Cost-effectiveness of using protons in breast cancer patients aiming at reducing cardiotoxicity: A risk-stratification analysis

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Research Article

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Abstract

Purpose

Incidental exposure of heart to ionizing irradiation is associated with an increased risk of ischemic heart disease (IHD) in breast cancer patients after radiotherapy. Intensity-modulated proton radiation therapy (IMPT) offers a promise in limiting the mean heart dose (MHD) in breast irradiation to a negligible level. However, the uncertainty in cost-effectiveness hinders its use. This cost-effectiveness analysis aims to identify patients in appropriate risk groups as targets for IMPT.

Methods

A Markov decision model was designed to evaluate the cost-effectiveness of IMPT versus intensity-modulated photon-radiation therapy (IMRT) in reducing the irradiation-related IHD risk. Baseline evaluation was performed on 50-year-old women patient without preexisting cardiac risk factor (CRF). Stratified for preexisting cardiac risk and photon MHD, cost-effective scenarios under different proton cost and willingness-to-pay (WTP) were identified for 40-, 50- and 60-year-old patients.

Results

With baseline set-ups, incremental effectiveness (IE) ranged from 0.025 quality-adjusted life-year (QALY) to 0.135 QALY when photon MHD varied from 3 to 16 Gy; IE increased from 0.043 QALY to 0.964 QALY when preexisting cardiac risk increased from the baseline level to its 10 times. IMPT was not cost-effective to patients without preexisting CRF. At the WTP of China, once proton cost reduced to $20,000, IMPT would be cost-effective to ≤ 50-year-old women patients having preexisting cardiac risk of general-population level.

Conclusion

Patient’s preexisting cardiac risk level should be a main consideration for the clinical decision of using protons; protons may become cost-effective to general-level patients if a substantial decrease in proton cost occurs in the future.

Introduction

Breast cancer (BC) has surpassed lung cancer as the most commonly diagnosed cancer. Every year, an estimated 2.3 million population worldwide are diagnosed with BC, accounting for 11.7% of all new cancer cases [1, 2]. Radiotherapy serves as a standard therapeutic procedure for BC patients after breast-conserving operation and BC patients of intermediate or high risk of locoregional recurrence after mastectomy. However, the effect of postoperative radiotherapy in improving overall survival is still in dispute [3, 4]. Most investigators believe that this should be due to the incidental exposure of heart to ionizing irradiation, which increases the risk of ischemic heart disease (IHD) and the subsequent mortality [5, 6]. In the era of photon irradiation, irradiation-related IHD is recognized as the leading cause of excess non-cancer death and a main deteriorating factor for life quality in BC survivors [7]. New technologies of low cardiotoxicity are urged to optimize the irradiation efficacy for BC patients.

Proton beam therapy is a rapidly evolving particle irradiation modality with superior dose distribution afforded by protons’ “Bragg peaks” [8]. Its advanced form, the intensity-modulated proton radiation therapy (IMPT) enabled to limit the mean heart dose (MHD) to a level of < 0.5 Gray (Gy) while maintaining excellent tumor control in breast irradiation; in comparison with the intensity-modulated photon-radiation therapy (IMRT), which often leads to an MHD range of 5 to 16 Gy [9–11]. However, proton irradiation is also associated with an increase of medical expense, with the cost ratio (cost of IMPT/ cost of IMRT) ranges from 3.2 to 4.8. The uncertainty in cost-effectiveness hinders its use in BC patients [12].

Previous cost-effectiveness analysis (CEA) studies indicated that protons could be cost-effective to BC patients when it enabled to reduce photon-induced IHD risk to a certain extent, and the absolute risk reduction mainly depends on the estimated MHD in photon irradiation and the patient’s preexisting cardiac risk status [13, 14]. A population-based case-control study by Darby et al. found a linear relationship between MHD and the incidence of IHD, which showed that each Gy increase in MHD correlates with a 7.4% increase in IHD risk, so the preexisting cardiac risk acted as the base in such irradiation-related IHD risk increase [15]. Preexisting cardiac risk in BC patients may be due to “traditional” cardiac risk factors (CRFs, such as abnormal lipids, high blood pressure, diabetes and smoking) or potential use of anticancer agents known to affect the heart (such as anthracycline, trastuzumab and taxanes) [16, 17]. In a population-based survey by Boekel et al., anthracycline-based chemotherapy was found to be associated with an increased IHD risk (HR = 1.5), and the effect doubled when combined with an internal mammary chain (IMC) irradiation [18]. Therefore, to identify the “cost-effective” risk groups as targets for protons, both the irradiated and non-irradiated (preexisting) cardiac risks of the BC patients should be stratified. Till present, no such risk-stratification study has been conducted.

