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Original article

Cost-effectiveness of postmastectomy hypofractionated radiation therapy vs conventional fractionated radiation therapy for high-risk breast cancer

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ABSTRACT

Background: The phase 3 NCT00793962 trial demonstrated that postmastectomy hypofractionated radiation therapy (HFRT) was noninferior to conventional fractionated radiation therapy (CFRT) in patients with high-risk breast cancer. This study assessed the cost-effectiveness of postmastectomy HFRT vs CFRT based on the NCT00793962 trial.

Methods: A Markov model was adopted to synthesize the medical costs and health benefits of patients with high-risk breast cancer based on data from the NCT00793962 trial. Main outcomes were discounted lifetime costs, quality-adjusted life-years (QALYs), and incremental cost-effectiveness ratio (ICER). We employed a time-dependent horizon from Chinese, French and USA payer perspectives. Model robustness was evaluated with one-way and probabilistic sensitivity analyses.

Results: Patients receiving CFRT versus HFRT gained an incremental 0.0163 QALYs, 0.0118 QALYs and 0.0028 QALYs; meanwhile an incremental cost of $2351.92, $4978.34 and $8812.70 from Chinese, French and USA payer perspectives, respectively. Thus CFRT versus HFRT yielded an ICER of $144,281.47, $420,636.10 and $3,187,955.76 per QALY from Chinese, French and USA payer perspectives, respectively. HFRT could maintain a trend of >50% probabilities of cost-effectiveness below a willingness-to-pay (WTP) of $178,882.00 in China, while HFRT was dominant relative to CFRT, regardless of the WTP values in France and the USA. Sensitivity analyses indicated that the ICERs were most sensitive to the parameters of overall survival after radiotherapy.

Conclusions: Postmastectomy HFRT could be used as a cost-effective substitute for CFRT in patients with high-risk breast cancer and should be considered in appropriately selected patients.

1. Introduction

Breast cancer is the most common cancer and the leading cause of cancer death among women worldwide [1]. Due to the high incidence, breast cancer treatment costs account for the largest portion of cancer-related expenditures because of the frequent need for multimodal therapy [2]. As an integral part of standard treatment for breast cancer, radiation therapy contributes heavily to this cost burden [3]. In addition, with the growing burden of cancer, there is a worldwide shortfall of radiation therapy services, with more patients lacking access to radiation therapy [4]. In the

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current circumstances, such as during the covid-19 pandemic, it is particularly crucial to breast cancer patients that radiation therapy resources be allocated judiciously [5]. Therefore, technologies to reduce the cost and expand global access to radiation therapy have become increasingly critical over the past years [6].

The intent of hypofractionated radiation therapy (HFRT) is to create shorter courses by reducing the number of total fractions, raising the prospect of reducing cost and increasing use of radiation therapy [3]. Data have even confirmed that adoption of shorter schedules in countries with limited radiation therapy resources could actually improve breast cancer survival and other endpoints [7]. Nowadays, HFRT has been able to replace conventional fractionated radiation therapy (CFRT) as the standard of care in early-stage breast cancer patients after breast-conserving surgery [8,9]. There is growing interest in continuing study of hypofractionation after postmastectomy [10]. Emerging evidence has suggested that postmastectomy HFRT may be as effective as CFRT for patients at high risk of locoregional recurrence [11–16].

The use of HFRT instead of CFRT may have a profound financial consequence while diffusing into practice. An overview has summed up a series of health economic evaluations that analysed the efficiency of new fractionation schedules and techniques for post-operative breast radiation therapy [17]. However, owing to the lack of high-level evidence on postmastectomy HFRT in women with high-risk breast cancer, the clinical significance of cost-effectiveness of HFRT in such patients remains unknown, and its economic impact on clinical decision-making has not been specifically addressed. A recently published randomized controlled trial (RCT; NCT00793962) has demonstrated that postmastectomy HFRT is noninferior to CFRT in a large cohort of patients with high-risk breast cancer [12]. This finding provides a critical opportunity to compare the relative cost of these two radiation fractionated modalities. Considering the impact of medical expenses and limited resources in clinical practice, a less expensive treatment strategy should be preferred on health economic grounds [18]. Hence, this accompanying study aims to provide an economic assessment of postmastectomy HFRT compared with CFRT based on the trial from Chinese, French and USA payer perspectives.

