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ORIGINAL ARTICLE – BREAST ONCOLOGY

Cost-Effectiveness Analysis of Intraoperative Radiation Therapy for Early-Stage Breast Cancer

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ABSTRACT

Background. Shortened courses of radiation therapy have been shown to be similarly effective to whole-breast external-beam radiation therapy (WB-EBRT) in terms of local control. We sought to analyze, from a societal perspective, the cost-effectiveness of two radiation strategies for early-stage invasive breast cancer: single-dose intraoperative radiation therapy (IORT) and the standard 6-week course of WB-EBRT.

Methods. We developed a Markov decision-analytic model to evaluate these treatment strategies in terms of life expectancy, quality-adjusted life years (QALYs), costs, and the incremental cost-effectiveness ratio over 10 years.

Results. IORT single-dose intraoperative radiation therapy was the dominant, more cost-effective strategy, providing greater quality-adjusted life years at a decreased cost compared with 6-week WB-EBRT. The model was sensitive to health state utilities and recurrence rates, but not costs. IORT was either the preferred or dominant strategy across all sensitivity analyses. The two-way sensitivity analyses demonstrate the need to accurately determine utility values for the two forms of radiation treatment and to avoid indiscriminate use of IORT.

Conclusions. With less cost and greater QALYs than WB-EBRT, IORT is the more valuable strategy. IORT offers a unique example of new technology that is less costly than the current standard of care option but offers similar efficacy. Even when considering the capital investment for the equipment ($425 K, low when compared with the investments required for robotic surgery or high-dose-rate brachytherapy), which could be recouped after 3–4 years conservatively, these results support IORT as a change in practice for treating early-stage invasive breast cancer.

Local control of early-stage breast cancer has improved dramatically as a result of less-invasive surgical strategies that combine breast-conserving surgery (BCS) followed by whole-breast external beam radiation (WB-EBRT).[1,2] Nonetheless, 21 % of North American women who undergo BCS do not complete the recommended radiation therapy (RT), partially because of cost and inconvenience.[3] Researchers have continued searching for opportunities to improve effectiveness and patient tolerability of both surgical and radiation interventions.

Accelerated shortened courses of radiation may provide a solution for ensuring that women complete breast irradiation by offering a more convenient and comparably effective alternative. The recently developed technique of intraoperative radiation therapy (IORT) delivered at the time of BCS has shown promising results. This technique has been tested in more than 3,000 patients in the TARGIT-A trial, an international randomized controlled trial, and in close to 2,000 patients in the ELIOT trial.[4,5] Several randomized controlled trials have also supported the use of hypofractionated RT. These trials established that accelerated shortened courses of RT are similarly effective in local control of breast cancer and comparable or better than conventional WB-EBRT in terms of complications and cosmetic effects.[4–6]

Shortened courses of RT not only make adjuvant radiation more convenient for women to complete, but also reduce the delay in starting adjuvant chemotherapy, decrease the radiation facility workload, lower the societal costs, and

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increase the number of women eligible for BCS.[7,8] Increasing pressure from public and private sectors to consider cost as well as quality necessitates an in-depth analysis of the societal impacts of breast cancer treatment options. We therefore conducted a cost-effectiveness analysis, from a societal perspective, of options for women with early-stage invasive breast cancer.[9] There were two treatment strategies evaluated for selected patients over a 10-year time period: IORT and standard 6-week WB-EBRT. We sought to determine if shorter courses of RT are cost effective by evaluating both the economic and quality-of-life impact.

METHODS

We developed a Markov decision-analytic model based on the protocol of the international TARGIT-A trial, the only randomized trial that compares the two strategies: single-dose targeted IORT (20 Gy that attenuates to 5–7 Gy at 1-cm depth) versus standard WB-EBRT (typically 40–56 Gy over 5–6 weeks).[4] We simulated the model for a 10-year period, a time frame sufficient to capture events of the natural progress of the disease. The analyses were conducted from a societal perspective using TreeAge Pro 11 Software (Williamstown, MA).

Patient Population

Early-stage was defined as stage I–IIA estrogen-receptor positive (ER+), breast cancer.[4] We based our model on a cohort of 55-year old women because more than 80 % of patients in the TARGIT-A trial were ≥55 years old.

