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Regional Nodal Irradiation and Post-Mastectomy Radiation Therapy After Up-Front Surgery

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Abstract

Purpose of Review This review serves to summarize available data impacting treatment decisions for the use of post-mastectomy radiation (PMRT) and regional nodal irradiation (RNI).

Recent Findings In the last decade, there have been ongoing shifts in breast cancer management, including changes in the type and sequencing of systemic therapy tailored to receptor subtype and molecular profiling, changes to the surgical management of the regional nodes, and improvements in radiation treatment planning and delivery technology. In this chapter, we will consider historic and modern indications for PMRT and RNI after up-front surgery and discuss how the changing paradigms of surgical and systemic management continue to impact the role of PMRT and RNI.

Summary The majority of patients with lymph node-positive breast cancer will have some benefit from PMRT and/or RNI, but in the modern era, the impact may be modest, particularly for patients with low-volume nodal involvement. Clinical trial enrollment, tailored recommendations, and shared decision making are important to optimize treatment decisions.

Keywords Post-mastectomy radiation therapy (PMRT) · Regional nodal irradiation (RNI) · Patient-reported outcomes (PRO) · Internal mammary nodes (IMN) · Locoregional recurrence (LRR) · Hypofractionation

Introduction

Post-mastectomy radiation therapy (PMRT), inclusive of the chest wall and regional lymphatics, has been consistently shown to reduce the relative risk of locoregional recurrence (LRR) by about two-thirds in patients selected for inclusion in PMRT studies, typically on the basis of larger tumor size and/or lymph node positivity [1–4]. PMRT may also improve breast cancer-specific or overall survival by treating reservoirs of microscopic cells that seed distant metastases [2, 5]. Because studies of PMRT have generally included regional nodal irradiation (RNI) as a component, some of the benefits of PMRT may be extrapolated to RNI as well, and more modern studies have shifted to evaluating the impact of RNI, independent of the primary breast surgery type (mastectomy or beast conserving surgery (BCS). The RNI component of PMRT or BCS is variably defined by different studies and often depends on the extent of lymph node surgery done (Table 1), with the most common approach comprising "comprehensive" treatment of the undissected axillary lymph nodes (levels I–III), as well as the supraclavicular nodal basin (SCV) and the internal mammary lymph nodes (IMN). Early studies of PMRT demonstrated significant benefits, particularly with longer-term follow-up. For example, the 2014 Oxford Overview of studies accruing between 1964 and 1986 showed that PMRT inclusive of RNI reduced breast cancer recurrence and mortality in women with any lymph node-positive disease, with 10-year LRR decreased from 21 to 4%, and 20-year breast cancer-specific mortality decreased from 49 to 41% [4]. These relatively dramatic benefits must be put in the context that early studies addressing PMRT/RNI generally included patients with more significant nodal burden in an era prior to tailored systemic therapies, which likely resulted in an increased impact of radiotherapy. Newer studies of PMRT and RNI after up-front surgery have focused on earlier-stage breast cancer, generally

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Table 1 Nodal volume stations defining regional nodal irradiation by study

	Definition of internal mammary node coverage	Definition of axillary coverage	Definition of supraclavicular coverage
EORTC 22922	First 3 interspaces of IMN. Note: exception made in the case of medial lower quadrant lesions wherein IMNs will be contoured to the first 5 interspaces	Axillary levels upper II, III (ALND done)	Supra/infraclavicular nodes
Z011	No IMN	No dedicated axillary RT*	No planned SCV coverage*
AMAROS**	No IMN	Axillary levels I–III	Supra/infraclavicular nodes
MA.20	First 3 interspaces	Axillary levels upper II, III (ALND done)	Supra/infraclavicular nodes
DBCG-IMN	First 4 interspaces	Axillary levels II–III (included level I if > 6 nodes with macrometastases)	Supra/infraclavicular nodes

ALND, axillary node dissection; *IMN*, internal mammary nodes; *SCV*, supraclavicular