2. Materials and methods

The results were reported following the consolidated health economic evaluation reporting standards statement (CHEERS).

2.1. Markov model

We developed a Markov-based state transition model to estimate the costs and effectiveness of postmastectomy HFRT and CFRT for women with high-risk breast cancer. The model assumed that women with high-risk breast cancer who met the NCT00793962 trial inclusion criteria moved through four possible states: disease-free, locoregional recurrence, distant metastasis, or any death from breast cancer or other unrelated causes (Fig. 1). Transition-state cycles were 1 month in duration, and a lifetime horizon was used to calculate direct medical costs and health benefits. The primary outputs of the model were used to calculate the incremental cost for CFRT compared with HFRT in 2020 US dollars for an additional quality-adjusted life-year (QALY) gained (ie. incremental cost-effectiveness ratio [ICER]). We assumed a willingness-to-pay (WTP) threshold of $30,828 (ie. three time of the gross domestic product per capital in 2019) per QALY gained in China and $100,000 per QALY gained in France and USA [19].

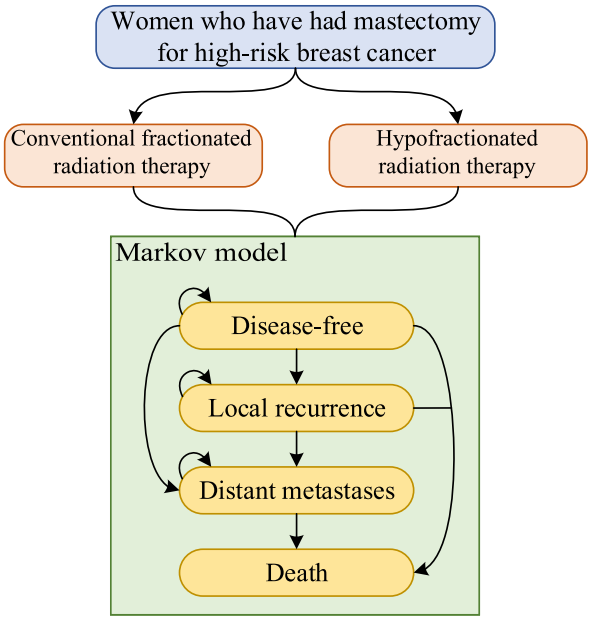

Fig. 1. Markov-model diagrams. Schematic model is shown representing health states of clinical and economic significance. At the beginning of the model, all women enter in a disease-free health state. As time progresses, women transition from one health state to another and acquire cost and utilities associated with that health state. Women at any stage may transition to death attributed to breast cancer or other unrelated causes. Base case model is structured over the time horizon of lifetime.

2.2. Survival estimations

This modelling study was based on publicly available data and the aggregated identified results of the NCT00793962 trial. No institutional board approval or patient consent was required. As described previously [12], eligibility criteria in the NCT00793962 trial included female patients who were aged 18–75 years; had a Karnofksy performance score of 60% or higher; had invasive breast cancer; had undergone mastectomy and axillary dissection; and had at least four pathological positive axillary lymph nodes or primary tumor stage T3–4 disease if patients had undergone primary surgery, or clinical stage III disease or pathological positive axillary lymph nodes if patients had received neoadjuvant chemotherapy. Patients were randomly assigned to receive either CFRT (50 Gy/25 fractions/5 weeks) or HFRT (43.5 Gy/15 fractions/3 weeks).

