

Radiotherapy in Cancer care: estimating the Optimal Utilisation from a review of evidence-based Clinical Guidelines

October 2003

***Collaboration for Cancer Outcomes Research and Evaluation (CCORE)
Liverpool Hospital, Locked Bag 7103 Liverpool BC, NSW 1871 Australia***

For the National Cancer Control Initiative

***Funded by the Commonwealth Department of Health and Ageing,
Commonwealth of Australia, GPO Box 9848, Canberra ACT 2601
Australia***



AUTHORS

- ***Dr. Geoff Delaney, MBBS, MD, FRANZCR. Director of Radiation Oncology, Liverpool and Campbelltown Hospitals, Senior lecturer, University of N.S.W.***
- ***Dr. Susannah Jacob, MBBS, MD. Project Manager, Collaboration for Cancer Outcomes Research and Evaluation (CCORE), Liverpool Hospital.***
- ***Dr. Carolyn Featherstone, MBChB, MRCP, MSc, FRCR. Clinical Fellow, Collaboration for Cancer Outcomes Research and Evaluation (CCORE), Liverpool Hospital.***
- ***A/Prof Michael Barton, MBBS, FRANZCR. Director, Collaboration for Cancer Outcomes Research and Evaluation (CCORE), Liverpool Hospital, Staff specialist Radiation Oncologist, Liverpool Hospital and Senior lecturer, University of N.S.W.***

Suggested Citation:

Delaney GP., Jacob S., Featherstone C., Barton MB. Radiotherapy in cancer care: estimating optimal utilisation from a review of evidence-based clinical guidelines. Collaboration for Cancer Outcomes Research and Evaluation (CCORE), Liverpool Hospital, Sydney, Australia, 2003.

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Executive Summary

The planning of efficient, equitable radiotherapy services for a population requires a rational estimate of demand. In this project we have calculated an estimate of ideal radiotherapy utilisation based on the incidence of each type of cancer, the evidence-based indication for radiotherapy in the treatment of that cancer, and the proportion of cancer patients included in that indication for radiotherapy.

Background

The radiotherapy utilisation rate is defined as the proportion of a defined population of patients with a notifiable cancer that receives radiotherapy during their lifetime. (Notifiable cancers are cancers for which statutory requirements exist to notify a state cancer registry. Statutory notification excludes non-melanomatous skin cancers and benign tumours.) Radiotherapy utilisation rates vary substantially throughout Australia. Variations have also been reported in other countries such as Canada and the Nordic countries, where utilisation ranges from 20–55% of all new cancer cases. These variations stress the importance of using rigorous evidence-based methods to estimate an optimal radiotherapy utilisation rate that can act as a benchmark against which actual utilisation rates can be compared.

It has been widely stated by Commonwealth and State agencies that 50% of all new cases of cancer in Australia will require radiotherapy at some stage of their illness. This 50% treatment rate is based almost entirely on expert opinion, and it is not responsive to changing clinical indications.

Objectives

The objectives of this project were:

- To estimate, using the best available evidence, the ideal proportion of new cases of registered cancer that should receive megavoltage external-beam radiotherapy at some time during the course of their illness. This estimate should be useful in planning for future radiotherapy facilities.
- To develop a model of radiotherapy utilisation that can be used to estimate the impact of future changes in cancer incidence rates, changes in stage at presentation and changes in indications for radiotherapy on the optimal radiotherapy utilisation rate.

Methodology

In this study, an indication for radiotherapy is defined as a clinical situation in 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 treatment guidelines issued by reputed national and international institutions. If guidelines did not exist for particular cancer types and tumour sites, or where the guidelines did not adequately address radiotherapy use, other sources of evidence were identified. These included treatment reviews, randomised controlled trials, population-based studies of care, and single-institution studies.

The evidence for the indications for radiotherapy was classified using the National Health and Medical Research Council (NHMRC) hierarchy of levels of evidence. As our purpose was to make recommendations for radiotherapy services in Australia, the highest priority was given to Australian evidence-based clinical practice guidelines issued by national institutions such as the NHMRC or the National Breast Cancer Centre.

Software by TreeAge™ (Data version 3.5) was used to construct radiotherapy utilisation trees for each cancer site. This software has been used for decision analyses in health and economic assessments of the cost-effectiveness of various treatments. We used the software to illustrate the indications for radiotherapy in a diagrammatic form (as a tree), to perform basic calculations such as multiplication of factors and summation of the results, and to perform statistical analyses such as sensitivity analyses of variability. Parameters can be readily adjusted in the tree if indications for radiotherapy or epidemiological data distributions change in the future and the software can then rapidly estimate the adjusted utilisation rates.

The utilisation trees depict the clinical conditions for which radiotherapy is indicated. Each terminal branch of the tree shows whether or not radiotherapy is recommended for a particular type of cancer in individuals with specific clinical attributes. In some circumstances, the indication for radiotherapy occurred in the initial stages of management. In other circumstances, radiotherapy was given later in the disease course (for instance, in patients who developed a local recurrence and who had not previously had an indication for treatment with radiotherapy). 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 had multiple indications at different stages in their illness.

The radiotherapy utilisation trees also depict the proportion of patients in each branch of the tree. These epidemiological data are displayed below the branch. Australian epidemiological data were used wherever possible. The relative quality of epidemiological data from various sources was ranked according to a scoring system that gave greatest importance to Australian national and state registry data. Where national or state registry data were unavailable for particular decision-tree branches, population-based datasets from other countries were used, for example, the US National Cancer Institute SEER (Surveillance, Epidemiology, and End Results) Database 1973-1997. Population-based databases were preferred because they were considered less likely to be affected by the problems of referral bias or selection bias and

therefore were more likely to be representative of the entire population of patients with cancer.

The proportion of patients in whom radiotherapy would be recommended was calculated for each cancer site by calculating the frequency of each indication for radiotherapy and then summing the frequencies to give the total optimum rate of use. The overall optimum radiotherapy utilisation rate was calculated by summing the optimum utilisation rates derived for each cancer site, calculated as a proportion of all cancers.

Sensitivity analysis was undertaken to assess the impact on the radiotherapy utilisation rate that would result from variations in epidemiological data, different probabilities of benefit from treatment or uncertainty in the indication for radiotherapy. The TreeAge Data version 3.5 software was used to permit different variable estimates to model the effect of uncertainty in some variables with one-way sensitivity analysis and Monte Carlo simulation techniques.

Peer Review

An expert steering committee was convened for this project by the National Cancer Control Initiative (NCCI), with representation from major cancer organisations, consumers, epidemiologists, radiation and medical oncologists, surgeons, palliative care specialists, and experts in evidence and treatment guidelines. The steering committee (consisting of fifteen members) was chaired by the Director or the Deputy Director of the NCCI. The steering committee met with the investigators on a regular basis to agree on the scope of the project and the methods, and to review the drafts.

A multidisciplinary court of reviewers was also established, comprising ninety-one nationally recognised oncology experts from the fields of medical, surgical and radiation oncology, palliative care and oncology nursing. Drafts of each of the chapters were sent to the designated expert reviewers. Reviewers who specialised in one or two particular tumour sites were sent only the relevant chapters. General radiation oncology, medical oncology, surgery and palliative care reviewers received all the chapters for review.

Forty-two of the reviewers provided comments, with 43% of these reviewers being from a non-radiation oncology specialty. Many reviewers provided comments for more than one chapter. We collated 271 specific comments related to the review. This resulted in 139 changes to the text, radiotherapy utilisation trees, epidemiological data or evidence cited including a number of offers of additional epidemiological data. The review also resulted in two major reconstructions of the radiotherapy utilisation trees for two tumour sites. The radiotherapy utilisation trees for breast and lung cancer have recently been published in international general oncology journals.

Results

The recommended overall optimal radiotherapy utilisation rate based upon the best available evidence was estimated to be 52.3%.

Table 1 summarises the results for each of the cancers studied and represents the cohort receiving radiotherapy as a proportion of all cancer patients.

Table 1: Optimal radiotherapy utilisation rate by cancer type.

Tumour type	Proportion of all cancers	Patients receiving radiotherapy (%)	Patients receiving radiotherapy (% of all cancers)
Breast	0.13	83	10.8
Lung	0.10	76	7.6
Melanoma	0.11	23	2.5
Prostate	0.12	60	7.2
Gynaecological	0.05	35	1.8
Colon	0.09	14	1.3
Rectum	0.05	61	3.1
Head and Neck	0.04	78	3.1
Gall Bladder	0.01	13	0.1
Liver	0.01	0	0.0
Oesophageal	0.01	80	0.8
Stomach	0.02	68	1.4
Pancreas	0.02	57	1.1
Lymphoma	0.04	65	2.6
Leukaemia	0.03	4	0.1
Myeloma	0.01	38	0.4
Central Nervous System	0.02	92	1.8
Renal	0.03	27	0.8
Bladder	0.03	58	1.7
Testis	0.01	49	0.5
Thyroid	0.01	10	0.1
Unknown Primary	0.04	61	2.4
Other	0.02	50	1.0
Total	1.00		52.3

The optimal radiotherapy utilisation rates in Table 1 varied from a low rate of 0% for liver cancer patients to a high rate of 92% for patients with Central Nervous System tumours.

Multivariate sensitivity analysis using Monte Carlo analysis indicates that the 95% confidence limits were 51.7% and 53.1%. The tightness of the confidence interval suggests that the overall estimate is robust. This final estimate is remarkably precise despite uncertainty existing in relation to data for some indications for radiotherapy and occasional uncertainty between treatment options of approximately equal efficacy (such as radiotherapy, surgery or watchful waiting for early prostate cancer). The tight confidence interval may be explained by the fact that good quality data existed for the initial branches of the tree (for example, data such as tumour type and stage at presentation). Most of the uncertainty existed in the distal or near-terminal branches of the tree, and therefore affected only very small proportions of the cancer population and had little effect on the overall estimate. In addition, the effect of these variations was such that some would increase the overall utilisation rate while others would reduce it, so that to a large extent they cancelled each other.

Applications of the Model

The estimated overall optimal radiotherapy utilisation rate is 52.3%. The model of radiotherapy utilisation developed in this project has many current and future benefits. In addition, the study has highlighted a number of controversies within cancer management that may have a moderate impact on this estimate and therefore may provide some priority to future research. The following recommendations are made regarding the potential applications of the model and the final estimate of optimal radiotherapy utilisation derived from it.

Planning radiotherapy services on a population basis

The radiotherapy utilisation rate can be used as a benchmark in planning future radiotherapy services. A readily adaptable model of the type described in this study will allow easy recalculation should cancer incidence or treatment recommendations change in the future. The model can be adapted for use in other populations that have differing distributions of cancers and stages at diagnosis, for example, in countries such as India where cervical cancer is much more common than in Australia.

However, there are other uses for radiotherapy that are not included in this estimate and that will need consideration when planning radiotherapy resources. Radiotherapy has an established role in the management of non-malignant conditions (benign tumours and non-cancerous conditions) as well as a role in the management of non-registered cancers such as non-melanomatous skin cancers. The overall need for radiotherapy resources is difficult to estimate as the overall incidence for these conditions is unknown. However, it remains important to consider this additional workload in resource planning.

In the absence of a reasonable estimate, it was considered appropriate to consider the actual workload of radiation oncology departments with respect to the above conditions. We therefore examined actual radiotherapy activity rates for non-malignant and non-registered cases. The William Buckland

Cancer Centre in Victoria, reported on the case mix and outcomes of 9838 patients treated at the centre between 1992 and 2002. The treatment of non-melanomatous skin cancers, heterotopic bone, benign neoplasms and other non-malignant conditions accounted for 12% of radiotherapy activity. In a similar analysis over the same period, 10.4% of the 30,583 patients treated with radiotherapy at the Queensland Radium Institute (Royal Brisbane and Brisbane Mater Hospitals) had non-notifiable conditions. It should be noted that some cases of skin cancer may be treated by kilovoltage radiotherapy, but in many centres electrons produced by linear accelerators are the only modality available to treat skin cancers.

Taking a middle figure of 11% of cases treated by linear accelerators as an estimate of the proportion of non-notifiable conditions receiving radiotherapy, this can then assist in the planning of appropriate resources using the following calculations.

For every 1000 cancer cases in a population:

- 523 patients would need radiation as an optimal part of their management based upon the results of this project (calculated optimal radiotherapy utilisation rate of 52.3%).
- A further 131 patients, of the above 523 patients, will require re-treatment (based upon an actual re-treatment rate of 25%).

This means that an estimated 654 courses of treatment will be required for every 1000 cancer patients diagnosed with a registered cancer. These calculations are summarised in Table 2.

Table 2: Estimated optimal number of courses of treatment per 1000 registered cancers.

	Proportion	Total
Number of new registered cancers		1000
Number of patients requiring radiation	52.3%	523
Number of re-treatments	25%	131
Total number of courses		654

If a linear accelerator has a capacity of delivering 450 courses of treatment per annum we need to factor in treatment of the non-notifiable conditions as well as the need for treatment of notifiable cancers, using the following calculation:

- 11% of a linear accelerator load is for non-malignant and non-registered cancer reasons (based upon the actual estimates from the William Buckland Cancer Centre and the Queensland Radium Institute). For a linear accelerator with an overall capacity of 450 courses per year, this non-registered cancer load would represent 50 courses. This would leave a further 400 courses for registered cancers.
- Using the figure of 654 courses required per 1000 registered cancers, this means that we need 1.6 linear accelerators per 1000 registered

cancers to provide sufficient resources to manage all patients including those with non-registered cancers (this figure does not factor in the brachytherapy resources needed).

Estimating shortfalls between optimal and actual rates of radiotherapy utilisation and providing a benchmark for service delivery

The radiotherapy utilisation trees that have been developed for each of the tumour sites are a diagrammatic representation of optimal evidence-based cancer care from a radiotherapy perspective. Epidemiological data from patterns of care studies will allow comparisons to be made between the actual rates of radiotherapy delivery and the evidence-based ideal rate. Further details can be determined by analysing the distributions of tumour stage, histology, age, performance status and other factors, in order to better define areas of discrepancy between the actual and ideal utilisation rates.

Modelling the effects on the overall recommended radiotherapy utilisation rate of changes to a particular cancer incidence or changes in staging

The TreeAge Data software used to construct the radiotherapy utilisation trees can readily modify the overall model should there be changes in the incidence of certain cancers, a change in the stage distribution or a change in therapy recommendations based on clinical trials. For example, if another country with a very different cancer incidence profile were to use the model then the only requirement to recalculate the optimal radiotherapy utilisation rate would be to alter the incidence of each of the cancers. Similarly, a change in stage distribution of cancer due to the development of superior staging investigations (such as the impact of Positron Emission Tomography on staging non-small cell lung cancer), or following the introduction of a screening programme could easily be incorporated into the model.

Determining optimal rates and resources for other treatment modalities

Throughout the course of this project, the methodology has been refined and improved upon. The radiotherapy utilisation tree model and methodology could be readily adapted to consider other treatments (such as surgery or chemotherapy) for cancer. It could also be used to plan other services if criteria were known for the use of a particular service. For instance, if we knew the factors that predict the need for palliative care referral or genetics review, then resource planning could be assisted by calculating the optimal utilisation rate in a similar fashion to that described here for radiotherapy.

Identifying areas of research that would have the greatest impact on radiotherapy service delivery

As well as the research opportunities discussed above, this project has identified several potential future research activities that would directly impact on the accuracy of this model. A few of these general areas are discussed below:

- (a) Epidemiological studies – The construction of the radiotherapy utilisation tree has identified a number of areas where there is uncertainty about the proportion of patients with certain conditions

and has highlighted the need for better data. The main areas identified as being sub-optimal are those near terminal branches of the utilisation tree and those identified as showing variation requiring sensitivity analysis. More meaningful data, particularly longitudinal population-based data, would be valuable in the following areas:

- the incidence of metastasis over time and by stage, and treatment for the more common cancers
- the proportion of patients who develop metastases to organs other than bone and brain, and the need for symptomatic control
- patterns of metastatic spread with time and the proportion of patients who develop metastases of differing types
- the proportion of patients who develop symptoms as an indication for palliative radiation treatment over time
- performance status and how this changes with relapse, and the effect of patient choice when two treatment modalities are considered similar in efficacy and are equally available.

(b) Identification of controversial areas of practice where further clinical trials are needed – The tornado diagrams identified the controversial areas of practice that will have the most impact on the overall optimal radiotherapy utilisation rate. The main controversies identified in terms of their impact on the optimal radiotherapy utilisation rate are:

- the role of radiotherapy (as opposed to observation or surgery) for localised prostate cancer
- the role of radiotherapy for T4 colon cancer
- the criteria for adjuvant radiotherapy for node-positive melanoma (need to be better defined)
- the role of radiotherapy for positive margins post-prostatectomy (should be clearly determined)
- the role of lymph node dissection for endometrial cancer
- the role of surgery (versus radiotherapy) for localised bladder cancer.

In addition, a large number of radiotherapy treatment recommendations are based upon level IV evidence and it is strongly recommended that the levels of evidence should be improved through randomised controlled trials.

(c) Prediction of future radiotherapy workload

The radiotherapy utilisation trees that have been constructed allow an assessment of the overall proportion of cancer patients for which a recommendation for radiotherapy would be likely throughout the course of their illness. However, the utilisation tree does not assess whether the treatment intent would be palliative or radical, and does not predict the number of fractions of treatment that would be evidence-based, nor the complexity of the patient's care. Various models of complexity have been reported in the literature that might

be used in future studies so that even more accurate predictions of radiotherapy workload could be determined.

Conclusion

The overall estimate for radiotherapy utilisation is 52.3% based upon the best available evidence. Although the scope of this study is confined to exploring the optimal utilisation of radiotherapy (limited to external beam megavoltage radiotherapy) for notifiable cancers only, the overall estimate provides a useful tool for assisting in the planning of adequate radiotherapy resources. Based upon actual re-treatment rates of 25% and actual radiotherapy treatment rates for non-registered conditions of 11% of total linear accelerator capacity, we estimate that at least 1.6 linear accelerators will be required per 1000 registered cancers in order to meet demand.

Introduction

Background

Radiotherapy is an essential mode of cancer treatment and contributes to the cure or palliation of many cancer patients. Radiotherapy facilities have high capital costs and their operation is staff intensive. The planning of efficient, equitable radiotherapy services for a population requires a rational estimate of need. In this project we have undertaken to calculate such an estimate, based on the occurrence of each type of cancer, the evidence-based indication for radiotherapy in the treatment of each type of cancer, and the probability that radiotherapy will be chosen as a form of treatment.

Previous reports from Commonwealth and State agencies have proposed that 50 percent of all new cases of registered cancer in Australia should be treated with external beam radiotherapy (1) (2-5). Although this figure is based almost entirely on expert opinion, it is currently accepted as the guide for estimating utilisation and is used to plan for the distribution and number of linear accelerators. However, its validity is questionable, it is not responsive to changing clinical indications, and it does not include an assessment of the rate of re-treatment (about 25% of radiotherapy cases are currently re-treated with radiotherapy) (5). The population's need for radiotherapy is obviously determined by both the number of new cases requiring radiotherapy, and the number of cases requiring re-treatment with radiotherapy.

Radiotherapy utilisation rates vary substantially throughout Australia. Such variations have also been reported in other countries, such as Canada and the Nordic countries, where utilisation ranges from 20 to 55 percent of all new cancer cases (6) (7) (8) (9). In Australia, higher radiotherapy utilisation rates are reported for urban patients or where rural patients have ready access to a radiotherapy consultation (such as remote centres with radiation oncology outpatient clinics) (10) (11). Radiotherapy utilisation rates decrease as the distance from patients' place of residence to radiotherapy services increase. While this may reflect reduced access for patients living further from radiotherapy departments, an alternative explanation is that radiotherapy may be over-utilised in areas that are well-resourced (6). Other possible explanations for variations in utilisation rates include differences in casemix across regions, either due to regional differences in epidemiological factors such as socioeconomic status or prevalence of smoking that may impact on the risk of certain cancers, or to variations in referrals based on perceived differences in expertise by medical professionals in certain hospitals. For instance, some centres may be a centre of excellence for a particular type of cancer or type of surgical procedure.

The existence of these variations stresses the importance of using rigorous evidence-based methods to estimate a recommended radiotherapy utilisation rate. Such methods make use of the recent proliferation of evidence-based guidelines for cancer management that specify the indications for various treatment modalities. Tyldesley et al. (6) described their use of such an evidence-based approach to the determination of 'ideal' referral rates for the management of lung cancer. Their approach can be adopted for other cancers, using epidemiological information on the incidence of each cancer

type. By summation over all cancer types, a more accurate estimate of the overall requirement for radiotherapy can be obtained than the current opinion-based figure.

Project objectives

The objectives of the project were

- To estimate the ideal proportion of new cases of registered cancer that should receive megavoltage external beam radiotherapy at some time during the course of their illness from the best available evidence available. This estimate should be useful in aiding the planning for future radiotherapy facilities.
- To develop a model of radiotherapy utilization that may be used for future changes in cancer incidence rates, changes in stage at presentation and changes in indications for radiotherapy.

Issues

The following issues present some difficulties and limit the certainty of the estimate of optimal utilisation.

- *Rare tumours.* Guidelines exist for the common cancers only. In Australia, evidence-based national guidelines exist for the management of breast cancer, colorectal cancer and melanoma. Prostate and lung cancer guidelines are being developed. These cancers account for just over half of the new cancer cases treated in NSW radiotherapy departments. No national level Australian guidelines are available, and indeed few randomised controlled trials have been published, for many of the recognised indications of radiotherapy, such as head and neck cancers.
- *Non malignant diseases.* Radiotherapy is recognised as an effective treatment, and is often the optimal treatment, for benign conditions such as pituitary tumours, and for premalignant conditions such as ductal carcinoma-in-situ of the breast that may not be recorded in cancer registries. Population incidence figures for such conditions may be difficult to find. Recommendations for the utilisation of radiotherapy in non-malignant diseases are only just emerging for some conditions (notably post-angioplasty coronary irradiation).
- *Palliation.* Many randomised controlled trials exist on the use of radiotherapy for the palliation of pain from metastases to bone. Much less Level I-II evidence exists for other palliative indications for radiotherapy which are in widespread clinical use, such as obstruction of the superior vena cava and spinal cord compression.

- *Non-melanomatous skin cancer.* This group represents a significant component of workload in most radiation oncology departments. However, the methodology of this study was to use registered cancers as the denominator for calculating the optimal radiotherapy rate. Therefore, these were excluded from the calculation. However, this workload will need to be considered when planning radiotherapy resources.

These issues are discussed and possible solutions are presented in the discussion section of this report.

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Methods

The following steps were employed to develop a model of optimum radiotherapy utilisation for each cancer site.

Step 1: Evidence for the efficacy of radiotherapy

In this study, an indication for radiotherapy is defined as a clinical situation in 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 treatment guidelines issued by reputed national and international institutions. As our purpose was to make recommendations for radiotherapy services in Australia, 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) or the National Breast Cancer Centre.

If guidelines did not exist for particular cancer types and tumour sites, or where the guidelines did not adequately address radiotherapy use, other sources of evidence were identified. These included randomised controlled trials, population-based studies of care, and single-institution studies. Systematic reviews of published English-language literature were undertaken to find evidence of indications for radiotherapy. We based our assessment of the quality of published studies on the National Health and Medical Research Council (NHMRC) hierarchy of levels of evidence (see Table 1).

Table 1. Levels of evidence for indications for radiotherapy (1)

Level	Description
I	Systematic review of all relevant randomised studies
II	At least 1 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

Step 2: Indications for radiotherapy and radiotherapy utilisation trees

Radiotherapy was defined as efficacious in any clinical situation where there was evidence that radiotherapy was superior to other treatment modalities (or no treatment) for one or more of the following clinical endpoints:

- survival,
- local control,
- disease-free survival,
- quality of life,
- symptom control, and
- cost.

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.

The same attributes were used by Tyldesley et al (2), who described their use of such an evidence-based approach in the determination of 'ideal' referral rates for the management of lung cancer.

Any indications for radiotherapy identified in clinical practice guidelines or other literature were included in the analysis. We recognise that some indications were universally accepted while others were not. Radiotherapy utilisation trees developed for the project (described below) were constructed to be modifiable in the light of changing practice and emerging evidence.

For each type of cancer, we developed a radiotherapy utilisation tree in which each branch point represented an attribute (such as the stage of the tumour, or whether or not surgery was clear of the tumour margins) that affected a management decision. TreeAge software version 3.5™ was used to construct the 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 (3). This particular software was chosen for the following reasons - it depicts indications for a particular treatment modality in a diagrammatic form, provides a convenient way to perform multiplication of various factors and the summation of the results, it provides tools to perform statistical analyses such as sensitivity analyses of variability and can easily adapt the tree parameters should indications for the treatment modality or epidemiological data distributions change over time. Each branch of the tree ended in either 'radiotherapy' or 'no radiotherapy' as the final outcome. In some circumstances, the indication for radiotherapy occurs in the initial stages of management. In other circumstances, radiotherapy may be delayed (for instances, in patients who develop a local recurrence, and who

have not previously required radiotherapy). Because the purpose of our project was to determine the proportion of all cancer patients who have an indication for radiotherapy at some time in the course of their illness, patients requiring radiotherapy were counted only once, even if they had multiple indications at different stages in their illness. Each terminal branch of the tree showed whether or not radiotherapy was recommended for a particular type of cancer in individuals with particular attributes.
[Further information on the use of radiotherapy utilisation trees is provided at the end of this section.]

Step 3: Epidemiology of cancer types, tumour sites and stages

Searches for information on the epidemiology of the different attributes associated with each cancer type and each tumour site (using Australian data wherever possible) were performed. The relative quality of epidemiological data from various sources was ranked as shown in Table 2.

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

National cancer incidence figures, such as those published by the Australian Institute of Health and Welfare (4) were used to determine the incidence of cancer types and tumour sites. Tumour staging information and other clinical characteristics relevant to the need for radiotherapy were sought from national databases, or national surveys of representative samples of Australian cancer patients (e.g. the 1995 National Breast Cancer Management survey, 2000-2001 National Colorectal cancer management survey. When national data were unavailable, more specific datasets (such as those of State Cancer Registries) were used for information pertaining to tumour stage and pathology.

Where clinical details in surveys were incomplete, additional details were obtained from multi-institutional settings. One such source was the South

Australian Network of Hospital-based Cancer Registries (SA-HBCR) (5). The Registries in the Network are based in major teaching hospitals and include data on patients attending the five largest cancer centres in South Australia, which manage more than half of all cancer cases in the State. It was assumed that, where SA-HBCR data were used, the distribution of attributes such as tumour site and stage and patients' performance status were representative of the general population of Australian cancer cases. The validity of this assumption is supported by the following points:

- In 1995, the distribution of stages of breast cancer in the SA-HBCR was almost identical to that found in the 1995 National survey of breast cancer management (12).
- SA-HBCR survival rates were very similar to those reported from other Australian studies of cancer survival, both at the national level and in NSW, Queensland and Western Australia (A/Professor David Roder, personal communication). Since stage is the major determinant of survival for most cancer types and tumour sites, it is likely that the distribution of stages in South Australia was the same as corresponding distributions from elsewhere in Australia.
- The survival of cases attending South Australian hospitals that had hospital-based cancer registries was similar to the survival of all South Australian cancer cases. Thus, again, it is likely that the distribution of stages in the SA-HBCR was similar to that of the overall population.
- The cancer types and tumour sites covered by the SA-HBCR represent 88 percent of all cancers in South Australia and, by inference, Australia as a whole (excluding non-melanoma skin cancers). The collective disease-specific five-year survival for cases in the SA-HBCR was 51 percent, very similar to the figure of 53 percent given by the South Australian Cancer Registry for all cases with cancers at these sites (after weighting by site to be similar to the distribution observed in the SA-HBCR).

Where national or State Registry data were unavailable for particular radiotherapy utilisation-tree branches, population-based datasets from other countries were used, for example, the US National Cancer Institute Surveillance, Epidemiology, and End Results Database 1973-1997 (6). Population-based databases were preferred because they were considered less likely to be affected by the problems of referral bias and biases associated with selection for treatment.

Where population-based datasets could not be found in Australia or internationally for particular branches in the tree, overseas databases (such as the US National Cancer Database) were used, or incidence data were drawn from historical reports of regional patterns of care and longitudinal studies identified in the literature search. The MEDLINE database was searched for epidemiological incidence data for specific branches in the radiotherapy utilisation tree where there was no available epidemiological data from registries or from institutional databases. This often involved the smallest branches in the tree where searches were conducted for published data on very specific clinical situations in which radiotherapy is indicated. Secondary manual searches of bibliographies were performed to follow up on

additional references identified in the guidelines or in retrieved papers. Historical reports and longitudinal studies were interpreted with care because they were considered to be susceptible to referral bias and bias in the selection of cases for treatment. Greater value was placed on random samples of populations than on multi-institutional databases because referral bias was considered to be less likely. Comprehensive reports of the entire experience of an individual institution were ranked higher than reports of highly-selected groups of cases involved in clinical trials; although both would be subject to referral bias, the latter is also subject to bias relating to selection for treatment, while the former is not. Where two or more sources of data of equivalent quality (based on the criteria in Table 2) were found, the source with the larger sample size was chosen. If large differences in incidences existed between similar studies then both sets of data were used in the sensitivity analysis.

Step 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.

Step 5: Sensitivity analysis

Sensitivity analyses was undertaken 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.

The TreeAge software allowed different estimates to be modelled using one-way sensitivity analysis and Monte Carlo simulation techniques.

One-way sensitivity analyses allow a single uncertain variable to be modelled to assess the impact that the uncertainty has on the final optimal radiotherapy utilisation. Monte Carlo simulations allow for assessments of the various uncertain data and their overall impact on the radiotherapy utilisation rate in a multivariate fashion. Monte Carlo simulations are based upon the random sampling of variables from discrete and continuous distributions during individual trials. Observing the statistical properties of many trials using random sampled values allows additional insight into the performance of a model. Further description of the Monte Carlo simulations are presented in the results section (Chapter 19).

Step 6: Modelling of projections

Once the model of radiotherapy utilisation has been established for each cancer site and tumour site, projections can be made, based on observed trends. These projections can incorporate:

- changes in the age distribution of the population,
- the introduction of new diagnostics tools,
- the advent of screening programs,
- new techniques, and
- the outcomes of current randomised trials.

This could be the subject of future research but was not performed as part of this project.

Steering Group and Court of Reviewers

The final results of this project had to be credible to all parties who may be affected by it, including State and Commonwealth governments, consumers, non-government organisations such as State Anti-Cancer Councils, and medical, surgical and radiation oncologists. To ensure that the project outcomes met expectations of rigour and that points of interpretation were resolved, an expert steering group was appointed. The steering group was convened by the National Cancer Control Initiative (NCCI), with representation from major cancer organisations, consumers, epidemiologists, radiation and medical oncologists, surgeons, palliative care specialists, and experts in evidence and treatment guidelines, and was chaired by the Director of the NCCI. The steering group met with the investigators on a regular basis to agree on the scope of the project and the methods, and later to review the first and final drafts.

It was recognised that the indications for radiotherapy and the radiotherapy utilisation trees for each cancer type and tumour site should be peer-reviewed for validity. The draft results were scrutinised through a process of consultation prior to final adoption of the model. A Court of Reviewers was established comprised of experts drawn from the fields of surgical oncology, medical oncology, radiation oncology, palliative medicine, public health and oncological nursing. The Faculty of Radiation Oncology of the Royal Australian and New Zealand College of Radiologists called for expressions of interest from its Radiation Oncology Fellows to act as reviewers for this project. Reviewers from other fields were nominated by members of the National Cancer Control Initiative Steering Committee or by members of the Medical and Scientific Committee of the Clinical Oncological Society of Australia. Representatives of the guideline committees that were responsible for the existing Australian treatment guidelines were also invited to act as reviewers. The Court of Reviewers was consulted regularly during the review process and the reviewers who responded to our requests are gratefully acknowledged in Appendix 1. Appendix 2 lists the comments and the actions that resulted from the reviewer's comments.

A description of the layout of the rest of this report

The tumour sites that have a cancer incidence of 1% or greater of the entire population of registered cancers were reviewed and appear in each of the following chapters. Each chapter discusses a particular cancer site and contains:

- a table consisting of indications for radiotherapy and the guideline sources where these recommendations came from,
- a table listing the epidemiological data on the specific attributes that contribute branches to the trees and the sources of data and their level of importance,
- a list of explanatory notes that provide comment about the data sources relevant to the epidemiological data and/or the guideline recommendation for radiotherapy,
- a sensitivity analysis for each tumour. Some chapters contain a tornado diagram. The tornado diagram is a diagrammatic representation of the one way sensitivity analysis. Each variable is represented by a horizontal bar with the variable that has the most impact appearing on the top and as the bars decrease in importance they go down the page until the least important variable in terms of the impact on the final result appears,
- a summary of the final result for the cancer being discussed
- a radiotherapy utilisation tree with each terminal branch ending in an outcome of either 'no radiotherapy' (outcome '0') or 'radiotherapy' (outcome '1'). The results for each of the end nodes is shown as a proportion of all patients with that particular cancer.

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Breast Cancer

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

Outcome No.	Clinical Scenario	Treatment indicated	Level of Evidence	References	Notes	Proportion of all breast cancer cases
1	DCIS, breast –conserving surgery	Adjuvant radiotherapy	II	<ul style="list-style-type: none"> • NBCC guidelines on DCIS (1) • National Cancer Institute PDQ guidelines (2) • NCCN guidelines (3) • CCOP guidelines on DCIS (4) • BCCA guidelines (5) • Canadian consensus guidelines (6) 	3	0.09
2	DCIS treated with mastectomy, local recurrence	Radical or adjuvant radiotherapy	III	<ul style="list-style-type: none"> • NBCC advanced breast cancer guidelines (7) • National Cancer Institute PDQ guidelines (2) • NCCN guidelines (3) • BCCA guidelines (5) • COIN guidelines (8) 	4	< 0.01
4	T1-2 N0-1 M0 breast-conserving surgery	Adjuvant radiotherapy	II	<ul style="list-style-type: none"> • NBCC early breast cancer guidelines (9) • National Cancer Institute PDQ guidelines (2) • NCCN guidelines (3) • CCOP guidelines on invasive breast cancer (10) • BCCA guidelines (5) • Scottish SIGN guidelines (11) 	6	0.62

Outcome No.	Clinical Scenario	Treatment indicated	Level of Evidence	References	Notes	Proportion of all breast cancer cases
5	T1-2 N0-1 M0 mastectomy 0-3 lymph nodes involved, local recurrence	Radical or Adjuvant radiotherapy	III	<ul style="list-style-type: none"> NBCC advanced breast cancer guidelines (7) National Cancer Institute PDQ guidelines (2) NCCN guidelines (3) BCCA guidelines (5) COIN guidelines (8) 	8	0.01
12	T1-2 N0-1 M0 mastectomy > 3 lymph nodes involved	Adjuvant radiotherapy	I	<ul style="list-style-type: none"> NBCC post -mastectomy guidelines (12) ASCO post-mastectomy guidelines (13) National Cancer Institute PDQ guidelines (2) NCCN guidelines (3) NIH consensus guidelines (14) 	7	0.03
13	T3-4 Any N M0, good/fair PS or Any T N2-3 M0, good/fair PS	radiotherapy +/- systemic therapy +/- surgery	III	<ul style="list-style-type: none"> NBCC advanced breast cancer guidelines (7) ASCO post-mastectomy guidelines (13) NCCN guidelines (3) BCCA guidelines (5) 	9 7	0.06

[illegible]

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

Key	Population or subpopulation of interest	Attribute	Proportion of population with this attribute	Quality of information	References	Notes
0	All registry cancers	Breast cancer	0.13	α	AIHW (18)	
1a	All breast cancer	DCIS	0.09	β	Kricker et al (19)	1
1b	All breast cancer	T1-2 N0-1 M0	0.80	α	Hill et al (20)	5
1c	All breast cancer	T3-4 Any N M0, or Any T N2-3 M0	0.08	α	Hill et al (20)	5
1d	All breast cancer	Any T Any N M1	0.03	α	Hill et al (20)	5
2	DCIS	Mastectomy	0.33	ζ	Morrow (21)	2,3
3	DCIS, mastectomy	Local recurrence	0.014	ϵ	Boyages et al (22)	4
4	T1-2 N0-1 M0	Breast-conserving surgery	0.81	ζ	Morrow et al (21)	6
5	T1-2N0-1M0 mastectomy	0-3 lymph nodes	0.82	ϵ	SA Hosp Reg (23)	7
6	T1-2 N0-1 M0, mastectomy, 0-3 lymph nodes	Local recurrence	0.09	ζ	Wilking et al (24)	8

Key	Population or subpopulation of interest	Attribute	Proportion of population with this attribute	Quality of information	References	Notes
7	T1-2 N0-1M0 mastectomy, 0-3 lymph nodes, no local recurrence	distant recurrence	0.12	ζ	Wilking et al (24)	8
8	T1-2 N0-1 M0 mastectomy, 0-3 lymph nodes, 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. (25) Solomayer et al. (26) Coleman et al. (27) Leone et al. (28)	10
9	All bone metastases	Painful bone metastases	0.95 0.8	ζ	Pivot et al. (25) Solomayer et al. (26)	11
10	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. (25)	12

Key	Population or subpopulation of interest	Attribute	Proportion of population with this attribute	Quality of information	References	Explanatory Notes
12	T3-4 Any N M0, or Any T N2-3 M0	good/fair PS	0.91	ε	SA Hosp Reg (23)	9
15	Non-symptomatic bone metastases +/- visceral metastases	Symptomatic brain metastases	0.12	ζ	Pivot et al. (25)	12

Key to Abbreviations in Breast Cancer Tables

DCIS –Ductal Carcinoma in-situ

PS – Performance status

NBCC – National Breast Cancer Centre (Australia)

NCCN - National Comprehensive Cancer Network (US)

BCCA – British Columbia Cancer Agency (Canada)

ASCO – American Society of Clinical Oncology

CCOP – Cancer Care Ontario Practice Guidelines Initiative

NIH – National Institute of Health (US)

SIGN – Scottish Intercollegiate Guidelines Network

Breast Cancer

Treatment guidelines

Peer-reviewed Australian national-level guidelines for the treatment of breast cancer have been published by the NHMRC National Breast Cancer Centre (Clinical Practice guidelines for the management of early breast cancer, advanced breast cancer, DCIS, post-mastectomy radiotherapy). In addition there are several international guidelines on the treatment of breast cancer. These include the guidelines issued by the National Cancer Institute's Physician Data Query (PDQ), the British Columbia Cancer Agency (BCCA), the National Comprehensive Cancer Network (NCCN), the American Society of Clinical Oncology (ASCO), the Cancer Care Ontario Practice Guideline Initiative (CCOP), the Royal College of Radiologists Clinical Oncology Information Network (COIN), the Scottish Intercollegiate Guidelines Network (SIGN) and the American College of Radiologists.

Indications for radiotherapy

In accordance with guideline recommendations, radiotherapy is indicated in the treatment of breast cancer in the following clinical situations:

- In patients who undergo breast-conserving surgery for ductal carcinoma in situ (DCIS)
- In patients who undergo breast-conserving surgery for early invasive cancer
- In patients who develop local recurrence following mastectomy for DCIS
- In patients who develop local recurrence following mastectomy for early invasive cancer
- In patients with Stage IIA (T1-2 N0-1 M0) breast cancer who undergo mastectomy and are found to have microscopic tumour involvement of more than three axillary lymph nodes
- In patients with Stage III (T3-4 Any N M0 or Any T N2-3 M0) breast cancer and good or fair performance status
- For the palliation of painful bone metastases
- For the palliation of symptomatic brain metastases

There are other palliative indications for radiotherapy including symptomatic pulmonary, nodal, subcutaneous and choroidal metastases. However, these are relatively uncommon and patients with metastatic disease to these sites will also commonly have brain and/or bone metastases and hence already appear in the tree and receive radiation. It was thought that omission of these extra sites of metastatic disease would have little impact on the overall radiotherapy utilisation estimate.

Explanatory Notes to Tables 1 and 2

1. Incidence of breast cancer

Breast Cancer constitutes 12.8 % of all cancers occurring in Australia (18). The data on the proportion of all breast malignancy that is ductal carcinoma in situ (DCIS) was obtained from Kricker (19) from cross-referencing of Australian Institute of Health and Welfare (AIHW) (29) and National Breast Cancer Centre (NBCC) data.

2. Breast conserving surgery vs mastectomy for DCIS

When determining whether patients were suitable for breast conserving surgery for early breast cancer and DCIS in the decision trees, it was important to look at the **clinical criteria** for breast conservation as opposed to the actual mastectomy rates reported in some areas. The aim of this study was not to review current practice but to assess the management of patients according to the best available evidence. Current mastectomy rates may not necessarily reflect evidence-based best practice and may be influenced by factors such as the selection biases of the treating clinician, level of access to radiotherapy services, the type of information provided to the patient etc. For example, the South Australian Registry reports a 1987-1998 mastectomy rate for DCIS of 45% (23). However, this mastectomy rate may reflect instances where radiotherapy was not an option due to non-availability of convenient radiotherapy services. Therefore, when determining the appropriate proportion of patients suitable for breast conservation in this study, prospective studies assessing the suitability for breast conservation of a random cohort of patients with early breast cancer or DCIS were preferred over patterns of practice studies. A study of 96 patients with DCIS treated in one multi-disciplinary setting by Morrow et al (21) attempted to prospectively categorise all patients into two categories – “breast conservation possible” or “breast conservation not possible”. This was based on rigid *a priori* criteria such as the patient’s breast size and the likelihood of a good cosmetic result if conservative surgery with clear margins were undertaken. This study showed that 33 % of cases of DCIS had contraindications to breast conserving surgery (BCS). The most common contraindication to BCS was multicentric or multifocal disease, which was present in 40 % of patients with contraindications to BCS. Other contraindications to BCS were a diffusely abnormal mammogram and a large tumour/breast ratio.

3. Radiotherapy following breast conserving surgery for DCIS

All patients who have undergone breast conserving surgery (BCS) for DCIS were considered to have an indication for radiotherapy. This was because 2 randomised controlled trials (30) (31) have shown a statistically significant improvement in local control for DCIS treated with BCS and radiotherapy over BCS alone, for all pathologic sub-types. The draft NBCC DCIS guidelines (1) suggest that the small but significant improvement seen for low-grade DCIS may mean that radiotherapy may be omitted for some subgroups, but this must be discussed with the patient and radiotherapy must have been considered and offered to all DCIS patients.

The proportion of patients that may fall into the low-risk category is difficult to determine since criteria have not yet been established to adequately define these patients. As the guidelines suggest that radiotherapy should be offered to all patients with DCIS lesions who have been treated with conservative surgery, the decision tree reflects the fact that radiotherapy should be made available if necessary to all these patients.

4. Local recurrence after mastectomy for DCIS

Local recurrence data for DCIS patients treated by mastectomy was taken from a review of all reported series of mastectomy for DCIS by Boyages et al (22). This includes studies that were predominantly pre-screening and therefore the estimate of recurrence may be slightly high but no other data exist to provide a more accurate estimate. It is recommended that all patients who develop local recurrence will require radiotherapy. The NHMRC Locally Advanced Breast Cancer Guidelines state that “[In the event of locoregional recurrence] radiotherapy should be administered to the entire chest wall and draining nodal areas if they have not been previously irradiated”.

5. Stage data for invasive breast cancer

Estimates of the proportions of all invasive breast cancers by stage are taken from the 1995 national survey of breast cancer management by Hill et al (20). If DCIS comprises 9% of all breast malignancies, then the proportions of invasive cancers are proportions of the remaining 91% of breast malignancy. The stages reported in this decision tree are based on the clinical pre-operative stages reported by Hill et al. (20) rather than the stages based upon the pathological findings. The decision to use the clinical stage was based on the fact that most of the decisions about management will mainly be based on the pre-operative stage and the decision trees reflect clinical decision-making.

6. Breast conserving surgery for invasive breast cancer

The NHMRC Early Breast Cancer Guidelines recommend that all patients undergoing BCS for early breast cancer should receive radiotherapy. Randomised trials show an improvement in local control in patients who receive radiotherapy following BCS when compared to patients treated with BCS alone.

In the Australian patterns of care study (20), 53% of patients with early disease received BCS. However, some of the stated reasons for BCS being denied to the remaining 47% are not necessarily contraindications to BCS according to the NBCC Early Breast Cancer Guidelines (9). In the Breast Cancer Patterns of Care survey in Greater Western Sydney (32), 47.5 % of T1-2 had BCS. Breast surgeons in this study with a significant clinical load of breast cancer cases had a 53% BCS rate for T1-2. The SA Hosp Registry data (23) shows that breast conservation rates have increased with time, from 38% in 1987-1991, to 55% in 1992-1998 to 70% in 1999. The problem with using these proportions in the decision tree is that they reflect actual practice and are not necessarily evidence-based, as discussed in explanatory note 2 for DCIS. The proportion of breast

cancer patients who undergo conservative management will be influenced by factors such as the experience of the treating clinician, the treatment biases of the clinician, access to radiotherapy services and the type of information provided to the patient. The best study on the proportion of patients with contraindications to breast conserving surgery is by Morrow et al (21). They reported on 336 invasive breast cancers referred to a multi-disciplinary clinic in NorthWestern University, U.S. between 1988 and 1993. Forty percent of the cases were mammographically detected (similar to the experience in many other centres and to the experience in Australia). The contraindications to BCS in the study were established *a priori* as follows: multiple gross or mammographic tumours in separate quadrants of the breast, diffuse suspicious or indeterminate microcalcifications on mammogram, first or second trimester pregnancy, prior irradiation to the breast area, inability to resect a tumour with clear margins with 2 surgical procedures exclusive of the diagnostic biopsy and a large tumour to breast ratio. Sixty-five of the 336 patients (19 %) were found to have contraindications to BCS, resulting in a proportion of 81% in whom BCS and radiotherapy was considered appropriate. Morrow et al also found that 19 % of patients who were eligible to have BCS chose to have a mastectomy. No reasons were sought for these patients choosing mastectomy. Age was not found to predict patient choice.

7. Radiotherapy in patients with positive lymph nodes following mastectomy

Recent randomised trials suggest that node positive patients undergoing mastectomy benefit from post-mastectomy radiotherapy (both in terms of local control and survival). Most guidelines such as the National Breast Cancer Centre Radiation Oncology Advisory Group guidelines (12) and the American Society of Clinical Oncology (ASCO) guidelines (13) suggest that radiotherapy should be recommended for patients with the highest risk of loco-regional failure (>3 axillary nodes positive). However the guidelines remain cautious about recommending radiotherapy for patients with N 0-3 axillary nodes positive. The NBCC Radiation Oncology Advisory Group guidelines (12) suggest that patients with 1-3 nodes should “be considered for irradiation” if adverse pathological features are present (lymph-vascular space invasion, high grade, oestrogen receptor negativity etc). At present, the decision tree reflects the recommendation of radiotherapy for patients with > 3 nodes positive. However, sensitivity analysis examined the possibility that ALL patients (including those with 1-3 nodes positive) who have node positive disease following mastectomy will be offered radiotherapy. A recent sub-group analysis of the Danish randomised trial presented at the European Society of Therapeutic Radiation Oncology 2001 (ESTRO) suggested that patients with 1-3 nodes involved do derive benefits in local control and survival following radiotherapy (M.Overgaard, unpublished data).

SA Hospital Registry data on a selected group of 241 cases undergoing axillary dissection with T1-2 breast cancer show no node involvement in 66%, 1-3 nodes involved in 16 % and N >3 in 18% for T1-2 breast cancers (23). The decision tree used the figure of 18% for the proportion of patients

with >3 nodes as the value requiring radiotherapy to reflect the guideline recommendations. For the sensitivity analysis, to examine the effect of including patients with N1-3 nodes, the proportion of “4+ nodes patients” was modelled at 34% of all patients being recommended for radiotherapy (this represents the 18% with 4+ nodes and the 16% having 1-3 nodes from SA Hospital Registry data).

8. Local recurrence after mastectomy for invasive breast cancer

“Local recurrence” following mastectomy refers to any locoregional recurrence including the axilla, internal mammary chain or supraclavicular fossa nodes as well as the chest wall. The local recurrence rates for T1-2 with N0-3 nodes treated by mastectomy were obtained from a Swedish population based study (24) that reported a recurrence of 8.8 % for N0-3. For the proportion estimate, it has been assumed that the proportion of N 0-3 (82 %) in Stage I and II patients (most surgical series) does not differ between those deemed BCS appropriate and those in whom BCS is considered inappropriate. Most of the other large studies and randomised trials reported recurrence rates for T1-2 with N1-3 (but not N0).

It is assumed that all patients who develop local recurrence will require radiotherapy. The NHMRC Advanced Breast Cancer Guidelines (7) state “[In the event of locoregional recurrence] radiotherapy should be administered to the entire chest wall and draining nodal areas if they have not been previously irradiated”.

9. Stage III invasive breast cancer

Radiotherapy is recommended for all patients with locally advanced breast cancer, provided that they are fit enough (this could be with chemotherapy +/- surgery). SA Hospital Registry data (23) shows that 91 % of Stage III patients were ECOG 0-2, and it has been assumed that these patients would be fit enough for radiotherapy.

10. Indications for radiotherapy in metastatic breast cancer

The vast majority of patients in whom radiotherapy is recommended in stage IV would be those with brain and/or bone metastases. Other sites of metastatic disease where radiotherapy could be recommended are for supraclavicular disease, other lymph node groups and retinal metastases. However, obtaining accurate epidemiological data on proportions of Stage IV patients with these attributes was not possible. They are a small subgroup of patients and their omission from the decision tree is unlikely to dramatically affect the overall proportion of cancer patients in whom radiotherapy is recommended.

The proportion of patients with distant recurrence who develop brain or bone metastases as part of their disease has been assumed to remain constant irrespective of the initial stage of the patient at presentation. Thus although the overall proportion of patients who develop distant metastases will increase with increasing initial stage, once distant metastases are diagnosed, then the proportion of patients with metastatic disease who have brain metastases, bone metastases etc. has been assumed to

remain constant throughout the tree. For example, although patients with N0-3 nodal involvement have less chance of developing bone metastases than those with N>4, of the patients who do develop distant metastases, the distribution of the metastases according to site was assumed to remain constant.

Pivot et al (25) reported on 1125 patients with metastatic breast cancer treated at MD Anderson Cancer Centre from 1973-1980, and 42% had bone metastases during their illness. This figure was lower than that reported by others (see below). This may reflect the fact that detection was on the basis of clinical symptoms, unlike other studies, which depended on investigations such as bone scans. In the study by Pivot et al, a substantial proportion of patients (95%) were symptomatic - this proportion is higher than in other reported studies. Coleman and Rubens (27) in a retrospective study of 587 patients who died of breast cancer, found that 69 % had radiological evidence of skeletal metastases before death. Solomayer et al (26) in a retrospective study of 648 patients with metastatic breast cancer reported that 71 % of patients had bone metastases during their illness course. Leone et al. (28) reported bone metastases in 57% of patients with metastatic breast cancer.

Randomised controlled trials where patients were treated with systemic therapy and followed could not be used in this dataset. For instance, Colleoni et al. (33) reported on groups of breast cancer patients recruited onto treatment protocols of the International Breast Cancer Study Group (IBCSG) and reported on the incidence of bone metastases in various subcategories based on nodal status. The reason for not including these studies was that the sample was likely to have selection biases that make the large single-institutional databases quoted above more reliable. The patients on the IBCSG trials of systemic therapy may have been patients with good performance status and adverse pathological features which put them at a higher risk of developing metastases as compared to a general population of patients with early breast cancer.

11. The proportion of patients with bone metastases who are symptomatic

There were several alternate approaches to determining the proportion of patients with bone metastases in whom radiotherapy is indicated. Pivot et al. (25) reported that of the 440 patients in their study who had bone metastases, 95% were symptomatic (bone pain, fractures or cord compression). This was higher than the symptomatic rates reported by others (see below); however, Pivot reported a lower overall incidence of bone metastases (diagnosed on the basis of clinical symptoms and not bone scans) thus counterbalancing the over-estimate. Solomayer et al (26) reported that 80% of patients with bone metastases had bone pain. The NHMRC Clinical Practice Guidelines for the management of advanced breast cancer (7) state that "Palliative radiotherapy remains the most effective single modality for the treatment of local metastatic bone pain." The Swedish Council on Technology Assessment in Health Care (SBU) (34) state that palliative radiotherapy is both clinically effective and

economically justified and is therefore “the treatment method of choice in patients who have pain localised to a skeletal region with a verified metastatic tumour”. For the purpose of this analysis, we assumed that all patients with bone pain should ideally receive radiotherapy. This may over-represent the situation although no quality of life comparisons have ever been performed to prove that radiotherapy is inferior to other modalities in palliating pain. Domchek et al (35) reported on 718 patients with bone metastases (+/- visceral disease) and found that 41 % received radiotherapy. This represents actual practice and not the ideal utilisation rate. The SBU study found that palliative radiotherapy was under-utilised as a treatment modality for painful bone metastases and perhaps this may partly explain the low figure reported by Domchek et al.

Another approach to estimate the proportion of patients with bone metastases that **should ideally** receive radiation (rather than accepting that all patients in pain should have radiotherapy) would be to look at randomised clinical trials involving patients with bone metastases from breast cancer, where treatment with radiotherapy is an endpoint of the study. The best example was in the study by Paterson et al., (36) where 173 patients were treated with oral clodronate or placebo following a diagnosis of metastatic breast cancer with bone metastases. In this trial, 34/85 (40%) received radiotherapy following clodronate therapy and 42/88 (47.7%) following placebo. For the entire study group, this represented an overall utilisation rate for palliative radiotherapy of 43.9%. However, this figure may reflect under-utilisation of radiotherapy since only patients who did not respond to systemic treatments were given radiotherapy. This trial did not discuss whether there were specific indications that had to be present for the radiotherapy to be recommended. In addition, the follow up in the study was relatively short for a breast cancer trial (median follow-up was 14 months, range 4-37 months) and it is presumed that the requirement for radiotherapy will increase with increasing follow-up as more patients will relapse with time.

After careful consideration of all the options, it was decided to use the figures reported by Pivot et al. in the tree as this was a large population based study based on clinical symptoms rather than on investigations. A sensitivity analysis was conducted in which the other alternatives were also considered (see below).

The Level I evidence for bone radiotherapy quoted in the Advanced Breast Cancer Guidelines for radiotherapy for bone metastases is based on randomised controlled trials and systematic reviews of bone radiotherapy for the palliation of pain (37), (38), (39), (40), (41), (42), (43). Although these studies do not assess the overall efficacy of radiotherapy **when compared with no radiotherapy**, they do highlight that the vast proportion (60-80%) of patients received palliative benefit with radiation and that a dose response was evident.

12. The proportion of patients with brain metastases

Single institution data reported rates of brain metastases of 10–36 % for patients with metastatic breast cancer (Valagussa et al (44), Lee (45), Tsukada et al (46)). The largest reported series from MD Anderson Cancer Centre of 1125 patients with metastatic breast cancer by Pivot et al. (25) reported a brain metastasis rate of 12%. Carty et al (47) analysed 100 patients who died of breast cancer and found that 23 had brain metastases. The 12% figure of Pivot et al. was used as it comes from the largest study and sensitivity analysis for the range of 10-36% brain metastases has been performed.

Optimal Radiotherapy Utilisation Rate

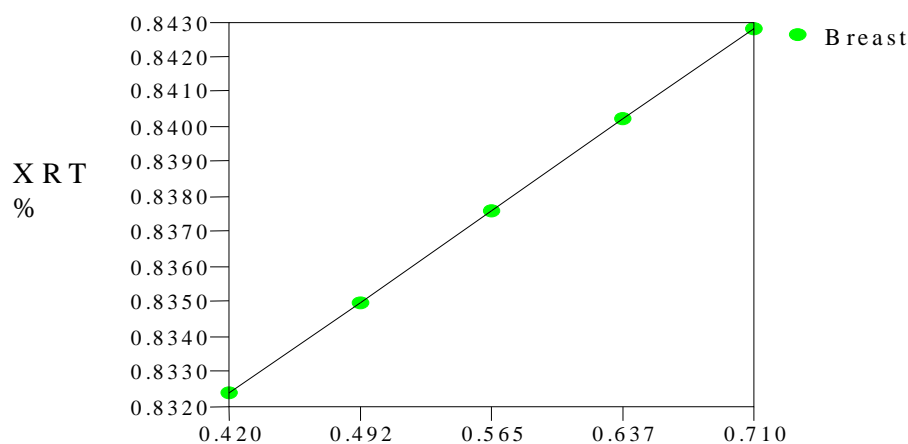
Using the proportions as described in Table 2, the calculation of the proportion of ALL patients with breast malignancy (DCIS or invasive breast cancer) in whom at least one course of radiotherapy is recommended is calculated as 0.83 or 83% of patients according to the best available guideline evidence. As breast cancer comprises 13% of all cancer patients, breast cancer patients in whom radiotherapy is indicated comprise a total percentage of the entire cancer population of $0.13 \times 0.83 = 0.1079$ or 10.79%.

Sensitivity Analysis

1. Bone metastases and bone pain requiring radiotherapy

The data with the greatest uncertainty or variation in the published literature is the data on the proportion of patients with distant relapse who have bone metastases, and the proportion of patients with bone metastases who are symptomatic (see explanatory notes 10 and 11). Two sources of data were identified as the best available. Pivot et al (25) reported on 1125 patients with metastatic breast cancer treated at MD Anderson Cancer Centre from 1973-1980, of whom 42% had bone metastases during their illness. This figure was used in the decision tree. Solomayer et al (26) in a retrospective study of 648 patients with metastatic breast cancer reported that 71% of patients had bone metastases during their illness course. They reported that 80% of patients with bone metastases in their series had bone pain. Sensitivity analysis was performed using these two sets of data. (When we used the data that 42% of patients with distant disease have bone metastases then we assumed that 95% should receive palliative radiation for bone metastases; and when we used the incidence data of 71% of patients with distant relapse having bone metastases we assumed that 80% of them should receive palliative radiotherapy due to the presence of symptoms. This is called correlating the 2 variables). A sensitivity calculation with the correlation of these two variables as described appears below.

Sensitivity Analysis on Proportion of patients with bone metastases from breast



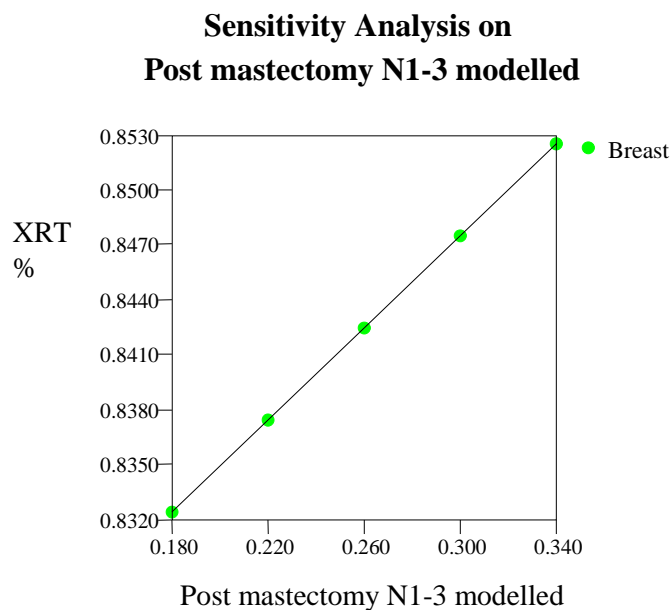
Proportion of patients with bone metastases from breast cancer

The analysis shows that as the proportion of patients with bone metastases is varied from 0.42 to 0.71, and the proportion receiving radiotherapy due to pain is varied between 0.95 and 0.80 (does not appear on the graph), this alters the proportion of breast cancer patients in whom radiotherapy is indicated from 83.2% to 83.9%. The effect on the overall proportion of cancer patients would be an overall increase in the proportion having radiotherapy by 0.09%.

The other available data on the incidence of bone metastases in breast cancer were not subjected to sensitivity analysis as these data lie within the range of 0.42-0.71 and therefore would alter the overall result less than the most extreme example shown above.

2. Proportion of node positive patients in whom post-mastectomy radiotherapy is recommended

As discussed in explanatory note 7, guidelines (10) (11) recommend radiotherapy for patients undergoing mastectomy and axillary node dissection who are found to have node positive disease with >3 nodes involved, and to consider radiotherapy in some patients with 1-3 nodes involved. However, randomised controlled trials of post-mastectomy radiotherapy have also identified benefits for patients with less nodal involvement. Therefore, although the proportion of patients with >3 nodes involved was used in the tree, sensitivity analysis was performed to assess the overall impact of treating all node positive patients.

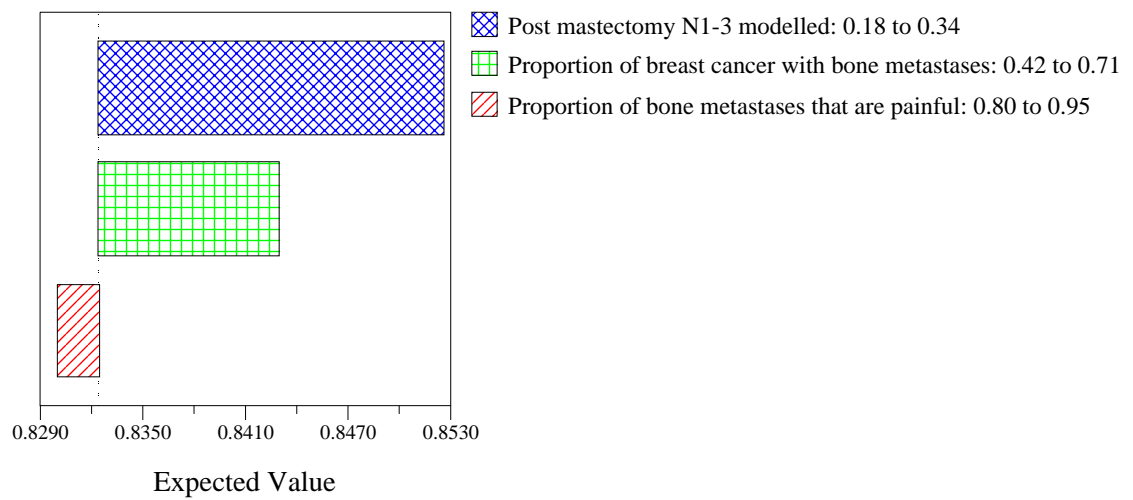


This analysis reveals that if ALL node positive patients were treated with post-mastectomy radiotherapy (34% of all mastectomy patients) instead of only those with >3 nodes (18% of mastectomy patients), the overall impact would be to increase the proportion of breast cancer patients recommended to receive radiotherapy from 83.2% to 85.3%. The effect on the overall proportion of cancer patients would be an overall increase in the proportion having radiotherapy by 0.2%.

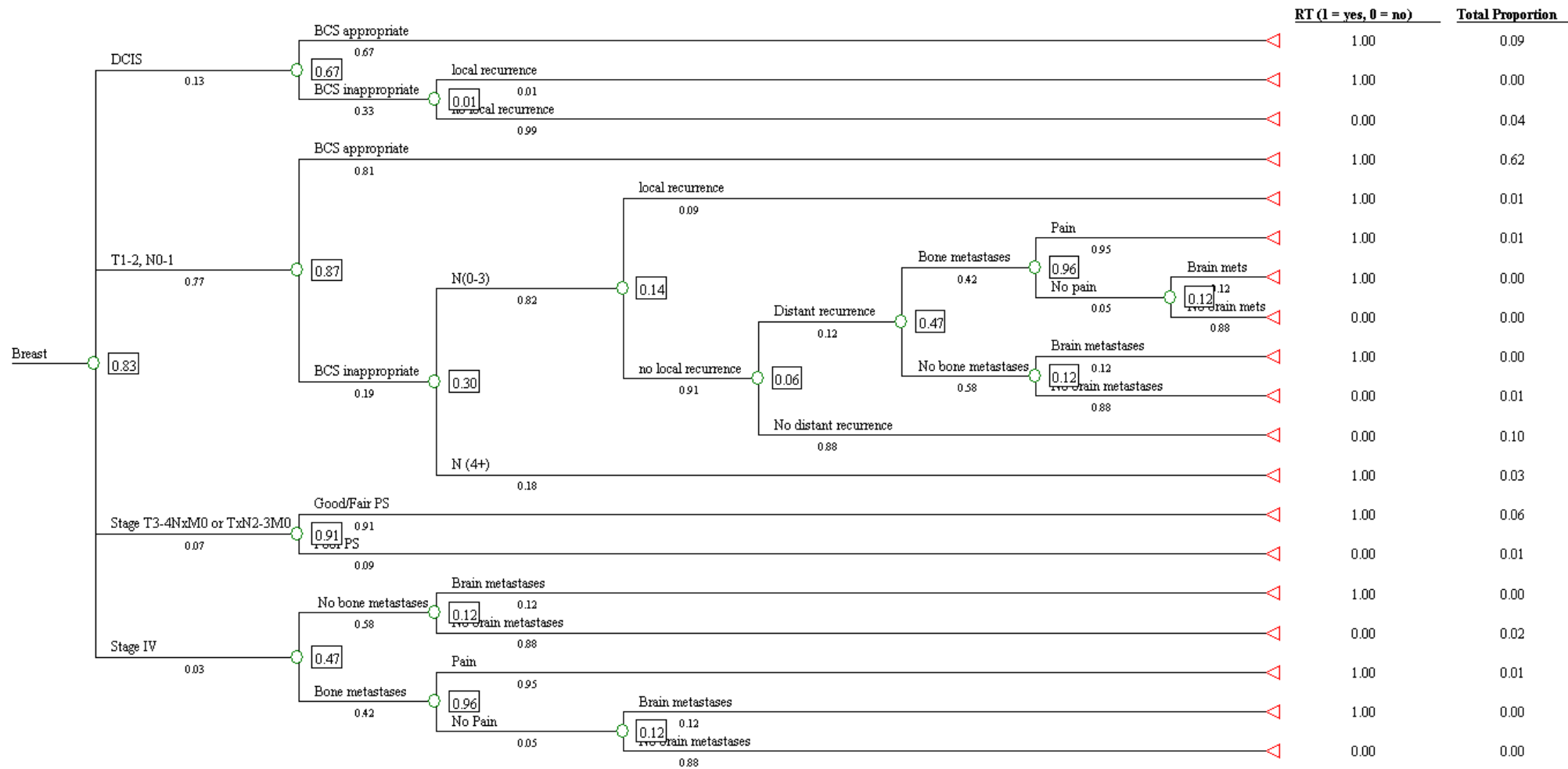
Tornado Diagram

A tornado diagram is a set of one-way sensitivity analyses brought together in a single graph. The expected value is displayed on the horizontal axis, so each bar represents the selected node's ranges of expected values generated by altering the variable. A wide bar indicates that the associated variable has a large potential effect on the expected value. The graph is called a tornado diagram because the bars are arranged in order, with the widest bar (reflecting the greatest uncertainty) at the top and the narrowest at the bottom, resulting in a funnel-like appearance.

Tornado Diagram at Breast



This tornado diagram reveals that the figure of 83% of breast cancer patients in whom radiotherapy is indicated will vary between 82.95% and 85.25% depending on the variables identified.



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Lung Cancer

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

Outcome No.	Clinical Scenario	Treatment Indicated	Level of Evidence	References	Explanatory Notes	Proportion of all lung cancer patients
1	Small-cell lung cancer, limited stage, good PS	CT/RT	I	<ul style="list-style-type: none"> ▪ National Cancer Institute PDQ Statement on Small Cell lung cancer (1) ▪ SIGN clinical guideline for management of lung cancer (2) ▪ NCCN Small Cell lung cancer clinical practice guidelines (3) 	1	0.07
3	Small-cell lung cancer, extensive, good PS, local symptoms	RT	III	<ul style="list-style-type: none"> ▪ SIGN clinical guideline for management of lung cancer (2) ▪ National Cancer Institute PDQ Statement on Small Cell lung cancer (1) ▪ NCCN Small Cell lung cancer clinical practice guidelines (3) 	2	0.05
4	Small-cell lung cancer, extensive, good PS, no local symptoms, brain metastases	RT	II	<ul style="list-style-type: none"> ▪ National Cancer Institute PDQ Statement on Small Cell lung cancer (1) ▪ SIGN clinical guideline for management of lung cancer (2) ▪ NCCN Small Cell lung cancer clinical practice guidelines (3) 	3	0.01

Outcome No.	Clinical Scenario	Treatment Indicated	Level of Evidence	References	Notes	Proportion of all lung cancer patients
5	Small-cell lung cancer, extensive, good PS, no local symptoms, no brain metastases, painful bone metastases	RT	I	<ul style="list-style-type: none"> National Cancer Institute PDQ Statement on SCLC (1) SIGN clinical guideline for the management of lung cancer (2) NCCN Small Cell lung cancer clinical practice guidelines (3) 	3	<0.01
8	NSCLC, Stage I-II, Good PS, surgery, positive margins	RT	IV	<ul style="list-style-type: none"> Royal College of Radiologists COIN guidelines on the non-surgical management of lung cancer (4) SIGN clinical guideline for management of lung cancer (2) NCCN Non-small cell lung cancer clinical practice guidelines (5) 	7	<0.01
9	NSCLC, Stage I-II, Good PS, surgery, negative margins, symptomatic local relapse	RT	III	<ul style="list-style-type: none"> BC Cancer Agency Cancer Management Guidelines for NSCLC (6) Royal College of Radiologists COIN guidelines on the non-surgical management of lung cancer (4) SIGN clinical guideline for the management of lung cancer (2) National Cancer Institute PDQ Statement on NSCLC (7) NCCN Non-small cell lung cancer clinical practice guidelines (5) 	8	0.04

Outcome No.	Clinical Scenario	Treatment Indicated	Level of Evidence	References	Notes	Proportion of all lung cancer patients
11	NSCLC, Stage I-II, Good PS, surgery, negative margins, no local relapse, brain metastases	RT	II	<ul style="list-style-type: none"> National Cancer Institute PDQ Statement on NSCLC (7) BC Cancer Agency Cancer Management Guidelines for NSCLC (6) SIGN clinical guideline for the management of lung cancer (2) NCCN Non-small cell lung cancer clinical practice guidelines (5) 	9	0.01
12	NSCLC, Stage I-II, Good PS, surgery, negative margins, no local relapse, no brain metastases, painful bone metastases	RT	I	<ul style="list-style-type: none"> National Cancer Institute PDQ Statement on NSCLC (7) SIGN clinical guideline for the management of lung cancer (2) 	10,11	<0.01
15	NSCLC, Stage I-II, Good PS, no surgery.	RT	III	<ul style="list-style-type: none"> National Cancer Institute PDQ Statement on NSCLC (7) SIGN clinical guideline for the management of lung cancer (2) NCCN Non-small cell lung cancer clinical practice guidelines (5) 	6	0.08

Outcome No.	Clinical Scenario	Treatment Indicated	Level of Evidence	References	Notes	Proportion of all lung cancer patients
16	NSCLC, Stage I-II, Poor PS, no surgery, symptomatic local or distant relapse requiring RT	RT	III	<ul style="list-style-type: none"> Royal College of Radiologists COIN guidelines on the non-surgical management of lung cancer (4) SIGN clinical guideline for the management of lung cancer (2) BC Cancer Agency Cancer Management Guidelines for NSCLC (6) National Cancer Institute PDQ Statement on NSCLC (7) NCCN Non-small cell lung cancer guidelines (5) 	12	<0.01
18	NSCLC, Stage IIIA, Good PS, surgery, N0 or N1, positive margins	RT	IV	<ul style="list-style-type: none"> Royal College of Radiologists COIN guidelines on the non-surgical management of lung cancer (4) SIGN clinical guideline for management of lung cancer (2) NCCN Non-small cell lung cancer guidelines (5) 	7	<0.01

Outcome No.	Clinical Scenario	Treatment Indicated	Level of Evidence	References	Notes	Proportion of all lung cancer patients
19	NSCLC, Stage III A, Good PS, surgery, N0 or N1, negative margins, symptomatic local relapse	RT	III	<ul style="list-style-type: none"> Royal College of Radiologists COIN guidelines on the non-surgical management of lung cancer (4) SIGN clinical guideline for the management of lung cancer (2) BC Cancer Agency Cancer Management Guidelines for NSCLC (6) National Cancer Institute PDQ Statement on NSCLC (7) NCCN Non-small cell lung cancer guidelines (5) 	8	0.01
20	NSCLC, Stage IIIA, Good PS, surgery, N0 or N1, negative margins, no local relapse, distant relapse, brain metastases	RT	II	<ul style="list-style-type: none"> National Cancer Institute PDQ Statement on NSCLC (7) BC Cancer Agency Cancer Management Guidelines for NSCLC (6) SIGN clinical guideline for the management of lung cancer (2) NCCN Non-small cell lung cancer guidelines (5) 	9	<0.01

Outcome No.	Clinical Scenario	Treatment Indicated	Level of Evidence	References	Notes	Proportion of all lung cancer patients
21	NSCLC, Stage IIIA, Good PS, surgery, N0 or N1, negative margins, no local relapse, distant relapse, no brain metastases, painful bone metastases	RT	I	<ul style="list-style-type: none"> National Cancer Institute PDQ Statement on NSCLC (7) SIGN clinical guideline for the management of lung cancer (2) 	10, 11	<0.01
25	NSCLC, Stage IIIA, Good PS, surgery, N2 disease	PORT	II	<ul style="list-style-type: none"> National Cancer Institute PDQ Statement on NSCLC (7) SIGN clinical guideline for the management of lung cancer (2) NCCN Non-small cell lung cancer guidelines (5) 	14	0.01

Outcome No.	Clinical Scenario	Treatment Indicated	Level of Evidence	References	Notes	Proportion of all lung cancer patients
26	NSCLC, Stage IIIA, Good PS, no surgery	RT	II	<ul style="list-style-type: none"> ▪ National Cancer Institute PDQ Statement on NSCLC (7) ▪ SIGN clinical guideline for the management of lung cancer (2) ▪ Royal College of Radiologists COIN guidelines on the non-surgical management of lung cancer (4) ▪ CCOP practice guideline on Stage III lung cancer (8) 	15	0.10
27	NSCLC, Stage III A, Poor PS, no surgery, local or distant symptoms requiring RT	RT	III	<ul style="list-style-type: none"> ▪ Royal College of Radiologists COIN guidelines on the non-surgical management of lung cancer (4) ▪ SIGN clinical guideline for the management of lung cancer (2) ▪ BC Cancer Agency Cancer Management Guidelines for NSCLC (6) ▪ National Cancer Institute PDQ Statement on NSCLC (7) ▪ NCCN Non-small cell lung cancer guidelines (5) 	12	<0.01

Outcome No.	Clinical Scenario	Treatment Indicated	Level of Evidence	References	Notes	Proportion of all lung cancer patients
29	NSCLC, Stage IIIB, good PS	CT/RT	II	<ul style="list-style-type: none"> ▪ CCOP Practice Guideline on Stage III lung cancer (8) ▪ National Cancer Institute PDQ Statement on NSCLC (7) ▪ ASCO guidelines for the treatment of unresectable NSCLC (9) ▪ NCCN Non-small cell lung cancer guidelines (5) 	15	0.14
30	NSCLC, Stage IIIB, poor PS, local symptoms	RT	III	<ul style="list-style-type: none"> ▪ Royal College of Radiologists COIN guidelines on the non-surgical management of lung cancer (4) ▪ SIGN clinical guideline for the management of lung cancer (2) ▪ BC Cancer Agency Cancer Management Guidelines for NSCLC (6) ▪ National Cancer Institute PDQ Statement on NSCLC (7) ▪ NCCN Non-small cell lung cancer guidelines (5) 	12	0.02

Outcome No.	Clinical Scenario	Treatment Indicated	Level of Evidence	References	Notes	Proportion of all lung cancer patients
32	NSCLC, Stage IV, symptomatic local disease	RT	III	<ul style="list-style-type: none"> ▪ Royal College of Radiologists COIN guidelines on the non-surgical management of lung cancer (4) ▪ SIGN clinical guideline for the management of lung cancer (2) ▪ BC Cancer Agency Cancer Management Guidelines for NSCLC (6) ▪ National Cancer Institute PDQ Statement on NSCLC (7) 	12	0.19
33	NSCLC, Stage IV, no local symptoms, brain metastases	RT	II	<ul style="list-style-type: none"> ▪ National Cancer Institute PDQ Statement on NSCLC (7) ▪ BC Cancer Agency Cancer Management Guidelines for NSCLC (6) ▪ SIGN clinical guideline for the management of lung cancer (2) ▪ NCCN Non-small cell lung cancer guidelines (5) 	9	0.02

Outcome No.	Clinical Scenario	Treatment Indicated	Level of Evidence	References	Notes	Proportion of all lung cancer patients
34	NSCLC, Stage IV, no local symptoms, no brain metastases, painful bone metastases	RT	I	<ul style="list-style-type: none"> National Cancer Institute PDQ Statement on NSCLC (7) SIGN clinical guideline for the management of lung cancer (2) 	10, 11	0.01
Total proportion of patients with lung cancer where radiotherapy is recommended						0.76 (76%)
Total proportion of all cancer patients = 0.76 X 0.10 =						0.076 (7.6%)

Key to Abbreviations

NSCLC - Non small-cell lung cancer

PS – Performance status

PDQ - Physician data query

NCCN - National Comprehensive Cancer Network (US)

BCCA – British Columbia Cancer Agency (Canada)

ASCO – American Society of Clinical Oncology

CCOP – Cancer Care Ontario Practice Guidelines Initiative

SIGN – Scottish Intercollegiate Guidelines Network

COIN - Clinical Oncology Information Network

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

Key	Population or subpopulation of interest	Attribute	Proportion of population with this attribute	Quality of information	References	Explanatory Notes
0	All registry cancers	Lung cancer	0.1	α	AIHW (10)	1
1	All lung cancers	Small cell	0.16	β	Richardson et al. (11)	1
2	Small cell (SC)	Limited stage	0.43	γ	American College of Surgeons (12)	4
3	Small cell (SC) Limited stage	Good PS (ECOG 0-2)	0.94	ϵ	SA Hosp Reg (13)	5
4	Small cell (SC) extensive	Good PS	0.80	ϵ	SA Hosp Reg (13)	5
5	Small cell (SC) extensive, good PS	Local symptoms	0.61/0.43	θ	Souhami et al. (14)	2
6	SC, extensive, good PS, no local symptoms	Brain metastases	0.49	ζ	Nugent et al. (15)	3
			0.27	ζ	Hirsch et al. (16)	
7	SC, extensive, good PS, no local symptoms, no brain metastases	Bone metastases	0.26	θ	Abrams et al. (17)	3

Key	Population or subpopulation of interest	Attribute	Proportion of population with this attribute	Quality of information	References	Explanatory Notes
8	SC, extensive, good PS, no local symptoms, no brain metastases, bone metastases	Painful bone metastases	0.80	ζ	Estimate based on bone metastases from breast cancer.	11
9	NSCLC	Stage I-II	0.33	ε	SA Hosp Registry (13)	5
10	NSCLC, Stage I-II	Good PS	0.90	ε	SA Hospital Registry (13)	5
11	NSCLC, Stage I-II, Good PS	Surgery	0.68	γ	US College of Surgeons (12)	6
12	NSCLC, Stage I-II, Good PS, Surgery	Positive margins	0.02 0.005	ζ	Kaiser et al (18) Sawyer et al. (19)	7
13	NSCLC, Stage I-II, Good PS, Surgery, negative margins	Symptomatic local relapse	0.23 0.23 0.24	θ λ λ	Stephens et al. (20) Van Houtte et al. (21) Ramacciato et al. (22)	8
14	NSCLC, Stage I-II, Good PS, Surgery, negative margins, no local relapse	Distant relapse	0.27 0.32 0.18	λ λ λ	Ramacciato et al. (22) Van Houtte et al. (21) Martini et al. (23)	8

Key	Population or subpopulation of interest	Attribute	Proportion of population with this attribute	Quality of information	References	Notes
15	NSCLC, Stage I-II, Good PS, Surgery, negative margins, no local relapse, distant relapse	Brain metastases	0.30	θ	Stephens et al. (20)	9
16	NSCLC, Stage I-II, Good PS, Surgery, negative margins, no local relapse, distant relapse no brain metastases	Bone metastases	0.19	ϵ	Hart et al. (24)	10
17	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	Estimate based on bone metastases from breast cancer.	11
18	NSCLC, Stage I-II, Poor PS	Symptomatic local or distant disease requiring RT	0.12	ϵ	Muers et al. (25)	12
19	NSCLC	Stage IIIA	0.16	ϵ	SA Hosp Registry (13)	5
20	NSCLC, Stage IIIA	Good PS	0.94	ϵ	SA Hosp. Registry (13)	5

Key	Population or subpopulation of interest	Attribute	Proportion of population with this attribute	Quality of information	References	Notes
21	NSCLC, Stage III A, Good PS	Surgery	0.22 0.25	γ ϵ	US College of Surgeons (12) SA Hospital Registry (13)	13
22	NSCLC, Stage III A, Good PS, surgery	N0 or N1	0.32	ζ	Mayer et al. (26)	14
23	NSCLC, Stage III A, Good PS, surgery, N0 or N1	Positive margins	0.02	ζ	Kaiser et al. (18)	7
24	NSCLC, Stage III A, Good PS, surgery, N0 or N1, negative margins	Local relapse	0.44 0.24 0.31	θ	Stephens et al. (20) Smolle-Juettner et al. (27) Feng (N1 only) (28)	8
25	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	See text Van Houtte (N0 only) (21) Feng (N1 only) (28) Stephens et al.(N1-2) (20) Mayer et al. (26)	16
26	NSCLC, Stage III A, Good PS, surgery, N0 or N1, negative margins, no local symptoms, distant relapse	Brain metastases	0.30	θ	Stephens et al. (20)	9

Key	Population or subpopulation of interest	Attribute	Proportion of population with this attribute	Quality of information	References	Notes
27	NSCLC, Stage III A, Good PS, surgery, N0 or N1, negative margins, no local symptoms, distant relapse no brain metastases	Bone metastases	0.19	ε	Hart et al. (24)	10
28	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	Estimate based on bone metastases from breast cancer.	11
29	NSCLC, Stage IIIA, poor PS	Local or distant symptoms requiring RT	0.12	ε	Muers et al. (25)	12
30	NSCLC	Stage IIIB	0.19	ε	SA Hospital Registry (13)	5
31	NSCLC, Stage IIIB	Good PS	0.84	ε	SA Hospital Registry (13)	5

Key	Population or subpopulation of interest	Attribute	Proportion of population with this attribute	Quality of information	References	Notes
32	NSCLC, Stage IIIB, poor PS	Local or distant symptoms requiring RT	0.71 0.56 0.69		Anderson et al. (29) Cullen et al. (30) Thongprasert et al. (31)	12
33	NSCLC	Stage IV	0.32	ϵ	SA Hospital registry (13)	5
34	NSCLC, Stage IV	Local symptoms	0.71 0.56 0.69		Anderson et al. (29) Cullen et al. (30) Thongprasert et al. (31)	12
35	NSCLC, Stage IV, no local symptoms	Brain metastases	0.30	θ	Stephens et al. (20)	9
36	NSCLC, Stage IV, no local symptoms, no brain metastases	Bone metastases	0.19	ϵ	Hart et al. (24)	10
37	NSCLC, Stage IV, no local symptoms, no brain metastases, bone metastases	Painful bone metastases	0.80	ζ	Estimate based on bone metastases from breast cancer.	11

Lung Cancer

Treatment guidelines

The Australian NHMRC guidelines for the management of lung cancer are being drafted and were not available at the time this project was conducted. Therefore, other international lung cancer guidelines were used to determine indications for radiotherapy in the decision tree. The guidelines used were the National Cancer Institute's Physician Data Query (PDQ), the British Columbia Cancer Agency (BCCA) guidelines, the National Comprehensive Cancer Network (NCCN) guidelines, the American Society of Clinical Oncology (ASCO) guidelines, the Cancer Care Ontario Practice Guideline Initiative guidelines, the Royal College of Radiologists Clinical Oncology Information Network (COIN) guidelines and the Scottish Intercollegiate Guidelines Network (SIGN) guidelines. The Australian national recommendations for radiotherapy in the treatment of lung cancer will be incorporated into this study as soon as the guidelines are published. Personal communications with members of the guideline committee suggests that there are likely to be no major changes to the design of the radiotherapy utilisation tree.

Indications for radiotherapy

In accordance with guideline recommendations, radiotherapy is indicated in the treatment of lung cancer in the following clinical situations:

- In limited stage small cell lung cancer (together with chemotherapy)
- In the palliation of symptomatic local disease, brain or bone metastases in extensive stage small cell lung cancer
- In Stage I-IIIa non-small cell lung cancer patients who are inoperable
- In Stage I-IIIa non-small cell lung cancer patients who have positive margins following surgery
- In Stage IIIa non-small cell lung cancer patients who have surgery and are node-positive
- In Stage IIIB non-small cell lung cancer patients who have good performance status
- In the palliation of symptomatic local disease, brain or bone metastases in all stages of non-small cell lung cancer

The lung cancer decision tree is particularly complex compared to decision trees for other tumour sites, because of the paucity of high level data on the incidence of populations with palliative indications for radiotherapy. As a consequence, finding the proportions of the sub-populations in some branches of the tree was more difficult than for other tumour sites such as breast cancer. A number of patterns of care studies are currently being conducted but data from these audits are not available at present. These data sources include a Lung Cancer Patterns of Care study for the South-western Sydney Area Health service (SWSAHS), the Hunter region, the Central Sydney Area Health Service and the Northern Sydney Area Health Service. There are plans for a prospective patterns of care review for N.S.W. under the auspices of the N.S.W. Cancer Council, but data collection has not been completed. If in the future data become available that supersedes data that

we have currently used in the decision trees, than the higher quality data will be incorporated into the tree.

In some parts of the decision tree, the incidence figures available in the literature were widely disparate. In such cases, all the available figures (with references) were included in the table. The figure that is based on the highest level of evidence (as defined in the hierarchy of evidence outlined in the study methodology) will ultimately be chosen for analysis on the decision tree. Sensitivity analysis was then performed to model the extent to which the different estimates of incidence affected the overall radiotherapy utilisation rate.

Explanatory Notes to Tables 1 and 2

SMALL CELL LUNG CANCER

1. **Proportion of all lung cancer that small cell lung cancer represents**

The Australian Institute of Health and Welfare (AIHW) (1) reports that lung cancer represents 10% of all cancers in Australia. Small cell lung cancer comprises 14% of all lung cancers according to the 1993 Victorian Patterns of Care study by Richardson et al (11).

Two published meta-analyses show a local control and survival benefit with the addition of thoracic radiotherapy to chemotherapy for limited stage small cell lung cancer [Pignon et al (32). and Warde et al.(33)].

There is therefore a Level I indication for thoracic radiotherapy in guidelines written by the National Cancer Institute (1) and the Scottish Intercollegiate Guidelines Network (2).

2. **The proportion of patients with metastatic small cell lung cancer who develop respiratory symptoms warranting palliative radiotherapy to the lung or mediastinum**

Guidelines (1),(2) recommend the use of palliative radiotherapy when symptomatic relapse from chemotherapy occurs. These recommendations are based upon single arm studies assessing the palliative efficacy of thoracic radiotherapy. Souhami et al (14) reported that the first site of symptomatic relapse for patients with extensive disease treated with chemotherapy was local disease for 61% of patients treated with a commonly used three-weekly chemotherapy regimen. They also reported that patients treated with a less common weekly regimen developed local symptoms as first sign of relapse in 43% of cases. The 61% figure was used for our study as the chemotherapy regimen used equates to widespread clinical practice in Australia, but the lower figure was incorporated into sensitivity analysis.

3. **Incidence of brain and/or bone metastases**

Nugent et al. (15) report that 49% of all extensive stage small cell lung cancer patients develop brain metastases and that 85% received radiotherapy. Therefore, 15% did not receive radiotherapy. It would be reasonable to presume that the majority of those patients not undergoing radiotherapy were poor performance status patients. This poor performance status figure of 15% correlates well with the 16% incidence of extensive stage small cell lung cancer having a poor performance status reported from the SA Cancer Registry. Hirsch et al. (16) report that 27% of their patients with extensive disease developed brain metastases. This smaller proportion was included in the sensitivity analysis.

Abrams et al. (17) report that a mean of 26% of patients with metastatic small cell lung cancer have bone metastases.

4. **Proportion of all small cell lung cancer that is limited disease following staging investigations**

The proportion of patients with limited stage Small Cell lung cancer has been obtained from the U.S. College of Surgeons (12) report. This is a large population based data source and supersedes local registry and institutional databases. The 1993 Victorian Patterns of Care study (11) reports limited stage disease in 25% of small cell cancer patients. However, a substantial proportion of patients in this study (22%) had inadequate staging information and therefore the data from the US College of Surgeons was thought to be more reliable.

5. **Performance status**

The South Australian Hospital Registry (13) contains information on 2745 patients diagnosed with small or non-small cell lung cancer in South Australia in 1987-1998. This database has performance status data for approximately 80% of lung cancer patients. Information from this database on histology/stage/performance status has been used to calculate the incidence for a number of branches of the decision tree.

NON SMALL CELL LUNG CANCER (NSCLC)

6. **Proportion of early stage NSCLC that have indications for radiotherapy rather than surgery**

The National Cancer Institute guidelines (7) and the Scottish Intercollegiate Guidelines Network (2) recommend radiotherapy for the treatment of patients with early stage (Stage I and II) disease who do not undergo surgery. The proportion that do not undergo surgery will include patients who have surgically inoperable disease, patients who are medically inoperable due to poor performance status, poor pulmonary reserve or other co-morbidities, and patients who refuse surgery. The American College of Surgeons (12) reports that 68% of

patients with Stage I or II NSCLC underwent surgery from a database of 183,297 cases in the U.S. in the two years 1986-1987 and 1992.

7. **Positive surgical margins following attempted resection of NSCLC**

It is contentious whether radiotherapy is indicated in cases of NSCLC treated by surgical resection who have a positive surgical margin at histopathologic assessment. The proportion is a small sub-set of all surgical series and is unlikely to have a significant impact on the overall decision tree model. Kaiser et al. (18) report the incidence of margin positivity or “residual disease post-resection” to be 1.6%. Sawyer et al. (19) report 2/370 (0.5%). Two sets of guidelines (4), (2) discuss radiotherapy in this context and provide a recommendation based on expert opinion (Level IV).

8. **Locoregional recurrence following curative lung resection**

Radiotherapy has been shown to be of benefit for the palliation of symptoms related to locoregional recurrence (Level III) following surgical resection. The proportion with post-operative local recurrence for each stage will vary.

For Stage I-II patients – Ramacciato et al (22) reported on a series of 270 patients with N0-1 disease treated with surgery, who had a local recurrence rate of 24%. Van Houtte et al. (21) reported that 23% of patients with Stage I and II disease treated with surgery alone developed symptomatic local relapse. These data correlate well with Sawyer et al. (19) reporting a five-year actuarial recurrence rate of 15% for 370 patients treated with resection for Stage I disease only. Ramacciato et al. (22) in their surgical series of N0-1 patients, reported that 27% developed distant recurrence. Van Houtte et al. (21) also report on the risk of distant recurrence for Stage I and II patients who were treated with surgery alone. The distant recurrence rate for all patients treated with surgery and who did not develop isolated local recurrence is 26/71 (32%). The data from Ramacciato et al. is preferred as it is a larger and more recent series compared with the study by Van Houtte et al. Martini et al. (23) reported that distant metastases represented the site of first relapse in 18% of 598 T1-2N0M0 patients treated with surgery.

For Stage IIIa N 0-1 Mayer et al. (26) report a local recurrence of 17/72 (23.6%) for stage T1-2, N1-2, M0 NSCLC. They found no prognostic significance of nodal involvement for local recurrence. But this study did not include N0 patients. Stephens et al. (20) report the local recurrences for patients with T1-2, N1-2, M0 NSCLC randomised between surgery alone and surgery and post-operative radiotherapy. The locoregional recurrence rate for N1 patients treated with surgery alone was 27% and a further 17% had suspected locoregional recurrence. Feng et al. (28) report local recurrence of 31.4% for N1 disease treated with surgery. Smolle-Juettner et al. (27) report a local recurrence of 17/72 (24%) for N0-2 patients randomised to surgery alone. None of these studies reported the recurrence rate for the specific population of N0-1. The data above was used in our study but

may slightly over-estimate the risk. A similar strategy was adopted by Tyldesley et al. (34) when calculating the radiotherapy utilisation rate for lung cancer.

9. **Proportion of patients with brain metastases**

Patients with NSCLC with brain metastases are best palliated with radiotherapy in almost all instances (Level III). The proportion of patients with distant recurrence who develop brain metastases has been assumed to remain constant irrespective of the initial stage of presentation of the patient. (Although the overall proportion of patients with distant metastases will increase with increasing stage, it is assumed that once distant metastases are diagnosed, then the proportion of these patients developing brain metastases, bone metastases etc. will remain constant).

Stephens et al. (20) report that patients with T1-2N1-2M0 NSCLC treated by surgery +/- radiotherapy had a distant metastatic rate of 182/308 (59%). Of that group of M1 patients, 55/182 (30%) had brain metastases and 82/182 (45%) had bone metastases. Similarly, Andre et al. (35) reported that 21/70 (30%) of patients developed metastatic disease after surgery +/- pre-operative chemotherapy for N2 disease. Newman and Hansen (36) report brain metastases in 23% of 247 consecutive patients treated at The VA Hospital, Washington D.C. who had previously received chemotherapy or radiotherapy. It is likely that some more data will become available from the South-Western Sydney Lung Cancer Patterns of Care study due for completion in 12/01.

10. **Proportion of patients with bone metastases**

The proportion of patients with distant recurrence who develop bone metastases has been assumed to remain constant irrespective of the initial stage of presentation. Although the overall proportion of patients with distant metastases will increase with increasing stage, once distant metastases are diagnosed then the proportions of patients with brain metastases, bone metastases etc have been assumed to remain the same.

For non small cell lung cancer, Hart et al. (24) report on the SEER data for the Detroit area 1993-1995. They report that 19% of all patients who developed metastatic NSCLC had bone metastases from a database of 15 416 patients.

11. **Guidelines for giving radiotherapy for bone metastases**

The Level I evidence for treatment of bone metastases with radiotherapy is based on randomised controlled trials and systematic reviews of bone radiotherapy for the palliation of pain (37), (38), (39), (40), (41) (42), (43). Although these studies do not assess the overall efficacy of radiotherapy **when compared with no radiotherapy**, they

do highlight that the vast proportion (60-80%) of patients receive palliative benefit with radiation and that a dose response is evident.

The Swedish Council on Technology Assessment in Health Care (44) states that palliative radiotherapy is both clinically effective and economically justified and is therefore “the treatment method of choice in patients who have pain localised to a skeletal region with a verified metastatic tumour”. For the purpose of this analysis, we assumed that all patients with bone pain should ideally receive radiotherapy. This may over-estimate the situation although no quality of life comparisons have ever been performed to prove that radiotherapy is inferior to other modalities in palliating pain. A study of patients with bone metastases from breast cancer (45) reports that 80% of bone metastases are painful. No comparable studies could be identified for patients with bone metastases from lung cancer and it was thought reasonable for the decision tree analysis that the 80% figure be used for the incidence of pain in patients with small or non-small cell lung cancer as most studies quoted here are based on clinical findings of bone metastases rather than investigation-based diagnosis.

