Public Comment Draft

Postmastectomy Radiation Therapy: An ASTRO/ASCO/SSO Clinical Practice Guideline

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Abstract

Purpose: This guideline provides evidence-based recommendations on the use of postmastectomy radiation therapy (PMRT) in the treatment of breast cancer. Updated recommendations detail indications for PMRT in the upfront surgical setting and after neoadjuvant systemic therapy, as well as provide guidance on appropriate target volumes, dosing, and treatment techniques.

Methods: The American Society for Radiation Oncology (ASTRO) convened a multidisciplinary task force to address 4 key questions focused on radiation management of patients with breast cancer who undergo mastectomy. The key questions emphasized (1) indications for PMRT after upfront surgery, (2) indications for PMRT after neoadjuvant systemic therapy, (3) appropriate PMRT treatment volumes and dose-fractionation regimens, and (4) treatment techniques. Recommendations were based on a systematic literature review and created using a predefined consensus-building methodology and system for quality of evidence grading and strength of recommendation.

Results: PMRT is recommended in the upfront surgical setting for lymph node positive, and select lymph node negative, disease. PMRT is also recommended after neoadjuvant systemic therapy both for patients presenting with locally advanced disease and for those with residual nodal disease at the time of surgery. PMRT is conditionally recommended for patients with clinical N1 disease who become node negative after neoadjuvant systemic therapy. When PMRT is delivered, treatment to the ipsilateral chest wall and regional lymphatics is recommended, with either conventional or moderate hypofractionation approaches for patients without breast reconstruction. The use of moderate hypofractionation is conditionally recommended for patients with breast reconstruction. Computed tomography-based volumetric treatment planning with 3-dimensional conformal radiation therapy (3-D CRT) is recommended, with intensity modulated RT when 3-D CRT is unable to achieve treatment goals. For patients receiving intensity modulated RT, daily image guidance is recommended. Deep inspiration breath hold techniques are also recommended for cardiac sparing purposes. For patients with cancer involving the skin and chest wall, the use of bolus is recommended; otherwise, the routine use of tissue-equivalent bolus is not recommended.

Conclusions: Based on published data, the ASTRO task force has proposed evidence-based recommendations regarding the use of PMRT in patients with breast cancer.

Preamble

As a leading organization in radiation oncology, the American Society for Radiation Oncology (ASTRO) is dedicated to improving quality of care and patient outcomes. A cornerstone of this goal is the development and dissemination of clinical practice guidelines based on systematic methods to evaluate and classify evidence, combined with a focus on patient-centric care and shared decision making. ASTRO develops and publishes guidelines without commercial support, and members volunteer their time.

Disclosure Policy—ASTRO has detailed policies and procedures related to disclosure and management of industry relationships to avoid actual, potential, or perceived conflicts of interest. All task force members are required to disclose industry relationships and personal interests from 12 months before initiation of the writing effort. Disclosures for the chair and vice chair go through a review process with final approval by ASTRO's Conflict of Interest Review Committee. For the purposes of full transparency, task force members' comprehensive disclosure information is included in this publication. Peer reviewer disclosures are also reviewed and included (Supplementary Materials, Appendix E1). The complete disclosure policy for Formal Papers is online.

Selection of Task Force Members—ASTRO strives to avoid bias and is committed to creating a task force that includes a diverse and inclusive multidisciplinary group of experts considering race, ethnicity, gender, experience, practice setting, and geographic location. Representatives from organizations and professional societies with related interests and expertise are also invited to serve on the task force.

Methodology—ASTRO's task force uses evidence-based methodologies to develop guideline recommendations in accordance with the National Academy of Medicine standards.[1,2] The evidence identified from key questions (KQs) is assessed using the **P**opulation, **I**ntervention, **C**omparator, **O**utcome, **T**iming, **S**etting (PICOTS) framework. A systematic review of the KQs is completed, which includes creation of evidence tables that summarize the evidence base task force members use to formulate recommendations. Table 1 describes ASTRO's recommendation grading system. See Appendix E2 in Supplementary Materials for a list of abbreviations used in the guideline.

Consensus Development—Consensus is evaluated using a modified Delphi approach. Task force members confidentially indicate their level of agreement on each recommendation based on a 5-point Likert scale, from "strongly agree" to "strongly disagree". A prespecified threshold of ≥75% (≥90% for expert opinion recommendations) of raters who select "strongly agree" or "agree" indicates consensus is achieved. Recommendation(s) that do not meet this threshold are removed or revised. Recommendations edited in response to task force or reviewer comments are resurveyed before submission of the document for approval.

Annual Evaluation and Updates—Guidelines are evaluated annually beginning 2 years after publication for new, potentially practice-changing studies that could result in a guideline update. In addition, ASTRO's Guideline Subcommittee will commission a replacement or reaffirmation within 5 years of publication.

Table 1 ASTRO recommendation grading classification system

ASTRO's recommendations are based on evaluation of multiple factors including the QoE and panel consensus, which among other considerations, inform the strength of recommendation. QoE is based on the body of evidence available for a particular key question and includes consideration of number of studies, study design, adequacy of sample sizes, consistency of findings across studies, and generalizability of samples, settings, and treatments.

Strength of Recommendation	Definition	Overall QoE Grade	Recommendation Wording
Strong	• Benefits clearly outweigh risks and burden, or risks and burden clearly outweigh benefits. • All or almost all informed people would make the recommended choice.	Any (usually high, moderate, or expert opinion)	"Recommend/ Should"
Conditional	• Benefits are finely balanced with risks and burden, or appreciable uncertainty exists about the magnitude of benefits and risks. • Most informed people would choose the recommended course of action, but a substantial number would not. • A shared decision-making approach regarding patient values and preferences is particularly important.	Any (usually moderate, low, or expert opinion)	"Conditionally Recommend"

Overall QoE Grade	Type/Quality of Study	Evidence Interpretation
High	• 2 or more well-conducted and highly generalizable RCTs or meta-analyses of such trials.	The true effect is very likely to lie close to the estimate of the effect based on the body of evidence.
Moderate	• 1 well-conducted and highly generalizable RCT or a meta-analysis of such trials **OR** • 2 or more RCTs with some weaknesses of procedure or generalizability **OR** • 2 or more strong observational studies with consistent findings.	The true effect is likely to be close to the estimate of the effect based on the body of evidence, but it is possible that it is substantially different.
Low	• 1 RCT with some weaknesses of procedure or generalizability **OR** • 1 or more RCTs with serious deficiencies of procedure or generalizability or extremely small sample sizes **OR** • 2 or more observational studies with inconsistent findings, small sample sizes, or other problems that potentially confound interpretation of data.	The true effect may be substantially different from the estimate of the effect. There is a risk that future research may significantly alter the estimate of the effect size or the interpretation of the results.
Expert Opinion*	• Consensus of the panel based on clinical judgment and experience, due to absence of evidence or limitations in evidence.	Strong consensus (≥90%) of the panel guides the recommendation despite insufficient evidence to discern the true magnitude and direction of the net effect. Further research may better inform the topic.

Abbreviations: ASTRO = American Society for Radiation Oncology; QoE = quality of evidence; RCTs = randomized controlled trials.

*A lower quality of evidence, including expert opinion, does not imply that the recommendation is conditional. Many important clinical questions addressed in guidelines do not lend themselves to clinical trials, but there still may be consensus that the benefits of a treatment or diagnostic test clearly outweigh its risks and burden.

ASTRO's methodology allows for use of implementation remarks meant to convey clinically practical information that may enhance the interpretation and application of the recommendation. While each recommendation is graded according to recommendation strength and QoE, these grades should not be assumed to extend to the implementation remarks.

1. Introduction

According to the World Health Organization, in 2022 breast cancer was the second most common cancer and the fourth leading cause of cancer mortality worldwide.[3] While some patients may undergo breast conservation therapy, others undergo mastectomy either by medical necessity or by choice. For these patients, postmastectomy radiation therapy (PMRT), which delivers radiation therapy (RT) to the residual skin and soft tissue of the ipsilateral chest wall and regional draining lymphatics, can decrease the risk of a locoregional recurrence (LRR) and potentially improve breast cancer mortality.[4] As the absolute benefit of PMRT can vary according to patient and tumor characteristics, it is important to identify which patients are at higher risk of LRR to individualize treatment decision-making.

ASTRO, the American Society of Clinical Oncology, and the Society of Surgical Oncology sought to develop a new guideline to clarify patient selection criteria and appropriate technical approaches for the delivery of PMRT. This evidence review was completed to replace the 2016 PMRT guideline[5] and to reflect the evolving understanding of the benefit of PMRT. With advancements in the management of breast cancer, including improved diagnostic imaging, trends in de-escalation of axillary surgery, newer and more tailored systemic therapy agents, and advances in RT techniques, there is a need to provide updated guidance regarding the appropriate indications for, and approaches to, PMRT in the modern era.

