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Clinical Practice Guideline

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

Rachel B. Jimenez, MD,[a,*] Yara Abdou, MD,[b] Penny Anderson, MD,[c] Parul Barry, MD,[d] Lisa Bradfield, BA,[e] Julie A. Bradley, MD,[f] Lourdes D. Heras, MPH,[g] Atif Khan, MD, MS,[h] Cindy Matsen, MD,[i] Rachel Rabinovitch, MD,[j] Chantal Reyna, MD, MHA,[k] Kilian E. Salerno, MD,[l] Sarah E. Schellhorn, MD,[m] Deborah Schofield, PhD,[n] Kekoa Taparra, MD, PhD, MPH,[o] Iman Washington, MD,[p] Jean L. Wright, MD,[q] Youssef H. Zeidan, MD, PhD,[r] Richard C. Zellars, MD,[s] and Kathleen C. Horst, MD[t]

[a]Department of Radiation Oncology, Massachusetts General Hospital, Boston, Massachusetts; [b]Department of Medical Oncology, University of North Carolina, Chapel Hill, North Carolina; [c]Department of Radiation Oncology, Fox Chase Cancer Center, Philadelphia, Pennsylvania; [d]Department of Radiation Oncology, UPMC Hillman Cancer Center, University of Pittsburgh, Pittsburgh, Pennsylvania; [e]American Society for Radiation Oncology, Arlington, Virginia; [f]Department of Radiation Oncology, University of Florida, Jacksonville, Florida; [g]Patient Representative, Surviving Breast Cancer, Gilbert, Arizona; [h]Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, New York; [i]Department of Surgery, Huntsman Cancer Institute at the University of Utah, Salt Lake City, Utah; [j]Department of Radiation Oncology, University of Colorado Denver, Aurora, Colorado; [k]Department of Surgery, Loyola University Medical Center, Chicago, Illinois; [l]Radiation Oncology Branch, National Cancer Institute, Bethesda, Maryland; [m]Department of Medicine, Yale School of Medicine, New Haven, Connecticut; [n]Department of Radiation Physics, University of Texas MD Anderson Cancer Center, Houston, Texas; [o]Department of Radiation Oncology, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, California; [p]Department of Radiation Oncology, Moffitt Cancer Center, Tampa, Florida; [q]Department of Radiation Oncology, University of North Carolina, Chapel Hill, North Carolina; [r]Department of Radiation Oncology, Florida International University and Lynn Cancer Institute, Boca Raton, Florida; [s]Department of Radiation Oncology, Indiana University School of Medicine, Indianapolis, Indiana; and [t]Department of Radiation Oncology, Stanford University, Stanford, CA

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*Corresponding author: Rachel Jimenez, MD; Email: rbjimenez@mgb.org

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Purpose: This guideline provides evidence-based recommendations on the use of postmastectomy radiation therapy (PMRT) in the treatment of breast cancer. PMRT refers to the treatment of the chest wall and ipsilateral regional nodes, including at-risk axillary, supra/infraclavicular, and internal mammary nodes. Updated recommendations detail indications for PMRT in the upfront surgical setting and after neoadjuvant systemic therapy, and provide guidance on appropriate target volumes, dosing, and treatment techniques.

Methods: The American Society for Radiation Oncology, American Society of Clinical Oncology, and the Society of Surgical Oncology convened a multidisciplinary task force to address 4 key questions focused on radiation therapy (RT) in patients with breast cancer who undergo mastectomy including (1) indications for PMRT after upfront surgery, (2) indications for PMRT after neoadjuvant systemic therapy followed by surgery, (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: After upfront mastectomy, PMRT is indicated for most patients with node-positive breast cancer and select patients with 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 cT1-3N1 or cT3N0 breast cancer with pathologically negative nodes after neoadjuvant systemic therapy (ypN0). When PMRT is delivered, treatment to the ipsilateral chest wall/reconstructed breast and regional lymphatics is recommended, with moderate hypofractionation preferred, but with conventional fractionation approaches acceptable in rare cases. Computed tomography-based volumetric treatment planning with 3-dimensional conformal RT is recommended, with intensity modulated RT advised when 3-dimensional conformal RT is unable to achieve treatment goals. Deep inspiration breath hold techniques are also recommended for normal tissue sparing. For patients with skin involvement, positive superficial margins, and/or lymphovascular invasion, the use of a bolus is recommended, but the routine use of tissue-equivalent bolus is not recommended.

Conclusions: These evidence-based recommendations guide clinical practice on 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 the 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 submitting 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

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 well-conducted meta-analyses of such randomized 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 including such a trial **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 the 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 QoE, 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 is still consensus that the benefits of a treatment or diagnostic test clearly outweigh its risks and burden.

ASTRO's methodology allows for the 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.

Guideline Subcommittee will commission a replacement or reaffirmation within 5 years of publication.

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] Although 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 improve breast cancer mortality.[4] As the absolute benefit of PMRT can vary according to patient and tumor characteristics, it is important to individualize treatment decision-making to balance considerations of LRR and breast cancer mortality with the side effects of treatment.

ASTRO, the American Society of Clinical Oncology (ASCO), and the Society of Surgical Oncology (SSO) sought to jointly 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.

Methods

Task force composition

The ASTRO/ASCO/SSO joint 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 also developed in collaboration with the European Society for Radiotherapy and Oncology, which provided representatives and peer reviewers.

Document review and approval

The guideline was reviewed by 17 official peer reviewers (Appendix E1) and revised accordingly. The modified guideline was posted on the ASTRO website for public comment from September to October 2024. The final guideline was approved by the ASTRO Board of Directors, ASCO Evidence-Based Medicine Committee, and SSO Executive Committee; and endorsed by the American Society of Breast Surgeons and the Royal Australian and New Zealand College of Radiologists.

Evidence review

Key questions (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 and Embase databases was conducted for English-language publications between January 1, 2005, through October 2023, and then the search was updated through October 15, 2024. Allowable publication types included prospective randomized controlled trials (RCTs), prospective nonrandomized studies, meta-analyses, and retrospective studies. The population of interest was adults (age ≥18 years) who received a diagnosis of breast cancer and 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 on 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.