Herein, we designed a CEA model to evaluate the cost-effectiveness of IMPT versus IMRT in terms of reducing the irradiation-related IHD risk, in light of photon MHD and preexisting cardiac risk. Our aim is to estimate the cost-effective scenarios as to facilitate the medicoeconomic decision making on protons in BC population.

Methods

Model design

The TreeAge Pro 2018 software (TreeAge, Williamstown, Massachusetts) was used for model building and statistical analyses. A two-arm Markov decision model (IMPT versus IMRT) was built based on the following assumptions: (1) the advantage of IMPT over IMRT lied in its ability in reducing the IHD risk. The IHD risk includes the risk of fatal IHD (IHD death) and the risk of nonfatal IHD (including nonfatal acute myocardial infarction, angina pectoris, and ischemic heart failure) [15, 19, 20]; (2) a constant 0.5 Gy of MHD was assumed for all proton irradiations, in comparison to different MHD yielded in photon irradiations [9, 13]; (3) tumor control was identical between the two strategies.

General structure of Markov model is illustrated in Figure 1. Five states of “healthy”, “nonfatal IHD”, “IHD death”, “cancer death” and “other death” were used to simulate the natural process of BC patient after radiotherapy. The two strategies experienced a background 5-year survival rate of 94% due to cancer death [21]. The risk of “other death” was calculated based on the 2016 Life Tables of the United States [22]. A 1-year cycle length was used and the Markov models were cycled from the end of radiotherapy until the age of 80-year-old, to evaluate the cost-effectiveness over a lifetime horizon.

Risk of ischemic heart disease

The risk of “IHD death” in CEA model was set according to the annual IHD death risk data reported by Darby et al. [15] (**Supplementary Table S1**). The risk of “nonfatal IHD” was set to be 5 times, 4 times, 2 times, and one times the corresponding “IHD death” risk for the age levels of <50, 50-59, 60-69, and <70, respectively [15]. The final cumulative IHD death risk and total IHD risk by the 80-year-old were calibrated to be exactly the same as the cumulative risk data reported by Darby et al. [15] (**Supplementary Table S2 and Table S3**), in which irradiation-related IHD risk increased linearly with the MHD by 7.4% per Gy. General-population IHD risk data from the Framingham Heart Study was applied to estimate the cost-effective scenarios in patients having preexisting cardiac risk of non-irradiated general-population level [18]; and the preexisting cardiac risk in BC patients who received anthracycline-based chemotherapy was assumed to be 1.5 times that in those patients who did not receive (**Supplementary Table S4**) [23].

Baseline set-ups

Baseline evaluation was performed on a 50-year-old postmenopausal women patient who had a stage II (T2N1M0) left-sided invasive ductal carcinoma and no preexisting CRF. The patient received breast irradiation after the breast-conserving operation. We initially assumed that the photon MHD in the irradiation using IMRT was 5 Gy. Accordingly, her IHD death risk and IHD risk by the age of 80-year-old were set to be 2.0% and 4.6% in the IMPT irradiation (proton MHD of 0.5 Gy); 2.7% and 6.1% in the IMRT irradiation (photon MHD of 5 Gy) [15].

Stratified analysis

CEA model were set and analyzed separately for 40-, 50- and 60-year-old patients. Stratified analyses were performed to evaluate the cost-effectiveness under different photon MHD and preexisting cardiac risk. The photon MHD range from a minimum of 1 Gy to a maximum of 20 Gy was analyzed. 1 to 8 Gy was considered to be the photon MHD range of ordinary breast irradiations; 9 to 20 Gy was considered to be the photon MHD range of certain special irradiations, such as IMC irradiation or synchronous bilateral BC (SBBC) irradiation [9, 18, 24]. Using no preexisting CRF as baseline, cost-effectiveness under different preexisting cardiac risk levels were analyzed by gradually increasing such risk level from 1 to 10 times.

Costs and utilities

The treatment regimens of the 2 compared strategies were similar except for the irradiation technique (IMPT/IMRT). The prescription dose for postoperative breast irradiation was a 50 Gy (at 2 Gy per fraction) to the breast / chest wall and lymph node regions plus an additional 16 Gy (at 2 Gy per fraction) to the tumor bed / mastectomy incision [25]. All costs were adjusted to US dollars ($), using a Sino-US exchange rate of $1 = 6.47 RMB (February 28, 2021). Our method for cost estimation has been reported previously [26, 27]. The cost of IMPT for breast irradiation in China was assumed as $50,000 based on the current charge standard in the Shanghai proton and heavy Ion Center in China; other 3 proton cost levels ($40,000 / $30,000 / $20,000) were adopted to simulate potential cost variation due to regional differences, different dose-fractionation schedules, or proton technology upgrade. A constant $12,000 was estimated as the cost for breast irradiation using IMRT. The management of IHD followed the guidelines recommended by the American College of Cardiology [28, 29]. We assumed that “nonfatal IHD” patients would receive once percutaneous coronary intervention (PCI) to treat ischemic symptoms, and the cost for PCI was estimated as $10,000, simulating the costs for the interventional cardiology materials (1.5 stents, catheters, guide wires, balloons and microcatheters) and other costs for operation, anticoagulant drug, blood tests, and hospitalization. The annual treatment costs for nonfatal IHD were estimated as $2,000, simulating medical care for ischemic symptoms or the maintenance after PCI (including a daily b-blocker, aspirin, angiotensin-converting enzyme inhibitor, and statin, in addition to tests at diagnosis of both rest and stress electrocardiogram, hemoglobin level, and fasting lipid panel).