Model Structure and Strategies

All women were assumed to have had BCS followed by either IORT or 6-week WB-EBRT. Women in the 6-week WB-EBRT arm received a standard 33 fractions of WB-EBRT. All women in the IORT arm received IORT at the time of BCS. In the TARGIT-A trial, 14.1 % of women who underwent IORT received an additional 5 weeks (28 fractions) of WB-EBRT if their final pathology findings revealed high-risk features such as positive margins.[4] We incorporated this additional treatment for 14.1 % of women in our model.

After initial BCS and allocated radiation treatment, women were modeled to begin in a healthy state without evidence of disease. Women then transitioned annually between this disease-free health state and multiple other health states (Fig. 1). Recurrence in women who initially had WB-EBRT could only be treated with salvage mastectomy followed by immediate reconstruction. However, recurrence in patients who received IORT had the option of salvage lumpectomy followed by WB-EBRT. Death as a result of breast cancer was only possible for women with metastatic breast cancer (MBC); death due to other causes was possible at any time in the model. All inputs for costs and effectiveness (Table 1) were discounted at 3 % per cost-effectiveness guidelines (Fig. 2).[10]

Model Inputs

Health State Utilities Where possible, we used health state utilities obtained via standard gamble preference.[11] We valued the utilities of IORT and IORT followed by 5 week WB-EBRT as equal to 6-week WB-EBRT (0.92) and varied these values within clinically relevant ranges in sensitivity analyses.[11,12]

Rates and Probabilities Probabilities and 10-year local recurrence rates (LRR) were derived from the literature (Table 1).[5] The 4-year LRRs from the TARGIT-A trial were converted to annual transition probabilities and projected over 10 years. The rates were assumed to progress linearly over 10 years. Kaplan–Meier estimate of local recurrence in the conserved breast at 4 years was 1.20 % (95 % CI 0.53–2.71) for the IORT arm and 0.95 % (95 % CI 0.39–2.31) in the EBRT arm (difference between groups 0.25 %, −1.04 to 1.54; $p = .41$).[4] For women treated with IORT followed by WB-EBRT, we conservatively assumed that they would incur the same LRR as women who had IORT alone.[13]

Costs Direct medical costs for surgical and radiation procedures were estimated using medicare reimbursements, whereas costs of metastatic states and indirect costs were derived from published data. Direct medical costs include