Scope of the guideline

The scope of this guideline is to define the role of PMRT in the curative-intent management of invasive breast cancer, including the indications for PMRT after upfront surgery and following neoadjuvant systemic therapy, and to discuss the appropriate target volumes and technical specifications for PMRT. Given the rapid

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 (including VMAT) • Electrons • Protons • Set-up 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.

adoption of biologically tailored neoadjuvant systemic therapy and the de-escalation of axillary surgery with the use of 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 mortality, 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 inflammatory breast cancer, management of ductal carcinoma in situ after mastectomy, management of locally or regionally recurrent disease, and detailed discussions of chemotherapy regimens and surgical approaches, including axillary management. This guideline also does not encompass recommendations on reirradiation, RT in the setting of oligometastatic/palliative disease, phyllodes tumors, or sarcomas of the breast.

KQs and Recommendations

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?

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 and/or node-positive breast cancer who receive PMRT.[4,6-8,13-15] Support for the use of PMRT in patients with nodal involvement comes from the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis.[4,10] 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.[4,10] 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 still with significant benefits for those with 1 to 3 positive nodes (pN1). Notably, there was no differentiation between patients with pN1 or pN1mic status after axillary dissection in these trials. However, among patients with pN1mic disease, the magnitude of benefit of PMRT is often considered to be lower than in those with higher nodal burden, and therefore, requires assessment of other clinicopathological features, as noted in the discussion of patients with node-negative disease to follow.

It should also be acknowledged that the EBCTCG meta-analysis was limited to trials initiated by 1995,[4,16] 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, human epidermal growth factor receptor 2 [HER2]-directed therapy) which have been recognized to further confer a locoregional control and DFS benefit.[6,7,15] 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

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 remarks: • Omission of PMRT may be appropriate for select patients with pN1mic or low nodal burden pN1a disease following ALND who have favorable clinicopathologic features. • Favorable clinicopathologic features include pT1-2 disease, low-to-intermediate grade HR positive/HER2-negative subtype, postmenopausal status, absence of LVI, and a low 21-gene recurrence score.	Strong	High 4,6-10
2. For patients with any pT4 breast cancer, PMRT is recommended even in the absence of any other risk factors.	Strong	High 4,6
3. For patients with pT3N0 breast cancer, PMRT is conditionally recommended. Implementation remark: PMRT may be omitted or treatment volumes reduced (eg, chest wall alone) for patients with favorable clinicopathologic features including l ow-to-intermediate grade, HR positive/HER2-negative subtype, postmenopausal status, absence of LVI, and a low 21-gene recurrence score.	Conditional	High 4,6,8
4. For patients with pT1-2N0 breast cancer, PMRT is **not** recommended. Implementation remark: Select patients with pT1-2N0 breast cancer who have multiple unfavorable clinicopathologic features (eg, triple-negative, high histologic grade, LVI, young age, and/or central/medially located tumors) may benefit from PMRT.	Strong	Low 4,11,12
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: ALND = axillary lymph node dissection; HR/HER2 = hormone receptor/human epidermal growth factor receptor 2; KQ = key question; LVI = lymphovascular invasion; PMRT = postmastectomy radiation therapy; RT = radiation therapy.

evaluated the impact of PMRT on OS for patients with limited nodal disease in the upfront surgical setting after axillary lymph node dissection with at least 8 lymph nodes removed. Final results from this study will provide additional insights regarding the value of PMRT in this favorable-risk population.[17] 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 estrogen-receptor (ER)-positive, HER2-negative pT1-2N1a disease and a non-high-risk recurrence score (recurrence score ≤25) to PMRT or no PMRT, with a primary endpoint of recurrence-free interval. The results from this trial will also inform recommendations for PMRT for patients receiving upfront surgery with limited axillary nodal disease including pN1mic and favorable ER-positive tumor biology. Notably, in this study, axillary lymph node dissection is not mandatory; however, there can be no more than 2 positive lymph nodes present if sentinel lymph node biopsy alone is performed.[18] While this study evaluates selective omission of PMRT in favorable-risk ER-positive, HER2-negative breast cancer, it should be noted that in historical studies evaluating the mortality benefit of PMRT, the magnitude of benefit was higher for patients with ER-positive biology, despite a comparatively lower local recurrence risk,[19] largely due to the competing risk for distant failure. Therefore, while LRR is an important endpoint, it need not be the sole consideration in recommendations for PMRT.

In the node-negative setting, data support the use of PMRT in patients with high-risk features. Larger tumor size (≥5 cm), younger age (<40 years), and hormone receptor-negative disease have all independently been associated with a greater benefit of PMRT in node-negative patients.[15,20,21] Although specific RCTs directly focusing on T4N0 breast cancer are limited, there are data supporting the benefits of PMRT in reducing LRR and improving survival outcomes in this patient population.[4,6-8,22,23] Invasion of the skin and pectoralis muscle has also been associated with higher rates of LRR,[8] and were considered high-risk criteria for eligibility in both the Danish 82b/c trials.[22,23] For patients with pT3N0 breast cancer, who were included in these RCTs, there was a >50% reduction in LRR with PMRT.[22,23] However, this group comprised <10% of the study cohorts, modern systemic regimens known to reduce LRR were not used, and neither trial demonstrated a significant improvement in breast cancer-specific or OS in patients with pT3N0 breast cancer.[24] Multiple population data set analyses have demonstrated no breast cancer-specific survival benefit of PMRT across unselected patients with pT3N0 disease, even for patients <50 years of age.[25-27] Patients with pT3N0 disease were included in the European Organization for Research and Treatment of Cancer (EORTC) 22922 trial, which demonstrated a benefit of regional nodal irradiation (RNI) in terms of any breast cancer recurrence and breast cancer mortality, with no significant difference in OS. However, only 3.5% of the patients had pT3N0 disease.[12] Given the demonstrated local regional control benefit and uncertain survival benefit of PMRT for patients with pT3N0 breast cancer, PMRT is conditionally recommended and when employed, smaller treatment volumes (eg, chest wall RT alone) may be used at the discretion of the provider.[4,6] PMRT may be omitted for patients with favorable clinicopathological features including low-to-intermediate grade, ER-positive/HER2-negative subtype, postmenopausal status, absence of lymphovascular invasion (LVI), and low 21-gene recurrence score. These patients are included in both the SUPREMO (*NCT00966888*) and the TAILOR-RT (*NCT03488693*) trials, and these results may better define the impact of PMRT in this patient population.

