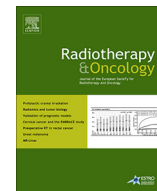




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Original article

Impact of radiotherapy underutilisation measured by survival shortfall, years of potential life lost and disability-adjusted life years lost in New South Wales, Australia

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ABSTRACT

Background and purpose: Despite evidence of the benefits of radiotherapy (RT) in the treatment of cancer patients, its underutilisation has been reported for various tumour sites. The aim of this study was to estimate survival shortfall, 'years of potential life lost' (YPLL) and 'disability-adjusted life years lost' (DALY) to demonstrate the impact of radiotherapy underutilisation in Australia.

Materials and methods: Optimal and actual RT utilisation (RTU) was compared to assess RT underutilisation to estimate 5-year overall survival shortfall using 2006 data from New South Wales (NSW) for 26 common tumour sites. 5-year overall survival shortfall is defined as number of people not surviving for 5-years due to RT underutilisation [=benefit proportion × shortfall [(optimal-actual RTU)/optimal RTU] proportion × No. of new cases]. YPLL = survival shortfall × estimated years of life lost per person (overall life expectancy – median age at death for specific cancer). DALY = (Years lived with disability + Years of life lost) × survival shortfall.

Results: The total number of new cases with cancer in 2006 in NSW was 20,741. Optimal RTU was 48% while actual RTU was 26%, resulting in estimated of 411 deaths due to underutilisation. Each death resulted in an average of 10.4 YPLL and 17.5 DALY. It was estimated RT underutilisation resulted in a total of 4,289 YPLL and 7,192 DALY overall.

Conclusion: This study illustrates the value of considering different mortality statistics, which include measures of the burden of cancer deaths on both the population and patients.

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Cancer is one of the leading causes of morbidity and mortality worldwide, with approximately 14 million new cases in 2012 [1]. It is the second leading cause of death globally, and was responsible for 8.8 million deaths in 2015 [1]. Radiotherapy is a major component of cancer management for up to 50% of patients [2]. Despite this, not all cancer patients who have an indication for radiotherapy actually receive it. Observed radiotherapy utilisation rates (i.e. the proportion of all cancer patients who receive radiotherapy) have been shown to be consistently below optimum benchmark rates [2]. Benchmark rates estimate the proportion of patients in a population who have an indication for radiotherapy based on

evidence-based guidelines [3–9]. The difference between optimal and actual radiotherapy utilisation provides an indication of radiotherapy underutilisation.

The impact that radiotherapy underutilisation has on mortality is not well studied. Along with assessing the impact of radiotherapy underutilisation on crude mortality or survival shortfall, other measures of population cancer burden effects should be considered. The concept of years of potential life lost (YPLL) involves estimating the average time a person would have lived had he or she not died prematurely [10]. It is a population-based mortality indicator, which gives more weight to those diseases that kill younger people. Another measure, disability-adjusted life years lost (DALY), is a measure of overall disease burden, expressed as the number of years lost due to ill-health, disability or early death [11]. One DALY can be thought of as one lost year of "healthy" life.

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The aim of this study was to estimate survival shortfall, YPLL and DALY for a population to demonstrate the impact of radiotherapy underutilisation in New South Wales, Australia.

Materials and methods

The methodology used to estimate optimal radiotherapy utilisation has been previously reported in detail by our group [2,3] and is briefly outlined. The indications for radiotherapy for each cancer site were derived from evidence-based treatment guidelines issued by reputed national and international organisations. An optimal radiotherapy utilisation model was developed for each cancer site using TreeAge Pro™ (Williamstown, MA) software. In the optimal radiotherapy utilisation (RTU) models each branch point represented an attribute (such as the stage of the tumour, performance status or whether clear surgical margins were present) that affects a clinical management decision of whether to use radiotherapy or not. The proportion of patients for whom radiotherapy was recommended during the first year from the time of diagnosis was determined using epidemiological observations from the literature. The addition of all these indication proportions determined the optimal utilisation rate for the specified cancer site. Univariate sensitivity analyses were undertaken to assess changes in the recommended radiotherapy utilisation rate that would result from variations in epidemiological data or where there was conflict in radiotherapy recommendations between treatment guidelines. Multivariate analysis with Monte Carlo simulation was used for the sensitivity analysis of the whole tree.

