


ORIGINAL ARTICLE

Individualised selection of left-sided breast cancer patients for proton therapy based on cost-effectiveness

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Abstract

Introduction: The significantly greater cost of proton therapy compared with X-ray therapy is frequently justified by the expected reduction in normal tissue toxicity. This is often true for indications such as paediatric and skull base cancers. However, the benefit is less clear for other more common indications such as breast cancer, and it is possible that the degree of benefit may vary widely between these patients. The aim of this work was to demonstrate a method of individualised selection of left-sided breast cancer patients for proton therapy based on cost-effectiveness of treatment. **Methods:** 16 left-sided breast cancer patients had a treatment plan generated for the delivery of intensity-modulated proton therapy (IMPT) and of intensity-modulated photon therapy (IMRT) with the deep inspiration breath-hold (DIBH) technique. The resulting dosimetric data was used to predict probabilities of tumour control and toxicities for each patient. These probabilities were used in a Markov model to predict costs and the number of quality-adjusted life years expected as a result of each of the two treatments. **Results:** IMPT was not cost-effective for the majority of patients but was cost-effective where there was a greater risk reduction of second malignancies with IMPT. **Conclusion:** The Markov model predicted that IMPT with DIBH was only cost-effective for selected left-sided breast cancer patients where IMRT resulted in a significantly greater dose to normal tissue. The presented model may serve as a means of evaluating the cost-effectiveness of IMPT on an individual patient basis.

Introduction

Comparative planning studies have suggested that proton therapy has the potential to increase sparing of critical structures in the treatment of breast cancers for certain patients.^{1,2} However, Weber et al.² noted that the issues of treatment cost and availability for a common disease could limit the routine clinical use of protons in the post-operative treatment of breast cancer.

While proton therapy is a more expensive treatment than conventional X-ray therapy, it may be justified when costs other than that of the initial treatment are considered over the lifetime of a patient. For some patients, savings may be made if they are treated with

proton therapy, even if the initial cost is greater. When comparing the breast cancer treatment costs associated with proton and photon radiation, Taghian et al.³ found proton treatments to be significantly more expensive. However, they acknowledge that they consider initial treatment costs only and do not include costs of treatment side effects. Lundkvist et al.^{4,5} have utilised Markov modelling with a hypothetical cohort to investigate whether improved outcomes for breast cancer patients who receive proton therapy are sufficient to justify a greater treatment cost. They found the treatment to be cost-effective for patients who had a high risk of developing a cardiac complication as a result of the radiation. Mailhot Vega et al.⁶ have explored dosimetric

scenarios for which proton therapy could be cost-effective in treating breast cancer, with a consideration for the risk of radiation-induced cardiac toxicity. Proton therapy was found to be cost-effective for cases where a patient had a cardiac risk factor and would receive a mean heart dose of greater than 5 Gy if treated with photons. The study did not explore the effects of lung toxicity, radiation-induced cancers, or differences in the probability of tumour control between proton and photon therapies.

Deep inspiration breath hold (DIBH) with X-rays is becoming increasingly common for the treatment of left-sided breast cancer.⁷ This technique can increase the distance between the breast and the heart, reducing heart dose and thereby the risk of radiation-induced heart complications. For patients capable of the breath hold technique, the reduction in risk of radiation-induced toxicity may be negligible with proton therapy. Proton therapy still has the potential to reduce dose to the lung and contralateral breast compared with DIBH with X-rays, however.^{8,9} These organs are sensitive to radiation-induced second primary cancers.¹⁰ It is important these organs at risk are included in an analysis of cost-effectiveness of proton therapy compared with state-of-the-art X-ray therapy.

The objective of the current work was to demonstrate a method for selecting left-sided breast cancer patients for proton therapy based on cost-effectiveness of treatment. As an alternative to the approaches of Lundkvist *et al.*^{4,5} and Mailhot Vega *et al.*,⁶ this work assesses cost-effectiveness through a dosimetric analysis of real comparative treatment plans, on an individual basis. A cohort of 16 real DIBH-capable early-stage breast cancer patients were considered in this work for the purposes of the demonstration. In addition to cardiac toxicity, pneumonitis and second primary cancer induction were included in a Markov chain cost-effective analysis comparing intensity-modulated proton therapy (IMPT) with hybrid three-dimensional conformal radiotherapy (3DCRT)/intensity-modulated radiotherapy (IMRT) with X-rays. The transition probabilities of the Markov model were based on radiobiological models of tumour control probability (TCP), normal tissue complication probability (NTCP) and second primary cancer induction probability (SPCIP). The effect of second malignancy induction can be significant for breast cancer patients.¹⁰ These probabilities were derived on an individual basis from their comparative proton/X-ray radiotherapy treatment plans. The model was used to predict the likely outcome after a given treatment for each of the patients in the cohort in terms of life expectancy and quality-adjusted life expectancy (QALE). Costs of primary and subsequent treatment were also included to determine the cost per quality-adjusted life year (QALY) gained for protons

compared to X-rays, also known as the incremental cost-effectiveness ratio (ICER).

