterns of treatment’, ‘extent of disease’, ‘neck recurrence’, ‘follow up’, ‘outcomes’, ‘unresectable’ in various combinations. This has been applied particularly to the early branches in the tree for which national or state level data on cancer incidence rates and stages are available. The epidemiological data together with their sources and hierarchical level are documented in Table 2.

Incidence of Thyroid Cancer:

Since the publication of the previous radiotherapy utilisation project, the Australian national cancer incidence data published by the Australian Institute of Health and Welfare (AIHW) have been updated, with the most recent data available being 2007 data. The latest ACIM (Australian Cancer Incidence and Mortality) book published by AIHW in 2010 reports that in 2007, thyroid cancer accounted for 1.6% of all cancer in Australia (11). In the original radiotherapy utilisation study, thyroid cancer accounted for only 1% of all cancer in Australia (based on AIHW data for the year 1998). This increased incidence of thyroid cancer in Australia corresponds to the increased incidence reported internationally (12;13).

Thyroid cancer incidence patterns in the United States by histologic type have been reported for the years 1992-2006 using SEER data (14). These data have been used in the optimal utilisation tree since they are of higher quality and more recent than the previous data used. Papillary cancer is the predominant histological type of differentiated thyroid cancer in developed countries (follicular cancer is common in developing and iodine-deficient countries) (15). The ratio of papillary to follicular cancer in Australia is likely to be similar to the United States.

Data were extracted from the SEER database for the years 2002-2007 to determine the proportion of all papillary and follicular carcinomas that were unresectable (16). The most recent data available were used, since surgical techniques are assumed to have advanced with time. We found that 99 out of a total of 40,118 cases of papillary carcinoma either had EBRT and no surgery, or had pre-operative EBRT. This indicates that 0.25% of papillary carcinomas diagnosed in the above period were unresectable. For follicular carcinoma, 30 out of a total of 2936 cases had either EBRT and no surgery, or had pre-operative EBRT, indicating that 1.0% of all cases were unresectable. These data have been used in the optimal utilisation tree.

Hay reported that in 107 out of 2444 cases (4%) of papillary carcinoma who underwent definitive primary surgical therapy at the Mayo clinic, the surgeon reported that the tumour excision was incomplete with the persistence of gross residual disease at the conclusion of the initial neck operation (17). Andersen et al reported that 8 out of a total of 163 patients (5%) with follicular cancer treated by the head and neck service of Memorial Sloan-Kettering Cancer Center were found to have had extrathyroidal extension during surgery (18). Extrathyroidal extension was defined as extension of the primary tumour outside the capsule of the thyroid gland with invasion into surrounding structures such as the trachea, larynx, strap muscles and recurrent laryngeal nerve (all patients were treated surgically).

Verburg et al reported on a retrospective review of 51 patients with papillary carcinoma and lymph node metastases who were treated with I^{131} ablation (19). After a median follow-up of 84 months, 34 patients received additional treatment (I^{131} or surgery or both) and of these 34 patients, 3 patients also required EBRT for lymph node metastases that did not take up I^{131}. Creach et al reported that of 95 patients with differentiated thyroid cancer and persistent lymph node disease treated with I^{131}, 9% developed recurrent disease within cervical lymph nodes during follow-up of whom 6 were treated with surgery and 3 were treated with additional I^{131} therapy (no patients were reported to receive EBRT) (20). Based on these two studies, in the optimal utilisation model we have assumed that 3% of patients with neck recurrences would require treatment with EBRT (average rate of Verburg and Creach).

Sciuto et al reported on the natural history and clinical outcome of 1503 patients with differentiated thyroid carcinoma treated by total thyroidectomy and radioactive iodine (21). The patient stage distribution was 82% in stages I or II, 16% in stage III and 2% in stage IV. A complete response to

I^{131} therapy was achieved in 1281 patients (85%) while a further 165 patients (11%) had a partial response to I^{131}. The response rate to I^{131} of 85% has been used in the optimal utilisation tree to represent the proportion of patients with differentiated thyroid carcinoma and gross residual disease after surgery that would respond to RAI (not all of the patients in the series of Sciuto et al had gross residual disease, however it has been assumed that this would not affect the response rate to RAI and no better data could be sourced).

Panigrahi et al reported on American practice patterns with regard to 2033 patients with medullary thyroid carcinoma identified from the SEER database (22). Of the 1514 patients with surgical information available, 209 (14%) had a gross incomplete resection.

Abraham et al reported on the long-term outcomes of surgical treatment of 94 cases of medullary cancer in Sydney (23). All patients had total thyroidectomy with bilateral central neck dissection +/- lateral neck dissection (there was no mention of any cases of incomplete resection). The patients were followed up for a mean of 6.2 years, over which 22% developed local recurrence and 16% developed distant recurrence.

Estimation of the Optimal Radiotherapy Utilisation Rate

Based on the most recent evidence on the efficacy of radiotherapy and on epidemiological data on the occurrence of indications for radiotherapy, the proportion of all thyroid cancer patients in whom radiotherapy would be recommended is 4% (Table 1 and Figure 1). The original optimal radiotherapy utilisation rate derived in 2003 for thyroid cancer was 10%. The reduction in the optimal utilisation rate can be partly attributed to the change in the histological distribution of thyroid cancer (with an increased proportion of papillary cancer) and partly to changes that have been made to the optimal utilisation model. Changes to the optimal utilisation model have resulted in the proportion of patients with papillary cancer in whom EBRT is recommended falling from 4% in the original model to 2% in the revised model (the reduction is mainly due to EBRT being recommended only for 3% of neck recurrences instead of for all neck recurrences). In follicular cancer, the optimal utilisation rate has fallen from 6.5% in the original model to 6% in the revised model. The proportion of patients with medullary cancer in whom EBRT is optimally recommended is reduced from 79% in the original model to 21% in the revised model, due to the removal of recommendation of EBRT for locally advanced disease in the revised model. A SEER review of patients with medullary cancer diagnosed between 1973 and 2006 reported that post-operative EBRT was administered to 33% of patients who had incomplete resection and 6% of patients with complete resection (22).

Sensitivity Analysis

Univariate sensitivity analysis was undertaken (Figure 2) to assess any changes in the optimal radiotherapy utilisation rate that would result from different estimates of the proportions of patients with particular attributes as mentioned in Table 2. The variability in the estimate of optimal radiotherapy utilisation due to these uncertainties was 1% and the expected value ranged from 4% to 5% as shown in the Tornado diagram (Figure 2).

Concurrent Chemoradiotherapy in Thyroid Cancer

The indications for radiotherapy in thyroid cancer were reviewed to identify any indications where radiotherapy is recommended in conjunction with concurrent chemotherapy as the first treatment. The guidelines currently do not recommend concurrent chemo-radiotherapy in thyroid cancer except as part of a clinical trial. The NCI PDQ guidelines mention concurrent chemoradiotherapy as a “treatment option under clinical evaluation” in anaplastic thyroid cancer, stating that “the combination of chemotherapy plus radiation therapy in patients following complete resection may provide prolonged survival but has not been compared to any one modality alone.” The NCCN guidelines also mention concurrent chemoradiotherapy as a treatment option to “consider” in anaplastic thyroid cancer. Since none of the guidelines specifically recommend concurrent chemoradiotherapy, it has not been implemented into the optimal utilisation tree.

Figure 1. Revised Optimal Radiotherapy Utilisation Tree for Thyroid Cancer

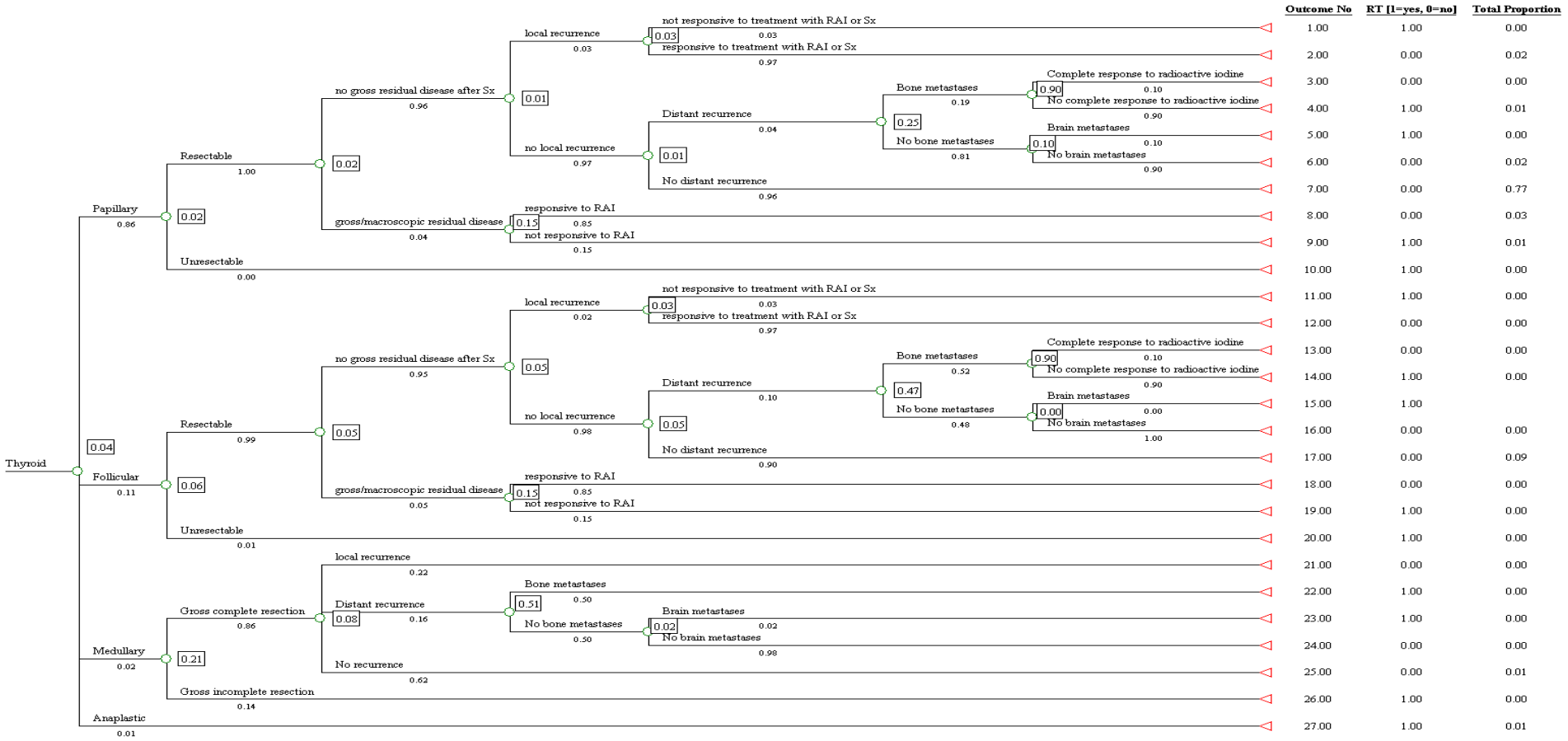


Figure 2. Tornado diagram for univariate sensitivity analyses

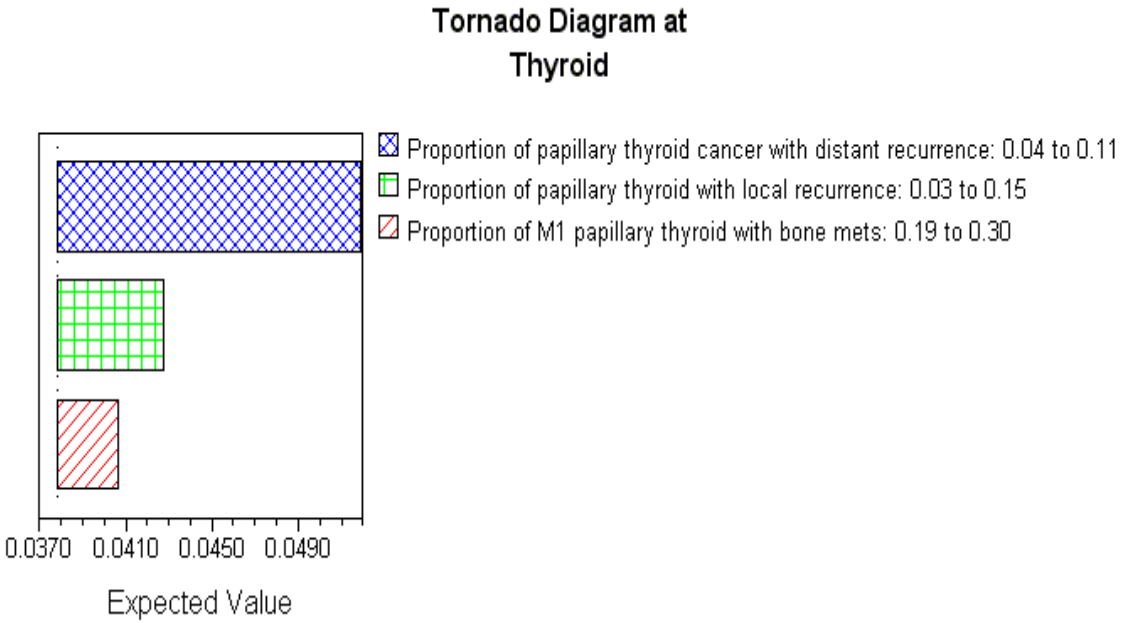


Table 1: Thyroid Cancer. Indications for radiotherapy - Levels and sources of evidence

Updates 2011							
Outcome No. in Tree	Clinical Scenario	Change of Indication	Guideline updated	Current level of evidence	Change to proportion of all thyroid cancer with that indication		References
					Yes/ No	Updated value	
1	Papillary thyroid cancer, resectable, local recurrence not responsive to RAI or Sx	Yes	Yes	III	Yes	<0.01	ATA (1), BTA (2), ETA(3), ESMO (4), NCCN (5), PDQ (6)
4	Papillary thyroid cancer, resectable, no local recurrence, bone metastases not responsive to RAI	No	Yes	I	Yes	0.01	ATA (1), BTA (2), ETA(3), ESMO (4), NCCN (5), PDQ (6)
5	Papillary thyroid cancer, resectable, no local recurrence, brain metastases	No	Yes	II	Yes	<0.01	ATA (1), BTA (2), ETA(3), ESMO (4), NCCN (5), PDQ (6)

Updates 2011							
Outcome No. in Tree	Clinical Scenario	Change of Indication	Guideline updated	Current level of evidence	Change to proportion of all thyroid cancer with that indication		References
					Yes/ No	Updated value	
9	Papillary thyroid cancer, resectable, gross residual disease not responsive to RAI	Yes	Yes	III	Yes	0.01	ATA (1), BTA (2), ETA(3), ESMO (4), NCCN (5), PDQ (6)
10	Papillary thyroid cancer, unresectable	Yes	Yes	III	Yes	<0.01	ATA (1), BTA (2), ETA(3), ESMO (4), NCCN (5), PDQ (6)
11	Follicular thyroid cancer, resectable, local recurrence not responsive to RAI or Sx	Yes	Yes	III	Yes	<0.01	ATA (1), BTA (2), ETA(3), ESMO (4), NCCN (5), PDQ (6)
14	Follicular thyroid cancer, resectable, no local recurrence, bone metastases not responsive to RAI	No	Yes	I	Yes	<0.01	ATA (1), BTA (2), ETA(3), ESMO (4), NCCN (5), PDQ (6)

Updates 2011							
Outcome No. in Tree	Clinical Scenario	Change of Indication	Guideline updated	Current level of evidence	Change to proportion of all thyroid cancer with that indication		References
					Yes/ No	Updated value	
15	Follicular thyroid cancer, resectable, no local recurrence, brain metastases	No	Yes	II	Yes	<0.01	ATA (1), BTA (2), ETA(3), ESMO (4), NCCN (5), PDQ (6)
19	Follicular thyroid cancer, resectable, gross residual disease not responsive to RAI	Yes	Yes	III	Yes	<0.01	ATA (1), BTA (2), ETA(3), ESMO (4), NCCN (5), PDQ (6)
20	Follicular thyroid cancer, unresectable	Yes	Yes	III	Yes	<0.01	ATA (1), BTA (2), ETA(3), ESMO (4), NCCN (5), PDQ (6)
22	Medullary thyroid cancer, complete resection, bone metastases	No	Yes	I	Yes	<0.01	ATA (7), ETA (3), ESMO (4), NCCN (5), PDQ (6)
23	Medullary thyroid cancer, complete resection, brain metastases	No	Yes	II	Yes	<0.01	ATA (7), ETA (3), ESMO (4), NCCN (5), PDQ (6)

Updates 2011							
Outcome No. in Tree	**Clinical Scenario**	**Change of Indication**	**Guideline updated**	**Current level of evidence**	**Change to proportion of all thyroid cancer with that indication**		**References**
					Yes/ No	**Updated value**	
26	Medullary thyroid cancer, gross incomplete resection	Yes	Yes	III	Yes	<0.01	ATA (7), ETA (3), ESMO (4), NCCN (5), PDQ (6)
27	Anaplastic thyroid cancer	No	Yes	III	Yes	0.01	ETA (3), ESMO (4), NCCN (5), PDQ (6)
Updated proportion of all patients with thyroid cancer in whom radiotherapy is recommended						**0.04 (4%)**	
Original proportion of all patients with thyroid cancer in whom radiotherapy is recommended (2002 study)						0.10 (10%)	

Abbreviations: RAI – radioactive iodine, Sx – surgery, ATA – American Thyroid Association, BTA – British Thyroid Association, ETA – European Thyroid Association, ESMO – European Society of Medical Oncology, NCCN – National Comprehensive Cancer Network, PDQ – National Cancer Institute Physician Data Query
Levels of Evidence for Indications for Radiotherapy: Level I – evidence obtained from a systematic review of all relevant randomised controlled trials; Level II – evidence obtained from at least one properly-designed randomised controlled trial; Level III – evidence obtained from well-designed controlled trials without randomisation -these include trials with 'pseudo-randomisation' where a flawed randomisation method was used (eg. alternate allocation of treatments) or comparative studies with either comparative or historical controls; Level IV – evidence obtained from case series . Taken from the National Health and Medical Research Council (NHMRC) hierarchy of levels of evidence (24)

Table 2: Thyroid Cancer. The incidence of attributes used to define indications for radiotherapy

Population or subpopulation of interest	Attribute	Proportion of populations with this attribute	Quality of information	References
All registry Cancers	Thyroid Cancer	0.016 (1.6%)	α	AIHW 2007(11)
Thyroid Cancer	Papillary histology	0.86	γ	SEER (14)
Thyroid Cancer	Follicular histology	0.11	γ	SEER (14)
Thyroid Cancer	Medullary histology	0.02	γ	SEER (14)
Papillary cancer	Un-resectable	0.0025	γ	SEER (16)
Papillary cancer, (resectable), surgery	gross residual disease following surgery	0.04	ζ	Hay et al (17)
Papillary cancer, (resectable), surgery	Local recurrence	0.03 (0.03- 0.15)	ζ	Data and sources unchanged from original model
Papillary cancer, surgery, local recurrence	Not responsive to treatment with RAI or Sx	0.03	λ	Verburg et al (19) Creach et al (20)
Papillary cancer, surgery, no local recurrence	Distant recurrence	0.04 (0.03- 0.11)	ζ	Data and sources unchanged from original model

Population or subpopulation of interest	Attribute	Proportion of populations with this attribute	Quality of information	References
Papillary cancer, surgery, distant recurrence	Bone metastases	0.19 (0.19-0.30)	ζ	Data and sources unchanged from original model
Papillary cancer, surgery, distant recurrence, bone metastases	Complete response to RAI	0.10	ζ	Data and sources unchanged from original model
Papillary cancer, surgery, distant recurrence, no bone metastases	Brain metastases	0.10	ζ	Data and sources unchanged from original model
Papillary cancer, resectable, gross residual disease following surgery	Responsive to RAI	0.85	ζ	Sciuto et al (21)
Follicular Cancer	Un-resectable	0.01	γ	SEER (16)
Follicular cancer, (resectable), surgery	gross residual disease following surgery	0.05	ζ	Andersen et al (18)
Follicular cancer, (resectable), surgery	Local recurrence	0.02	ζ	Data and sources unchanged from original model
Follicular cancer, surgery, local recurrence	Not responsive to treatment with RAI or Sx	0.03	λ	Verburg et al (19) Creach et al (20)
Follicular cancer, surgery, no local recurrence	Distant recurrence	0.10	ζ	Data and sources unchanged from original model
Follicular cancer, surgery, distant recurrence	Bone metastases	0.52	ζ	Data and sources unchanged from original model

Population or subpopulation of interest	Attribute	Proportion of populations with this attribute	Quality of information	References
Follicular cancer, surgery, distant recurrence, bone metastases	Complete response to RAI	0.10	ζ	Data and sources unchanged from original model
Follicular cancer, resectable, gross residual disease following surgery	Responsive to RAI	0.85	ζ	Sciuto et al (21)
Medullary cancer	Gross incomplete resection	0.14	γ	Panigrahi et al (SEER) (22)
Medullary cancer, complete resection	Local recurrence	0.22	λ	Abraham et al (23)
Medullary cancer, complete resection	Distant recurrence	0.16	λ	Abraham et al (23)
Medullary cancer, distant recurrence	Bone metastases	0.50	ζ	Data and sources unchanged from original model
Medullary cancer, distant recurrence, no bone metastases	Brain metastases	0.02	ζ	Data and sources unchanged from original model

References

1. Cooper DS, Doherty GM, Haugen BR, Kloos RT, et al. Revised American Thyroid Association Management Guidelines for patients with thyroid nodules and differentiated thyroid cancer. The American Thyroid Association (ATA) Guidelines Taskforce. *Thyroid* 2009;19:1167-214.

2. British Thyroid Association and Royal College of Physicians. Guidelines for the management of thyroid cancer. 2nd edition. Report of the Thyroid Cancer Guidelines Update Group. http://www.british-thyroid-association.org/news/Docs/Thyroid_cancer_guidelines_2007.pdf . 2007. Royal College of Physicians, London. 1-11-2011.
   Ref Type: Electronic Citation

3. Pacini F, Schlumberger M, Dralle H, et al. European consensus for the management of patients with differentiated thyroid carcinoma of the follicular epithelium. *Eur J Endocrinol* 2006;154:787-803.

4. Pacini F, Castagna MG, Brilli L, et al. Thyroid cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann.Oncol* 2010;21:v214-v219.

5. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology - Thyroid Carcinoma. v.3.2011. http://www.nccn.org/professionals/physician_gls/PDF/thyroid.pdf . 2011. 7-10-0011.
   Ref Type: Electronic Citation

6. National Cancer Institute. PDQ Cancer Information Summaries: Treatment of Thyroid Cancer. http://www.cancer.gov/cancertopics/pdq/treatment/thyroid/HealthProfessional . 6-1-2012. 16-1-2012.
   Ref Type: Electronic Citation

7. The American Thyroid Association Guidelines Task Force. Medullary Thyroid Cancer: Management Guidelines of the American Thyroid Association. *Thyroid* 2009;19:565-612.

8. Coburn M, Teates D, Wanebo HJ. Recurrent thyroid cancer. Role of surgery versus Radioactive Iodine (I131). *Ann Surg* 1994;219:587-95.

9. Biermann M, Pixberg MK, Schuck A, et al. Multicenter study differentiated thyroid carcinoma (MSDS). Diminished acceptance of adjuvant external beam radiotherapy. *Nuklearmedizin* 2003;42:244-50.

10. Biermann M, Pixberg MK, Riemann B, et al. Clinical outcomes of adjuvant external beam radiotherapy for differentiated thyroid cancer - results after 874 patient-years of follow-up in the MSDS trial. *Nuklearmedizin* 2009;48:89-98.

11. Australian Institute of Health and Welfare (AIHW). Australian Cancer Incidence and Mortality (ACIM) Books. http://www.aihw.gov.au/acim-books/ . 2010. 10-8-2011.
    Ref Type: Electronic Citation

12. Kilfoy BA, Zheng T HT, et al. International patterns and trends in thyroid cancer incidence, 1973-2002. *Cancer Causes and Control* 2009;20:525-31.

13. Davies L, Welch HG. Increasing incidence of thyroid cancer in the United States, 1973-2002. *JAMA* 2006;295:2164-7.

14. Aschebrook-Kilfoy B, Ward MH, Sabra MM, Devesa SS. Thyroid cancer incidence patterns in the United States by histologic type, 1992-2006. *Thyroid* 2011;21:125-34.

15. Woodruff SL, Arowolo OA, Akute OO, et al. Global variation in the pattern of differentiated thyroid cancer. *Am J Surg* 2010;200:462-6.

16. National Cancer Institute and Surveillance, Epidemilogy and End Results SEER Program. Surveillance, Epidemiology and End Results (SEER) Program SEER*Stat Database: Incidence - SEER 17 Regs Research Data, Nov 2009 Sub (1973-2007 varying) - Linked to county attributes-Total US., 1969-2007 Counties. 2010.
Ref Type: Data File

17. Hay ID, Thompson GB, Grant CS, Bergstralh EJ, et al. Papillary thyroid carcinoma managed at the Mayo Clinic during six decades (1940-1999): temporal trends in initial therapy and long-term outcome in 2444 consecutively treated patients. *World J Surg* 2002;26:879-85.

18. Andersen PE, Kinsella J, Loree TR, et al. Differentiated carcinoma of the thyroid with extrathyroidal extension. *Am J Surg* 1995;170:467-70.

19. Verburg FA, de Keizer B, Lam MGEH, et al. Persistent disease in patients with papillary thyroid carcinoma and lymph node metastases after surgery and Iodine-131 ablation. *World J Surg* 2007;31:2309-14.

20. Creach KM, Gillanders WE, Siegel BA, et al. Management of cervical nodal metastasis detected on I-131 scintigraphy after initial surgery of well-differentiated thyroid carcinoma. *Surgery* 2012;148:1198-204.

21. Sciuto R, Romano L, Rea S, et al. Natural history and clinical outcome of differentiated thyroid carcinoma: a retrospective analysis of 1503 patients treated at a single institution. *Ann Oncol* 2009;20:1728-35.

22. Panigrahi B, Roman SA, Sosa JA. Medullary thyroid cancer: are practice patterns in the United States discordant from American Thyroid Association guidelines? *Ann Surg Oncol* 2010;17:1490-8.

23. Abraham DT, Low T, Messina M, Jackson N, et al. Medullary thyroid carcinoma: long-term outcomes of surgical treatment. *Ann Surg Oncol* 2011;18:219-25.

24. National Health and Medical Research Council. Guide to the development, implementation and evaluation of clinical practice guidelines. Appendix B, 56. 1998.
Ref Type: Report

UNKNOWN PRIMARY CANCER

Evidence-based treatment guidelines for unknown primary cancer management issued by major international, national and provincial organisations reviewed for the model are those published after the previous radiotherapy utilisation study was completed (July 2003) up to the most recent ones published in 2012.

Updated Guidelines

The following new or updated guidelines were identified and reviewed since the original RTU study:

- NCCN clinical practice guidelines on occult primary cancer, version 1, 2013 (1)
- NCI carcinoma of unknown primary treatment PDQ, 2012 (2)
- BC Cancer Agency primary unknown cancer management guidelines, 2005 (3)
- NICE guidelines on diagnosis and management of metastatic malignant disease of unknown primary origin, 2010 (4)

Indications for radiotherapy

As in the original CCORE model, “unknown primary cancer” refers to patients presenting with metastatic cancer (most commonly adenocarcinoma of unknown primary, and also including carcinoma not otherwise specified, poorly differentiated carcinoma, melanoma or neuroendocrine carcinoma) in whom the primary tumour site is not detected. Metastatic cervical squamous cell carcinomas from a probable skin or head and neck primary are not discussed here, since they have been included in the head and neck section.

All the indications for external beam radiotherapy in the original model have been reviewed and updated in the optimal utilisation tree based on the latest guideline recommendations (Table 1). The previous indications remain supported by current guidelines and there are no new indications recommended.

Level of evidence

According to the methods applied for the previous radiotherapy utilisation model the indications for radiotherapy for unknown primary cancer have been derived from evidence-based treatment guidelines issued by major international, national and provincial organisations. Based on guidelines review, all indications of radiotherapy for unknown primary cancer are supported by level I-III evidence, unchanged from the previous model. Three outcomes in the model have radiotherapy indications and 2 of these are supported by level I or II evidence comprising 33% of the unknown primary cancer population (Table 1 and Figure 1).

Epidemiology of cancer stages

The epidemiological data in the unknown primary cancer utilisation tree have been reviewed to see if more recent data are available through extensive electronic search using the key words 'Australia', 'epidemiology unknown primary cancer', 'epidemiology carcinoma of unknown primary', 'incidence', 'radiotherapy treatment', 'distant metastases', 'survival', 'treatment outcome' in various combinations. If there is a change in the hierarchical quality of the epidemiological data, this has also been noted (Table 2).

Since the completion of the previous radiotherapy utilisation project the national data on cancer statistics published by AIHW have been updated to more recent years till 2008 (5). The incidence of unknown primary cancer has decreased from 4% to 2% in Australia.

In the original CCORE model of optimal radiotherapy utilisation for unknown primary cancer (6), data from Hess et al (7) were used to determine the proportion of patients with brain, bone or lymph node metastases (6%, 29% and 42% respectively), as their study was the largest single institutional study identified (N=1000). An updated search identified studies with smaller sample sizes (N=79 to 100) which reported proportions of patients with these metastases (8-10) (Table 2). In view of the significantly larger sample size, data from Hess et al (7) were used in the updated model.

An alternative approach would be to use the weighted mean values of the 3 smaller studies in preference to the data of the much larger but older series. Culine et al (10) reported the number of patients with lymph node metastases by site, and it was unclear whether patients with multiple sites of lymph node involvement were counted more than once. Excluding the data on lymph node metastases from this series, the weighted mean values from these 3 studies were 6%, 25% and 44% for brain, bone and lymph node metastases respectively, which are very similar to the proportions reported by Hess et al (7). In the updated model, data from Hess et al (7) were used, with sensitivity analysis being undertaken to assess changes in the optimal utilisation rate that would result from the different proportions reported in the 3 smaller, more recent studies.

Estimation of the optimal radiotherapy utilisation

From the evidence on the efficacy of radiotherapy and the most recent epidemiological data on the occurrence of indications for radiotherapy, the proportion of unknown primary cancer patients in whom radiotherapy would be recommended is 61% (Table 1 and Figure 1), unchanged from the original estimate.

Estimation of the optimal combined radiotherapy and chemotherapy utilisation

The indications of radiotherapy for unknown primary cancer were reviewed to identify those indications where radiotherapy is recommended in conjunction with concurrent chemotherapy as the first treatment. According to the best available evidence there are no indications identified for which concurrent chemoradiation is beneficial over radiotherapy alone as the first indicated treatment.

Sensitivity analysis

Univariate sensitivity analysis has been undertaken to assess changes in the recommended unknown primary cancer radiotherapy utilisation rate that would result from different estimates of the proportions of patients with particular attributes as mentioned in Table 2. The variability in the estimate of optimal radiotherapy utilisation due to these uncertainties ranged from 55% to 68% as shown in the Tornado diagram (Figure 2).