Clinical efficacy data including local recurrence, distant metastases, and mortality after either HFRT or CFRT were derived from the NCT00793962 trial. According to the results of goodness of fit measured by the weighted residual sum of squares, the Weibull survival function and log-normal survival function were employed for fitting the Kaplan–Meier probabilities of the HFRT or CFRT strategies respectively (Table 1). The estimated parameters were used to measure the time-dependency transition probabilities from the disease-free, local recurrence, and distant metastases states. Age-specific all-cause mortality was derived from the Global Burden of Disease Study 2017 (GBD 2017) results where the mortality risk exceeded that in the NCT00793962 trial [20]. The hazard ratio of distant metastases between patients with local-recurrence and disease-free patients was 3.55 (95% CI: 2.63–4.78), while the

Table 1
Parameters in the Markov model.

Parameters	Values (95% CI)	Distribution	Source
Overall survival of HF	meanlog: 5.2312 (5.1981–5.2623) sdlog: 1.0651 (1.0413–1.0868)	Lognormal	[12]
Overall survival of CF	meanlog: 5.2260 (5.1826–5.2685) sdlog: 0.9776 (0.9482–1.0125)	Lognormal	[12]
Local recurrence of HF	meanlog: 6.8443 (6.6488–6.9870) sdlog: 2.0615 (1.9684–2.1250)	Lognormal	[12]
Local recurrence of CF	meanlog: 6.6910 (6.473–6.7976) sdlog: 1.8307 (1.7062–1.8739)	Lognormal	[12]
Disease-free survival of HF	meanlog: 4.9302 (4.8304–5.0035) sdlog: 1.4139 (1.3247–1.4640)	Lognormal	[12]
Disease-free survival of CF	meanlog: 4.7815 (4.7460–4.8235) sdlog: 1.1896 (1.1549–1.2387)	Lognormal	[12]
Distant metastases of HF	meanlog: 4.9755 (4.8623–5.089) sdlog: 1.3923 (1.2937–1.4824)	Lognormal	[12]
Distant metastases of CF	meanlog: 4.8869 (4.8504–4.9258) sdlog: 1.2226 (1.1985–1.2548)	Lognormal	[12]
China[a]			
Cost of CF	10875 (10704–11047)	Gamma	Estimated
Cost of HF	8796 (8630–8964)	Gamma	Estimated
Cost of local recurrence treatment	8334 (7352–9378)	Gamma	Estimated
Cost of distant metastases treatment	18975 (16956–21105)	Gamma	Estimated
France			
Cost of CF	12519 (10015–15023)	Gamma	[26]
Cost of HF	9063 (7251–10876)	Gamma	[26]
Cost of local recurrence treatment	33575 (15714–84330)	Gamma	[27]
Cost of distant metastases treatment	97970 (49111–346194)	Gamma	[27]
United States			
Cost of CF	18635 (14908–22362)	Gamma	[28]
Cost of HF	12402 (9922–14882)	Gamma	[28]
Cost of local recurrence treatment	33584 (27692–39475)	Gamma	[29]
Cost of distant metastases treatment	157405 (152866–162380)	Gamma	[30]
Utilities (quality of life)			
Utilities during radiation therapy	0.680 (0.638–0.720)	Beta	[31]
Utilities of disease-free	0.935 (0.912–0.955)	Beta	[31]
Utilities of local recurrence (first year)	0.779 (0.742–0.814)	Beta	[31]
Utilities of local recurrence (subsequent year)	0.850 (0.817–0.880)	Beta	[31]
Utilities of distant metastases	0.685 (0.644–0.725)	Beta	[31]
Discount rate of cost	0.03 (0–0.06)	..	..
Discount rate of QALY	0.03 (0–0.06)	..	..

Abbreviations: CI = confidence interval; HF = hypofractionated radiation therapy; CF = conventional fractionated radiation therapy; QALY = quality-adjusted life-year.
[a] Costs of breast cancer treatment in China were estimated from the same center of the clinical trial.

hazard ratios of overall survival between the distant-metastases and disease-free states, and between the local-recurrence and disease-free states were 3.90 (2.78–5.45) and 1.38 (1.03–2.12), respectively [21,22].