Methods

Patient cohort and treatment planning

The cohort of patients considered in this retrospective study consisted of 16 female left-sided breast cancer patients treated with X-ray radiotherapy. The median age was 56 years (range 36-74). 50% of diagnoses were invasive ductal carcinoma, but diagnoses also included invasive lobular carcinoma, papillary carcinoma, ductal carcinoma in situ, and apocrine carcinoma. A majority of patients were stage T1 (68%) and N0 (87.5%). As patients with metastatic disease were excluded from the study, most patients were M0, with one patient Mx (unable to be assessed for distant metastases). All patients had breasts intact and the whole breast was modelled in treatment planning.

Each patient had a computed tomography (CT) scan acquired with DIBH. The clinical target volume (CTV) included apparent CT glandular breast tissue and lumpectomy CTV. In this retrospective analysis, each patient had two new treatment plans created. The prescribed dose was 40 Gy_{RBE} in 15 fractions. Planning objectives for the heart were $D_{\text{mean}} < 3$ Gy and $V_{21.5\text{Gy}} < 10\%$, for the left lung $V_{18\text{Gy}} < 15\%$ and as low as reasonably achievable doses to the left anterior descending artery, right lung, and right breast.

The X-ray treatment plan made use of the 3DCRT/IMRT hybrid technique (h-IMRT). The plans consisted of opposing tangential fields with 70% and 30% weighting of the 3DCRT and IMRT beams in each tangent respectively. 6 MV beams were used unless the size of the breast required the use of 10 MV beams in the 3DCRT beam to reduce lateral hotspots and improve target coverage. IMRT beams were optimised to a planning target volume, defined as the CTV with a 5 mm margin limited to within the exterior of the patient minus 5 mm and excluding the left lung. Treatment plans were created to achieve 98% coverage of the planning target volume (PTV) with 95% of the prescribed dose.

IMPT plans were created with a single *en-face* beam. A range-shifter was used to allow the placement of Bragg peaks close to the patient surface. A beam-specific PTV was generated with an expansion of 5 mm laterally and 3% of the beam range distally. Two patients were duplicated and replanned to test planning consistency. These data have been reviewed by the Royal Adelaide Hospital Research Ethics Committee. Informed consent was obtained from all individual participants included in the study.

Markov model

A discrete-time Markov chain model was applied in this work.¹¹ The time period modelled begins immediately after the final fraction of radiotherapy treatment and ends when the patient is deceased. The cycle length was chosen to be one year.

A patient can occupy only a single Markov state at a given time. These states are summarised in Figure 1. The toxicities considered included pneumonitis and heart disease. The possibility of developing a second primary cancer (SPC) as a result of the initial radiation treatment was also included.

The following assumptions were made when determining the Markov states to be used in the model:

- Pneumonitis, if developed, is likely to resolve many years prior to the induction of a second primary cancer. Therefore, there are no states for the situation where a patient is affected by both pneumonitis and a second primary cancer.
- If a treatment is unsuccessful, it is assumed that it is highly unlikely that the patient will still be alive when the probability of developing a second malignancy is significant. Therefore, there are no states where the initial cancer and a second cancer coexist.

Markov state transition probabilities

Markov models in medical applications assume that a patient occupies a single state for the duration of a cycle. At the end of each cycle, it is possible for a patient to transition to another state. The allowed transitions are summarised in Figure 1.

The following assumptions were made when determining the allowed transitions in the model:

- It is not possible to recover from heart disease or a second cancer once it has developed.
- The patient may begin the Markov process in either the Well state or the Cancer state (details in Locoregional control Section). It is not possible to transition between these two states once the first Markov cycle has begun.
- There is a large difference in the time point after treatment at which the second primary cancer induction probability (SPCIP) becomes significant compared to the time point where the NTCP is significant for the toxicities considered. Therefore, the probability of simultaneously developing an injury and second cancer is negligible. Similarly, the probability of developing an injury after a second cancer is also negligible.