Table 1: Unknown Primary Cancer. Indications for radiotherapy - Levels and sources of evidence

Original RTU study				Updates 2012					
Outcome No. in Tree	Clinical Scenario	Level of evidence	Proportion of all unknown primary cancer	Change of Indication	Guideline updated	Current level of evidence	Change to proportion of all unknown primary cancer		References
							Yes/ No	Updated value	
1	Unknown primary, brain metastases	II	0.06	No	Yes	II	No	0.06	NCCN (1), NICE (4)
2	Unknown primary, no brain metastases, bone metastases	I	0.27	No	Yes	I	No	0.27	NCCN (1)
3	Unknown primary, no brain metastases, no bone metastases, symptomatic node metastases.	III	0.28	No	Yes	III	No	0.28	NCCN (1)
Proportion of all unknown primary cancer patients in whom radiotherapy is recommended			0.61 (61%)	**Updated proportion of all unknown primary cancer patients in whom radiotherapy is recommended**				**0.61 (61%)**	

Table 2: Unknown Primary Cancer. The incidence of attributes used to define indications for radiotherapy

Original RTU study				Updates 2012				
Population or sub-population of interest	**Attribute**	**Proportion of population with the attribute**	**Quality of Information**	**Change in proportion of population with attribute Yes/ No**	**Altered Proportion**	**Updated Quality of Information**	**Updated Reference**	**Comments**
All registry cancers	Unknown primary cancer	0.04	α	Yes	0.02	α	AIHW 2012 (5)	
Unknown primary	Brain metastases	0.06 0.07 0.05 0.07	ζ ζ ζ ζ	No	0.06 0.09 0.03 0.05	ζ ζ ζ θ	Hess et al 1999 (7) Ponce Lorenzo et al 2007 (8) Yakushiji et al 2006 (9) Culine et al 2003 (10)	
Unknown primary, no brain metastases	Bone metastases	0.29 0.13 0.45 0.20	ζ ζ ζ ζ	No	0.29 0.24 0.17 0.33	ζ ζ ζ θ	Hess et al 1999 (7) Ponce Lorenzo et al 2007 (8) Yakushiji et al 2006 (9) Culine et al 2003 (10)	

Original RTU study				Updates 2012				
Population or sub-population of interest	**Attribute**	**Proportion of population with the attribute**	**Quality of Information**	**Change in proportion of population with attribute Yes/ No**	**Altered Proportion**	**Updated Quality of Information**	**Updated Reference**	**Comments**
Unknown primary , no brain metastases, no bone metastases	Symptomatic node metastases	0.42 0.35 0.45 0.32	ζ ζ ζ ζ	No	0.42 0.37 0.52	ζ ζ ζ	Hess et al 1999 (7) Ponce Lorenzo et al 2007 (8) Yakushiji et al 2006 (9)	

Figure 1. Unknown primary cancer radiotherapy utilisation tree

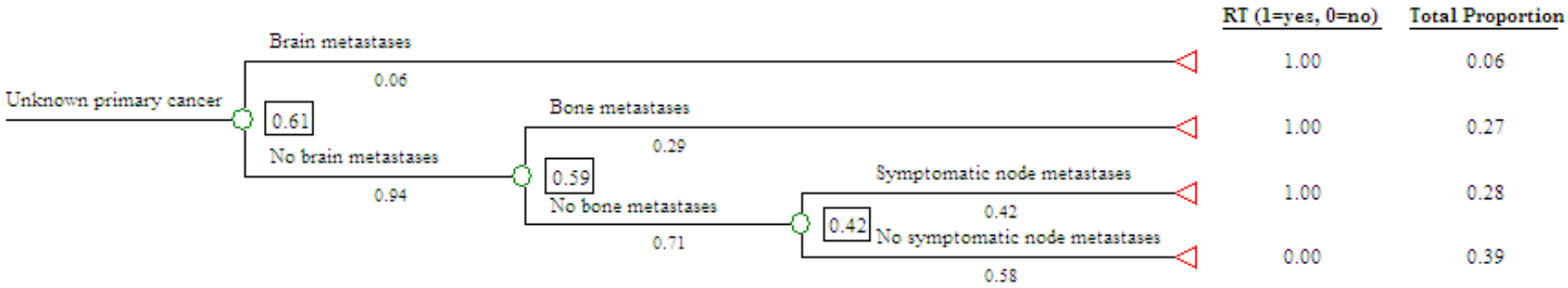
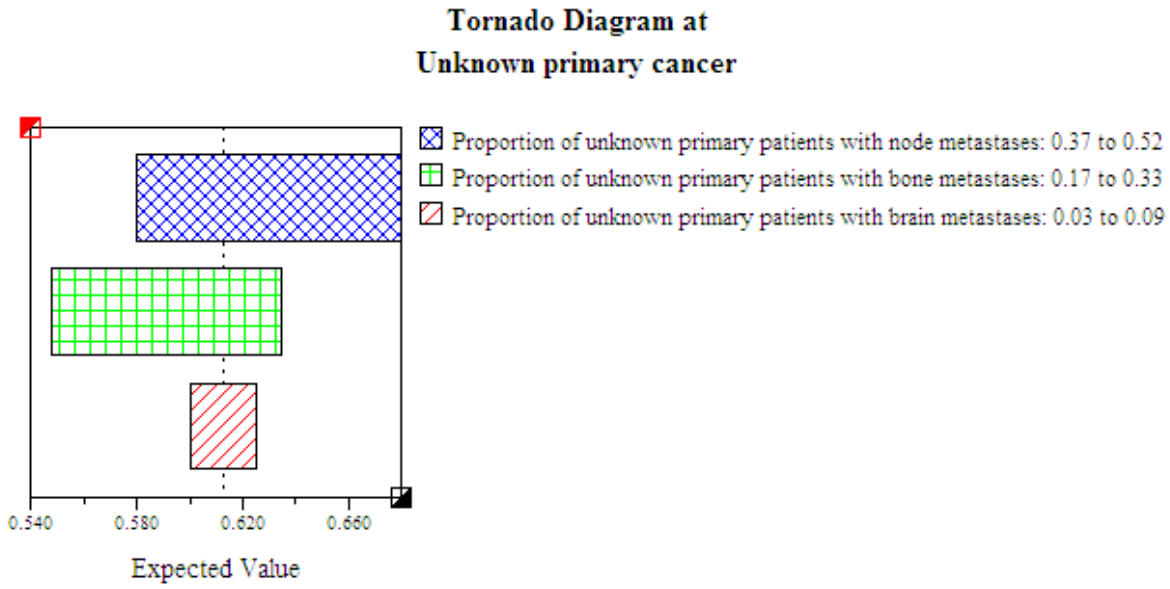


Figure 2. Tornado diagram for univariate sensitivity analyses



References

1. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Occult Primary (Cancer of Unknown Primary) Version 1.2013: www.nccn.org; 2012. Accessed 17/9/2012.

2. National Cancer Institute. PDQ Summary: Carcinoma of Unknown Primary Treatment: www.cancer.gov; 2012. Accessed 17/9/2012.

3. British Columbia Cancer Agency. Cancer Management Guidelines: Primary Unknown Cancer: www.bccancer.bc.ca; 2005. Accessed 17/9/2012.

4. National Institute for Clinical Excellence. Metastatic Malignant Disease of Unknown Primary Origin: Diagnosis and Management of Metastatic Malignant Disease of Unknown Primary Origin: www.nice.org.uk/guidance/CG104; 2010. Accessed 17/9/2012.

5. Australian Institute of Health and Welfare (AIHW). Australian Cancer Incidence and Mortality (ACIM) books. : www.aihw.gov.au/acim-books/; 2012. Accessed 17/09/2012.

6. Delaney G, Jacob S, Barton M. Estimating the optimal radiotherapy utilization for carcinoma of the central nervous system, thyroid carcinoma, and carcinoma of unknown primary origin from evidence-based clinical guidelines. *Cancer* 2006;106:453-465.

7. Hess KR, Abbruzzese MC, Lenzi R*, et al.* Classification and regression tree analysis of 1000 consecutive patients with unknown primary carcinoma. *Clin Cancer Res* 1999;5:3403-3410.

8. Ponce Lorenzo J, Segura Huerta A, Diaz Beveridge R*, et al.* Carcinoma of unknown primary site: development in a single institution of a prognostic model based on clinical and serum variables. *Clin Transl Oncol* 2007;9:452-458.

9. Yakushiji S, Ando M, Yonemori K*, et al.* Cancer of unknown primary site: review of consecutive cases at the National Cancer Center Hospital of Japan. *Int J Clin Oncol* 2006;11:421-425.

10. Culine S, Lortholary A, Voigt JJ*, et al.* Cisplatin in combination with either gemcitabine or irinotecan in carcinomas of unknown primary site: results of a randomized phase II study--trial for the French Study Group on Carcinomas of Unknown Primary (GEFCAPI 01). *J Clin Oncol* 2003;21:3479-3482.

UTERINE CORPUS MALIGNANCIES

In the original EBRT and BT utilisation models the indications for EBRT and BT for uterine corpus malignancies were derived from evidence-based treatment guidelines issued by major national and international organisations until December 2004. The current updated model includes guidelines published until February 2012.

Updated Guidelines

The following clinical practice guidelines for the management of uterine corpus malignancies have not been updated:

- (BCCA STS) British Columbia Cancer Agency: Cancer Management Guidelines >> Gynecology >> 6. Gynecological Sarcomas (1)
- (SGOG) The Sydney Gynaecologic Oncology Group, Royal Prince Alfred and Liverpool Hospitals: Clinical Practice and Management Policies (2)
- (ABS) ABS: American Brachytherapy Society Recommendations for High-Dose-Rate Brachytherapy for Carcinoma of the Endometrium (3)

The following new or updated clinical practice guidelines for the management of uterine corpus malignancies were identified:

- (FIGO) Federation Internationale de Gynecologie et d'Obstetrique: Staging classifications and clinical practice guidelines for gynaecologic cancers (4)
- (PDQ) CancerNet PDQ Cancer Information Summaries: Treatment of Endometrial Cancer (5)
- (PDQ) CancerNet PDQ Cancer Information Summaries: Treatment of Uterine Sarcomas (6)
- (NCCN) National Comprehensive Cancer Network: Clinical Practice Guidelines in Oncology - v1.2012 – Uterine Neoplasms (7)
- (INC/SFOG) Clinical Practice Guidelines for the Management of Patients With Endometrial Cancer in France (8)
- (JSGO) Evidence-based guidelines for treatment of uterine body neoplasm in Japan: Japan Society of Gynecologic Oncology (9)
- (NSW) NSW Gynaecological Oncology Group Best Practice Guideline, 2009 (10)
- (CCO) Cancer Care Ontario: Adjuvant Radiotherapy in Women with Stage I Endometrial Cancer: A Clinical Practice Guideline (11)
- (BCCA Ca) British Columbia Cancer Agency: Cancer Management Guidelines >> Gynecology >> 3. Endometrium (12)
- (YCN) Yorkshire Cancer Network Guidelines for the Management of Gynaecological Cancers (13)
- (ESMO) Endometrial Cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up (14)

The following previously used clinical practice guideline for the management of uterine corpus malignancies has been removed from the internet in order to be updated:

- START: State of the Art Oncology in Europe. Cancer of the Endometrium (15)

Indications for radiotherapy

All the indications for EBRT and for BT in the original CCORE models of optimal RT and BT utilisation for uterine corpus malignancies were reviewed based on the latest guideline recommendations (Figures 1 and 2 and Tables 1 and 2*).* A number of changes to the tree design have occurred as a result of changes in evidence and guideline recommendations.

Endometrioid cancer, Stage I. Previously, for endometrioid cancer, stage I, adjuvant RT was indicated if there were high risk pathological features, with BT being recommended if lymph nodes dissection (LND) had been performed and EBRT if not. In 2009, meta-analysis of ASTEC and NCIC EN.5 randomised trials of LND was published, as well as the Italian randomised trial in the previous year, showing no disease control benefit from the addition of LND (16) (17), and two randomised trials have been published showing that patients with intermediate risk pathological features, without LND, have clinically, albeit not statistically, similar rates of pelvic control with BT or EBRT (18) (19). Therefore, in accordance with the guidelines that have been updated since some or all of this evidence emerged, including the NSW guidelines (10), the LND branches have been removed and BT is the recommended adjuvant treatment for intermediate risk disease (7) (8) (9) (10) (12) (14) and EBRT (5) (7) (8) (9) (11) (13) (2) (14) or EBRT and BT (5) (7) (8) (9) (10) (11) (12) (13) for high risk disease (8) (10) (12). Not all guidelines were explicit in defining risk categories, but defining Low Risk Disease as Grade 1-2 and Stage IA; Intermediate Risk Disease as Grade 3 and Stage IA, or Grade 1-2 and Stage 1B, or Low Risk with lympho-vascular invasion; and High Risk Disease as Grade 3 and Stage IB fits most closely to the majority of the guideline definitions (5) (8) (9) (11) (12) (13) (14), as well as being similar to the definitions used in the trials (18) (19).

Endometrioid cancer, Stage II. Stage IIA disease has been removed from the latest FIGO staging system and is classified (and treated as) stage I disease.

Endometrioid cancer, Stage III. Stage IIIA, positive peritoneal cytology only, has been removed from the latest FIGO staging system and is classified (and treated as) stage I disease.

Papillary Serous/Clear Cell Carcinoma. In the previous utilization trees, EBRT (and BT if loco-regional disease) were recommended for all patients. Guideline recommendations are now more heterogenous. Priority is given to the national guidelines over the state/provincial ones: for loco-regional disease adjuvant RT is optional (NCCN), or adjuvant EBRT is recommended (INC/SFOG, JSGO), with addition of BT optional (INC/SFOG) (7) (8) (9) (10) (13) (2).

Uterine Tumours with Sarcomatous Elements. These tumours were not included in the previous RT utilization study. In the subsequent BT utilization study, EBRT (with or without BT), was incorporated into the utilization tree based on level III evidence and guideline recommendations. Subsequently, a Euorpean randomised trial of adjuvant EBRT for these tumours has been published, providing level II data in the favour of adjuvant EBRT for carcinosarcomas (improved pelvic control), but against this for true uterine sarcomas (20). BT was not included in the trial. Guidelines published since this trial recommend adjuvant EBRT alone (7) (8) (9) (10) (13) or with BT (7) (8) (9) (10) for carcinosarcomas, but not for true uterine sarcomas (9) (13).

Changes to Epidemiological Data

The epidemiological data in the uterine corpus malignancy utilization trees have been reviewed to identify whether more recent data are available through extensive electronic searches. These have been applied to the early branches in the trees for which national or state level data on cancer incidence rates, histologies, and stages are available. No changes to the hierarchical quality of the epidemiological data were identified, but there were changes in the magnitude of the indications based on up-dated SEER stage data (21) (Table 3).

Incidence of Uterine Corpus Malignancies:

Since the publication of the previous radiotherapy utilisation project, the Australian national cancer incidence data published by the Australian Institute of Health and Welfare (AIHW) has been updated, with the most recent data available being 2008 data. In 2008, uterine corpus malignancies accounted for 44.5% of gynaecological cancers, and 1.8% of all cancer in Australia (22). Table 3.

Histopathological and Stage proportions for Uterine Corpus Malignancies

The SEER database (21) provided the most recent population level data for stage distribution and histopathological subtype of uterine corpus malignancies, and these 2004-07 data were substituted for the previous 1973-1995 data used for the RTU tree and the 1997-2001 data used for the BTU tree (Table 3).

Estimation of the Optimal External Beam Radiotherapy Utilisation Rate

Based on the evidence of the efficacy of radiotherapy and the most recent epidemiological data on the occurrence of indications for EBRT, EBRT is recommended in 38% of all patients with uterine corpus malignancies in Australia (Table 1 and Figure 1). The previous optimal EBRT rate for uterine corpus malignancies derived in 2003 was 46%. The decrease in the revised optimal utilisation rate is predominantly due to identification of intermediate risk stage I endometrioid disease, requiring adjuvant BT only rather than EBRT, based on two randomised trials published since the previous report (18) (19) and incorporated into guidelines (7) (8) (9) (10) (12) (14). The contribution of stage I (including previous IIA) endometrioid disease (representing some 2/3 of all uterine malignancies) to the optimal RTU decreased from 22% to 9% absolute.

Estimation of the Optimal Brachytherapy Utilisation Rate

Based on the evidence of the efficacy of BT and the most recent epidemiological data on the occurrence of indications for BT, BT is recommended in 39% of all patients with uterine corpus malignancies in Australia (Table 2 and Figure 2). The previous optimal BT rate for uterine corpus malignancies derived in 2004 was 40%. The small decrease in the revised optimal utilisation rate is due to changes in the epidemiological data, and to changes in indications for BT. The new indication for BT for endometrioid cancer, stage I, intermediate risk, was balanced by reduced optimal utilisation for BT for other stages/histologies.

Estimation of the Optimal Concurrent Chemoradiotherapy Utilisation Rate

The indications for radiotherapy for uterine corpus malignancies were reviewed to identify the indications where radiotherapy is recommended in conjunction with concurrent chemotherapy (CRT) as the first treatment. None of the guidelines supported concurrent CRT for uterine malignancies, which is currently considered experimental, and being tested in the PORTEC 3 randomised trial. Since none of the guidelines specifically recommend concurrent CRT, it has not been implemented into the optimal utilisation tree.

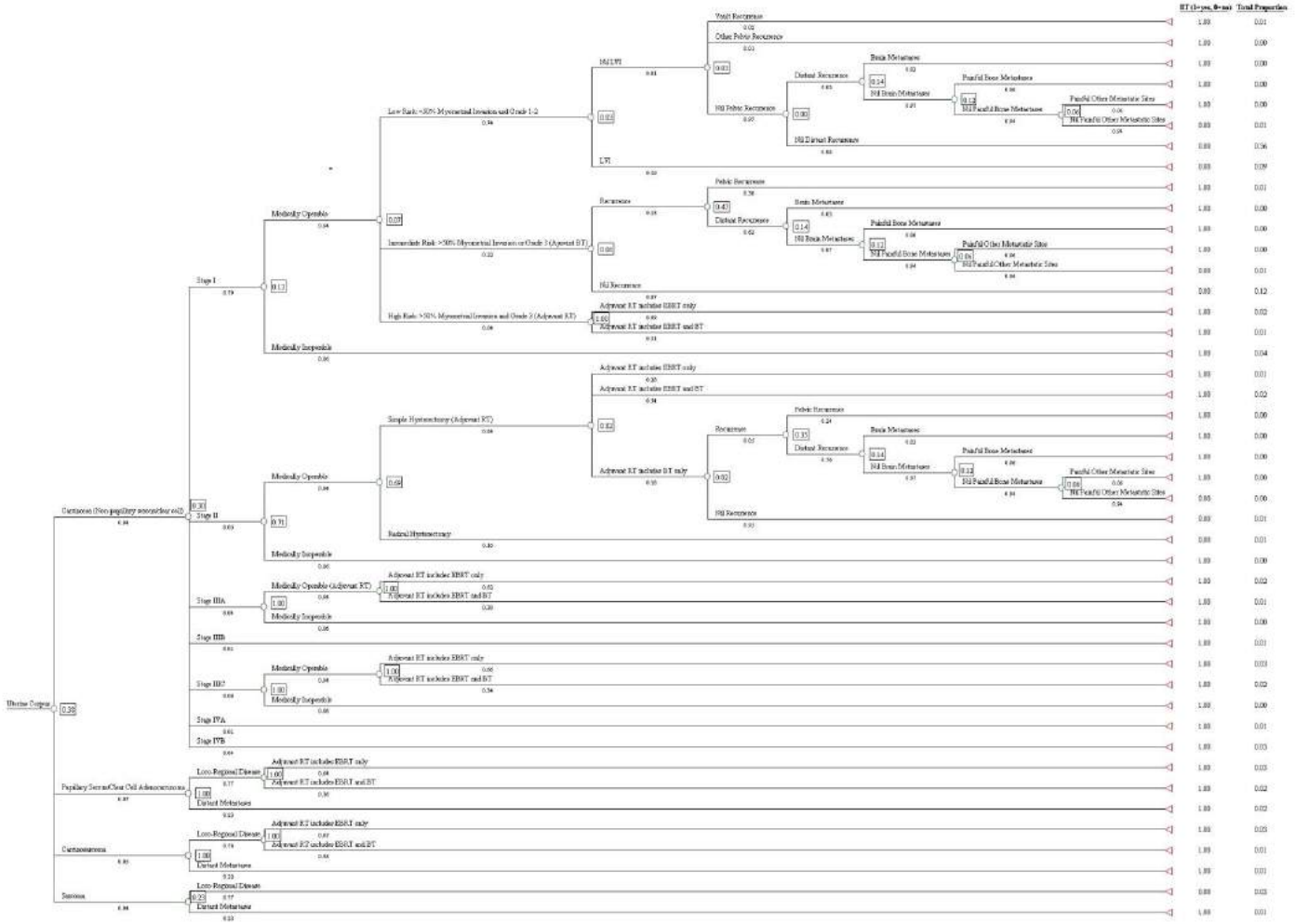
Level of evidence

The levels of evidence supporting the indications for EBRT and BT are essentially unchanged, the main difference being that BT is substituted for EBRT for endometrioid cancer, stage I, intermediate risk, based on level II evidence. Level I-II evidence supports the indications for 6.5% (absolute) of the total 38% EBRT optimal utilisation and 14% (absolute) of the total 39% BT optimal utilisation.

Sensitivity Analyses

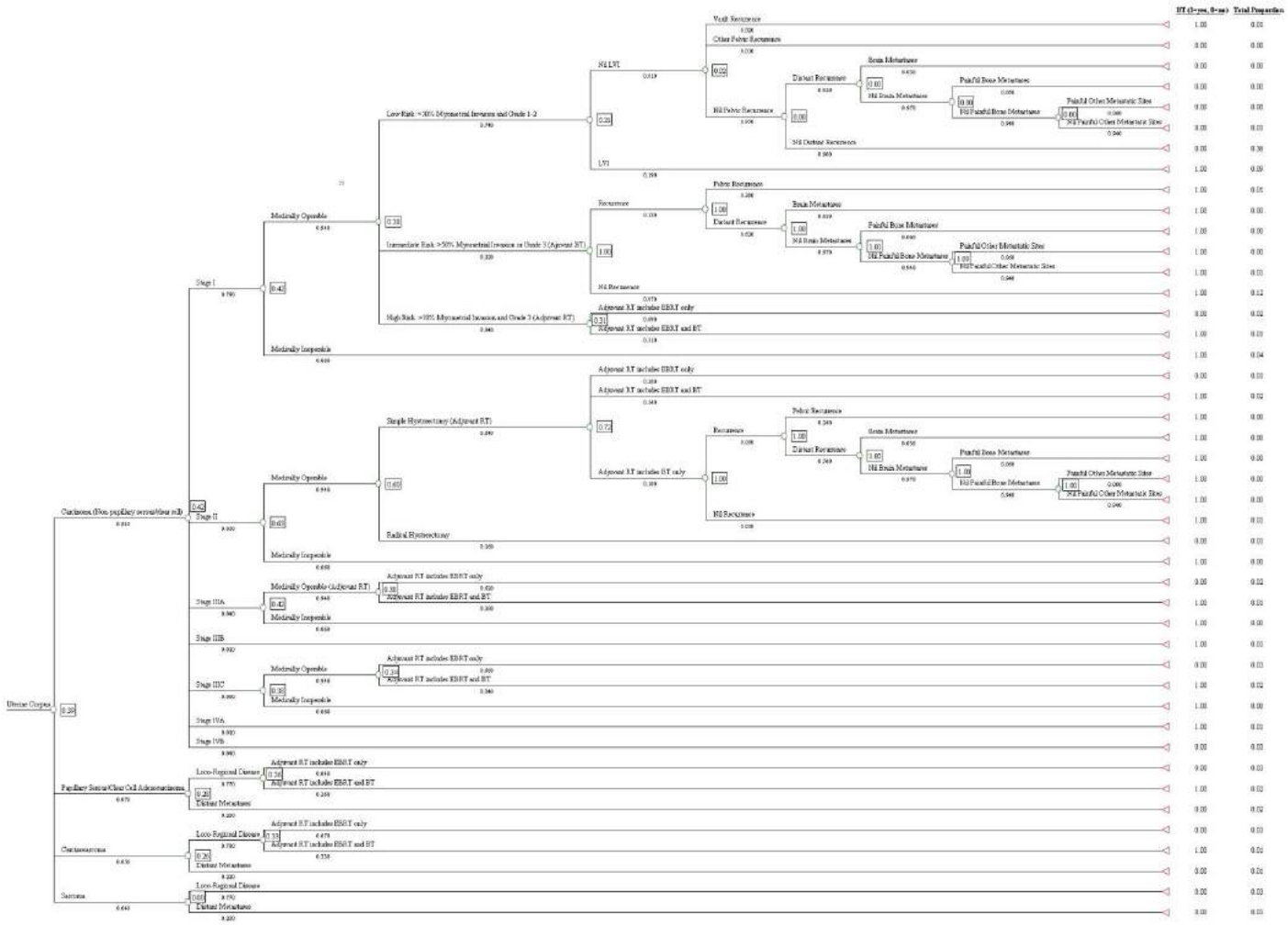
Univariate sensitivity analyses were undertaken (Figures 3) to assess any changes in the optimal utilisation rate that would result from different estimates of the proportions of patients with particular attributes as mentioned in Table 3. There were no variables with significant uncertainty in the EBRT utilisation tree. In the previous model, the proportion of patients who undergo lymph node dissection in Australia was uncertain – as discussed above in “notes”, this factor has now been removed from the tree. In the case of optimal BT utilisation, there are a number of circumstances in which adjuvant RT is clearly indicated, but whether or not BT should be added to EBRT may be controversial, with disagreement between the guidelines and lack of or conflicting evidence. Therefore, Patterns Of Care Studies, generally from SEER (23) (24), were used to provide an estimate of the likely proportion of patients in whom BT is indicated in addition to EBRT, and a range from 0% -100% was modelled. Optimal BT utilisation was 39%, and the range in the estimate due to these uncertainties was 37% - 42%, as shown in the Tornado Diagram (Figure 3).

Figure 1. Revised Optimal External Beam Radiotherapy Utilisation Tree for Uterine Corpus Malignancies



LVI, Lymphatic Vascular Space Invasion; RT, Radiotherapy; EBRT, External Beam Radiotherapy; BT, Brachytherapy

Figure 2. Revised Optimal Brachytherapy Utilisation Tree for Uterine Corpus Malignancies



LVI, Lymphatic Vascular Space Invasion; RT, Radiotherapy; EBRT, External Beam Radiotherapy; BT, Brachytherapy

Table 1: Uterine Corpus Malignancies. Indications for External Beam Radiotherapy - Levels and sources of evidence

Outcome Nos. in Updated Tree	Clinical Scenario	Original RTU study			Updates 2012					References
		Treatment Indicated	Level of Evidence for EBRT	Proportion of all Uterine Cancers	Treatment Indicated	Guideline updated	Current level of evidence for EBRT	Change to proportion of all Uterine Cancers		
								Yes/No	Updated value	
1	Carcinoma (non-PS/CC); Stage I; Medically operable; Low Risk Disease; Nil LVI; Vault recurrence without distant metastases	RT for Stage I (and IIA), Medically Operable: Adjuvant if Adverse Histology and no LND; or for Recurrence	IV	0.19	EBRT and BT	Yes	IV	n/a	0.01	FIGO (4), PDQ (5), NCCN (7), JSGO (9), NSW (10), YCN (13), SGOG (2), ESMO (14), ABS (3)
2	Carcinoma (non-PS/CC); Stage I; Medically operable; Low Risk Disease; Nil LVI; Other Pelvic Recurrence		IV		EBRT	Yes	IV	n/a	<0.01	FIGO (4), PDQ (5), NCCN (7), JSGO (9), NSW (10), YCN (13), SGOG (2), ESMO (14), ABS (3)

Outcome Nos. in Updated Tree	Clinical Scenario	Original RTU study			Updates 2012					References
		Treatment Indicated	Level of Evidence for EBRT	Proportion of all Uterine Cancers	Treatment Indicated	Guideline updated	Current level of evidence for EBRT	Change to proportion of all Uterine Cancers		
								Yes/No	Updated value	
3	Carcinoma (non-PS/CC); Stage I; Medically operable; Low Risk Disease; Nil LVI; Nil Pelvic Recurrence; Distant Recurrence; Brain Metastases		II*		EBRT	Yes	II	n/a	<0.01	FIGO (4), PDQ (5), NCCN (7), INC/SFOG (8), JSGO (9), NSW (10), SGOG (2), ESMO (14)
4	Carcinoma (non-PS/CC); Stage I; Medically operable; Low Risk Disease; Nil LVI; Nil Pelvic Recurrence; Distant Recurrence; Nil Brain Metastases; Painful Bone Metastases		I		EBRT	Yes	I	n/a	<0.01	FIGO (4), PDQ (5), NCCN (7), INC/SFOG (8), JSGO (9), NSW (10), SGOG (2), ESMO (14)

Outcome Nos. in Updated Tree	Clinical Scenario	Original RTU study			Updates 2012					References
		Treatment Indicated	Level of Evidence for EBRT	Proportion of all Uterine Cancers	Treatment Indicated	Guideline updated	Current level of evidence for EBRT	Change to proportion of all Uterine Cancers		
								Yes/No	Updated value	
5	Carcinoma (non-PS/CC); Stage I; Medically operable; Low Risk Disease; Nil LVI; Nil Pelvic Recurrence; Distant Recurrence; Nil Brain Metastases; Nil Painful Bone Metastases; Painful Other Metastatic Sites		III		EBRT	Yes	III	n/a	<0.01	FIGO (4), PDQ (5), NCCN (7), INC/SFOG (8), JSGO (9), NSW (10), SGOG (2), ESMO (14)
9	Carcinoma (non-PS/CC); Stage I; Medically operable; Intermediate Risk Disease (Adjuvant BT); Recurrence; Pelvic Recurrence		IV		(BT then) EBRT	Yes	IV	n/a	0.01	FIGO (4), PDQ (5), NCCN (7), JSGO (9), NSW (10), YCN (13), SGOG (2), ESMO (14), ABS (3)

Outcome Nos. in Updated Tree	Clinical Scenario	Original RTU study			Updates 2012					References
		Treatment Indicated	Level of Evidence for EBRT	Proportion of all Uterine Cancers	Treatment Indicated	Guideline updated	Current level of evidence for EBRT	Change to proportion of all Uterine Cancers		
								Yes/No	Updated value	
10	Carcinoma (non-PS/CC); Stage I; Medically operable; Intermediate Risk Disease (Adjuvant BT); Recurrence; Distant Recurrence; Brain Metastases		II*		(BT then) EBRT	Yes	II	n/a	<0.01	FIGO (4), PDQ (5), NCCN (7), INC/SFOG (8), JSGO (9), NSW (10), SGOG (2), ESMO (14)
11	Carcinoma (non-PS/CC); Stage I; Medically operable; Intermediate Risk Disease (Adjuvant BT); Recurrence; Distant Recurrence; Nil Brain Metastases; Painful Bone Metastases		I		(BT then) EBRT	Yes	I	n/a	<0.01	FIGO (4), PDQ (5), NCCN (7), INC/SFOG (8), JSGO (9), NSW (10), SGOG (2), ESMO (14)