Few RCTs have evaluated PMRT in the pT1-2N0 setting.[11] 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.[11] 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.[11] EORTC 22922 also included patients with stage I and II breast cancer with lymph node-negative, central or medially located tumors, and identified a breast cancer recurrence and breast cancer mortality benefit with the addition of chest wall and RNI, though mastectomy patients comprised only approximately 25% of participants.[12] 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%.[4,28] However, these data also suggest that LVI, young age, high histologic grade disease, and positive margins increase the risk of LRR such that PMRT may be beneficial, particularly for patients with multiple high-risk features.[28]

Finally, there are no RCTs evaluating the role of RT in patients with positive margins following mastectomy. Positive margins, however, are consistently associated with a greater risk of local recurrence.[29] 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 re-excision is not feasible.[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.

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?

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.[48,49] Several studies have shown that patients with initial cT4 or cN2-3 (also defined by the American Joint Committee on Cancer 6th edition as stage III) breast cancer who receive neoadjuvant systemic therapy have improved LRR with PMRT regardless of their response to neoadjuvant therapy.[30-34] Some studies have also shown an improvement in OS, but these were small retrospective evaluations.[30,31] Based on the current evidence, PMRT is recommended for patients with initial presentation of cT4 or cN2-3 disease who receive neoadjuvant systemic therapy, regardless of pathological response.[30-34]

In addition, several studies have demonstrated that residual nodal disease after neoadjuvant systemic therapy (ypN+) is associated with an increased risk of LRR.[36,38,39] The extent of axillary nodal disease after neoadjuvant systemic therapy (ie, ypN1 vs ypN2-3) is also an important risk factor.[36,37] This risk is further elevated in patients with cT3 tumors.[38] The addition of PMRT in patients with ypN+ improves locoregional control with incremental benefit noted in patients with increased axillary burden.[37,39] An OS benefit for PMRT has been reported for patients with ypN2-3 disease.[37] 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 the Alliance A011202 trial (*NCT01901094*), evaluating whether RT to the undissected axilla and other regional lymph nodes after SLN biopsy is noninferior to axillary lymph node dissection (with RT only to the undissected regional lymph nodes), will further clarify the value of extensive axillary surgery after neoadjuvant systemic therapy and provide guidance regarding the appropriate RT treatment volumes needed in this patient population.

In patients who begin treatment with clinically involved axillary lymph nodes (cN1) and convert to pathologically node negative after neoadjuvant systemic therapy (ypN0), the full reporting of the NSABP B-51/Radiation Therapy Oncology Group 1304 trial (*NCT01872975*), which randomized these patients to PMRT or no RT, will help to resolve the clinical equipoise that exists on the use of PMRT in this setting. On this protocol, patients were eligible if they had clinical axillary nodal involvement (cN1) as assessed before neoadjuvant chemotherapy by palpation, ultrasound, computed tomography (CT) scan, MRI, PET

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 who receive neoadjuvant systemic therapy, PMRT is recommended regardless of pathologic response.	Strong	Moderate 30-34
2. For patients with positive lymph nodes after neoadjuvant systemic therapy (ypN+), PMRT is recommended.	Strong	Moderate 35-39
3. For patients with cT1-3N1 or cT3N0 breast cancer with pathologic negative nodes after neoadjuvant systemic therapy (ypN0), PMRT is conditionally recommended. Implementation remarks: • Patients with high-risk features (eg, young age, LVI, high residual cancer burden in the breast) may derive a greater benefit from PMRT. • PMRT may be omitted in the setting of complete pathologic response in the breast and lymph nodes (ypT0N0).	Conditional	Moderate 35-38,40-47
4. For patients with cT1-2N0 breast cancer with pathologic negative nodes after neoadjuvant systemic therapy (ypN0), PMRT is **not** recommended. Implementation remark: Patients with multiple high-risk features (eg, young age, LVI, high residual cancer burden in the breast) may benefit from PMRT.	Strong	Moderate 36,38,40,42,43,45-47
5. For patients with positive surgical margins after neoadjuvant systemic therapy, PMRT is recommended.	Strong	Expert Opinion

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

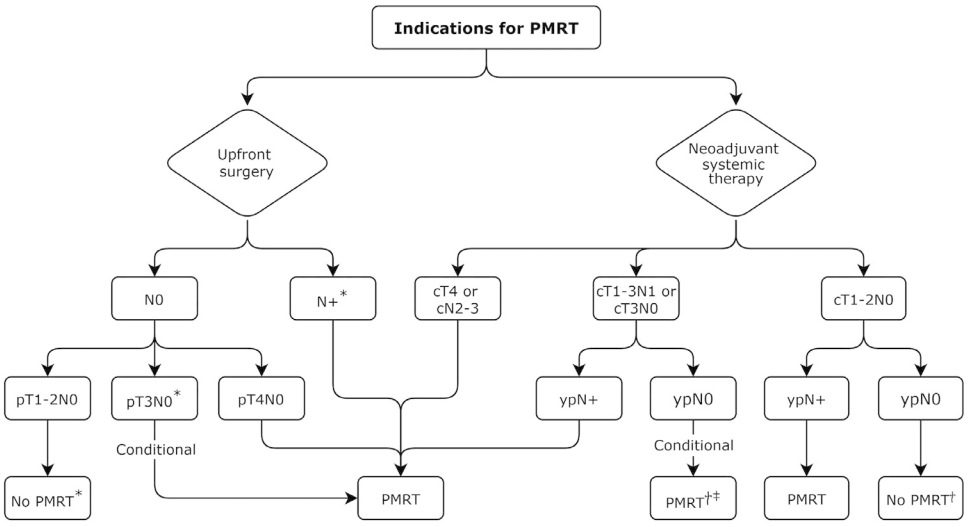

Figure 1 Indications for PMRT.
Abbreviation: PMRT = postmastectomy radiation therapy. *See implementation remarks in Table 3 for details. †See implementation remarks in Table 4 for details. ‡PMRT may be omitted in the setting of complete pathological response in the breast and lymph nodes (ypT0N0).