The utility was adjusted to quality-adjusted life-year (QALY) using health state utility values (HSUVs). On the basis of published data, the HSUVs for the states of “healthy” were standardized as 0.95, simulating a disease-free state after the radical anticancer treatment [30]; HSUVs for the states of “nonfatal IHD” were standardized as 0.695, simulating the cardiovascular symptoms caused by nonfatal IHD (angina pectoris) [13, 31]. Half-cycle corrections were performed to minimize discretization errors in the continuous Markov process [32]. The costs and QALY were discounted at an annual rate of 3% [33].

Sensitivity analysis

Probabilistic sensitivity analysis (PSA) was performed to examine the robustness of the model in light of a joint uncertainty for cost and utility parameters by running over 50,000 iteration trials, and 90% confidence interval (CI) of the parameters were identified. The parameters of utility were tested using beta distributions, and the parameters of cost were tested using uniform distributions. Tornado diagram was used to evaluate the influences of the parameters on cost-effectiveness by varying each parameter over their 90% CI identified in PSA.

Outcome measures

The outcome measure of the CEA was the incremental cost-effectiveness ratio (ICER), which represents the ratio of the difference in costs to the difference in treatment effectiveness (incremental cost / incremental effectiveness [IE]) between IMPT and IMRT. IMPT was considered cost-effective if the ICER value was below an established societal willingness-to-pay (WTP) threshold. According to the World Health Organization guidelines, a strategy is defined as cost-effective if the ICER value is below 3 times the gross domestic product (GDP) per capita [34]. Thus, $33,558 / QALY (3 times the Chinese GDP per capita in 2020) was applied as the societal WTP threshold of China in 2021 [35]. Other 2 common WTP thresholds ($50,000/QALY and $100,000/QALY) were also adopted in this study.

Results

Model robustness verification

The model information and set-ups are summarized in Table 1. The model robustness verification was conducted with the baseline set-ups. **Supplementary Figure S1** displayed the results of Markov cohort analyses and confirmed that the cumulative IHD death risk and total IHD risk by 80-year-old were 2.0% and 4.6% in the IMPT strategy, and 2.7% and 6.1% in the IMRT strategy; such exactly corresponded to the data of Darby et al. [15]. The tornado diagram examining the robustness of utility and cost parameters demonstrated that only the cost of IMPT had an obvious impact on ICER. When the cost of IMPT varied from $37,060.5 to $62,933.8 (90% CI in PSA), ICER ranged from $579,499.2/QALY to $1,179,828.2/QALY. The impacts from the utility of “healthy”, the utility of “nonfatal IHD” and the cost of IMRT were relatively limited and changing individual parameters did not lead to a notable change in ICER; the impact from other parameters was insignificant (**Supplementary Fig. S2**). In the baseline case, IMPT provided 0.043 QALY at an additional cost of $37,915.1, the ICER (IMPT versus IMRT) was $879,729.9/QALY.

Table 1
Model information and set-ups

Parameters	Input information	Source / Reference
Evaluated treatment strategies	IMPT versus IMRT	
IHD risk		
Annual death risk from IHD	Supplementary Table 1	[15]
Cumulative risk of IHD death	Supplementary Table 2	[15]
Cumulative risk of IHD	Supplementary Table 3	[15]
Non-irradiated general-population IHD risk	Supplementary Table 4	[18, 23]
Utilities (QALY)		
Healthy	0.950	[30]
Nonfatal IHD	0.695	[31]
Death	0	
Cost ($)[a]		
IMPT	20,000 / 30,000 / 40,000 / 50,000	[26, 27]
IMRT	12,000	[26, 27]
PCI	10,000	[28, 29]
Treatment for nonfatal IHD / year	2,000	[28, 29]
Follow-up / year	1,000	[26, 27]
Baseline set-ups		
Patient age	50-year-old	Assumption
Tumor stage	T2N1M0, Stage II	Assumption
Proton MHD	0.5 Gy	Assumption
Photon MHD	5 Gy	Assumption
Preexisting cardiac risk factor	None	Assumption
IMPT cost ($)	50,000	[26, 27]
Markov model basic set-ups		
Cancer death risk	0.06 (5-year)	[21]
Non-cancer death risk	Life Tables 2016	[22]
Cycle length	1-year	
Number of cycles[b]	80 - patient age	
Discount rate / year	3%	[33]
Willingness-to-pay ($/QALY)	33,558 / 50,000 / 100,000	[35]