Outcome Nos. in Updated Tree	Clinical Scenario	Original RTU study			Updates 2012					References
		Treatment Indicated	Level of Evidence for EBRT	Proportion of all Uterine Cancers	Treatment Indicated	Guideline updated	Current level of evidence for EBRT	Change to proportion of all Uterine Cancers		
								Yes/No	Updated value	
12	Carcinoma (non-PS/CC); Stage I; Medically operable; Intermediate Risk Disease (Adjuvant BT); Recurrence; Distant Recurrence; Nil Brain Metastases; Nil Painful Bone Metastases; Painful Other Metastatic Sites		III		(BT then) EBRT	Yes	III	n/a	<0.01	FIGO (4), PDQ (5), NCCN (7), INC/SFOG (8), JSGO (9), NSW (10), SGOG (2), ESMO (14)
15	Carcinoma (non-PS/CC); Stage I; Medically operable; High Risk Disease (Adjuvant RT); Adjuvant RT includes EBRT only		II		EBRT	Yes	II	n/a	0.02	FIGO (4), PDQ (5), NCCN (7), JSGO (9), CCO (11), YCN (13) SGOG (2), ESMO (14)

Outcome Nos. in Updated Tree	Clinical Scenario	Original RTU study			Updates 2012					References
		Treatment Indicated	Level of Evidence for EBRT	Proportion of all Uterine Cancers	Treatment Indicated	Guideline updated	Current level of evidence for EBRT	Change to proportion of all Uterine Cancers		
								Yes/No	Updated value	
16	Carcinoma (non-PS/CC); Stage I; Medically operable; High Risk Disease, (Adjuvant RT); Adjuvant RT includes EBRT and BT		II		EBRT and BT	Yes	II	n/a	0.01	INC/SFOG (8), NSW (10), BCCA (12)
17	Carcinoma (non-PS/CC); Stage I; Medically Inoperable	RT	IV**	0.03	EBRT and BT	Yes	IV	Yes	0.04	FIGO (4), PDQ (5), NCCN (7), JSGO (9), NSW (10), SGOG (2), ABS (3)
18	Carcinoma (non-PS/CC); Stage II; Medically operable; Simple Hysterectomy (Adjuvant RT); Adjuvant RT includes EBRT only	RT for all Stage IIB disease	III	0.10 for all Stage IIB and III	EBRT	Yes	III	n/a	0.01	PDQ (5), NCCN (7) JSGO (9), YCN (13), SGOG (2)

Outcome Nos. in Updated Tree	Clinical Scenario	Original RTU study			Updates 2012					References
		Treatment Indicated	Level of Evidence for EBRT	Proportion of all Uterine Cancers	Treatment Indicated	Guideline updated	Current level of evidence for EBRT	Change to proportion of all Uterine Cancers		
								Yes/No	Updated value	
19	Carcinoma (non-PS/CC); Stage II; Medically operable; Simple Hysterectomy (Adjuvant RT); Adjuvant RT includes EBRT and BT		III		EBRT and BT	Yes	III	n/a	0.02	PDQ (5), NCCN (7), INC/SFOG (8), NSW (10), BCCA (12), ESMO (14)
20	Carcinoma (non-PS/CC); Stage II; Medically operable; Simple Hysterectomy (Adjuvant RT); Adjuvant RT includes BT only; Recurrence; Pelvic Recurrence		n/a		(BT then) EBRT	Yes	IV	n/a	<0.01	FIGO (4), PDQ (5), NCCN (7), JSGO (9), NSW (10), YCN (13), SGOG (2), ESMO (14), ABS (3)

Outcome Nos. in Updated Tree	Clinical Scenario	Original RTU study			Updates 2012					References
		Treatment Indicated	Level of Evidence for EBRT	Proportion of all Uterine Cancers	Treatment Indicated	Guideline updated	Current level of evidence for EBRT	Change to proportion of all Uterine Cancers		
								Yes/No	Updated value	
21	Carcinoma (non-PS/CC); Stage II; Medically operable; Simple Hysterectomy (Adjuvant RT); Adjuvant RT includes BT only; Recurrence; Distant Recurrence; Brain Metastases		n/a		(BT then) EBRT	Yes	II	n/a	<0.01	FIGO (4), PDQ (5), NCCN (7), INC/SFOG (8), JSGO (9), NSW (10), SGOG (2), ESMO (14)
22	Carcinoma (non-PS/CC); Stage II; Medically operable; Simple Hysterectomy (Adjuvant RT); Adjuvant RT includes BT only; Recurrence; Distant Recurrence; Nil Brain Metastases; Painful Bone Metastases		n/a		(BT then) EBRT	Yes	I	n/a	<0.01	FIGO (4), PDQ (5), NCCN (7), INC/SFOG (8), JSGO (9), NSW (10), SGOG (2), ESMO (14)

Outcome Nos. in Updated Tree	Clinical Scenario	Original RTU study			Updates 2012					References
		Treatment Indicated	Level of Evidence for EBRT	Proportion of all Uterine Cancers	Treatment Indicated	Guideline updated	Current level of evidence for EBRT	Change to proportion of all Uterine Cancers		
								Yes/No	Updated value	
23	Carcinoma (non-PS/CC); Stage II; Medically operable; Simple Hysterectomy (Adjuvant RT); Adjuvant RT includes BT only; Recurrence; Distant Recurrence; Nil Brain Metastases; Nil Painful Bone Metastases; Painful Other Metastatic Sites		n/a		(BT then) EBRT	Yes	III	n/a	<0.01	FIGO (4), PDQ (5), NCCN (7), INC/SFOG (8), JSGO (9), NSW (10), SGOG (2), ESMO (14)
27	Carcinoma (non-PS/CC); Stage II; Medically Inoperable		n/a		EBRT and BT	Yes	IV	n/a	<0.01	FIGO (4), PDQ (5), NCCN (7), JSGO (9), NSW (10), SGOG (2), ABS (3)

Outcome Nos. in Updated Tree	Clinical Scenario	Original RTU study			Updates 2012					References
		Treatment Indicated	Level of Evidence for EBRT	Proportion of all Uterine Cancers	Treatment Indicated	Guideline updated	Current level of evidence for EBRT	Change to proportion of all Uterine Cancers		
								Yes/No	Updated value	
28	Carcinoma (non-PS/CC); Stage IIIA; Medically Operable (Adjuvant RT); Adjuvant RT includes EBRT only	RT for all Stage III disease	III		EBRT	Yes	III	n/a	0.02	PDQ (5), NCCN (7), NSW (10), SGOG (2), ESMO (14)
29	Carcinoma (non-PS/CC); Stage IIIA; Medically Operable (Adjuvant RT); Adjuvant RT includes EBRT and BT		III		EBRT and BT	Yes	III	n/a	0.01	NCCN (7), INC/SFOG (8), BCCA (12), YCN (13)
30	Carcinoma (non-PS/CC); Stage IIIA; Medically Inoperable		n/a		EBRT and BT	Yes	IV	n/a	<0.01	FIGO (4), PDQ (5), NCCN (7), JSGO (9), NSW (10), SGOG (2), ABS (3)

Outcome Nos. in Updated Tree	Clinical Scenario	Original RTU study			Updates 2012					
		Treatment Indicated	Level of Evidence for EBRT	Proportion of all Uterine Cancers	Treatment Indicated	Guideline updated	Current level of evidence for EBRT	Change to proportion of all Uterine Cancers		References
								Yes/No	Updated value	
31	Carcinoma (non-PS/CC); Stage IIIB		n/a		EBRT and BT	Yes	III	n/a	0.01	FIGO (4), PDQ (5), NCCN (7), INC/SFOG (8), NSW (10), BCCA (12), ESMO (14), ABS (3)
32	Carcinoma (non-PS/CC); Stage IIIC; Medically Operable; Adjuvant RT includes EBRT only		n/a		EBRT	Yes	III	n/a	0.03	FIGO (4), PDQ (5), NCCN (7), NSW (10), SGOG (2), ESMO (14)
33	Carcinoma (non-PS/CC); Stage IIIC; Medically Operable; Adjuvant RT includes EBRT and BT		n/a		EBRT and BT	Yes	III	n/a	0.02	INC/SFOG (8), NSW (10), BCCA (12), YCN (13)

Outcome Nos. in Updated Tree	Clinical Scenario	Original RTU study			Updates 2012					References
		Treatment Indicated	Level of Evidence for EBRT	Proportion of all Uterine Cancers	Treatment Indicated	Guideline updated	Current level of evidence for EBRT	Change to proportion of all Uterine Cancers		
								Yes/No	Updated value	
34	Carcinoma (non-PS/CC); Stage IIIC; Medically Inoperable		n/a		EBRT and BT	Yes	IV	n/a	<0.01	FIGO (4), PDQ (5), NCCN (7), JSGO (9), NSW (10), SGOG (2), ABS (3)
35	Carcinoma (non-PS/CC); Stage IVA	RT only for Stage IV with brain metastases or sympt. other sites	n/a	0.01	EBRT and BT	Yes	IV	n/a	0.01	PDQ (5), NCCN (7), INC/SFOG (8), JSGO (9), NSW (10), SGOG (2), ESMO (14), ABS (3)

Outcome Nos. in Updated Tree	Clinical Scenario	Original RTU study			Updates 2012					References
		Treatment Indicated	Level of Evidence for EBRT	Proportion of all Uterine Cancers	Treatment Indicated	Guideline updated	Current level of evidence for EBRT	Change to proportion of all Uterine Cancers		
								Yes/No	Updated value	
36	Carcinoma (non-PS/CC); Stage IVB		n/a		EBRT	Yes	IV	n/a	0.03	FIGO (4), PDQ (5), NCCN (7), INC/SFOG (8), JSGO (9), NSW (10), CCO (11), SGOG (2), ESMO (14), ABS (3)
37	Carcinoma (PS/CC); Loco-Regional Disease Only; Adjuvant RT includes EBRT only	RT	IV**	0.13	EBRT	Yes	IV	n/a	0.03	NCCN (7), INC/SFOG (8), JSGO (9), NSW (10), YCN (13), SGOG (2)

Outcome Nos. in Updated Tree	Clinical Scenario	Original RTU study			Updates 2012					References
		Treatment Indicated	Level of Evidence for EBRT	Proportion of all Uterine Cancers	Treatment Indicated	Guideline updated	Current level of evidence for EBRT	Change to proportion of all Uterine Cancers		
								Yes/No	Updated value	
38	Carcinoma (PS/CC); Loco-Regional Disease Only; Adjuvant RT includes EBRT and BT		IV**		EBRT and BT	Yes	IV	n/a	0.02	NCCN (7), INC/SFOG (8), YCN (13), SGOG (2)
39	Carcinoma (PS/CC); Distant Metastases		IV**		EBRT	Yes	IV	n/a	0.02	FIGO (4), PDQ (5), NCCN (7), INC/SFOG (8), JSGO (9), NSW (10), CCO (11), SGOG (2), ESMO (14), ABS (3)
40	Carcinosarcoma; Loco-Regional Disease; Adjuvant RT includes EBRT only	Nil	n/a	n/a	EBRT	Yes	II	Yes	0.03	NCCN (7), INC/SFOG (8), JSGO (9), NSW (10), YCN (13)

Outcome Nos. in Updated Tree	Clinical Scenario	Original RTU study			Updates 2012					References
		Treatment Indicated	Level of Evidence for EBRT	Proportion of all Uterine Cancers	Treatment Indicated	Guideline updated	Current level of evidence for EBRT	Change to proportion of all Uterine Cancers		
								Yes/No	Updated value	
41	Carcinosarcoma; Loco-Regional Disease; Adjuvant RT includes EBRT and BT	Nil	n/a	n/a	EBRT and BT	Yes	II	Yes	0.01	NCCN (7), INC/SFOG (8), JSGO (9), NSW (10)
42	Carcinosarcoma; Distant Metastases	Nil	n/a	n/a	EBRT	Yes	IV	Yes	0.01	FIGO (4), PDQ (5), NCCN (7), INC/SFOG (8), JSGO (9), NSW (10), CCO (11), SGOG (2), ESMO (14), ABS (3)

Outcome Nos. in Updated Tree	Clinical Scenario	Original RTU study			Updates 2012					References
		Treatment Indicated	Level of Evidence for EBRT	Proportion of all Uterine Cancers	Treatment Indicated	Guideline updated	Current level of evidence for EBRT	Change to proportion of all Uterine Cancers		
								Yes/No	Updated value	
44	Sarcoma; Distant Metastases	Nil	n/a	n/a	EBRT	Yes	IV	Yes	0.01	FIGO (4), PDQ (5), NCCN (7), INC/SFOG (8), JSGO (9), NSW (10), CCO (11), SGOG (2), ESMO (14), ABS (3)
Proportion of all patients with uterine corpus malignancies in whom EBRT was recommended				0.46 (46%)	**Updated Proportion of all patients with uterine corpus malignancies in whom EBRT is recommended**				**0.38 (38%)**	

*Level of evidence in original RTU study erroneously reported to be III rather than II
**Level of evidence in original RTU study erroneously reported to be III rather than IV
Abbreviations: Nos, Numbers; RTU, Radiotherapy Utilisation; PS/CC, Papillary Serous / Clear Cell Carcinoma; LVI, Lymphatic Vascular Space Invasion; RT, Radiotherapy; EBRT, External Beam Radiotherapy; BT, Brachytherapy

Table 2: Uterine Corpus Malignancies. Indications for Brachytherapy - Levels and sources of evidence

Outcome Nos. in Updated Tree	Clinical Scenario	Original BTU study			Updates 2012					References
		Treatment Indicated	Level of Evidence For BT	Proportion of all Uterine Cancers	Change of Indication	Guideline updated	Current level of evidence For BT	Change to proportion of all Uterine Cancers		
								Yes/No	Updated value	
1	Carcinoma (non-PS/CC); Stage I; Medically operable; Low Risk Disease; Nil LVI; Vault recurrence without distant metastases	No IR Group BT for Stage I (and IIA), Medically Operable: Adjuvant if Adverse Histology and LND; or for Vault	IV	0.21	EBRT and BT	Yes	IV	n/a	0.01	FIGO (4), PDQ (5), NCCN (7), JSGO (9), NSW (10), YCN (13), SGOG (2), ESMO (14), ABS (3)
8	Carcinoma (non-PS/CC); Stage I; Medically operable; Low Risk Disease; LVI		IV		BT	Yes	IV	n/a	0.09	NSW (10)

Outcome Nos. in Updated Tree	Clinical Scenario	Original BTU study			Updates 2012					
		Treatment Indicated	Level of Evidence For BT	Proportion of all Uterine Cancers	Change of Indication	Guideline updated	Current level of evidence For BT	Change to proportion of all Uterine Cancers		References
								Yes/No	Updated value	
9	Carcinoma (non-PS/CC); Stage I; Medically operable; Intermediate Risk Disease (Adjuvant BT); Recurrence; Pelvic Recurrence	Recurrence	n/a		BT (then EBRT)	Yes	II	n/a	0.01	NCCN (7), INC/SFOG (8), JSGO (9), NSW (10), BCCA (12), ESMO (14)
10	Carcinoma (non-PS/CC); Stage I; Medically operable; Intermediate Risk Disease (Adjuvant BT); Recurrence; Distant Recurrence; Brain Metastases		n/a		BT (then EBRT)	Yes	II	n/a	<0.01	NCCN (7), INC/SFOG (8), JSGO (9), NSW (10), BCCA (12), ESMO (14)

Outcome Nos. in Updated Tree	Clinical Scenario	Original BTU study			Updates 2012					References
		Treatment Indicated	Level of Evidence For BT	Proportion of all Uterine Cancers	Change of Indication	Guideline updated	Current level of evidence For BT	Change to proportion of all Uterine Cancers		
								Yes/No	Updated value	
11	Carcinoma (non-PS/CC); Stage I; Medically operable; Intermediate Risk Disease (Adjuvant BT); Recurrence; Distant Recurrence; Nil Brain Metastases; Painful Bone Metastases		n/a		BT (then EBRT)	Yes	II	n/a	<0.01	NCCN (7), INC/SFOG (8), JSGO (9), NSW (10), BCCA (12), ESMO (14)

Outcome Nos. in Updated Tree	Clinical Scenario	Original BTU study			Updates 2012					References
		Treatment Indicated	Level of Evidence For BT	Proportion of all Uterine Cancers	Change of Indication	Guideline updated	Current level of evidence For BT	Change to proportion of all Uterine Cancers		
								Yes/No	Updated value	
12	Carcinoma (non-PS/CC); Stage I; Medically operable; Intermediate Risk Disease (Adjuvant BT); Recurrence; Distant Recurrence; Nil Brain Metastases; Nil Painful Bone Metastases; Painful Other Metastatic Sites		n/a		BT (then EBRT)	Yes	II	n/a	<0.01	NCCN (7), INC/SFOG (8), JSGO (9), NSW (10), BCCA (12), ESMO (14)

Outcome Nos. in Updated Tree	Clinical Scenario	Original BTU study			Updates 2012					References
		Treatment Indicated	Level of Evidence For BT	Proportion of all Uterine Cancers	Change of Indication	Guideline updated	Current level of evidence For BT	Change to proportion of all Uterine Cancers		
								Yes/No	Updated value	
13	Carcinoma (non-PS/CC); Stage I; Medically operable; Intermediate Risk Disease (Adjuvant BT); Recurrence; Distant Recurrence; Nil Brain Metastases; Nil Painful Bone Metastases; Nil Painful Other Metastatic Sites		n/a		BT	Yes	II	n/a	0.01	NCCN (7), INC/SFOG (8), JSGO (9), NSW (10), BCCA (12), ESMO (14)
14	Carcinoma (non-PS/CC); Stage I; Medically operable; Intermediate Risk Disease (Adjuvant BT); Nil Recurrence		n/a		BT	Yes	II	n/a	0.12	NCCN (7), INC/SFOG (8), JSGO (9), NSW (10), BCCA (12), ESMO (14)

Outcome Nos. in Updated Tree	Clinical Scenario	Original BTU study			Updates 2012					References
		Treatment Indicated	Level of Evidence For BT	Proportion of all Uterine Cancers	Change of Indication	Guideline updated	Current level of evidence For BT	Change to proportion of all Uterine Cancers		
								Yes/No	Updated value	
16	Carcinoma (non-PS/CC); Stage I; Medically operable; High Risk Disease, (Adjuvant RT); Adjuvant RT includes EBRT and BT		III		EBRT and BT	Yes	III	n/a	0.01	INC/SFOG (8), NSW (10), BCCA (12)
17	Carcinoma (non-PS/CC); Stage I; Medically Inoperable	EBRT and BT	IV	0.04	EBRT and BT	Yes	IV	No	0.04	FIGO (4), PDQ (5), NCCN (7), JSGO (9), NSW (10), SGOG (2), ABS (3)

Outcome Nos. in Updated Tree	Clinical Scenario	Original BTU study			Updates 2012					References
		Treatment Indicated	Level of Evidence For BT	Proportion of all Uterine Cancers	Change of Indication	Guideline updated	Current level of evidence For BT	Change to proportion of all Uterine Cancers		
								Yes/No	Updated value	
19	Carcinoma (non-PS/CC); Stage II; Medically operable; Simple Hysterectomy (Adjuvant RT); Adjuvant RT includes EBRT and BT	EBRT and BT for all IIB post simple hyst.	III	0.03	EBRT and BT	Yes	III	Yes	0.02	NCCN (7), INC/SFOG (8), ESMO (14)
20	Carcinoma (non-PS/CC); Stage II; Medically operable; Simple Hysterectomy (Adjuvant RT); Adjuvant RT includes BT only; Recurrence; Pelvic Recurrence				BT (then EBRT)	Yes	III	Yes	<0.01	FIGO (4), NCCN (7), NSW (10), YCN (13), ESMO (14)

Outcome Nos. in Updated Tree	Clinical Scenario	Original BTU study			Updates 2012					References
		Treatment Indicated	Level of Evidence For BT	Proportion of all Uterine Cancers	Change of Indication	Guideline updated	Current level of evidence For BT	Change to proportion of all Uterine Cancers		
								Yes/No	Updated value	
21	Carcinoma (non-PS/CC); Stage II; Medically operable; Simple Hysterectomy (Adjuvant RT); Adjuvant RT includes BT only; Recurrence; Distant Recurrence; Brain Metastases				BT (then EBRT)	Yes	III	Yes	<0.01	NCCN (7), NSW (10), YCN (13), ESMO (14)

Outcome Nos. in Updated Tree	Clinical Scenario	Original BTU study			Updates 2012					
		Treatment Indicated	Level of Evidence For BT	Proportion of all Uterine Cancers	Change of Indication	Guideline updated	Current level of evidence For BT	Change to proportion of all Uterine Cancers		References
								Yes/No	Updated value	
22	Carcinoma (non-PS/CC); Stage II; Medically operable; Simple Hysterectomy (Adjuvant RT); Adjuvant RT includes BT only; Recurrence; Distant Recurrence; Nil Brain Metastases; Painful Bone Metastases				BT (then EBRT)	Yes	III	Yes	<0.01	NCCN (7), NSW (10), YCN (13), ESMO (14)

Outcome Nos. in Updated Tree	Clinical Scenario	Original BTU study			Updates 2012					
		Treatment Indicated	Level of Evidence For BT	Proportion of all Uterine Cancers	Change of Indication	Guideline updated	Current level of evidence For BT	Change to proportion of all Uterine Cancers		References
								Yes/No	Updated value	
23	Carcinoma (non-PS/CC); Stage II; Medically operable; Simple Hysterectomy (Adjuvant RT); Adjuvant RT includes BT only; Recurrence; Distant Recurrence; Nil Brain Metastases; Nil Painful Bone Metastases; Painful Other Metastatic Sites				BT (then EBRT)	Yes	III	Yes	<0.01	NCCN (7), NSW (10), YCN (13), ESMO (14)

Outcome Nos. in Updated Tree	Clinical Scenario	Original BTU study			Updates 2012					References
		Treatment Indicated	Level of Evidence For BT	Proportion of all Uterine Cancers	Change of Indication	Guideline updated	Current level of evidence For BT	Change to proportion of all Uterine Cancers		
								Yes/No	Updated value	
24	Carcinoma (non-PS/CC); Stage II; Medically operable; Simple Hysterectomy (Adjuvant RT); Adjuvant RT includes BT only; Recurrence; Distant Recurrence; Nil Brain Metastases; Nil Painful Bone Metastases; Nil Painful Other Metastatic Sites				BT	Yes	III	Yes	<0.01	NCCN (7), NSW (10), YCN (13), ESMO (14)

Outcome Nos. in Updated Tree	Clinical Scenario	Original BTU study			Updates 2012					References
		Treatment Indicated	Level of Evidence For BT	Proportion of all Uterine Cancers	Change of Indication	Guideline updated	Current level of evidence For BT	Change to proportion of all Uterine Cancers		
								Yes/No	Updated value	
25	Carcinoma (non-PS/CC); Stage II; Medically operable; Simple Hysterectomy (Adjuvant RT); Adjuvant RT includes BT only; Nil Recurrence				BT	Yes	III	Yes	0.01	NCCN (7), NSW (10), YCN (13), ESMO (14)
27	Carcinoma (non-PS/CC); Stage II; Medically Inoperable	EBRT and BT	n/a	<0.01	EBRT and BT	Yes	IV	No	<0.01	FIGO (4), PDQ (5), NCCN (7), JSGO (9), NSW (10), SGOG (2), ABS (3)

Outcome Nos. in Updated Tree	Clinical Scenario	Original BTU study			Updates 2012					References
		Treatment Indicated	Level of Evidence For BT	Proportion of all Uterine Cancers	Change of Indication	Guideline updated	Current level of evidence For BT	Change to proportion of all Uterine Cancers		
								Yes/No	Updated value	
29	Carcinoma (non-PS/CC); Stage IIIA; Medically Operable (Adjuvant RT); Adjuvant RT includes EBRT and BT	EBRT and BT	IV	<0.01	EBRT and BT	Yes	IV	Yes	0.01	NCCN (7), INC/SFOG (8), BCCA (12), YCN (13)
30	Carcinoma (non-PS/CC); Stage IIIA; Medically Inoperable	EBRT and BT	IV	<0.01	EBRT and BT	Yes	IV	No	<0.01	PDQ (5), NCCN (7), JSGO (9), NSW (10), SGOG (2), ABS (3)
31	Carcinoma (non-PS/CC); Stage IIIB	EBRT and BT	IV	0.01	EBRT and BT	Yes	IV	No	0.01	FIGO (4), INC/SFOG (8), NSW (10), BCCA (12), ESMO (14), ABS (3)

Outcome Nos. in Updated Tree	Clinical Scenario	Original BTU study			Updates 2012					References
		Treatment Indicated	Level of Evidence For BT	Proportion of all Uterine Cancers	Change of Indication	Guideline updated	Current level of evidence For BT	Change to proportion of all Uterine Cancers		
								Yes/No	Updated value	
33	Carcinoma (non-PS/CC); Stage IIIC; Medically Operable; Adjuvant RT includes EBRT and BT	EBRT and BT	III	0.04	EBRT and BT	Yes	III	Yes	0.02	INC/SFOG (8), NSW (10), BCCA (12), YCN (13)
34	Carcinoma (non-PS/CC); Stage IIIC; Medically Inoperable	EBRT and BT	IV	<0.01	EBRT and BT	Yes	IV	No	<0.01	FIGO (4), PDQ (5), NCCN (7), JSGO (9), NSW (10), SGOG (2), ABS (3)
35	Carcinoma (non-PS/CC); Stage IVA	EBRT and BT	IV	0.01	EBRT and BT	Yes	IV	No	0.01	PDQ (5), NCCN (7), INC/SFOG (8), NSW (10), ABS (3)

Outcome Nos. in Updated Tree	Clinical Scenario	Original BTU study			Updates 2012					References
		Treatment Indicated	Level of Evidence For BT	Proportion of all Uterine Cancers	Change of Indication	Guideline updated	Current level of evidence For BT	Change to proportion of all Uterine Cancers		
								Yes/No	Updated value	
38	Carcinoma (PS/CC); Loco-Regional Disease Only; Adjuvant RT includes EBRT and BT	EBRT and BT	IV	0.02	EBRT and BT	Yes	IV	No	0.02	NCCN (7), INC/SFOG (8), NSW (10), YCN (13), SGOG (2)
41	Carcinosarcoma; Loco-Regional Disease; Adjuvant RT includes EBRT and BT	EBRT and BT	IV	0.01	EBRT and BT	Yes	IV	No	0.01	NCCN (7), INC/SFOG (8), JSGO (9), NSW (10)
Proportion of all patients with uterine corpus malignancies in whom BT was recommended				0.40 (40%)	**Updated Proportion of all patients with uterine corpus malignancies in whom BT is recommended**				**0.39 (39%)**	

Abbreviations: Nos, Numbers; BTU, Brachytherapy Utilisation; PS/CC, Papillary Serous / Clear Cell Carcinoma; LND, Lymph Node Dissection; LVI, Lymphatic Vascular Space Invasion; RT, Radiotherapy; EBRT, External Beam Radiotherapy; BT, Brachytherapy; Hyst, Hysterectomy

Table 3: Uterine Corpus Malignancies. The incidence of attributes used to define indications for radiotherapy

Population or sub-population of interest	Attribute	Original RTU/BTU studies		Updates 2012			
		Proportion of population with the attribute	Quality of Information	Change in proportion population with attribute	Updated Proportion	Updated Quality of Information	Updated Reference
All registry cancers	Gynaecological cancer	0.037 (RTU) 0.045 (BTU)	α	Yes	0.039	α	AIHW 2011 (22)
All gynaecological cancer	Uterine corpus malignancies	0.37 (RTU) 0.41 (BTU)	α	Yes	0.45	α	AIHW 2011 (22)
Uterine corpus malignancies	Carcinoma (non-PS/CC)	0.87 (RTU) 0.90 (BTU)	γ	Yes	0.84	γ	SEER 2004-2007 (21)
Carcinoma (non-PS/CC)	Stage I	0.72 (RTU) 0.76 (BTU)	γ	Yes	0.79	γ	SEER 2004-2007 (21)
Carcinoma (non-PS/CC), Stage I	Medically operable	0.95 (RTU) 0.94 (BTU)	ζ β	Yes No	0.94	No	n/a
Carcinoma (non-PS/CC), Stage I; Medically operable	Low Risk Disease: Stage IA and Grade 1-2	n/a	n/a	Yes	0.74	γ	SEER 1997-2001 (23)
Carcinoma (non-PS/CC), Stage I; Medically operable; Low Risk Disease	Nil LVI	0.81 (BTU)	ζ	No	0.81	No	n/a
Carcinoma (non-PS/CC), Stage I; Medically operable; Low Risk Disease; Nil LVI	Vault recurrence without distant metastases	0.02 (BTU)	θ	No	0.02	No	n/a

Population or sub-population of interest	Attribute	Original RTU/BTU studies		Updates 2012			
		Proportion of population with the attribute	Quality of Information	Change in proportion population with attribute	Updated Proportion	Updated Quality of Information	Updated Reference
Carcinoma (non-PS/CC), Stage I; Medically operable; Low Risk Disease; Nil LVI	Pelvic side-wall recurrence without distant metastases	0.01 (BTU)	θ	No	0.01	No	n/a
Carcinoma (non-PS/CC), Stage I; Medically operable; LND; Low Risk Disease; Nil Pelvic Recurrence	Distant Recurrence	0.02 (RTU)	ζ	No	0.02	No	n/a
Carcinoma (non-PS/CC), Stage I; Medically operable; Low Risk Disease; Nil LVI; Nil Pelvic Recurrence; Distant Recurrence	Brain Metastases	0.03 (RTU)	ζ	No	0.03	No	n/a
Carcinoma (non-PS/CC), Stage I; Medically operable; Low Risk Disease; Nil LVI; Nil Pelvic Recurrence; Distant Recurrence; Nil Brain Metastases	Painful Bone Metastases	0.06 (RTU)	ζ	No	0.06	No	n/a
Carcinoma (non-PS/CC), Stage I; Medically operable; Low Risk Disease; Nil LVI; Nil Pelvic Recurrence; Distant Recurrence; Nil Brain Metastases; Nil Painful Bone Metastases	Painful Other Metastatic Sites	0.06 (RTU)	ζ	No	0.06	No	n/a

Population or sub-population of interest	Attribute	Original RTU/BTU studies		Updates 2012			
		Proportion of population with the attribute	Quality of Information	Change in proportion population with attribute	Updated Proportion	Updated Quality of Information	Updated Reference
Carcinoma (non-PS/CC), Stage I; Medically operable	Intermediate Risk Disease: Stage IA and Grade 3, or Stage IB and Grade 1-2	n/a	n/a	Yes	0.22	γ	SEER 1997-2001 (23)
Carcinoma (non-PS/CC), Stage I; Medically operable; Intermediate Risk Disease (Adjuvant BT)	Recurrence	n/a	n/a	Yes	0.13	θ	Nout et al (18)
Carcinoma (non-PS/CC), Stage I; Medically operable; Intermediate Risk Disease (Adjuvant BT); Recurrence	Pelvic Recurrence	n/a	n/a	Yes	0.38	θ	Nout et al (18)
Carcinoma (non-PS/CC), Stage I; Medically operable; Intermediate Risk Disease (Adjuvant BT); Recurrence; Distant Recurrence	Brain Metastases	0.03 (RTU)	ζ	No	0.03	No	n/a
Carcinoma (non-PS/CC), Stage I; Medically operable; Intermediate Risk Disease (Adjuvant BT); Recurrence; Distant Recurrence; Nil Brain Metastases	Painful Bone Metastases	0.06 (RTU)	ζ	No	0.06	No	n/a