*Per protocol, no axillary RT permitted; 50% patients had axillary RT

*Per protocol, no SCV RT permitted; 19% patients had SCV RT with 3 fields

**In axillary nodal dissection arm, if N2, RT allowed to levels I–III

addressing patients with low-volume lymph node positivity and/or centrally/medially located primary breast tumors (increasing likelihood of drainage via the IMN pathway). In these more modern studies, inclusive of optimal and tailored systemic therapies, outcomes overall are markedly improved compared to earlier data, and the impact of radiotherapy is therefore more modest. In two recent studies, MA.20 and EORTC 22922, RNI decreased 10-year LRR by up to 2.5%, and also conferred a 3% decrease in distant metastasis disease-free survival (DM-DFS), with no overall survival benefit [6–8]. It is thus increasingly clear that while the primary role of PMRT and RNI is to impact LRR in the treated areas, with a relatively modest benefit in more modern series, the effect of RNI is also systemic—an important consideration when weighing its benefits against potential toxicity implications during treatment selection.

The last major consensus guideline in the US regarding PMRT was published in 2016 as a joint statement by ASCO/ASTRO/SSO [9]. Since that time, there have been ongoing shifts in breast cancer management, including changes in the type and sequencing of systemic therapy, generally tailored to receptor subtype and molecular profiling, changes to the surgical management of the regional nodes, and improvements in radiation treatment planning and delivery technology. In this chapter, we will consider historic and modern indications for PMRT and RNI after up-front surgery and discuss how the changing paradigms of surgical management of the axilla and the role of receptor profile and biomarkers continue to impact the role of PMRT and RNI. Note that the role of PMRT and RNI after preoperative systemic therapy will be addressed separately in ***the following chapter, Radiation Management after Neoadjuvant Therapy***.

Interrelationship Between Changes in Axillary Lymph Node Surgery and the Use of PMRT/RNI

The evolution toward de-escalation of axillary surgical management in breast cancer emerged in the context of breast cancer screening, which permitted for detection of earlier stage breast cancer with lower nodal disease burden at the time of diagnosis. Concomitant with this was increased utilization of tailored systemic therapy. In turn, the role of radiotherapy has evolved along with these changes in surgical approach.

In early breast cancer studies, nodal status was determined at the time of up-front surgery with the use of full axillary lymph node dissection (ALND), and the number of lymph nodes involved was the major determinant for the need for both chemotherapy and PMRT/RNI. The role of ALND was felt to include both the gathering of prognostic information (primarily the number of nodes affected) and conferring an oncologic benefit in terms of improving local control and potentially even survival (though axillary surgery is now understood not to impact survival). In turn, past indications for PMRT/RNI were formulated around the premise that the absolute number of involved axillary nodes was critical

for determining the potential benefit of radiotherapy, with most studies and guidelines limiting the use of PMRT/RNI to patients with ≥ 4 involved nodes. Unless frankly unresectable, up-front surgery was used for most breast cancers, and ALND was the standard prior to the advent of sentinel lymph node biopsy (SLNB).

In this context, PMRT was found to reduce the risk of LRR by greater than 15% and ultimately to improve survival [1–4]. The first trials to demonstrate an overall survival (OS) advantage with PMRT were the Danish and British Columbia trials [1–3, 10]. The Danish 82b and 82c studies assessed the addition of PMRT to chemotherapy in pre-menopausal patients and tamoxifen in post-menopausal women, respectively, irrespective of receptor profile [1, 2]. The British Columbia study assessed the impact of PMRT in patients with at least one positive lymph node [3]. All three studies showed improvement in LRR, DFS, and OS with the addition of PMRT. Lastly, the EBCTCG meta-analysis, comprised of 14 trials of over 13,000 patients (inclusive of the Danish and British Columbia studies), demonstrated an absolute reduction of LRR of 17% at 5 years and a 5% improvement in breast cancer-specific survival (BCSS) at 15 years [4].

