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Partial Breast Irradiation Versus Whole-Breast Irradiation For Early-Stage Breast Cancer: A Decision-Analysis

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Abstract

Purpose—To compare the quality-adjusted life expectancy (QALE) between women treated with whole-breast radiation therapy (WBRT) and partial-breast irradiation (PBI) for estrogen-receptor (ER)-positive early-stage breast cancer.

Methods and materials—We developed a Markov model to describe health states in the 15 years following radiotherapy (RT) for ER-positive early-stage breast cancer. Breast recurrences were separated into local recurrences (LR) and elsewhere failures (EF). Ipsilateral breast tumor recurrence (IBTR) risk was extracted from the Oxford overview, and rates and utilities were adapted from the literature. We studied two cohorts of women (aged 40 years and aged 55 years), both of whom received adjuvant tamoxifen.

Results—Assuming a NED-PBI (no evidence of disease) utility of 0.93, QALE after PBI (and WBRT) was 12.61 (12.57) and 12.10 (12.06) years for 40-year-old and 55-year-old women, respectively. The NED-PBI utility thresholds for preferring PBI over WBRT were 0.923 and 0.921 for 40-year-old and 55-year-old women, respectively, both slightly greater than the NED-WBRT utility. Outcomes were sensitive to the utility of NED-PBI, the PBI hazard ratio (HR) for local recurrence, the baseline IBTR risk, and the percentage of IBTRs that were local. Overall, the degree of superiority of PBI over WBRT was greater for 55-year-old women than for 40-year-old women.

Conclusions—For most utility values of the NED-PBI health state, PBI was the preferred treatment modality. This result was highly sensitive to patient preferences and was also dependent upon patient age, PBI efficacy, IBTR risk, and the fraction of IBTRs that were local.

Introduction

The past 30 years has witnessed a dramatic shift in the local treatment of breast cancer. First, the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-04 study confirmed that

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the Halsted radical mastectomy does not confer a survival benefit over the less morbid total mastectomy with irradiation.¹ The landmark NSABP B-06 trial then showed that lumpectomy and whole breast radiotherapy (WBRT) results in survival outcomes similar to modified radical mastectomy,² and since its publication breast-conserving therapy (BCT) has largely replaced mastectomy as the standard-of-care for early-stage breast cancer.³

Additional data on patterns of local recurrence after lumpectomy and irradiation have suggested that the majority of ipsilateral breast tumor recurrences (IBTR) occur in the same quadrant as the original tumor.⁴⁻⁷ These local recurrences (LR) are distinguished from elsewhere failures (EF), which is tumor reappearance in a different quadrant of the breast. Given the inconvenience and side effects associated with a 6-week course of conventional whole-breast radiotherapy, there has been a movement to treat only part of the breast, termed partial-breast irradiation (PBI). PBI was initially delivered using low-dose rate brachytherapy, but more recently other techniques have been developed to accelerate treatment, provide superior dosimetry, and improve the convenience and tolerability of radiotherapy. Currently there are three main modalities of PBI practiced in North America: three-dimensional external-beam radiotherapy (EB-PBI), MammoSite brachytherapy, and high- and low-dose rate interstitial brachytherapy. PBI is generally given in twice-daily fractions over a period of 4-5 days.

Preliminary experience using PBI has generally been encouraging, resulting in local control rates comparable to those seen after WBRT.⁸ One notable exception was the Christie Hospital randomized trial of EB-PBI versus WBRT, which found inferior local control and cosmetic outcome in the PBI arm, although overall survival was similar between the two arms.⁹ This study has been heavily criticized for its older radiation technique and poor quality control, inadequate axillary and systemic management, and incomplete pathologic examination.¹⁰ Given the rapidly increasing acceptance of partial breast irradiation, NSABP has recently initiated B-39, a multi-institutional cooperative group trial which is randomizing women with ductal carcinoma *in situ* (DCIS), stage I or II breast cancer to conventional WBRT or PBI.