12. **Poor performance status patients**

Palliative radiotherapy is recommended in patients with any stage NSCLC and poor performance status, if symptoms of local disease or distant metastases treatable with radiotherapy (e.g. brain or bone metastases, supraclavicular disease etc.) are present. Neither the SA hospital registry nor the lung cancer patterns of care studies collect information on the incidence of local symptoms by stage. This information was unable to be located from any other published sources. The only available data on the proportions of patients with these attributes were in studies of patients treated with best supportive care. However, the vast majority of these best supportive care studies focus on patients with Stage IIIB-IV disease and, to date, no best supportive care studies for patients with earlier stages of disease have been found. Some studies assess the impact of chemotherapy for Stage IIIB-IV disease by comparing chemotherapy treatment arms with best supportive care, and report the rates of use of radiotherapy as endpoints. However, there are wide variations in the use of radiotherapy between studies, reflecting different study durations and the potential subjectivity of the indication for delivery of radiotherapy. No firm criteria were established in any study to justify the use of radiotherapy. Numico et al. (46) reviewed seven randomised trials of various experimental chemotherapy regimens versus best supportive care, in an attempt to assess the palliative efficacy of chemotherapy for non-small cell lung cancer. They found that radiotherapy was used in 9 - 49% of cases in the trial chemotherapy arms, versus 23 - 79% in the best supportive care arms of the trials. Most of these studies reported on the overall use of radiotherapy, without differentiating between patients with local primary symptoms requiring radiotherapy and those requiring radiotherapy for distant symptomatic disease.

Cullen et al. (30) reported that 56% of patients in their trial assessing chemotherapy for advanced disease required radiotherapy for progressive primary symptoms. They reported that 40% of patients treated with mitomycin, ifosfamide and cisplatin required radiotherapy for local symptoms. Similarly, Thongprasert et al. (31) found that 69% of patients warranted radiotherapy when treated with best supportive care, while 16% of patients who were randomised to either iphosphomide, mesna, epirubicin and cisplatin or to mitomycin, cisplatin and vinblastine required thoracic radiotherapy. Anderson et al. (29) reported that 71% of patients treated with best supportive care required radiotherapy to the chest or mediastinum, whereas 37% of patients treated with gemcitabine and best supportive care required chest or mediastinal radiotherapy. For the calculation of the proportion of Stage IIIB patients treated with best supportive care who should get radiotherapy, the data in the study by Anderson et al. (29) was used as it is the largest, most recent and best designed study. In addition, sensitivity analysis using the data from these other studies was performed.

For earlier stage disease where best supportive care was used because of poor performance status, information provided in the study by Muers et al. (25) was used. In this population-based study, once a decision was made on initial treatment, all non small cell lung cancer patients were followed up. One hundred and three patients in this study received best supportive care due to poor performance status, refusal of treatment and co-morbidity. Some of these patients had early stage disease but the overall proportion of early stage disease patients in this supportive care group was not reported. Twelve percent of the patients who received best supportive care ultimately required radiotherapy for progressive local or distant symptomatic disease. This study is based on actual practice rather than on evidence and therefore may either over- or under-estimate the actual need for radiotherapy based on evidence. However, we could not identify any other study that reports on a lung cancer population with a proportion of early stage disease where best supportive care was used and then the patient developed local or distant relapse.

13. **Proportion of stage IIIA patients with operable disease**

The proportion of patients with Stage IIIA disease that undergo surgery has been obtained from both the South Australian Hospitals Registry (13) and the U.S. College of Surgeons (12) reports. The US College of Surgeons report is a national report and supersedes the SA Hospital Registry but the proportions quoted are similar. Further data from local Patterns of Care studies are expected. The National Cancer Institute (7), the Cancer Care Ontario practice guidelines (8) and the Scottish Intercollegiate Guidelines Network (2) recommend that patients with good performance status and Stage IIIA disease who do not undergo surgery and patients with good performance status and IIIB disease, should be treated with radiotherapy +/- chemotherapy (if the patient is

fit for chemotherapy). This is based on a number of randomised trials showing superior survival compared to other treatments (Level II). The National Cancer Institute (7), the Cancer Care Ontario practice guidelines (8) and the Scottish Intercollegiate Guidelines Network (2) recommend that patients with good performance status and Stage IIIA disease who do not undergo surgery, and patients with good performance status and IIIB disease, should be treated with radiotherapy +/- chemotherapy (Level II).

14. **N2 node positivity and radiotherapy**

The role of radiotherapy in patients who undergo surgical resection and have N2 disease on pathology assessment is highly controversial. A meta-analysis of post-operative radiotherapy following surgical resection by the PORT meta-analysis Trialists Group (47) showed no survival benefit. This study included patients with N0, N1 and N2 disease. There was no difference in survival and no statistical difference in local control when pooling the results (local recurrence = 195/1056 (18.4%) for PORT, 276/1072 (25.7%) for surgery alone, and 471/2128 (22%) for the entire group. Sub-group analysis revealed that radiotherapy was detrimental to survival for N0 disease, with no difference in survival for N1 and N2 disease. No raw local control data was presented in the paper to assess whether there was a difference in local control according to nodal status.

In terms of guideline recommendations, there was conflict as to whether radiotherapy is recommended for N2 patients. It is accepted that radiotherapy is not routinely recommended for N0-1. The Scottish Intercollegiate Guidelines Network (2) states that there is evidence from randomised controlled trials for an increase in local control from giving radiotherapy following surgery to patients with N2 disease. The British Columbia guidelines (6) state that "... (post-operative radiotherapy) can be considered ... (if there is) limited involvement of completely resected N2 nodal stations, particularly in a young, fit patient with significant nodal extension." The guidelines also state that if the endpoint of treatment is survival then radiotherapy should not be considered but if the endpoint was local control then radiotherapy can be considered. The Royal College of Radiologists (4) suggest "post-operative radiotherapy for residual disease may reduce locoregional relapse." However, no definition of residual disease was given (i.e. extent of nodal involvement).

In the decision tree, we have included the recommendation for post-operative radiotherapy for N2 on the basis of improved local control. Mayer et al. (26) report that for 155 patients treated with radical surgery the incidence of N2 nodal involvement was 32%.

15. **Locally advanced non-metastatic NSCLC**

The National Cancer Institute (7), the Cancer Care Ontario practice guidelines (8) and the Scottish Intercollegiate Guidelines Network (2) recommend that patients with good performance status and Stage IIIA disease who do not undergo surgery and patients with good performance status and IIIB disease, should be treated with radiotherapy +/- chemotherapy (if the patient is fit for chemotherapy). These guideline recommendations are based on a number of randomised trials showing superior survival compared to other treatments (Level II).

16. **Distant recurrence following surgery**

Mayer et al. (26) report a crude distant recurrence rate of 70/155 (45%) for patients with N0-2 operable disease who were randomised to post-operative radiotherapy or observation. There was no difference in survival between the groups and no difference in the distant metastatic rate. Stephens et al. (20) studied a similar group of patients and reported a distant recurrence rate of 182/308 (59%). Note that these two studies include N2 patients whereas the branch point includes N0-1 only. Feng et al. (28) report a distant metastasis rate for N1 patients of 42%. Alternatively, Van Houtte et al. (21) report a distant recurrence rate of 32% for N0 patients treated with surgery and radiation. The SWSAHS Lung Cancer Patterns of Care study or the SA Cancer Registry data may provide more meaningful data specific to this group of N0-1. Arbitrarily we have taken a mark halfway between the data from Van Houtte et al. (21) for N0 patients and Feng et al. (28) for N1 resulting in a recurrence rate of 37% for the decision tree.

Optimal Radiotherapy Utilisation Rate

Using the proportions as described in Table 2, the calculation of the proportion of ALL patients with lung cancer in whom at least one course of radiotherapy was recommended according to the best available guideline evidence was calculated as 0.76 or 76% of all patients with lung cancer. The proportion of small cell lung cancer patients in whom radiotherapy was recommended at least once was 79%, and the proportion for non small cell lung cancer is 75%. As lung cancer represents 10% of all cancers (AIHW data) (1), the group of lung cancer patients who should ideally receive at least one course of radiotherapy comprised 7.6% of all cancer patients.

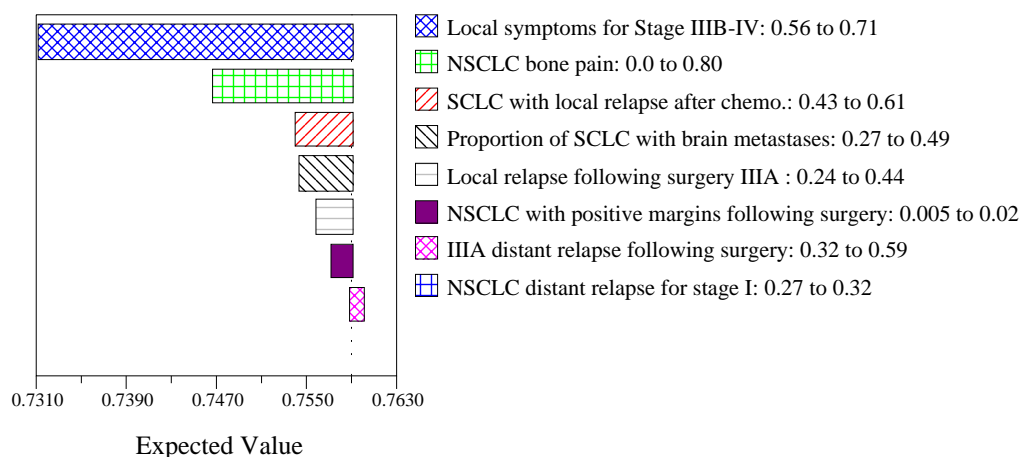
Sensitivity Analysis

There are several data elements where there was uncertainty because of different proportions reported in the literature. This includes the proportion of patients with small cell lung cancer with good performance status and local symptoms (0.43 - 0.61), the proportion of small cell lung cancer with distant relapse in brain (0.27 - 0.49), the proportion of patients undergoing resection

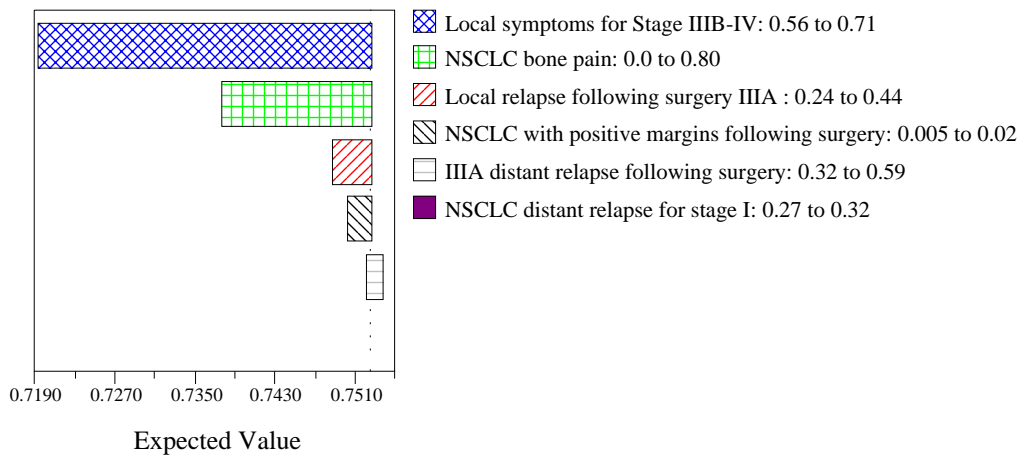
for non small cell lung cancer and having positive margins (0.005 – 0.02), the proportion of Stage IIIA patients with 0-1 node involved who develop local recurrence (0.24 - 0.44), the proportion of patients with non small cell lung cancer Stage IIIA who develop local relapse (0.32 -0.59) and the proportion of Stage IIIB or IVA non small cell lung patients with local symptoms (0.56 - 0.71). To assess the impact of these uncertainties on the overall estimate of the need for radiotherapy in all lung cancers, and for small and non small cell lung cancer respectively, a one-way sensitivity analysis was performed for each of the variables. The impact of these variables on the overall results is illustrated by tornado diagrams (see graphs below).

The graphs below show that the proportion of lung cancer patients that should receive radiotherapy based on evidence and incidence of attributes for radiotherapy was 73-76%, the proportion of small cell lung cancer to receive radiotherapy was 76-79%, and the proportion for non small cell lung cancer was 72-75%.

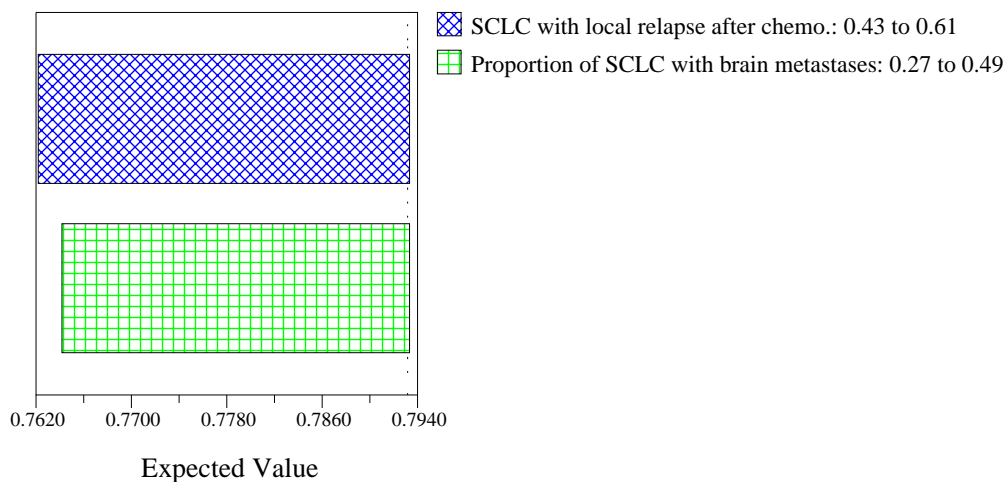
**Tornado Diagram at
Lung cancer**



Tornado Diagram at Non Small cell



Tornado Diagram at Small cell



Discussion

The finding that 76% (range 73 - 76%) of all lung cancer patients should receive radiotherapy based upon evidence, guideline recommendations and the incidence of specific attributes differs from the findings of Tyldesley et al. (34) who conducted a similar study in Canada. Tyldesley et al reported that 61.0% +/- 3.9% of all lung cancer patients should receive radiotherapy. A comparison of the results by histology and stage between the two studies is shown below.

Comparison between 2 studies of the proportions of lung cancer patients recommended to receive radiotherapy.

Clinical group	RT recommendation (%) <i>Tyldesley et al. (34)</i>	RT recommendation (%) <i>Current study</i>
All lung cancers	61	76
Small cell	54	79
Non small cell	64	75
Stage I	41	50*
Stage II	55	50*
Stage III	84	95
Stage IV	66	83

* Stages I and II were combined on the same branch of the decision tree in the current study. The management of both stages is usually the same.

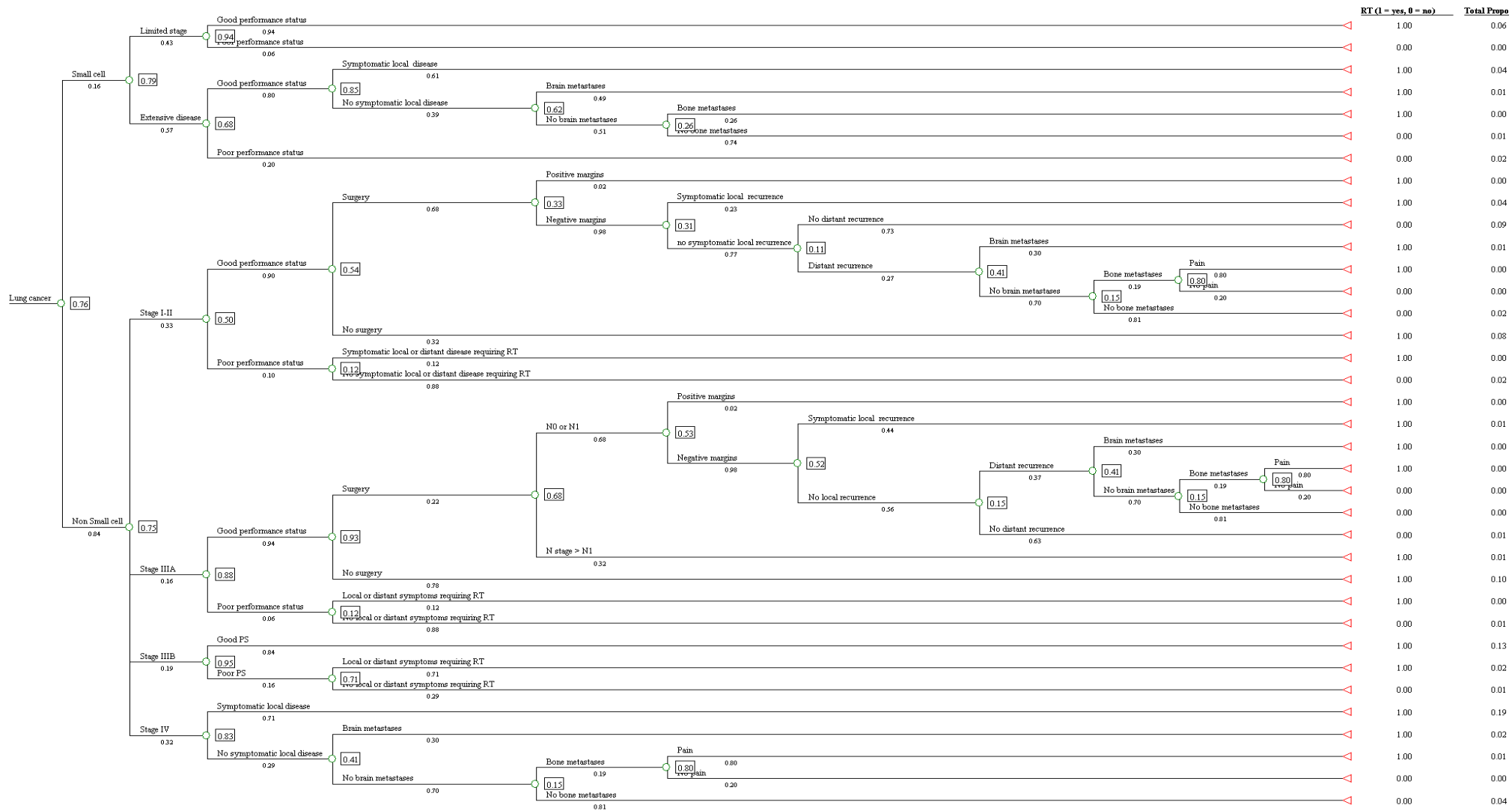
The differences between the studies in terms of methodology and data are summarised below:

- ❖ In this study, Australian data on the incidence of the different decision node attributes was used wherever possible. Tyldesley et al. (34) used Canadian data wherever possible.
- ❖ The differences in data included
 - The proportion of patients with good performance status for limited stage SCLC for the current study was 0.94, whereas the Canadian study was 0.84.
 - The proportion of early non small cell lung cancers with good/fair performance status was 90% in the current study versus 80% in the Canadian study.
 - The Canadian study identified that 21% of operable T1-3N0-2M0 patients who undergo resection will develop a symptomatic local or distant recurrence requiring RT. Our study identifies that this proportion is at least 10% higher when you factor in local and distant recurrences.
- ❖ Some branches in the decision tree differed between the 2 studies in the following ways:-
 - The Canadian study did not subdivide metastatic disease into specific metastatic sites where radiotherapy may be indicated. Instead they reported on the actual use of radiotherapy for symptoms of metastatic disease. As a consequence the incidence data used was often from patterns of care studies where the use of radiotherapy was reported. We have attempted to avoid doing this wherever possible as it is based on actual practice rather than on evidence, and it is likely that this under-represents the indications for radiotherapy. In contrast, our study relied on branches indicating the incidence of bone and brain metastases rather than reporting on

the use of radiotherapy. In some instances it was necessary to use radiotherapy utilisation data as no other information was available.

- The Canadian study does not recommend radiotherapy for all patients with good performance status and limited stage small cell lung cancer. They recommend radiotherapy only if the patient responds to chemotherapy, which removes the 4% who do not respond. Our recommendations are based on guidelines where early radiotherapy is suggested and hence waiting for a response to chemotherapy is not recommended. This recommendation is based on randomised trial evidence of early radiotherapy improving survival over delayed radiotherapy (48) (49). (50)
- The Canadian study does not allow provision for any patients with poor performance status to receive radiotherapy. This will under-predict the use of radiotherapy as there are instances where short palliative radiotherapy is recommended to palliate symptoms in patients with poor performance status.
- The Canadian study has a number of branches where patients either accept or decline radiotherapy. The current study avoids the incorporation of patient choice into the decision tree. The reason is that the acceptance or refusal of radiotherapy by patients will depend upon factors such as the availability of and access to radiotherapy services, and the selection biases and the type of information given to the patient by their doctor, and thus may not reflect best evidence. This may also under-predict the use of radiotherapy.

Following a review of the differences between the current study and the study by Tyldesley et al (34), we concluded that the differences in the radiotherapy utilisation rates for lung cancer between the two studies can be explained by the above factors and further modification of our tree was unnecessary.



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Gastrointestinal Cancers

Oesophageal Cancer

Table 1: Oesophageal Cancer: Indications for radiotherapy: Levels and sources of evidence

Outcome Number	Clinical Scenario	Treatment Indicated	Level of Evidence	References	Notes	Proportion of all Oesophageal Cancer patients
1	TxNxM0, Fit for surgery, resection with clear margins, locoregional recurrence	Surgery Or RT or supportive care	IV	<ul style="list-style-type: none"> National Cancer Institute PDQ statement on Esophageal cancer (1) NCCN practice guidelines on Esophageal cancer (2) 	7	0.06
2	TxNxM0, Fit for surgery, resection with clear margins, No locoregional recurrence, distant recurrence, brain metastases	RT	II	<ul style="list-style-type: none"> Priestman et al. (3) Kurtz et al. (4) Borgelt et al. (5) 	8	<0.01
3	TxNxM0, Fit for surgery, resection with clear margins, No locoregional recurrence, distant recurrence, No brain metastases, painful bone metastases	RT	I	<ul style="list-style-type: none"> Steenland et al. (6) Nielsen et al. (7) Tong et al. (8) 	8	0.01

Outcome Number	Clinical Scenario	Treatment Indicated	Level of Evidence	References	Notes	Proportion of all Oesophageal Cancer patients
6	TxNxM0, Fit for surgery, No resection performed or margins not clear	RT	IV	<ul style="list-style-type: none"> Dexter et al. (9) Fok et al. (10) Blazeby and Alderson (11) 	6	0.06
7	TxNxM0, Not fit for surgery	RT +/- chemo	III	<ul style="list-style-type: none"> National Cancer Institute PDQ statement on Esophageal cancer (1) NCCN practice guidelines on Esophageal cancer (2) 	3, 4	0.40
8	TxNxM1, Symptomatic loco-regional disease	RT	IV	<ul style="list-style-type: none"> National Cancer Institute PDQ statement on Esophageal cancer (1) NCCN practice guidelines on Esophageal cancer (2) 	7	0.24

[illegible]

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

Key	Population or subpopulation of interest	Attribute	Proportion of population with this attribute	Quality of information	References	Notes
A	All registry cancers	Oesophageal Cancer	0.01	α	AIHW (12)	1
B	Oesophageal cancer	Stage TxNxM0	0.68	γ	Daly et al. (13)	2
			0.66	ζ	Junginger and Datkowski (14)	
C	Stage TxNxM0	Proceed to Surgery	0.42 0.59 0.40-0.60	δ ζ Review	Sagar et al. (15) Junginger and Datkowski (14) Geh et al. (16)	4
D	Stage TxNxM0, proceed to surgery	Resection performed with clear margins	0.80 0.79 0.91 0.72 0.80 0.62 0.80-0.90 0.70	δ δ ζ ζ ζ ζ Review θ	Pye et al.(17) Sagar et al. (15) Junginger and Datkowski (14) Molloy et al. (18) Alexiou et al. (19) Sugimachi et al. (20) Geh et al. (16) MRC Oesophageal Working Party	4

Key	Population or subpopulation of interest	Attribute	Proportion of population with this attribute	Quality of information	References	Notes
E	Stage TxNxM0, fit for surgery, resection performed with clear margins	Locoregional recurrence	0.27 0.25 0.31	ζ ζ ζ	Dresner and Griffin (21) Law et al. (22) Fok et al (10)	7
F	Stage TxNxM0, surgical resection with clear margins, no locoregional recurrence	Distant recurrence	0.18 0.30	ζ ζ	Dresner and Griffin (21) Fok et al. (10)	8
G	Stage TxNxM0, fit for surgery, resection with clear margins, no locoregional recurrence, distant recurrence	Brain metastases	0.10	ζ	Dresner and Griffin (21)	8
H	Stage TxNxM0, fit for surgery, resection with clear margins, no locoregional recurrence, distant recurrence, no brain metastases	Painful bone metastases	0.33 0.16	ζ ζ	Dresner and Griffin (21) Law et al. (22)	8

Key	Population or subpopulation of interest	Attribute	Proportion of population with this attribute	Quality of information	References	Notes
I	Stage TxNxM1	Symptomatic locoregional disease	0.75 0.80	ζ ζ	Welt et al. Taieb et al.(23)	9
J	Stage TxNxM1, no symptomatic locoregional disease	Brain metastases	0.10	ζ	Dresner and Griffin (21)	8
K	Stage TxNxM1, no symptomatic locoregional disease, no brain metastases	Painful bone metastases	0.33 0.16	ζ ζ	Dresner and Griffin (21) Law et al. (22)	8

Oesophageal cancer

Treatment Guidelines

There are two clinical practice guidelines for the management of oesophageal cancer, one issued by the National Cancer Institute (Physicians Data Query or PDQ statement on oesophageal cancer) (1) and the other by the National Comprehensive Cancer Network (NCCN) (2).

Indications for Radiotherapy

Based on published treatment guideline recommendations, radiotherapy in oesophageal cancer is indicated in the following clinical situations:

- In patients who develop a local recurrence following surgical resection
- In patients with non-metastatic disease who undergo resection and are found to have positive margins or who have unresectable disease (T4)
- In patients presenting with non-metastatic disease who are medically inoperable or do not choose to undergo surgery (this might be in conjunction with chemotherapy for fitter patients)
- Palliative radiotherapy is indicated in patients presenting with metastatic disease who have symptomatic local disease
- Palliative radiotherapy is indicated in patients with symptomatic bone metastases
- Palliative radiotherapy is indicated in patients with symptomatic brain metastases

Explanatory Notes for Tables 1 and 2

1. Incidence of oesophageal cancer

Oesophageal cancer constitutes 1% of all cancers in Australia according to the Australian Institute of Health and Welfare (AIHW) 1998 statistics (12).

2. Stage at presentation

From a management decision perspective, patients with oesophageal cancer can be divided into those with apparent locoregional cancer (stages I to III - any T, any N, M0) and those with obvious metastatic disease (stage IV - any T, any N, M1).

The patterns of care and outcomes of oesophageal cancer in the United States between 1988-1993 are described in the U.S. National Cancer Data Base (13). It is reported that 11% of patients were >80 years old and 29% were 70-79 years old. The stage distribution of patients at diagnosis was 32% Stage IV disease, 25% Stage III, 27% Stage II and 16% Stage I and in situ. Junginger and Dutkowski (14) reported that of a consecutive 322 patients diagnosed with oesophageal cancer in their department in Germany, 109 (34%) had evidence of metastatic disease at diagnosis and no curative therapy was contemplated.

3. **Management of non-metastatic disease**

The management of non-metastatic oesophageal cancer remains controversial. For fit patients, the options are surgery (with or without pre-operative chemotherapy or chemoradiotherapy) or chemoradiotherapy alone. For patients who are unfit for chemotherapy, radiotherapy alone is considered appropriate in most circumstances (PDQ guidelines).

There are no randomised trials that definitively indicate the most efficacious treatment for localised oesophageal cancer. Two small trials showed slight benefit for surgery over radiotherapy alone without chemotherapy (24). Subsequently radiotherapy alone has been shown to be inferior to chemoradiotherapy in a randomised trial (25).

Current Australian practice in most institutions is to offer surgery as definitive treatment to patients with good performance status and resectable disease (26) (27). This treatment approach has been incorporated into the tree, since surgery has the advantages of having a quicker recovery period and providing better local control. Radiotherapy is reserved for patients who refuse surgery, who have unresectable disease due to tumour size or position, or who have an increased risk of complications and peri-operative mortality due to advanced age or reduced performance status. This is despite the fact that overall survival reported in reviews of radiotherapy and surgery suggest similar outcomes (28).

4. **Proportions of patients with operable disease after staging and those found to have resectable disease at surgery**

The term "operable" denotes that the pre-operative opinion of the surgeon is that the tumour is surgically removable. The term "resectable" refers to patients who are found to have technically removable tumours during surgery.

Proportion of patients considered operable

Not all patients with "localised" or non-metastatic disease at presentation will be eligible to undergo surgery due to advanced presentation or due to age, co-morbidity or general performance status reasons. In addition, some patients will refuse oesophagectomy and prefer other treatment alternatives. The proportion of patients with localized disease who are thought operable at diagnosis was estimated from the literature.

A patterns of care study from Leeds 1975-1988 by Sagar et al (15) showed that out of a total of 316 patients presenting with oesophageal cancer, surgical exploration was carried out in 134 patients (42%). Junginger and Dutkowski (14) reported that of 322 consecutive patients diagnosed with oesophageal cancer, 109 (34%) had evidence of metastatic disease and no curative therapy was contemplated. A total

of 190 patients (59 % of all oesophageal cancer patients) underwent surgery. These data correlate well with the review from Geh et al. (16) where an estimate of 40-60% of patients with localised disease have contraindications to surgery.

Proportion of operable patients found to have resectable disease during surgery

Some patients who undergo surgery are found to have unresectable disease intra-operatively. Sagar et al (15) found that resection of the tumour was possible in 79% of patients (106) who underwent surgery. Junginger and Dutkowski (14) reported that 173 patients (91%) undergoing surgery had an oesophageal resection. Histological examination found that 121 patients who underwent resection had clear margins, while 52 had tumour involvement of the margins. Molloy et al. (18) reported a lower rate of resectability of 72% of patients who were considered operable after laparoscopic assessment. Alexiou et al. (19) reported a resectability rate of 80% in 686 surgical patients treated at Nottingham. The resectability rates in the surgery alone arms of randomised trials testing pre-operative therapy were 55-86% (16). The review by Geh et al (16) found that 10-20% of patients are found to have inoperable disease at surgery.

A one year epidemiological study from Wales by Pye et al. (17) describes 910 patients with oesophagus and stomach cancer. 61% of patients were > 70 years old. No stage distribution data were reported. 337 oesophagus cancer patients were included in the study. Of the 90 that underwent resection, 72 (80%) had successful resection, whereas the other 20% had exploration only due to the extent of disease found at surgery.

A review by Sugimachi (20) states that resectability increases with more modern imaging and surgical techniques. In their series, the patients treated in the latter stages of the study (1987-1996) had a complete resection rate of 62% suggesting that a further 38% had residual disease either macro- or micro-scopic. They do not report locoregional control data.

The randomised trial performed and reported by the Medical Research Council Oesophageal Working Party of surgical resection with or without pre-operative chemotherapy reported a resection rate of 83% and a macroscopic clearance rate of 70% for the group treated with surgery alone.

The data of Pye et al. (17) was used in the utilisation tree as this was considered the best quality evidence (it is regional epidemiological data rather than institutional and therefore is not subject to the biases associated with single institutional databases or surgical databases especially from specialist surgical units). Regional epidemiological data was also considered superior to data from randomised trials since it is more representative of a population.

5. Pre-operative therapy

No definite role for the routine use of pre- or post-operative radiotherapy in patients undergoing oesophagectomy has been established. At least 50 trials have been published on the use of pre-operative chemoradiotherapy. Most of the earlier studies were non-randomised. Some randomised trials have found differences on subgroup analysis (29) (30). However, these studies have had methodological flaws (29) or have not completed the period of planned follow-up (30). Other studies have found no differences between groups undergoing combined treatment versus surgery alone. A recent meta-analysis of pre-operative radiotherapy by Arnott et al (31) found that pre-operative therapy may result in a reduction in mortality of 11% but statistical significance was not reached ($p=0.06$). They concluded that the role of pre-operative radiotherapy is unresolved and therefore not recommended outside a clinical trial. Furthermore, a recent Medical Research Council (MRC) randomised trial (32) found a survival benefit for pre-operative chemotherapy for patients undergoing oesophagectomy that may require further trials to confirm the finding. However, some patients in both arms of the trial were also given optional radiotherapy. Therefore, no definite role for radiotherapy prior to surgery currently exists outside of a clinical trial and hence it is not incorporated into the decision tree. Newer agents are currently being investigated with radiotherapy.

6. Post-operative therapy

The PDQ guidelines (1) are not specific about when, if ever, radiotherapy may be considered post-operatively. However, a number of studies have highlighted high recurrence rates following surgery when residual microscopic or macroscopic disease remains following resection. A prospective randomised trial reported by Fok et al. (10) suggests an improvement in local control for those with residual macroscopic disease following resection but no benefit for patients who have resection with clear surgical margins. Dexter et al. (9) report that margin involvement is an independent prognostic factor for locoregional recurrence and advocate post-operative radiotherapy. It would be considered reasonable to offer radiotherapy to aid local control. In the randomised pre-operative chemotherapy study conducted and reported by the Medical Research Council (32), 11% of operations were macroscopically incomplete and a further 17% were microscopically incomplete. A further 16% had no surgery due to disease extent or patient refusal. Local recurrence occurred in 8% of both groups. However, this may be a gross under-estimate, because 22% of patients who died of disease did not have a site of relapse recorded. Dexter et al. (9) reported that 47% of patients in their series of 135 patients had margin positive disease. The authors found worse survival in the group with positive margins and recommend the use of adjuvant or neo-adjuvant therapy.

7. Locoregional recurrence following surgery

For patients with locoregional recurrence and no evidence of distant disease, radiotherapy is recommended to palliate symptoms (1) (33) and in some instances, in the absence of metastatic disease, may be curative. Raoul et al. (33) report durable symptomatic improvement in 74% of patients with local recurrence treated with radiotherapy. To estimate the rate of local recurrence, Dresner and Griffin (21) reported on 520 oesophagus cancer patients selected for oesophagectomy in the period 1990-1999 at the Royal Victoria Infirmary, Newcastle upon Tyne, U.K. 216 patients underwent resection (42%). They reported that the locoregional recurrence rate following oesophagectomy and lymph node dissection for the 176 patients who had a "curative" resection was 27% with a median time to recurrence of 11 months. Law et al. (22) reported on 108 oesophageal cancers treated at Queen Mary Hospital, Hong Kong. Intrathoracic recurrence occurred in 25% and distant recurrence in 41%. Fok et al. (10) reported a randomised trial comparing radiotherapy and surgery. Those undergoing surgery alone had a recurrence rate of 31% although some of these patients had palliative resections due to the presence of distant metastatic disease.

8. Distant recurrence and site of recurrence following surgery

Dresner and Griffin (21) reported that of 176 oesophageal cancer patients who had oesophagectomy, 18% developed metastatic disease without locoregional recurrence. Of the patients with metastatic disease, 33% had bone metastases, 33% liver, 10% brain, 6% skin or soft tissue metastases. Law et al. (22) reported on the failure patterns of 44 patients with metastatic disease after attempted curative resection. Bone metastases occurred in 7 (16%) while a further 25% had cervical lymph node recurrences. Brain metastases were not specifically mentioned although 6% were classified with "other" metastases. Fok et al. (10) reported distant recurrence in 30% of 28 patients treated with curative surgery alone. The largest series (21) was taken as the most appropriate figure for estimating the risk of distant metastases. Sensitivity analysis was performed to assess the impact of the variation of this data on the overall radiotherapy utilisation assessment.

It would be reasonable to consider palliative radiotherapy for patients with symptomatic brain or bone metastases and who have sufficiently good performance status (although this proportion of patients is unknown). It is presumed that all of the patients with metastatic disease in the study were symptomatic as routine screening for metastatic disease was not part of the treatment protocol (21). It might be reasonable also to offer palliative radiotherapy for patients with symptomatic pulmonary, nodal, skin or soft tissue lesions. However, it is not possible to determine the proportions of patients with these characteristics in whom radiotherapy would be considered reasonable.

This group make up only a small proportion and therefore are unlikely to significantly impact upon the overall radiotherapy utilisation estimate.

9. Palliation of locoregional disease

There are several options available to palliate local disease particularly when it causes dysphagia. Stents, laser therapy, external beam radiotherapy and intracavitary brachytherapy or a combination of these therapies have all been established as effective in the relief of dysphagia (34). A major drawback of using laser therapy alone is that the procedure commonly requires repeating at frequent intervals (35). Palliative resection of the oesophagus is not recommended due to high surgical mortality rates, poor prognosis and the existence of effective, less invasive procedures (34) (36). Stents have been shown to improve swallowing in most cases but problems include migration and odynophagia post-insertion (37).

External beam radiotherapy has been established as effective in the palliation of dysphagia (38) (39) (40), (41) (37), (42). When laser resection was appropriate, the addition of radiotherapy was shown to significantly reduce the number of laser treatments necessary and to lengthen the time from repeat endoscopy until symptoms in a British randomised clinical trial of laser resection +/- 30Gy external beam radiotherapy (35). Kubba and Krasner (43) in their review of palliation of dysphagia suggest that radiotherapy is appropriate in combination with other palliative modalities such as stent or laser to prolong the period of functional swallowing. Therefore, in the vast majority of patients with either symptomatic locoregional disease with distant metastases or for the palliation of recurrence with pain and/or dysphagia following oesophagectomy, it is appropriate to consider external beam radiotherapy. It appears at least equal in efficacy to stent insertion. The role of chemoradiotherapy for palliation is currently undergoing evaluation and may potentially be of greater palliative benefit than current options. However, insufficient data are available at present for this to be recommended.

Data on the proportion of patients with M1 disease who have locoregional symptoms were unavailable. However, the next best alternative was to review the proportion of patients with incurable disease undergoing a trial of chemotherapy who develop dysphagia. For example, Petrasch et al. (44) report on 20 patients with advanced oesophageal cancer who underwent a trial of cisplatin and paclitaxel for either recurrent, inoperable or metastatic disease. Their rate of dysphagia pre-treatment was 15/20 (75%). Similarly, Taieb et al. (23) reported that 81% of patients with metastatic oesophageal cancer undergoing a trial of chemotherapy had dysphagia. Therefore, it may be reasonable to suggest that 75-80% of patients with M1 disease may have dysphagia for which radiotherapy could be considered reasonable treatment.

Optimal radiotherapy utilisation rate and Sensitivity Analysis

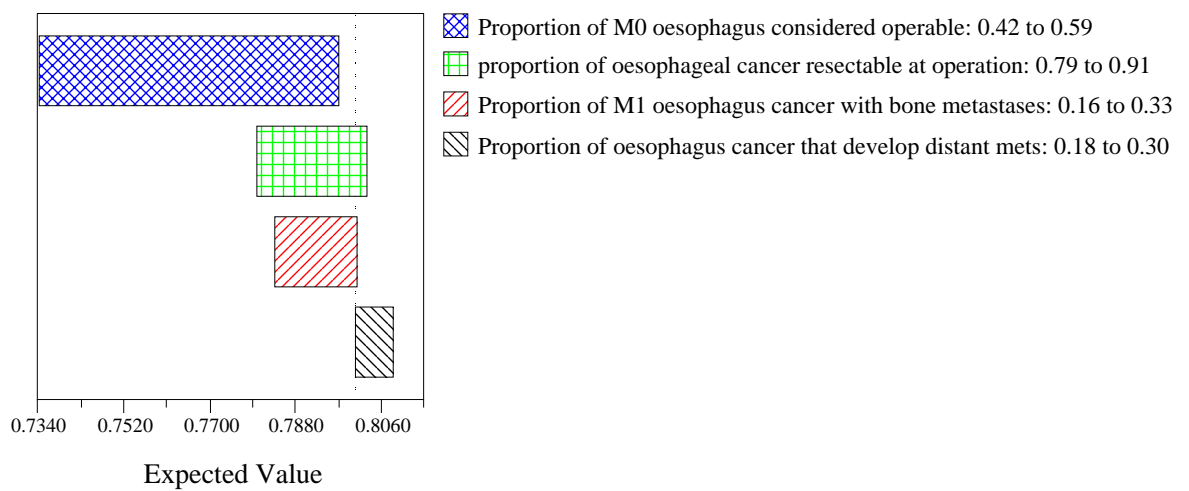
Sensitivity analysis assesses the impact of changing the values of variables on the overall result. This is advantageous when the data used are uncertain. For the oesophagus cancer decision tree, the data items identified as being uncertain were:

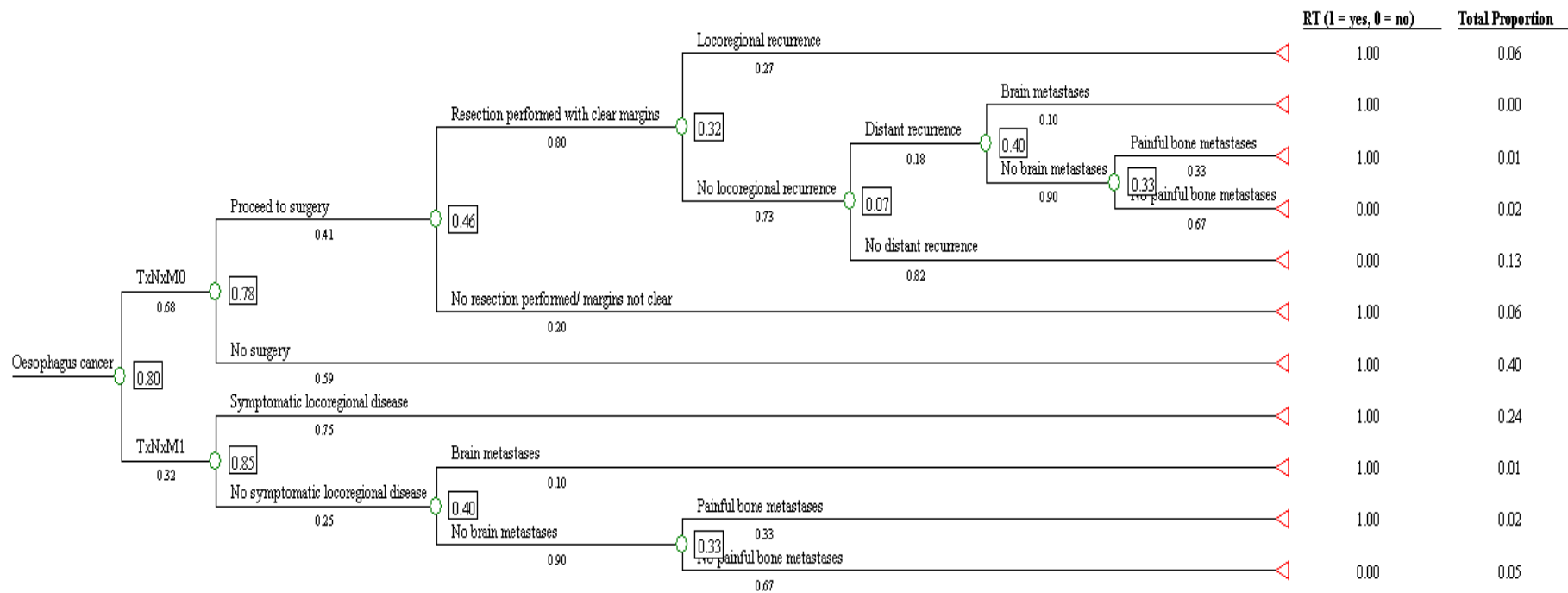
- the proportion of non-metastatic oesophageal cancer patients considered operable after pre-operative assessment (0.41-0.61)
- the proportion of patients with operable disease who go on to have a complete resection (0.62-0.90)
- the proportion of patients who develop distant disease following surgical treatment (0.18-0.30)
- the proportion of patients with metastatic disease who have painful bone metastases (0.16-0.33)

To assess the impact of this uncertainty on the overall estimate of the need for radiotherapy in all oesophageal cancers, a sensitivity analysis was performed for each of the variables and is illustrated by the tornado diagram below.

The graph below shows that the optimal proportion of oesophageal cancer patients who should receive radiotherapy based on evidence and incidence of attributes for radiotherapy is 80%. Depending on the data used this utilisation rate could vary from 73% to 81%. As oesophageal cancer represents 1% of all cancers, the contribution to the overall radiotherapy utilisation rate is 0.08% and may vary between 0.07% and 0.08%.

Tornado Diagram at Oesophagus





Gastric Cancer

Table 3: Gastric Cancer. Indications for radiotherapy: Levels and sources of evidence

Outcome Number	Clinical Scenario	Treatment Indicated	Level of Evidence	References	Notes	Proportion of all Gastric Cancer patients
13	TxNxM0, medically fit for surgery, T1N0, distant relapse, brain metastases	RT	II	<ul style="list-style-type: none"> • Priestman et al. (3) • Kurtz et al. (4) • Borgelt et al. (5) 	5	<0.01
14	TxNxM0, medically fit for surgery, T1N0, distant relapse, no brain metastases, painful bone metastases	RT	I	<ul style="list-style-type: none"> • Steenland et al. (6) • Nielsen et al. (7) • Tong et al. (8) 	5	<0.01
16	TxNxM0, medically fit for surgery, all Stage I-III other than T1N0M0	Post-operative Chemo-RT	II	<ul style="list-style-type: none"> • National Cancer Institute PDQ statement - Gastric cancer (45) • NCCN Practice Guidelines on gastric cancer (46) • Macdonald et al (47) 	2	0.68
18	TxNxM1, brain metastases	RT	II	<ul style="list-style-type: none"> • Priestman et al. (3) • Kurtz et al. (4) • Borgelt et al. (5) 	5	<0.01
19	TxNxM1, No brain metastases, painful bone metastases	RT	I	<ul style="list-style-type: none"> • Steenland et al. (6) • Nielsen et al. (7) • Tong et al. (8) 	5	<0.01
Proportion of all stomach cancer patients in whom radiotherapy is recommended					0.68 (68%)	
Proportion of all cancer patients = 0.68 X 0.02 =					0.013 (1.3%)	

Table 4: Gastric Cancer. The incidence of attributes used to define indications for radiotherapy

Key	Population or subpopulation of interest	Attribute	Proportion of population with this attribute	Quality of information	References	Explanatory Notes
A	All registry cancers	Gastric cancer	0.02	α	AIHW (12)	1
B	Gastric cancer	Stage TxNxM0	0.83	γ	National Cancer database (U.S.) (48) German Gastric cancer study (49)	3
			0.71	γ		
C	Stage TxNxM0	Medically fit for surgery	0.87	γ	U.S. National Cancer database	4
D	Stage TxNxM0, Medically fit for surgery	T1N0	0.06	γ	National Cancer database (U.S.) (48) German Gastric cancer study (49) Santoro et al.(50)	3
			0.20	γ		
			0.10	ζ		
E	Stage TxNxM0, Medically fit for surgery, T1N0	Distant relapse	0.05	ζ	Kitamura et al (51)	5
F	Stage TxNxM0, Medically fit for surgery, T1N0, distant relapse	Brain metastases	0	N/A	No data identified	5

Key	Population or subpopulation of interest	Attribute	Proportion of population with this attribute	Quality of information	References	Explanatory Notes
G	Stage TxNxM0, Medically fit for surgery, T1N0, distant relapse, no brain metastases	Painful bone metastases	0	N/A	No data identified	5
H	Stage TxNxM1	Brain metastases	0	N/A	No data identified	5
I	Stage TxNxM1, no brain metastases	Painful bone metastases	0	N/A	No data identified	5

Gastric cancer

Treatment Guidelines

Two clinical practice guidelines for the management of gastric cancer were identified, one issued by the National Cancer Institute (Physicians Data Query or PDQ statement on gastric cancer) (45) and the other by the National Comprehensive Cancer Network (NCCN) (46).

Indications for Radiotherapy

Based on guideline recommendations, radiotherapy in gastric cancer is indicated in the following clinical situations:

- Patients presenting with non-metastatic disease (Stages I-III) who have node-positive (N+) cancer are recommended to undergo postoperative chemoradiotherapy (PDQ and NCCN guidelines).
- The PDQ and NCCN guidelines also recommend postoperative chemoradiotherapy in patients with muscle-invasive (T2-4) disease.
- Palliative radiotherapy is indicated in patients with symptomatic bone metastases
- Palliative radiotherapy is indicated in patients with symptomatic brain metastases

Explanatory Notes for Tables 3 and 4

1. Incidence of gastric cancer

Gastric cancer constitutes 2% of all cancers in Australia according to the Australian Institute of Health and Welfare (AIHW) statistics (12).

2. Post-operative radiotherapy (+ chemotherapy)

In patients with node-positive (T1N1) and muscle invasive (T2-4 N1-3 M0) disease, post-operative chemoradiotherapy is recommended by the PDQ guidelines (45) and the NCCN guidelines (46). Treated with gastrectomy alone, recurrence rates in this group of patients ranges from 40-65%, thus making post-operative radiotherapy an attractive option. Intergroup study 0116 was a prospective randomised multi-institutional phase III trial evaluating the role of post-operative chemoradiation following gastric resection (including a D1 or D2 node dissection) for Stage IB-IV M0 (T2-4NXM0, T1N1M0) adenocarcinoma of the stomach in 556 patients (47). The study reported that there was a survival benefit and a local control benefit with the addition of post-operative chemoradiotherapy. Median survival was 36 months versus 27 months for surgery alone. A subsequent consensus conference and report supported the use of chemoradiotherapy for this sub-group of patients (52). The NCCN guidelines consider omitting chemoradiotherapy for patients who have undergone an R2 resection (i.e. a more extensive nodal dissection), but there is no evidence-based justification for this as the randomised trial found no statistically significant difference when analysing the different surgical procedures. In addition, a pre-operative radiotherapy trial showed superiority over surgery alone for gastric cancer (53).

3. Incidence of T1N1M0 or T2-4NxM0 disease

A recent National Cancer database report on gastric cancer in the US by Hundahl et al. (48) found that T1N0 represents 5.5% of all gastric cancers, and 6% of all M0 patients. In this report M1 disease represents 17% of all gastric cancers.

The German Gastric Cancer Study (49) reported a prospective, multi-institutional study in patients with gastric cancer treated with surgery from 1986-89. A total of 1999 patients were studied. 1654/1999 had a curative resection (83%). 29% had M1 disease. The German study does have substage of disease (Of the M0 patients, Stages IB-III = 80% and IA=20%).

Santoro et al. (50) reported on 100 consecutive patients treated in their department in Rome from 1971-1987. They reported that Stage IA represented 10% of patients with adenocarcinoma of the stomach and no metastatic disease, and the remainder were >IA (90%).

The preferred epidemiological data used for the decision tree was from the U.S. National Cancer Database report of Hundahl et al. (48) as it is a national database and is the most recent report. Sensitivity analysis was performed using data from the German study to assess the impact of this uncertainty of the data on the overall radiotherapy estimate.

4. Unfit for surgery

Data from the US National Cancer Database (48) shows that for patients with Stage I-III disease, 8% had no anti-cancer therapy and a further 5% had chemotherapy alone suggesting that this group was not of sufficient performance status to undergo surgery. A breakdown by age group was not reported.

5. Metastatic disease

Occasionally, palliative radiotherapy may be considered for patients with metastatic disease who have a symptomatic primary stomach cancer that is either too large to resect or the patient is not considered appropriate for a palliative resection. The main symptoms requiring palliation would be bleeding or pain. Radiotherapy could be considered although this is a rare indication for radiotherapy and is not considered in the decision tree as the incidence would be considered so small that it will have little impact on the overall radiotherapy utilisation.

The proportion of patients with stage T1N0M0 who undergo distant relapse could not be identified. However Kitamura et al reported a five-year survival rate for patients with Stage I gastric cancer of 95%; the main cause of death among the remaining 5% was metastatic disease (51).

Therefore the proportion of T1N0M0 patients undergoing distant relapse was assumed to be 5%.

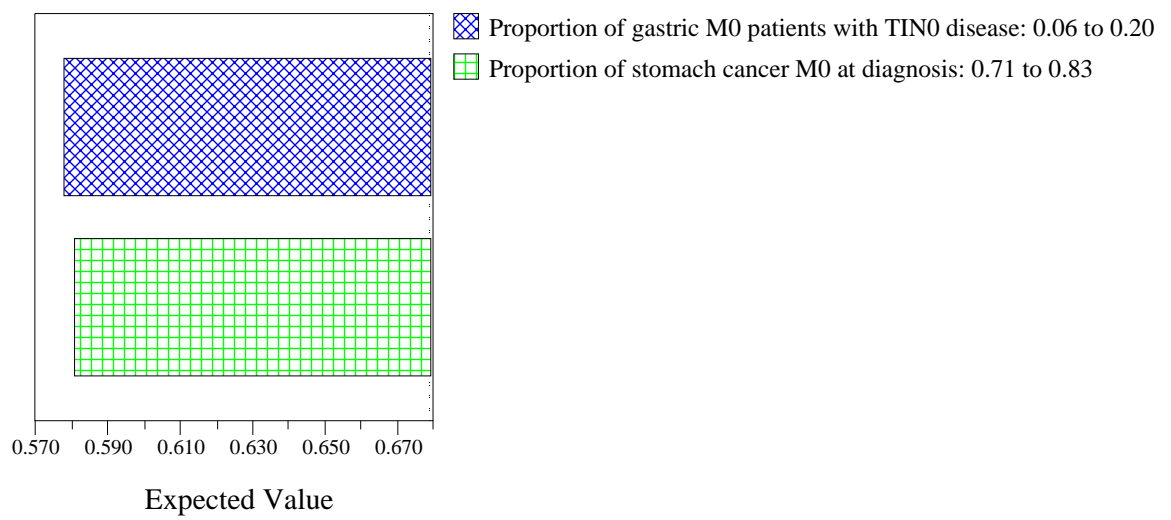
Radiotherapy is also considered for palliation of bone or brain metastases that are symptomatic. However, these are quite rare in gastric cancer. In a randomised trial assessing chemotherapy for advanced or metastatic disease no mention was made of the presence of bone or brain metastases with the majority of metastases being in the abdomen (distant nodes, liver, peritoneum) as well as pulmonary. However, approximately 29% had “other” metastases without stipulation of site (54). No data on the incidence of metastases to the brain or bone were identified and therefore values of 0 were chosen.

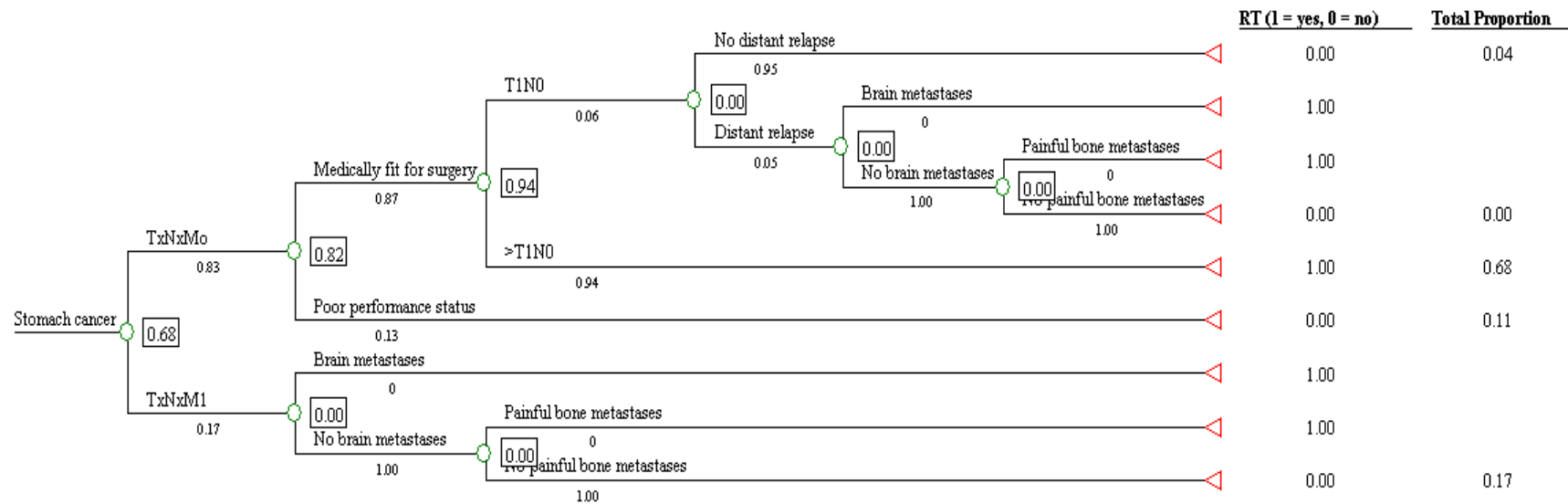
Optimal radiotherapy utilisation rate and Sensitivity analysis

There was uncertainty or variation concerning some of the epidemiological data. To assess the impact that this data uncertainty has on the overall estimate of radiotherapy utilisation, sensitivity analysis was performed. There was uncertainty regarding the incidence data for T1N0 stomach cancer, which varied between 0.06 and 0.20 and the data for the absence of metastatic disease at diagnosis, which ranged from 0.62 to 0.83. Therefore, sensitivity analysis assessed the impact of this variation on the overall estimate.

The graph below shows that the optimal proportion of stomach cancer patients who should receive radiotherapy based on evidence and the incidence of attributes for radiotherapy is 68% and could vary between 58% and 68% depending on the data used. As stomach cancer represents 2% of all cancers, the contribution to the overall radiotherapy utilisation rate is 1.4% and may vary between 1.2% and 1.4%.

Tornado Diagram at Stomach





Pancreatic Cancer

Table 5: Pancreatic Cancer. Indications for radiotherapy: Levels and sources of evidence

Outcome Number	Clinical Scenario	Treatment Indicated	Level of Evidence	References	Explanatory Notes	Proportion of all pancreatic cancer patients
21	Pancreatic cancer, localised, operable	Adjuvant chemoRT	II	<ul style="list-style-type: none"> • GITSG (Moertel et al.) (55) • Farnell et al.(56) • Kalser et al.(57) • Poen et al.(58) • National Cancer Institute PDQ statement on Pancreatic cancer (59) • NCCN Practice Guidelines on pancreatic adenocarcinoma (60) 	4	0.07
22	Pancreatic cancer, localised, inoperable	RT	II	<ul style="list-style-type: none"> • National Cancer Institute PDQ statement on Pancreatic cancer (59) • NCCN Practice Guidelines on pancreatic adenocarcinoma (60) • Moertel et al. (55) • Farnell et al. (56) • Poen et al. (58) 	5	0.36
23	Pancreatic cancer, metastatic disease, symptomatic primary or metastases	Palliative RT	III	<ul style="list-style-type: none"> • National Cancer Institute PDQ statement on Pancreatic cancer (59) • NCCN Practice Guidelines on pancreatic adenocarcinoma (60) 	6	0.14
Total proportion of pancreatic cancer where radiotherapy recommended:						0.57 (57%)
Total proportion of all cancers = 0.57 X 0.02 =						1.4%

Table 6: Pancreatic Cancer: The incidence of attributes used to define indications for radiotherapy

Key	Population or subpopulation of interest	Attribute	Proportion of population with this attribute	Quality of information	References	Explanatory Notes
A	All registry cancers	Pancreatic cancer	0.02	α	AIHW (12)	1
B	Pancreatic cancer	Localised disease	0.58	γ	Janes Jr. et al. (61)	2
C	Pancreatic cancer, localised disease	Operable	0.16 0.49	γ λ	Janes Jr. et al (61) Hosotani et al. (62)	3
D	Pancreatic cancer, metastatic disease,	Symptomatic primary or metastases	0.24	ϵ	Storniolo et al. (63)	6

Pancreatic cancer

Treatment Guidelines

There are two clinical practice guidelines for the management of pancreatic cancer, one issued by the National Cancer Institute (Physicians Data Query or PDQ statement on pancreatic cancer) (59) and the other issued by the National Comprehensive Cancer Network (NCCN) (60).

Indications for Radiotherapy

Based on guideline recommendations, radiotherapy in pancreatic cancer is indicated in the following clinical situations:

- Adjuvant radiotherapy (along with chemotherapy) following pancreatic resection
- Radiation therapy (with chemotherapy) in patients with locally unresectable disease
- For palliation of symptoms (arising from the primary or from secondaries) in metastatic pancreatic cancer

Explanatory Notes for Tables 5 and 6

1. Pancreatic carcinoma incidence

The incidence of pancreatic carcinoma is approximately 1% of all cancers according to the Australian Health and Welfare statistics (12).

2. Incidence of metastases at presentation

The main decision regarding the management of pancreatic cancer is to determine whether the patient is operable. Patients with metastases (M1 disease) are usually not recommended for surgical resection although a palliative bypass procedure may be appropriate in selected patients (56). The proportion of patients with M1 disease at diagnosis is reported by Janes Jr et al (61). They reported a patterns of care survey by the Commission of Cancer of U.S. institutions 1983-1985 and 1990 which includes data on 14 826 cases treated in 978 institutions. 57% had M1 disease at diagnosis.

3. Proportion of M0 patients that undergo surgical excision

Surgery is regarded as the mainstay of treatment in patients with localised operable disease who are considered fit for surgery. However, some patients are found to have localised but unresectable disease at diagnosis. This proportion varies between 10 and 25% in most series (64) (65). The largest report comes from Janes Jr. et al (61). Of the 6375 patients with M0 disease in their series, 16% of patients (1023) in Stages I-III underwent cancer directed surgery. The surgery altered with the presentation stage and age of the patient. Performance status measures were not stated. In a smaller series by Hosotani et al. (62), 49% of 309 patients who underwent exploratory laparotomy were found to have disease amenable to pancreatectomy. With increasing stage at presentation, the resectability rate decreased. Even though the resectability data varies widely between these 2

studies, sensitivity analysis was not performed because the variation in resection rate will have no impact on the decision tree. Patients with resectable disease are recommended to undergo post-operative radiotherapy (see explanatory note 4) and patients with unresectable tumours are also recommended to undergo radiotherapy if they have no evidence of metastatic disease (see explanatory note 5).

4. The role of adjuvant radiotherapy

The role of adjuvant radiotherapy remains controversial. A randomised trial conducted in the 1980s by the U.S. National Gastrointestinal Tumour Group (GITSG) reported superior local control and survival for post-operative radiotherapy compared with no adjuvant therapy following complete resection of pancreatic cancer (66) (57). This resulted in increased use of adjuvant therapy in the United States and Australia. Review articles and other non-randomised trials also support the use of adjuvant therapy with chemoradiation following resection of pancreatic cancer (65), (67) (68) (56) (69) (70) (58) (62). An EORTC trial failed to show a difference between patients treated with adjuvant chemoradiotherapy versus surgery alone (71). However, the dose of radiotherapy was lower, the radiotherapy technique was poor and the administration of chemotherapy was different compared with the study from the GITSG and therefore the negative result does not necessarily exclude a benefit from high-dose chemoradiation. The European Study Group for Pancreatic Cancer trial showed no benefit for adjuvant radiotherapy (72). The Mayo Clinic and a review article by Poen et al. still recommend adjuvant chemoradiotherapy (56) (58). Currently a number of adjuvant and neoadjuvant trials are underway testing various chemotherapy/radiotherapy combinations. At the present time it would appear reasonable, based on Level II evidence (randomised trial) that post-operative adjuvant chemoradiation should be offered to patients who have undergone complete resection as this project is based largely on treatment guideline recommendations. However, given that there is controversy, sensitivity analysis was also performed with no adjuvant radiotherapy being given as the alternative (see sensitivity analysis).

5. The role of radiotherapy in unresectable disease

The role of radiotherapy for the treatment of unresectable pancreatic cancer has been addressed by a GITSG randomised controlled trial comparing chemoradiotherapy with radiotherapy alone. Patients treated with chemoradiotherapy were better palliated and had longer median survival (55). Other studies and reviews have confirmed the palliative benefits of radiotherapy in the management of locally advanced pancreatic cancer (65) (73) (58) (67) (74) (56). Therefore, locally advanced pancreatic cancer would reasonably be treated with palliative radiotherapy with concurrent chemotherapy. Alternative palliative procedures such as biliary bypass procedures, coeliac plexus blocks or chemotherapy have not been formally tested against radiotherapy to assess their better efficacy in terms of palliative benefit or prolongation of survival (67).

6. Radiotherapy for metastatic disease

Patients with metastatic disease usually have a very limited life expectancy, with Janes et al (61) reporting a 2-year relative survival rate of 5% in patients with Stage IV disease. The most common sites of metastases from pancreatic carcinoma are to the lymph nodes, liver, peritoneum and lung. Treatment of metastases with radiotherapy would be very rare and hence would have no significant effect on the overall radiotherapy utilisation rate. In most instances, if the patient is of reasonable performance status, they may receive palliative chemoradiotherapy for pain related to the pancreatic primary.

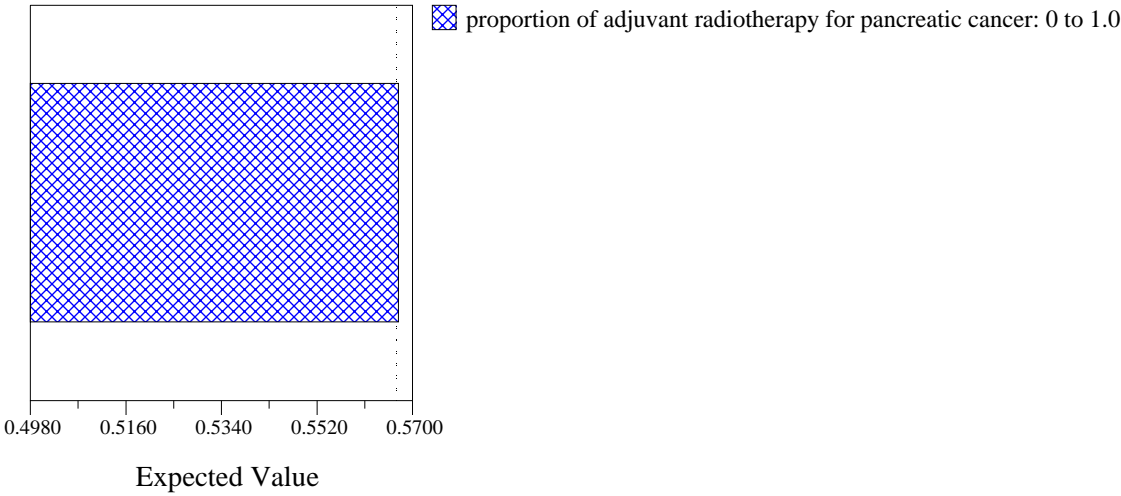
Trying to determine the proportion of metastatic pancreatic cancer with symptoms warranting radiotherapy is very difficult as such specific data was not available. The chemotherapy treatment that appears to have reasonable activity in pancreatic cancer is Gemcitabine. It would be reasonable to consider patients for palliative radiotherapy if they have progressive pancreatic pain following a trial of Gemcitabine. Storniolo et al. (63) reported on a series of patients treated with Gemcitabine for advanced pancreatic cancer. 24% of patients had worsening pain after 4 cycles of treatment. The actual radiotherapy utilisation rate for this study is not reported. A further 33% of patients had “stable” pain after 4 cycles of treatment. It might be argued that some of these patients also may warrant radiotherapy, however in view of the poor prognosis of the patient group the conservative approach of considering radiotherapy only in those with worsening pain was taken for this decision tree.

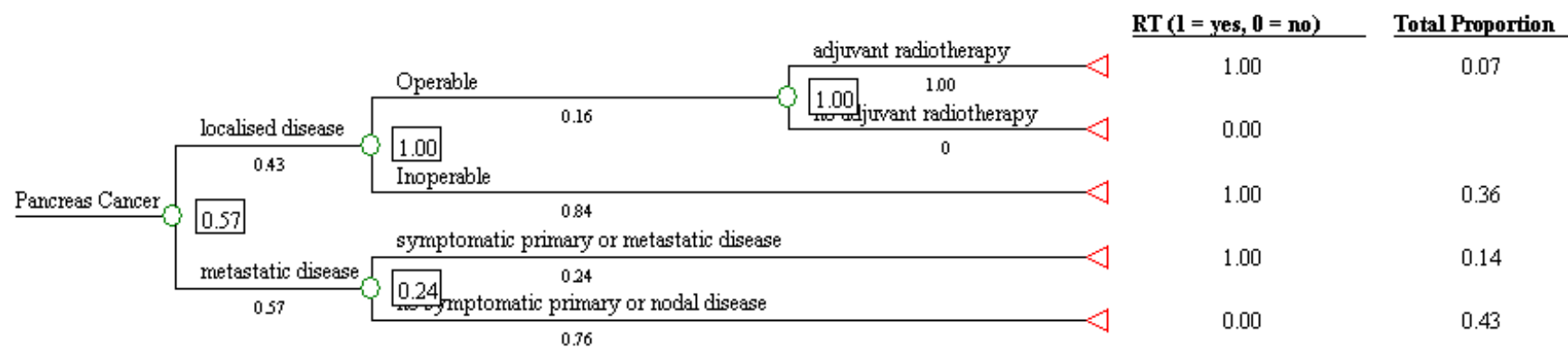
Optimal radiotherapy utilisation rate and Sensitivity analysis

Based on the data and indications for radiotherapy discussed above, 57% of pancreatic cancer patients have clinical indications where radiotherapy may be considered appropriate at some time during their treatment course. As pancreatic cancer represents 2% of all cancers, this represents 1.0 and 1.1% of all cancer patients.

There was some uncertainty about the recommendation that all pancreatic cancer patients who undergo resection should receive radiation, so the alternative of no patients receiving post-operative analysis was modelled in sensitivity analysis (see graph below). This uncertainty varied the expected value between 50% and 57%.

**Tornado Diagram at
Pancreas**





Liver Cancer

For localised primary liver tumours the treatment of choice is surgery. Pre-operative radiotherapy (+/- chemotherapy) has been described in some anecdotal cases. In addition, recent reports have suggested external beam radiotherapy using modern conformal techniques to treat unresectable hepatocellular carcinoma. However, no defined role for radiotherapy has currently been established, according to the U.S. National Cancer Institute PDQ treatment guidelines on adult primary liver cancer (75) and the NCCN guidelines on hepatobiliary cancers (76). Patients with unresectable tumours have a very limited life expectancy. The majority of treatments are aimed at conservative palliation of symptoms or the use of chemotherapy or chemo-embolisation. There are currently no indications to give radiotherapy in this setting outside of a clinical trial (75). Therefore, it is estimated that no patients with primary liver cancer receive radiotherapy.

Cancer of the Gall bladder

Table 7: Gall Bladder Cancer. Indications for radiotherapy: Levels and sources of evidence

Outcome Number	Clinical Scenario	Treatment Indicated	Level of Evidence	References	Proportion of all Gall Bladder Cancer patients	Explanatory Notes
27	No metastatic disease, good PS, inoperable	RT	IV	National Cancer Institute PDQ statement – Gall bladder cancer (77) NCCN Clinical Practice guidelines on Hepatobiliary cancers (76)	0.13	1
Proportion of all gall bladder cancer patients in whom radiotherapy is recommended					0.13 (13%)	
Proportion of all cancer patients = $0.13 \times 0.01 =$					0.0013 (0.13 %)	

Table 8: Gall Bladder Cancer. The incidence of attributes used to define indications for radiotherapy

Key	Population or subpopulation of interest	Attribute	Proportion of population with this attribute	Quality of information	References	Explanatory Notes
A	All registry cancers	Gall Bladder cancer	0.01	α	AIHW	1
B	Gall Bladder cancer	Metastatic disease	0.62 0.50	ζ ζ	Carty and Johnson (78) Schauer et al.(79)	2
C	Gall bladder cancer, no metastatic disease	Good PS	0.97	ϵ	Cubertafond et al.(80)	3
D	Gall bladder cancer, no metastatic disease, good PS	Operable	0.58 0.97 0.43	ζ ζ ζ	Schauer et al.(79) Carty and Johnson (78) Nakamura et al.(81)	4

Abbreviations: PS - Performance Status

Treatment Guidelines

There are two clinical practice guidelines for the management of gall bladder cancer, one issued by the National Cancer Institute (Physicians Data Query or PDQ statement on gall bladder cancer) (77) and the other by the National Comprehensive Cancer Network (NCCN) (76) .

Indications for Radiotherapy

The guidelines make the following recommendations on cancer of the gall bladder.

- Gall bladder cancer that is resectable is uncommon and usually discovered incidentally during a surgical procedure rather than presenting with specific symptoms
- Localised disease that is resectable should be treated with surgery alone. In these cases, isolated local recurrence is rare with either cure or development of distant disease the more likely outcome (82),(83), (80). There is no definite evidence that post-operative radiotherapy is of benefit. Small series suggest tolerable toxicity and reasonable local control compared to historical controls (84),(85).
- For patients with unresectable disease, radiation with or without concurrent chemotherapy has been reported to provide short-term response and local control ((86), (87),(88), (89), (90), (91), (92), (93). However, results are poor and the NCI guidelines (77) recommend consideration of these patients for chemoradiation trials.
- Chemotherapy alone has not been shown to be of palliative benefit in the management of metastatic gall bladder cancer. In most instances radiotherapy is also of limited value as most metastases are hepatic, peritoneal or nodal.
Therefore, based on these guidelines, radiotherapy is recommended for inoperable, non-metastatic disease in patients with good performance status.

Explanatory Notes for Tables 7 and 8

1. Incidence of gall bladder cancer

Gall bladder cancer constitutes 0.01 % of all cancers in Australia according to the Australian Institute of Health and Welfare (AIHW) 1998 statistics (12).

2. Proportion of patients with metastatic disease at presentation

Patients with metastatic disease at diagnosis have a very short average life expectancy and therefore the vast majority would not have any indications for palliative radiotherapy. In a patterns of care study from Wessex, Carty and Johnson (78) reported that 62% of 95 patients with a diagnosis of gall bladder cancer had metastases or major liver involvement (Nevin stage V) at diagnosis. Gagner et al. (94) reviewed four series of gall bladder cancers according to diagnosis by stage and reported that 55.5% of patients had Nevin stage V disease at diagnosis. Schauer et al. (79) reported that of 127 gall bladder cancer cases in their department, 50% had metastatic disease at diagnosis.

3. Proportion of gall bladder cancer patients who have poor performance status

A survey of 73 institutions mainly in France as well as other European centres by Cubertaft et al (80) resulted in a database of 724 cases of histologically proven carcinoma of the gall bladder. They reported that 3% of cases were of such poor performance status that conservative palliation was the recommended treatment approach. They reported that 23% were fit and of a tumour stage that warranted radical surgery. The majority of surgical patients had T4N0M0 disease (53% of operative group).

4. Proportion of non-metastatic disease that is resectable

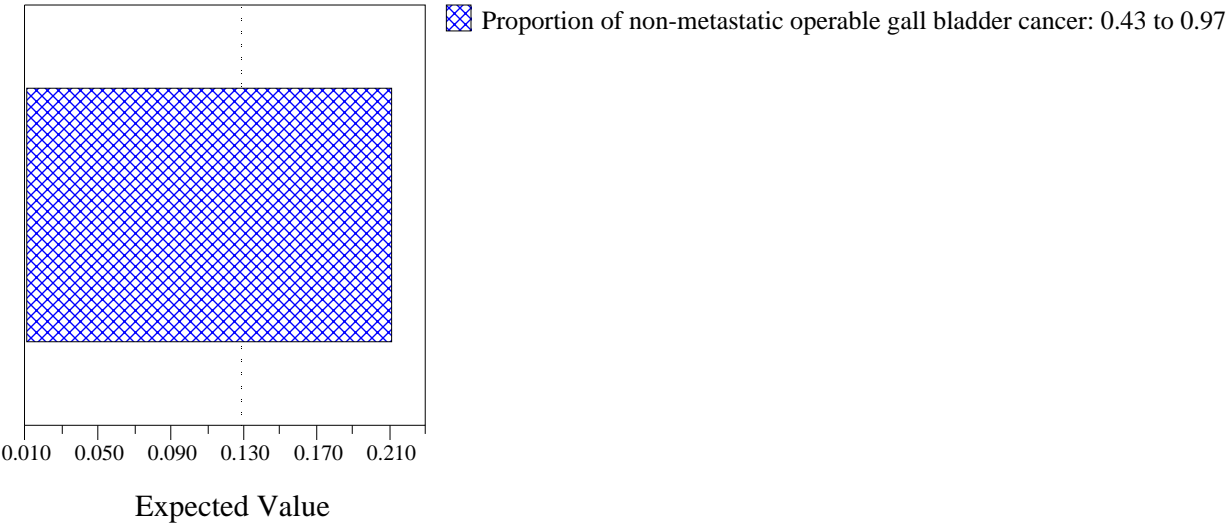
Carty and Johnson (78) reported that 97% of the 36 patients with non-metastatic disease (38%) in their study underwent a curative procedure. The other 3% underwent biopsy only. According to the PDQ guidelines (77), there is evidence that radiotherapy may be of benefit for patients with no evidence of metastatic disease and unresectable tumours. Schauer et al. (79) reported that of their 63 patients that were M0, 37(59%) were operable. For the 35 patients undergoing surgery at Hamamatsu University Hospital (81), 43% had operable disease.

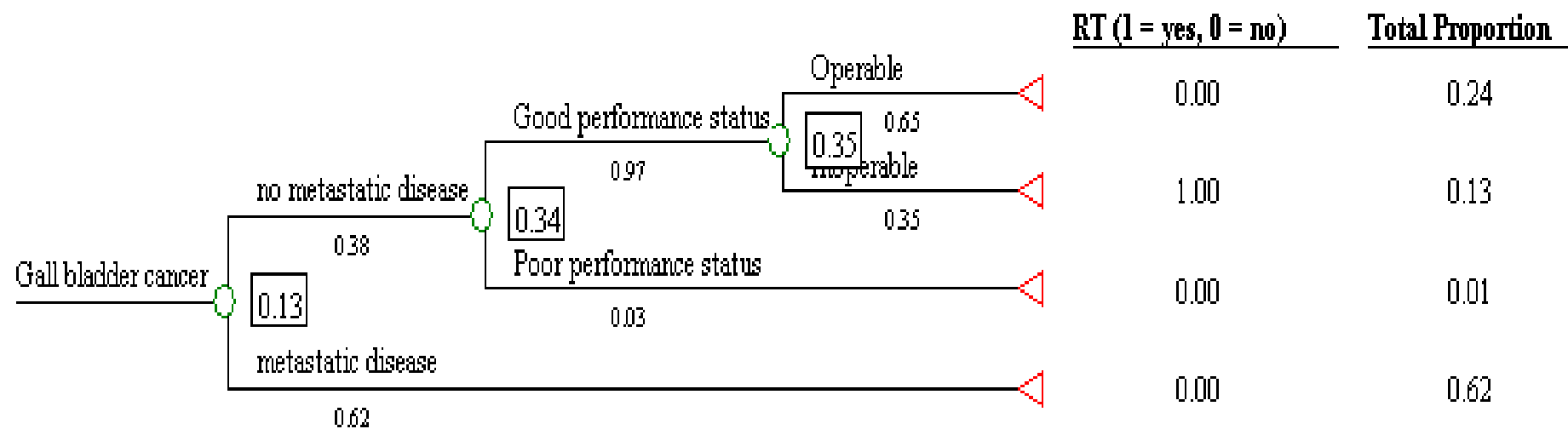
The above data suggest that there are wide variations in the proportion of non-metastatic gall bladder cancer that have resectable disease. All of the above studies were of equivalent quality (single institution, retrospective, surgical series with similar numbers of patients). Therefore a weighted mean of 65% was calculated and used in the decision tree. A sensitivity analysis was then performed to model the impact that using the extreme values would have on the overall utilisation rate. The extreme values used were 43% and 96%.

Optimal radiotherapy utilisation rate and sensitivity analysis

It was estimated that 13% of all gall bladder cancers should optimally receive radiotherapy. The one value associated with significant uncertainty and variation was the proportion of patients with non-metastatic gall bladder cancer who have resectable disease. Therefore, a sensitivity analysis was performed to establish the impact of this variation on the overall radiotherapy utilisation estimate. The tornado diagram below shows the range in the radiotherapy utilisation rate when the variable is varied between 43% and 97%. This results in an estimate for radiotherapy utilisation that varies from 1% to 21% of all gall bladder cancers. As gall bladder cancer represents 1% of all cancers, this estimate represents 0.01% of all cancers (range = 0.001% - 0.02%).

**Tornado Diagram at
Gall bladder**





Colon Cancer

Table 9: Colon Cancer. Indications for radiotherapy – Levels and sources of evidence

Outcome No.	Clinical Scenario	Treatment Indicated	Level of Evidence	References	Explanatory Notes	Proportion of all colon cancer patients
30	Stage T1-3 any N M0 Bone metastases	Palliative radiotherapy	I	<ul style="list-style-type: none"> NHMRC guidelines for the prevention, early detection and management of colorectal cancer (95) 	1	0.03
31	Stage T1-3 any N M0 No bone metastases Brain metastases	Palliative radiotherapy	II	<ul style="list-style-type: none"> NHMRC guidelines for the prevention, early detection and management of colorectal cancer (95) 	1	0.01
33	Stage T4 any N M0	Adjuvant radiotherapy	III	<ul style="list-style-type: none"> Willett et al (96) 	2	0.10
34	Any T any N M1 non-resectable due to fixation to other organs	Palliative radiotherapy	IV	<ul style="list-style-type: none"> Willett et al (97) 	3	<0.01

Outcome No.	Clinical Scenario	Treatment Indicated	Level of Evidence	References	Explanatory Notes	Proportion of all colon cancer patients
36	Stage any T any N M1, Bone metastases	Palliative radiotherapy	I	<ul style="list-style-type: none"> NHMRC guidelines for the prevention, early detection and management of colorectal cancer (95) 	1	<0.01
37	Stage any T any N M1, No bone metastases, brain metastases	Palliative radiotherapy	II	<ul style="list-style-type: none"> NHMRC guidelines for the prevention, early detection and management of colorectal cancer (95) 	1	<0.01
Proportion of colon cancer patients in whom radiotherapy is recommended					0.14 (14%)	
Total proportion of all cancer patients = 0.14x 0.09 =					0.012 (1.2%)	

Table 10: Colon cancer. The incidence of attributes used to define indications for radiotherapy

Key	Population or subpopulation of interest	Attribute	Proportion of populations with this attribute	Quality of information	References	Explanatory Notes
A	All registry cancers	Colon cancer	0.09	α	AIHW (12)	1
B	All Colon cancers	any T any N M0	0.80	γ	SA Cancer Registry (98)	2
C	Colon Cancer, any T any N M0	T4 any N M0	0.07 0.25	ζ	Russell et al (99) Willett et al (97)	2
D	Stage T1-3 any N M0	Bone metastases	0.04	ζ	Bonnheim et al (100)	4
E	Stage T1-3 any N M0 and no bone metastases	Brain metastasis	0.01	ζ	Hammoud et al (101)	5
F	Stage any T any N M1	Unresectable due to fixation to other organs	0.22	ζ	Willett et al (96)	3
G	Stage any T any N M1	Bone metastases	0.02	ζ	Russell et al (99)	4
H	Stage any T any N M1 no bone metastases	Brain metastases	0.01	ζ	Russell et al (99)	5

Colon cancer

Treatment guidelines

The following national level clinical practice guidelines for the management of colon cancer were identified:- NHMRC guidelines for the prevention, early detection and management of colorectal cancer (1999), NCCN clinical practice guidelines on colon cancer (v 2, 2003), National Cancer Institute PDQ guidelines on colon cancer (2003), BC Cancer Agency Cancer management guidelines (2002), Cancer Care Ontario (CCOP) guidelines on adjuvant therapy for stage II and stage III colon cancer (2000), SIGN Scottish national clinical guideline for the management of colorectal cancer (1997), Royal College of Surgeons guidelines for the management of colorectal cancer (1996) and the NIH consensus statement on adjuvant therapy for patients with colorectal cancer (1990). In this study, preference was given to the Australian national guidelines issued by the National Health and Medical Research Council (NHMRC) since the results of this study will be used to plan future radiotherapy facilities in Australia based on recommended Australian practice.

Indications for Radiotherapy

Based on guideline recommendations, radiotherapy in colon cancer is indicated in the following clinical situation:

- Palliative radiotherapy for patients with symptomatic brain or bone metastases
- In addition, adjuvant radiotherapy has been advocated for patients with tumours that penetrate the bowel wall or are fixed to adjacent structures (see below).

Explanatory Notes for Tables 9 and 10

1. Incidence of colon cancer

Colon cancer constitutes 9% of all cancers in Australia (12) based on data from the Australian Institute of Health and Welfare.

2. Adjuvant radiotherapy for colon cancer

Adjuvant radiotherapy has been advocated for those patients with tumours that penetrate the bowel wall and involve other organs (T4 any N M0) (96). Studies indicate improved local control and survival for patients with T4 any N M0 in retrospective data. The proportion of patients with Stage T4 any N M0 tumours was only reported in hospital series and varied from 7% (99) to 25% (97). In practice not all those cases would be suitable for radiotherapy because of patient fitness and the site of organ involvement. The proportion with this attribute was therefore varied in the sensitivity analysis from 0% to 25% (see below). An arbitrary value of 50% of cases (i.e. 12%) was chosen for the decision tree analysis.

3. Radiotherapy for unresectable tumours

Willett (96) reported that 22% of Stage any T any N M1 patients had tumours that were not resectable because of attachment to other organs

(11). Not all of these cases would be suitable for radiotherapy because of poor overall performance status or tumour site. Asymptomatic patients would usually be observed. The value for this attribute has been set at 0% with the upper boundary of the sensitivity analysis assuming that an arbitrarily chosen 50% of patients would receive radiotherapy.

4. Incidence of bone metastases

Data for the incidence of bone metastases were obtained from 2 sources. Russell et al. (99) report on a series of colon patients with metastatic disease on presentation. The rate of bone involvement was 2%. Bonnheim et al. (100) report on the development of bone metastases for patients that originally have M0 disease who then subsequently develop metastatic disease. Bone metastasis rate was 1%.

5. Incidence of brain metastases

Data for the incidence of brain metastases was obtained from 2 sources. Russell et al. (99) report on a series of colon patients with metastatic disease on presentation. The rate of brain involvement was 1%. Hammoud et al. (101) report on the development of brain metastases for patients that originally have M0 disease who then subsequently develop metastatic disease. The proportion was 1%.

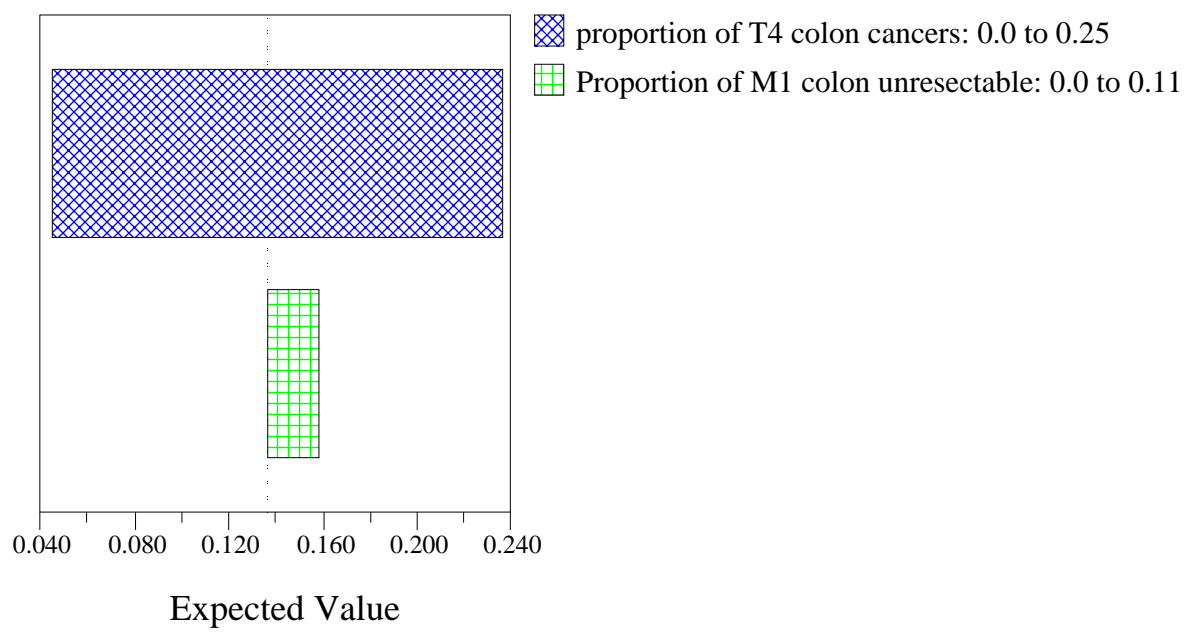
Optimal radiotherapy utilisation rate and sensitivity analysis

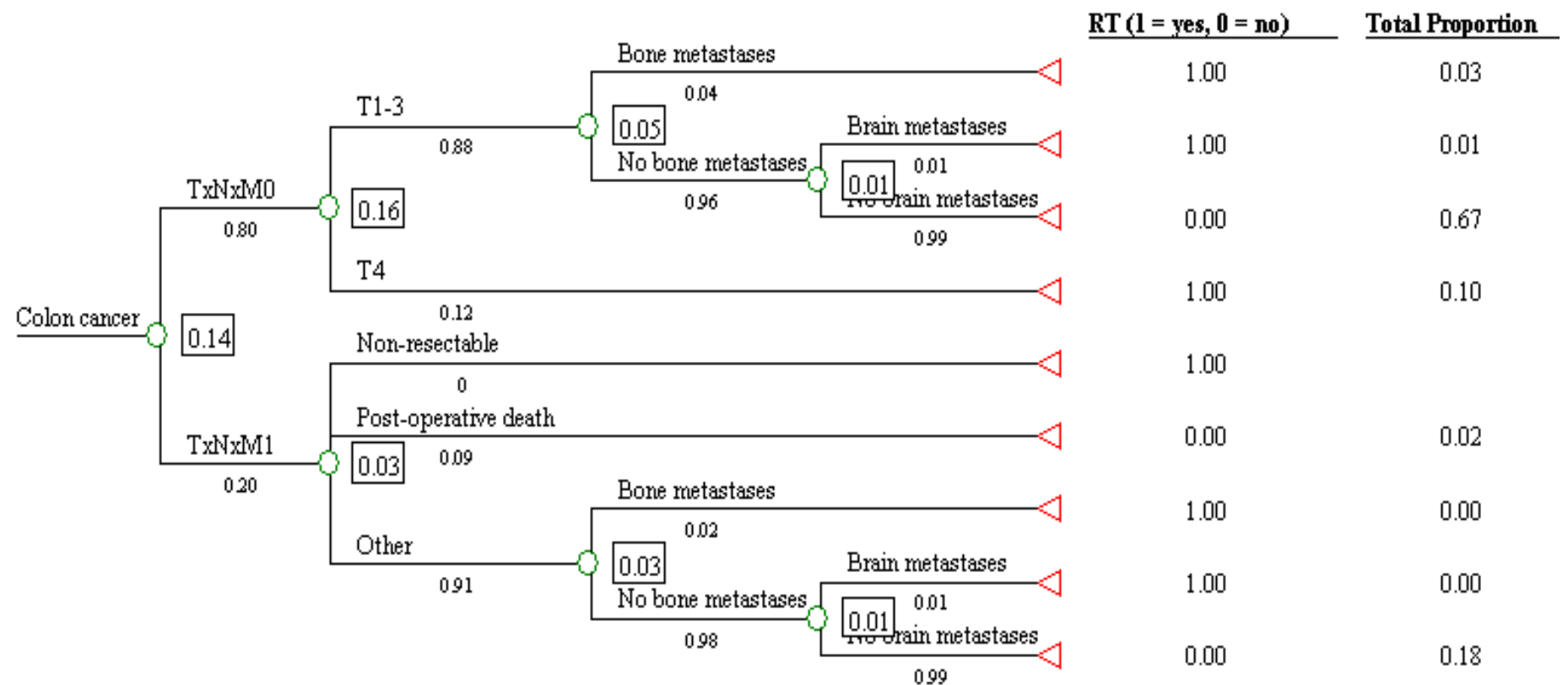
Using the proportions as described in Table 2, the calculation of the proportion of ALL patients with colon cancer in whom at least one course of radiotherapy is recommended according to the best available guideline evidence is calculated as 14% of all patients with colon cancer. As colon cancer represents 9% of all cancers (AIHW data) (12) the group of colon cancer patients who should ideally receive at least one course of radiotherapy comprises 1.2% of all cancer patients

As discussed above, there were no data that indicated the proportion of patients with tumours that invade into other organs (Stages T4NxM0 and TxMxM1 unresectable) that might benefit from radiotherapy either as an adjuvant or for palliation. Therefore a sensitivity analysis was performed to examine the effect of varying the proportion that received radiotherapy for these indications for 0%-50% of the 22% of patients with this attribute. Similarly, the proportion of patients with T4 colon cancer that may benefit from radiotherapy was varied between 0% and 25% (i.e no patients get radiotherapy through to all T4 patients). The sensitivity analysis graph appears below.

The variation in the estimate of the proportion of patients for whom radiotherapy may be indicated ranges from 4.1% to 23%. As colon cancer represents 9% of all cancers (AIHW data) (12), the group of colon cancer patients who should ideally receive at least one course of radiotherapy varies from 0.37% to 2.1% of all cancer patients.

