Personalized Approaches to Breast Radiotherapy: Strategies for Treatment Refinement

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Abstract: Radiotherapy (RT) is a crucial component of the adjuvant treatment of breast cancer that often follows breast conservation or mastectomy to further reduce the risk of local recurrence. As outcomes improve and our understanding of disease biology advances, interest is growing in de-escalating RT to minimize the treatment burden and side effects while maintaining oncologic outcomes. This review examines the evidence and summarizes the results of ongoing trials evaluating RT de-escalation strategies in breast cancer. We discuss hypofractionation and ultrahypofractionation for whole breast irradiation, showing efficacy comparable with that of conventional fractionation with improved convenience. The role of accelerated partial breast irradiation is explored, with an emphasis on its benefits and the importance of patient selection. We review data supporting omission of RT in selected patients with low-risk, early-stage disease, particularly older women with hormone receptor–positive disease. Ongoing research into biomarker-guided RT de-escalation is addressed, including trials using genomic assays and immunohistochemistry. Emerging data on RT de-escalation in HER2-positive and triple-negative breast cancers are discussed. Finally, we explore de-escalation strategies for locally advanced disease, including hypofractionation for post-mastectomy RT and potential omission of regional nodal irradiation after neoadjuvant chemotherapy for those with an excellent response. These strategies may allow more personalized approaches to RT, potentially improving quality of life without compromising oncologic outcomes.

Keywords
Breast cancer, hypofractionation, partial breast irradiation, radiotherapy, whole breast irradiation

Introduction

Adjuvant radiotherapy (RT) is a standard component of breast-conserving therapy for early-stage invasive breast cancer, significantly reducing the risk of local recurrence (LR).[1,2] The meta-analysis of the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) demonstrated that adjuvant RT reduced the 10-year recurrence risk from 35% to 19% and reduced 15-year breast cancer mortality from

25% to 21%.[3] In patients with node-negative breast cancer following lumpectomy, the recurrence rate was reduced from 31% to 16% with the addition of RT, and breast cancer mortality was reduced from 21% to 17%.[3] Although RT confers oncologic benefits, it also carries risks of acute and long-term side effects. These include dermatitis, fatigue, cosmetic changes, fibrosis, lymphedema, rib fracture, brachial plexopathy, cardiac and pulmonary toxicity, and a small risk of secondary malignancy.

Over time, advances in imaging, surgical techniques, pathologic assessments, molecular and biomarker stratification of disease subtypes, and systemic therapies have led to significant improvements in oncologic outcomes.[4] In parallel, RT techniques have improved in recent decades. Increasing hypofractionation has resulted in shorter, more cost-effective, and less burdensome treatment regimens, while at the same time broadened indications for partial breast irradiation (PBI) have made possible shorter courses of RT with decreased side effect profiles.[5,6] Substantial efforts have been made to identify patients with sufficiently low-risk disease—on the basis of age, pathologic features, or multigene assays—to support omission of RT altogether. This review examines the existing literature and ongoing clinical trials evaluating various approaches to de-escalation of RT for patients with breast cancer, including shorter courses of treatment to decrease the treatment burden, reduced treatment volumes, and omission of RT for both early-stage and locally advanced disease.

Early-Stage Disease

Hypofractionation and Ultrahypofractionation

Historically, adjuvant whole breast irradiation (WBI) has been delivered to a dose of 45 to 50 Gy over 25 fractions, with conventional dosing of 1.8 to 2 Gy daily.[7] Such a protracted course of RT is burdensome for patients and health care systems, in addition to being costly, all of which have the potential to limit access to RT.[8-13] Hypofractionation, the use of shorter courses of RT delivering more than 2 Gy/day, has been increasingly utilized for WBI in recent decades. Hypofractionated WBI is typically delivered to a dose of 40 to 42.5 Gy at 2.6 to 2.7 Gy per fraction in 15 to 16 fractions. Such hypofractionated courses may be uniquely advantageous for the treatment of breast cancer from a radiobiological perspective.[14,15] Breast cancer is considered to have an α:β ratio of approximately 4 Gy.[16] This α:β ratio, similar to that of late-responding normal tissues, eliminates the potential benefit of more fractionated RT schedules from the perspective of allowing repair and reducing the risk of late toxicity.[17] A relatively low α:β ratio of breast cancer cells also translates into a higher equivalent dose in fractions of 2 Gy (EQD2), potentially enhancing tumor control.[18]