Population or sub-population of interest	Attribute	Original RTU/BTU studies		Updates 2012			
		Proportion of population with the attribute	Quality of Information	Change in proportion population with attribute	Updated Proportion	Updated Quality of Information	Updated Reference
Carcinoma (non-PS/CC), Stage I; Medically operable; Intermediate Risk Disease (Adjuvant BT); Recurrence; Distant Recurrence; Nil Brain Metastases; Nil Painful Bone Metastases	Painful Other Metastatic Sites	0.06 (RTU)	ζ	No	0.06	No	n/a
Carcinoma (non-PS/CC), Stage I; Medically operable	High Risk Disease: Stage IB and Grade 3	n/a	n/a	Yes	0.04	γ	SEER 1997-2001 (23)
Carcinoma (non-PS/CC), Stage I; Medically operable; High Risk Disease	Adjuvant RT includes EBRT only	n/a	n/a	Yes	0.69*	γ	SEER 1988-2006 (24)
	Adjuvant RT includes EBRT and BT				0.31*		
Carcinoma (non-PS/CC)	Stage II**	0.08 (BTU)	γ	Yes	0.05	γ	SEER 2004-2007 (21)
Carcinoma (non-PS/CC); Stage II	Medically Operable	0.95 (RTU) 0.94 (BTU)	ζ β	Yes No	0.94	No	n/a
Carcinoma (non-PS/CC); Stage II; Medically operable	Simple Hysterectomy (Adjuvant RT)	0.84	γ	No	0.84	No	n/a

Population or sub-population of interest	Attribute	Original RTU/BTU studies		Updates 2012			
		Proportion of population with the attribute	Quality of Information	Change in proportion population with attribute	Updated Proportion	Updated Quality of Information	Updated Reference
Carcinoma (non-PS/CC); Stage II; Medically operable; Simple Hysterectomy (Adjuvant RT)	Adjuvant RT includes EBRT only	n/a	n/a	Yes	0.28	γ	SEER 1995-2005 (25)
Carcinoma (non-PS/CC); Stage II; Medically operable; Simple Hysterectomy (Adjuvant RT)	Adjuvant RT includes EBRT and BT	n/a	n/a	Yes	0.54	γ	SEER 1995-2005 (25)
Carcinoma (non-PS/CC); Stage II; Medically operable; Simple Hysterectomy (Adjuvant RT)	Adjuvant RT includes BT only	n/a	n/a	Yes	0.18	γ	SEER 1995-2005 (25)
Carcinoma (non-PS/CC); Stage II; Medically operable; Simple Hysterectomy (Adjuvant RT); Adjuvant RT includes BT only	Recurrence	n/a	n/a	Yes	0.05	θ	Rittenberg et al (26)
Carcinoma (non-PS/CC); Stage II; Medically operable; Simple Hysterectomy (Adjuvant RT); Adjuvant RT includes BT only; Recurrence	Pelvic Recurrence	n/a	n/a	Yes	0.24	θ	Rittenberg et al (26)

Population or sub-population of interest	Attribute	Original RTU/BTU studies		Updates 2012			
		Proportion of population with the attribute	Quality of Information	Change in proportion population with attribute	Updated Proportion	Updated Quality of Information	Updated Reference
Carcinoma (non-PS/CC); Stage II; Medically operable; Simple Hysterectomy (Adjuvant RT); Adjuvant RT includes BT only; Recurrence; Distant Recurrence	Brain Metastases	0.03 (RTU)	ζ	No	0.03	No	n/a
Carcinoma (non-PS/CC); Stage II; Medically operable; Simple Hysterectomy (Adjuvant RT); Adjuvant RT includes BT only; Recurrence; Distant Recurrence; Nil Brain Metastases	Painful Bone Metastases	0.06 (RTU)	ζ	No	0.06	No	n/a
Carcinoma (non-PS/CC); Stage II; Medically operable; Simple Hysterectomy (Adjuvant RT); Adjuvant RT includes BT only; Recurrence; Distant Recurrence; Nil Brain Metastases; Nil Painful Bone Metastases	Painful Other Metastatic Sites	0.06 (RTU)	ζ	No	0.06	No	n/a
Carcinoma (non-PS/CC)	Stage IIIA	0.04 (BTU)	γ	No	0.04	γ	SEER 2004-2007 (21)

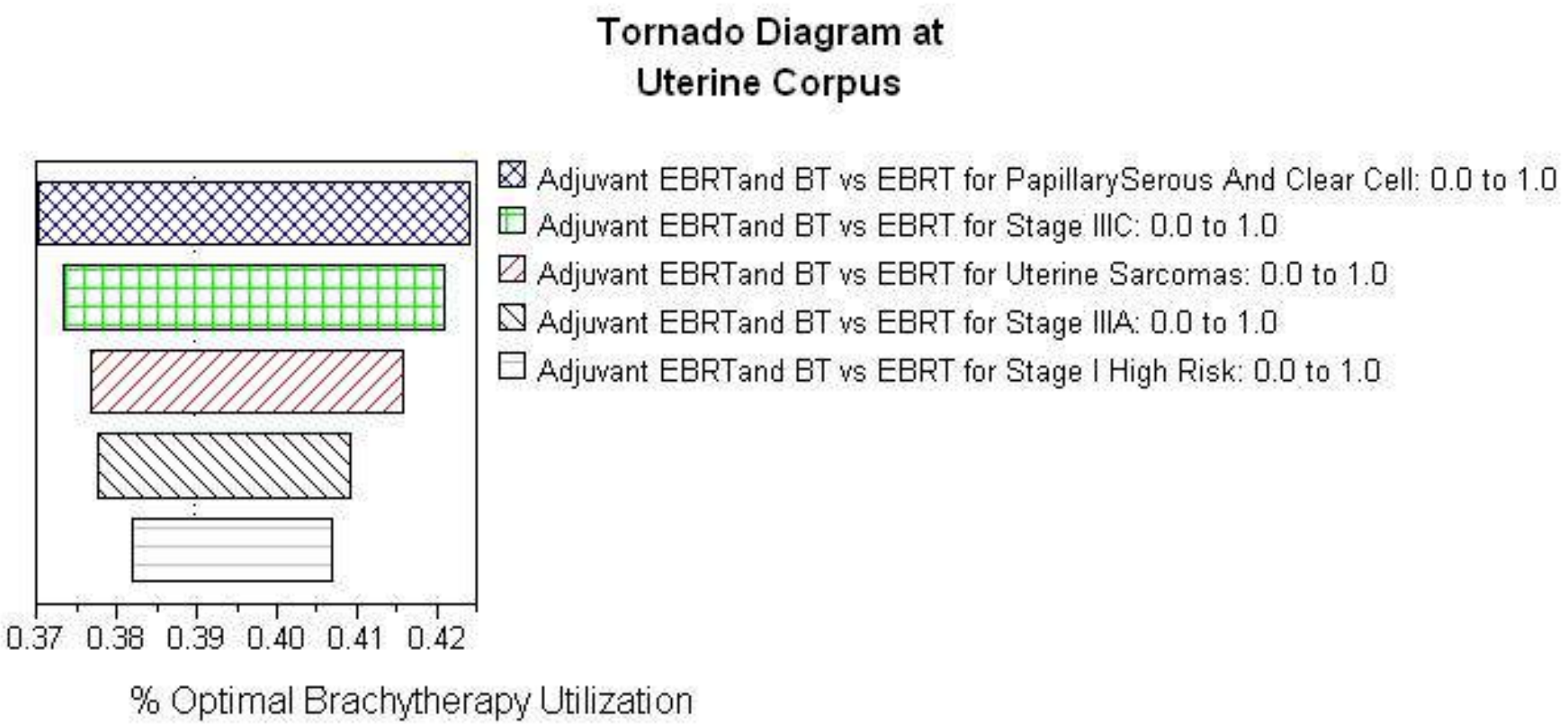
Population or sub-population of interest	Attribute	Original RTU/BTU studies		Updates 2012			
		Proportion of population with the attribute	Quality of Information	Change in proportion population with attribute	Updated Proportion	Updated Quality of Information	Updated Reference
Carcinoma (non-PS/CC); Stage IIIA	Medically Operable	0.95 (RTU) 0.94 (BTU)	ζ β	Yes No	0.94	No	n/a
Carcinoma (non-PS/CC); Stage IIIA; Medically Operable (Adjuvant RT)	Adjuvant RT includes EBRT only	0.62 (BTU)	γ	No	0.62*	No	n/a
	Adjuvant RT includes EBRT and BT	0.38 (BTU)			0.38*		
Carcinoma (non-PS/CC)	Stage IIIB	0.01 (BTU)	γ	No	0.01	γ	SEER 2004-2007 (21)
Carcinoma (non-PS/CC)	Stage IIIC	0.05 (BTU)	γ	Yes	0.06	γ	SEER 2004-2007 (21)
Carcinoma (non-PS/CC); Stage IIIC	Medically Operable	0.95 (RTU) 0.94 (BTU)	ζ β	Yes No	0.94	No	n/a
Carcinoma (non-PS/CC); Stage IIIC; Medically Operable (Adjuvant RT)	Adjuvant RT includes EBRT only	0.10 (BTU)	γ	Yes	0.66*	No	SEER 2001 (23)
	Adjuvant RT includes EBRT and BT	0.90 (BTU)			0.34*		

Population or sub-population of interest	Attribute	Original RTU/BTU studies		Updates 2012			
		Proportion of population with the attribute	Quality of Information	Change in proportion population with attribute	Updated Proportion	Updated Quality of Information	Updated Reference
Carcinoma (non-PS/CC)	Stage IVA	0.09 for all IV (RTU) 0.01 (BTU)	γ	Yes No	0.01	γ	SEER 2004-2007 (21)
Carcinoma (non-PS/CC)	Stage IVB	0.09 for all IV (RTU) 0.05 (BTU)	γ	Yes Yes	0.04	γ	SEER 2004-2007 (21)
Uterine corpus malignancies	PS/CC carcinoma	0.13 (RTU) 0.02 (BTU)	γ	Yes	0.07	γ	SEER 2004-2007 (21)
Uterine corpus malignancies; PS/CC carcinoma	Loco-regional disease	0.84 (BTU)	γ	Yes	0.77	γ	SEER 2004-2007 (21)
Uterine corpus malignancies; PS/CC carcinoma; Loco-regional disease (Adjuvant RT)	Adjuvant RT includes EBRT only	n/a	n/a	Yes	0.64*	γ	SEER 2001 (23)
	Adjuvant RT includes EBRT and BT				0.36*		
Uterine corpus malignancies	Carcinosarcoma	0.04 (BTU)	γ	Yes	0.05	γ	SEER 2004-2007 (21)

Population or sub-population of interest	Attribute	Original RTU/BTU studies		Updates 2012			
		Proportion of population with the attribute	Quality of Information	Change in proportion population with attribute	Updated Proportion	Updated Quality of Information	Updated Reference
Uterine corpus malignancies; Carcinosarcoma	Loco-regional disease	0.81 (BTU)	γ	Yes	0.78	γ	SEER 2004-2007 (21)
Uterine corpus malignancies; Carcinosarcoma; Loco-regional disease	Adjuvant RT includes EBRT only	0.67 (BTU)	γ	No	0.67*	No	n/a
	Adjuvant RT includes EBRT and BT	0.33 (BTU)			0.33*		
Uterine corpus malignancies	Sarcoma	0.04 (BTU)	γ	Yes	0.04	γ	SEER 2004-2007 (21)
Uterine corpus malignancies; Sarcoma	Loco-regional disease	0.81 (BTU)	γ	Yes	0.77	γ	SEER 2004-2007 (21)

* Sensitivity Analysis, varying proportion from 0.0-1.0 ** Stage II disease now excludes previous IIA disease.
Abbreviations: RTU, Radiotherapy Utilization; BTU, Brachytherapy Utilization; PS/CC, Papillary Serous/Clear Cell; AIHW, Australian Institute of Health and Welfare; SEER, Surveillance, Epidemiology, End Results Database; LVI, Lymphatic Vascular Space Invasion; PS/CC, Papillary Serous / Clear Cell Carcinoma; RT, Radiotherapy; EBRT, External Beam Radiotherapy; BT, Brachytherapy

Figure 3. Uterine Corpus Malignancies, Brachytherapy. Tornado Diagram for Univariate Sensitivity Analysis



References

1. BC Cancer Agency. Cancer Management Guidelines/Gynecology/Gynecological Sarcomas. http://www.bccancer.bc.ca/HPI/CancerManagementGuidelines/default.htm . 2000. 4-8-2004.
   Ref Type: Electronic Citation

2. Sydney Gynaecologic Oncology Group, Royal Prince Alfred and Liverpool Hospitals Sydney. Clinical Practice and Management Policies. Johnathan Carter. 1-6-2004. Sydney, Johnathan Carter.
   Ref Type: Serial (Book,Monograph)

3. Nag S, Erickson B, Parikh S, Gupta N, Varia M, Glasgow G. The American Brachytherapy Society recommendations for high-dose-rate brachytherapy for carcinoma of the endometrium. *Int J Radiat Oncol Biol Phys* 2000;48:779-90.

4. FIGO Committee on Gynecologic Oncology. Staging classifications and clinical practice guidelines for gynaecologic cancers. www.figo.org . 2006. 12-9-2012.
   Ref Type: Electronic Citation

5. National Cancer Institute. National Cancer Institute: PDQ® Endometrial Cancer Treatment. http://www.cancer.gov/cancertopics/pdq/treatment/endometrial/HealthProfessional . 6-1-2012. 8-2-0012.
   Ref Type: Electronic Citation

6. National Cancer Institute. National Cancer Institute: PDQ® Uterine Sarcoma Treatment. http://www.cancer.gov/cancertopics/pdq/treatment/uterinesarcoma/HealthProfessional/ . 22-5-2008. 8-2-2012.
   Ref Type: Electronic Citation

7. National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology - v1.2012 - Uterine Neoplasms. http://www.nccn.org/professionals/physician_gls/pdf/uterine.pdf . 13-10-2011. 8-2-2012.
   Ref Type: Electronic Citation

8. Institut National du Cancer, Societe Francaise d'Oncologie Gynecologique. Clinical Practice Guidelines for the Management of Patients With Endometrial Cancer in France. *Int Gynecol Cancer* 2011;21:945-50.

9. Japan Society of Gynecologic Oncology. Evidence-based guidlines for treatment of uterine body neoplasm in Japan: Japan Society of Gynecologic Oncology (JSGO). *Int J Clin Oncol* 2010;15:531-42.

10. Greater Metropolitan Clinical Taskforce (GMCT). Best clinical practice: Gynaecological cancer guidelines 2009. 2009. Sydney, NSW Depatment of Health. 2009.
    Ref Type: Serial (Book,Monograph)

11. Cancer Care Ontario. Adjuvant Radiotherapy in Women with Stage I Endometrial Cancer: A Clinical Practice Guideline. https://www.cancercare.on.ca/common/pages/UserFile.aspx?fileId=14080 . 2006. 8-2-2012.
    Ref Type: Electronic Citation

12. BC Cancer Agency. Cancer Management Guidelines >> Gynecology >> 3. Endometrium. http://www.bccancer.bc.ca/HPI/CancerManagementGuidelines/Gynecology/Endometrium . 2011. 8-2-2012.
    Ref Type: Electronic Citation

13. Yorkshire Cancer Network Gynaecology NSSG. Guidelines for the Management of Gynaecological Cancers. http://www.ycn.nhs.uk/ . 2011. 19-10-2011.
    Ref Type: Electronic Citation

14. European Society of Medical Oncology. Endometrial Cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2011;22:vi35-vi39.

15. European School of Oncology - START: State of the Art Oncology in Europe. Endometrial Cancer. http://www.startoncology.net/default.jsp . 2001. 8-3-2002.
Ref Type: Electronic Citation

16. ASTEC/EN.5 Study Group. Adjuvant external beam radiotherapy in the treatment of endometrial cancer (MRC ASTEC and NCIC EN.5 randomised trials): pooled trial results, systematic review and meta-analysis. *Lancet* 2009;373:137-46.

17. Benedetti PP, Basile S, Maneschi F, et al. Systematic pelvic lymphadenectomy vs. no lymphadenectomy in early-stage endometrial carcinoma: Randomized clinical trial. *J Natl Cancer Inst* 2008;100:1707-16.

18. Nout RA, Smit VTHBN, Putter H, et al. Vaginal brachytherapy versus pelvic external beam radiotherapy for patients with endometrial cancer of high-intermediate risk (PORTEC-2): an open-label, non-inferiority, randomised trial. *Lancet* 2010;375:816-23.

19. Sorbe B, Horvath G, Andersson H, et al. External beam and vaginal irradiation versus vaginal irradiation alone as postoperative therapy in medium-risk endomtrial carcinoma - a prospective randomised study. *Int J Radiat Oncol Biol Phys* 2012;82:1249-55.

20. Reed NS, Mangioni C, Malmstrom H, et al. Phase III randomised study to evaluate the role of adjuvant pelvic radiotherapy in the treatment of uterine sarcomas stage I and II: an European Organisation for Research and Treatment of Cancer Gynaecological Cancer Study Group. *Eur J Cancer* 2008;44:808-18.

21. National Cancer Institute (Cancer Statistics Branch). SEER*Stat 6.6.2 Surveillance, Epidemiology and End Results Cancer Incidence Public-Use Database, 1973-2007. 2010. Bethesda, US Department of Health and Human Services.
Ref Type: Data File

22. Australian Institute of Health and Welfare (AIHW). Australian Cancer Incidence and Mortality (ACIM) books. http://www.aihw.gov.au/acim-books/ . 2007. 8-3-2012.
Ref Type: Electronic Citation

23. National Cancer Institute (Cancer Statistics Branch). SEER*Stat 5.2.2. Surveillance, Epidemiology and End Results Cancer Incidence Public-Use Database, 1973-2001. 2004. Bethesda, US Department of Health and Human Services.
Ref Type: Report

24. Chino JP, Jones E, Berchuck A, Secord AA, Havrilevsky LJ. The influence of radiation modality and lymph node dissection on survival in early-stage endometrial cancer. *Int J Radiat Oncol Biol Phys* 2012;82:1872-9.

25. Patel MK, Cote ML, Ali-Fehmi RA, etal. Trends in the utilization of adjuvant vaginal cuff brachytherapy and/or external beam radiation treatment in stage I and II endometrial cancer: a Surveillance, Epidemiology, and End-Results study. *Int J Radiat Oncol Biol Phys* 2011;83:178-84.

26. Rittenberg PVC, Lotocki RJ, Heywood MS, Krepart GV. Stage II endometrial carcinoma: Limiting post-operative radiotherapy to the vaginal vault in node-negative tumors. *Gynecol Oncol* 2005;98:434-8.

VAGINAL CANCER

In the original external beam radiotherapy (EBRT) and brachytherapy (BT) utilisation models the indications for EBRT and BT for vaginal cancer were derived from evidence-based treatment guidelines issued by major national and international organisations until December 2004. The current updated model includes guidelines published until February 2012.

Updated Guidelines

The following clinical practice guidelines for the management of vaginal cancer have not been updated since the last review:

- (SGOG) The Sydney Gynaecologic Oncology Group, Royal Prince Alfred and Liverpool Hospitals: Clinical Practice and Management Policies (1)

The following updated clinical practice guidelines for the management of vaginal cancer were identified:

- (FIGO) Federation Internationale de Gynecologie et d'Obstetrique: Staging classifications and clinical practice guidelines for gynaecologic cancers (2)
- (PDQ) National Cancer Institute PDQ Statement on the Management of Vaginal Cancer (3)
- (NSW) NSW Gynaecological Oncology Clinical Practice Guideline 2009 (4)
- (BCCA) British Columbia Cancer Agency Guidelines on Vaginal Cancer (5)
- (YCN) Yorkshire Cancer Network Guidelines for the Management of Gynaecological Cancers (6)

Indications for radiotherapy

All the indications for EBRT and for BT in the original CCORE models of optimal RT utilisation for vaginal cancer were reviewed based on the latest guideline recommendations (Figures 1 and 2 and Table 1). For EBRT, the original model included EBRT as indicated for all patients with vaginal cancer, based on PDQ recommendations (7). In the construction of the subsequent BT utilisation tree, a small sub-group of patients was identified for whom guidelines recommended primary surgical management, with RT only being required in the event of local recurrence (3) (4). This recommendation that operable patients undergo primary surgery has been included in the current combined EBRT/BT utilisation tree (3) (4) (5) (6). The tree has been further modified to differentiate between BT and EBRT indications, as outlined in Table 1.

Level of evidence

The levels of evidence supporting the indications for EBRT and BT are unchanged. None of the indications were supported by level I-II evidence.

Changes to Epidemiological Data

The epidemiological data in the vaginal cancer utilisation tree have been reviewed to see if more recent data are available through extensive electronic searches. This has been applied to the early branches in the tree for which national or state level data on cancer incidence rates and stages are available. No changes to the hierarchical quality of the epidemiological data were identified, but there were changes in the magnitude of the indications based on updated SEER data (8) (Table 2).

Incidence of Vaginal Cancer:

Since the publication of the previous radiotherapy utilisation project, the Australian national cancer incidence data published by the Australian Institute of Health and Welfare (AIHW) has been updated, with the most recent data available being 2007 data. In 2007, vaginal cancer accounted for 1.6% of gynaecological cancers and for 0.10% of all cancers in Australia (9).

Stage proportions for Vagina Cancer

The SEER database provided the most recent population level data for vaginal cancer stage distribution, and these 2004-07 data were substituted for the previous 1997-2001 data (Table 2).

Estimation of the Optimal External Beam Radiotherapy Utilisation Rate

Based on the evidence of the efficacy of radiotherapy and the most recent epidemiological data on the occurrence of indications for EBRT, the therapy is recommended in 94% of all vaginal cancer patients in Australia (Table 1 and Figure 1). The previous optimal EBRT rate for vaginal cancer derived in 2003 was 100%. The decrease in the revised optimal utilisation rate is due to the identification of a sub-group of patients in whom guidelines recommend primary surgical management (3) (4) (5) (6).

Estimation of the Optimal Brachytherapy Utilisation Rate

Based on the evidence of the efficacy of radiotherapy and the most recent epidemiological data on the occurrence of indications for BT, BT is recommended in 80% of all vagina cancer patients in Australia (Table 1 and Figure 2). The previous optimal BT rate for vaginal cancer derived in 2004 was 85%. The decrease in the revised optimal utilisation rate is due to changes in the epidemiological data, rather than any changes in the indications for BT.

Estimation of the Optimal Concurrent Chemo-Radiotherapy Utilisation Rate

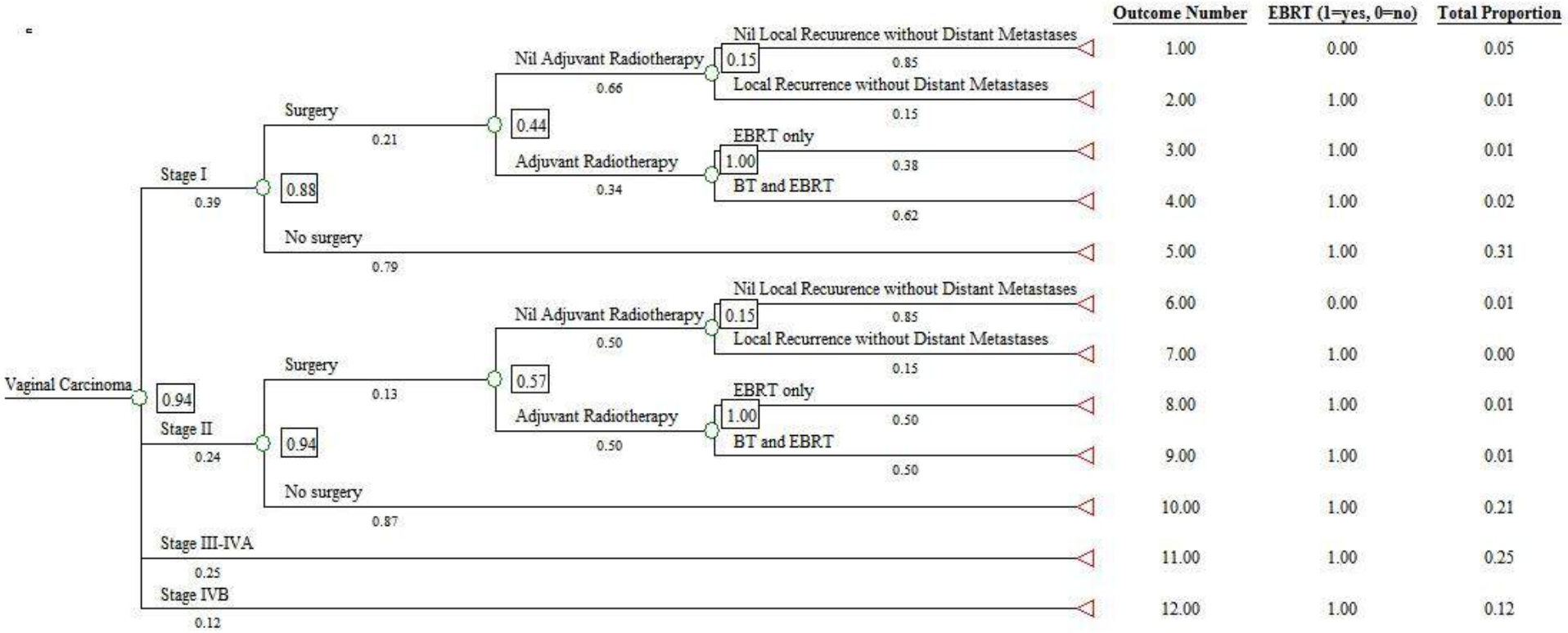
The indications for radiotherapy for vaginal cancer were reviewed to identify the indications where radiotherapy is recommended in conjunction with concurrent chemotherapy as the first treatment. Guidelines support concurrent chemo-radiotherapy (CRT) for selected (“fit enough”) patients being treated with curative EBRT based on level IV evidence (2) (4) (5) (6). In the model of optimal utilisation CRT, all patients being treated with radical EBRT and BT are recommended to receive CRT. It is acknowledged that some of these patients will not be fit to receive concurrent chemotherapy and this is dealt with by sensitivity analysis of the combined utilisation tree. Based on

this model, 78% of all vaginal cancer patients should receive concurrent radiotherapy with chemotherapy (Figure 3 and Table 3).

Sensitivity Analysis

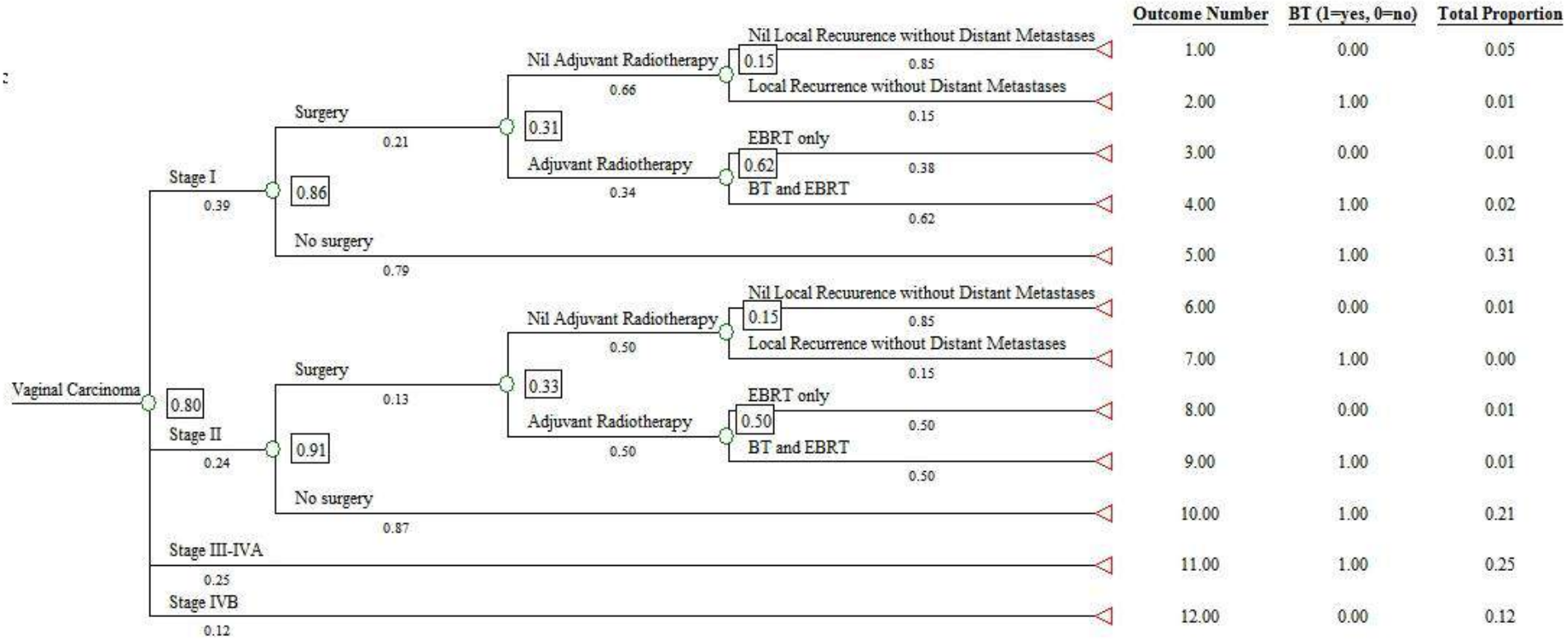
Univariate sensitivity analyses were undertaken (Figures 4-6) to assess any changes in the optimal utilisation rate for EBRT, BT and CRT that would result from different estimates of the proportions of patients with particular attributes as mentioned in Table 2. The variability in the estimate of optimal EBRT utilisation due to these uncertainties was 4% and the expected value ranged from 92% to 96% as shown in the Tornado diagram (Figure 4). The variability in the estimate of optimal BT utilisation due to these uncertainties was 6% and the expected value ranged from 77% to 83% as shown in the Tornado diagram (Figure 5). The variability in the estimate of optimal CRT utilisation due to these uncertainties was 7% and the expected value ranged from 74% to 81% as shown in the Tornado diagram (Figure 6).

