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ORIGINAL ARTICLE – BREAST ONCOLOGY

# The Landmark Series: Adjuvant Radiation Therapy for Breast Cancer

**Stephanie A. Valente, DO[1], and Chirag Shah, MD[2]**

[1]Division of Breast Surgery, Department of General Surgery, Cleveland Clinic, Cleveland, OH; [2]Department of Radiation Oncology, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH

**ABSTRACT** Radiation therapy represents a cornerstone of breast cancer treatment both for patients undergoing breast conservation and for those receiving mastectomy. Trials evaluating breast-conserving therapy have established the benefit of adjuvant radiation therapy in terms of both local control and breast cancer mortality, whereas trials evaluating post-mastectomy radiation therapy have demonstrated improved survival for appropriately selected patients. More recent trials have confirmed that axillary node dissection can be omitted for patients who have positive sentinel nodes with no impairment at locoregional recurrence and improved outcomes. Additionally, new studies have validated the finding that the addition of regional nodal irradiation to patients with limited nodal disease provides improved outcomes. With a growing focus on treatment de-intensification, studies evaluating partial-breast irradiation with brachytherapy and external beam have demonstrated outcomes comparable with those of whole-breast irradiation, whereas further study is needed regarding intraoperative radiation therapy. This study reviews these landmark studies to present a roadmap for how adjuvant radiation therapy is used to treat breast cancer patients at this time.



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S. A. Valente, DO
e-mail: Valents3@ccf.org

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## BREAST-CONSERVING THERAPY AND MASTECTOMY

### *Background*

For decades before the seminal trials comparing modified radical mastectomy and breast conservation, patients with the diagnosis of breast cancer, regardless of stage, were offered the same radical surgical treatment option. The trials described in this report represent some of the first attempts to tailor treatment paradigms in breast cancer to the patient's disease and to de-escalate treatment in appropriate cases. These studies aimed to compare mastectomy with breast conservation. We hypothesized that outcomes between the two surgical treatments would be equivalent.

### *National Surgical Adjuvant Breast and Bowel Project B06*[1]

The National Surgical Adjuvant Breast and Bowel Project B06 trial was a three-arm randomized trial that included 2163 women with tumors smaller than 4 cm (stage 1 or 2 breast cancer) from 1976 to 1984. All the patients underwent axillary lymph node (LN) dissection (ALND) (levels 1 and 2), and those with positive nodes received adjuvant chemotherapy.

The women were randomized to total mastectomy, lumpectomy with adjuvant RT (50 Gy to the whole breast without regional nodal irradiation [RNI] and no boost), or lumpectomy alone. For the patients undergoing lumpectomy, adjuvant radiation therapy (RT) reduced the risk of ipsilateral breast tumor recurrence (IBTR) found 20 years later (no-RT39% vs RT 14%; $p < 0.001$), which was independent of nodal status.

At 20 years, no difference in disease-free survival, distant disease-free survival, or overall survival were noted among the mastectomy and breast-conserving surgery (BCS) groups. With long-term follow-up evaluation, the study concluded that BCS is an appropriate option for patients.

*EORTC 1080*[2,3]

The EORTC 10,801 trial was a randomized trial from 1980 to 1986 that included 868 women younger than 70 years with tumors smaller than 5 cm. The women were randomized to modified radical mastectomy (MRM) or lumpectomy (BCS) with adjuvant RT (50 Gy to the whole breast with a 25-Gy Ir-192 boost). In the study, negative surgical margins were not required (217 of 448 margins were involved), and all the patients underwent ALND, with chemotherapy given to node-positive patients younger than 55 years. The primary end point of the trial was time to distant metastasis. At 22 years, no difference in the rates of distant metastases (MRM 42% vs BCS 46%) or survival was observed. With long-term follow-up evaluation, the study concluded that BCS was appropriate for women with early breast cancers.