Tornado Diagram at Colon





Rectal Cancer

Table 11: Rectal Cancer. Indications for radiotherapy - Levels and sources of evidence

Outcome No.	Clinical Scenario	Treatment indicated	Level of evidence	References	Notes	Proportion of all rectal cancer patients
65	Stage T1N0M0, radical surgery, local recurrence	Radiotherapy +/- Chemotherapy	III	<ul style="list-style-type: none"> NHMRC guidelines for the prevention, early detection and management of colorectal cancer (95) 	4	0.01
67	Stage T1N0M0, local excision, observation (category 2), local recurrence	Radiotherapy	III	<ul style="list-style-type: none"> NHMRC guidelines for the prevention, early detection and management of colorectal cancer (95) 	5	<0.01
69	Stage T1N0M0, local excision, category 3 and 4	Radiotherapy +/- Chemotherapy	III	<ul style="list-style-type: none"> Russell et al (102) 	6	0.03
70	Stage T2N0M0, radical surgery, local recurrence	Radiotherapy and Chemotherapy	III	<ul style="list-style-type: none"> NHMRC guidelines for the prevention, early detection and management of colorectal cancer (95) 	6	0.01

Outcome No.	Clinical Scenario	Treatment indicated	Level of evidence	References	Notes	Proportion of all rectal cancer patients
72	Stage T2N0M0, local excision	Radiotherapy	III	<ul style="list-style-type: none"> NHMRC guidelines for the prevention, early detection and management of colorectal cancer (95) 	5	0.04
73	Stage T3-4N0M0	Surgery + CMT (Chemotherapy and Radiotherapy)	II	<ul style="list-style-type: none"> NHMRC guidelines for the prevention, early detection and management of colorectal cancer (95) 	2, 3	0.19
74	Stage TxN1-2M0	Surgery + CMT (Chemotherapy and Radiotherapy)	II	<ul style="list-style-type: none"> NHMRC guidelines for the prevention, early detection and management of colorectal cancer (95) 	2,3	0.29
75	Stage TxNxM1, symptomatic primary disease	Palliative Radiotherapy	III	<ul style="list-style-type: none"> NHMRC guidelines for the prevention, early detection and management of colorectal cancer (95) 	8	0.03
76	Stage TxNxM1, brain metastases	Radiotherapy	II	<ul style="list-style-type: none"> NHMRC guidelines for the prevention, early detection and management of 	9	<0.01

				colorectal cancer (95)		
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Outcome No.	Clinical Scenario	Treatment indicated	Level of evidence	References	Notes	Proportion of all rectal cancer patients
77	Stage TxNx M1, no brain metastases, symptomatic bone metastases	Radiotherapy	I	<ul style="list-style-type: none"> NHMRC guidelines for the prevention, early detection and management of colorectal cancer (95) 	10	0.01
Proportion of all rectal cancer patients in whom radiotherapy is recommended						0.61 (61%)
Proportion of all cancer patients = 0.61 x 0.05 =						0.0305 (3.05%)

Key to Abbreviations in Rectal cancer decision tree and tables

CMT – combined modality therapy

NHMRC – National Health and Medical Research Committee

Table 12: Rectal Cancer. The incidence of attributes used to define indications for radiotherapy

Key *	Population or subpopulation of interest	Attribute	Proportion of populations with this attribute	Quality of Information	References	Explanatory Notes
0	All registry cancers	Rectal cancer	0.05	α	AIHW (12)	
1a	All rectal cancer	Stage T1N0M0	0.09	α	National Colorectal Cancer survey (103)	1
1b	All rectal cancer	Stage T2N0M0	0.22	α	National Colorectal Cancer survey (103)	1
1c	All rectal cancer	Stage T3-4N0M0	0.26	α	National Colorectal Cancer survey (103)	1
1d	All rectal cancer	Stage TxN1-2M0	0.26	α	National Colorectal Cancer survey (103)	1
1e	All rectal cancer	Stage TxNxM1	0.17	α	National Colorectal Cancer survey (103)	1
2	Stage T1N0M0	Radical surgery	0.96	α	National Colorectal Cancer survey (103)	4
3	Stage T1N0M0, radical surgery	Local relapse	0.06 0.09	ζ	Bethune et al. (104) Nymann et al. (105)	5
4	Stage T1N0M0, local excision	Category 2 (see explanatory note 6)	0.22	ε	Russell et al. (102)	6
5	Stage T1N0M0, local excision, Category 2	Local relapse	0.01	ε	Russell et al. (102)	6
6	Stage T2N0M0	Radical surgery	0.99	α	National Colorectal Cancer survey (103)	4

Key *	Population or subpopulation of interest	Attribute	Proportion of populations with this attribute	Quality of Information	References	Explanatory Notes
7	Stage T2N0M0 Radical surgery	Local relapse	0.14	ζ	Bethune et al. (104)	7
8	Stage T2N0M0	Local excision	0.33	ε	Russell et al. (102)	6
9	Stage TxNxM1	Symptomatic local disease	0.16	δ	Berthelsen (personal communication, SWSAHS data)	8
10	Stage TxNxM1	Symptomatic brain metastases	0.02	ζ	Patanaphan et al. (106)	9
11	Stage TxNxM1, no symptomatic brain metastases	Symptomatic bone metastases	0.01 0.09	ζ ζ	Talbot et al. (107) Besbeas et al. (108)	10

Rectal Cancer

Treatment Guidelines

The following national level clinical practice guidelines for the management of colon cancer were identified:- NHMRC guidelines for the prevention, early detection and management of colorectal cancer (1999), NCCN clinical practice guidelines on rectal cancer (v 2, 2003), National Cancer Institute PDQ guidelines on rectal cancer (2003), BC Cancer Agency Cancer management guidelines (2002), Cancer Care Ontario guidelines on the use of preoperative radiotherapy in the management of patients with clinically resectable rectal cancer (2003), Cancer Care Ontario guidelines on postoperative adjuvant radiotherapy and/or chemotherapy for resected Stage II or III rectal cancer (2001), SIGN Scottish national clinical guideline for the management of colorectal cancer (1997), the Royal College of Surgeons guidelines for the management of colorectal cancer (1996) and the NIH consensus statement on adjuvant therapy for patients with colorectal cancer (1990). In this study, preference was given to the Australian national guidelines issued by the National Health and Medical Research Council (NHMRC) since the results of this study will be used to plan future radiotherapy facilities in Australia based on recommended Australian practice. However the NHMRC Colorectal treatment guidelines did not define either any specific criteria for local excision in the treatment of early rectal cancer, or the criteria for recommendation of radiotherapy in patients with early rectal cancer who were treated with local excision. Other studies have therefore been used to define these branches in the decision tree.

Indications for Radiotherapy

According to the guidelines, radiotherapy is recommended for rectal cancer in the following situations:

- All patients undergoing curative rectal surgery who have node positive disease (NHMRC guidelines)
- All patients undergoing curative surgery who have penetration of tumour through the muscularis mucosae (NHMRC guidelines)
- Patients who have undergone local excision and who have intermediate to high risk of recurrence (see explanatory note 6)
- Patients with symptomatic bone or brain metastases
- Patients who develop recurrence locoregionally following curative surgery.

Explanatory Notes for Tables 11 and 12

1. Stage

The issue of the staging system to be used in the decision tree for rectal cancer was problematic. There are several recognised staging systems and different staging systems are used in the published literature and reports on incidence. The NHMRC Colorectal Cancer treatment guidelines recommend the Australian ClinicoPathological Staging System (ACPS) and the Tumour Node Metastasis (TNM) staging system. When recommending treatment, the NHMRC guideline does not specifically refer

to any particular staging system. The proportions of each stage were sourced from the National Colorectal Cancer survey which was conducted in 2000 (103). Due to the available epidemiological data it was most practical to use the TNM staging system.

2. Performance status

Ideally, it would be appropriate to split the decision tree according to performance status by stage of rectal cancer. However, no reliable database reporting on both stage and performance status was found. Performance status by stage for rectal cancer was not available from the SA Hospital Registry. In the current decision tree, ALL rectal cancer patients who are fit for surgery and have T3-4N0M0 and TxN1-2M0 disease are recommended to have radiotherapy. This is not an unreasonable assumption, as almost all patients who are fit enough for radical surgery are usually fit enough for radiotherapy. A small minority of patients may be unfit for radiotherapy; however this group would be so small that it will not significantly influence the end result of the study.

3. Justification for radiotherapy for T3 or N1-2 tumours in the era of total mesorectal excision

Radiotherapy is routinely recommended for tumours that penetrate through the muscularis mucosae and/or have nodal involvement (T3NxM0 and TxN1-2 M0) for two reasons. (This is despite the opinion of some colorectal surgeons who may advocate total mesorectal excision (TME) and no adjuvant radiotherapy). First, the objective of this Radiotherapy Utilisation study was to base decision-points on recommendations as they appear in current available guidelines. The NHMRC Colorectal treatment guidelines recommend routine radiotherapy for this group of patients. Second, a recent randomised controlled trial (109) has reported a statistically significant reduction in local recurrence with the addition of post-operative radiotherapy to TME (2.4% local recurrence) compared with treatment with TME alone (8.2% local recurrence; $p < 0.001$). This study therefore further justifies the recommendation for radiotherapy in these patients.

4. Incidence of radical excision for stage T1-2N0M0

The radical excision rates of 96% for Stage T1N0M0, and 99% for Stage T2N0M0 were taken from the results from the National Colorectal Cancer survey of practice (103).

The issue of whether or not radiotherapy is indicated after local excision is far from clear-cut, either from the guidelines or from published literature. The NHMRC colorectal cancer guidelines (95) do not discuss the role of radiotherapy after local excision of rectal cancer other than stating (page 97) that only 5 – 10% of all rectal tumours fit the criteria for local excision. However, this recommendation was not well referenced. Published reports vary considerably in terms of the selection criteria for local excision with/without adjuvant RT and also the treatment recommendations for

these patients. No study reports on the selection criteria in sufficient detail to calculate the proportion of Stage T1-2N0M0 patients who undergo local excision and radiotherapy. Willett et al. (110) reported that approximately 45% of T1 and T2 tumours had local excision during their study period. Killingback (111) published a local excision rate of 13.2% of all tumours but does not provide a breakdown by stage. Bethune et al. (104) reported a 10% local excision rate of all tumours and Grigg et al. (112) reported a 6% local excision rate for all rectal tumours, but neither study states a breakdown of this rate according to Stage.

5. Local recurrence rates for T1N0M0 disease treated with surgery only

For patients with Stage T1N0M0 disease, very few studies have reported on local recurrence rates according to stage. Bethune et al (104) reported a recurrence rate of 5/86 (6%) and Nymann et al. (105) had a rate of 3/33 (9%) for stage T1N0M0. Sengupta (113) in a review of 41 studies on curative local excision for rectal cancer, reported an overall local recurrence rate of 9.7 % for T1, 25 % for T2 and 38 % for T3 rectal cancers treated with local excision alone. The Australian National Colorectal Cancer survey (103) has outcome data but with very short follow up at this point in time and therefore was not included in this study.

This branch of the tree does not consider the occurrence of any metastatic disease following surgery where patients may then receive radiotherapy, as this number is difficult to obtain and is assumed to be extremely low. Although we recognise that this is a slight underestimate as a small proportion will develop metastases that would be appropriately treated with radiotherapy, the omission of metastatic disease is justified on the basis of the low incidence and the fact that it is unlikely to influence the ultimate result.

All locoregional recurrences are assumed to require radiotherapy in the decision tree for rectal cancer. Most series report that radiotherapy is “commonly used” for recurrence (114). In addition, the NHRMC Clinical Guidelines for Colorectal cancer (95) state that “The vast majority of local recurrences are inoperable and incurable. Their management is palliative and it should include consideration of radiotherapy and/or chemotherapy..... the use of radiotherapy can relieve these symptoms in the majority of cases, but the duration of relief is often short-lived. The benefits of palliative radiation in these patients may translate into improved quality of life.....”

6. The proportion of patients with early rectal cancers treated by local excision who have indications for adjuvant radiotherapy

Determination of the proportion of patients who have undergone local excision and in whom radiotherapy is considered “appropriate” was difficult. Some studies recommend that radiotherapy should be given to selected patients post-operatively following local excision, based on local policy or selection criteria (110) (115) (116). Other studies either

recommended that radiotherapy should not be given following local excision, or report on institutional results of local excision without radiation in highly selected patients (117) (118) (119) and justify the omission of radiotherapy on the low recurrence rates. The inclusion criteria for post-operative radiotherapy following local excision vary between studies.

Russell et al (102) developed rigid pathological criteria for radiotherapy following local excision in a Phase II RTOG study. They reported acceptable local control results in a prospective trial of patients treated in accordance with their protocol. With a minimum follow-up of 5 years, they reported on 65 patients with clinically mobile rectal tumours located below the peritoneal reflection, <4 cm in size and occupying 40% or less of the rectal circumference, who would have required abdominoperineal resection if undergoing radical surgery. These 65 patients instead underwent sphincter-sparing local excision (called Category 1).

Protocol surgery was en bloc resection of tumour (by trans-anal, trans-coccygeal or trans-sacral approach), followed by either post-operative observation or radiotherapy +/-chemotherapy, based on pathologic criteria. Patients with tumours less than 3 cm in diameter, well- or moderately-differentiated, with absence of lymphatic or vascular space invasion, surgical microscopic margin > 3 mm and a normal post-op CEA were deemed to have “low-risk” disease (Category 2) and were observed. This group comprised 14/65 (22%) of the entire group. Patients with tumours not meeting these criteria were deemed “high or intermediate risk” (Categories 3 and 4). These patients comprised 51/65 (78%) of the study group and were treated with radiotherapy with or without chemotherapy.

Although this study was not randomised and therefore does not adequately address the question of the utility of radiotherapy, it does provide some guidance in specifying the criteria that increase the risk of local recurrence. The proportions of patients who are assigned to various risk groups could be calculated, and it was possible to determine the proportion of patients undergoing local excision for whom radiotherapy might be recommended.

The NHMRC Colorectal treatment guidelines (95) mention very little about the criteria for consideration of post-operative radiotherapy following local excision. The guidelines recommended local excision only in patients who correspond to those deemed as Category 2 in the RTOG study. The guidelines made no mention of patients in Category 3 or 4, and whether post-operative radiotherapy was appropriate in those cases. We followed a treatment rationale based on the RTOG study (15) in which the patients with Category 2 disease or “favourable” histopathology should not receive adjuvant radiotherapy, but may be considered for radiotherapy if local recurrence occurs. Patients with Category 3 or 4 disease or “less favourable” histopathology following local excision should be considered for adjuvant radiotherapy. This included all T2N0M0 patients who undergo local excision.

7. Local recurrence rate in patients in stage T2N0M0 treated with surgery alone

Bethune et al. (104) reported that 9/64 (14%) patients undergoing radical surgery for T2N0M0 disease developed a local recurrence. Other surgical series have not reported on local recurrence rates according to stage or have not broken Stage B data into the various sub-stages.

8. Incidence of local pelvic symptoms in patients with metastatic disease

The NHRMRC guidelines for the management of colorectal cancer (95) state that radiotherapy may be used for the treatment of symptomatic pelvic disease. The indications for palliative radiotherapy would be pain, bleeding or partial obstruction. No published data sources provide proportion data for this population of patients. The South Western Sydney Colorectal Tumour Group have recently completed a Patterns of Care study on all colorectal patients in South West Sydney 1997-2001 (A.Berthelsen, personal communication). In this study, 32 patients had metastatic disease at diagnosis. Of that group, 5/32 (16%) had local pelvic symptoms which required palliative radiotherapy of the primary disease site.

9. Radiotherapy for brain metastases

The Level II evidence for radiotherapy of brain metastases was based on randomised trials that have shown improvements in the quality of life when patients receive radiotherapy, although there are no randomised trials of brain radiotherapy versus no brain radiotherapy. The Level II allocation of evidence was derived directly from the NHMRC Colorectal treatment guidelines.

Information on the incidence of brain metastases in patients presenting with metastatic colorectal cancer has been difficult to obtain. Most studies report on brain metastases from multiple tumour origins, or from the colon and the rectum together, or on the overall incidence of brain metastases in rectal cancer without reference to the stage at presentation. Patanaphan and Salazar (106) in a retrospective review reported that 2% of all patients with metastatic colorectal cancer develop symptomatic brain metastases.

10. Radiotherapy for bone metastases

Talbot et al (107) reviewed 4000 patients with rectal cancer from 1943 - 1986 and reported that 48 patients had bone metastases. All of these patients were diagnosed with symptomatic bone metastases (rather than undergoing screening for the presence of asymptomatic bone metastases). Therefore, it would be appropriate to consider radiotherapy in the total proportion of patients in this series with bone metastases. Besbeas et al. (108) reported an osseous metastasis rate for rectal cancer of 9%. The larger study from Talbot et al. was used as the data source.

The Swedish Council on Technology Assessment in Health Care (SBU) (120) states that palliative radiotherapy for bone metastases is both clinically effective and economically justified and is “the treatment method of choice in patients who have pain localised to a skeletal region with a verified metastatic tumour”. Although the NHMRC guidelines recommend radiotherapy for bone metastases, no guidelines report specific indications for radiotherapy in the treatment of bone metastases. For the purpose of this analysis, we assume that all patients with bone pain should ideally receive radiotherapy. This may over-represent the situation although no quality of life comparisons have ever been performed to prove that radiotherapy is inferior to other treatment modalities in palliating pain. This overestimate may be counteracted to some extent by our assumption that patients with visceral metastases never receive radiotherapy, although it is likely that some visceral metastases will in fact receive radiotherapy.

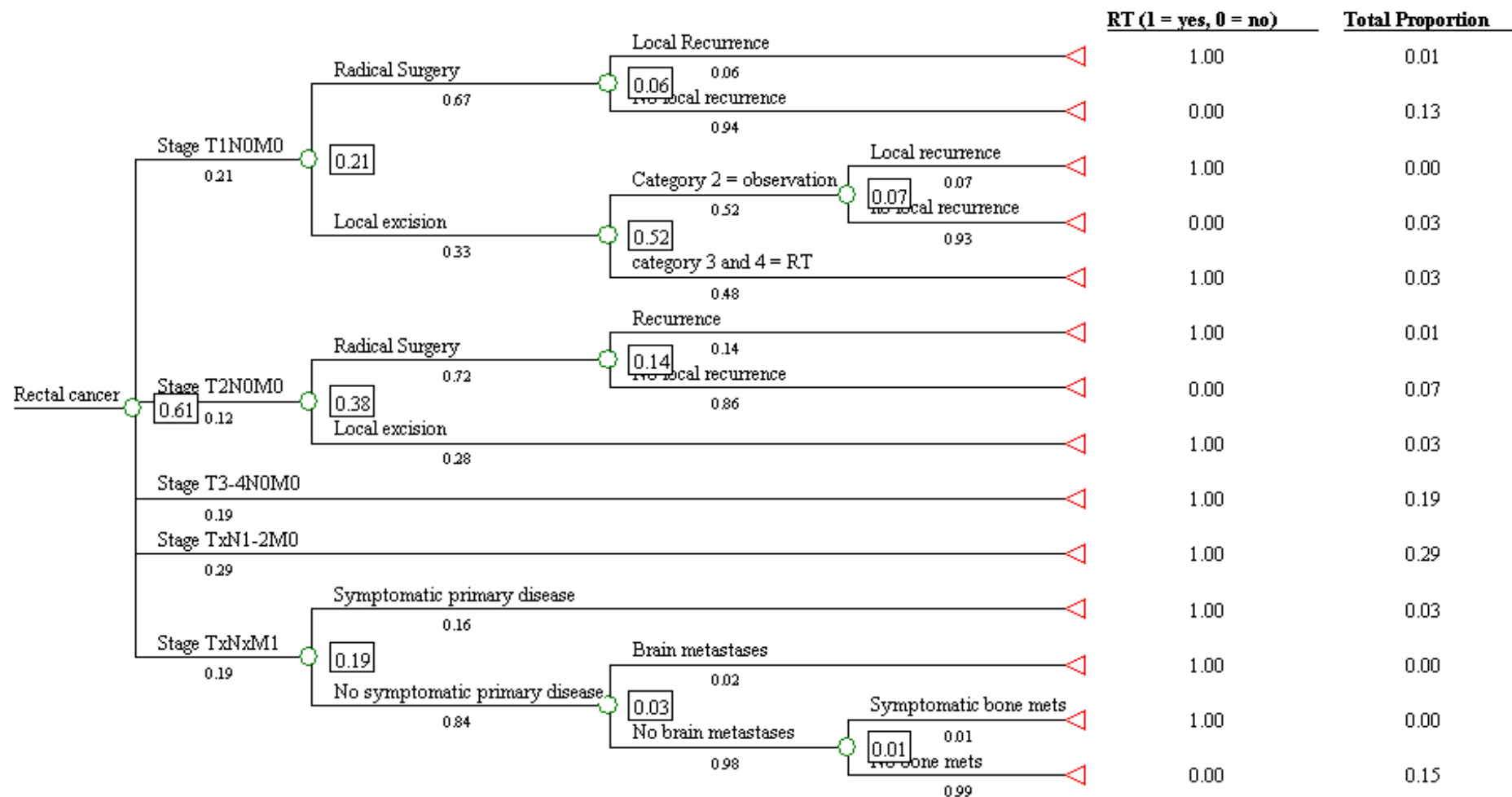
The Level I evidence quoted for radiotherapy for bone metastases is based on the randomised controlled trials and systematic reviews of bone radiotherapy for the palliation of pain (6) (121) (7) (8) (122) (123) (124). Although these studies did not assess the overall efficacy of radiotherapy when compared with no radiotherapy, they demonstrated that the vast proportion (60-80%) of patients receive palliative benefit with radiation and that a dose response was evident. The evidence is therefore acknowledged as Level I in the NHMRC Colorectal guidelines (95).

Note: The rectal cancer decision tree included local recurrence as the only indication for radiotherapy when patients with Stages T1-2N0M0 rectal cancer relapse, i.e. it did not consider the possibility of distant recurrence. (Incidence figures could not be found for this small subset). This was a practical decision for the purposes of constructing a decision tree, as the incidence of metastatic disease in this group is small. The incidence of that metastatic group then developing brain or bone metastases was extremely small and was unlikely to significantly affect the overall RT utilisation rate.

Optimal radiotherapy utilisation rate and sensitivity analysis

Using the proportions as described in Table 2, the calculation of the proportion of ALL patients with rectal cancer in whom at least one course of radiotherapy is indicated in the overall treatment course, according to the best available guideline evidence, was calculated as 0.61 or 61%. Since rectal cancer represents 0.05 of all cancers, rectal cancer patients for whom radiotherapy was recommended represent $0.05 \times 0.61 = 0.0305$ or 3.0 % of all cancer patients.

In terms of the incidence data, no data were found to be inconsistent or contradictory. Where more than one source of data was available to provide incidence information, it was found that the data did not vary significantly. As a consequence, sensitivity analysis was not required for the rectal cancer radiotherapy utilisation tree.



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Prostate Cancer

Table 1: Prostate Cancer. Indications for radiotherapy – Levels and sources of evidence

Outcome No.	Clinical Scenario	Treatment Indicated	Level of Evidence	References	Notes	Proportion of all prostate cancer patients
1	Stage T1N0M0, good PS, preference - surgery, positive margins	RT	IV	<ul style="list-style-type: none"> National Cancer Institute PDQ statement on prostate cancer (1) NCCN Clinical Practice guidelines (2) 	2,3	0.02
2	Stage T1N0M0, good PS, preference - surgery, negative margins, local recurrence/ PSA rise with no bone metastases	RT	IV	<ul style="list-style-type: none"> National Cancer Institute PDQ statement on prostate cancer (1) 	4	0.01
4	Stage T1N0M0, good PS, preference - surgery, negative margins, no local recurrence, distant relapse with symptomatic progressive disease	RT	I	<ul style="list-style-type: none"> National Cancer Institute PDQ statement on prostate cancer (1) NCCN Clinical Practice guidelines (2) 	5	0.01

Outcome No.	Clinical Scenario	Treatment Indicated	Level of Evidence	References	Notes	Proportion of all prostate cancer patients
6	Stage T1N0M0, good PS, preference - RT	RT	IV	<ul style="list-style-type: none"> ▪ National Cancer Institute PDQ statement on prostate cancer (1) ▪ NCCN Clinical Practice guidelines (2) ▪ Royal College of Radiologists/British Association of Urological Surgeons COIN guidelines (3) 	1	0.04
7	Stage T1N0M0, good PS, preference -observation, progressive symptomatic disease following hormonal therapy	RT	I	<ul style="list-style-type: none"> ▪ National Cancer Institute PDQ statement on prostate cancer (1) 	6	<0.01
9	Stage T1N0M0, poor PS, hormonal Rx, progressive symptomatic disease	RT	I	<ul style="list-style-type: none"> ▪ National Cancer Institute PDQ statement on prostate cancer (1) 	5	<0.01

Outcome No.	Clinical Scenario	Treatment Indicated	Level of Evidence	References	Notes	Proportion of all prostate cancer patients
11	Stage T2N0M0, good PS, preference - surgery, positive margins	RT	IV	<ul style="list-style-type: none"> National Cancer Institute PDQ statement on prostate cancer (1) NCCN Clinical Practice guidelines (2) 	2, 3	0.07
12	Stage T2N0M0, good PS, preference - surgery, negative margins, local recurrence/ PSA rise with no bone metastases	RT	IV	<ul style="list-style-type: none"> National Cancer Institute PDQ statement on prostate cancer (1) American Society of Therapeutic Radiation Oncology (ASTRO) guidelines (4) 	3	0.02
14	Stage T2N0M0, good PS, preference - surgery, negative margins, no local recurrence, distant relapse with symptomatic progressive disease	RT	I	<ul style="list-style-type: none"> National Cancer Institute PDQ statement on prostate cancer (1) NCCN Clinical Practice guidelines (2) 	7	0.01

Outcome No.	Clinical Scenario	Treatment Indicated	Level of Evidence	References	Notes	Proportion of all prostate cancer patients
16	Stage T2N0M0, good PS, preference -radiotherapy	RT	IV	<ul style="list-style-type: none"> National Cancer Institute PDQ statement on prostate cancer (1) NCCN Clinical Practice guidelines (2) Royal College of Radiologists/ British Association of Urological Surgeons (3) 	1	0.10
17	Stage T2N0M0, good PS, observation, progressive local or distant symptoms warranting radiotherapy	RT	I	<ul style="list-style-type: none"> National Cancer Institute PDQ statement on prostate cancer (1) 	6	0.01
19	Stage T2N0M0, poor PS, hormonal Rx, progressive symptomatic disease	RT	I	<ul style="list-style-type: none"> National Cancer Institute PDQ statement on prostate cancer (1) NCCN Clinical Practice guidelines (2) 	5	0.01
21	Stage T3-4N0M0, good PS	RT	III	<ul style="list-style-type: none"> National Cancer Institute PDQ statement on prostate cancer (1) 	2	0.10

Outcome No.	Clinical Scenario	Treatment Indicated	Level of Evidence	References	Notes	Proportion of all prostate cancer patients
22	Stage T3-4N0M0, poor PS, hormonal therapy, progressive symptomatic disease	RT	I	<ul style="list-style-type: none"> National Cancer Institute PDQ statement on prostate cancer (1) NCCN Clinical Practice guidelines (2) 	5	<0.01
24	Stage TxN+M0 or TxNxM1, hormonal therapy, symptomatic progression	RT	I	<ul style="list-style-type: none"> National Cancer Institute PDQ statement on prostate cancer (1) NCCN Clinical Practice guidelines (2) 	5	0.20
Total proportion of patients with prostate cancer in whom radiotherapy is recommended						0.60 (60%)
Total proportion of all cancer patients = 0.60 x 0.12 =						0.072 (7.2 %)
<u>Abbreviations</u> PS – Performance Status PSA – Prostate Specific Antigen RT - Radiotherapy NCCN - National Comprehensive Cancer Network						

Table 2: Prostate cancer. The incidence of attributes used to define indications for radiotherapy

Key	Population or subpopulation of interest	Attribute	Proportion of populations with this attribute	Quality of information	References	Explanatory Notes
A	All registry cancers	Prostate cancer	0.12	α	AIHW (5)	1
B	All prostate cancer	Stage T1N0M0	0.19	ϵ	SA Hosp Registry (6)	1
C	Stage T1N0M0	Good PS	0.89	γ	Harlan et al (7)	2
D	Stage T1N0M0, good PS	Preference for Surgery	0.55	γ	Harlan et al (7)	1
E	Stage T1N0M0, good PS, surgery	Positive margins	0	γ	See explanatory note 3	3
			0.22		Pooled data (Table 4)	

Key	Population or subpopulation of interest	Attribute	Proportion of populations with this attribute	Quality of information	References	Explanatory Notes
F	Stage T1N0M0, good PS, surgery, negative margins	Local or PSA recurrence	0.18	ε	Quinn et al (8)	4
			0.17	ζ	Ohori et al. (9)	
			0.15	ζ	Pound et al. (10)	
			0.10	ζ	Babaian et al. (11)	
			0.12	ζ	Bentvelsen et al. (12)	
			0.22	ζ	Frazier et al. (13)	
			0.07	ζ	Obek et al. (14)	
G	Stage T1N0M0, good PS, surgery, negative margins, no local recurrence	Distant relapse	0.15	ζ	Zincke et al (15)	7
			0.04	ζ	Bentvelsen et al (12)	
H	Stage T1N0M0, good PS, surgery, negative margins, no local recurrence, distant relapse	Symptomatic progressive disease	0.70	θ	Sarosdy et al. (16)	5
I	Stage T1N0M0, good PS	Preference - Radiotherapy	0.25	γ	Harlan et al (7).	1

Key	Population or subpopulation of interest	Attribute	Proportion of populations with this attribute	Quality of information	References	Explanatory Notes
J	Stage T1N0M0, good PS	Preference - Observation	0.2	γ	Harlan et al (7)	1
K	Stage T1N0M0, good PS, observation, hormone therapy	Progressive symptomatic disease	0.07	ϵ	Koppie et al. (17)	6
			0.10	ζ	Adolfsson et al. (18)	
			0.07	ζ	Epstein et al. (19)	
L	Stage T1N0M0, poor PS, hormonal therapy	Progressive symptomatic disease	0.10	ζ	Adolfsson et al. (18)	6
M	All prostate cancer	Stage T2N0M0	0.42	ϵ	SA Hosp Registry (6)	1
N	Stage T2N0M0	Good PS	0.89	γ	Harlan et al. (7)	2
O	Stage T2N0M0, good PS	Surgery	0.52	γ	Harlan et al. (7)	1
P	Stage T2N0M0, good PS, surgery	Positive margins	0.35	γ	Pooled data (see Table 4)	3

Key	Population or subpopulation of interest	Attribute	Proportion of populations with this attribute	Quality of information	References	Explanatory Notes
Q	Stage T2N0M0, good PS, surgery, negative margins	Local or PSA recurrence	0.18	ε	Quinn et al (8)	4
			0.17	ζ	Ohori et al. (9)	
			0.15	ζ	Pound et al. (10)	
			0.12	ζ	Bentvelsen et al. (12)	
			0.22	ζ	Frazier et al.(13)	
			0.17	ζ	Babaian et al. (11)	
R	Stage T2N0M0, good PS, surgery, negative margins, no local recurrence	Distant relapse	0.15	ζ	Zincke et al (15).	7
			0.04	ζ	Bentvelsen et al. (12)	
S	Stage T2N0M0, good PS, surgery, negative margins, no local recurrence, distant relapse	Symptomatic progressive disease	0.70	θ	Sarosdy et al. (16)	5
T	Stage T2N0M0, good PS	Radiotherapy	0.48	γ	Harlan et al. (7)	1
U	Stage T2N0M0, good PS	Preference - Observation	0.20	γ	Harlan et al. (7)	1

Key	Population or subpopulation of interest	Attribute	Proportion of populations with this attribute	Quality of information	References	Explanatory Notes
V	Stage T2N0M0, good PS, observation, hormone therapy	Progressive symptomatic disease	0.07	ϵ	Koppie et al. (17)	6
			0.10	ζ	Adolfsson et al. (18)	
			0.07	ζ	Epstein et al. (19)	
W	Stage T2N0M0, poor PS	Progressive symptomatic disease	0.10	ζ	Adolfsson et al. (18)	6
X	All prostate cancer	Stage T3-4N0M0I	0.11	ϵ	SA Hosp Registry (6)	1
Y	Stage T3-4N0M0	Good PS	0.89	γ	Harlan et al. (7)	2
Z	Stage T3-4N0M0, poor PS, hormonal therapy	Progressive symptomatic disease	0.12	ζ	Adolfsson et al. (18)	6
ZZ	All prostate cancer	Stage TxN+M0 or TxNxM1	0.28	ϵ	SA Hosp Registry (6)	1
ZZZ	Stage TxNM0 or TxNxM1	Progressive symptomatic disease	0.70	θ	Sarosdy et al. (16)	5

Abbreviations: PS – Performance Status
PSA – Prostate Specific Antigen

Prostate Cancer

Treatment Guidelines

Clinical practice guidelines for the management of prostate cancer have been published by the National Cancer Institute (Physicians Data Query or PDQ statement on prostate cancer), the National Comprehensive Cancer Network (NCCN), the Royal College of Radiologists/British Association of Urological Surgeons COIN (3) and the American Society of Therapeutic Radiation Oncology (ASTRO) (4).

Indications for Radiotherapy

Based on guideline recommendations, radiotherapy in prostate cancer is indicated in the following clinical situations:

- Early prostate cancer patients with good performance status who choose to undergo radical external radiotherapy
- Early prostate cancer patients with good performance status who choose to undergo radical surgery and have positive margins
- Early prostate cancer patients with good performance status who choose to undergo radical surgery and have negative margins but develop either a local recurrence or a PSA rise with no bone metastases
- Locally advanced prostate cancer with good performance status
- Patients of poor performance status or with nodal or distant metastatic disease, with symptomatic local disease following hormonal therapy
- Patients presenting with any stage of prostate cancer who develop symptomatic bone metastases
- Issues where radiotherapy were considered controversial were in the treatment of a PSA relapse after surgery, as adjuvant therapy post-prostatectomy in the presence of positive margins. The explanatory notes below discuss the ways in which these controversies have been addressed.

The construction of a treatment decision tree for early prostate cancer posed one of the biggest problems in this project. The management options for early prostate cancers include no treatment (watchful waiting), radical prostatectomy (+/- post-operative radiotherapy), radical external radiotherapy (+/- brachytherapy boost) and brachytherapy alone. There is no conclusive evidence to prove that any one of these options is superior to the others.

Published treatment guidelines reflect this lack of data. Any comparison of the therapeutic options based on current published series is flawed because of the selection factors affecting the choice of treatment and the lack of well-designed randomised clinical trials. Randomised studies to date have not identified the supremacy of one treatment over the alternatives. Therefore, radiotherapy could be considered appropriate treatment for ALL early prostate cancer patients provided that they have good performance status and life expectancy. However, other treatment alternatives may be equally appropriate (20) and therefore, the treatment choice lies with the patient.

Explanatory Notes for Tables 1 and 2

1. Radical treatment for localised disease

In this study, wherever possible, we have tried to avoid using data from studies that report on actual radiotherapy utilisation rates because of the inherent biases in these studies. For instance, treatment may depend heavily upon the patient's access to radiotherapy advice and treatment resources and also the way that the choice was discussed with the patient and who provided the information. A proportion of patients with early prostate cancer referred to urologists will not have been referred to a radiation oncologist before making a treatment decision (21) (22). Patient choice may rely upon the urologist's views and description of radiotherapy (7). The type and amount of information that the specialist believes is relevant to aid decision-making has been shown to vary greatly between specialists (23).

Since there is no available data on optimal treatment for early prostate cancer, we have assessed patient choice by using actual radiotherapy utilisation data. Sensitivity analysis was then performed to derive the maximum and minimum possible proportion of patients for whom radiotherapy would be considered appropriate treatment. Sensitivity analysis of these extremes will allow an estimate of the influence these variations would have on the overall radiotherapy utilisation rate.

The aim of this study is to estimate optimal radiotherapy utilisation for external beam radiotherapy only and therefore the use of brachytherapy for prostate cancer is not included. However, it needs to be recognised that brachytherapy has a role to play in the management of prostate cancer and needs to be included in the planning of radiotherapy services.

Therefore, treatment alternatives considered for early prostate cancer were conservative therapy (either observation or hormonal therapy), radical surgery and radical radiotherapy.

Actual practice – radical prostatectomy versus radiotherapy versus observation versus hormone therapy

The incidence of prostate cancer by stage provided in the tree and Table 2 are from the South Australian Hospital-Based Cancer Registry (6) and are representative of the rest of Australia and New Zealand.

Radical therapy (either radiotherapy or surgery) would only be contemplated when the patient is fit enough to undergo therapy, has a life expectancy sufficiently long and is free of serious co-morbidities that may compromise the life expectancy. The studies that describe the actual utilisation rates of surgery, radiotherapy, hormonal therapy and observation are summarised in Table 3. These reports are either large population-based databases of prostate cancer management or institutional experiences.

The decision tree ideally should have multiple branch points based on grade, performance status, age etc to determine the group of patients who, according to the best available evidence, should not receive radical treatment.

Insufficient data were presented in the studies with an observation treatment arm to determine the reason why observation was chosen in the population described. As this data is lacking it was decided that the branch point for those with a bad prognosis be grouped into “poor performance status”. See further discussion on performance status in explanatory note 2.

The best and most recent data on utilisation rates for radiotherapy, surgery and observation in early prostate cancer was provided by Harlan et al (7) who reported on a large well-defined population based study in the United States. It reports on 3073 patients with T1-2N0M0 from the Prostate Cancer Outcomes Study (PCOS) treated 1/10/94-31/10/95. Radical prostatectomy (RP) = 47.6%, Radiotherapy (RT) = 23.4%, Hormones = 10.5%, watchful waiting 18.5%. Patients having hormone therapy should be excluded as they are likely to have had “poor performance status”. For the remaining patients, the treatment figures by stage are: T1 – RP = 55%, RT = 25% and observation = 20%. T2 – RP= 52%, XRT = 28%, observation = 20%. The disadvantage of using this data is that American practice appears to favour more surgery for patients as opposed to practice in Europe and Australasia.

Two Australian sources of data were considered before deciding upon Harlan et al (7) as the benchmark source of data. The SA Hospital Registry data (6) reports on 1081 patients diagnosed with prostate cancer in 1990-1997. Overall, 72% of all prostate cancer patients had surgery as part of their primary treatment, but there is no breakdown of the surgical data so as to separate radical surgery such as radical prostatectomy from other surgery such as orchidectomy. Frydenberg et al. (24) reported on 1993 Victorian patterns of care for prostate cancer. However, this study was conducted prior to the widespread use of radical prostatectomy or radical radiotherapy as curative treatment for prostate cancer. Australian Health Insurance Commission data shows that significant increases in the utilisation of both radical radiotherapy and radical prostatectomy occurred after this study reflecting that this study is too old to be of practical use.

Table 3 summarises the radical treatment data that were considered for this report.

Table 3: Summary of radical treatment data

<u>Reference</u>	<i>Data Source</i>	<i>Years</i>	<i>No.</i>	<i>T detail</i>	<i>RP (%)</i>	<i>XRT (%)</i>	<i>WW or hormones (%)</i>	<i>criticisms</i>
Harlan et al. (7)	PCOS	1994-1995	3073	All T1-2N0M0	48 T1=55 T2=52	23 T1=25 T2=27	29 T1=20 T2=20	10% had hormones
Harlan et al. (25)	SEER	1984-1991	67 693	Local/ regional	32	30	38	25% regional, long study period
Potosky et al. (26)	PCOS	1994	1591	Age 55-74	73	27		No men >74
Shaw et al (27)	SEER	1989-1996	71 249	All T1-2 patients	52	48		
SA Hospitals registry (6)	SA-HBCR	1990-1997	1081	Stage T1N0M0 II III IV	89 63 76 71	16 36 27 21	4 8 4 5	Sx. Includes TURP and orchidectomy
Johansson et al. (28)	Orebro community	1977-1984	648	M0			47	Large deferred treatment group. Very old study. Pre PSA
Demark-W et al. (21)	N. Carolina community		240	50-74				Age bias
Yan et al. (29)	Washington PSA screening	1989-1998	1809		79	12	8	Screening only

Frydenberg et al. (24)	Victorian patterns of care	1993	1048	all	13.5	11.2	35.6	Others (39.8%) = hormones
Mettlin et al. (30)	US National Cancer database	1992+ 1995	176 316	all	34	26	22	Others + hormones or implant No breakdown of data by stage
Brandeis et al.(31)	US Medicare costs	1993-1996	10 107	All radical patients	35.6	64.4	0	No WW. All stages with no stage breakdown
Koppie et al. (17)	CaPSURE	?	4 459	All prostate cancers			10.6	No breakdown of the radical treatments
Chamberlain et al. (32)	South Thames	1992	842	"localised"		16%		

Abbreviations

PCOS – Prostate Cancer Outcomes Study

SEER – Surveillance, Epidemiology and End Results

SA-HBCR – South Australian- Hospital Based Cancer Registry

CaPSURE – Cancer of the Prostate Strategic Urological Research Endeavour.

Sx – surgery

WW – watchful waiting

RP- radical prostatectomy

XRT – radical radiotherapy

PSA – Prostate specific antigen

Patient-choice studies

A number of studies have assessed patient choice in the management of localised prostate cancer. These studies are summarised below. These studies may reflect patient choice as the information given to patients was controlled and tested to ensure “adequacy” as defined by the study protocols. However, these studies are based on hypothetical scenarios in that the trial subjects did not have prostate cancer. Studies have previously demonstrated that the hypothetical situation does not necessarily reflect real practice (17).

- Mazur and Merz (33) reported on 148 patients in a veteran’s general medical clinic who did not have prostate cancer. A hypothetical scenario of early low grade prostate cancer was described and the therapeutic options of surgery or watchful waiting discussed including details on possible side effects. 43% preferred surgery even when the scenario included no expected survival benefit. This percentage dropped to 26% when the life expectancy benefit of surgery was 0-10 years and 27% preferred watchful waiting when the surgical survival benefit was >10 years. Five percent preferred the clinician making the choice and 1.4% preferred radiation despite the fact that this wasn’t offered. The proportion of patients requesting watchful waiting increased with increasing age.
- Feldman-Stewart et al. (34) reported on the testing of a decision aid to assist patients to come to a management decision for treatment for prostate cancer. 69 healthy Canadian men were used to test the decision aid instrument (ages 50-83). 44% indicated a preference for observation, 17% radiotherapy, 12% surgery and 25% remained undecided.
- O’Rourke (22) reported on 18 newly diagnosed prostate cancer patients and their partners in a clinic in North Carolina where the decision process was observed and described. These were not structured interviews and the information was provided exclusively by the urologist to most patients. 12/18 chose surgery, 5 chose radiotherapy and 1 observation.

Summary of the modelling of management for early stage prostate cancer

After consideration of all the possible data that could be used to model early prostate cancer management it was decided to use the data of Harlan et al (7) because this was the most recent and comprehensive information on actual utilisation rates. Sensitivity analysis was then undertaken to model the possible extremes of varying the surgical and radiotherapy proportion and keeping the observation proportion constant (it is not possible to vary 3 variables at the same time with the software being used). A **maximum radiotherapy utilisation** model was assumed to have the treatment proportions of surgery to equal 0.1, radiotherapy 0.7 and observation 0.2 for stages T1-2N0M0. For a **maximum surgery utilisation**, surgery was modelled at 0.7, radiotherapy 0.1 and observation 0.2. It is highly likely that

the optimal radiotherapy utilisation will lie between these 2 extremes (see sensitivity analysis section below).

2. Performance status

For early stage disease the decision to proceed with radical treatment (radical prostatectomy or radical radiation) will largely depend upon the performance status of the patient and his life expectancy. The most comprehensive data comes from the U.S. PCOS reported by Harlan et al. (7). They reported that of 3073 T1-2N0M0 prostate cancer patients registered, 89% had a performance status of 0-1, 6% had a score of 2 and 5% >2. No distribution of performance status by stage was provided. For the purposes of the decision tree it was assumed that the performance status proportions would be similar for all Stages TxN0M0 as the age range would be the same and the vast majority of patients with non-metastatic prostate cancer are unlikely to have cancer symptoms that alter their overall performance status.

A decision to treat early prostate cancer in a non-radical manner (with either observation or hormonal therapy) is not only based on performance status but also on factors such as co-morbidities, Gleason score, PSA etc. However, the studies identified did not adequately breakdown these other factors by stage in a manner that could be used in the decision tree. Personal communication with a number of prostate cancer experts suggested that a poor performance status or poor life expectancy of 10% would be a reasonable estimate.

For good performance Stage T3-4N0M0 patients, radical radiotherapy is recommended according to the National Cancer Institute PDQ guidelines (1). It might be argued that the decision whether to treat radically will be based also on the PSA level, Gleason grade etc. However, studies from Pilepich et al., (35) Roach et al (36) Hanks et al. (37) , Lawton et al. (38) and Kattan et al. (39) show that there are long term survivors for Stage T3-4N0M0 patients even when other adverse prognostic features exist. Neo-adjuvant hormone therapy in addition to radiotherapy has been shown to be of benefit even in the presence of adverse pathologic or clinical features. Therefore, according to evidence, it would be reasonable to consider all good performance status Stage T3-4N0M0 patients for radiotherapy. In addition, the PDQ guidelines do not stipulate a PSA level, Gleason score or any other adverse prognostic feature to totally exclude them from radiotherapy.

3. Post surgery – positive margins, adjuvant radiotherapy and recurrence rates with negative margins

Guidelines recommend that radiotherapy should be considered when surgical margins are positive following radical prostatectomy (1). This is because there are higher local recurrence rates reported for margin positive disease when compared with margin negative disease (40) (41) (42) (43) (44) (45) (46) (47) (48) (49) (50) (51).

However, the standard use of post-operative radiotherapy for positive margins remains contentious. Both radiotherapy and observation are currently considered acceptable management options. In Australia, a randomised trial of radiotherapy versus observation for positive margins was recently closed early without achieving the expected recruitment rates.

Although no randomised studies have been published to assess the benefit of adjuvant therapy, failure to achieve local control almost certainly impacts on survival. Anscher et al (42) reported that 37.5% of patients with local relapse develop metastatic disease versus 7% without local relapse.

As no definitive data currently exists to adequately answer the question, it was considered reasonable in the decision tree to offer radiotherapy to ALL patients with positive margins due to their significantly increased risk of local failure. However due to the remaining uncertainty, sensitivity analysis was performed for the alternative scenario of patients with positive margins not receiving a routine recommendation for radiotherapy, but being given radiotherapy at relapse.

A literature review was undertaken to determine the proportion of cases with positive margins. Margin positivity rates in the literature varied widely (see Table 4). All studies reviewed are large retrospective studies with no one study being methodologically superior. The weighted mean rate of margin positivity for T1 and T2 according to the data presented in Table 4 was calculated.

Table 4 Margin positive rate

Reference	Study period	Number of patients	Positive margins (T1) %	Positive margins (T2) %	Overall positive margins (%)
Zincke et al, 1994 (15)	1966-1987	1143	12	12	---
Zincke et al, 1994 (52)	1966-1991	3170	16	25	---
Grossfeld 2000 (51)	1995-1998	1383	---	---	34
Kattan 1999 (53)	1983-1997	996	---	---	14.4
Kupelian 1997 (54)	1987-1993	423	36	48	---
Babaian 2001 (11)	1987-1993	265	---	---	20
Ohori 1995 (9)	1983-1993	478	12	18	16
Obek 1999 (14)	1991-1998	495	29	32	31

Alsikafi 1998 (55)	1995-1997	144	10	14	11
Ramos 1999 (56)	1988-1998	1620	20	26	---
Epstein 1996 (57)	1982-1990	721	---	---	16
Graefen 2002 (58)	NR	2465			33.7
Murphy 1994 (59)	1990	2122	---	---	23.2
Stamey 1999 (60)	1983-1992	379	---	---	29
Paulson 1990 (61)	1974-1989	441	---	---	28
Smitt 1996 (62)	1990-1993	100	---	---	30
Total			Weighted mean = 22%	Weighted mean = 35%	Weighted mean = 26%

NR= not reported

4. Local recurrence or PSA relapse and no evidence of metastatic disease following radical surgery with negative margins.

A significant proportion of patients who develop a PSA rise following surgery with no evidence of nodal or distant metastatic disease are salvageable with local radiotherapy (4) (1) (63) (64) (65) (66) (50) (67). A survey conducted by Ornstein et al (68) reported that of 4467 American Urological Association members (including 28% non-urologists), 81% felt that radiation therapy was the most appropriate therapy at PSA relapse or local relapse. We have assumed that anyone fit enough to have undergone their initial surgery would retain fitness at the time of diagnosis of local recurrence to be offered radiotherapy. The proportion of cancer patients with good performance status (95%) remains stable up to the age of 75 years (69). It is reasonable to assume that only a very small proportion of patients will have deteriorated sufficiently at the time of diagnosis of local recurrence to be ineligible for salvage radiotherapy.

A number of retrospective studies (11), (10), (13) have reported rates of recurrence for “early” stage disease. These reports do not express recurrence data according to initial stage and therefore the same recurrence proportions are used in the decision tree for initial Stage T1N0M0 and Stage T2N0M0 patients for patients with margin negative status following prostatectomy.

Quinn et al (8) reported on Australian post-prostatectomy data between 1986 and 1999. They studied 732 men treated with radical prostatectomy, of whom 18% developed a PSA or clinically detected local recurrence. Ohori et al. (9) reported a margin positivity rate of 78/478 (16%) in a retrospective review

1983-1993. For T1 the rate was 13/113 (12%) and T2 65/365 (18%). Of 28 patients with positive surgical margins who did not undergo adjuvant radiotherapy, 31% had recurrence. 17% of margin negative patients had evidence of progression. This is the best PSA recurrence data because they give relapse by margin status. The other data cited in Table 2 are similar to that of Ohori et al. and therefore no sensitivity analysis based on varying the proportion was necessary as it would not significantly affect on the overall optimal radiotherapy estimate.

5. Hormonal therapy – development of symptomatic local or metastatic disease despite androgen deprivation therapy

Sarosdy et al. (16) reported a trial of 813 patients randomised to goserelin and/or leuprolide in various combinations for patients with metastatic disease. All treatment arms had similar times to progression and rates of progression. Seventy percent of patients had progressed at a median follow-up of 160 weeks. This result is similar to that reported by Vogelzang et al (70) who randomised 283 patients to orchidectomy or goserelin. Fifty percent of patients had relapsed by 52 weeks and the median survival was 125 weeks suggesting that well over 50% of patients had relapsed prior to death. Although no breakdown of symptoms by site was provided, it is reasonable to assume that the vast majority of patients who developed progressive disease were considered for radiotherapy for progressive symptoms from bone metastases, local progression or nodal disease.

The impact of Samarium and other radio-nuclides has not been factored into this decision tree. This is because inadequate data were provided in the radio-nuclide studies to determine the overall symptomatic progression rate following treatment as most of these studies assess initial response and do not follow the patients for sufficiently long periods. It has been assumed that the vast majority of patients treated with radionuclides will ultimately progress and that palliative radiotherapy will be considered at some point in the remainder of the patient's lifetime.

6. Deferred hormonal therapy following observation and the subsequent need for radiotherapy

The proportion of patients requiring radiotherapy who have previously had conservative management for low grade early stage disease will depend upon the selection criteria of the study.

Koppie et al. (17) reported on the CaPSURE (The Cancer of the Prostate Strategic Urological Research Endeavour) database of 4458 men in a database collected from 29 community and academic urological practices regionally throughout the United States. 329 patients elected for watchful waiting. The patients that underwent watchful waiting were more likely to have had low grade and/or earlier stage and/or be of older age. Of the patients on watchful waiting, 39% developed progression warranting clinical intervention

(the vast majority receiving hormonal therapy). Of this entire group 22 patients (6.7%) had progression of disease to warrant radiotherapy. This represents actual practice rather than being based on guideline recommendations and has relatively short follow-up. However, very few studies provide sufficient information to determine the proportions for the decision points needed for the decision tree. Being an ongoing database, with time further patients will progress and require radiotherapy so this estimate may under-represent the recommended proportion requiring radiotherapy.

Adolfsson et al. (18) reported on 172 patients with T1-3NxM0 prostate cancer between 1972-1982 in Sweden treated with watchful waiting. At progression (either local progression on digital rectal examination or the development of distant metastatic disease) most patients received hormone treatment. The mean follow up period was 80 months, which might be criticised as being too short to provide an accurate estimate. 58% of patients had developed local progression and 19% distant progression. 52% of patients had received orchidectomy for progressive disease. Of the total group, 18 patients underwent radiotherapy for symptomatic progression (10.4%). For the 122 patients who had T1-2NxM0 disease, 12 patients (9.8%) received radiotherapy. For T3 6/50 patients had radiotherapy (12%). These estimates also reflect actual practice rather than treatment given according to guideline-based evidence for radiotherapy. Most surveillance studies have not given a breakdown of the recurrences according to site of recurrence. The relatively short follow-up in most studies would suggest that the reported proportion of patients who receive radiotherapy is an under-estimate as the proportion requiring radiotherapy would increase with increasing follow-up.

Epstein et al. (19) reported on 94 men diagnosed with early prostate cancer and treated conservatively. Of these men, 26 died of other diseases without evidence of progressive prostate cancer, 42 were alive and well without evidence of progression at a minimum follow up of 8 years, 18 alive without progression at 4-8 years follow up and 8 had evidence of progression. The average interval from diagnosis to progression was 7 years. Six died of prostate cancer at an average interval from progression of 2 years. All had extensive stage disease at death suggesting that they all had further progression following hormonal therapy. No report of radiotherapy utilisation was made. If we assume all 6 patients required radiotherapy due to progressive bone disease, plus the one patient with progressive local disease (progressed to B2) then 7/94 patients (7.4%) required radiotherapy in this series.

Zietman et al. (71) reported on 199 men with T1-2 prostate cancer and PSA<20 ng/ml who elected for watchful waiting. The median follow up was 3.4 years and the median age was 71 years. Of the 37 men who died during the observation period, only 2 died of prostate cancer and only 6 underwent treatment suggesting that observation was the correct decision in almost all cases. A total of 64 patients (32%) underwent treatment either due to patient wish or evidence of progression biochemically or clinically. Radiotherapy was the treatment of choice in 46 (23% of entire population). This may under-represent the group where radiotherapy is considered reasonable as a further

8% of the entire population received androgen deprivation therapy and the reasons for this choice were not described. In addition, with longer follow up some of the remaining 98 patients may receive radiotherapy in the future.

Johansson (72) reported on 223 consecutive T1-2NxM0 treated by observation in Sweden. A total of 77 (34%) had progression with 49 (22%) having local progression only. Actual radiotherapy utilisation was not reported but the majority received hormonal therapy. However, with local disease alone it would have been equally reasonable to treat them with radiation.

A review article on the management of Stage A prostate cancer (73) suggests that the local relapse rate for observation alone ranges between 2 and 26%.

Due to the variation in the data sensitivity analysis was performed to assess the impact that the uncertainty in the data has on the overall radiotherapy utilization estimate. The data from Koppie et al. using a local recurrence of 7% was used in the decision tree as the best available epidemiological data for relapse and the effect of changing this variable between 7% and 26% was also performed (see sensitivity analysis).

7. Distant relapse following surgery

The vast majority of patients with distant relapse after definitive surgery would be initially treated with hormonal therapy at diagnosis of relapse. A proportion of these patients will not respond or will relapse at a later date and some symptoms would be alleviated with palliative radiotherapy.

- Zincke et al. (15) reported on 1143 patients treated with radical prostatectomy at the Mayo clinic between 1966 and 1987. This is a retrospective study. Age range = 38-79 years. Mean follow up is 9.7 years. Of the 1143 patients, 15% developed distant metastases.
- Bentvelsen et al. (12) reported on a retrospective review of 85 patients treated with prostatectomy and followed for 1-4 years. This estimate of recurrence may therefore be low as further relapses would be detected with longer duration of follow-up. 2 of 59 (4%) patients with negative margins had distant relapse.

Due to the concerns about the validity of both sets of data, both proportions were tested in sensitivity analysis for their overall effect on the optimal radiotherapy utilisation rate.

Optimal Radiotherapy Utilisation Rate

Using the proportions as described in Table 2, the calculation of the proportion of ALL patients with prostate cancer in whom at least one course of radiotherapy is recommended according to the best available guideline evidence is calculated as 60% of all patients with prostate cancer. As prostate cancer represents 12% of all cancers (AIHW data) (1), the group of prostate cancer patients who should ideally receive at least one course of radiotherapy

comprises 7.2% of all cancer patients. However, the limitations of this study are the lack of guideline evidence for superiority of any treatment modality for early stage disease and the lack of data on the possible benefit of treating margin positive disease. In addition, the decision tree design relied on a number of assumptions, they are:-

- That patients with varying stages of localised prostate cancer (T1-3N0M0) have a similar distribution of performance status,
- That the observation rate for good performance status patients with early prostate cancer is 20% based on Harlan et al. (If the observation rate is changed to 10%, the optimal radiotherapy utilisation rate increases from 60% to 65% of all patients with prostate cancer and increases the overall utilisation rate for all cancers from 7.2% to 7.8%),
- That patients with progressive symptomatic disease following hormones require radiotherapy (either for bone pain, symptomatic local disease or symptomatic nodal disease),
- That patients who relapse after prostatectomy and have not developed metastatic disease maintain sufficient performance status to warrant radiotherapy as salvage therapy (as no data exists on changing performance status with time),
- As strontium is not a curative therapy, all patients having strontium for bone pain will either ultimately fail strontium or have marrow toxicity precluding further strontium therapy and then require external beam radiotherapy for progressive bone symptoms.

Sensitivity Analysis

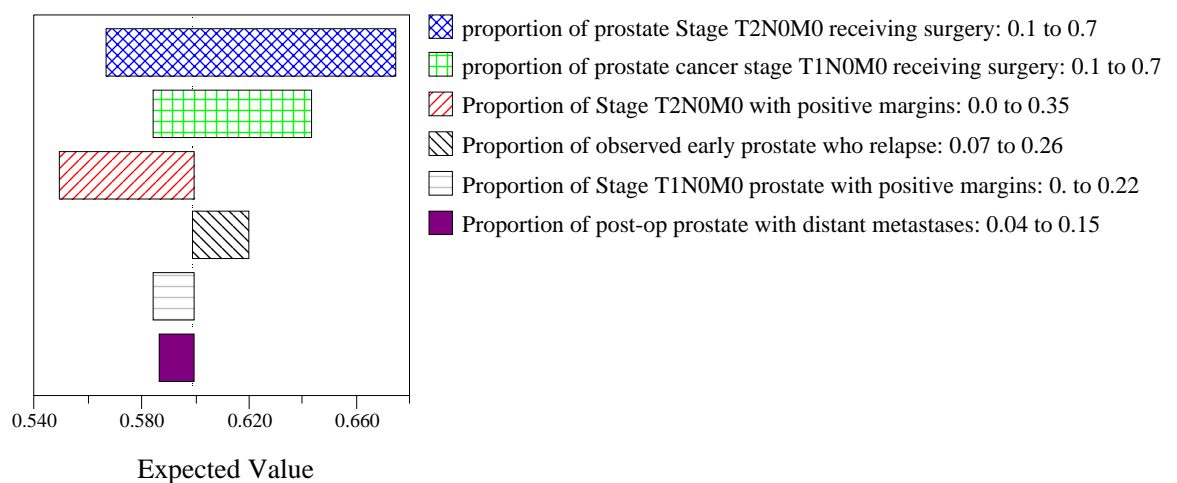
At several points of the decision tree there was uncertainty because of different proportions reported in the literature or due to lack of data to support a particular use of radiotherapy. These include the rate of surgery or radiotherapy for Stages I and II disease, the proportion of patients who develop distant metastases after prostatectomy and the uncertainty of the benefit for post-prostatectomy radiotherapy for margin positive disease.

- For the management of Stage I and II disease a “highest” and “lowest” case scenario were used to assess the extremes. For the lowest radiotherapy utilisation extreme Stages T1-2 had a surgery utilisation rate set at 0.7, observation at 0.2 and radiotherapy 0.1. For the highest radiotherapy utilisation, surgery was estimated at 0.1, radiotherapy 0.7 and observation 0.2. It is likely that the optimal rates lie within these extremes.
- In addition, modelling was performed between a scenario of not routinely irradiating margin positive patients (radiotherapy utilisation = 0) and routinely irradiating them (radiotherapy utilisation rate = margin positive rate for T1 and T2 patients), as discussed in explanatory note 3.
- The reported data on the proportion of early stage (T1-2N0M0) patients who undergo observation and later progress varied between 0.07 and 0.24.

To assess the impact that these uncertainties have on the overall estimate of the need for radiotherapy in all prostate cancers, a sensitivity analysis was performed for each of the variables. It is illustrated by the tornado diagram below. Once the decision trees for all tumours are completed, a tornado analysis will be performed whereby the impact each of these variables have on the overall estimate of the proportion of cancer patients needing radiotherapy will be examined.

The graphs below show that the optimal proportion of prostate cancer patients who should receive radiotherapy based on evidence and incidence of attributes for radiotherapy is between 55 and 67 %. The radiotherapy utilisation rate would decrease from 60% of prostate cancer patients to 54% if margin positive patients were not routinely irradiated unless they relapsed (an decrease in prostate radiotherapy utilisation rate of 1% for T1N0M0 and 5% for T2 N0M0).

Tornado Diagram at Prostate



Prostate brachytherapy

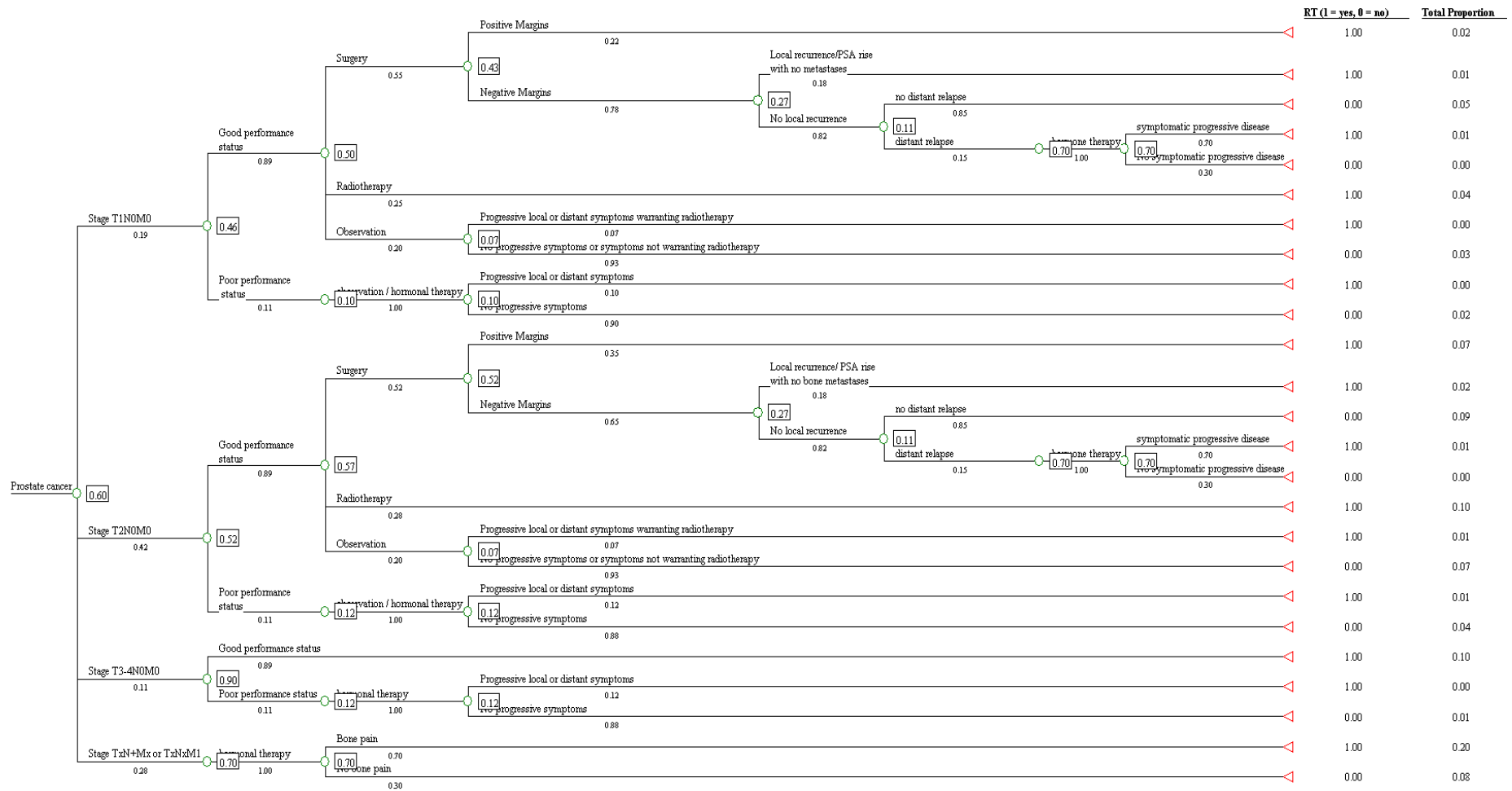
The aim of this project was to estimate the overall optimal radiotherapy utilisation for external beam radiotherapy only, and therefore brachytherapy was not considered in this study. Prostate brachytherapy has been described as an alternative treatment for localised prostate cancer, and excellent results have been achieved using radiotherapy seed implants alone in early stage prostate cancer. The role of prostate brachytherapy is yet to be fully established and there are currently no randomised data available indicating the proportion of patients that will derive a benefit from this treatment.

Any consideration of the overall resources required to provide adequate radiotherapy services for cancer will need to take into account external beam radiotherapy as well as the resources necessary for brachytherapy. In terms of the overall impact on radiotherapy, prostate brachytherapy may find a place in the management of patients who currently appear in the decision tree as undergoing surgery, external beam radiotherapy or observation.

Conclusion

The optimal radiotherapy utilisation rate is estimated to be 60% of all prostate cancer patients, which represents 7.2% of all cancer patients. It is likely that this is an under-estimate in that the studies are limited by short follow up compared to the natural history of the disease. It would be expected that with greater durations of follow-up the need for radiotherapy would increase particularly as other therapeutic options fail. The estimate is also limited by the lack of evidence to support a treatment decision for early disease as discussed above. The estimate used to calculate the optimal rate is a US study of actual utilisation rates and therefore may over-estimate the practice of prostatectomy compared to other places in the world.

It is likely that optimal radiotherapy utilisation falls between 55-67% of prostate cancer patients (6.6 - 8.0% of all cancer patients).



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Head & Neck Cancer

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

Outcome Number	Clinical Scenario	Treatment Indicated	Level of Evidence	References	Notes	Proportion of all Head & Neck cancers
1	Oral Cavity, Stages I-II, surgery, adverse pathology	Surgery + post-op RT	IV	<ul style="list-style-type: none"> • National Cancer Institute PDQ statement -lip and oral cavity cancer (1) • NCCN Guidelines on Head and Neck cancer (2) • BC Cancer Agency Guidelines – cancer of the oral cavity (3) • British Association of Otorhinolaryngologists Head & Neck surgeons (4) • Jones et al. (5) 	4	0.02
2	Oral Cavity, Stages I-II, surgery, no adverse pathology, locoregional recurrence	Surgery + post-op RT	IV	<ul style="list-style-type: none"> • National Cancer Institute PDQ statement -lip and oral cavity cancer (1) • BC Cancer Agency Guidelines – cancer of the oral cavity (3) 	4	0.03

Outcome Number	Clinical Scenario	Treatment Indicated	Level of Evidence	References	Notes	Proportion of all Head & Neck cancers
4	Oral Cavity, Stages I-II, radiotherapy	Radical RT	III	<ul style="list-style-type: none"> • National Cancer Institute PDQ statement -lip and oral cavity cancer (1) • NCCN Guidelines on Head and Neck cancer (2) • BC Cancer Agency Guidelines – cancer of the oral cavity (3) • British Association of Otorhinolaryngologists Head & Neck surgeons (4) 	4	0.01
5	Oral Cavity, Stages III-IV	Surgery + RT	III	<ul style="list-style-type: none"> • National Cancer Institute PDQ statement- lip and oral cavity cancer (1) • BC Cancer Agency Guidelines – cancer of the oral cavity (3) • NCCN Guidelines on Head and Neck cancer (2) • British Association of Otorhinolaryngologists Head & Neck surgeons (4) 	4	0.15

Outcome Number	Clinical Scenario	Treatment Indicated	Level of Evidence	References	Notes	Proportion of all Head & Neck cancers
6	Lip, cosmetically excisable, locoregional recurrence	RT +/- surgery	IV	<ul style="list-style-type: none"> National Cancer Institute PDQ statement - lip and oral cavity cancer (1) NCCN Guidelines on Head and Neck cancer (2) 	5	0.02
8	Lip, not cosmetically excisable	RT	III	<ul style="list-style-type: none"> National Cancer Institute PDQ statement -lip and oral cavity cancer (1) BC Cancer Agency guidelines – Cancer of the lip (6) NCCN Guidelines on Head and Neck cancer (2) British Association of Otorhinolaryngologists Head & Neck surgeons (4) 	5	0.06
9	Larynx, supraglottic, treated with conservative surgery, locoregional recurrence	RT	IV	<ul style="list-style-type: none"> National Cancer Institute PDQ statement - laryngeal cancer (7) NCCN Guidelines on Head and Neck cancer (2) 	6	0.00

Outcome Number	Clinical Scenario	Treatment Indicated	Level of Evidence	References	Notes	Proportion of all Head & Neck cancers
11	Larynx, supraglottic, not suitable for larynx preserving surgery	RT	III	<ul style="list-style-type: none"> • National Cancer Institute PDQ statement -laryngeal cancer (7) • NCCN Guidelines on Head and Neck cancer (2) • START treatment guidelines for larynx cancer (8) • BC Cancer Agency guidelines on the management of laryngeal cancer (9) • British Association of Otorhinolaryngologists Head & Neck surgeons (4) 	6	0.00
12	Larynx, glottic and subglottic, Stage I-II	RT	III	<ul style="list-style-type: none"> • National Cancer Institute PDQ statement -laryngeal cancer (7) • NCCN Guidelines on Head and Neck cancer (2) • START treatment guidelines for larynx cancer (8) • BC Cancer Agency guidelines in the management of laryngeal cancer (9) • British Association of Otorhinolaryngologists Head & Neck surgeons (4) 	6	0.10

Outcome Number	Clinical Scenario	Treatment Indicated	Level of Evidence	References	Notes	Proportion of all Head & Neck cancers
13	Larynx, glottic and subglottic, Stage III	chemoRT	III	<ul style="list-style-type: none"> National Cancer Institute PDQ statement - laryngeal cancer (7) NCCN Guidelines on Head and Neck cancer (2) START treatment guidelines for larynx cancer (8) 	6	0.04
14	Larynx, glottic and subglottic, Stage IV	Sx + post-op RT or RT +/- chemoRT	III	<ul style="list-style-type: none"> National Cancer Institute PDQ statement - laryngeal cancer (7) NCCN Guidelines on Head and Neck cancer (2) START treatment guidelines for larynx cancer (8) British Association of Otorhinolaryngologists Head & Neck surgeons (4) 	6	0.06
15	Oropharynx	RT +/- chemotherapy or Sx + RT	III	<ul style="list-style-type: none"> START guidelines – Cancer of the Oropharynx (10) BC Cancer Agency cancer management guidelines – carcinoma of the oropharynx (11) NCCN Guidelines on Head and Neck cancer (2) British Association of Otorhinolaryngologists Head & Neck surgeons (4) 	7	0.08

Outcome Number	Clinical Scenario	Treatment Indicated	Level of Evidence	References	Notes	Proportion of all Head & Neck cancers
16	Salivary gland, Stage I-II, low grade, node positive	Post-operative RT	IV	<ul style="list-style-type: none"> • START guidelines- salivary gland cancer (12) • NCCN Guidelines on Head and Neck cancer (2) • British Association of Otorhinolaryngologists Head & Neck surgeons (4) 	8	0.00
17	Salivary gland, Stage I-II, low grade, node negative, locoregional recurrence	Radical or post-operative RT	IV	<ul style="list-style-type: none"> • National Cancer Institute PDQ statement -salivary gland cancer (13) • NCCN Guidelines on Head and Neck cancer (2) • BC Cancer Agency guidelines for salivary gland tumours (14) 	8	0.00
19	Salivary gland, high grade	Post-operative RT	IV	<ul style="list-style-type: none"> • National Cancer Institute PDQ statement -salivary gland cancer (13) • NCCN Guidelines on Head and Neck cancer (2) • BC Cancer Agency guidelines for salivary gland tumours (14) • British Association of Otorhinolaryngologists Head & Neck surgeons (4) 	8	0.03

Outcome Number	Clinical Scenario	Treatment Indicated	Level of Evidence	References	Notes	Proportion of all Head & Neck cancers
20	Salivary gland, Stage III-IV	Post-operative RT	IV	<ul style="list-style-type: none"> National Cancer Institute PDQ statement - salivary gland cancer (13) NCCN Guidelines on Head and Neck cancer (2) BC Cancer Agency guidelines for salivary gland tumours (14) British Association of Otorhinolaryngologists Head & Neck surgeons (4) 	8	0.02
21	Hypopharynx	Radical or post-operative RT +/- chemotherapy	III	<ul style="list-style-type: none"> National Cancer Institute PDQ statement - hypopharyngeal cancer (15) NCCN Guidelines on Head and Neck cancer (2) BC Cancer Agency cancer management guidelines – carcinoma of the hypopharynx (16) British Association of Otorhinolaryngologists Head & Neck surgeons (4) 	9	0.05

Outcome Number	Clinical Scenario	Treatment Indicated	Level of Evidence	References	Notes	Proportion of all Head & Neck cancers
22	Paranasal sinus	Radical or post-operative RT	III	<ul style="list-style-type: none"> National Cancer Institute PDQ statement - paranasal sinus and nasal cavity cancer (17) NCCN Guidelines on Head and Neck cancer (2) British Association of Otorhinolaryngologists Head & Neck surgeons (4) 	10	0.05
23	Nasopharynx	ChemoRT or RT alone	III	<ul style="list-style-type: none"> National Cancer Institute PDQ statement - nasopharyngeal cancer (18) BC Cancer Agency cancer management guidelines – carcinoma of the nasopharynx (19) NCCN Guidelines on Head and Neck cancer (2) British Association of Otorhinolaryngologists Head & Neck surgeons (4) 	11	0.04

Outcome Number	Clinical Scenario	Treatment Indicated	Level of Evidence	References	Notes	Proportion of all Head & Neck cancers
24	Unknown primary, N1-2a, local or regional recurrence	RT alone or Sx + RT	IV	<ul style="list-style-type: none"> NCCN Guidelines on Head and Neck cancer (2) British Association of Otorhinolaryngologists Head & Neck surgeons (4) 	12	0.00
28	Unknown primary, N2b-N3	RT alone or Sx + RT	IV	<ul style="list-style-type: none"> National Cancer Institute PDQ statement - metastatic squamous neck cancer with occult primary (20) NCCN Guidelines on Head and Neck cancer (2) 	12	0.02
Proportion of head and neck cancer patients in whom radiotherapy is recommended						0.78
Total proportion of all cancer patients = 0.78 X 0.04 =						3.1%

Abbreviations: RT – radiotherapy Sx - surgery

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

Key	Population or sub-population of interest	Attribute	Proportion of population with this attribute	Quality of information	References	Notes
A	All registry cancers	Head and Neck cancers	0.04	α	AIHW (21)	1
B	All Head and Neck cancers	Oral cavity cancers	0.28	α	AIHW (21)	1,4
C	Oral cavity cancers	Stages I – II	0.45	β	SA Cancer Registry (22)	4
D	Oral cavity cancers, Stages I – II	Surgery	0.90	β	SA Cancer Registry (22)	4
E	Oral cavity cancers, Stages I – II, surgery	Adverse pathology	0.20	ζ	Jones (5)	4
F	Oral cavity cancers, Stages I – II, surgery, no adverse pathology	Locoregional recurrence	0.31	ζ	McGuirt et al (23)	4
G	All Head and Neck cancers	Lip cancer	0.22	α	AIHW (21)	5
H	Lip cancer	Cosmetically excisable	0.89	ζ	Zitsch et al. (24)	5
I	Lip cancer, cosmetically excisable	Locoregional recurrence	0.14 0.09	ζ ζ	Zitsch et al (24) Rowe et al (25)	5
J	All Head and Neck cancers	Cancer of the Larynx	0.20	α	AIHW (21)	6

Key	Population or sub-population of interest	Attribute	Proportion of population with this attribute	Quality of information	References	Notes
K	Larynx cancer	Supraglottic larynx cancer	0.28	ζ	Spitz et al. (26)	6
L	Supraglottic larynx cancer	Suitable for larynx preserving surgery	0.00 0.16 0.26	- ζ ζ	See explanatory note 6 Lee et al. (27) Hinerman et al. (28)	6
M	Supraglottic larynx cancer treated with larynx preserving surgery	Locoregional recurrence	0.16	ζ	Orus et al. (29)	6
N	Larynx cancer	Stage I – II	0.51	β	SA Cancer Registry (22)	6
O	Larynx cancer	Stage III	0.21	β	SA Cancer Registry (22)	6
P	Larynx cancer	Stage IV	0.28	β	SA Cancer Registry (22)	6
Q	All Head and Neck cancers	Cancer of the Oropharynx	0.08	α	AIHW (21)	7
R	All Head and Neck cancers	Salivary gland cancer	0.06	α	AIHW (21)	8
S	Salivary Gland cancer	Stage I-II	0.66 0.67 0.67	ζ ζ ζ	Calearo et al.(30) Spiro et al. (31) O'Brien et al. (32)	8

Key	Population or sub-population of interest	Attribute	Proportion of population with this attribute	Quality of information	References	Notes
T	Salivary gland cancer, Stage I-II	Low grade	0.28 0.24 0.32	ζ ζ ζ	Spiro et al. (31) North et al. (33) O'Brien et al. (32)	8
U	Salivary gland cancer, low grade	Node positive	0.05	ζ	Spiro et al. (31)	8
V	Salivary gland cancer, low grade, negative margins	Locoregional recurrence	0.26	ζ	North et al. (33)	8
W	All Head and Neck cancers	Cancer of the Hypopharynx	0.05	α	AIHW (21)	9
X	All Head and Neck cancers	Cancer of the Paranasal Sinus	0.05	α	AIHW (21)	10
Y	All Head and Neck cancers	Nasopharyngeal Cancer	0.04	α	AIHW (21)	11
Z	All Head and Neck cancers	Unknown primary (Head and Neck)	0.02 0.02	ζ ζ	Sinnathamby et al. (34) Grau et al.(35)	12
Z-2	Unknown primary (Head and Neck)	N1-2a	0.22 0.61	ζ ζ	Sinnathamby et al (34) Nguyen et al (36)	12
Z-3	Unknown primary (Head and Neck), N1-2a	Local or regional recurrence	0.54	ζ	Grau et al.(35)	12

Head and Neck Cancer

Treatment guidelines

There are no Australian National peer-reviewed guidelines for the management of head and neck cancer. The guidelines for the management of head and neck cancer included the treatment guidelines published by the U.S. National Cancer Institute (PDQ), the National Comprehensive Cancer Network (NCCN), the British Association of Otorhinolaryngologists Head and Neck Surgeons, the British Columbia Cancer Agency and the European School of Oncology/START. To reflect Australian practice, non peer-reviewed institutional guidelines from the Peter MacCallum Cancer Institute (L. Peters, personal communication) were also examined wherever management was controversial.

Indications for radiotherapy

For many Head and Neck cancers, the treatment guidelines state that different treatment modalities (such as surgery and radiotherapy) have similar cure rates, and that the choice of treatment should depend on individual clinical features and resource availability. The PDQ guidelines state that “it is difficult to unequivocally state the ideal therapy for a specific site or stage of cancer originating in the head and neck, since there is a paucity of well-designed and controlled prospective studies comparing treatment modalities”. In addition, as can be seen in Table 1, all of the recommendations for radiotherapy are based upon Level III-IV evidence, further reflecting the lack of good randomised data comparing radiotherapy with surgery.

Historically, radiotherapy has been used in the treatment of head and neck cancer as an alternative to radical surgery in an attempt to preserve function of the upper aero-digestive tract. Over the last century, it has become firmly established as an effective method of managing a variety of different head and neck cancers, either alone or in combination with chemotherapy. Trials to compare radiotherapy against surgery have been difficult to establish due to the biases of treating doctors and the difficulties associated with acceptance of a randomised trial that involves two treatments that are widely separated in terms of their delivery and toxicity.

Over the last four decades, a large body of clinical research based on randomised clinical trials has been performed to improve the efficacy of radiotherapy for head and neck cancer. Indeed, locoregionally advanced head and neck cancer has become one of the predominant clinical models for randomised trials involving radiotherapy. Examples include trials of altered fractionation, combinations with drugs designed to overcome or exploit tumour hypoxia, alternative forms of radiotherapy and combinations with cytotoxic chemotherapy.

Against this backdrop of the established role for radiotherapy in the management of head and neck cancer, alone or combined with systemic therapy, it is not surprising that very few randomised clinical trials have been performed in which radiotherapy was omitted from one treatment arm. Indeed, this would only be ethically possible for early stage disease for certain head

and neck sub-sites with favourable pathology where surgery alone is a viable single modality treatment option and where function is not compromised. Given that the overall control rates in non-randomised trials using surgery alone or radiotherapy for such lesions are similar, the enthusiasm for doing such trials is low and unlikely to make a significant difference to the overall radiotherapy utilisation.

The head and neck cancers included in this portion of the tree include cancers of the oral cavity, lip, oropharynx, hypopharynx, nasopharynx, larynx, paranasal sinuses and salivary glands. The tree also includes the management of cervical lymph node metastases where the primary is unknown. The significant majority of all head and neck cancers in the tree (except for paranasal sinuses and salivary glands) are squamous cell carcinomas and therefore these trees apply to the management of squamous cell carcinomas. Melanoma and lymphoma have been addressed in the melanoma and lymphoma trees. The histopathology of paranasal sinus cancers and salivary cancers is not important as the management does not significantly vary by histopathological group except where indicated on the tree (e.g. high grade and low grade salivary gland cancers).

Patients with locally advanced skin cancer in the head and neck region have not been included in the tree. Radiotherapy, either alone or in addition to surgery, is frequently used in these patients in the management of unresectable primary disease, significant nodal disease or perineural spread. This is a moderate caseload in many radiotherapy departments and can be a significant caseload for some departments with rural consultative clinics or large head and neck practices. This group was not included in this study because the aim of this study is to identify the appropriate, evidence-based use of radiotherapy for **registered cancers**. Unfortunately, advanced head and neck skin cancers are not included in state or federal cancer registry data and therefore the incidence of these cancers remains unknown. Adding non-registered cases such as locally advanced head and neck skin malignancies would falsely inflate the numerator. Thus, without minimising their significance, they have been omitted from the report. It is recommended that advanced head and neck skin cancers should be factored into the planning of radiotherapy services and considered for separate studies into their impact on radiotherapy workload.

Explanatory Notes for Tables 1 and 2

Table 1 lists the appropriate indications that were identified for external beam radiotherapy in head and neck cancer. The aim of this study was to estimate the ideal utilisation rate for external beam radiotherapy only and therefore appropriate use of brachytherapy has not been included.

There is little discussion in any treatment guidelines about the management of recurrent disease after surgical management. The guidelines generally recommend that recurrent disease should be treated on an individual basis depending upon the size and site of recurrence, previous surgery and the

performance status of the patient. Although occasional patients could develop a small recurrence that would be adequately treated with surgery alone, the vast majority of patients with recurrent disease will have a recurrence of a size that would warrant radiotherapy, either alone for patients with inoperable disease or poor patient performance status, or in combination with surgical salvage. The proportion of patients in whom radiotherapy would not be considered as treatment for recurrence after surgical salvage cannot be obtained from existing data. However, it is likely to be very small and have little impact on the overall estimate of radiotherapy utilisation. Therefore wherever locoregional recurrence appears in the tree, the branch signifies treatment with radiation.

1. Head and Neck incidence by sub-site and tumour stage

The incidences of head and neck cancers of the various sub-sites are derived from the Australian Institute of Health and Welfare (AIHW) 1998 data (21). However, AIHW data does not include head and neck cancers of unknown primary origin in the overall head and neck category, instead grouping unknown primary head and neck cancers with the other unknown primary cancers such as adenocarcinoma of unknown primary site. The proportion of head and neck unknown primary cancer was obtained from Sinnathamby et al.(34), who reported that 2.4% of all head and neck cancers are SCC unknown primary. This proportion was confirmed by Grau et al. (35).

2. Performance status

Performance status data specific to a population of head and neck cancer patients could not be identified. In general, head and neck cancer is associated with a worse performance status stage-for-stage than other cancer sites because patients with head and neck cancer are usually heavy smokers and can have significant co-morbidities. Most studies that investigate performance status usually do it retrospectively and therefore may not be reliable. Jones et al. (37) examined the effect of performance status on the prognosis of 1701 head and neck cancer patients at the Department of Otolaryngology/Head and Neck surgery, University of Liverpool and Clatterbridge Centre for Oncology, Clatterbridge, U.K. However, this study mainly involved patients referred for surgery and does not necessarily reflect population-based performance status. They provide no proportion data for the respective performance status levels. This study reported that even patients with poor performance status (ECOG levels of 3 or 4) had a 30% 6-month survival and 20% 12-month survival. Chen et al. (38) reported a 60% 2 year survival for patients with T3-4 laryngeal cancer treated at MD Anderson Cancer Center. These data suggest that the prognosis of at least some of this group would be sufficient to consider palliative radiotherapy in symptomatic patients.

For most patients with locoregional disease, the performance status will have little impact on overall radiotherapy utilisation but may impact more on

treatment intent. There have been reports showing that performance status strongly correlates with survival (37). For instance, a patient with an advanced head and neck primary who would receive radiotherapy (+/- chemotherapy) as radical treatment if his performance status is good, will most likely still undergo radiotherapy (but with palliative intent) in the setting of poor performance status. Occasionally a patient with an early head and neck cancer, who would be normally best treated with surgery due to early stage of disease, will instead undergo radiation due to severe co-morbidities or poor performance status. This subgroup is relatively small and there are no available data on the proportion of the subgroup. Similarly, there will be occasional patients with such poor performance status that no treatment is considered appropriate. It is not possible from the literature to accurately estimate the proportion for this group and it is considered to be too small to significantly impact on the overall radiotherapy utilisation estimate as very few patients present with a performance status level of 4. Most patients with a performance status of 4 would have had sufficiently good performance status at presentation to have considered radiotherapy. Therefore, performance status was not used as a discriminator for treatment decisions in the head and neck tree.

3. Stage

The issue of stage in the decision tree is problematic since several different staging systems have been used in the past and published reports frequently do not specify the staging system that was used. In addition, the incidence data was derived from different time periods and hence different staging systems have been used. For the decision tree, the most recent staging system, ie the 1997 AJCC Staging system (39) has been used. Where old prevalence data has been used then the old staging system is used and applied to the tree despite the fact that the actual prevalence may differ between the old and new staging systems. This was a pragmatic decision as it is unlikely that these changes in the staging system would dramatically alter the prevalence of a particular stage and therefore any minor differences would have no significant effect on the calculated optimal radiotherapy utilisation rate.

Tumour sub-sites

4. Oral cavity

The 1987-1998 SA Hospital Cancer Registry data indicates that 45% of all oral cancers were Stage I-II and the remainder Stage III-IV.

Primary treatment of early disease

For patients with Stage I-II cancers, treatment may consist of either surgery or radiotherapy and actual treatment may therefore be affected by the biases of the treatment group. The British Columbian treatment guidelines (3)

recommend the predominant use of radiotherapy alone for early stage oral cavity cancers, citing excellent local control and functional results (mainly Level III or IV). The National Cancer Institute PDQ statement on lip and oral cavity cancer (1) states that for early cancers (stage I and II) of the oral cavity, surgery or radiation therapy produce similar cure rates. The PDQ recommends that the choice of treatment should therefore be dictated by the anticipated functional and cosmetic results of treatment and by the availability of specialist expertise and patient preference. In Australia, the majority of early oral cancers are treated with surgery. To reflect current practice in Australia, we took a base proportion of patients treated by surgery from the SA Hospital Cancer Registry, which indicates that 90% of Stage I-II patients had surgery. Some of these patients also had radiotherapy presumably due to the presence of adverse pathological features. For sensitivity analysis, the proportion of patients in Stage I-II receiving surgery as primary therapy was modelled between 90% and 0% (i.e. that at one extreme 90% of patients had surgery and at the other extreme all patients had radiation). This modelling was performed to assess the effect of varying this proportion on the overall radiotherapy utilisation rate.

For patients with early disease who undergo surgery, a subset may have adverse pathological features that would warrant consideration for adjuvant radiotherapy. Jones et al. (5) report on a retrospective study from the University of North Carolina. They reviewed the recurrence patterns of 49 patients treated with surgery for Stage I-II oral cavity cancer (oral tongue, retromolar trigone, floor of mouth, alveolar ridge, buccal mucosa and hard palate), to identify pathological features that predicted locoregional recurrence. Pathological factors associated with an unacceptably high recurrence rate were depth of invasion >5 mm or positive margins. This represents approximately 20% of the entire surgical group. The recurrence rate in patients with no adverse pathology was not reported. Patients who have recurrence following surgery alone will most likely be treated with radiotherapy at relapse (either alone or combined with surgery).

The PDQ guidelines recommend that patients with stage III or IV tumours of the oral cavity are candidates for treatment by a combination of surgery and radiation therapy or radiotherapy alone.

Treatment and incidence of recurrence

McGuirt et al. (23) reported on a series of 129 patients with N0 SCC of the floor of mouth. No other studies were identified that would provide more general (ie including other sites in the oral cavity) recurrence rates after surgery alone for early disease. A subset of 116 had T1-2N0 tumours. Patients with positive margins were excluded from analysis. The total locoregional recurrence rate was 36/116 (31%). Not all of these recurrences would necessarily receive radiotherapy, however in this study 33/36 patients (92%) received radiation either alone or with surgery for salvage. For the decision tree all patients with locoregional recurrence are designated as having radiotherapy as part of their treatment (either alone or in combination with surgery).

5. Lip Cancer

The National Cancer Institute PDQ statement on lip and oral cavity cancer states that early cancers (stage I and II) of the lip are highly curable with surgery or radiation therapy, and that the choice of treatment should be dictated by the anticipated functional and cosmetic results of treatment and by the availability of specialist expertise.

It is reasonable to consider surgery as the primary treatment modality when excision with a clear surgical margin would not compromise the cosmetic result. For the purposes of the decision tree, a tumour size of 3 cm was arbitrarily chosen as surgically excisable with a reasonable cosmetic result. Sensitivity analysis modelling was undertaken by varying the tumour size cut-off for surgery between 2-4 cm. The PDQ statement also recommends that most patients with stage III or IV tumours of the lip are candidates for treatment by a combination of surgery and radiation therapy.

Zitsch et al. (24) reported on 1252 squamous carcinomas of the lip treated at the University of Missouri-Columbia School of Medicine from 1940-1987. Cancers were treated with radiotherapy, surgery or a combination based on size, position of the tumour and the performance status of the patient although specific selection criteria were not stated. 11% of patients had lesions >3cm in size. Sensitivity analysis was conducted by varying the decision to treat with radiotherapy in preference to surgery from any tumour >2cm (25% of cases in Zitsch et al.) to any tumour >4cm (6%). Of the T1 group, 3.3% had positive margins. Recurrence rates were 14% for T1.

Rowe et al. (25) reported on a literature review of local recurrence and distant metastases for lip cancer. They reported a locoregional recurrence rate of 759/7974 (9.5%) for patients treated with surgery who had >5 years follow-up. Radiotherapy would be an appropriate method of treatment either alone or in combination with surgery for the vast majority of cases of locoregional recurrence of lip cancer previously treated with surgery alone.

6. Larynx

The 1987-1998 SA Cancer Registry (22) reported on 191 laryngeal cancers treated at Royal Adelaide Hospital. 51% were Stage I, 21% Stage III and 28% had advanced stage disease (Stage IV- either T4 or N2-3 or M1). We have assumed that the stage distribution for the various sub-sites of laryngeal cancer (i.e. supraglottic, glottic and sub-glottic) are similar. Data from the M.D. Anderson institute indicate that supraglottic larynx cancer comprises 28% of all larynx cancer (26).

Stage I-II

The National Cancer Institute PDQ statement (7) indicates that Stage I and II laryngeal cancers can be treated with either radiotherapy or surgery. However the PDQ guidelines state that “irradiation should be preferred because of good results, preservation of voice and possibility of surgical salvage in patients whose disease recurs locally.” No randomised trials exist that compare “voice-preserving” surgery with definitive radiotherapy. The British Columbia Cancer Agency guidelines suggest that radiotherapy is appropriate although surgery “may be an option in selected cases”.

The START guidelines (8) specifically recommend against RT in supraglottic T1-2N0. There are many reports of laryngeal conservation surgery without radiotherapy in the literature but these studies are single-institutional non-randomised studies where selection of good prognosis patients may have occurred. Orus et al. (29) reported on a non-randomised trial to define the treatment of choice (partial laryngectomy vs radiotherapy) in the early stage of supraglottic squamous cell cancer (ESSC). One hundred and fifteen patients with ESSC were treated with either partial laryngectomy (25 patients) or with radiotherapy (90 patients) between January 1984 and December 1996. All patients had a follow-up of over 29 months. Radiotherapy (RT) had a local control rate of 79%, which increased to 90% with salvage surgery, and a high larynx preservation rate (83%). Partial laryngectomy (PL) offered a similar initial local control rate of 84% increasing to 88% with salvage surgery, and functional results were also good (80%). No statistically significant differences were found between RT and PL. RT was less costly, showed better suitability for treatment, produced moderate morbidity and sequelae, and local recurrence was easier to rescue. PL showed higher immediate postoperative morbidity, higher cost and lower suitability for treatment but had fewer long-term sequelae and offered the best initial local control. No clear oncological arguments were found in the series to define whether PL or RT is the treatment of choice for ESSC. Both are effective therapies. Secondary factors such as suitability for treatment, morbidity, cost and applicability should be individually evaluated when choosing the type of treatment.

An extensive literature search identified one source of data on the proportion of all supraglottic larynx cancers that are suitable for partial laryngectomy without adjuvant radiotherapy. The largest series is from Lee et al. from MD Anderson Cancer Center (27). They reported a conservation rate of 16% among 404 consecutive patients. Hinerman et al. (28) reported on 274 consecutive supraglottic larynx cancers at the University of Florida Head and Neck Unit, 26% of whom had clinical attributes amenable to laryngeal preservation surgery. Due to the controversy surrounding the best form of treatment for early supraglottic larynx cancers, the decision tree depicts all supraglottic larynx cancers having radiation, reflecting the majority view of the guidelines reviewed (i.e. the proportion of supraglottic larynx cancers suitable for larynx preservation set at zero). The sensitivity analysis then assesses the

impact on the overall estimate by altering the proportion suitable for larynx preserving surgery at 30%.

Similar arguments can support larynx-preserving surgery for glottic cancer although the guidelines all tend to recommend radiotherapy in preference to any form of surgery. Cordectomy in a small proportion of patients or vertical partial laryngectomy have both been proven to have similar local control to radiotherapy although their impact on voice quality have been shown to be worse than for radiotherapy (40) (41). Therefore, the tree depicts all glottic larynx cancer having radiotherapy.

Stage III

The management of Stage III laryngeal cancer is controversial with several treatment options recommended by different guidelines. There have been no randomised trials to compare outcomes between these different treatment modalities. The PDQ guidelines (7) state that Stage III patients may be treated either with surgery with or without postoperative radiotherapy, or by definitive radiotherapy with surgery for salvage of radiation failures. The START guidelines recommend that laryngeal preservation should be the aim. The British Columbia treatment guidelines suggest that locally advanced laryngeal cancer usually requires a combined approach although many patients may be curable with either modality alone and that multidisciplinary assessment is recommended.

Contemporary Australian practice is to preserve the larynx. Larynx preservation with chemoradiotherapy (using laryngectomy for salvage) has been shown in randomised trials (42) (43) (44) (45) (46) (47) (48) (49) (50) to provide laryngeal preservation in the majority of cases without any detrimental effect on survival when compared with laryngectomy. Therefore, it would be considered reasonable to offer radiotherapy to all patients with T3 laryngeal cancer and to reserve surgery for salvage.

Stage IV

All cases of Stage IV laryngeal cancer are recommended to receive radiotherapy according to NCI guidelines, either as postoperative treatment or as definitive treatment. It is recognized that M1 disease is included in Stage IV. However, this is likely to be a small group and the majority of these will usually have locoregional symptoms requiring palliative radiotherapy. It may be possible in rare instances for a patient to have extensive M1 disease at diagnosis and not be recommended for radiotherapy. This would be a very small group and exclusion of these patients from the decision tree is unlikely to impact on the optimal radiotherapy utilisation estimate.

7. Oropharynx

There are no randomised trials addressing the treatment options (radiotherapy versus surgery) in oropharyngeal cancer. The START guidelines (10) and the BC Cancer Agency guidelines (11) recommend the use of radiotherapy, either as definitive or as adjuvant therapy, for all sites and stages of oropharyngeal cancer. Therefore for the purposes of the decision tree, all oropharyngeal cancers are treated with radiotherapy. The PDQ guidelines (51) state that either surgery or radiation is equally successful in controlling Stage I or II oropharyngeal cancer. Radiation may be the preferred modality where the functional deficit will be great, and surgery may be the preferred modality where the functional deficit will be minimal. Stage III and operable stage IV cancers are most commonly managed with a combination of radiation therapy and surgery. Non-resectable Stage IV patients are managed with radiotherapy alone.

Parsons et al. (52) reported on a large review of North American academic institutions that used surgery with or without adjuvant radiotherapy or radiotherapy alone for squamous cell carcinoma of the oropharynx. The results were identical in terms of relapse and survival between surgery and radiotherapy but the severe or fatal complication rate was substantially higher in the surgery group. The authors concluded that radiotherapy is the preferred primary treatment modality with surgical salvage reserved for persistent disease.

8. Salivary Gland

The START guidelines (12) recommend that surgery is the treatment modality of choice for most resectable salivary gland tumours. The National Cancer Institute PDQ statement (53), British Columbia treatment guidelines and the START guidelines (12) recommend post-operative radiotherapy for high-grade tumours, perineural infiltration, nodal involvement or advanced disease. We have therefore included Stages III-IV or high grade as the 2 branch points where radiotherapy is given (either definitive radiotherapy alone or, more frequently, where radiotherapy is recommended post-operatively).