2.3. Cost and utility estimations

A cost-effectiveness analysis was conducted from Chinese, French and USA payer perspectives, using a standard rate of 3% annually to discount future costs and benefits [23]. Only direct medical costs were considered and reported in early-2020 US dollars (US$1 = 7.0 Chinese Yuan). The costs associated with healthcare services were converted to 2020 values according to the consumer price index [24]. Considering that intensity-modulated radiation therapy offers high conformal plans, limited hotspots, and protection of the organ at risk in patients receiving regional nodal irradiation for breast cancer [25], the supraclavicular nodal region was treated with intensity-modulated radiation therapy instead of a conventional treatment technique in the RCT on which the present study was based. Direct medical care costs were estimated through data from the same institution with the NCT00793962 trial and the literatures (Table 1) [26–30].

We derived utility values (i.e., values from 0 to 1 indicating the quality of a person's state of health, with 0 indicating death and 1 indicating perfect health) from the results on the EuroQol Group 5-Dimension (EQ-5D) self-report questionnaire from the published literature (Table 1) [31]. To reflect the effect of adverse events on patient quality of life for the period during radiation therapy, a weighted utility value of 0.68 was applied to the period during radiation therapy [31]. We assumed the mean duration of HFRT or CFRT were 1 month and 1.5 months, respectively. Delayed adverse events associated with radiation therapy were assumed to extend an additional 1 month after the last exposure, i.e., for 2 months and 2.5 months for HFRT or CFRT, respectively.

2.4. Sensitivity analysis

We performed a series of sensitivity analyses to evaluate the robustness of our conclusions. We varied the value of model parameters one at a time during one-way sensitivity analysis to examine the individual effects on the ICER. During probabilistic sensitivity analysis, we performed 10,000 Monte Carlo simulations, each time randomly sampling from the distributions of model inputs. Bivariate normal distributions were assigned to all Weibull or log-normal parameters; health utilities were represented by beta distributions, whereas costs were represented by gamma distributions.

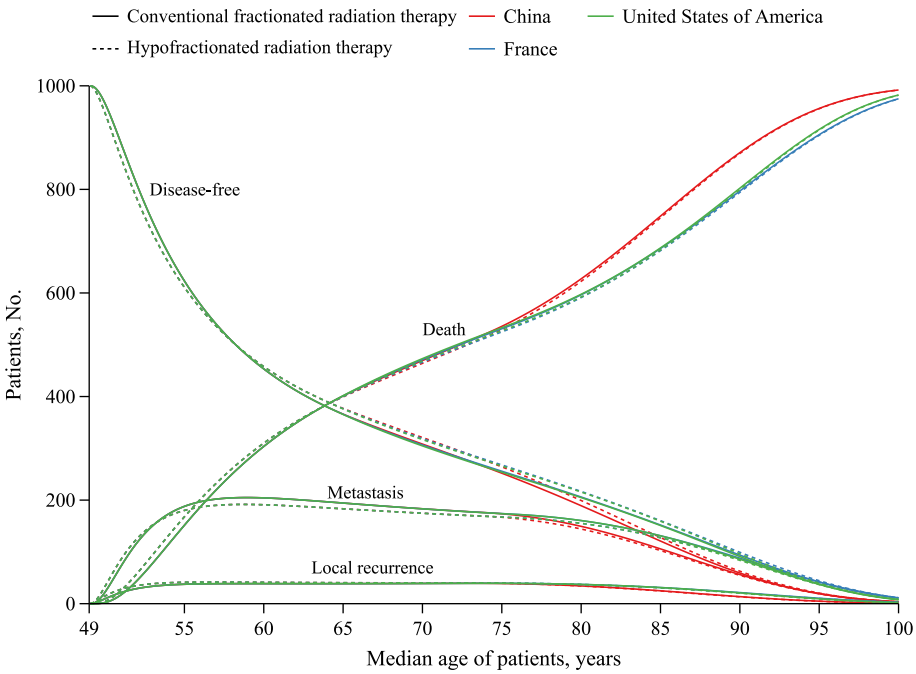

Fig. 2. Patient counts by model state. The model begins with 1000 patients in the disease-free state. Their progression through the other model states by model iteration is indicated for the conventional fractionated radiation therapy and hypofractionated radiation therapy groups.