IMPT intensity-modulated proton radiation therapy, *IMRT* intensity-modulated photon-radiation therapy, *MHD* mean heart dose, *Gy* Gray, *IHD* ischemic heart disease, *QALY* quality-adjusted life-year, *$* US dollars, *PCI* percutaneous coronary intervention

[a] All costs were derived from institutional chart review.

[b] Markov models were to be cycled “80 - patient age” times to evaluate the outcomes over a time-period from the age of receiving the radiotherapy to the age of 80-year-old. The number of cycles for 40-, 50-, and 60-year-old patients were 40, 30, and 20, respectively.

Cost-effectiveness and irradiated/non-irradiated cardiac risk

With the baseline set-ups, the IE (IMPT versus IMRT) ranged from 0.025 QALY to 0.135 QALY when the photon MHD varied from 3 to 16 Gy (Fig. 2a), the corresponding ICERs ranged from $1,528,810.0/QALY to $280,919.6 /QALY under a IMPT cost of $50,000; the IE ranged from 0.043 QALY to 0.964 QALY when the preexisting (non-irradiated) cardiac risk varied from the baseline to its 10 times (Fig. 2b), the corresponding ICERs ranged from $879,729.9/QALY to $39,299.2/QALY under a IMPT cost of $50,000. The corresponding ICERs under different proton cost levels ($50,000, $40,000, $30,000 and $20,000) were evaluated separately for 40-, 50- and 60-year-old patients (**Supplementary Table S5 - S10**).

Cost-effective scenarios

Using 3 different WTP thresholds ($33,558/QALY, $50,000/QALY and $100,000/QALY), the cost-effective thresholds of the photon MHD (beyond which protons was considered as “cost-effective”) were identified for different preexisting cardiac risk levels and different proton cost levels, displayed in Fig. 3a,b,c separately for 40-, 50- and 60-year-old patients. Under the costs and WTP set-ups of this study, IMPT was found not cost-effective to women patients without preexisting CRF.

For women BC patients who have preexisting cardiac risk of non-irradiated general-population level, under the current IMPT cost ($50,000) and WTP ($33,558 / QALY) of Chinese society, IMPT was cost-effective to 40-year-old patients with anthracycline use or photon MHD ≥ 13Gy and 50-year-old patients with anthracycline use combined with photon MHD ≥ 12Gy; once the IMPT cost reduced to $20,000, IMPT would be cost-effective to 40- and 50-year-old patients and those 60-year-old patients with anthracycline use or photon MHD ≥ 9 Gy.

Discussion

BC is the most commonly diagnosed cancer worldwide and it is also a potential target for proton beam therapy [9, 10, 36]. This is the first CEA study stratifying both irradiated and non-irradiated (preexisting) cardiac risks to assess the cost-effectiveness of IMPT versus IMRT in BC patients. Upon assumption-based CEA modeling, our analyses demonstrated that the patient’s preexisting cardiac risk level contributed a substantial impact on the cost-effectiveness of protons and should be a main consideration for the clinical decision of using protons; further, patients in appropriate risk groups were identified to facilitate proton decision making from the perspective of cost-effectiveness and the potential future trends.

Model robustness examinations were performed with the baseline set-ups (50-year-old, no preexisting CRF, a photon MHD of 5Gy). Markov cohort analysis was applied as a calibration tool, it confirmed that the cancer-related survival rates in IMPT strategy and IMRT strategy were identical, and the model-predicted IHD death risk and total IHD risk corresponded to the natural process previously reported [15]; tornado diagram evaluating the model parameter uncertainty showed that only the IMPT cost had an obvious impact on the ICER value. As such, the benefits of IMPT over IMRT in reducing IHD risk and the cost difference between the two radiotherapy modalities would be the determinants of the cost-effectiveness (ICERs) in the CEA modeling, which indicated that the CEA model was robust.

A similar CEA study conducted by Mailhot Vega et al. also evaluated the IHD risk difference between protons and photons by using the data of Darby et al., but the effect of preexisting cardiac risk was only evaluated as presence/absence of a CRF in that study [13]. In our modeling, both the photon MHD and the patient’s preexisting cardiac risk have been quantified to estimate the absolute IHD risk reduction from IMPT. Using the baseline set-ups as a contrast, our analyses showed that either an increase in photon MHD or an increase in preexisting cardiac risk would cause the IE value increased and ICER value decreased, and the impact of the preexisting cardiac risk was even greater than the impact of photon MHD (Fig. 2). In BC radiotherapy practice, the increasing use of prone positioning and breath-holding techniques makes a high photon MHD less common [37], so we supposed that preexisting cardiac risk level should be a main consideration in clinical decision making of using protons.

