Evaluating Radiotherapy Options in Breast Cancer: Does Intraoperative Radiotherapy Represent the Most Cost-Efficient Option?

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Abstract

Increasingly intraoperative radiation therapy is being utilized in the management of early stage breast cancer despite a lack of data supporting its efficacy based in part on potential cost savings with the technique. While cost minimization demonstrates a reduction in cost with intraoperative therapy, this is misleading. When factoring additional medical and non-medical costs whole breast irradiation and accelerated partial breast irradiation represent cost effective modalities with more quality data supporting their safety and efficacy.

Introduction: This study analyzed the cost-efficacy of intraoperative radiation therapy (IORT) compared with whole-breast irradiation (WBI) and accelerated partial-breast irradiation (APBI) for early-stage breast cancer.

Materials and Methods: Data for this analysis came from 2 phase III trials: the TARGIT (Targeted Intraoperative Radiotherapy) trial and the ELIOT (Electron Intraoperative Radiotherapy) trial. Cost analyses included a cost-minimization analysis and an incremental cost-effectiveness ratio analysis including a quality-adjusted life-year (QALY) analysis. Cost analyses were performed comparing IORT with WBI delivered using 3-dimensional conformal radiotherapy (3D-CRT), APBI 3D-CRT, APBI delivered with intensity-modulated radiotherapy (IMRT), APBI single-lumen (SL), APBI multilumen (ML), and APBI interstitial (I). Results: Per 1000 patients treated, the cost savings with IORT were $3.6-$4.3 million, $1.6-$2.4 million, $3.6-$4.4 million, $7.5-$8.2 million, and $2.8-$3.6 million compared with WBI 3D-CRT, APBI IMRT, APBI SL, APBI ML, and APBI I, respectively, with a cost decrement of $1.6-$2.4 million compared with APBI 3D-CRT based on data from the TARGIT trial. The costs per QALY for WBI 3D-CRT, APBI IMRT, APBI SL, APBI ML, and APBI I compared with IORT were $47,990-$60,002; $17,335-$29,347; $49,019-$61,031; $108,162-$120,173; and $36,129-$48,141, respectively, based on data from the ELIOT trial. These results are consistent with APBI and WBI being cost-effective compared with IORT. Conclusion: Based on cost-minimization analyses, IORT represents a potential cost savings in the management of early-stage breast cancer. However, absolute reimbursement is misleading, because when additional medical and nonmedical costs associated with IORT are factored in, WBI and APBI represent cost-effective modalities based on cost-per-QALY analyses. They remain the standard of care.

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Introduction

Breast-conserving therapy continues to be the standard of care in the management of early-stage breast cancer. Traditionally, adjuvant radiation therapy is delivered after breast-conserving surgery and entails 5 to 6 weeks of treatment with whole-breast irradiation (WBI) with or without a boost. Unfortunately, owing to the...
IORT Cost Efficacy

Intraoperative radiation therapy (IORT) represents an alternative to WBI or APBI and allows for delivery of radiation therapy at the time of surgery or in a single session after pathology review, eliminating adjuvant treatment for more than 80% of patients; IORT can be delivered using low-energy x-rays or electrons, and both techniques have been evaluated in randomized studies. Given the nature of the technique, IORT has been suggested as a modality that could reduce costs associated with breast cancer, but limited data have emerged regarding this hypothesis.7

When evaluating new radiation therapy techniques such as IORT, the focus is often on absolute differences in reimbursement rather than on evaluating reimbursement in light of differences in outcomes, toxicity profiles, or both. More recently, radiation therapy techniques for breast cancer have been evaluated using multiple cost-effectiveness modalities including incremental cost-effectiveness ratios (ICER) and the associated cost per quality-adjusted life-year (QALY); these techniques are able to provide a more meaningful understanding of the costs associated with novel radiation therapy techniques compared with traditional modalities, and they incorporate differences in outcomes, toxicity, and quality of life. Therefore, the purpose of this study was to evaluate the cost-efficacy of IORT via a cost-minimization analysis, an ICER analysis, and a cost-per-QALY analysis based on local recurrence data from 2 recently updated randomized trials comparing IORT with WBI.