Decision analysis using Markov modeling is a technique that can compare the expected outcomes of different treatment strategies using existing data before the complete results of clinical trials are available. The decision to use PBI in early-stage breast cancer lends itself to this analytic technique, and sensitivity analyses can also provide insight into characteristics of PBI that would make it the preferred treatment modality. Since the findings of NSABP B-39 will not be available for 5-10 years, this type of modeling can yield important information on potential outcomes and implications of this study in the interim. We report the results of a decision analysis of radiotherapy techniques for women with estrogen-receptor (ER)-positive stage I breast cancer.

Methods and Materials

Decision model

We designed a Markov model to simulate the clinical history of two hypothetical cohorts of women with stage I breast cancer (pT1N0 by the tumornode-metastasis system) after lumpectomy. Cohort 1 consisted of 40-year old, pre-menopausal women, and cohort 2 consisted of 55-year old, post-menopausal women. Markov simulation allows these women to transition between different health states in fixed increments of time.¹¹

The model starts patients off in the well state (no evidence of disease, NED), having received either WBRT or PBI. These states are titled NED-PBI or NED-WBRT (Figure 1). The other potential health states are local recurrence (LR), defined as recurrence in the same quadrant of the breast, elsewhere failures (EF), defined as recurrence in a different quadrant of the breast,

well after salvage mastectomy (NED-MTX), distant metastasis (DM), death from other causes, and death from breast cancer.

The primary outcome studied was quality-adjusted life expectancy. A 15-year time horizon was used, due to evidence that improved local control manifests a survival benefit over this period.¹² The model was created and analyzed using Data TreeAge Pro (Williamstown, MA).

External validity

The external validity of this model was assessed by comparing the 10-year overall survival (OS) and breast-cancer specific mortality (BCSM) with the predicted results from Adjuvant! Online.¹³ This online prognostic tool has been validated using a large, population-based sample.¹⁴ For the purposes of this model, the 10-year OS and BCSM were estimated for women aged 40 and 55 years, with negative lymph nodes, tumor size 1-2 cm, and intermediate-grade ER-positive cancer; all patients received tamoxifen.

Model assumptions and data

Patterns of failure and mortality—Rates of local recurrence after radiotherapy were extracted from the recent Oxford overview, which performed a meta-analysis of trials comparing lumpectomy alone with lumpectomy plus radiotherapy.¹² In this meta-analysis, the risk of IBTR was highest during the first 5 years after treatment, became lower during the subsequent 5 years, and thereafter approximated the risk seen in the lumpectomy-alone cohort. Therefore in our model, we altered baseline rates of IBTR according to time period since completion of RT. The rate was highest in the first five-year time period following radiation treatment and was lowered in the subsequent five years. It was assumed that the rate within these 5-year time periods was constant. The risk of IBTR was doubled at all time periods for women younger than 50 years.¹⁵⁻¹⁹ We did not consider axillary failures, since among the modeled population the risk of isolated axillary recurrence is very low (<0.1%) in modern series using sentinel-lymph node biopsy.²⁰

Data regarding the fraction of ipsilateral breast tumor recurrences that are local (versus elsewhere in the breast) vary by institution and by time since lumpectomy. For the baseline analysis, we chose the Beaumont experience, a recent analysis of patterns of failure,⁶ but varied this proportion using sensitivity analyses.

The risk of distant metastases as site of first failure in lymph node-negative cancer was extracted from the results of NSABP B-14 trial²¹ and calibrated to obtain survival estimates comparable to published reports. The rate of distant metastasis was assumed to be constant over the first 10 years of follow-up, and then declined over the following 5 years. This rate of distant metastases as first failure was assumed to be equal in both WBRT and PBI arms.

The rate of distant metastasis subsequent to the appearance of IBTR (both LR and EF) was assumed to be constant throughout the time window and the same in both PBI and WBRT arms. The 10-year risk of developing a metastasis after an IBTR was 20%.²² The transition rate between distant metastasis and death was obtained from the Surveillance, Epidemiology and End Results database.²³ All deaths from breast cancer were assumed to have arisen from the metastatic state.²²

Patients could die from other causes after any health state, and these rates were derived from standard life-tables based on 2003 data.²⁴ All rates, probabilities and utilities are shown in table 1.