To facilitate proton decision making, we identified the cost-effective scenarios in the form of the minimum photon MHDs for BC patients at different preexisting cardiac risk levels, using different set-ups for proton cost and WTP (Fig. 3). Further, we applied the general-population cardiac risk data from the Framingham Heart Study to estimate the cost-effective scenarios from a Chinese perspective. In China, there is currently only 1 operational proton center on the mainland of China and the proton costs is not yet covered by the Chinese public medical insurance. Meanwhile, the Chinese government has authorized 16 new licenses for operating proton centers in 2021, and more than 70 proton centers are in the planning stage. Applying the current unfavorable settings (a WTP of $33,558 / QALY and a IMPT cost of $50,000), we found that for the BC patients having non-irradiated general-population cardiac risk, the cost-effective scenarios existed in 40-year-old women patients who received anthracycline-based chemotherapy or special breast irradiation (IMC/SBBC). But considering the potential future trends, such as market competition, proton technology upgrades, hypofractionated schedule, the introduction of newly China-made compact proton treatment system, the gradual coverage of medical insurance as well as the economic growth [38, 39], substantial reduction in proton cost or gradual increase in WTP may occur in the near future. Of particular note, it has been observed in our study that the cost-effective scenarios would be extended to the general-level BC patients (40- and 50-year-old women BC patients having non-irradiated general-population cardiac risk) if the current IMPT cost reduced to $20,000. Such indicated the huge market potential of protons in BC patients in China.

There were several limitations in this study worth mentioning. First, the benefits of protons in reducing the irradiation-related pneumonia and secondary cancer were not evaluated in this study, considering the relatively low absolute incidences and the opportunistic occurrences of the two events [40]. Second, due to the current data limitation, our analyses only involved 40-, 50- and 60-year-old women patients. Theoretically, younger (< 40-year-old) BC patients could benefit more from protons compared to those ≥ 40-year-old, because they usually have higher cumulative lifetime IHD risk and more Markov cycles in the CEA modeling; and protons should be more cost-effective to men BC patients than women BC patients because of their higher preexisting IHD risk level [23]. Third, the IEs in 40-year-old patients were not greater than that in the 50-year-old patients in our CEA modeling, especially in those at low levels of preexisting cardiac risk (Fig. 2). This phenomenon had also been observed in the study of Mailhot Vega et al. [13], it should be attributed to the survey of Darby et al. which excluded the patients with only an angina in counting the total IHD risk [15]. Lastly, as our study suggests, BC patient’s preexisting cardiac risk should be individually assessed prior to proton decision making, but the current cardiac risk prediction algorithms, such as the Framingham Heart Study who applied traditional risk factors (sex, blood pressure, lipoprotein cholesterol, smoking, and diabetes) [23], could hardly accurately estimate the cardiac risk for BC patients who had received cardiotoxic anticancer agents. In this study, based on the survey of Boekel et al. [18], we assumed that the BC patients who received anthracycline-based chemotherapy experienced 1.5-fold preexisting IHD risk compared with those who did not receive, but the potential impacts of the other cardiotoxic agents (such as paclitaxel, trastuzumab or taxanes) have not been evaluated in Boekel’s study nor in our study. Besides, it has been reported that the IHD death risk in non-irradiated BC population might be lower than that in general population [41], the risk inconsistency between BC population and general population may affect our estimation for general-level cost-effective scenarios. Therefore, we call for the establishment of a cardiac risk prediction algorithm dedicated to BC patients in future studies [42].

Conclusions

On the basis of assumption-based CEA modeling and cardiac risk data from population-based surveys, the cost-effectiveness of protons in BC patients were evaluated in risk-stratification analyses for photon MHD and preexisting cardiac risk. Our analyses demonstrated that the patient's preexisting cardiac risk level should be a main consideration in the clinical decision making of using protons; the cost-effective scenarios of protons do exist in BC patients with preexisting cardiac risk factors, especially in those who receive anthracycline-based chemotherapy or have a high photon MHD; if a substantial decrease in proton cost occurs in the future, protons may become cost-effective to the general-level BC patients.

Declarations

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Competing interests The authors declare that they have no competing interests.

Data availability The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Compliance with ethical standards

- Conflict of interest The authors declare that they have no conflict of interest.

- Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

- Informed consent No individual patient was approached and no individual patient data was used, obtaining informed consent was not application to this study.