Figure 1. Revised Optimal External Beam Radiotherapy Utilisation Tree for Vaginal Cancer



EBRT, External Beam Radiotherapy; BT, Brachytherapy

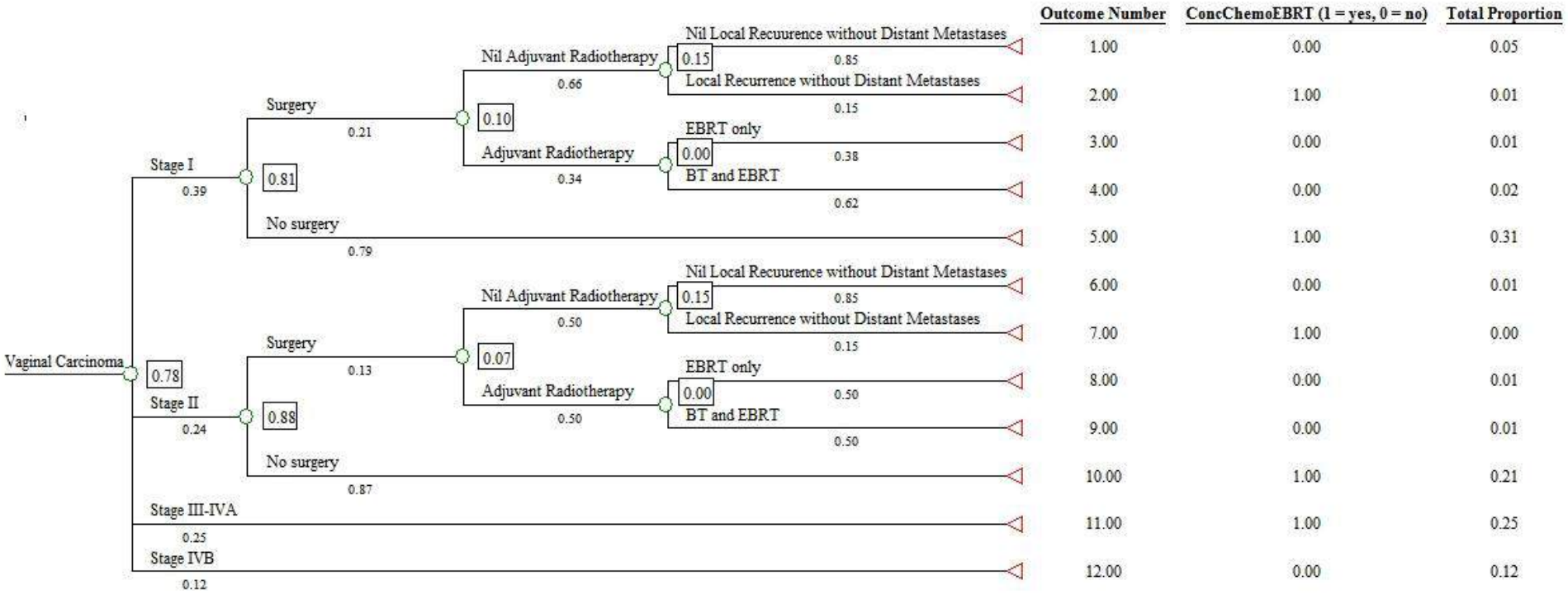
Figure 2. Revised Optimal Brachytherapy Utilisation Tree for Vaginal Cancer



Outcome Number	BT (1=yes, 0=no)	Total Proportion
1.00	0.00	0.05
2.00	1.00	0.01
3.00	0.00	0.01
4.00	1.00	0.02
5.00	1.00	0.31
6.00	0.00	0.01
7.00	1.00	0.00
8.00	0.00	0.01
9.00	1.00	0.01
10.00	1.00	0.21
11.00	1.00	0.25
12.00	0.00	0.12

EBRT, External Beam Radiotherapy; BT, Brachytherapy

Figure 3. Vaginal cancer - Optimal Utilisation Tree for Concurrent Chemo-radiation



Outcome Number	ConcChemoEBRT (1 = yes, 0 = no)	Total Proportion
1.00	0.00	0.05
2.00	1.00	0.01
3.00	0.00	0.01
4.00	0.00	0.02
5.00	1.00	0.31
6.00	0.00	0.01
7.00	1.00	0.00
8.00	0.00	0.01
9.00	0.00	0.01
10.00	1.00	0.21
11.00	1.00	0.25
12.00	0.00	0.12

EBRT, External Beam Radiotherapy; BT, Brachytherapy; ConcChemoEBRT, Concurrent Chemo-Radiotherapy

Table 1: Vaginal Cancer. Indications for radiotherapy - Levels and sources of evidence

Original BTU study[a]					Updates 2012					
Outcome Nos. in Updated Tree	Clinical Scenario	Treatment Indicated	Level of Evidence	Proportion of all Vaginal Cancer	Change of Indication	Guideline updated	Current level of evidence	Change to proportion of all vaginal cancer		References
								Yes/No	Updated value	
2	Stage I; Surgery; Nil adjuvant RT; Local recurrence without distant metastases	EBRT and BT	IV	<0.01	No	Yes	IV	No	<0.01	PDQ (3), NSW (4)
3	Stage I; Surgery; Close or positive margin (adjuvant RT); Adjuvant RT includes EBRT only	EBRT	IV	0.01	Yes[b]	Yes	IV	No	0.01	PDQ (3)
4	Stage I; Surgery; Close or positive margin (adjuvant RT); Adjuvant RT includes BT	EBRT and BT	IV	0.02	No	Yes	IV	No	0.02	PDQ (3)

Original BTU study[a]					Updates 2012					
Outcome Nos. in Updated Tree	Clinical Scenario	Treatment Indicated	Level of Evidence	Proportion of all Vaginal Cancer	Change of Indication	Guideline updated	Current level of evidence	Change to proportion of all vaginal cancer		References
								Yes/No	Updated value	
5	Stage I; No surgery	EBRT and BT	III	0.32	No	Yes	III	Yes	0.31	FIGO (2), PDQ (3), NSW (4), BCCA (5), YCN (6), SGOG (1)
7	Stage II; Surgery; Nil adjuvant RT; Local recurrence without distant metastases	EBRT and BT	IV	<0.01	No	Yes	IV	No	<0.01	PDQ (3), NSW (4)
8	Stage II; Surgery; Close or positive margin (adjuvant RT); Adjuvant RT includes EBRT only	EBRT	IV	<0.01	Yes[b]	Yes	IV	No	<0.01	PDQ (3)

Original BTU study[a]					Updates 2012					
Outcome Nos. in Updated Tree	Clinical Scenario	Treatment Indicated	Level of Evidence	Proportion of all Vaginal Cancer	Change of Indication	Guideline updated	Current level of evidence	Change to proportion of all vaginal cancer		References
								Yes/No	Updated value	
9	Stage II; Surgery; Close or positive margin (adjuvant RT); Adjuvant RT includes BT	EBRT and BT	IV	<0.01	No	Yes	IV	No	<0.01	PDQ (3)
10	Stage II; No surgery	EBRT and BT	III	0.24	No	Yes	III	Yes	0.21	FIGO (2), PDQ (3), NSW (4), BCCA (5), YCN (6), SGOG (1)
11	Stage III-IVA	EBRT and BT	III	0.24	No	Yes	III	Yes	0.25	FIGO (2), PDQ (3), NSW (4), BCCA (5), YCN (6), SGOG (1)
12	Stage IVB	EBRT	IV	0.07	Yes[b]	Yes	IV	Yes	0.12	PDQ (3), YCN (6)
Proportion of all vaginal cancer patients in whom EBRT was recommended[a]				1.00 (100%)	**Updated Proportion of all vaginal cancer patients in whom EBRT is recommended**				**0.94 (94%)**	
Proportion of all vaginal cancer patients in whom BT was recommended				0.85 (85%)	**Updated Proportion of all vaginal cancer patients in whom BT is recommended**				**0.80 (80%)**	

[a]Original RTU study had EBRT indicated for all vaginal cancer patients
[b]EBRT monotherapy not included in original BT utilisation tree
Abbreviations: BTU, Brachytherapy Utilisation; RT, Radiotherapy; EBRT, External Beam Radiotherapy; BT, Brachytherapy; PDQ, National Cancer Institute PDQ Statement on the Management of Vaginal Cancer; NSW, Gynaecological Oncology Clinical Practice Guidelines, NSW, Australia; FIGO, Federation Internationale de Gynecologie et d'Obstetrique staging classifications and clinical practice guidelines in the management of gynaecologic cancers; BCCA, British Columbia Cancer Agency Guidelines on Vaginal Cancer; YCN, Yorkshire Cancer Network Guidelines for the Management of Gynaecological Cancers; SGOG, Clinical Practice and Management Policies, The Sydney Gynaecologic Oncology Group, Royal Prince Alfred and Liverpool Hospitals, Sydney

Table 2: Vaginal Cancer. The incidence of attributes used to define indications for radiotherapy

Original BTU Study[a,b]				Updates 2012			
Population or sub-population of interest	**Attribute**	**Proportion of population with the attribute**	**Quality of Information**	**Change in proportion of population with attribute Yes/ No**	**Updated Proportion**	**Updated Quality of Information**	**Updated Reference**
All registry cancers	Gynae cancer	0.045	α	Yes	0.039	α	AIHW 2011 (9)
Gynae cancer	Vaginal Cancer	0.017	α	Yes	0.016	α	AIHW 2011 (9)
Vaginal cancer	Stage I	0.41	γ	Yes	0.39	γ	SEER 2004-2007 (8)
Stage I	Surgery	0.21	γ	No	N/A	N/A	N/A
Stage I; Surgery	Nil adjuvant RT	0.66	γ	No	N/A	N/A	N/A
Stage I; Surgery; Nil adjuvant RT	Local recurrence without distant metastases	0.15	ζ	No	N/A	N/A	N/A
Stage I; Surgery; Adjuvant RT	Adjuvant RT includes EBRT	1.0	γ	No	N/A	N/A	N/A
Stage I; Surgery; Adjuvant RT	Adjuvant RT includes BT	0.62	γ	No	N/A	N/A	N/A

Original BTU Study[a,b]				Updates 2012			
Population or sub-population of interest	**Attribute**	**Proportion of population with the attribute**	**Quality of Information**	**Change in proportion of population with attribute Yes/ No**	**Updated Proportion**	**Updated Quality of Information**	**Updated Reference**
Vaginal cancer	Stage II	0.28	γ	Yes	0.24	γ	SEER 2004-2007 (8)
Stage II	Surgery	0.13	γ	No	N/A	N/A	N/A
Stage II; Surgery	Nil adjuvant RT	0.50	γ	No	N/A	N/A	N/A
Stage II; Surgery; Nil adjuvant RT	Local recurrence without distant metastases	0.15	ζ	No	N/A	N/A	N/A
Stage I; Surgery; Adjuvant RT	Adjuvant RT includes EBRT	1.0	γ	No	N/A	N/A	N/A
Stage II; Surgery; Adjuvant RT	Adjuvant RT includes BT	0.50	γ	No	N/A	N/A	N/A
Vaginal cancer	Stage III-IVA	0.24	γ	Yes	0.25	γ	SEER 2004-2007 (8)
Vaginal cancer	Stage IVB	0.07	γ	Yes	0.12	γ	SEER 2004-2007 (8)

[a]Original RTU study had EBRT indicated for all vaginal cancer patients
[b]EBRT monotherapy not included in original BT utilisation tree
Abbreviations: BTU, Brachytherapy Utilization; Gynae, Gynaecological; RT, Radiotherapy; EBRT, External beam radiotherapy; BT, Brachytherapy; N/A, Not Applicable

Table 3: Vaginal Cancer. Indications for concurrent chemoradiotherapy - levels and sources of evidence

Outcome no. in tree	Clinical scenario	Level of evidence	References	Proportion of all Vaginal Cancer patients
2	Stage I; Surgery; Nil adjuvant RT; Local recurrence without distant metastases	IV	FIGO (2) NSW (4) BCCA (5) YCN (6)	<0.01
5	Stage I; No surgery	IV	FIGO (2) NSW (4) BCCA (5) YCN (6)	0.31
7	Stage II; Surgery; Nil adjuvant RT; Local recurrence without distant metastases	IV	FIGO (2) NSW (4) BCCA (5) YCN (6)	<0.01
10	Stage II; No surgery	IV	FIGO (2) NSW (4) BCCA (5) YCN (6)	0.21
11	Stage III-IVA	IV	FIGO(2) NSW (4) BCCA (5) YCN (6)	0.25
The total proportion of all patients with Vaginal Cancer in whom concurrent chemoradiotherapy is recommended				**0.78 (78%)**

Abbreviations: RT, Radiotherapy; FIGO, Federation Internationale de Gynecologie et d'Obstetrique staging classifications and clinical practice guidelines in the management of gynaecologic cancers; NSW, Gynaecological Oncology Clinical Practice Guidelines, NSW, Australia; BCCA, British Columbia Cancer Agency Guidelines on Vaginal Cancer; YCN, Yorkshire Cancer Network Guidelines for the Management of Gynaecological Cancers

Figure 4. Vaginal Cancer External Beam Radiotherapy. Tornado Diagram for Univariate Sensitivity Analysis

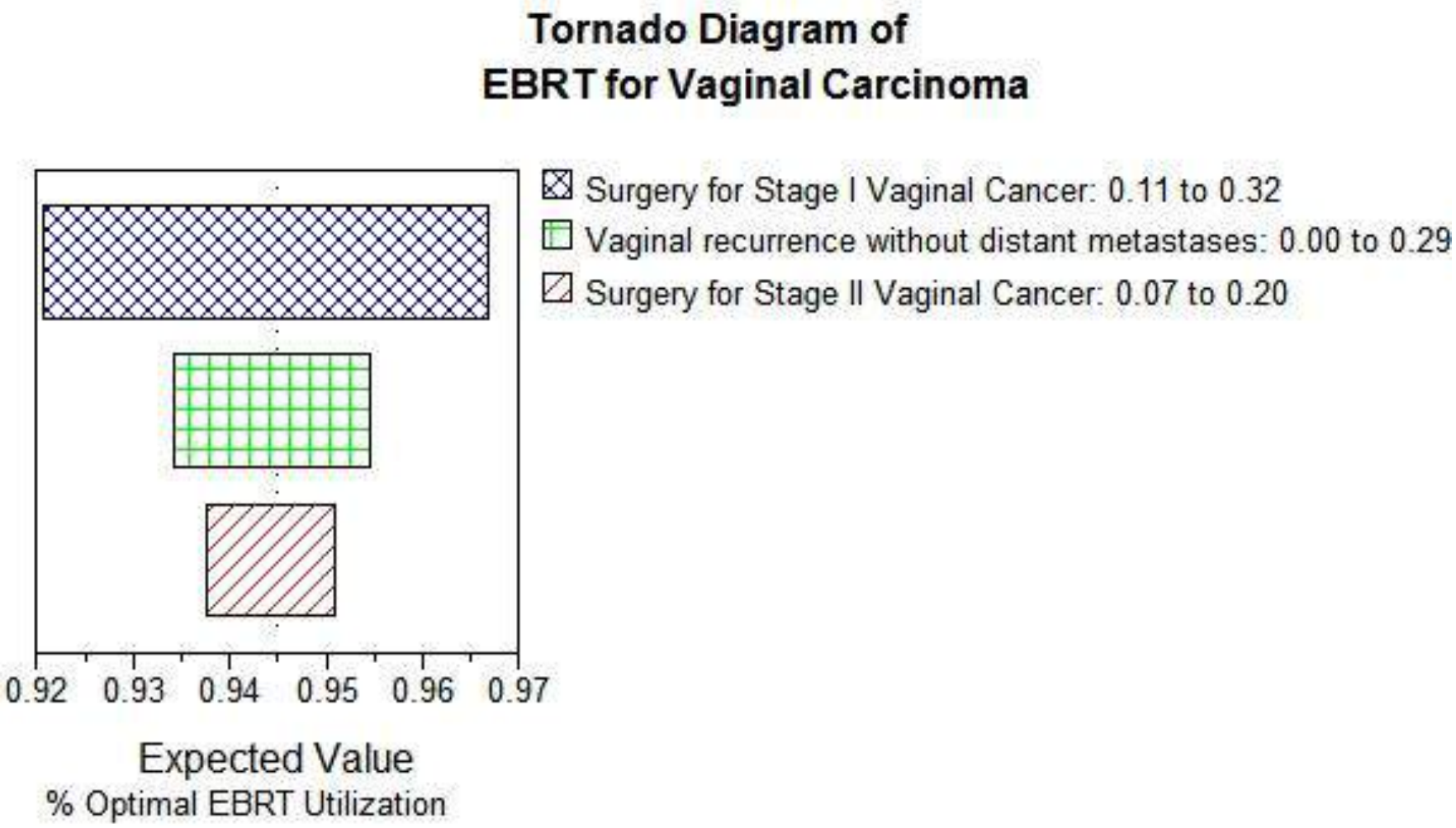


Figure 5. Vaginal Cancer Brachytherapy. Tornado Diagram for Univariate Sensitivity Analysis

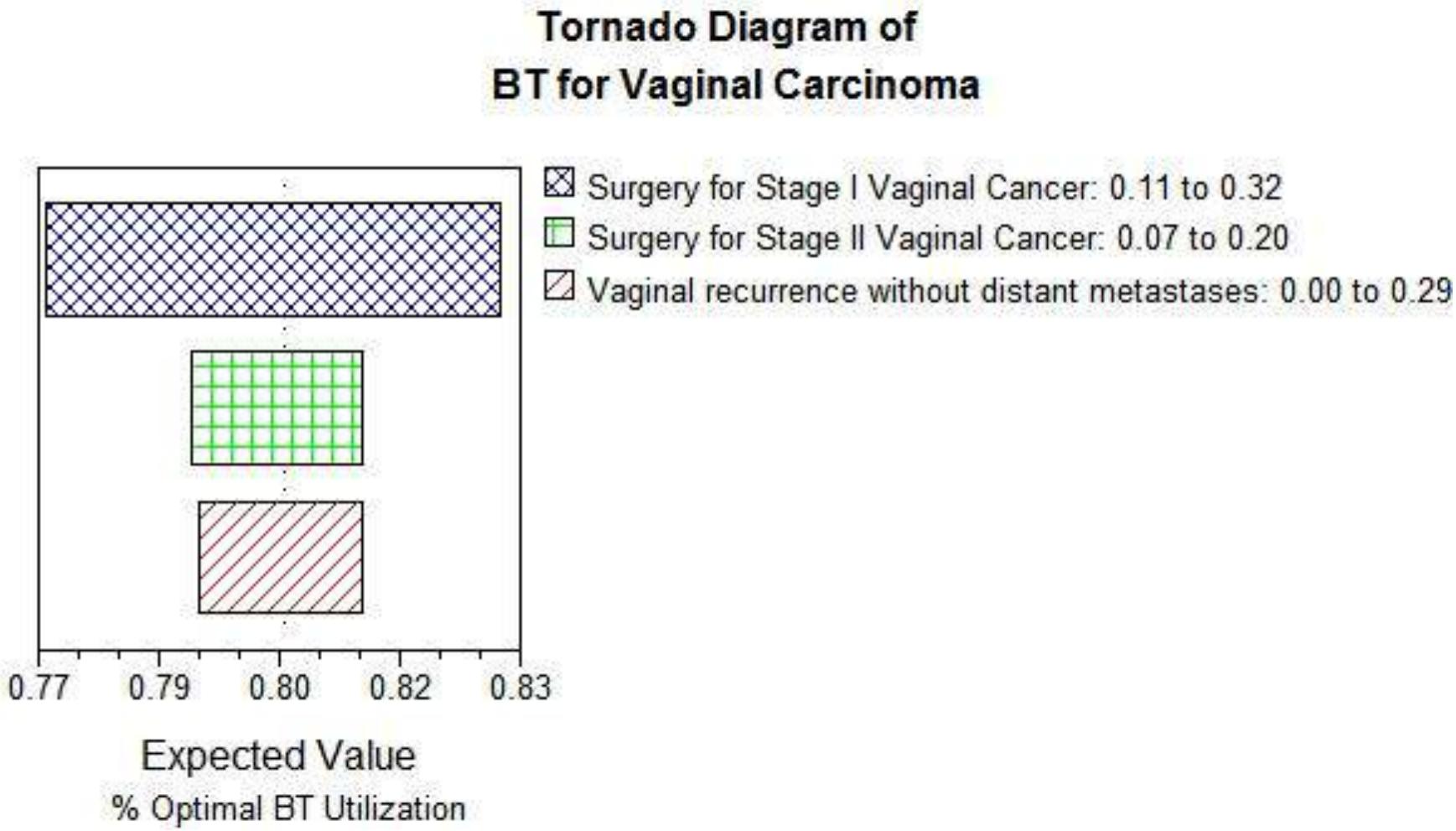
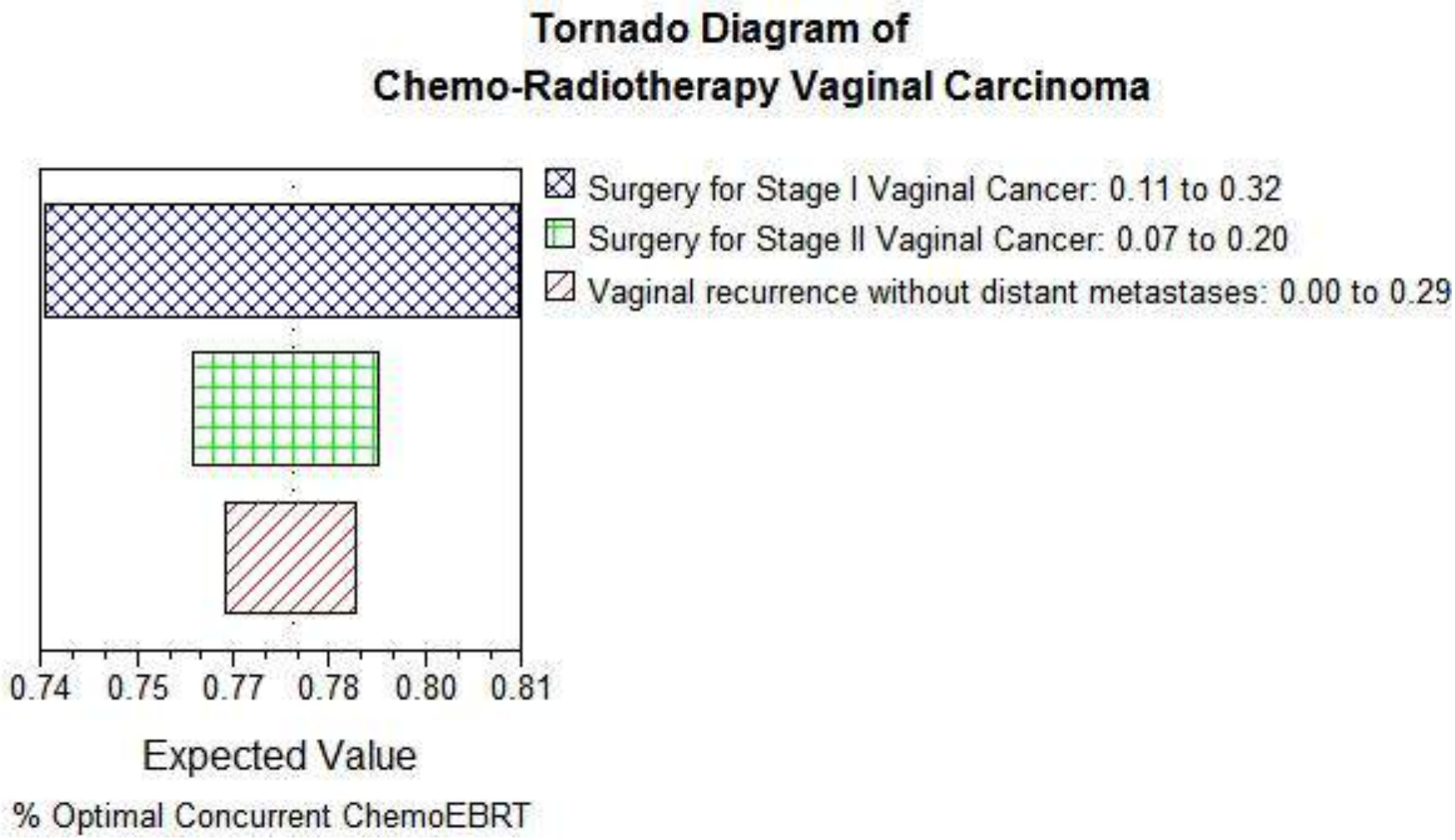


Figure 6. Vaginal Cancer Concurrent Chemo-Radiation. Tornado Diagram for Univariate Sensitivity Analysis



References

1. Sydney Gynaecologic Oncology Group, Royal Prince Alfred and Liverpool Hospitals Sydney. Clinical Practice and Management Policies. Johnathan Carter. 1-6-2004. Sydney, Johnathan Carter.
   Ref Type: Serial (Book,Monograph)

2. FIGO Committee on Gynecologic Oncology. Staging classifications and clinical practice guidelines for gynaecologic cancers. www.figo.org . 2006. 12-9-2012.
   Ref Type: Electronic Citation

3. National Cancer Institute. PDQ Vaginal Cancer Treatment. http://cancer.gov/cancertopics/pdq/treatment/vaginal/HealthProfessional . 28-7-2011. 19-10-2011.
   Ref Type: Electronic Citation

4. Greater Metropolitan Clinical Taskforce (GMCT). Best clinical practice: Gynaecological cancer guidelines 2009. 2009. Sydney, NSW Department of Health. 2009.
   Ref Type: Serial (Book,Monograph)

5. BC Cancer Agency. Cancer Management Guidelines >> Gynecology >> 9. Vagina. http://www.bccancer.bc.ca . 2010. 19-10-2011.
   Ref Type: Electronic Citation

6. Yorkshire Cancer Network Gynaecology NSSG. Guidelines for the Management of Gynaecological Cancers. http://www.ycn.nhs.uk/ . 2011. 19-10-2011.
   Ref Type: Electronic Citation

7. National Cancer Institute. PDQ Cancer Information Summaries: Treatment of vaginal cancer. www.nci.nih.gov . 2002. 8-3-2002.
   Ref Type: Electronic Citation

8. National Cancer Institute (Cancer Statistics Branch). SEER*Stat 6.6.2 Surveillance, Epidemiology and End Results Cancer Incidence Public-Use Database, 1973-2007. 2010. Bethesda, US Department of Health and Human Services.
   Ref Type: Data File

9. Australian Institute of Health and Welfare (AIHW). Australian Cancer Incidence and Mortality (ACIM) books. http://www.aihw.gov.au/acim-books/ . 2007. 8-3-2012.
   Ref Type: Electronic Citation

VULVAL CANCER

Evidence-based treatment guidelines for vulval cancer published by major national and international organisations since the completion of the previous radiotherapy utilisation study in July 2003 have been identified and reviewed.

Updated Guidelines

The following new or updated guidelines were reviewed:

- NSW Greater Metropolitan Clinical Taskforce (GMCT) Gynaecological Oncology Group best practice guidelines, 2009 (1)
- National Cancer Institute (NCI). Vulvar cancer Treatment (PDQ®), 2012 (2)
- NHS Pan Birmingham Cancer Network guidelines on management of vulval cancer, 2011 (3)
- BC Cancer Agency gynaecology cancer management guidelines, 2011 (4)
- International Federation of Gynaecology and Obstetrics (FIGO) guidelines on gynaecological cancers, 2006 (5)
- Society of Obstetricians and Gynaecologists of Canada (SOGC) guidelines on management of vulval cancer, 2006 (6)
- Royal College of Obstetricians and Gynaecologists (RCOG) guidelines on management of vulval cancer, 2006 (7)

Indications for radiotherapy

All the indications for external beam radiotherapy (RT) in the original CCORE model of optimal radiotherapy utilisation for vulval cancer have been reviewed and updated based on the latest guideline recommendations (Table 1 and Figure 1). *The tree is newly designed based on TNM stage distribution.*

Level of evidence

The indications of RT for vulval cancer have been derived from evidence-based treatment guidelines issued by major national and international organisations. Eight outcomes in the model have RT indications and four these are supported by level II evidence comprising 30% population with vulval cancer (Table 1 and Figure 1).

Epidemiology of cancer stages

The published recent epidemiological data on vulval cancer have been identified through extensive electronic search using the key words ‘epidemiology vulval cancer’, ‘vulval cancer stage‘, ‘incidence’, ‘local control’, ‘radiotherapy treatment’, ‘survival’, ‘treatment outcome’ in various combinations. Table 2 provides an updated list of data used and assessment of the hierarchical quality of that data. According to the updated national data on cancer statistics published by AIHW, vulval cancer

accounted for 0.25% of all cancers and 6% of all gynaecological cancers in Australia in 2008 (8). For epidemiological data of most of the clinical scenarios in the model SEER data have been used (9).

Low incidence of vulval cancer combined with low proportion of recurrences lead to scarcity and variability of good quality published studies on recurrent cancers; according to the Royal College of Gynaecology guidelines, the proportion of patients with post-surgical local recurrence for vulval cancer varied in the range of 15-33% (7). For our model, a multi-institutional European study (Portuguese Cancer Institute) data been used for the proportion with recurrence (10) and a British retrospective study (11) with relatively large sample size and detailed treatment description been selected for epidemiological data on treatment scenarios (outcomes 3 and 9) for recurrent cancers (Table 2).

Estimation of the optimal radiotherapy utilisation

From the evidence on the efficacy of RT and the most recent epidemiological data, the proportion of vulval cancer patients in whom RT would be recommended is 39% (Table 1 and Figure 1) compared with the original estimate of 34%. The change is due to the revised epidemiological data for the newly designed model.

Estimation of the optimal combined radiotherapy and chemotherapy utilisation

The indications of RT for vulval cancer were reviewed to identify those indications where the therapy is recommended in conjunction with concurrent chemotherapy (CRT). According to the best available evidence concurrent CRT is indicated as definitive treatment for initial or recurrent disease that is unresectable, usually because of location, extent, or fixity (7;12). Our model predicted that 15% of all vulval cancer patients would benefit from addition of CRT to their treatment (Table 3 and Figure 2).

Sensitivity analysis

Guidelines recommend that patients with early vulval cancer with either two or more lymph node metastasis, with extracapsular spread, or with bilateral microscopic groin metastases should receive postoperative bilateral groin and pelvic radiation (1;5;6); till now there is no international consensus regarding indication of adjuvant RT for node positive vulval cancers where only one groin node is involved; a large German study presented at the 2012 ASCO conference indicated that only 57% of lymph node positive vulval cancer patients received RT postoperatively (13). Epidemiological data on the proportion of patients with node positive vulval cancer for whom RT is indicated varied from 65% to 76% (14;15); also single institute based epidemiological data on local recurrence (15-33%) (12) and related treatment data (23-38%) varied (11;16) (Table 2). Hence, a sensitivity analysis was carried out including all these data variability that showed a variation in RT optimal utilisation from 37% to 42% (Figure 3).