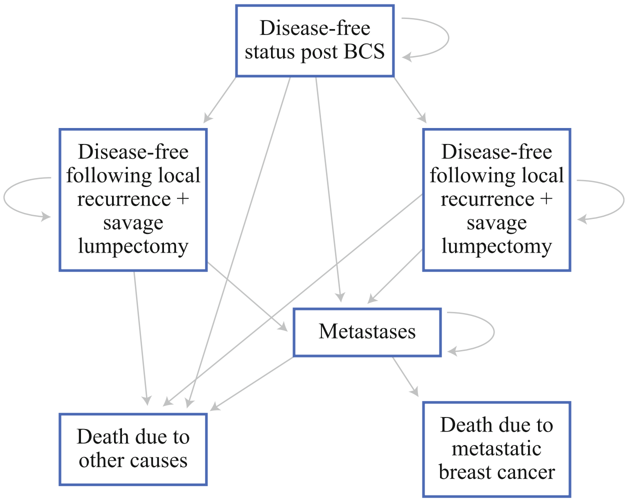

FIG. 1 Health-state diagram depicting model structure

TABLE 1 Model inputs

	Base case value	Range values
Health state utilities		
IORT[a]	0.92 [11,b]	0.87–0.97
3-week WB-EBRT[a]	0.92 [11]	0.87–0.97
6-week WB-EBRT[a]	0.92 [11]	0.87–0.97
IORT followed by 5-week WB-EBRT[a]	0.92 [11,b]	0.87–0.97
Salvage mastectomy	0.82 [11]	0.77–0.87
Salvage lumpectomy and WB-EBRT[a]	0.87 [11,b]	0.82–0.92
Metastatic BC	0.70 [11]	0.60–0.80
Death	0 [11]	–
Rates and probabilities		
LRR after BCS and IORT[a]	3.0 %[4] (10-year)	1.5–4.5 %
LRR after BCS and 6-week WB-EBRT[a]	2.4 %[4] (10-year)	1.2–3.6 %
LRR after BCS and IORT followed by WB-EBRT	3.0 %[4,b] (10-year)	1.5–4.5 %
LRR after BCS and 3-week WB-EBRT	6.2 %[7] (10-year)	3.1–9.3 %
LRR after salvage lumpectomy and WB-EBRT following first recurrence	38.0 %[23] (10-year)	28.4–47.8 %
Rate of metastasis after initial BCS (independent of radiation type)[a]	11.0 %[15] (10-year)	5.0–22.0 %
Rate of metastasis after salvage mastectomy[a]	20.0 %[15] (10-year)	10.0–40.0 %
Annual rate of BC death after metastasis	34.0 %[24] (annual)	30.0–38.0 %
Percent of women who can undergo salvage lumpectomy and radiation after a local recurrence in the IORT arm	65.5 %[23]	49.1–81.9 %
Percent of women in the IORT arm who receive IORT followed by WB-EBRT[a]	14.1% [4]	7.1–28.2 %
Costs (2011 $US)		
IORT	$5,547[25,26]	$2,774–11,094
6-week WB-EBRT	$10,464[25,26]	$7,848–13,079
IORT followed by 5-week WB-EBRT	$13,640[25,26]	$10,230–17,050
3-week WB-EBRT	$6,640[25,26]	$4,890–8,230
Salvage mastectomy and reconstruction	$9,411[27]	$7,059–11,764
Salvage lumpectomy	$2,446[27]	$1,835–3,058
Indirect costs (6-week WB-EBRT)	$1,467[28–31]	$1,100–1,834
Indirect costs (IORT followed by 5-week WB-EBRT)	$1,244[28–31]	$934–1,556
Indirect costs (3-week WB-EBRT)	$667[28–31]	$500–834
Routine disease-free follow-up care (annual)	$1,883[24]	$1,413–2,355
First year of metastatic disease care	$35,743[32]	$26,807–44,678
Annual treatment of metastatic patients in remission	$8,069[32]	$6,052–10,086
Death due to BC	$29,238[32]	$21,928–36,547
Death due to other causes	$775[33]	$581–969

BC breast cancer, *BCS* breast cancer surgery, *LRR* local recurrence rate, *IORT* intraoperative radiation therapy, *WB-EBRT* whole-breast external-beam radiation therapy

[a] Model was sensitive to this parameter

[b] Adapted from the literature

physician and facility fees for various surgical and radiotherapy treatments, as well as costs associated with the metastatic health state.

Model Analysis

All strategies were evaluated in terms of life expectancy, quality-adjusted life-years (QALYs), and costs over a 10-year period. The incremental cost-effectiveness ratio (ICER) was calculated by dividing the difference in expected cost by the difference in expected QALYs between the two RT arms. An ICER of lesser value is considered more cost effective because it indicates more quality gained for less cost. The outcomes were evaluated against each other as well as against the assumed societal willing-to-pay threshold of $75,000 per QALY gained.[14]

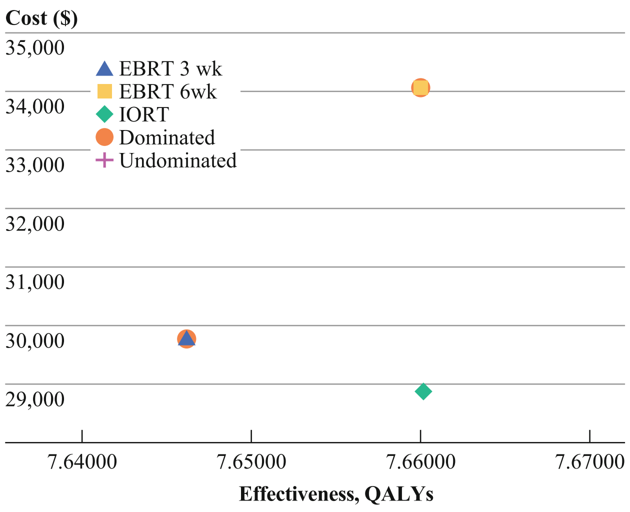

FIG. 2 Cost-effectiveness graph showing expected 10-year cost versus QALYs for various strategies

Sensitivity Analyses

A series of one-way and two-way sensitivity analyses were conducted to examine the impact of varying all inputs over their clinically and economically relevant ranges. Specific variables that held significant uncertainty or influence on the model results were explored in detail, including the utility, LRR, and cost of IORT (Table 1).