New models of 5-year overall survival benefit for all major cancer sites were developed by supplementing the RTU models. The details of the methods of development of radiotherapy benefit models were published previously [12–14]. Radiotherapy benefit proportion was the absolute proportion of patients in the cancer population alive at 5 years due to radiotherapy. The radiotherapy benefit for each indication in the model was based on the highest level of evidence identified in systematic review. Meta-analysis was utilised where multiple sources of the same evidence level were identified. We determined the proportion of the cancer population deriving a benefit when radiotherapy was optimally utilised according to evidence based guidelines. The population benefit was derived by multiplying the optimal proportion of patients with each curative radiotherapy indication in the optimal RTU model by the proportional benefit of radiotherapy, and summing all such products.

The method used to calculate actual radiotherapy utilisation has been reported previously [15]. The actual radiotherapy utilisation rate was defined as the proportion of cancer patients receiving radiotherapy for their initial treatment within one year of their diagnosis amongst those diagnosed with cancer in that region during the specified time. This retrospective study cohort consisted of all patients diagnosed with cancer in New South Wales (NSW) in 2006 to estimate actual radiotherapy utilisation. Patients were followed for one year after their diagnosis to capture their first episode of radiotherapy.

The difference between optimal and actual radiotherapy utilisation (RTU) was determined to estimate 5-year overall survival shortfall as described elsewhere [16]. Survival shortfall in this study is defined as number of patients who were estimated not to survive 5-years due to lack of appropriate radiotherapy treatment for their cancer (Eq. (1)). A uniform gap between actual and optimal RTU was applied in the absence of actual RTU data on each specific indication. Australia-wide data on cancer site specific actual radiotherapy utilisation rates were not available and hence, for the analysis presented in this study NSW data were used to predict the nationwide survival shortfall. This was assessed

for 26 tumour sites for which radiotherapy is indicated where the incidence was more than 1% of all registered cancers; bladder, brain, breast, cervix, colon, gall bladder, head and neck, kidney, leukaemia, liver, lung, lymphoma, melanoma, myeloma, oesophagus, ovary, pancreas, prostate, rectum, stomach, testis, thyroid, uterus, vulva, unknown primary and other (anus, non-melanoma skin cancer, soft tissue sarcoma) cancers. YPLL (Eq. (2)) and DALY (Eq. (3)) were estimated for all tumour sites. To calculate the YPLL and DALY, an average life expectancy of 85 was used for the Australian population [17].

$$\begin{aligned} \text{Survival shortfall (in person)} &= \text{benefit proportion} \\ &\times \text{shortfall proportion} \\ &\times \text{number of new cases with cancer} \end{aligned} \quad (1)$$

where benefit proportion is defined as absolute proportion of patients in the cancer population alive at 5 years due to radiotherapy. Shortfall proportion = (Optimal RTU – Actual RTU)/(Optimal RTU).

$$YPLL = (\text{survival shortfall}) \times (\text{years of life lost}) \quad (2)$$

where years of life lost is calculated by subtracting the median age at death for specific tumour type [18] from the average life expectancy.

$$\begin{aligned} \text{DALY} &= [(\text{years lived with disability}) + (\text{years of life lost})] \\ &\times (\text{survival shortfall}) \end{aligned} \quad (3)$$

where years lived with disability is calculated by subtracting the median age at diagnosis from the median age at death for specific tumour type [18], and years of life lost is calculated as Eq. (2).

A detailed example for breast cancer is shown in [Supplementary Material 1](#). [Supplementary Material 2](#) lists the benefit proportion, number of new cases with cancer, and median age at diagnosis and death for all tumour sites.

Results

The estimated optimal RTU in 2006 for all cancer was 48% while actual RTU was 26% (Table 1). A shortfall proportion in radiotherapy utilisation was seen in 22 out of the 26 tumour sites investigated. In contrast, for several tumour sites (leukaemia, liver, ovary and thyroid), the actual RTU was greater than the optimal RTU but the survival shortfall in these sites was zero.

Survival shortfall, YPLL and DALY due to radiotherapy underutilisation from the 26 tumour sites are shown in Table 2. It was estimated that radiotherapy underutilisation resulted in a total of survival shortfall in 411 people, 4289 YPLL and 7192 DALY for all tumour sites. Survival shortfall was estimated for 16 out of 26 tumour sites investigated ranging from 1 to 64 deaths. The five tumour sites with the highest survival shortfall were lung, lymphoma, other, prostate and head and neck. For 10 tumour sites (colon, gall bladder, kidney, leukaemia, liver, melanoma, ovary, pancreas, thyroid and unknown primary) no survival shortfall due to radiotherapy underutilisation was estimated. Each death due to underutilization of radiotherapy was estimated to result in an average of 10.4 YPLL and 17.5 DALY. The top three ranking tumour sites in terms of YPLL due to radiotherapy underutilisation were lung, head and neck and testis, while the top three ranking tumour sites in terms of DALY due to radiotherapy underutilisation were lymphoma, prostate and other cancer.