Treatment—We assumed that all patients underwent lumpectomy and sentinel lymph node biopsy, consistent with standard surgical practice. Unlike NSABP B-39, all women were

assumed to be lymph node-negative. We further assumed that all patients were ER-positive, and these individuals received tamoxifen for five years. The benefit of tamoxifen on both local and distant disease is dependent on the time since initiation of therapy;¹² this variation was incorporated into this model. In accordance with common practice for ER-positive stage I breast cancer, patients in the model were assumed not to have received chemotherapy.²⁵

All patients underwent mastectomy after any IBTR, irrespective of the location of recurrence and treatment modality. Although there is preliminary experience with repeat lumpectomy and salvage PBI,²⁶ this approach is still experimental. Following salvage local treatment, patients did not receive additional chemotherapy, because there are no prospective data suggesting a survival benefit to such treatment.

Throughout each time period, the rate of local recurrence was assumed to be equal in PBI and WBRT in the baseline analysis. In other words, PBI and WBRT are equally efficacious at reducing the risk of failure within the tumor bed. Therefore the hazard ratio (HR) for LR after PBI was set to 1; however, this ratio was varied in sensitivity analyses. The Oxford overview¹² showed that WBRT reduces the risk of any IBTR by two-thirds. Partial breast irradiation does not treat other quadrants of the breast, so the rate of EF during the first five years after PBI was assumed to be 3 times the rate of EF after WBRT. This ratio was varied in sensitivity analyses. As shown in several retrospective reviews, the ratio of elsewhere to local recurrences increases over time.⁴⁻⁷ Therefore it is unlikely that whole breast irradiation successfully reduces EF after five years, and at that point the further improvement in IBTR after conventional radiotherapy is most likely due to a reduction in local recurrences. Consequently we assumed that the rate of EF was equivalent in the two arms after 5 years but varied this in sensitivity analyses.

Utilities—Hayman et al. elicited patient-perspective utilities for health states associated with treatment using standard gambles with women treated for early-stage breast cancer.²⁷ We used their derived utility for NED-WBRT of 0.92 (on a scale of 0-1, 1=optimal health, 0=being dead) for the well-state after treatment with whole-breast radiotherapy.

There have been no studies evaluating patient preferences after PBI. However, preliminary quality-of-life data have shown persistent benefits of PBI in several domains.²⁸ Though it is plausible that the utility of the NED-PBI state exceeds that of NED-WBRT, we chose 0.92 as the base case utility for NED-PBI to avoid biasing our model towards PBI, and tested this value in sensitivity analyses. One potential concern with hypofractionation therapy is late radiation fibrosis and skin changes, so the late NED-PBI utility was also adjusted in sensitivity analyses.

Utilities for health states after salvage mastectomy and distant metastases were extracted from published literature.²⁹ The disutility in taking tamoxifen was assumed to be 0.05,³⁰ and we assumed an additive relationship between the disutility of tamoxifen use and the value of the total health state.

Sensitivity analyses

Sensitivity analyses allow the modeler to adjust the assumptions of the model, and we tested this analysis over a wide range of assumptions. All parameters that are listed with a range in table 1 were placed into a sensitivity analysis.

One-way sensitivity analyses were performed in both cohorts to determine the threshold NED-PBI utility at which PBI was the preferred treatment choice. The difference in utilities between PBI and WBRT was only assumed to exist for 5 years; between years 6-15, the well states after both treatments were assumed to be equal in the baseline analysis. This analysis was repeated

for a hypothetical ER-negative population who would not receive tamoxifen or cytotoxic chemotherapy.

Tornado diagrams are graphs which display the difference in expected utility between two strategies as various parameters are changed. A compilation of 1-way sensitivity analyses, tornado diagrams were performed for cohorts of 40 year-old and 55 year-old women. The utility of NED-PBI was set at 0.93 in this diagram.