Johns and Goldsmith (54) reviewed the literature and defined 4 groups of salivary gland tumours. The authors based their treatment of salivary gland malignancies on the size of the primary and the histopathologic diagnosis. Group 1 includes smaller tumours in the T1 and T2 classification with cell types that are associated with slow growth. A parotidectomy is usually sufficient therapy for tumours in this group. Group 2 contains T1 and T2 tumours with more aggressive behaviour. Total parotidectomy is indicated here, with postoperative radiotherapy. T3 tumours and patients with nodal metastasis or recurrent tumours make up group 3. Radical parotidectomy with sacrifice of the facial nerve is usually required for a sufficient tumour-free margin in these patients, and postoperative radiotherapy is recommended. Group 4 includes T4 lesions and the extent of disease dictates excision and postoperative radiotherapy.

Spiro et al. (31) reported on 470 patients with salivary gland tumours treated at Memorial Sloan Kettering Cancer Centre. Of all salivary gland tumours treated definitively, 81% were parotid, 18% submandibular, 1% sublingual. By stage, 56% were Stage I, 10% Stage II, 23% Stage III and 10% Stage IV. 130/470 (28%) were low grade (low grade muco-epidermoid, oncocytoma or acinic carcinoma). The remainder were high grade muco-epidermoid, adenocarcinoma, adenoid cystic, squamous cell carcinoma, malignant mixed or anaplastic tumours. Of the low-grade lesions, 5% had node positive disease. Spiro et al. stated that radiotherapy was generally given to patients with more extensive tumours, involved nodes, positive surgical margins or other adverse pathology. No recurrence data by treatment modality are presented.

Calearo et al. (30) reported on 167 consecutively treated parotid cancer patients from the University of Florence. 112/167 (67%) had T1-2N0-1 disease, which is a similar stage distribution to that reported by Spiro et al. 41% of their patients underwent post-operative radiotherapy based on advanced stage or high grade.

O'Brien et al. (32) reported on 113 patients with malignant salivary tumours treated at the University of Alabama between 1959-1984. 68% were Stage I-II and 32% Stage III-IV. 32% were low grade. Locoregional recurrence data for low-grade lesions treated with surgery alone were not reported.

Local recurrence following surgery alone in the absence of adverse pathological features is reported by North et al. (33). From 1975-1987, 87 patients with carcinomas of the major salivary glands (70 parotid and 17 submandibular) were treated by either surgery or surgery followed by postoperative radiotherapy (RT). Surgical procedures included superficial (24%) or total (56%) parotidectomies and submandibular gland resection (20%). Low grade lesions were present in 21/87 (24%). Postoperative RT (when administered) usually began 2 to 4 weeks following surgery and was administered to 64/87 (74%) of patients. For patients with previously untreated disease, 26% treated by surgery alone experienced local recurrence, whereas only 4% recurred locally following surgery plus postoperative RT ($p = 0.01$).

9. Hypopharynx

The National Cancer Institute PDQ guidelines (15) recommend surgery followed by postoperative radiation therapy for all Stage I and Stage II cancers, except for very early T1N0 cancers. Since malignancy of the hypopharynx is generally clinically silent until the advanced stages, it is very unusual to diagnose these tumours at the T1 N0 stage. In addition, if the surgery of choice is pharyngolaryngectomy, then radiotherapy must be the preferred treatment to maintain function, using surgery for salvage. The proportion of these tumours that can be treated with conservative surgery alone would be so small as to make no significant difference to the overall

utilisation rate. The BC Cancer agency guidelines (16) recommend that T1-2N0 lesions should be treated with radiation with surgery for salvage of radiation failure.

Both the PDQ and BC Cancer guidelines recommend treatment of Stage III-IV cancers with a combination of surgery and radiation. Therefore, all stages of hypopharynx cancer are recommended to have radiation for at least part of the treatment.

10. Paranasal sinus

The PDQ recommendations (17) are for radiotherapy alone or in combination with surgery for all stages of paranasal sinus cancer. The British Columbia group have not published guidelines for the management of paranasal sinus cancer.

11. Nasopharynx

All the established guidelines (National Cancer Institute PDQ, BC Cancer Agency) state that high-dose radiotherapy is the primary treatment for nasopharyngeal carcinoma, both for the primary tumour site and the neck. Accordingly in the decision tree, all non-metastatic nasopharyngeal carcinomas are designated to receive radiotherapy. In many cases, the addition of concurrent chemotherapy is indicated (55).

The proportion of patients with M1 disease at diagnosis is small - 5% in a series of 564 patients from Prince of Wales Hospital, Hong Kong (56), and 6% in 1555 patients with nasopharyngeal carcinoma treated at the National Taiwan University Hospital (57).

M1 disease is predominantly treated with palliative chemotherapy. A large proportion of these patients will however require radiotherapy for either locoregional symptoms or symptoms related to metastases to bone or brain. A small proportion of patients with liver and/or lung metastases will die from their disease without requiring radiotherapy. However, a detailed literature search failed to satisfactorily identify the proportion of patients that do not require radiotherapy. Most chemotherapy series for metastatic nasopharyngeal carcinoma either include radiation as part of the routine treatment (thus indicating the high need for radiotherapy even in patients with M1 disease) or patients developed metastases after previous “curative” radiotherapy (+/- chemotherapy). Therefore, the decision tree denotes that all patients receive radiation. A study of all nasopharyngeal cancers treated in Finland 1980-1989 (58) revealed that 13/107 patients (12%) were treated palliatively due to age, severe co-morbidity or refusal to undergo radical radiotherapy. All received palliative radiotherapy to the primary. A further 3/107 (3%) had distant metastases at diagnosis. They all received palliative radiotherapy to the primary due to symptoms.

12. Metastatic squamous neck cancer with occult primary

Indications for radiotherapy

Most squamous carcinomas metastatic to lymph nodes of the upper half of the neck will originate from a head and neck primary site. However, in these patients the primary remains occult following standard head and neck examination and investigations.

The indications for the use of radiotherapy either as definitive treatment or as an adjuvant to surgery for patients with metastatic squamous cell carcinoma of the head and neck where the primary is unidentified is controversial. Some groups such as Maulard et al. (59) advocate routine radiotherapy in patients with localised disease. The main intent is to not only maximise locoregional control in the neck but also to attempt to prevent the occult primary from becoming symptomatic. However, others like Sinnathamby et al. (34) hold the view that modern staging techniques obviate the routine use of radiotherapy for unknown primary, and radiotherapy should be reserved for particular groups of patients who are at higher risk of locoregional failure (particularly those with advanced disease). O'Mara et al. (60) suggest neck dissection alone for N1-2a and Sinnathamby et al. discuss omitting radiotherapy for solitary nodes up to 6 cm (N1-2a). The Peter MacCallum Cancer Institute has developed treatment pathways for unknown primary squamous cell carcinoma of the head and neck (personal communication Prof. LJ Peters). In their treatment pathway, routine radiotherapy either pre- or post-operatively is recommended for >N2a disease and radiotherapy is considered optional for disease N1-2a. For the decision tree, the branch point for radiotherapy is for N1-2a not to receive radiotherapy. However, in the sensitivity analysis the branch point underwent modelling with the prevalence varying between the proportion with >N1 disease and > N2A disease receiving routine post-operative radiotherapy to assess the impact that this variation has on the overall radiotherapy utilisation rate.

The Incidence

Sinnathamby et al. (34) reported on the experience of head and neck cancer at the Peter MacCallum Cancer Institute. From 1983-1992, 69 patients with unknown primary cancers of the head and neck were treated. 15/69 patients (22%) were N1-2a and 9% were N1. Of the 67 patients with recorded performance status, only 1 had a performance status worse than ECOG performance level 2. Only 4/69 (6%) patients did not receive radiotherapy (i.e. were treated with surgery alone). The remainder had radiotherapy either alone or in combination with surgery. Of the 15 who had N1-2a disease, 3 (20%) had surgery alone. All patients in this group maintained locoregional control (but the number of patients was very small).

These data differs from that of Nguyen et al from the McGill University teaching hospital (36), who reported on 54 patients with metastatic squamous

cell carcinoma to cervical lymph nodes. In this group, 61% had N1-2a disease (9% N1 and 52% N2a). 98% of the patients underwent radiotherapy either alone or in combination with surgery.

The decision tree uses the Sinnathamby rate of 9-22% of patients not receiving routine radiotherapy since this is the largest series and being Australian, this data is more likely to reflect incidence rates in other Australian treatment centres.

Incidence of Recurrence

Grau et al. (35) reported the results of a national Danish survey of unknown primary head and neck cancer. 51% had N1-2a disease. Only 9% of the 352 patients were treated with surgery alone. The vast majority of N2a disease received radiation to the neck and head and neck mucosal sites. Recurrence or development of a symptomatic primary occurred in 54% of the N1-2 surgery alone group.

None of the identified guidelines discuss the management of recurrent disease in this situation. However, it seems reasonable to assume that the vast majority of patients who develop recurrent disease would receive radiotherapy as part of their management, either alone for unresectable disease or post-operatively.

Optimal Radiotherapy Utilisation Rate and Sensitivity Analysis

Sensitivity analysis allows the assessment of the impact of varying the value of uncertain data items on the overall optimal radiotherapy utilisation rate. For the head and neck decision tree, 4 data items were identified as being uncertain.

- No data were identified to estimate the proportion of early stage oral cavity cancer that should be treated with surgery. An arbitrary value of 0.9 was chosen based on reported practice in South Australia (see explanatory note 4) and the sensitivity analysis varied this proportion between 0% patients having surgery (and all being treated with radiation) and 90% patients having surgery,
- Similarly, the ideal proportion of lip cancers that should undergo surgery alone is uncertain as there are no clear guidelines of when surgery is appropriate and when radiotherapy is appropriate. We therefore used incidence data to model between patients having radiotherapy for tumours > 4 cm in size as the smallest case scenario for radiotherapy (6% incidence) and >2 cm as the greatest case scenario for radiotherapy (25% incidence).
- The proportion of supraglottic larynx cancer that could undergo larynx-preserving surgery in preference to radiotherapy was varied between zero (i.e all supraglottic larynx cancers treated radiotherapeutically) and

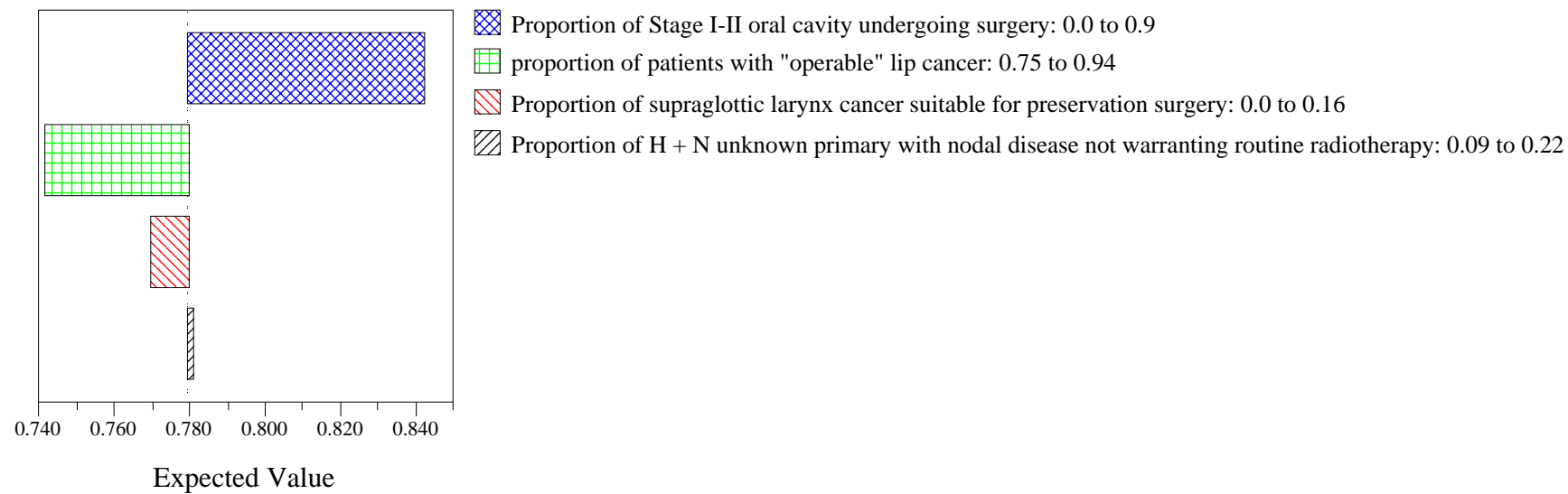
26% (i.e. the proportion of supraglottic larynx cancers identified as being suitable for larynx preservation in one large head and neck practice.).

- The proportion of patients with SCC unknown primary was varied between those with nodal status > N1 getting radiation (22%) and >N2a (9%) getting radiation.

To assess the impact of this uncertainty on the overall estimate of the need for radiotherapy in all head and neck cancers, a sensitivity analysis was performed for each of the variables. It is illustrated by the tornado diagram below. Once the decision trees for all tumours are completed, a tornado analysis will be performed whereby the impact of each of these variables on the overall estimate of the proportion of cancer patients needing radiotherapy will be examined.

The graphs below show that the optimal proportion of head and neck cancer patients who should receive radiotherapy based on evidence is 78%. As head and neck cancer comprises 4% of all cancers, head and neck cancer patients suitable for radiotherapy represent 3.1% of all cancer patients. This optimal proportion can range between 74% and 84% (3.0% and 3.3% of all cancers), largely depending on the values used for surgery being appropriate for early oral cancer and lip cancer. If early oral cancer were more routinely treated with radiotherapy then the utilisation rate would increase from 78% to 84%. This represents an increase in utilisation for head and neck cancer of 6% and an increase in the utilisation for all cancer by 0.2%.

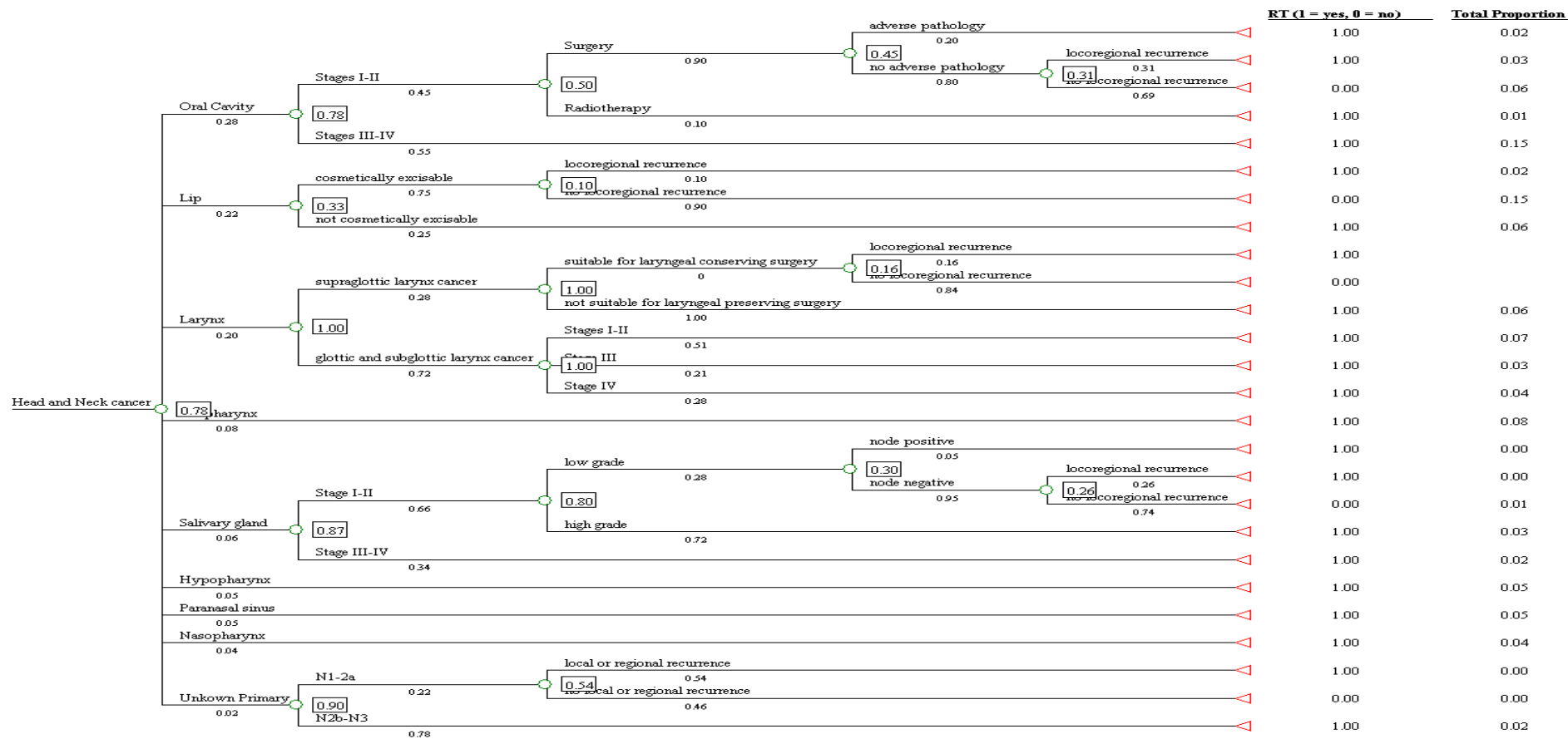
Tornado Diagram at Head and neck



The overall optimal radiotherapy utilisation rate for head and neck cancer is 78% (74% - 84%). This group represents 3.1% (3.0 -3.4%) of all cancer patients. For the 9 tumour sub-sites, the optimal utilisation rates are shown in Table 4.

Table 4: Optimal radiotherapy utilisation rates by head and neck sub-type

Tumour Sub-site	% of head and neck cancer	Overall optimal radiotherapy utilisation rate for sub-site (%)	Proportion of all cancer patients that should receive radiotherapy (%)
Oral Cavity	28	78	0.9
Lip	22	33	0.2
Larynx	20	100	0.8
Oropharynx	8	100	0.3
Salivary Gland	6	87	0.2
Hypopharynx	5	100	0.2
Paranasal sinus	5	100	0.2
Nasopharynx	4	100	0.2
Metastatic unknown primary	2	90	0.1
TOTAL	100	78	3.1



RT (1 = yes, 0 = no)

Total Proportion

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Melanoma

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

Outcome Number	Clinical Scenario	Treatment Indicated	Level of Evidence	References	Notes	Proportion of all Melanoma patients
1	Mucosal melanoma	Post-operative Radiotherapy	IV	<ul style="list-style-type: none"> NHMRC guidelines for the management of cutaneous melanoma (1) European school of oncology START guidelines (2) 	1, 2	0.01
3	Cutaneous, Stage I-III, desmoplastic	Surgery and Radiotherapy	III	<ul style="list-style-type: none"> NHMRC guidelines for the management of cutaneous melanoma (1) 	4	0.02
5	Cutaneous, Stage I-III, non-desmoplastic, head and neck, pT1-3, nodal/systemic recurrence	Palliative Radiotherapy	III	<ul style="list-style-type: none"> NHMRC guidelines for the management of cutaneous melanoma (1) NCCN clinical practice guidelines (3) 	5, 8	< 0.01
7	Cutaneous, Stage I-III, non-desmoplastic, head and neck, pT4	Post-operative Radiotherapy	III	<ul style="list-style-type: none"> NHMRC guidelines for the management of cutaneous melanoma (1) European school of oncology START guidelines (2) 	5	0.02

Outcome Number	Clinical Scenario	Treatment Indicated	Level of Evidence	References	Notes	Proportion of all Melanoma patients
9	Cutaneous, Stage I-III, non-desmoplastic, Not head and neck, node negative, nodal/systemic recurrence	Palliative Radiotherapy	III	<ul style="list-style-type: none"> NHMRC guidelines for the management of cutaneous melanoma (1) 	7, 8	0.03
12	Cutaneous, Stage I-III, non-desmoplastic, Not head and neck, node positive, 1-3 nodes involved nodal/systemic recurrence	Palliative Radiotherapy	III	<ul style="list-style-type: none"> NHMRC guidelines for the management of cutaneous melanoma (1) 	6, 8	0.07
14	Cutaneous, Stage I-III, non-desmoplastic, Not head and neck, node positive, > 4 nodes involved	Postoperative Radiotherapy	III	<ul style="list-style-type: none"> NHMRC guidelines for the management of cutaneous melanoma (1) European school of oncology START guidelines (2) 	6	0.08

Outcome Number	Clinical Scenario	Treatment Indicated	Level of Evidence	References	Notes	Proportion of all Melanoma patients
15	Cutaneous, Stage IV, symptomatic brain/bone/node metastases	Palliative Radiotherapy	III	<ul style="list-style-type: none"> NHMRC guidelines for the management of cutaneous melanoma (1) European school of oncology START guidelines (2) 	8	< 0.01
The proportion of all melanoma patients in whom radiotherapy is recommended						0.23
Proportion of all cancer patients = 0.23 x 0.11 =						0.025 (2.5%)

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

Key	Population or subpopulation of interest	Attribute	Proportion of population with attribute	Quality of information	References	Notes
0	All registry cancers	Melanoma	0.11	α	AIHW (4)	1
1	Melanoma	Cutaneous	0.97	ε	SA Hospital Registry (5)	1
2	Melanoma	Ocular	0.02	ε	SA Hospital Registry (5)	1
3	Cutaneous melanoma	Stage I - III	0.99	ζ	Sydney Melanoma Unit (6)	3
4	Cutaneous melanoma, Stage I - III	Non-desmoplastic	0.98	ε	SA Hospital Registry (5)	4
5	Cutaneous melanoma, Stage I - III, non-desmoplastic	Head and neck	0.12	ζ	O'Brien et al (7)	5
6	Cutaneous melanoma, Stage I - III, non-desmoplastic, head and neck	PT1-3	0.84	ζ	O'Brien et al (7)	5

Key	Population or subpopulation of interest	Attribute	Proportion of population with attribute	Quality of information	References	Notes
7	Cutaneous melanoma, Stage I - III, non-desmoplastic, head and neck, pT1-3	Nodal or systemic recurrence	0.08	ζ	O'Brien et al (7)	5
8	Cutaneous melanoma, Stage I - III, non-desmoplastic, head and neck, pT1-3, nodal or systemic recurrence	Nodal/brain/ bone recurrence	0.51 0.21 (0.38 if subcutaneous metastases counted)	ζ	Slingluff Jr. et al. (8) Cohn- Cedermark et al. (9)	8
9	Cutaneous melanoma, Stage I - III, non-desmoplastic, non - head and neck	Node negative	0.64 0.54	E ζ	Balch et al. (10) Calabro et al. (11)	6
10	Cutaneous melanoma, Stage I - III, non-desmoplastic, non - head and neck, node negative	Nodal/ systemic recurrence	0.11	ε	Gershenwald et al (12)	7

Key	Population or subpopulation of interest	Attribute	Proportion of population with attribute	Quality of information	References	Notes
11	Cutaneous melanoma, Stage I - III, non-desmoplastic, non - head and neck, node negative, Nodal/ systemic recurrence	Nodal/brain/ bone recurrence	0.51 0.21 (0.38 if subcutaneous metastases counted)	ζ	Slingluff Jr. et al. (8) Cohn- Cedermark et al. (9)	8
12	Cutaneous melanoma, Stage I - III, non-desmoplastic, non - head and neck, node positive	1-3 nodes involved	0.26 (3+ nodes positive) 0.55 (1+ node positive)	ε ε	Balch et al. (10) Balch et al. (10)	6
13	Cutaneous melanoma, Stage I - III, non-desmoplastic, non - head and neck, node positive, 1-3 nodes involved	Nodal/ systemic recurrence	0.60	ζ	Calabro et al (11)	6

Key	Population or subpopulation of interest	Attribute	Proportion of population with attribute	Quality of information	References	Notes
14	Cutaneous melanoma, Stage I - III, non-desmoplastic, non - head and neck, node positive, 1-3 nodes involved, Nodal/ systemic recurrence	Nodal/brain/ bone recurrence	0.51 0.21 (0.38 if subcutaneous metastases counted)	ζ	Slingluff Jr. et al. (8) Cohn- Cedermark et al. (9)	8
15	Cutaneous melanoma, Stage IV	Symptomatic brain/bone/ node metastases	0.51 0.21 (0.38 if subcutaneous metastases counted)	ζ	Slingluff Jr. et al. (8) Cohn- Cedermark et al. (9)	8

Melanoma

Treatment Guidelines

Australian national-level guidelines for the treatment of melanoma have been published by the National Health and Medical Research Council (NHMRC). Clinical practice guidelines for melanoma have also been issued by the US National Comprehensive Cancer Network (NCCN) and by the European School of Oncology. Since this study will be used in the planning of radiotherapy facilities in Australia, the recommendations of the Australian guidelines have been given precedence over the other guidelines. In addition issues such as the treatment of desmoplastic and mucosal melanoma are discussed only in the NHMRC guidelines.

Indications for radiotherapy

In accordance with the NHMRC guideline recommendations for melanoma, radiotherapy is indicated in the following clinical situations:

- Following resection of mucosal melanomas
- Following resection of desmoplastic melanomas
- Post-operatively in cutaneous melanomas arising in the head and neck region that are likely to recur locally (>4mm thick)
- Post-operatively in cutaneous melanomas with multiple lymph node involvement
- For palliative management of cerebral and bone metastases and for other metastases where temporary local control is needed, eg. nodal masses

1. **Incidence data**

According to Australian Institute of Health and Welfare (AIHW) data, melanoma represents 11% of all cancer.

The incidence of mucosal melanoma in the South Australian Hospitals Based Cancer Registry (SA-HBCR) database (5) was 1% of all melanoma. This includes melanomas of the vagina, anus, oesophagus, nasal cavity and sinuses, oral cavity and other miscellaneous sites. Choroidal melanoma represented 2% of all melanomas in the SA-HBCR database. The remaining 97% were cutaneous melanomas.

2. **Mucosal melanoma**

The NHMRC guidelines (1) state that post-operative radiotherapy should be considered for mucosal melanomas as they usually present late and are usually unresectable. Therefore the decision tree indicates that all mucosal melanomas should be considered for recommendation of radiotherapy, although this is likely to be an over-estimate as an occasional early mucosal melanoma might be considered resectable. Given the rare nature of these lesions, this will not have a significant impact on the estimate of the overall proportion of patients needing radiotherapy.

3. Stage Incidence

The Stage data for cutaneous melanoma is reproduced with the permission of the Sydney Melanoma Unit and Professor McCarthy. They reported that 1% of all patients in the Sydney Melanoma Unit database had stage IV disease leaving 99% with Stages I-III. This differs somewhat from the experience reported by Balch et al (10). Balch reported on pooled data from 13 institutions and co-operative study groups (including the Sydney Melanoma Unit) and reported a Stage IV incidence of 1158/17600 (6.6%). Therefore there may be a difference in stage distribution between the United States and Australia. This may reflect media campaigns for early detection of melanoma in Australia and a greater awareness of melanoma. To reflect Australian conditions, the Sydney Melanoma Unit data was used as the most relevant source of data. No state registry data were available for melanoma by stage.

4. Radiotherapy for primary disease post-operatively

The NHMRC guidelines for melanoma (1) recommend that radiotherapy should be considered for “tumours that have a high incidence of local recurrence” (page 39). They also state that desmoplastic melanoma is “a type of melanoma prone to local recurrence” (page 48). Therefore, it would be reasonable to recommend consideration of radiotherapy for all cases of desmoplastic melanoma. While it is accepted that there will be some patients with poor performance status and/or co-morbidities that exclude them from consideration for adjuvant radiotherapy, there was no available data on performance status correlated with histological type of melanoma. Therefore for the purposes of this decision tree it was assumed that all patients with melanoma with desmoplastic features are considered for radiotherapy. A review by Geara et al. (13) suggests that local recurrence rates for desmoplastic melanoma approaches 50% and radiotherapy should be considered in these patients. The incidence of desmoplastic melanoma in the South Australian Hospital Registry (5) was 1.7%.

5. Melanoma depth and adjuvant radiotherapy for T4 head and neck melanoma

South Australian Hospital Registry data (5) indicate that 90% of melanomas were pT1-3 and 10% were pT4. The NHMRC melanoma guidelines recommend that radiotherapy should be considered for pT4 lesions. However, expert opinion (Level IV) suggests that surgical clearance would be considered adequate in most anatomical sites. Therefore, it was considered unnecessary that all pT4 melanomas receive routine radiotherapy. Expert opinion (Dr Hughes, melanoma surgeon, personal communication) suggests that the use of radiotherapy could be reserved for pT4 lesions on the head and neck where there is difficulty in achieving clear deep surgical margins (due to the thin tissue in areas of the head and neck) and the need for conservative surgery to maintain function. In addition, O'Brien et al. (7) report a high incidence of local recurrence for head and neck melanomas when thickness was >4 mm

(24% recurrence) which could perhaps have been improved with the addition of radiotherapy and therefore may justify radiotherapy in this group.

Therefore, for the purposes of the decision tree, head and neck melanomas were treated differently from melanomas in sites other than head and neck whereby the pT4 lesions were recommended radiotherapy. O'Brien et al. (7) report that of 8000 cases in the Sydney Melanoma Unit database, 12% were from the head and neck and of this group, 16% were pT4. Slingluff Jr. et al. (8) reported a head and neck melanoma incidence of 12%.

The recurrence rate in pT1-3 tumours treated with surgery alone was 8% in the series reported by O'Brien et al.

6. Adjuvant nodal radiotherapy

The NHMRC guidelines for the management of melanoma (1) recommend the consideration of radiotherapy for "multiple" lymph node involvement, but the guidelines do not specifically indicate the number of involved nodes that warrant treatment with radiation.

Randomised trial evidence is lacking for adjuvant nodal radiotherapy. The MD Anderson Center has reported the largest prospective series on head and neck adjuvant radiotherapy in high-risk cases for regional relapse (14). They report 88% local control versus 50% treated surgically. Similar data from Australia suggests better local control with adjuvant radiotherapy for node positive melanoma (15) (16) (17).

The number of positive lymph nodes that a patient should have before radiotherapy is recommended is controversial. The NHMRC melanoma treatment guidelines suggest considering radiotherapy when multiple nodes are involved. This could be interpreted as consideration of radiotherapy if > 1 node is involved, whereas others (18), M. Hughes (personal communication) state that it would be reasonable to consider radiotherapy only when >3 nodes are involved. Locoregional recurrence data from Miller et al. (18) indicate that the recurrence rate for 1-3 nodes positive is 14% and for >3 nodes is 53%. This suggests a very high recurrence rate for >3 nodes and therefore it would be reasonable to consider radiotherapy for > 3 nodes. Sensitivity analysis was performed to assess the impact on the overall radiotherapy utilisation rate if patients with > 1 node involved were recommended for radiotherapy.

In terms of epidemiological incidence data, Balch et al. (10) report on pooled data from 13 cancer centres from a total of 17 600 melanoma patients. Of the entire patient population, 16 442 were M0 stage. Of this group, 5995 patients (36%) were node positive either macro- or microscopically when treated at diagnosis (either by node dissection or sentinel lymph node dissection). Of a sub-section of 1528 patients with full details of their node positivity, 55% had > 1 node involved and 26% had > 3 nodes involved.

Slingluff Jr. et al. (8) reported on 4682 patients treated at Duke University who were diagnosed with locoregional melanoma (i.e. no metastatic disease at diagnosis). 46% were node positive either clinically or at dissection.

The recurrence rate for node positive disease was estimated from Calabro et al. (11) who reported on 1001 consecutive node positive patients treated at the MD Anderson Cancer Center and found that 60% of patients with 1 node involved developed distant metastatic disease.

7. Recurrence for node negative melanoma

The incidence of nodal and/or systemic recurrence for node negative melanoma is reported by Gershenwald et al. (12). They reported on the recurrence (locoregional and distant) for 243 patients who had a negative sentinel node biopsy and were therefore pN0. The incidence of recurrence (local, in-transit, nodal and distant recurrences all included) reported is 11%.

8. Radiotherapy for distant metastases

The NHMRC cutaneous melanoma guidelines (1) recommend consideration of radiotherapy for symptomatic metastases to “brain, bone, nodal recurrences and extensive cutaneous metastases” (page 39).

Slingluff et al (8) reported that 51% of patients with metastatic or recurrent melanoma developed brain, bone or nodal metastases including those with more than one site of metastatic spread. It is presumed that the majority of these sites were symptomatic. Cohn-Cedermark et al. (9) reported on 569 patients who developed metastases to distant sites including distant skin sites and distant nodal sites. The group with brain, bone or nodal recurrence represents 21% of their entire patient group (this 21% consists of 10% brain, 4% bone and 7% distant nodes and does not count those with multiple sites (39%) where no breakdown according to location of site was reported. If we consider those with only one site of involvement and exclude the data on multiple sites of metastatic disease then brain, bone and distant nodes represents 50% of all solitary metastatic sites. Therefore the figure of 21% may represent an underestimate of all patients with brain, bone and nodal metastases). The NHMRC melanoma guidelines also recommend consideration of radiotherapy for ‘extensive’ cutaneous metastases. No published report or study has been identified that differentiates ‘extensive’ cutaneous metastases from ‘less extensive’ metastases. If one includes all skin metastases along with bone, brain and nodal recurrence then the incidence of the potential radiotherapy group in the study reported by Cohn-Cedermark et al. increased to 38% (i.e. 17% of their cohort have cutaneous metastases in addition to the previous 21% discussed above).

Sensitivity analysis using these extremes will be performed. The data used for the decision tree were from Slingluff et al. as it included data on patients with more than one metastatic site whereas the data from Cohn-

Cedermark may be inaccurate because patients with multiple sites were not considered. When they are considered (see above), the metastatic rate where radiotherapy would be considered is 50% which is similar to that reported by Slingluff et al.

Estimated Optimal Radiotherapy Utilisation Rate

Using the proportions as described in Table 2, the proportion of ALL patients with melanoma in whom at least one course of radiotherapy is indicated in the overall treatment course according to the best available guideline evidence is 23%. As melanoma comprises 11% of all cancers, the group of melanoma patients where radiotherapy is recommended is $0.11 \times 0.23 = 0.024$ or 2.4%.

Sensitivity Analysis

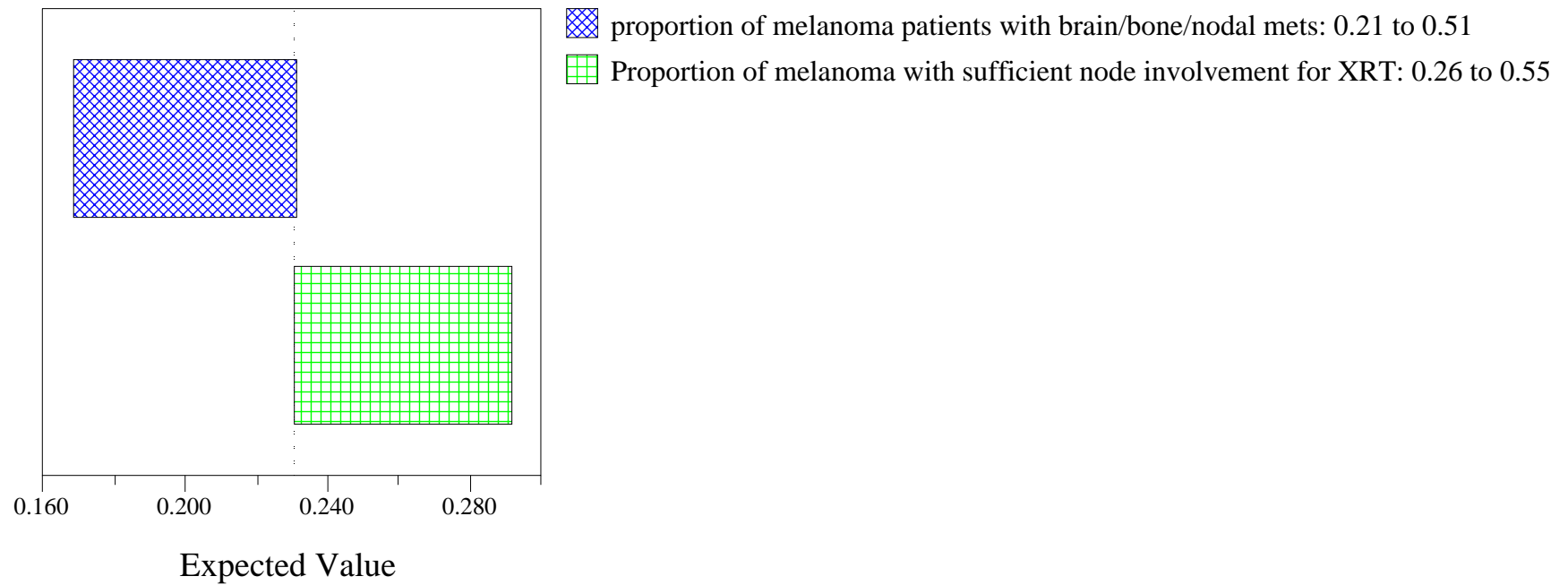
The data or treatment guidelines with the most uncertainty in melanoma were

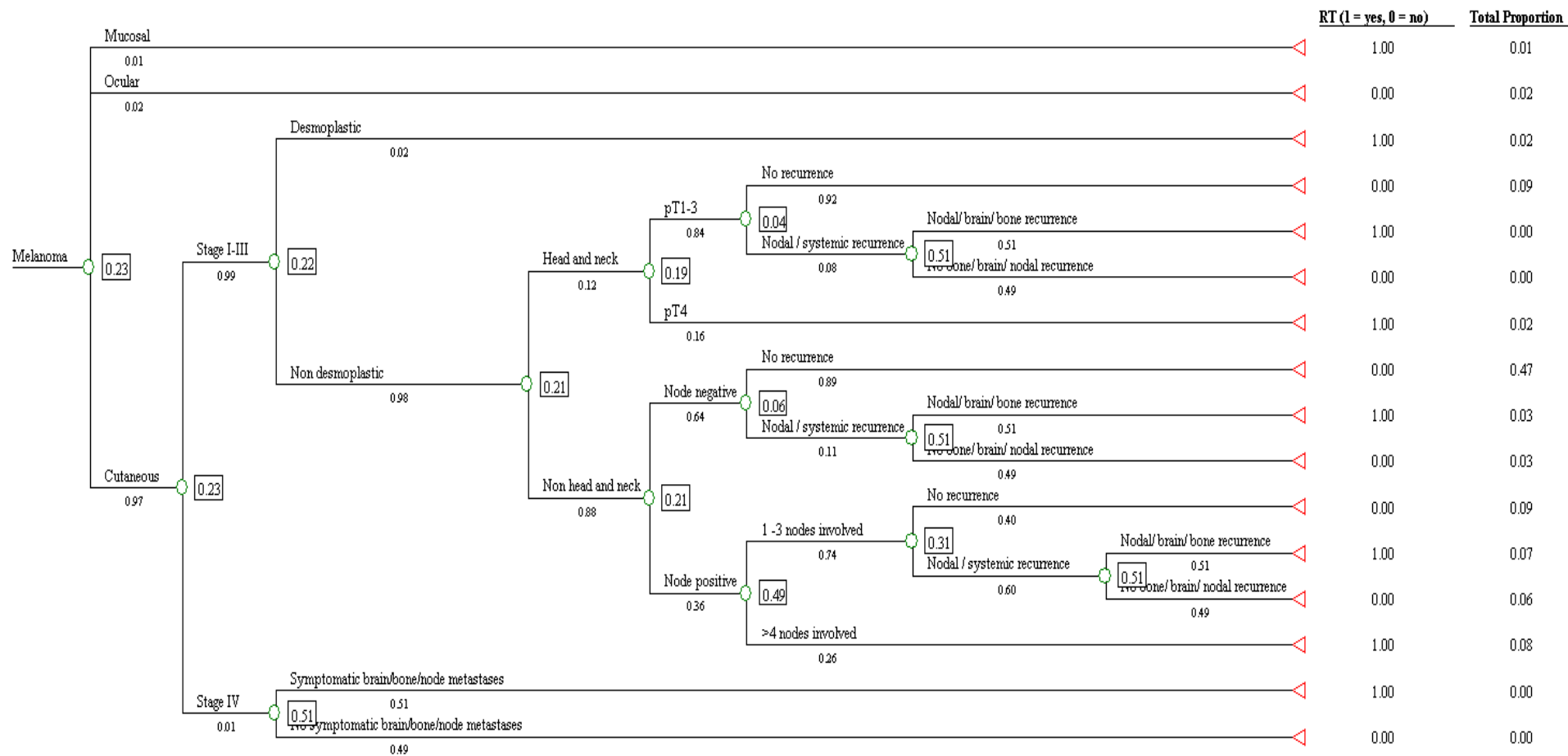
- the estimated proportion of patients with melanoma and evidence of distant disease who have symptomatic brain, bone or nodal metastases (+/- subcutaneous metastases) in whom radiotherapy may be considered. The range quoted in the literature was 0.21 – 0.51. The 0.51 proportional estimate from Slingluff et al. was used in the decision tree as this was identified as the most reliable study as it did not exclude patients with >1 metastatic site of involvement. However, to assess the impact that this uncertainty can have on the estimate of the need for radiotherapy, a sensitivity analysis was performed varying the proportion to 0.21 for patients with a single site of metastatic involvement cited by Cohn-Cedermark et al.
- the estimated proportion of Stage I-III patients with nodal disease high enough to justify the use of radiotherapy to improve loco-regional control. As indicated in explanatory note 6, The NHMRC guidelines for the management of melanoma (1) recommend the consideration of radiotherapy for “multiple” lymph node involvement, but the guidelines do not specifically indicate the number of involved nodes that warrant treatment with radiation.

The number of positive lymph nodes that a patient should have before radiotherapy is recommended is controversial. The NHMRC melanoma treatment guidelines suggest considering radiotherapy when multiple nodes are involved. This could be interpreted as consideration of radiotherapy if > 1 node is involved, whereas others (18), (M. Hughes personal communication) state that it would be reasonable to consider radiotherapy only when >3 nodes are involved. The tree reflects this opinion where only those with >3 nodes positive are recommended for radiotherapy. Sensitivity analysis was performed to assess the impact on the overall radiotherapy utilisation rate if patients with > 1 node involved were recommended for radiotherapy. Incidence data for >3 nodes (36%) and > 1 node involved (55%) were taken from Balch et al.

By varying the values of the two variables, the estimates for the proportion of melanoma patients where radiotherapy is recommended at least once in their illness course is 23% and ranges between 17% and 29%. As melanoma comprises 11 % of all cancers in Australia, the group of melanoma patients in whom radiotherapy is recommended ranges from 1.9% ($0.11 \times 0.17 = 0.019$) to 3% ($0.11 \times 0.29 = 0.03$) of all cancers.

Tornado Diagram at Melanoma





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Gynaecological Cancer

Cervical Cancer

Table 1: Cervical Cancer. Indications for radiotherapy – Levels and sources of evidence

Outcome No.	Clinical Scenario	Treatment Indicated	Level of Evidence	References	Notes	Proportion of all cervical cancer patients
2	Stage IB/IIA, good PS non-bulky disease, surgery, positive lymph nodes	Adjuvant RT	II	<ul style="list-style-type: none"> • National Cancer Institute PDQ Statement on Cervical Cancer (1) • NIH Consensus statement (2) • FIGO Committee on Gynaecologic Oncology (3) • BC Cancer Agency guidelines on Cervical Cancer (4) • NCCN Clinical practice guidelines (5) 	1, 7	0.06
3	Stage IB/IIA, good PS non-bulky disease, surgery, negative lymph nodes, close or positive margins	Adjuvant RT	III	<ul style="list-style-type: none"> • National Cancer Institute PDQ Statement on Cervical Cancer p 13, 15 (1) • NIH Consensus statement (2) • FIGO Committee on Gynaecologic Oncology (3) • NCCN Clinical practice guidelines (5) • BC Cancer Agency guidelines on Cervical Cancer (4) 	1, 7	0.01

Outcome No.	Clinical Scenario	Treatment Indicated	Level of Evidence	References	Notes	Proportion of all cervical cancer patients
4	Stage IB/IIA, good PS non-bulky disease, surgery, negative lymph nodes, negative margins, high risk for local failure (GOG score > 120)	Adjuvant RT	III	<ul style="list-style-type: none"> National Cancer Institute PDQ Statement on Cervical Cancer (1) NCCN Clinical practice guidelines (5) 	1, 8	0.03
5	Stage IB/IIA, good PS non-bulky disease, surgery, no lymph nodes, negative margins, not high risk for local failure (GOG score<120), local recurrence	Radical or palliative RT	III	<ul style="list-style-type: none"> NIH Consensus statement (2) NCCN Clinical practice guidelines (5) 	1, 8	0.01
6	Stage IB/IIA, good PS non-bulky disease, surgery, negative lymph nodes, negative margins, not high risk for local failure (GOG score<120), distant recurrence with brain metastases	Palliative RT	II	<ul style="list-style-type: none"> Priestman et al (6) Kurtz et al (7) Borgelt et al (8) 	1, 12	0.00

Outcome No.	Clinical Scenario	Treatment Indicated	Level of Evidence	References	Notes	Proportion of all cervical cancer patients
7	Stage IB/IIA, good PS non-bulky disease, surgery, negative lymph nodes, negative margins, not high risk for local failure (GOG score <120), distant recurrence with painful bone metastases	Palliative RT	I	<ul style="list-style-type: none"> • NIH Consensus statement (2) • NCCN Clinical practice guidelines (5) 	1, 11	0.00
11	Stage IB/IIA, good PS, bulky disease	Radical or adjuvant (pre- or post-op) RT	III	<ul style="list-style-type: none"> • National Cancer Institute PDQ Statement on Cervical Cancer (1) • FIGO Committee on Gynaecologic Oncology (2) 	1, 6	0.10
12	Stage IB/IIA, poor PS	Radical or palliative RT	III	<ul style="list-style-type: none"> • NIH Consensus statement (2) • FIGO Committee on Gynaecologic Oncology (3) 	1, 5	0.02

Outcome No.	Clinical Scenario	Treatment Indicated	Level of Evidence	References	Notes	Proportion of all cervical cancer patients
13	Stage IIB-IVA	Radical RT (palliative if poor performance status)	II	<ul style="list-style-type: none"> • NIH Consensus statement (2) • FIGO Committee on Gynaecologic Oncology (3) • NCCN Clinical practice guidelines (5) • BC Cancer Agency guidelines on Cervical Cancer (4) 	1, 5	0.26
14	Stage IVB	Palliative RT	IV	<ul style="list-style-type: none"> • NIH Consensus statement (2) • FIGO Committee on Gynaecologic Oncology (3) 	1, 13	0.09
Proportion of cervical cancer patients in whom radiotherapy is recommended						0.58
Total proportion of all cancer patients = 0.58 X 0.23 x 0.05 =						0.7%

ABBREVIATIONS FIGO – Federation Internationale de Gynaecologie et d'Obstetrique

PS – Performance Status

GOG – Gynaecological Oncology Group

RT - Radiotherapy

NIH – National Institute of Health

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

Key	Population or subpopulation of interest	Attribute	Proportion of population with this attribute	Quality of information	References	Explanatory Notes
A	All registry cancers	Gynaecological cancer	0.05	α	AIHW (9)	2
B	All gynaecological cancer	Cervical cancer	0.23	α	AIHW (9)	2
C	All Cervical cancer	Stage IA	0.30	γ	SEER (10)	3
D	All cervical cancer	Stage IB/IIA	0.35	γ	SEER (10)	3
E	Stage IB/IIA	Good/ fair PS	0.95	ζ	Roila et al. (11)	4
F	Stage IB/IIA, Good PS	Non “bulky” disease	0.69	ζ	Fuller Jr. et al. (12)	6
			0.67	θ	Landoni et al. (13)	
G	Stage IB/IIA, Good PS, Non “bulky” disease, Surgery	Lymph node positive	0.25	θ	Landoni et al. (13)	7
			0.16	ζ	Kim et al. (14)	
			0.14	ζ	Kamura et al (15)	
H	Stage IB/IIA, Good PS, Non “bulky” disease, Surgery, Lymph node negative	Positive margins	0.06	θ	Landoni et al. (13)	7
			0.04	ζ	Estape et al. (16)	

Key	Population or subpopulation of interest	Attribute	Proportion of population with this attribute	Quality of information	References	Explanatory Notes
I	Stage IB/IIA, Good PS, Non “bulky” disease, Surgery, Lymph node negative, negative margins	“high risk” for local failure (GOG score > 120)	0.16 0.24 0.27	ε θ ζ	Delgado et al. (17) Landoni et al (13) Kridelka et al. (18)	8
J	Stage IB/IIA, Good PS, Non “bulky” disease, Surgery, Lymph node negative, negative margins, not high risk	Local relapse	0.11 0.08	ε θ	Delgado et al. (17) Landoni et al. (13)	9
K	Stage IB/IIA, Good PS, Non “bulky” disease, Surgery, Lymph node negative, negative margins, not high risk, no local relapse	Distant relapse	0.06 0.03	θ Θ	Landoni et al. (13) Samlal et al. (19)	10
L	Stage IB/IIA, Good PS, Non “bulky” disease, Surgery, Lymph node negative, negative margins, not high risk, no local relapse, distant relapse	Brain metastases	0.09 0.11	ζ ζ	Saphner et al. (20) Wang et al. (21)	12

Key	Population or subpopulation of interest	Attribute	Proportion of population with this attribute	Quality of information	References	Explanatory Notes
M	Stage IB/IIA, Good PS, Non “bulky” disease, Surgery, Lymph node negative, negative margins, not high risk, no local relapse, distant relapse, no brain metastases	Bone metastases	0.16	ζ	Fagundes et al. (22)	11
			0.31	ζ	Wang et al. (21)	
N	Stage IB/IIA, Good PS, Non “bulky” disease, Surgery, Lymph node negative, negative margins, not high risk, no local relapse, distant relapse, no brain metastases, bone metastases	Painful bone metastases	0.80	ζ	Solomayer et al. (23)	11
O	All cervical cancer	Stage IIB-IV A	0.26	γ	SEER (10)	3
P	All cervical cancer	Stage IVB	0.09	γ	SEER (10)	3

Cervical cancer

Treatment guidelines

There are no published peer-reviewed Australian guidelines for the management of cervical cancer and therefore international consensus guidelines were sought. The following guidelines on the management of cervical cancer were identified: NIH consensus conference guidelines (2), FIGO Committee on Gynaecologic Oncology (3), National Cancer Institute PDQ statement on the management of cervical cancer (1), BC Cancer Agency guidelines on Cervical Cancer (4) and NCCN clinical practice guidelines on cervical cancer (5).

Indications for radiotherapy

The guidelines recommend consideration of radiotherapy for cervical cancer in the following situations: -

- Stage IB/IIA disease where radiotherapy is considered an equal alternative to surgery with differing toxicity. The vast majority of good performance status patients undergo surgery and therefore the decision tree depicts surgery as the primary treatment for all good performance status patients, with consideration of radical radiotherapy as definitive treatment in patients with poor performance status (ECOG performance status = 4).
- Stage IIB-IVA as definitive treatment (usually with concurrent chemotherapy) for patients with good performance status.
- Post-operative therapy in the presence of positive pelvic nodes, positive surgical margins, or other adverse pathological features (such as GOG score > 120 – see explanatory note 8).
- As palliative treatment in patients with any stage disease and poor performance status or advanced disease with local primary symptoms, symptoms related to bone metastases or for recurrent disease following surgery.

Explanatory Notes for Tables 1 and 2

1. Incidence of cervical cancer

AIHW data (9) show that gynaecological cancer represents approximately 5% of all cancers and cervical cancer represents 23% of all gynaecological cancer. For this decision tree no distinction was made between squamous cell carcinoma and adenocarcinoma, as the treatment recommendations for both histological types of cervical cancer are the same.

2. Stage

The FIGO (Federation Internationale de Gynecologie et d'Obstetrique) staging system was used in preference to the TNM or other staging systems. Most of the treatment guidelines base their treatment recommendations on FIGO stage. In addition, published incidence data is reported according to initial FIGO stage.

The SA Hospital registry (24) contains data by Stages I, II, III and IV but is not broken down into sub-stage categories for stages above stage I. The 1998 SEER database (10) contains data on 9601 invasive cervical carcinomas (excluding cervical intra-epithelial neoplasia) and this database does report substages. The data from the two databases are shown in Table 3. 2830 (30%) are Stage IA, Stage IB = 3024 (31%), Stage IIA = 385 (4%), Stage IIB = 700 (7%), Stage IIIA = 101 (1%), Stage IIIB = 1601 (18%), Stage IVA = 82 (1%) and Stage IVB = 878 (9%).

Table 3: Stage data on cervical carcinoma

Stage substage		SA Cancer Registry	SEER
I		56%	61%
	IA	14%	30%
	IB	42%	31%
II		25%	11%
	IIA	NR	4%
	IIB	NR	7%
III		13%	19%
IV		6%	10%
	IVA	NR	1%
	IVB	NR	9%
NR = Not Reported			

The branch points for the decision tree are for Stage IA (SEER data = 0.30), Stages IB-IIA (SEER = 0.35), Stages IIB-IVA (SEER = 0.26) and Stage IVB (SEER = 0.09). These stage groupings were chosen as branch points to reflect the treatment guideline recommendations. The SEER incidence data was therefore used in preference to local data due to the lack of sub-stage data from the local registries. Local departmental databases were not used because of the potential for the stage data to be influenced by referral bias.

For Stage IA disease, several studies (25) (26) (27) (28) (29) (30) (31) (32) and the NIH consensus statement (2) report a recurrence rate of <1% for patients undergoing surgical excision of IA disease. Similarly the rate of distant metastases is <1%. Therefore for the purpose of the decision tree all patients with Stage IA disease do not require radiotherapy and there are no branches signifying recurrence (the very low numbers will not have an impact on the overall optimal radiotherapy utilisation rate). Occasional patients with Stage IA disease may not be medically fit for surgery but these patients would most

probably be treated by intracavitary radiotherapy only without external beam radiotherapy (33).

3. Performance status

Very little data exist on performance status by stage for cervical cancer. The only data identified specific to cervical cancer were that of the US radiotherapy Patterns of Care studies for the years 1973 and 1978 by Lanciano et al (34) and 1973 by Hanks et al. (35). They report that approximately 22% had a Karnofsky score of <80. Both of these datasets may have been biased, as they only included patients undergoing radiotherapy and not other treatment modalities (therefore the data may be skewed towards more advanced disease or patients with a poorer performance status) and include all stages of disease.

There were no specific reports on the proportions of cervical carcinoma patients by performance status or on the basis of medical operability, and so sources describing performance status in general oncology were used. Roila et al. (11) report on the performance status of 209 consecutive cancer patients treated at an Italian oncology centre. The vast majority of patients had breast, haematological, lung, genito-urinary or gastro-intestinal malignancy. One hundred and twenty of the 209 patients had disseminated disease. Eleven of the patients (5%) were classified as having ECOG performance status of 4. It should be noted that in fact this proportion is also similar to the proportion of patients with low performance status in the prostate cancer and lung cancer populations where specific data are available (36) (37) (38). It was assumed that these patients would not be fit for radical surgical resection. These patients would commonly be referred for radiotherapy instead.

4. Surgery versus radiotherapy for Stages IB-IIA

This remains a contentious issue. A randomised trial (13) reported identical 5-year overall and disease-free survival rates when comparing radiation therapy to radical hysterectomy (1). Both the National Cancer Institute PDQ Statement on Cervical Cancer (1) and the NIH Consensus statement (2) state that radiotherapy and surgery are equally efficacious for this stage of disease and therefore both options should be put to the patient. If surgery is chosen then post-operative radiotherapy is recommended for lymph node positive disease, close or positive margins or when other risk factors are present.

The NIH Consensus statement (2) clearly states that radiotherapy is the standard of care for stages above Stage IIA. The NIH Consensus also justifies radiotherapy for recurrence after surgery.

Given that there are no definitive studies proving the superiority of either surgery or radiotherapy in early stage cervix cancer, actual utilisation rates were used in this study. In Australian practice, the vast

majority of early stage cervical cancer is treated by radical gynaecological surgery. The exceptions are usually those patients with poor performance status, significant co-morbidity or who refuse surgery. The proportion of patients where radiotherapy could be considered appropriate was not readily available from the literature. Therefore, for the purposes of the optimal radiotherapy utilisation tree it was decided that patients with ECOG 0-3 receive surgery and ECOG IV receive radiation (either palliative or radical depending upon age, prognosis etc.). For poor performance status patients, it would still be appropriate to treat them with radical or palliative radiotherapy in most instances.

5. Patients with “bulky” early stage disease

These patients have a high risk of locoregional recurrence with surgery alone and therefore radiotherapy is recommended either definitively or post-operatively in this group of patients by most peer-reviewed guidelines. Landoni et al. (13) described a randomised trial for Stages IB and IIA in which patients were randomised to either radical hysterectomy or radical radiotherapy. 33% of patients had bulky (defined as >4 cm) tumours. Fuller Jr. et al. (12) report that 31% of Stage IB-IIA cervical cancer patients at the Memorial Sloan Kettering Cancer Center from 1939-1977 had bulky disease.

6. Proportion of early stage cervical cancer of ‘non-bulky’ size that have positive nodes or positive margins

Post-operative radiotherapy is recommended for non-bulky disease with positive lymph nodes or positive surgical margins in order to reduce the incidence of locoregional relapse (2). Landoni et al (13) in a randomised trial reported on 114 patients with non-bulky tumours (< 4cm) who underwent surgery; 7 (6%) had positive surgical margins and 28 (25%) had positive lymph nodes. A further 27 (24%) of the patients with non-bulky tumours, negative margins and negative lymph nodes had “high risk” disease warranting adjuvant radiotherapy. The criteria for offering radiotherapy were at least one of the following – surgical stage > Pt2a, <3mm uninvolved cervical stroma, cut-through and positive lymph nodes. Patients with no “high risk” features treated with surgery alone had a local recurrence rate of 8% and a distant relapse rate of 6%. Estape et al. (16) reported on 1223 Stage IA2-IIA patients treated in 1965-1995 with radical hysterectomy. Fifty-one patients (4%) were considered to have margins of <0.5cm from the surgical resection edge. However, patients with positive margins were excluded from the study. Patients with close margins treated with radiation had a substantial improvement in local control compared with those not treated with adjuvant radiotherapy.

Kim et al. (14) reported on 366 patients who underwent radical hysterectomy and lymph node dissection in Chonnam University Hospital, Korea from 1985 to 1994. 16% of tumours <4cm were lymph node positive. Kamura et al. (15) report lymph node metastases in

34/249 (14%) patients undergoing hysterectomy for Stage IB-IIA disease in 1979-1988.

7. Intermediate risk (node negative, presence of other adverse prognostic features)

A subgroup of node-negative, margin-negative patients have been identified as being at intermediate risk of recurrence and post-operative radiotherapy is recommended in these patients (39) (15) (31). The PDQ and NIH treatment guidelines recommend consideration of radiotherapy for adverse pathological features such as presence of lymphovascular invasion, increasing tumour size and increasing depth of invasion, but do not specifically state at what point they would recommend that the adverse features are sufficiently bad to warrant treatment with post-operative radiotherapy. Therefore, surrogate measures of locoregional recurrence risk where prevalence data could be identified were sought.

A Gynaecological Oncology Group (GOG) randomised trial reported by Sedlis et al. (39) indicates better local control rate for patients with “adverse pathology” who receive post-operative radiotherapy. Delgado et al. (17) describe a GOG study in which 545 patients with node negative disease were observed after radical hysterectomy. Three independent prognostic factors – clinical tumour size, depth of invasion and presence of lymph-vascular invasion – predicted for a higher rate of recurrence (40%) and radiotherapy was advised in these patients. Recurrence rates by GOG score were 11% when GOG score <120 and 70% when GOG score >120. In this series, 16% have a GOG score >120. Kridelka et al. (18) reported that 27% of 92 node negative Stage IB patients had a GOG score > 120 in their series. A GOG score cut-off of >120 has been taken arbitrarily as the decision-point to proceed routinely to radiotherapy for this decision tree as the treatment guidelines reviewed were not specific enough to provide this information. It is acknowledged that some gynaecological oncology units may use a slightly different cut-off and that the importance of the GOG score has not been validated by a randomised controlled trial.

8. Locoregional recurrence rates for “good prognosis” patients

Recurrence data: For those patients not given radiotherapy because of the absence of adverse pathology, radiotherapy is recommended if they develop recurrence as either salvage radical therapy or in palliation (40) (21). The proportion of patients with “favourable” pathology is estimated from Delgado et al (17). They report a locoregional recurrence rate of 11% for patients with a GOG score <120. Radiotherapy has been identified as good palliative treatment for patients with post-surgical disease recurrence (2).

9. Distant metastases

In the randomised trial of Landoni et al (13), 114 patients with non-bulky tumours (< 4cm) received surgery. Patients treated with surgery alone with no “high risk” features had a local recurrence rate of 8% and

a distant relapse rate of 6%. Samlal et al. (19) reported on the distant metastatic rate in early stage cervical carcinoma with negative pelvic nodes treated by surgery. They reviewed 15 studies and calculated an overall distant metastatic rate of 120/3702 (3%).

10. Pattern of metastatic disease

A comprehensive single-institution study from the Mallinckrodt Institute of Radiology reported on 1211 patients treated with radiation alone 1959-1986 (22). Since studies have shown a similar outcome following surgery and radiotherapy for early stage disease, the sites of distant metastases following radiotherapy quoted in the paper is assumed to also reflect similar metastatic patterns for patients who undergo surgery. 322 of the patients developed distant metastases. Of all patients with metastatic disease, 16% (CI+/-4%) developed bone metastases. The metastatic rates for squamous cell carcinoma and adenocarcinoma were comparable. Other metastatic rates reported where radiotherapy may be considered were para-aortic nodes 11%, lung 21%, supraclavicular nodes 7%, and inguinal nodes 3%. No report on the rate of symptomatic disease or actual palliative radiotherapy utilisation was provided in the report.

Wang et al. (21) reported on 45 patients with metastatic disease, of whom 31% (CI+/-16%) had bone metastases. This was double the rate reported by Fagundes et al (22) but the wide confidence intervals reflect the small dataset. Therefore, the 16% quoted in the larger study was used.

There was no available information on the proportion of patients with metastatic cervical carcinoma and bone metastases who have bone pain warranting palliative radiotherapy. However, it is reasonable to assume that the vast majority of patients who are clinically diagnosed to have bone metastases are symptomatic as bone scans or x-ray screening for metastases are not usually part of routine practice. It was also assumed that the proportion of patients with bone pain who require palliative radiotherapy would be similar to that of breast carcinoma. In fact, this may under-estimate the proportion of patients where palliative radiotherapy may be appropriate as more palliative systemic treatment options are available in breast cancer management than for other cancers. Solomayer et al. (23) report that approximately 80% of all breast cancer patients with bone metastases have pain, and this proportion was used to estimate the palliative role of radiotherapy in cervical carcinoma patients with bone metastases.

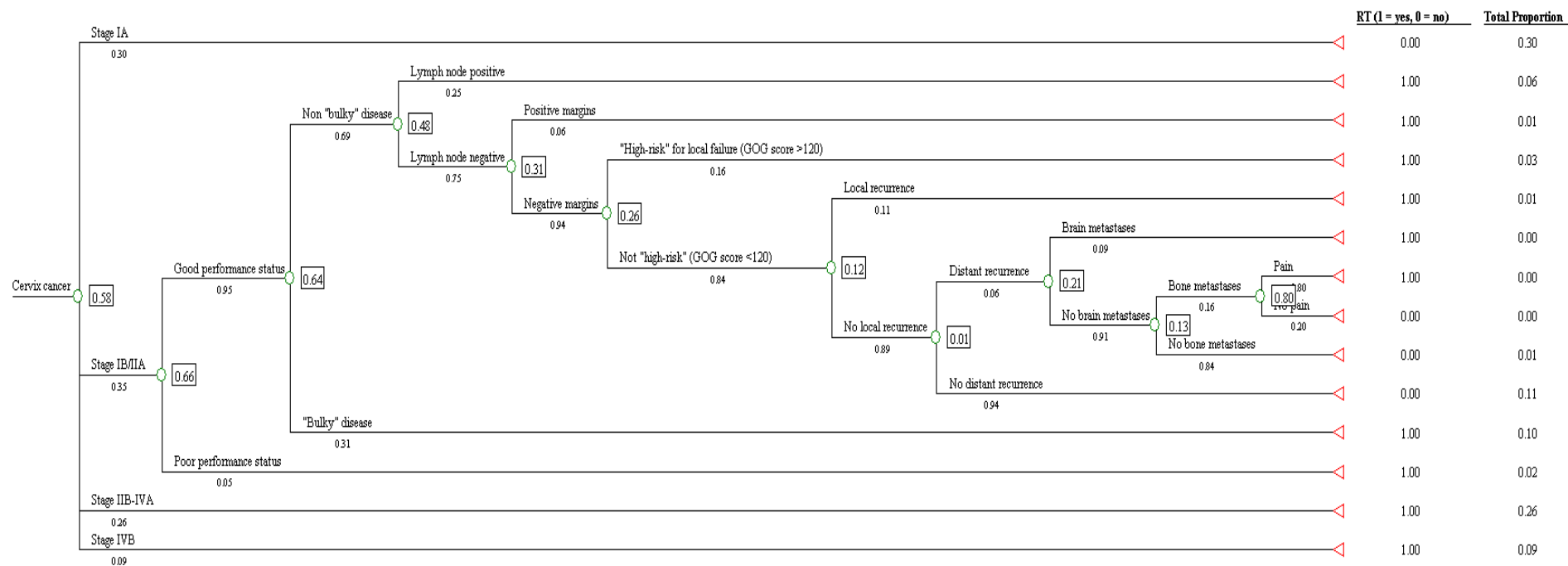
11. Proportion of metastatic disease that occurs in the brain

A commonly recommended role for radiotherapy is for palliative treatment of symptomatic brain metastases (8) (7) (6). The proportion of patients with metastatic cervical carcinoma who develop brain metastases was obtained from several sources. Saphner et al. (20)

reported that 6 patients had brain metastases out of 67 with Stage IV disease (9%) in a study of 1219 patients with cervical cancer. Wang et al. (21) reported on 45 cervical carcinoma patients who developed distant metastases at a median follow-up of 5.9 years. 5 patients (11%) had brain metastases.

12. Proportion of patients with metastatic disease and local symptoms

For patients with Stage IVB disease, it is recommended that the vast majority of these patients receive radiotherapy for palliation of local symptoms (41). It is uncommon for patients with Stage IVB disease to be completely asymptomatic from their primary tumour and therefore palliative radiotherapy is recommended to alleviate symptoms such as pain, bleeding or symptoms secondary to metastases to bone or lymph nodes. This may even be the case for patients with very poor performance status where treatment with single fractions of radiotherapy, with acceptable toxicity, have led to improvements of symptoms (42). The actual proportion that this represents is not possible to obtain from the published literature. Interviews with several gynaecological oncology experts revealed that their experience was that almost all patients have local symptoms such as pain or bleeding and warrant a radiotherapy opinion. Therefore, for the decision tree, it was decided that treating all patients with radiotherapy was the most appropriate option.



Endometrial Cancer

Table 4: Endometrial Cancer. Indications for radiotherapy – Levels and sources of evidence

Outcome No.	Clinical scenario	Treatment indicated	Level of Evidence	References	Notes	Proportion of all endometrial cancer patients
15	Endometrioid, Stage I, good PS, lymph node dissection, node negative, local recurrence	Palliative or radical RT (+/-) surgery	III	<ul style="list-style-type: none"> • PDQ Statement on Treatment of Endometrial cancer (43) • FIGO Committee on Gynaecologic Oncology (3) 	6	0.01
16	Endometrioid, Stage I, good PS, lymph node dissection, node negative, no local recurrence, distant recurrence, brain metastases	Palliative RT	III	<ul style="list-style-type: none"> • FIGO Committee on Gynaecologic Oncology (3) 	11	<0.01
17	Endometrioid, Stage I, good PS, lymph node dissection, node negative, no local recurrence, distant recurrence, no brain metastases, painful bone metastases	Palliative RT	I	<ul style="list-style-type: none"> • FIGO Committee on Gynaecologic Oncology (3) 	11	<0.01

Outcome No.	Clinical scenario	Treatment indicated	Level of Evidence	References	Notes	Proportion of all endometrial cancer patients
18	Endometrioid, Stage I, good PS, lymph node dissection, node negative, no local recurrence, distant recurrence, no brain metastases, no painful bone metastases, painful other metastases	Palliative RT	III	<ul style="list-style-type: none"> NCCN Clinical Practice Guidelines on Uterine cancer (44) 	11	<0.01
21	Endometrioid, Stage I, good PS, no lymph node dissection, adverse pathology	Adjuvant RT	II	<ul style="list-style-type: none"> Royal Marsden protocol (45) BC Cancer Agency guidelines on endometrial cancer (46) NCCN Clinical Practice Guidelines on Uterine cancer (44) 	7	0.14
22	Endometrioid, Stage I, good PS, no lymph node dissection, no adverse pathology, local recurrence	Radical or palliative RT	III	<ul style="list-style-type: none"> PDQ Statement on Treatment of Endometrial cancer (43) FIGO Committee on Gynaecologic Oncology (3) BC Cancer Agency guidelines on endometrial cancer (46) NCCN Clinical Practice Guidelines on Uterine cancer (44) 	10	0.01

Outcome No.	Clinical scenario	Treatment indicated	Level of Evidence	References	Notes	Proportion of all endometrial cancer patients
23	Endometrioid, Stage I, good PS, no lymph node dissection, no adverse pathology, no local recurrence, distant recurrence, brain metastases	Palliative RT	III	<ul style="list-style-type: none"> FIGO Committee on Gynaecologic Oncology (3) 	11	<0.01
24	Endometrioid, Stage I, good PS, no lymph node dissection, no adverse pathology, no local recurrence, distant recurrence, no brain metastases, painful bone metastases	Palliative RT	I	<ul style="list-style-type: none"> FIGO Committee on Gynaecologic Oncology (3) 	11	<0.01
25	Endometrioid, Stage I, good PS, no lymph node dissection, no adverse pathology, no local recurrence, distant recurrence, no brain metastases, no painful bone metastases, painful other metastases	Palliative RT	III	<ul style="list-style-type: none"> NCCN Clinical Practice Guidelines on Uterine cancer (44) 	11	<0.01

Outcome No.	Clinical scenario	Treatment indicated	Level of Evidence	References	Notes	Proportion of all endometrial cancer patients
28	Endometrioid, Stage I, poor PS	Palliative or Radical RT +/- chemotherapy	III	<ul style="list-style-type: none"> • PDQ Statement on Treatment of Endometrial cancer (43) • FIGO Committee on Gynaecologic Oncology (3) • American Brachytherapy Society (47) • NCCN Clinical Practice Guidelines on Uterine cancer (44) 	12	0.03
29	Endometrioid, Stage I, good PS, lymph node dissection, node negative, local recurrence	Palliative or radical RT (+/-) surgery	III	<ul style="list-style-type: none"> • PDQ Statement on Treatment of Endometrial cancer (43) • FIGO Committee on Gynaecologic Oncology (3) • BC Cancer Agency guidelines on endometrial cancer (46) • NCCN Clinical Practice Guidelines on Uterine cancer (44) 	10	<0.01

Outcome No.	Clinical scenario	Treatment indicated	Level of Evidence	References	Notes	Proportion of all endometrial cancer patients
30	Endometrioid, Stage IIA, good PS, lymph node dissection, node negative, no local recurrence, distant recurrence, brain metastases	Palliative RT	III	<ul style="list-style-type: none"> FIGO Committee on Gynaecologic Oncology (3) 	11	<0.01
31	Endometrioid, Stage IIA, good PS, lymph node dissection, node negative, no local recurrence, distant recurrence, no brain metastases, painful bone metastases	Palliative RT	I	<ul style="list-style-type: none"> FIGO Committee on Gynaecologic Oncology (3) 	11	<0.01
32	Endometrioid, Stage IIA, good PS, lymph node dissection, node negative, no local recurrence, distant recurrence, no brain metastases, no painful bone metastases, painful other metastases	Palliative RT	III	<ul style="list-style-type: none"> NCCN Clinical Practice Guidelines on Uterine cancer (44) 	11	<0.01

Outcome No.	Clinical scenario	Treatment indicated	Level of Evidence	References	Notes	Proportion of all endometrial cancer patients
35	Endometrioid, Stage IIA, good PS, no lymph node dissection, adverse pathology	Adjuvant RT	II	<ul style="list-style-type: none"> Royal Marsden protocol (45) NCCN Clinical Practice Guidelines on Uterine cancer (44) 	7	0.02
36	Endometrioid, Stage IIA, good PS, no lymph node dissection, no adverse pathology, local recurrence	Radical or palliative RT	III	<ul style="list-style-type: none"> PDQ Statement on Treatment of Endometrial cancer (43) FIGO Committee on Gynaecologic Oncology (3) NCCN Clinical Practice Guidelines on Uterine cancer (44) 	9	<0.01
37	Stage IIA, good PS, no lymph node dissection, no adverse pathology, no local recurrence, distant recurrence, brain metastases	Palliative RT	III	<ul style="list-style-type: none"> FIGO Committee on Gynaecologic Oncology (3) 	11	<0.01

Outcome No.	Clinical scenario	Treatment indicated	Level of Evidence	References	Notes	Proportion of all endometrial cancer patients
38	Endometrioid, Stage IIA, good PS, no lymph node dissection, no adverse pathology, no local recurrence, distant recurrence, no brain metastases painful bone metastases	Palliative RT	I	<ul style="list-style-type: none"> FIGO Committee on Gynaecologic Oncology (3) 	11	<0.01
39	Endometrioid, Stage IIA, good PS, no lymph node dissection, no adverse pathology, no local recurrence, distant recurrence, no brain mets, no painful bone metastases, painful other metastases	Palliative RT	III	<ul style="list-style-type: none"> NCCN Clinical Practice Guidelines on Uterine cancer (44) 	12	<0.01

Outcome No.	Clinical scenario	Treatment indicated	Level of Evidence	References	Notes	Proportion of all endometrial cancer patients
42	Endometrioid, Stage IIA, poor PS	Palliative or Radical RT +/- chemotherapy	III	<ul style="list-style-type: none"> • PDQ Statement on Treatment of Endometrial cancer (43) • FIGO Committee on Gynaecologic Oncology (3) • American Brachytherapy Society (47) • NCCN Clinical Practice Guidelines on Uterine cancer (44) 	10	<0.01
43	Endometrioid, Stage IIB-III	Palliative or radical RT (+/- chemotherapy)	III	<ul style="list-style-type: none"> • FIGO Committee on Gynaecologic Oncology (3) • BC Cancer Agency guidelines on endometrial cancer (46) • NCCN Clinical Practice Guidelines on Uterine cancer (44) 		0.10
44	Endometrioid, Stage IV, brain metastases	Palliative RT	III	<ul style="list-style-type: none"> • FIGO Committee on Gynaecologic Oncology (3) 	11	<0.01
45	Endometrioid, Stage IV, no brain metastases, painful bone metastases	Palliative RT	I	<ul style="list-style-type: none"> • FIGO Committee on Gynaecologic Oncology (3) 	11	<0.01

Outcome No.	Clinical scenario	Treatment indicated	Level of Evidence	References	Notes	Proportion of all endometrial cancer patients
46	Endometrioid, Stage IV, no brain metastases, no painful bone metastases, painful other metastases	Palliative RT	III	<ul style="list-style-type: none"> NCCN Clinical Practice Guidelines on Uterine cancer (44) 	11	<0.01
48	Papillary serous and clear cell carcinoma	RT as definitive, adjuvant or palliative treatment	III	<ul style="list-style-type: none"> BC Cancer Agency Guidelines (46) NCCN Clinical Practice Guidelines on Uterine cancer (44) 	3	0.13
Proportion of patients with endometrial cancer in whom radiotherapy is recommended						0.46
Total proportion of all cancer patients = 0.46 X 0.37 x 0.05 =						0.9%

ABBREVIATIONS

PS – Performance Status

GOG – Gynaecological Oncology Group

RT - Radiotherapy

NIH – National Institute of Health

FIGO – Federation Internationale de Gynaecologie et d'Obstetrique

Table 5: Endometrial cancer. The incidence of attributes used to define indications for radiotherapy

Key	Population or Sub-population of interest	Attribute	Proportion of populations with this attribute	Quality of information	References	Explanatory Notes
A	All registry cancers	Gynaecological cancer	0.05	α	AIHW (9)	1
B	All gynaecological cancer	Endometrial cancer	0.37	α	AIHW (9)	1
C	All endometrial cancer	Endometrioid histology	0.87	ζ	Cirisano et al. (48)	3
D	All endometrioid cancer	Stage I	0.72	γ	SEER (10)	2
E	Stage I	Good PS	0.95	ζ	Roila et al. (11)	4
F	Stage I, Good PS	Lymph node dissection	0.50	μ	Expert opinion	5
G	Stage I, good PS, lymph node dissection, node negative	Local recurrence	0.05	ζ	Ayhan et al. (49)	6
H	Stage I, good PS, lymph node dissection, node negative, no local recurrence	Distant recurrence	0.02	ζ	Ayhan et al. (49)	6
I	Stage I, good PS, lymph node dissection, node negative, no local recurrence, distant recurrence	Brain metastases	0.03 0.06 0.03	δ ζ ζ	Salvesen et al. (50) Aalders et al. (51) Shumsky et al. (52)	11

Key	Population or Sub-population of interest	Attribute	Proportion of populations with this attribute	Quality of information	References	Explanatory Notes
J	Stage I, good PS, node negative, no local recurrence, distant recurrence, no brain metastases	Painful bone metastases	0.06 0.12 0.11	δ ζ ζ	Salvesen et al. (50) Aalders et al. (47) Shumsky et al. (52)	11
K	Stage I, good PS, Node negative, no local recurrence, distant recurrence, no brain metastases, no painful bone metastases	Painful other site metastases	0.06	δ	Salvesen et al. (50)	11
L	Stage I, good PS, no lymph node dissection	Adverse pathology	0.37 0.43 0.44 0.46	ϵ ζ ζ ζ	Thomas et al. (45) Creasman et al. (53) Irwin et al. (54) Ayhan et al. (49)	7
M	Stage I, good PS, no lymph node dissection, no adverse pathology	Local recurrence	0.07 0.01	ζ ζ	Irwin et al. (54) Eltabbakh et al. (55)	8
N	Stage I, good PS, no lymph node dissection, no adverse pathology, no local recurrence	Distant recurrence	0.02 0.03	ζ ζ	Irwin et al. (54) Eltabbakh et al. (55)	8
O	Stage I, good PS, no lymph node dissection, no adverse pathology, no local recurrence, distant recurrence	Brain metastases	0.03 0.06 0.03	δ ζ ζ	Salvesen et al. (50) Aalders et al. (51) Shumsky et al. (52)	11

Key	Population or Sub-population of interest	Attribute	Proportion of populations with this attribute	Quality of information	References	Explanatory Notes
P	Stage I, good PS, no lymph node dissection, no adverse pathology, no local recurrence, distant recurrence, no brain metastases	Painful bone metastases	0.06 0.12 0.11	δ ζ ζ	Salvesen et al. (50) Aalders et al. (51) Shumsky et al. (52)	11
Q	Stage I, good PS, no lymph node dissection, no adverse pathology, no local recurrence, distant recurrence, no brain metastases, no painful bone metastases	Painful other site metastases	0.06	δ	Salvesen et al. (50)	11
R	All endometrioid cancer	Stage IIA	0.08	γ	SEER (10)	2
S	Stage IIA	Good PS	0.95	ζ	Roila et al. (11)	4
T	Stage IIA, good PS	Lymph node dissection	0.50	μ	Expert opinion	5
U	Stage IIA, good PS, lymph node dissection, node negative	Local recurrence	0.12	ζ	Calais et al. (56)	6
V	Stage IIA, good PS, lymph node dissection, node negative, no local recurrence	Distant recurrence	0.10	ζ	Calais et al. (56)	6

Key	Population or Sub-population of interest	Attribute	Proportion of populations with this attribute	Quality of information	References	Explanatory Notes
W	Stage IIA, good PS, lymph node dissection, node negative, no local recurrence, distant recurrence	Brain metastases	0.03 0.06 0.03	δ ζ ζ	Salvesen et al. (50) Aalders et al. (51) Shumsky et al. (52)	11
X	Stage IIA, good PS, lymph node dissection, node negative, no local recurrence, distant recurrence, no brain metastases	Painful bone metastases	0.06 0.12 0.11	δ ζ ζ	Salvesen et al. (50) Aalders et al. (51) Shumsky et al. (52)	11
Y	Stage IIA, good PS, lymph node dissection, node negative, no local recurrence, distant recurrence, no brain metastases, no painful bone metastases	Painful other site metastases	0.06	δ	Salvesen et al. (50)	11
Z	Stage IIA, good PS, no lymph node dissection	Adverse pathology	0.37 0.43 0.40	ε ζ ζ	Thomas et al. (45) Creasman et al. (53) Eltabbakh et al. (57)	7
A2	Stage IIA, good PS, no lymph node dissection, no adverse pathology	Local recurrence	0.07	ζ	Eltabbakh et al. (57)	9
B2	Stage IIA, good PS, no lymph node dissection, no adverse pathology, no local recurrence	Distant recurrence	0	ζ	Eltabbakh et al. (57)	9

Key	Population or Sub-population of interest	Attribute	Proportion of populations with this attribute	Quality of information	References	Explanatory Notes
C2	Stage IIA, good PS, no lymph node dissection, no adverse pathology, no local recurrence, distant recurrence	Brain metastases	0.03 0.06 0.03	δ ζ ζ	Salvesen et al. (50) Aalders et al. (51) Shumsky et al. (52)	11
D2	Stage IIA, good PS, no lymph node dissection, no adverse pathology, no local recurrence, distant recurrence, no brain metastases	Painful bone metastases	0.06 0.12 0.11	δ ζ ζ	Salvesen et al. (50) Aalders et al. (51) Shumsky et al. (52)	11
E2	Stage IIA, good PS, no lymph node dissection, no adverse pathology, no local recurrence, distant recurrence, no brain metastases, no painful bone metastases	Painful other site metastases	0.06	δ	Salvesen et al. (50)	11
F2	All endometrioid cancer	Stage IIB-III	0.11	γ	SEER (10)	2
G2	All endometrioid cancer	Stage IV	0.09	γ	SEER (10)	2
H2	Stage IV	Brain metastases	0.03 0.06 0.03	δ ζ ζ	Salvesen et al. (50) Aalders et al. (51) Shumsky et al. (52)	11
I2	Stage IV, no brain metastases	Painful bone metastases	0.06 0.12 0.11	δ ζ ζ	Salvesen et al. (50) Aalders et al. (51) Shumsky et al. (52)	11
J2	Stage IV, no brain metastases,	Painful other site	0.06	δ	Salvesen et al. (50)	11

	no painful bone metastases	metastases				
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Endometrial cancer

Treatment guidelines

There are no published peer-reviewed Australian guidelines for the management of endometrial cancer and therefore international consensus guidelines were sought. The following international guidelines on the treatment of endometrial cancer were identified: National Cancer Institute PDQ statement on the management of endometrial cancer (1), NIH consensus conference (2), FIGO Committee on Gynaecologic Oncology (3), NCCN Clinical Practice guidelines on uterine cancer (44) and BC Cancer Agency Guidelines on endometrial cancer (46).

Indications for radiotherapy

The guidelines state that radiotherapy in endometrial cancer should be considered in the following situations: -

- For patients with Stage I-IIA disease who do not undergo lymph node dissection but have adverse pathology (based on deep myometrial invasion, grade and margin status)
- For patients with brain metastases
- For patients with bone metastases
- For patients with local recurrence where the previous treatment was surgery alone
- For patients with Stages I-IIA with poor performance status unsuitable for surgery
- For patients with Stages IIB-III disease (usually in conjunction with surgery for the fit patient or as definitive treatment for the patient unfit for surgery)
- For patients with pathologic sub-types papillary-serous or clear cell carcinoma (usually in conjunction with surgery).

Explanatory Notes for Tables 4 and 5

1. Incidence of endometrial cancer

AIHW data indicates that endometrial cancer comprises 37% of all gynaecological malignancy (9).

2. Stage

The FIGO (Federation Internationale de Gynecologie et d'Obstetrique) staging system was used in preference to the TNM or other staging systems. Most of the guidelines base their treatment recommendations on FIGO stage. In addition, most published incidence data report according to initial FIGO stage.

No Australian cancer registry data provided Stage data in sufficient detail to allow subdivision into substages IA, IB, IIA, IIB etc. Therefore 1998 SEER data (10) on 27,271 patients were used –

- Stage I = 19 795 (72%) ,
- II = 3755 (14%),
- III = 1288 (5%),
- IV = 2433 (9%)

There was no break down for Stage II into IIA and IIB. However, 58% of Stage II are IIA according to the surgical series reported by Eltabbakh et al. This results in a stage proportion of 72% Stage I, 8% Stage IIA, 6% Stage IIB, 5% Stage III and 9% Stage IV.

3. **Radiotherapy recommendations based on papillary serous histology**

The BC Cancer Agency guidelines (46) recommend adjuvant radiotherapy (or palliative radiotherapy for inoperable disease) for all stages of endometrial cancer of the papillary serous and clear cell pathological sub-types. The other histological variants of endometrial malignancy such as sarcoma comprise a very small proportion and were not considered in the decision tree.

Cirisano et al. (48) report on 573 patients treated in their institution. Thirteen percent were papillary serous or clear cell sub-types of endometrial carcinoma. It is assumed that all patients with these histological sub-types receive post-operative radiotherapy irrespective of stage because of the higher than average risk of recurrence (48). Corn et al. (58) reported on 394 women treated at the Hospital of the University of Pennsylvania and Fox Chase Cancer Centre, and 43/394 (11%) had papillary-serous or clear cell histologies.

4. **Performance status**

For the purposes of the decision trees when deciding on radical or adjuvant therapy, poor performance status was taken as ECOG performance level of 4 and good-fair was ECOG performance level 0-3. This was done to exclude those patients with such poor performance status that conservative palliation would be preferred to radiation. However, when determining the use of palliative radiotherapy, the vast majority of symptomatic patients with ECOG of 4 would most likely warrant radiotherapy and therefore patients of ALL performance status levels were included when palliative radiotherapy was considered appropriate.

Very little data exists on performance status by stage for endometrial cancer. Therefore, performance status data from general cancer populations was sought. Roila et al. (11) reported on the performance status of 209 consecutive cancer patients treated at an Italian oncology centre. The vast majority of patients had breast, haematological, lung, genito-urinary or gastro-intestinal malignancy. One hundred and twenty of the 209 patients had disseminated disease. Eleven of the patients (5%) were classified as having an ECOG performance status of 4. The SA Hospital Registry data (24) for performance status in breast cancer patients (i.e. 91% of patients having a good performance status – ECOG 0-2) was used. It should be noted that this proportion is similar to the

reported performance status of prostate cancer and lung cancer patients, for whom specific data on performance status was available. This data is therefore used for endometrial cancer on the assumption that performance status levels would be similar for these cancers.

5. The controversies of the role of lymph-node dissection for early stage endometrial cancer

It is controversial whether patients who undergo hysterectomy for clinical Stage I-IIA disease should undergo pelvic lymph node dissection (59). Proponents of lymph node dissection argue that it results in more accurate staging and reduces the proportion of patients who require radiotherapy. Proponents of post-operative radiotherapy argue that the risk of lymph node positivity can be predicted based on adverse pathologic features such as deep myometrial invasion or grade. Studies have shown improvement in locoregional control with the addition of adjuvant radiotherapy in the presence of adverse pathology such as node positivity or deep myometrial invasion but no improvement in survival (60) (61) (62) (39).

The PDQ guidelines (43) recommend lymph node dissection and recommend adjuvant radiotherapy only for node positive disease. The START guidelines (63) state that "... in patients (Stage I-IIA) with high risk features for pathological lymph nodes (i.e. grade 3 lesions, >50% myometrial invasion, vascular space invasion, cervical stromal invasion and adenosquamous carcinoma, clear cell or papillary adenocarcinoma) a lymph node dissection is recommended to enable the selection of patients who need adjuvant radiotherapy. Several centres find selective lymph node dissection sufficient to determine whether adjuvant radiotherapy is required and therefore do not recommend radiotherapy in the presence of other adverse pathological features if the nodes are negative for malignancy. However, other centres consider the presence of adverse prognostic factors as sufficient indication for radiotherapy without the need for lymph node dissection. Although there is suggestion that lymph node dissection per se has a therapeutic benefit, it is not clear whether it improves survival."

This differs from the guidelines from the British Columbia Cancer Agency (46) who recommend no lymph node dissection and post-hysterectomy radiotherapy for high-risk patients. A comparison, using SEER data, of the survival of patients according to whether nodes were examined shows that lymph node sampling has no impact on overall survival (64). Other reports also indicate a policy of no routine node dissection and the use of post-operative radiotherapy when adverse pathological parameters are present (45;65).

Maggino et al. (66) surveyed 82 leading centres of gynaecological oncology in Western Europe in 1994. Only 24.4% of centres reported routine lymphadenectomy. All centres in the survey recommended radiotherapy if the patient was found to be node-positive. The centres that did not consider lymphadenectomy routine, usually reserved

lymphadenectomy for specific pathological indications based on stage, grade, myometrial invasion, enlarged nodes or histological sub-type. For lymph node negative cases, radiotherapy was omitted in 29.5% of centres, whereas 70.5% stated that radiotherapy was still considered in the presence of high-grade tumours (46%) or deep myometrial invasion (33%).

The prevalent practice amongst Australian gynaecological oncologists is for lymph node dissection to be performed routinely on patients with adverse pathology and to consider adjuvant external beam radiotherapy for lymph node positive patients (personal communication with multiple gynaecological oncology specialists). This does not necessarily occur in practice, as a significant proportion of patients with endometrial cancer are treated by gynaecologists without formally accredited training in gynaecological oncology. The patients treated by this group often do not undergo lymph node dissection and are referred for radiation if adverse pathological features predicting for lymph node positivity are found (such as deep myometrial invasion, high grade, lymph vascular space invasion). In addition, not all patients in a gynaecological oncology practice will undergo lymph node dissection because of patient factors such as operative risk and co-morbidity including obesity. Unfortunately it is not possible to determine the proportion of patients with endometrial cancer who undergo lymph node dissection. Australian HIC data allows analysis by hysterectomy +/- lymph node dissection but it is not possible to separate those undergoing hysterectomy for endometrial cancer versus other clinical indications.

A number of reviewers of this study contributed educated guesses of the proportion of patients who would undergo lymph node dissection. The expert reviewers estimated that the proportion of endometrial cancer treated by gynaecological oncologists who would be likely to do node dissections is likely to be 50%. Therefore, 50% was chosen as the proportion for the tree and used for the calculation of the optimal radiotherapy rate. Sensitivity analysis was performed to vary this value between 2 extremes 10-90% to assess the impact that the uncertainty in this proportion has on the overall radiotherapy utilisation estimate.

In the radiotherapy utilisation tree, 50% of patients in Stages I and IIA (with sufficient performance status) are shown to undergo pelvic lymph node dissection. If these patients are found during surgery to have positive lymph nodes, then their surgical staging status changes to Stage III, and all these patients are depicted in the tree to receive radiotherapy. If they are node negative, then they remain in Stage I or IIA and proceed through the relevant branches of the tree for that stage.

6. **Proportion of patients with Stage I and II disease, lymph node negative at pelvic dissection that develop local or distant recurrence**
– For Stage I, Irwin et al. (54) report a locoregional recurrence for node negative patients was 7/150 (5%) and distant recurrence 2%. For Stage IIA – specific data were not identified. However, Calais et al. (56) report a recurrence rate of 12% for node negative cases (including some Stage I

cases). The authors comment that the pelvic recurrence rates were similar for Stages I and II. The distant metastatic rate for this group was 10%.

7. Proportion of patients that do not undergo lymph node dissection and have “adverse” pathology

There are pathological features that predict for locoregional recurrence and warrant a recommendation for radiotherapy in patients who do not undergo lymph node dissection. These features are high-grade histology and/or myometrial invasion either >50% or >2/3. Most reports quote the various pathological factors individually, thus not allowing an accurate estimate of the proportion of patients with grade III **OR** >50% myometrial invasion (in whom external beam radiotherapy to the pelvis is recommended).

Thomas and Blake (45) published a review of 964 patients. Table 6 indicates the risk of myometrial invasion based on grade. Creasman et al. (67) report that deep myometrial penetration and/or grade II-III disease occurs in 426/621 (69%) patients. Both factors were present in 268/621 (43%).

Table 6– Correlation of tumour grade with depth of myometrial invasion (taken from Thomas and Blake).

Myometrial invasion	GRADE I N(%)	GRADE II N(%)	GRADE III N(%)
0-1/2	261 (27)	351 (36)	123 (13)
>1/2	36 (4)	88 (9)	105 (11)

This includes patients in varying stages of endometrial cancer. If these results are assumed to be generalisable by stage, we can estimate the proportion that have adverse pathology warranting radiotherapy. If we recommend radiotherapy to Grade III patients and to Grade I-II patients with myometrial penetration >1/2, then a total of 37% have adverse pathology warranting a recommendation of radiotherapy.

Specific Stage I data - Ayhan et al. (49) reported 183 patients with surgical stage I disease, of whom 46% had >50% myometrial invasion. Irwin et al (54) found that myometrial invasion >50% was present in 44% of Stage I patients treated surgically, 24% of patients had lymph space invasion and 16% had grade III disease. They reported a local recurrence rate of 8% for <50% myometrial involvement. The recurrence rate among all patients with Stage I disease treated without external beam radiotherapy was 7%. Distant recurrence rate in this group was 2%.

Specific Stage IIA data: No data specific to Stage IIA exists. Eltabbakh et al. (57) reported that myometrial extension > 50% occurred in 40%

(19/48) of patients with Stage II endometrial cancer. Fifteen percent had grade III disease although presumably at least a moderate proportion of these patients would also have had myometrial invasion.

The absence of good data on the prevalence of adverse pathology by stage led to the decision to use the data from Thomas and Blake for both Stage I and Stage IIA.

8. Proportion of “low risk” Stage I patients that developed local and distant recurrence

Irwin et al. (54) reported a recurrence rate of 7% among 550 patients with low risk Stage I disease who did not undergo either lymph node dissection or external beam radiotherapy. The distant recurrence rate in this group was 2%. Eltabbakh et al. (55) reported on 303 patients with surgical stage I disease who were considered low risk (defined as Grade I-II, <50% myometrial invasion) and were treated with radical hysterectomy, no lymph node dissection and vaginal brachytherapy. They were followed for a median of 8 years. One percent of patients developed pelvic recurrence and 3% developed distant metastatic disease. The data from the larger of the two series (Irwin et al.) were used for the analysis as both studies were similar in quality.

9. Proportion of low risk Stage IIA patients that develop local and distant recurrence

Eltabbakh et al. (57) reported on Stage IIA patients treated in their department, some of whom did not have lymph node dissection but considered low risk based on <50% myometrial invasion and/or low grade. These patients were not treated with adjuvant radiotherapy. Of these patients, 1% developed local recurrence and no patients had distant recurrence. However, these results indicate lower recurrence rates than were reported in explanatory note 10 for low risk Stage I patients. This probably reflects the small sample reported by Eltabbakh et al. (only 23 patients did not have radiotherapy). Median follow up was 6 years. Due to the absence of other specific data for Stage IIA their data were used in the decision tree.

10. Management of local recurrences

The vast majority of patients with an isolated local recurrence will be treated with either surgery and radiotherapy or radiotherapy alone depending upon the extent of disease and the fitness of the patient (51) (59). A small minority may be treated with progestins alone, although data on this proportion is not available in the literature. Patients treated only with progestins may develop further recurrence and receive radiotherapy at a later date. Because this group is small it is not included in the decision tree, which assumes that local recurrences will largely be treated with radiation (either alone or in combination with surgery).