A one-way sensitivity analysis was performed for each variable by setting upper and lower data limits. The survival shortfall varied from 387 to 426 people, while the YPLL and DALY from 2336 to

Table 1
Optimal and actual radiotherapy utilisation rate by tumour site.

Tumour site	Optimal RTU (%)	Actual RTU (%)	Shortfall proportion* (%)
Bladder	49	24	51
Brain	90	53	41
Breast	82	54	34
Cervix	58	52	10
Colon	10	5	53
Gall Bladder	13	8	42
Head and neck	70	52	26
Kidney	16	11	31
Leukaemia	3	8	-160
Liver	0	5	0
Lung	70	42	41
Lymphoma	59	26	55
Melanoma	13	5	58
Myeloma	38	30	22
Oesophagus	72	43	40
Ovary	4	19	-352
Pancreas	57	4	93
Prostate	55	7	87
Rectum	63	25	60
Stomach	68	27	60
Testis	48	16	67
Thyroid	7	33	-371
Unknown Primary	61	4	93
Uterus	46	21	54
Vulva	34	30	12
Other cancers	50	21	58
All Cancer	48	26	46

Shortfall proportion = [(optimal RTU – actual RTU)/optimal RTU].

Abbreviation: RTU-radiotherapy utilisation.

6342 and 5239 to 9245, respectively. This translated to 5.7–15.4 average YPLL and 12.8–22.5 average DALY per death.

Fig. 1 shows a simple plot of percentage of YPLL (a) and DALY (b) versus survival shortfall for the 16 tumour sites with survival shortfall. Tumour sites with zero or negative survival shortfall

are not shown as these sites will not have a negative impact on YPLL and DALY. The line of equality ($y = x$) is shown, so that tumour sites whose population burden (i.e. YPLL and DALY) exceed their survival shortfall are shown above and to the left of the line. This graph shows absolute differences in percentage for the three mortality indicators being considered (YPLL versus survival shortfall and DALY versus survival shortfall). For YPLL, the majority of points lie close to the line of equality except for testis and prostate, and to a lesser extent breast and brain. The absolute differences between DALY and survival shortfall are comparatively small except for lung, breast and testis.

Fig. 2 shows the percentage of survival shortfall and percentage of YPLL, as well as the ratio percent YPLL divided by percent survival shortfall for the 16 specified tumour sites. The figures are normalised to sum to 100% for these tumour sites. The ratio is a helpful way to show the relative difference between the two parameters. Most tumour types have very similar death rates with either mortality indicator, and a number of others have little difference between the two measures. However, five tumour sites (bladder, brain, cervix, prostate and testis) have a rather large difference, with ratios <0.6 or >1.4 . The population burden from bladder and prostate is rather less than suggested by percent survival shortfall. On the other hand, the population burden of cancers of the brain, cervix and testis is rather higher than percent survival shortfall suggesting that crude survival shortfall rate may underestimate burden of these tumours on population.

Discussion

This study reports a comparative assessment of optimal versus actual radiotherapy utilisation as well as the potential effect of shortfalls in utilisation that may lead to benefit shortfall at the population level. This is a projection of the maximum benefit averted due to underutilisation of radiotherapy. Using the YPLL and DALY parameters to represent population burden from radiotherapy underutilisation has added value in quantifying the overall

Table 2
Survival shortfall, years of potential life lost and disability adjusted life years due to radiotherapy underutilisation by tumour site.

Site	Survival shortfall	No. of YPLL per survival shortfall	No. of YPLL per tumour site	No. of DALY per survival shortfall	No. of DALY per tumour site
Bladder	13	3	40	9	121
Brain	15	20	306	23	352
Breast	29	15	428	24	684
Cervix	5	24	110	41	189
Colon	0	0	0	0	0
Gall Bladder	0	0	0	0	0
Head and Neck	49	12	587	17	831
Kidney	0	0	0	0	0
Leukaemia	0	0	0	0	0
Liver	0	0	0	0	0
Lung	64	12	767	13	831
Lymphoma	57	8	454	17	966
Melanoma	0	0	0	0	0
Myeloma	1	10	10	16	16
Oesophagus	3	12	38	14	45
Ovary	0	0	0	0	0
Pancreas	0	0	0	0	0
Prostate	54	3	161	17	911
Rectum	41	10	407	14	570
Stomach	4	14	53	15	57
Testis	12	37	455	50	615
Thyroid	0	0	0	0	0
Unknown Primary	0	0	0	0	0
Uterus	7	10	65	20	130
Vulva	1	7	9	17	22
Other cancers	57	7	398	15	854
Total = 411			Total = 4289		Total = 7192

Abbreviations: YPLL – years of potential life lost; DALY – disability adjusted life years.