Conventional and hypofractionated WBI have been compared in several phase 3 randomized clinical trials (RCTs), which demonstrated comparable or improved locoregional control, overall survival (OS), and cosmesis and comparable or reduced adverse effects.[19-21] The suitability of hypofractionated WBI delivered over 13 to 16 fractions was firmly established in the 2000s in 4 key studies. Overall, these studies demonstrated no detriment in oncologic outcomes with hypofractionation and comparable, if not improved, cosmesis and toxicity.[22-24] A combined analysis of 2 of these classic studies, the START A and START B trials, showed that patient-reported cosmesis was improved and breast symptoms reduced with hypofractionation.[25] Modern data continue to support the use of hypofractionation for WBI. A randomized study from the MD Anderson Cancer Center found that physician-reported acute dermatitis, pruritus, breast pain, hyperpigmentation, and fatigue were decreased with hypofractionation.[26] On the basis of this evidence, hypofractionated WBI is considered the standard of care per the 2018 American Society for Radiation Oncology (ASTRO) executive summary.[7]

More recently, efforts have focused on further hypofractionation of WBI with ultrahypofractionation, the delivery of at least 5 Gy per fraction. In the FAST trial from the United Kingdom, more than 900 women older than 50 years with low-risk, early-stage (pT1-2N0) breast cancer were randomized to conventional RT (50 Gy in 25 fractions delivered over 5 weeks) or ultrahypofractionated RT (30 or 28.5 Gy in 5 fractions delivered once per week). The authors reported no significant difference in effects on normal breast tissue (shrinkage, induration, telangiectasia, edema) when the 28.5-Gy regimen was compared with conventional fractionation. The 30-Gy regimen was associated with increased breast toxicities. Oncologic outcomes were excellent across the treatment arms.[5] Similarly, the FAST-Forward trial compared hypofractionated RT at 40 Gy in 15 fractions vs 2 ultrahypofractionated regimens. The researchers demonstrated that the administration of 26 Gy in 5 fractions was similar to the 3-week course of RT with regard to oncologic outcomes and breast toxicities.[6] This study has so far published 5-year results, and we eagerly await more mature data to expand the use of ultrahypofractionated RT.

Accelerated Partial Breast Irradiation

Most ipsilateral breast tumor recurrences (IBTRs) occur within or in the vicinity of the initial lumpectomy cavity.[27] This observation led to the concept of PBI, in which RT is delivered only to the lumpectomy cavity with a margin of 1 to 2 cm. Accelerated PBI (APBI) can be delivered in more than 2 Gy per fraction in a limited number of fractions. Multiple APBI delivery techniques have been

validated, including single- or multi-channel catheter brachytherapy; intraoperative RT (IORT); and external beam RT (EBRT), either 3-dimensional conformal RT (3DCRT) or intensity-modulated RT (IMRT).

Comparisons of WBI and PBI in numerous RCTs have generally demonstrated similar rates of disease control and side effect profiles, with some variability attributable to dose and technique.[28-38] The phase 3 Florence trial established what is now one of the most frequently used APBI regimens. More than 500 patients were randomized to conventional WBI (50 Gy in 25 fractions) or APBI planned via IMRT (30 Gy in 5 fractions delivered every other day). At a median follow-up of more than 10 years, the rates of IBRT did not differ significantly between the 2 groups, at 2.5% for WBI vs 3.7% for APBI. OS and breast cancer–specific survival also did not differ between the 2 arms. APBI was associated with significantly decreased acute and late toxicities, as well as with improved patient- and clinician-reported cosmesis.[34] However, to ensure low rates of IBTR with the use of APBI, appropriate patient selection is critical. For example, NSABP B-39/RTOG 0413 was a phase 3 RCT designed to compare local control, OS, and cosmesis after WBI or APBI in women with early-stage breast cancer following lumpectomy. Notably, the authors were unable to meet their endpoint of noninferiority of IBTR with APBI vs WBI. This trial enrolled relatively high-risk patients, including those younger than 40 years, with invasive lobular histology, multifocal disease, tumors larger than 2 cm, N1 disease, and hormone receptor–negative disease. Overall, the absolute difference in IBTR was less than 1%.[35] In addition to careful patient selection, the use of appropriate APBI technique is important. IORT, in which a single fraction of RT is delivered directly to the lumpectomy cavity after excision of the tumor, has been evaluated in 2 RCTs. ELIOT demonstrated a significantly increased LR rate with the use of IORT, whereas TARGIT-A demonstrated comparable LR rates with WBI vs IORT but required the addition of WBI for patients found to be at high risk on final pathology.[39,40] Although IORT is extremely convenient from the patient's perspective, on the basis of these results, the most recent ASTRO PBI guidelines do not recommend IORT alone as an approach to adjuvant RT.[41]