We performed a two-way sensitivity analysis to determine the optimal treatment when both the early NED-PBI utility (years 0-5) and late NED-PBI utility (years 6-15) were varied. This latter analysis represents the potential for an initial quality-of-life benefit from PBI, followed by a quality-of-life decrement from late fibrosis.

Several three-way analyses were performed for both cohorts, where one axis was the NED-PBI utility, which was varied between 0.92 and 0.96. We tested for the influence of HR_{PBI} and percentage of recurrences that are local in a three-way analysis, and we also examined the relationship between HR_{PBI} and the baseline risk of IBTR over the first 5 years. For most HR_{PBI} tested, WBRT was more effective at preventing IBTRs than PBI, such that WBRT was almost always be preferred if the NED utility states were equivalent. Therefore we chose to present the graphs in which the outcome was more dependent upon a difference in NED utilities.

Results

Model validity

The external validity of this model was assessed by comparing the 10-year overall survival (OS) and breast-cancer mortality (BCSM) with the predicted results from Adjuvant! Online. For a 55-year old woman with lymph node-negative cancer, Adjuvant! Online estimated a 10-year OS and BCSM of 85.1% and 5.4%, respectively. Our model predicted a 10-year OS and BCSM of 86.3% and 5.5%, respectively. For a 40 year-old woman, Adjuvant! Online predicted a 10-year OS and BCSM of 92.6% and 5.5%, respectively. Our model predicted a 10-year OS and BCSM of 91.9% and 6.0%, respectively.

One-way sensitivity analyses

One-way threshold analyses for the model sensitivity to the early (i.e. years 0-5) NED-PBI utility found that the threshold for preferring PBI was 0.921 and 0.923 for 55 and 40 year-old women, respectively. This difference is extremely small and almost impossible to distinguish during a preferences elicitation. This low threshold reflects the majority of time the cohort spent in the well state. Tornado diagrams for 55 and 40 year-old women are shown in Figure 2. The model composed of 40 year-old women was particularly sensitive to the NED-PBI utility, the baseline risk of IBTR, the PBI hazard ratio, and to a lesser extent the fraction of IBTR that were local. The outcomes for the 55 year-old cohort were also dependent upon the NED-PBI utilities but were less influenced by the IBTR risk and pattern of failure. The results were not significantly related to the risk of distant metastasis, which affected both arms equally. Other parameters listed in table 1 but not shown in the tornado diagrams did not change the conclusions of the analysis and were omitted from the diagram.

For patients who were ER-negative and not candidates for adjuvant hormonal or cytotoxic chemotherapy, the thresholds for preferring PBI were 0.923 and 0.926 for 55 and 40 year-old women, respectively.

Two- and three-way sensitivity analyses

The previous analyses assumed that the late NED-PBI health state (i.e. years 6-15) was valued equally to the late NED-WBRT health state. If late fibrosis caused a decrement in quality-of-life over this time, conventional whole-breast radiotherapy became the preferred treatment modality over a wide range of utility values, as seen in a two-way sensitivity analysis in Figure 3.

Three-way sensitivity analysis of the baseline risk of IBTR, the HR_{PBI} , and the utility of the early NED-PBI state was consistent with the dominant influence of the well state (Figure 4). For example, when the utility of NED-PBI was 0.94, PBI was the preferred strategy in the majority of the sample space. A three-way analysis of the percentage of IBTR that were local, the HR_{PBI} , and the utility of NED-PBI reflected the fact that partial breast irradiation only treats the tumor bed and surrounding tissue (Figure 5). As the likelihood of elsewhere failures increases, conventional whole breast radiation therapy became an increasingly preferred approach.

Discussion

Partial breast irradiation has the potential to strike a balance between local control and quality-of-life, both with respect to treatment morbidity and duration and convenience-of-care. Although preliminary experience suggests PBI is better tolerated than WBRT, the key research question is whether this benefit is large enough to overwhelm a likely increase in the IBTR risk. NSABP B-39 is a large, cooperative group non-inferiority trial designed to compare WBRT with PBI. However, the definitive results of this trial will not be available for 5-10 years.