2. Methods

2.1. Task force composition

The task force consisted of a multidisciplinary team of radiation, medical, and surgical oncologists; a radiation oncology resident; a medical physicist; and a patient representative. This guideline was developed in collaboration with the American Society of Clinical Oncology, European Society of Radiotherapy and Oncology, and Society of Surgical Oncology, who provided representatives and peer reviewers.

2.2. Document review and approval

The guideline was reviewed by XX official peer reviewers (Appendix E1) and revised accordingly. The modified guideline was posted on the ASTRO website for public comment from September 2024. The final guideline was approved by the ASTRO Board of Directors and endorsed by the TBD.

2.3. Evidence Review

KQs were developed by the ASTRO guideline subcommittee in conjunction with the guideline chairs, and then reviewed by the full task force. Using the PICOTS framework (Table 2), a systematic search of human participant studies retrieved from the Ovid MEDLINE database was conducted for English-language publications between January 1, 2005, through October 3, 2023. Allowable publication types included prospective randomized controlled trials (RCTs), prospective nonrandomized studies, meta-analyses, and large retrospective studies. The population of interest was adults (age ≥18 years) with a diagnosis of breast cancer who underwent mastectomy. Trial size required for inclusion was ≥50 patients for RCTs and meta-analyses, and ≥100 patients for prospective nonrandomized and retrospective studies. KQ1 addresses indications for PMRT in patients who receive mastectomy as their initial treatment. Retrospective studies were excluded for KQ1 given the strength of the prospective data available for this question. Universal exclusion criteria included the following: preclinical and nonhuman studies; publication types such as abstract only, review articles, case reports, comments, or editorials; study types such as dosimetric/contouring studies, health economics/cost analysis studies or large registry/database studies. For specific subquestions where limited data were available, expert opinion was relied upon to support recommendations. Full-text articles were assessed by the task force to determine the final included study list resulting in 104 studies (see the Preferred Reporting Items for Systematic Reviews and Meta-Analyses [PRISMA] flow diagram showing the number of articles screened, excluded, and included in the evidence review and Appendix E3 in Supplementary Materials for the literature search strategy, which includes the evidence search parameters and inclusion/exclusion criteria).

The data used by the task force to formulate recommendations are summarized in evidence tables available in Supplementary Materials, Appendix E4. References selected and published in this document are representative and not all-inclusive. Additional ancillary articles not in the evidence tables are included in the text; these were not used to support the evidence-based recommendations but may have informed expert opinion.

2.4. Scope of the guideline

The scope of this guideline is to define the role of RT after mastectomy for invasive breast cancer with curative intent, including the indications for PMRT after upfront surgery and after neoadjuvant systemic therapy, and to discuss the appropriate target volumes and technical specifications for PMRT. Given the rapid adoption of neoadjuvant systemic therapy and sentinel lymph node biopsy/targeted axillary dissection, this guideline seeks to address the indications and approaches for PMRT in the context of these advances in the multidisciplinary care of breast cancer. In this guideline, “PMRT” refers to treatment of the chest wall and

ipsilateral regional nodes, including at-risk axillary, supra/infraclavicular, and internal mammary nodes (IMN). Specific situations where treatment volumes may be less comprehensive are noted in the text.

The key outcomes of interest include LRR, disease-free survival (DFS), breast cancer-specific survival, distant metastasis-free survival, and overall survival (OS). Other key outcomes of interest include appropriate dose-fractionation regimens, nodal volumes considered for treatment, and optimal RT techniques to minimize toxicities. This guideline addresses only the subjects specified in the KQs (Table 2). There are several important questions in the management of patients with breast cancer that are outside the scope of this guideline, including the management of locally or regionally recurrent disease, reirradiation, RT in the setting of oligometastatic disease, palliative RT, and detailed discussions of surgical approaches and chemotherapy regimens. This guideline also does not encompass recommendations on RT for metastatic cancer, phyllodes tumors, sarcomas of the breast, nuances related to the treatment of inflammatory breast cancer, or management of ductal carcinoma in situ (DCIS) after mastectomy.

Table 2 KQs in PICO format

KQ	Population	Intervention	Comparator	Outcomes
1	**What are the indications for PMRT in patients who receive mastectomy as their initial treatment for breast cancer?**			
	• Adult patients with breast cancer	• PMRT	• No PMRT	• Local recurrence • Regional recurrence • Locoregional recurrence • Disease-free survival • Breast cancer mortality • Distant metastasis-free survival • Overall survival
2	**What are the indications for PMRT in patients who receive neoadjuvant systemic therapy before mastectomy?**			
	• Same as KQ1	• PMRT after neoadjuvant systemic therapy	• No PMRT after neoadjuvant systemic therapy	• Local recurrence • Regional recurrence • Locoregional recurrence • Disease-free survival • Breast cancer mortality • Distant metastasis-free survival • Overall survival
3	**What are the appropriate treatment volumes (eg, chest wall/reconstructed breast, regional nodes, boost) and dose-fractionation regimens for patients who receive PMRT?**			
	• Same as KQ1	• Hypofractionation • Chest wall/reconstructed breast without RNI • RNI including IMNs • Boost	• Conventional fractionation • Chest wall/reconstructed breast with RNI • RNI without IMNs • No boost	• Local recurrence • Regional recurrence • Locoregional recurrence • Disease-free survival • Breast cancer mortality

				• Distant metastasis free survival • Toxicity and adverse effects
4	**What are the appropriate techniques (eg, 3-D CRT, IMRT, protons, breath hold, bolus) for treating patients who receive PMRT?**			
	• Same as KQ1	• IMRT/VMAT • Electrons • Protons • Setup verification, image guidance/surface guidance • Respiratory management, gating, breath hold • Bolus	• 3-D CRT • PMRT with photons • No bolus	• Local recurrence • Regional recurrence • Locoregional recurrence • Disease-free survival • Breast cancer mortality • Distant metastasis free survival • Toxicity and adverse effects

Abbreviations: 3-D CRT = 3-dimensional conformal radiation therapy; IMN = internal mammary nodes; IMRT = intensity modulated radiation therapy; KQs = key questions; PICO = Population, Intervention, Comparator, Outcome; PMRT = postmastectomy radiation therapy; RNI = regional nodal irradiation; RT = radiation therapy; VMAT = volumetric modulated arc therapy.

3. Key Questions and Recommendations

3.1. KQ1: Indications for PMRT with mastectomy as initial treatment (Table 3)

See evidence tables in Supplementary Materials, Appendix E4, for the data supporting the recommendations for KQ1 and Fig 1.

What are the indications for PMRT in patients who receive mastectomy as their initial treatment for breast cancer?

Table 3 Indications for PMRT with mastectomy as initial treatment

KQ1 Recommendations	Strength of Recommendation	Quality of Evidence (Refs)
1. For patients with node-positive (pN+) breast cancer, PMRT is recommended. Implementation remark: PMRT may be omitted for select patients with low volume, node-positive (pN+) disease at low risk for locoregional recurrence after axillary dissection.	Strong	High [4,6-9]
2. For patients with pT4 breast cancer, PMRT is recommended even in the absence of lymph node involvement.	Strong	Expert Opinion
3. For patients with pT3N0 breast cancer, PMRT is recommended to reduce locoregional recurrence but may not improve overall survival.	Strong	Low [4,6,8]

4. For patients with pT1-2N0 breast cancer, PMRT is not recommended. Implementation remark: Select patients with pT1-2N0 breast cancer at high-risk for locoregional recurrence may be suitable for PMRT.	Strong	Low [4,10]
5. For patients with positive surgical margins after mastectomy and no other indication for PMRT, RT to the chest wall/reconstructed breast alone is conditionally recommended.	Conditional	Expert Opinion

Abbreviations: KQ = key question; PMRT = postmastectomy radiation therapy; RT = radiation therapy.

Over the last 4 decades, multiple RCTs and pooled analyses have shown a significant reduction in LRR and improved DFS and OS in women with pT3-4 or node-positive breast cancer who receive PMRT.[4,6-8,11-13] Support for the use of PMRT in patients with nodal involvement comes from the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis.[4,14] This analysis included women who underwent mastectomy and axillary dissection and were enrolled in trials evaluating PMRT to the chest wall and regional lymph nodes. PMRT significantly reduced breast cancer recurrence, breast cancer mortality, and all-cause mortality in patients with positive lymph nodes.[4,14] Among these patients, the risk of LRR and the benefit of PMRT increased with nodal burden, with the greatest absolute reduction of LRR and improvement in DFS and OS observed in patients with ≥4 positive nodes (pN2), but with still significant benefits for those with 1 to 3 positive nodes (pN1).

