Published in final edited form as:

Expert Rev Pharmacoecon Outcomes Res. 2022 July ; 22(5): 735–741.

doi:10.1080/14737167.2022.2044309.

Comparative cost-effectiveness of radiotherapy among older women with hormone receptor positive early-stage breast cancer

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Abstract

Objective: The aim was to examine the real-world cost-effectiveness of breast-conserving surgery (BCS) plus hormonal therapy with radiotherapy, compared to hormonal therapy alone among women 66 and older with hormone receptor positive early-stage breast cancer in the United States (US).

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Authors' contributions

A Ali, R Tawk, V Diaby, R Moussa conceptualized and drafted the manuscript. All authors critically revised the manuscript and approved the final version.

Declaration of interest

V Diaby and R Tawk have disclosed that they were funded by the National Institute on Minority Health and Health Disparities of the National Institutes of Health under Award Number G12MD007582. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute on Minority Health and Health Disparities of the National Institutes of Health. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Ethics approval

The study was approved by the FAMU Institutional Review Board.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Methods: This study was conducted from a U.S. Centers for Medicare and Medicaid Services perspective and an eight-year time horizon. Both costs (2020 US$) and health utilities (quality-adjusted life years, QALYs) were obtained from retrospective studies using the SEER linked with Medicare and Medicare Health Outcomes Survey, respectively. The incremental cost-effectiveness ratio (ICER) of the addition of radiotherapy to hormonal therapy versus hormonal therapy alone after BCS was estimated by an unbiased doubly robust estimator. Sensitivity analyses were conducted through bootstrapping to estimate credible intervals.

Results: The addition of radiotherapy to hormonal therapy after BCS yielded the highest clinical benefits (2.66 QALYs) and costs ($19,424.27) compared to its hormonal therapy alone after BCS (0.77 QALYS; $2,028.58). The ICER was estimated to be $9,174.94/QALY. Sensitivity analyses did not change the direction of the findings.

Conclusions: The results implicated that the combination of radiotherapy and hormonal therapy is cost-effective in the US.

Keywords

Comparative cost-effectiveness; doubly robust estimator; radiotherapy; hormonal therapy; early-stage breast cancer; elderly women

1. Introduction

Breast cancer is a global health concern that imposes a huge economic burden on patients, their families, the healthcare system, and overall society [1]. The estimated direct medical costs associated with breast cancer were $25.5 billion in 2015 which represent about 14% of all direct costs attributed to cancer care in the US, and this is projected to be about $34.3 billion dollars by the year 2030 [2].

The choice of breast cancer treatment options depends on several factors, including the patient age, the disease stage, and breast cancer type [3,4]. Radiotherapy remains a standard component of treatment for women that underwent BCS for patients diagnosed with hormone receptor-positive (HR+) breast cancer [5], although research has so far proved inconclusive in regard to the clinical benefits of the addition of radiotherapy to hormonal therapy in women 70 and over [6–10]. Previously, comparative effectiveness studies [8,9,11–15], assessing the clinical benefits associated with the use of the addition of radiotherapy to hormonal therapy compared to hormonal therapy alone after BCS, have failed to provide clear evidence for the development of guidelines to assist clinicians and their patients in making optimal shared decisions. The limitations inherent in the designs of these comparative effectiveness studies [8,9,11–15] may have contributed toward the conflicting findings reported. Consequently, there is a critical need to generate robust evidence to meet the evidentiary requirements for both shared clinical decision-making between clinicians and patients (comparative effectiveness data) as well as reimbursement decision-making about the use of adjuvant radiotherapy.

Sen et al. 2014 estimated the cost-effectiveness of external beam radiotherapy (EBRT) or newer radiation therapy compared to non-radiotherapy in older women with early-stage hormone receptor-positive breast cancer [16]. This analysis used a decision-analytic model

(Markov) that simulated costs and effectiveness associated with the treatment options over a 10-year time horizon. The results of the study suggest that EBRT is cost-effective for older women with early-stage hormone receptor-positive breast cancer. This study is informative and provides a basis for clinical and reimbursement decision- making. That being said, the availability of real-world data offered by claims and registry data such as surveillance, epidemiology, and end results linked to Medicare administrative and claims data (SEER-Medicare) may help generate real-world evidence on whether the total costs associated with the addition of radiotherapy to hormonal therapy as a treatment for HR+ early- stage breast cancer patients who underwent BCS correlates with better outcomes such as quality-adjusted life years (QALYs). The results of such studies would also help allocate cancer care resources optimally.