In the 1990s, a movement began to identify women with lower risk of axillary lymph node metastases for whom ALND could be safely avoided. This was supported by data from the National Surgical Adjuvant Breast and Bowel Project (NSABP) B04 trial, which demonstrated equivalent survival through 25 years of follow-up in patients with clinically node-negative breast cancer randomized to either mastectomy with ALND, mastectomy with radiation, or mastectomy with no dedicated axillary therapy, with delayed ALND if the patient later developed nodal metastases [11]. Ultimately, this led to the era of SLNB alone for patients with negative sentinel nodes; studies confirmed that a sentinel lymph node could be identified in more than 95% of women with breast cancer, and SLNB was associated with a false-negative rate of 4–8% and axillary recurrence rate of < 1%, with no survival benefit over ALND [12, 13]. Thereafter, a number of prospective studies evaluated the role of SLNB in replacing ALND as the standard management of the axilla for patients with low-volume sentinel node positivity, including IBCSG 23-01, ACOSOG Z0011, AMAROS, and OTOASOR trials [14–17]. In these trials, patients with clinically negative nodes on physical examination experienced equivalent local control and survival to those with ALND whether managed with SLNB alone or SLNB with RNI. Importantly, most patients across these studies had only 1 or 2 sentinel lymph node metastases, and the potential benefit of ALND in the setting of higher nodal disease burden remains unclear. Over the same time frame, there has been a shift toward the utilization of preoperative systemic therapy for most patients with clinically apparent axillary nodes, with subsequent implications regarding residual nodal positivity and appropriate management [18].

This evolution of axillary management over the last 20 years has led to a dramatic reduction in the use of ALND as up-front management of the axilla. The morbidity of ALND can now be minimized with the various alternatives to ALND including SLNB alone and SLNB with RNI, with the use of neoadjuvant systemic therapy to expand eligibility for SLNB in patients with clinically apparent nodal involvement at diagnosis. Overall, de-escalation of axillary surgical management in combination with compelling results from the EBCTCG regarding improved LRR and BCSS benefit from PMRT has supported an expanded role for RT in node-positive patients, with RNI replacing definitive surgical management of the axilla in many cases [4]. Yet, it is not clear which patients with positive nodes will truly benefit from PMRT and/or RNI, and this is the focus of current research.

Role of Radiotherapy in Low-Volume Node-Positive and Higher Risk or Node-Negative Breast Cancer

The question of when to utilize RT for patients with limited axillary disease burden (defined as 1–3 positive lymph nodes) has been addressed in 3 seminal prospective trials: MA.20, EORTC 22922, and the Danish Breast Cancer Group, DBCG-IMN study [6, 7, 19]. MA.20 primarily enrolled patients who had undergone lumpectomy and were found to have positive nodes, with the vast majority having 1–3 involved nodes, although a minority (10%) of patients enrolled had high-risk node-negative disease. All patients received both whole breast RT and ALND (reflective of the era in which the study was designed) and were then randomized to either receive RNI or not. The patients who received RNI had a 2.5% improvement in LRR (6.8% without RNI versus 4.3% with RNI, primarily driven by regional recurrence since both cohorts received RT to the breast), a 5% improvement in DFS (82% versus 77%), and a 4% improvement in distant metastasis-free survival (86.3% versus 82.4%), all $p < 0.05$. However, no significant differences in OS or BCSS were found between the two groups [20]. EORTC 22922 also aimed to assess the benefits of RNI and enrolled patients treated with mastectomy or lumpectomy who had either positive nodes or had central/medial tumor location irrespective of nodal status. Participants were randomized to undergo RNI or not. Similar to MA.20, EORTC22922 did not demonstrate a statistically significant overall survival benefit for RNI (82.3% versus 80.7%). However, there was a statistically significant decrease in regional recurrence (2.7% after RNI versus 4.2% without), distant recurrence (15.9% with RNI versus 19.6% without), and breast cancer-specific mortality (16% with RNI and 19.8% without) [7], all $p < 0.05$. In both of these studies, the majority of patients