It should be noted that the EBCTCG meta-analysis was limited to trials initiated by 1995,[4,15] so while the majority of the included studies reflected the receipt of appropriate systemic therapies for the time period, most did not use current evidence-based systemic regimens (eg, immunotherapy, HER2-directed therapy) which have been recognized to further confer a locoregional control benefit.[6,7,13]

In this context, the benefit of PMRT for low volume, node-positive disease (pN1) has been questioned. The SUPREMO (Selective Use of Postoperative Radiotherapy after Mastectomy; *NCT00966888)* trial evaluated the value of PMRT for patients with limited nodal disease in the upfront surgical setting. Data are maturing for this study and the results will provide additional insights regarding the value of PMRT in this favorable risk population. Additionally, in an era where the biology of breast cancer guides systemic therapy, questions arise as to whether biology should also inform RT recommendations. Indeed, MA.39/TAILOR-RT (A Randomized Trial of Regional Radiotherapy in Biomarker Low-Risk Node-Positive Breast Cancer, *NCT03488693*) randomizes patients with pT1-2N1a disease and a non-high-risk recurrence score (RS ≤25) to PMRT or no PMRT. The results from this trial will also inform recommendations for PMRT for patients receiving upfront surgery with limited axillary nodal disease and favorable estrogen receptor (ER)-positive tumor biology. Notably, in this study

axillary lymph node dissection is not mandatory; however, if a sentinel lymph node biopsy alone is performed, there can be no more than 2 positive nodes to meet inclusion criteria.

In the node-negative setting, data support the use of PMRT in patients with high-risk features. Younger age (<40 years), hormone receptor-negative disease, and larger tumor size (≥5 cm) have also all independently been associated with a greater benefit of PMRT.[13] Although specific RCTs directly focusing on T4N0 breast cancer are limited, there are some data that support the benefits of PMRT in reducing LRR and improving survival outcomes in this patient population.[4,6-8,16,17] Invasion of the skin and pectoralis muscle (not included in the AJCC definition of pT4, but often treated as such) has been associated with higher rates of LRR,[8] and were considered high-risk criteria for eligibility in both the Danish 82b and c trials.[16,17] For patients with pT3N0 breast cancer, which were also included in these RCTs, there was a >50% reduction in LRR with PMRT.[16,17] However, this group comprised <10% of the study cohorts and neither trial demonstrated a significant improvement in breast cancer-specific or OS in patients with pT3N0 breast cancer.[6] Multiple population dataset analyses have demonstrated no breast cancer-specific survival benefit of PMRT across unselected patients with pT3N0 disease, even for patients <50 years of age.[18,19] Patients with pT3N0 disease were also included in the EORTC 22922 trial, which demonstrated a benefit of RNI in terms of any breast cancer recurrence and breast cancer mortality, with no significant difference in overall survival. However, only 3.5% of the patients had pT3 disease.[20] Given the benefit of PMRT in terms of LRR, but the limited impact on survival outcomes for patients with pT3N0 breast cancer, these patients are also included in both the SUPREMO and the TAILOR RT trials to better define the impact of PMRT in this patient population in a more modern era of systemic therapy and biologic risk stratification.

Few RCTs have evaluated PMRT in the pT1-2N0 setting.[10] A single study in patients with stage I or II triple-negative breast cancer demonstrated a relapse-free survival and OS benefit with PMRT following total mastectomy, partial axillary dissection, and adjuvant chemotherapy; however, the systemic therapy regimens used are no longer considered standard of care.[10] Additionally, 19% of patients had node-positive disease and no subset analysis was performed to determine if the benefit of PMRT was primarily in the node-positive subgroup. Overall, meta-analyses and retrospective studies of patients with pT1-2N0 breast cancer demonstrate excellent outcomes without PMRT for most patients, with reported 10-year LRR rates between 2.1% and 12.8% and the majority reporting rates of 3% to 7%.[4,21] However, these data also suggest that lymphovascular invasion (LVI), young age, high-grade disease, and positive margins increase the risk of LRR such that PMRT may be beneficial, particularly for patients with multiple high-risk features.[22]

Finally, there are no RCTs evaluating the role of RT in patients with positive or close margins following mastectomy. Positive margins, however, are consistently associated with a greater risk of local recurrence following mastectomy.[23] Recognizing the consistent reduction in local recurrence of approximately 50% with

the use of PMRT, PMRT is conditionally recommended in the setting of positive margins when this feature is considered sufficient to raise the absolute risk of local recurrence such that PMRT is deemed worthwhile for a local control benefit.[6] The extent and location of positive margins, tumor biology, consideration of other high-risk features (eg, LVI, young age, tumor grade) and plan for adjuvant therapies should be weighed together to determine the value of PMRT for an individual patient.

3.2. KQ2: Indications for PMRT with neoadjuvant systemic therapy (Table 4)

See evidence tables in Supplementary Materials, Appendix E4, for the data supporting the recommendations for KQ2 and Fig 1.

What are the indications for PMRT in patients who receive neoadjuvant systemic therapy before mastectomy?

Table 4 Indications for PMRT with neoadjuvant systemic therapy

KQ2 Recommendations	Strength of Recommendation	Quality of Evidence (Refs)
1. For patients with initial cT4 or cN2-3 breast cancer receiving neoadjuvant systemic therapy, PMRT is recommended regardless of pathologic response.	Strong	Moderate [24-28]
2. For patients with any positive lymph nodes after neoadjuvant systemic therapy (ypN+), PMRT is recommended.	Strong	Moderate [29-33]
3. For patients with positive surgical margins after neoadjuvant systemic therapy, PMRT is recommended.	Strong	Expert Opinion
4. For patients with cT1-3N1 who convert to ypN0 after neoadjuvant systemic therapy, PMRT is conditionally recommended.	Conditional	Moderate [29-32,34-41]

Abbreviations: KQ = key question; PMRT = postmastectomy radiation therapy.

Over the past decade, the use of neoadjuvant systemic therapy has increased for specific subsets of patients with breast cancer, notably those with cT2 or greater or clinically node-positive disease to downstage the breast and axilla, and in those with HER2-positive or triple negative biology.[42,43] Several studies have shown that patients with initial cT4 or cN2-3 (also defined by AJCC 6th edition as stage III) breast cancer who receive neoadjuvant systemic therapy have improved LRR with PMRT regardless of their response to neoadjuvant therapy.[24-28] Some studies have also shown an improvement in OS, but these were small retrospective evaluations.[24,25] Based on the current evidence, PMRT is recommended for patients with initial presentation with cT4 or cN2-3 disease who receive neoadjuvant systemic therapy , regardless of pathologic response.[24-28]

In addition, several studies have demonstrated that residual nodal disease after neoadjuvant systemic therapy (ypN+) is associated with an increased risk of LRR.[30,32,33] The extent of axillary nodal disease after neoadjuvant systemic therapy (ie, ypN1 vs ypN2-3) is also an important risk factor.[30,31] This risk is further

elevated in patients with T3 tumors.[32] The addition of PMRT in patients with ypN+ improves locoregional control with incremental benefit noted in patients with increased axillary burden.[31,33] An OS benefit for PMRT has been reported for patients with ypN2-3 disease.[31] It is worth noting that the benefit of PMRT for residual nodal disease in these studies was evaluated in the setting of axillary nodal dissection. Results from ongoing trials such as Alliance A011202 (*NCT01901094)* will further clarify the impact of axillary nodal dissection compared with sentinel lymph node biopsy alone after neoadjuvant systemic therapy.