scan, or PET/CT scan, and patients with N2-3 disease detected clinically or by imaging were ineligible.[50] Data from a 2022 prospective Dutch registry, in which patients with cT1-2N1 breast cancer (defined as 1-3 suspicious nodes on imaging before neoadjuvant chemotherapy), and had negative nodes at surgery (ypN0) and did not receive PMRT, demonstrated a low LRR rate of 2.1% at 5 years, supporting de-escalation of PMRT in patients with ypN0 disease after neoadjuvant systemic therapy.[51] Another pooled analysis showed a 5-year LRR rate of 3% after mastectomy without PMRT in patients with HER2-positive disease achieving ypN0.[39] Although several retrospective studies have shown similar LRR-free survival rates with and without PMRT after achieving ypN0,[45,47] a meta-analysis including 12 studies of over 17,000 patients who achieved a pathological complete response in the lymph nodes (ypN0) demonstrated a significant benefit with PMRT in all stages, with the greatest benefit in stage III disease.[33] For patients who achieve a pathological complete response in the nodes, certain features appear to increase the risk of LRR and may suggest a continued benefit with PMRT. For example, several reports have suggested that baseline clinicopathological factors including young age, cT3-4 disease, triple-negative subtype, and LVI may predict higher rates of LRR, so PMRT is conditionally recommended in patients with multiple high-risk factors.[31,36,38,42,44,45,52] Similarly, other pathological features after neoadjuvant systemic therapy are associated with demonstrably higher risks of LRR (eg, high-volume residual invasive disease in the breast, persistent LVI, residual HER2-positive and triple-negative disease, close margins) and may be indications for PMRT after neoadjuvant systemic therapy.[35-37,40,42,46,47,53,54] The benefits of PMRT may be higher in younger women compared with older women.[30,45,55] 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.[30] This finding is consistent with a study from Korea that found age ≤40 years to be an independent predictor of LRR.[45] Treatment decision-making regarding the role for PMRT should include a discussion of risks and benefits, particularly for young patients. For those who have residual invasive disease in the breast, the advances in adjuvant systemic therapy (eg, CDK 4/6 inhibitors, capecitabine, ado-trastuzumab emtansine-1, pembrolizumab) may further impact the risk-benefit ratio of PMRT.[56-58]

Although neoadjuvant systemic therapy is most often used for larger tumors and those with nodal involvement, there may be some patients with cT1-2N0 disease who receive neoadjuvant treatment, particularly those with HER2+ and triple-negative biological subtype. For these patients, PMRT is not recommended if the nodes are pathologically negative (ypN0) as the risk of an LRR after mastectomy alone is low.[38] However, the presence of multiple clinical and pathological risk factors (eg, young age, LVI, high residual cancer burden in the breast) increases the risk of an LRR such that PMRT may be an option.[36,38,40,42,43,45-47]

Finally, there are limited data to inform PMRT recommendations for patients with positive surgical margins after neoadjuvant therapy. However, given that positive margins are a conditional indication for PMRT in the upfront surgery setting,[29] PMRT is recommended for positive margins after neoadjuvant systemic therapy when re-excision is not feasible based on expert opinion.

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.

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

In the EBCTCG meta-analysis of 8135 women pooled from trials comparing no PMRT with PMRT, inclusive of the chest wall and regional lymph nodes, 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,[7,15] 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 are 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.[12,59,78] The 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 and RNI (inclusive of IMNs) or whole breast/chest wall irradiation alone.[59] 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 in breast cancer mortality and any breast cancer

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, at-risk axillary nodes, supra/infraclavicular nodes, and IMNs) is recommended. Implementation remarks: • Treatment to the chest wall/reconstructed breast alone may be used in select patients (eg, pT3N0). • Coverage of the IMNs may be individually determined based on tumor location (medial/central), tumor size, and extent of nodal involvement.	Strong	High 4,9,59-63
2. For patients *without* breast reconstruction receiving PMRT, moderate hypofractionation is recommended. Implementation remarks: • Moderate hypofractionation is preferred given equivalent oncologic outcomes and reduced toxicity. • Conventional fractionation may be an option in rare circumstances.	Strong	High 64-71
3. For patients *with* breast reconstruction receiving PMRT, moderate hypofractionation (preferred) or conventional fractionation is recommended.	Strong	Moderate 63,72 (Moderate hypofx) High 12,59,62,64,66-69,73 (Conventional fx)
4. For patients with T4 breast cancer or close/positive margins receiving PMRT, a boost to the chest wall/scar is conditionally recommended.	Conditional	Low 67,69,72,74-77
5. For patients with nodal disease not surgically addressed and at risk of harboring residual disease, a nodal boost is recommended.	Strong	Expert Opinion