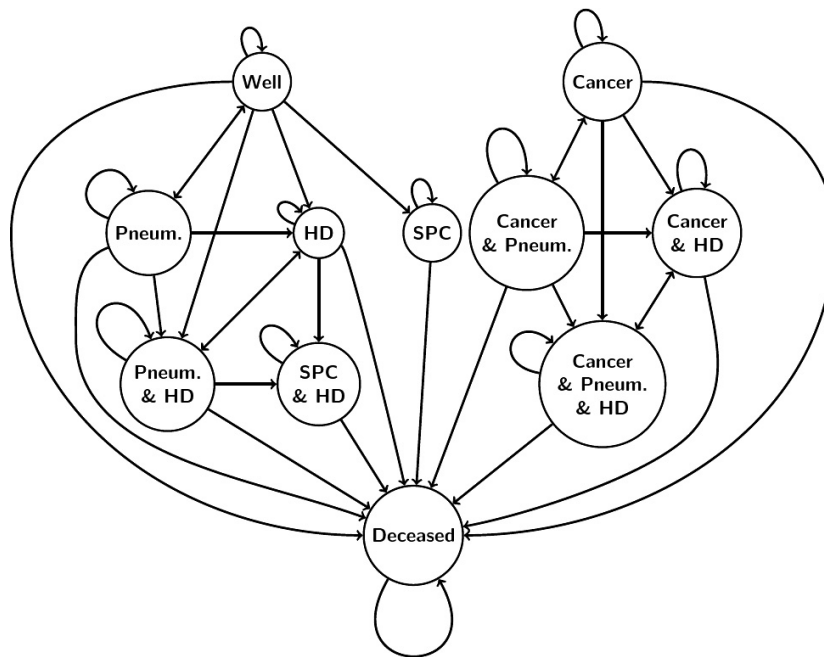


Figure 1. The Markov state transition diagram showing the allowed transitions between states. 'Well' represents perfect health. 'Cancer' represents the situation where the patient still has the initial primary breast cancer, 'SPC' represents a second primary cancer, 'Pneum' refers to pneumonitis and 'HD' represent heart disease.

- Once pneumonitis has been recovered from, the model ensures that it is not possible to relapse.

The transition probabilities are explained in more detail in Locoregional control, Normal tissue complications, Second primary cancer induction and Death probabilities Sections.

Locoregional control

The probability of the patient beginning in the Well state is equal to the dose-dependent TCP (defined in the Supporting Information), while the probability of beginning in the Cancer state is the complement of the TCP. Re-treatments are not directly included in the model. This is assumed as the outcome of the initial treatment is the focus of this selection tool. Similarly, while there were no explicit states for metastases, the cancer death probabilities incorporate this implicitly in the model.

Normal tissue complications

The probability of pneumonitis is calculated using the radiation dose to both lungs. The probability of heart disease is calculated with the dose to the heart. These transition probabilities are time-dependent to allow for a more realistic estimation of costs and QALYs. The details of the calculations are described in the Supporting Information.

The majority of patients with pneumonitis recover.¹² It was assumed that recovery would occur after 1 year as all estimated costs associated with treating this injury applied within the first year only. It was assumed that heart disease was chronic, and the possibility of recovery was neglected in this work.

Second primary cancer induction

The SPCIP is the probability of developing a radiation-induced cancer as a result of the treatment. This is an important consideration due to the expected difference in integral dose between a proton and photon plan. This is also a dose- and time-dependent quantity and was calculated using the model developed by Schneider *et al.*¹³ The relevant formula and input data are described in the Supporting Information.

Death probabilities

Unlike the other transition probabilities described in this section, the probability of transitioning to the Deceased state is dose-independent. The purpose of this study was

to evaluate the cost-effectiveness from a dosimetric point of view and while the death probabilities are not dosimetric quantities, they allow for a more realistic estimate of the number of QALYs gained as a result of a given treatment. Depending on the Markov state of a patient, there are a number of possible transitions that can be made to the Deceased state:

- Death due to breast cancer as a result of an unsuccessful treatment. Survival of breast cancer patients was found to be 55% at 10 years for the case of local failure.¹⁴ A constant yearly death probability, denoted $Pr(Die)$, was derived from this data, where $S = (1 - Pr(Die))^n$, $n = 10$ is the number of years after treatment, and $S = 0.55$ is the surviving fraction. Solving for the death probability gives 0.06.
- Death due to a second malignancy. The 5-year survival for all cancers combined is 68%.¹⁵ Using the same method for the breast cancer death described above, a yearly death probability of 0.08 was derived.
- Death due to heart disease. The probability was assumed to be 0.01 per year which was estimated using 2007 prevalence (3.5 million) and death rates (48, 456) associated with cardiovascular disease in Australia.¹⁶
- Unrelated death. This time-dependent probability is based on data from life tables obtained from the Australian Bureau of Statistics (ABS).¹⁷

Note that as recovery from pneumonitis is highly likely, it was assumed that this injury was non-fatal.

Estimation of quality of life utilities

The quality of life (QoL) utility value of each Markov state represents the quality of life associated with the state relative to perfect health (with $QoL = 1$). By default, the quality of life associated with death is 0. The utilities used in the current work are listed in Table 1.

For states where there is more than one injury or cancer, the assigned utility is a multiplication of the utilities of the states where there is only one of each injury or cancer. The state representing the cases of second primary cancers was assigned a value of 0.8 in

Table 1. Estimates for the yearly costs and quality of life utilities for states in the Markov model. Details of the cost estimations are given in the Supporting Information.

State	Utility	Cost (AUD \$)
Breast cancer	0.89 ²²	15,960
Heart disease	0.8 ²³	13,658
Pneumonitis	0.8 ²³	4,037
Second primary cancer	0.8 ¹⁸	15,960

accordance with the Eastern Cooperative Oncology Group (ECOG) performance status¹⁸ as their definition of a grade 1 complication gives the most accurate description of this state.

Estimation of costs

In addition to the cost of the breast cancer treatment, costs of side-effect treatments were also incorporated into the model to allow for a more realistic representation of the costs associated with a given treatment. The costs of re-treatments and treatments of second cancers were not included. No costs were assumed for fatal events, only loss of QALYs. For states where several injuries affect a patient, the cost applied was the sum of the costs for the individual injuries. Furthermore, if a cancer is present along with at least one injury, then this cost is also added to the total cost of the state. Costs and QALYs were discounted by 3% annually, to adjust for differences in timing of costs and effects. Where possible, Australian costs were applied for consistency and all costs are in Australian dollars (AUD). These are summarised in Table 1. The details of the cost estimation are given in the Supporting Information.

Results

The ICER was calculated for each patient in the cohort. The results are given in Table 2. In accordance with the NICE guidelines,¹⁹ IMPT was considered cost-effective if it cost £20,000 (\$36,000) per QALY gained or less compared with h-IMRT.

Proton therapy was cost-effective for one patient in the cohort and cost-ineffective for 15 patients. Both members of both sets of the duplicated patients were classified as cost-ineffective. The difference in the ICER calculated for patient 3 and the ICER calculated for its replanned duplicate was approximately \$8,000. For patient 8, the difference between the ICER and the ICER of the duplicate was \$6,000.

Sensitivity analysis

Variation of selected parameters altered the fraction of the cohort that could be treated with IMPT cost-effectively.

Parameters related to second cancers were varied as these had a large impact on whether a patient was classified as cost-effective. These included costs, the utility, and the death probability. In contrast, the TCP difference between the treatments did not exceed 0.01 for any of the patients. Therefore, it is unlikely that variation of related parameters would impact the results.

Table 2. Predicted life expectancies and costs for each patient. The cost of protons per QALY gained is listed. Duplicated patients are denoted by an asterisk. QALY = quality-adjusted life year. QALE = quality-adjusted life expectancy = number of QALYs lived. ICER = incremental cost-effectiveness ratio.