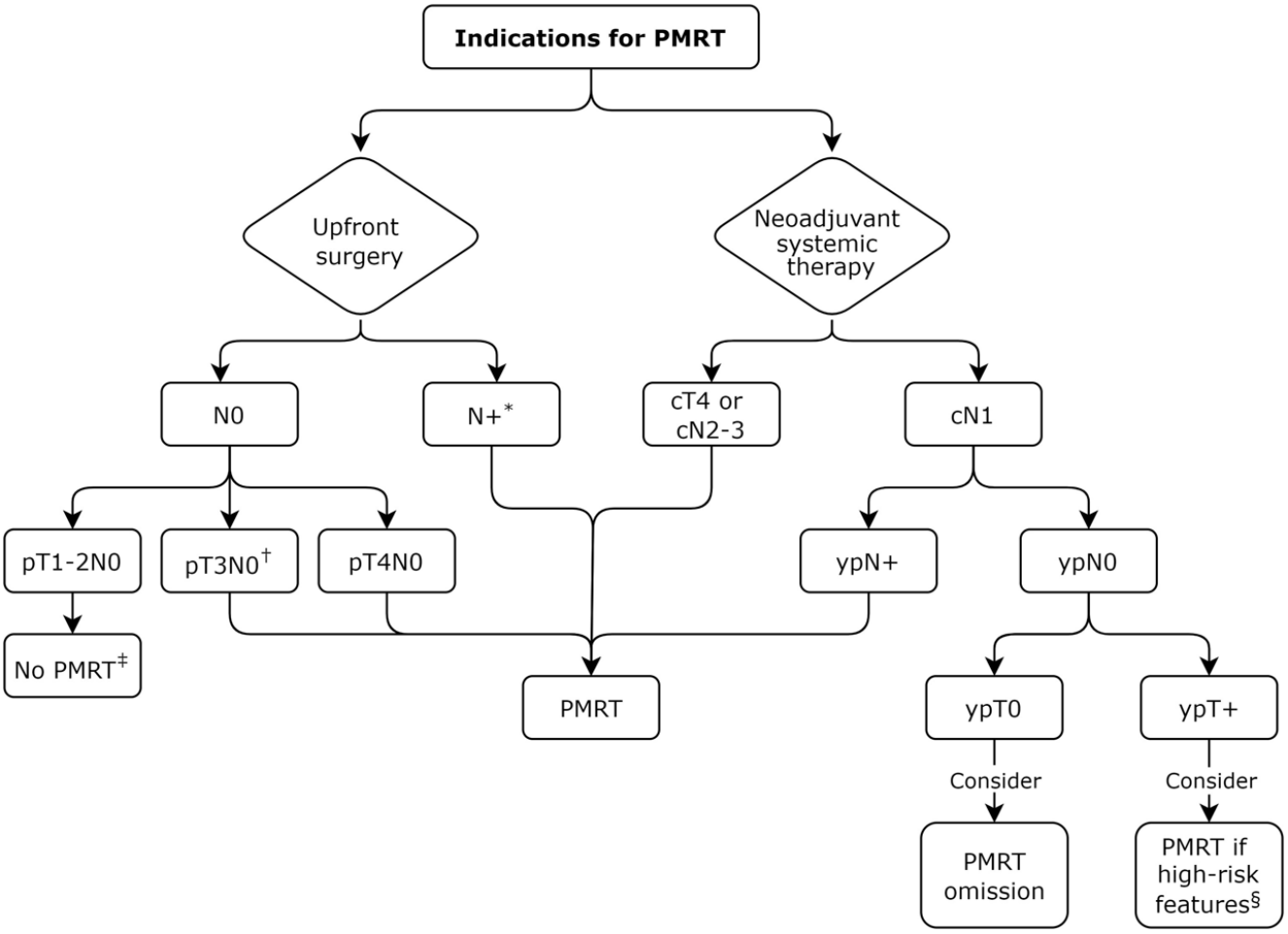
There are limited data to inform PMRT recommendations for patients with positive surgical margins after neoadjuvant therapy. However, given that positive margins are an indication for PMRT in the upfront surgery setting,[23] PMRT is also recommended for positive margins after neoadjuvant systemic therapy based on expert opinion.

In patients who begin treatment with clinically involved mobile axillary lymph nodes (cN1) but convert to being pathologically node-negative after neoadjuvant systemic therapy (ypN0), the full reporting of NSABP B51/RTOG1304 (*NCT01872975*) will help to resolve the clinical equipoise that exists on the use of PMRT and regional nodal irradiation (RNI) in this setting. Data from a 2022 prospective Dutch registry reported a low LRR of 2.1% at 5 years without PMRT, supporting de-escalation of PMRT in patients with ypN0 disease after neoadjuvant systemic therapy.[44] Another pooled analysis showed a 5-year LRR rate of 3% after mastectomy without PMRT in patients with HER-2 positive disease achieving ypN0.[33] LRR risks may be particularly modest for patients with cN1 breast cancer who manifest a pathologic complete response in both the breast and the lymph nodes (ypT0N0), such that the risks of PMRT may outweigh the benefits. However, certain features appear to increase the risk of LRR and may suggest a benefit with PMRT. For example, several reports have suggested that baseline clinicopathologic factors including young age, cT3-4 disease, triple-negative subtype, LVI, and high-volume clinical nodal disease may predict higher rates of LRR so PMRT is conditionally recommended in patients with multiple high-risk factors.[25,30,32,38,39,45] Similarly, post neoadjuvant systemic therapy /postoperative factors (eg, high-volume residual disease in the breast, the presence of LVI, and close or involved margins) may be indications for PMRT after neoadjuvant systemic therapy based on demonstrably higher risks of LRR on multivariable analyses.[31,34,36,40,41] The benefits of PMRT may be higher in younger women compared with older women.[24,39] In a retrospective study of young women (age <35 years) who received neoadjuvant anthracycline-based chemotherapy, the use of PMRT reduced LRR and improved OS;[24] this finding is consistent with a study from Korea that found age ≤40 years to be an independent predictor of LRR.[39]

Lack of pathologic complete response (ie, residual disease) in the breast, particularly in triple-negative breast cancers, is associated with higher rates of LRR.[29,30,34,46,47] Additionally, among patients who achieve a pathologic complete response in the lymph nodes (ypN0), PMRT was associated with a significantly improved

5-year LRR-free survival for patients with triple-negative breast cancer compared with other histologies (91.9% vs 75.0%).[36] Although several retrospective studies have shown similar LRR-free survival rates with and without PMRT after achieving ypN0,[39,41] a meta-analysis including 12 studies of over 17,000 patients who achieved a pathologic complete response in the lymph nodes (ypN0) demonstrated a benefit with PMRT, particularly in patients with stage III breast cancer.[27]

Figure 1 Indications for PMRT



Abbreviation: LVI = lymphovascular invasion; PMRT = postmastectomy radiation therapy.

*PMRT may be omitted for select patients with low volume, node-positive (pN+) disease after axillary dissection at low risk for locoregional recurrence.

†PMRT may be omitted for select patients with low-risk disease.

‡Select patients with pT1-2N0 breast cancer at high-risk for locoregional recurrence may be suitable for PMRT.

§High-risk features include age <40 years, cT3, LVI, or triple negative subtype.

3.3. KQ3: PMRT treatment volumes and dose-fractionation regimens (Table 5)

See evidence tables in Supplementary Materials, Appendix E4, for the data supporting the recommendations for KQ3 and Fig 2.

What are the appropriate treatment volumes (eg, chest wall/reconstructed breast, regional nodes, boost) and dose-fractionation regimens for patients who receive PMRT?

Table 5 PMRT treatment volumes and dose-fractionation regimens

KQ3 Recommendations	Strength of Recommendation	Quality of Evidence (Refs)
1. For patients receiving PMRT, treatment to the ipsilateral chest wall/reconstructed breast and regional lymphatics (ie, axilla at-risk, supraclavicular, and IMN) is recommended. Implementation remarks: • Treatment to the chest wall/reconstructed breast alone may be used in select patients. • Coverage of the IMN may be individually determined based on location and size of the tumor and extent of nodal involvement.	Strong	High 4,9,48-51
2. For patients *without* breast reconstruction receiving PMRT, conventional fractionation (5000 cGy in 25 fractions) or moderate hypofractionation (4005-4256 cGy in 15-16 fractions) is recommended.	Strong	High 52-59
3. For patients *with* breast reconstruction receiving PMRT, conventional fractionation (5000 cGy in 25 fractions) is recommended.	Strong	High 20,48,51,52,54-57,60
4. For patients *with* breast reconstruction receiving PMRT, moderate hypofractionation (4005-4256 cGy in 15-16 fractions) is conditionally recommended.	Conditional	Low 61
5. For patients with T4 breast cancer or close/positive margins receiving PMRT, a boost to the chest wall/scar is conditionally recommended.	Conditional	Low 55,57,61-65
6. For patients with nodal disease not surgically addressed and at risk for residual disease, a nodal boost is recommended.	Strong	Expert Opinion

Abbreviations: IMN = internal mammary nodes; KQ = key question; PMRT = postmastectomy radiation therapy.

In the EBCTCG meta-analysis of 8135 women pooled from trials comparing PMRT, inclusive of the chest wall and regional lymph nodes, with surgery alone, PMRT significantly reduced both LRR, overall recurrence and breast cancer mortality, with the chest wall being the most common site of LRR.[4] The meta-analysis also included 8 trials that did not include the chest wall in the treatment fields (ie, only treated the regional lymph node basins) and found that RT in those studies did not have a significant impact on overall recurrence or breast cancer mortality. As 50% to 80% of all local recurrences identified in RCTs were located in the chest wall,[7,13] inclusion of the chest wall as a PMRT target structure is recommended regardless of surgical margins, although direct comparisons of RT with versus without chest wall volumes is limited.