11. Metastatic pattern

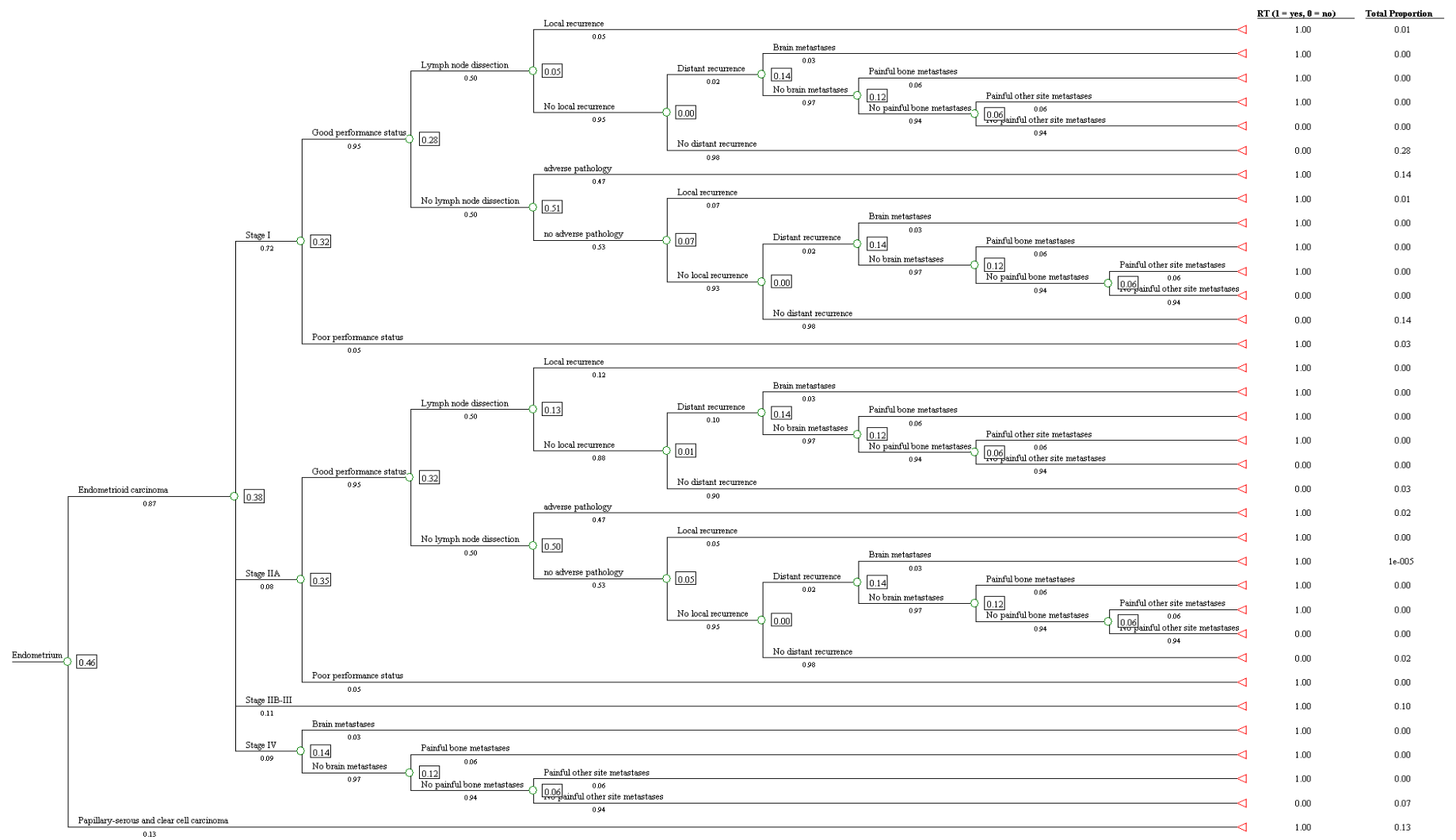
Salvesen et al. (50) reported on the recurrence of endometrial cancer in 249 women from Hordaland county, Norway. A total of 32 patients developed metastatic disease. Of these patients 6% had painful bone metastases, 6% had metastases in other sites (abdominal wall, lymph nodes) where the main symptom was pain and 3% had symptomatic brain metastases.

Aalders et al. (51) reported on the pattern of recurrence among 379 patients who developed endometrial cancer recurrence. 108 patients developed only distant recurrence and a further 81 patients developed local and distant recurrence together. Of the total of 189 patients with distant recurrence, sites of recurrence were lung 63 (33%), multiple sites 26 (14%), upper abdomen 48 (25%), bone 22 (12%), and brain 11 (6%). Shumsky et al. (52) reported on 28 patients with metastatic disease. Of this group 10% had symptomatic bone metastases and 3% had symptomatic brain metastases.

12. Utility of radiotherapy to treat local symptoms in patients with poor performance status or metastatic disease

The FIGO Committee on Gynaecologic Oncology guidelines (3) on endometrial carcinoma state that radiotherapy is an effective modality to treat symptomatic disease in patients with poor performance status for any stage of disease or in those patients with incurable Stage IV disease.

Unlike cervical carcinoma, patients with Stage IV endometrial carcinoma do not usually need palliative radiotherapy for localised pelvic symptoms in the presence of metastatic disease. No data was available to estimate the proportion of endometrial cancer patients with Stage IV disease and local symptoms sufficient to justify the use of palliative radiotherapy. It is estimated to be sufficiently low as to not influence the overall estimate of radiotherapy utilisation. Therefore, the tree denotes that patients with Stage IV disease require radiation only in the presence of symptomatic brain or bone metastases.



Ovarian Cancer

Table 7: Ovarian Cancer. Indications for radiotherapy – Levels and sources of evidence

Outcome No.	Clinical Scenario	Treatment Indicated	Level of Evidence	References	Notes	Proportion of all ovarian cancer patients
50	Stage IV Ovarian cancer, bone/lymph node/CNS metastases	Palliative RT	II	<ul style="list-style-type: none"> • Priestman et al (6) • Kurtz et al (7) • Borgelt et al (8) • Steenland et al (68) • Nielsen et al (69) • Tong et al (70) 	See notes	0.04

Table 8: Ovarian Cancer. The incidence of attributes used to define indications for radiotherapy

Key	Population or subpopulation of interest	Attribute	Proportion of population with this attribute	Quality of information	References	Notes
A	All registry cancers	Gynaecological cancer	0.05	α	AIHW (9)	2
B	All gynaecological cancer	Ovarian cancer	0.33	α	AIHW (9)	2
C	Ovarian Cancer	Stages I -III	0.62	ζ	Dauplat et al (71)	
D	Ovarian cancer, Stage IV	Bone/lymph node/ CNS metastases	0.11	ζ	Dauplat et al (71)	

Ovarian Cancer

Treatment guidelines

There are no published peer-reviewed Australian guidelines for the management of ovarian cancer and therefore international consensus guidelines were sought. The following international guidelines on the management of ovarian cancer were identified: National Cancer Institute PDQ guidelines, National Comprehensive Cancer Network (NCCN) guidelines and the British Columbia Cancer Agency (BCCA) guidelines.

Indications for radiotherapy

The guidelines concentrate on the roles of surgery and systemic therapy in the management of ovarian cancer. Discussion on radiotherapy in the guidelines is confined to a comparison of whole abdominal radiotherapy with combination chemotherapy. The guidelines favour the use of combination chemotherapy and therefore whole abdominal radiotherapy was not included in the tree. It may be appropriate in some situations to use whole abdominal radiotherapy, either in preference to chemotherapy or as salvage after failure. The proportion of patients in this category is considered small and appropriate epidemiological data to determine this proportion were unavailable. As the proportion is small, it is unlikely that the omission of whole abdominal radiotherapy will significantly impact on the overall radiotherapy utilisation estimate.

The treatment guidelines do not discuss any roles for radiotherapy to palliate symptomatic metastases. However radiotherapy has a recognised role in the palliation of specific metastatic sites such as bone, brain and lymph nodes for a variety of different cancers and therefore is recommended in the tree for the palliation of metastatic ovarian cancer.

Radiotherapy may be considered in the following situations for patients with ovarian cancer:

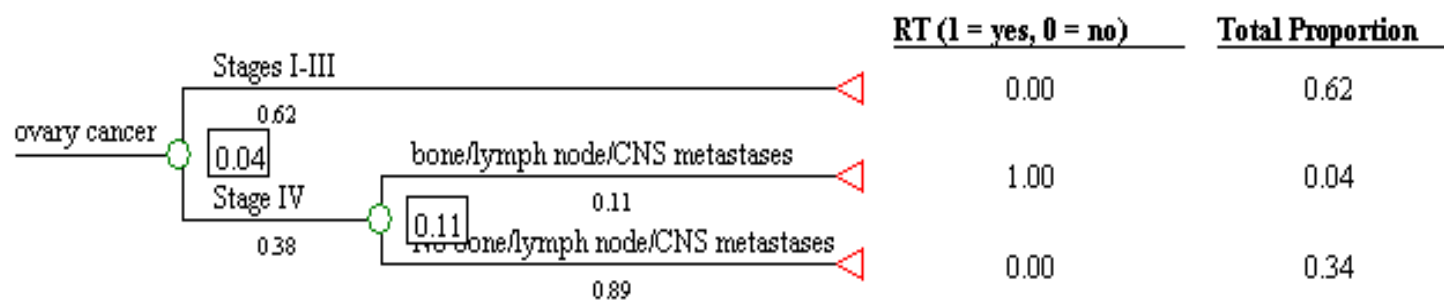
- in patients with advanced stage disease who progress following systemic therapy and have uncontrolled pelvic symptoms such as pain
- in symptomatic brain, bone or nodal metastases that have not been successfully palliated by systemic therapy, or
- when systemic therapy is considered inappropriate (72).

All of the above examples comprise very small proportions of the entire ovarian cancer population. For example, a study from the UCLA School of Medicine (71) reported on 255 patients with ovarian cancer, of whom 38% ultimately developed distant metastatic disease. The proportion of patients with metastatic disease who developed distant metastases at sites where radiotherapy may be considered appropriate were central nervous system (2%), bone (2%) and distant lymph nodes (7%). Therefore, it can be estimated that the overall optimal utilisation of radiotherapy would be 11% in Stage IV disease and substantially less than this for non-Stage IV disease. If 11% of the 38% of patients with metastases had disease that warranted radiotherapy,

then this would represent 4% of ovarian cancer. A Victorian Patterns of Care survey showed that 2.1% of all ovarian cancer patients studied received radiotherapy as part of their treatment (73). This will be an under-estimate of the overall radiotherapy use as this study was a snapshot of treatment and further relapses with time will occur. The proportion of patients with uncontrolled pelvic symptoms with pain and the proportion of patients in whom palliative radiotherapy would be preferred over palliative systemic therapy were not identified in the literature. However, these estimates were thought to be small and unlikely to significantly affect the final estimate.

Optimal Radiotherapy Utilisation Rate

The calculated overall rate of optimal radiotherapy utilisation in ovarian cancer was 4%. As ovarian cancer represents 33% of all gynaecological cancers, and in turn gynaecological cancer accounts for 5 % of all cancers, this population of patients represents 0.07% of all cancer patients.



Vulvar Cancer

Table 9: Vulvar Cancer. Indications for radiotherapy – Levels and sources of evidence

Outcome No.	Clinical scenario	Treatment indicated	Level of Evidence	References	Notes	Proportion of all vulvar cancer patients
53	Vulvar cancer, low risk, nodal recurrence following surgery	Radiotherapy or Surgery and radiotherapy.	III	<ul style="list-style-type: none"> • PDQ Statement on Treatment of Vulvar cancer (74) 	5	<0.01
55	Vulvar cancer, intermediate risk	Post-operative RT	II	<ul style="list-style-type: none"> • Berek and Hacker (75) • Homesley et al. (76) 	4	0.18
56	Vulvar cancer, high locoregional recurrence risk	Chemoradiotherapy or post-operative radiotherapy.	II	<ul style="list-style-type: none"> • PDQ Statement on Treatment of Vulvar cancer (74) • Berek and Hacker (75) • Homesley et al. (76) 	4	0.15
Proportion of vulvar cancer patients for whom radiotherapy is recommended						0.34
Total proportion of all cancer patients = 0.34 X 0.05 x 0.05 =						0.085%

Table 10: Vulvar cancer. The incidence of attributes used to define indications for radiotherapy

Key	Population or Sub-population of interest	Attribute	Proportion of populations with this attribute	Quality of information	References	Explanatory Notes
A	All registry cancers	Gynaecological cancer	0.05	α	AIHW (9)	1
B	All gynaecological cancer	Vulvar Cancer	0.05	α	AIHW (9)	1
C	All vulvar cancer	Low risk	0.67	θ	Homesley et al. (76)	4
D	Vulvar cancer, low risk	Nodal recurrence	0.02	ζ	Hacker et al. (77)	5
			0.00	θ	Stehman et al. (78)	
E	All vulvar cancer	Intermediate risk	0.18	θ	Homesley et al. (76)	4
F	All vulvar cancer	High risk	0.15	θ	Homesley et al. (76)	4

Vulvar Cancer

Treatment guidelines

There are very few international guidelines on the management of vulvar carcinoma. Only two guidelines were identified – the PDQ guidelines of the US National Cancer Institute (74) and the British Columbia Cancer Agency (BCCA) guidelines (79). In addition, a gynaecological oncology textbook by Berek and Hacker lists evidence-based recommendations for radiotherapy in the management of vulvar cancer (75).

Indications for radiotherapy

- The PDQ guidelines indicate that surgery is the main treatment in early stage disease for patients who are fit to undergo surgery. Radiotherapy may be reserved for use in the treatment of locoregional recurrence (either as adjuvant therapy with surgical excision or as definitive or palliative treatment depending upon the patient's health and stage status at recurrence).
- In Stage II, the definitive treatment is surgery for patients fit for surgery. However, adjuvant radiotherapy “should be considered” in the presence of “adverse” pathology (defined as margins <8mm, capillary lymphatic space invasion, thickness>5mm, positive nodes) (80) (81) . This differs from the radiotherapy recommendations of Berek and Hacker, who suggest post-operative radiotherapy in patients with > 2 micro-metastases, one macrometastasis, extra-capsular spread or surgical margins <5mm clear.
- Adjuvant radiotherapy is routinely recommended for Stage III and IV disease in the PDQ guidelines.
- It is also recommended in preference to surgery for patients with any stage who are unfit for surgery (82) (83).

Explanatory Notes for Tables 9 and 10

1. Vulvar carcinoma incidence

Vulvar carcinoma represents 5% of all gynaecological malignancy in Australia (9).

2. **Stage.** Most of the radiotherapy utilisation trees use stage as a major branch point in determining the need for radiotherapy. However, stage was not used for vulvar carcinoma. This is because most of the reported epidemiological data were not supported with additional data regarding prognostic factors that help determine the risk of locoregional recurrence and hence the need for radiotherapy. The AJCC staging system divides patients into Stages I, II, III and IV but no data is available about the proportions of patients within each stage that have attributes that require radiotherapy. Surgical series provided good data on locoregional recurrence risk but not by surgical stage. The approach taken was therefore to use the locoregional recurrence risk factor analyses rather than stage to

help determine the proportions of vulvar carcinoma patients in whom radiotherapy would be recommended.

3. Performance status

No data exists on performance status by stage for vulvar cancer. However, several gynaecological oncology reviewers commented that even frail and elderly patients can tolerate surgical excision. Therefore, it was recommended that almost all patients should receive surgery as primary treatment. The decision as to whether to give post-operative radiotherapy should be made based upon the presence or absence of adverse pathological features.

4. Determining the risk group that require radiotherapy

The PDQ guidelines recommend surgery for Stage I and II disease (small primary, node negative) and the use of radiotherapy (+/- chemotherapy and +/- surgery) for disease involving nodes or lesions with involvement of the anus or vagina (Stages III and IV) (74) (84). Post-operative radiotherapy is not routinely recommended for Stage I and II disease. However, for early vulvar disease a sub-group has been identified in whom radiotherapy is recommended. In the PDQ guidelines these patients are defined as patients with surgical margins < 8mm, tumour thickness > 5mm, capillary space invasion or node positive disease. However, according to some gynaecological oncologists, there is no evidence to support the pathological parameters quoted in the guidelines. These experts state that evidence for post-operative radiotherapy exists only in patients with > 1 macro-metastasis, > 2 micro metastases, extranodal spread or margins < 5mm. These patients are considered to be at intermediate or high risk for recurrence and significant failure rates occur in the absence of radiotherapy (75) (85) (86) (87). A randomised GOG (Gynaecological Oncology Group) trial found that patients with >1 positive lymph nodes benefited from post-operative radiotherapy (76). They published incidence proportions for "low", "intermediate" and "high" risk as 67%, 18% and 15% respectively. Intermediate and high risk patients are defined as patients with 2 unilateral lymph nodes, tumours of > 2 cm with 1 positive node and lesions > 8 cm with no positive nodes. In view of the slight differences of opinion between the PDQ guidelines and Australian gynaecological oncologists, we have adopted the recommendations of Australian experts. We have indicated the use of radiotherapy for intermediate and high risk patients as identified by the GOG trial, as these indications correspond best to the recommendations of Berek and Hacker.

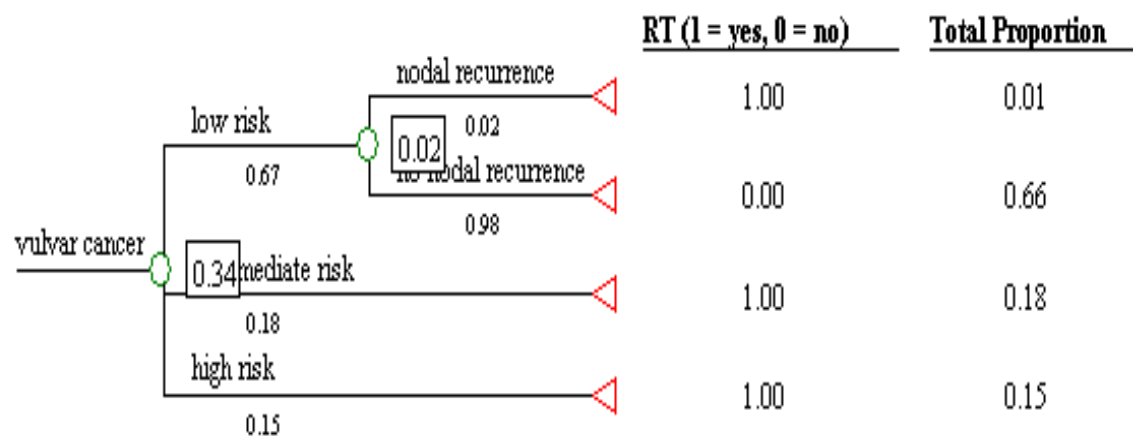
5. Incidence of post-surgical recurrence

The treatment of recurrent vulvar cancer has not been standardized due to the various ways in which recurrence may present. The PDQ guidelines state that wide local excision and/or radiotherapy may be

used to treat recurrences. Two expert reviewers in this report both suggested that surgery is almost always the treatment of choice for local recurrence but nodal recurrences will almost always require radiation (either alone or in combination with surgery).

The proportion of patients with early vulvar cancer who do not undergo radiation (all Stage I and Stage II without the presence of adverse pathology) and who develop local recurrence is reported to be 7% based on a review of multiple series by Marsden and Hacker (84). However, this report does not provide data on nodal recurrence. Hacker et al. (77) reported on the largest study of 177 cases of stage I vulva carcinoma treated with radical surgery at the University of California (UCLA). Three patients developed local recurrence and all were successfully salvaged with further radical surgery. However, there were 4 (1.7%) regional recurrences, all of whom subsequently developed further disease after surgery. In the Gynaecological Oncology Group (GOG) trial of surgery versus lymph node dissection for T1-3N0-1 vulvar cancer, there were no nodal recurrences amongst the 25 patients treated with surgery (78). The 2% recurrence rate from Hacker et al. was used since it is derived from a larger series.

The development of distant metastases is rare without local recurrence and therefore a branch on the decision tree has been omitted. The omission of a branch on the decision tree corresponding to those who did not receive radiotherapy at initial treatment or at recurrence, and who subsequently developed isolated distant recurrence amenable to palliation with radiotherapy (such as brain or bone metastases) is unlikely to alter the overall estimate for optimal radiotherapy utilisation.



Vaginal cancer

Vaginal cancer comprises 2% of all gynaecological cancers. The National Cancer Institute PDQ guidelines (88) recommend radiotherapy (either alone or with chemotherapy and/or surgery) for all stages of vaginal cancer. This would even be the case for symptomatic Stage IV disease. Therefore, 100% of vaginal cancer patients will be recommended for radiotherapy.

Sensitivity Analysis

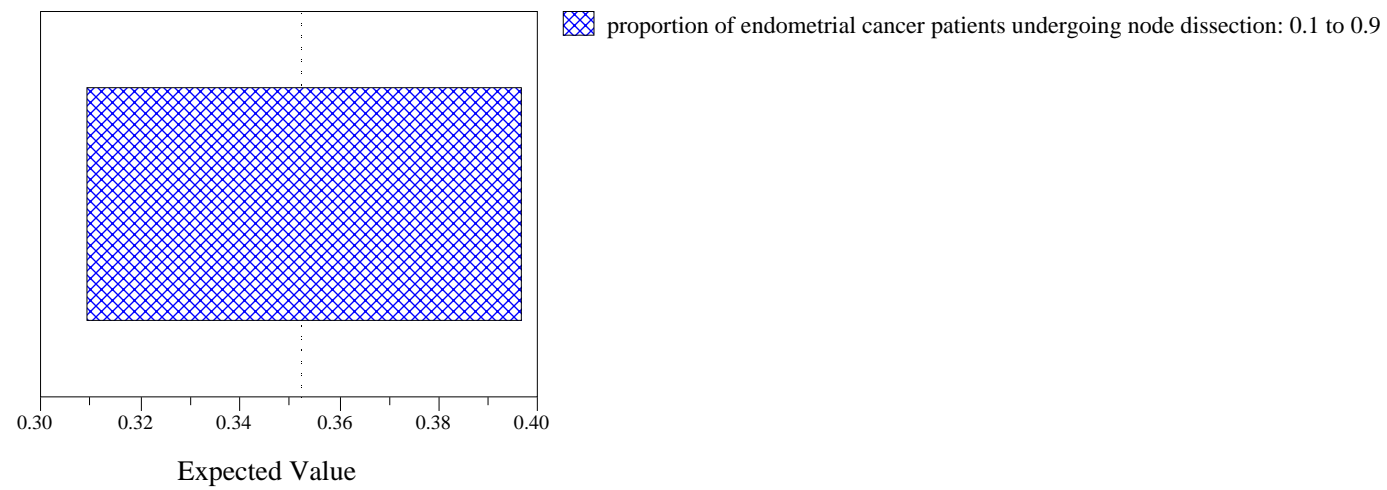
Sensitivity analysis allows the assessment of the impact of changing the value of the variables on the overall end result. This is advantageous when the data used are uncertain. For the gynaecological decision tree, one data item was identified as being uncertain. In endometrial cancer, no data could be identified to estimate the proportion of early stage endometrial cancer patients who undergo a lymph node dissection. An arbitrary value of 0.5 was chosen based on discussion with gynaecological oncology experts, and the sensitivity analysis varied this proportion between 0.1 and 0.9 to assess the impact that this uncertainty had on the overall rate.

To assess the impact of this uncertainty on the overall estimate of the need for radiotherapy in all gynaecological cancers, a sensitivity analysis was performed for each of the variables. It is illustrated by the tornado diagram below. Once the decision trees for all tumours are completed, a tornado analysis will be performed whereby the impact that each of these variables has on the overall estimate of the proportion of cancer patients needing radiotherapy will be examined.

The graphs below show that the optimal proportion of gynaecological cancer patients who should receive radiotherapy based on evidence and incidence of attributes for radiotherapy is 35%. This proportion could vary from a low of 31% to a high of 39% depending on the proportion of patients undergoing endometrial cancer surgery who also have a lymph node dissection (varied between the extremes of 10% to 90%).

Tornado diagram of sensitivity analysis for gynaecological cancer

**Tornado Diagram at
Gynae cancer**



Optimal radiotherapy utilisation rate

The overall optimal radiotherapy utilisation rate for gynaecological cancer is 35%. This group represents 1.75% of all cancer patients for whom radiotherapy is indicated, according to the best available evidence. The optimal utilisation rates for the five gynaecological tumour sub-sites are shown in Table 8.

Table 8: Optimal radiotherapy utilisation rates by gynaecological sub-type

Tumour Sub-site	% of gynaecological cancer	Overall optimal radiotherapy utilisation rate for sub-site (%)	Proportion of all cancer patients that should receive radiotherapy
Cervix	23	58	0.7%
Endometrium	37	46	0.85%
Ovary	33	4	0.1%
Vulva	5	60	0.1%
Vagina	2	100	0.1%
TOTAL	100	35	1.975%

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Genitourinary Cancers

(excluding prostate cancer)

Renal Cancer

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

Outcome Number	Clinical Scenario	Treatment Indicated	Level of Evidence	References	Proportion of all Renal Cancer patients	Notes
1	TxNxM0, Fit for surgery, local recurrence	XRT	IV	<ul style="list-style-type: none">• Expert opinion of Dr Sandra Turner during expert review.	0.03	5
2	TxNxM0, Fit for surgery, no local recurrence, distant recurrence with brain metastases	XRT	II	<ul style="list-style-type: none">• National Cancer Institute PDQ statement on treatment of renal cell cancer (1)• BC Cancer Agency guidelines for the management of renal cancer (2)	0.02	8
3	TxNxM0, Fit for surgery, no local recurrence, distant recurrence with no brain metastases and painful bone metastases	XRT	I	<ul style="list-style-type: none">• National Cancer Institute PDQ statement on treatment of renal cell cancer (1)• BC Cancer Agency guidelines for the management of renal cancer (2)• NCCN Clinical Practice guidelines (3)	0.07	7
7	TxNxM1, no symptomatic primary, brain metastases	XRT	II	<ul style="list-style-type: none">• National Cancer Institute PDQ statement on treatment of renal cell cancer (1)• BC Cancer Agency guidelines for the management of renal cancer (2)	0.03	8

Outcome Number	Clinical Scenario	Treatment Indicated	Level of Evidence	References	Proportion of all Renal Cancer patients	Notes
8	TxNxM1, no symptomatic primary, no brain metastases, painful bone metastases	XRT	I	<ul style="list-style-type: none"> National Cancer Institute PDQ statement on treatment of renal cell cancer (1) BC Cancer Agency guidelines for the management of renal cancer (2) NCCN Clinical Practice guidelines (3) 	0.11	7
9	TxNxM1, no symptomatic primary, no brain metastases, no bone metastases, symptomatic lymph node or skin metastases	XRT	IV	<ul style="list-style-type: none"> National Cancer Institute PDQ statement on treatment of renal cell cancer (1) 	0.02	10
11	TxNxM1, symptomatic primary	XRT	III	<ul style="list-style-type: none"> National Cancer Institute PDQ statement on treatment of renal cell cancer (1) BC Cancer Agency guidelines for the management of renal cancer (2) 	0	9
Proportion of all patients with renal cancer in whom radiotherapy is recommended =					0.28	
Proportion of all cancer patients in whom radiotherapy is recommended = 0.03 X 0.28 =					0.008 (0.8 %)	

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

Key	Population or subpopulation of interest	Attribute	Proportion of population with this attribute	Quality of information	References	Notes
A	All registry cancers	Renal cancer	0.03	α	AIHW (4)	1
B	Renal cancer	TxNxM0	0.69	β	SA Hosp Registry (5)	2
C	TxNxM0	Fit for surgery	0.98	β	SA Hosp Registry (5)	3
D	TxNxM0, Fit for surgery	Local recurrence	0.04	ϵ	Campbell and Novick (6)	5
E	TxNxM0, fit for surgery, no local recurrence	Distant recurrence	0.30	ζ	Ljungberg et al. (7)	6
			0.24	ζ	Levy et al. (8)	
			0.23	ζ	Sandock et al. (9)	
			0.35	ζ	Nativ et al. (10)	
			0.58	ζ	Aref et al. (11)	

Key	Population or subpopulation of interest	Attribute	Proportion of population with this attribute	Quality of information	References	Notes
F	TxNxM0, fit for surgery, no local recurrence, distant recurrence	Brain metastases	0.10	δ	Schouten et al. (12)	8
			0.07	ζ	Ljungberg et al. (13)	
			0.07	ζ	Ljungberg et al. (7)	
			0.17	ζ	Harada et al. (14)	
			0.19	ζ	Aref et al. (11)	
G	TxNxM0, fit for surgery, no local recurrence, distant recurrence, no brain metastases	Bone metastases	0.39	ζ	Ljungberg et al. (13)	7
			0.43	ζ	Ljungberg et al. (7)	
			0.30	ζ	Sandock et al. (9)	
			0.25	ζ	Aref et al. (11)	
			0.23	θ	Mickisch et al. (15)	

Key	Population or subpopulation of interest	Attribute	Proportion of population with this attribute	Quality of information	References	Notes
H	TxNxM1	Symptomatic primary	0.20	ζ	Ljungberg et al. (13)	9
I	TxNxM1, no symptomatic primary	Brain metastases	0.10	δ	Schouten et al. (12)	8
			0.07	ζ	Ljungberg et al. (13)	
			0.07	ζ	Ljungberg et al. (7)	
			0.17	ζ	Harada et al. (14)	
			0.19	ζ	Aref et al. (11)	
J	TxNxM1, no symptomatic primary, no brain metastases	Bone metastases	0.39	ζ	Ljungberg et al. (13)	7
			0.43	ζ	Ljungberg et al. (7)	
			0.25	ζ	Aref et al. (11)	
			0.23	θ	Mickisch et al. (15)	
K	TxNxM1, no symptomatic primary, no brain metastases, no bone metastases	Symptomatic lymph node or skin metastases	0.10	ζ	Ljungberg et al. (7)	10

Renal Cancer Notes

Treatment guidelines

Guidelines on the treatment of renal cancer have been issued by the National Cancer Institute's Physician Data Query (PDQ) (1), the British Columbia Cancer Agency (BCCA) (2) and the National Comprehensive Cancer Network (NCCN) (3).

Indications for radiotherapy

The primary treatment modality for renal cancer is radical surgical resection. Radiotherapy, according to the guidelines, should be considered in the following clinical situations:

- As palliative treatment for a local recurrence that is inoperable (Level III, PDQ guidelines)
- As palliative radiotherapy for bone metastases causing pain, spinal cord compression or other local symptoms or at risk of pathological fracture (PDQ and BC Cancer Agency guidelines, Level I)
- As palliative therapy for symptomatic skin or lymph node metastases
- As palliative radiotherapy for brain metastases (Level II PDQ and BC Cancer Agency)
- As palliative radiotherapy for a symptomatic primary in the presence of metastatic disease (PDQ and BC Cancer Agency, Level III).
- As adjuvant therapy following radical nephrectomy for positive margins (Level III, PDQ guidelines). While this has not been validated by randomised trial data, there are some Level III studies that support the use of radiotherapy on the basis of an improvement in local control compared to similar series where patients did not receive adjuvant radiotherapy. However, the BC Cancer Agency guidelines suggest that there is no evidence to support radiotherapy either pre- or post-operatively. The decision tree has not included positive margins as a reason for giving radiotherapy.

There are also other less common clinical scenarios that may be considered for radiotherapy such as symptomatic lung metastases. However, these situations are rare enough that their omission from the tree is unlikely to have a significant impact on the overall radiotherapy utilisation rate for renal cancer.

Explanatory Notes for Tables 1 & 2

1. Overall incidence

Renal cancer comprises 3% of all cancers according to the Australian Institute of Health and Welfare statistics for 1998. (4)

2. Stage proportions

The treatment of renal cancer is predominantly radical surgery (total or partial nephrectomy) in patients with no metastatic disease. Surgery is also sometimes indicated in patients with limited

metastatic disease (16), (15). Therefore, the first branch point divides patients into M1 and M0. The proportion of patients diagnosed with M1 disease at initial presentation, according to the South Australian Hospital Registry, is 31% (5). A report from the SEER database by Hock et al. (17) contains data on 43 685 cases of renal cancer 1973-1998 in a cumulative population of 585 million. 25% of cases were metastatic at diagnosis and a further 8.2% were unstaged. By excluding the data on unstaged patients, patients with metastatic disease represent 27%, which is similar to the South Australian figure.

3. Operability rate

Not all patients with M0 disease will be fit enough for a radical nephrectomy. No direct accurate data on performance status or incidence of co-morbidities in renal cancer were available. According to the South Australian Hospital Registry data, the proportion of M0 patients not undergoing any surgical therapy is 2%. It is presumed this is due mainly to poor performance status or poor life expectancy from co-morbidities. In the tree, these patients also receive no radiotherapy. An occasional patient may receive palliative radiotherapy but this number would be very small and an estimate of this proportion is unlikely to have an impact on the overall radiotherapy utilisation estimate.

4. Positive margins post-nephrectomy

The issue of whether radiotherapy is recommended is contentious. The PDQ guidelines (1) suggest that "External beam irradiation has been given before or after nephrectomy without conclusive evidence that this improves survival compared with results of surgery alone, but may be of benefit in selected patients with more extensive tumours." The BC Cancer Agency guidelines (2) suggest ".....Radiotherapy has no established role as primary definitive therapy of early renal cancer or as an adjuvant to surgery." Therefore, there is perhaps some conflict between the 2 guidelines. Two randomised trials have failed to show any benefit for post-operative radiotherapy (18) (19). Reviews by Aref et al. (11), Pittman and Selby (20), Rabinovitch et al. (21) and Savage (22) suggest that local recurrences are rare and are more likely to be associated with distant metastases, and therefore recommend no routine adjuvant radiotherapy following nephrectomy. The statement from the BC Cancer Agency is more specific and therefore for the purposes of the decision tree positive margins post-nephrectomy are not routinely recommended for radiotherapy.

5. Proportion of patients developing isolated local recurrence post-nephrectomy

The PDQ guidelines (1) suggest that radiotherapy may be used to treat an isolated local recurrence. Gill et al. (23) reviewed 4 retrospective studies of patients with localised renal carcinoma who had undergone either laparoscopic radical nephrectomy or open resection. Local recurrence occurred in 1% of open radical nephrectomies. Campbell and Novick report that of 7 studies identified, 24/668 (4%) developed an isolated local recurrence. As this was the largest study in the literature this value of 4% was used in the utilisation tree.

However, the management of an isolated local recurrence is controversial. Schrodter et al. (24), Campbell and Novick (6) and Skinner et al. (25) reported that some local recurrences are operable and should undergo resection. Therefore the literature seems to contradict the guidelines. To address this controversy sensitivity analysis was performed whereby the proportion of local recurrences to receive radiation was set at 4% as this correlated with the guideline recommendation and in the sensitivity analysis the alternative of no patients receiving radiation was considered.

6. Proportion of patients with distant recurrence after nephrectomy

Lgungberg et al. (7) reported on 187 patients who underwent radical nephrectomy 1982-1997 in Umea, Sweden. The median follow up was 66 months (5-179 months) and patients were followed prospectively using a pre-determined follow up protocol. Thirty percent of patients had metastatic disease diagnosed at follow up. Levy et al. (26) reported a distant metastatic rate of 24% in 286 patients who were followed for a median time of 37 months following nephrectomy. In the series of Sandock et al. (9), 137 patients were treated by nephrectomy. The duration of follow up was not reported but 32/137 (23%) recurred. Aref et al. (11) found that in their series of 116 nephrectomy patients, 67 (58%) developed distant metastases at a median follow-up of 44 months. Nativ et al. (10) reported on a smaller group of patients but with a median follow up of 7.6 years, which is significantly longer than most series. They found that in 54 patients treated with nephrectomy for M0 renal cell carcinoma, 19 patients (35%) developed distant recurrence.

The best incidence data for development of metastases in terms of lengthy duration of follow up, prospective design and large sample size is Lgungberg et al. (7) and therefore their distant metastatic rate of 0.30 is used in the tree. Sensitivity analysis was performed to assess the impact that the variability of this data (23-58%) has on the overall estimate.

7. Proportion of patients with M1 disease who have metastases to bone

Radiotherapy is recommended for symptom control in patients with symptomatic bone metastases. Tumours such as renal cancers have previously been reported as being radioresistant. However, specific examination of the palliation of symptoms for bone metastases for renal cancer show benefit for >50% of patients (27). Ljungberg et al. (13)(2000) reported on 106 consecutive patients with metastatic renal cancer treated in Sweden. The duration of follow up was 6 months-17 years. No mean or median follow up time was reported but 101/106 (95%) of patients were deceased at the study cut-off date. Bone metastases were present in 39% of patients.

Mickisch et al. (15) reported on a randomised trial of patients with M1 renal cancer. Patients were randomised to interferon or interferon and nephrectomy. Bone metastases were present in 23% of the patients in this study. However, no data are presented as to the proportion of M1 patients who subsequently develop bone metastases prior to death and therefore this may under-represent the final rate.

Ljungberg et al. (7) (1999) reported that of 56 patients who developed metastatic disease after nephrectomy, 24 (43%) had bone metastases at a median follow up of 66 months.

Aref et al. (11) reported that of 67 patients who developed metastatic disease following nephrectomy, 17/67 (25%) had bone metastases.

Sandock et al. (9) reported that of 32 patients with metastatic disease following initial nephrectomy, 30% had bone metastases. All patients with bone metastases in the study had bone pain. In the tree, it has been assumed all patients with metastatic bone disease will be symptomatic at some point of their remaining life to warrant consideration of radiotherapy. The data from Sandock et al. (9) supports this assumption. The data from Ljungberg et al. (13) (2000) was used in the radiotherapy utilisation tree, as it represented the most mature data as 95% of their patients were deceased at the time of the report.

8. Proportion of patients with M1 disease who have metastases to the brain

Radiotherapy is recommended for symptom control in patients with brain metastases. Tumours such as renal cancers have previously been reported as being radioresistant. However, specific examination of the palliation of symptoms for brain metastases for renal cancer show benefit for >50% of patients (27). Schouten et al. (12) reported on a population-based study designed to assess the incidence of brain metastases. They reported that of 114 renal

cancer patients studied, the cumulative incidence of brain metastases was 10% for all stages at diagnosis. Ljungberg et al. (13) in 2000 reported on 106 consecutive patients with metastatic renal cancer treated in Umea, Sweden. The duration of follow up was 6 months-17 years. No mean or median follow up time was reported but 101/106 (95%) of patients were deceased at the study cut-off date. Brain metastases were present in 7% of patients. Ljungberg et al. (7) in 1999 reported that of 56 patients who developed metastatic disease after nephrectomy, 4 (7%) had brain metastases. Harada et al. (14) reported that of 108 patients with distant metastases, 18 (17%) developed brain metastases at a median follow up of 44 months.

Aref et al. (11) reported that of 67 patients who developed metastatic disease following nephrectomy, 13/67 (19%) patients had brain metastases.

Therefore, the data on incidence of brain metastases ranges from 7-19%. The 10% figure from Schouten et al. (12) was used as it is a population-based study without the selection biases that reports from comprehensive cancer centres may have. However, sensitivity analysis was conducted to assess the impact that this variation in data had on the overall optimal radiotherapy utilisation rate.

9. Proportion of patients with M1 disease who have a symptomatic primary

The PDQ guidelines suggest consideration of palliative radiotherapy to the primary site when patients have metastatic disease and the primary tumour causes symptoms of pain or bleeding. However, radical nephrectomy could also be considered in this setting. Randomised, controlled trials of adjuvant systemic therapy +/- nephrectomy have revealed a survival benefit for nephrectomy in selected patients with good performance status and limited metastatic disease (15). Treatment options for patients with metastatic disease and symptomatic primary therefore include nephrectomy without radiation, palliative radiotherapy alone or radiation followed by nephrectomy in patients who fail to respond to radiotherapy. Sensitivity analysis was conducted to assess the impact of this treatment uncertainty on the overall radiotherapy utilisation estimate. The tree will use a value of 0 for patients with symptomatic primary who receive palliative radiotherapy (i.e. take the option that all may get nephrectomy) and this value will be varied to include the possibility that all symptomatic primaries receive radiotherapy. The true value will be somewhere within this range.

10. Proportion of patients with M1 disease who have symptomatic lymph node or skin metastases

A study by Ljungberg et al. reviewed the type of metastatic disease seen in a cohort of 56 patients and 98 metastatic sites (7). They report an incidence of symptomatic lymph node or skin involvement of 10%.

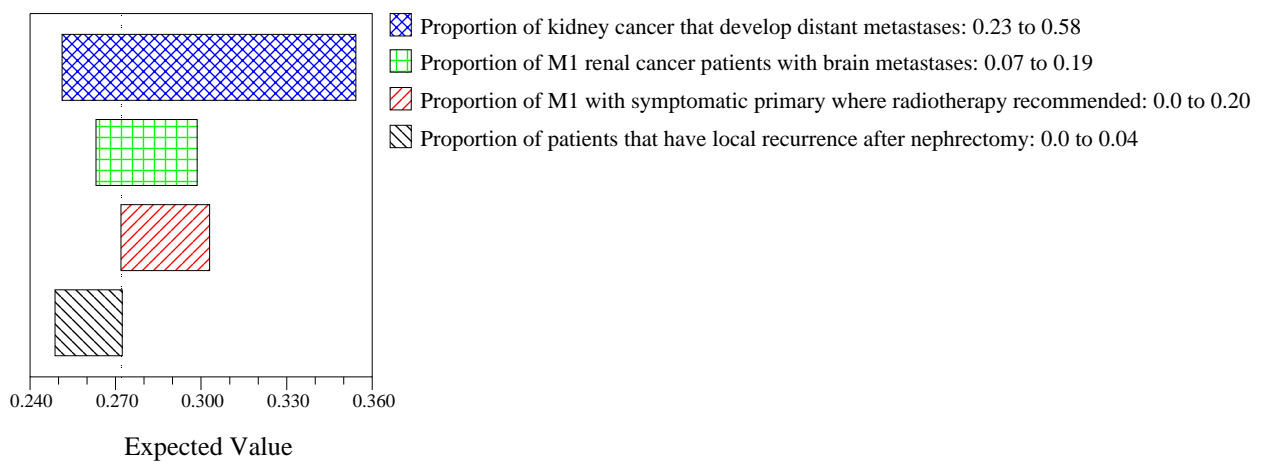
In terms of frequency of symptomatic primary in patients with metastatic disease, Ljungberg et al. (13) reported on 106 consecutive patients with metastatic renal cancer treated in Umea, Sweden. Of these patients, 21 had symptoms of haematuria (20%). A further 11 (10%) had “other symptoms” and it is not clear whether these included symptoms such as flank pain where radiotherapy may be considered. In the entire group with metastatic disease, 34 (32%) required radiotherapy but no details were provided about whether this was to a symptomatic primary or to secondary disease. Follow up period was 6 months-17 years but no mean or median follow up time was reported.

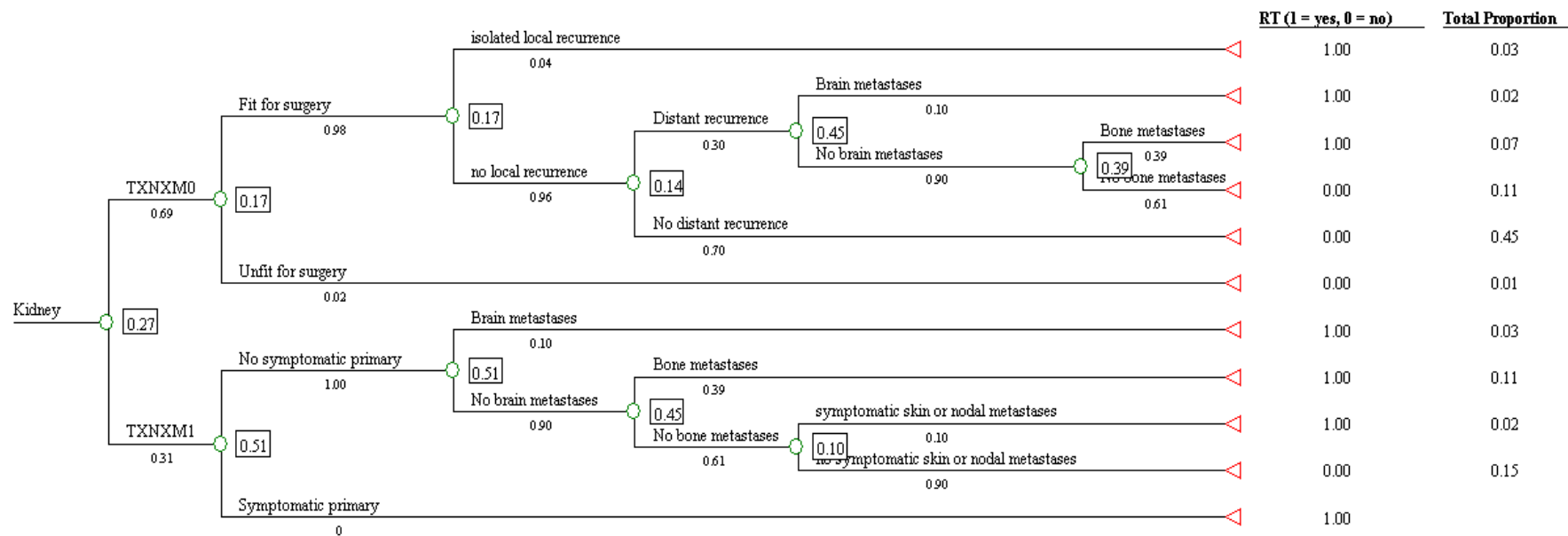
Expected value and sensitivity analysis

The calculated overall rate of optimal radiotherapy utilisation in renal cancer was 28%. As renal cancer represents 3% of all cancers, this population of patients represents 0.8% of all cancer patients.

There were two treatment branches where uncertainty of treatment recommendations existed. These were whether patients with M1 disease and a symptomatic primary (e.g. haematuria, flank pain etc.) would be recommended for radiotherapy or nephrectomy, and whether radiotherapy would be recommended for patients with an isolated local recurrence after nephrectomy. Therefore, sensitivity analysis was necessary to assess the impact of this uncertainty on the optimal radiotherapy utilisation rate. In addition, there were two data items (proportion of patients with metastatic disease who have brain involvement and proportion of patients who develop distant metastases post-nephrectomy), where the reported values varied significantly. The graph below shows that varying the proportions for each of these two values altered the renal cancer optimal utilisation rate from 25% to 35%. This would affect the overall rate between 0.75-1.05%.

Tornado Diagram at Kidney





Bladder Cancer

Table 3: Bladder Cancer. Indications for radiotherapy - Levels and sources of evidence

Outcome Number	Clinical Scenario	Treatment Indicated	Level of Evidence	References	Notes	Proportion of all Bladder Cancer patients
1	Stage I, local recurrence after conservative treatment, cystectomy (age <75 yrs), repeat local recurrence	RT	III	<ul style="list-style-type: none">• NCCN Urothelial Cancer Practice Guidelines (28)	3,4	<0.01
2	Stage I, local recurrence after conservative treatment, cystectomy (age <75 yrs), no repeat local recurrence, distant recurrence, brain metastases	RT	II	<ul style="list-style-type: none">• Priestman et al. (29)• Kurtz et al. (30)• Borgelt et al. (31)	4, 7	<0.01
3	Stage I, local recurrence after conservative treatment, cystectomy (age <75 yrs), no repeat local recurrence, distant recurrence, no brain metastases, painful bone metastases	RT	I	<ul style="list-style-type: none">• Steenland et al. (32)• Nielsen et al. (33)• Tong et al (34)	4, 7	<0.01
6	Stage I, local recurrence after conservative treatment, age>75 years, no cystectomy	RT	III	<ul style="list-style-type: none">• NCCN Urothelial Cancer Practice Guidelines (28)	4	0.07
7	Stage I, no local recurrence after conservative treatment, distant recurrence, brain metastases	RT	II	<ul style="list-style-type: none">• Priestman et al. (29)• Kurtz et al. (30)• Borgelt et al. (31)	7	<0.01

Outcome Number	Clinical Scenario	Treatment Indicated	Level of Evidence	References	Notes	Proportion of all Bladder Cancer patients
8	Stage I, no local recurrence after conservative treatment, distant recurrence, no brain metastases, painful bone metastases	RT	I	<ul style="list-style-type: none"> • Steenland et al. (32) • Nielsen et al. (33) • Tong et al (34) 	7	0.01
11	Stages II-III, cystectomy (medically operable), local recurrence	RT	III	<ul style="list-style-type: none"> • National Cancer Institute PDQ statement on treatment of bladder cancer (35) • NCCN Urothelial Cancer Practice Guidelines (28) 	5	<0.01
12	Stages II-III, cystectomy (medically operable), no local recurrence, distant recurrence, brain metastases	RT	II	<ul style="list-style-type: none"> • Priestman et al. (29) • Kurtz et al. (30) • Borgelt et al. (31) 	7	<0.01
13	Stages II-III, cystectomy (medically operable), no local recurrence, distant recurrence, no brain metastases, painful bone metastases	RT	I	<ul style="list-style-type: none"> • Steenland et al. (32) • Nielsen et al. (33) • Tong et al (34) 	7	<0.01

Outcome Number	Clinical Scenario	Treatment Indicated	Level of Evidence	References	Notes	Proportion of all Bladder Cancer patients
16	Stages II-III, medically inoperable	RT	II	<ul style="list-style-type: none"> National Cancer Institute PDQ statement on treatment of bladder cancer (35) BC Cancer Agency guidelines (36) NCCN Urothelial Cancer Practice Guidelines (28) 	6	0.38
17	Stage IV, symptomatic primary	Palliative RT	II	<ul style="list-style-type: none"> National Cancer Institute PDQ statement on treatment of bladder cancer (35) BC Cancer Agency guidelines (36) Duchesne et al. 	8	0.07
18	Stage IV, no symptomatic primary, brain metastases	RT	II	<ul style="list-style-type: none"> Priestman et al. (29) Kurtz et al. (30) Borgelt et al. (31) 	7	0.01
19	Stage IV, no symptomatic primary, no brain metastases, painful bone metastases	RT	I	<ul style="list-style-type: none"> Steenland et al. (32) Nielsen et al. (33) Tong et al (34) 	7	0.04
Proportion of all bladder cancer in whom radiotherapy is recommended =						0.58
Proportion of all cancer patients in whom radiotherapy is recommended = 0.03 X 0.58 =						1.7%

Table 4: Bladder Cancer. The incidence of attributes used to define indications for radiotherapy

Key	Population or subpopulation of interest	Attribute	Proportion of population with this attribute	Quality of information	References	Notes
A	All registry cancers	Bladder cancer	0.03	α	AIHW (4)	1
B	Bladder cancer	Stage I	0.46	β	SA Hosp Registry (5)	2
C	Bladder cancer, Stage I treated with intra-vesical therapy and/or local excision	Local recurrence	0.32	ϵ	Holmang et al. (37)	3
D	Bladder cancer, stage I treated with intra-vesical therapy and/or local excision, local recurrence	Age< 75 years to undergo cystectomy	0.53	β	SA Hosp Registry (5)	4
E	Stage I, local recurrence treated with radical cystectomy	Locoregional recurrence	0.04	ζ	Freeman et al. (38)	3
F	Stage I, Local recurrence, no repeat local recurrence	Distant recurrence	0.09	θ	Herr et al. (39)	3

Key	Population or subpopulation of interest	Attribute	Proportion of population with this attribute	Quality of information	References	Notes
G	Stage I, Local recurrence, no repeat local recurrence, distant recurrence	Brain metastases	0.01	ζ	Slaton et al. (40)	5
H	Stage I, Local recurrence, operable, no repeat local recurrence, distant recurrence, no brain metastases	Painful bone metastases	0.17	ζ	Slaton et al. (40)	5
I	Stage I, no local recurrence	Distant recurrence	0.05	ζ	Slaton et al. (40)	7
J	Stage I, no local recurrence, distant recurrence	Brain metastases	0.01 0.12	ζ ζ	Slaton et al. (40) Sternberg et al. (41)	7
K	Stage I, no local recurrence, distant recurrence, no brain metastases	Painful bone metastases	0.43 0.17	ζ ζ	Sengelov et al. (42) Slaton et al. (40)	7
L	Bladder Cancer	Stages II-III	0.38	β	SA Hosp Registry (5)	2
M	Bladder cancer, Stages II-III	Medically operable	0.0 0.47	μ β	See explanatory note 6. SA Hosp Registry (5)	6

Key	Population or subpopulation of interest	Attribute	Proportion of population with this attribute	Quality of information	References	Notes
N	Stages II-III, operable	Locoregional recurrence	0.08 0.16	ζ ζ	Slaton et al. (40) Herr et al. (43)	4
O	Stages II-III, medically operable, no local recurrence	Distant recurrence	0.31 0.30	ζ ζ	Slaton et al. (40) Thomas et al. (44)	7
P	Stages II-III, medically operable, no local recurrence, distant recurrence	Brain metastases	0.01	ζ	Slaton et al. (40)	7
Q	Stages II-III, medically operable, no local recurrence, distant recurrence, no brain metastases	Painful bone metastases	0.17	ζ	Slaton et al. (40)	7
R	Bladder Cancer, Stage IV	Symptomatic primary tumour	0.43	ζ	Sengelov et al. (42)	8
S	Stage IV, no symptomatic primary	Brain metastases	0.01 0.12	ζ ζ	Slaton et al. (40) Sternberg et al. (41)	7
T	Stage IV, no symptomatic primary, no brain metastases	Painful bone metastases	0.43 0.18	ζ ζ	Sengelov et al. (42) Slaton et al. (40)	7

Bladder Cancer Notes

Treatment guidelines

The treatment guidelines available for bladder cancer were:

- National Cancer Institute Physician Data Query guidelines (PDQ) 2002
- British Columbia Cancer Agency guidelines (BCCA) 2001
- American Urological Association (AUA) bladder cancer treatment guidelines (which did not discuss the role of radiotherapy at all)(45)
- National Comprehensive Cancer Network (NCCN) guidelines 2002.

Indications for radiotherapy

The treatment guidelines recommended consideration of radiotherapy in the management of bladder cancer for the following situations:

- As definitive treatment (with or without concomitant chemotherapy) for muscle invasive bladder cancer (Stage T2-T4a). The BCCA (36), NCCN (28) and PDQ guidelines (35) suggest that either radical cystectomy or radical radiotherapy are both reasonable treatment options with the choice being influenced by the extent of disease, the fitness and co-morbidities of the patient, patient age and patient wishes. The BCCA guidelines favour radiotherapy since it has the advantage of bladder preservation with only patients who relapse requiring bladder removal.
- As palliation for locally advanced or recurrent tumours in the presence of symptoms such as haematuria (28), (46).

The bladder cancer treatment guidelines do not specifically recommend radiotherapy for the palliation of metastases from bladder cancer as the predominant focus of the guidelines is on the management of non-metastatic disease. However the role of radiotherapy in the palliation of certain metastatic sites is well established and therefore radiotherapy is also recommended

- As palliative treatment of metastases to bone or brain (29) (30) (31) (32) (33) (34).

Explanatory notes for Tables 3 and 4.

1. Bladder cancer incidence

The Australian Institute of Health and Welfare (4) states that bladder cancer represents 3% of all reportable cancers in 1998.

2. Stage of bladder cancer

The South Australian Hospital Cancer Registry (5) reports that of all bladder cancers in their series, 46% presented in Stage I, 38% in Stage II-III and 16% in stage IV.

3. Local recurrence and distant recurrence after intra-vesical therapy

The management of Stage I bladder cancer is trans-urethral resection and intravesical therapy (NCCN). Holmang et al. (37) reported on a population-based sample of patients from Western Sweden treated by

a variety of conservative techniques. They reported a recurrence rate for Stage I disease of 32%. These data correlate well with those reviewed by Soloway et al. (47) and being population-based data it should reflect wider practice than single institution data.

A randomised trial of intra-vesical therapy for superficial bladder cancer by Herr et al (39) reported a local recurrence rate of 42/86 (49%) and 8/86 (9%) patients developed distant metastases as the first site of recurrence.

Patients who have a local recurrence are usually considered for cystectomy. Freeman et al. (38) reported on a group of patients treated with radical cystectomy due to recurrent or high-risk disease. They reported a local recurrence risk of 4% and distant recurrence of 8%.

4. Local recurrence and the use of cystectomy for salvage following conservative therapy

The guidelines state that partial or radical cystectomy is the treatment of choice for patients who have developed recurrent or progressive disease following conservative therapy. However, a significant proportion of patients will not be fit to undergo surgery due to age or co-morbidities. There were no data available on performance status in order to estimate the proportion of patients in whom surgery would not be recommended due to poor performance status. Therefore, we used age as a surrogate of performance status with an age cut-off for surgery of 75 years. In the South Australian Hospital Registry (5), 47% of patients were above the age of 75 years. We have indicated that these patients would be given radiotherapy and the other 53% below the age of 75 receive surgery. It is acknowledged that there will be some fit patients above 75 years in whom cystectomy is appropriate and likewise there will be some unfit patients below the age of 75 in whom surgery is inappropriate. Patients considered unfit for surgery may still be fit enough for radical radiation. If not, palliative radiotherapy has been shown to be effective in symptom control (42) (48).

5. Local recurrence following complete or partial cystectomy

Patients who have undergone radical or partial cystectomy and then develop local recurrence may be considered for radiotherapy. There are many single institution series that report outcome following cystectomy in these patient groups. The largest and most recent series have been chosen for an estimate of the locoregional recurrence risk. Slaton et al. (40) described the cystectomy experience of the M.D. Anderson cancer centre 1986-1994 (382 patients). They reported locoregional recurrence in 23/304 (8%) Stage II-III patients. Herr et al. (43) reported on the outcome of 322 patients treated by cystectomy for muscle-invasive bladder cancer. They reported a 16% rate of locoregional recurrence. The 8% locoregional recurrence risk of Slaton et al was chosen due to the larger sample size of their study, with sensitivity analysis performed to assess the impact of this data variation on the overall estimate of radiotherapy utilisation.

6. Management of stage II-IVA bladder cancer

The management of Stage II-IVA bladder cancer is controversial with advocates for surgery and advocates for radiotherapy. A meta-analysis of 5 randomised trials for pre-operative radiotherapy by Huncharek et al showed no benefit over surgery alone (49) but no comparison of (chemo)radiotherapy versus surgery occurred. Some reviews such as that by Sternberg (41) state that “surgery is the gold standard for muscle-invasive bladder cancer” in patients who are fit to undergo surgery. However, no evidence-based justification for the statement is presented and choice of treatment is affected by a patient's overall medical condition and consideration of the adverse effects of therapy. Some reviews quote superior survival results for non-randomised surgical series compared with radiotherapy series. However these comparisons are inappropriate due to selection bias as patients found to have more extensive disease at the time of surgery are usually excluded from the surgical series and the fitter patients are more likely to have had surgery. Conversely advocates for radiotherapy cite bladder preservation rates of 38-50%, justifying routine radiotherapy (+/- chemotherapy) with reservation of cystectomy for salvage in patients who fail to achieve a complete response, recur or develop radiation cystitis (41) (50), Shipley et al. (51), Hayter et al. 2000(52), Kachnic et al (53)., Tester et al.(54), Brown et al.(55).

A Cochrane review purported to compare surgery with radiotherapy suggested that surgery was superior (56) but this review did not adequately address the question and has been strongly criticised. The trials in the review included pre-operative radiotherapy and surgery versus surgery alone, included trials of radiation alone (without chemotherapy), used outdated radiotherapy techniques and had severe methodological flaws that make such a conclusion inappropriate (57) (58). Opponents to a radiotherapy approach argue that following radiotherapy the bladder is prone to bleed and is non-functional. However, a case-controlled questionnaire of patients post-radiotherapy showed no difference in bladder outcome symptom measures compared with patients having no radiation (59). A survey of British urologists (60) revealed that 54% of them would refer a 66 year old man with muscle-invasive bladder cancer for radiotherapy and 44% would perform a cystectomy. A patterns of care study from North Alberta 1984-1993 (61) reported that of 184 patients treated with radical intent, 44% had cystectomy alone with all other patients undergoing radiotherapy (either alone or in combination with chemotherapy and/or surgery).

As there is no definitive randomised evidence of superiority for one modality over the other we have modelled various options in the radiotherapy utilisation tree. For the calculation of the optimal radiotherapy utilisation rate we have modelled radiotherapy being given to all patients with muscle-invasive bladder cancer by estimating the medically inoperable group as 100% (i.e. all patients are preferentially

treated with radiotherapy). Sensitivity analysis was then performed where this estimate was changed to the other extreme where all medically fit patients receive surgery and only those considered unfit on the basis of age or co-morbidity receive radiation at the time of diagnosis. The proportion of patients in whom surgery would not be recommended due to poor performance status is not known, as there were no specific data available on performance status. Therefore, we used age as a surrogate with an age cut-off for surgery of 75 years. In the South Australian Hospital Registry (5), 47% of patients were above the age of 75 years. Therefore, when modelling surgery as the preferred option we assumed that this would represent the other 53%. Patients considered unfit for surgery may still be fit enough for radical radiation. If not, palliative radiotherapy has been shown to be effective in symptom control in several studies including a randomised trial (42;48).

7. Proportion of patients with distant metastases

Patients who develop distant metastases in either brain or bone would be considered for palliative radiotherapy. Slaton et al. (40) reported on the cystectomy experience of the M.D. Anderson cancer centre 1986-1994 (382 patients). The rate of metastatic disease was 5% for Stage I and 31% for stages II-III. Of the 97 patients who developed metastatic disease, 17 (18%) developed bone metastases and 1 (1%) developed brain metastases. Sengelov et al. (42) reported that of 155 patients with metastatic disease in their series, 66 (43%) had bone metastases. They did not report on the proportion with brain metastases. Sternberg et al. (41) reported on the outcomes of 133 metastatic urothelial cancer patients treated with chemotherapy, of whom 12% ultimately developed brain metastases.

To estimate the overall radiotherapy utilisation, the rates of bone and brain metastases were taken from the largest series of Sengelov et al. (42) and Sternberg et al. (41) respectively, with sensitivity analysis performed to calculate the effect of the uncertainty in data on the overall radiotherapy utilisation rate.

8. Proportion of patients with stage IV disease and a symptomatic primary

Patients with stage IV disease and a symptomatic primary would be considered suitable for palliative radiotherapy. Petrovich et al. reviewed the benefits of palliative radiotherapy in patients with incurable disease (46). In terms of reports on the proportion of patients with symptomatic primary disease, the best report was from Sengelov et al. (42). They reported on the pattern of recurrence in patients with disseminated bladder cancer treated in the Copenhagen University Hospital, 1976-1991. In this series of 155 patients with metastatic disease, 67 (43%) had symptomatic locoregional disease and the remainder had metastatic disease with no locoregional disease.

Expected value and sensitivity analysis

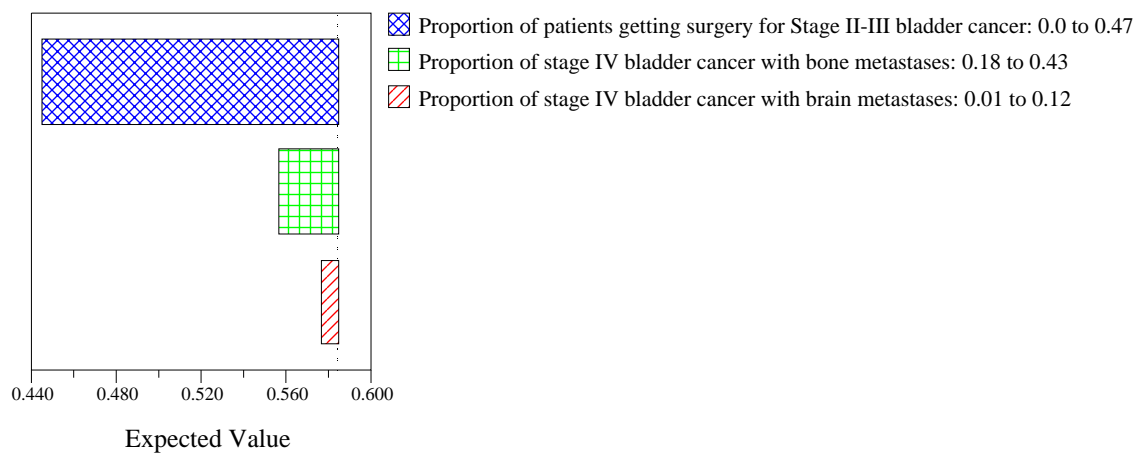
The calculated overall rate of optimal radiotherapy utilisation in bladder cancer was 58%. As bladder cancer represents 3% of all cancers, this population of patients represents 1.7% of all cancer patients.

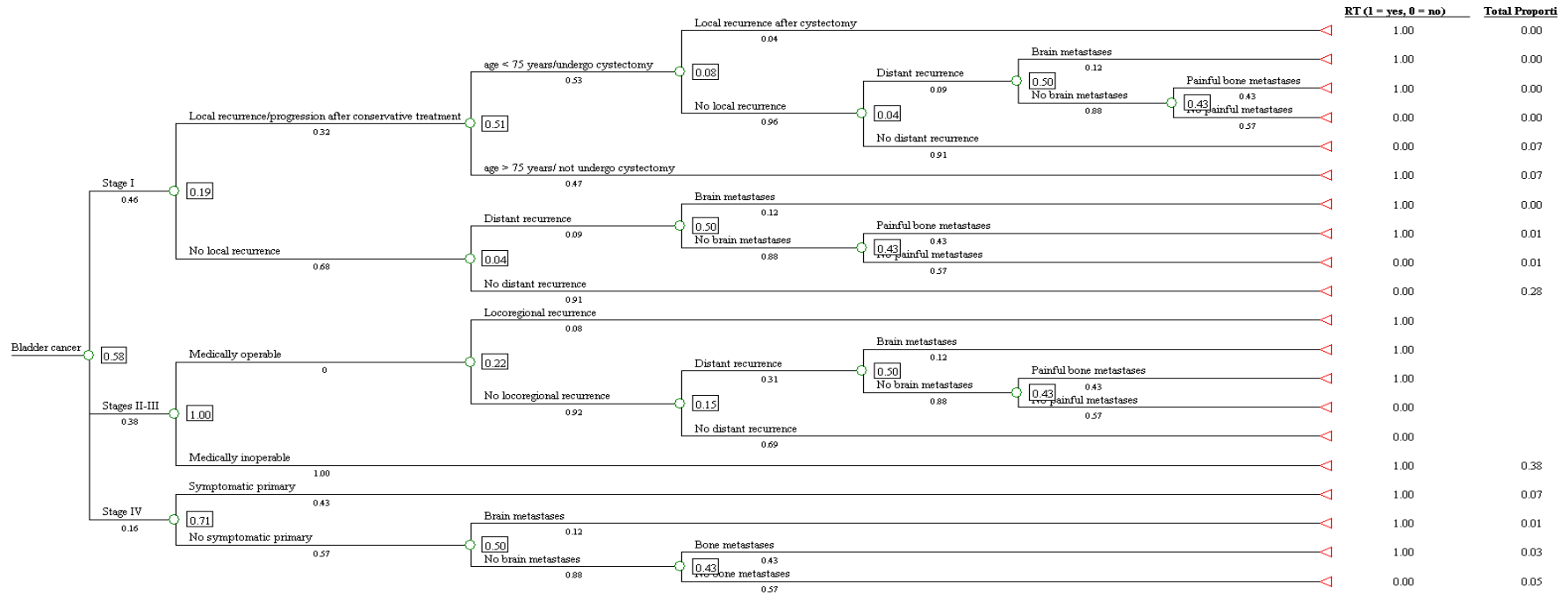
There were several instances where the data varied significantly. They were:

- The proportion of patients with stage II-III bladder cancer in whom surgery is appropriate was varied between 0% (i.e. all patients to receive radiation) and 0.47 (i.e. only those patients that are unfit for surgery to get radiation),
- The proportion of patients with stage IV disease with bone metastases (0.18-0.43) and
- The proportion of patients with stage IV disease with brain metastases (0.01-0.12).

Therefore, sensitivity analysis was necessary to assess the impact of this overall uncertainty on the optimal radiotherapy utilisation rate. The graph below shows that varying the proportions for each of these values, altered the bladder cancer optimal utilisation rate from 44.5% to 58.3%. This would mean that the radiotherapy rate as a proportion of all cancers would be between 1.3 and 1.7%.

Tornado Diagram at Bladder cancer





Testicular Cancer

Table 5: Testicular Cancer. Indications for radiotherapy - Levels and sources of evidence

Outcome Number	Clinical Scenario	Treatment Indicated	Level of Evidence	References	Notes	Proportion of all Testicular Cancer patients
30	Seminoma, Stage I, radiotherapy	Adjuvant RT	III	<ul style="list-style-type: none">• National Cancer Institute PDQ statement on treatment of testicular cancer (62)• COIN/SIGN guidelines on the management of adult testicular germ cell tumours (63)	2	0.41
31	Seminoma, Stage I, observation, nodal recurrence	RT	IV	<ul style="list-style-type: none">• National Cancer Institute PDQ statement on treatment of testicular cancer (62)	3,4	0.01
32	Seminoma, Stage I, observation, no nodal recurrence, distant recurrence, brain metastases	RT	II	<ul style="list-style-type: none">• COIN/SIGN guidelines on the management of adult testicular germ cell tumours (63)• German Testicular Cancer Study Group (64)	6	<0.01
33	Seminoma, Stage I, observation, no nodal recurrence, distant recurrence, no brain metastases bone metastases	RT	I	<ul style="list-style-type: none">• Steenland et al. (32)• Nielsen et al. (33)• Tong et al (34)	6	<0.01

Outcome Number	Clinical Scenario	Treatment Indicated	Level of Evidence	References	Notes	Proportion of all Testicular Cancer patients
36	Seminoma, Stage II, non-bulky disease (Stage IIA/IIB)	RT	III	<ul style="list-style-type: none"> National Cancer Institute PDQ statement on treatment of testicular cancer , p 14 (62) COIN/SIGN guidelines on the management of adult testicular germ cell tumours, p20, (63) 	7	0.07
37	Seminoma, Stage II, bulky disease, residual disease post-chemotherapy	RT	IV	<ul style="list-style-type: none"> EAU guidelines on testicular cancer (65) 	8	<0.01
38	Seminoma, Stage II, bulky disease, no residual disease post-chemotherapy, no nodal recurrence, distant recurrence with brain metastases	RT	II	<ul style="list-style-type: none"> COIN/SIGN guidelines on the management of adult testicular germ cell tumours, p 26, (63) German Testicular Cancer Study Group (64) 	6	<0.01

Outcome Number	Clinical Scenario	Treatment Indicated	Level of Evidence	References	Notes	Proportion of all Testicular Cancer patients
39	Seminoma, Stage II, bulky disease, no residual disease post-chemotherapy, no nodal recurrence, distant recurrence, no brain metastases, bone metastases	RT	I	<ul style="list-style-type: none"> • Steenland et al. (32) • Nielsen et al. (33) • Tong et al (34) 	6	<0.01
42	Seminoma, Stage III, residual disease post-chemotherapy	RT	IV	<ul style="list-style-type: none"> • EAU guidelines on testicular cancer (65) 	9	<0.01
43	Seminoma, Stage III, no residual disease post-chemotherapy, distant recurrence with brain metastases	RT	II	<ul style="list-style-type: none"> • COIN/SIGN guidelines on the management of adult testicular germ cell tumours , p 26) (63) • German Testicular Cancer Study Group (64) 	6	<0.01

Outcome Number	Clinical Scenario	Treatment Indicated	Level of Evidence	References	Notes	Proportion of all Testicular Cancer patients
44	Seminoma, Stage III, no residual disease post-chemotherapy, distant recurrence, no brain metastases, bone metastases	RT	I	<ul style="list-style-type: none"> • Steenland et al. (32) • Nielsen et al. (33) • Tong et al (34) 	6	<0.01
47	Seminoma, Stage IV, brain metastases	RT	II	<ul style="list-style-type: none"> • COIN/SIGN guidelines on the management of adult testicular germ cell tumours, p 26 (63) • German Testicular Cancer Study Group (64) 	6	<0.01
48	Seminoma, Stage IV, no brain metastases, bone metastases	RT	I	<ul style="list-style-type: none"> • Steenland et al. (32) • Nielsen et al. (33) • Tong et al (34) 	6	<0.01
49	Seminoma, Stage IV, no brain or bone metastases, persistent disease after chemotherapy	RT	IV	<ul style="list-style-type: none"> • EAU guidelines on testicular cancer (65) 	10	<0.01

Outcome Number	Clinical Scenario	Treatment Indicated	Level of Evidence	References	Notes	Proportion of all Testicular Cancer patients
51	Non-seminomatous germ cell and non-germ cell, Stages I-III, distant recurrence with brain metastases	RT	II	<ul style="list-style-type: none"> National Cancer Institute PDQ statement on treatment of testicular cancer, p 21 (62) 	12	<0.01
54	Non-seminomatous germ cell and non-germ cell, Stage IV, brain metastases	RT	II	<ul style="list-style-type: none"> National Cancer Institute PDQ statement on treatment of testicular cancer, p21 (62) German Testicular Cancer Study Group (64) 	12	<0.01
Proportion of testicular cancer patients in whom radiotherapy is recommended						0.49
Proportion of all cancer patients in whom radiotherapy is recommended = 0.49 X 0.01 =						0.5%

Table 6: Testicular Cancer - The incidence of attributes used to define indications for radiotherapy

Key	Population or subpopulation of interest	Attribute	Proportion of population with this attribute	Quality of information	References	Notes
A	All registry cancers	Testicular cancer	0.01	α	AIHW (4)	1
B	Testicular cancer	Seminoma	0.56	β	Toner et al. (66)	1
			0.54	γ	Weir et al. (67)	
C	Seminoma	Stage I	0.83	β	Toner et al. (66)	1
D	Seminoma, Stage I	Radiotherapy	0.89	β	Toner et al. (66)	2, 3
E	Seminoma, Stage I, Observation	Nodal recurrence	0.19	ε	von der Maase et al. (68)	4
			0.14	ζ	Gospodarowicz et al. (69)	
F	Seminoma, Stage I, Observation, no nodal recurrence	Distant Recurrence	0.08	ζ	Duchesne et al. (70)	5
G	Seminoma, Stage I, Observation, no nodal recurrence, distant recurrence	Brain metastases	0.01	ε	International Germ Cell Cancer Collaborative Group (71)	6

Key	Population or subpopulation of interest	Attribute	Proportion of population with this attribute	Quality of information	References	Notes
H	Seminoma, Stage I, Observation, no nodal recurrence, distant recurrence, no brain metastases	Bone metastases	0.05	ε	International Germ Cell Cancer Collaborative Group (71)	6
I	Seminoma	Stage II	0.14	β	Toner et al. (66)	1
J	Seminoma, Stage II	Bulky disease	0.16	ζ	Warde et al. (72)	7
K	Seminoma, Stage II, bulky disease	Residual disease post-chemotherapy	0.0	θ	Duchesne et al. (70)	8
			0.07	θ	Duchesne et al. (70)	
L	Seminoma, Stage II, bulky disease, no residual disease post-chemotherapy	Recurrence	0.0	ζ	Warde et al. (72)	9
M	Seminoma, Stage II, bulky disease, no residual disease post-chemotherapy, distant recurrence	Brain metastases	0.01	ε	International Germ Cell Cancer Collaborative Group (71)	6

Key	Population or subpopulation of interest	Attribute	Proportion of population with this attribute	Quality of information	References	Notes
N	Seminoma, Stage II, bulky disease, no residual disease post-chemotherapy, distant recurrence, no brain metastases	Bone metastases	0.05	ε	International Germ Cell Cancer Collaborative Group (71)	6
O	Seminoma	Stage III	0.03	β	Toner et al. (66)	1
P	Seminoma, Stage III	Residual disease post-chemotherapy	0.0	θ	Duchesne et al. (70)	8
			0.15	ζ	Logothetis et al. (73)	
Q	Seminoma, Stage III No residual disease post-chemotherapy	Recurrence	0.25	λ	Pooled data - See explanatory note 5.	5
R	Seminoma, Stage III No residual disease post-chemotherapy, distant recurrence	Brain metastases	0.01	ε	International Germ Cell Cancer Collaborative Group (71)	6

Key	Population or subpopulation of interest	Attribute	Proportion of population with this attribute	Quality of information	References	Notes
S	Seminoma, Stage III No residual disease post-chemotherapy, distant recurrence, no brain metastases	Bone metastases	0.05	ε	International Germ Cell Cancer Collaborative Group (71)	6
T	Seminoma	Stage IV	0.0	β	Toner et al. (66)	1
U	Seminoma, Stage IV	Brain metastases	0.01	ε	International Germ Cell Cancer Collaborative Group (71)	6
V	Seminoma, Stage IV, no brain metastases	Bone metastases	0.05	ε	International Germ Cell Cancer Collaborative Group (71)	6
W	Seminoma, Stage IV, no brain metastases	Persistent disease after chemotherapy	0.0	θ	Duchesne et al (70) Logothetis et al. (73) Loehrer et al. (74)	10
			0.09	ζ		
			0.32	θ		
X	Testicular cancer	Non-seminomatous germ cell and non-germ cell	0.44	β	Toner et al. (66)	1
Y	Testicular cancer, non-seminomatous germ cell and non-germ cell	Stages I-III	1.0	β	Toner et al. (66)	1

Key	Population or subpopulation of interest	Attribute	Proportion of population with this attribute	Quality of information	References	Notes
Z	Testicular cancer, non-seminomatous germ cell and non-germ cell, Stages I-III	Distant recurrence	0.12	ζ	Kelty et al. (75)	11`
Z-1	Testicular cancer, non-seminomatous germ cell and non-germ cell, Stages I-III, distant recurrence	Brain metastases	0.06 0.03 0.04 0.01	ζ ζ θ ε	Motzer et al. (76) Howard et al.(77) Ozols et al. (78) International Germ Cell Cancer Collaborative Group (71)	12
Z-2	Testicular cancer, non-seminomatous germ cell and non-germ cell, Stages I-III, distant recurrence, no brain metastases	Bone metastases	0.01	ε	International Germ Cell Cancer Collaborative Group (71)	12
Z-3	Testicular cancer, non-seminomatous germ cell and non-germ cell, Stage IV	Brain metastases	0.06 0.03 0.04 0.01	ζ ζ θ ε	Motzer et al. (76) Howard et al.(77) Ozols et al. (78) International Germ Cell Cancer Collaborative Group (71)	12
Z-4	Testicular cancer, non-seminomatous germ cell and non-germ cell, Stages I-III, distant recurrence, no brain metastases	Bone metastases	0.01	ε	International Germ Cell Cancer Collaborative Group (71)	12

Testicular Cancer Notes

Treatment guidelines

The guidelines available on the management of testicular cancer are:

- National Cancer Institute Physicians Data Query (PDQ) 2002 (62)
- British Columbia Cancer Agency (BCCA) 2001 (79)
- Royal College of Radiologists Clinical Oncology Information Network (COIN) 2001 (63)
- National Comprehensive Cancer Network (NCCN) 1998 (80)
- European Association of Urologists (EAU) 2001. (65)
- German Testicular Cancer Study Group 1996 (64)

Indications for radiotherapy

The guidelines recommend the use of radiotherapy in testicular cancer in the following clinical situations:

- As prophylactic treatment following inguinal orchidectomy for Stage I seminoma (62) (79) (63) (80) (65).
- In Stage II seminoma, radiotherapy is routinely recommended if the nodal disease is non-bulky (62) (79) (63) (80) (65). Bulky Stage II-III seminoma may be treated either by chemotherapy alone or by a combination of chemotherapy and radiation. The main controversy is whether residual masses after chemotherapy should be routinely irradiated (62) (79) (63) (80). This is discussed further in explanatory note 8.
- Brain metastases from seminoma or non-seminoma (62) (63) (80) (65) (64).
- Recurrent seminoma not previously irradiated (62) (80).

Explanatory Notes for Tables 5 and 6

1. Stage data

There are two main histological types of testicular cancer – seminoma and non-seminoma. Toner et al. reported on the patterns of care of testicular cancer in Victoria from 1988-1993 (66). There were 633 patients in their series who were classified histologically as follows: seminoma 56%, non-seminomatous germ cell tumour 43% and non-germ cell tumours 1%. This data is used in preference to hospital registry data because of the larger sample size and the fact that the Victorian study is population-based rather than hospital registry-based. The US National Cancer Data Base of testicular cancer 1985-1996 (81) reported on 15409 testicular cancers diagnosed between 1985-1986, 1990-1991 and 1995-1996. Seminoma comprised 56%, 38% were non-seminomatous germ cell tumours and 6% were non-germ cell tumours. The incidence of seminoma in Ontario 1964-1996 was 54% of all testicular tumours (67). As the management in terms of radiotherapy is largely limited to the

palliation of brain metastases for both non-seminomatous germ cell tumours and non-germ cell tumours, they were grouped together in the tree.

The SA Hospital Cancer Registry database (5) does not report AJCC stage groupings according to histology. The US National Cancer Database (81) only reported by crude stage groupings (early or advanced). 62% of patients with both seminoma and non-seminoma had early disease, and 38% had advanced disease. The Victorian Patterns of Care study in testis cancer (66) reports both seminoma and non-seminoma by stage. The stage distributions were:

Stage	Seminoma	Non Seminoma
I	83%	72%
II	14%	23%
III	3%	19%

There were no Stage IV tumours reported.

2. **Stage I seminoma management controversies**

All the guidelines recommended prophylactic radiotherapy over other treatment alternatives. The option of adjuvant chemotherapy was discussed in the BCCA guidelines. However, they state that this is still undergoing evaluation in Phase II and III studies and the data is too immature to replace other established treatments.

All the treatment guidelines suggest that radical inguinal orchidectomy followed by observation is a reasonable option but has largely fallen from favour due to the low treatment toxicity with radiotherapy and the problems of compliance with prolonged surveillance. The COIN guidelines (63) state that: "A policy of surveillance for patients with Stage I "pure" seminoma is not recommended routinely but may be considered in rare instances where radiotherapy has previously been given or in patients who are medically or mentally unable to tolerate treatment." The BCCA guidelines (79) state that the standard treatment for Stage I seminoma is surgery followed by para-aortic +/- pelvic radiotherapy, which leads to control rates of 95% and cure in 99%. They state that surveillance could be considered an alternative but no long-term randomised trials exist to prove that surveillance is as successful as radiotherapy. Relapse rates after surveillance are 15-20%. Both the PDQ (62) and EAU guidelines (65) discuss surgery followed by observation and radiotherapy as equal treatment options. Sharda et al.(82) in an economic analysis of the treatment options found adjuvant radiotherapy to be more cost-effective than surveillance.

3. Proportion of Stage I seminoma patients who elect to have surveillance rather than radiotherapy

The US National Cancer Data Base for testicular cancer 1985-1996 (81) reports an increase in the rates of observation following orchidectomy for early stage seminoma (15% in 1985-1986, 19% for 1990-1991, 21% for 1995-1996). This compares with radiation being given post-operatively in approximately 73% of cases in 1995-1996. The Victorian Patterns of Care study (66) reported that of 295 patients with Stage I seminoma, 33 patients (11%) chose observation over radiotherapy. It is not clear whether access to radiotherapy was an important factor in the patient choice. A survey of 74 Australasian Radiation Oncologists (83) revealed that 54% of radiation oncologists routinely discussed surveillance of Stage I disease with their patients and estimated that approximately 5% (range 0-30%) would choose observation over prophylactic radiotherapy. This compared with 79% of 79 Canadian radiation oncologists and 75% of 36 US radiation oncologists regularly discussing surveillance with their patients (84). The median estimated uptake of surveillance was 20% in Canada (range 0-100%) and 7.5% in the US (range 0-50%).

4. Nodal relapse after surveillance

Most treatment guidelines recommend radiotherapy to patients who develop nodal relapse while undergoing surveillance for Stage I seminoma. There are a large number of prospective single institution studies reporting relapse incidence rates for patients treated with orchidectomy and then enrolled onto a surveillance programme. This study is not intended to review all of this literature but to use the best epidemiological data available. Therefore, only a limited number of studies were reviewed to estimate this proportion.

The Danish Testicular Carcinoma Study Group (DATECA) (68) described the largest series of seminoma patients treated with orchidectomy and surveillance. They reported a 19% recurrence rate at 4 year median follow-up. This result is consistent with most of the other literature. A series with longer follow-up (73 months) by Warde et al. (72) reported a recurrence rate of 14%. The Princess Margaret Hospital Group reported that their standard therapy for para-aortic recurrence is radiotherapy with <20% risk of further recurrence (72). Sharda et al. (82) when performing a cost-analysis for surveillance assumed a recurrence rate of 15%. A review by Gospodarowicz et al. of 8 trials and a total of 800 patients reported a recurrence rate of 16% (69).

5. Distant relapse after surveillance

Duchesne et al. reported on 113 patients with Stage I seminoma treated by orchidectomy and surveillance (70). They reported an overall recurrence rate of 12%. Of these 13 relapsed patients, 1(8%) had distant recurrence. The remainder had nodal recurrence. All nodal recurrences were treated with radiotherapy +/- chemotherapy.

6. Proportion of patients with distant metastases who develop brain or bone metastases

The treatment guidelines recommend consideration of radiotherapy to the brain for patients with symptomatic brain metastases (65) (64). In addition, a large study of high-dose radiotherapy advocates radiotherapy for metastatic germ cell tumours of seminoma and non-seminoma type (85). None of the treatment guidelines discuss the use of palliative radiotherapy of bone metastases. However, radiotherapy for bone metastases is well established for other cancers and therefore there is good evidence to consider radiotherapy for patients with seminoma and bone metastases to palliate pain or to prevent pathological fracture (32;33) (34).

The incidence of brain or bone metastases for stage IV seminoma is not frequently reported in the literature. The best data was from a collaborative study of 5,800 germ cell cancer patients with metastatic disease treated on chemotherapy protocols across 10 collaborating countries (71). They reported that seminoma with brain metastases represented 1% of the entire group of seminoma patients, and bone metastases 5%. These may be under-estimates as assessment was at the time of inclusion into the study and does not include the development of subsequent metastases in these patients. However, no other studies were available and therefore these estimates were used.

7. Proportion of patients with Stage II seminoma who have bulky disease

The recommended treatment for non-bulky seminoma (<5 cm) is radiotherapy. However, for bulky stage II disease (tumours >5 cm in size) chemotherapy is considered the treatment of choice because of the higher failure rates with radiotherapy alone (86). In terms of the estimate of the proportion with bulky nodes, Warde et al. reported on a series of 99 patients with Stage II disease treated at Princess Margaret Hospital, Toronto, Canada from 1981-1993 (72). Of these patients, 16% were bulky (stages IIc-IIId).

8. Proportion of patients with Stage II or III seminoma who have residual masses after chemotherapy

Duchesne et al. reported that of patients with abdominal disease with nodes >5 cm in size, 7% had residual masses following chemotherapy (70). Logothetis et al. reported that in 52 patients with Stage III disease, 85% achieved a complete response to cyclophosphamide and platinum (73).

Patients without a complete response following completion of chemotherapy were recommended to have post-chemotherapy radiotherapy by some of the guidelines (65) (EAU) but not others (PDQ(62), NCCN (80)). Motzer et al. (76) in a retrospective review of 52 patients with >3cm of nodal residual mass after chemotherapy, reported that 42% of patients either were found to have viable tumour at surgery or relapsed at a later time and suggest further therapy in these patients. Duchesne et al. (70) reported that radiotherapy to residual masses does not have any impact upon overall survival rates.

The majority of treatment guidelines recommended against routine radiotherapy for patients with residual masses. Therefore, in the tree it was decided to recommend radiotherapy for the branch “proportion of patients with residual disease after chemotherapy” but with the proportion requiring radiotherapy set at 0 indicating that this is appropriate in no patients for the overall radiotherapy utilisation estimate. This figure was then varied to reflect the other extreme view where all residual masses get radiotherapy [proportion = 15% according to Logothetis et al. (73)] in sensitivity analysis to assess the impact of this uncertainty on the overall utilisation rate.

9. Proportion of patients with Stages II-III seminoma treated with chemotherapy, who develop recurrence following chemotherapy

Warde et al. (72) reported on the Princess Margaret Hospital, Toronto experience of treating 99 patients with stage II seminoma. Of 19 patients treated with chemotherapy alone, none developed a recurrence.

The relapse rate for stage III disease was difficult to determine as most studies had very small patient numbers. The table below shows the crude rates of recurrence, the numbers of patients and the average value for the overall recurrence rate of stage III patients treated with chemotherapy in the radiotherapy utilisation tree.

Table 7: Relapse rate for stage III disease from selected series.

Study	Patient number	Number of recurrences	Failure rate
Fossa et al. (87)	12	2	17%
Pizzocarro et al. (88)	3	1	33%
Wilkinson et al. (89)	13	4	31%
Schmoll et al. (90)	12	3	25%
Total	40	10	25%

10. Proportion of patients with stage IV seminoma who have persistent disease after chemotherapy

Loehrer et al. (74) reported on the SouthEastern Cancer Study Group experience of 62 patients with metastatic seminoma treated with various chemotherapy regimens. A total of 41 patients (68%) had no evidence of disease after chemotherapy (and surgical resection of residual masses in some patients). This leaves a further 32% of patients with residual disease who may potentially benefit from radiotherapy. Logothetis reported on 55 patients with metastatic seminoma (73). 9% of patients had evidence of persistent disease requiring radiotherapy following chemotherapy.

However, a large review of 10 European centres by Duchesne et al. (70) suggests that routine radiotherapy is not beneficial after chemotherapy for patients with Stage IV seminoma with residual masses following chemotherapy. They suggested consideration of radiotherapy only for those patients with evidence of progressive disease. In the tree it was decided that the branch of “proportion of patients with residual disease after chemotherapy” should show radiotherapy being given but the proportion would be set at 0 indicating that this is appropriate in no patients for the overall radiotherapy utilisation estimate. This figure was then varied to reflect the other extreme where all patients with residual disease receive radiotherapy [proportion = 32% according to Loehrer et al. (74)] in sensitivity analysis to assess the impact of this uncertainty on the overall utilisation rate.

11. Proportion of patients with non-seminomatous germ cell tumours (NSGCT) and non-germ cell tumours, Stages I-III who develop distant metastases

Kelty et al. (75) reported on their 15-year experience of patients with testicular tumours treated at the National Naval Medical Centre in Bethesda, U.S.A. They reported on 122 cases of NSGCT Stages I-III that were initially treated with either retroperitoneal lymph node dissection or observation. The stage distributions were similar to that seen in population based series. Of the 122 cases, 15 relapsed with distant metastases (12%).

12. Proportion of patients with metastatic non-seminomatous germ cell and non-germ cell tumours that develop brain or bone metastases

The guidelines discuss the management of brain metastases in little detail except for the German Testicular Cancer Study Group(64) who suggest that appropriate treatment would include brain radiotherapy. In addition, a large study of high-dose radiotherapy advocates radiotherapy for metastatic germ cell tumours of seminoma and non-seminoma type (85). As was the case with seminoma, no treatment guidelines discussed the use of radiotherapy for palliation of bone metastases. Considering the utility of radiotherapy for bone metastases from other tumour sites, it was considered appropriate to use radiotherapy in this setting.

In terms of brain metastasis incidence data, Motzer et al. (76) reported on the characteristics of 124 advanced germ cell tumours treated at Memorial Sloan Kettering Hospital from 1979-1989. Of those with metastatic disease, 6% had brain metastases. Howard et al.(77) reported that 3% of their series of 34 patients had brain metastases. Ozels et al. (78) reported 4% incidence in a chemotherapy study.

A collaborative study across 10 countries enrolled 5,800 germ cell cancer patients with metastatic disease who were treated on chemotherapy protocols (71). The study reported that non-seminoma with brain metastases represented 1% of the entire group of non-seminoma patients, and bone metastases 1%. These may be under-estimates as this was an assessment at the time of inclusion of the study and did not study the development of subsequent metastases in these patients. As there was better brain metastasis incidence data from Motzer et al. (76) (in that their study reported on the progress of patients), the 6% figure from Motzer et al. was used. Since there were no better data on the incidence of bone metastases, the 1% derived from the collaborative study was used.

There are other metastatic sites where palliative radiotherapy may be considered such as lung or soft tissue. However, it is

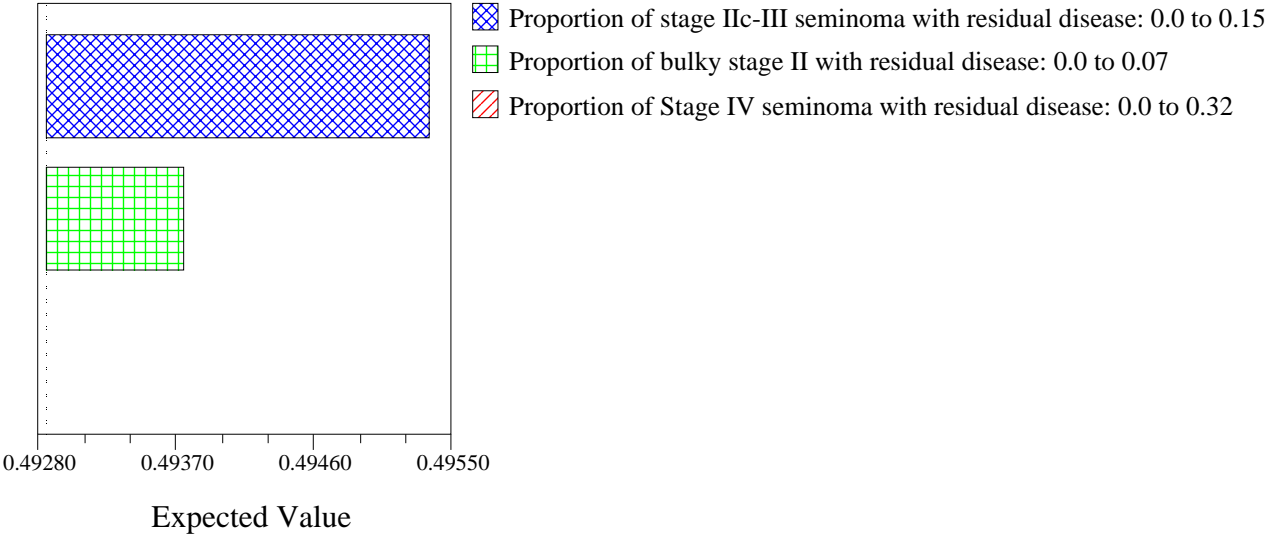
impossible to determine an accurate incidence of patients with these clinical features in whom the use of radiotherapy is considered appropriate. It is assumed that the incidence is small and unlikely to significantly alter the overall estimate of optimal radiotherapy utilisation.