Considering the increased use of hypofractionated WB-EBRT, we modeled a scenario analysis of the 3-week accelerated WB-EBRT schedule of 16 fractions.[6] This scenario is based on the Ontario Clinical Oncology Group (OCOG) trial, a randomized trial with a patient population similar to TARGIT-A with a long follow-up period.[7] Without a previously reported utility for 3-week WB-EBRT, we used a value of 0.92 (equivalent to the utility of 6-week WB-EBRT; see Table 1).

RESULTS

Model Validity

The model's external validity was assessed by comparing our results with the TARGIT-A trial's published results and other prediction tools. For a 55-year-old woman, our model predicted a 4-year recurrence rate for IORT of 1.2 %, equal to the 4-year value in the TARGIT-A trial. Our model's 10-year overall survival was also compared with the predicted results of Adjuvant!Online, an online tool for adjuvant therapy, and a cost-effectiveness model evaluating partial-breast irradiation versus WB-EBRT by Sher et al.[15] Our model predicted a 10-year overall survival of 86.5 %, compared with 86.3 % in Sher et al.'s model and 79.9–95.3 % in Adjuvant!Online's model. These comparisons suggest that our model was able to replicate the initial results from the TARGIT-A trial and is comparable to other prediction tools.

Baseline Analyses

Under our baseline assumptions, the model results showed that IORT is the dominant strategy: It was both less costly and offered more QALYs than the 6-week WB-EBRT regimen. On average, IORT cost $5191 <6-week WB-EBRT. The effectiveness analysis showed that IORT was slightly preferred over the WB-EBRT strategy when measured in QALYs (a difference of 0.00026 QALYs, or 0.95 quality-adjusted days). This result was driven by the improved utility values for the proportion of women who have salvage lumpectomy after IORT, whereas all women who undergo WB-EBRT have a salvage mastectomy. However, when measured in life-years gained, IORT was slightly less effective than 6-week WB-EBRT (a difference of 0.00017 life-years, or 0.062 days). Local recurrence rate was the driving factor for this result, as WB-EBRT has a slightly lower LRR than IORT.

When calculating the ICER for moving from the most effective strategy (IORT) to the least effective (WB-EBRT) strategy, IORT dominates the WB-EBRT strategy in terms of QALYs: IORT offers greater QALYs at less cost. However, in terms of life expectancy, the ICER for moving from IORT to WB-EBRT was calculated to be $29.9 million/life year.

Sensitivity Analyses

The model was most sensitive to health state utilities and local and distant recurrence rates. IORT was always preferred, and in most cases, the dominant strategy across the variables (Table 2). For the utility of IORT, within the studied range of 0.87–0.97, IORT is always preferred. When the utility of IORT is greater than 0.91996 (base case value is 0.92), IORT dominates the WB-EBRT strategy. When we varied the LRR of IORT, IORT dominates when its 10-year LRR is <3.11 %. The ICER for WB-EBRT is >$75,000/QALY unless the LRR for IORT is >22.9 %. In all of the probability and rate sensitivity analyses, the ICER for WB-EBRT was significantly greater than the society willingness-to-pay of $75,000/QALY. For the hypofractionated scenario analysis, IORT was the dominant strategy compared with 3-week WB-EBRT in terms of both QALYs and life expectancy.