Several large, RCTs have evaluated the value of RNI in patients with medially- or centrally-located tumors, positive lymph nodes, or in patients with high-risk node-negative breast cancer.[20,48,66] The European Organization for Research and Treatment of Cancer (EORTC) 22922 trial randomly assigned patients who had centrally or medially located primary tumors, irrespective of axillary involvement, or laterally located tumors with axillary involvement, to either whole breast/chest wall irradiation in addition to comprehensive RNI (inclusive of the IMN) or whole breast/chest wall irradiation alone.[48] Approximately one-quarter of these patients were treated with mastectomy. At 10 years, the addition of RNI resulted in a significantly improved breast cancer mortality rate, improved DFS, and a trend toward improved OS. The 15-year results continued to demonstrate a significant reduction of breast cancer mortality and any breast cancer recurrence with the addition of IMN/supraclavicular irradiation in patients with stage I-III breast cancer.[20] The Canadian Cancer Trials Group MA.20 trial also evaluated the addition of RT of the supraclavicular lymph nodes, axillary apical lymph nodes, and the IMNs for patients with node-positive disease or high-risk node-negative disease.[66] Although it did not include patients treated with mastectomy, it did demonstrate that the addition of comprehensive RNI reduced the rate of any breast cancer recurrence, further supporting the use of comprehensive RNI when defining target coverage for patients with node-positive or high risk node-negative breast cancer. For those patients who have undergone an axillary dissection and receive PMRT, data do not support a benefit to including the dissected stations of the axilla, typically axillary levels I and II; however, an increasing number of studies support the omission of axillary lymph node dissection after a positive sentinel lymph node biopsy and in these circumstances, coverage of all axillary nodal basins is advised.[4,7,67]Although it is a departure from traditional PMRT to irradiate the chest wall without inclusion of the regional lymph node stations, this approach may be considered in patients with positive surgical chest wall margins or large tumors in the absence of lymph node involvement or other high-risk factors given the concern for local over regional recurrences in this patient population.[4]

While comprehensive RNI in the EORTC 22922 and MA.20 trials included treatment of the IMNs, there is debate as to which patients might benefit most from IMN irradiation, particularly with the higher cardiopulmonary exposure with this approach and the potential for increased toxicity.[20,66] The benefit of IMN RT was specifically evaluated in studies from Denmark, France, and South Korea in which patients with breast cancer were treated with whole breast or chest wall RT, supraclavicular, and axillary apex irradiation with or without IMN RT.[49-51] The DBCG trial was a prospective, nonrandomized population-based cohort study that assigned IMN irradiation only to patients with right-sided disease to mitigate concerns for cardiac RT exposure among patients with left-sided cancer.[49] This study demonstrated a significant improvement in distant recurrence, death from breast cancer, and a 4.7% improvement in overall survival at 15 years among right-sided patients who received IMN RT. A French RCT enrolled patients with positive axillary lymph nodes or

central/medial tumors with or without positive axillary lymph nodes, randomly assigning patients to receive RT to the chest wall and supraclavicular nodes with or without IMN RT.[50] This study did not demonstrate an OS benefit for IMN RT. However, in subgroups with a high risk of IMN involvement, including patients with medial or central tumors and positive axillary lymph nodes, a small benefit was observed in favor of IMN RT. Finally, the Korean Radiation Oncology Group (KROG) 08-06 trial similarly randomized patients with pathologically confirmed, node-positive disease after mastectomy or breast conservation surgery with axillary lymph node dissection to RNI with or without IMN RT.[51] The study demonstrated a 2.6% absolute decrease in distant metastases without a significant improvement in DFS. However, in a subgroup analysis of patients with medial or centrally located tumors, both DFS and breast cancer-specific mortality at 7 years was significantly improved with the addition of IMN RT, suggesting that IMN RT in this subgroup of patients is beneficial.[51] Importantly, none of these trials, nor the aforementioned RNI studies, demonstrated an increased risk of cardiac toxicity with treatment of the IMNs, lending support for the routine inclusion of IMN RT for patients with clinically or radiographically detected IMN nodes and those with central or medially located breast tumors, particularly when axillary lymph nodes are positive.[48-51,66]

Most of the studies evaluating PMRT have largely used conventional fractionation with doses approximating 5000 cGy, EQD2.[9] However, there are emerging data on the safety and efficacy of moderately hypofractionated PMRT. A number of retrospective analyses have suggested that hypofractionated PMRT regimens result in reduced acute and late toxicity compared with conventional regimens, with comparable survival outcomes.[55,57,61,68-70] There is also some precedent from RCTs to support the use of moderately hypofractionated regimens. In the landmark British Columbia study, 3750 cGy in 16 fractions was used to deliver PMRT.[9] Additionally, the United Kingdom START (Standardization of Breast Radiotherapy) B trial involved 2215 women with breast cancer, with approximately 8% receiving PMRT. They found that 4000 cGy in 15 fractions over 3 weeks yielded comparable outcomes in terms of locoregional tumor control and late normal tissue effects, as assessed by patient and physician-reported arm and shoulder symptoms, to the standard regimen of 5000 cGy in 25 fractions over 5 weeks.[59] In China, a noninferiority study involving 820 randomized patients compared moderate hypofractionation (15 fractions) with conventional fractionation (25 fractions), demonstrating similar efficacy and toxicity profiles between the 2 approaches.[53] An additional RCT confirmed that there were no discernible differences in toxicities, LRR, distant failure rate, or DFS between PMRT regimens of 4000 cGy in 15 fractions and 5000 cGy in 25 fractions.[54]

None of these trials were specifically designed to evaluate the impact of hypofractionation on cosmetic outcomes in the setting of breast reconstruction. As such, there has been hesitancy to transition to shorter treatment schedules for patients who opt for breast reconstruction, but there are increasing data forthcoming to support its use.[61,68] The phase 3 FABREC (Fractionated Accelerated Boost Radiotherapy in

Breast Conservation) trial randomized 400 patients after mastectomy with implant-based reconstruction to hypofractionated RT (4256 cGy over 3 weeks) or conventional RT (5000 cGy over 5 weeks).[71,72] The primary endpoint was improvement in the FACT-B (Physical Well-Being domain of Functional Assessment of Cancer Therapy-Breast) at 6 months. Results showed that 7.7% of patients in the conventionally-fractionated arm required a treatment break (average = 3.3 days), as compared with 2.7% of patients in the hypofractionated arm (average = 2.8 days).[71,72] Another completed RCT, Alliance A221505 (RT CHARM: Hypofractionated Post Mastectomy Radiation with Breast Reconstruction; *NCT03414970*) randomized patients undergoing mastectomy with immediate or delayed reconstruction to hypofractionated PMRT (4256 cGy in 16 fractions) or conventional PMRT (5000 cGy in 25 fractions) with a primary endpoint of reconstruction complication rate.[61,68] We expect the published results of both trials to inform practice.

Evidence supporting the administration of a chest wall scar boost to improve local control rates is limited and has never been established prospectively. Although the majority of locoregional recurrences after mastectomy occur on the chest wall,[7] only retrospective studies have examined the use of chest wall boosts for high-risk patients and have provided some support for doses up to 6600 cGy using conventional fractionation.[73-76] Despite this, a survey among breast radiation oncologists demonstrated that 55% routinely use a chest wall boost following PMRT and an additional 18% prescribe a boost depending on margin status.[77] Pragmatically, the administration of a chest wall boost is conditionally recommended in cases of T4 disease and positive margins where concern for residual disease is enhanced.

Similarly, there are no randomized studies examining the use of a boost to gross disease in undissected nodal basins, such as the supraclavicular fossa or internal mammary chain, despite recognition that involvement of these nodes is a poor prognostic factor in breast cancer.[49,50] A single institutional retrospective analysis suggested that an additional boost to involved supraclavicular and internal mammary chain nodes can be delivered safely and may improve local control rates, but these data are limited by small sample sizes.[78]

3.4. KQ4: Appropriate PMRT delivery techniques (Table 6)

See evidence tables in Supplementary Materials, Appendix E4, for the data supporting the recommendations for KQ4 and Fig 2.

KQ4: What are the appropriate techniques (eg, 3-D CRT, IMRT, protons, breath hold, bolus) for treating patients who receive PMRT?

Table 6 Appropriate PMRT delivery techniques

KQ4 Recommendations	Strength of Recommendation	Quality of Evidence (Refs)
1. For patients receiving PMRT, CT-based volumetric treatment planning with 3-D CRT is recommended.	Strong	High 20,49-51,79-82

2. For patients receiving PMRT, IMRT including VMAT, is recommended when 3-D CRT is unable to achieve treatment goals (ie, target coverage and normal tissue avoidance). Implementation remark**:** Use of IMRT, including VMAT, may increase OAR low-dose exposure compared with 3-D CRT.	Strong	Low 83-87
3. For patients receiving PMRT, deep inspiration breath hold is recommended when lower doses to the heart can be achieved compared with free breathing. Implementation remark: Other cardiac sparing techniques may be used.	Strong	Moderate 83,88,89
4. For patients receiving PMRT treated with IMRT, including VMAT, daily image guidance is recommended.	Strong	Expert Opinion
5. For patients with cT1-3 breast cancer receiving PMRT, the routine use of tissue-equivalent bolus is not recommended. Implementation remark: Bolus may be used in circumstances where improved dosimetric coverage of the skin is desired.	Strong	Moderate 90-95
6. For patients with T4 breast cancer, the use of tissue-equivalent bolus is recommended.	Strong	Expert Opinion

Abbreviations: 3-D CRT = 3-dimensional conformal radiation therapy; CT = computed tomography; IMRT = intensity modulated radiation therapy; KQ = key question; OAR = organ at risk; PMRT = postmastectomy radiation therapy; VMAT = volume-modulated arc therapy.