*Early Breast Cancer Trialists Meta-Analysis*[4]

The Early Breast Cancer Trialists (EBCTG) meta-analysis was a patient-level study of 10,801 women from 17 randomized trials evaluating the role of adjuvant RT after BCS with the goal of evaluating differences in recurrence. Radiation therapy reduced the 10-year risk of recurrence 15.7% (no-RT 35.0% vs RT 19.3%), which translated to a 3.8% reduction in breast cancer mortality at 15 years (25.2% vs 21.4%). These benefits were seen in both node-negative and node-positive patients, with outcomes demonstrating that for every four recurrences prevented with adjuvant radiation at 10 years, one breast cancer death was avoided at 15 years.

*Commentary and Implications for Practice*

Taken together, these studies and additional trials have defined the role of breast conservation for patients, providing an alternative standard-of-care approach and surgical options for patients with breast cancer. With these data, patients can be assured that BCS provides equivalent rates of cancer survival. Additionally, the data presented support the role of adjuvant RT after breast-conserving surgery, with not only a reduction in locoregional recurrence (LRR), but also an improved breast cancer mortality at 15 years.

## POST-MASTECTOMY RADIATION THERAPY

*Background*

In the late 1970s and early 1980s, the role of adjuvant systemic therapy after surgery continued to expand. Although older studies had evaluated adjuvant RT, only limited data were available to guide clinicians on the role of post-mastectomy RT (PMRT) with modern treatment paradigms. These studies evaluated the impact of PMRT on LRR and survival for high-risk patients.

*British Columbia*[5]

The British Columbia trial from 1979 to 1986 evaluated the impact of PMRT on LRR and survival for women undergoing MRM. The trial included 318 *pre*-menopausal women who were node-positive after MRM. All the patients received adjuvant cyclophosphamide methotrexate fluorouracil (CMF) chemotherapy and were randomized to the receipt of PMRT or not. Radiation therapy was delivered to the chest wall and regional LNs (supraclavicular/axillary fields) between the fourth and fifth cycles of chemotherapy. The radiation was delivered with older techniques (nonlinear accelerator-based, Cobalt-60). At 20 years, the addition of PMRT was associated with a reduction in isolated LRR (PMRT 10% vs no-PMRT 26%; $p = 0.002$), with improved systemic relapse-free survival and breast cancer-specific survival, as well as a 10% improvement in overall survival, with lower rates of long-term side effects.

*Danish 82b/c*[6,7]

The Danish 82b randomized trial included 1708 *pre*-menopausal women with stage 2 or 3 high-risk cancer (node-positive tumor $> 5$ cm and/or invasion of skin/pectoral fascia) after MRM (median of 7 LNs removed), whereas 82c included 1375 *post*-menopausal women, and both accrued patients from 1982 to 1989. All of the 82b patients received CMF chemotherapy, whereas the 82c patients received tamoxifen.

All the patients were randomized to the receipt of PMRT or not. RT was delivered to the chest wall and regional nodes (supraclavicular/infraclavicular/axillary/internal mammary fields) between the first and second cycles of chemotherapy. At 10 years, the addition of PMRT reduced LRR (32% vs 9%; $p < 0.001$), translating into an improvement in disease-free survival and a 9% clinically significant improvement in overall survival for *pre*-menopausal women. For *post*-menopausal women, PMRT reduced LRR (35% vs 8%; $p < 0.001$), translating into an improvement in disease-free survival and a 9% significant

improvement in overall survival. Pooled analyses confirmed a benefit of PMRT for patients with one to three positive lymph nodes.

*EBCTG Meta-Analysis*[8]

The EBCTG meta-analysis was a study of 8135 women from 22 randomized trials evaluating the role of PMRT for LRR and breast cancer mortality of women treated with mastectomy and axillary surgery. The meta-analysis included studies between 1964 and 1986. A total of 3786 women received ALND. The 10-year follow-up assessment showed that for the 700 women who had N0 disease, PMRT offered no benefit. A total of 1314 patients received ALND for one to three positive LNs, and PMRT significantly reduced LRR ($p < 0.00001$) and improved breast cancer mortality, with the benefit persisting among the patients who received systemic therapy. The patients with more than four positive LNs also had a significant reduction in LRR, translating into improvements in breast cancer mortality.