3. Results

3.1. Status transition and survival

The Markov model began with 1000 patients in the disease-free state. Their progression through the other model states by model iteration was indicated for the HFRT and CFRT groups in Fig. 2. Assigned Markov transition probabilities yielded survival outcomes closely approximating those reported for the NCT00793962 trial. Detailed information about survival probabilities and hazard ratios of every state dependent on survival time was listed in Supplementary Figure S1. There were subtle differences between patients receiving CFRT and HFRT in each health state. Transition probabilities for patients who received CFRT and HFRT were shown in detail in Supplementary Figure S2.

3.2. Lifetime ICER of HFRT vs CFRT

The lifetime costs and QALYs for each month were presented in Supplementary Figure S3a and the cost for each month within one year were presented in Supplementary Figure S3b. The costs were equivalent in the first month for patients receiving CFRT or HFRT. In the second month, CFRT had a much higher expenditure because of a longer radiation therapy course. From the third month onwards, the differences of costs between the two groups were driven by disparities in treatments of locoregional recurrence and distant metastasis. Lower QALYs in CFRT were observed at the third month, because of the longer duration of side effects for patients in the CFRT cohort. Afterwards, the incremental QALYs were dependent on the different probabilities from locoregional recurrence and distant metastasis.

The results of base case analysis were presented in Table 2. From a Chinese payer perspective, it cost $21,018.23 and $18,666.32 per patient for the CFRT and HFRT groups, with 13.1254 and 13.1091 QALY gained, respectively. Thus, patients receiving CFRT encountered an incremental cost of $2351.92 and an incremental 0.0163 QALYs. This yielded an ICER of $144,281.47 per QALY. Using a French payer perspective, the cost of CFRT compared with HFRT ($64,010.31 vs $59,031.97, respectively) and the QALY (13.4244 vs 13.4125, respectively) resulted in an incremental cost of $4978.34 and an incremental 0.0118 QALYs, which led to an ICER of $420,636.10 per QALY. From a USA payer perspective, the cost of CFRT compared with HFRT ($99,111.58 vs $90,298.88, respectively) and the QALY (13.8036 vs 13.8009, respectively) resulted in an incremental cost of $8812.70 and an incremental 0.0028 QALYs, which led to an ICER of $3,187,955.76 per QALY. This finding

Table 2
Lifetime costs, effectiveness, and incremental cost-effectiveness for conventional fractionated radiation therapy vs. hypofractionated radiation therapy.

Strategy	Costs (US$)	Effectiveness (QALY)	ICER (US$/QALY)
China			
Conventional fractionated radiation therapy	21018.23	13.1254	144281.47
Hypofractionated radiation therapy	18666.32	13.1091	..
France			
Conventional fractionated radiation therapy	64010.31	13.4244	420636.10
Hypofractionated radiation therapy	59031.97	13.4125	..
United States			
Conventional fractionated radiation therapy	99111.58	13.8036	3187955.76
Hypofractionated radiation therapy	90298.88	13.8009	..

Abbreviations: QALY = quality-adjusted life-year; ICER = incremental cost-effectiveness ratio.

indicated that the small predicted QALY gains from CFRT probably contributed to the large variability in the cost-effectiveness predictions, given that the QALY gains represent the denominator of the ICERs.

3.3. ICER as a function of time horizon

The ICER was exquisitely sensitive to the time horizon of analysis (Fig. 3). Through each time horizon across the periods in which the radiation therapy might have an effect on either clinical or economic outcomes (i.e., range from 5 to 51 years after the treatment), none of the ICERs in China could be considered very cost-effective. Nevertheless, within a range of time horizons from 8 to 18 years for China and 7–15 years for the USA, the ICER of CFRT compared with HFRT could be considered cost-effective. In France, the ICER of CFRT compared with HFRT could be considered cost-effective until 25 years after the treatment. This finding indicated that the ICER of CFRT vs HFRT was time horizon-dependent, and that HFRT could yield a greater health gain when the model was structured over longer time horizons.