Although the literature broadly demonstrates improved cosmesis and reduced RT side effects with APBI, as demonstrated in the Florence trial, the choice of regimen is important. The RAPID trial, which compared WBI vs APBI delivered via 3DCRT at 38.5 Gy in 10 fractions twice a day, did show worse adverse events with APBI, particularly poor cosmesis. This was potentially due to the twice-a-day treatment schedule and the limited (6-8 hours) interval between fractions.[19] NSABP B-39/RTOG 0413 used a similar EBRT regimen and also noted worse physician-reported cosmesis with APBI.[35] Many excellent reviews of the critical trials comparing WBI and PBI have been published. In particular, Ambrosio and colleagues provide a summary table of study inclusion criteria, treatment techniques, and oncologic outcomes.[42]

In November of 2023, ASTRO published a clinical practice guideline that updated the 2017 guidelines and significantly broadened the appropriateness criteria for PBI. For patients with early-stage, favorable-risk breast cancer, including patients 40 years or older with a primary tumor no larger than 2 cm, grade 1 or 2, and estrogen receptor–positive (ER+), the guidelines strongly recommend PBI. In comparison, the 2017 guidelines classified patients 50 years and older as suitable for PBI and recommended caution in those 40 to 49 years. According to the updated guidelines, PBI is conditionally recommended for patients with pathologic risk factors such as grade 3, ER negativity, and primary tumor larger than 2 cm but no larger than 3 cm.[41,43]

Omission of Radiotherapy

Early-Stage ER+ Disease. Several randomized trials support the omission of RT in appropriately selected low-risk patients. The CALGB 9343 trial enrolled women 70 years or older with stage I ER+ breast cancer managed with breast-conserving surgery (BCS). These women were randomized to either tamoxifen alone or tamoxifen plus adjuvant RT. The 10-year locoregional recurrence (LRR) rate was 2% in the RT arm vs 10% with omission of RT.[44,45] Other oncologic outcomes, including distant metastases, breast cancer mortality, and OS, did not differ between the groups. The PRIME II study included 1326 women at least 65 years old with pT1-2N0 tumors up to 3 cm in size and ER+ or progesterone receptor–positive (PR+) disease treated with BCS. These women were similarly randomized to either tamoxifen or tamoxifen plus adjuvant RT; the IBTR rate was 0.9% with RT and 9.8% without RT. Again, no detriment in OS was seen with omission of RT.[46,47] Such trials consistently demonstrate improvements in local control with RT, and overall the rates of recurrence are acceptably low, without OS detriment from the omission of RT. Current National Comprehensive Cancer Network guidelines allow omission of adjuvant RT in women at least 70 years old with T1N0, hormone receptor–positive breast cancer who intend to complete 5 years of adjuvant endocrine therapy. It is critical to note the importance of adherence to endocrine therapy, as unacceptably high rates of recurrence are otherwise observed.[48,49]

Traditionally, trials of omission of RT have relied on patient age, stage, and basic pathologic features. More recently, genomic and immunohistochemistry-based biomarkers have been increasingly used to identify patients

Table. Ongoing Trials of Omission of Radiotherapy

	Design	Age, y	N	Results
IHC				
LUMINA	Single arm; Ki-67 ≤13.25%	≥55	501	5-y LR rate, 2.3%
PRIMETIME	Randomized; IHC4+C with Ki-67	≥60	2400	*Accrual completed*
Oncotype DX				
IDEA	Single arm; RS ≤18	50-69	200	400 person-years, 0 events
DEBRA/NRG BR007	Randomized; RS ≤18	50-70	1670	*In accrual*
Prosigna PAM50				
PRECISION	Single arm; ROR ≤40	50-75	350	2-y incidence of LRR, 0.3%
EXPERT	Randomized; ROR ≤60	≥50	1167	*In accrual*
HER2+: HERO/ NRG BR008	Randomized; T1N0 HER2+	≥40	1300	*In accrual*