*Commentary and Implications for Practice*

The results of these randomized trials and meta-analyses defined the role of PMRT for high-risk patients after mastectomy, including those with T3 disease or axillary node involvement. Although these considerations remain appropriate, guidelines continue to evolve, accounting for the consideration of tumor biology and new systemic therapies.[9] Patients with T3N0 disease continue to be evaluated for PMRT on a case-by-case basis.

For patients with N1 disease after mastectomy with ALND, adjuvant RT can be considered based on the aforementioned data, with current studies evaluating the omission of RT for these patients.[10] However, it should be noted that the MA20 trial[11] (primarily breast conservation), which included patients with a low nodal burden (1 to 3 positive nodes 85%), found that the addition of regional RT reduced LRR and improved distant metastatic survival, suggesting a continued role for PMRT in cases with low nodal involvement. Ongoing studies, such as the TAILOR RT trial, are evaluating the role of regional nodal irradiation versus no RT for patients with low-risk biomarkers. Results are expected in the future.[12]

## EXTERNAL BEAM RADIATION THERAPY: HYPOFRACTIONATION

*Background*

After the publication of trials comparing mastectomy and BCS, whole-breast irradiation (WBI) represented the standard of care after breast surgery.[13] The WBI was delivered during 5 to 7 weeks, administered in standard fractions (1.8–2.0 Gy/fx) with or without a tumor bed boost.[14] However, studies demonstrated poor rates of compliance with adjuvant RT, with one factor being the duration of treatment.[15] Hypofractionation, or giving larger than standard fractions per treatment emerged as an alternative RT, allowing for the completion of adjuvant RT in a shorter time of 3 to 4 weeks. The purpose of these studies was to compare standard WBI with hypofractionated WBI (HWBI).

*Ontario Oncology Group*[16]

The Ontario Oncology Group trial was a randomized study of 1234 women with T1-2N0 (by ALND) breast cancer who underwent BCS with negative margins from 1993 to 1996. After surgery, the women were randomized to standard WBI (50 Gy/25 fx) for 5 weeks or to HWBI (42.56 Gy/16 fx) for 16 days without a boost in either arm of the study. At 10 years, no difference in the rates of LRR was noted (6.7% with standard WBI vs 6.2% with HWBI) and no difference in survival. With respect to toxicity and cosmetic outcomes, HWBI was not associated with increased rates of skin toxicity or inferior cosmetic outcomes.

*START A/B*[17–19]

Standardization of Breast Radiotherapy (START) A and B were two randomized trials run simultaneously between 1999 and 2002 evaluating WBI compared with HWBI. The primary end points were LRR and radiation effects on breast tissue. The START A study was a three-arm randomized trial that included 2236 women with T1-3aN0-1 breast cancer after surgery (BCS 85%) randomized to standard WBI (50 Gy/25 fx) or HWBI (41.6 Gy/13 fx or 39 Gy/13 fx, each completed during 5 weeks). Boost was at the discretion of the treating physician (16%). At 10 years follow up, no difference in rates of LRR were noted between the HWBI arm (WBI 7.4% vs HWBI 41.6 Gy per arm 6.3% vs HWBI 39 Gy per arm 8.8%), whereas the 39-Gy arm was associated with reductions in breast induration, telangiectasias, and breast edema.

The START B trial randomized 2215 patients with T1-3aN0-1 breast cancer after surgery (BCS 92%) to standard WBI (50 Gy/25 fx during 5 weeks) or HWBI (40 Gy/15 fx during 3 weeks). Boost was at the discretion of the treating physician (43%). At 10 years, no difference in LRR was noted (standard WBI 5.5% vs HWBI 4.3%). With respect to toxicities, HWBI was associated with less breast shrinkage, telangiectasias, and breast edema than standard WBI.