The purpose of this study was to assess the real-world comparative cost-effectiveness of breast-conserving surgery plus hormonal therapy with or without radiotherapy, according to the U.S. Centers for Medicare and Medicaid Services (CMS) perspective.

2. Methods

2.1. Data sources

Data were obtained from the SEER cancer registry linked to Medicare Administration and Claims Data (SEER-Medicare), representing two large population-based sources of data that offer information about Medicare beneficiaries suffering from cancer. Data from this linked database is collected by 18 SEER cancer registries with Medicare claim files from the Centers for CMS. SEER provides patient demographics, clinical, and vital status information for cancer patients, while Medicare (Part A, B) data include Medicare Provider Analysis and Review (MEDPAR), the Carrier Claims, outpatient (OUTPAT), Home Health Agencies (HHA), Hospice, Durable Medical Equipment (DME), and Part D Event (PDE) files. The MEDPAR file contains hospital claims for all short- and long-term and skilled nursing facility stays. The NCH file contains claims from physicians and other non-institutional care providers and has procedure codes according to the Health Care Procedure Classification Code (HCPCS) and the Common Procedural Terminology, 4th Edition (CPT-4), and the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) procedure codes with service dates. The OUTPAT file contains claims from institutional outpatient providers, including hospitals, rural health clinics, and mental health centers. In addition, we used the Surveillance, Epidemiology, and End Results (SEER) – Medicare Health Outcomes Survey (MHOS). SEER-MHOS contains patient demographics, clinical, and cause of death information from nation-wide registries and patient reported outcomes of elderly patients who are enrolled in Medicare advantage organizations (managed care health plans). SEER-MHOS provides HRQOL information measured via Veteran Rand-12 (VR-12) starting 2006. A baseline survey is administered every year to a new cohort. Each cohort is resurveyed 2 years after baseline to provide two waves of data.

The Florida Agricultural and Mechanical University institutional review board exempted this study.

2.2. Study design and population

Using the 2007 January–2011 December SEER-Medicare, we conducted a retrospective cohort study of incident HR+ early-stage BC (Stage 1 and 2) women who underwent breast-conserving surgery (BCS). The date of the first use of treatments was the index date. We used the SEER site recode International Classification of Diseases for Oncology (ICD-O-3) to identify Medicare beneficiaries in the SEER cancer registry files with a new diagnosis of female breast cancer. A woman's cancer-stage status was defined based on the American Joint Committee on Cancer (AJCC) Staging Manual 6th edition. We restricted the study cohort to patients who met the following criteria: (1) female patients aged ≥66 years at diagnosis (to allow 1 year baseline period to ascertain baseline characteristics) and alive at diagnosis, (2) breast is the first or only cancer site, (3) patients had ≥12 months continuous Medicare Parts A & B enrollment and were not enrolled in an HMO before their diagnosis, (4) patients had Medicare Part D enrollment starting the month of index date for at least a year, and (5) patients had HR+ early-stage BC (Figure 1).

2.3. Treatments

Treatment options were a combination of radiotherapy and hormonal therapy after BCS (referred to as the treatment group) and hormonal therapy alone after BCS (referred to as the control group). BCS, radiotherapy, and hormonal therapy were identified using HCPCS, ICD-9 diagnosis and procedure codes, CPT codes, and revenue center codes (see Supplemental Table 1) [17–19]. The variable 'receipt of treatment' was treated as a dichotomous variable with the respective coding: 1 if the patient received radiotherapy plus hormonal therapy after BCS and 0 if the patient did not receive radiotherapy after BCS (hormonal therapy alone).

2.4. Outcome measures

The outcome measures used in this population-based cost-effectiveness are presented in the next sections.