HER2+, human epidermal growth factor receptor 2–positive; IHC, immunohistochemistry; IHC4+C, IHC4+clinical; LR, local recurrence; LRR, locoregional recurrence; PAM50, Prosigna Prediction Analysis of Microarray 50; ROR, PAM50 risk of recurrence; RS, Oncotype DX recurrence score; y, year.

at low risk of recurrence. Oncotype DX is a 21-gene expression assay used for hormone receptor–positive, human epidermal growth factor receptor 2–negative (HER2–) breast cancer. This test provides a recurrence score that estimates the risk of distant recurrence of disease and the likelihood of benefit from chemotherapy. The Prosigna Prediction Analysis of Microarray 50 (PAM50) test is a 50-gene expression test that provides a risk-of-recurrence score and categorizes breast cancers into luminal A, luminal B, HER2-enriched, basal-like, and normal-like subtypes.[50] Immunohistochemical staining of Ki-67 is used to estimate the proliferation rate and aggressiveness of tumor growth.[51] In the modern era, such tests are increasingly being used to identify patients at low risk for recurrence for whom omission of RT may be appropriate.

The multicenter, single-arm, prospective IDEA trial is evaluating women aged 50 to 69 years with invasive breast cancer that is unifocal pT1N0M0, ER+/PR+/HER2– and with an Oncotype DX recurrence score of 18 or less who are being managed with BCS and endocrine therapy. The primary endpoint is the 5-year LRR rate; this trial has closed to accrual. Among 186 patients with clinical follow-up of at least 56 months, the authors have reported excellent oncologic outcomes, with OS and breast cancer–specific survival rates of 100%. Crude rates of overall recurrence were 5% for patients aged 50 to 59 years and 3.6% for patients aged 60 to 69 years.[52]

Ongoing Trials of Omission of Radiotherapy. Many of the ongoing trials exploring omission of RT parallel IDEA, using immunohistochemistry-based biomarkers to identify patients at low risk of recurrence who are suitable for omission of RT (Table).

A 5-year interim analysis of the multicenter, single-arm, prospective LUMINA trial (NCT01791829) was presented at the 2022 American Society of Clinical Oncology Annual Meeting. This trial enrolled patients aged 55 years or older with pT1N0M0, grade 1 to 2, luminal A disease (ER+ ≥1%, PR+ >20%, HER2–, and Ki-67 ≤13.25%) managed with BCS and endocrine therapy without RT. Among 501 enrolled patients, the 5-year LR rate was only 2.3%. Rates of contralateral breast cancer, relapse-free survival, disease-free survival, and OS were also favorable.[36]

The PRECISION trial (NCT02653755) is a single-arm, prospective phase 2 study evaluating patients aged 50 to 75 years with pT1N0M0, grade 1 or 2, ER+/PR+/HER2– disease and a low PAM50 recurrence score, managed with lumpectomy and endocrine therapy alone.[53] A 2-year cumulative incidence of LRR of 0.3% has been reported.[54] This trial has accrued more than 600 patients and is now closed.

PRIMETIME (ISRCTN41579286) is a multicenter, prospective case-cohort trial from the United Kingdom that is evaluating omission of adjuvant RT after lumpectomy in women at least 60 years of age (or <60 years with significant comorbidities) who have pT1N0M0, grade 1 or 2, ER+/PR+/HER2– disease and are classified as at very low risk of recurrence on the IHC4+C score. This algorithm combines immunohistochemistry of ER, PR, HER2, and Ki-67 with a clinical treatment score (age, tumor size, nodal status, tumor grade, and type of

endocrine therapy treatment). This study has a primary endpoint of 5-year IBTR.[55-58]

DEBRA-NRG BR007 is a multicenter phase 3 RCT through NRG Oncology that is evaluating BCS and endocrine therapy with or without adjuvant RT (NCT04852887). This trial is currently enrolling women aged 50 to 70 years with unicentric pT1N0M0 breast cancer that is ER+/PR+/HER2– and with an Oncotype DX recurrence score no higher than 18.[59] In addition to oncologic outcomes, DEBRA will report on quality of life, breast pain, cosmesis, breast function status, fatigue, and anxiety regarding recurrence of disease.