*Commentary and Implications for Practice*

These randomized studies have defined the role of HWBI for patients undergoing BCS. As such, current practice guidelines support HWBI for patients with node-negative breast cancer after BCS. With limited exceptions, HWBI reduced the duration of treatment without having an impact on clinical outcomes or toxicity profiles.[20] Moving forward, these trials have laid the framework to extend HWBI to shorter courses as in the UK-FAST trial.[21]

Additionally, hypofractionation is being evaluated in cases involving regional nodal irradiation (RNI) and PMRT. The RT CHARM trial is evaluating the role of hypofractioatned PMRT for patients undergoing reconstruction.[22] For patients undergoing mastectomy without reconstruction, a previously published randomized trial demonstrated no difference in clinical outcomes at 5 years for hypofractionated PMRT, with similar toxicity profiles.[23]

## EXTERNAL BEAM RADIATION THERAPY: ADJUVANT RADIATION WITH POSITIVE SENTINEL LYMPH NODE

*ACOSOG-Z011*[2426]

The ACOSOG-Z0011 trial randomized 891 women between 1999 and 2004 with clinical T1-2 N0 breast cancer who were undergoing BCS and sentinel lymph node (SLN) biopsy. The patients found to have one or two positive SLNs at surgery were randomized to receive either ALND or no further surgery. The patients with more than three positive LNs, matted nodes, or gross extracapsular extension were excluded from the trial.

All the patients received WBI specifically excluding third-field nodal irradiation. A median of two SLNs per patient were removed, with a median number of one positive LN. The patients randomized to ALND had a median of 17 LNs removed, with 27.3% of the patients having additional positive LNs. At the 10-year follow-up evaluation, LRR was 6.2% for ALND versus 5.3% for the SLN-only group ($p = 0.36$). Axillary regional recurrences did not differ statically between the groups (ALND 0.5% vs SLN biopsy only 1.5%). The results supported the conclusion that despite residual axillary nodal disease after SLN biopsy, ALND did not improve LRR or survival ($p = 0.13$) and was not necessary for regional disease control.

*AMAROS Trial*[27]

The EORTC 10,981–22,023 AMAROS trial evaluated 4806 patients from 2001 to 2010 with T1-2 N0 disease undergoing either lumpectomy or mastectomy and SLN biopsy. A total of 1425 patients were found to have a positive SLN and randomized to receive either radiotherapy or ALND. A median of two SLNs were removed, with a median of one positive LN. The patients with ALND had a median of 15 LNs removed, with 33% having additional positive LNs. The findings showed 82% of the patients with BCS, with 18% undergoing mastectomy. Axillary radiotherapy included all three levels of the axilla and the medial portion of the supraclavicular fossa (2 Gy/25 fx).

At the 5-year follow-up evaluation, regional axillary recurrence was not significant among the groups (0.43% in the ALND arm vs 1.19% in the radiotherapy arm and 0.72% in the negative-SLN cohort). The type of axillary management (ALND vs radiotherapy for a positive LN) did not affect LRR or survival but did add the morbidity of increased lymphedema (13% vs 11%; $p = 0.0009$).

*Commentary*

These two randomized studies demonstrated the safe de-escalation of surgical management of the axilla in T1-2N1 disease. Both studies showed that in more than 30% of patients with at least one positive SLN, additional LNs will contain disease. Despite this potential residual nodal burden, ALND is not required to improve regional control. Regional nodal irradiation may add benefit, although a radiation field sub-analysis in Z0011 suggests that additional research is needed to determine the extent of nodal radiation necessary for this subset of patients. Importantly, these data can be extrapolated to the management of the axilla in mastectomy patients, but at this writing, no large randomized trial has specifically addressed the benefit of ALND versus radiation for these surgical patients.[9]

## EXTERNAL BEAM RADIATION THERAPY: ADJUVANT RADIATION WITH AXILLARY DISSECTION

*Background*

After BCS or mastectomy, the role of RNI for patients undergoing ALND with nodal involvement has been an area of continued research. For patients with four or more LNs involved or extracapsular extension, adjuvant radiation including RNI is a standard approach. For patients with one to three nodes involved after ALND, controversy exists. However, older data after mastectomy have demonstrated a benefit with adjuvant RT.[8] An additional area of controversy has been the role of internal mammary (IMN) RT. Although trials evaluating PMRT and RNI have included IMN RT, studies have failed to demonstrate a

consistent benefit, with concerns regarding cardiac and pulmonary toxicity.[28]

*NCIC MA20*[11]