enrolled had 1–3 positive nodes, although 44% in EORTC were enrolled on the basis of central/medial tumor location with negative nodes. While pre-planned subgroup analyses failed to demonstrate how other clinicopathologic features might be considered in clinical decision making, it is notable that in MA.20, patients with estrogen receptor (ER)-positive disease were noted to have improved DFS on multivariable analysis. This finding from MA.20 highlights the increasing role of tumor biology in estimating LRR risk and the benefit of radiotherapy [6].

Improved understanding of the intrinsic biologic subtypes in breast cancer, including hormone receptor and HER2 status, as well as the molecular genetic profile of the cancer, has helped to define a patient's risk for recurrence. In a retrospective review of a large national database, the benefit of PMRT on preventing LRR was highest for patients with luminal A subtype and lowest for patients with triple-negative disease. Notably, the risk of LRR was particularly low in patients with HER2-positive disease treated with HER2-directed therapy [21]. A retrospective review of the Danish 82b/c studies was done to examine tumor subtype and gene profile and demonstrated that the LRR and survival benefit of PMRT was greatest in luminal A tumors [20]. The impact of genomic profiling is further supported by the combined analysis of the 21-gene Oncotype DX® recurrence score (RS), in patients treated in the NSABP B14, B20, and B28 studies, which demonstrated a significant association between the RS and the risk of LRR in patients with node-positive disease [22].

Taken together, the current data show that patients with lower RS, stronger ER positivity, and/or lower volume nodal involvement may have the lowest risk of LRR without RT, yet may also have the most significant relative risk reduction with the use of RT. The discrete impact of RT in these lower-risk populations still needs to be elucidated. As a natural extension of the data supporting consideration of receptor subtype and molecular profiling into PMRT/RNI treatment decisions, the focus of current clinical trials in node-positive breast cancer is risk stratification and recommendations regarding PMRT and RNI according to these features. In the RxPONDER study of post-menopausal patients with hormone-receptor positive early-stage breast cancer with 1–3 positive nodes and a RS of ≤ 25, chemotherapy conferred a minimal advantage and could be safely omitted [23]. This sets the stage to similarly investigate patients for whom RNI could be de-escalated based on molecular profiling in the Canadian Cancer Trials Group's TAILOR-RT/MA.39 study (NCT03488693) [24]. This is an ongoing randomized study of RNI or no RNI among patients with ER-positive, HER2-negative tumors with low-risk biomarkers (Oncotype Dx® Recurrence Score ≤ 25) and 1–2 node positive or T3N0 disease. The study is agnostic to surgery type, allowing both mastectomy and lumpectomy as well as SLNB or ALND, though the use of ALND is quite rare in this population at this time.

While we await the results of the ongoing MA.39 study, outside of clinical trial participation, physicians and patients must rely on a complex balance of considerations, from the modest but measurable benefits of PMRT/RNI to the side effect profile of radiotherapy—which is generally seen as quite safe but can clearly confer negative quality of life (QOL) impact for the majority of patients. The effects of PMRT on QOL have been assessed in the SUPREMO trial [25]. In this study, patients with study-defined intermediate-risk breast cancer were randomized to receive or not receive PMRT (notably using a moderately hypofractionated regimen in about 70% of enrolled patients, hypofractionation will be addressed in a later section). While the primary endpoint of OS at 10 years has not been published, the results of a pre-specified secondary endpoint of QOL at 2 years of follow-up demonstrated a small but significant worsening of chest wall symptoms with RT, but no differences in shoulder symptoms, body image, fatigue, overall QOL, physical function, anxiety, or depression [25]. The ASCO/ASTRO/SSO guideline encourages strong consideration of PMRT for patients with T1-2 breast cancer with 1–3 positive axillary nodes (and clearly recommends PMRT for patients with more advanced stages), but it is clear that the benefit in this cohort will vary with risk factors like age, receptor profile, and genomic expression, and is likely to be quite small for some patients fitting these criteria. Thus, the specific impact of PMRT and RNI on quality of life and the balance with its impact on LRR and DFS are likely to vary among patients, and shared decision-making remains paramount in this setting.