We completed two-way sensitivity analyses to determine the preferred strategy when (1) the utilities of IORT and EBRT were varied and (2) the LRR of IORT and the proportion receiving EBRT after IORT were varied. Both two-way analyses were conducted in QALYs. In the first analysis, IORT and EBRT are virtually indistinguishable in

TABLE 2 Baseline results and sensitivity analyses

	Baseline results				
	IORT	3-week WB-EBRT	6-week WB-EBRT	Differential between 3-week WB-EBRT and IORT	Differential between 6-week WB-EBRT and IORT
Life expectancy (life-years)	8.38240	8.38152	8.38257	−0.00088	0.00017
QALYs	7.66020	7.64618	7.65994	−0.01402	−0.00026
Cost	$28,879	$29,789	$34,070	$910	$5,191
ICER	–	Dominated	Dominated	–	–

	Sensitivity analyses						
	Parameter ranges	IORT		6-week WB-EBRT		ICER ($/QALY)	Cost-effectiveness results
		QALYs	Mean cost ($)	QALYs	Mean cost ($)		
Utilities							
Utility of IORT							
High	0.97	8.0073	28,879	7.6599	34,070	Dominated	WB-EBRT is dominated when utility of IORT surpasses 0.91996.
Low	0.87	7.3131	28,879	7.6599	34,070	12,820	
Utility of 6-week WB-EBRT							
High	0.97	7.6602	28,879	8.0651	34,070	14,965	WB-EBRT is dominated when utility of WB-EBRT <0.92003.
Low	0.87	7.6602	28,879	7.2548	34,070	Dominated	
Utility of IORT followed by 5-week WB-EBRT							
High	0.97	7.7172	28,879	7.6599	34,070	Dominated	WB-EBRT is dominated when utility of IORT followed by WB-EBRT surpasses 0.91977.
Low	0.87	7.6032	28,879	7.6599	34,070	91,517	
Utility of salvage lumpectomy after IORT							
High	0.92	7.6627	28,879	7.6599	34,070	Dominated	WB-EBRT is dominated when utility of salvage lumpectomy surpasses 0.86486.
Low	0.82	7.6577	28,879	7.6599	34,070	2,284,464	
Probabilities and rates							
LRR of IORT (10-year)							
High	6.0 %	7.6534	29,193	7.6599	34,070	746,158	WB-EBRT is dominated when LRR of IORT <3.1 %.
Low	1.5 %	7.6636	28,719	7.6599	34,070	Dominated	
LRR of 6-week WB-EBRT (10-year)							
High	3.6 %	7.6602	28,879	7.6578	34,124	Dominated	WB-EBRT is dominated when LRR of WB-EBRT surpasses 2.3 %.
Low	1.2 %	7.6602	28,879	7.6621	34,015	2.7 million	
Proportion of women who receive IORT followed by 5-week WB-EBRT							
High	28.2 %	7.6600	29,916	7.6599	34,070	267 million	WB-EBRT is dominated when proportion <22.9 %.
Low	7.1 %	7.6604	28,360	7.6599	34,070	Dominated	
Rate of MBC after salvage lumpectomy or mastectomy (10-year rates)							
High	40.0 %	7.6582	28,981	7.6585	34,152	21 million	WB-EBRT is dominated when rate of MBC is <29.9 %.
Low	10.0 %	7.6612	28,823	7.6607	34,025	Dominated	
Rate of metastasis after initial BCS (10-year rates)							
High	22.0 %	7.4592	34,081	7.4587	39,290	Dominated	WB-EBRT dominated
Low	5.0 %	7.7644	26,110	7.7643	31,291	Dominated	
Costs							
Cost of IORT							
High	$11,094	7.6602	33,643	7.6599	34,070	Dominated	WB-EBRT dominated
Low	$2,774	7.6602	26,497	7.6599	34,070	Dominated	
Cost of 6-week WB-EBRT							
High	$13,079	7.6602	28,914	7.6599	31,454	Dominated	WB-EBRT dominated
Low	$7,848	7.6602	28,843	7.6599	36,685	Dominated	

TABLE 2 continued

	Sensitivity analyses						
	Parameter ranges	IORT		6-week WB-EBRT		ICER ($/QALY)	Cost-effectiveness results
		QALYs	Mean cost ($)	QALYs	Mean cost ($)		
Other							
Discount rate							
High	7.0 %	6.5822	25,610	6.5820	30,823	Dominated	WB-EBRT dominated
Low	0 %	8.8689	31,999	8.6866	37,169	Dominated	

All outcomes discounted at 3 % in the model

BCS breast cancer surgery, *ICER* incremental cost-effectiveness ratio, *IORT* intraoperative radiation therapy, *LRR* local recurrence rate, *MBC* metastatic breast cancer, *QALYS* quality-adjusted life years, *WB-EBRT* whole-breast external-beam radiation therapy