The National Cancer Institute of Canada MA.20 trial was a randomized trial from 2000 to 2007 that evaluated the survival benefit of RNI for positive LNs or high-risk node-negative tumors. This trial investigated 1832 women with invasive breast cancer who underwent BCS (SLN or ALND), had positive axillary nodes or were node-negative with high-risk features (> 5 cm or 2 cm with < 10 nodes removed and either grade 3, estrogen-negative or lymphovascular space invasion [LVSI]), < AQ6 > and received adjuvant systemic therapy. The patients were randomized to WBI (50 Gy/25 fx) with or without RNI (internal mammary, supraclavicular, axillary). In both study arms, approximately 85% of the patients had one to three nodes involved, and 90% received chemotherapy. At 10 years, no difference in survival was noted, although in a pre-planned analysis, estrogen receptor (ER)-negative patients had better survival (81.3% vs 73.9%; $p = 0.05$) with RNI. The RNI was associated with improvement of 3% in LRR and 3.5% in distant recurrences. Addition of RNI was not associated with increased cardiac toxicity but with was associated with a 4% increase in lymphedema.

*EORTC 22922*[29]

The EORTC 22,922 was a randomized trial of 4004 women who had stages 1 to 3 invasive breast cancer with axillary node involvement that evaluated RNI and survival from 1996 to 2004. After surgery (75% breast conservation), the women were randomized to WBI/chest wall irradiation with or without regional nodal irradiation (50 Gy/25 fx, internal mammary and medial supraclavicular). In both study arms, approximately 43% of the patients had one to three nodes involved, and 55% received chemotherapy. At 10 years, no difference in overall survival was noted (RNI 82.3% vs 80.7%; $p = 0.06$), but a statically significant improvement in breast cancer mortality (12.5% vs 14.4%; $p = 0.02$) with RNI was observed as well as disease-free survival and the first recurrence of breast cancer. The addition of RNI was not associated with increased cardiac toxicity or pulmonary fibrosis.

*Danish Breast Cancer Cooperative Group–Internal Mammary Node Trial*[30]

The Danish Breast Cancer Cooperative Group–Internal Mammary Node trial was a population-based cohort study of 3089 women younger than 70 years with unilateral, node-positive breast cancer treated from 2003 to 2007. After surgery with ALND, the patients with right-sided disease received IMN RT, whereas those with left-sided disease did not because of concern with radiation-associated heart disease. The primary end point of the trial was overall survival. At 8 years, receipt of IMN RT was associated with improved survival (75.9% vs 72.2%; $p = 0.005$) and breast cancer mortality. No difference in deaths due to ischemic heart disease was noted.

*Commentary and Implications for Practice*

The results of the MA20 and EORTC studies confirm a benefit with adjuvant RT, particularly RNI, for patients with low-volume axillary disease after ALND despite the use of relatively modern systemic therapy. Importantly, it is appropriate to extrapolate findings to patients undergoing mastectomy, and as such, these studies validate the need to consider adjuvant RT for patients with one to three nodes involved after ALND, whether after BCS or mastectomy.[9] With respect to IMN RT, the results suggest that IMN RT should be considered if cardiac and pulmonary dose constraints can be met such that the clinical benefit of IMN treatments is not outweighed by potential toxicity risks.

## PARTIAL-BREAST IRRADIATION: BRACHYTHERAPY

*GEC-ESTRO*[31]

The GEC-ESTRO randomized trial included 1184 patients between 2004 and 2009 with early-stage invasive ductal cancer or ductal carcinoma in situ (DCIS) randomized to WBI or alternate partial-breast irradiation (APBI) delivered with interstitial brachytherapy (32 Gy/8 fractions twice daily; 30.1 Gy/7 fx twice daily; 50 Gy delivered with a pulsed dose rate during 60 to 85 h). At 5 years, no difference in the rates of LRR (APBI 1.4% vs WBI 0.9%; $p = 0.42$) were noted, and reduced skin toxicity was noted, with interstitial PBI, including late grades 2 to 3 skin toxicity and subcutaneous side effects.[32]

*MammoSite Registry Trial*[33,34]