Patient ID	Treatment	Raw LE (y)	QALE (QALYs)	Costs (AUD \$)	ICER (\$/y)
1	IMPT	48.2	25.48	39,040	73,950
	IMRT	47.6	25.26	22,470	
2	IMPT	19.0	14.38	31,430	107,130
	IMRT	18.8	14.21	13,650	
3	IMPT	38.9	22.91	38,040	122,700
	IMRT	38.6	22.77	20,740	
3*	IMPT	38.9	22.88	38,160	128,640
	IMRT	38.6	22.75	21,050	
4	IMPT	22.3	16.16	31,720	49,610
	IMRT	21.9	15.80	13,960	
5	IMPT	19.0	14.40	31,430	79,660
	IMRT	18.8	14.17	13,660	
6	IMPT	33.4	21.02	37,000	89,980
	IMRT	33.1	20.83	20,000	
7	IMPT	25.6	17.78	33,760	46,640
	IMRT	25.2	17.41	16,450	
8	IMPT	33.5	21.07	36,490	54,730
	IMRT	33.0	20.77	20,180	
8*	IMPT	33.4	21.01	37,050	60,910
	IMRT	33.0	20.74	20,550	
9	IMPT	18.2	13.94	31,360	67,800
	IMRT	18.0	13.67	13,600	
10	IMPT	21.4	15.69	31,650	87,370
	IMRT	21.2	15.48	13,910	
11	IMPT	36.2	22.00	37,660	237,110
	IMRT	36.0	21.92	20,110	
12	IMPT	15.0	12.03	31,040	99,620
	IMRT	14.9	11.85	13,410	
13	IMPT	18.1	13.92	31,360	90,840
	IMRT	18.0	13.73	13,920	
14	IMPT	30.7	19.96	36,450	26,750
	IMRT	29.9	19.38	20,780	
15	IMPT	40.6	23.42	38,660	52,680
	IMRT	40.0	23.12	22,540	
16	IMPT	29.0	19.26	35,480	45,820
	IMRT	28.5	18.90	18,800	

Due to the relatively small NTCP for pneumonitis (see Supporting Information), no parameters relevant to pneumonitis were considered to have a significant effect on the results. Even if the NTCP difference were larger between the two treatments, the relatively small cost and duration of pneumonitis would result in a minimal effect on the results. The exception was the possibility of this injury becoming chronic in a fraction of patients.

There was not a significant difference in the heart disease NTCP between IMPT and h-IMRT for any of the patients (see Supporting Information). The only parameter

Table 3. The effect of model parameter variation on the percentage of the cohort that could be treated with IMPT cost-effectively. The ratio of the treatment costs was varied by varying the proton treatment cost.

Scenario	Percentage cost-effective
No parameter variation	6
Decreased proton/photon cost ratio to 1.5	88
Increased proton/photon cost ratio to 3.5	0
Decreased recovery rate of pneumonitis to 80%	6
Decreased second cancer death probability by 50%	0
Increased second cancer death probability by 50%	6
Decreased second cancer cost to 75%	6
Increased second cancer cost to 125%	6
Decreased second cancer utility by 10%	6
Increased second cancer utility by 10%	6
Doubled baseline risk of heart disease	6

related to heart disease that was varied was the baseline risk. This parameter was doubled in the sensitivity analysis to investigate whether high risk groups could be treated with protons cost-effectively. Treatment cost ratios were varied by varying the proton treatment cost, as this was considered to have the greatest uncertainty.

After selecting parameters that were most likely to influence the results, a sensitivity analysis was performed for each. The results are presented in Table 3. As expected, if IMPT could be delivered at a lower cost (1.5 times that of IMRT), then a significantly greater proportion of the cohort could be treated with IMPT cost-effectively. Proton therapy was also less likely to be cost-effective where there was a reduced probability of death due to second cancer induction. The results were stable with variation of other model parameters.

Discussion

The Markov model predicted that IMPT could not be delivered cost-effectively to the majority of patients in the cohort investigated. The patient that could be treated cost-effectively had a comparatively high lung dose (see Supporting Information) which increased the second cancer risk. The higher lung dose was necessary to spare breast tissue in this patient who had relatively larger breasts. This was also a younger patient (less than the assumed retirement age at the time of treatment), and hence, in the model they had the potential to be less productive in society as a result of second malignancy. Alternatively, the difference in normal tissue doses between treatments was smaller for the remainder of the cohort. The differences in ICER for the replanned (duplicated) patients are due to small differences (up to 0.1 years) in the number of QALYs in the denominators.

The sensitivity analysis indicated that, as expected, the initial cost of the proton treatment had the largest impact on whether a patient could be treated cost-effectively. However, it is anticipated that the cost of proton therapy will decrease over time as it is a newer treatment. Furthermore, it is likely that the initial cost of building a proton clinic would have a large contribution to this cost. This cost can be increasingly justifiable with an increasing number of patients who are expected to benefit from the treatment. If breast cancer patients could be included in this category, then proton clinics may be more viable as current standard indications are predominantly relatively rare or paediatric cases.