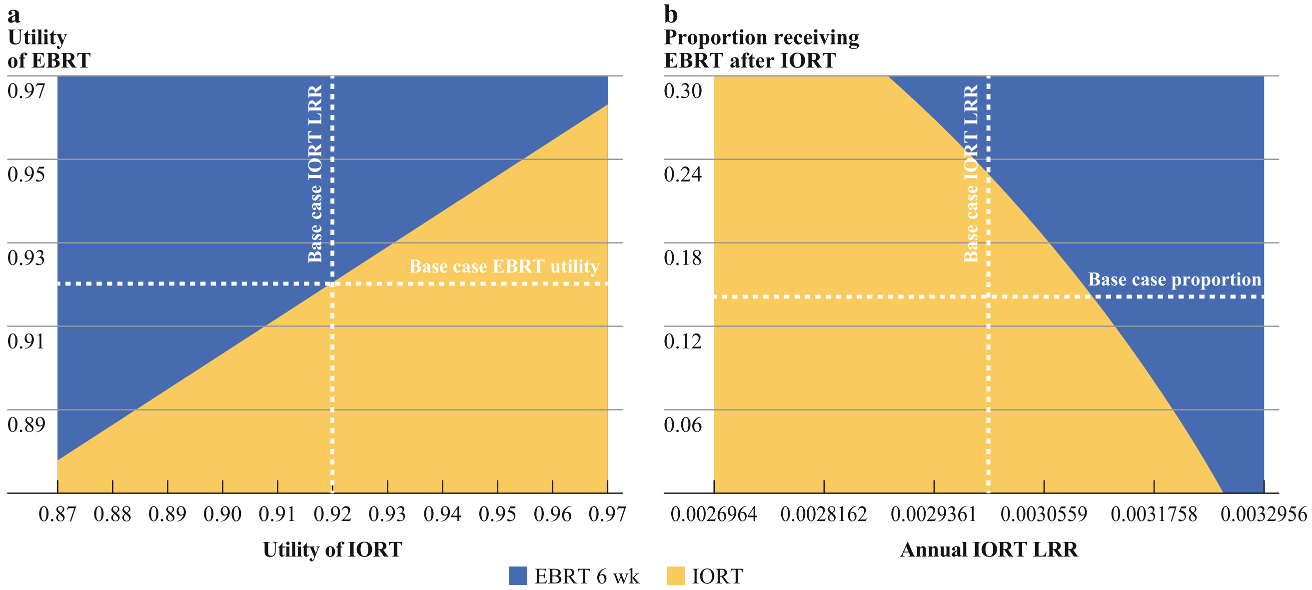

FIG. 3 **a** The two-way sensitivity analysis of the utilities for radiation therapy. The *yellow* area represents the combination of utility values for IORT and EBRT where IORT offers higher QALYs. The *blue* area represents the combination of utility values where WB-EBRT offers higher QALYs. **b** The two-way sensitivity analysis of local recurrence rate of IORT and proportion receiving EBRT after IORT. The *yellow* area represents the combination of these values where IORT offers more QALYs, and the remaining area (*blue*) represents the combination of values where WB-EBRT offers greater QALYs. The base case is represented by the *dotted lines*

terms of which strategy is preferred when the utilities of the two strategies are similar (approximating the base case) (Fig. 3). In the second two-way analysis, IORT is the preferred strategy except when the 10-year LRR of IORT is high (>3.11 %) or the proportion receiving EBRT after IORT is high (>24 %).

DISCUSSION

Our study, the first cost-effectiveness analysis of IORT following BCS for early-stage breast cancer treatment, shows that IORT is less expensive and more effective than the standard of care. In contrast to most new technology, which results in higher cost, this is an example of a disruptive innovation—one that provides a less costly and more convenient option, ultimately creating a new market.[16] Within the baseline model, IORT dominates WB-EBRT, implying that if IORT were the standard strategy today, WB-EBRT would never be adopted.