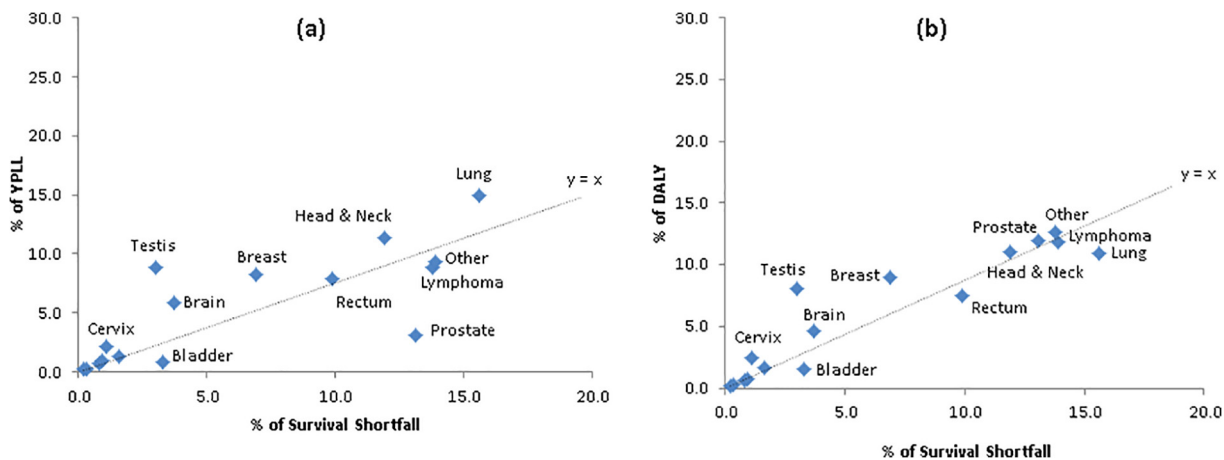


Fig. 1. (a) Years of potential life lost (YPLL) versus survival shortfall, (b) Disability adjusted life years (DALY) versus survival shortfall.

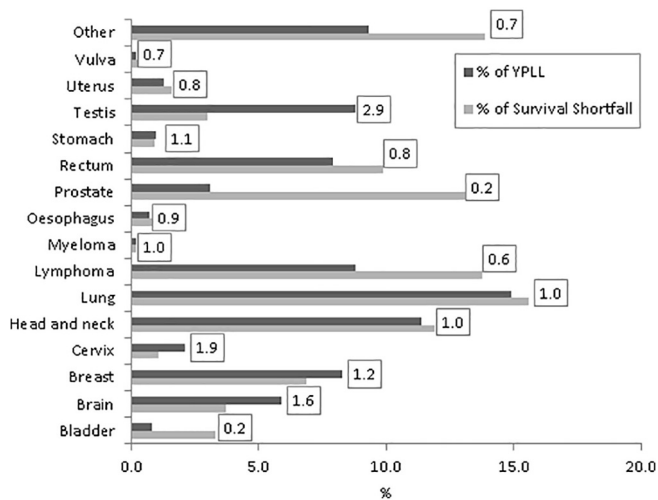


Fig. 2. Percentage of survival shortfall and percentage of years of potential life lost (YPLL). The relative difference between the two parameters of mortality is given by the ratio % YPLL divided by % survival shortfall as shown in the text box.

population effect of underutilisation for individual tumour sites. These measures reflect the impact of radiotherapy underutilisation in terms of human cost better than crude mortality data as estimated by survival shortfall in this study. For each death due to radiotherapy underutilisation, an average of 10 years of potential life before the age of 85 years is lost. The results of this study emphasise the unfortunate impact of radiotherapy underutilisation. Consideration of YPLL and DALY as a survival parameter might therefore be important if cancer deaths from individual tumour sites are to be used to make decisions concerning research support and make a case for investment in radiotherapy resources for specific tumours. Another notable aspect in this comparison of optimal and actual RTU is the potential effect of overutilisation of radiotherapy for some of the cancer sites. For example, in cases of haematological cancer leukaemia, the actual utilisation is 5% over the optimal RTU rate in NSW. This may be because the model underestimates the demand for palliative radiotherapy. The effect of overutilization of radiotherapy on YPLL and DALY was not assessed in this study. Similarly, tumour sites with zero survival shortfalls due to radiotherapy underutilisation were excluded in the YPLL and DALY estimation as these would not have a negative impact on YPLL and DALY.