Author Contributions

All authors contributed to the study conception and design. Jin Gao and Guo Li collected data for analysis. Yi-Xiang Huang, Deniz Okat, Jerome Doyen and Bo Qiu performed the analyses and interpreted the results. Guo Li and Chao-Nan Qian prepared a first draft of the manuscript. Pierre-Yves Bondiau, Karen Benezery and Yun-Fei Xia provided critical revisions. All authors reviewed and approved the final version of the manuscript. Chao-Nan Qian is the guarantor of the manuscript.

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Figures

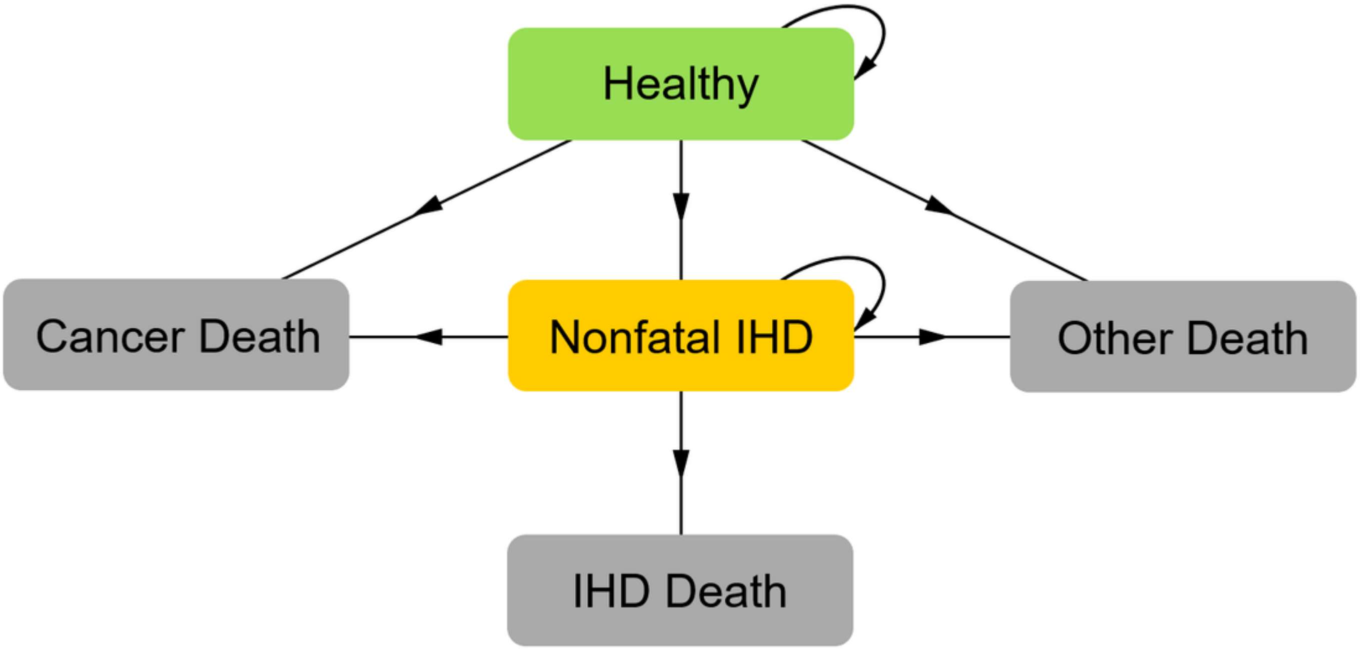
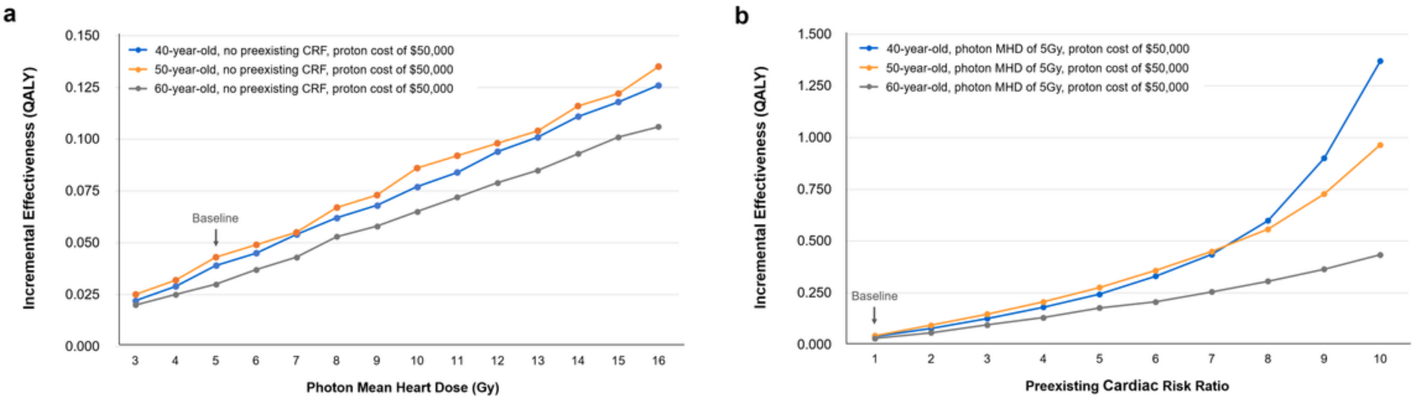