Table 1: Vulval cancer. Indications for radiotherapy - Levels and sources of evidence

Outcome No. in Tree	Clinical Scenario	Guideline updated	Level of evidence	Proportion of all vulval cancer patients	References
1	Vulval cancer, Stage I-II, operable, adjuvant therapy indicated	Yes	III	0.03	GMCT (1), FIGO (5), SOGC (6), RCOG (7)
3	Vulval cancer, Stage I-II, operable, no adjuvant therapy, local recurrence, RT with or without surgery indicated	Yes	III	0.04	NCI (2), NHS (3), SOGC (6), RCOG (7), Salom (12)
5	Vulval cancer, Stage I-II, inoperable	Yes	II	0.03	GMCT (1), NCI (2), NHS (3), FIGO (5), SOGC (6)
6	Vulval cancer, stage III-IVA, operable, node positive	Yes	II	0.15	GMCT (1), NCI (2), BCA (4), FIGO (5), SOGC (6), RCOG (7)
7	Vulval cancer, Stage III-IVA, operable, node negative, adjuvant therapy indicated	Yes	III	0.01	GMCT (1), FIGO (5), SOGC (6)
9	Vulval cancer, Stage III-IVA, operable, node negative, no adjuvant therapy, local recurrence, RT with or without surgery indicated	Yes	III	0.01	NCI (2), NHS (3), SOGC (6), RCOG (7), Salom (12)
11	Vulval cancer, Stage III-IVA, inoperable	Yes	II	0.08	GMCT (1), NCI (2), NHS (3), BCA (4), FIGO (5), SOGC (6), RCOG (7)
12	Vulval cancer, stage IVB	Yes	II	0.04	NCI (2), SOGC (6), RCOG (7)
Updated proportion of all vulval cancer patients in whom radiotherapy is recommended				**0.39 (39%)**	
Original proportion of all vulval cancer patients in whom radiotherapy was recommended				0.34 (34%)	

Table 2: Vulval cancer. The incidence of attributes used to define indications for radiotherapy

Population or subpopulation of interest	Attribute	Proportion of population with the attribute	Quality of Information	References
All registry cancers	Vulval cancer	0.25	α	AIHW 2008 (8)
Vulval cancer	Stage I-II	0.67	γ	SEER 2011 (9)
Vulval cancer , Stage I-II	Operable	0.96	γ	SEER 2011 (9)
Stage I-II, operable	Adjuvant therapy indicated	0.05	γ	SEER 2011 (9)
Stage I-II, operable, no adjuvant therapy	Local recurrence	0.27	ε	Fonseca-Moutinho et al 2000 (10)
Stage I-II, operable, no adjuvant therapy, local recurrence	RT with or without surgery indicated	0.23 0.38	ζ ζ	Piura et al 1993 (11) Hruby et al 2000 (16)
Vulval cancer, stage III-IVA	Operable	0.71	γ	SEER 2011 (9)
Vulval cancer, stage III-IVA, Operable	Node positive	0.75 0.57 0.76 0.65	γ ε ζ ζ	SEER 2011 (9) Mahner et al 2012 (13) Van der Velden et al 1995 (14) Paladini et al 1994 (15)

Population or subpopulation of interest	Attribute	Proportion of population with the attribute	Quality of Information	References
Vulval cancer, stage III-IVA, Operable, node negative	Adjuvant therapy indicated	0.28	γ	SEER 2011 (9)
Vulval cancer, stage III-IVA, operable, node negative, no adjuvant therapy, local recurrence	RT with or without surgery indicated	0.77 0.62	ζ ζ	Piura et al 1993 (11) Hruby et al 2000 (16)
Vulval cancer	Stage IVB	0.04	γ	SEER 2011 (9)

Table 3: Vulval cancer. Indications for concurrent chemoradiotherapy (CRT) - Levels and sources of evidence

Outcome No. in Tree	Clinical Scenario	Level of Evidence	References	Proportion of all vulval cancer patients
3	Vulval cancer, Stage I-II, operable, no adjuvant therapy needed, local recurrence, RT with or without surgery indicated	III	NCI (2), NHS (3), Salom (12)	0.04
5	Vulval cancer, stage I-II, inoperable	III	GMCT (1), NCI (2), NHS (3), BCA (4), FIGO (5), SOGC (6), RCOG (7)	0.03
9	Vulval cancer, Stage III-IVA, operable, no adjuvant therapy needed, local recurrence, RT with or without surgery indicated	IIII	NCI (2), NHS (3), Salom (12)	<0.01
11	Vulval cancer, Stage III-IVA, inoperable	III	GMCT (1), NCI (2), NHS (3), BCA (4), FIGO (5), SOGC (6), RCOG (7)	0.08
The total proportion of all patients with vulval cancer in whom concurrent chemoradiotherapy (CRT) is recommended				**0.15 (15%)**

Figure 1. Vulval cancer Radiotherapy (RT) Utilization Tree

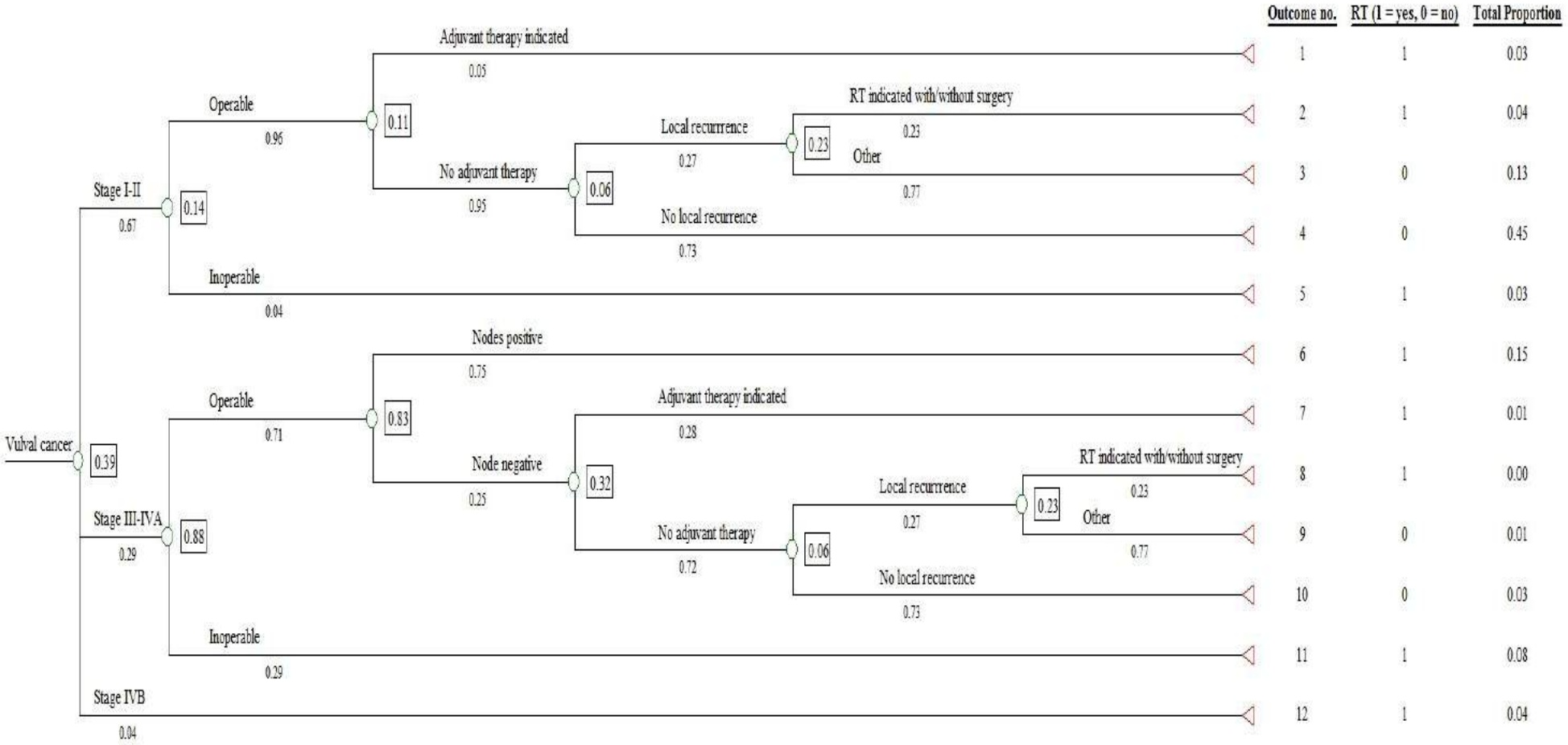


Figure 2. Vulval cancer Concurrent ChemoRadiotherapy (CRT) Utilization Tree

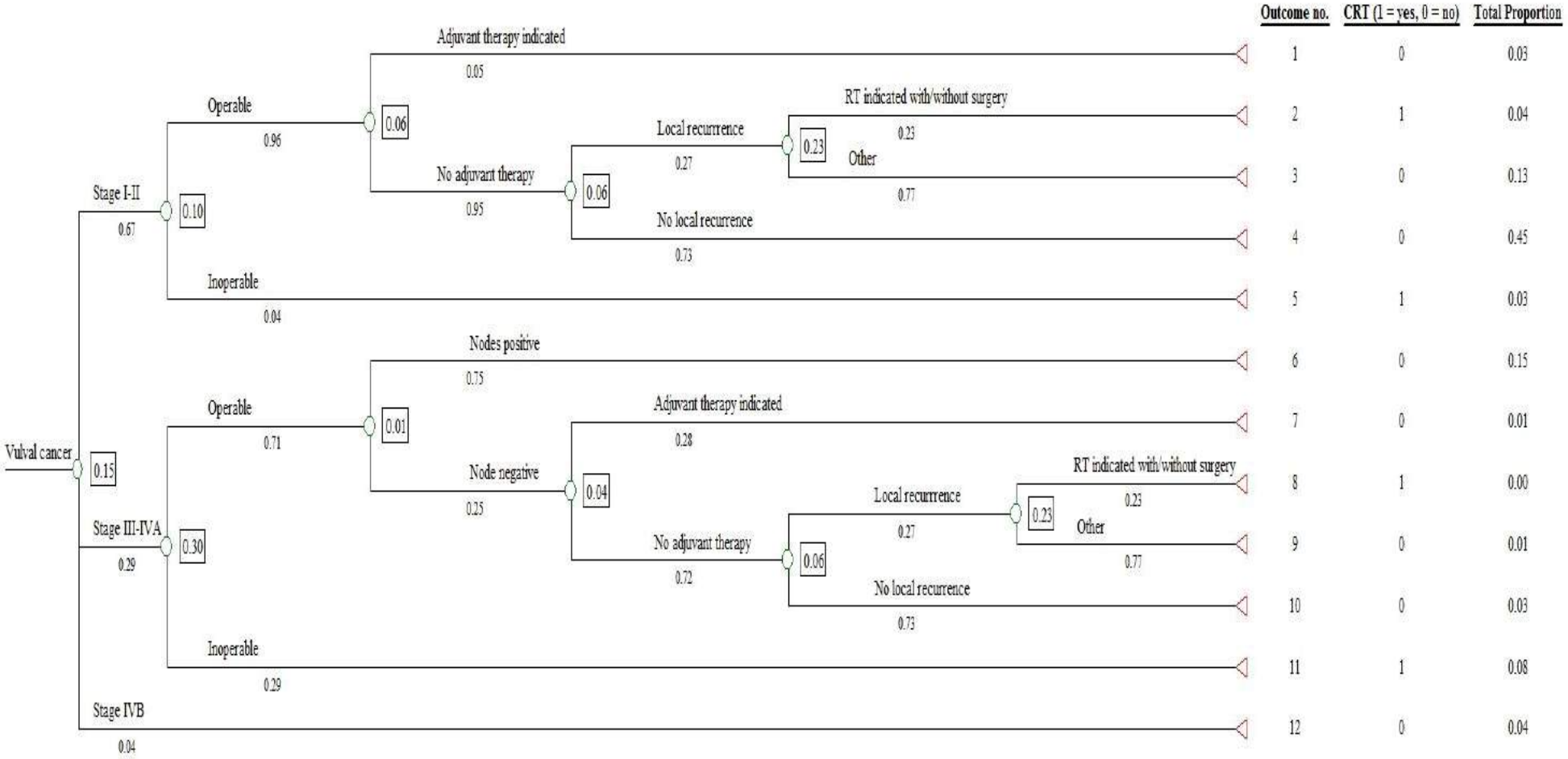
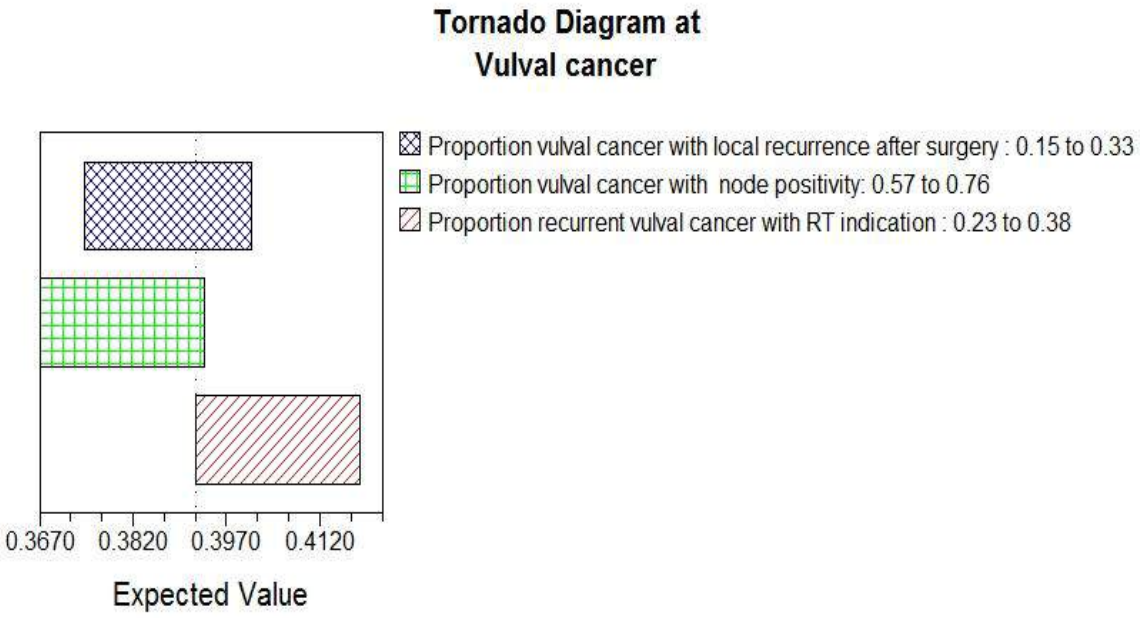


Figure 3. Tornado diagram: univariate sensitivity analyses for RT utilisation



References

1. Greater Metropolitan Clinical Taskforce (GMCT). Best clinical practice: Gynaecological cancer guidelines 2009. Sydney: NSW Department of Health; 2009.

2. National Cancer Institute (NCI). Vulvar cancer treatment (PDQ). Available at: http://www cancer gov/cancertopics/pdq/treatment/vulvar/HealthProfessional 2012 [cited 2012 Aug 31];

3. NHS Pan Birmingham Cancer Network. Guideline for the management of vulval cancer . Available at: http://www birminghamcancer nhs uk/uploads/document_file/document/4df20ca0358e987b4a00199a/guideline_for_the_management_of_vulval_cancer_version_3 0 pdf 2011 [cited 2012 Aug 31];

4. BC Cancer Agency. Cancer management guidelines: Gynecology. Available at: http://www bccancer bc ca/HPI/CancerManagementGuidelines/Gynecology/Vulva/default htm 2011 [cited 2012 Aug 31];

5. FIGO Committee on Gynecologic Oncology. FIGO staging classifications and clinical practice guidelines in the management of gynecologic cancers. 2006 Oct.

6. Society of Obstetricians and Gynaecologists of Canada (SOGC). Management of squamous cell cancer of the vulva. 2006.

7. Royal College of Obstetricians and Gynaecologists (RCOG). Management of vulval cancer. 2006.

8. Australian Institute of Health and Welfare (AIHW). Australian Cancer Incidence and Mortality (ACIM) books. Available from http://www aihw gov au/acim-books/ 2012 [cited 2012 Apr 16];

9. Surveillance Research Program, National Cancer Institute SEER*Stat software (seer.cancer.gov/seerstat). Version 7.0.5. [computer program]. Bethesda, MD: National Cancer Institute (NCI); 2011.

10. Fonseca-Moutinho JA, Coelho MC, Silva DP. Vulvar squamous cell carcinoma. Prognostic factors for local recurrence after primary en bloc radical vulvectomy and bilateral groin dissection. J Reprod Med 2000 Aug;45(8):672-8.

11. Piura B, Masotina A, Murdoch J, et al. Recurrent squamous cell carcinoma of the vulva: a study of 73 cases. Gynecol Oncol 1993 Feb;48(2):189-95.

12. Salom EM, Penalver M. Recurrent vulvar cancer. Curr Treat Options Oncol 2002 Apr;3(2):143-53.

13. Mahner S, et al. Impact of adjuvant therapy in lymph-node positive vulvar cancer: The AGO CARE 1 study. OncoLink Scientific Meetings Coverage; OncoLink at ASCO 2012. Available from: http://www oncolink org/Conferences/conferences cfm?c=3 2012 [cited 2012 Sep 12];

14. van der V, van Lindert AC, Lammes FB, et al. Extracapsular growth of lymph node metastases in squamous cell carcinoma of the vulva. The impact on recurrence and survival. Cancer 1995 Jun 15;75(12):2885-90.

15. Paladini D, Cross P, Lopes A, Monaghan JM. Prognostic significance of lymph node variables in squamous cell carcinoma of the vulva. Cancer 1994 Nov 1;74(9):2491-6.

16. Hruby G, MacLeod C, Firth I. Radiation treatment in recurrent squamous cell cancer of the vulva. Int J Radiat Oncol Biol Phys 2000 Mar 15;46(5):1193-7.

OTHER CANCERS

In this project, models of optimal radiotherapy utilisation have been constructed for all cancers with an incidence of > 1% in Australia based on the primary site of origin. In addition there are a number of comparatively rarer cancers that each have an incidence of <1% in Australia. These are designated as “other cancers” in the optimal radiotherapy utilisation tree and together comprised 5.4% of all cancers in Australia in 2008 according to data from the Australian Institute of Health and Welfare (1). These “other” cancers include mesotheliomas, skin cancers (excluding melanoma, squamous and basal cell carcinomas) and primary cancers of the small intestine, anus, soft tissue, bone and biliary tract as well as other rarer malignancies arising from other cancer sites. A few of these malignancies are commonly treated with radiotherapy (such as soft tissue sarcomas, anal cancers and Merkel cell cancers) and others are rarely treated with radiation.

A simplified tree (Figure 1) has been created for the group of miscellaneous “other” cancers. All cancer sites that constitute 5% or more of this group of miscellaneous “other” cancers based on AIHW incidence rates in 2008 (1) have been shown separately in the tree and end in either a recommendation for radiotherapy or no radiotherapy. Radiotherapy is indicated for all anal cancers (2;3) and all soft tissue sarcomas (4) based on guideline recommendations. Radiotherapy is indicated for half of all non-melanoma, non-squamous/basal cell skin cancers based on an assumption that this group would be recommended radiation for Merkel cell carcinomas (5) or for close/positive margins. (Squamous and basal cell skin cancers are not registered cancers in Australia and therefore are not included in national or state cancer registry data; a separate radiotherapy utilisation tree has been constructed for melanoma).

The management of the commonest paediatric cancers, i.e. brain cancer, leukaemias and lymphomas are included in the relevant chapters for those cancer sites. Other paediatric cancers either arise from uncommon primary sites with incidence of <1% (eg. retinoblastoma, neuroblastoma) or constitute a tiny proportion of a particular cancer site [eg. only 1% of kidney cancers in Australia in 2008 arose in patients aged under 20 years (1)] and hence have not been discussed separately.
According to the revised model, radiotherapy is indicated in 19% of this group of “other” cancers. This is likely to be an under-estimate since rare indications for radiotherapy such as palliative radiotherapy for mesothelioma are not included in the model. A different approach was taken in the original radiotherapy utilisation model, where an arbitrary assumption was made that 50% of this group of “other” cancers would receive radiotherapy and sensitivity analysis was conducted for a recommendation for radiotherapy from 0-100% of the group.

Figure 1. Revised Optimal Radiotherapy Utilisation Tree for "Other Cancers"

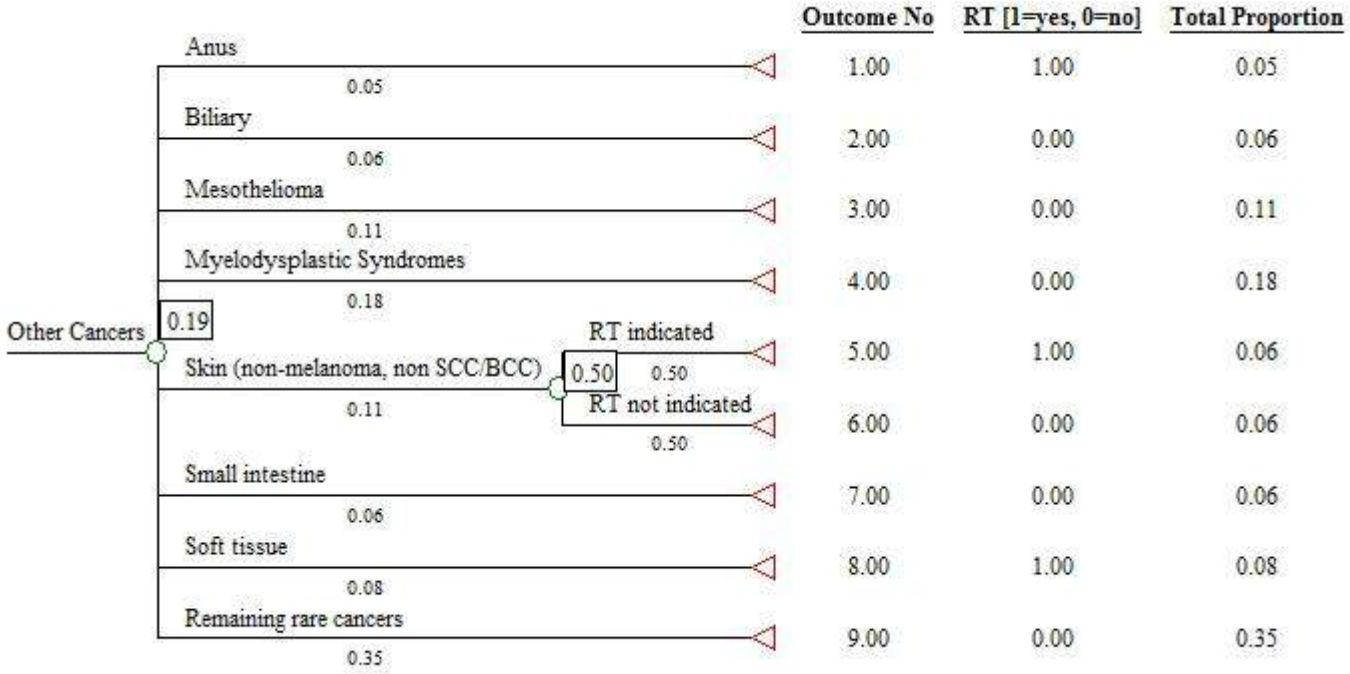


Table 1: "Other" Cancers. Indications for radiotherapy - Levels and sources of evidence

Updates 2012							
Outcome No. in Tree	**Clinical Scenario**	**Change of Indication**	**Guideline updated**	**Current level of evidence**	**Change to proportion of all "other" cancer**		**References**
					Yes/ No	**Updated value**	
1	Anal Cancer	N/A (new tree)	N/A (new tree)	II	Yes	0.05	NCCN (2), NCI PDQ (3)
5	Skin - Merkel Cell Cancer	N/A (new tree)	N/A (new tree)	I	Yes	0.06	NCCN (5)
8	Soft tissue sarcomas	N/A (new tree)	N/A (new tree)	III	Yes	0.08	NCCN (4)
Updated proportion of all patients with "Other" cancers in whom radiotherapy is recommended						**0.19 (19%)**	
Original proportion of all patients with "Other" cancers in whom radiotherapy is recommended (2003 study)						0.50 (50%)	

Table 2: "Other" Cancers. The incidence of attributes used to define indications for radiotherapy

Population or subpopulation of interest	Attribute	Proportion of populations with this attribute	Quality of information	References
All Registry Cancers	"Other" Cancers	0.054 (5.4%)	α	AIHW 2008 (1)
Other Cancers	Anal Cancer	0.05	α	AIHW 2008 (1)
Other Cancers	Biliary Cancer	0.06	α	AIHW 2008 (1)
Other Cancers	Mesothelioma	0.11	α	AIHW 2008 (1)
Other Cancers	Myelodysplastic Syndromes	0.18	α	AIHW 2008 (1)
Other Cancers	Skin (non-melanoma, non-SCC/BCC)	0.11	α	AIHW 2008 (1)
Skin (non-melanoma, non-SCC/BCC)	Proportion treated with radiotherapy	0.50	N/A	Assumption
Other Cancers	Small Intestine	0.06	α	AIHW 2008 (1)
Other Cancers	Soft tissue	0.08	α	AIHW 2008 (1)
Other Cancers	Remaining rare cancers	0.35	α	AIHW 2008 (1)

References

1. Australian Institute of Health and Welfare (AIHW). Cancer Data (Excel Pivot Table). http://www.aihw.gov.au/cancer-data/ . 2012. 8-10-2012.
   Ref Type: Electronic Citation

2. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Anal Carcinoma V1.2013. http://www.nccn.org/professionals/physician_gls/pdf/anal.pdf. 2012. 21-10-2012.
   Ref Type: Electronic Citation

3. National Cancer Institute. PDQ Anal cancer treatment. http://www.cancer.gov/cancertopics/pdq/treatment/anal/HealthProfessional/page4 . 2012. 21-10-2012.
   Ref Type: Electronic Citation

4. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Soft tissue sarcome V2.2012. http://www.nccn.org/professionals/physician_gls/pdf/sarcoma.pdf. 2012. 21-10-2012.
   Ref Type: Electronic Citation

5. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Merkel Cell Carcinoma V1.2012. http://www.nccn.org/professionals/physician_gls/pdf/mcc.pdf. 2012. 21-10-2012.
   Ref Type: Electronic Citation

RADIOTHERAPY UTILISATION FOR AUSTRALIAN STATES AND TERRITORIES

The distribution of cancer sites is the factor that has the greatest effect on the radiotherapy utilisation rate. There are variations in the distribution of cancer sites between Australian States and Territories. We have used publicly available data on the distribution of tumour types to estimate optimal radiotherapy utilisation rates. Data were obtained from jurisdictional central cancer registries for the residence of patients diagnosed with cancer. Data on cancer treatment for individual cancer sites are not available by jurisdiction.

The most recent year available has been used for each jurisdiction ranging from 2001-2005 to 2011. The Northern Territory has reported on the new cases of cancer for the period 2001 to 2005 because the numbers for an individual year were too small for some cancer sites.

The distribution of cancer sites by State and Territory is shown in Table 1 along with the year for which they were reported. Further customisation to each jurisdiction was not possible because of the lack of jurisdiction-based staging data.

Table 2 shows the proportion of new cases of cancer with an indication for radiotherapy by State and Territory and the optimal utilisation rate for that cancer site. The proportion of new cases of cancer with an indication for radiotherapy was 48.3% for Australia and ranged from 46.6% in Queensland to 50.8% in the Northern Territory. The slight variation is due to the slightly different distributions of cancer sites across jurisdictions. Northern Territory had higher proportions of Head and Neck, oesophagus and lung cancers than other jurisdictions. Smoking prevalence is higher in the Northern Territory and may result in higher proportions of aerodigestive tract cancers. Tasmania has a higher proportion of cases of prostate cancer perhaps due to the older average age of the population. Overall the differences in proportions are not great and this is reflected in the narrow range for the estimation of the optimal utilisation rate for each jurisdiction.

Table 1. Distribution of cancer sites by State and Territory of residence for the most recent year available

Proportions	ACT	NSW	NT	QLD	SA	TAS	VIC	WA	AUS
YEAR	2011	2008	2001-2005	2009	2008	2009	2010	2010	2008
Reference	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
Bladder	1.5%	1.9%	1.4%	1.9%	2.2%	0.5%	2.4%	2.3%	2.0%
Bone and connective tissue	1.0%	0.0%	1.1%	0.1%	1.0%	0.6%	0.9%	0.7%	
Brain	1.7%	1.4%	2.0%	1.5%	1.6%	1.0%	1.8%	1.5%	1.4%
Breast	15.4%	12.1%	12.6%	12.0%	12.1%	11.4%	12.5%	13.3%	12.2%
Cancer at Indefinite & Unspecified Sites	2.9%	2.9%	4.9%	2.7%	2.6%	2.2%	2.7%	2.2%	2.4%
Cervix	0.7%	0.7%	1.9%	0.7%	0.7%	0.5%	0.6%	0.8%	1.0%
Colon	8.3%	8.4%	10.8%	8.3%	9.2%	9.3%	8.5%	8.3%	8.4%
Gall Bladder	0.6%	0.0%	0.0%	0.6%	0.6%	0.4%	0.6%	0.7%	0.6%
Head and Neck	2.1%	3.3%	9.2%	3.6%	3.2%	5.8%	3.0%	4.1%	3.3%
Kidney	2.8%	2.7%	1.8%	2.9%	3.2%	2.7%	2.4%	2.3%	2.3%
Leukaemia	3.6%	2.5%	2.6%	2.4%	2.9%	2.5%	2.8%	2.7%	2.3%
Liver	1.1%	1.3%	1.4%	0.9%	1.3%	0.9%	1.2%	1.0%	1.2%
Lung	7.2%	8.9%	10.9%	8.9%	9.1%	7.4%	8.3%	8.9%	9.0%
Lymphoma	4.2%	3.8%	4.0%	3.8%	4.1%	3.8%	4.6%	4.5%	4.2%
Melanoma	10.3%	9.8%	10.3%	12.8%	7.9%	8.8%	8.0%	9.4%	9.9%
Myeloma	1.3%	1.1%	0.0%	1.1%	1.3%	1.1%	1.5%	1.2%	1.2%
Oesophagus	0.7%	1.2%	3.3%	1.1%	1.2%	1.7%	1.3%	1.3%	1.2%
Ovary	1.4%	1.2%	1.4%	1.1%	1.1%	1.1%	1.2%	0.9%	1.1%
Pancreatic	1.8%	2.3%	1.5%	1.9%	2.0%	2.0%	2.4%	2.1%	2.1%
Prostate	18.2%	18.9%	11.7%	16.9%	18.5%	21.3%	17.4%	17.2%	18.4%
Rectum	4.9%	4.6%	0.0%	3.6%	3.4%	5.1%	4.5%	3.8%	4.2%
Stomach	1.7%	1.8%	0.0%	1.4%	1.8%	1.7%	1.8%	1.4%	1.8%
Testis	0.9%	0.6%	1.0%	0.7%	0.6%	0.7%	0.7%	0.6%	1.0%
Thyroid	1.5%	2.1%	1.9%	2.0%	1.3%	1.1%	1.6%	2.3%	1.8%
Uterus	1.7%	1.7%	1.6%	1.7%	1.9%	1.6%	2.1%	1.6%	1.8%
Vagina	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%	0.1%
Vulva	0.0%	0.0%	0.7%	0.2%	0.2%	0.6%	0.4%	0.2%	0.3%
Other Cancers	2.4%	4.2%	2.3%	1.8%	0.3%	3.2%	4.5%	4.3%	5.0%

Table 2: The proportion of new cases of cancer with an indication for radiotherapy by State and Territory of residence and the optimal utilisation rate for that cancer site

	New RTU	ACT	NSW	NT	QLD	SA	TAS	VIC	WA	AUS
Bladder	47%	0.7%	0.9%	0.7%	0.9%	1.0%	0.2%	1.1%	1.1%	0.9%
Brain	80%	1.4%	1.1%	1.6%	1.2%	1.3%	0.8%	1.4%	1.2%	1.1%
Breast	87%	13.4%	10.5%	10.9%	10.5%	10.5%	9.9%	10.8%	11.6%	10.6%
Cancer at Indef & Unspec Site	61%	1.8%	1.8%	3.0%	1.7%	1.6%	1.4%	1.7%	1.3%	1.5%
Cervix	71%	0.5%	0.5%	1.3%	0.5%	0.5%	0.3%	0.4%	0.6%	0.7%
Colon	4%	0.3%	0.3%	0.4%	0.3%	0.4%	0.4%	0.3%	0.3%	0.3%
Gall Bladder	17%	0.1%	0.0%	0.0%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%
Head and Neck	74%	1.6%	2.4%	6.8%	2.7%	2.4%	4.3%	2.2%	3.1%	2.4%
Kidney	15%	0.4%	0.4%	0.3%	0.4%	0.5%	0.4%	0.4%	0.3%	0.3%
Leukaemia	4%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%
Liver	0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Lung	77%	5.5%	6.9%	8.4%	6.9%	7.0%	5.7%	6.4%	6.8%	6.9%
Lymphoma	73%	3.1%	2.8%	2.9%	2.8%	3.0%	2.8%	3.4%	3.2%	3.1%
Melanoma	21%	2.2%	2.1%	2.2%	2.7%	1.7%	1.8%	1.7%	2.0%	2.1%
Myeloma	45%	0.6%	0.5%	0.0%	0.5%	0.6%	0.5%	0.7%	0.5%	0.5%
Oesophagus	71%	0.6%	0.9%	2.5%	0.8%	0.9%	1.3%	1.0%	1.0%	0.8%
Ovary	4%	0.0%	0.0%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Pancreatic	49%	0.9%	1.1%	0.7%	0.9%	1.0%	1.0%	1.2%	1.0%	1.0%
Prostate	58%	10.6%	10.9%	6.8%	9.8%	10.7%	12.4%	10.1%	10.0%	10.7%
Rectal	60%	3.0%	2.7%	0.0%	2.1%	2.0%	3.1%	2.7%	2.3%	2.5%
Stomach	27%	0.5%	0.5%	0.0%	0.4%	0.5%	0.4%	0.5%	0.4%	0.5%
Testis	7%	0.1%	0.0%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
Thyroid	4%	0.1%	0.1%	0.1%	0.1%	0.1%	0.0%	0.1%	0.1%	0.1%
Uterus	38%	0.6%	0.6%	0.6%	0.7%	0.7%	0.6%	0.8%	0.6%	0.7%
Vagina	94%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%	0.1%
Vulva	39%	0.0%	0.0%	0.3%	0.1%	0.1%	0.2%	0.2%	0.1%	0.0%
Other Cancers	19%	0.5%	0.8%	0.4%	0.3%	0.1%	0.6%	0.9%	0.8%	1.0%
ALL		49.1%	48.0%	50.8%	46.6%	47.4%	48.8%	48.6%	49.2%	48.3%

RTU = radiotherapy utilisation rate

References

1. ACT Cancer Registry. Cancer in the ACT, 2004-08. Canberra: 2011.

2. Tracey E, Kerr T, Dobrovic A, Currow D. Cancer In NSW: Incidence and Mortality Report 2008. Sydney: 2010.

3. Zhang X, Condon JR, Dempsey K, Garling L. Cancer incidence and mortality, Northern Territory 1991–2005. Darwin: 2008.

4. Queensland Cancer Registry. Cancer in Queensland 1982 to 2009. Brisbane: 2012.

5. South Australian Cancer Registry. Cancer in South Australia 2008 – with projections to 2011. Adelaide: 2011.

6. Dalton M, Venn A, Albion T, P. O. Cancer in Tasmania: Incidence and Mortality 2009. Hobart: 2012.

7. Thursfield V.J. T, Farrugia H. Cancer in Victoria: Statistics and trends 2010. Melbourne: 2011.

8. Threlfall TJ, J.R. T. Cancer incidence and mortality in Western Australia, 2010. Perth: 2012.

9. Australian Insititute of Health and Welfare (AIHW). ACIM (Australian Cancer Incidence and Mortality) Books. Canberra: 2011.