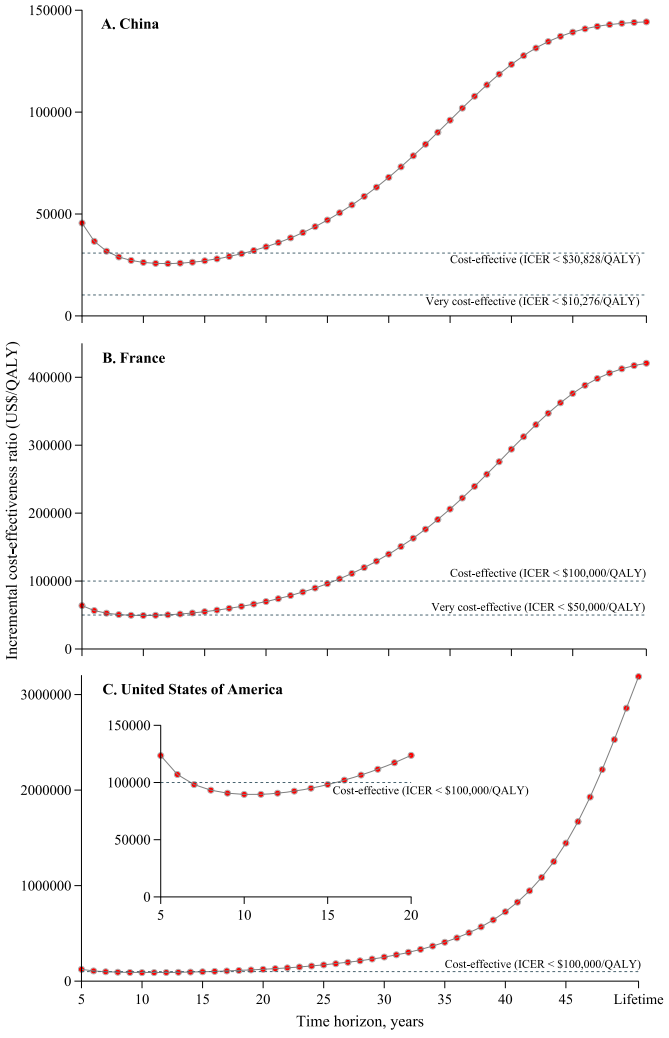

Fig. 3. ICER as a function of time horizon. Time horizon ranged from 5 years to lifetime (i.e., 51 years). The vertical lines indicate the ICER thresholds of $10,276 (per capita GDP of China in 2019) and $30,838 (three times per capita GDP) in China (A), and the ICER threshold of $50,000 and $100,000 in France and the USA (B and C). ICER, incremental cost-effectiveness ratio; GDP, gross domestic product; QALY, quality-adjusted life-year.

3.4. Willingness-to-pay

The cost-effectiveness acceptability curves suggested that HFRT maintained a >50% probability of cost-effectiveness before the WTP threshold of $178,882/QALY in China (Fig. 4). However, in France and the USA, HFRT always had a >50% probability of being cost-effective regardless of the WTP thresholds, i.e., CFRT was dominated by HFRT. This finding indicated that the cost-effectiveness of HFRT vs CFRT in a given WTP threshold varied under different assumptions about payment systems and background all-cause mortality, though HFRT would be cost-effective in China, France and the USA.

3.5. Sensitivity analysis

Probabilistic sensitivity analysis showed that in China CFRT gained a slightly effective benefit compared with HFRT, while the incremental cost was almost 100% positive, while the gap in health effect was even smaller in France and the US (Supplementary Figure S4). The influence of upper and lower limits of different parameters on the incremental cost and effect was shown in Supplementary Figure S5. One-way sensitivity analyses suggested that the results were most sensitive to the parameters of overall survival in each group. Additional parameters with significant contributions to model results were the distant metastases of HFRT and CFRT, discount rate of QALY, local recurrence of HFRT and CFRT. Variations in other values had small to moderate effects on cost-effectiveness (Supplementary Figure S6).