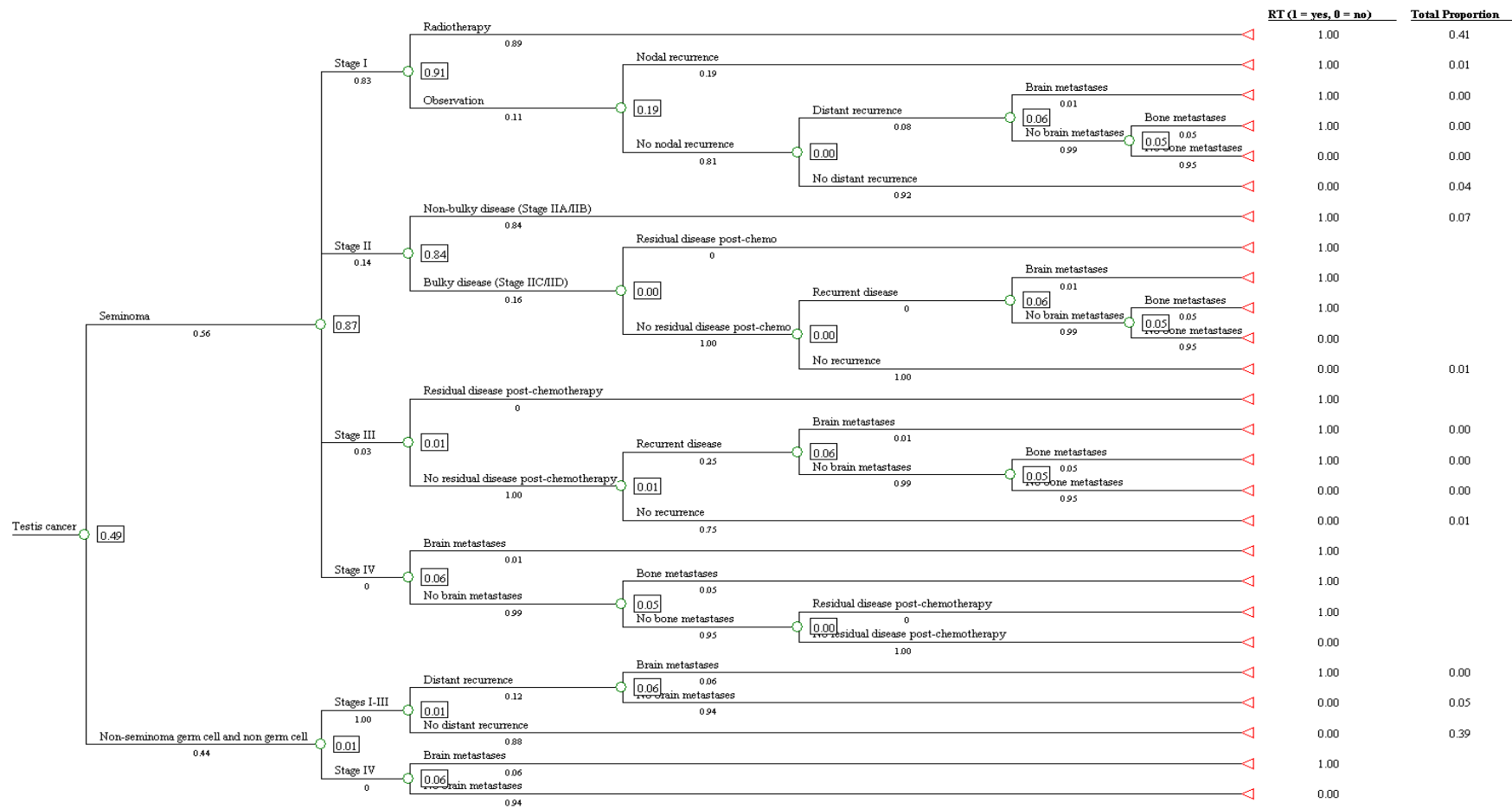
Expected value and sensitivity analysis

The calculated overall rate of optimal radiotherapy utilisation in testicular cancer was 49%. The optimal utilisation rates for seminoma and non-seminoma/non-germ cell tumours were 87% and 1% respectively. As testicular cancer represents 1% of all cancers, the proportion of testicular cancer patients in whom radiotherapy is recommended represents 0.5% of all cancer patients.

There were several branches in the testicular cancer tree where uncertainty of treatment recommendation existed. This mainly concerned seminoma patients with nodal disease and residual masses after chemotherapy. The issue of whether radiotherapy should be given to residual masses with the majority of the treatment guidelines not recommending routine radiation is controversial. Therefore, the optimal radiotherapy rate was calculated based upon none of these patients getting radiation and then sensitivity analysis was performed to model the impact of a policy of routine radiotherapy on the overall estimate. This is illustrated by the tornado diagram below. The graph below shows that varying the proportions for each of these branches, altered the testicular cancer optimal utilisation rate from 49.3% to 49.5%%. This would affect the overall cancer radiotherapy utilisation rate by 0.02%.

**Tornado Diagram at
Testis**





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Lymphoma

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

Outcome Number	Clinical Scenario	Treatment Indicated	Level of Evidence	References	Notes	Proportion of all lymphoma patients
1	Hodgkin's Disease Stage I-IIA	RT	III	<ul style="list-style-type: none">•National Cancer Institute PDQ Statement on Hodgkin's Disease (1)•National Comprehensive Cancer Network Guidelines on Hodgkin's Disease (2)•European Society of Medical Oncology Guidelines (3)	3	0.05
2	Hodgkin's Disease Stage IIB-IV <60 years Bulky Disease	RT	III	<ul style="list-style-type: none">•National Cancer Institute PDQ Statement on Hodgkin's Disease(1)• National Comprehensive Cancer Network Guidelines on Hodgkin's Disease (2)•European Society of Medical Oncology Guidelines (3)	5	0.01
4	Hodgkin's Disease Stage IIB-IV < 60 years no bulky disease complete response to chemotherapy relapse suitable for HDCT/BMT residual disease	RT	IV	<ul style="list-style-type: none">• National Comprehensive Cancer Network Guidelines on Hodgkin's Disease (2)	8	<0.01

Outcome Number	Clinical Scenario	Treatment Indicated	Level of Evidence	References	Notes	Proportion of all lymphoma patients
6	Hodgkin's Disease Stage IIB-IV < 60 years no bulky disease complete response to chemotherapy relapse Not suitable for HDCT/BMT Relapse at nodal site	RT	IV	<ul style="list-style-type: none"> • National Comprehensive Cancer Network Guidelines on Hodgkin's Disease (2) 	8	<0.01
8	Hodgkin's Disease Stage IIB-IV < 60 years no bulky disease partial response to chemotherapy	RT	III	<ul style="list-style-type: none"> • European Society of Medical Oncology Guidelines(3) • National Comprehensive Cancer Network Guidelines on Hodgkin's Disease (2) 	9	<0.01
9	Hodgkin's Disease Stage IIB-IV < 60 years no bulky disease progressive disease/stable disease with chemotherapy, residual disease after HDCT	RT	IV	<ul style="list-style-type: none"> • European Society of Medical Oncology Guidelines (3) • National Comprehensive Cancer Network Guidelines on Hodgkin's Disease (2) 	9	<0.01

Outcome Number	Clinical Scenario	Treatment Indicated	Level of Evidence	References	Notes	Proportion of all lymphoma patients
12	Hodgkin's Disease Stage IIB-IV >60 years no bulky disease Complete response Relapse at nodal site	RT	IV	<ul style="list-style-type: none"> •NCI PDQ Statement on Hodgkin's Disease (1) • NCCN Guidelines on Hodgkin's Disease (2) •ESMOGuidelines (3) 	11	<0.01
14	Hodgkin's Disease Stage IIB-IV >60 years no bulky disease Incomplete response	RT	III	<ul style="list-style-type: none"> • National Comprehensive Cancer Network Guidelines on Hodgkin's Disease (2) • European Society of Medical Oncology Guidelines (3) 	12	0.01
15	Hodgkin's Disease Stage IIB-IV > 60 years Bulky Disease	RT	IV	<ul style="list-style-type: none"> •National Cancer Institute PDQ Statement on Hodgkin's Disease (1) • National Comprehensive Cancer Network Guidelines on Hodgkin's Disease (2) •European Society of Medical Oncology Guidelines (3) 	11	<0.01

Outcome Number	Clinical Scenario	Treatment Indicated	Level of Evidence	References	Notes	Proportion of all lymphoma patients
16	Non-Hodgkin's lymphoma (NHL) Low Grade, MALT Gastric, stage I-II Complete response to helicobacter eradication Relapse	RT	III	<ul style="list-style-type: none"> • National Comprehensive Cancer Network Guidelines on Non-Hodgkin's Lymphoma (4) 	17	<0.01
18	Non-Hodgkin's lymphoma (NHL) Low Grade, MALT Gastric, stage I-II Incomplete response to helicobacter eradication	RT	IV	<ul style="list-style-type: none"> • National Comprehensive Cancer Network Guidelines on Non-Hodgkin's Lymphoma (4) 	16	<0.01
20	Non-Hodgkin's lymphoma (NHL) Low Grade MALT lymphoma Not gastric Stage I-II	RT	IV	<ul style="list-style-type: none"> • National Comprehensive Cancer Network Guidelines on Non-Hodgkin's Lymphoma (4) • British Committee for Standards in Haematology- Non-Hodgkin's Lymphoma Guidelines (5) 	18	0.03

Outcome Number	Clinical Scenario	Treatment Indicated	Level of Evidence	References	Notes	Proportion of all lymphoma patients
22	Non-Hodgkin's lymphoma (NHL), Low Grade Non-MALT lymphoma Stage I-II	RT	III	<ul style="list-style-type: none"> • National Comprehensive Cancer Network Guidelines on Non-Hodgkin's Lymphoma (4) • British Committee for Standards in Haematology- Non-Hodgkin's Lymphoma Guidelines (5) • National Cancer Institute PDQ Statement on Non-Hodgkin's lymphoma (6) 	19	0.08
24	NHL, Low Grade Non-MALT, Stage III-IV Require treatment at presentation Complete response to chemotherapy Relapse, partial/no response second line chemotherapy	RT	IV	National Comprehensive Cancer Network Guidelines on Non-Hodgkin's Lymphoma (4) <ul style="list-style-type: none"> • British Committee for Standards in Haematology- Non-Hodgkin's Lymphoma Guidelines (5) 	22	0.02

Outcome Number	Clinical Scenario	Treatment Indicated	Level of Evidence	References	Notes	Proportion of all lymphoma patients
27	NHL, Low Grade Non-MALT, Stage III-IV Require treatment at presentation incomplete response to initial chemotherapy partial/no response second line chemotherapy	RT	III	National Comprehensive Cancer Network Guidelines on Non-Hodgkin's Lymphoma (4) •British Committee for Standards in Haematology-Non-Hodgkin's Lymphoma Guidelines (5)	23	0.02
29	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 chemotherapy	RT	III	National Comprehensive Cancer Network Guidelines on Non-Hodgkin's Lymphoma (4) •British Committee for Standards in Haematology-Non-Hodgkin's Lymphoma Guidelines (5)	25	0.01

Outcome Number	Clinical Scenario	Treatment Indicated	Level of Evidence	References	Notes	Proportion of all lymphoma patients
32	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 chemotherapy	RT	III	National Comprehensive Cancer Network Guidelines on Non-Hodgkin's Lymphoma (4) •British Committee for Standards in Haematology-Non-Hodgkin's Lymphoma Guidelines (5)	26	<0.01
35	NHL, intermediate Grade Stage I-II	RT	II	<ul style="list-style-type: none"> • National Comprehensive Cancer Network Guidelines on Non-Hodgkin's Lymphoma (4) • British Committee for Standards in Haematology-Non-Hodgkin's Lymphoma Guidelines (5) •European Society of Medical Oncology Guidelines (7) 	27	0.3

Outcome Number	Clinical Scenario	Treatment Indicated	Level of Evidence	References	Notes	Proportion of all lymphoma patients
37	NHL, intermediate Grade, Stage III-IV, complete response to chemotherapy, age < 70 years, relapse with 'bulky' disease	RT	III	<ul style="list-style-type: none"> • National Comprehensive Cancer Network Guidelines on NHL (4) • British Committee for Standards in Haematology-NHL Guidelines (5) • European Society of Medical Oncology Guidelines (8) 	29	0.01
40	NHL, intermediate Grade Stage III/IV, complete response to chemotherapy, age > 70 years, relapse with 'bulky' disease	RT	IV	<ul style="list-style-type: none"> • British Committee for Standards in Haematology-Non-Hodgkin's Lymphoma Guidelines (5) • European Society of Medical Oncology Guidelines (8) 	30	<0.01
42	NHL , Intermediate Grade Stage III/IV, incomplete response to chemotherapy, age < 70 years, with 'bulky' disease	RT	III	<ul style="list-style-type: none"> • British Committee for Standards in Haematology-Non-Hodgkin's Lymphoma Guidelines (5) • European Society of Medical Oncology Guidelines (7) 	29	0.03

Outcome Number	Clinical Scenario	Treatment Indicated	Level of Evidence	References	Notes	Proportion of all lymphoma patients
44	NHL Intermediate Grade Stage III/IV incomplete response to chemotherapy age >70 years	RT	IV	<ul style="list-style-type: none"> • British Committee for Standards in Haematology- NHL Guidelines (5) • European Society of Medical Oncology Guidelines (7) 	31	0.06
45	NHL, high Grade, lymphoblastic lymphoma adult, prophylactic cranial irradiation	RT	III	<ul style="list-style-type: none"> •British Committee for Standards in Haematology- Non-Hodgkin's Lymphoma Guidelines (5) 	32	0.01
48	NHL Mycosis Fungoides, Stage I-II Complete response to PUVA/topical agents Relapse	RT	IV	<ul style="list-style-type: none"> •National Cancer Institute PDQ Statement on Mycosis Fungoides (9) 	33	<0.01
50	NHL Mycosis Fungoides, Stage I-II Incomplete response to PUVA/topical agents	RT	IV	<ul style="list-style-type: none"> •National Cancer Institute PDQ Statement on Mycosis Fungoides (9) 	33	<0.01

Outcome Number	Clinical Scenario	Treatment Indicated	Level of Evidence	References	Notes	Proportion of all lymphoma patients
51	NHL Mycosis Fungoides Stage III-IV	RT	IV	•National Cancer Institute PDQ Statement on Mycosis Fungoides (9)	33	<0.01
Proportion of all Lymphoma patients in whom radiotherapy is recommended =						0.65
Proportion of all cancer patients = 0.04 x 0.65 = 3% of all cancer patients						0.03 (3 %)

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

Key	Population or subpopulation of interest	Attribute	Proportion of population with this attribute	Quality of information	References	Notes
A	All registry cancers	All lymphomas	0.04	α	AIHW (10)	1
B	All lymphomas	Hodgkin's Disease	0.1	α	AIHW (10)	1
C	Hodgkin's Disease	Stage I-IIA	0.45	δ	Glimelius et al (11)	2
D	Hodgkin's Disease Stage IIB-IV	Age <60 years	0.63	δ	Glimelius et al (11)	4
			0.8	δ	Taylor et al (12)	
E	Hodgkin's Disease Stage IIB-IV < 60 years	Bulky Disease	0.4	θ	Amini et al (13)	5
F	Hodgkin's Disease Stage IIB-IV Age<60 years no bulky disease Response to chemotherapy	Complete Response	0.84	θ	Amini et al (13)	6
		Partial Response	0.09			
		Progressive or Stable Disease	0.07			

Key	Population or subpopulation of interest	Attribute	Proportion of population with this attribute	Quality of information	References	Notes
G	Hodgkin's Disease, Stage IIB-IV, age<60 years, no bulky disease, complete response to chemotherapy	No Relapse	0.78	θ	Amini et al (13)	7
H	Hodgkin's Disease Stage IIB-IV Age<60 years no bulky disease Complete response to chemotherapy Relapse	Suitable for transplant	0.32	θ	Amini et al (14)	8
I	Hodgkin's Disease Stage IIB-IV Age<60 years no bulky disease Complete response to chemotherapy Relapse Proceed to transplant	Proportion with residual mass	0.23	θ	Linch et al (15)	8

Key	Population or subpopulation of interest	Attribute	Proportion of population with this attribute	Quality of information	References	Notes
J	Hodgkin's Disease Stage IIB-IV Age<60 years no bulky disease incomplete response to chemotherapy Proceed to transplant	Proportion with residual mass	0.23	θ	Linch et al (15)	8
K	Hodgkin's Disease Stage IIB-IV Age >60 years	Non-Bulky disease	0.85	δ	Glimelius et al (11)	11
L	Hodgkin's Disease Stage IIB-IV Age >60years Non-bulky disease	Complete response to chemotherapy	0.59	δ	Glimelius et al (11)	11
M	Hodgkin's Disease Stage IIB-IV, age >60years, non-bulky disease, complete response	Relapse	0.26	δ	Glimelius et al (11)	11
N	Hodgkin's Disease Stage IIB-IV, age >60years, non-bulky disease, complete response, relapse	Relapse at nodal site	0.73	λ	Young et al (16)	12

Key	Population or subpopulation of interest	Attribute	Proportion of population with this attribute	Quality of information	References	Notes
O	NHL Classification by Grade (working formulation)	Low (A-D) Intermediate (E-H) High (I-J) Mycosis	0.32 0.61 0.05 0.02	γ	SEER (17)	15
P	NHL, Low Grade	MALT lymphoma	0.21	ζ	International Non-Hodgkin's Lymphoma Project (18;19)	15
Q	NHL, low Grade MALT lymphoma	Gastric	0.16	γ	Groves et al (20)	15
R	NHL, low Grade MALT lymphoma Gastric	Stage I-II	0.88	ζ	Thieblemont et al (21)	15
S	NHL, low Grade MALT lymphoma Gastric	Complete response to HP eradication	0.81 0.56 0.89 0.81	θ θ λ λ	Stolte et al (22) Ruskone-Formestaux et al (22;23) Fischbach (22;24) Thiede et al (25)	16
T	NHL, low Grade MALT lymphoma Gastric Complete response to HP eradication	relapse	0.1	θ	Neubauer et al (26)	17

Key	Population or subpopulation of interest	Attribute	Proportion of population with this attribute	Quality of information	References	Notes
U	NHL, low Grade MALT lymphoma Non-gastric	Stage I-II	0.35	ζ	Thieblemont et al (21)	18
V	Low grade Non-MALT	Stage I-II	0.33	ε	International Non-Hodgkin's Lymphoma Project (18;19)	19
W	NHL Low Grade Stage III-IV	Requires Treatment at presentation	0.61	λ	Horning et al (27)	21
X	NHL Low Grade Stage III-IV Require treatment at presentation	Complete response to chemotherapy	0.38 0.65 0.66	ε ε θ	Maartense et al (28) Federico et al (29) Peterson et al (30)	21
Y	NHL Low Grade Stage III-IV Require treatment at presentation, CR to initial chemotherapy	relapse	0.65	ζ	Johnstone et al (31)	22

Key	Population or subpopulation of interest	Attribute	Proportion of population with this attribute	Quality of information	References	Notes
Z	NHL Low Grade Stage III-IV Require treatment at presentation, CR to initial chemotherapy, relapse,	complete response to second line chemotherapy	0.41	λ	Montoto et al (32)	22
AA	NHL Low Grade Stage III-IV Require treatment at presentation, incomplete response to chemotherapy	complete response to second line chemotherapy	0.41	λ	Montoto et al (32)	23
BB	NHL, Low Grade Stage III-IV Suitable for surveillance at presentation	Requires treatment	0.61	λ	Horning et al (27)	24
CC	NHL, Low Grade Stage III-IV Suitable for surveillance at presentation Requires treatment	nodal disease	0.72	λ	Portlock et al (33)	24

Key	Population or subpopulation of interest	Attribute	Proportion of population with this attribute	Quality of information	References	Notes
DD	NHL, Low Grade Stage III-IV Suitable for surveillance at presentation Requires treatment	Complete response to initial chemotherapy	0.38 0.65 0.66	ε ε θ	Maartense et al (28) Federico et al (29) Peterson et al (30)	24
EE	NHL, Low Grade Stage III-IV Suitable for surveillance at presentation Requires treatment Complete response to initial chemotherapy	relapse	0.65	ζ	Johnstone et al (31)	25
FF	NHL, Low Grade Stage III-IV Suitable for surveillance at presentation Requires treatment Complete response to initial chemotherapy Relapse	complete response to second line chemotherapy	0.41	λ	Montoto et al (32)	25

Key	Population or subpopulation of interest	Attribute	Proportion of population with this attribute	Quality of information	References	Notes
GG	NHL Low Grade Stage III-IV Suitable for surveillance at presentation Requires treatment Complete response to initial chemotherapy	complete response to second line chemotherapy	0.41	λ	Montoto et al (32)	26
HH	NHL Intermediate Grade	Stage I-II	0.54 0.54	θ θ	Glass et al (33) Armitage et al (18)	27
II	NHL Intermediate Grade Stage III-IV	Complete Response to chemotherapy	0.44	ε	Maartense (28)	28
JJ	NHL Intermediate Grade Stage III-IV Complete response to chemotherapy	Age <70	0.56	ε	Maartense (28)	28

Key	Population or subpopulation of interest	Attribute	Proportion of population with this attribute	Quality of information	References	Notes
KK	NHL, intermediate Grade, Stage III-IV Complete response to chemotherapy, Age <70 years	Relapse	0.41	ϵ	Maartense (28)	29
LL	NHL, intermediate Grade, stage III-IV CR to chemotherapy Age <70 years, relapse	'Bulky' disease	0.3	θ	Phillips et al (34)	29
MM	NHL Intermediate Grade Stage III-IV Complete response to chemotherapy Age >70 years	relapse	0.36	ϵ	Maartense (28)	30
NN	NHL Intermediate Grade Stage III-IV Complete response to chemotherapy Age >70 years Relapse	bulky disease	0.3 0.36		Phillips (34) Maartense (28)	30

Key	Population or subpopulation of interest	Attribute	Proportion of population with this attribute	Quality of information	References	Notes
OO	NHL, intermediate Grade Stage III-IV Incomplete response to treatment	Age < 70 years	0.59	δ	Maartense et al (28)	31
PP	NHL, intermediate Grade, Stage III-IV, Incomplete Response to chemotherapy < 70 years	'Bulky' Disease	0.3	θ	Phillips et al (34)	31
QQ	NHL, high Grade	Lymphoblastic Lymphoma	0.26	γ	SEER (17)	32
RR	NHL, high Grade Lymphoblastic	Adult (> 15 years)	0.77	γ	SEER (17)	32
SS	NHL Mycosis fungoides	Stage I-II	0.65	ε	Green et al (35)	33
TT	Mycosis fungoides Stage I-II	Complete response to either PUVA or topical agents	0.66	λ	Hermann et al (36)	33
UU	Mycosis fungoides Stage I-II Complete response to either PUVA or topical agents	Relapse	0.58	λ	Hermann et al(36)	33

Lymphoma

Treatment guidelines

The guidelines available on the management of lymphoma are:

- National Cancer Institute PDQ Statement on Hodgkin's Disease (1)
- National Comprehensive Cancer Network Guidelines on Hodgkin's Disease(2)
- European Society of Medical Oncology Guidelines on Hodgkin's Disease 2001(3)
- National Comprehensive Cancer Network Guidelines on Non-Hodgkin's Lymphoma 2002(4)
- British Committee for Standards in Haematology (BCSH) (Draft) 2001(5)
- National Cancer Institute PDQ Statement on Non-Hodgkin's Lymphoma 2002(6)
- European Society of Medical Oncology Guidelines on newly diagnosed Non-Hodgkin's Lymphoma 2001 (7)
- European Society of Medical Oncology Guidelines on relapsed Non-Hodgkin's Lymphoma 2001 (8)
- National Cancer Institute PDQ Statement on Mycosis Fungoides (9)

Indications for Radiotherapy

The clinical situations where radiotherapy is recommended for Hodgkin's Disease and Non-Hodgkin's Lymphoma are:

- Stage I-II Hodgkins Disease radiotherapy is routinely recommended as curative treatment, usually in combination with chemotherapy. (PDQ, NCCN, ESMO)
- Stage IIB-IV Hodgkin's Disease involved field radiotherapy is recommended after chemotherapy to all patients presenting with bulky disease (NCCN, ESMO),
- Stage IIB-IV Hodgkin's Disease involved field radiotherapy is recommended after a partial response to chemotherapy (NCCN).
- Stage IIB-IV Hodgkin's Disease involved field radiotherapy is recommended after high dose chemotherapy to residual masses (PDQ)
- As palliation
- As definitive treatment for Stage I-II low grade non-Hodgkin's lymphoma (PDQ, BCSH, NCCN)
- Relapsed follicular lymphoma: extended field radiotherapy (BCSH)
- Relapsed follicular lymphoma: palliative treatment to relieve symptoms (BCSH, NCCN) or to treat bulky or persistent lesions as a supplement to chemotherapy (BCSH, NCCN)
- Stage I-IIA Intermediate grade non-Hodgkin's lymphoma as definitive treatment in combination with chemotherapy (PDQ, BCSH, NCCN, ESMO)
- Intermediate grade non-Hodgkin's lymphoma: initial sites of bulky disease or residual masses after chemotherapy (BCSH, NCCN, ESMO)
- Intermediate grade non-Hodgkin's lymphoma: Residual masses after high dose chemotherapy (ESMO)
- Prophylactic cranial irradiation of Lymphoblastic lymphoma (BCSH)

- Recurrent and chemotherapy resistant disease to symptomatic palliative sites (BCSH, ESMO)
- Mycosis Fungoides: for early stage disease on progression after PUVA or topical agents (PDQ).
- Mycosis Fungoides: As palliation for stage III-IV disease (PDQ).

Explanatory notes for Tables 1 and 2

1. **Incidence of lymphoma:** Lymphoma constitutes 4% of all cancers in Australia according to the Australian Institute of Health and Welfare (AIHW) 1998 statistics(10), with Non-Hodgkin's Lymphoma and Hodgkin's Disease accounting for 90% and 10% respectively of all reported cases of lymphoma in Australia.
2. **Hodgkin's Disease: Stage distribution at diagnosis:** The Ann Arbor staging system is recommended, which categorises stage using number of sites of nodal or extranodal involvement above and below the diaphragm, and the presence/absence of well-defined generalised "B" symptoms.

In the Swedish patterns of care study stage I-IIA Hodgkin's Disease accounts for 45% of cases (11). The reason for identifying this subdivision is that patients with stage IIB disease should be considered for chemotherapy and are usually treated in the same way as patients presenting with more advanced disease (1).

3. **Management of stage I-IIA Hodgkin's Lymphoma (all ages):** The management of early stage Hodgkin's Disease includes radiotherapy in all cases (1-3). This can either be 'involved-field' radiotherapy in combination with chemotherapy or subtotal nodal irradiation depending upon patient age, performance status, site and extent of disease. The use of chemotherapy alone is not currently recommended by the guidelines, although it may need to be considered if there is a young female who will require her breast to be irradiated. It should not be excluded if there is a bulky mediastinal mass but only if bilateral axilla require treatment. This subgroup is so small that it will not be included in the tree.
4. **Management of Hodgkin's Disease, (stage IIB-IV), Age:** Management of stage IIB-IV Hodgkin's Disease is primarily with chemotherapy. Patients over the age of 60 are less likely to be fit enough to tolerate and complete radical treatment, and will not be considered for bone marrow transplant for an incomplete response or on relapse. It was therefore decided to split the group by age at this stage of the radiotherapy utilisation tree.

Australian population data reported that 85% of patients diagnosed with Hodgkin's Disease are younger than 65 years, however they do not divide this group by stage (37). From a Swedish population based

registry, 37% of patients with stage IIB-IV were over the age of 60 (11). This appears lower than the UK population where only 20% of patients over the age of 60 were diagnosed with stage 3-4. Because the Swedish study separates the patients by stage and age, this data will be used in the analysis. A sensitivity analysis will be performed using the UK data (12).

5. **Management of Hodgkin's Disease, (stage IIB-IV), age <60 years, Bulky Disease:** With the majority of chemotherapy relapses occurring at sites of initial bulky disease, guidelines recommend radiotherapy (2;3) to reduce local recurrence.

A population based Swedish study reported on the presence of bulky disease in 40% of patients presenting with stage IIB-IV disease, younger than 60 years (13).

6. **Management of Hodgkin's Disease, stage IIB –IV, Age <60 years No Bulky Disease:** Guidelines recommend that these patients should be treated with combination chemotherapy (1;2). The population based study from Sweden reports an 84% complete response, 9% partial response and 7% progressive disease rates for patients with non-bulky disease treated with MOPP/ABVD chemotherapy alone (13). Guidelines recommend that radiotherapy should be considered for all patients who achieve a partial response to chemotherapy to improve local control rates(3) (38). Radiotherapy to sites of non-bulky disease after a complete response to chemotherapy is not routinely recommended.
7. **Hodgkin's Disease, age < 60 years, no bulky disease, achieve a complete response to initial chemotherapy, proportion that relapse:** In a Swedish population based study the relapse rate after a complete response to initial chemotherapy was 22%, with 52% relapsing within 1 year (14).
8. **Hodgkin's Disease, age <60 years, no bulky disease, treatment on relapse:** Guideline options to treat relapsed disease include conventional chemotherapy +/-RT, high dose chemotherapy or transplant +/-RT, radiotherapy alone and palliative care and are dependent on age, stage at relapse, performance status and associated comorbidities (1;2).

Bone Marrow Transplant: Indications for bone marrow transplant include progressive disease on initial conventional chemotherapy, or relapse within 1 year of initial treatment (2). Not all of these patients will be suitable for transplant, with the actual percentage of patients' transplanted being 32% (14).

The role of radiotherapy in conjunction with high dose chemotherapy (HDCT)/bone marrow transplant (BMT) for relapsed Hodgkin's disease

remains to be clearly defined. Retrospective studies have shown that the use of IFRT result in lower relapse rates in sites of prior disease involvement than those not treated with radiotherapy (39). Prospective trials have not been reported. Guidelines recommend that patients should receive post transplant RT if they are refractory to reinduction or salvage treatment (1). This groups account for 23% of patients treated with HDCT/BMT (15).

The role of total body irradiation conditioning prior to transplant remains controversial. Although studies have reported on a non-significant improvement in outcome using a TBI conditioning regimen there is concern regarding the risk of development of leukaemia and myelodysplasia (40). For the purpose of this study radiotherapy has not been used for this indication.

No Bone Marrow Transplant: This group have chemoresistant disease, have relapsed greater than 1 year after initial treatment or are considered inappropriate for bone marrow transplant. Seventy-three percent have relapsed at previous sites of disease (16).

Patients with chemoresistant disease should be treated with radiotherapy. Single institution case series of radiotherapy alone for relapsed disease report relapse-free survivals of 30-48% (41).

Relapse after bone marrow transplant:

Forty-five percent of patients relapse after bone marrow transplant, usually at sites of previous disease (39). These patients should now have radiotherapy considered as part of their further management.

9. **Hodgkin's Disease, age < 60 years, stable or progressive disease after first line chemotherapy:** These patients should be considered for HDCT/BMT and radiotherapy to residual disease as per patients who relapse after a complete response to initial chemotherapy. The role of radiotherapy in conjunction with high dose chemotherapy (HDCT)/bone marrow transplant (BMT) for relapsed Hodgkin's disease remains to be clearly defined. Retrospective studies have shown that the use of IFRT result in lower relapse rates in sites of prior disease involvement than those not treated with radiotherapy (39). Prospective trials have not been reported. Guidelines recommend that patients should receive post transplant RT if they are refractory to reinduction or salvage treatment (1). This groups account for 23% of patients treated with HDCT/BMT(15).

The role of total body irradiation conditioning prior to transplant remains controversial. Although studies have reported on a non-significant improvement in outcome using a TBI conditioning regimen there is concern regarding the risk of development of leukaemia and myelodysplasia (40). For the purpose of this study radiotherapy has not been used for this indication.

10. **Hodgkin's Disease, >60years, Bulky Disease:** With the majority of chemotherapy relapses occurring at sites of initial bulky disease, guidelines recommend radiotherapy (2;3) to reduce local recurrence. If not fit enough for treatment with radical intent they will still benefit from palliative radiotherapy to sites of bulky disease. A population based study reports 15% of patients with stage IIB-IV Hodgkin's disease present with bulky disease (11).
11. **Hodgkin's Disease, >60years, non-bulky disease, complete response to chemotherapy:** A complete response to ABVD/MOPP chemotherapy was recorded in 59% of patients over the age of 60 years (11). Although this is lower than the younger population the rate of relapse is similar, at 26%. The response reflects the inability to administer certain drugs and adequate doses to the older population.
12. **Hodgkin's Disease, > 60 years, incomplete response/relapse in patients:** Patients who achieve a partial response are treated with radiotherapy (1-3).

Treatment of relapsed disease in this older population, if considered appropriate, is with second line chemotherapy for those who are fit enough. Radiotherapy is considered for limited nodal relapse, symptomatic nodal or extranodal disease if unfit for chemotherapy and as consolidation after a second complete response. Seventy three percent of patients relapse at sites of nodal disease (42). These patients are recommended to be treated with radiotherapy

13. **Non-Hodgkin's lymphoma** accounts for 90% of all reported cases of lymphoma in Australia (10). Stage distribution at diagnosis, is classified using the Ann Arbor staging system which categorises stage using number of sites of nodal or extranodal involvement above and below the diaphragm, and the presence or absence of well-defined generalised "B" symptoms.
14. **Non-Hodgkin's Lymphoma Classification:** There have been several classification systems for Non-Hodgkin's lymphoma proposed and used. Prior to the introduction of the Revised European American Lymphoma (REAL) Classification in 1994 (43) either the Working Formulation (WF) (44) or the Kiel Classification was commonly used. Most of the studies used in this report and population data from the South Australian Hospital and SEER cancer registries use the Working Formulation.

In the Working Formulation three groups are identified as low, intermediate and high grade. Within each group there are several pathological entities. The SEER Database data has been used to subclassify the clinical groups relevant to the guidelines. The commonest group is the intermediate grade, which accounts for 61% of non-Hodgkin's lymphoma, with low grade, high grade and mycosis fungoides accounting for 32%, 5% and 2% respectively (17).

15. **Low Grade Non-Hodgkin's Lymphoma, stage at diagnosis:** MALT lymphomas are a newer entity. The tree is divided here to include them with respect to a proportion of gastric MALT that are unlikely to require radiotherapy having responded to Helicobacter eradication therapy. The proportion of patients diagnosed with MALT (21%) was identified from the International lymphoma Classification Project (18;19). The percentage of MALT lymphomas that are gastric in origin was identified from a large US database as 16% (20). Eighty-eight percent of gastric MALT lymphomas are diagnosed with stage I-II disease (21).
16. **Gastric MALT, complete response to Helicobacter Pylori eradication:** Guidelines on the management of gastric MALT were identified in the NCCN NHL guidelines. There have been a number of reports on the response of gastric MALT lymphomas to Helicobacter Pylori eradication therapy. Most of these report on response of the complete group, although some only report on HP positive patients. Response rates can vary from 35-100%, although most report complete response of about 80%. I have selected the larger reports from 2 international groups rather than single institutional case series. The response rate ranged from 56% to 81% (22-25). A sensitivity analysis will be performed to reflect this. Those who do not achieve a complete response are likely to be offered alternative treatment with radiotherapy.
17. **Gastric MALT, relapse rate after a complete response:** This is not well reported in the literature. One study who followed 40 'cured' patients of which 10% have relapsed after a median follow-up of 2 years (26).
18. **MALT Lymphoma, non gastric:** About two-thirds of patients present with localised stage I-II disease (21). These should be treated with curative radiotherapy.
19. **Low grade lymphoma, non-MALT. Stage I-II:** The majority of patients with low grade lymphoma are diagnosed with advanced disease. The International lymphoma Classification Project reports that only 33% of patients present with stage I/II follicular lymphoma (18;19). Studies have shown that localised radiotherapy for low grade non-Hodgkin's lymphoma is curative (45). In keeping with guidelines curative or palliative radiotherapy is indicated for these patients (4-6).
20. **Treatment of stage III/IV low grade lymphoma:** Studies have shown that initiating treatment only on symptomatic progression has no detriment on overall survival (27). Patients presenting with advanced low grade lymphoma to a single US institution were put on a surveillance program if they had asymptomatic indolent disease (39%) (46).

21. Patients with stage III/IV low grade non-Hodgkin's lymphoma who require treatment at the time of diagnosis: Chemotherapy is recommended for patients diagnosed with low grade stage III-IV non-Hodgkin's lymphoma that require treatment at presentation (61%). Complete response rates for advanced low-grade non-Hodgkin's lymphoma, to initial chemotherapy will depend upon what regimen is used. Reports from multi-institutional databases, which is the highest ranking evidence, range from 38-65%. Two other recent reports on the use of chemotherapy for advanced disease, although lower ranking, also report on response rates of 65%. This has been used in the analysis although a sensitivity analysis will be performed.

22. Patients who relapse after a complete response to chemotherapy: A UK single institution study with 20 years follow-up reported that 65% of patients relapsed after a complete response to initial therapy (31). Treatment for relapse is heterogeneous, with most patients receiving further chemotherapy. Two single institutions report on response rates to second line chemotherapy of about 70% overall. Montoto et al reported a higher complete response rate than Johnson et al of 41%. This proportion, which included patients treated with Fludarabine and stem cell transplant, will be used (32;46). Guidelines recommend palliative radiotherapy for symptomatic disease or for residual masses after chemotherapy. The patients who did not respond to or achieved an incomplete response to second line chemotherapy should be considered for palliative radiotherapy.

23. Patients with stage III/IV low grade non-Hodgkin's lymphoma who require treatment at the time of diagnosis, incomplete response to chemotherapy: Guidelines would recommend palliative radiotherapy for symptomatic disease. This group have required treatment for symptoms, but have failed to respond to chemotherapy. Prior to being considered for palliative radiotherapy they are likely to be treated with an alternative chemotherapy regimen.

Two single institutions report on response rates to second line chemotherapy of about 70% overall. Montoto et al reported a higher complete response rate than Johnson et al of 41%. This proportion, which included patients treated with Fludarabine and stem cell transplant, will be used (32;46). Guidelines recommend palliative radiotherapy for symptomatic disease or for residual masses after chemotherapy. The patients who did not respond to or achieved an incomplete response to second line chemotherapy should be considered for palliative radiotherapy.

24. Patients with stage III/IV low grade non-Hodgkin's lymphoma who require treatment after surveillance: With a median follow-up period of 50 months (range 11 months to 17 years), 61% of patients on a surveillance programme have required treatment, with progressive bulky lymphadenopathy being the reason to initiate therapy in 72% of cases (46). Initial treatment for patients presenting with low grade,

stage III-IV non-Hodgkin's lymphoma is chemotherapy. Complete response rates for advanced low-grade non-Hodgkin's lymphoma, to initial chemotherapy will depend upon what regimen is used. Reports from multi-institutional databases, which is the highest ranking evidence, range from 38-65%. Two other recent reports on the use of chemotherapy for advanced disease, although lower ranking, also report on response rates of 65% (22-25). This has been used in the analysis although a sensitivity analysis will be performed.

25. Treatment of stage III/IV low grade non-Hodgkin's lymphoma, bulky lymphadenopathy, complete response to chemotherapy, who relapse: A UK single institution study with 20 years follow-up reported that 65% of patients relapsed after a complete response to initial therapy. (31). Treatment for relapse is heterogeneous, with most patients receiving further chemotherapy. Two single institutions report on response rates to second line chemotherapy of about 70% overall. Montoto et al reported a higher complete response rate than Johnson et al of 41%. This proportion, which included patients treated with Fludarabine and stem cell transplant, will be used (32;46). Guidelines recommend palliative radiotherapy for symptomatic disease or for residual masses after chemotherapy. The patients who did not respond to or achieved an incomplete response to second line chemotherapy should be considered for palliative radiotherapy

26. Treatment of stage III/IV low grade non-Hodgkin's lymphoma, bulky lymphadenopathy, incomplete response to chemotherapy: Guidelines would recommend palliative radiotherapy for symptomatic disease. This group have required treatment for symptoms, but have failed to respond to chemotherapy. Prior to being considered for palliative radiotherapy they are likely to be treated with an alternative chemotherapy regimen.

Two single institutions report on response rates to second line chemotherapy of about 70% overall. Montoto et al reported a higher complete response rate than Johnson et al of 41%. This proportion, which included patients treated with Fludarabine and stem cell transplant, will be used (32;46). Guidelines recommend palliative radiotherapy for symptomatic disease or for residual masses after chemotherapy. The patients who did not respond to or achieved an incomplete response to second line chemotherapy should be considered for palliative radiotherapy.

27. Stage I-II Intermediate Grade Lymphoma: Stage I-II accounts for 54% of intermediate grade lymphoma (33) Guidelines recommend that patients should receive CHOP chemotherapy followed by involved field RT (4-7). Elderly patients or patients considered unfit for chemotherapy would be considered for radiotherapy with either curative or palliative intent (47).

28. **Stage III-IV Intermediate Grade Lymphoma:** These patients should all be considered for chemotherapy. Guidelines recommend radiotherapy for bulky disease (4), however the proportion of patients who present with advanced in the chemotherapy trials for the advanced intermediate group. This data was used and therefore there is no subdivision for bulky disease.

Most population based data includes heterogeneous groups with a small proportion being treated for early disease and some with radiation only. In a population based study the complete response rate for advanced intermediate disease was 44%. A higher response was documented in patients under the age of 70 years (51%) when compared to patients over 70 years (33%) (28). CHOP chemotherapy is standard treatment for patients of all ages (48;49), with newer regimens not improving overall survival. Fisher et al report on a randomised controlled trial a complete response rate of 44% to CHOP chemotherapy, reflecting our population based figure that includes elderly patients excluded from clinical trials. Complete response rates for intermediate grade Non-Hodgkin's Lymphoma in other trials have ranged from 44% to 61% (50).

Younger patients who relapse after a complete response are likely to be considered for high dose chemotherapy and bone marrow transplant. This data could not be identified and it was therefore decided to split the tree by age at this point. In a population based study from the Netherlands the complete response rate to treatment for patients with stage II-IV intermediate grade lymphoma was recorded by age, with 56% of patients obtaining a complete response being under the age of 70 years(28).

29. **Stage III-IV Intermediate Grade Lymphoma, non bulky disease, (relapsed, <70 years) or progressive disease on chemotherapy:** In a population based study from the Netherlands the relapse rate after a complete response to treatment for patients <70 years with stage II-IV intermediate grade lymphoma was 41%. A multi-institutional study of bone marrow transplant in patients with relapsed intermediate grade non-Hodgkin's lymphoma, addressing the role of radiotherapy has been reported. This study randomised patients to high dose treatment after a response to second line conventional chemotherapy. Radiotherapy was recommended in both arms of the study to sites of bulky disease >5cm or T3/T4 extranodal disease (30%). The addition of radiotherapy reduced the incidence of local recurrence observed in both the transplant and non-transplant arm (34). Relapse at the primary site was recorded in 50% of patients treated with chemotherapy alone compared to 26% when radiotherapy was also delivered. From this information radiotherapy should be considered to initial sites of disease in patients who relapse with these indications.
30. **Intermediate grade lymphoma, treatment for relapse after a complete response, > 70 years:** Forty-four percent of patients >70

years subsequently relapsed (28). Treatment at this time will be individualised depending on the ability of the patient to tolerate further chemotherapy. Greil has published a review article on management strategies of lymphatic neoplasms in the elderly (51). Although initial curative treatment is warranted he identified that a significant proportion of elderly patients received reduced dose chemotherapy and were unable to adequately tolerate treatment. Their chance of receiving adequate treatment with chemotherapy alone on relapse is unlikely. These patients should be considered for palliative radiotherapy in the presence of bulky disease. Both a population based study and a multi-institutional report identify similar proportions of elderly and young patients presenting with bulk disease. These reports did not distinguish by stage or grade. It was therefore concluded that a similar proportion of elderly patients would relapse with bulky disease as the younger trial group (34). This proportion (30%) was included in the analysis to distinguish a proportion of patients who should receive radiotherapy.

31. **Intermediate grade lymphoma, incomplete response to chemotherapy, > 70 years:** In a population-based study 59% of patients who did not obtain a complete response to first line chemotherapy were under the age of 70 years (28). Treatment at this time will be individualised. Guidelines would recommend radiotherapy to either initial sites of bulky disease or residual masses. Radiotherapy can also be considered on disease progression, with further chemotherapy more dependent on the patient's initial tolerance to treatment. Radiotherapy is therefore considered for this group of patients.
32. **High Grade Lymphoma:** This subgroup includes Burkitt's Lymphoma (74%) and Lymphoblastic Lymphoma (26%). Patients presenting with Lymphoblastic Lymphoma are at risk of developing CNS disease. Guidelines recommend that they should be treated on leukaemic protocols, which include prophylactic cranial irradiation. In one study adults had significantly fewer episodes of CNS relapse (52). To prevent toxicity the recommended CNS prophylaxis in childhood is with intrathecal chemotherapy.
33. **Mycosis Fungoides:** Mycosis Fungoides accounts for 2% of all lymphomas (33). Data from the Mycosis Fungoides Cooperative Group (MF CG) includes information collected from 20 USA institutions. They report that 65% of patients present with T1 or T2 disease. Guidelines recommend that topical treatment is suitable as initial therapy (9). Reported complete response rates of about 66% are similar whether topical treatment is with PUVA or topical chemotherapy (36). Patients who do not respond completely or who relapse (36) should be considered for either involved field RT or TSEBT (Total Skin Electron Beam Therapy) (9).

Patients presenting with more advanced disease should be considered for TSEBT +/- chemotherapy. TSEBT will penetrate to the dermis

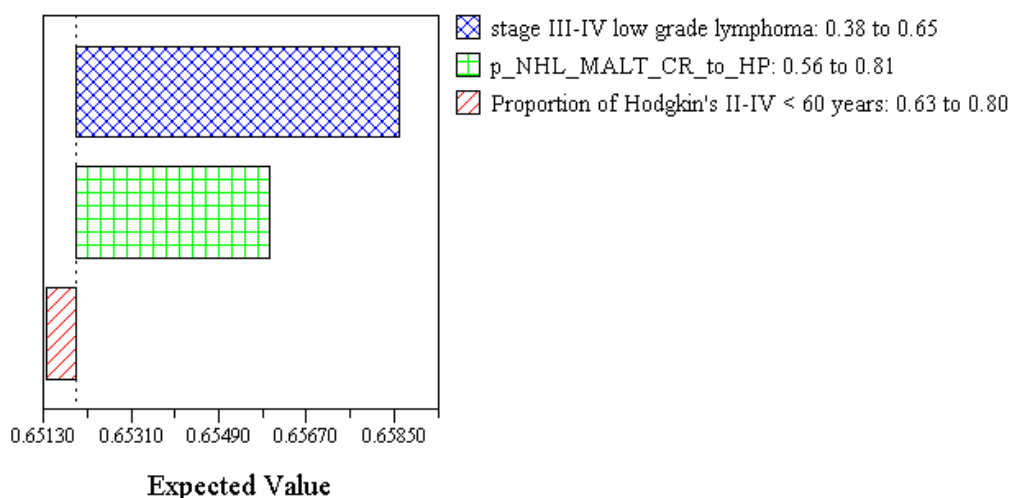
producing excellent palliation with complete response rates of up to 80% (9). For unfit patients, palliative radiotherapy to symptomatic lesions is recommended.

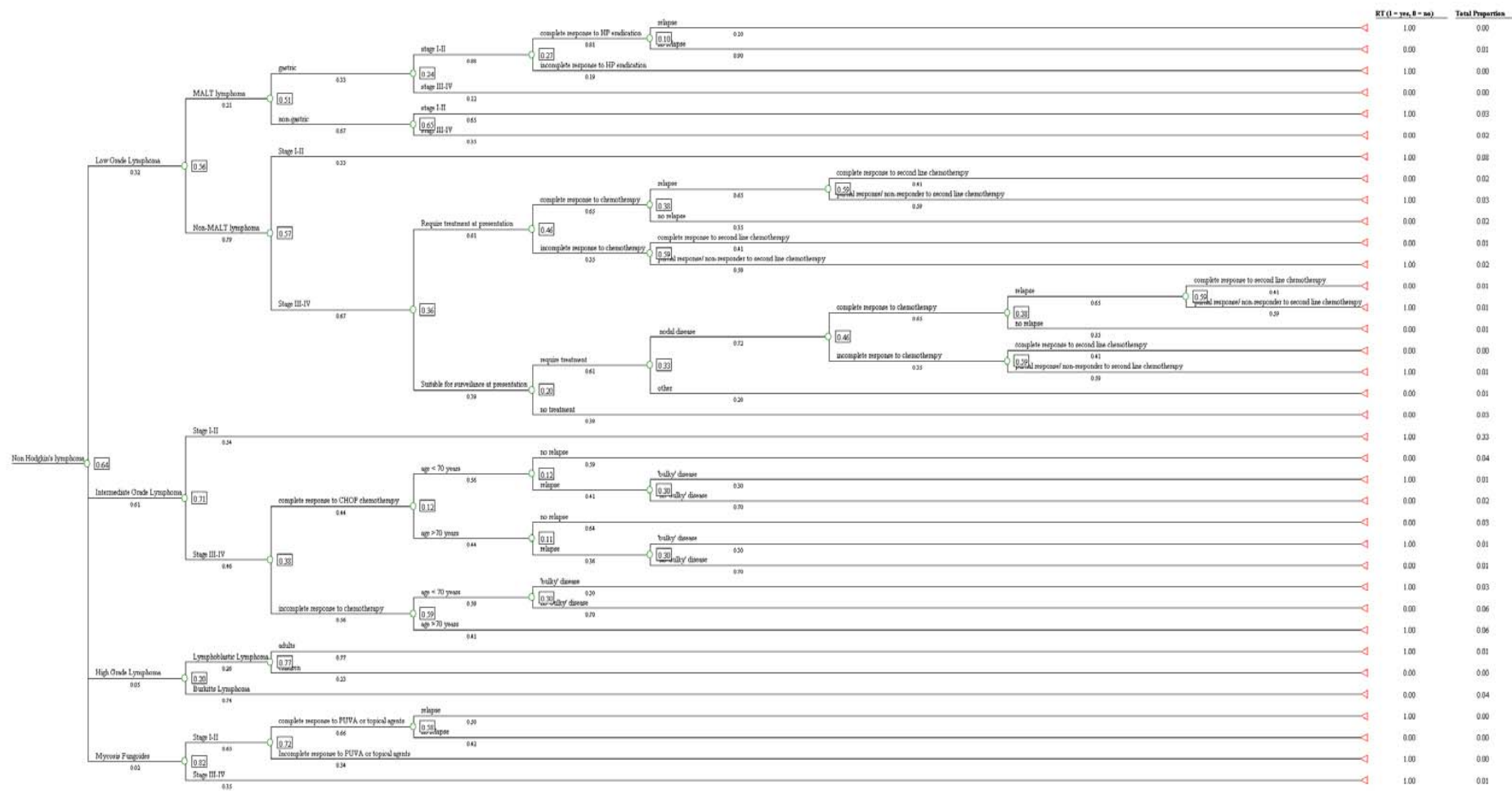
Optimal Radiotherapy Utilisation Rate and Sensitivity Analysis

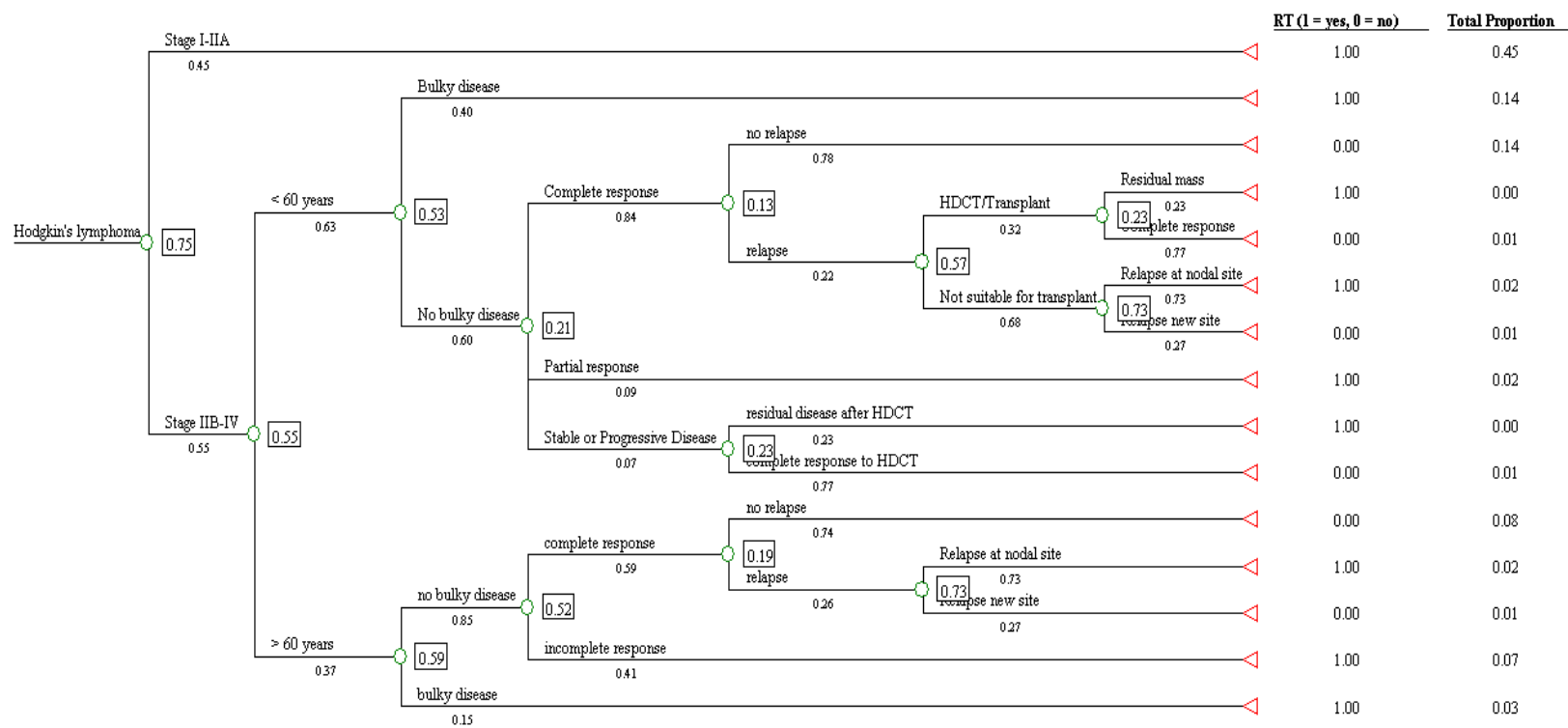
The proportion of lymphoma patients in whom at least one course of radiotherapy is indicated is 65%, based on guideline recommendations. There are several data elements where there was uncertainty because of different proportions reported in the literature. This includes the proportion of patients with Stage IIB-IV Hodgkin's Disease over the age of 60 (0.2-0.37), the proportion of patients presenting with Low Grade MALT gastric Non-Hodgkin's Lymphoma who respond to *Helicobacter pylori* therapy (0.56-0.81) and the proportion of patients with stage III/IV low grade non-Hodgkin's lymphoma who respond to chemotherapy (0.38-0.65).

To assess the impact that these uncertainties have on the overall estimate of the need for radiotherapy in all lymphoma patients, a one-way sensitivity analysis was performed for each of the variables and the impact that these variables have on the overall results is illustrated by a tornado diagram. The graph shows that the proportion of lymphoma patients that should receive radiotherapy based on evidence and incidence of attributes for radiotherapy was 65-66%. As lymphoma represents 4% of all reported malignancies, the proportion of lymphoma patients where radiotherapy is indicated represents 2.6% of all cancer patients.

**Tornado Diagram at
Lymphoma**







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Leukaemia

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

Outcome Number	Clinical Scenario	Treatment Indicated	Level of Evidence	References	Notes	Proportion of all Leukaemia patients
1	Acute Lymphocytic Leukaemia Age < 15 years CNS disease at presentation	RT	III	•National Cancer Institute PDQ Statement on Acute Lymphocytic Leukaemia in children (1)	4	<0.01
2	Acute Lymphocytic Leukaemia Age < 15 years No CNS disease at presentation High risk	RT	II	•National Cancer Institute PDQ Statement on Acute Lymphocytic Leukaemia in children (1)	5	0.01
3	Acute Lymphocytic Leukaemia Age < 15 years No CNS disease at presentation. Not high risk. Relapse CNS/testicular	RT	III	•National Cancer Institute PDQ Statement on Acute Lymphocytic Leukaemia in children (1)	7	<0.01

Outcome Number	Clinical Scenario	Treatment Indicated	Level of Evidence	References	Notes	Proportion of all Leukaemia patients
4	Acute Lymphocytic Leukaemia Age < 15 years No CNS disease at presentation Not high risk Relapse Bone marrow, within 3 years HLA compatible donor	RT	IV	•National Cancer Institute PDQ Statement on Acute Lymphocytic Leukaemia in children (1)	8	<0.01
8	Acute Lymphocytic Leukaemia Age > 15 years, but <60 years, relapse HLA compatible donor	RT	III	•National Cancer Institute PDQ Statement on Acute Lymphocytic Leukaemia in Adults (2)	11	<0.01

[illegible]

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

Key	Population or subpopulation of interest	Attribute	Proportion of population with this attribute	Quality of information	References	Notes
A	All Cancers	Leukaemia	0.03	α	AIHW (6)	1
B	All leukaemia	Acute Lymphocytic Leukaemia	0.11	θ	South Australia Cancer Registry (7)	2
		Acute Myeloid Leukaemia	0.46			
		Chronic Lymphocytic Leukaemia	0.3			
		Chronic Myeloid Leukaemia	0.13			
C	Acute Lymphocytic Leukaemia (ALL)	<15 Years	0.45	β	New South Wales Cancer Registry (8)	3
D	Acute Lymphocytic Leukaemia Age < 15 years	CNS disease at presentation	0.02	θ	Chessells JM et al (9)	4
			0.02	θ	Schrapppe M et al BMF-90 (10)	

Key	Population or subpopulation of interest	Attribute	Proportion of population with this attribute	Quality of information	References	Notes
E	Acute Lymphocytic Leukaemia Age < 15 years No CNS disease at presentation	high risk	0.11	θ	Schrappe M et al (10)	5
			0.13	θ	Wheeler KA et al (11)	
F	Acute Lymphocytic Leukaemia Age < 15 years No CNS disease at presentation Not high risk	relapse	0.21	θ	Reiter et al (12)	7
			0.12	θ	Schrappe et al (10)	
			0.12	θ	Silverman et al (13)	
			0.37	θ	Rivera et al (14)	
			0.18	θ	Kamps et al (15)	
G	Acute Lymphocytic Leukaemia Age < 15 years No CNS disease at presentation Not high risk Relapse	CNS/testicular	0.34	θ	Reiter et al (12)	7
			0.35	θ	Schrappe (10)	
			0.25	θ	Silverman (13)	
			0.38	θ	Rivera et al (14)	
			0.35	θ	Kamps et al (15)	
H	Acute Lymphocytic Leukaemia Age < 15 years No CNS disease at presentation Not high risk Relapse bone marrow	Early relapse	0.7	ε	Barrett et al (16)	8

Key	Population or subpopulation of interest	Attribute	Proportion of population with this attribute	Quality of information	References	Notes
I	Acute Lymphocytic Leukaemia Age < 15 years No CNS disease at presentation Not high risk Relapse in bone marrow	HLA compatible donor	0.35	ϵ	Wheeler KA et al (11)	8
J	Acute Lymphocytic Leukaemia Age > 15 years	>60 years	0.33	δ	SEER (17)	9
K	ALL Age >15 years	Complete remission	0.82	ϵ	Hoelzer et al (18)	10
L	ALL Age >15 years Complete remission	relapse	0.46 0.54	ϵ ϵ	Larson (19) Hussein (20)	11
M	ALL Age >15 years Complete remission relapse	HLA donor	0.33	θ	Cassileth (21)	11
N	Acute Myeloid Leukaemia, age at diagnosis	<15 years 16-54 >55	0.03 0.28 0.69	γ	SEER (17)	12

Key	Population or subpopulation of interest	Attribute	Proportion of population with this attribute	Quality of information	References	Notes
O	AML, age 16-54	Low risk	0.23	θ	Grimwade (22)	14
P	AML age 16-54years low risk	Complete remission	0.91	θ	Grimwade et al (22)	14
Q	AML age 16-54 years low risk Complete remission	Relapse	0.51	θ	Burnett(23)	15
R	AML age 16-54 years low risk Complete remission relapse	HLA donor	0.33	θ	Cassileth (21)	15
S	AML age 16-54 years low risk Complete remission Relapse HLA donor	Refuse/ relapse pre BMT	0.19	θ	Cassileth (21)	15
T	AML, age 16-54 years intermediate/high risk	Complete response to induction therapy	0.83	θ	Grimwade(22)	14

Key	Population or subpopulation of interest	Attribute	Proportion of population with this attribute	Quality of information	References	Notes
T	AML age 16-54years high/ intermediate risk	HLA compatible donor	0.33		Cassileth (21)	16
U	AML age 16-54 years high/ intermediate risk HLA compatible donor	Refuse/ relapse pre BMT	0.19	θ	Cassileth (21)	16

Leukaemia

Treatment guidelines

The following guidelines on the treatment of Leukaemia are available:

- National Cancer Institute PDQ Statement on Acute Lymphocytic Leukaemia in children (1)
- National Cancer Institute PDQ Statement on Acute Lymphocytic Leukaemia in Adults (2)
- National Cancer Institute PDQ Statement on Acute Myeloid Leukaemia in Adults (3)
- National Comprehensive Cancer Network Guidelines on Acute Myeloid Leukaemia (4)
- National Cancer Institute PDQ Statement on Acute Myeloid Leukaemia in Children (24)
- National Cancer Institute PDQ Statement on Chronic Myelogenous Leukaemia (25)
- National Comprehensive Cancer Network Guidelines on Chronic Myelogenous Leukaemia (26)
- National Cancer Institute PDQ Statement on Chronic Lymphocytic Leukaemia (27)

Indications for Radiotherapy

The indications for radiotherapy from the guidelines are:

- Acute Lymphocytic Leukaemia (ALL)(children): Presentation or relapse with central nervous system involvement. Prophylactic cranial irradiation in high-risk patients (PDQ).
- ALL Adults: Prophylactic cranial irradiation, Bone marrow transplant if failed induction therapy, < 60 years
- Acute Myeloid Leukaemia (AML): Bone marrow transplant if complete response to induction therapy, < 60 years, 'high/intermediate risk'
- AML complete response to chemotherapy, on relapse < 60 years

Explanatory notes for Tables 1 and 2

1. **Incidence of Leukaemia:** Leukaemia accounts for 3% of all new cancers reported in Australia according to the 1998 Australian Institute of Health Welfare statistics 1998(6).
2. **Major Leukaemia subtypes:** The four major subtypes recognised by the South Australian Cancer Registry are acute lymphocytic leukaemia (ALL) (11%), Chronic lymphocytic leukaemia (CLL) (30%), acute myeloid leukaemia (AML) (46%) and chronic myeloid leukaemia (CML) (13%) (7).

The treatment of leukaemia differs between the paediatric age group (defined here as patients < 15 years) and the adult age group

3. **Acute Lymphocytic Leukaemia:** ALL has a bimodal age distribution. After ages 2-4 years, ALL rates decline rapidly with age, then begins to rise after the age of 40 years, increasing thereafter to almost the same level in the elderly as in children. In NSW 45% of registered cases were under the age of 15 years (8).
4. **Central nervous system treatment in children diagnosed with ALL:** Cranial irradiation is also recommended by guidelines when patients present with documented CNS leukaemia. This accounts for 2% of children diagnosed (9;10).
5. **Acute Lymphocytic leukaemia: <15 years, estimating the incidence of high risk disease:** Central nervous system prophylaxis is required for all children diagnosed with ALL. Concerns about potential late effects of cranial irradiation prompted a reappraisal of its role in childhood.
Over the past decade, prophylactic cranial irradiation has been replaced by intrathecal chemotherapy (15;28) except for patients classified as 'high risk'. This definition varies amongst different groups usually including the presence of one of the following criteria: inadequate cytoreductive response, >1000/ul leukaemic cells in the peripheral blood on day 8, incomplete response within 1 month, translocation t (9;22) or t (4;11) and age(10;12;29).
Children are usually treated on National/International protocols or clinical trials. Thus information available on prognostic factors is available from multicentre trials rather than population databases but they probably reflect population distributions better than clinical trials in solid tumours. Approximately 12% of children are classified as high risk, which is similar among studies even allowing for the slight variation in the definition between groups (10;11).
6. **The Role of Bone Marrow Transplant (BMT) in ALL:** A UK randomised trial reported that the reduction in relapse rate using BMT in first remission is outweighed by the increased treatment related mortality. Therefore, allogeneic BMT should be confined to groups of patients with clearly defined very poor prognosis such as those with Philadelphia chromosome (30) or those failing to achieve remission after induction chemotherapy, or in second remission.
7. **Proportion of low risk patients who relapse:** This proportion was identified from several of the large multicentre trials that treated low risk patients without cranial radiotherapy. The median relapse rate was 21% (range 12-37%). The prognosis of a child with ALL whose disease recurs depends on the time and site of relapse. Sites of relapse involved the CNS or testes in about one-third of cases. These patients should receive radiotherapy as part of their further treatment in combination with aggressive systemic therapy (31;32).
8. **Proportion of patients with bone marrow relapse:** The patients who relapse early should be considered at high risk and considered for

BMT. 70% relapse within 3 years of diagnosis (16). From the UKALL high risk study, 35% of patients had an HLA-matched donor (11). Which children should have TBI included as pre-BMT conditioning is difficult to determine. I contacted a Paediatric haematologist who recommended that the majority of children with Allogeneic BMT will be treated by TBI. Davies et al report on behalf of the IBMTR that TBI/Cy resulted in improved survival over Bu/Cy (33).

9. **Adult ALL:** As in childhood ALL, adults are at risk of developing central nervous system involvement during the course of their disease. Prophylactic treatment can be with either chemotherapy or cranial irradiation. Although a proportion of patients will be treated with cranial irradiation it is difficult to identify which patients. Different trials either used cranial or intrathecal therapy exclusively rather than identifying risk groups. It was therefore decided not to give any patients cranial irradiation.
In the SEER database 33% of adult with ALL are older than 60 years. These older patients are often unfit for aggressive treatment and will not be considered for BMT.
10. **ALL, age 16-60 years, response to chemotherapy:** There have been a number of studies trying to improve the response and survival for this group of patients, which is not as good as for children. Hoelzer et al has produced tables including some of the more recent publication from multiinstitutional groups. The weighted mean complete remission rate was 82% (18).
11. **ALL, age 16-60 years, relapse after chemotherapy and treatment:** Relapse rates are higher in adults than in children at around 50% (19;20). Guidelines recommend reinduction chemotherapy followed by allogeneic bone marrow transplant if a suitable donor is identified. Patients without a donor should be enrolled in trials. The proportion of adult patients with ALL who have a suitable donor was identified as 33% (34). Most of these patients will get TBI conditioning.
12. **Acute Myeloid Leukaemia:** This subtype accounts for 46% of all leukaemia (7). It is uncommon in children, accounting for only 3% of cases reported by SEER. The majority of patients are elderly with 69% of patients presenting over the age of 55 years(17).
13. **Acute Myeloid Leukaemia, <15 years:** Although there is a higher rate of central nervous disease at presentation treatment is with systemic and intrathecal chemotherapy. A recently published study from the Australian And New Zealand Children's Cancer Study Group treated all patients with intrathecal methotrexate, even in the presence of craniospinal disease. All were considered for bone marrow transplant after remission-induction therapy, using a conditioning regimen of busulphan and cyclophosphamide (35).

- 14. Acute Myeloid Leukaemia, > 15 years, risk group and response to initial treatment:** Initial treatment is with chemotherapy using a combination of an anthracycline and cytarabine. Allogeneic bone marrow transplant in first remission is recommended for patients under 60 years presenting with unfavourable cytogenetics (NCCN) and, by consensus, is the preferred therapy for intermediate risk patients. It is also recommended for patients with induction failure. Complete remission rates are usually about 80%. We have stratified the patients by risk to identify a high/intermediate risk group who should be considered for early bone marrow transplant. The MRC AML X study, with an overall response rate of 82% to induction therapy, gives response rates for these risk groups. These percentages will be used in this project. Complete remission for the low risk group was 91%. The intermediate/ high risk response being 83% after all treatment. This figure being the same as the response rate to induction therapy will be used for the high/ intermediate risk group (22).

There is no consensus on the recommended post remission strategy for the favourable features group. They will therefore not receive BMT at this point but on relapse.

- 15. Patients with AML, favourable features who develop relapse:** A relapse rate of 49% was reported for patients with favourable features (19;20). These patients should now be considered for BMT. Allogeneic bone marrow transplant is the preferred treatment and is possible due to the identification of a matched donor in 33% of patients, however a proportion of these patients will never proceed to transplant due to refusal or disease progression(34).

The conditioning regimens should include cyclophosphamide with total body irradiation (TBI) following the publication of a metaanalysis that reported trends for an improved survival and disease free survival with TBI conditioning regimens for patients with AML (5).

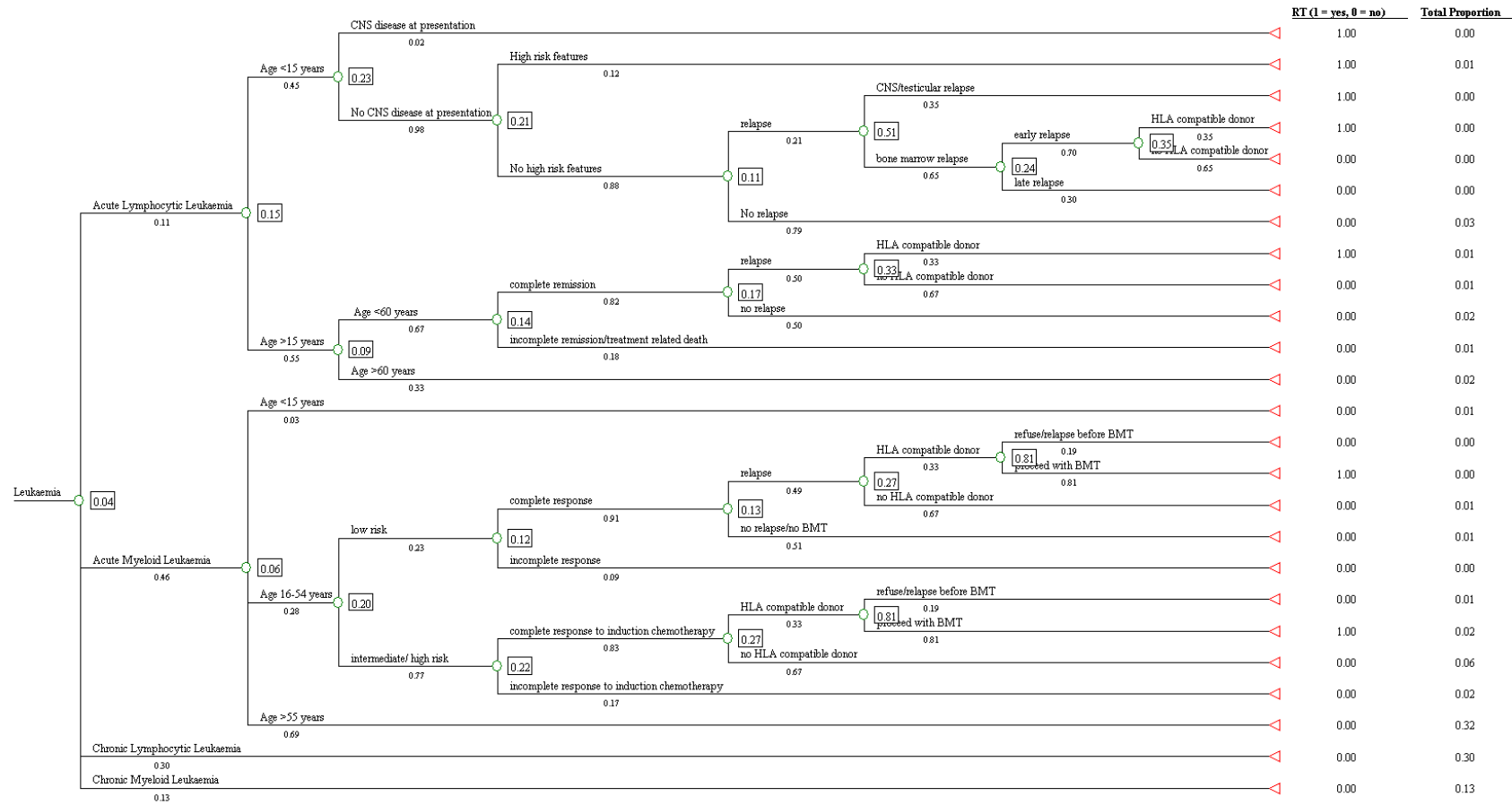
- 16. Patients with AML, high/intermediate risk:** Allogeneic bone marrow transplant in first remission is recommended for patients under 60 years presenting with unfavourable cytogenetics (NCCN) and, by consensus, is the preferred therapy for intermediate risk patients. It is also recommended for patients with induction failure. All patients with high/intermediate risk are therefore considered for allogeneic BMT, if a suitable donor is identified. The proportion identified with a suitable donor is 33% however a proportion of these patients will never proceed to transplant due to refusal or disease progression (34).

The conditioning regimens should include cyclophosphamide with total body irradiation (TBI) following the publication of a metaanalysis that reported trends for an improved survival and disease free survival with TBI conditioning regimens for patients with AML (36).

17. **Chronic Lymphocytic Leukaemia:** The only indication for radiotherapy in patients diagnosed with CLL is involved field radiotherapy for stage I-II disease. Splenic irradiation may be helpful in a very small proportion of patients with hypersplenism. These numbers are small, will not influence the utilisation rate and will not be included in this analysis.
18. **Chronic Myeloid Leukaemia:** This subtype accounts for 13% of patients diagnosed with leukaemia. It is characterised by a biphasic or triphasic clinical course in which a benign chronic phase is followed by transformation into an accelerated or blastic phase. There are three effective therapies available to treat CML: allogeneic bone marrow transplant, alpha-interferon with or without cytarabine or imatinib mesylate. Randomised studies have been useful in comparing approaches within a single modality, however no studies have directly compared transplant and non-transplant therapies. An evidence-based analysis prior to the introduction of imatinib mesylate into clinical practice did not provide a definitive answer regarding the relative roles of allogeneic BMT versus interferon-based therapy because appropriately designed well controlled trials have not been performed (37). Current guidelines would recommend that all 3 options are discussed with patients. There is a proportion of patients who will be treated with BMT, however the preparative regimen is likely to be chemotherapy following the report of a similar probability of cure with Cyclophosphamide either in combination with oral Busulphan (Cy-Bu) or TBI (Cy-TBI) (36).
19. **Other considerations for radiotherapy:** Occasionally on relapse patients will be referred for palliative RT for symptomatic splenomegaly. These numbers are small, difficult to estimate from published data, will not influence the utilisation rate and will not be included in this analysis.

Optimal Radiotherapy Utilisation Rate

The proportion of all patients with leukaemia in whom at least one course of radiotherapy was recommended according to the best available guideline evidence was calculated to be 0.04 or 4% of all patients with leukaemia. A one-way sensitivity analysis was performed for one variable and the impact that this had varied the proportion from 0.04 to 0.046. As leukaemia represents 3% of all cancers, the group of leukaemia patients who should ideally receive at least one course of radiotherapy comprised 0.1% of all cancer patients.



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Myeloma

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

Outcome Number	Clinical Scenario	Treatment Indicated	Level of Evidence	References	Notes	Proportion of all myeloma patients
1	Age < 60 years Relapse after initial therapy Palliative treatment for bone pain	RT	I	National Cancer Institute PDQ Guidelines on myeloma(1) National Comprehensive Cancer Network on Multiple Myeloma (2) British Haematological Society (3)	4	0.03
5	Age < 60 years Unable to tolerate initial therapy Palliative treatment for bone pain	RT	I	National Cancer Institute PDQ Guidelines on myeloma (1) National Comprehensive Cancer Network on Multiple Myeloma (2) British Haematological Society (3)	6	0.02
7	Age < 60 years Relapse after initial therapy Palliative treatment for bone pain	RT	I	National Cancer Institute PDQ Guidelines on myeloma (1) National Comprehensive Cancer Network on Multiple Myeloma (2) British Haematological Society (3)	7	0.01

[illegible]

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

Key	Population or subpopulation of interest	Attribute	Proportion of population with this attribute	Quality of information	References	Notes
A	All registry cancers	Patients diagnosed with myeloma	0.01	α	AIHW (4)	1
B	Patients diagnosed with myeloma	Symptomatic	0.97	λ	Dimopoulos et al (5)	1
C	Patients diagnosed with myeloma Symptomatic	Age <60 years	0.22	γ	SEER (6)	1
D	Patients diagnosed with myeloma Symptomatic Age < 60 years	Suitable for bone marrow transplant	0.86	ε	Lenhoff et al (7)	2
E	Patients diagnosed with myeloma Symptomatic Age < 60 years Suitable for bone marrow transplant	Able to complete transplant	0.78	ε	Lenhoff et al (7)	2

Key	Population or subpopulation of interest	Attribute	Proportion of population with this attribute	Quality of information	References	Notes
F	Patients diagnosed with myeloma Symptomatic Age < 60 years Suitable for bone marrow transplant Able to complete transplant	Proportion who relapse	0.62	0	Attal et al (8)	3
G	Patients diagnosed with myeloma Symptomatic Age < 60 years Suitable for bone marrow transplant Able to complete transplant Relapse	Suitable for salvage treatment	0.89	0	Attal et al (8)	3

Key	Population or subpopulation of interest	Attribute	Proportion of population with this attribute	Quality of information	References	Notes
H	Patients diagnosed with myeloma Symptomatic Age < 60 years Suitable for bone marrow transplant Able to complete transplant relapse Suitable for salvage treatment	Bone pain after bisphosphonates	0.42	θ	Metaanalysis (9)	4
I	Patients diagnosed with myeloma Symptomatic Age < 60 years suitable for bone marrow transplant unable to complete transplant	Bone pain after bisphosphonates	0.42	θ	Metaanalysis (9)	2
J	Patients diagnosed with myeloma Symptomatic Age > 60 years	Bone pain after bisphosphonates	0.42	θ	Metanalysis (9)	10

Myeloma

Treatment guidelines

The following guidelines have been identified to treat multiple myeloma:

- National Cancer Institute PDQ Statement on Multiple Myeloma(1)
- National Comprehensive Cancer Network Guidelines on Multiple Myeloma (2)
- British Haematological Society Guidelines on Multiple Myeloma (3)

Indication for Radiotherapy

Radiotherapy is indicated as a palliative treatment for uncontrolled pain in multiple myeloma (PDQ, NCCN, British Guidelines).

Explanatory notes for Tables 1 and 2

1. **Myeloma** accounts for 1% of all new cancers diagnosed in Australia (4). It is an indolent disease, normally running a prolonged natural course. Fifteen percent of patients are diagnosed prior to the development of symptoms, however the majority will become symptomatic with time. Progression has occurred in 97%, with a median time to disease progression of 26 months (5).

Most patients diagnosed are elderly, 22% of patients registered by SEER being under the age of 60 years (6).

2. **Myeloma, < 60 years, suitable for bone marrow transplant:**
Younger fit patients should be considered for high dose chemotherapy and bone marrow transplant following reports of superior survival when compared to standard chemotherapy in a multi-institutional randomised controlled trial (8).

A Nordic population-based study (1994-1997) collected data on 348 new patients under the age of 60 who were diagnosed with myeloma of whom 86% were suitable for bone marrow transplant (7).

In both the Nordic population based study and the French randomised controlled trial a further 22% of patients who were deemed suitable for bone marrow transplant were unable to complete treatment.

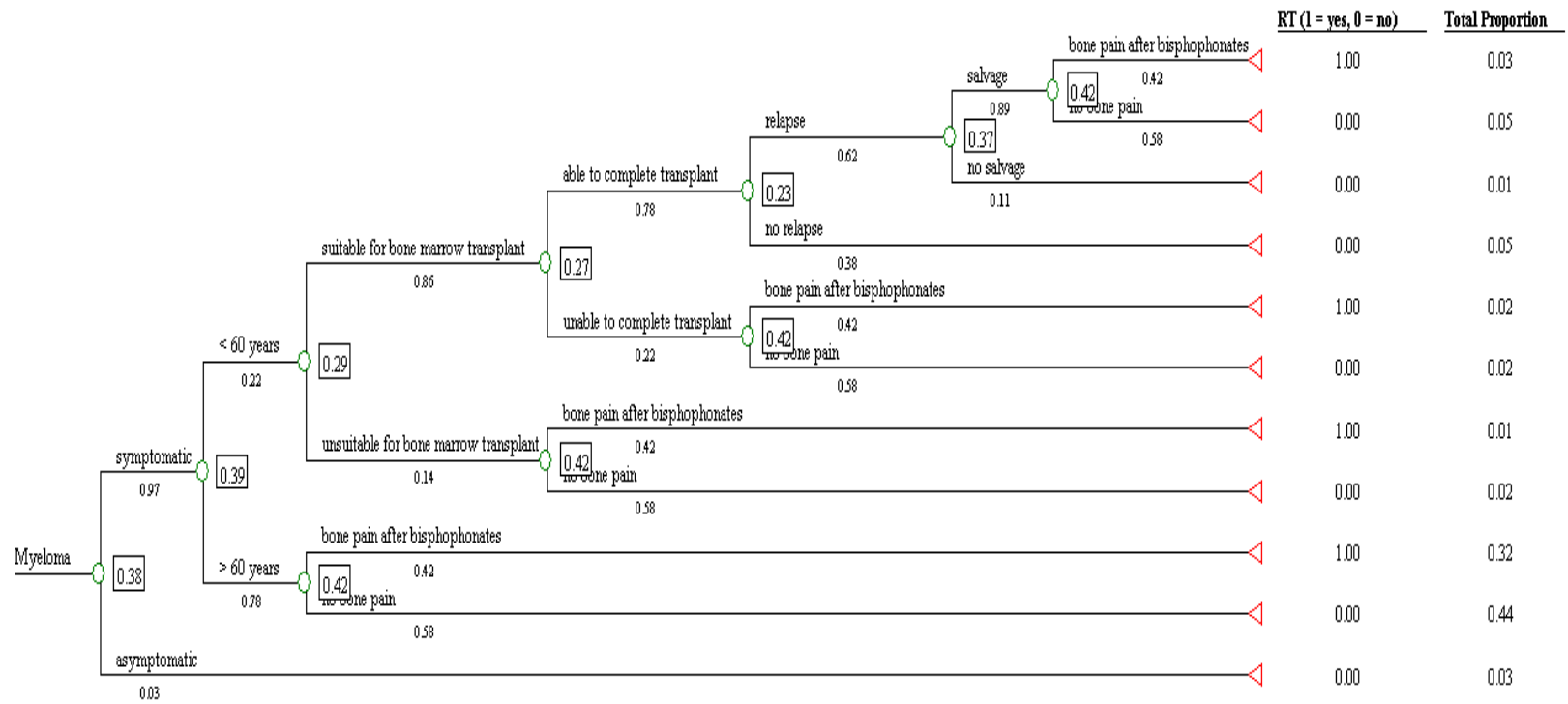
Although the conditioning regimen used in the French trial included Melphalan and Total Body Irradiation (TBI), this is a not standard recommendation. The European Bone Marrow Registry reported an inferior survival with the use of regimens that included TBI in 1905 patients treated for myeloma (10).

3. **Patients who progress after high dose therapy:** In the French randomised study 62% of patients treated with high dose chemotherapy relapsed. Salvage chemotherapy was recommended in 89%, with the remainder receiving no salvage treatment (8).
4. **Patients who progress after high dose therapy who require radiotherapy:** Radiotherapy is indicated for the palliation of painful metastases. We used the meta-analysis addressing the use of bisphosphonates in the treatment of multiple myeloma to determine the proportion of patients who require radiotherapy. Although pain outcome data are not uniformly described in the clinical trials included in the meta-analysis, data extracted from 8 eligible trials with a total on 1281 patients identified 276/657 (42%) patients still reporting pain after treatment with bisphosphonates (9).
5. **Patients unsuitable for bone marrow transplant or unable to complete transplant:** The patients who were not suitable for BMT would be treated with conventional chemotherapy. Patients treated with conventional chemotherapy should receive alkylator-based therapy with melphalan and prednisolone. Newer aggressive combination chemotherapy regimes achieve higher initial response rates of 60-70% but no survival advantage (11). Whatever chemotherapy is used all of these patients with symptomatic disease should be considered for bisphosphonates at the time of initial treatment (12).
6. **Patients unsuitable for bone marrow transplant who require radiotherapy:** Radiotherapy is indicated for the palliation of painful metastases. We used the meta-analysis addressing the use of bisphosphonates in myeloma to determine the proportion of patients who require radiotherapy. Although pain is not uniformly described in the clinical trials included in the meta-analysis, data extracted from 8 eligible trials with a total of 1281 patients identified 276/657 (42%) patients still reporting pain after treatment with bisphosphonates (9).
7. **Patients over the age of 60:** Although some patients aged between 60-70 years will be suitable for BMT, 42% of patients between 60 and 65 years included in the French randomised trial did not manage to undergo transplantation(8). This group will therefore be included here in the no transplant arm.
8. **Treatment of patients >60 years:** Patients over the age of 60 years who are fit enough to be treated with conventional chemotherapy should receive alkylator-based therapy with melphalan and prednisolone. All of these patients should be considered for bisphosphonates at the time of initial treatment. Radiotherapy is indicated for the palliation of painful metastases. We used the meta-analysis addressing the use of bisphosphonates in myeloma to determine the proportion of patients who require radiotherapy (10).

Although pain is not uniformly described in the clinical trials included in the meta-analysis, data extracted from 8 eligible trials with a total of 1281 patients identified 276/657 (42%) patients still reporting pain after treatment with bisphosphonates (9).

Optimal Radiotherapy Utilisation Rate

The proportion of all patients with myeloma in whom at least one course of radiotherapy was recommended according to the best available guideline evidence was calculated to be 0.38 or 38% of all patients with myeloma. As myeloma represents 1% of all cancers, the group of myeloma patients who should ideally receive at least one course of radiotherapy comprised 0.4% of all cancer patients.



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Central Nervous System Cancers

Table 1: Malignant CNS tumours. Indications for radiotherapy – Levels and sources of evidence

Outcome No.	Clinical Scenario	Treatment Indicated	Level of Evidence	References	Notes	Proportion of all CNS cancer patients
1	Malignant CNS tumour, good PS, astrocytoma, pilocytic, complete excision, recurrence.	RT	III	<ul style="list-style-type: none"> National Cancer Institute PDQ treatment guidelines - adult brain tumors (1) 	7	<0.01
3	Malignant CNS tumour, good PS, astrocytoma, pilocytic, incomplete excision	Post-op RT	III	<ul style="list-style-type: none"> National Cancer Institute PDQ treatment guidelines - adult brain tumors (1) 	6	<0.01
4	Malignant CNS tumour, good PS, astrocytoma, low grade, incomplete excision	Post-op RT	III	<ul style="list-style-type: none"> National Cancer Institute PDQ treatment guidelines - adult brain tumors (1) NCCN practice guidelines on CNS cancers (2) 	4	0.10
5	Malignant CNS tumour, good PS, astrocytoma, low grade, complete excision, older age (>45 years)	Post-op RT	III	<ul style="list-style-type: none"> National Cancer Institute PDQ treatment guidelines - adult brain tumors (1) NCCN practice guidelines on CNS cancers (2) 	5	0.03

Outcome No.	Clinical Scenario	Treatment Indicated	Level of Evidence	References	Notes	Proportion of all CNS cancer patients
6	Malignant CNS tumour, good PS, astrocytoma, low grade, complete excision, young age, recurrence	RT	III	<ul style="list-style-type: none"> National Cancer Institute PDQ treatment guidelines - adult brain tumors (1) NCCN practice guidelines on CNS cancers (2) 	5, 9	0.02
8	Malignant CNS tumour, good PS, astrocytoma, high grade	RT +/- chemo	II	<ul style="list-style-type: none"> National Cancer Institute PDQ treatment guidelines - adult brain tumors (1) NCCN practice guidelines on CNS cancers (2) 	4	0.65
9	Malignant CNS tumour, good PS, ependymoma	RT +/- chemo	III	<ul style="list-style-type: none"> National Cancer Institute PDQ treatment guidelines - adult brain tumors (1) NCCN practice guidelines on CNS cancers (2) 	12	0.04
10	Malignant CNS tumour, good PS, embryonal tumour	RT + chemo	II	<ul style="list-style-type: none"> National Cancer Institute PDQ treatment guidelines - adult brain tumors (1) NCCN practice guidelines on CNS cancers (2) 	13	0.04
11	Malignant CNS tumour, good PS, oligodendroglioma, incomplete excision	Post-op RT	III	<ul style="list-style-type: none"> National Cancer Institute PDQ treatment guidelines - adult brain tumors (1) NCCN practice guidelines on CNS cancers (2) 	10	0.03

[illegible]

Table 2: Malignant CNS tumours. The incidence of attributes used to define indications for radiotherapy

Key	Population or subpopulation of interest	Attribute	Proportion of populations with this attribute	Quality of information	References	Notes
A	All registry cancers	Malignant CNS tumours	0.02	α	AIHW (3)	1
B	Malignant CNS tumours	Good performance status	0.94	ϵ	SA Hospital Registry (4)	2
C	Malignant CNS Tumours, good PS	Astrocytoma	0.88	γ	SEER (5)	3
D	Malignant CNS tumours, good PS, astrocytoma	Pilocytic	0.02	γ	SEER (5)	3
		Low grade	0.19 0.24	δ δ	Fleury et al. (6) Van der Sanden et al. (7)	
		High grade	0.79	δ	Fleury et al. (6)	
E	Malignant CNS tumours, good PS, pilocytic astrocytoma	Complete resection	0.82 0.69 0.64 0.60	ζ ζ ζ ζ	Desai et al. (8) Dirven et al. (9) Krieger et al. (10) Hojer et al. (11)	6
F	Malignant CNS tumours, good PS, pilocytic astrocytoma, complete resection, no radiotherapy	Recurrence	0.13 0.27	ζ ζ	Krieger et al. (10) Pan et al. (12)	7

Key	Population or subpopulation of interest	Attribute	Proportion of populations with this attribute	Quality of information	References	Notes
G	Malignant CNS tumours, good PS, low grade astrocytoma	Incomplete resection	0.66	θ	Pignatti et al. (13)	8
H	Malignant CNS tumours, good PS, low grade astrocytoma, complete resection	Older age (> 45 years)	0.47	θ	Pignatti et al. (13)	5
I	Malignant CNS tumours, good PS, low grade astrocytoma, complete resection, younger age, no radiotherapy	Recurrence	0.61	θ	Karim et al. (14)	9
J	Malignant CNS tumours, good PS	Ependymoma	0.04	γ	SEER (5)	3
K	Malignant CNS tumours, good PS	Embryonal tumour	0.04	γ	SEER (5)	3
L	Malignant CNS tumours, good PS	Oligodendro-glioma	0.04	γ	SEER (5)	3

Key	Population or subpopulation of interest	Attribute	Proportion of populations with this attribute	Quality of information	References	Notes
M	Malignant CNS tumours, good PS, oligodendroglioma	Incomplete resection	0.75 0.72 0.78 0.78 0.94 0.85 0.74 0.71	ε ζ ζ ζ ζ ζ ζ ζ	Lindegard et al. (15) Celli et al. (13) Olson et al. (16) Nijjar et al. (17) Bullard et al. (18) Gannett et al. (19) Wallner et al. (20) Reedy et al. (21)	10
N	CNS tumours, good PS, oligodendroglioma, complete resection	Age > 45 years	0.50 0.50	ζ ζ	Nijjar et al. (17) Gannett et al. (19)	5
O	CNS tumours, good PS, oligodendroglioma, complete resection, age <45 years	Recurrence	0.54 0.50	ζ ζ	Bullard et al. (18) Gannett et al. (19)	11

Abbreviations: CNS – Central Nervous system, PS – Performance Status

Malignant CNS tumours - Notes

Treatment Guidelines

Guidelines on the management of CNS tumours have been published by the U.S. National Cancer Institute (Physician Data Query or PDQ guidelines) (1) and by the National Comprehensive Cancer Network (NCCN) (2). There are currently no national Australian guidelines for the management of CNS tumours.

Indications for radiotherapy

The guidelines make the following recommendations on the role of surgery and radiotherapy in the management of CNS tumours:

- For all malignant brain tumours, surgical removal is recommended provided that the lesion is accessible and that preservation of reasonable neurological function is possible. Stereotactic biopsy is preferred if significant morbidity can be predicted with surgery.
- Radiotherapy plays a major role in the management of most types of malignant brain tumours as sole treatment, as post-operative treatment or at recurrence if surgery was the sole treatment.
- Radiotherapy is recommended (with surgery if possible) for anaplastic astrocytoma, glioblastoma multiforme, incompletely-excised oligodendroglioma, mixed glial tumours, brain stem glioma, ependymoma, pineal tumours, medulloblastoma, primitive neuroectodermal tumours (PNETs) and germ cell tumours.
- Omission of radiotherapy is considered reasonable for completely excised juvenile pilocytic astrocytoma; however radiotherapy should be used if there is recurrence
- Radiotherapy is recommended post-operatively for all grades of glioma in the PDQ guidelines (1). The guidelines state that some physicians treat well-differentiated mildly and moderately anaplastic astrocytoma with surgery alone if the patient is <35 years old and the tumour does not enhance on CT. No evidence is quoted for this approach and it is mentioned as an alternative practice rather than advocated. Similarly, the PDQ guidelines mention that some physicians may consider omission of radiotherapy in patients <45 years old, with a non-contrast enhancing low grade oligodendroglioma that has been completely resected.

The NCCN guidelines (2) cite retrospective studies that suggest superior outcomes for patients treated with surgery followed by immediate rather than delayed radiotherapy for completely resected low-grade astrocytomas and oligodendrogliomas. Shimizu et al. (22) reported a “meta-analysis” of retrospective studies suggesting superior outcome for radiotherapy when the results from all studies are pooled. However, the NCCN guidelines also state that omission of radiotherapy is a reasonable treatment alternative for low grade astrocytomas and oligodendrogliomas when the patient is < 45 years and the tumour has been completely resected. They recommend consideration of radiotherapy for all patients > 45 years because these tumours tend to be higher grade and have a shorter time to relapse. Explanatory note 5

below explains how this guideline uncertainty was dealt with in the radiotherapy utilisation tree.

- The guidelines do not discuss chemotherapy as primary or post-operative treatment of choice for oligodendrogliomas despite some recent studies suggesting dramatic and sometimes sustained responses to chemotherapy (23). As they are not discussed in the guidelines, the use of chemotherapy has not been factored into the radiotherapy utilisation trees. Further data on chemotherapy will be needed. Omission of chemotherapy from the tree is unlikely to make a substantial difference to the overall radiotherapy utilisation. Peterson and Cairncross stated that the large majority of patients treated with chemotherapy will relapse at a later date and subsequently need radiotherapy (23).
- The NCCN guidelines recommend radiotherapy for low-grade astrocytomas and oligodendrogliomas following recurrence even if the recurrence is completely excised.

CNS lymphoma is not discussed in this section as it has been included in the lymphoma utilisation tree.

Explanatory Notes for Tables 1 and 2

1. Incidence of brain tumours

Malignant brain tumours constitute 2% of all cancers in Australia in 1998 (3). The cancer registries that contribute to Australian national statistics collect information on malignant brain tumours only and do not include benign tumours such as meningiomas, craniopharyngiomas and pituitary adenomas. Radiotherapy has a role in the management of benign tumours although they are not included in the cancer statistics. Because the aim of this project is to estimate the optimum proportion of new cases of registered cancers that should receive radiotherapy at some time during the course of their illness from the best available evidence, benign diseases treated with radiation are not included. It should be recognised that the role of radiotherapy in the management of CNS tumours, both benign and malignant, is under-estimated (24). The incidence of benign brain tumours is at least 50% of all CNS tumours (25) and hence any estimation of radiotherapy workload must also take into consideration the treatment of conditions not covered by this project.

2. Performance status

The guidelines do not specify an age cut-off for radiotherapy despite the fact that the benefits of radiotherapy, at least for high-grade astrocytomas, decrease with increasing age. There will be some patients with poor performance status in whom conservative treatment would be considered the most appropriate. Determining this performance status cut-off is difficult with little data available to provide an appropriate cut-off. Therefore, surrogate data was used

to determine the proportion of high-grade glioma patients in whom radiotherapy would not be appropriate given their poor performance status. The South Australian Hospital Registry registered 1035 brain tumours from 1977-1998 (4). Of these cases, 94% had some form of primary therapy (largely surgery and/or radiotherapy). This means that 6% did not undergo any form of active therapy. We presume that this was based on age/co-morbidity although the specific reasons for omission of therapy are not known and the appropriateness of a conservative treatment approach is also not known.

3. **Incidence by histological type**

A number of studies have been published on the incidence of various types of brain tumours. Some studies include data on benign conditions and brain metastases; in these instances the incidence has been recalculated by removing the data on benign and metastatic cases.