EFFECT OF PATIENT CHOICE ON RADIOTHERAPY UTILISATION

Where evidence is lacking for a benefit from one particular treatment option over another, the treatment choice lies with the patient. Even when there is clear and significant evidence in favour of a treatment, a patient may choose to have an alternate less effective treatment or to have no treatment at all. The right to make a choice is recognised as the right of autonomy in the National Statement on Research Ethics (1) and more broadly in the community.

Jansen et al conducted a review of determinants of patients' preferences for adjuvant therapy in cancer (2). A total of 40 determinants of patients' preferences were classified into seven categories: (i) treatment-related determinants (such as potential benefits of treatment, degree of toxicity, previous experience of treatment) (ii) socio-demographic characteristics and current quality of life (age, sex, marital status, dependents living at home etc) (iii) clinical characteristics (type of cancer, stage of disease, lymph node status, disease recurrence, tumour size) (iv) determinants related to methodology (effects of framing of questions with regards to survival, side effects, dying, treatment benefits, level of starting point of questions, order of starting point and interviewer) (v) time-related determinants (impact of the passing of time on determinants) (vi) cognitive/affective determinants (belief in treatment benefits, negative emotions, feeling a need to take action, anticipated regret) and (vii) specialist-related determinants.

Newcomb and Carbone showed that physicians exert a significant influence on their patients' treatment choices (3). Several studies of cancer patients have noted the importance of the treating specialist's recommendation on patients' treatment preferences (4-7). Yellen and Cella state that the most important determinant of patient willingness to undergo aggressive treatment may be the way in which the treatment is described by the oncologist as well as the strength of the recommendation (4).

Patients' preferences for taking responsibility for treatment decisions vary, with some patients wanting to make their own treatment decisions while others wish to receive information but not to be actively involved in treatment decisions (8-13). Several studies report that older patients and those with fewer qualifications are more likely to want the doctor to make treatment decisions (11-13). Degner and Sloan reported that patients close to a life-threatening event were more passive with respect to treatment decision preference than a comparison group of healthy individuals (14). An analysis of 729 cancer patients' preferences for involvement in decision making showed that patients tended to prefer a decreasing level of involvement over time (15).

There are two situations in which patient choice can have a significant effect on the overall optimal radiotherapy utilisation model since they involve commonly occurring cancers where there is no clear evidence of benefit for any one treatment option. These are in the management of early prostate cancer and of early breast cancer. The major concern about including patient preference into a study of optimal utilisation is the concern that empirical studies of patient choice may be affected by

patients' socio-demographic factors, by issues of access and by other confounding factors that the study aims to overcome by providing a benchmark of optimal access.

Prostate Cancer

In the management of early prostate cancer, evidence-based guidelines suggest that there is no evidence of the superiority of any one of the four available treatment options, i.e. brachytherapy (BT), external beam radiotherapy (EBRT), surgery - radical prostatectomy (RP) or active surveillance (AS). Patterns of practice studies have not been described here since these studies have the disadvantages that there is a wide variation in treatments administered between countries (16) (17) and even within countries (18) (19), reflecting the fact that patterns of care studies reveal what treatment is being administered and perhaps what is more accessible, and not necessarily the optimal treatment that should be administered. Patterns of care studies are biased by such issues as geographical access to treatments and to medical practitioners and by varying costs to patients of different treatments.

Patient choice studies used or considered in previous optimal utilisation models for prostate cancer (20) (21-23) have disadvantages that include: not all treatment options being offered (24-27), hypothetical scenarios being offered to well men without prostate cancer (24;25), small sample size (25;26), or inadequate pre-choice counselling without consultation with both a radiation oncologist and a urologist (24-26;28;29).

Diefenbach et al (28) examined the decision making processes of 654 American men of whom 52% chose EBRT, 25% chose BT, 17% chose prostatectomy and 6% chose watchful waiting. Patients who decided on surgery were significantly younger than those who received radiation therapy and brachytherapy. Patients indicated that physician recommendation was the most important reason influencing their treatment decision.

Sommers et al surveyed 167 men with clinically localised prostate cancer who had not yet undergone treatment regarding treatment choices (30). They reported that 37% chose RP, 24% chose BT and 19% chose EBRT.

The only well conducted patient choice study that systematically presented all four treatment options to patients with localised prostate cancer was performed by the UK North-West Uro-Oncology Group (31;32). All deficiencies listed in the patient choice studies above were addressed. All patients discussed all management options with a urologist, a radiation oncologist, and a specialist nurse, were given comprehensive information leaflets, and then were offered a second appointment to further discuss matters. The majority of men who opted for surgery were motivated by the need for physical removal of the cancer. External beam radiotherapy was mainly chosen by patients who feared other treatments while most men chose brachytherapy because it was more convenient for their lifestyle. Of the 768 patients, 40% chose surgery, 31% chose external beam radiotherapy, 21%

chose brachytherapy and 8% opted for active surveillance. These data were therefore used for all branches on the decision tree where equivalent treatment options were applicable.

In the optimal radiotherapy utilisation model for non-metastatic prostate cancer, since there is no evidence of superiority of any one treatment option, data on patient preferences between the four treatment options have been used at several decision nodes in the tree. This is less than ideal for the reasons highlighted above; however, in the absence of a clear patient choice study that definitively identifies what the patients choice would be under ideal conditions this was thought to be the most pragmatic approach.

Breast Cancer

There is no difference in survival between women with operable breast cancer treated with mastectomy or breast conservation therapy (BCT) followed by radiotherapy. The Australian NHMRC guidelines state that “the choice of surgery is an individual one and each woman should be fully informed of her options, including the risks and benefits of each procedure” (33).

There are a number of patterns of practice studies reporting on rates of mastectomy vs BCT, and studies reporting on patients’ preferences for being involved in decision-making but few studies report on actual patient preferences for treatment in early breast cancer.

Staradub et al reported on 578 women with breast cancer who did not have contraindications for BCT or mastectomy and were eligible to choose between BCT, mastectomy or mastectomy with immediate reconstruction (MIR) after viewing an informational video (34). Among this group, 85.2% of women chose BCT, 9.2% chose mastectomy and 5.6% chose MIR. Patients who chose BCT were significantly younger than patients who opted for mastectomy alone. The group that underwent MIR were more likely to have private health insurance than the group that underwent mastectomy alone.
Morrow et al reported on 432 patients with early breast cancer and found that among those with no contraindications for BCT, 81% chose BCT independent of age (35). However Katz et al reported that more patient involvement in decision making was associated with greater use of mastectomy (36), possibly due to the increasing use of immediate breast reconstruction. Collins et al reported that out of 125 women who were eligible for either mastectomy or BCS, 35% chose mastectomy (37).

A recent NCCN study of 8 multidisciplinary cancer centres found that there is substantial variation in the surgical treatment of early breast cancer across institutions and showed that the use of BCS and mastectomy with reconstruction substantially varies by institution and correlates with the supply of subspecialty care (38). Lazovich et al reported that the presence of a radiation therapy facility in the county of residence influences the rate of BCT (39). Patient age at diagnosis also has an impact on the BCT rate (40). Due to the lack of suitable patient preference data in early breast cancer, population-based actual practice data was instead used in the model of optimal radiotherapy utilisation.

References

1. National Health and Medical Research Council and Australian Vice-Chancellors Committee. National Statement on Ethical Conduct in Human Research. http://www.nhmrc.gov.au/_files_nhmrc/publications/attachments/e72.pdf . 2007. 15-11-2012. Ref Type: Electronic Citation

2. Jansen SJT, Otten W, Stiggelbout AM. Review of determinants of patients' preferences for adjuvant therapy in cancer. *J Clin Oncol* 2004;22:3181-90.

3. Newcomb PA, Carbone PP. Cancer treatment and age: patient perspectives. *J Natl Cancer Inst* 1995;85:1580-4.

4. Yellen SB, Cella DF. Someone to live for: social well-being, parental status and decision-making in oncology. *J Clin Oncol* 1995;13:1255-64.

5. Cullen MH, Billingham LJ, Cook J, et al. Management preferences in stage I non-seminomatous germ cell tumors of the testis: an investigation among patients, controls and oncologists. *Br J Cancer* 1996;74:1487-91.

6. Whelan T, Sawka C, Levine M, et al. Helping patients make informed choices: A randomized trial of a decision aid for adjuvant chemotherapy in lymph node-negative breast cancer. *J Natl Cancer Inst* 2003;95:581-7.

7. Whelan TJ, Levine MN, Gafni A, et al. Breast irradiation postlumpectomy: development and evaluation of a decision instrument. *J Clin Oncol* 1995;13:847-53.

8. Robinson A, Thomson R. Variability in patient preferences for participating in medical decision making: implication for the use of decision support tools. *Quality in Health Care* 2001;10:i34-i38.

9. Deber R. Physicians in health care management. 8. The patient-physician partnership: decision-making, problem-solving and the desire to participate. *Can Med Assoc J* 1994;151:423-7.

10. Deber R. The patient-physician partnership: 7. Changing roles and the desire for information. *Can Med Assoc J* 1994;151:171-6.

11. Strull W, Bernard L, Charles G. Do patients want to participate in medical decision making? *JAMA* 1984;252:2990-4.

12. Vick S, Scott A. Agency in health care. Examining patients' preferences for attributes of the doctor-patient relationship. *J Health Econ* 1998;17:587-605.

13. Ende J, Kazis L, Ash A, et al. Measuring patients' desire for autonomy: decision making and information seeking preferences among medical patients. *J Gen Intern Med* 1989;4:23-30.

14. Degner LF, Sloan JA. Decision making during serious illness: what role do patients really want to play? *J Clin Epidemiol* 1992;45:941-50.

15. Mallinger JB, Shields CG, Griggs JJ, et al. Stability of decisional role preference over the course of cancer therapy. *Psycho-Oncology* 2006;15:297-305.

16. Harlan LC, Potosky A, Gilliland FD, Hoffman R, Albertsen PC, et al. Factors associated with initial therapy for clinically localized prostate cancer: prostate cancer outcomes study. *J Natl Cancer Inst* 2001;93:1864-71.

17. Spapen SJJC, Damhuis RAM, Kirkels WJ. Trends in the curative treatment of localized prostate cancer after the introduction of prostate-specific antigen: data from the Rotterdam Cancer Registry. *BJU International* 2000;85:474-80.

18. Harlan LC, Brawley O, Pommerenke F, Wali P, Kramer B. Geographic, age and racial variation in the treatment of local/regional carcinoma of the prostate. *J Clin Oncol* 1995;13:93-100.

19. Mettlin CJ, Murphy GP, Cunningham MP, Menck HR. The National Cancer Data Base Report on Race, Age, and Region Variations in Prostate Cancer Treatment. *Cancer* 1997;80:1261-6.

20. Delaney GP, Jacob S, Featherstone C, and Barton MB. Radiotherapy in cancer care: estimating optimal utilisation from a review of evidence-based clinical guidelines. www.ncci.org.au . 2003.
Ref Type: Electronic Citation

21. Thompson SR, Delaney G, and Barton MB. Estimating the optimal utilization of brachytherapy for the treatment of cancer. 2004. Submitted to NSW Department of Health.
Ref Type: Report

22. Thompson SR and Barton M. Optimal utilization of permanent seed brachytherapy for the treatment of prostate cancer. 2009. Submitted to NSW Department of Health.
Ref Type: Report

23. Foroudi F, Tyldesley S, Barbera L, Huang J, Mackillop WJ. Evidence-based estimate of appropriate radiotherapy utilization rate for prostate cancer. *Int J Radiat Oncol Biol Phys* 2003;55:51-63.

24. Mazur DJ, Merz JF. How older patients' treatment preferences are influenced by disclosures about therapeutic uncertainty: surgery versus expectant management for localized prostate cancer. *J Am Geriatr Soc* 1996;44:934-7.

25. Feldman-Stewart D, Brundage MD, Van Manen L. A decision aid for men with early stage prostate cancer: theoretical basis and a test by surrogate patients. *Health Expectations* 2001;4:221-34.

26. O'Rourke ME. Narrowing the options: the process of deciding on prostate cancer treatment. *Cancer Investigation* 1999;17:349-59.

27. The North-West Uro-Oncology Group. A preliminary report on a patient preference study to compare treatment options in early prostate cancer. *BJU International* 2002;90:253-6.

28. Diefenbach MA, Dorsey J, Uzzo RG, et al. Decision-Making Strategies for Patients With Localized Prostate Cancer. *Sem in Urol Oncol* 2002;20:55-62.

29. Sommers BD, Beard CJ, D'Amico AV, et al. Predictors of Patient Preferences and Treatment Choices for Localized Prostate Cancer. *Cancer* 2008;113:2058-67.

30. Sommers BD, Beard CJ, E'Amico AV, et al. Predictors of patient preferences and treatment choices for localized prostate cancer. *Cancer* 2008;113:2058-67.

31. Anandadas CN, Clarke NW, Davidson SE, et al. Early prostate cancer - which treatment do men prefer and why? *BJU International* 2010;107:1762-8.

32. Anandadas CN, Clarke NW, Davidson SE, et al. Early prostate cancer - which treatment do men prefer and why? *BJU International* 2010;107:1762
1768.

33. NHMRC National Breast Cancer Centre. Clinical Practice Guidelines for the management of early breast cancer. Second stage consultation draft. 2001. National Health and Medical Research Council.
Ref Type: Serial (Book,Monograph)

34. Staradub VL, Hsieh Y, Clauson J, et al. Factors that influence surgical choices in women with breast carcinoma. *Cancer* 2002;95:1185-90.

35. Morrow M, Bucci C, Rademaker A. Medical contraindications are not a major factor in the underutilisation of breast conserving therapy. *J Am Coll Surg* 1998;186:269-74.

36. Katz SJ, Lantz PM, Janz NK, et al. Patient involvement in surgery treatment decisions for breast cancer. *J Clin Oncol* 2005;23:5526-33.

37. Collins ED, Moore CP, Clay KF, et al. Can women with early-stage breast cancer make an informed decision for mastectomy? *J Clin Oncol* 2009;27:519-25.

38. Greenberg CC, Lipsitz SR, Hughes ME, et al. Institutional variation in the surgical treatment of breast cancer. A study of the NCCN. *Ann Surg* 2011;254:339-45.

39. Lazovich DA, White E, Thomas DB, et al. Underutilization of breast-conserving surgery and radiation therapy among women with Stage I or II breast cancer. *JAMA* 1991;266:3433-8.

40. Samet JM, Hunt WC, Farrow DC. Determinants of receiving breast-conserving surgery. The Surveillance, Epidemiology and End Results Program, 1983-1986. *Cancer* 1994;73:2344-51.

FACTORS THAT AFFECT ACTUAL AND OPTIMAL RADIOTHERAPY UTILISATION

A comparison of actual radiotherapy utilisation rates with optimal rates shows that actual rates are lower than optimal in Australia, the United States, the United Kingdom and Canada, showing that barriers exist that limit guideline-recommended, evidence-based radiotherapy utilisation (1-5).
A literature review was conducted to determine the factors that can affect actual and optimal radiotherapy utilisation rates.

Actual Radiotherapy Utilisation

Factors that can affect actual radiotherapy utilisation can be classified as follows, based on a review of barriers to accessing radiotherapy in Canada (6). Many of these factors are inter-related and may exert combined effects on radiotherapy utilisation rates.

A. Health System Factors

1. Distance to treatment centre: Many studies demonstrate an adverse impact of increasing distance on radiotherapy utilisation. Mackillop et al found that the rates of radiotherapy use varied significantly from county to county across Ontario and the highest rates were recorded in communities close to radiotherapy centres (7). Tyldesley and McGahan reported higher radiotherapy rates (closer to optimal rates) for breast and lung cancer patients in urban than in rural areas in British Columbia, but found that radiotherapy rates did not vary with drive time for patients with prostate cancer (8). Jones et al found that in northern England, the likelihood of receiving radiotherapy was reduced for most common cancer sites with increasing travel time to the nearest radiotherapy hospital (9). However a study of radiotherapy utilisation in New South Wales from 1996 to 1998 found that rural area health services had an identical average rate to urban area health services, although both were significantly below the optimal rate (10). A study conducted in the south of England concluded that travel times of up to one hour did not affect the uptake of radiotherapy (11). The NSW Cancer Council reported on the effect of remoteness (as measured by ARIA score of residence) on cancer incidence and mortality in NSW (12) (13) and found that, when considering all cancers together, there was no statistically significant effect on incidence; but, after adjusting for age and stage, there was a 30% relative increase in risk of death at 5 years for those patients living in remote locations with this excess risk being due to excess mortality from cancers of the head and neck, rectum, breast, cervix and prostate. Brachytherapy has a major role in the treatment of cancers of the latter two tumour sites. The authors pointed out possible contributing factors that have been identified in the literature, such as the association between

geographical remoteness and disadvantage in terms of SES, race and educational levels (all factors that have been associated with worse cancer outcome), less screening, more advanced disease at diagnosis, and less access to treatment. Young et al found that NSW patients treated in metropolitan hospitals compared to rural hospitals were more likely to be treated with adjuvant chemotherapy (node positive colon cancer) but not radiotherapy (high risk or tethered/fixed rectal cancers) but did not analyse for the potential confounder of SES (14). In the lung cancer Patterns of Care Study conducted by Vinod et al (15), there were similar care and outcomes in the two socioeconomically and ethnically dissimilar metropolitan area health services, but less pathological diagnoses, surgery, radiotherapy and chemotherapy in the partly rural area health service, implying geographical rather than socioeconomic or cultural barriers to lung cancer care. Barton et al found increased rates of mastectomy amongst Western Australian patients living in non-Highly Accessible postcodes, implying reduced access to breast conservation (16). Several studies have analysed RTU in NSW. Denham reported that in 1990-91, metropolitan RTU was 36% compared to 19% in non-metropolitan NSW (17). By 1996-98, Barton found that this urban/rural difference was no longer evident, although a slight difference in RTU between AHS with RT facilities (39%) compared to without (36%) was noted (10). A study of South Australian RT for the years 1990-94 described reduced likelihood of being treated with RT amongst patients who were older, female, or resident in a country region (probability 0.91), with socioeconomic status not being significant (18).

2. Waiting times: Waiting times depend on the capacity of the facility to meet the demand for radiotherapy services. Capacity is affected by equipment levels, workforce and productivity. The risk of local recurrence increases with increasing waiting times for radiotherapy (19). In patients with high grade glioma, delay in radiotherapy can shorten survival (20;21). National audits of waiting times for radiotherapy in the United Kingdom have found that waiting times for radical radiotherapy have improved over time from 2003 to 2005 to 2007 (22).

3. Treatment centre characteristics: Gillan et al in their review found that a patient has a greater likelihood of receiving radiotherapy if the initial diagnosis is made in an academic hospital or one with an affiliated cancer centre (6;23;24). French et al reported that palliative radiotherapy utilisation rates in British Columbia were lower where there was difficult or limited access to a cancer centre (25). Thompson et al found reduced likelihood of being treated with brachytherapy amongst patients resident in Area Health Services not equipped with brachytherapy facilities, independent of socioeconomic or geographical factors (26).

B. Patient Socio-demographic factors

1. Race/Ethnicity: Race and ethnicity has been reported to have an effect on radiotherapy utilisation rates. In Australia, a study of indigenous and non-indigenous Queenslanders with lung cancer found that 31% of indigenous patients received radiotherapy as opposed to 42.8% of non-indigenous patients (27). In Los Angeles, African American and Hispanic women were found to be less likely to receive adjuvant radiotherapy after breast conserving surgery (BCS) for breast cancer (28).

2. Socioeconomic status (SES): Deprivation has a major influence on radiotherapy access rates; even in the United Kingdom where there is access to universal health care, Williams et al found that in regions with higher levels of deprivation, fewer patients with cancer receive radiotherapy (22). Parise et al found that in Los Angeles, lower SES was associated with decreasing odds of receiving adjuvant radiation therapy after BCS for breast cancer (28). Lavergne et al found that the rate of palliative radiotherapy in Nova Scotia, Canada, declined with increased community deprivation (29). Vinod et al and Hui et al performed lung cancer Patterns of Care Studies and compared treatment and outcomes between two metropolitan area health services (thereby eliminating rural location as a factor), and found that there were no differences in care or outcomes based on patient SES (30) (31). Luke et al addressed the issue of access to RT in the South Australian setting for the years 1990-94 and found that SES of residential area was not significant (18). Barton et al (16) performed an overview of cancer treatment services in Western Australia and did not find a correlation between IRSD of postcode of residence and radical prostatectomy rates for prostate cancer or of chemotherapy rates for breast, lung or colorectal cancer. Mastectomy rates for breast cancer increased with low SES postcodes (implying reduced breast conservation), but this may have been confounded by increased mastectomy rates amongst patients living in non-Highly Accessible locations.

C. Patient Factors

1. Age and co-morbidity: Tyldesley et al found that the rate of RT use declined with age in Ontario, particularly for adjuvant and palliative indications (32). The relative decline in receipt of radiotherapy with age exceeded the relative decline in functional status with age in the general population. Most of the decline in radiotherapy use was related to a decline in referral to cancer centres. Vulto et al reported that in the South Netherlands, age and comorbidity had an influence over whether patients received radiotherapy, and for most tumour types age appeared to be a stronger predicting factor (33). Vinod et al showed that older age is a factor in some patients in South Western Sydney receiving no treatment for lung cancer (34).

2. Cultural beliefs: The effect of cultural or religious beliefs among aboriginals or ethnic groups who refuse radiotherapy based on these beliefs have been described in Australia, Canada and Pakistan (35-37).

3. Beliefs re efficacy/burden of treatment: The effect of patient choice on radiotherapy utilisation and the factors affecting patient choice have been described separately in the chapter on patient choice.

4. Life expectancy: The Canadian review of barriers to radiotherapy by Gillan et al found that reduced life expectancy was associated with lower rates of consultation and treatment for palliation (6).

5. Other: Gillan et al in their review of Canadian literature found that patient education level was associated with longer radiotherapy waiting times (6). Kane et al studied the impact of patient educational level on patients with prostate cancer in the United States, and found that among older men, those with a higher education level received more aggressive treatment (radiotherapy versus hormonal therapy) than those with less education (38).

D. Provider Factors

1. Referral: Cancer patients are generally referred for radiation oncology consultations by other medical specialists or by general practitioners, who act as gatekeepers. Hence a lack of referral can affect radiotherapy utilisation rates. Gillan et al reported that higher referral rates are associated with having a university academic appointment, being a specialist in a cancer centre, performing a higher volume of surgeries for cancers potentially requiring adjuvant radiotherapy, being more knowledgeable about radiotherapy or having formal training in radiotherapy (6). In certain clinical situations referral for radiation oncology consultation may be affected because the evidence for radiotherapy is weak or there is no evidence in favour of radiotherapy over other treatment modalities. Wong et al hypothesised that the quality of evidence would interact with geographical resource factors: they compared the use of adjuvant radiotherapy amongst 10198 American patients operated on in hospitals with and without on-site radiotherapy services, and found that for cancer of the rectum (with well-established randomized evidence for adjuvant RT), there was no difference in RTU, but for pancreatic cancer, in which the role of adjuvant RT remains controversial, RTU was almost double in hospitals with on-site RT services (39).

2. Multidisciplinary care: It is probable that patients with access to multidisciplinary care would be more likely to be seen by a radiation oncologist. A recent study of 13,722 women with breast cancer in the United Kingdom found that the introduction of

multidisciplinary care was associated with improved survival (40). Among patients with lung cancer, Freeman et al reported that a multidisciplinary thoracic malignancy care conference increased the percentage of patients receiving treatment that adhered to nationally accepted guidelines (41).

3. Understanding and awareness: Gillan et al noted that "low referral rates can be attributed in part to limited radiotherapy-related knowledge of the referring physician" (6). A majority of survey respondents reported poor levels of knowledge about palliative radiotherapy in two surveys of family physicians and other referring practitioners (42;43).

Optimal Radiotherapy Utilisation

The factors that affect the rate of optimal radiotherapy utilisation have been described in the individual cancer site chapters in this report. The main factors that affect the overall optimal radiotherapy utilisation rate are:

1. Changes in Cancer incidence

   The relative incidence of the various cancer sites can change over time. In the original model of optimal radiotherapy utilisation, the incidence of prostate cancer was 12% of all cancers. In the revised model, prostate cancer constitutes 18% of all registered cancers. In the revised model, the incidence of each of the cancer sites has been updated according to national data from the Australian Institute of Health and Welfare (AIHW) for the year 2008.

2. Changes in Stage Distribution

   Over time, there have been changes in the stage distribution of various cancers due to increased screening, new diagnostic tools or other factors leading to earlier diagnosis. This can lead to changes in the overall optimal utilisation rate.

3. Changes in indications for radiotherapy

   Some indications for radiotherapy are no longer valid as compared to the original model, while there are a few new indications for radiotherapy. Some controversial areas still remain where there is no clear evidence in favour of radiotherapy over another treatment modality; ongoing clinical trials may resolve these areas of treatment uncertainty in the future.

4. Other changes in epidemiological data

   Changes in other data such as in the rates of local relapse or distant metastases based on the latest available epidemiological can also affect the radiotherapy utilisation rate. Any changes to these data have been described in detail in the relevant chapters.

References

1. Delaney G, Jacob S, Featherstone C, Barton MB. The role of radiotherapy in cancer treatment. Estimating optimal utilization from a review of evidence-based clinical guidelines. *Cancer* 2005;104:1129-37.

2. Williams MV, Summers ET, Drinkwater K, Barrett A. Radiotherapy dose fractionation, access and waiting times in the countries of the UK in 2005. *Clin Oncol* 2007;19:273-86.

3. Erridge SC, Featherstone C, Chalmers R, Campbell J, et al. What will be the radiotherapy machine capacity required for optimal delivery of radiotherapy in Scotland in 2015? *Eur J Cancer* 2007;43:1802-9.

4. Kerba M, Qun Miao, Zhang-Salomoms J, Mackillop WJ. Defining the need for prostate cancer radiotherapy in the general population: a criterion-based benchmarking approach. *Clinical Oncology* 2010;22:801-9.

5. Kerba M, Miao Q, Zhang-Salomons J, Mackillop WJ. Defining the need for breast cancer radiotherapy in the general population: a criterion-based benchmarking approach. *Clin Oncol (R Coll Radiol)* 2007;19:481-9.

6. Gillan C, Briggs K, Pazos A, and et al. Barriers to accessing radiation therapy in Canada: a systematic review. Radiation Oncology . 2012.
   Ref Type: In Press

7. Mackillop WJ, Groome PA, Zhang-Salomoms J, et al. Does a centralised radiotherapy system provide adequate access in care? *J Clin Oncol* 1997;15:1261-71.

8. Tyldesley S, McGahan C. Utilisation of radiotherapy in rural and urban areas in British Columbia compared with evidence-based estimates of radiotherapy needs for patients with breast, prostate and lung cancer. *Clin Oncol* 2010;22:526-32.

9. Jones AP, Haynes R, Sauerzapf V, Crawford SM, et al. Travel time to hopsital and treatment for breast, colon, rectum, lung, ovary and prostate cancer. *Eur J Cancer* 2008;44:992-9.

10. Barton MB. Radiotherapy utilisation in New South Wales from 1996 to 1998. *Australas Radiol* 2000;44:483-4.

11. Cosford P, Garrett C, Turner K. Travel times and radiotherapy uptake in two English counties. *Public Health* 1997;111:47-50.