4. Discussion

This study is the first to demonstrate that postmastectomy HFRT tends to be cost-effective than CFRT for women with high-risk breast cancer in China, France and the USA. In China, HFRT could maintain >50% probabilities of cost-effectiveness due to its trends toward gaining net health benefits before the WTP of $178,882. In France and the USA, HFRT was dominant relative to CFRT regardless of the WTP threshold. The ICERs of CFRT vs HFRT varied in a time-dependent manner and increased with time horizon. One-way sensitivity analysis demonstrated that the parameters of overall survival were the most influential model inputs, particularly in the setting of CFRT. These findings provide additional evidence supporting the clinical utilization of postmastectomy HFRT in patients with high-risk breast cancer.

Several RCTs have demonstrated equivalent treatment outcomes and toxicities between HFRT and CFRT after breast-conserving surgery in favorable-prognosis patients with early-stage breast cancer [32–36]. The first large RCT offered high-level evidence supporting the noninferior efficacy of postmastectomy HFRT vs CFRT in women with high-risk breast cancer [12]. Generally, if there is no difference in efficacy and toxicities between different fractionated modalities, the reduced fractionation by HFRT in a large cohort of patients can result in substantial savings and increased radiation therapy access [37]. Previous studies have reported that the clinical use of HFRT instead of CFRT after breast-conserving surgery can significantly reduce direct medical costs based on the Medicare paying system in the USA [28,38]. For instance, HFRT instead of CFRT after breast-conserving surgery saved $2467 and $4462 per patient in MarketScan and SEER-Medicare respectively for patients with early-stage breast cancer [38]. Furthermore, considering both efficiency and medical cost, Deshmukh and colleagues had demonstrated that the cost-effectiveness of HFRT after breast-conserving surgery was dominant relative to CFRT in early-stage breast cancer patients from a lifetime horizon [39]; the ICER was most sensitive to the probability

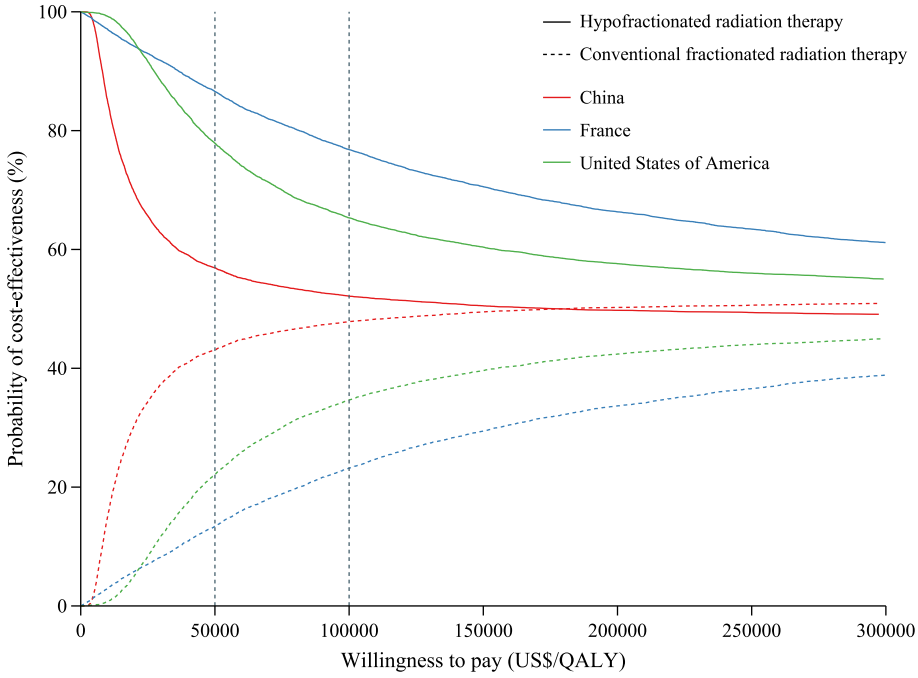

Fig. 4. Cost-effectiveness acceptability curves. Results of the probabilistic sensitivity analysis based on 10,000 iterations of the Markov model in China, France and the USA. QALY, quality-adjusted life-year.

of metastasis and treatment cost.