Pobereskin and Chadduck reported the incidence of brain tumours in two English counties from 1992-1997 by identifying cases from abnormal CT and MRI reports (25). They proposed that this was a better method than by using hospital inpatient data sources as not all brain tumours are treated or referred to specialist units within the county areas. They then obtained histopathology details of all cases. 2483 intracranial cancers were found, of which 861 were found to be metastases. This left 1622 primary brain tumours of which 830 were malignant. Kuratsu et al. reported on brain tumours identified from a hospital registry in Kumamoto Prefecture, Japan from 1989-1994 (26). Davis et al. reported on primary brain tumours in Connecticut and Utah from 1985-1994 (27). Jukich et al. reported the incidence data by histology of 16 000 benign and malignant brain tumours from 6 U.S. population-based registries from 1985-1994 (28). Giles and Gonzalez reported on the epidemiology of CNS tumours in Victoria, Australia 1982-1995 (29). Van der Sanden et al. reported on 1100 brain tumours (benign and malignant) in South and East Netherlands (7). The data from these studies are presented in Table 3.

The data from SEER was used as the primary data source as it was the most comprehensive database. However, the data from the other studies shows little variations from the SEER data. Only CNS tumours with an incidence >2% were included in the tree as tumours with lower incidences would be unlikely to significantly influence the radiotherapy utilisation rate as they contribute such a minor proportion.

Table 3: Prevalence of malignant CNS tumours by histological type by report.

Tumour type	Pobereskin (2000) (25)	SEER 1973-1994 (5)	Kuratsu et al. 1996 (26)	Davis et al. 2001 (27)	Jukich et al. 2001 (28)	Giles et al. 1982-1995. (29)	Van der Sanden et al. 1998 (7)
Astrocytoma	710 (86%)	19 135 (88%)	261 (77%)	2 761 (90%)	7 455 (88%)	2 927 (91%)	740 (82%)
Astrocytoma NOS	NS	6 268 (29%)	NS	719 (24%)	3 001 (36%)	976 (30%)	NS
Anaplastic	NS	1473 (7%)	NS	289 (9%)	537 (6%)	NS	NS
Pilocytic	NS	518 (2%)	NS	95 (3%)	NS	NS	NS
Diffuse	NS	522 (2%)	NS	53 (2%)	NS	NS	NS
GBM	NS	10 354 (48%)	NS	1 543 (50%)	3 756 (45%)	1 707 (53%)	NS
Mixed glioma	NS	NS	NS	62 (2%)	161 (2%)	244 (8%)	NS
Ependymoma	27 (3%)	755 (4%)	22 (7%)	90 (3%)	296 (3%)	92 (3%)	43 (5%)
Embryonal	25 (3%)	921 (4%)	4 (1%)	99 (3%)	285 (3%)	107 (3%)	31 (3%)
Pineal	10 (1%)	NS	NS	NS	NS		3 (<1%)
Oligodendroglioma	7 (<1%)	955 (4%)	NS	121 (4%)	310 (4%)	76 (2%)	71 (8%)
Haemangioblastoma	19 (2%)	NS	NS	NS	NS	NS	NS
Primary CNS Lymphoma	29 (3%)	NS	31 (9%)	NS	NS	NS	NS
Germ cell	3 (<1%)	NS	20 (6%)	NS	NS	NS	15 (2%)
Total malignant tumours	830 (100%)	21 766 (100%)	338 (100%)	3071 (100%)	8346 (100%)	3202	903 (100%)

4. **Incidence of astrocytoma by grade**

McKinley et al. reported on glial tumours in New York State from 1976-1995 (30). They classified the astroglial tumours as Glioblastoma Multiforme (GBM), Anaplastic Astrocytoma (AA), and Astrocytoma Not Otherwise Specified (ANOS). The overall cases were 11 204 (67%) GBM, 4613 (28%) ANOS and 878 (5%) AA. However, no description is available to indicate the proportion of astrocytomas with low-grade histology. Fleury et al. reported on incidence data from 6 French cancer registries (6). They state that low-grade astrocytoma constituted 19% of all astrocytomas. They do not actually state the grading system used but refer to lesions either being “malignant” or “low-grade”. Van der Sanden et al. reported on brain tumour incidence in South and East Netherlands 1989-1994; of 695 astrocytomas where the grade was known, 166 (24%) were low grade (7).

5. **Age**

There are 2 aspects to age that might impact upon the decision to deliver radiotherapy:

a) Older patients with brain tumours have a particularly bad prognosis and there will be clinical situations where conservative supportive care rather than radiotherapy (+/- surgery) is chosen. The Central Brain Tumour Registry of the United States (31) reports that of all CNS tumours, 3% occur in patients above the age of 85 years, and 19% in those above the age of 75 years. However, age alone is not necessarily a sensitive enough measure for appropriateness of treatment (see explanatory note 2 on performance status above). With reference to gliomas in the radiotherapy utilisation tree, we used performance status rather than old age as a determinant of whether an elderly patient with glioma was appropriately treated with radiation.

b) For completely resected, low-grade astrocytomas and oligodendrogliomas, there is controversy as to whether post-operative radiotherapy is routinely recommended. It is beyond the scope of this project to review all of the literature for and against post-operative therapy for completely resected low-grade glioma. Morantz provides an excellent summary of the main studies (32). The first completed randomised trial comparing surgical resection alone versus surgical resection and post-operative radiotherapy in low-grade glioma has completed patient recruitment. The interim trial results at a median follow-up of 5 years have been reported by Karim et al (14). They found that post-operative radiotherapy significantly improved the time to progression but there was no statistically significant improvement in overall survival. The authors conclude, based on their findings, that post-operative radiotherapy should be used to delay recurrence. The NCCN

guidelines state that omission of radiotherapy for patients younger than 45 years may be considered reasonable although they also state that immediate radiotherapy is an alternative option. Some retrospective reviews suggest superior outcome for patients undergoing immediate post-operative radiotherapy compared with radiotherapy delayed until recurrence.

Fortin et al. reviewed the literature on oligodendrogliomas (33). They found no dose response for radiotherapy raising the possibility that there is little effect. They advocate chemotherapy as the post-operative treatment of choice and suggest use of radiotherapy for recurrence. However, they concede that the majority of cases will ultimately recur after chemotherapy. As stated previously, the guidelines suggest observation or radiotherapy with little discussion about chemotherapy for oligodendroglioma.

Because of this lack of definitive evidence, a variable was inserted into the radiotherapy utilisation tree to model this guideline uncertainty, based on an age cut-off of 45 years (the NCCN guidelines suggest the option of no radiation for patients < 45 years). All patients > 45 years with completely resected oligodendroglioma or low-grade glioma (a very small sub-group) are indicated to undergo radiotherapy because the guidelines suggest that these tumours are more aggressive in the older age group. All patients < 45 years of age were recommended to undergo observation with radiotherapy for recurrence. However, the alternative view that all patients irrespective of age should be given radiotherapy was factored into the tree by changing the proportion of people < 45 years to 0% in the sensitivity analysis (i.e. all patients now go down the radiotherapy branch irrespective of age).

For data on age in oligodendroglioma, both Gannett et al. (19) and Nijjar et al. (17) reported that 50% of their series of patients were above the age of 45 years. Pignatti et al. published pooled data from two randomised trials of low-grade glioma/oligodendroglioma randomised to radiotherapy versus no radiotherapy (13). They used an age cut-off of 40 years; 47% of their patients were above the age of 40 years. Therefore in this study, 50% of patients are assumed to be <45 years and hence undergo observation and only receive radiation at recurrence. The data was then modelled by varying the proportion of patients <45 years to 0% to indicate that all patients receive radiotherapy at diagnosis.

6. Proportion of pilocytic astrocytomas that are not completely resected

Desai et al. reported on the outcome of 102 children with pilocytic astrocytoma treated at King Edward Hospital, Mumbai, India (8). They reported total resection in 82% of cases. This was the largest series identified in the literature. However, the next three largest series had quite different total resection rates. Dirven et al. reported

on 73 cases of pilocytic astrocytoma treated at Free University Hospital, in the Netherlands (9). They had a complete resection rate, proved by a negative post-operative scan, of 69%. Krieger et al. reported that of 36 patients treated at the Children's Hospital, Los Angeles, 64% had complete excision and the remaining 36% had residual disease (10). Hojer et al. reported on 33 cases treated at University of Cologne, Germany with a complete resection rate of 60% (11). Due to the large discrepancy in the data we used a total resection rate of 82% from the largest series (Desai et al.) and also used the 69% quoted by the next largest series (Dirven et al) in the sensitivity analysis (see below).

7. **Proportion of completely resected pilocytic astrocytomas that recur**

Krieger et al. reported that of 23 cases of completely excised pilocytic astrocytoma at the Children's Hospital, Los Angeles, 3 (13%) had recurrence (10). Pan et al. reported on 15 cases of completely resected, paediatric cerebellar pilocytic astrocytoma treated at Veterans General Hospital, Taipei (12). Four patients (27%) had evidence of recurrence or persistence on MRI. The larger series of Krieger et al. was the data source used for the radiotherapy utilisation tree.

8. **Proportion of low-grade astrocytoma treated with complete surgical resection**

The best available data comes from a meta-analysis of two randomised trials conducted by the European Organization for Research and Treatment of Cancer (EORTC) reported by Pignatti et al (13). The two trials included in the analysis were trials assessing the timing and dose of radiation therapy required for low-grade gliomas. Of the entire data set of 610 patients, 206 (34%) were quoted as having had resection of 90-100% of the low-grade glioma. The remaining 66% had <90% tumour resection.

9. **Proportion of completely-resected, low-grade astrocytomas treated by surgery alone that recur**

This data was difficult to find as there have been many old reports about recurrence rates after complete surgical resection but these reports were largely in the pre-CT/MRI era and therefore not particularly relevant to neuro-oncological management today. In addition, a lot of the old studies had follow-up periods of < 5 years which is an inadequate duration for a determination of the true recurrence rate. Furthermore, the reports identify that a proportion of the study population had radiotherapy and others did not; however the recurrence data is not reported in accordance with the completeness of excision and the omission of radiotherapy. The recurrence data is usually presented in a univariate fashion or only as overall survival data, without providing any disease-specific or local recurrence data.

The best data available was the control arm of the randomised EORTC trial of low-grade glioma, which tested post-operative radiotherapy versus observation following resection (14). These data are multi-institutional in that multiple departments contributed to the study as opposed to using single institutional data. However, this study does include a small proportion of patients who had less than a complete resection although the investigators were prepared to allow these patients the possibility of being randomised to no radiotherapy. The recurrence rate for this group was 85/140 (61%) at a median follow-up of 5 years.

10. **Proportion of oligodendrogliomas that undergo complete excision**

The best data source was from Lindegaard et al. who reported a population-based study of 208 cases of oligodendroglioma treated in Norway 1953-1977 (15). They found that of the 175 evaluable cases, 43 (25%) were totally resected and the other 75% had subtotal resection. This study was considered superior to other studies that were evaluated, which are single institutional studies. Celli et al. reported on 137 patients with oligodendroglioma treated at La Sapienza University, Italy, of whom 38 (28%) had complete or subtotal excision (34). Olson et al. reported on 106 oligodendrogliomas and mixed gliomas treated at the Memorial Sloan Kettering Cancer Center (16). They reported a gross total excision rate of 22%. Nijjar et al. reported on 68 patients with oligodendroglioma treated at Princess Margaret Hospital, Toronto between 1958 and 1984 (17). 10 patients (15%) were treated with surgery alone. 15/68 (22%) were completely excised. Bullard et al. reported on 71 patients treated at the Duke University Medical Centre, U.S.A. between 1940 and 1983 (18). Their complete resection rate was 6%. Gannett et al. treated 41 oligodendroglioma patients at the University of Washington, Seattle 1956-1984 and reported that 37 (90%) were incompletely macroscopically excised (19). Wallner et al. reported that of 42 patients undergoing resection at UCSF from 1940-1983, 31 (74%) had subtotal resection (20). Reedy et al. reported that 15/21 (71%) had subtotal resection at Cleveland Clinic 1950-1980 (21).

11. **Proportion of completely-resected oligodendrogliomas treated by surgery alone that recur**

Lindegaard et al. (15), Wallner et al. (20), Reedy et al. (21) and Nijjar et al. (17) do not report their recurrence rates for patients treated with surgery alone. Bullard reported that of the 24 patients treated with surgery alone in their series, with long-term data available, 54% have recurred (18). Gannett et al. reported that of the 4 patients in their series who did undergo complete resection, 2 (50%) had recurrence (19). The other two patients have survived > 10 years without a recurrence.

12. **Radiotherapy for ependymoma**
The PDQ (1) and NCCN (2) guidelines both recommend radiation treatment for ependymoma due to an improvement in survival and reduction in recurrence.
13. **Radiotherapy for embryonal tumours such as medulloblastomas/ primitive neuro-ectodermal tumours (PNET).** The PDQ (1) and NCCN (2) guidelines both recommend radiation treatment for embryonal tumours such as medulloblastomas and PNETs because of the superior survival outcome and the high recurrence risk with surgery alone.

Optimal Radiotherapy Utilisation Rate and Sensitivity analysis

The calculated expected value or optimal radiotherapy utilisation rate for CNS tumours was 92%. As CNS tumours make up 2% of all primary cancers, this 92% represents 1.8% of all cancers.

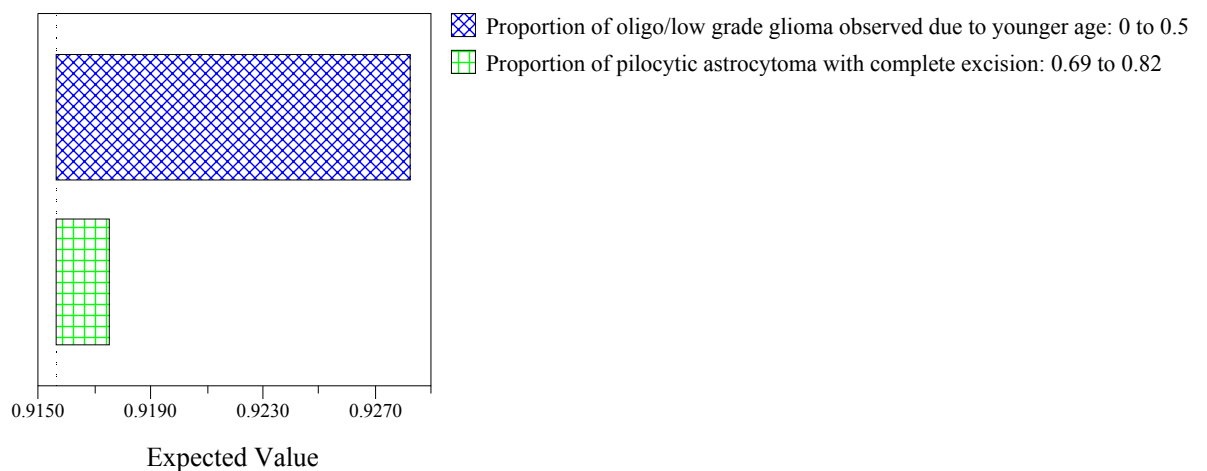
There were two areas in the tree where either the data or the evidence to support radiotherapy were uncertain. The main controversy in the management of CNS tumours relates to the conflicting evidence in the management of low-grade astrocytomas and oligodendrogliomas, particularly after complete or almost complete macroscopic excision. The PDQ and NCCN guidelines suggest the use of radiotherapy when the patients are > 45 years because of the tumours' more aggressive natural history. However, the uncertainty is whether those <45 years should receive radiation. A randomised trial reported by Karim et al. suggests an improvement in time to progression but not to overall survival. The authors conclude by recommending radiotherapy to all patients, although advocates for delayed radiation suggest that the lack of an overall survival benefit shows that delayed radiotherapy (with or without other therapy such as surgery or chemotherapy), may be effective. To model this uncertainty and the impact on the overall optimal radiotherapy utilisation rate for CNS tumours, two scenarios were used. Firstly, because the guidelines suggested that radiotherapy be omitted for completely resected, low-grade, < 45 years (approximately half the patients are <45 years), then the tree indicates that they do not receive radiation. However, the other scenario was that the proportion getting radiotherapy due to age was re-set at 1.0 (100%) in that all patients should get immediate treatment and not wait for recurrence.

The second controversy was the complete resection data rates for pilocytic astrocytoma. There was considerable difference between the largest series (82%) and the next three largest series. The data analysis incorporated sensitivity analysis using data from the two largest series.

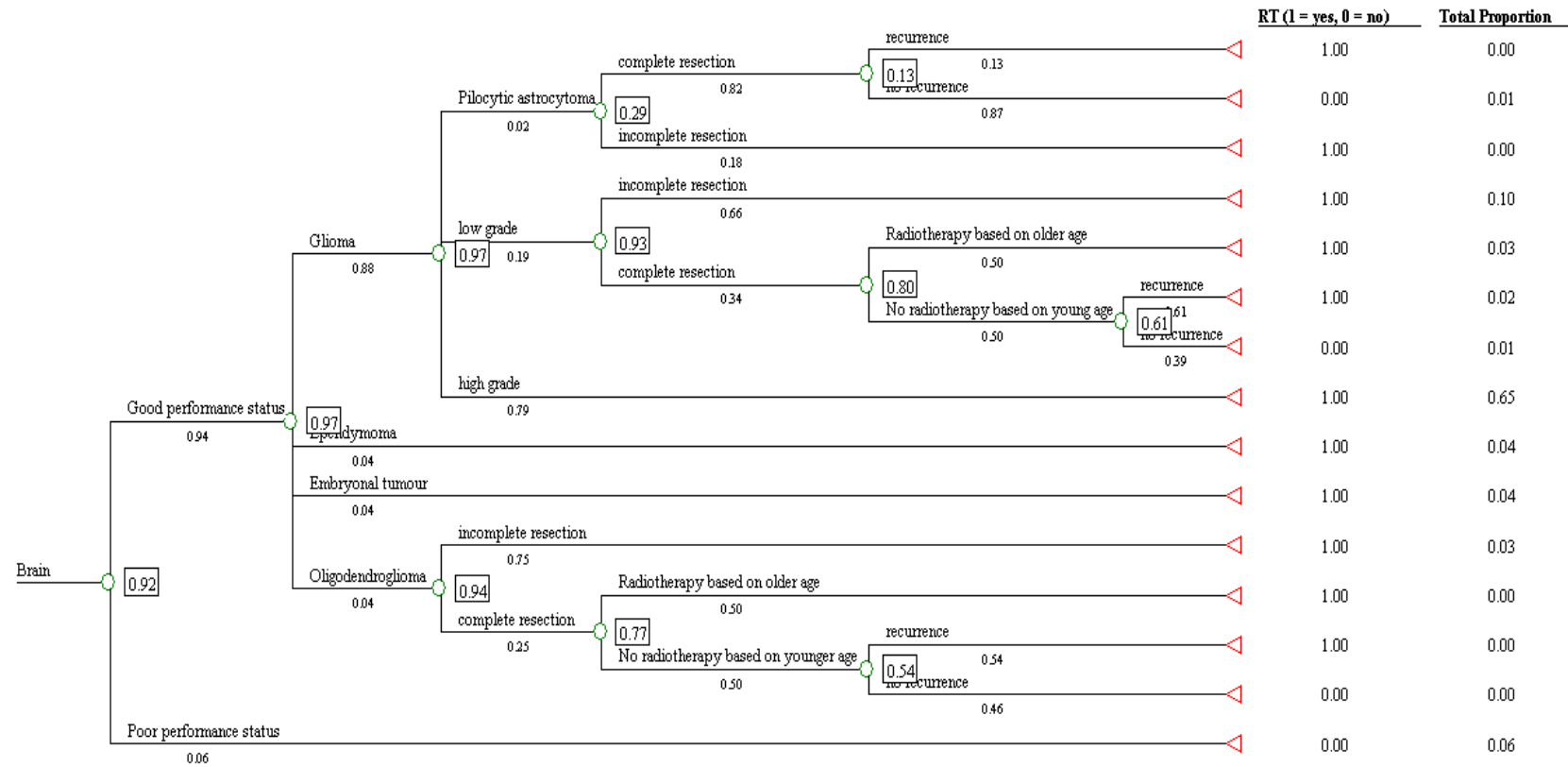
Another area where the data varied was for the complete resection rates for oligodendroglioma. However, this was not included into the sensitivity analysis

because the best evidence was higher in the hierarchy of evidence as described in the study outline and therefore the best data source was used.

Tornado Diagram at Brain



The sensitivity analysis varies the overall radiotherapy utilisation estimate between 91.6% and 92.8%. For instance, irradiation of all oligodendrogliomas and low-grade astrocytomas that have been completely resected increases the rate from 91.6% (no radiation for completely resected tumours in the < 45 years age group) to 92.8%. As malignant CNS tumours make up only 2% of all cancers, the effect of this uncertainty on the overall radiotherapy utilisation rate estimate is small (varying between 1.8% and 1.9% of all cancers).



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Thyroid Cancer

Table 1: Thyroid Cancer. Indications for radiotherapy – Levels and sources of evidence

Outcome No.	Clinical Scenario	Treatment Indicated	Level of Evidence	References	Notes	Proportion of all thyroid cancer patients
1	Thyroid cancer, papillary, persistent local recurrence	RT	III	<ul style="list-style-type: none"> ▪ RTCG (1) ▪ AACE/ACE/AAES (2) ▪ BTA/RCP (3) ▪ Vini and Harmer (4) 	3	0.02
3	Thyroid cancer, papillary, no local recurrence, distant recurrence, bone metastases that do not completely respond to radioactive iodine	Palliative RT	I	<ul style="list-style-type: none"> ▪ AACE/ACE/AAES (2) ▪ BTA/RCP (3) ▪ National Cancer Institute PDQ guidelines (5) ▪ NCCN guidelines (6) 	5, 6	0.01
4	Thyroid cancer, papillary, no local recurrence, distant recurrence, brain metastases	Palliative RT	II	<ul style="list-style-type: none"> ▪ AACE/ACE/AAES (2) ▪ BTA/RCP (3) ▪ NCCN guidelines (6) 	7	<0.01
7	Thyroid cancer, follicular, persistent local recurrence	RT	III	<ul style="list-style-type: none"> ▪ RTCG (1) ▪ AACE/ACE/AAES (2) ▪ BTA/RCP (3) ▪ Vini and Harmer (4) 	8	<0.01

RTCG – Regional Thyroid Cancer Group (U.K.), AACE -American Association of Clinical Endocrinologists, ACE - American College of Endocrinology, AAES - American Association of Endocrine Surgeons, BTA – British Thyroid Association, RCP – Royal College of Physicians, U.K.

Outcome No.	Clinical Scenario	Treatment Indicated	Level of Evidence	References	Notes	Proportion of all thyroid cancer patients
9	Thyroid cancer, follicular, no local recurrence, distant recurrence, bone metastases that do not respond to radioactive iodine	Palliative RT	I	<ul style="list-style-type: none"> ▪ AACE/ACE/AAES (2) ▪ BTA/RCP (3) ▪ National Cancer Institute PDQ guidelines (5) ▪ NCCN guidelines (6) 	5, 6	0.01
10	Thyroid cancer, follicular, no local recurrence, distant recurrence, brain metastases	Palliative RT	II	<ul style="list-style-type: none"> ▪ AACE/ACE/AAES (2) ▪ BTA/RCP (3) ▪ NCCN guidelines (6) 	7	<0.01
13	Thyroid cancer, medullary, not locally advanced, locoregional recurrence	RT	III	<ul style="list-style-type: none"> ▪ RTCG (1) ▪ AACE/ACE/AAES (2) ▪ BTA/RCP (3) ▪ Vini and Harmer (4) 	11	0.02
14	Thyroid cancer, medullary, not locally advanced, no local recurrence, distant recurrence, bone metastases	Palliative RT	I	<ul style="list-style-type: none"> ▪ AACE/ACE/AAES (2) 	5	<0.01

RTCG – Regional Thyroid Cancer Group (U.K.), AACE -American Association of Clinical Endocrinologists, ACE - American College of Endocrinology, AAES - American Association of Endocrine Surgeons, BTA – British Thyroid Association, RCP – Royal College of Physicians, U.K.

[illegible]

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

Key	Population or subpopulation of interest	Attribute	Proportion of populations with this attribute	Quality of information	References	Explanatory Notes
A	All registry cancers	thyroid cancer	0.01	α	AIHW (9)	1
B	Thyroid cancer	Papillary	0.78 0.72 0.77 0.76	γ γ γ γ	Hundahl et al. (10) Mulla and Margo (11) Iribarren et al. (12) Haselkorn et al. (13)	2
C	Thyroid cancer, papillary	Persistent local recurrence	0.03 0.06 0.15 0.02	ζ ζ ζ ζ	Samaan et al. (14) McConahey et al. (15) Hoie et al. (16) Lerch et al. (17)	3
D	Thyroid cancer, papillary, no local recurrence	Distant recurrence	0.04 0.05 0.11 0.03	ζ ζ ζ ζ	Samaan et al. (14) McConaghey et al. (15) Hoie et al. (16) Lerch et al. (17)	4
E	Thyroid cancer, papillary, no local recurrence, distant recurrence	Bone metastases	0.19 0.23 0.30 0.20	ζ ζ ζ ζ	Hoie et al. (18) McConaghey et al. (15) Samaan et al. (14) Lerch et al. (17)	5
F	Thyroid cancer, papillary, no local recurrence, distant recurrence, bone metastases	Complete response to radioactive iodine	0.10	ζ	Schlumberger et al. (19)	6

Key	Population or subpopulation of interest	Attribute	Proportion of populations with this attribute	Quality of information	References	Explanatory Notes
G	Thyroid cancer, papillary, no local recurrence, distant recurrence, no bone metastases	Brain metastases	0.10 0.15	ζ ζ	Hoie et al. (18) McConaghey et al. (15)	7
H	Thyroid cancer	Follicular	0.15 0.21 0.13 0.15	γ γ γ γ	Hundahl et al. (10) Mulla and Margo (11) Iribarren et al. (12) Haselkorn et al. (13)	2
I	Thyroid cancer, follicular	Persistent local recurrence	0.02 0.01	ζ ζ	Samaan et al. (14) Lerch et al. (17)	8
J	Thyroid cancer, follicular, no local recurrence	Distant recurrence	0.10 0.04	ζ ζ	Samaan et al. (14) Lerch et al. (17)	9
K	Thyroid cancer, follicular, no local recurrence, distant recurrence	Bone metastases	0.52 0.86	ζ ζ	Samaan et al. (14) Lerch et al. (17)	5
L	Thyroid cancer, follicular, no local recurrence, distant recurrence, bone metastases	Complete response to radioactive iodine	0.10	ζ	Schlumberger et al. (19)	6
M	Thyroid cancer, follicular, no local recurrence, distant recurrence, no bone metastases	Brain metastases	0.0 0.10	ζ ζ	Samaan et al. (14) Lerch et al. (17)	7

Key	Population or subpopulation of interest	Attribute	Proportion of populations with this attribute	Quality of information	References	Explanatory Notes
N	Thyroid cancer	Medullary	0.05 0.05 0.02 0.03	γ γ γ γ	Hundahl et al. (10) Mulla and Margo (11) Iribarren et al. (12) Haselkorn et al. (13)	2
O	Thyroid cancer, medullary	T1-3N0-1a	0.54 0.53	ϵ ζ	Modigliani et al. (20) Hyer et al. (21)	10
P	Thyroid cancer, medullary, T1-3N0-1a	Locoregional recurrence	0.59 0.53	ζ ζ	Hyer et al. (21) Simpson et al.	11
Q	Thyroid cancer, medullary, T1-3N0-1a, no local recurrence	Distant recurrence	0.06	ϵ	Modigliani et al. (20)	12
R	Thyroid cancer, medullary, T1-3N0-1a, no local recurrence, distant recurrence	Bone metastases	0.50	ζ	Saad et al. (22)	5
S	Thyroid cancer, medullary, T1-3N0-1a, no local recurrence, distant recurrence, no bone metastases	Brain metastases	0.02	ζ	Saad et al. (22)	7
T	Thyroid cancer	Anaplastic	0.02 0.02 0.01 0.02	γ γ γ γ	Hundahl et al. (10) Mulla and Margo (11) Iribarren et al. (12) Haselkorn et al. (13)	12

Thyroid cancer

A large component of the management of thyroid cancer (particularly follicular and papillary carcinoma) involves the use of unsealed radioactive iodine, which is delivered either by radiation oncology departments or by nuclear medicine departments, depending on individual hospital protocols. The aim of this project is to estimate the overall optimal rate of all cancers that should receive external beam radiotherapy at least once in their treatment course. Therefore, the use of radioactive iodine is not included in this analysis. However from a resource point of view, radioactive iodine treatment may need to be included in the overall planning for a radiotherapy service.

The four commonest histologic types of thyroid cancer are papillary, follicular, medullary and anaplastic. The optimal radiotherapy utilisation rate for lymphoma of the thyroid is discussed in the section on non-Hodgkins lymphoma.

Treatment guidelines

The American Association of Clinical Endocrinologists (AACE), the American College of Endocrinologists (ACE) and the American Association of Endocrine Surgeons (AAES) have published joint guidelines for the management of thyroid carcinoma (2). The Northern Cancer Network is a United Kingdom collaborative group that has issued guidelines for the management of thyroid cancer (Regional Thyroid Cancer Group) (1). Guidelines have also been issued by the British Thyroid Association/Royal College of Physicians (3), by the National Cancer Institute (PDQ) (5) and the NCCN (6).

Indications for radiotherapy

The guidelines make the following recommendations about the use of external beam radiotherapy in the management of thyroid cancer.

The American Association of Clinical Endocrinologists (AACE), the American College of Endocrinologists (ACE) and the American Association of Endocrine Surgeons (AAES) recommend external beam radiotherapy for

- Advanced follicular or papillary carcinoma if there has been residual disease identified that does not take up iodine
- Advanced follicular or papillary carcinoma for locally advanced disease in the neck
- For anaplastic carcinoma

The Regional Thyroid Cancer Group recommend the use of external beam radiotherapy in the following situations:

- occasionally recommended for advanced papillary or follicular thyroid cancer
- recommended as post-operative adjuvant therapy for high grade or locally advanced papillary, follicular or medullary thyroid cancers that do not take up radioactive iodine
- recommended as adjuvant therapy if extensive residual disease is found following thyroidectomy,

- recurrent disease not amenable to radioactive iodine treatments or recurrent despite radioactive iodine therapy (referred to in the tree as locally persistent cancer)
- recommended in anaplastic thyroid cancer (+/- palliative surgery),
- inoperable disease
- for palliation of metastatic disease in bone, brain etc.

The British Thyroid Association of the Royal College of Physicians recommend consideration of external beam radiotherapy in the following situations:

- unresectable tumours that do not take up iodine
- residual disease post-operatively especially if there is little or no radioactive iodine uptake
- recurrent disease not amenable to radioactive iodine therapy or further surgery
- palliation of metastatic disease to bone, brain, mediastinum, spine etc.

The National Cancer Institute PDQ guidelines recommend consideration of external beam radiotherapy in the following clinical situations:

- Stage III papillary or follicular tumours that do not take up iodine
- Stage IV papillary or follicular thyroid cancer with localised lesions that are unresponsive to I¹³¹
- Anaplastic thyroid cancer which is unresectable

A review by Vini and Harmer (4) discusses the beneficial role of external beam radiotherapy in the treatment of recurrent or inoperable disease. They additionally recommend adjuvant radiotherapy in medullary carcinoma if node positive, based upon a study in the Institut Gustav-Roussy which showed substantially better survival in patients treated with adjuvant therapy (86% at 5 years) compared with those that did not have radiotherapy (36% 5 year survival) (23).

Reviews of medullary carcinoma of the thyroid recommend consideration of post-operative radiotherapy following thyroidectomy for patients with locally advanced disease (7) (8).

Explanatory Notes for Tables 1 and 2

1. **Incidence of thyroid cancer.** The Australian Institute of Health and Welfare reports that thyroid cancer comprises 1% of all registered cancers (9).
2. **Incidence of thyroid cancer by histology.** The U.S. National Cancer Database for thyroid cancer contains records on 53 856 cases of thyroid cancer from 1985-1996. Papillary cancer comprised 79%, follicular 15%, medullary 4% and anaplastic 2% (10). The Florida Cancer Data System reported on 5746 thyroid cancers that occurred in Florida, from 1981-1993 (11). They reported that of the 4 common histological types (excluding lymphoma and other less common thyroid

cancers such as squamous carcinoma of the thyroid), papillary carcinoma = 72%, follicular = 21%, medullary = 5% and anaplastic = 2%. Iribarren et al. (12) reported on a large health plan study of 205 000 people in the San Francisco Bay area 1964-1973. The incidence by histology for the 196 incident cases of thyroid cancer was papillary (77%), follicular (13%), medullary (2%) and anaplastic (1%). "Other" histology represented 7%. Haselkorn et al. reported on 8820 thyroid cancer cases in the Los Angeles county 1972-1995 and stated that papillary carcinoma comprised 76% of all thyroid cancer, follicular 15%, medullary 3% and anaplastic 2% (13).

3. **Proportion of papillary thyroid cancer that recurs locally requiring external beam radiotherapy.** Samaan et al. (14) reported that of 1289 patients with papillary thyroid cancer treated at M.D. Anderson Cancer Center, 43 (3%) recurred in the neck. McConaghey et al. (15) reported on 800 patients with papillary thyroid cancer treated at the Mayo clinic with a recurrence rate of 6%. Hoie et al. (16) reported on 730 patients treated with surgery in the Norwegian Radium Hospital from 1956-1978. They reported a local recurrence rate of 15% after thyroidectomy and radioactive iodine. A smaller series reported similar results to that of Samaan et al - Lerch et al. (17) reported on 301 papillary thyroid cancer patients treated at the University of Munster. Their locoregional recurrence rate was found to be 6/301 (2%). The largest series by Samaan et al. (14) was chosen as the data source. Sensitivity analysis of the widest variables was also performed to assess the impact of this data uncertainty on the overall radiotherapy estimate.
4. **Proportion of papillary thyroid cancer that recurs with distant metastases.** Samaan reported that of the 1289 papillary thyroid cancers treated at M.D. Anderson Cancer Center, 49 (4%) developed distant metastases (14). McConaghey et al. (15) reported a distant metastatic rate for the Mayo Clinic series of 40/800 (5%). Hoie et al. (16) reported that of 730 patients with papillary thyroid cancer treated with surgery and radioactive iodine, 11% ultimately developed distant metastases. Lerch et al. (17) reported a distant recurrence rate of 3% (10/301). The largest data source of Samaan et al. (14) was used for the utilisation tree. Due to the large variation in incidence, sensitivity analysis was performed (between the 4% and 11% data values) to assess the impact of this data uncertainty on the overall radiotherapy utilisation estimate (see sensitivity analysis).
5. **Proportion of bone metastases by histology.**
Papillary cancer
 Hoie et al. (18) reported on the distribution of metastatic disease in 91 papillary thyroid cancer patients with metastases outside regional lymph nodes. There were 17 patients (19%) with bone metastases. Samaan et al. (14) reported that of 49 patients with metastatic papillary thyroid cancer in their series, 15 (30%) had bone metastases. McConahey et al. (15) reported a bone involvement rate of 23% in their series of 40 patients with metastases (15). Lerch et al. (17) reported

that of 10 patients with distant disease, 2 (20%) had bone metastases. The largest series by Hoie et al. (18) was used for the tree, with sensitivity analysis assessing the range of 19-30%.

Follicular cancer

Samaan et al. (14) reported that bone metastases occurred in 14/27 (52%) follicular cancer patients who had metastatic disease. They found that bone metastases were much more common for follicular than papillary cancers. Lerch et al. (17) reported that of 7 patients who developed metastatic disease in their series, 6 (86%) developed bone metastases. The data from Samaan et al was used with no sensitivity analysis because the study from Lerch et al was considered too small to be reliable.

Medullary cancer

Saad et al. (22) described the outcome of 47 patients with medullary thyroid cancer who developed metastatic disease during follow up. Bone metastases occurred in 23 patients (50%).

6. **Proportion of papillary and follicular thyroid cancer with bone metastases responsive to radioactive iodine.** Schlumberger et al. (19) reported on 394 patients with bone and/or lung metastases, out of 2200 thyroid cancer patients (pooled data for both papillary and follicular cancers). They reported that 10% of patients achieved a complete response in bone to radioactive iodine, suggesting that the other 90% may continue having symptoms and hence external beam radiotherapy may be used as palliation for the bone metastases in those patients. It is possible that patients who have a complete response may ultimately relapse. However, they could be retreated with radioactive iodine. The proportion of patients with complete response who ultimately need external beam radiotherapy due to progressive disease not sensitive to further radioactive iodine has not been reported.

7. **Proportion of brain metastases in metastatic thyroid cancer by histology.**

Papillary Cancer

Hoie et al. (18) reported on the distribution of metastatic disease in 91 papillary thyroid cancer patients treated at the Norwegian Radium Institute. There were 9 patients (10%) with brain metastases. McConaghey et al. (15) reported a brain involvement rate of 15% in their series of 40 patients with metastases. The series by Samaan et al. did not provide data on incidence of brain metastases.

Follicular Cancer

Samaan et al. (14) described the M.D.Anderson Cancer Center results for follicular thyroid cancer. Among 236 follicular cancers seen, there were no brain metastases. Lerch et al. (17) reported that of 10 patients with metastatic disease, 1 (10%) had brain metastases.

Medullary Cancer

Saad et al. (22) described the course of 47 patients with medullary thyroid cancer who developed metastatic disease during follow up. Brain metastases occurred in 1 patient (2%).

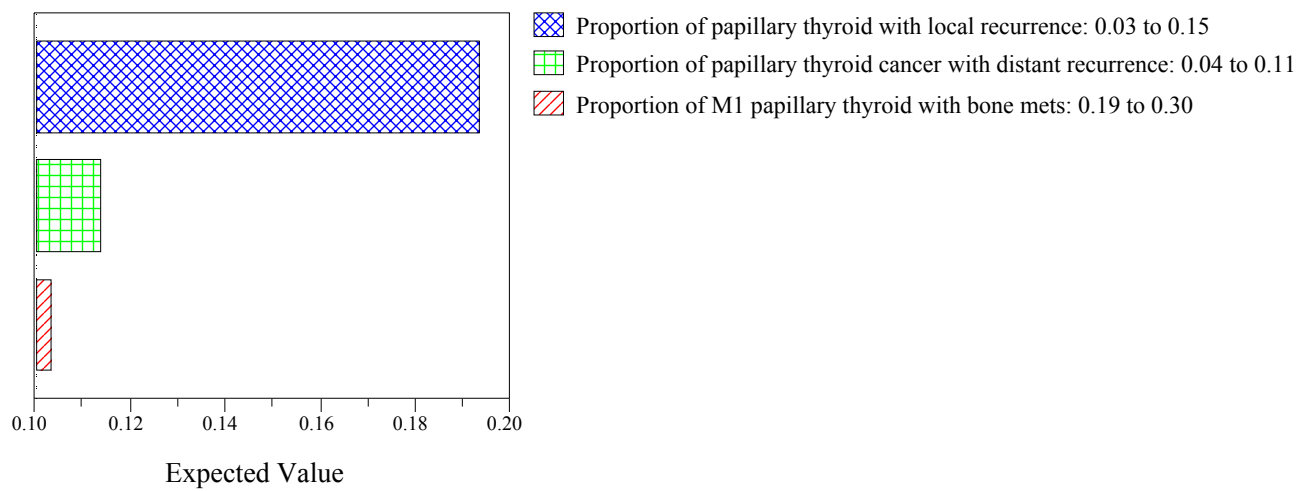
- 8. Proportion of locally recurrent follicular thyroid cancer requiring external beam radiotherapy.** Samaan et al. (14) reported a 2 % recurrence rate in the neck following thyroidectomy for follicular thyroid cancer in 236 patients treated at M.D. Anderson Cancer Center. Lerch et al. (17) reported a locoregional recurrence rate of 2/199 (1%) in a series of 199 patients with follicular cancer treated at the University of Munster.
- 9. Proportion of follicular thyroid cancer that recurs distantly.** Samaan et al. (14) reported that of the 236 follicular thyroid cancers treated at M.D. Anderson Cancer Center, 23/236 (10%) developed metastatic disease. Lerch et al. (17) reported a distant recurrence rate of 7/199 (4%).
- 10. Proportion of medullary cancer that is locally advanced at diagnosis (T4 or >N1a).** Modigliani et al. (20) reported on 899 cases of medullary carcinoma registered in the French Calcitonin Tumours Study Group. They found that 46.5% had locally advanced disease at presentation. Hyer et al. (21) described their experience with 162 patients treated with surgery for medullary carcinoma between 1949-1998 at the Royal Marsden Hospital, U.K. Sixty-three percent had node-positive neck dissections and 23% had T4 disease. They used radiotherapy as post-operative therapy for advanced disease such as extra-thyroid extension or multiple node involvement or symptomatic metastatic disease. This represented 76/162 (47%) of the entire group. Survival was similar in patients receiving or not receiving radiotherapy despite the radiotherapy group having significantly more advanced disease at presentation.
- 11. Proportion of early medullary cancer that recurs locoregionally.** In the study by Hyer et al.(21), the locoregional relapse rate in patients with early medullary cancer who did not receive radiotherapy was 59%. They do not report on distant metastatic rate. Simpson et al. (24) reported that of 13 medullary thyroid cancers treated with surgery alone and no post-operative radiotherapy (due to absence of adverse prognostic features), 7 (53%) recurred.
- 12. Proportion of early medullary thyroid cancer that recurs distantly.** No crude data on distant recurrence rates were available specifically for early stage thyroid cancer. Modigliani et al. (20) reported that early stage medullary cancers were alive in 94% of cases (survival of stages I and II combined). This suggests a distant metastatic rate of 6% although the specific causes of death are not described.
- 13. Anaplastic thyroid cancer.** Anaplastic carcinoma of the thyroid has a dismal prognosis. All guidelines recommend consideration of chemotherapy and radiotherapy in fit patients and palliative

radiotherapy alone in non-fit patients in the management of anaplastic carcinoma of the thyroid. No randomised trials exist but there are institutional reports from many centres on the improved survival with a radiotherapy +/- chemotherapy treatment approach (25) (26) (27).

Estimated optimal radiotherapy utilisation rate and sensitivity analysis

Based upon the evidence-based radiotherapy tree and the epidemiological data described, the optimal rate of radiotherapy for thyroid cancer patients is 10%. As thyroid cancer comprises 1% of all cancers, the patient group with thyroid cancer in whom radiotherapy is recommended represents 0.1% of the entire cancer population.

**Tornado Diagram at
Thyroid**



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Unknown Primary Cancer

Table 1: Indications for radiotherapy for unknown primary carcinoma: Levels and sources of evidence

Outcome	Clinical Scenario	Treatment indicated	Levels of evidence	References	Proportion of unknown primary patients
1	Unknown primary, brain metastases	Palliative RT	II	• NCCN Practice Guidelines (1)	0.06
2	Unknown primary, no brain metastases, bone metastases	Palliative RT	I	• NCCN Practice Guidelines (1)	0.27
3	Unknown primary, no brain metastases, no bone metastases, symptomatic node metastases.	Palliative RT	III	• NCCN Practice Guidelines (1)	0.28
Proportion of unknown primary patients in whom radiotherapy is recommended					0.61
Total proportion of all cancer patients = 0.61 x 0.04 =					0.024 (2.4%)

Abbreviations: NCCN – National Comprehensive Cancer Network (U.S.)

RT - radiotherapy

Table 2: The incidence of attributes used to define indications for radiotherapy for unknown primary

Key	Population or subpopulation of interest	Attribute	Proportion of population with this attribute	Quality of information	References
0	All registry cancers	Unknown primary	0.04	α	AIHW (2)
1	Unknown primary	Brain metastases	0.06 0.07 0.05 0.07	ζ ζ ζ ζ	Hess et al. (3) Zuur et al. (4) Culine et al. (5) Greco and Hainsworth (6)
2	Unknown primary, no brain metastases	Bone metastases	0.29 0.13 0.45 0.20	ζ ζ ζ ζ	Hess et al. (3) Zuur et al. (4) Culine et al. (5) Greco and Hainsworth (6)
3	Unknown primary , no brain metastases	Symptomatic node metastases	0.42 0.35 0.45 0.32	ζ ζ ζ ζ	Hess et al. (3) Zuur et al. (4) Culine et al. (5) Greco and Hainsworth (6)

Explanatory notes

Definition

In this study, “carcinoma of unknown primary” refers to patients presenting with metastatic cancer (most commonly adenocarcinoma of unknown primary (ACUP), and also including carcinoma not otherwise specified, poorly differentiated carcinoma, melanoma or neuroendocrine carcinoma) in whom the primary tumour site is not detected. This group of patients usually share common clinical characteristics such as rapid progression and random atypical metastases (7). Metastatic cervical squamous cell carcinomas from a skin or head and neck primary are not discussed here, since they have been included in the head and neck section.

At autopsy, the most common primary sites were found to be in the lung and pancreas, although 25% of primaries remained undetermined even at autopsy (7) (8). The median survival of this group of patients is 4 months. The Australian Institute of Health and Welfare (AIHW) reported that in 1998, unknown primary cancer represented 4% of all registered malignancies (2).

Treatment guidelines

Guidelines for the treatment of carcinoma of unknown primary origin have been issued by the National Cancer Institute (PDQ) (8), the British Columbia cancer agency (9) and the National Comprehensive Cancer Network (NCCN) (1). There are many ways in which unknown primary cancer can manifest and therefore the presenting symptoms can vary significantly. The treatment guidelines are not explicit because of the varying clinical presentations and therapeutic options that exist as well as the lack of Level I and II evidence for treatment.

Indications for radiotherapy

The NCCN guidelines are the most specific and recommend radiotherapy for bone pain, imminent pathological fracture, brain metastases and node disease such as axillary or supraclavicular fossa disease.

When determining the indications for radiotherapy for this section of the radiotherapy utilisation tree, it was decided that emphasis would be placed on the more common sites of metastasis in which radiotherapy is considered appropriate. For instance, palliative radiotherapy for the management of brain, nodal disease and bone metastases is well established (10) (11) (12) (13) (14) (15) (4) and these clinical conditions are not uncommon.

It is recognised that palliative radiotherapy is considered appropriate in many other clinical settings including symptomatic subcutaneous, pulmonary, or hepatic metastases. However, the incidence of these conditions is low (and therefore would have little effect on the estimate of optimal radiotherapy utilisation) and hence these indications have not been included in the radiotherapy utilisation tree.

The data on the incidence of the various manifestations of unknown primary was obtained almost exclusively from medical oncology department series. Many of these series were very small as they reported on a single institution experience over a limited timeframe with a particular chemotherapy regimen. Therefore, we limited the data that we used to series with > 70 patients.

The fact that data comes from medical oncology departments could potentially lead to reporting biases; however this could not be factored into calculations, as the degree of bias was unknown. For instance, patients treated in a medical oncology practice may not represent the population of unknown primary patients. They are likely to be younger and fitter on average as they were considered for chemotherapy. They may also be more likely to have a longer prognosis than all patients with unknown primary. In addition, the reported series do not report follow up of all patients until death. In fact, the majority of reports report on the manifestations of unknown primary when the patients were first seen. This means that with time, more patients may go on to develop a manifestation that warrants radiotherapy (such as a brain metastasis). However, insufficient data were available to assess this effect. It is likely that our approach may under-estimate the role of radiotherapy for unknown primary.

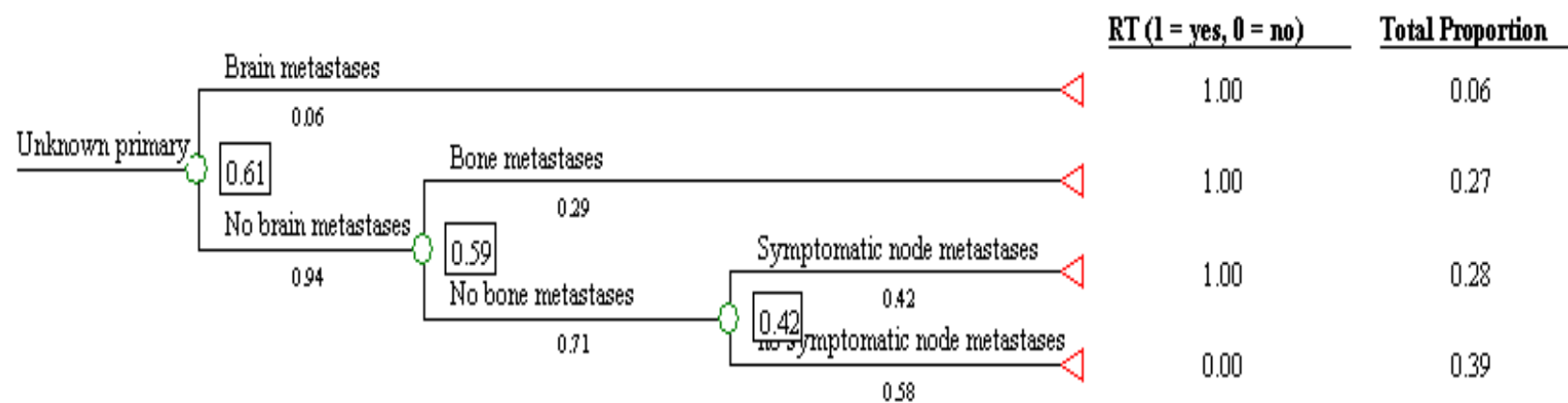
Five published series comprising > 70 patients each were identified. These studies were used to provide data on the incidence of brain, bone and nodal metastases and are summarised below in Table 3. One study from the M.D. Anderson institute by Abbruzzese et al. (16) was excluded because there was a larger study [Hess et al. (3)] from the same institution. The incidences of each metastatic manifestation were similar in all the series except for bone metastases. For the radiotherapy utilisation tree, the largest data series from Hess et al. (3) was used. An alternative approach would be to take the weighted mean of these 4 series in preference to just taking the largest series. Little difference occurs in either option as the weighted mean values were 6%, 27% and 41% for brain, bone and node metastases respectively which are very similar to the largest study. The data on bone metastases was quite varied and hence sensitivity analysis of the extreme values was performed to assess the impact of the uncertainty of data on the overall radiotherapy estimate. This is explained further in the section on sensitivity analysis.

Table 3: Incidence of unknown primary cancer by metastatic site.

Series (author)	No. of patients	% brain metastases	%bone metastases	% node metastases
M.D. Anderson Cancer Centre (Hess et al.) (3)	1000	6	29	42
Netherlands Cancer Institute (Zuur et al.) (4)	270	7	13	35
Montpellier Cancer Center, France (Culine et al.) (5)	150	5	45	45
Vanderbilt University Cancer Center (Greco and Hainsworth) (6)	71	7	20	32

Optimal radiotherapy utilisation rate and sensitivity analysis

The estimated rate of optimal radiotherapy utilisation is 61%. As unknown primary cancer represents 4% of registered cancers, the population of unknown primary cancers that warrant consideration of radiotherapy constitutes 2.4% of all cancers. One area where the data showed variation was in the proportion of patients with unknown primary and bone metastases, which varied between 13% and 45%. Sensitivity analysis allows the assessment of the impact that altering the value of the variables would have on the overall end result. This is advantageous when the data used are uncertain. Sensitivity analysis was performed to estimate the effect of the variable bone metastasis data on the overall radiotherapy utilisation rate, which can vary from 53% to 70% due to the uncertainty in the estimate of bone metastases. As unknown primary cancer represents 4% of all cancer, this represents a range for the entire cancer population of between 2.1% and 3.5%.



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Miscellaneous Cancers

Miscellaneous Other Cancers

This project involved determining estimates for radiotherapy utilisation for all cancer. All cancers with an incidence of $> 1\%$ were depicted in the trees. A further group comprise the remaining cancers that have an incidence of $<1\%$. These have been called “other cancers” in the radiotherapy utilisation tree and comprise 2% of the entire cancer population according to the Australian Institute of Health and Welfare report (1). These cancers include paediatric cancers, sarcomas of soft tissue and bone, cancers of the mediastinum, orbit, peritoneum, retroperitoneum, penis, and pleura as well as other rare malignancies. Some of these malignancies are commonly treated with radiotherapy (such as soft tissue sarcomas) and others are rarely treated with radiation (eg. peritoneal tumours).

The method of estimating the impact of the requirement for radiotherapy of these other cancers on the overall estimate of radiotherapy utilisation was to estimate that the requirement for radiotherapy was 50% and then perform sensitivity analysis where the use of radiotherapy for other cancers ranges between 0 and 100%. Review of the chapter on sensitivity analysis will indicate the impact of this uncertainty on the final estimate.

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Results and Sensitivity Analyses

In the radiotherapy utilisation tree, a total of 415 branches were constructed for all the cancers that represented 1% or greater of the entire registrable-cancer population. The branches that ended with the recommendation for radiotherapy numbered 250 and a further 165 branches ended with no radiotherapy being recommended.

In terms of peer review, drafts of each of the chapters were sent to the designated expert reviewers. This comprised 15 National Cancer Control Initiative steering committee members and 91 expert reviewers. Reviewers who were specialised in one or two particular tumour sites were sent only the relevant chapters. General radiation oncology, medical oncology, surgery, palliative care and nursing reviewers were sent all chapters to comment on. Some reviewers who felt that they were not sufficiently expert enough in a particular area often indicated that they had passed the responsibility on to an expert within their department or specialty. Forty-two of the reviewers provided comments, with 43% of reviewers being from a non-radiation oncology specialty. Many reviewers provided comments for more than 1 chapter. We collated 271 specific comments related to the review. This resulted in 139 changes to the text, trees, epidemiological data or evidence cited including a number of offers of additional epidemiological data. The review also resulted in 2 major reconstructions of the radiotherapy utilisation trees for 2 tumour sites.

It was calculated that, based on the best available evidence, 52.3 % of all cancer patients should ideally receive radiotherapy at least once during the course of their illness. The radiotherapy branches that represented the greatest proportion of cancer patients receiving radiation were early breast cancer treated by breast conserving surgery and post-operative radiotherapy (8% of all cancer diagnoses), pre- or post-operative radiotherapy for T3-4 or N2-3 rectal cancer (1%), early prostate cancer (2%) and metastatic prostate cancer (2%). In addition, there were many branches that ended in radiotherapy being recommended for symptom control for Non Small Cell Lung Cancer (3-6%).

Table 1 summarises the results for each of the cancers studied and represents the cohort receiving radiotherapy as a proportion of all cancer patients. These data are based on the estimates most likely to be closest to the real value for each of the variables within the tree. As the table shows, the overall proportion of patients who would receive radiotherapy in an optimal situation based upon the evidence available is 52.3% (see Table 1).

The optimal radiotherapy utilisation rates in Table 1 vary from a low rate of 0% for liver cancer patients to a high of 92% of Central Nervous System tumour patients recommended to have radiotherapy during the course of their illness. Table 1: The overall optimal radiotherapy utilisation rate by cancer type.

Tumour type	Proportion of all cancers	Proportion receiving XRT	Sensitivity Analysis	Proportion of all cancer receiving radiotherapy
Breast	0.13	83	82.95 - 85.25	10.8
Lung	0.10	76	73 - 76	7.6
Melanoma	0.11	23	17 - 29	2.5
Prostate	0.12	60	55 - 67	7.2
Gynae	0.05	35	32 - 39	1.8
Colon	0.09	14	4 - 23	1.3
Rectum	0.05	61	NA*	3.1
Head and Neck	0.04	78	74 - 84	3.1
Gall Bladder	0.01	13	1 - 21	0.1
Liver	0.01	0	0	0.0
Oesophageal	0.01	80	73 - 81	0.8
Stomach	0.02	68	58 - 68	1.4
Pancreas	0.02	57	50 - 57	1.1
Lymphoma	0.04	65	65 - 66	2.6
Leukaemia	0.03	4	4 - 4.6	0.1
Myeloma	0.01	38	NA*	0.4
CNS	0.02	92	91.6 - 92.8	1.8
Renal	0.03	28	25 - 35	0.8
Bladder	0.03	58	44.5 - 58.3	1.7
Testis	0.01	49	49.3 - 49.5	0.5
Thyroid	0.01	10	NA*	0.1
Unknown Primary	0.04	61	53 - 70	2.4
Other	0.02	50	0 - 100	1.0
Total	1.00			52.3

NA* - Sensitivity Analysis was not conducted since there was no significant variation in the data.

Data Uncertainty

As indicated in many of the chapters on specific tumour sites, there were variables for which there was significant uncertainty. These uncertainties can be categorized as:

1. Uncertainty in the data (i.e. where data from multiple sources were obtained and there were large differences in the prevalence estimates). Typically these were near the terminal ends of the trees where large studies on prevalence rates were lacking,

2. Uncertainty in the indication for radiotherapy (i.e. there are guidelines that indicate a range of criteria for consideration of radiotherapy. For example, the guidelines reviewed for breast cancer recommended radiotherapy for post-mastectomy patients with > 3 axillary nodes involved, but also “to consider” radiotherapy for patients with any nodal involvement.),
3. Uncertainty in the choice of radiotherapy between treatment options of approximately equal efficacy such as surgery, observation or radiotherapy for localised prostate cancer.

The uncertain variables are listed under each of the three types of uncertainty along with the range of values applied in the sensitivity analyses.

Uncertainty 1: Variations in prevalence rates across different datasets.

- Proportion of unknown primary cancer with bone metastases 0.13-0.45
- Proportion of stomach cancer M0 at diagnosis 0.71-0.83
- Proportion of M0 stomach cancer who have T1N0 disease 0.06-0.20
- Proportion of M0 oesophageal cancer that are considered operable 0.42-0.59
- Proportion of “operable” oesophageal cancer that actually undergo complete resection 0.79-0.91
- Proportion of M0 oesophagus cancer that develop distant metastatic disease 0.18-0.30
- Proportion of M1 oesophageal cancer with bone metastases 0.16-0.33
- Proportion of melanoma patients with brain or bone or nodal metastases 0.21-0.51
- Proportion of kidney cancer that undergo nephrectomy and then develop distant metastases 0.23-0.58
- Proportion of M1 kidney cancer with brain metastases 0.07-0.19
- Proportion of M1 bladder cancer with bone metastases 0.18-0.43
- Proportion of M1 bladder cancer with brain metastases 0.01-0.12
- Proportion of stage IIIB-IV non small cell lung cancer with local symptoms where radiotherapy is warranted 0.56-0.71
- Proportion of post-operative non small cell lung cancer Stage III with local recurrence 0.24-0.44
- Proportion of post-operative non small cell lung cancer Stage III with distant recurrence 0.32-0.59
- Proportion of operable non small cell lung cancer with positive surgical margins 0.005-0.02
- Proportion of small cell lung cancer extensive stage with local relapse following chemotherapy 0.43-0.61
- Proportion of extensive stage small cell lung cancer with brain metastases 0.27-0.49
- Proportion of prostate cancer treated by observation only who subsequently develop local recurrence 0.07-0.24
- Proportion of localised prostate post-operative who develop distant metastases 0.04-0.15
- Proportion of low-grade non Hodgkin’s lymphoma stage I-II 0.33-0.49

- Proportion of low grade MALT lymphoma, CR to Helicobacter Pylori eradication 0.56-0.89
- Proportion of Hodgkin's disease stage II-IV < 60 years old 0.63-0.80
- Proportion of Acute Lymphoblastic Leukaemia patients < 15 years who undergo a complete response 0.12-0.37.
- Proportion of pilocytic astrocytoma undergoing local excision 0.69-0.82
- Proportion of M0 operable gall bladder cancer 0.43-0.97
- Proportion of M1 breast cancer patients with bone metastases 0.42-0.71
- Proportion of breast cancer patients with bone metastases and pain 0.80-0.95
- Proportion of papillary thyroid cancer with persistent local recurrence warranting radiotherapy 0.03-0.15
- Proportion of papillary thyroid cancer with distant recurrence 0.04-0.11
- Proportion of M1 papillary thyroid cancer with bone metastases 0.19-0.30.

Uncertainty 2: Variations in the recommendation for radiotherapy based on treatment guideline uncertainty

- Whether adjuvant radiotherapy recommended for T4 colon cancer = 0.25 (0-0.25)
- When melanoma patients have sufficient nodal involvement to warrant adjuvant radiotherapy 0.26 (0.26-0.55)
- Whether prostate stage T1N0M0 with positive margins should receive radiation 0.22 (0-0.22)
- Whether prostate stage T2N0M0 with positive margins should receive radiation 0.35 (0-0.35)
- The proportion of post-mastectomy breast cancer patients with sufficient axillary nodal disease to recommend radiotherapy 0.18 (0.18-0.34)
- Whether M1 colon cancer that is unresectable should receive radiation 0 (0-0.11)
- The size criteria to estimate the proportion of lip cancers that are small enough to be operable with good cosmesis in preference to radiotherapy 0.75 (0.75-0.94)
- Whether adjuvant radiotherapy is recommended for all pancreatic cancer 0 (0-1.0)
- Whether local recurrence after nephrectomy should receive radiotherapy 0.04 (0-0.04)
- Whether a proportion of patients with supraglottic cancer can undergo conservative surgery in preference to radiation 0 (0-0.16)
- Whether palliative radiotherapy for a symptomatic primary renal cancer (in the presence of M1 disease) is warranted 0 (0-0.2)
- Whether consolidation radiotherapy is recommended after complete response to chemotherapy for bulky stage III-IV low grade non Hodgkin's lymphoma 0.65 (0.65-1.0)

- Whether radiotherapy is omitted from young patients with low grade gliomas when the tumour has been completely resected 0.5 (0-0.5)
- Whether radiotherapy is used for seminoma stage IIc-III with residual disease post chemotherapy 0 (0-0.15)
- Whether radiotherapy is used for seminoma stage II with residual disease post-chemotherapy 0 (0-0.07)
- Whether radiotherapy is used for stage IV seminoma with residual disease post-chemotherapy 0 (0- 0.32)
- The criteria to be used for head and neck with unknown primary depending on the extent of nodal involvement 0.22 (0.09-0.22)

Uncertainty 3: Where radiotherapy may be considered but other efficacious treatment could also be available and therefore variations in practice have been modelled.

- What proportion of prostate cancer T1N0M0 undergo surgery in preference to radiotherapy 0.55 (0.1-0.7)
- What proportion of prostate cancer T2N0M0 undergo surgery in preference to radiotherapy 0.52 (0.1-0.7)
- Proportion of early stage bladder cancer getting surgery 0 (0-0.47)
- Proportion of early stage oral cancer undergoing surgery 0.9 (0-0.9)
- Proportion of patients with endometrial cancer undergoing node dissection [based upon expert opinion] 0.5 (0.1-0.9)
- Proportion of lung cancer patients with pain warranting radiotherapy over other modalities of treatment 0.8 (0-0.8)
- Proportion of “other cancers” that were not specifically studied in the tree because they represented <1% of all registered cancer was estimated as 0.5 needing radiotherapy (assumed range 0-1.0)

Sensitivity analysis allows an assessment of the effect that the data uncertainty may have on the overall radiotherapy utilisation estimate. Two different types of sensitivity analyses were performed. The methodology, differences between the analyses and the results are described below. TreeAge Software version 3.5 was used in the construction of the tree and in the sensitivity analyses described here.

Sensitivity Analyses

(i) Tornado analysis (one-way sensitivity analysis).

One-way sensitivity analysis allows an assessment or estimate to be made of the impact of varying the value of one of the branches of the tree on the overall radiotherapy utilisation estimate. This was done by setting upper and lower data limits and modelling the radiotherapy utilisation tree using these extreme values. One-way sensitivity analyses were described in each of the tumour-specific chapters and have been aggregated here as a tornado diagram.

A tornado diagram is a set of one-way sensitivity analyses brought together in a single graph. Further details on the description and interpretations of tornado diagrams can be found in the section on materials and methods. The tornado diagrams for each of the individual tumour sites can be found in the relevant chapters. The full tornado diagram is shown below.

Each bar represents a single one-way sensitivity analysis and the legend provides details of each of the analyses depicted. The variables are ranked on their effect on the overall radiotherapy utilisation estimate with the variables that have most impact appearing at the top of the graph and those with smaller impact appearing below. The tornado analysis shows that the 52.2% estimate could vary between 51.6% and 53.1%, depending upon the data used in the calculation. The model is seen to be robust as the overall impact that any one of these uncertainties have on the radiotherapy utilisation rate is relatively minor.

(ii) Monte Carlo analysis

The main limitation of the tornado analysis is that this form of analysis only assesses the impact of one factor at a time. However, Monte Carlo simulations can be done in order to assess the impact that these data uncertainties have on the overall radiotherapy utilisation rate in a multivariate fashion. Monte Carlo simulations are based upon the random sampling of variables from discrete and continuous distributions using individual trial data. Observing the statistical properties of many trials using random sampled values allows additional insight into the performance of a model. The main weakness of the Monte Carlo analysis in this study is that the relative importance of all of the data used are weighted by study size and may not necessarily be ranked by study quality.

For the various different types of data uncertainties described above, assumptions were made on the distribution of data as described below. For data uncertainties where various different trial data sets were used (Type 1 data uncertainty above), the available trial data were used to calculate beta-distributions using FastPro version 1.8. For most conventional Bayesian calculations of differing datasets, it is usually assumed that these data follow a beta distribution (1).

For this Monte Carlo analysis, beta distributions were calculated for each of the uncertain data parameters. These distribution calculations were based upon the sample size and the proportion data quoted in the original paper. For variations in the radiotherapy treatment indication (Type 2 above), the guideline uncertainty could not be modelled for Monte Carlo analysis and therefore the preferred practice as recommended by the guidelines was used in the Monte Carlo analysis. For situations where there was uncertainty in the use of radiotherapy compared to equally efficacious treatment or where the reasonable use of radiotherapy would fluctuate between two extremes based upon subjective criteria (Type 3 above), an estimate based upon current practice was used for the optimal radiotherapy utilisation estimate. To obtain upper and lower bounds we made estimates on the absolute extremes,

beyond which it was thought to be unreasonable for the true value to lie, according to expert opinion. These bounds were used in the tornado sensitivity analysis. For the Monte Carlo simulations these data were modelled assuming a triangular distribution of values which assumes that the estimate based upon current practice is the most likely value and as the values move further away from this value the less frequently they occur in the Monte Carlo simulations. For situations where a range could be estimated but no patterns of practice data existed to assist with an “optimal” figure, then a flat distribution was assumed whereby any value within the range would be equally likely to be used in the Monte Carlo simulations.

The Monte Carlo analysis performed in this study involved 10 000 simulations. The result was an optimal radiotherapy utilization rate of 52.3% (95% confidence limits: 51.7%; 53.1%). The tightness of the confidence intervals demonstrates that the overall figure is robust. This final estimate is remarkably precise despite uncertainty existing in relation to data (i.e. where data from multiple sources differed in their prevalence estimates), uncertainty in some indications for radiotherapy and occasional uncertainty between treatment options of approximately equal efficacy (such as radiotherapy, surgery or watchful waiting for early prostate cancer). These tight confidence intervals can be explained by the fact that good quality data existed for the initial branches of the tree (eg. data such as stage data which is collected by most cancer registries). Most of the uncertainty existed in the distal or near-terminal branches of the tree and hence affected very small proportions of the cancer population, thus having very little effect on the overall figure. In addition, the effect of these variations was such that some would increase the overall utilisation rate while others would reduce it, so that to a large extent they would cancel each other.

Limitations of this study

Some limitations of the study have been identified and are discussed below:

(a) Quality of data

This study has identified the areas where good quality epidemiological data (based on stage, performance status etc.) are lacking, and we recommend that some of these deficiencies be improved by collecting further data. In the meantime, we have overcome the problem by performing modelling and sensitivity analysis to indicate the relatively minor impact that any of these data uncertainties might have on the overall utilisation rate. However, this does not alter the recommendation that better epidemiological data be available in future.

(b) Skin cancer and benign diseases provide workload for radiation oncology departments but are not included as registered cancers and therefore have not been factored into the model

This study was intended as a benchmark for planning of external beam radiotherapy based upon cancers reported by statutory Cancer Registries, as this is the benchmark against which most radiotherapy

resources are planned. Cancer Registries do not report non-melanomatous skin cancers or benign tumours. To include non-registered cancers would inflate the numerator of the utilisation rate.

The Australian Institute of Health and Welfare (AIHW) estimates that approximately 270 000 new cases of non-melanocytic skin cancers are diagnosed every year (2). Radiotherapy has been identified as an effective treatment for skin cancers and represents a large caseload in some departments. In addition, metastatic involvement of neck lymph nodes by skin cancers in the head and neck is an indication for radiotherapy. The proportion of patients with non-melanomatous skin cancer in the community who, in an ideal, evidence-based world should see a radiation oncologist for treatment is not known. Reports of actual numbers of new cases of skin cancer treated in radiotherapy departments suggest that this indication accounts for 4 to 7 percent of the new cases treated by megavoltage radiation (3-5).

In addition, a moderate workload in any radiation oncology department relates to the treatment of benign diseases such as keloid, pterygia, heterotopic ossification and exophthalmos secondary to Grave's disease, just to name a few. In addition, there are a large number of benign tumours that are treated with radiotherapy either definitively or in the adjuvant setting. These benign tumours include pituitary adenomas, pleomorphic adenomas of the parotid gland, meningiomas, craniopharyngiomas and desmoid tumours. These also should be considered when planning radiotherapy resources.

For both benign disease and advanced non-melanomatous skin cancers, treatment techniques are often complex and this significantly adds to the radiotherapy resources required to provide quality care for all patients. The only data that could be obtained on the significance of this workload come from productivity statistics from The Alfred Hospital, Melbourne and the Queensland Radium Institute, Brisbane (3-5). Their data showed that non-registered conditions such as benign disease and non-melanomatous skin cancer comprised 12% of their overall workload, underlining the importance of factoring this into the radiotherapy planning process.

It is important that this issue is resolved by future research into the optimal rate of utilisation of radiotherapy for skin cancer and benign disease. Non-melanomatous skin cancer (and benign conditions treated by radiotherapy) are not included in the statistics of registered cancers collected by cancer registries; however most radiation oncology departments will count radiotherapeutic treatment of skin cancers in their workload statistics. This is likely to falsely inflate the actual radiotherapy rate for registered cancers, which further confuses the correct rate for planning of resources.

We describe how the information (on utilisation of radiotherapy for purposes other than the treatment of registered cancers) might be used in conjunction with the results from this report to assist in determining an appropriate radiotherapy workload in Chapter 20.

(c) Other forms of radiotherapy have not been considered

Inclusion of other forms of radiotherapy such as brachytherapy (interstitial and intracavitary) and/or with radio-isotopes (iodine, yttrium, samarium, strontium etc.) are beyond the scope of this project. However these other forms of radiotherapy should be considered when planning radiotherapy resources and could be the subject of a further study.

(d) Controversies in the recommended use of radiotherapy

Despite using treatment guidelines to determine indications for radiotherapy, there are many areas where the role of radiotherapy remains poorly defined or where the indications for the use of radiotherapy remain vague. This is mainly due to poor evidence and the lack of good quality trials. We have identified some areas where future research would be useful. The best way to deal with this problem is with the modelling used in the sensitivity analysis. Although it is only as good as the available evidence, the sensitivity analysis does indicate that most of these uncertainties, even if resolved, would have only a minor effect on the optimal radiotherapy utilisation rate.

(e) Patient choice considerations

The available data on patient choice between two equally effective treatment modalities is limited. It was our original intent to include the impact of patient choice on the overall radiotherapy utilisation estimate, particularly as patient choice has a significant role to play. However, the estimate for this study was based upon an ideal situation with no resource constraints. Very few patient-choice studies provided information about whether resource constraints and displacement from home for patients were discussed in the clinical scenario given to the patient. It has been shown that the mastectomy rates for breast cancer among women living in country areas are higher than the mastectomy rates for urban women (6). This difference can be attributed to a relative lack of access to radiotherapy in country areas, leading women to choose mastectomy over radiotherapy and breast-conserving surgery. In addition, some of the studies do not discuss the content of discussions with patients or how information was presented to patients. In situations where descriptions of content and mode of discussion were discussed, the studies were usually hypothetical in that either the subjects were not actually cancer patients or their treatment had already been determined and they were asked to consider a

hypothetical situation. It was thought that due to these limitations, patient choice would be flagged as a need for future research but would not be incorporated into the tree.

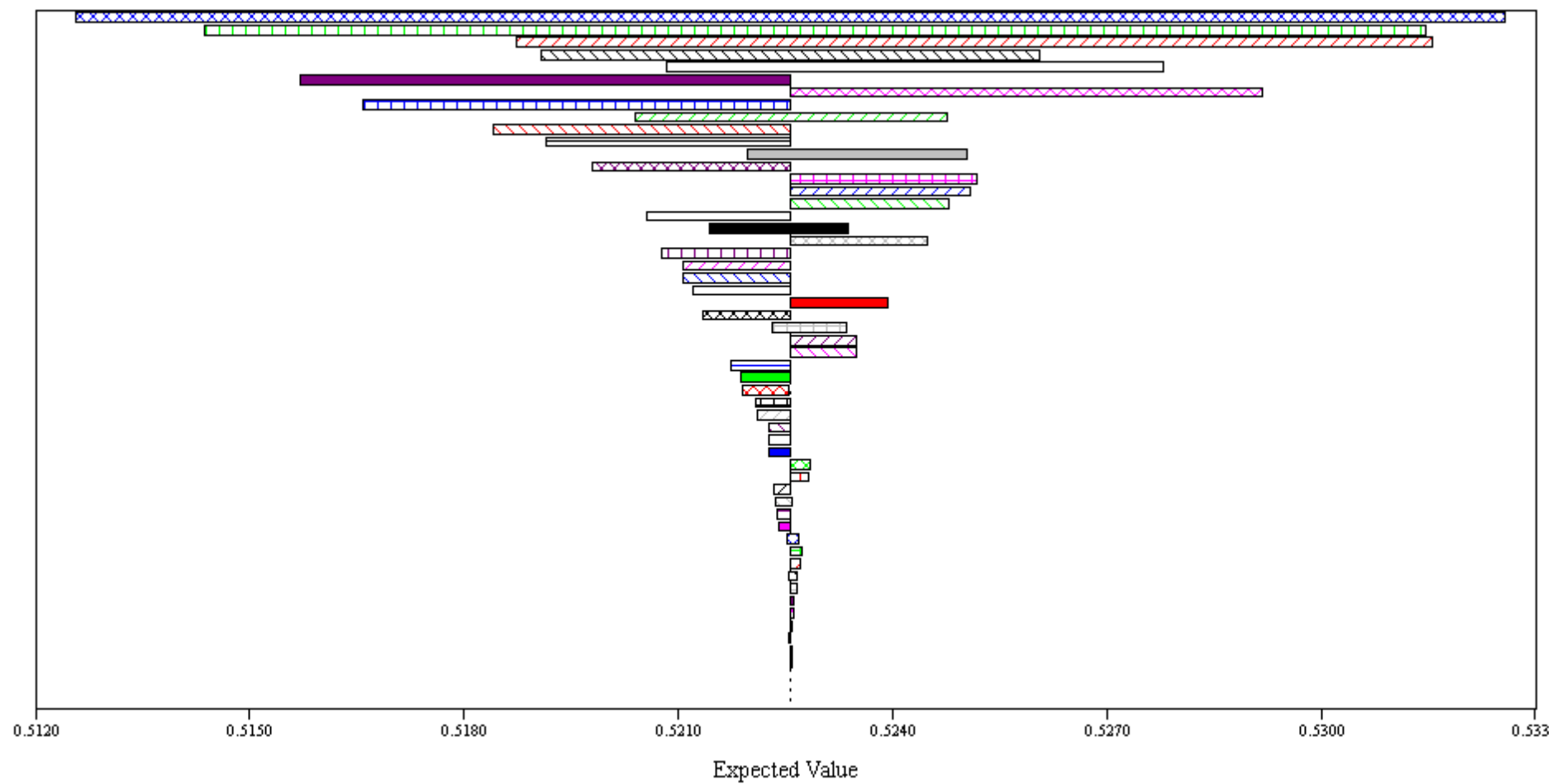
(f) Rare indications for radiotherapy have not been included in the overall estimate

The methodology of this study involved studying indications for radiotherapy that would impact upon the overall radiotherapy utilisation rate. However, data for some indications for radiotherapy were lacking and likely to be exceedingly small. For instance, for patients with metastatic disease, we have included only the more common examples of metastatic disease where radiotherapy might be recommended (e.g. brain and bone metastases). However, in many cancers there will be a small proportion of patients who might receive appropriate radiotherapy for metastases at less common sites such as lung, liver, subcutaneous tissue etc. Although only of small overall impact in their own right, the cumulative total of these indications might increase the overall radiotherapy utilisation estimate by 1-2%. Sufficient epidemiological data on the incidence of these metastatic manifestations do not exist to calculate a more accurate figure.

Summary of results

The overall estimate for radiotherapy utilisation is 52.2% based upon the best quality data and may vary between 51.6% and 53.1% based upon univariate analysis of variables where data values are uncertain. Monte Carlo analysis, which allows multivariate assessment of data uncertainty, indicates that the overall radiotherapy utilisation estimate is 52.3%. Monte Carlo analysis demonstrates that, even if there is data uncertainty, our estimate and the overall model is robust. Although the scope of this study is confined to exploring the optimal utilisation of radiotherapy (limited to external beam megavoltage radiotherapy) for registered cancers only, the overall estimate provides a useful tool for assisting in the planning of adequate radiotherapy resources.

Tornado Diagram at
Cancer



- ☒ Proportion of other cancers receiving radiotherapy: 0.0 to 1.0
- ☒ proportion of T4 colon cancers to receive RT: 0.0 to 0.25
- ☒ proportion of prostate Stage T2N0M0 receiving surgery: 0.1 to 0.7
- ☒ Proportion of melanoma with sufficient node involvement for XRT: 0.26 to 0.55
- ☒ Proportion of unknown primary with bone metastases: 0.13 to 0.45
- ☒ proportion of prostate cancer stage T1N0M0 receiving surgery: 0.1 to 0.7
- ☒ Proportion of Stage T2N0M0 with positive margins: 0.0 to 0.35
- ☒ proportion of endometrial cancer patients undergoing node dissection: 0.1 to 0.9
- ☒ Proportion of patients getting surgery for Stage II-III bladder cancer: 0.0 to 0.47
- ☒ Proportion of stomach cancer M0 at diagnosis: 0.62 to 0.83
- ☒ proportion of melanoma patients with brain/bone/nodal mets: 0.21 to 0.51
- ☒ Proportion of kidney cancer that develop distant metastases: 0.23 to 0.58
- ☒ proportion of NSCLC IIIB IV local symptoms: 0.56 to 0.71
- ☒ proportion for post mastectomy XRT N1-3 modelled: 0.18 to 0.34
- ☒ Proportion of Stage I-II oral cavity undergoing surgery: 0.0 to 0.9
- ☒ Proportion of observed early prostate who relapse: 0.07 to 0.24
- ☒ Proportion of gastric M0 patients with T1N0 disease: 0.06 to 0.20
- ☒ Proportion of non-metastatic operable gall bladder cancer: 0.43 to 0.96
- ☒ Proportion of M1 colon unresectable: 0.0 to 0.11
- ☒ Proportion of Stage T1N0M0 prostate with positive margins: 0. to 0.22
- ☒ Proportion of post-op prostate with distant metastases: 0.04 to 0.15
- ☒ proportion of patients with "operable" lip cancer: 0.75 to 0.94
- ☒ proportion of adjuvant radiotherapy for pancreatic cancer: 0 to 1.0
- ☒ Proportion of patients with bone metastases from breast cancer: 0.42 to 0.71
- ☒ Proportion of NSCLC with bone mets & pain: 0.0 to 0.80
- ☒ Proportion of M1 renal cancer patients with brain metastases: 0.07 to 0.19
- ☒ Proportion of papillary thyroid with local recurrence: 0.03 to 0.15
- ☒ Proportion of renal M1 with symptomatic primary where radiotherapy recommended: 0.0 to 0.20
- ☒ Proportion of stage IV bladder cancer with bone metastases: 0.18 to 0.43
- ☒ Proportion of patients that have local recurrence after nephrectomy: 0.0 to 0.04
- ☒ Proportion of M0 oesophagus considered operable: 0.42 to 0.59
- ☒ Proportion of SCLC post-chemo local relapse: 0.43 to 0.61
- ☒ Proportion of SCLC with brain metastases: 0.27 to 0.49
- ☒ Proportion of NSCLC IIIA post-op local recurrence: 0.24 to 0.44
- ☒ Proportion of bone metastases that are painful: 0.80 to 0.95
- ☒ Proportion of supraglottic larynx cancer suitable for preservation surgery: 0.0 to 0.16
- ☒ p_NHL_low_grade_CR: 0.38 to 0.66
- ☒ Proportion of oligo/low grade glioma observed due to younger age: 0 to 0.5
- ☒ Proportion of stage IV bladder cancer with brain metastases: 0.01 to 0.12
- ☒ proportion of oesophageal cancer resectable at operation: 0.79 to 0.91
- ☒ Proportion of NSCLC with positive margins : 0.005 to 0.02
- ☒ Proportion of M1 oesophagus cancer with bone metastases: 0.16 to 0.33
- ☒ children with ALL who relapse: 0.12 to 0.37
- ☒ response to Helicobacter eradication: 0.56 to 0.81
- ☒ Proportion of papillary thyroid cancer with distant recurrence: 0.04 to 0.11
- ☒ Proportion NSCLC IIIA distant relapse : 0.32 to 0.59
- ☒ Proportion of oesophagus cancer that develop distant mets: 0.18 to 0.30
- ☒ Proportion of H + N unknown primary with nodal disease not warranting routine radiotherapy: 0.09 to 0.22
- ☒ Proportion of pilocytic astrocytoma with complete excision: 0.69 to 0.82
- ☒ Proportion of M1 papillary thyroid with bone mets: 0.19 to 0.30
- ☒ Proportion of Hodgkin's II-IV < 60 years: 0.63 to 0.80
- ☒ Proportion of stage IIc-III seminoma with residual disease: 0.0 to 0.15
- ☒ Proportion of bulky stage II with residual disease: 0.0 to 0.07
- ☒ Proportion of Stage IV seminoma with residual disease: 0.0 to 0.32
- ☒ p_NHL_intermed_stIII_IV_CR: 0.44 to 0.61
- ☒ Ext, stage SCLC with local symptoms: 0.43 to 0.61

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Potential Uses

Potential Uses for the Optimal Radiotherapy Utilisation Estimate and the Treatment Model

The model of radiotherapy utilisation developed in this project has many current and future benefits. In addition, this study has highlighted a number of controversies within cancer management. The following discussion outlines some of the possible future uses of this study.

To plan radiotherapy services on a population basis

The main reason for calculating an evidence-based assessment of radiotherapy utilisation is because it is invaluable for radiotherapy resource planning. Australian Commonwealth and State agencies have previously assumed that 50 % of all cancer patients will require radiotherapy at some stage (1-5). However, critics have suggested that the figure of 50% is not evidence-based and is perhaps biased. This study recommends an optimal 52% treatment rate figure using an evidence-based approach. An evidence-based estimate will allow more accurate planning of future radiotherapy services. A readily adaptable model of the type described in this paper will allow easy re-calculation should cancer incidence or treatment recommendations change in the future. The model can also be adapted for use in other populations that have differing distributions of cancers and stages at diagnosis such as in countries like India where cervical cancer is much more common than in Australia.

However, the evidence-based radiotherapy utilisation estimate needs to be used in context with other indications of radiotherapy not considered by the model when planning radiotherapy. The model uses cancer incidence data on registrable cancers from the cancer registry to estimate demand. This does not account for patients with conditions that are treated by megavoltage radiotherapy but are not registered in the statutory notification of cancer incidence. In particular benign brain tumours and metastatic and complex non-melanomatous skin cancers may add appreciably to the demand for radiotherapy. There are currently no evidence-based estimates of the utilisation of radiotherapy for non-registered cases. We examined actual radiotherapy activity rates for non-registered cases as the next best solution. The William Buckland Cancer Centre, Victoria reported on the case mix and outcomes of 9838 patients treated at the centre between 1992 and 2002 (Table 1). The treatment of skin cancers, heterotopic bone, benign neoplasms and other non-malignant conditions accounted for 12% of radiotherapy activity. A similar analysis of 16530 patients treated at the Queensland Radium Institute between 1992 and 1997 showed that the proportion of conditions treated by radiotherapy but not registered with the Cancer Registry was 11%. Some skin cancers may be treated by Kilovoltage equipment but in many centres electrons produced by linear accelerators is the only modality available to treat skin cancers. Prospective, longitudinal studies of appropriate, evidence-based use of radiotherapy are recommended to get a more accurate assessment.

Table 1: Workload at the William Buckland Centre and at the Queensland Radium Institute according to registered and non registered conditions.

William Buckland Radiotherapy Centre, The Alfred Hospital	Year of treatment	92 - 98	98-99	99-00	00-01	01-02	All years
	Malignant excluding skin	4762	1010	959	1169	1243.00	9143
Cases treated by radiotherapy that would not be registered by a cancer registry	Skin (malignant)	388	77	79	70	81	695
	Benign neoplasms	118	27	33	37	42.00	257
	Uncertain neoplasms	7	3	9	5	8.00	32
	Heterotopic bone	49	12	10	9	2.00	82
	Other	53	19	10	17	24	123
	Total non-registered	615	138	141	138	157	1189
	% of all treatment	11%	12%	13%	11%	11%	12%
Queensland Radium Institute	Year of treatment	93	94	95	96	97	All years
	Malignant excluding skin	3261	3119	2906	2623	2871	14780
Cases treated by radiotherapy that would not be registered by a cancer registry	Skin (malignant)	238	211	172	137	113	871
	Benign neoplasms	60	65	69	82	102	378
	Uncertain neoplasms	16	16	17	23	16	88
	Other	52	73	90	101	97	413
	Total non-registered	366	365	348	343	328	1750
	% of all treatment	10%	10%	11%	12%	10%	11%

The accepted benchmark for linear accelerator throughput used for planning resources is 450 treatment courses per annum (1). The data in Table 1 imply that each linear accelerator could treat 396 courses for registered malignancies and 54 for non-registered conditions. Those 396 courses would consist of 297 courses for patients who had never received radiotherapy and 99 courses for patients who had been treated before (assuming a 25% retreatment rate (5) which has been commonly reported as a reasonable benchmark) (see Table 2).

Table 2: The distribution of treatment for a linear accelerator including treatment for non-registered conditions.

		Linac capacity for new cases of cancer per year
1. Number of new cancers treated by radiotherapy	52%	
2. Linear accelerator capacity (new courses per year)	450	450
3. Treated cases not registered by cancer registry	Less 12%	396
4. Retreated registered cases	Less 25%	297

In addition, the planning parameters that were used assume that the linear accelerators will be used at 100% capacity. They make no allowance for spare capacity to avoid long and increasing waiting lists (6). New equipment such as multileaf collimators and new techniques such as Intensity Modulated Radiotherapy have appreciably altered the capacity of linear accelerators to treat new cases.

(2) To determine shortfalls between optimal and actual rates of radiotherapy utilisation and providing a benchmark for service delivery.

The radiotherapy utilisation trees that have been developed for each of the tumour sites are a diagrammatic representation of optimal evidence-based cancer care from a radiotherapy perspective. Epidemiological data from patterns of care studies will allow comparisons to be made between the actual rates of radiotherapy delivery and the evidence-based ideal rate. Further details can be ascertained by analysing the distributions of tumour stage, histology, age, performance status and other factors, in order to better define areas of discrepancy between the actual and ideal utilisation rates. For example, the Collaboration for Cancer Outcomes Research and Evaluation (CCORE) have recently analysed differences between actual and optimal rates of utilisation for the common cancers (7;8).

(3) Modelling changes to a particular cancer incidence or changes in staging. Assessment of the impact of the changes on the overall recommended radiotherapy utilisation rate.

The TreeAge software used to construct the radiotherapy trees can be readily used to change the overall model should there be changes in the incidence of certain cancers, a change in the stage distribution or a change in therapy recommendations based on clinical trials. For example, if another country with a very different cancer incidence profile were to use the model then the only requirement to recalculate the optimal radiotherapy utilisation rate would be to alter the incidence of each of the cancers. Similarly, a change in stage distribution of cancer due to the development of superior staging investigations (such as the impact that Positron Emission Tomography has had on non-small cell lung cancer staging), or following the introduction of a screening programme could easily be incorporated into the model.

(4) Use of this study methodology to determine optimal rates and resources for other treatment modalities.

Throughout the course of this project, the methodology has been refined and improved upon. The radiotherapy utilisation tree model and methodology could be readily adapted to consider other treatments (such as surgery or chemotherapy) for cancer. It could also be used to plan other services if criteria were known for the use of a particular service. For instance, if we knew the factors that predict the need for palliative care referral or genetics review, then resource planning could be assisted, by calculating the optimal utilisation rate in a similar fashion to that described here for radiotherapy.

(5) Use of the model to identify areas of research that would have the greatest impact on radiotherapy service delivery.

This research has identified several potential future research projects in a number of different areas. A few of these general areas are discussed below:

- (a) Further utilisation tree constructions – as discussed above, this methodology has been validated and has been approved by external reviewers as an appropriate approach to the research question. Therefore applying similar utilisation tree methodology to services such as surgery, chemotherapy, palliative care or genetics would be feasible and useful. In addition, other non-oncological medical therapies could use similar methodology to assess the need for services and provide a guide for health planners. The methodology could also be used to study the proportions of patients who have benign diseases in whom radiotherapy would be considered appropriate.

- (b) Use of this radiotherapy tree to predict future changes in radiotherapy service delivery – There will be a constant need to examine changes (such as changes in incidence, presenting stage or new treatments) with respect to radiotherapy service delivery. For example, if PET staging leads to greater diagnosis of metastatic disease at presentation there will be a shift in the stage proportions of lung cancer. This will have an impact on the overall radiotherapy utilisation rate. This model will also allow population projections to be used to calculate future radiotherapy need.
- (c) Patterns of Care studies – Actual radiotherapy utilisation rates may be examined and compared with optimal utilisation rates to identify particular areas of shortfall that require increased services to improve patient care.
- (d) Epidemiological studies – The construction of the radiotherapy utilisation tree has identified a number of areas that have very poor data and highlighted the need for better data. The main data identified as being sub-optimal are areas of the tree that are near the terminal branches and those identified as having variable data in sensitivity analysis. More meaningful data, particularly longitudinal population-based data, would be valuable in the following areas: metastasis incidence with time and by stage and treatment for the more common cancers, the proportion of patients who develop metastases to organs other than bone and brain and the need for symptomatic control, patterns of metastatic spread with time and the proportion of patients who develop metastases of differing types, the proportion of patients who develop symptoms as an indication for palliative radiation treatment over time, performance status and how this changes with relapse and patient choice when two treatment modalities are considered similar in efficacy and are equally available.
- (e) Identification of controversial areas of practice where further clinical trials are needed – The tornado diagrams have shown the controversial areas that will have the most impact on the overall optimal radiotherapy utilisation rate. Therefore, the controversial clinical areas where clinical trials may make a substantial difference to the optimal radiotherapy utilisation rate can be identified. The main controversies identified in terms of their impact on the optimal radiotherapy utilisation rate are the role of radiotherapy (as opposed to observation or surgery) for localised prostate cancer and the role of radiotherapy for T4 colon cancer. Other areas of uncertainty which impact on the optimal utilisation rate are the following: the criteria for adjuvant radiotherapy for node-positive melanoma need to be better defined, the role of radiotherapy for positive margins post-prostatectomy is to be better determined, the role of lymph node

dissection for endometrial cancer and the role of surgery (versus radiotherapy) for localised bladder cancer also need further study. In addition, a large number of the radiotherapy treatment recommendations are based upon level IV evidence and it is strongly recommended that the levels of evidence should be improved through randomised control trials to better define the role for radiotherapy.

(f) Prediction of future radiotherapy workload

The trees that have been constructed allow an assessment of the overall proportion of cancer patients where a recommendation for radiotherapy would be likely throughout their illness course. However, the tree does not assess whether the treatment intent would be palliative or radical, does not predict the number of fractions of treatment that would be evidence-based, nor the complexity of the patients care. Various models of complexity have been reported in the literature that might be used in future studies so that even more accurate predictions of radiotherapy workload could be performed.

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Conclusions

Conclusions

This study has found that the proportion of all patients with registered cancers that should receive at least one course of megavoltage external beam radiotherapy during the course of their illness is 52.3%. One-way and Monte Carlo sensitivity analyses show this estimate to be robust, despite the limitations of some data. The 95% confidence limits using Monte Carlo analysis were 51.7% and 53.1%.

This estimated optimal utilisation rate will assist in planning for radiotherapy resource needs. The optimal radiotherapy utilisation rate can function as a valuable benchmark against which patterns of care data may be compared. The methodology allows easy adaptation of the model to allow for future changes in treatment recommendations and/or tumour stage distribution. The methodology also provides an excellent framework that can be used to determine optimal utilisation rates for other oncological and non-oncological services. Further assessment of the model against current practice is recommended.

Acknowledgements

Appendix 1: Acknowledgements

The investigators in this study would like to thank the following people for their input into the study.

Assistance in study design, report writing and/or chapter development

- A/Prof. Michael Frommer, Australian Health Policy Institute, for assistance with the study design and tender response.
- A/Prof. David Roder, Consultant Epidemiologist, Anti-Cancer Foundation of SA, for assistance in study design, data provision, tender response and statistical methodology advice.
- Dr. Carolyn Featherstone, Research Fellow in radiation oncology, Collaboration for Cancer Outcomes, Research and Evaluation, Liverpool Hospital, Sydney, for chapter development and report writing for the chapters on myeloma, leukaemia and lymphoma.
- A/Prof Bin Jalaludin, Deputy Director, School of Public Health, South Western Sydney Area Health Service, for study design, tender response, statistical methodology.
- Dr. Narcyz Ghinea , Research Officer (Mathematician), Dept. of Neurosurgery, Liverpool Hospital, Sydney for statistical methodology advice.
- Dr. James van Gelder, neurosurgeon and statistician, Liverpool Hospital, Sydney, for statistical methodology advice.

Provision of Epidemiological Data

- Prof David Speakman, colorectal surgeon, for epidemiological data on colorectal cancer
- Prof Allan Spigelman, Newcastle, for epidemiological data on colorectal cancer
- Prof William McCarthy, Director, Sydney Melanoma Unit, Royal Prince Alfred Hospital (retired), for epidemiological data on melanoma

- A/Prof. David Roder, Consultant Epidemiologist, Anti-Cancer Foundation of SA, for epidemiological data on melanoma, breast and lung cancer from the South Australian Hospital Based Cancer Registry.
- Dr Kwun Fong, Department of Thoracic Medicine, The Prince Charles Hospital, Brisbane, for epidemiological data on lung cancer
- Dr Michael Veness, radiation oncologist, Westmead Hospital, for data on the number of non melanomatous skin cancers treated at Westmead Hospital.
- Dr Chris Dalrymple, Gynaecologist, Royal Prince Alfred Hospital, Sydney, for epidemiological data on gynaecological stage.
- Dr Anne Kricker, National Breast Cancer Centre, NSW Cancer Council, for epidemiological data on Ductal Carcinoma in situ.
- Dr Richardson and Ms Vicky J Thursfield, Director and data manager, Victorian Cancer Registry, for epidemiological data on prostate cancer.
- Ms Angela Berthelsen, Data Manager, SWS Colorectal Cancer Tumour Group, for data on colorectal cancer
- Dr Claire Vajdic, Cancer Epidemiology Research Unit, NSW Cancer Council, for data on ocular melanoma
- Professor Allan Rodger, Director of William Buckland Cancer Centre, Melbourne for data on the radiotherapy workload for non-registered conditions at their centre.
- Professor Roger Allison, Director of Queensland Radium Institute, Royal Brisbane Hospital, Brisbane for data on the radiotherapy workload for non-registered conditions at their centre.