2.4.1. Total direct medical costs—According to the U.S. CMS perspective, only direct medical costs were considered and included costs associated with the acquisition of treatments [20], medical visits [21], and imaging. The cost of the management of adverse events was not included in this study. Cost data were extracted from all Medicare files, including inpatient (Medicare Provider Analysis and Review [MedPAR]), hospital outpatient, carrier/National Claims History (NCH), and durable medical equipment (DME) files covering the study period. For each patient, we calculated the total direct medical cost as the sum of payments made to the provider by Medicare. All costs were adjusted for inflation to represent the year 2020 US dollars, using the Consumer Price Index (CPI) inflation calculator from the Bureau of Labor Statistics (available at http://www.bls.gov/data/inflation_calculator.htm). Supplemental Table 2 shows the average cost per cost per resource used.

2.4.2. Life years (Lys) gained—Lys were defined as the time from index date to death or the last encounter date with the healthcare system, whichever occurred first. Details about the estimation of the Lys can be found in the paper by Ali et al. 2019 [22].

2.4.3. Quality-adjusted life years—The clinical effectiveness of the treatment options was captured using quality-adjusted life years (QALYs), which were estimated based on health utility weight and overall survival time of patients (i.e. Lys gained). Health utility weights were estimated for patients who had Medicare advantage plans using SEER-Medicare Health Outcomes Survey (SEER-MHOS) data. Health utility weights for patients in the treatment and control groups were derived from the VR-12 health-related quality of life instrument using a multi-stage mapping algorithm [23] and averaged across treatment groups. Further details on the estimation of health utility weights can be found in our previous publication [24]. The overall survival rate was calculated as the number of years from the index date to death or the end of the study period (31 December 2013).

2.4.4. Incremental cost-effectiveness ratio (ICER) and net monetary benefit (NMB)—The ICER was expressed as the ratio of the difference in costs over the difference in effectiveness (Lys, QALYs) between the treated and the control groups. The NMB represents the difference between the benefits (effectiveness measure) associated with the combination of hormonal therapy and radiotherapy after BCS, expressed in monetary value and the total costs attributable to the use of that treatment combination. The next section provides details about the implementation of the comparative cost-effectiveness analysis.

2.5. Comparative cost-effectiveness analysis

The cost-effectiveness of radiotherapy + hormonal therapy compared to hormonal therapy alone was assessed using the ICER, expressed as the incremental cost (ΔC) between the treated group and the control group divided by the incremental effectiveness (ΔE) between the treated group and the control group. The ΔC is defined as the difference in the average total costs between the two groups and Δ⁏ is defined as the difference in the average survival between the same groups. We used doubly robust estimators tailored for cost-effectiveness analysis [25] to estimate Δ and Δ⁏. The doubly robust estimation is predicated upon the Neyman- Rubin causal framework [26], where one could estimate the causal effect of a drug (e.g. drug A) on a patient by taking the difference between the observed outcome following exposure to drug A and the predicted outcome have that patient not been exposed to drug A in an alternative scenario. The observed and predicted outcomes are referred to as potential outcomes. Below are the steps conducive to the estimation of ΔC and ΔE in this study.

First, we estimated propensity score models (logit model) and obtained the predicted probability for every patient in the entire patient cohort. The propensity scores were used to balance the groups based on the covariates for which there. Then, we estimated the probability of not being censored using a Kaplan–Meier estimator for every patient in the entire cohort to adjust for loss to follow-up. Additionally, we estimated outcome regression models for cost and survival for each group separately and predicted values for the entire sample using each estimated model. The predicted values from the model estimated based on the treated group are the counterfactual outcomes had all subjects received radio-therapy + hormonal therapy, while the predicted values from the model estimated based on the control group are the counterfactual outcomes had all subjects received hormonal therapy alone. Finally, we calculated ΔC and ΔE by averaging the differences between

the two potential outcomes across all breast cancer patients." Appropriate benchmarks for willingness-to-pay (WTP) thresholds ($50,000, $100,000, $150,000, and $200,000 per QALY) [27–30] were used to establish the cost-effectiveness of the alternative under evaluation.