Decision analysis provides a mechanism to compare the predicted outcome after treatment with WBRT or PBI, and sensitivity analyses enable the modeler to test these results against a wide range of assumptions. We have shown that PBI is the preferred treatment for most utility values of NED health states. These results speak to the fact that most breast recurrences occur within the first 5 years, and most of those failures occur within the tumor bed. Since high-intensity partial breast radiotherapy presumably will prevent these recurrences equally well as conventional breast RT, the model results are highly dependent on patients residing in the well state. Thus, the utility threshold for preferring PBI was 0.921 for 55 year-old women and 0.923 for 40 year-old women, minutely larger than the assumed utility value of 0.92 for WBRT.

To put these extremely small values into perspective, consider that a utility difference of 0.001 is equivalent to the following statement. If a woman was presented with two alternatives: to live the next ten years of her life with the morbidity of whole breast RT or a shorter period of time to live with the morbidity of PBI, she would only have to give up 4 *days* out of 10 years to prefer the less morbid and more convenient treatment. Such a preference is so small that we have difficulty measuring such a value.

These results were sensitive to other characteristics of the disease, such as the location of the recurrence and the efficacy of PBI at reducing local recurrences. Nevertheless, for many of the sensitivity analyses, PBI was still the preferred option a majority of the time.

This study has several limitations. First and foremost, a decision analysis cannot replace a properly performed randomized, controlled trial, which actually tests these treatments in real patients. This model was based wholly on existing data, although we used widely-accepted probabilities and utilities from the literature whenever available. Sensitivity analyses are tools to investigate the validity of model assumptions, and in general our model proved to be robust. In fact, we intentionally biased our model against PBI in a number of ways, such as equalizing

the NED utilities after five years. We also did not model the possibility that PBI patients may be more likely to undergo repeat breast conserving therapy at recurrence, but this potential option would increase the quality-of-life benefit of PBI. In addition, we assumed that the rate of distant metastasis subsequent to IBTR was equivalent after WBRT and PBI. It is conceivable that an EF after PBI may be less aggressive than an EF after WBRT, because the latter recurred after receiving a full course of irradiation. However, any difference in metastatic progression is likely to be quite small and would only minimally affect the model. Finally, we did not distinguish between the different modalities of partial breast irradiation. As experience accumulates with these different techniques, it is possible that recurrence rates and morbidity will differ among them, thereby changing the calculus of this decision analysis.

We also showed that any early gain in QALE from PBI can be nullified by late complications such as fibrosis or cosmetically unappealing telangiectasias. This finding is also an important conclusion from this analysis. However, radiobiologic models suggest that the risk of these complications is comparable to that following conventional breast radiotherapy.³¹ Ultimately, long-term quality-of-life data are needed to resolve the tension between the potential of late fibrosis and the early benefits from treatment tolerance.

NSABP B-39 will help to determine the IBTR rate after WBRT and PBI, and investigators have attached several quality-of-life instruments to this trial. However, utilities cannot be elicited or derived from the instruments used in this study, and further work should be performed to compare patient preferences after different modalities of radiotherapy for early-stage breast cancer.

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Figure 1.

Markov model. NED = no evidence of disease. The utilities of the NED health states vary according to modality of radiotherapy (WBRT vs. PBI) and to time since RT (0-5 years versus 6-15 years).

Figure 2.

Tornado diagrams of a series of 1-way sensitivity analyses for cohorts of 40 year-old (panel A) and 55 year-old (panel B) women. The utility of the NED-PBI health state was set at 0.93 for the first 5 years after treatment, and it was lowered to 0.92 for the remainder of the cycles. The majority of parameters do not influence the optimal decision, even over a wide range of values. The X-axis reflects the difference in expected utility between the two models. Parameters to the right of the line favor whole breast radiotherapy, and parameters to the left of the line favor PBI.

Figure 3.