Defining Radiation Fields in RNI and PMRT

Definition of the specific nodal volumes of the axilla, SCV, infraclavicular, and IMN remains controversial. Among the most challenging aspects of defining RNI are the inclusion and extent of the IMN as well as the level I/II axillary node targets, the latter of which may vary with the extent of nodal surgery. Moreover, different approaches to axillary surgery and varying definitions of coverage of fields used in trials regarding RNI management further complicate our ability to standardize an approach to RNI [7, 15, 16, 19, 24, 26, 27].

The coverage of IMN is supported both by broad inclusion of IMN in historic studies of regional nodal RT as well as dedicated studies evaluating its specific role in improving cancer outcomes. In the EBCTCG meta-analysis, 20 of the 22 trials that demonstrated benefit with PMRT included some form of IMN coverage [4]. Among studies that specifically evaluated inclusion of IMNs, coverage of this nodal region has generally been associated with a 1–5%

improvement in endpoints including LRR, BCSS, and/or OS rates [4, 18, 28, 29]. Other trials have attempted to define subsets of patients for whom IMN coverage is most beneficial. While a recent randomized clinical trial of 735 women with node-positive breast cancer demonstrated that 7-year DFS did not significantly differ in women who received RNI with IMN coverage versus those without, a subgroup analysis of patients with inner central tumors showed that 7-year DFS was improved by 10% when IMNs were included [30•]. Due to potential for long-term risk of cardiac toxicity with treatment of the IMNs, the DBCG-IMN study assessed treatment of the IMNs based on tumor laterality. Patients requiring RNI were treated with IMN coverage if their tumor was right-sided and without IMN coverage if left-sided. The benefit of RT to the IMN was demonstrated to be the greatest in patients with positive nodes and central/medial disease, as well as in patients with ≥ 4 nodes regardless of primary tumor location [19]. Informing the extent of the IMN treatment field needed, a retrospective study by Jethwa et al. analyzed IMN recurrences with respect to the IMN CTV and demonstrated 78% of recurrences occurring in the first 3 intercostal spaces, with 14% occurring below the third intercostal space and 8% superior to the first intercostal space [31].

Commensurate with the measurable but perhaps modest impact of IMN coverage, there is variability in inclusion and definitions of IMN coverage in recent studies of regional nodal RT as well as in consensus guidelines. Table 1 describes the range of IMN coverage utilized in recent key prospective trials regarding regional nodal management. The 2016 ASCO/ASTRO/SSO PMRT consensus guideline does specify the inclusion of IMN in its standard definition of RNI without clarifying the extent of the treatment field. Given lack of consensus regarding IMNs for RNI, clinicians must weigh the benefits of the inclusion and extent of IMN coverage against risks such as substantial evidence of the relationship between RT dose to the heart and lungs and adverse cardiopulmonary consequences in breast RT [32–34]. Drawing from the studies cited above, patient-specific features that may guide the clinical decision to treat all or part of the IMN nodal chain include target laterality, tumor location within the breast (central/medial versus not), anatomical position of the heart and lungs relative to the treatment target, and access to and tolerance of breath hold procedures that may mitigate incidental cardiac and lung doses.