Since the economic analysis of patient-level data is in essence stochastic, it is important to characterize the sampling uncertainty around the ICER estimate. As a result, we used a nonparametric statistical technique called bootstrapping to estimate the distribution of the base case ICER from our SEER-Medicare data (patients with HR+ early-stage breast cancer). In other words, the bootstrapping technique was utilized to calculate the confidence interval around the ICER estimate (2.5th and 97.5th percentiles corresponding to the lower and upper bounds of the confidence interval). This technique consists of drawing (with replacement) the same size patient samples from the SEER-Medicare data, called replicates. We simulated 1000 replicates for this analysis. The scatter diagram of ICERs obtained from the replicates shows the uncertainty around the estimates of the expected costs and effects associated with the addition of radiotherapy to hormonal therapy compared with hormonal therapy alone after BCS. This sampling uncertainty was summarized using cost-effectiveness acceptability curves (CEACs).

All analyses were conducted using STATA (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC.).

3. Results

3.1. Base case analysis

The study included 5,688 women diagnosed with early-stage hormone receptor breast cancer who received BCS. The results of the base-case analysis showed that the average life year gained was 3.81 and 1.25 for patients receiving hormonal therapy plus radiotherapy and hormonal therapy alone, respectively. The incremental life-year gain was 2.56 (SD 0.03). The average QALYs associated with the addition of radiotherapy to hormonal therapy after BCS (2.66 QALYs) were 3.5 times higher than the QALYs associated with hormonal therapy alone (0.77 QALYs) (Table 1). As for the costs, the total cost of the combination of radiotherapy and hormonal therapy following BCS ($19,424.27) was 9.4 times higher than the cost associated with hormonal therapy alone ($2,058.58). The ICER was estimated to be $6,795.19 and $9,174.94 per life- year gained and QALY gained, respectively. Based on the WTP threshold of $50,000/life-year gained and QALY, the combination of radiotherapy to hormonal therapy after BCS was cost-effective. In subgroup analyses, the incremental cost-effectiveness ratio increased to more than $50,000 per life year gain and QALY for women aged 80 and above.

3.2. Sensitivity analyses

Sensitivity analyses conducted in this study showed that the base-case results were robust to sampling uncertainty, i.e. the direction, magnitude, and interpretation of the base-case results remained unchanged. The bootstrapping analysis indicated results that were very similar to the base-case analysis. The mean ICER of hormonal therapy combined with

radiotherapy after BCS, obtained from bootstrap replicates of the individual-level pairs of costs and survival for the treatment and control, was $6,407.58 (CI: $6,375.42; $6,439.89). The individual-level pairs of costs and QALY for the treatment and control were $9,016.00 (CI: $8,971.24; $9,060.77). Figure 2 A & B shows that more than 99% of the expected ICER pairs [ICER scatter plot when the outcome is survival (2A) and QALY (2B)] are concentrated in the north-east quadrant of the cost- effectiveness plane, indicating occurrences where the addition of radiotherapy to hormonal therapy is cost-effective or does not depend upon the WTP. The CEACs (Figure 3 A &B) suggest that if a QALY were worth $50,000, the combination therapy would have had 100% probability of being cost-effective (Figure 2).

4. Discussion

In this study, we conducted a population-based comparative cost-effectiveness analysis of the addition of radiotherapy to hormonal therapy use after BCS for elderly patients suffering HR+ early-stage breast cancer in the U.S. setting. The strength of this study is the concomitant use of two unique breast cancer quality of care datasets, the SEER-Medicare, and SEER- MHOS datasets. SEER-Medicare and SEER-MHOS cover wide geographic areas across the US. SEER-Medicare encompasses cancer registry data and claims from Medicare, while SEER-MHOS contains cancer registry data and patient-reported outcomes. Thus, these data sources allow the study of the real-world treatment effects of radiotherapy and hormonal therapy in patients with early-stage hormone receptor-positive breast cancer. In addition, a doubly robust estimator was used to reduce selection bias and right-censoring in the estimation of the ICER. According to the results of our base case analysis, combined adjuvant radiation and endocrine therapy was cost- effective compared to hormonal therapy alone as the ICER ($6,795.19 and $9,174.94 per life year gained and QALY, respectively) was below the WTP thresholds considered in this evaluation. Our results were robust to sampling uncertainty as illustrated by the sensitivity analysis conducted (Figure 2A, 2B, 3A, and 3B). The probability of being cost-effective for the combination therapy at $50,000 WTP is 1.