Abbreviations: fx = fractionation; hypofx = hypofractionation; IMNs = internal mammary nodes; KQ = key question; PMRT = postmastectomy radiation therapy.
Moderate hypofractionation is most frequently defined as 266 to 267 cGy per fraction for 15 to 16 fractions. Conventional fractionation is most frequently defined as 180 to 200 cGy per fraction for 25 to 28 fractions.[64-71]

recurrence with the addition of IMN/supraclavicular irradiation in patients with stage I-III breast cancer.[12] The Canadian Cancer Trials Group MA.20 trial also evaluated the addition of RT to the supraclavicular lymph nodes, axillary apical lymph nodes, and the IMNs for patients with node-positive disease or high-risk node-negative disease.[78] Although it did not include patients treated with mastectomy, it did demonstrate that the addition of RNI reduced the rate of any breast cancer recurrence, further supporting the use of 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.[4,7,79] Additionally, among patients who undergo an inadequate axillary dissection or whose pathological specimens demonstrate tumor deposits/emboli into the axillary fat, coverage of the dissected axilla is indicated. 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 select patients (eg, positive surgical chest wall margins as the only indication for PMRT or pT3N0 tumors in the absence of other high-risk factors), given the concern for local over regional recurrence risk.[4,15]

Although 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 associated with this approach and the potential for increased toxicity.[12,78] 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.[60-62] 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.[60,80] This study demonstrated a significant improvement in distant recurrence, death from breast cancer, and a 4.7% improvement in OS 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 and randomly assigned patients to receive RT to the chest wall and supraclavicular nodes with or without IMN RT.[61] This study did not demonstrate an OS benefit for IMN RT. In patients with positive axillary lymph nodes, a small but nonsignificant benefit was observed in favor of IMN RT. This study was underpowered and was performed in the 2-dimensional era of treatment planning, limiting its applicability.[61] Finally, the Korean Radiation Oncology Group 08-06 trial randomized patients with pathologically confirmed, node-positive disease after mastectomy or breast conservation surgery and axillary lymph node dissection to RNI with or without IMN RT.[62] The study demonstrated a nonstatistically significant 2.6% absolute decrease in distant metastases without a significant improvement in DFS. However, in an ad hoc subgroup analysis of patients with medial or centrally located tumors, both DFS and breast cancer-specific mortality at 7 years were significantly improved with the addition of IMN RT, suggesting that IMN RT in this subgroup of patients is beneficial.[62] Importantly, none of these trials, or the aforementioned RNI studies, demonstrated an increased risk of cardiac toxicity with treatment of the IMNs within the reported follow-up periods, 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.[59-62,78]

Most of the studies evaluating PMRT have used conventional fractionation with doses approximating 5000 cGy, EQD2.[9] However, a number of retrospective analyses have suggested that moderately hypofractionated PMRT regimens result in reduced acute and late toxicity compared with conventional regimens, with comparable survival outcomes.[67,69,72,81-83] There is also 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] In the United Kingdom Standardization of Breast Radiotherapy A trial, enrolling 2236 women with breast cancer, 15% underwent PMRT, and hypofractionated schedules resulted in similar locoregional failure rates, and lower adverse events, compared with conventional fractionation.[70] Additionally, the United Kingdom Standardization of Breast Radiotherapy B trial involved 2215 women with breast cancer, with approximately 8% receiving PMRT.[71] At a median follow-up of 10 years, they found that 4005 cGy in 15 daily fractions yielded comparable outcomes to 5000 cGy in 25 daily fractions in terms of locoregional tumor control and lower late normal tissue effects, as assessed by both patient and physician-reported photographs, and arm and shoulder symptoms.[71] In China, a noninferiority study randomized 820 patients with at least 4 positive axillary nodes or T3-4 disease, excluding those with internal mammary or supraclavicular nodal involvement, to moderate hypofractionation (4350 cGy in 15 fractions) or conventional fractionation (5000 cGy in 25 fractions). At a median follow-up of 58.4 months, locoregional failure was deemed noninferior between arms (8.3% hypofractionation vs 8.1% conventional fractionation), and there was a lower rate of grade 3 skin toxicity in the hypofractionation arm.[65] An additional RCT confirmed that there were no discernible

differences in toxicities, LRR, distant failure rate, or DFS between PMRT regimens of 4005 cGy in 15 fractions and 5000 cGy in 25 fractions.[66] Given equivalent oncological outcomes and reduced toxicity, moderate hypofractionation is recommended for patients without breast reconstruction who are receiving PMRT, with careful consideration of dose selection for those with more advanced disease (eg, T4 and cN3 disease) or those with limited response to neoadjuvant systemic therapy.

None of these trials, however, 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 to support its use.[72,81] The phase 3 Fractionation on Patient Outcomes After Breast REConstruction trial randomized 400 patients with stage 0-III breast cancer, excluding T4 disease, after mastectomy with implant-based reconstruction to hypofractionated RT (4256 cGy in 16 fractions) or conventional RT (5000 cGy in 25 fractions).[63] The primary endpoint was improvement in the Physical Well-Being domain of Functional Assessment of Cancer Therapy-Breast at 6 months. Results showed a significant reduction in patients requiring a treatment break with hypofractionation compared with conventional fractionation (2.7% vs 7.7%). There was no difference in chest wall toxicity between the 2 groups at a median follow-up of 40.4 months.[63,84] Based on these data, the use of moderate hypofractionation is recommended as the preferred PMRT approach in the setting of implant-based reconstruction.[63]

Another completed RCT, Alliance A221505 (RT CHARM: Hypofractionated Post Mastectomy Radiation with Breast Reconstruction; *NCT03414970*)[85] randomized nearly 900 patients with T1-3N1-2 or T3N0 disease undergoing mastectomy with immediate or delayed reconstruction (implant-based or autologous) to hypofractionated PMRT (4256 cGy in 16 fractions) or conventional PMRT (5000 cGy in 25 fractions) with a primary endpoint of reconstruction complication rate. In this trial, patients with T4 and N3 disease, including IMN involvement, were excluded.[85] Final published results from this study will provide additional data on the clinical outcomes and toxicity of hypofractionated PMRT with reconstruction.[85] Until then, conventional fractionation is also recommended as an option.

It is important to note the variability in dose regimens and eligibility criteria used in each of the above trials,[63-65,84,85] reflecting uncertainties regarding biologically effective dosing between conventional fractionation and moderate hypofractionation. Because of the evolving understanding of both the alpha/beta ratio of breast cancer and the effect of shorter treatment regimens on repopulation, care should be taken when selecting hypofractionated regimens, particularly for patients with high-risk features (eg, T4 or N3 disease), to ensure that definitive RT doses are used. In these scenarios, a separate boost to suspected residual disease, as could be employed in the conventional fractionation setting, may also be appropriate (see the subsequent discussion of a boost).