Although interstitial brachytherapy was shown to be an effective form of APBI, the technical complexity associated with the technique limited its widespread dissemination. The single-entry MammoSite radiation device represented an alternative APBI brachytherapy technique, offering clinicians the ability to perform APBI with a single-entry catheter. The MammoSite registry was a 1449-patient prospective registry study evaluating outcomes with the APBI device from 2002 to 2004 for women

with early-stage breast cancer or DCIS (23%). At 5 years, the rate of IBTR was 3.8% (3.7% for invasive cancer and 4.1% for DCIS). Higher IBTR was found with larger tumors ($p = 0.03$) and estrogen-negative tumors ($p = 0.0009$). Complication rates were low and included infections (9.6%), symptomatic seroma (13.4%), and fat necrosis (2.5%).[32]

*Commentary and Implications for Practice*

Together, randomized trials have demonstrated equivalent rates of LR between APBI delivered via interstitial brachytherapy and WBI. The rates of toxicity were comparable between APBI and WBI, with data suggesting a potential for reduced late-skin toxicities and improved cosmetic outcomes with interstitial APBI. Applicator-based APBI has been shown in non-randomized prospective studies to offer low rates of recurrence and toxicity during a 5-year follow-up period.

## PARTIAL-BEAM IRRADIATION: EXTERNAL BEAM

*NSABP B39*[35]

The NSABP B-39 trial was a randomized trial of 4216 women with invasive cancer smaller than 3 cm or DCIS (24%) after BCS from 2005 to 2013. Patients with one to three LNs were included in the trial. The patients were stratified by stage, tumor biology, and menopausal status, then randomized to APBI (multi-catheter APBI [6%] vs single-entry APBI [21%] vs 3D-CRT [73%]) or WBI (50 Gy/25 fx). The primary outcome was IBTR and survival. At 10 years, equivalence between the two groups was not reached, showing that WBI had a slightly lower IBTR (APBI 4.6% vs WBI 3.9%), although the rate of IBTR was lower in the 3D-CRT cohort. The overall survival among the groups was similar. The results indicated that women older than 50 years with hormone-positive DCIS or stage 1 cancer undergoing lumpectomy would benefit equally well from APBI or WBI.

*RAPID*[36]

The RAPID trial was a randomized trial of 2135 women 40 years of age or older with DCIS or node-negative breast cancer after BCS from 2006 to 2011. The patients were randomized to 1 week of external-beam APBI with 3D-CRT (Gy/10 fx 38.5 twice daily) or WBI (42.5 Gy/16 fx, 50 Gy/25 fx). The primary outcome was IBTR. At 8 years, no difference in IBTR was noted between the two groups (APBI 3.0% vs WBI 2.8%), with similar toxicities. Adverse cosmetic outcomes were noted in the 3D-CRT APBI group.

*IMPORT LOW*[37]

The Intensity Modulated Partial Organ Radiotherapy Trial (IMPORT) LOW study included 1347 women 50 years of age or older with tumors smaller than 3 cm and zero to three positive LNs after breast-conserving surgery from 2007 to 2010. The patients were randomized to WBI (40 Gy/15 fx), intensity modulated (IMRT) APBI (40 Gy/15 fractions), or WBI with a simultaneous boost (40 Gy to tumor bed, 36 Gy WBI). The primary end point was LRR. At 5 years, no difference in LRR was noted (1·1% WBI 40 Gy, 0·2% WBI 36 Gy vs 0·5% IMRT APBI), with comparable toxicity and cosmetic outcomes. The patient-reported outcomes demonstrated fewer adverse events with IMRT APBI.[38]

*University of Florence*[39]

The University of Florence randomized trial included 520 women 40 years of age or older with tumor smaller than 2.5 cm who underwent BCS. The patients were randomized to WBI (50 Gy/25 fx) or APBI delivered with IMRT (30 Gy/5 fx, delivered every other day). The primary end point was IBTR. At 5 years, APBI was found to have no difference in IBTR (1.5% for both groups), with reduced rates of acute late toxicities and improved cosmetic outcomes seen with APBI, confirmed at 10 years.