Materials and Methods

Randomized Trials

Local recurrence data were extracted from 2 randomized trials comparing outcomes between IORT and WBI. The first randomized trial was the TARGIT (Targeted Intraoperative Radiotherapy) trial, which was an international, multicenter, prospective, noninferiority trial comparing IORT with WBI among 2232 patients. Eligibility included women aged 45 years or older with early-stage ductal breast cancer, with individual institutions able to add additional inclusion criteria. WBI was delivered with a variety of dose schemes (40 to 56 Gy with or without a boost of 10 to 16 Gy) using tangents. IORT was delivered using a 50-kV x-ray source delivering 20 Gy to the surface and 5 to 7 Gy to 1 cm over a period of 20 to 35 minutes. This trial initially reported 4-year outcomes, with no difference noted in local recurrence between IORT and WBI (1.2% vs. 0.95%); however, a recent update of this trial noted increased 5-year rates of local recurrence with IORT (3.3% vs. 1.3%; P = .04) and increased overall recurrences with IORT (8.2% vs. 5.7%), albeit with a median follow-up of 29 months.5

The second randomized trial was the ELIOT (Electron Intraoperative Radiotherapy) trial, which was a single-institution, prospective trial that randomized women to IORT delivered with electrons or to WBI, with a total of 1306 patients enrolled. Eligibility included women older than 45 years with unicentric cancer less than 2.5 cm. No women in the IORT arm received WBI, regardless of margin or nodal status. WBI patients received 50 Gy delivered with tangents, along with a 10-Gy boost, whereas patients receiving IORT received 21 Gy prescribed to the 90% isodose line using electrons with a 1.5- to 3.0-cm expansion around the tumor bed. Recent presentation of this study noted statistically significant increases in the rates of local recurrence with IORT (5.3% vs. 0.7%).6

Cost-Effectiveness Analyses

Reimbursement models were generated based on a previous publication from the present authors’ group for each treatment technique with the exception of IORT; models for the latter were based on a publication from Grobmyer et al (Table 1).7,8 In these models, WBI costs were assessed without boosts owing to the heterogeneity of techniques (and therefore reimbursement); however, indirect costs did incorporate a traditional 6-week schedule with boost. Reimbursement models were calculated in several ways: (1) reimbursement only (professional and facility); (2)

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**Table 1 Reimbursements by Treatment Technique**

<table>
<thead>
<tr>
<th>Technique</th>
<th>Total Reimbursement</th>
<th>Reimbursement Including Additional Medical Costs</th>
<th>Reimbursement Including Medical and Nonmedical Costs</th>
<th>Reimbursements Including Medical, Nonmedical, and Recurrence Costs (TARGIT)</th>
<th>Reimbursements Including Medical, Nonmedical, and Recurrence Costs (ELIOT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IORT</td>
<td>$3094</td>
<td>$8003-$8706</td>
<td>$8192-$8971</td>
<td>$9399-$10179</td>
<td>$9230-$10,009</td>
</tr>
<tr>
<td>WBI 3D-CRT</td>
<td>$11,726</td>
<td>$11,726</td>
<td>$12,985</td>
<td>$13,743</td>
<td>$13,122</td>
</tr>
<tr>
<td>APBI 3D-CRT</td>
<td>$6578</td>
<td>$6578</td>
<td>$7028</td>
<td>$7786</td>
<td>$7165</td>
</tr>
<tr>
<td>APBI IMRT</td>
<td>$10,547</td>
<td>$10,547</td>
<td>$10,997</td>
<td>$11,755</td>
<td>$11,134</td>
</tr>
<tr>
<td>APBI SL</td>
<td>$12,602</td>
<td>$12,602</td>
<td>$13,052</td>
<td>$13,810</td>
<td>$13,189</td>
</tr>
<tr>
<td>APBI ML</td>
<td>$16,439</td>
<td>$16,439</td>
<td>$16,889</td>
<td>$17,646</td>
<td>$17,025</td>
</tr>
<tr>
<td>APBI Interstitial</td>
<td>$11,765</td>
<td>$11,765</td>
<td>$12,215</td>
<td>$12,974</td>
<td>$12,353</td>
</tr>
</tbody>
</table>