One limitation of these trials is the relatively small number of Black, Hispanic, or Asian patients enrolled, which limits the understanding of potential cosmetic differences in these populations. Prior studies have demonstrated, Asian, Black, and Hispanic patients experience worse acute and long-term skin quality of life outcomes after breast RT than White patients.[86,87] Therefore, extra consideration in treatment planning and supportive care is advised in these patient populations, recognizing that their relative lack of representation on the available trials should not unduly limit their access to shorter, more convenient treatment schedules, particularly given recognized disparities in the receipt of PMRT among Black and Hispanic patients with stage III breast cancer.[88,89]

Finally, there is increasing interest in the use of ultrahypofractionated treatment regimens (ie, 2600 cGy in 5 fractions) in breast cancer, although there are limited data in patients receiving PMRT. Early reports suggest comparable outcomes with ultrahypofractionation to the chest wall and nodal regions,[90] and additional trials are underway to further evaluate these abbreviated treatment regimens for patients requiring PMRT.[91,92]

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 LRRs 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.[93-96] 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.[97] 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. Of note, an evaluation of women who had undergone PMRT from the California Cancer Registry identified disparities in the receipt of a chest wall boost, with poor and Hispanic women more commonly receiving a chest wall boost than affluent and non-Hispanic women of similar cancer stage and biology.[98] This suggests that objective criteria for using a chest wall boost may not be uniformly applied and care should be taken, whenever possible, not only to follow consistent criteria, as detailed here, but to ensure representative enrollment of diverse patient populations in prospective studies evaluating treatment techniques.

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.[60,61] Institutional retrospective analyses 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.[99,100] However, if adding a boost to an undissected node, doses of 6000 cGy EQD2 should be considered for microscopic disease and at least 6600 cGy EQD2 for gross or residual disease.

KQ4: Appropriate PMRT delivery techniques (Table 6)

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

What are the appropriate techniques (eg, 3-dimensional conformal RT [3-D CRT], intensity modulated radiation therapy [IMRT], protons, breath hold, bolus) for treating patients who receive PMRT?

High-quality evidence from RCTs directly evaluating various RT techniques for PMRT is limited, and most foundational studies used 2-dimensional or 3-D photon therapy, with or without an electron component.[6,9,12,60-62,80,103,118] 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 ventricle, left anterior descending [LAD] artery/right coronary artery, bilateral lungs, contralateral breast, spinal cord, thyroid, esophagus, humeral head, stomach, liver, and/or brachial plexus).[119,120] Use of contouring guidelines, such as those provided by the Radiation Therapy Oncology Group atlas, RADCOMP (Radiotherapy Comparative Effectiveness),[119] and European atlases,[120,121] may be used to assist with accurate target and OAR delineation. The goal of volumetric treatment planning is to use 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 disease sites, CT-based volumes should be used for individualized RT planning for breast cancer. The task force acknowledges that in many cases

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	Moderate 12,60-62,80,101-103
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	Moderate 104-108
3. For patients receiving PMRT, DIBH is recommended when lower doses to normal tissues, including the heart and lungs, can be achieved compared with free breathing. Implementation remarks: • Other normal tissue sparing techniques may be used. • For DIBH, use of a real-time monitoring device (eg, SGRT, spirometry-based systems, chest wall monitoring system) and image-guided verification are advised.	Strong	Moderate 104,109,110
4. For patients receiving PMRT treated with IMRT (including VMAT), daily image guidance, in conjunction with regular 3-D assessments (eg, CBCT, SGRT), is recommended.	Strong	Low 111
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 needed.	Strong	Moderate 112-117
6. For patients with skin involvement, positive superficial margins, and those with dermal lymphatic involvement and/or extensive LVI, the use of tissue-equivalent bolus is recommended.	Strong	Expert Opinion

Abbreviations: 3-D CRT = 3-dimensional conformal radiation therapy; CBCT = cone beam computed tomography; CT = computed tomography; DIBH = deep inspiration breath hold; IMRT = intensity modulated radiation therapy; KQ = key question; LVI = lymphovascular invasion; OAR = organ at risk; PMRT = postmastectomy radiation therapy; SGRT = surface-guided radiation therapy; VMAT = volumetric modulated arc therapy.

Table 7 Guidance on target coverage

Structure	Goal	5000-5040 cGy in 25-28 fx	4000-4256 cGy in 15-16 fx
Ipsilateral chest wall[50,85]	Ideal	D95 ≥95% PTV	D95 ≥95% PTV
	Acceptable	D90 ≥90% PTV	D90 ≥90% PTV
	Ideal	D0.1 cc ≤110%	D0.1 cc ≤107%[†]
	Acceptable	D0.1 cc ≤115% Rx	D0.1 cc 115% Rx
Axilla[*][50,85]	Ideal	D95 ≥95% PTV	D95 ≥95% PTV
	Acceptable	D90 ≥90% PTV	D90 ≥90% PTV
	Ideal	D0.1 cc 110% Rx	D0.1 cc 107% Rx[†]
	Acceptable	D0.1 cc ≤115% Rx	D0.1cc 115% Rx
Supraclavicular fossa[50,85]	Ideal	D95 ≥95% PTV	D95 ≥95% PTV
	Acceptable	D90 ≥90% PTV	D90 ≥90% PTV
	Ideal	D0.1 cc 115% Rx	D0.1 cc 112% Rx[†]
	Acceptable	D0.1 cc ≤120% Rx	D0.1 cc 115% Rx
Internal mammary nodes[50,85]	Ideal	D95 ≥90% PTV	D95 ≥90% PTV
	Acceptable	D90 ≥80% PTV	D90 ≥80% PTV

Abbreviations: PTV = planning target volume; Rx = prescription dose.
[*]If patient has undergone a completion axillary dissection, coverage goals apply only to the targeted axilla.
[†]Extrapolated from conventionally fractionated data.
This table is a combination of evidence-based constraints and expert opinion.

more stringent planning parameters can be achieved than what is detailed in Table 7 and the concept of as low as reasonably achievable should prevail for all RT treatment plans. However, it is also recognized that the guidance provided may not be uniformly achievable for all patients' plans given anatomic concerns. When intensity modulated planning is employed, attention to low doses delivered to OARs that do not typically receive dose exposure with 3-D planning is advised (eg, spinal cord, stomach, liver).[12,60-62,80,101-103] Finally, given the current state of the data, specific dose constraints are not provided for all relevant vulnerable normal tissues (eg, LAD artery or right coronary artery); however, contouring of these structures is still advised to rationally constrain unnecessary exposure during treatment planning.