High-quality evidence from RCTs directly evaluating various RT techniques for PMRT is limited, and most foundational studies used 2-D or 3-D photon therapy, with or without an electron component.[6,9,20,49-51,81,82,96] Modern RT design is based on contouring of the target areas (chest wall and nodal basins as indicated) and the adjacent relevant organs at risk (OARs) as appropriate (ie, heart, left anterior descending [LAD] artery or right coronary artery, bilateral lungs, contralateral breast, spinal cord, thyroid, esophagus and/or brachial plexus).[97,98] Use of contouring guidelines, such as those provided by the RTOG atlas, RADCOMP (Radiotherapy Comparative Effectiveness),[97] and European atlases,[98] may be used to assist with accurate target and OAR delineation. The goal of volumetric treatment planning is to use the computed tomography (CT) information to adequately cover the target volumes while minimizing dose to normal tissues, taking individual anatomic variation into account. While this approach has historically been underutilized in RT treatment planning for breast cancer compared with other organ sites, CT-based volumes should be used for individualized breast RT planning.[20,49-51,79-82]

For PMRT field design, 3-D conformal radiation therapy (3-D CRT) treatment planning can use a variety of techniques, for example, partially wide tangent fields to include the IMN contour, a medial electron field matched to narrow photon tangents, or electrons to the chest wall alone with a match to a photon

supraclavicular field with or without a posterior axillary field.[99] Advanced planning techniques (eg, intensity modulated radiation therapy (IMRT), including VMAT), can be used to improve high-dose conformality and target coverage. Studies evaluating treatment of patients with breast cancer using tomotherapy or VMAT have also shown feasibility.[100,101] Studies comparing various techniques have shown low LRR rates regardless of technique.[55,80,81,84]

Treatment with IMRT/VMAT can also decrease the high-dose exposure of OARs compared with 3-D CRT, and in some cases decrease the risk of toxicity.[55,87,102] A retrospective study of patients receiving PMRT comparing 3-D CRT with VMAT reported a reduction in RT pneumonitis in the cohort treated with VMAT.[55] Another study demonstrated that adequate target coverage was achieved with both 3-D CRT and IMRT, with a decrease in moist desquamation in the cohort treated with IMRT (14.3% vs 3.8%, respectively).[87] A third study described a decrease in moderate and high dose exposure to the shoulder in patients undergoing RNI with IMRT compared with 3-D CRT.[102] One potential trade-off of reduced high-dose exposure to OARs with IMRT/VMAT is an increase in low-dose OAR exposure. For example, one study described acute radiation-induced nausea associated with low-dose exposure of the upper abdominal structures,[103] side effects that are uncommon with 3-D CRT. Therefore, the technique used (eg, 3-D CRT versus IMRT/VMAT) should be selected on an individual basis based on what optimizes target coverage and normal tissue avoidance, as appropriate.

Historically, a key cause of noncancer related morbidity and mortality from PMRT came from undue cardiac exposure. Therefore, numerous studies comparing treatment planning techniques have done so with the goal of improving cardiac sparing.[104,105] Although a dose dependent relationship between cardiac exposure to RT and heart disease has been demonstrated in several landmark studies,[106-110] no safe threshold has been established to prevent major cardiovascular events. Therefore, it is generally accepted that mean heart dose should be as low as reasonably achievable. Special consideration should be given to minimizing RT exposure to the heart for patients with pre-existing heart disease and certain risk factors (eg, diabetes, hypertension, and smoking), as these have been shown to be synergistic with cardiac RT exposure in increasing the risk of cardiac disease development.[111,112]

A deep inspiration breath hold (DIBH) technique is one strategy for reducing dose to the heart. Suitability for DIBH should be evaluated based on patient tolerance and individual cardiac anatomy.[88,89] Among patients for whom DIBH can be successfully implemented, cardiac and cardiac substructure dose can be reduced compared with a free-breathing 3-D CRT technique.[88] Notably, there is an understanding that dose exposure to cardiac substructures including the left ventricle and the LAD artery do not correlate with mean heart dose. Both have been implicated in RT-associated cardiac toxicity in patients receiving RT for breast cancer, so particular consideration should be given to these substructures.[109,113] An RCT comparing IMRT-DIBH with free-breathing 3-D CRT for patients with node-positive breast cancer showed lower mean doses for the

ipsilateral lung, heart and LAD artery, suggesting that patients receiving IMRT can also benefit from DIBH.[83] Although there was no difference in single-photon emission CT perfusion defects in the LAD territory or lung perfusion/function between groups, most patients in the IMRT-DIBH arm had stable or improved left ventricular ejection fraction at 1 year compared with a slightly declining left ventricular ejection fraction in the free-breathing cohort.[83]

The use of proton therapy remains under investigation at the time of guideline development. Single institution series, prospective registry reports, and retrospective studies have demonstrated improved dosimetric target coverage, alongside preservation of cardiac function, over 3-D CRT and IMRT, particularly in the setting of RNI, including IMN irradiation.[114-118] The RADCOMP trial evaluating major cardiac events between patients treated with proton versus photon RT completed accrual in April 2024 and it is anticipated that these results will provide more data on the appropriate role of proton PMRT in the future.[97]

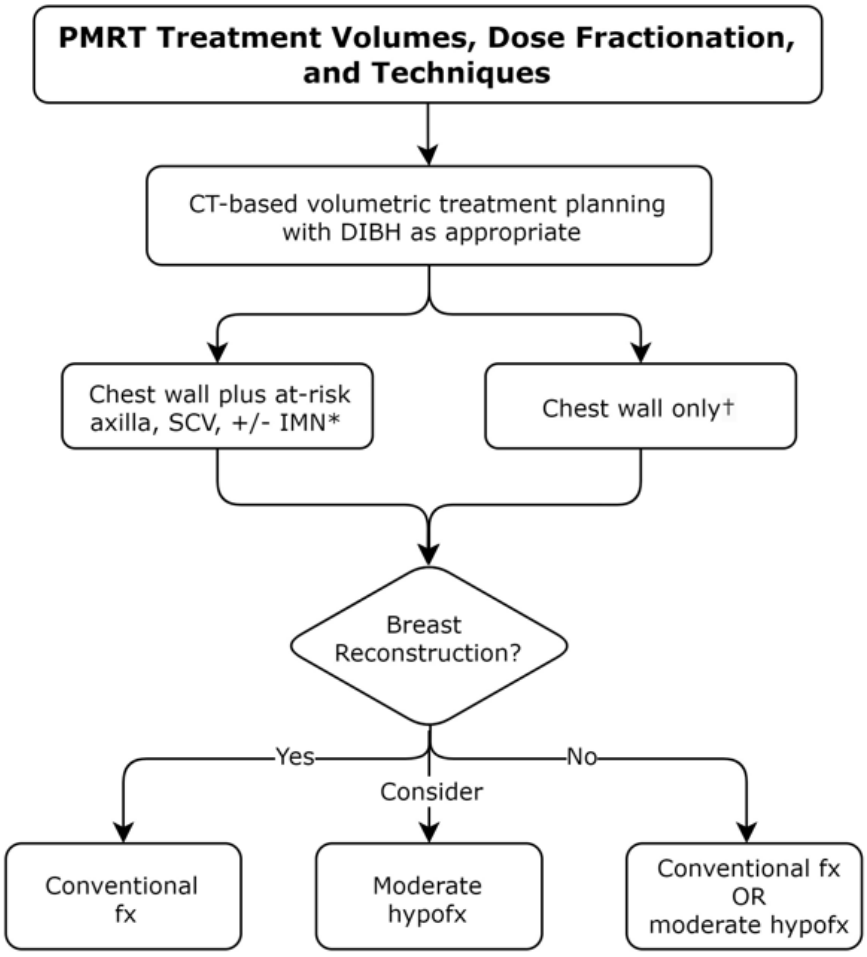
There is currently a lack of evidence to support an optimal strategy for image guidance in the PMRT setting. Minimally, daily planar imaging is recommended for patient localization when an intensity modulated delivery technique is used; however, this is based on expert opinion since there are limited data.[119,120] Volumetric imaging (eg, cone beam CT) can be acquired during treatment to assess for significant anatomic changes or set up variability that may adversely affect treatment accuracy. However, the planning target volume margins should account for set-up variability and the type and frequency of image guidance used during treatment.[121]

Additionally, there is some evidence that surface guided radiation therapy (SGRT) using the patient's external surface and nonionizing RT can assist in PMRT patient setup,[88,122] monitor intrafraction motion[123] and verify breath hold position.[88,122] However, in addition to training and workflow issues,[124] significant tissue deformations and limitations in the technology to detect darker skin tones have been identified as drawbacks of these systems.[125] Currently, data are lacking to support the use of SGRT alone without image guidance. ESTRO-ACROP offers guidance for use of SGRT with image guidance, including common challenges and potential errors.[124]

Finally, tissue equivalent bolus has historically been used in PMRT with the recognition that most chest wall recurrences occur superficially or just under the skin. The skin and most superficial layer of chest wall tissue are key components of the RT target and depending on the RT technique and beam energy used, surface dose may only reach 70% to 80% of the prescribed dose. Tissue equivalent bolus can be used to bring the skin dose closer to prescription dose. However, the application of tissue equivalent bolus over the chest wall in PMRT can vary with respect to frequency and thickness, and several clinical trials have permitted bolus at the discretion of the treating physician,[71,126,127] thereby limiting the ability to formally evaluate the impact of bolus on clinical outcomes to help guide recommendations for the use of bolus with PMRT.