EXPERT is a randomized phase 3 trial of omission of RT following BCS through the Breast Cancer Trials group in Australia and New Zealand (NCT02889874). This trial is enrolling women at least 50 years old with pT1N0M0, grade 1 or 2, ER+/PR+/HER2– breast cancer and a low PAM50 score, with a primary endpoint of 10-year LR.

Many of the historical trials evaluating de-escalation of treatment for early-stage, low-risk breast cancer have evaluated receipt of endocrine therapy with omission of RT. However, endocrine therapy is associated with side effects, such as fatigue, hot flashes, vulvovaginal symptoms, arthralgias, and decreases in bone density. Adherence to endocrine therapy is far from perfect, and poor adherence is associated with compromised disease outcomes.[60] Such low-risk patients are anticipated to have excellent long-term oncologic outcomes with either endocrine therapy or RT, and the optimal treatment approach remains uncertain. The ongoing phase 3 EUROPA trial from the University of Florence (NCT04134598) is a RCT of women 70 years or older with low-risk, hormone receptor–positive invasive breast cancer. Participants are randomized to endocrine therapy alone or RT alone, with primary endpoints of health-related quality of life (QoL) and noninferior LRR. The 24-month results were recently presented at the 2024 San Antonio Breast Cancer Symposium. The authors reported that health-related QoL was superior and adverse events were reduced for patients receiving RT rather than endocrine therapy. Both treatment arms had excellent oncologic outcomes, with no noted IBTR, LRR, or breast cancer mortality.[61]

Omission of RT for HER2+ Disease. A minority of patients with invasive breast cancer, approximately 15% to 20%, have HER2+ disease, which historically portended a poor prognosis.[62-64] However, with the advent of modern HER2-targeted therapies, these patients now have excellent oncologic outcomes, on a par with those observed among patients with luminal A disease. As such, 2 recent studies have evaluated de-escalation of systemic therapy for patients with early-stage HER2+ breast cancer. The single-arm, multicenter phase 2 APT trial enrolled patients with T1-2N0-1mic HER2+ breast cancer managed with BCS and adjuvant RT. All patients received adjuvant paclitaxel and trastuzumab for 12 weeks, followed by continuation of trastuzumab for 1 year. The authors reported a 7-year LRR-free survival rate of 98.6%.[65-67] ATEMPT was a phase 2 trial enrolling similarly early-stage patients managed with BCS and adjuvant RT, but the patients were randomized to adjuvant trastuzumab emtansine, also known as T-DM1 (Kadcyla, Genentech), or to paclitaxel plus trastuzumab (TH). At 3 years, LR had developed in only 2 of 383 patients in the T-DM1 arm and in 1 of 114 patients in the TH arm.[68,69] The extremely low rates of LRR in this population suggest the possibility of de-escalation of treatment for these patients.

To date, no level 1 evidence is available regarding omission of RT in patients with HER2+ disease treated with BCS. A retrospective National Cancer Database (NCDB) analysis evaluated patients with T1N0 HER2+ disease managed with lumpectomy, adjuvant chemotherapy, and HER2-targeted therapy. Of the nearly 7000 patients evaluated, 509 did not receive RT. OS rates at 2 years were significantly worse in the patients who did not receive RT than in those who did receive RT, at 89% vs 99%, respectively. The retrospective database nature of this study makes it difficult to interpret the results and impossible to account for confounders. Because adjuvant RT would be the standard of care in this setting, omission of RT may be suggestive of patient comorbidities, limited access to care, or poor adherence to treatment.[70]

The HERO trial, NRG BR008, is a phase 3 RCT of patients at least 40 years of age with early-stage HER2+ invasive breast cancer managed with BCS and randomized to standard of care with or without RT (NCT05705401). Patients receiving adjuvant chemotherapy and HER2-targeted therapy must have pT1N0 disease, or cT2N0 disease with a primary tumor smaller than 3 cm and a pathologic complete response if they are receiving neoadjuvant chemotherapy (NAC) and HER2-targeting therapy. This trial is currently enrolling patients and evaluating the recurrence-free interval at 7 years. Secondary outcomes include IBTR, LRR, disease-free survival, OS, and patient-reported outcomes regarding pain and fear of recurrence.