Abbreviations: 3D-CRT = 3-dimensional conformal radiotherapy; APBI = accelerated partial-breast irradiation; ELIOT = Electron Intraoperative Radiotherapy trial; IMRT = intensity-modulated radiation therapy; IORT = intraoperative radiation therapy; ML = multilumen; SL = single-lumen; TARGIT = Targeted Intraoperative Radiotherapy trial; WBI = whole-breast irradiation.

*Range based on differences in whole breast irradiation rates (15%-21%).
reimbursement incorporating additional medical costs (eg, increased operative time with IORT, fraction of IORT patients requiring additional radiation); (3) reimbursement incorporating nonmedical costs; and (4) reimbursement incorporating costs associated with recurrences. Additional medical costs were factored in based on the study by Grobmyer et al; based on the TARGIT trial, which found that 15% to 21% of patients treated with prepathology verification required WBI; and based on data from ASTRO (the American Society for Radiation Oncology) and Stanford University regarding the increased operating time required with IORT and the cost for this additional time. For nonmedical costs, assumptions included that the average round-trip travel was 40 miles to the radiation center (36 cents per mile); that the time involved was 2 hours per treatment, including travel, of which 30 minutes were spent receiving treatment ($14.78 per hour); and that patients receiving twice-daily treatment returned to work during the interfraction interval. Based on these assumptions, the costs were $44.96 and $89.92 per day for once-daily and twice-daily schedules, respectively. Future follow-up costs after treatment were not included in this model owing to similar regimens after treatment. Costs associated with local recurrence or other recurrences (including salvage mastectomy) were based on the study by Stokes et al and were incorporated into the model by multiplying the costs by the percentage of patients in each group having an event; a general number was used for cost of recurrence, rather than breaking out costs by local technique, reconstruction, or systemic therapy. Recurrence rates for WBI in the randomized trials were extrapolated to APBI based on multiple prospective datasets that have found no difference in outcomes between APBI and WBI, including 10-year data from a randomized phase III trial. Further multiple phase III trials have accrued, with no differences noted to date. Toxicity data were not included in the TARGIT ICER analysis, because they were not available in the updated results and because previous publications from this trial found no difference in major toxicity between techniques. With regard to the ELIOT trial, the published abstract did not include a toxicity analysis. All assumptions and methodology were based on and consistent with previously published articles that reported on the ICER method or other cost-efficacy techniques.

Based on the absolute difference in reimbursements by technique, a cost-minimization analysis was performed. Cost savings per 1000 patients were subsequently calculated based on these absolute differences in reimbursement alone and also on reimbursement incorporating additional medical costs, nonmedical costs, and costs associated with recurrences. ICERs for IORT were calculated based on comparisons with the WBI and APBI modalities; the purpose of the ICER analysis was to provide a relative cost-effectiveness of WBI and APBI techniques compared with IORT. The ICER analysis, for the purpose of this analysis, provided the increased reimbursement required to use WBI or APBI compared with IORT per percentage point of improvement in local recurrence. For example, if IORT costs $3500 and has a local recurrence rate of 5%, whereas WBI costs $13,000 and has a local recurrence rate of 1%, the ICER for WBI would be $2500 per percentage point of improvement in local recurrence: ($13,000 − $3500)/(5 − 1). Unlike for QALY analyses, no definitive threshold for ICER analyses has been defined as cost-effective.

Cost per QALY was calculated for WBI and APBI compared with IORT based on the TARGIT and ELIOT data. To calculate the cost per QALY, mean utility values for the various outcome states (no recurrence = 0.92, local recurrence = 0.779, other recurrences = 0.685) were used based on data from Hayman et al; mean utility by technique was calculated at 10 years based on the mean utility values and the proportion of each cohort in each utility state; time to events was not available and therefore was not incorporated into the model. Total costs, including medical/nonmedical costs and costs associated with recurrences, were used for the cost for each modality.