Multiple studies have identified a relationship between the use of bolus and increased skin toxicity.[90,91,93-95] At the same time, despite the historical assumption of benefit, the impact of bolus on local control has been questioned, including 3 small retrospective studies none of which identified a local control benefit with bolus.[93-95] One RCT of 59 patients, employing a risk stratified bolus strategy with thicker and more frequent use of bolus in patients with frank skin involvement and no bolus versus 5 mm bolus on alternate days in standard-risk patients without skin involvement, found no decrement in chest wall local control within risk groups, although all patients in the high-risk group were treated with bolus.[90] Although these analyses are limited by patient and treatment heterogeneity, they suggest insufficient evidence for a local control benefit with the routine use of bolus for patients with cT1-3 disease without a high risk of skin involvement.[94,95] In these patients, bolus may be used in circumstances where improved dosimetric coverage of the skin is desired. However, for those patients with an increased risk of skin recurrence, including patients who present with T4 breast cancer, or other risk factors including dermal lymphatic invasion or extensive LVI, the use of bolus is recommended based on expert opinion.[90]

Figure 2 PMRT treatment volumes, dose fractionation, and techniques



Abbreviations: CT = computed tomography; DIBH = deep inspiration breath hold; fx = fractionation; hypofx = hypofractionation; IMN = internal mammary nodes; PMRT = postmastectomy radiation therapy; RNI = regional nodal irradiation; SCV = supraclavicular lymph nodes.
*Treatment to the chest wall/reconstructed breast alone may be used in select patients.
†RNI is an option for T3N0 with high-risk features or T1-2 central or medially located cancer.
Conventional fx = 5000 cGy in 25 once daily fx of 200 cGy.
Moderate hypofx = 4005-4256 cGy in 15-16 once daily fx of 266-267 cGy.

4. Conclusions and Future Directions

Multiple RCTs and the EBCTCG meta-analysis have confirmed that PMRT reduces the risk of LRR and improves breast cancer mortality for patients with high-risk disease. However, the absolute risk reduction varies across individuals. There are ongoing efforts to try to better characterize risk according to tumor biology and in the era of tailored systemic therapy to personalize treatment recommendations. Unfortunately, there are little data from available clinical trials to guide tailored management recommendations for patients based on sociodemographic characteristics, including race and access to health care. Future trials addressing some of these potentially important characteristics are needed.

In addition, there are several potentially practice changing trials that remain in active accrual or have not yet been published at the time of this guideline (SUPREMO, RT CHARM [*NCT03414970*], NSABP B-51 [*NCT01872975*], RADCOMP [*NCT02603341*], MA.39/TAILOR-RT [*NCT03488693*]) that will likely have influence on the recommendations provided above and future clinical practice.

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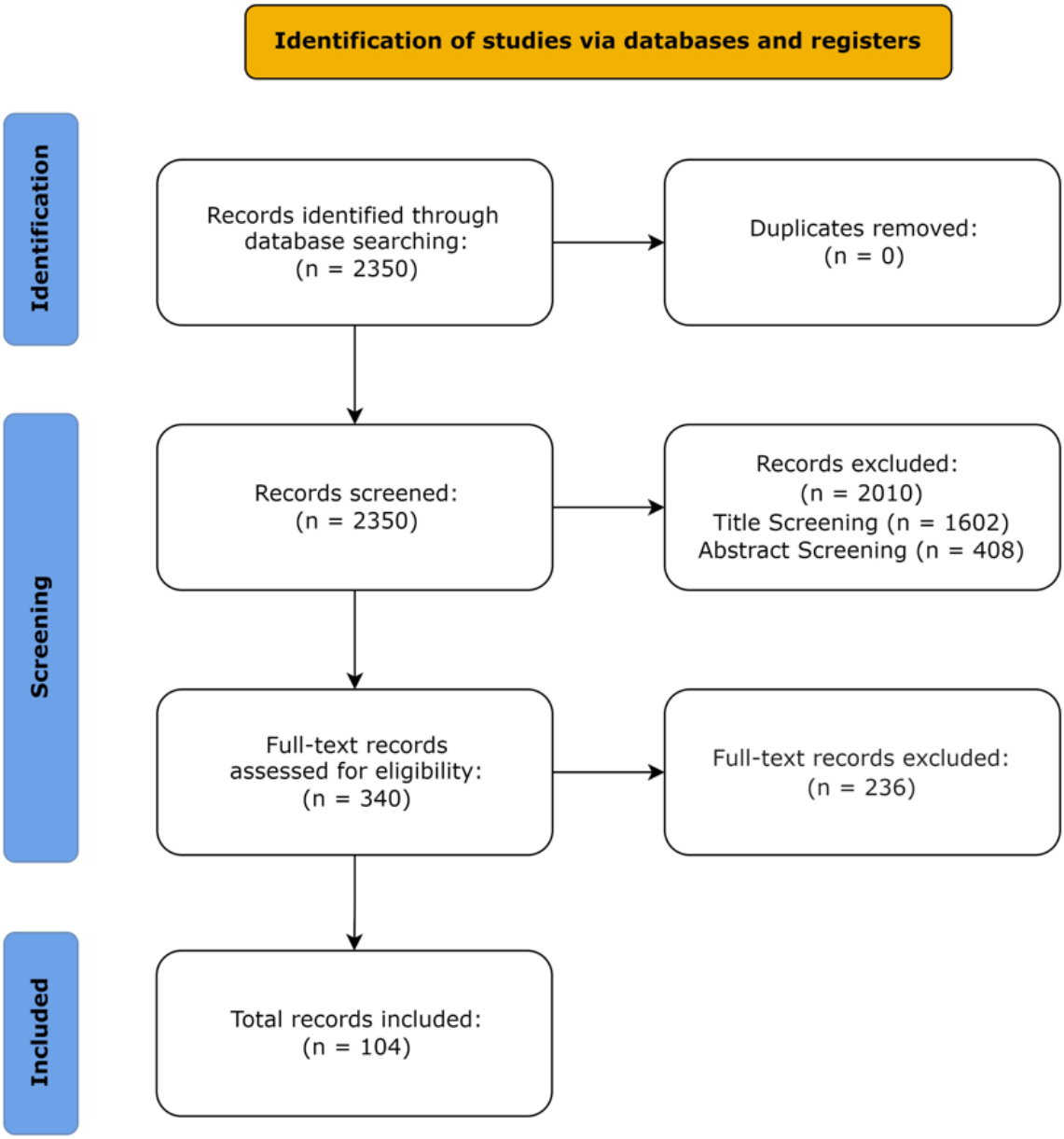

PRISMA 2020 Study Selection Diagram[128,129]

Abbreviation: PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

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Appendix E1 Peer Reviewers and Disclosures (Comprehensive)

Inserted after peer review

Appendix E2 Abbreviations

3-D CRT = 3-dimensional conformal radiation therapy
cGy = centigray
CT = computed tomography
DFS = disease-free survival
DIBH = deep inspiration breath hold
IMN = internal mammary nodes
IMRT = intensity modulated radiation therapy
KQ = key question
LAD = left anterior descending
LRR = locoregional recurrence
LVI = lymphovascular invasion
OAR = organ at risk
OS = overall survival
PICOTS = Population, Intervention, Comparator, Outcome, Timing, Setting framework
PMRT = postmastectomy radiation therapy
RNI = regional nodal irradiation
RT = radiation therapy
RCT = randomized controlled trial
SGRT = surface guided radiation therapy
VMAT = volume modulated arc therapy

Appendix E3 PICOTS Questions / Literature Search Strategy

Search Limits:

Search Date(s):	10/3/2023
Age Range	Adult (≥18 years old)
Language	English only
Species	Humans
Publication Types	RCTs (≥50 patients) Meta-analyses (≥50 patients) Prospective studies (≥100 patients) Retrospective studies (≥100 patients for KQs 2, 3, & 4; KQ1 excluded all retrospective studies)
Timeframe	1/1/2005-10/3/2023