Figure 1

General structure of Markov model. After radiotherapy, the patient might be in the state of “healthy”, “nonfatal IHD”, or “death” (“IHD death”, “cancer death” or “other death”). For each cycle, if the patient was in the state of “healthy”, s/he might stay in the state of “healthy”, develop into the state of “nonfatal IHD” or develop into the “death” states; if the patient was in the state of “nonfatal IHD”, s/he might stay in the state of “nonfatal IHD” or develop into the “death” states; and if the patient was in the absorbing “death” states, the loop operation would be terminated. IHD ischemic heart disease

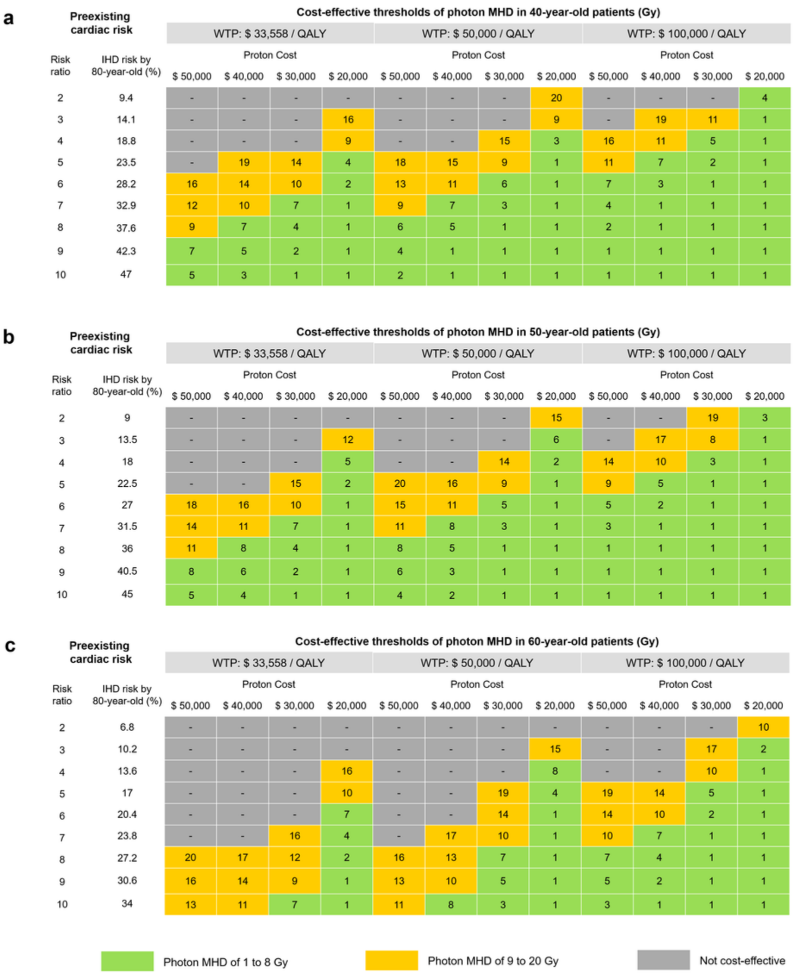


	3	4	5	6	7	8	9	10	11	12	13	14	15	16
40-year-old	0.022	0.029	0.039	0.045	0.054	0.062	0.068	0.077	0.084	0.094	0.101	0.111	0.118	0.126
50-year-old	0.025	0.032	0.043	0.049	0.055	0.067	0.073	0.086	0.092	0.098	0.104	0.116	0.122	0.135
60-year-old	0.020	0.025	0.030	0.037	0.043	0.053	0.058	0.065	0.072	0.079	0.085	0.093	0.101	0.106

	1	2	3	4	5	6	7	8	9	10
40-year-old	0.039	0.079	0.126	0.181	0.244	0.331	0.436	0.599	0.901	1.370
50-year-old	0.043	0.094	0.148	0.207	0.276	0.358	0.450	0.558	0.728	0.965
60-year-old	0.030	0.058	0.096	0.131	0.178	0.207	0.255	0.306	0.365	0.434