For PMRT field design, 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.[122] Advanced modulated planning techniques (eg, IMRT including volumetric modulated arc therapy [VMAT]), can be used to improve high-dose conformality and target coverage. Studies evaluating the treatment of patients with breast cancer using tomotherapy have also shown feasibility.[123,124] Studies comparing various techniques have shown low LRR rates regardless of technique.[67,102,103,105]

Treatment with inverse planned IMRT can decrease the high-dose exposure of OARs compared with 3-D CRT, and in some cases decrease the risk of toxicity.[67,107,108,125] 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.[67] 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).[108] 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.[125] One trade-off of reduced high-dose exposure to OARs with IMRT is an increase in low-dose OAR exposure. For example, 1 study described acute radiation-induced nausea associated with low-dose exposure of the upper abdominal structures,[126] side effects that are uncommon with 3-D CRT. Therefore, the use of IMRT (including VMAT) is recommended when 3-D CRT is unable to achieve treatment goals, with close attention to increased low-dose OAR exposure (see Table 8 for guidance on OARs).

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 been done with the goal of improving cardiac sparing.[132,133] Although a dose-dependent relationship between cardiac exposure to RT and heart disease has been demonstrated in several landmark studies,[134-138] 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 (Table 8). Special consideration

Table 8 Guidance on organs at risk*

Structure	Goal	5000-5040 cGy in 25-28 fx	4000-4256 cGy in 15-16 fx
Ipsilateral lung[50,85]		V5 Gy ≤75%	V4 Gy ≤65%‡
	Ideal	V10 Gy ≤65%	V8 Gy ≤55%‡
		V20 Gy ≤35%†	V17 Gy ≤25%‡
	Acceptable	V20 Gy ≤40%	V17 Gy ≤35%
Contralateral lung[85]	Ideal	V5 Gy ≤10%	V4 Gy ≤10%‡
	Acceptable	V5 Gy ≤15%	V4 Gy ≤15%‡
Heart§[85]	Ideal (left sided)	Dmean ≤3 Gy	Dmean ≤2.4 Gy‡
	Acceptable (left sided)	Dmean ≤5 Gy	Dmean ≤4 Gy‡
	Ideal (right sided)	Dmean <2 Gy	Dmean <1.6 Gy‡
	Acceptable (right sided)	Dmean ≤3 Gy	Dmean ≤2.4 Gy‡
Contralateral breast/chest wall[50,85]	Ideal	V3 Gy ≤10%	V3 Gy ≤10%
	Acceptable	V5 Gy ≤10%	V5 Gy ≤10%
Additional considerations			
Brachial plexus[90]	Suggested	D0.1 cc ≤105% Rx	D0.1 cc ≤105% Rx
Esophagus	Suggested	V10 Gy <30% / V20 Gy <15%[128]	V8 Gy <30% / V17 Gy <15%‡[127]
Left ventricle[129]	Suggested	V2 Gy <36%	V1.6 Gy <36%‡
Spinal cord†	Suggested	D0.1 cc 45 Gy	D0.1 cc 38.54 Gy
Thyroid[130,131]	Suggested	Dmean <21 Gy	Dmean <21 Gy
Humeral head	Suggested	Dmean <20 Gy	Dmean <17 Gy
Stomach (left sided)	Suggested	Dmean <3 Gy	Dmean <2.4 Gy
Liver (right sided)	Suggested	Dmean <7 Gy	Dmean <5.6 Gy

Abbreviations: Dmean = mean dose received by an organ; Rx = prescription dose.
*Where dose constraints differed by protocol, the more conservative guidelines were used.
†Based on the Hypofractionated Radiotherapy for Breast Cancer Nodal Irradiation (HYPOG)-1 trial protocol (*NCT03127995*).
‡Extrapolated from conventionally fractionated data.
§Cardiac dose should be constrained as low as reasonably achievable.
This table is a combination of evidence-based constraints and expert opinion and reflects guidance for routine treatments that do not employ a boost for gross or residual nodal disease.

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.[139,140]

A deep inspiration breath hold (DIBH) technique is one strategy for reducing dose to normal tissues, including the heart and lungs. Suitability for DIBH should be evaluated based on a patient's ability to maintain the breath hold and individual cardiac anatomy.[109,110] Among patients for whom DIBH can be successfully implemented, cardiopulmonary dose can be reduced compared with a free-breathing 3-D CRT technique.[109,141] Notably, there is an understanding that dose exposure to cardiac substructures including the left ventricle and the LAD artery does 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.[137,142] 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.[104] 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.[104] When DIBH is employed, use of a real-time monitoring device (eg, surface-guided radiation therapy [SGRT], spirometry-based or chest wall monitoring systems) and image-guided RT verification is advised to ensure the fidelity of respiratory displacement throughout treatment delivery.[104,109]

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, compared with 3-D CRT and IMRT, particularly in the setting of RNI, including IMN irradiation.[143-147] The RADCOMP trial as well as the PARABLE and Danish Breast Proton trials are all evaluating major cardiac events between patients treated with proton versus photon RT and it is anticipated that these studies will provide more data on the appropriate role of proton PMRT in the future.[119,127]