Universal Exclusion Criteria:

1. Pre-clinical/non-human studies
2. Health economics/cost analysis studies
3. Studies available in abstract only
4. Publication types: letters, editorials, discussions, comments/commentary, guidelines, review articles, case reports, surveys
5. Pediatric patients
6. SEER, SEER-Medicare, and National Cancer Database (NCDB) studies
7. Palliative or noncurative treatment
8. Metastatic cancer
9. Recurrent disease, unresectable
10. Intraoperative care
11. Phyllodes and sarcoma
12. Ductal carcinoma in situ (DCIS)

Item	Details
Key Question and PICO(TSS) Framework	
Key clinical question(s)	**Key Question 1:** What are the indications for PMRT in patients who receive mastectomy as their initial treatment for breast cancer?
Definitions	PMRT includes treatment to the chest wall and regional nodes (undissected axilla, Supraclavicular +/- IMNs)
Participants/ population	Patients treated with mastectomy *as the initial treatment for breast cancer.* Patients receiving RNI who have had mastectomy
Intervention(s)/ exposure(s)	PMRT: Chest wall and RNI (undissected axilla, supraclavicular, +/- internal mammary nodes (IMNs)) Chest wall RT without RNI
Comparator/ control	No PMRT
Outcomes: primary/critical	Local recurrence Regional recurrence Locoregional recurrence Disease-free survival

	Breast cancer mortality Distant metastasis-free survival Overall survival
Timing	Adjuvant
Setting/context	Any
Study design	RCTs (≥50 patients) Meta-analysis (≥50 patients) Prospective NR studies (≥100 patients)
Summary of the key selection criteria	**Inclusion criteria:** Adults ≥18 years with breast cancer treated with mastectomy as initial treatment Invasive breast cancer **Exclusion criteria:** Retrospective studies Universal exclusion criteria above Treatment with neoadjuvant/preoperative systemic therapy
Validation Set	PMID: 15657341 (British Columbia Study), PMID: 35288227 (Overgaard 82b/c), PMID: 24656685 (EBCT-2014), PMID: 16360786 (2015), PMID: 33152277 (EORTC- more results, less technique), PMID: 17306393 (subgroup analysis of Danish 82B/C for 1-3 LNs+), PMID: 24656685 (EBCTCG), PMID: 21852010 (RCT-Adj chemo/RT in triple-neg BC)

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Item	Details
Key Question and PICO(TSS) Framework	
Key clinical question(s)	**Key Question 2:** What are the indications for PMRT in patients who receive neoadjuvant systemic therapy?
Definitions	Neoadjuvant systemic therapy includes the use of chemotherapy, immunotherapy, or endocrine therapy before surgery. Concurrent systemic therapy is delivered during PMRT. Neoadjuvant=preoperative
Participants/ population	Adult patients with breast cancer who receive systemic therapy (chemotherapy, immunotherapy, or endocrine therapy) before undergoing mastectomy +/- use of concurrent therapies during PMRT
Intervention(s)/ exposure(s)	PMRT after neoadjuvant systemic therapy
Comparator(s)/ control	No PMRT after neoadjuvant systemic therapy RT alone
Outcomes: primary/critical	Toxicity Local recurrence Regional recurrence Locoregional recurrence Disease-free survival Breast cancer mortality Distant metastasis-free survival Overall survival
Timing	Adjuvant
Setting/context	Any
Study design	RCTs MAs Prospective NR studies (≥100 patients) Retrospective studies (≥100 patients) - (so that we capture the MDACC series listed in the validation set – e.g., Huang et al and McGuire et al)
Summary of the key selection criteria	**Inclusion criteria:**

	Patients with breast cancer treated with systemic therapy before mastectomy +/- concurrent with PMRT Invasive breast cancer **Exclusion criteria:** Patients with breast cancer who have mastectomy as the initial treatment.
Validation Set	PMID: 17418973 (McGuire MDA), PMID: 15570071 (Huang, MDA), PMID: 23032615 (Mamounas), PMID: 35952707 (neoadjuvant), PMID: 33564308 (neoadjuvant), PMID: 26130454 (neoadjuvant), PMID: 32407932 (neoadjuvant), PMID: 24161425 (neoadjuvant), PMID: 17855016 (neoadjuvant, age <35 y), PMID: 21885207 (neoadjuvant, cT3N0), PMID: 21377284 (ypN0)

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Item	Details
Key Question and PICO(TSS) Framework	
Key clinical question(s)	**Key Question 3:** What are the appropriate dose-fractionation regimens and treatment volumes (eg, chest wall, regional nodes, boost) for patients who receive PMRT?
Definitions	Radiation total dose and dose per fraction defines the prescription of radiation advised. Target volumes pertain to the areas of tissue intended to receive radiation dose.
Participants/ population	Patients with breast cancer who undergo mastectomy.
Intervention(s)/ exposure(s)	A. Hypofractionation B. Boost – scar boost only (may need retrospective studies, ≥100 patients) C. Chest wall without RNI D. RNI including IMNs
Comparator(s)/ control	A. Conventional fractionation B. No boost C. PMRT with comprehensive RNI D. RNI without IMNs
Outcomes: primary/critical	Local recurrence Regional recurrence Locoregional recurrence Disease-free survival Breast cancer mortality Distant metastasis free survival
Timing	Adjuvant
Setting/context	Any
Study design	RCTs MAs Prospective NR studies (≥100 patients) Retrospective data (≥100 patients)
Summary of the key selection criteria	**Inclusion criteria:** Invasive breast cancer Dose-fractionation regimens RNI Use of chest wall boost **Exclusion criteria:** Universal exclusion criteria above
Validation Set	PMID: 26598752 (DBCG-IMN), PMID: 28459606 (Khan JCO 2017), PMID: 30711522 (Wang 2019, hypofx), PMID: 35394824 (Thorsen), PMID: 34695841 (Kim-IMNs), PMID: 34102286 (bolus SR), PMID: 28459606 (hypofractionation PMRT), PMID: 31055108 (boost), PMID: 30926576 (electrons and bolus), PMID: 32289474 (5 y update of hypofx PMRT ph II), PMID: 33485893 (bolus), PMID: 36594077 (bolus, RCT), PMID: 31952507 (helpful for refs cited), PMID: 25835623 (bolus & skin toxicity), PMID: 23664327 (+/- IMN French IMN), PMID: 33152277-orig study

Item	Details
Key Question and PICO(TSS) Framework	
Key clinical question(s)	**Key Question 4:** What are the appropriate treatment techniques (eg IMRT, 3-D CRT, proton, breath hold, respiratory gating) for treating patients who receive PMRT?
Definitions	IMRT and 3-D CRT are treatment planning techniques. Breath hold and gating are techniques to help minimize dose to the heart and lung.
Participants/ population	Patients with breast cancer who undergo mastectomy and receive PMRT.
Intervention(s)/ exposure(s)	Setup verification, image guidance/surface guidance Respiratory management, gating, breath hold IMRT (VMAT) Use of electrons Use of protons Use of Bolus Will possibly include general info in text re toxicity related to resp mgmt., IMRT, protons
Comparator(s)/ control	PMRT with photons 3-D CRT No bolus
Outcomes: primary/critical	Local recurrence Regional recurrence Locoregional recurrence Disease-free survival Breast cancer mortality Distant metastasis free survival Toxicity and adverse effects (cardiac and pulmonary/radiation pneumonitis)
Timing	Adjuvant
Setting/context	Any
Study design	RCTs MAs Prospective NR studies (≥100 patients) Retrospective studies (≥100 patients)
Summary of the key selection criteria	**Inclusion criteria:** RT techniques (3-D CRT or IMRT) RT modalities (photons, electrons, protons) Set up verification techniques Respiratory management techniques Invasive breast cancer Use of bolus **Exclusion criteria:** Universal exclusion criteria above Will mention reconstruction/hypofractionation in text.
Validation Set	PMID: 31449469 (Jimenez JCO 2019), PMID: 35597698 (Ranger Clin Oncol 2022), PMID: 23199652 (DIBH: Nissen-mostly focused on toxicity), PMID: 22948692 (Prone), PMID: 24674086 (Wang 2012), PMID: 30926576 (electrons & bolus), PMID: 33152277 (Poortmans), PMID: 29621872, PMID: 30508620, PMID: 22270108, PMID: 33985547 (DIBH), PMID: 35481261 (surface-guided RT: SR), PMID: 35568284 (EORTC 22922)

Abbreviations: 3-D CRT = 3-dimensional conformal radiation therapy; KQ = key question; IMRT = intensity modulated radiation therapy; IMN = internal mammary nodes; PMRT = postmastectomy radiation therapy; MA = meta-analysis; NR = nonrandomized; PICO = Population, Intervention, Comparator, Outcome; RCT = randomized controlled trial; RNI = regional nodal irradiation; RT = radiation therapy; VMAT = volume-modulated arc therapy.