Omission of RT for Triple-Negative Disease. Triple-negative breast cancer (TNBC) is another molecular subtype associated with poor outcomes, both locoregional and distant, even in women with early-stage (pT1N0) disease.[71-73] Given the aggressive nature of TNBC, any de-escalation of treatment for this patient population must be approached with caution. However, there is support in the literature for low rates of locoregional and distant recurrence in a subset of patients with very small (<1 cm) node-negative TNBC.[74,75] A meta-analysis of more than

1800 patients with TNBC found a subset of patients with stage I disease and a high level of tumor-infiltrating lymphocytes who did not receive chemotherapy and had excellent outcomes. These data suggest that even among patients with TNBC, a certain subset may exist for whom de-escalation is suitable, including omission of RT.[76]

A Surveillance, Epidemiology, and End Results (SEER) database study evaluated women 70 years or older with pT1-2N0 ER– breast cancer that was diagnosed between 1993 and 2007 and treated with BCS. Because the SEER database does not report local failures, the authors used mastectomy rates as a surrogate. They noted a significantly higher rate of mastectomy at 5 years (8.3% vs 4.9%) among patients who did not receive RT. Similarly, the breast cancer mortality rate was increased among patients who did not receive RT (24% vs 11%).[77] A similar NCDB study evaluated women 70 years or older with pT1N0M0 TNBC. OS was significantly better in the patients who received adjuvant RT than in those who did not.[78] Ultimately, it is important to note that no level 1 evidence exists to support omission of RT for patients with TNBC, and any omission of RT in this population should be considered highly experimental.

Locally Advanced Disease

Rationale for Regional Nodal Irradiation in Node-Positive Disease

Regional nodal irradiation (RNI) involves RT of the axillary nodal basins (levels I-III), the supraclavicular lymph nodes, and often the internal mammary lymph nodes. In addition to the usual toxicities seen with WBI, treatment of the regional lymphatics also carries a risk of esophagitis and thyroiditis, as well as an increased risk of pneumonitis, cardiac toxicity, and lymphedema.

Optimal RT management of the regional lymph nodes for women with 1 to 3 positive lymph nodes has long been a source of controversy. Historically, several randomized studies established RNI as the standard of care in the setting of node-positive or high-risk node-negative disease.[79-81] The MA.20 trial enrolled 1832 women with high-risk, node-negative or N1 breast cancer managed with BCS and axillary sampling. Patients received WBI and were randomized to RNI or no RNI. At 10 years of follow-up, OS did not differ between the groups, but RT significantly improved the disease-free survival rate, which was 82% with RNI vs 77% without RNI.[82] The EORTC 22922/10925 study was a similar randomized, multicenter phase 3 trial evaluating the benefit of RNI. Eligible patients were node-negative with centrally/medially located tumors or were node-positive and could be managed with mastectomy or BCS. More than 4000 patients were randomized to RNI or to RT to the breast or chest wall only. With more than 15 years of median follow-up, the addition of RNI did not affect OS but improved rates of any recurrence and breast cancer mortality. A meta-analysis by the Early Breast Cancer Trialists' Collaborative Group demonstrated that among 1314 patients treated with mastectomy who had 1 to 3 positive lymph nodes, the addition of RNI following mastectomy significantly decreased the rates of any recurrence (34% vs 46%), LRR (3.8% vs 20.3%), and breast cancer mortality (42% vs 50%).[83]

Hypofractionation and Ultrahypofractionation

Hypofractionation was pursued in the setting of BCS and WBI because shortened courses of RT reduce the treatment burden for both patients and healthcare systems, improve access to care, and may be advantageous from a radiation biology perspective. Greater reluctance has been shown to shorten the courses of post-mastectomy RT (PMRT) and RNI, given the larger treatment volume, fear of increased toxicity, and concern regarding complications with breast reconstruction. Although conventional fractionation remains the standard of care for PMRT and RNI, hypofractionation is beginning to be explored. The existing literature is largely confined to retrospective work or small studies.[84-88] The first RCT of hypofractionated PMRT was conducted in China. A total of 820 patients treated with mastectomy without reconstruction were randomized to conventional (50 Gy in 25 fractions) or hypofractionated (43.5 Gy in 15 fractions) PMRT. Control of disease was excellent, with a 5-year LRR rate of approximately 8% in each arm. No significant differences between the 2 groups were found with regard to acute or late toxicities except that fewer patients in the hypofractionated arm had grade 3 or higher acute skin toxicity.[89] The multicenter FABREC trial enrolled 400 patients with breast cancer, who were managed with mastectomy and immediate placement of a tissue expander or implant. All patients received chest wall RT, with or without RNI. Patients were randomized to conventional RT (50 Gy in 25 fractions to the chest wall and RNI at 46-50 Gy) or hypofractionated RT (42.56 Gy in 16 fractions to the chest wall and RNI at 39.9 Gy in 15 fractions). In this study, adverse effects and oncologic outcomes did not differ significantly between conventional and hypofractionated RT. The RT regimen was not associated with chest wall toxicity. Hypofractionated RT resulted in fewer treatment breaks and work interruptions. Among the patients younger than 45 years, QoL at 6 months was better in those who received hypofractionated RT, and they were less bothered by the sequelae of treatment in comparison with those who received conventional fractionation.[90] Results of the Alliance A221505 RT CHARM study, a phase 3 noninferiority trial of conventional vs hypofractionated PMRT, were presented at the