Results

Reimbursement is presented in Table 1; when factoring in professional and facility reimbursement only, IORT was the least expensive modality, with a decrease in reimbursement ranging from $3484 (compared with APBI 3-dimensional conformal radiotherapy [3D-CRT]) up to $13,345 (compared with APBI multilumen [ML]). When factoring in additional medical costs, nonmedical costs, and cost of recurrences, APBI 3D-CRT had a lower overall cost ($7786/$7165 vs. $9399-$10,179/$9230-$10,009 for TARGIT and ELIOT, respectively). The cost-minimization analysis found that per 1000 patients treated, the cost savings with the use of IORT were $8.6 million, $7.5 million, $3.5 million, $9.5 million, $13.3 million, and $8.6 million compared with WBI 3D-CRT, APBI intensity-modulated radiotherapy (IMRT), APBI 3D-CRT, APBI single-lumen (SL), APBI ML, and APBI interstitial (I), respectively. However, when factoring in medical/nonmedical costs and the cost of recurrences, the savings were lower. Based on the TARGIT trial, the cost savings with the use of IORT were $3.6-$4.3 million, $1.6-$2.4 million, $3.6-$4.4 million, $7.5-$8.8 million, and $2.8-$3.6 million compared with WBI 3D-CRT, APBI IMRT, APBI SL, APBI ML, and APBI I, respectively, with a cost increase of $1.6-$2.4 million compared with APBI 3D-CRT. Based on the ELIOT trial, the cost savings with the use of IORT were $3.1-$3.9 million, $1.1-$1.9 million, $3.2-$4.0 million, $7.0-$7.8 million, and $2.3-$3.1 million compared with WBI 3D-CRT, APBI IMRT, APBI SL, APBI ML, and APBI I, respectively, with a cost increase of $2.1-$2.8 million compared with APBI 3D-CRT.

ICERs for local control are presented in Table 2. When all associated costs are incorporated, the ICERS for local control (cost per percentage point of improvement in local control) are $677-$846, $244-$433, $691-$861, $1525-$1694, and $509-$679 for WBI 3D-CRT, APBI IMRT, APBI SL, APBI ML, and APBI I, respectively, with a cost increase of $1.0-$1.9 million. Based on the ELIOT trial, the cost savings with the use of IORT were $3.1-$3.9 million, $1.1-$1.9 million, $3.2-$4.0 million, $7.0-$7.8 million, and $2.3-$3.1 million compared with WBI 3D-CRT, APBI IMRT, APBI SL, APBI ML, and APBI I, respectively, with a cost increase of $2.1-$2.8 million compared with APBI 3D-CRT. ICERs for local control are presented in Table 2. When all associated costs are incorporated, the ICERS for local control (cost per percentage point of improvement in local control) are $677-$846, $244-$433, $691-$861, $1525-$1694, and $509-$679 for WBI 3D-CRT, APBI IMRT, APBI SL, APBI ML, and APBI I, respectively, with a cost increase of $1.0-$1.9 million. Based on the ELIOT trial, the cost savings with the use of IORT were $3.1-$3.9 million, $1.1-$1.9 million, $3.2-$4.0 million, $7.0-$7.8 million, and $2.3-$3.1 million compared with WBI 3D-CRT, APBI IMRT, APBI SL, APBI ML, and APBI I, respectively, with a cost increase of $2.1-$2.8 million compared with APBI 3D-CRT.
for WBI 3D-CRT, APBI IMRT, APBI SL, APBI ML, and APBI I compared with IORT are $89,234/QALY-$108,735/QALY; $39,464/QALY-$58,966/QALY; $90,904/QALY-$110,405/QALY; $186,924/QALY-$206,425/QALY; and $69,978/QALY-$89,479/QALY, respectively, based on the TARGIT trial. The cost per QALY for WBI 3D-CRT, APBI IMRT, APBI SL, APBI ML, and APBI I compared with IORT are $47,990/QALY-$60,002/QALY; $17,335/QALY-$29,347/QALY; $49,019/QALY-$61,031/QALY; $108,162/QALY-$120,173/QALY; and $36,129/QALY-$48,141/QALY, respectively, based on the ELIOT trial, indicating that despite higher reimbursement, these techniques were cost-effective when factoring in recurrences and direct and indirect costs.