Sen et al., 2014 in their model-based economic evaluation concluded that external beam radiation therapy was cost- effective for older women with early-stage breast cancer [16]. However, this treatment option was not cost-effective for women who have shorter life expectancy. The authors reported that in order for the newer radiation therapy to be a cost-effective option, the new radiation therapy regimen has to be more effective than the existing treatment.

Our economic evaluation is prone to a number of limitations. These limitations are the fact that 1) Medicare is the secondary payer for some patients, and 2) Medicare data do not include claims for HMO enrollees, data regarding care provided in other settings such as the Veterans Administration. As a result, the above limitations may have limited the generalizability of the study results in other populations while potentially contributing to the underestimation of costs associated with their care. The dataset used in this comparative cost-effectiveness analysis only had information about charges and not costs per se. This could have contributed to overestimating the costs associated with the competing treatments.

The costs of the management of adverse events associated with the treatment options were not included in the analysis as it was not clear whether these adverse events (in the dataset) were related to the treatments under evaluation. The addition of these costs to the total cost of treatment could have changed the direction and magnitude of the ICER.

In this project, matching was done separately for the estimation of health utility weights and for the survival times, where different samples were used (Medicare managed care population for mean health utilities and the survival times from Medicare Part A and B populations). As a result, combining survival times and mean health utilities from these different samples (with potentially different characteristics), to estimate QALYs, may have introduced some degree of uncertainty in the final results. In this research, the bootstrapping analysis was done only for the final estimates of QALYs. We did not correct for the additional variance that is due to the fact that health utility weights and survival times were from different patient populations. This may have contributed toward underestimating the amount of uncertainty in the estimation of QALY. That being said, this approach was considered the best proxy for providing evidence from population data, in the absence of quality-of-life information from the SEER-Medicare data. Finally, the data timeframe used in this study is remote. This is due to the availability of our data at the time of conducting this study. However, we inflated cost values to represent $2020 US dollars and estimated quality-adjusted life-years benefits over a stable time horizon. The limitation of using this remote timeframe is the non-inclusion of newer therapies in this analysis. To our defense, our results are conservative given that radiation therapy + hormonal therapy after BCS was found to be very cost-effective (Less than 10 K/QALY). Given that hypofractionated whole-breast treatment regimens are purported to be safer than conventionally fractionated treatment regimens, we would anticipate this newer radiotherapy to be at worst very cost-effective or dominant strategies at best [31]. We can only offer a directional impact of the inclusion of these newer treatment modalities into historical cost-effectiveness. This represents an opportunity for further research in this area to augment the evidence base. This was added to the discussion section of the manuscript.

Although subject to limitations, the implication of the study findings would be that the addition of radiotherapy to hormonal therapy after BCS should be considered the optimal treatment for managing elderly patients suffering early-stage HR+ breast cancer, pending further research applying more advanced statistical techniques to fully control selection bias in observational-based studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This study used the linked SEER-Medicare data. The interpretation and reporting of these data are the sole responsibility of the authors. The collection of cancer incidence data used in this study was supported by the California Department of Public Health as part of the statewide cancer reporting program mandated by California Health and Safety Code Section 103885; the National Cancer Institute's (NCI) Surveillance, SEER Program under contract HHSN261201000140C awarded to the Cancer Prevention Institute of California, contract HHSN261201000035C awarded to the University of Southern California, and contract HHSN261201000034C

awarded to the Public Health Institute; and the Centers for Disease Control and Prevention's (CDC) National Program of Cancer Registries, under agreement # U58DP003862–01 awarded to the California Department of Public Health. The ideas and opinions expressed herein are those of the authors and endorsement by the State of California Department of Public Health, the NCI, and the CDC and Prevention or their Contractors and Subcontractors is not intended nor should it be inferred. The author acknowledges the efforts of the NCI; the Office of Research, Development and Information, CMS; Information Management Services Inc.; and the SEER Program tumor registries in the creation of the SEER-Medicare data.