*Commentary and Implications for Practice*

External-beam PBI offers a patient the ability to receive APBI without additional invasive procedures. Randomized trials have demonstrated no difference in clinical outcomes after 3D-CRT partial breast irradiation, with the potential for increased toxicities and worse long-term cosmetic outcomes. More recently, use of IMRT has shown clinical outcomes similar to those after WBI, with reduced toxicities, offering patients and clinicians an external-beam APBI technique with a comparable outcome and reduced toxicities.

## PARTIAL-BREAST IRRADIATION: INTRAOPERATIVE RADIATION THERAPY

Intraoperative radiation (IORT) is an RT technique that delivers radiation to the lumpectomy tumor bed and allows all local regional cancer treatment to be performed in one setting, which can improve convenience and compliance. Two prospective randomized trials have compared IORT

with conventional WBI. Each trial used a single fraction of IORT delivered at the time of lumpectomy or shortly after as a second procedure (post-pathology cohort). However, the radiation devices, IORT techniques, and patient inclusion criteria in each trial were unique.

### *ELIOT*[40]

The ELIOT trial prospectively randomized 1305 lumpectomy patients between 2000 and 2007 to receive either IORT or standard WBI. The IORT treatment was performed using electrons with 6 to 9 MeV energies to a dose of 21 Gy. No additional WBI was given. The study included women older than 48 years with tumors smaller than 2.5 cm undergoing BCS. Women with high-risk tumor biology and up to three positive axillary nodes were eligible for the study. The 5-year risk of LRR was 4.4% with IORT versus 0.4% with WBI ($p = 0.0001$), and survival was similar between the two groups. When a suitable (per ASTRO guidelines) group was analyzed, (tumor $< 2$ cm, node-negative, ER-positive), the in-breast LR or IORT was 1.5% at 5 years.[41]

### *TARGIT-A*[42,43]

The TARGIT-A trial prospectively randomized 3451 lumpectomy patients to receive IORT or standard WBI between 2000 and 2012. The trial used a spherical applicator to deliver 50-kV X-rays (20 Gy to applicator surface, 6 Gy at 1-cm depth). The study included women older than 45 years with invasive ductal cancer smaller than 3.5 cm undergoing BCS. The patients could receive IORT either at the time of lumpectomy, or as a second procedure. In the IORT group, 15.2% of the patients subsequently required WBI due to the final pathology showing positive lymph nodes, positive surgical margins, or high-risk tumor biology. The 5-year in-breast LR for all the women was 3.3% for IORT versus 1.3% for WBI ($p = 0.04$), which was within the non-inferiority threshold. For the patients who received IORT at the time of surgery, the risk of LR> was 2.1%, which did not differ significantly from that for the patients receiving WBI ($p = 0{\cdot}31$). The delayed cohort did have a significant increase in LR (5.4% vs 1.7%).

### *Commentary*

Unlike other APBI techniques, IORT has demonstrated slightly higher rates of recurrence despite limited long-term follow-up evaluation. At this writing, it is recommended that IORT be performed as part of a prospective study/registry.[41,44,45] For the treatment of low-risk, early-stage breast cancer, IORT may be an appropriate treatment option, but studies of long-term outcomes in terms of LRR and survival are necessary.

## FUTURE DIRECTIONS

Although adjuvant RT represents a key component of breast cancer treatment, its evolution continues. With regard to WBI after BCS, studies are underway evaluating shorter courses of RT including reduction of WBI duration to five fractions.[21] Similarly, ongoing studies are evaluating shorter courses of APBI as well as newer techniques to reduce toxicity profiles. Regarding the RT technique, the external-beam studies discussed earlier all used photon therapy. At this writing, the role of proton therapy in breast RT remains unclear, although studies including the RADCOMP trial are underway to compare outcomes between photon and proton radiotherapy, with effectiveness in reducing major cardiovascular events as the primary outcome.[46]

Conversely, a growing focus is on moving from treatment recommendations based solely on clinical and pathologic features to more individualized treatment recommendations. For patients with limited nodal involvement, studies to understand better which patients benefit from regional nodal irradiation are needed.[47] Finally, whereas trials have previously evaluated omitting RT in lieu of endocrine therapy for low-risk patients, new studies are evaluating omission of endocrine therapy rather than RT, partly due to shorter durations of treatment, improved compliance, and different toxicity profiles.[48,49]

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