2024 ASTRO Annual Meeting. In this study, patients undergoing mastectomy with planned breast reconstruction were randomized to conventional PMRT (50 Gy in 25 fractions) or a hypofractionated regimen (42.5 Gy in 16 fractions). With nearly 900 patients enrolled, the rate of reconstruction complications at 2 years was 11.7% with conventional fractionation vs 14% with hypofractionation, which was noninferior. Both acute and late adverse effects of RT did not differ significantly between the study arms. Interestingly, complication rates were lower with autologous reconstruction than with implant only. Local and regional recurrences were comparable in the 2 study arms.[91] In addition, attempts are ongoing to further shorten the courses of PMRT and RNI. The FAST-FORWARD trial includes a subset of 627 patients who received RNI, and results are eagerly awaited.[6]

De-escalation of Regional Nodal Irradiation

The Canadian Cancer Trials Group MA.39 TAILOR RT trial (NCT03488693) is exploring whether the Oncotype DX recurrence score can be used to identify node-positive patients for whom omission of RNI is appropriate. In this phase 3 RCT, women at least 35 years of age with ER+/HER2– N1 (1-3 positive axillary lymph nodes) breast cancer and an Oncotype DX recurrence score of 25 are randomized to receipt or omission of RNI (in the case of BCS) or PMRT (in the case of mastectomy). The primary endpoint is any recurrence event or breast cancer mortality.[92]

SUPREMO (NCT00966888) is an international RTC that is evaluating omission of PMRT. Women with breast cancer were managed with mastectomy and axillary surgery if they were node positive, after which those defined by the study group as intermediate risk (pT1-2N1, pT3N0, or pT2N0 if also grade 3 or with lymphovascular invasion) were randomized to PMRT or omission of RT. The trial is now closed to accrual, with more than 1600 patients enrolled. To date, results of a QoL substudy of approximately 1000 patients have been published. At 2 years, patients in the RT group had worse chest wall symptoms, whereas other QoL measures did not differ significantly between the groups. The primary endpoint of this study is 10-year OS, and these results are eagerly awaited.[93]

In recent years, NAC has been increasingly utilized, especially for locally advanced disease. NAC can shrink primary tumors, allowing BCS, and it provides key information regarding tumor response to chemotherapy because the extent of nodal disease following NAC is an important prognostic factor.[94-97] For patients with ypN+ disease, PMRT or RNI is generally recommended, given high recurrence rates. In the combined NSABP B-18 and B-27 analysis, in women with residual nodal disease following NAC who did not receive adjuvant PMRT or RNI, the 10-year LRR rate following BCS was 14.7% for women 50 years or older and 22.3% for women younger than 50 years. Following mastectomy, the rates of LRR at 10 years were 17% for tumors no larger than 5 cm and 22.4% for primary tumors larger than 5 cm.[98]