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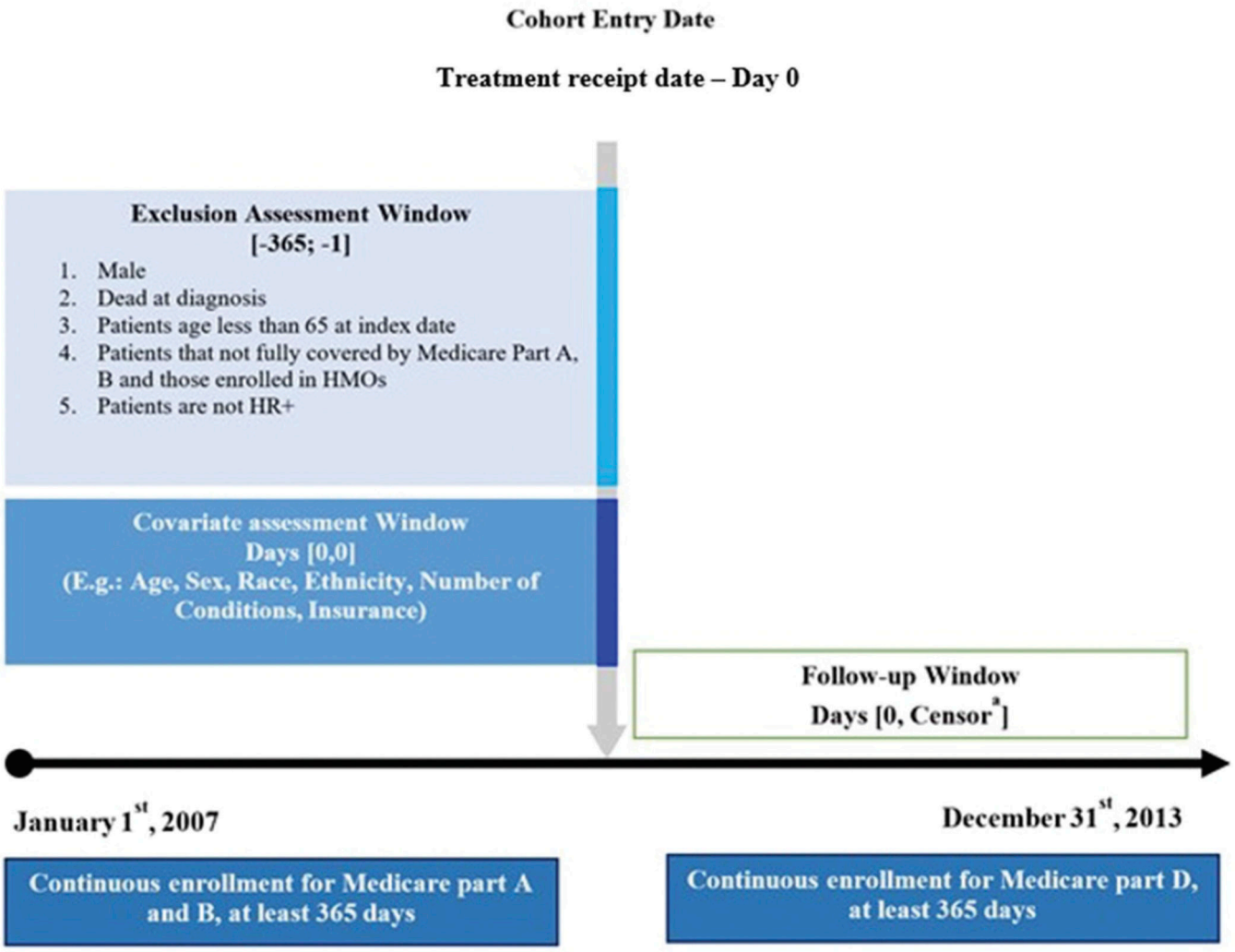


Figure 1.
Early-stage HR+ breast cancer cohort entry.