Project Steering Committee (convened by the National Cancer Control Initiative)

- Prof. Mark Elwood, Director NCCI (chair)
- Dr Paul Ireland, Deputy Director, NCCI (until December 2002)
- Dr Michael Ashby, Director of Palliative Care, Monash Medical Centre, Victoria

- Dr Stephen Begbie, Director of Medical Oncology, Port Macquarie Base Hospital, Port Macquarie, NSW
- Prof Gordon Clunie, Senior Medical Adviser, Anti-Cancer Council of Victoria, Melbourne
- Dr Paul Glare, Director of Palliative Care, Royal Prince Alfred Hospital, Sydney
- Dr Rosemary Knight, Director Cancer Control, Dept of Health and Aged Care, Canberra
- Ms Felicity Lehman, Consumer Representative (on the Steering Committee until December 2002)
- Prof Lester Peters, Radiation Oncologist, Peter MacCallum Cancer Institute, Victoria.
- Dr John Primrose, Senior Medical Advisor, Department of Health and Aging, Canberra
- Emeritus Professor Tom Reeve, Director, Australian Cancer Network, Sydney
- Professor Allan Rodger, Director and radiation oncologist, William Buckland Cancer Centre, Victoria (until May 2003)
- Dr Martin Stockler, Senior Lecturer, Sydney Cancer Centre, Royal Prince Alfred Hospital, Sydney
- Ms Elizabeth Tracey, Manager, Cancer Registers, NSW Cancer Council. Australian Association of Cancer Registers (AACR) representative on the steering committee.
- Professor Andrew Wilson, School of Population Health, University of Queensland

Court of Expert Reviewers

- Dr Stephen Ackland, Medical Oncologist, Newcastle Mater Misericordiae Hospital, Newcastle
- Dr Gordon Adler, Sydney Radiotherapy and Oncology Centre, Sydney
- Dr David Allen *, Department of Surgery, Peter MacCallum Cancer Institute, Melbourne

- Prof Roger Allison, Radiation Oncologist, Royal Brisbane Hospital, Brisbane
- Dr Chris Atkinson, Radiation Oncologist, Christchurch, New Zealand
- A/Professor David Ball *, Radiation oncologist, Peter MacCallum Cancer Institute, Melbourne
- Dr Sally B-Hay, Department of Medical Oncology, Royal North Shore Hospital, Sydney
- Dr Martin Berry *, Radiation Oncologist, Liverpool Hospital, Sydney
- Dr David Blakey *, Radiation Oncologist, Peter MacCallum Cancer Institute, Melbourne
- Dr Martin Borg *, Radiation oncologist, Royal Adelaide Hospital
- Dr Michael Boyer, Department of Medical Oncology, Royal Prince Alfred Hospital, Sydney
- Dr Fran Boyle *, Medical Oncologist, Royal North Shore Hospital, Sydney
- Prof Ken Bradstock *, Director of Haematology, Westmead Hospital, Sydney.
- Dr Brancatissano, Department of Surgery, Westmead Hospital, Sydney
- Dr Alison Brand *, Gynaecological Oncologist, Westmead Hospital, Sydney
- Dr Joe Bucci *, Department of Radiation Oncology, St George Hospital, Sydney
- Dr Colin Bull, Department of Radiation Oncology, Westmead Hospital Sydney
- A/Prof. B. Burmeister *, Radiation oncologist, Queensland Radium Institute, Brisbane.
- Ms Stacey Cail, Oncology Nurse, St George Hospital, Sydney
- Dr Robyn Cheuk, Radiation Oncologist, Royal Brisbane Hospital, Brisbane
- Dr John Childs, Radiation Oncologist, Sydney
- Dr. David Christie *, Radiation Oncologist, Wesley Hospital, Gold Coast

- Dr Katy Clark *, Palliative care physician, Royal Prince Alfred Hospital, Sydney
- Dr June Corry, Peter MacCallum Cancer Institute, Melbourne
- Dr Paul Cozzi, Urology Department, St George Hospital, Sydney
- A/Professor David Currow *, Department of Palliative Care, Daw Park Hospital, Adelaide
- Dr David Dalley *, Director, Department of Medical Oncology, St. Vincents Hospital, Sydney
- Dr Alison Davis *, Medical Oncologist, The Canberra Hospital
- Dr Margaret Davy, Department of Gynaecological Oncology, Royal Adelaide Hospital
- Prof Jim Denham, Department of Radiation Oncology, Newcastle Mater Misericordiae Hospital
- Prof. G. Duchesne *, Director of Radiation Oncology, Peter MacCallum Cancer Institute, Melbourne.
- Ms Heather Ferguson, Oncology Nurse, Peter MacCallum Cancer Institute, Melbourne
- Dr Allan Fowler *, radiation oncologist, Liverpool Hospital
- Dr Ian Franklin *, Radiation oncologist, Queensland Radium Institute, Brisbane.
- Dr Paul Glare, Department of Palliative Care, Royal Prince Alfred Hospital, Sydney
- Dr Peter Graham, Department of Radiation Oncology, St George Hospital.
- Dr P. Grant *, Gynaecological oncologist, Mercy Hospital for Women, Melbourne
- Dr John Gribbin, Department of Surgery, Monash Medical Centre, Victoria
- Dr John Grygiel, Radiation Oncologist, Sydney
- Prof Neville Hacker *, Director, Gynaecological Cancer Centre, Royal Hospital for Women, Randwick, NSW
- Dr Mark Hertzberg, Dept of Haematology, Westmead Hospital, Sydney
- Dr Elizabeth Hovey, Medical Oncologist, Liverpool Hospital, Sydney

- Dr Michael Hughes *, Oncology surgeon, Westmead Hospital, Sydney
- Dr Andrew Hui *, Radiation Oncologist, Peter MacCallum Cancer Institute, Melbourne
- Dr Keen Hun Tai *, Radiation oncologist, Peter MacCallum Cancer Institute, Melbourne.
- Dr Lyndell Kelly *, Radiation oncologist, Royal Brisbane Hospital, Brisbane
- Dr Liz Kenny, Queensland Radium Institute, Royal Brisbane Hospital
- Dr Andrew Kneebone *, Radiation Oncologist, Liverpool Hospital
- Dr Yee Leung, Gynaecological Oncologist, St John of God Hospital Murdoch WA
- Dr Robert Lindeman *, Haematologist, Prince of Wales Hospital, Sydney
- Dr Karen Luxford *, Evidence-based Medicine Manager, National Breast Cancer Centre, Sydney
- Dr Bernard Lyons, Department of Surgery, Peter MacCallum Cancer Institute, Melbourne
- Mr Bruce Mann, Department of Surgery, Royal Melbourne Hospital
- Dr Don Marsden, Gynaecological Oncologist, Royal Hospital for Women, Randwick NSW
- Ms Jane McEniery, Nurse Unit Manager, Royal Women's Hospital Melbourne
- Dr Gary Morgan, Department of Radiation Oncology, Westmead Hospital, Sydney
- Dr Graeme Morgan, Radiation Oncologist, St Vincents Hospital, Sydney
- Dr Kailash Narayan *, Radiation Oncologist, Peter MacCallum Cancer Institute, Melbourne.
- Dr Sam Ngan *, Radiation oncologist, Peter MacCallum Cancer Institute, Melbourne
- Prof Chris O'Brien, Radiation Oncologist, Royal Prince Alfred Hospital Sydney
- Dr Peter O'Brien *, Radiation Oncologist, Mater Hospital, Newcastle

- Ms Gabrielle O'Connor, Neuro-Oncology Nurse, Monash Medical Centre, Victoria
- Dr Malcolm Pell, Neurosurgeon, St Vincents Hospital, Sydney
- Prof Lester Peters *, Radiation oncologist, Peter MacCallum Cancer Institute, Melbourne.
- Dr Gary Pratt *, Radiation Oncologist, Royal Brisbane Hospital, Brisbane
- Prof. Allan Rodger *, Radiation Oncologist and Director, William Buckland Cancer Centre, Victoria.
- Dr Danny Roos, Dept of Radiation Oncology, Royal Adelaide Hospital
- Ms. Pauline Rose *, Radiation Oncology Clinical Nurse Consultant, Queensland Radium Institute, Brisbane.
- Dr Abraham Rubinfeld *, Deputy Director, Dept Respiratory Medicine, Royal Melbourne Hospital, Melbourne
- Professor John Seymour *, Haematologist, Peter MacCallum Institute, Melbourne
- Dr Robert Smee *, Radiation Oncologist, Prince of Wales Hospital, Sydney.
- Dr M Smithers, Department of Surgery, Princess Alexandra Hospital Brisbane
- Dr David Speakman *, Consultant Oncology Surgeon, Peter MacCallum Cancer Institute, Melbourne.
- Ms Liz Stickland, CSSP Project Officer, Austin and Repatriation Medical Centre, VIC
- Ms Deborah Stokes, Oncology Nurse, William Buckland Radiotherapy Centre, The Alfred Hospital, VIC
- Dr David Storey, Department of Surgery, Royal Prince Alfred Hospital Sydney
- Dr Noel Tait, Department of Surgery, The Canberra Hospital
- Dr Charles Teo, Neurosurgeon, Prince of Wales Hospital, Sydney
- Professor Robert Thomas *, Surgical Oncologist, Peter MacCallum Cancer Institute, Melbourne
- Ms Pauline Thomson Cancer Care Centre, St George Hospital.

- Dr Sandra Turner *, Radiation oncologist, Westmead Hospital, Sydney.
- Dr Michael Veness *, Radiation oncologist, Westmead Hospital, Sydney.
- Dr Shalini Vinod *, Radiation oncologist, Liverpool Hospital
- Dr Marianne Vonau, Neurosurgeon, Prince of Wales Hospital, Sydney
- Dr Margaret Wallington, Radiation Oncologist, Royal Hobart Hospital
- Dr Helen Wheeler, Medical Oncologist, Royal North Shore Hospital, Sydney
- Dr David Wigg *, Radiation Oncologist, Royal Adelaide Hospital, Adelaide
- Dr Jonathan Wood, Neurologist, Prince of Wales and Nepean Hospitals, Sydney
- Professor Patsy Yates, School of Nursing, Queensland University of Technology, Brisbane
- Dr Graham Young, Dept of Haematology, Royal Prince Alfred Hospital Sydney
- A/Prof Philip Yuile, Radiation oncologist, Mater Private Hospital, Crow's Nest

(NB: * indicates those who responded to the draft documents with their comments and suggestions)

Funding

The investigators would like to thank the National Cancer Control Initiative and The Federal Department of Health and Aged Care for providing the funding for this study.

Publications and Presentations


The following scientific papers have been published or presented as a result of the Radiotherapy Utilisation project.

Publications

- Delaney G, Barton M., Jacob S, Jalaludin B. A model for decision-making for the use of radiotherapy in lung cancer, *Lancet Oncology*, 4:120-128, 2003.
- Delaney G., Barton M. Jacob S. Estimation of an optimal radiotherapy utilisation rate for breast cancer: A review of the evidence. *Cancer* 98 (9):1977-1986, 2003.
- C Featherstone, G Delaney, S Jacob, MB Barton - Estimating optimal radiotherapy utilisation for haematological malignancies from clinical guidelines. *Clinical Oncology* 15(2) s25, 2003.
- Featherstone C., Delaney G., Barton M., Jacob S. Estimation of an optimal radiotherapy utilization rate for myeloma: A review of the evidence. Submitted to *Blood*, 2003.
- Featherstone C., Delaney G., Barton M., Jacob S. Estimation of an optimal radiotherapy utilization rate for leukaemia: A review of the evidence. Submitted to *Blood*, 2003.
- Featherstone C., Delaney G., Barton M., Jacob S. Estimation of an optimal radiotherapy utilization rate for lymphoma: A review of the evidence. Submitted to *Blood*, 2003.

- Delaney G., Barton M. Jacob S, Hughes M. Estimation of an optimal radiotherapy utilization rate for melanoma: A review of the evidence. Draft complete.
- Delaney G., Barton M., Jacob S. Estimation of an optimal radiotherapy utilization rate for rectal carcinoma: A review of the evidence. Draft in progress.

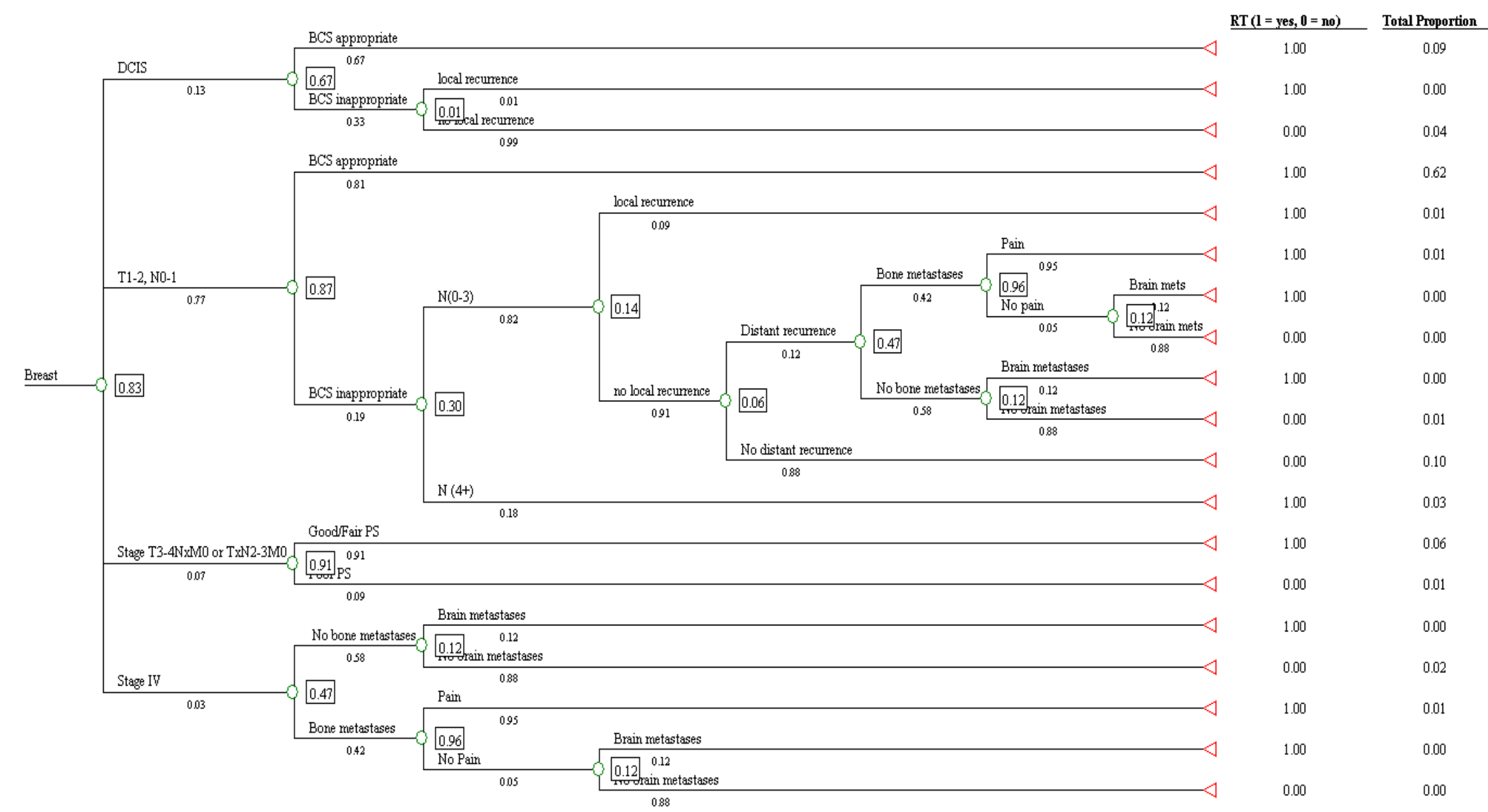
Oral presentations

- Stage I draft report to the NCCI steering committee – G. Delaney, M. Barton
- Stage II draft report to the NCCI steering committee – G. Delaney, M. Barton
- The actual versus optimal rates of melanoma and breast, lung and rectal cancer, M. Barton - NCCI Victorian Anti Cancer Council Dec 2002 
- Estimating the optimal radiotherapy utilisation rate from evidence. G. Delaney. S. Jacob, M. Barton, B. Jalaludin, M. Frommer. October 2002 RANZCR Annual General and Scientific Meeting, Adelaide, Australia. (G. Delaney awarded the Philips Award for the best scientific presentation at the conference).
- The optimal versus actual rates for lung cancer – the gaps in radiotherapy service delivery, Lung Cancer Workshop, Adelaide, 2003
- The optimal rate of radiotherapy utilisation for lung cancer, G. Delaney, accepted for presentation, International Lung Cancer conference August 2003, Vancouver, Canada.

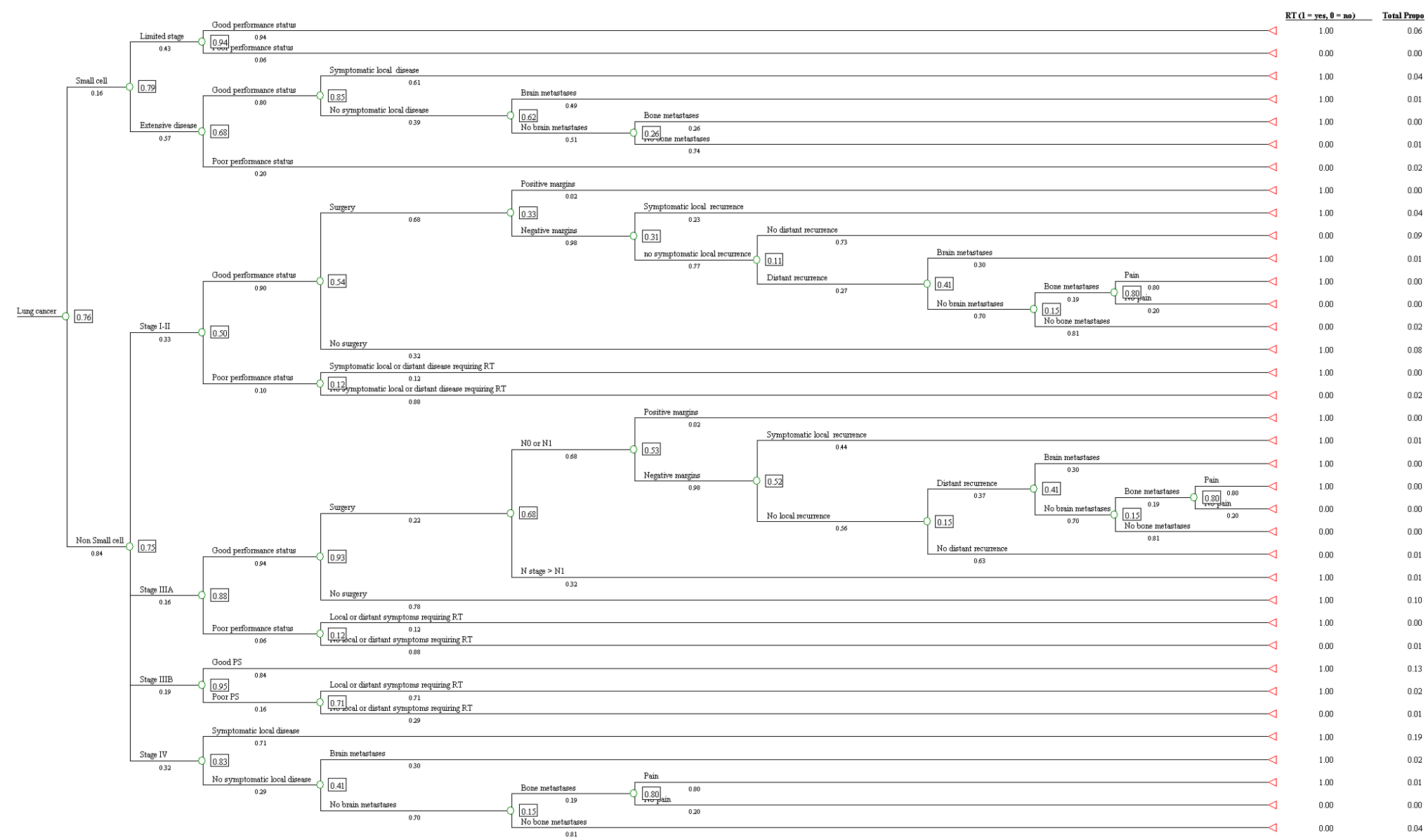
Poster presentations

- C Featherstone, G Delaney, S Jacob, MB Barton - Estimating optimal radiotherapy utilisation for haematological malignancies from clinical guidelines. Presented at United Kingdom Radiation Oncology (UKRO) meeting in Bath, England April 7-9th, 2003
- Estimating the optimal radiotherapy utilisation rate based on clinical guidelines and best available evidence and comparing it to current practice - to be presented at ASTRO in Salt Lake City in September 2003.

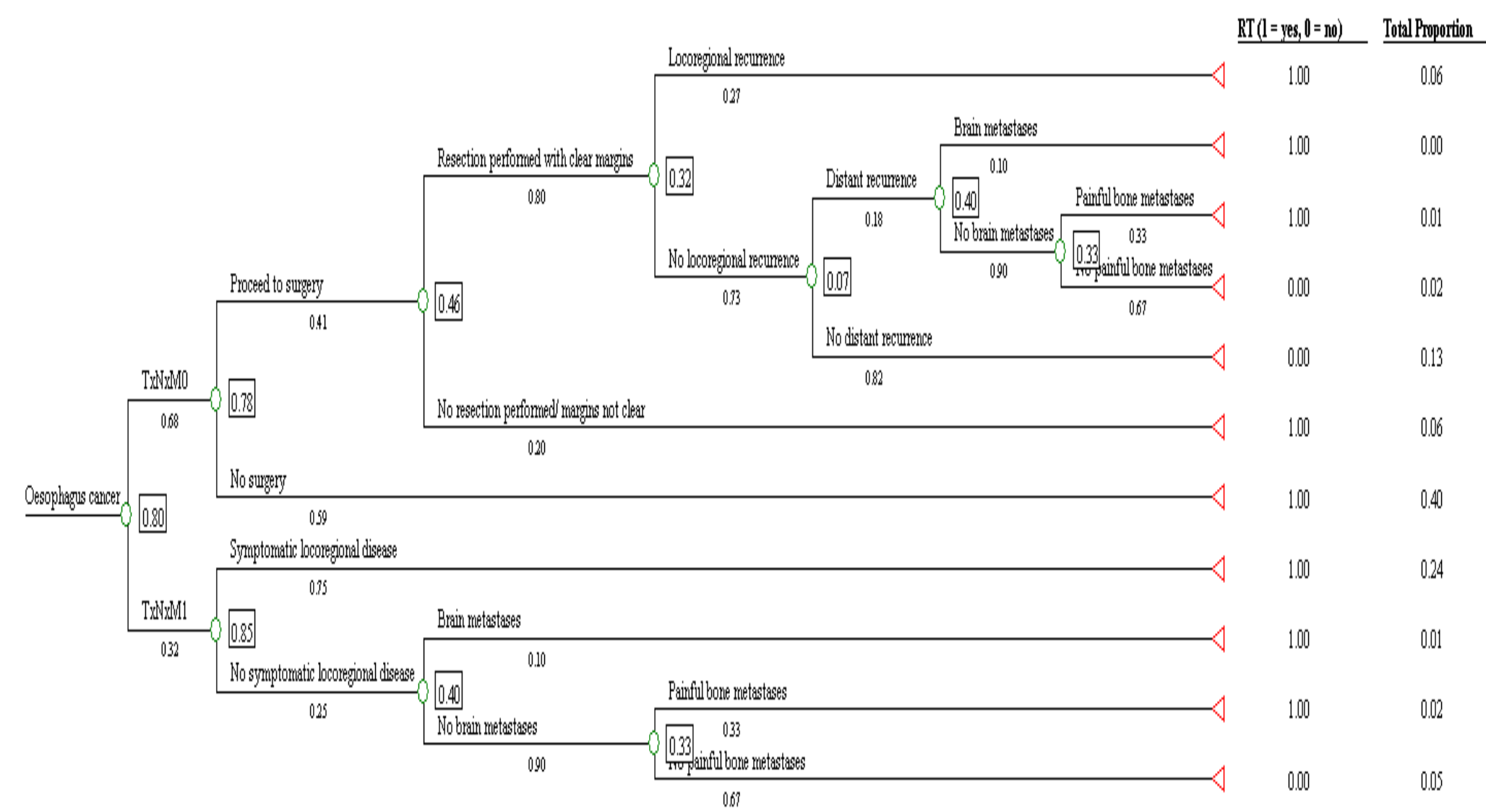
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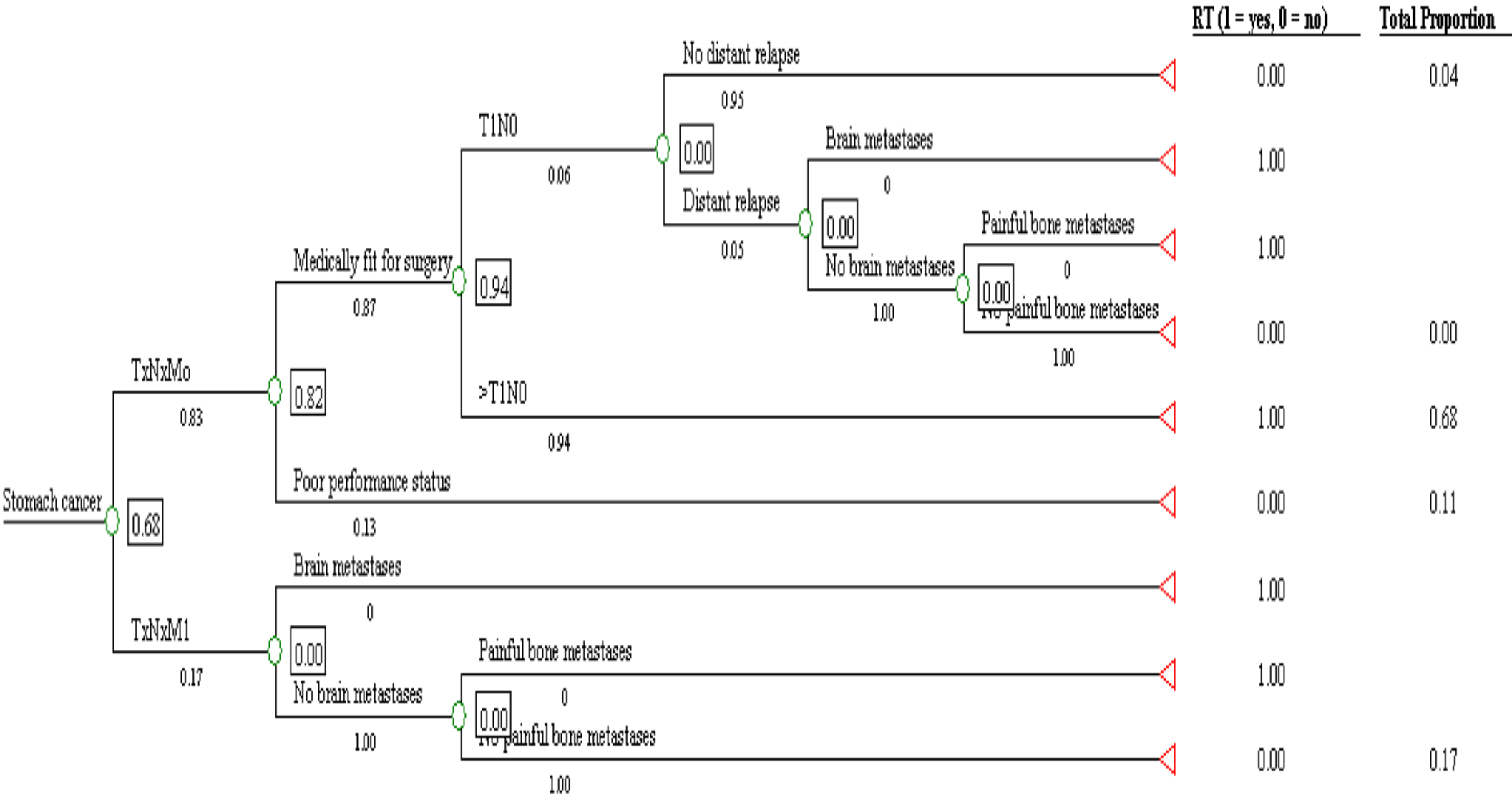
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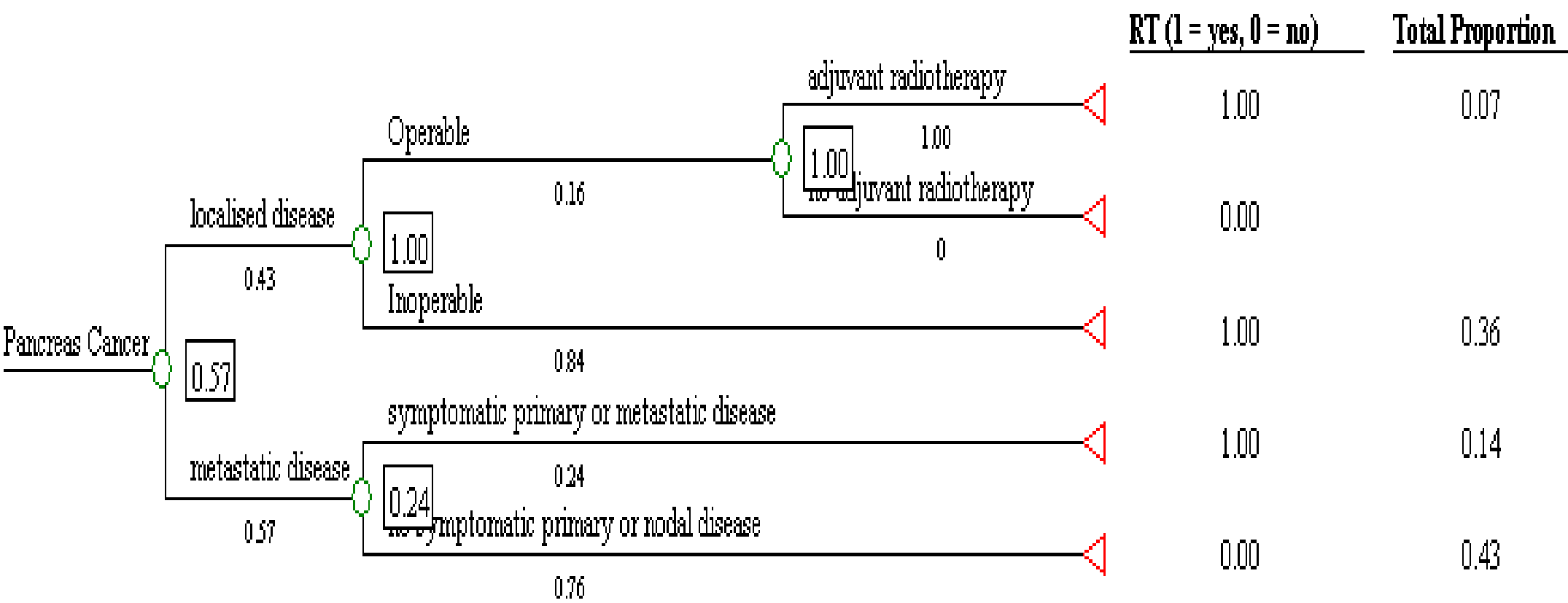
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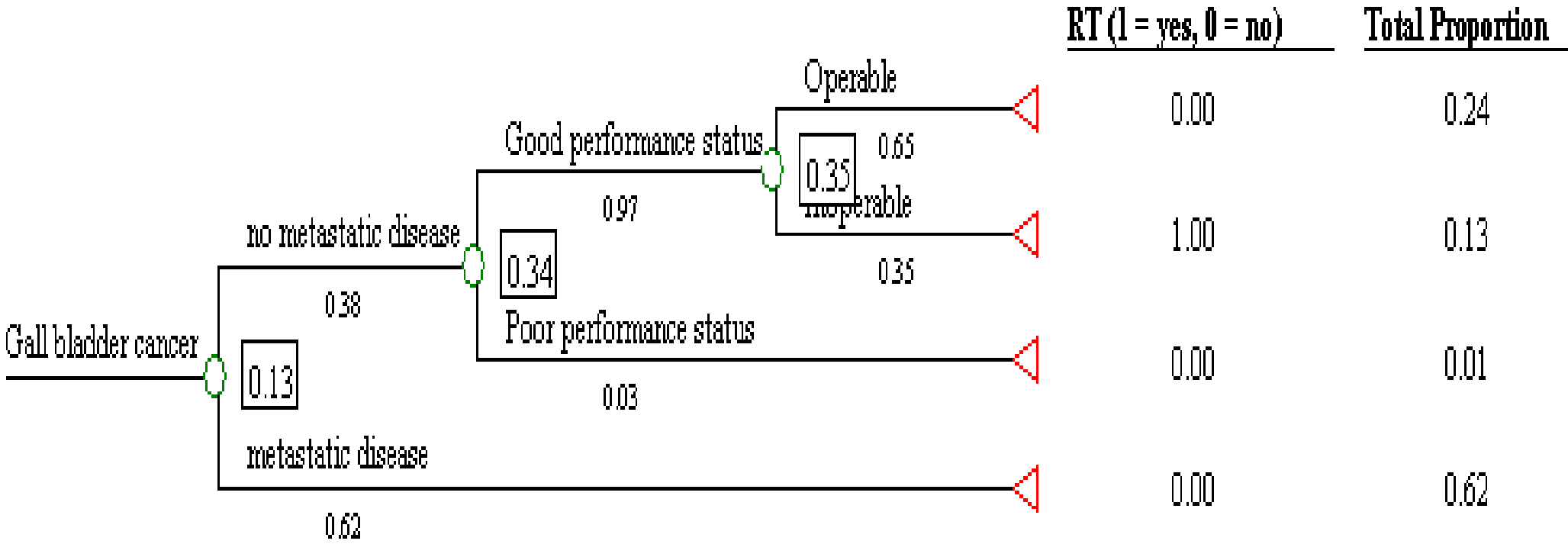
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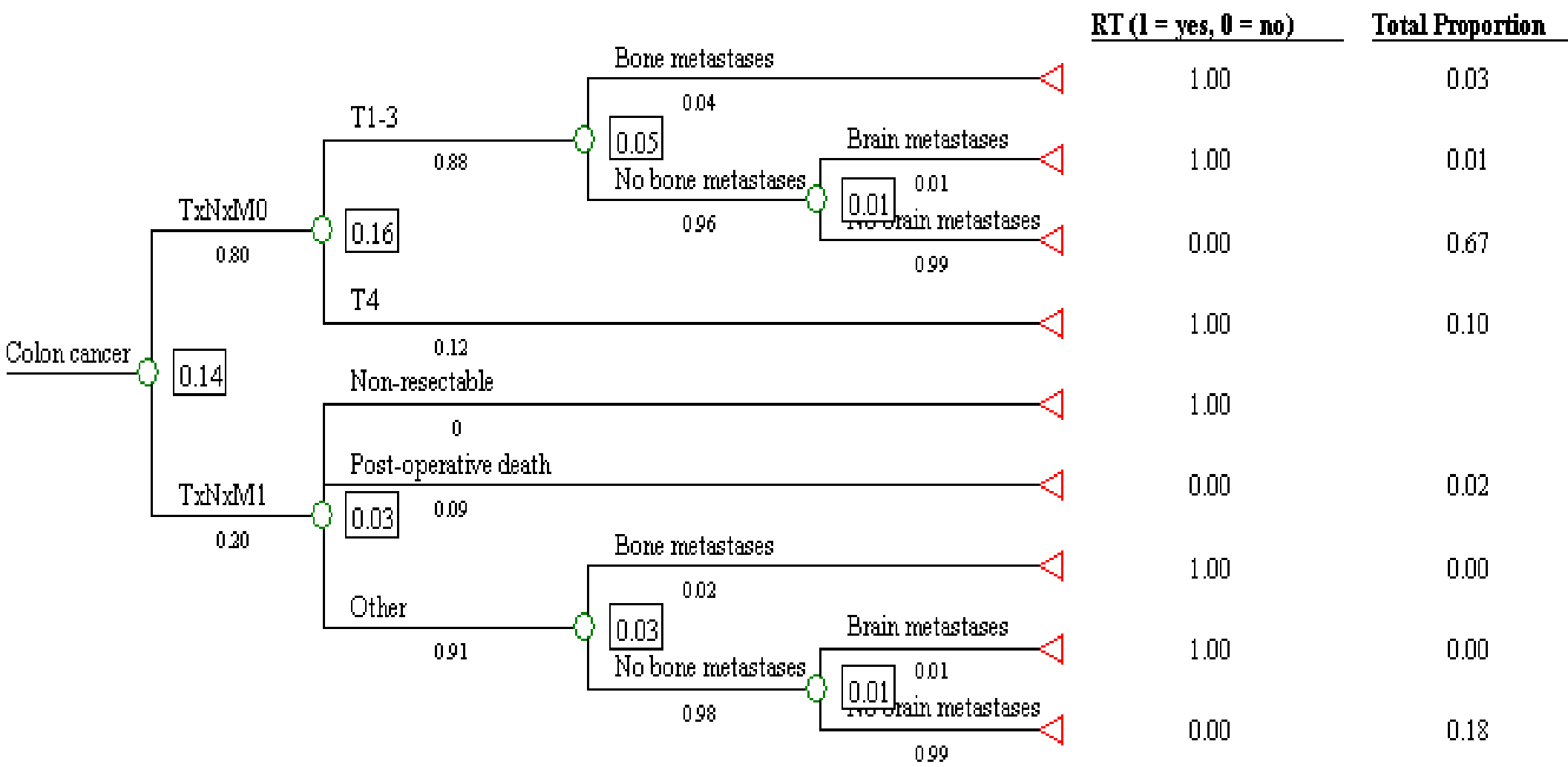
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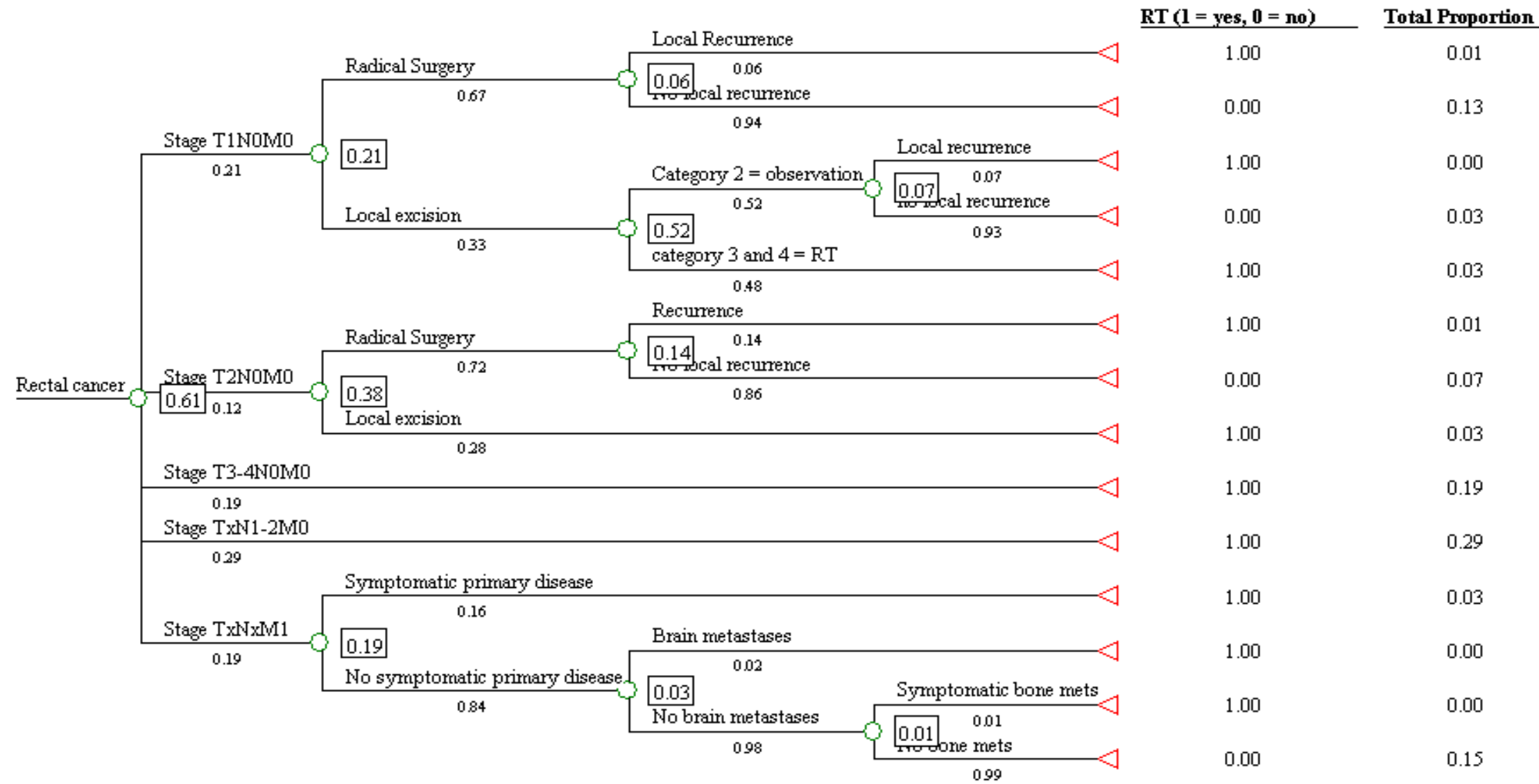
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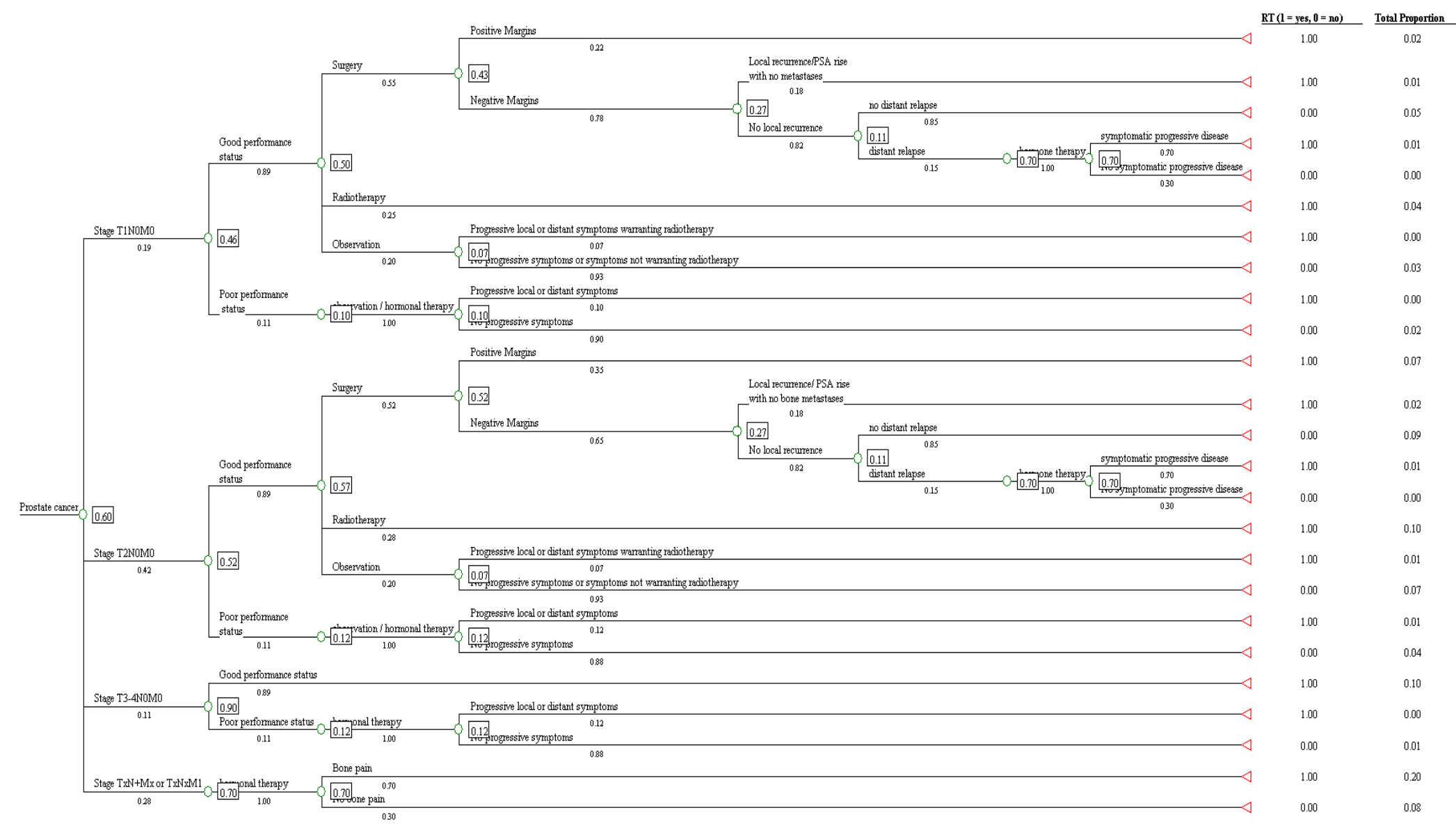
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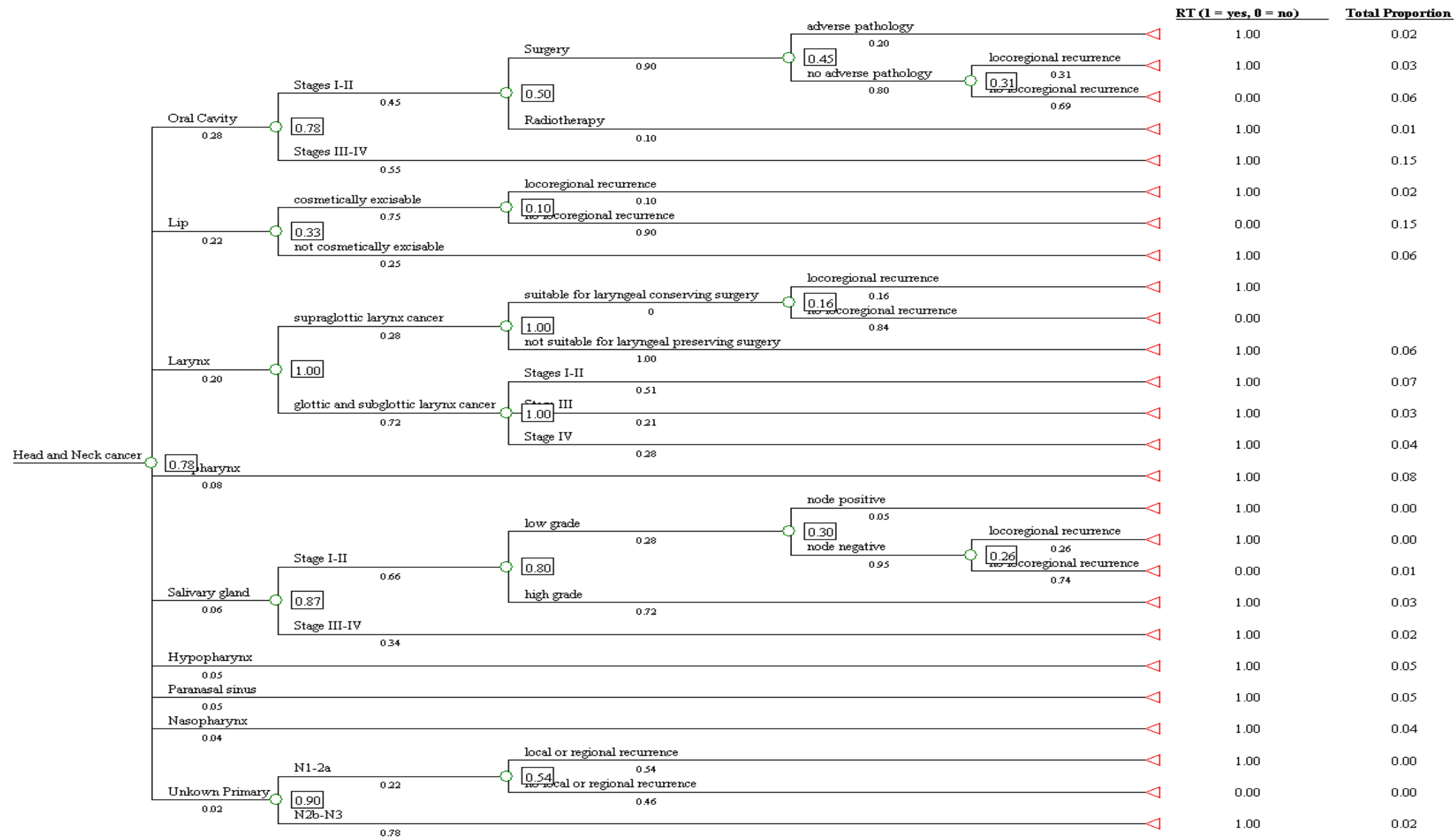
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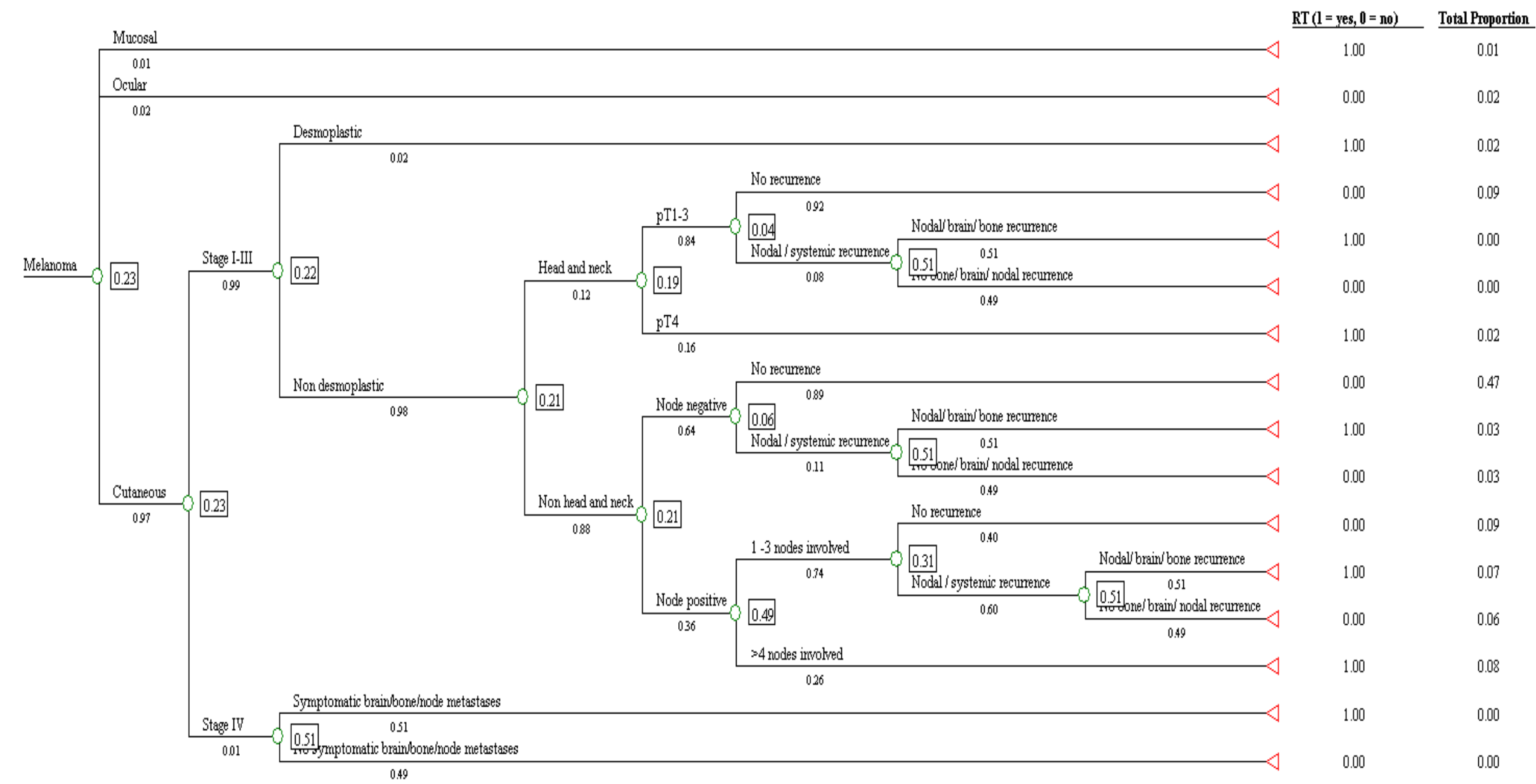
Prostate Cancer



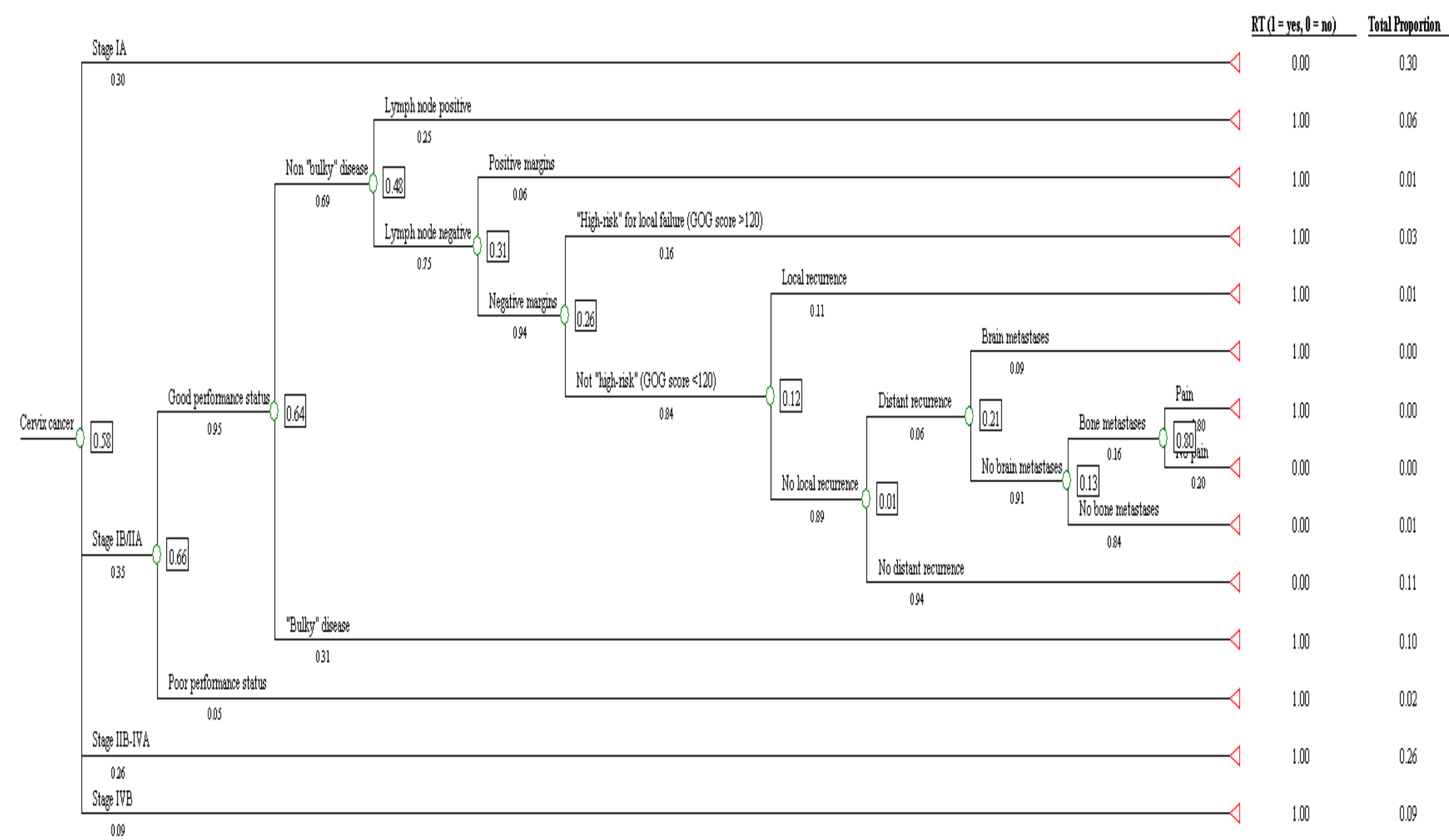
Head and Neck Cancers



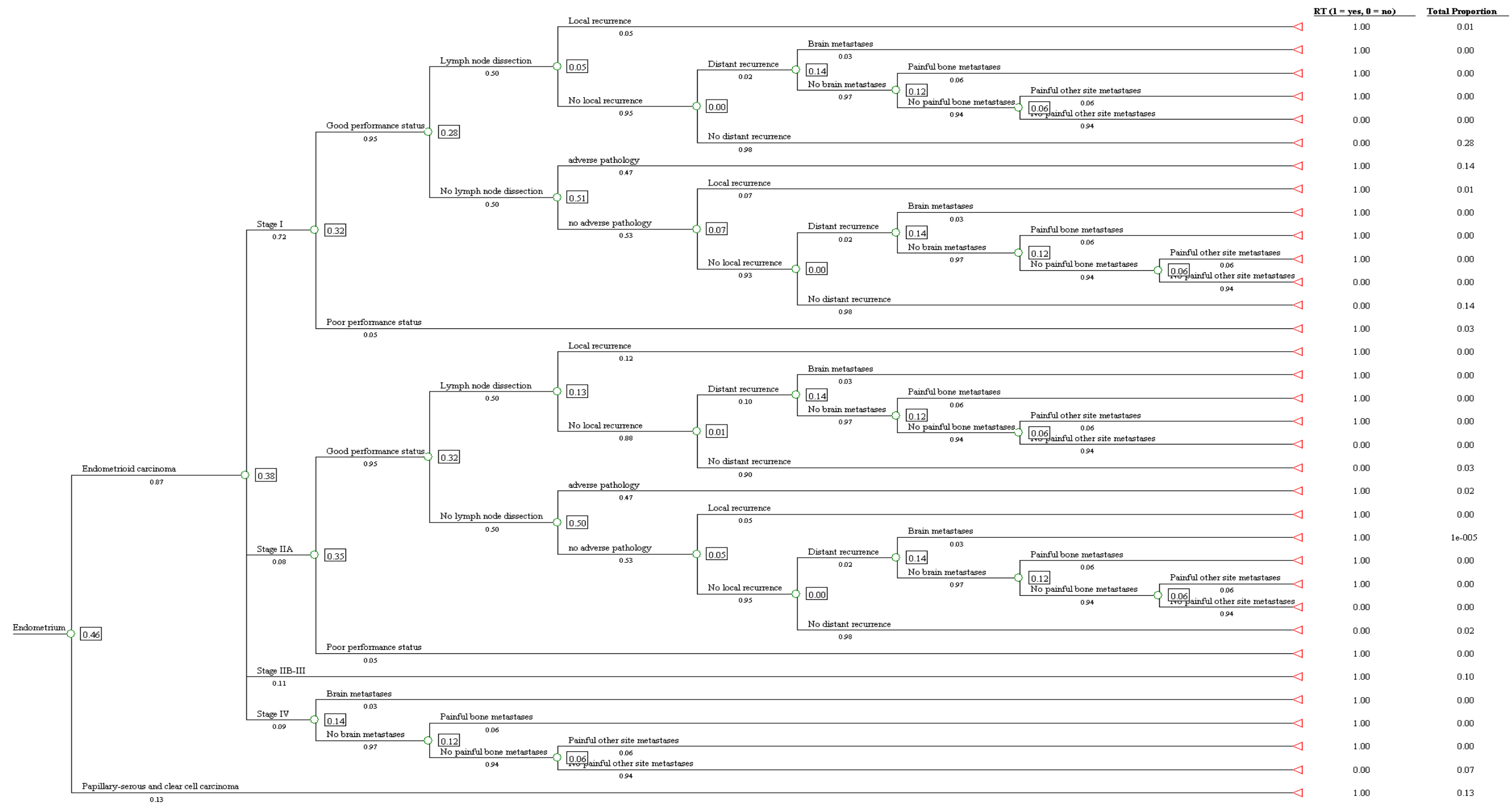
Melanoma



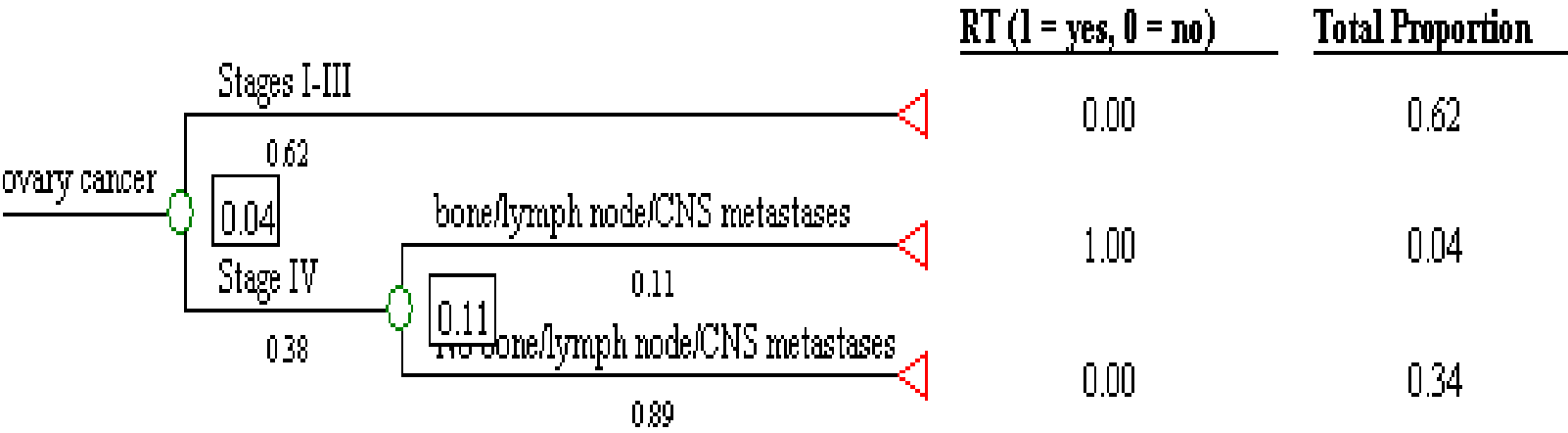
Cervical Cancer



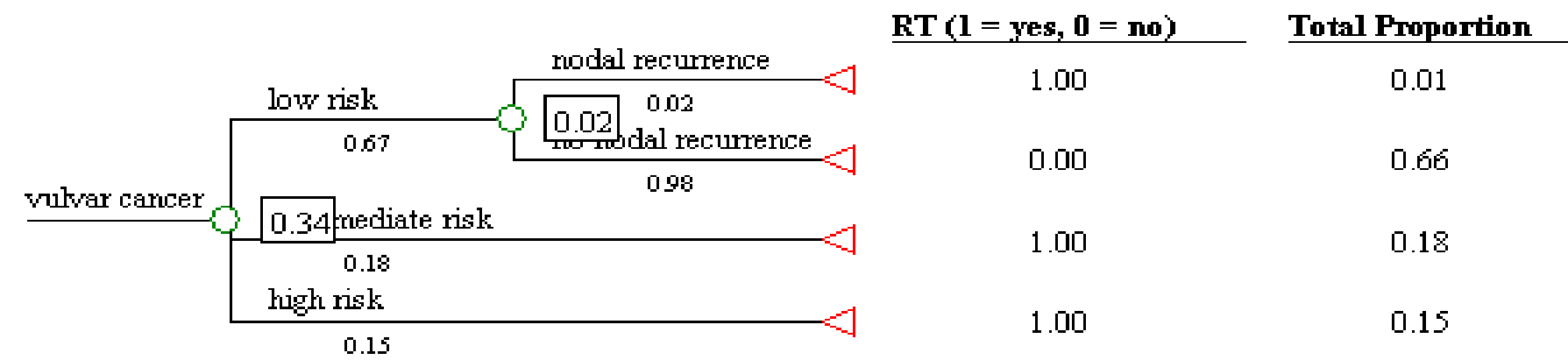
Endometrial Cancer



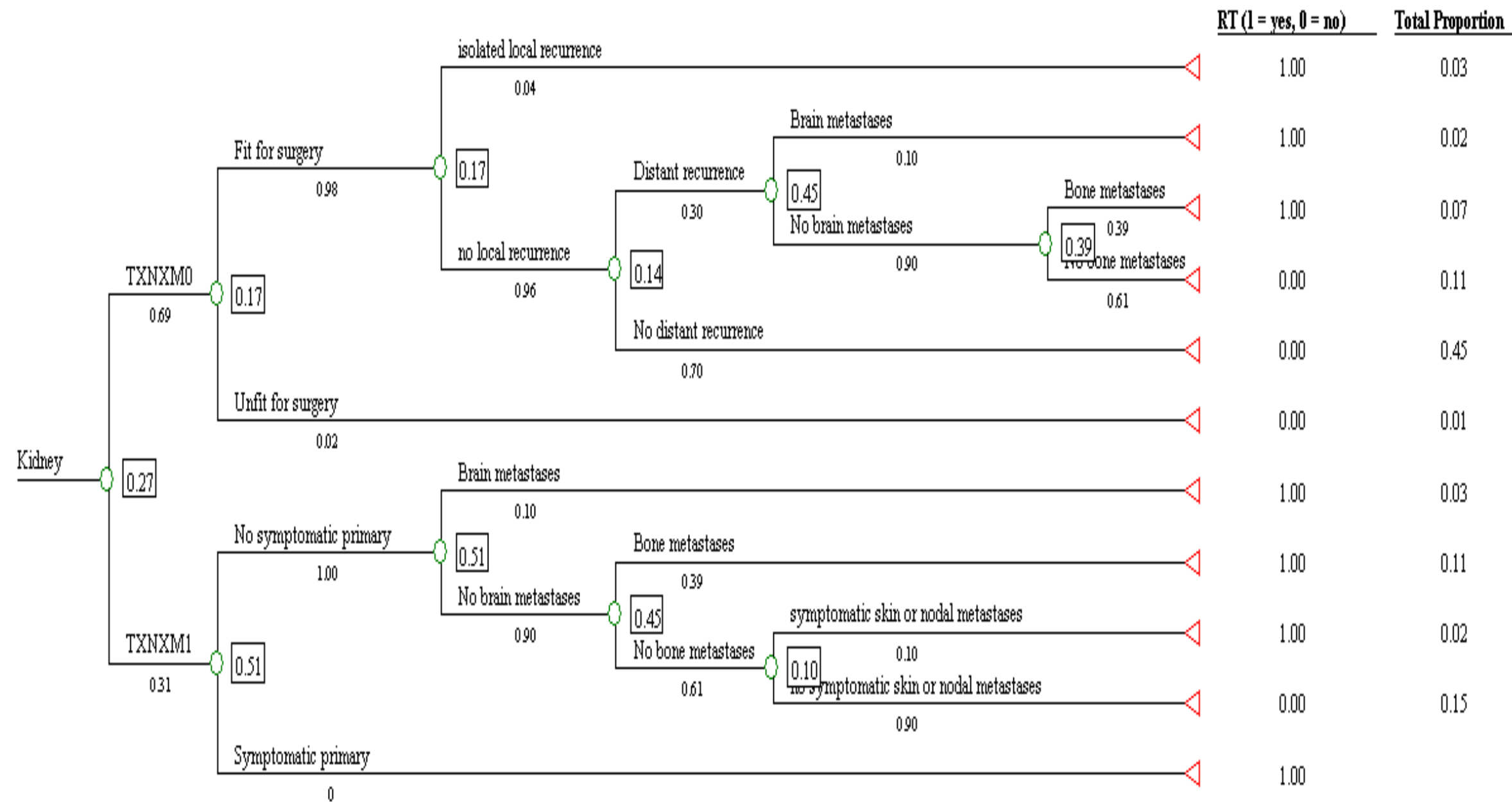
Ovarian Cancer



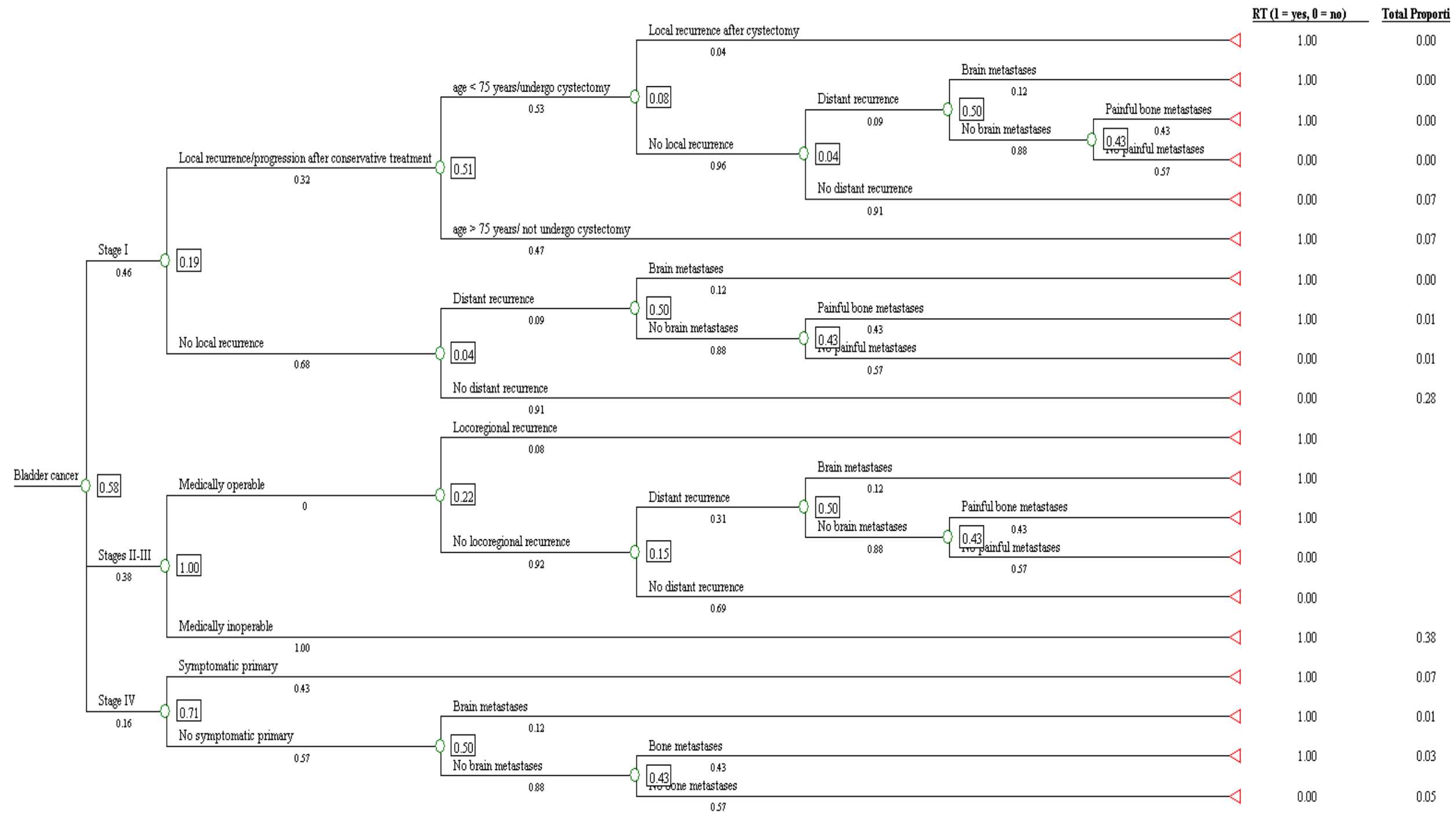
Vulvar Cancer



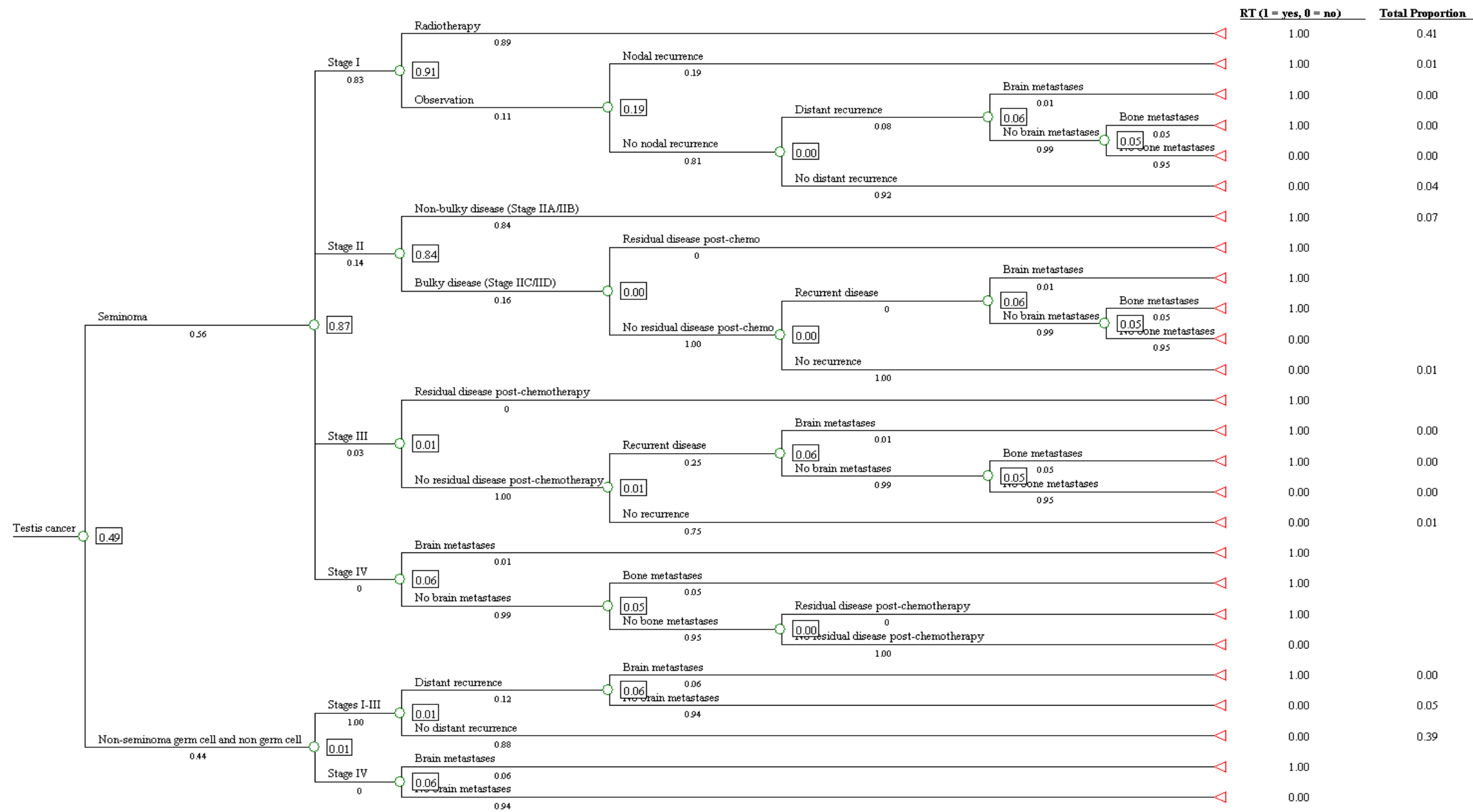
Renal Cancer



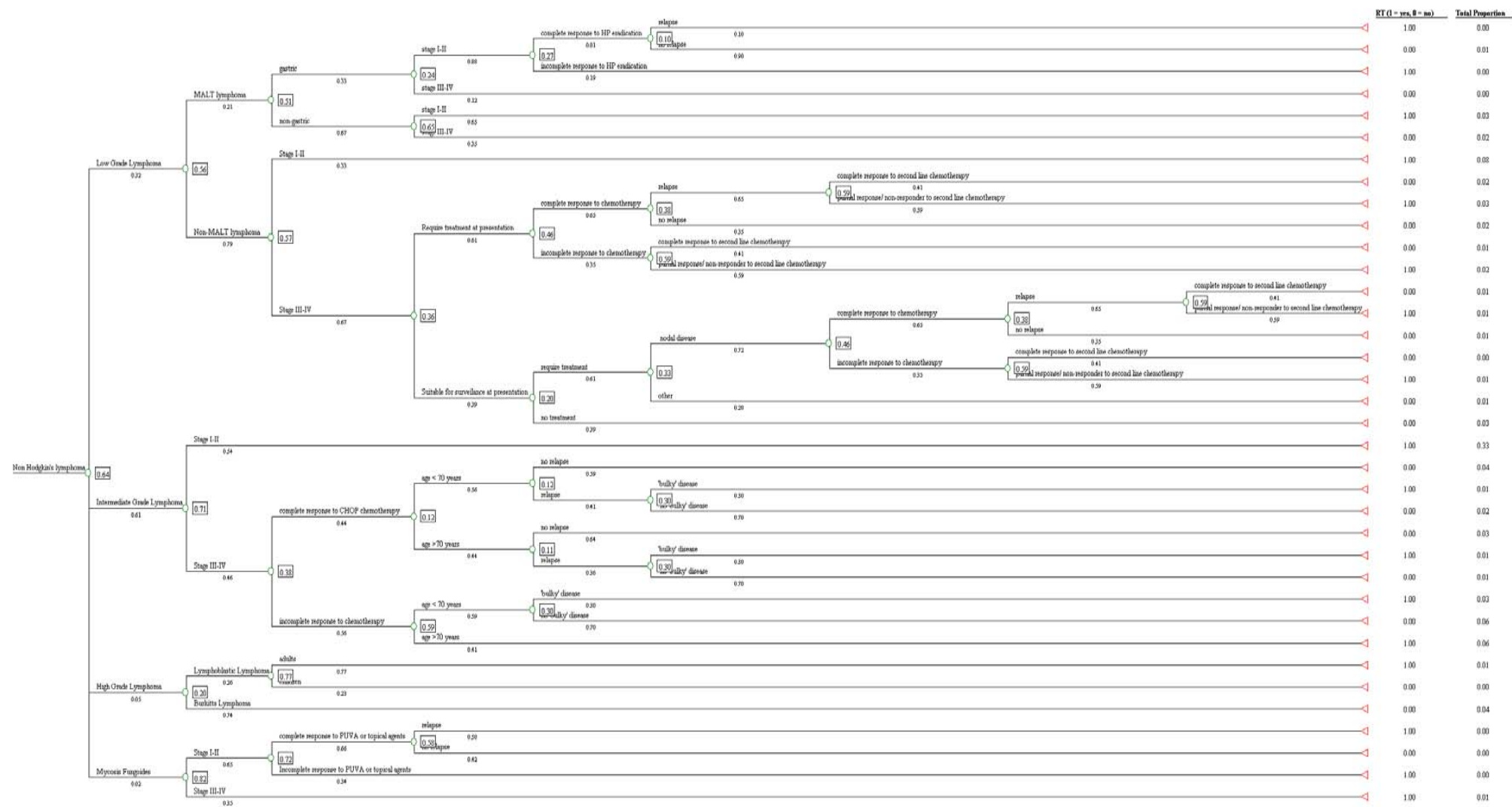
Bladder Cancer



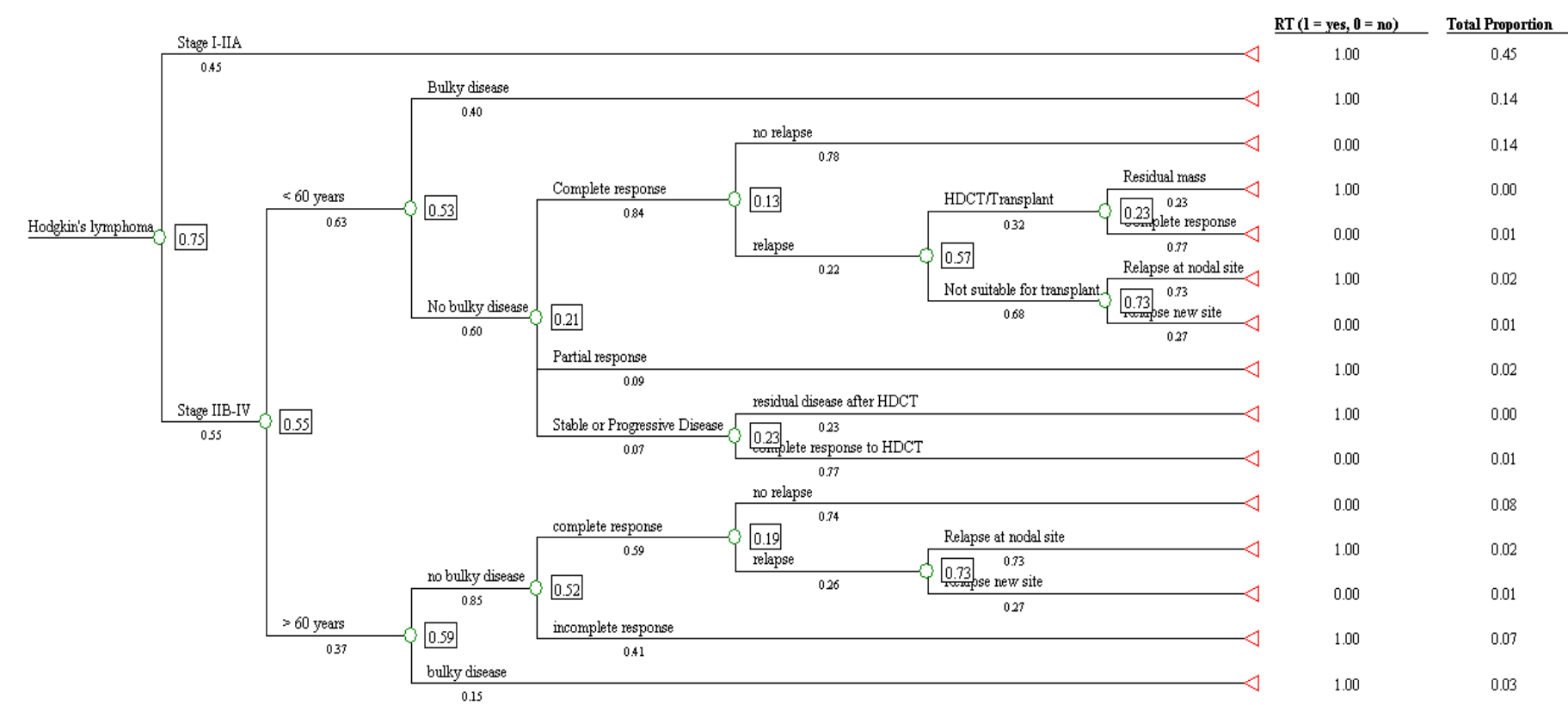
Testicular Cancer



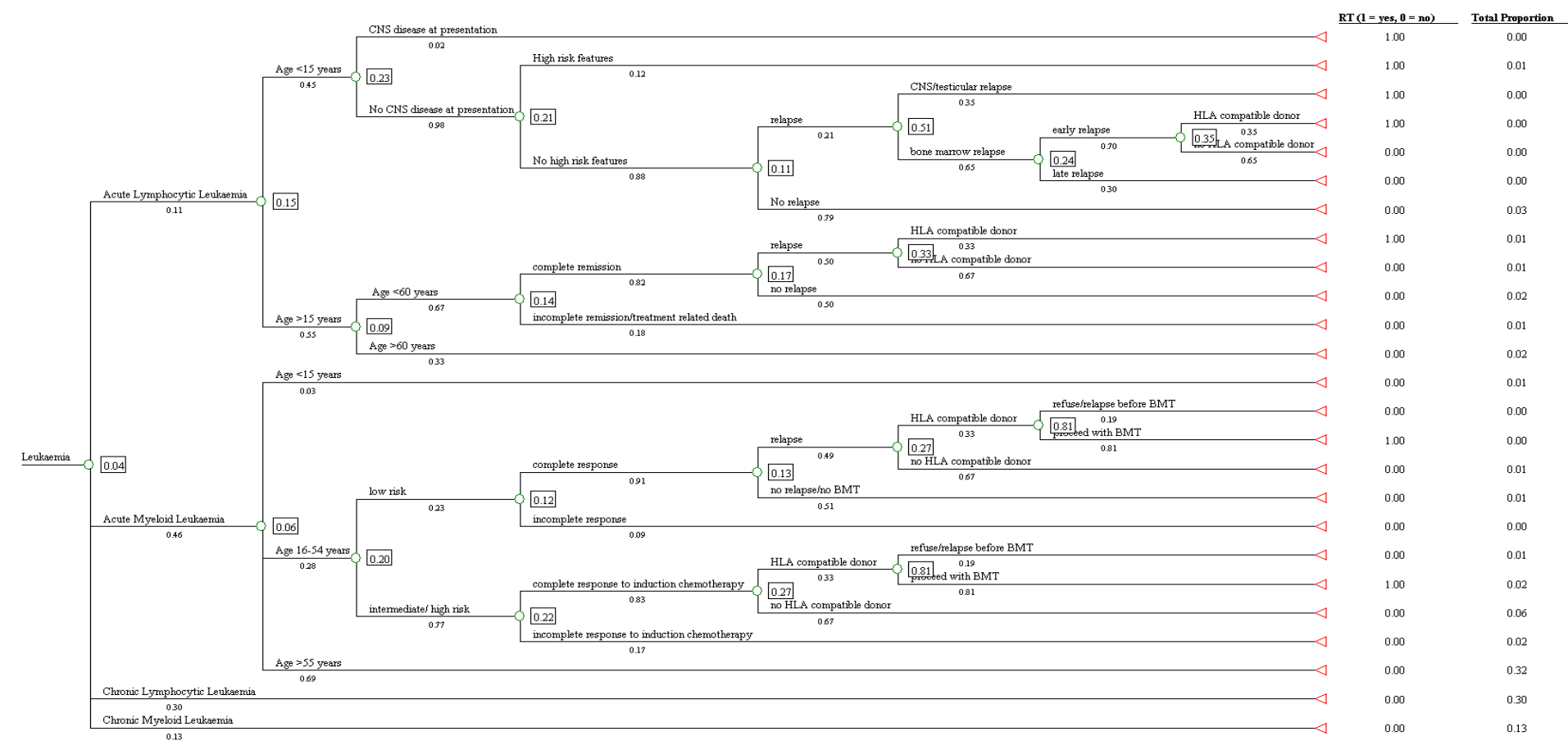
Non-Hodgkin’s lymphoma



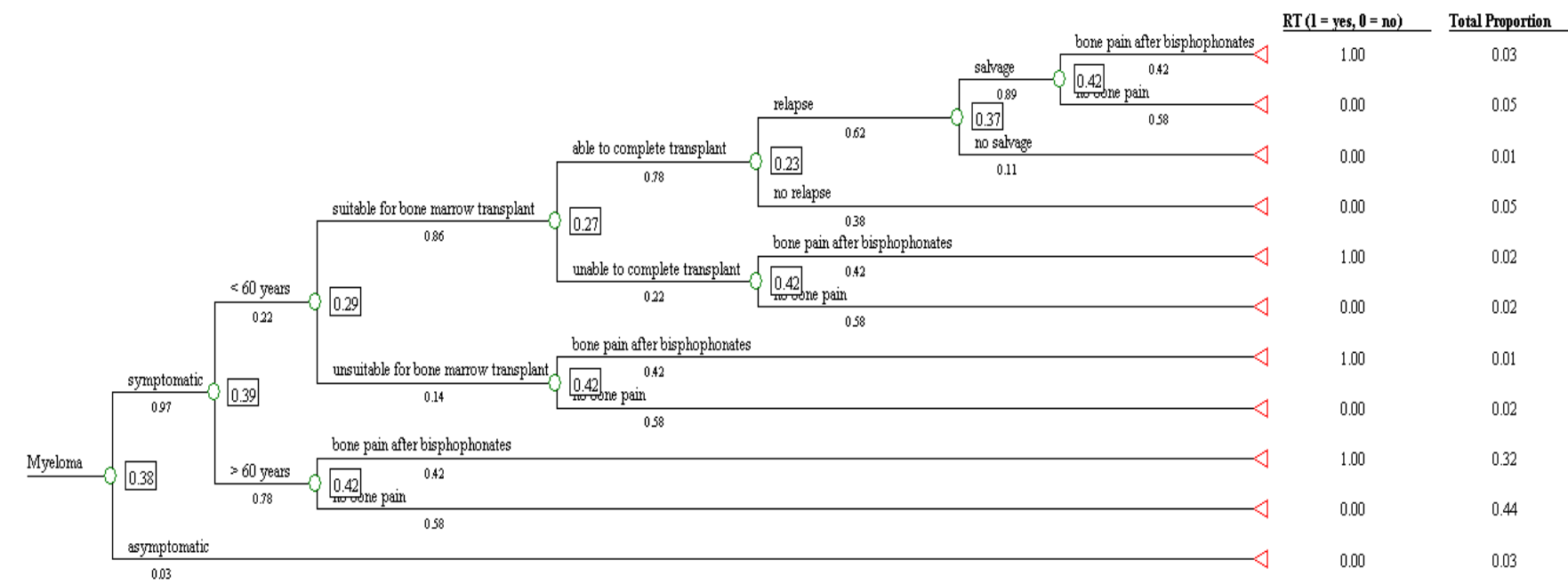
Non-Hodgkin’s lymphoma



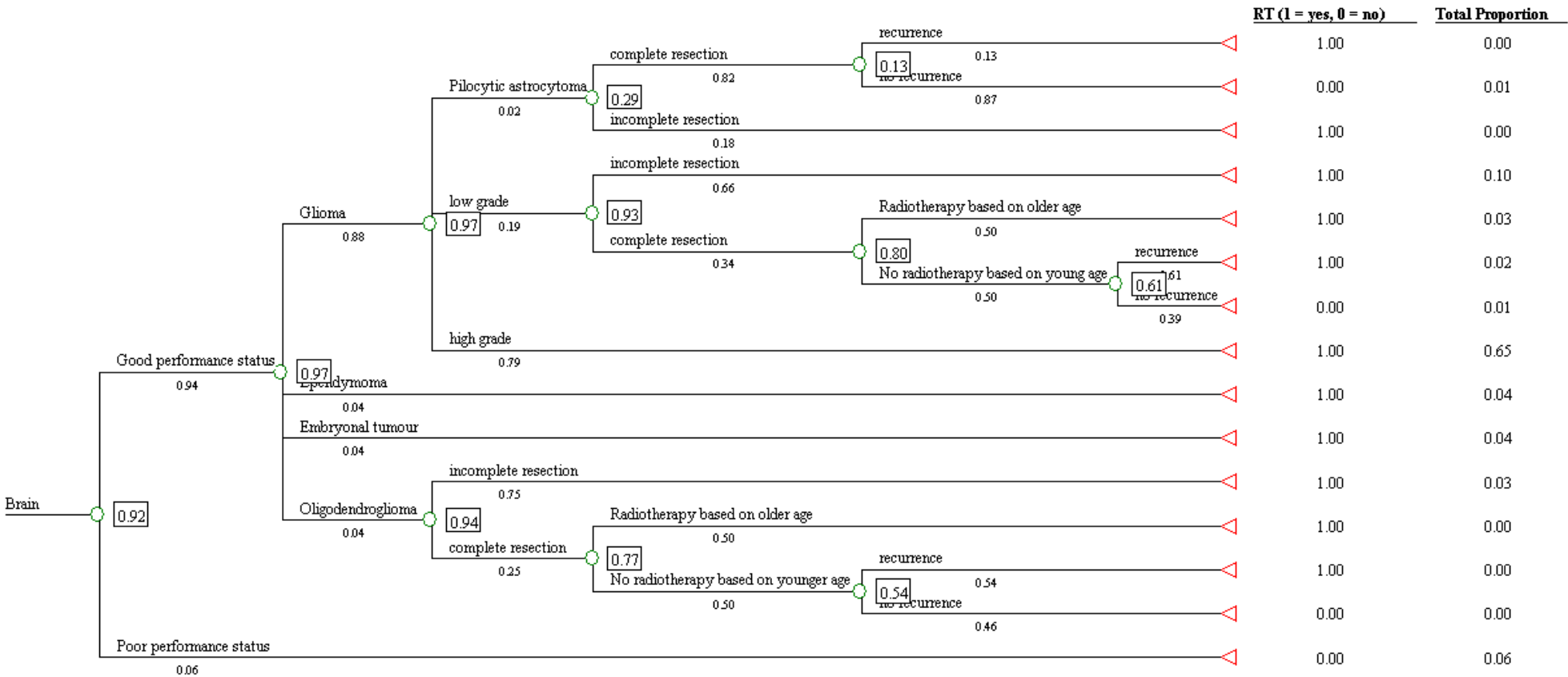
Leukaemia



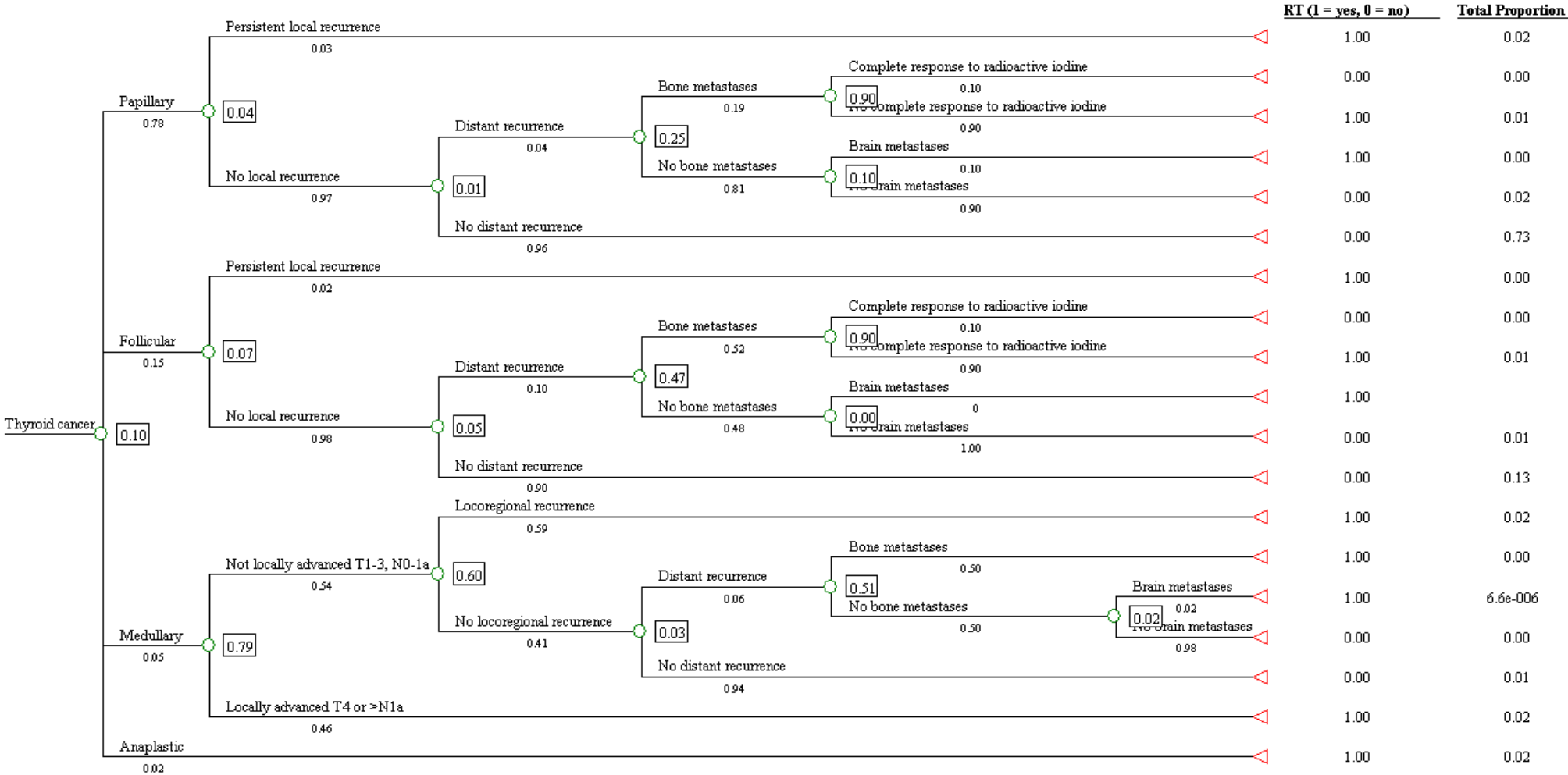
Myeloma



Central Nervous System Tumours



Thyroid Cancer



Adenocarcinoma - Unknown Primary Site