Consistent with previous findings, the present study has demonstrated that the use of postmastectomy HFRT could reduce health costs by $2351.92, $4978.34 and $8812.70 per patient from Chinese, French and USA perspectives, respectively. Similarly, an Australian study has estimated that the simple replacement of postmastectomy CFRT by HFRT could reduce health costs by over $2000 per patient from an Australian perspective [40]. For the first time, we also found that the cost-effectiveness of postmastectomy HFRT was dominant relative to CFRT in France and the USA, while HFRT could maintain >50% probabilities of cost-effectiveness before a high WTP threshold in China. The ICER in the present study was most sensitive to the hazard ratios of overall survival in each group, probably due to the low frequency of distant metastasis. Furthermore, the ICERs of postmastectomy HFRT vs CFRT varied with time horizon and were pronounced for patients who survived more than 15 years in the USA, 18 years in China, or 25 years in France. In contrast to the previous study on the cost-effectiveness analysis of HFRT after breast-conserving surgery [39], which considered only a lifetime horizon, our study offered more informed insights into changes of ICER with different time horizons.

The strengths of this study are the inclusion of solid individual data from a large-scale RCT, use of current-era economic modelling methods, and evaluation of cost-effectiveness from different countries. First, to our knowledge, this is the first analysis to compare the economic outcomes of postmastectomy HFRT with those of CFRT for patients with high-risk breast cancer through an economic modelling approach. Our generation and validation of economic models for describing the cost-effectiveness association between HFRT and CFRT is unique for such patients. Second, the incorporation of cost and efficiency parameters from both trial- and model-based methodologies in this study has allowed more precise analysis of cost-effectiveness in a time horizon–dependent manner. It has estimated a prominent health gain from HFRT in the context of long-term time horizon. Third, the cost-effectiveness analyses from three countries provide more precise insights into variations between countries and hence improve the generalizability of our study. Given the high incidence of breast cancer in the world, the wide use of postmastectomy HFRT based on high-level evidence of cost-effectiveness is clinically very relevant and suggests value for current practice, particularly in countries where medical resources might be limited. These findings would be helpful for decision-making by physicians and patients.

There are several limitations. Firstly, this model represented patient outcomes from only one randomized trial, and because sensitivity analyses identified transition probability assumptions as critically important to the ICER, small differences in rates of progression or survival in patients receiving two therapies will greatly influence the cost-effectiveness. Future studies should investigate these outcomes. Secondly, due to the lack of data, health benefits beyond the observation time of the NCT00793962 trial were estimated through the fitting of parametric survival functions to the reported data, which might have resulted in uncertainty in the model outputs. The current analysis needs to be updated as evidence becomes available. Finally, the cost data adopted in the present study were derived from one hospital and published literature, which may limit the generalizability of our findings to patients with different payment settings.

5. Conclusion

This study provides valuable new data on the cost-effectiveness of postmastectomy HFRT among women with high-risk breast cancer undergoing radiation therapy. HFRT could be used as a cost-effective substitute for CFRT without compromising clinical outcomes. This finding supports the clinical use of HFRT and enhances the range of its applications.

Author contributions

Drs Ye-Xiong Li and Shu-Lian Wang had full access to all of the

data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: Ye-Xiong Li, Shu-Lian Wang, Jing Yang. Acquisition, analysis, or interpretation of data: Ye-Xiong Li, Shu-Lian Wang, Jing Yang. Drafting of the manuscript: Ye-Xiong Li, Jing Yang. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: Ye-Xiong Li, Jing Yang. Obtained funding: Ye-Xiong Li, Shu-Lian Wang, Jing Yang. Administrative, technical, or material support: Ye-Xiong Li, Shu-Lian Wang. Supervision: Ye-Xiong Li, Shu-Lian Wang.

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Declaration of competing interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2021.04.002.

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