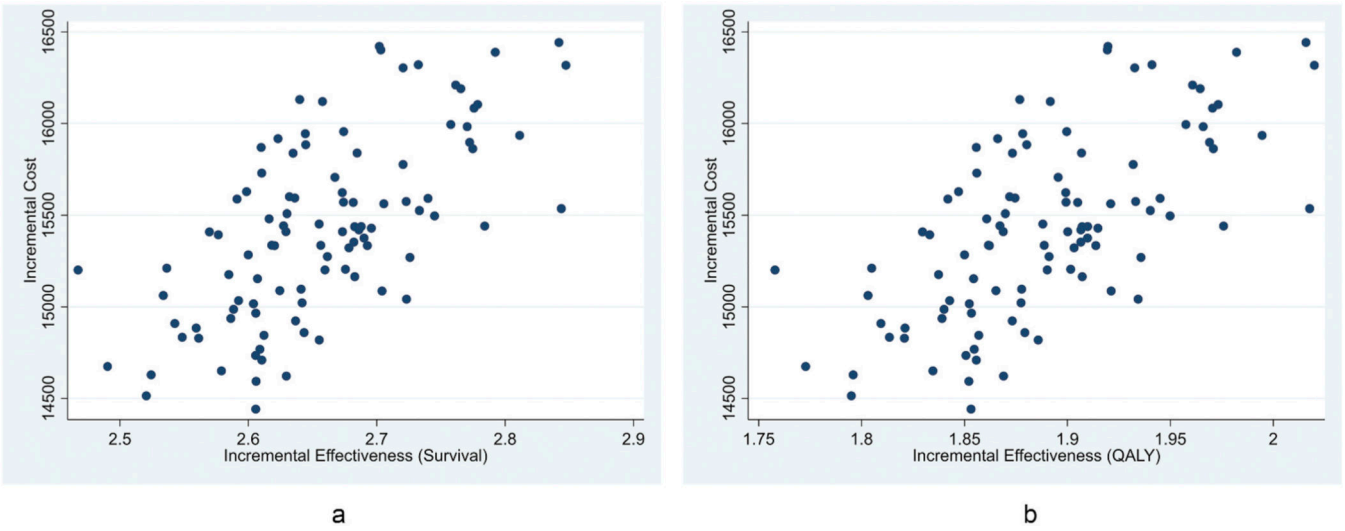
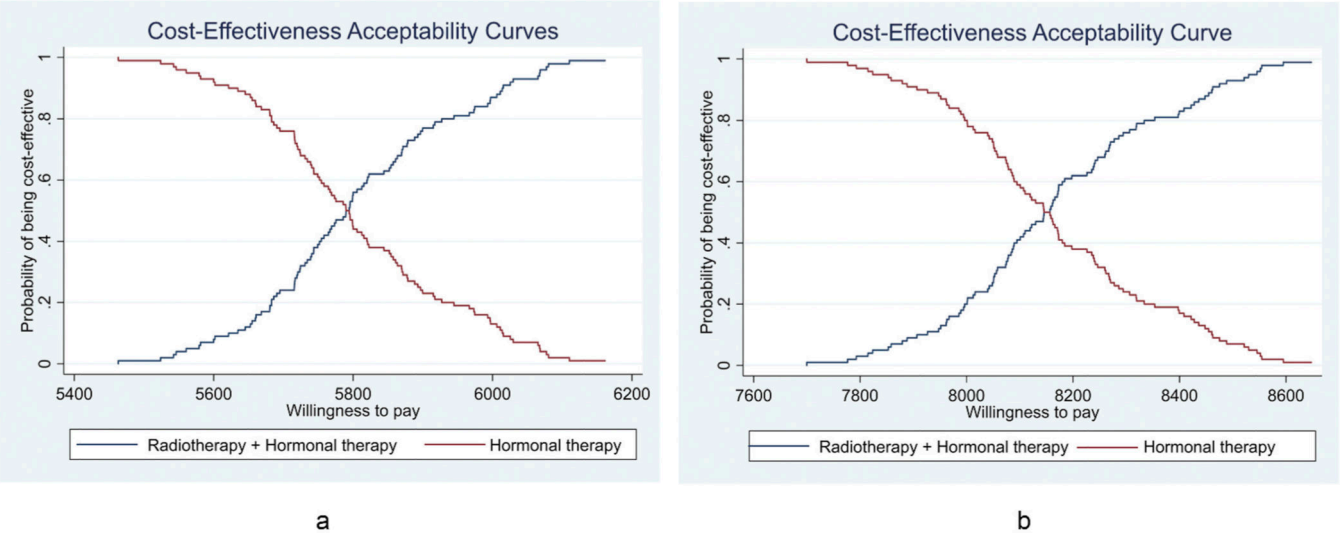


Figure 2.
(a). Cost-effectiveness plane. (b) Cost-effectiveness scatter plot.



a b

Figure 3.