In contrast, controversy surrounds the use of RT following a nodal pathologic complete response (pCR). In the pooled analysis of the NSABP B-18 and B-27 trials of patients receiving NAC without PMRT or RNI, the 10-year rate of regional recurrence was only 0% to 2.4% for patients who had clinically node-positive disease with a nodal pCR.[98] A French retrospective review evaluated patients with stage II or III breast cancer managed with NAC and surgical resection and demonstrated no benefit from the addition of PMRT in the setting of a nodal pCR.[99] The ACOSOG Z1071 trial evaluated patients with T0-4 N1-2 M0 breast cancer managed with NAC, with adjuvant RT at the discretion of the treating radiation oncologist. At more than 5 years of median follow-up, the LRR rate was only 6%. On subset analysis, for patients with a nodal pCR, omission of RNI or PMRT did not correlate with LRR risk.[100] The Dutch RAPCHEM BOOG 2010-03 multicenter prospective registry study enrolled 838 patients with cT1-2N1 disease who were managed with NAC followed by surgical resection. Patients were stratified into 3 groups: (1) low risk, ypN0; (2) intermediate risk, ypN1; and (3) high risk, ypN2-3. For the low- and intermediate-risk groups, PMRT/RNI was omitted. Overall, the 5-year LRR rate was only 2.2%, suggesting the appropriateness of omission of PMRT/RNI in patients with a low burden of residual nodal disease.[101] In contrast, some studies have suggested compromised locoregional control when RT is omitted.[102,103]

NSABP B51/RTOG 1304 is a multicenter phase 3 RCT evaluating the benefit of PMRT/RNI following a nodal pCR. This trial is now closed to accrual. The study enrolled patients with cT1-3N1 disease who after NAC and surgical resection (BCS or mastectomy) had a nodal pCR. Patients were randomized to receipt or omission of RNI/PMRT. Early results were presented at the 2023 San Antonio Breast Cancer Symposium. Receipt of RT did not affect the OS rate, which was 94% without RNI vs 93.6% with RNI, or the invasive breast cancer recurrence-free interval, which was 91.8% without RNI vs 92.7% with RNI. A few caveats should be noted in interpreting these results. First, this study has been presented in abstract form only, and the manuscript and full results are awaited. Second, the authors presented 5-year outcomes, but long-term results are needed to ensure the durability of these promising early results. Third, a subgroup analysis by cancer subtype was performed, and no group significantly benefited from RT. However, the

data suggested the possibility of a small benefit from RT in patients with ER+/HER2– disease. Further follow-up, especially more detailed subgroup results, will be of interest as the data mature. Finally, the majority of patients in the trial had a breast pCR, so these results should be applied with caution to patients with significant residual breast disease following NAC.[104]

Conclusion

The landscape of breast cancer RT is evolving rapidly, with a growing body of evidence supporting various de-escalation strategies. This review has highlighted several key approaches that are reshaping clinical practice and paving the way for more personalized treatment. Hypofractionation and ultrahypofractionation have emerged as effective alternatives to conventional fractionation, offering comparable oncologic outcomes with improved convenience and potentially reduced toxicity. These shorter courses of treatment have the added benefit of increasing access to RT and reducing healthcare costs. APBI has shown promise in selected patient populations, allowing significant reductions in treatment volume and duration. However, careful patient selection remains crucial to ensure optimal outcomes with this approach. The omission of RT in selected low-risk populations, particularly older women with hormone receptor–positive early-stage disease, is supported by robust evidence. Ongoing trials incorporating genomic and immunohistochemical biomarkers may further refine our ability to identify patients who can safely forgo RT without compromising oncologic outcomes. In locally advanced disease, emerging data on hypofractionation for PMRT and RNI are encouraging. Additionally, the potential to omit RNI in patients achieving a pCR after NAC represents an exciting area of ongoing research. Although these de-escalation and personalization strategies show great promise, it is important to note that many studies are still ongoing, and long-term follow-up data are needed to confirm the durability of outcomes. Furthermore, these approaches must be integrated into clinical practice thoughtfully, with careful consideration of individual patient factors and shared decision making. As our understanding of breast cancer biology continues to advance, and with the integration of novel biomarkers and imaging techniques, we anticipate further refinement of RT strategies. Future research should focus on identifying robust predictors of RT benefit, exploring the role of immunotherapy in modulating radiation response, and investigating the potential for further treatment intensification in high-risk subgroups.

Thus, RT de-escalation in breast cancer represents a paradigm shift toward more personalized and patient-centered care. By tailoring treatment intensity to individual risk profiles, we have the potential to maintain excellent oncologic outcomes while minimizing treatment burden and improving QoL for patients with breast cancer. As we move forward, continued rigorous clinical investigation and thoughtful implementation of these strategies will be essential to optimize breast cancer care in the modern era.

Disclosures

The authors have no conflicts of interest to disclose.

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