The decision to provide dedicated treatment of the axillary and supraclavicular nodes also presents a challenge in light of the design of past clinical trials. The ACOSOG Z0011 trial of omission of ALND specified tangential fields to the breast alone in the supine position, which likely incidentally included a portion of level I of the axilla; a detailed analysis of RT fields for a subset of included cases showed that about half of patients were treated with "high tangents" including most of the level I/II axilla, and approximately 20% were treated with dedicated nodal RT [28]. Thus, the extent to which RT contributed to the excellent locoregional outcomes in this study remains unclear. In the AMAROS trial, the radiation fields in patients who did not get ALND included the entire axilla and the supraclavicular lymph nodes, again limiting the ability to differentiate between the impact of RT and surgery in maintaining locoregional control [15]. Both MA.20 and EORTC 22922 prescribed RT to the IMN, axillary, and SCV nodes after the majority of participants received ALND. While patients with negative nodes comprised just 10% of patients on MA.20, they made up approximately 45% in EORTC 22922 [6, 15]. Together, these two studies suggest the potential benefit of RNI inclusive of the IMN for subsets of node-negative patients including those with central/medial tumors combine with one or more additional high-risk feature.

The primary trade-off in considering the toxicity of axillary RNI is its impact on lymphedema risk. In the AMAROS study, lymphedema risk was twice as high in patients treated with ALDN and RNI as compared to SLNB and RNI [15], and this has been substantiated in a systematic review of multiple other series [35]. Thus, it is generally acknowledged that when RNI is used in patients who had SLNB only, the radiation target should include the full axilla including levels I, II, and III, in addition to the supraclavicular nodes +/- IMN. In those patients who have ALND and still require RNI, whether to treat or avoid (and how to do so) radiation of the dissected portion of the axilla remains a significant challenge. In reality, most 3D conformal techniques will incidentally include much of the level I and part of the level II axilla in both BCS and PMRT [36]. Nonetheless, avoidance of the dissected areas of the axilla is preferred, if possible, after ALND, unless there is a marked risk of residual disease, such as in the case of extensive extranodal extension, tumor deposits in axillary tissue outside the nodes, and/or a large percent of removed nodes affected.

Variability in Contouring and Defining Regional Nodal Target Volumes

There are many resources for contouring of the nodal structures for RNI, which vary in style and in substance. The three major contouring atlases are the RTOG breast cancer atlas, RADCOMP atlas, and the ESTRO atlas [29, 37, 38]. The nodal target volumes are generally more extensive with the RTOG and RADCOMP atlases compared to the ESTRO atlas and rely on delineation of the fat planes between muscles, bones, and other normal structures. In contrast, the ESTRO atlas is primarily based on vessels. There are notable differences in the atlases;

for example, the cranial border of the supraclavicular clinical tumor volume (CTV) is located much more superiorly in both the RTOG and RADCOMP atlases compared to the ESTRO atlas, which has implications for both coverage of the supraclavicular nodal structures as well as dose to the esophagus, thyroid gland, and the shoulder neck/musculature. There are also differences in how the IMN target is defined. Further differences are delineated in an excellent review by Bazan et al. [39•]. When considering the optimal atlas for target delineation for an individual patient, clinical trial participation and radiotherapy technique are important considerations. The RADCOMP atlas was designed specifically for use on the RADCOMP study, taking into account the specific dosimetric considerations for proton radiotherapy. It is also a very useful atlas for IMRT planning, as its volumes are contiguous and avoid cold spots that could arise when applying the RTOG Breast Cancer Altas with the use of protons or IMRT. In contrast, the standard RTOG breast cancer atlas is used on RTOG-sponsored trials and is excellent for routine 3D conformal planning, as it closely mimics traditional field borders for this planning approach.