Our results show an interesting relationship between new technology implementation and its cost effectiveness. For IORT to be the more valuable strategy, it must be applied to the eligible patient population. If applied indiscriminately, the proportion of patients who will be eligible for salvage lumpectomy after recurrence decreases, reducing the expected QALYs from the IORT strategy as well as increasing the overall costs, making this a less-valuable strategy. These results, shown in the second two-way sensitivity analysis (Fig. 3b), will help guide future implementation of IORT.

When making a decision between mastectomy and BCS, women are concerned about the risk of recurrence, the need for radiation, and side effects from radiation.[17] These factors lead some women to choose mastectomy over BCS followed by conventional WB-EBRT. If BCS is offered with IORT, women may choose BCS over mastectomy, preferring the convenience, similar recurrence rates, and reduced side effects of IORT. Thus, patients' preferences play an important role in these treatment decisions.

The model's sensitivity to the utility values for both IORT and WB-EBRT should be considered in light of the conservative assumption of the equal utility values for IORT and EBRT.[12] Preliminary data from a patient preference study showed that women would prefer IORT over WB-EBRT and would even accept a small increase in risk of recurrence to have the convenience of a 1-time dose of radiation.[18]

Although early results from the TARGIT-A trial are promising, many researchers are waiting for longer follow-up to assess the efficacy of IORT. However, most studies of early-stage breast cancer indicate that the peak of breast cancer local recurrence occurs within 3 years, suggesting that the efficacy of IORT in the TARGIT-A trial is unlikely to change.[1,4,19] Our model implies that the LRR for IORT would need to be higher than 22.9 % over 10 years for WB-EBRT to be considered a cost-effective strategy when compared with IORT. Surgeons are critical to the adoption of IORT given RT is incorporated at the time of lumpectomy. The expected additional operating room time is 25–45 min. Presently, there is not a reimbursement code for surgeons to place the radiation applicator, as there is to place a brachytherapy balloon catheter; however, a reimbursement code is expected in the near future.

As patients are increasingly eligible for several RT regimes following lumpectomy, surgeons and radiation oncologists need to consider the most appropriate and cost-efficient treatment. A recent cost comparison of radiation regimens estimated that a cost-minimization strategy saved US$5.69 million per 1,000 patients treated.[20] Early adoption of IORT into clinical practice could safely further reduce the societal financial burden of breast cancer care, while allowing individuals to benefit from a less-intensive intervention.

Study limitations include a lack of long-term data for the IORT technology, though sensitivity analyses indicate that the results will hold across reasonable ranges of possible outcomes. Also, we used Medicare reimbursements as a proxy for procedural, treatment, and follow-up costs, even though the model cohort begins with 55-year-old women. Since Medicare reimbursements generally are greatly discounted, the model may underestimate total costs. However, the same costs were used in both the IORT and WB-EBRT arms of the model and should balance without impacting the cost-effectiveness estimates. Lastly, we recognize that the capital costs of delivering IORT are not trivial. For instance, the price of the Intrabeam device used for IORT is ~$425,000 (about half of the required investment for HDR brachytherapy). Overall, this investment and operating room time are relatively low compared with other medical technology such as robotic surgery. Additionally, these capital costs are accounted for in the cost-effectiveness analysis through the cost of the IORT procedure.[21]

Models can guide decision-making both at the policy and individual levels by exploring outcomes depending on different assumptions. Models allow the use of the best available data to project an estimate of expected outcomes and aggregate costs, which are rarely available. Importantly, while they cannot give us exact data, models let us test assumptions that have the highest impact and provide a rationale for where we should focus our efforts to gather better data to inform decisions.

Breast cancer is diagnosed in over 1 million women each year, worldwide, but the impact of the associated treatment decisions extends beyond these patients.[22] When WB-EBRT is compared with IORT, IORT is clearly the preferred treatment strategy for selected patients with early-stage breast cancer treated with BCS. The one-time treatment at the time of surgery is cost saving and also offers better quality of life. This is a promising outcome in the current health care environment where new technology tends to drive medical costs upward for minimal benefit.

DISCLOSURE Michael D. Alvarado, MD, and Laura J. Esserman, MD, MBA served as members of the International Steering Committee for the TARGIT-A trial. The study has previously been presented, in part, at the St. Gallen Breast Cancer Conference, March 16–19 2011, St. Gallen, Switzerland, and the American Society of Clinical Oncology, June 3–7, 2011, Chicago, IL.

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