Figure 2

The incremental effectiveness (IE) changing with (a) irradiated cardiac risk (photon mean heart dose [MHD]) and (b) non-irradiated (preexisting) cardiac risk. QALY quality-adjusted life-year, $ US dollars, CRF cardiac risk factor, Gy Gray



a

Cost-effective thresholds of photon MHD in 40-year-old patients (Gy)

Preexisting cardiac risk		WTP: $ 33,558 / QALY				WTP: $ 50,000 / QALY				WTP: $ 100,000 / QALY			
		Proton Cost				Proton Cost				Proton Cost			
Risk ratio	IHD risk by 80-year-old (%)	$ 50,000	$ 40,000	$ 30,000	$ 20,000	$ 50,000	$ 40,000	$ 30,000	$ 20,000	$ 50,000	$ 40,000	$ 30,000	$ 20,000
2	9.4	-	-	-	-	-	-	-	20	-	-	-	4
3	14.1	-	-	-	16	-	-	-	9	-	19	11	1
4	18.8	-	-	-	9	-	-	15	3	16	11	5	1
5	23.5	-	19	14	4	18	15	9	1	11	7	2	1
6	28.2	16	14	10	2	13	11	6	1	7	3	1	1
7	32.9	12	10	7	1	9	7	3	1	4	1	1	1
8	37.6	9	7	4	1	6	5	1	1	2	1	1	1
9	42.3	7	5	2	1	4	1	1	1	1	1	1	1
10	47	5	3	1	1	2	1	1	1	1	1	1	1

b

Cost-effective thresholds of photon MHD in 50-year-old patients (Gy)

Preexisting cardiac risk		WTP: $ 33,558 / QALY				WTP: $ 50,000 / QALY				WTP: $ 100,000 / QALY			
		Proton Cost				Proton Cost				Proton Cost			
Risk ratio	IHD risk by 80-year-old (%)	$ 50,000	$ 40,000	$ 30,000	$ 20,000	$ 50,000	$ 40,000	$ 30,000	$ 20,000	$ 50,000	$ 40,000	$ 30,000	$ 20,000
2	9	-	-	-	-	-	-	-	15	-	-	19	3
3	13.5	-	-	-	12	-	-	-	6	-	17	8	1
4	18	-	-	-	5	-	-	14	2	14	10	3	1
5	22.5	-	-	15	2	20	16	9	1	9	5	1	1
6	27	18	16	10	1	15	11	5	1	5	2	1	1
7	31.5	14	11	7	1	11	8	3	1	3	1	1	1
8	36	11	8	4	1	8	5	1	1	1	1	1	1
9	40.5	8	6	2	1	6	3	1	1	1	1	1	1
10	45	5	4	1	1	4	2	1	1	1	1	1	1

c

Cost-effective thresholds of photon MHD in 60-year-old patients (Gy)

Preexisting cardiac risk		WTP: $ 33,558 / QALY				WTP: $ 50,000 / QALY				WTP: $ 100,000 / QALY			
		Proton Cost				Proton Cost				Proton Cost			
Risk ratio	IHD risk by 80-year-old (%)	$ 50,000	$ 40,000	$ 30,000	$ 20,000	$ 50,000	$ 40,000	$ 30,000	$ 20,000	$ 50,000	$ 40,000	$ 30,000	$ 20,000
2	6.8	-	-	-	-	-	-	-	-	-	-	-	10
3	10.2	-	-	-	-	-	-	-	15	-	-	17	2
4	13.6	-	-	-	16	-	-	-	8	-	-	10	1
5	17	-	-	-	10	-	-	19	4	19	14	5	1
6	20.4	-	-	-	7	-	-	14	1	14	10	2	1
7	23.8	-	-	16	4	-	17	10	1	10	7	1	1
8	27.2	20	17	12	2	16	13	7	1	7	4	1	1
9	30.6	16	14	9	1	13	10	5	1	5	2	1	1
10	34	13	11	7	1	11	8	3	1	3	1	1	1

🟩 Photon MHD of 1 to 8 Gy
🟨 Photon MHD of 9 to 20 Gy
⬜ Not cost-effective

Figure 3

Cost-effective thresholds of photon mean heart dose (MHD) in (a) 40-year-old (b) 50-year-old and (c) 60-year-old patients. Protons was considered to be cost-effective to the patient if the estimated photon MHD ≥ the corresponding threshold value shown in the table. Green regions represented the photon MHD range of ordinary breast irradiations; yellow regions represented the photon MHD range of special irradiations (such as internal mammary chain irradiation or synchronous bilateral breast cancer irradiation). IHD ischemic heart disease, Gy Gray, WTP willingness-to-pay, $ US dollars, QALY quality-adjusted life-year

Supplementary Files

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- SupplementaryFigureS1.tif
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- SupplementaryTableS1S10.pdf