12. Jong KE, Smith DP, Yu XQ, and et al. Remoteness and cancer incidence, mortality and survival in New South Wales 1992 to 1996. 2002. The Cancer Council NSW.
    Ref Type: Report

13. Jong KE, Smith DP, Yu XQ, et al. Remoteness of residence and survival from cancer in New South Wales. *MJA* 2004;180:618-22.

14. Young J, Leong D, Armstrong K, et al. Concordance with national guidelines for colorectal cancer care in New South Wales: a population-based patterns of care study. *MJA* 2007;186:292-5.

15. Vinod SK, Hui AC, Esmaili N, Hensley MJ, Barton MB. Comparison of patterns of care in lung cancer in three area health services in New South Wales, Australia. *Intern Med J* 2004;34:683.

16. Barton MB, Gabriel GS, and Shefiq J. Overview of Cancer Treatment Services in Western Australia. 2008. CCORE.
    Ref Type: Report

17. Denham JW. How do we bring an acceptable level of radiotherapy services to a dispersed population? *Australas Radiol* 1995;39:171-3.

18. Luke C, Chapman P, Priest K, Roder D. Use of radiotherapy in the primary treatment of cancer in South Australia. *Australas Radiol* 2003;47:161-7.

19. Chen Z, King W, Pearcey R, et al. The relationship between waiting time for radiotherapy and clinical outcomes: a systematic review of the literature. *Radiother Oncol* 2008;87:3-16.

20. Irwin C, Hunn M, Purdie G, et al. Delay in radiotherapy shortens survival in patients with high grade glioma. *J Neuro-Oncol* 2007;85:339-43.

21. Do V, Gebski V, Barton MB. The effect of waiting for radiotherapy for grade III/IV gliomas. *Radiother Oncol* 2000;57:131-6.

22. Williams MV, Drinkwater KJ. Geographical variation in radiotherapy services across the UK in 2007 and the effect of deprivation. *Clin Oncol* 2009;21:431-40.

23. Chuah TK, et al. Management of primary rectal cancer by surgeons in Atlantic Canada: results of a regional survey. *Can J Surg* 2010;53:396-402.

24. Huang J, Zhou S, Groome P, Tyldesley S, et al. Factors affecting the use of palliative radiotherapy in Ontario. *J Clin Oncol* 2001;19:137-44.

25. French J, McGahan C, Duncan G, et al. Inequities in access: how utilization of palliative radiation therapy in British Columbia varies with geography. *J Med Imag Rad Sciences* 2008;39:75-80.

26. Thompson SR, Gabriel GS, Das P, and et al. Patterns of Care in Brachytherapy in NSW in 2003. 2008.
Ref Type: Personal Communication

27. Coory MD, et al. Survival of indigenous and non-indigenous Queenslanders after a diagnosis of lung cancer: a matched cohort study. *MJA* 2008;188:562-6.

28. Parise CA, Bauer KR, Caggiano V. Disparities in receipt of adjuvant radiation therapy after breast-conserving surgery among the cancer reporting regions of California. *Cancer* 2012;118:2516-24.

29. Lavergne MR, et al. Variation in the use of palliative radiotherapy at the end of life: examining demographic, clinical, health service and geographic factors in a population-based study. *Palliat Med* 2011;25:101-10.

30. Vinod SK, Delaney GP, Bauman AE, Barton MB. Lung cancer patterns of care in south western Sydney, Australia. *Thorax* 2003;58:690-4.

31. Hui AC, Vinod SK, Jalaludin BB, Yuile PG, Delaney PG, and Barton MB. Socioeconomic Status and Patterns of care in Lung Cancer. Lung Cancer . 2005.
Ref Type: In Press

32. Tyldesley S, Zhang-Salomons J, Groome PA, Zhou S, Schulze K, et al. Association between age and the utilization of radiotherapy in Ontario. *Int J Radiat Oncol Biol Phys* 2000;47:469-80.

33. Vulto AJ, Lemmens VE, Louwman MW, et al. The influence of age and comorbidity on receiving radiotherapy as part of primary treatment for cancer in South Netherlands, 1995 to 2002. *Cancer* 2006;106:2734-42.

34. Vinod SK, Sidhom MA, Gabriel GS, and et al. Why do some lung cancer patients receive no anticancer treatment? J Thorac Oncol 5(7), 1025-1032. 2010.
Ref Type: Abstract

35. Lowenthal RM, Grogan PB, Kerrins ET. Conference Report: reducing the impact of cancer in indigenous communities: ways forward. *MJA* 2005;182:105-6.

36. Yavari P, Barroetavena MC, Hislop TG, et al. Breast Cancer treatment and ethnicity in British Columbia, Canada. *BMC Cancer* 2010;10:154.

37. Kumar S, et al. Influence of patient's perceptions, beliefs and knowledge about cancer on treatment decision making in Pakistan. *Asian Pac J Cancer Prev* 2010;11:251-5.

38. Kane CJ, Lubeck DP, Knight SJ, et al. Impact of patient educational level on treatment for patients with prostate cancer: data from CaPSURE. *Urology* 2003;62:1035-9.

39. Wong SL, Wei Y, Birkmeyer JD. Use of adjuvant radiotherapy at hospitals with and without on-site radiation services. *Cancer* 2007;109:796-801.

40. Kesson EM, Allardice GM, George WD, and et al. Effects of multidisciplinary team working on breast cancer survival: retrospective, comparative, interventional cohort study of 13,722 women. BMJ 344, e2718. 2012.
Ref Type: In Press

41. Freeman RK, Van Woerkom JM, et al. The effect of a multidisciplinary thoracic malignancy conference on the treatment of patients with lung cancer. *Eur J Cardiothor Surg* 2010;38:1-5.

42. Samant RS, Fitzgibbon E, Meng J, et al. Family physicians' perspectives regarding palliative radiotherapy. *Radiother Oncol* 2006;78:101-6.

43. Fairchild A and Ghosh S. Referring practitioners' self-rated versus actual knowledge about palliative radiotherapy. Support Care Cancer 17(7), 965. 2009.
Ref Type: Abstract

NEW TECHNOLOGIES IN RADIOTHERAPY

It is possible that new technology in radiotherapy may affect the optimal utilisation rate because it

1. Increases the proportion of cases for whom radiotherapy would be the treatment of choice, or
2. Provides an alternative to standard external beam radiotherapy.

Of course not all new technologies result in improvements in patient outcomes. If the technologies discussed in this chapter had high levels of evidence to support their adoption then they would have been included in the specific tumour site reviews where relevant.

The Faculty of Radiation Oncology Position Paper on Techniques and Technologies in Radiation Oncology – 2011 Horizon Scan (1) was used as the major source of new technologies. It was produced by a multidisciplinary team and widely peer-reviewed. It identified six techniques that are not widely used in Australia at present but would in the future be considered essential for the good management of cancer patients in Australia. It should be noted that the wide acceptance of any new technology in the Australian Public Health System would depend on appropriate reviews and cost-effectiveness analysis.

A. New technology that involves external beam

1. Image Guided Radiation Therapy (IGRT)

IGRT is a broad term that can reasonably be applied to most radiotherapy techniques. It has been used recently to describe frequent 2-D or 3-D imaging of the treatment volume performed as close as possible to the time of treatment delivery to increase geometric accuracy.

IGRT offers greater accuracy and the ability to target tumours that are affected by body motion such as early stage lung or liver cancers or a small amount of metastatic disease to lung or liver, in conjunction with stereotactic body techniques.

IGRT may *increase* the proportion of lung and liver tumours with an indication for radiotherapy.

2. Intensity Modulated Radiation Therapy (IMRT)

IMRT is an external beam technique that individualises the fluence of the radiation beam to create better conformation of the radiation dose to the treatment volume. It reduces the dose to surrounding normal tissues which may decrease complications or allow dose escalation.

IMRT has a well-established role in external beam radiotherapy but has not created new treatment indications.

3. Stereotactic Radiation Treatments

Stereotactic radiation treatments include stereotactic radiosurgery (SRS), stereotactic radiotherapy (SRT) and stereotactic body radiotherapy (SBRT). SRS and SBRT use high doses of external beam radiotherapy delivered with a high precision stereotactic localisation system. SRT uses the high precision system to deliver fractionated radiotherapy.

SRS and SRT have been used to treat benign and malignant intracranial tumours and arteriovenous malformations. Benign lesions are outside the scope of this study because they are not notified to Central Cancer Registries and hence are not used in the calculation of utilisation rates.

SBRT has been used to deliver high doses to small mobile lung tumours and shows promising high tumour control rates. It may be used as a substitute for standard external beam, or for surgery in those patients of borderline medical inoperability. It has also been investigated for the treatment of liver tumours.

SBRT may increase the proportion of lung and liver tumours with an indication for radiotherapy.

B. New technology that may become an alternative to standard external beam radiotherapy

1. Particle Therapy

Particle therapy is a form of external beam radiotherapy using heavy particles known as hadrons. These include protons, neutrons and carbon ions. These particles may have advantages over X-rays because of different biological action or the differences in the physical deposition of dose. The major application is for the treatment of paediatric malignancies currently treated by X rays and base of skull tumours in adults. The number of cases is very small (2) and unlikely to have a significant effect on optimal radiotherapy utilisation rates.

2. Intra-operative Partial Breast Irradiation

Intra-operative partial breast irradiation was not discussed in the FRO Horizon Scanning document. There are several ways of delivering partial breast irradiation; Intra Operative Radiotherapy, radio-isotopes, needle implant and linear-accelerator treatment with electrons or photons. All of these techniques are considered investigational.

The use of a single high dose of low energy X-rays delivered into the tumour bed at the time of lumpectomy for breast cancer was the subject of a recent randomised trial (3) that showed non-inferiority for intra-operative partial breast irradiation compared with external beam. Intra-operative partial breast irradiation requires a dedicated 60kV X-ray emitter and trained staff.

Fourteen per cent of women who received intra-operative partial breast irradiation also required external beam radiotherapy because of adverse pathological findings.

External beam radiotherapy for early breast cancer (T1-2 N0-1) is indicated for 62% of all breast cancer. If 86% of these cases were suitable for intra-operative partial breast irradiation then 53% of all breast cancer patients would optimally be treated with partial breast irradiation rather than conventional fractionated megavoltage radiotherapy. Breast cancer accounts for 12% of all cancers and thus the uniform adoption of intra-operative partial breast irradiation could reduce the total optimal utilisation rate for all cancers by about 6%.

3. Hypofractionation

Hypofractionation is the use of fewer large radiation treatments (fractions) in a course of radiotherapy. The total dose must be reduced because larger doses per fraction cause greater late side effects. Hypofractionation with very large doses has been successful in stereotactic radiosurgery (see above).

Hypofractionation has been investigated in breast and prostate cancer to reduce the burden on patients and increase linear accelerator capacity. Hypofractionation has been shown to be equivalent to standard fractionation for selected early breast cancers (4). It is being investigated in prostate cancer (5, 6).

Hypofractionation has been incorporated into our existing fractionation model for breast cancer. If it is shown to be useful in prostate cancer it can be incorporated into the fractionation model.

Changes in the number of fractions per course do not affect the proportion of cases with an indication for radiotherapy but may reduce the number of treatments each patient requires and thus the total demand for megavoltage radiotherapy resources.

References

1. Faculty of Radiation Oncolgy, RANZCR. Techniques and Technologies in Radiation Oncology - 2011 Horizon Scan. Sydney: 2011 15 Nov 2011.

2. National Commissioning Group for highly specialised services. Guidance for the Referral of Patients Abroad for NHS Proton Treatment. London: National Health Service UK, 2010 March 2010. Report No.

3. Vaidya JS, Joseph DJ, Tobias JS, Bulsara M, Wenz F, Saunders C, et al. Targeted intraoperative radiotherapy versus whole breast radiotherapy for breast cancer (TARGIT-A trial): an international, prospective, randomised, non-inferiority phase 3 trial. Lancet. 2010;376(9735):91-102. Epub 2010/06/24.

4. Whelan TJ, Pignol JP, Levine MN, Julian JA, MacKenzie R, Parpia S, et al. Long-term results of hypofractionated radiation therapy for breast cancer. N Engl J Med. 2010;362(6):513-20. Epub 2010/02/12.

5. Lukka H, Hayter C, Julian JA, Warde P, Morris WJ, Gospodarowicz M, et al. Randomized trial comparing two fractionation schedules for patients with localized prostate cancer. J Clin Oncol. 2005;23(25):6132-8. Epub 2005/09/02.

6. Arcangeli S, Strigari L, Gomellini S, Saracino B, Petrongari MG, Pinnaro P, et al. Updated Results and Patterns of Failure in a Randomized Hypofractionation Trial for High-risk Prostate Cancer. Int J Radiat Oncol Biol Phys. 2012. Epub 2012/04/28.

OPTIMAL NUMBER OF RADIOTHERAPY FRACTIONS

Introduction

A radiotherapy treatment fraction is the fundamental unit of productivity in a radiotherapy department. A course of external beam radiotherapy is delivered in small doses called fractions, usually given once a day, five days a week, and a course of treatment can be delivered over several weeks, depending on the clinical situation. Radical radiotherapy, aiming to eradicate the tumour, requires a high total dose and is typically delivered over 2 to 8 weeks. On the other hand, palliative radiotherapy, which aims to improve symptoms, usually requires a lower total dose. A palliative radiotherapy course is delivered in fewer fractions and may last from one day to a few weeks.

Number of fractions per linear accelerator per department has been used for radiotherapy services planning and this parameter has been recognised as valuable (1-4). However, substantial variations in radiotherapy fractionation practices between radiotherapy departments or radiation oncologists have been observed in Australia and overseas (3, 5-7), and to date there has been no evidence-based benchmark for appropriate activity.

This chapter summarises the PhD thesis of Dr Karen Wong "Estimation of the optimal number of radiotherapy fractions for cancer patients: a review of the evidence**".** The objectives of the project were

- To develop a model of radiotherapy fractionation building on the previously published optimal radiotherapy utilisation model (8-9).
- To estimate the optimal number of radiotherapy fractions for the first course of radiotherapy per cancer patient and per treatment course from the best available evidence.
- To estimate the proportion of patients that should receive radical versus palliative radiotherapy as their first course of radiotherapy, and the optimal number of radiotherapy fractions per radical and per palliative course, based on best available evidence.

Methods

This current project was limited to the first course of radiotherapy in patients with a notifiable cancer with an incidence of ≥1% of the Australian cancer population, as was the optimal radiotherapy utilisation study from which this study is based (8-9). The reason why only the first treatment course for any patient was studied is that it is this parameter that is used for resource planning for radiation oncology. There is a component of a department's activity that involves retreatment (i.e. the patient undergoes subsequent radiotherapy) but this is factored into planning models in other ways and can be quite complex and beyond the scope of this study.

Evidence-based treatment guidelines, meta-analyses and randomised controlled trials were reviewed for fraction number recommendations for each clinical situation of each cancer site where

radiotherapy was indicated (i.e. each terminal branch of the optimal radiotherapy utilisation tree). In the radiotherapy utilisation tree, in some instances the branches did not differentiate whether the radiotherapy was recommended for curative or palliative intent, as the aim of the original study was purely to decide whether radiotherapy was recommended at all or not. In this current project, these branches were split to model more specific clinical situations where the fractionation schemes vary between branches.

Information on the proportions of patients with the different attributes associated with each additional branch of the tree was obtained by performing Medline searches, manual bibliographic searches and examination of review articles. The cancer incidence figures were updated using the national cancer incidence figures from 2005 published by the Australian Institute of Health and Welfare (10).

The radiotherapy utilisation tree was adapted so that each terminal branch ended in a "pay-off" with the number of radiotherapy fractions as the final outcome. For each cancer type, the optimal fraction number was calculated using the TreeAge software version 3.5™ (TreeAge Software, Williamstown, MA), taking into account the frequency of specific clinical conditions where radiotherapy is indicated and the recommended fraction number for each condition. In instances where a range of number of fractions was recommended for a terminal branch, the number of fractions best supported by evidence was used in the calculations. If there were a number of sources of equal quality that recommended different fractionation regimens, the number of fractions recommended in the Australian guidelines was used. When Australian guidelines did not exist for particular cancer sites or did not adequately address radiotherapy dose fractionation schedules, the *lowest* of the range of number of fractions recommended in the other clinical guidelines was used in the calculations. One-way and multivariate sensitivity analyses were performed to assess the impact of uncertainties on the overall optimal number of radiotherapy fractions.

Results

There were 15 cancer sites with 32 cancer sub-sites. It was estimated that, based on best available evidence, 48.3% of all cancer patients should ideally receive radiotherapy at least once during the course of their illness.

The optimal number of fractions for the first course of radiotherapy was calculated to be 18 per treatment course. For each cancer sub-site, the optimal number of fractions ranged from 0 to 30.8 per treatment course, with the highest being head and neck and central nervous system cancers. Table 1 summarises the results for each of the cancer sub-sites.

For the first course of radiotherapy, 78% of patients would ideally be treated with radical intent and 22% with palliative intent. For radical radiotherapy, the optimal number of fractions was 22.3 per treatment course. For palliative radiotherapy, the optimal number of fractions was 3.3 per treatment course.

Sensitivity analysis was performed to assess the effect of uncertainties on the overall optimal number of radiotherapy fractions. One-way sensitivity analysis showed that the optimal number of fractions varied from 17.2 to 19.2 per treatment course. For radical radiotherapy, the optimal fraction number ranged from 21.3 to 23.8 per treatment course. For palliative radiotherapy, the optimal fraction number ranged from 3.3 to 5.4 per treatment course.

Table 1. Optimal number of radiotherapy fractions by cancer sub-site

Cancer site	Cancer sub-site	Proportion of all cancers (%)	Optimal no. of fractions per treatment course	Range of no. of fractions per treatment course
Genitourinary cancer		24	19.6	17.8-22.1
	Prostate	18.4	22.2	20-25.1
	Kidney	2.3	2	2-3.6
	Bladder	2.0	9.5	7.8-14.5
	Testis	1.0	11.4	10.8-15
Gastrointestinal cancer		20	16.8	15.7-20
	Colon	8.4	17.9	2-21.3
	Rectum	4.2	10.7	10.7-25.8
	Pancreas	2.1	21.6	21.6-22.1
	Stomach	1.8	25.0	0-25
	Oesophagus	1.2	16.3	16.2-18.5
	Liver	1.2	0	N/A
	Gallbladder	0.6	24.6	20-25.2
	Small intestine	0.3	0	N/A
	Anus	0.3	26.1	25-27.1
Breast		12.2	17.3	17.3-21.8
Melanoma		9.9	19.1	18.1-19.6
Thoracic cancer		10	16.8	16.2-19.2
	Lung	9.0	16.6	16.1-19.1

Cancer site	Cancer sub-site	Proportion of all cancers (%)	Optimal no. of fractions per treatment course	Range of no. of fractions per treatment course
	Mesothelioma	0.6	0	N/A
Lymphoma		4.2	14.5	14.5-16.5
Gynaecological cancer		4	19.7	19.7-20
	Cervix	1.0	19.8	16.9-22.9
	Endometrium	1.8	20.2	18.4-20.7
	Ovary	1.1	7.5	7.5-10
	Vulva	0.3	25.3	24.1-30
	Vagina	0.1	23.1	23-24.6
Unknown primary		2.4	1.5	1.5-4.9
Head and neck		3.3	30.8	30.1-31.6
Leukaemia		2.3	6.9	6.8-7.3
Thyroid		1.8	20	20-22.6
Central nervous system		1.4	29.2	29.2-29.8
Myeloma		1.2	4.6	3.7-5.9
Sarcoma		1	21.1	21.1-27.4
	Soft tissue sarcoma	0.6	21.2	21.2-27.9
	Bone sarcoma	0.2	0	N/A
Other cancer		3.0	0	N/A
Total		**100**	**18**	**17.2-19.2**

Discussion

This is the first model to estimate the optimal number of radiotherapy fractions for cancer patients based solely on the evidence. The model has many potential uses. Results of this study can be applied to aid in the planning of radiotherapy services for a given population. The model can also be applied to predict future radiotherapy workload to aid in future planning of radiotherapy services. The model can be readily adapted for changes in cancer incidence, stage distribution, radiotherapy indication and dose fractionation schedule in the future. Results of clinical trials which have recently completed recruitment or are currently recruiting can be easily incorporated into the model to assess the impact on the optimal number of fractions. The model also provides a benchmark for service delivery and allows comparison with actual practice from population-based patterns of care studies. As an example, the 2007 patterns of care study of the UK (7) showed that, for the first course of radiotherapy, the average number of fractions per treatment course was 15.4. While this fell short of our optimal estimate of 18, the average number of fractions per radical course was 20.6 and that per palliative course was 4.0, which approximated our optimal estimates, suggesting that a higher than optimal proportion of patients were treated with palliative intent.

A number of limitations have been identified during the course of this research. Firstly, the model included only the first course of radiotherapy. It did not include retreatment after an initial course of either radical or palliative radiotherapy. The issue of retreatment modelling is highly complex and could be the focus of future research. Secondly, the model included only notifiable cancers in Australia. Thus, non-melanomatous skin cancers, benign tumours such as pituitary adenoma and meningioma, and other benign conditions such as keloid and heterotopic ossification, in which radiotherapy has an established role, were excluded as these are non-notifiable conditions in Australia. Additional workload for retreatment courses as well as for these non-notifiable conditions needs to be accounted for when this model is applied to the planning of radiotherapy services. Thirdly, there was a lack of high quality epidemiological data for some clinical situations in the model, particularly performance status and co-morbidity data. In order to overcome some of this limitation sensitivity analysis was performed for those branches where high quality epidemiological data were lacking and showed that the impact of these uncertainties on the model was minor. Lastly, on review of the clinical guidelines, it has been identified that there are differing recommendations on radiotherapy indication and dose fractionation schedule for many clinical situations. Sensitivity analysis was performed to estimate the effect of these variations and showed that the variables had a minor impact on the overall optimal number of fractions.

Conclusions

Based on best available evidence, it is estimated that 48.3% of all cancer patients should ideally receive radiotherapy at least once during the course of their illness, and that the optimal number of fractions for the first course of radiotherapy is 18 per treatment course. One-way and Monte Carlo sensitivity analyses show these estimates to be robust despite multiple variables in the model. These data serve as a benchmark for comparison with actual practice, and will be helpful in the planning of

radiotherapy services. Further research in the optimal number of fractions for non-melanomatous skin cancers and benign conditions in which radiotherapy plays a role will complement these data to better predict radiotherapy workload.

References

1. Morgan GW, Barton M, Atkinson C*, et al.* 'GAP' in radiotherapy services in Australia and New Zealand in 2009. *J Med Imaging Radiat Oncol* 2010;54:287-297

2. Erridge SC, Featherstone C, Chalmers R*, et al.* What will be the radiotherapy machine capacity required for optimal delivery of radiotherapy in Scotland in 2015? *Eur J Cancer* 2007;43:1802-1809.

3. Scottish Executive Health Department. Radiotherapy Activity Planning for Scotland 2011-2015: http://www.scotland.gov.uk/Resource/Doc/90297/0021749.pdf; 2006. Accessed 29/5/2012.

4. Jena R, Round C, Mee T*, et al.* The Malthus programme--a new tool for estimating radiotherapy demand at a local level. *Clin Oncol (R Coll Radiol)* 2012;24:1-3.

5. Statewide and Rural Health Services and Capital Planning. 2010 Radiotherapy management information system report. Sydney: NSW Ministry of Health; 2011.

6. Williams MV, Summers ET, Drinkwater K*, et al.* Radiotherapy dose fractionation, access and waiting times in the countries of the UK in 2005. *Clin Oncol (R Coll Radiol)* 2007;19:273-286.

7. Williams MV, Drinkwater KJ. Geographical variation in radiotherapy services across the UK in 2007 and the effect of deprivation. *Clin Oncol (R Coll Radiol)* 2009;21:431-440.

8. Delaney GP, Jacob S, Featherstone C*, et al.* Radiotherapy in cancer care: estimating optimal utilisation from a review of evidence-based clinical guidelines. Sydney: Collaboration for Cancer Outcomes Research and Evaluation (CCORE), Liverpool Hospital; 2003.

9. Delaney G, Jacob S, Featherstone C*, et al.* The role of radiotherapy in cancer treatment: estimating optimal utilization from a review of evidence-based clinical guidelines. *Cancer* 2005;104:1129-1137.

10. Australian Institute of Health and Welfare (AIHW) and Australasian Association of Cancer Registries (AACR). Cancer in Australia: an overview, 2008. Cancer series no. 46. Cat. no. CAN 42. Canberra, AIHW; 2008.

CONCLUSION

The result for all cancer sites are summarised in Table 1. Column A shows the proportion of cancer sites and the proportion of all cancers that they comprise. Columns B to D show the optimum utilisation rates for radiotherapy, chemo-radiotherapy and brachytherapy respectively. The chemo-radiation utilisation rate is a subset of the radiotherapy rate. Columns E to G show the proportion of each all cancers that are cancer sites with an indication for radiotherapy, chemo-radiation and brachytherapy, respectively. The sums of columns E to G are the proportion of all cancer cases with an indication for each modality.

Thus 48.3% of all cancers have an indication for radiotherapy (alone or with chemotherapy), 8.9% have an indication for chemo-radiotherapy and 3.3% have an indication for brachytherapy with or without external beam radiotherapy.

Table 1. Summary of Radiotherapy utilisation

	A	B	C	D	E	F	G
Cancer sites	**Proportion of all cancers**	**RTU**	**CT-RTU**	**Brachytherapy utilisation**	**Proportion of cancers with RT indication (A x B)**	**Proportion of cancers with CT-RT Indication (A x C)**	**Proportion of cancers with Brachytherapy Indication (A x D)**
Bladder	2.0%	47%	9%	0%	0.9%	0.2%	0%
Brain	1.4%	80%	53%	0%	1.1%	0.7%	0%
Breast	12.2%	87%	0%	0%	10.6%	0.0%	0%
Cervix	1.0%	71%	51%	53%	0.7%	0.5%	0.5%
Colon	8.4%	4%	0%	0%	0.3%	0.0%	0%
Gall bladder	0.6%	17%	17%	0%	0.1%	0.1%	0%
Head and Neck	3.3%	74%	26%	0%	2.4%	0.9%	0%
Kidney	2.3%	15%	0%	0%	0.3%	0.0%	0%
Leukaemia	2.3%	4%	0%	0%	0.1%	0.0%	0%
Liver	1.2%	0%	0%	0%	0.0%	0.0%	0%
Lung	9.0%	77%	26%	0%	6.9%	2.3%	0%
Lymphoma	4.2%	73%	0%	0%	3.1%	0.0%	0%
Melanoma	9.9%	21%	0%	2%	2.1%	0.0%	0.2%
Myeloma	1.2%	45%	0%	0%	0.5%	0.0%	0%
Oesophagus	1.2%	71%	33%	0%	0.8%	0.4%	0%
Ovary	1.1%	4%	0%	0%	0.0%	0.0%	0%
Pancreas	2.1%	49%	35%	0%	1.0%	0.7%	0%
Prostate	18.4%	58%	0%	10%	10.7%	0.0%	1.8%
Rectum	4.2%	60%	55%	0%	2.5%	2.3%	0%
Stomach	1.8%	27%	20%	0%	0.5%	0.4%	0%
Testis	1.0%	7%	0%	0%	0.1%	0.0%	0%
Thyroid	1.8%	4%	0%	0%	0.1%	0.0%	0%
Unknown Primary	2.4%	61%	0%	0%	1.5%	0.0%	0%
Uterus	1.8%	38%	0%	39%	0.7%	0.0%	0.7%
Vagina	0.1%	94%	78%	80%	0.1%	0.1%	0.1%
Vulva	0.3%	39%	15%	0%	0.0%	0.0%	0%
Other	5.0%	19%	5%	0%	1.0%	0.3%	0%
Total	**100.0%**				**48.3%**	**8.9%**	**3.3%**

RTU= optimal radiotherapy utilisation rate. CT-RT = chemo-radiation

Sensitivity Analysis

As indicated in the chapters on specific tumour sites, there was a level of uncertainly in the models due to

1) Variability in the epidemiological data for certain indications
2) Uncertainty in the indication for radiotherapy (RT) mentioned in the clinical practice guidelines
3) Uncertainty in the choice of radiotherapy, concurrent chemo-radiotherapy (CRT) and brachytherapy (BT) comparing with other treatment options such as surgery

These uncertainties for individual tumour models have been dealt with univariate analysis and presented as the Tornado diagram at the end of each individual tumour report. All individual models were merged at the end to get a single optimal utilisation proportion for cancer (48.3%). To deal with the data uncertainties in the merged model a tornado diagram was constructed including all the uncertain variables in the model. The variables that contributed to the greatest variability (up to 0.1% of the spread) in the model had been selected to do a multivariate sensitivity analysis using Monte Carlo simulation analysis with 10000 simulations that gave a ***95% confidence interval of 47.9% to 48.7% for the optimal RT utilisation, 8.5% to 9.3% for the CRT utilisation and 3.0% to 3.3% for BT utilisation.***

Table 2 compares the previous estimate of radiotherapy utilisation with the current ones. The proportion of all cancer cases that are prostate cancer has increased from 12% to 18% and the proportions of breast, lung and melanomas have decreased. Radiotherapy utilisation rates for bladder, brain, colon, kidney, pancreas, stomach and testis have decreased due to changed indications (colon, kidney, stomach and testis) or the availability of better data on the incidence of indications (bladder, brain, pancreas). Radiotherapy utilisation rates have increased substantially for cervix and lymphoma due to altered proportions with indications rather than the addition of new indications.

Table 2. Comparison between original and new estimates or radiotherapy utilisation by cancer site

Cancer sites	Proportion of all cancers (old)	Proportion of all cancers (new)	Old RTU	New RTU
Bladder	3.0%	2.0%	58%	47%
Brain	2.0%	1.4%	92%	80%
Breast	13.0%	12.2%	83%	87%
Cervix	1.0%	1.0%	58%	71%
Colon	9.0%	8.4%	14%	4%
Gall bladder	1.0%	0.6%	13%	17%
Head and Neck	4.0%	3.3%	74%	74%
Kidney	3.0%	2.3%	28%	15%
Leukaemia	3.0%	2.3%	4%	4%
Liver	1.0%	1.2%	0%	0%
Lung	10.0%	9.0%	76%	77%
Lymphoma	4.0%	4.2%	65%	73%
Melanoma	11.0%	9.9%	23%	21%
Myeloma	1.0%	1.2%	38%	45%
Oesophagus	1.0%	1.2%	80%	71%
Ovary	1.5%	1.1%	4%	4%
Pancreas	2.0%	2.1%	57%	49%
Prostate	12.0%	18.4%	60%	58%
Rectum	5.0%	4.2%	65%	60%
Stomach	2.0%	1.8%	68%	27%
Testis	1.0%	1.0%	49%	7%
Thyroid	1.0%	1.8%	10%	4%
Unknown Primary	4.0%	2.4%	61%	61%
Uterus	1.8%	1.8%	46%	38%
Vagina	0.1%	0.1%	100%	94%
Vulva	0.2%	0.3%	34%	39%
Other	2.0%	5.0%	50%	19%

RTU= optimal radiotherapy utilisation rate

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