Hypofractionation

In the management of early-stage breast cancer following BCS, hypofractionation is supported, with the obvious benefit to patients of shorter treatment courses, as well as lower acute and late toxicity [40–42]. These findings have led to studies evaluating the extension of this management strategy to PMRT and RNI. There have been several studies of hypofractionation that have included patients receiving PMRT/RNI, including a small percentage of patients in the UK START A and B studies that defined hypofractionation as a standard for RT to the intact breast [42]. A study from China randomized patients with mastectomy without reconstruction to 50 Gy in 25 fractions versus 43.5 Gy in 15 fractions and found no differences in LRR or acute or late toxicity at 6 years [43•]. A prospective phase II trial of 96 patients from Rutgers University delivered dose of 36.63 Gy in 11 fractions to the chest wall or reconstructed breast, and the regional lymphatics revealed no acute or late grade 3 and 4 non-reconstruction toxicities and comparable locoregional outcomes to historical controls [44]. These studies have laid the foundation for moderate hypofractionation as a very reasonable approach for patients receiving RNI or PMRT to the non-reconstructed chest wall. While the use of moderate hypofractionation in these settings is still gaining traction in the USA, it has been adopted as a standard in the UK and Canada and is one of the approved treatment approaches on the standard of care arm for RNI in the ongoing MA.39 study of RNI [24].

In addition to the MA.39 study, several studies are specifically addressing the role of moderate hypofractionation in the setting of chest wall reconstruction. Notably, the primary outcomes of these studies tend to focus on patient experience and reconstructive outcomes, from the perspective that existing data supports oncologic equivalence of conventional and moderately hypofractionated regimens. The RT-CHARM (ALLIANCE A221505; NCT03414970) non-inferiority trial comparing conventional versus moderate hypofractionation PMRT after reconstruction and mastectomy in stage IIA-IIIA breast cancer has accrued, and outcomes are awaited [45]. Similarly, the FABREC study (NCT03422003) for stage I–III breast carcinoma is a randomized trial of moderate hypofractionation RT versus conventional RT in women who have undergone mastectomy with immediate breast reconstruction [46]. Dose regimens were 50 Gy in 25 fractions (with 46 Gy in 23 fractions to the SCV) versus 42.56 Gy in 16 fractions (with 39.9 Gy in 15 fractions to the SCV). In both studies, primary endpoints address QOL with secondary evaluation of recurrence risk. Results from both studies are expected in late 2023–2024. In the meantime, the use of moderate hypofractionation for non-reconstructed patients receiving PMRT and/or RNI is increasingly common and well-supported and should be considered for most patients. Whether this approach can be reasonably extended to those patients with chest wall reconstructions will likely be known in the near future.

Locally Advanced Breast Cancer

Locally advanced breast cancer is a heterogeneous group with wide variability in disease presentation, varying from a large primary tumor with or without involvement of the skin and/or chest wall, and/or extensive regional nodal burden. Since locally advanced breast cancer is associated with a significant risk for systemic disease, its treatment includes controlling locoregional disease, as well as eradicating occult systemic metastases. As such most patients with locally advanced breast cancer receive chemotherapy in the neoadjuvant setting within the modern treatment paradigm. In those cases where surgery is done first, PMRT and RNI are generally recommended for patients with T3N1, T4, or N2-3 disease.

Conclusion

The majority of patients with lymph node-positive breast cancer will have some benefit from PMRT and/or RNI, but in the modern era, due to significant changes and improvements in systemic therapy, the impact of radiotherapy is much more modest than in earlier eras. As hypofractionation emerges as an option for more patients receiving PMRT and RNI, treatment accessibility and toxicity may improve, and thus,

the therapeutic ratio may continue to favor radiotherapy in many cases. Current and future research focuses on assessing the impact of PMRT and RNI in lower-risk cases and on expanding the role of hypofractionated regimens. Clinical trial enrollment, tailored recommendations, and shared decision making are important to optimize treatment decisions.

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Data Availability All material and data were prepared by the authors, and do not contain any third party material.

Declarations

Ethical Approval This article does not contain any studies with human or animal subjects performed by any of the authors.

Competing Interests Sara Alcorn, MD, MPH, PhD, has a leadership role as Breast Associate Editor for the International Journal of Radiation Oncology Biology and Physics. Jean L Wright MD is Chair of the ASTRO Clinical Affairs and Quality Committee, as well as serves as the Breast Section Editor for the International Journal of Radiation Oncology Biology and Physics. Teresa P Easwaran, MD, MS, declares no competing interests.

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