Discussion

The results of this cost-efficacy analysis led to several key findings. Although reimbursement for IORT is lower than that for WBI and APBI, when factoring in direct/indirect costs along with the costs associated with recurrences, the cost-minimization analysis found that the gains from switching to IORT are relatively modest for most modalities and that APBI delivered with 3D-CRT actually represents a cost savings compared with IORT. Although recent studies have suggested worse cosmetic outcomes with APBI 3D-CRT, this suggestion has not been confirmed by data from the NSABP (National Surgical Adjuvant Breast and Bowel Project) B-39 trial. The overall findings from the present study are consistent with the authors’ hypothesis that cost savings from IORT are likely lower than usually projected, once associated costs are factored in. A second conclusion from the present study is that based on the ICER analyses, WBI and APBI are cost-effective, with ICERs for local control ranging from $244-$1694 per percentage point of improvement in local control (based on the ELIOT data) to higher values (based on the TARGIT data). Unlike with cost per QALY, no consistent ICER values have been used to define cost-efficacy; however, a study examining the cost-efficacy of systemic therapy in early-stage breast cancer used a cutoff of $1000 per percentage point of reduction, and other studies examining radiation therapy techniques in breast cancer have used ranges of $1000-$2000 per percentage point of reduction. Using these thresholds, WBI and APBI are cost-effective techniques compared with IORT, based on the ICER analyses performed.

Another major conclusion from the present study is that, based on cost-per-QALY analyses, WBI and APBI are cost-effective techniques when compared with IORT. Compared with IORT, based on the ELIOT data, the cost per QALY was $48,000 for WBI and ranged from $17,000 to $120,000 with APBI; these findings are consistent with traditional thresholds used to define cost-efficacy in breast cancer, with ranges of $50,000-$100,000/QALY.

### Table 3 Mean Utility Values by Technique

<table>
<thead>
<tr>
<th>Technique</th>
<th>TARGIT</th>
<th>IORT</th>
<th>WBI/APBI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean Utility Value</td>
<td>Clinical Outcome</td>
<td>Overall Utility Value</td>
</tr>
<tr>
<td>No Recurrence</td>
<td>0.92</td>
<td>91.8%</td>
<td>8.45</td>
</tr>
<tr>
<td>Local Recurrence</td>
<td>0.779</td>
<td>3.3%</td>
<td>0.26</td>
</tr>
<tr>
<td>Other Recurrences</td>
<td>0.685</td>
<td>4.9%</td>
<td>0.34</td>
</tr>
<tr>
<td>Total Mean Utility Value</td>
<td>9.04</td>
<td>9.08</td>
<td></td>
</tr>
<tr>
<td>No Recurrence</td>
<td>0.92</td>
<td>94.7%</td>
<td>8.71</td>
</tr>
<tr>
<td>Local Recurrence</td>
<td>0.779</td>
<td>5.3%</td>
<td>0.41</td>
</tr>
<tr>
<td>Total Mean Utility Value</td>
<td>9.13</td>
<td>9.19</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: APBI = accelerated partial-breast irradiation; ELIOT = Electron Intraoperative Radiotherapy trial; IORT = intraoperative radiation therapy; TARGIT = Targeted Intraoperative Radiotherapy trial; WBI = whole-breast irradiation.
Frederix et al18 compared endocrine therapies (anastrozole vs. tamoxifen) and found the cost per QALY was up to $75,000/QALY for anastrozole; based on these data, the use of anastrozole was still advocated. Similarly, based on the present findings, the authors could continue to advocate for WBI or APBI compared with IORT. Unfortunately, limited data are available for comparison with the present study, as studies examining the cost-efficacy of IORT have focused on absolute reimbursement differences rather than relative cost-efficacy.7