(a) Cost-effectiveness acceptability curves life year gain. (b) Cost-effectiveness acceptability curves_QALY.

Table 1.

Cost-effectiveness estimates for women with early-stage hormone receptor-positive breast cancer.

Model results	Age	Radiotherapy plus hormonal therapy (SE)	Hormonal therapy alone (SE)	Incremental changes (SE)	95% Conf. interval for incremental changes	
					Lower	Upper
Mean total costs	All	19,424.27 (327.04)	2,028.58 (68.45)	17,395.69 (334.12)	16,672.68	18,118.69
	65–69	21,158.51 (555.87)	1,553.46 (66.07)	19,605.04 (559.78)	18,393.21	20,816.87
	70–74	20,306.73 (592.27)	2,153.38 (142.97)	18,153.34 (609.28)	16,834.17	19,472.42
	75–79	19,093.60 (676.34)	2,038.65 (69.53)	17,054.95 (679.90)	15,582.55	18,527.33
	80+	12,985.01 (968.85)	4,958.34 (723.77)	8,026.68 (1209.34)	5,403.89	10,649.46
Mean life year gained	All	3.81 (0.02)	1.25 (0.01)	2.56 (0.03)	2.62	2.72
	65–69	4.26 (0.04)	0.95 (0.01)	3.32 (0.04)	3.24	3.39
	70–74	3.90 (0.04)	1.08(0.01)	2.81 (0.04)	2.73	2.90
	75–79	3.81 (0.04)	1.25 (0.02)	2.56 (0.05)	2.47	2.65
	80+	2.29 (0.07)	2.19 (0.07)	0.11 (0.10)	−0.09	0.30
ICER, $ per year gained	All	-	-	6,795.19		
	65–69	-	-	5,905.13	-	-
	70–74	-	-	6,460.26	-	-
	75–79	-	-	6,662.09	-	-
	80+	-	-	72,969.82	-	-
NMB (50,000)	All	-	-	110,604.31 (1319.70)	114,327.32	117,881.31
	65–69	-	-	146,394.96 (1968.95)	143,606.79	148,683.13
	70–74	-	-	122,346.66 (2237.64)	119,665.83	125,527.58
	75–79	-	-	110,945.05 (2458.03)	107,917.45	113,972.67
	80+	-	-	−2,526.68 (5073.70)	−9,903.89	4,350.54
Mean QALY	All	2.66	0.77	1.896 (0.18)	1.55	2.25
	65–69	3.10	0.65	2.45 (0.03)	2.40	2.51
	70–74	2.77	0.75	2.02 (0.03)	1.96	2.08
	75–79	2.56	0.82	1.75 (0.03)	1.68	1.81
	80+	1.50	1.47	0.03 (0.07)	−0.10	0.16
ICER, $ per QALY	All	-	-	9,174.94	-	-
	65–69	-	-	8,002.06	-	-

Model results	Age	Radiotherapy plus hormonal therapy (SE)	Hormonal therapy alone (SE)	Incremental changes (SE)	95% Conf. interval for incremental changes	
					Lower	Upper
	70–74	-	-	8,986.80	-	-
	75–79	-	-	9,745.69	-	-
	80+	-	-	267,556	-	-
NMB (50,000)	All	-	-	77,404.31 (948.68)	60,827.32	94,381.31
	65–69	-	-	102,894.6 (1469.05)	101,606.79	104,683.13
	70–74	-	-	82,846.66 (1644.00)	81,165.83	84,527.58
	75–79	-	-	70,445.05 (1720.68)	68,417.45	71,972.67
	80+	-	-	−6,526.68 (3,463.91)	−10,403.89	−2,649.46

*All costs are expressed in 2020 US dollars; Incremental cost-effectiveness ratio

Expert Rev Pharmacoecon Outcomes Res. Author manuscript; available in PMC 2024 January 16.