Two-way sensitivity analysis of the NED-PBI utility values in the first 5 years after RT (X-axis) and in years 6-15 (Y-axis). The hatched area represents a combination of utility values for which WBRT is the preferred treatment, while the remaining solid area represents the combination of utility values for which PBI is the optimal therapy. Panel (A) is a cohort of 40-year old women, and panel (B) is a cohort of 55 year-old women.

Figure 4.

Three-way sensitivity analysis of early (i.e. 5-year) IBTR risk, PBI hazard ratio (PBI HR), and the early utility of NED-PBI. The X-axis represents the 5-year breast recurrence rate, and the Y-axis is the PBI HR. The hatched area represents conditions (i.e. a 5-year IBTR risk and a given PBI HR) under which WBRT is the preferred treatment. The remaining solid area reflects conditions under which PBI is the optimal strategy. As the IBTR risk decreases and PBI becomes more effective, PBI is more likely to be the preferred strategy. Panels (A) and (B) show the results of the analysis with the utility of NED-PBI set at 0.93 and 0.94, respectively, for a hypothetical cohort of 40 year-old women. Panels (C) and (D) show the results of the analysis with the utility of NED-PBI set at 0.93 and 0.94, respectively, for a hypothetical cohort of 55 year-old women.

Figure 5.

Three-way sensitivity analysis of fraction of early IBTR (i.e. years 0-5) that are local recurrences, PBI hazard ratio (PBI HR), and the early utility of NED-PBI. The X-axis represents the fraction of breast recurrences that are local recurrences instead of elsewhere failures, and the Y-axis is the PBI HR. The hatched area represents conditions (i.e. a given fraction of IBTRs that are LR and a given PBI HR) under which WBRT is the preferred treatment. The remaining solid area reflects conditions under which PBI is the optimal strategy. As the fraction of IBTRs increases and PBI becomes more effective, PBI is more likely to be the preferred strategy. Panels (A) and (B) show the results of the analysis with the utility of NED-PBI set at 0.93 and 0.94, respectively, for a hypothetical cohort of 40 year-old women. Panels (C) and (D) show the results of the analysis with the utility of NED-PBI set at 0.93 and 0.94, respectively, for a hypothetical cohort of 55 year-old women.

Table 1

Probabilities, hazard ratios, and utilities used in this study. *Years* refers to the years in which the probabilities apply. Tamoxifen hazard ratios are relative to no hormonal therapy. PBI hazard ratios for local recurrence (LR) and elsewhere failure (EF) are relative to WBRT.

Event	Years	Baseline Value	Range Studied	Reference
<i>Probabilities</i>				
NED⇒IBTR	0-5	6.7% (5-year)	2%-20%	12
	6-10	3.3% (5-year)	2-5%	
	11-15	0	--	
IBTR⇒Metastasis	0-15	20% (10-year)	10-40%	22
NED⇒Metastasis	0-10	11% (10-year)	5-20%	21
	11-15	6.7% (5-year)	--	
Metastasis⇒Death	0-15	32.8% (1-year)	--	23
% failures that are local	0-5	93%	50-93%	6
	6-10	62%	50-75%	
	11-15	N/A	--	
<i>Hazard ratios</i>				
Tamoxifen Distant HR	0-5	0.64	--	12
	6-10	0.69	--	
	11-15	1	--	
Tamoxifen IBTR HR	0-5	0.47	--	12
	6-10	0.69	--	
	11-15	1	--	
PBI LR HR	0-5	1	0.75-2.0	--
	6-10	1	0.75-2.0	
	11-15	1	--	
PBI EF HR	0-5	3	2-4	--
	6-10	1	1-3	
	11-15	1	--	
<i>Utilities</i>				
NED-WBRT	0-15	0.92	--	27
NED-PBI	0-5	0.92	0.92-0.96	--
	6-15	0.92	0.88-0.96	
Well after salvage mastectomy	0-15	0.82	--	27
Distant metastasis	0-15	0.62	--	29
Disutility of tamoxifen	0-10	0.05	0-0.05	30