The mean heart dose did not exceed 4 Gy for any treatment for any of the patients (see Supporting Information). This is likely a result of the DIBH technique, which is designed to reduce exposure to the heart. Mailhot Vega *et al.*⁶ found that for a proton treatment of breast cancer to be cost-effective, it was necessary for the mean dose to the heart from photons to be greater than 5 Gy. Hence, the results presented here are consistent with this finding.

The average predicted ICER of \$84,600 was smaller than the average predicted by Lundkvist *et al.* of €67,000 (\$105,000).⁴ Our estimation of the ratio of proton therapy to photon therapy costs is similar (2.5 in this work compared with 2.6). Their estimation of the probability of death due to breast cancer was lower than ours, but it is unlikely that this alone would influence our results significantly due to the relatively small difference in the expected TCP between IMPT and IMRT for the patients in our cohort. Therefore, the discrepancy is likely due to our inclusion of costs associated with the possibility of radiation-induced cancers.

While an ICER of £20,000 was assumed to be the threshold for a treatment to be cost-effective in this work, according to the NICE guidelines¹⁹ the threshold can be as large as £30,000 (\$54,000) if advisory bodies can make a strong case in support of the intervention. If this threshold were to be assumed here, an additional 4 patients would have a cost-effective proton treatment (31% of the cohort in total). These patients had relatively large lung dose differences between the two modalities, corresponding to larger SPCIP differences.

There are several assumptions in the Markov model that may have influenced the results. For example, re-treatments were omitted as the alternate treatments of the initial cancer are the subject of comparison in the model. However, the results may be less realistic as a consequence of this assumption. In reality, re-treatments would likely occur and this would contribute to costs. In addition, loss of life is assumed to have no cost. Including each of these factors would increase the

likelihood of a proton treatment being cost-effective, assuming it resulted in improved tumour control and reduced second cancer rates.

Acute toxicities are not included in this version of the model; however, this could easily be altered for a future version, if required. The Markov cycle length is a constant and was chosen to be one year. A result of this is that events that occur immediately after treatment, such as the onset and resolution of acute toxicities, cannot be modelled accurately in the temporal domain. However, the importance of computational efficiency must also be considered when selecting a cycle length for the model. While acute toxicities can have an important effect, the focus of this work was late effects which tend to have a greater effect on the model prediction due to the longer time spent in a state with a lower utility.

The radiobiological models that are built into the Markov model also have limitations. For example, the model used to estimate the probability of developing heart disease was developed using data from both left- and right-sided breast cancer patients. The effect of this is that the true NTCP may be underestimated, which could have contributed to the relatively small probabilities that were obtained for each of the patients despite a wide variation in mean heart dose. For the transition probabilities more generally, uncertainties in radiobiological model parameters and planned dose can influence model-based patient selection for proton therapy.²⁰

The sample size in this work is another limitation. The aim of this work was to demonstrate a method of patient selection for proton therapy, rather than to assess the cost-effectiveness of proton therapy as a treatment for breast cancer as an indication. Caution should be exercised when using these results for the latter purpose.

The effects of individual tumour characteristics were not considered directly. These characteristics can affect individual outcomes and therefore could have affected the results presented here. An example is HER2 status, as HER2 targeted therapies can increase the risk of cardiac toxicity.²¹ Therefore, patients with HER2 positive breast cancer could potentially benefit significantly from proton therapy. While variations in the baseline risk of heart disease were considered in this work, consideration of more specific risk factors could increase the accuracy of the predictions. These effects could possibly be incorporated in future work.

It is worth noting that the patients considered in this study represent a subset of breast cancer patients who are able to hold their breath during treatment. This is not the case for all breast cancer patients, particularly those who are elderly. It may be possible to treat patients cost-effectively if they are not able to hold their breath or have suspected nodal involvement and therefore would

experience a higher risk of cardiac toxicity if treated with X-rays.

Conclusion

The cost-effectiveness of proton therapy for a cohort of left-sided breast cancer patients capable of being treated with DIBH has been assessed with a Markov model. It was found that proton therapy was not a cost-effective treatment for the majority of the cohort. However, patients that would receive an increased lung dose if treated with X-rays, leading to an elevated risk of second malignancy, could be treated with IMPT cost-effectively. The presented model has the potential to evaluate the cost-effectiveness of treatments on a case-by-case basis, facilitating the delivery of individualised medicine and ensuring the efficient usage of healthcare resources.

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Conflicts of Interest

Scott Penfold works part-time for Commercial & General. The other authors have no conflicts to disclose.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Supporting Information: Additional details of Markov model input.