Both trials used in this study have found significant increases in local recurrences with IORT compared with WBI at 5 years, with the ELIOT trial finding a nearly 5% increase and the TARGIT trial finding a 2% increase. Although supporters of IORT have noted improved overall survival in the TARGIT trial for patients undergoing IORT, this is secondary to non-breast cancer–related deaths rather than to a reduction in breast cancer–related events.5 However, data from the Early Breast Cancer Trialists Group have indicated that increases in local recurrence for patients with early-stage breast cancer are associated with decrements in breast cancer–specific survival.19 The meta-analysis found that for every 4 recurrences prevented, there is a reduction of 1 breast cancer–related death. Using the ELIOT data, this translates to an additional 46 recurrences per 1000 patients and therefore to 11.5 additional breast cancer deaths per 1000 patients with IORT.6 Using the TARGIT data, IORT is associated with an additional 20 recurrences and 5 breast cancer deaths per 1000 patients.5 Based on these findings, IORT should be used with caution and may need to be limited at this time to patients enrolled in clinical protocols.

Recent data have indicated that axillary lymph node dissection (ALND) can be omitted in patients with limited nodal positivity who are receiving adjuvant WBI.20 The explanation for the equivalence in clinical outcomes is likely the ability of WBI to eradicate micrometastatic disease in the axilla. However, IORT provides minimal to no dose to the axilla; therefore, at this time IORT should be limited to those who are node negative, or, if it is used for those with limited nodal involvement, ALND would still be required. Therefore, the cost of IORT would be higher owing to the cost of the ALND and to the decrement in quality of life from higher rates of lymphedema.

There are several limitations to this analysis. Data from the WBI arm of the randomized trials were extrapolated to APBI. Although multiple studies have found equivalence in clinical outcomes between APBI and WBI, data from randomized phase III trials comparing the 2 techniques are still pending to provide final confirmation.2,3,13 Also, owing to data not being presented, costs associated with toxicity management were not included, and toxicity data were not incorporated into the ICER or cost-per-QALY analyses. Finally, there are limitations of ICER and cost-per-QALY analyses, including a lack of standardized utility scales and assumptions within the models that allow for variability in resultant outcomes; for example, the utility for no recurrence may be higher in IORT owing to improved quality of life, although this has not been proven.15 However, these assumptions and their rationales have been explained in the Materials and Methods section, and effort has been made to limit potential biases. Despite these limitations, this study is one of the only analyses to evaluate the cost-effectiveness of IORT compared with standard adjuvant radiation techniques and is the only one to evaluate cost-effectiveness with respect to clinical outcomes.

Conclusion

IORT represents a potentially cost-effective treatment option for women with early-stage breast cancer; however, despite reduced reimbursement rates with IORT, WBI and APBI represent cost-effective modalities to deliver radiation therapy based on cost-per-QALY analyses. Future studies will be required to look at associated costs with IORT, including the cost of managing recurrences and toxicities and the cost of additional axillary management when comparing with standard radiation modalities.

Clinical Practice Points

- Intraoperative radiation therapy (IORT) is an emerging radiation modality in early stage breast cancer with randomized Phase III trials performed.
- Recent results from these randomized trials have demonstrated increased rates of local recurrence with IORT compared with whole breast irradiation (WBI).
- IORT is often advocated for based on reductions in absolute cost which is misleading as it neglects additional costs associated with treatment.
- When factoring the costs associated with the higher rates of recurrence as well as medical and non-medical costs, standard modalities including WBI and accelerated partial breast irradiation (APBI) are cost effective compared to IORT.
- In light of higher recurrence rates with IORT and documented findings for anastrozole; based on these data, the use of anastrozole was still advocated.

Disclosure

The authors have stated that they have no conflicts of interest.

References

IORT Cost Efficacy