The biggest difference between YPLL and survival shortfall is seen for tumours of the brain, cervix and testis. These tumours have a substantial incidence in younger patients with median age at diagnosis of 62, 44 and 35 for brain, cervix and testis, respectively. By giving weight to each year of expected life lost, the YPLL measure values deaths at younger ages more. Reduction in the years of potential life lost is an important public health goal as it reflects a reduction in premature death. This might highlight the need to prioritise investigation into reasons for radiotherapy underutilisation in these groups of younger patients.

The different indicators of cancer deaths and cancer burden due to radiotherapy underutilisation show different aspects of the effect of mortality, and are complementary. Several studies have reported reasons for radiotherapy underutilisation, including travel distance, poor access to radiotherapy, lack of referral, and substitution of other treatments such as surgery or chemotherapy [3,7–9,15]. Analysis of cancer mortality and cancer burden together with reason for underutilisation can identify tumour types with extreme impact, either on society or on individual patients as a result of radiotherapy underutilisation. The economic impact of cancer is significant and is increasing. Estimates of the economic burden of cancer have been used to inform decision-making about the allocation of research funding [19,20]. The economic burden of cancer includes the loss of economic resources and opportunities from the perspective of the individual, the family and society [21]. This burden may be heightened for tumours of the brain and cervix with higher incidence in younger patients. Premature mortality due to radiotherapy underutilisation and its contribution to loss of economic opportunities is a key area for further research.

The methodology used in this study has several strengths including robustness to model uncertainties, rapid adaptability and transparency. In addition, these data elements are all derived from publicly available sources allowing for maximal flexibility and accessibility for the re-estimation of benefits in future when newer data become available. These models can also be used as the base models for further cost effectiveness analysis of optimal use of radiotherapy.

There are limitations to the approach described in this study. These include patient's choice of not receiving radiotherapy, variability in model estimates due to controversies in use of radiotherapy, and limitations due to the quality of the available data [12–14]. The methodology of this study assumes that the case mix of patients receiving treatment according to guidelines is identical to the case mix of patients not receiving treatment according

to guidelines. This may lead to inaccurate estimation of the survival impact of underuse of radiotherapy. Although all estimations in this study were based on data from 2006, this provides an indication of the likely impact of radiotherapy underutilisation in NSW.

The benefit models have calculated the potential gains in survival if the results of clinical trials are applied to all patients with indications for radiotherapy in the cancer population of the selected sites. Therefore variations on age, stage comorbidity, consideration of alternative treatment pathways and other demographic factors that are characteristics of population data were not uniformly represented in the data. Although population data sources would be ideally utilised to estimate survival benefit, quality and completeness of stage data in population-based cancer registries is considered as a major factor for variability in survival rates analysed from population based data [22]. To ensure that the literature describing the benefit for individual indications in the model accurately reflected the guideline indications, clinical trials with well-described stage and performance status data were used for the current model wherever possible. We are currently progressing a repeat study with data at the population level to address this limitation.

Gaps in RTU may be more related to patients receiving palliative radiotherapy than curative radiotherapy as optimally recommended [23]. The underuse of curative radiotherapy may also relate more to curative indications where there are acceptable alternatives such as surgery. In cases where there were acceptable alternatives to RT, sensitivity analysis was utilised. Where there is no standard-of-practice alternative treatment to radiotherapy, this indication for radiotherapy may be defined as 'irreplaceable' [12]. Future work could include estimation of the survival shortfall, YPLL and DALY for tumour sites with irreplaceable benefits of radiotherapy. Another limitation of this study is the use of median age at diagnosis and median age at death for specific tumour type when estimating YPLL and DALY. This may not be reflective of actual age of diagnosis and death, resulting in over-estimation or under-estimation of YPLL and DALY. Where there are known limitations of the data, sensitivity analysis was applied to provide some indication of the effect of these issues to the model.

This study illustrates the value of considering different mortality statistics, which include measures of the burden of cancer deaths on both the population and patients. The results suggest that a more subtle and comprehensive calculation of mortality statistics would be useful in relation to resource and research allocation. It also demonstrates the tumour sites that should be further targeted as a public health priority so that steps can be taken to prevent premature mortality due to radiotherapy underutilisation.

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Conflict of interest statement

The authors of this paper declare no actual or potential conflict of interests.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.radonc.2018.06.026>.

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