There is currently a lack of evidence to support a single optimal strategy for image guidance in the PMRT setting. Minimally, daily planar imaging, in conjunction with regular 3-D assessments (eg, cone beam CT, SGRT), is recommended for patient localization for complex planning and multifield techniques, such as IMRT (including VMAT).[148,149] Volumetric imaging (eg, cone beam CT) is valuable under these conditions to assess for evolving 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.[150]

Alternatively, SGRT using the patient's external surface and non-ionizing radiation can assist in PMRT patient set-up,[109,151] monitor intrafraction motion[152] and verify breath hold position.[110,151] However, in addition to training and workflow issues,[153] significant tissue deformations and limitations in the technology to detect darker skin tones have been identified as potential drawbacks.[154] Currently, data are lacking to support the use of SGRT alone for daily PMRT treatment delivery. When SGRT is employed, it is advised to use it in conjunction with image-guided RT for set-up verification. Guidance for the use of SGRT with image guidance, including common challenges and potential errors, has been published.[153]

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,[50,84,155] 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.[112,113,115-117,156] 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 which did not identify a local control benefit with bolus.[115-117] 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.[112] 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.[116,117] Understanding the value of bolus among patients with darker skin tones may be particularly critical given the higher likelihood of skin toxicity and late skin effects from RT among non-White patients, though no studies to-date have specifically evaluated the impact of bolus across different skin tones.[88,89] Therefore, the routine use of bolus is not advised for all patients, but may be used in circumstances where improved dosimetric coverage of the skin is needed. In addition, for those patients with an increased risk of skin recurrence, including patients who present with skin involvement, positive anterior surgical margins, dermal lymphatic invasion or extensive LVI, the use of bolus is recommended based on expert opinion.[112]

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. 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 further personalize treatment recommendations. Unfortunately, there are few data from available clinical trials to guide tailored management recommendations for patients based on sociodemographic characteristics, including race and access to health care. It is critical that future trials of PMRT ensure diverse trial enrollment and participation.

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 including trials related to PMRT in favorable-risk disease (SUPREMO, MA.39/TAILOR-RT [*NCT03488693*]), hypofractionation (RT CHARM [*NCT03414970*],[85] HYPOG-01 [*NCT03127995*], FAST FORWARD nodal substudy,[90] HYPORT-Adjuvant study[157]), PMRT after neoadjuvant chemotherapy (NSABP B-51 [*NCT01872975*]),[50] particle therapy (RADCOMP [*NCT02603341*], PARABLE (UK),[127] Danish Breast Proton Trial [*NCT04291378*]),[158] and the role of axillary surgery (Alliance A011202 [*NCT01901094*]) that will impact clinical decision-making and future clinical practice.

Disclosures

All task force members' disclosure statements were reviewed before being invited and were shared with other task force members throughout the guideline's development. Those disclosures are published within this guideline. Where potential conflicts were detected, remedial measures to address them were taken.

Yara Abdou (American Society of Clinical Oncology [ASCO] representative): AstraZeneca (consultant), Cancer Expert Now (consultant), CARISMA Therapeutics (research-site PI), CME Outfitters/CEConcepts (honoraria, meeting faculty), *Clinical Breast Cancer* (associate editor), Pfizer (consultant), MDedge/Medscape (honoraria/meeting faculty); **Parul Barry**: American Brachytherapy Society (ABS) (research-PI), American College of Radiation Oncology (ACRO) (board member, travel expenses, meeting faculty), ACRO New Practitioner grant (research-PI, travel expenses), ACRO Board of Chancellors (membership chair), ASTRO (research, meeting faculty, travel expenses; Health Equity, Diversity, and Inclusion council education chair), Beckwith Foundation (research-site PI), El-Sevier Pathways (consultant), *Rare Tumors* (senior associate editor), National Cancer Institute (research-co-PI), Silverlon (research-site PI), Pittsburgh Foundation (research-site PI), Women in Medicine Summit (research director, scientific cmt chair); **Julie Bradley**: Conquer Cancer ASCO/Pfizer grant (research-PI-ended 6/2023), Florida Breast Cancer Foundation (research-PI-ended 6/2023), Particle Therapy Cooperative Group - North America (vice president), Tissue Expander Re-Design (provisional patent); **Lourdes Heras (patient representative)**: Indian Health Services (member), Surviving Breast Cancer Organization (Director of engagement); **Rachel Jimenez (vice chair)**: *Advances in Radiation Oncology Journal* (editor-in-chief), Alexion (consultant-ended 11/2024), ASCO (research, ethics cmt chair), *JCO Oncology Practice* (associate editor), Surviving Breast Cancer Organization (medical advisory director); **Atif Khan**: American Board of Radiology (oral exam cmt breast section chair), Clovis Oncology (research-ended 3/2023), Merck (research-PI), Novavax & Xtrava Health (stock), Rutgers University (patent/copyright), Varian (research-PI); **Cindy Matsen (Society of Surgical Oncology [SSO] representative)**: American College of Surgeons (Utah chapter president), American Society of Breast Surgeons (Ethics cmt vice chair), Department of Defense (research), National Institutes of Health (research-PI), Utah Cancer Action Network (research-PI-ended 7/2024); **Rachel Rabinovitch**: Abbott Labs, Bristol Myers Squibb, Intuitive Surgical, Pfizer, Zimmer Biomet (all stock), NRG Oncology (membership cmt vice chair), Prelude DCISion RT Test (advisory board); **Chantal Reyna (SSO representative)**: Association of Women Surgeons (executive cmt, secretary, publications chair), Elucent Medical (consultant-ended 1/2023), Japanese Team Science Oncology Program (honoraria, meeting faculty), Latino Surgical Society (executive cmt-secretary); **Kilian Salerno (Guideline Subcommittee representative)**: *International Journal of Radiation Oncology, Biology, and Physics* (senior editor, pediatric/sarcoma section), *Journal of Surgical Oncology* (associate senior editor), *Practical Radiation Oncology* (associate senior editor); **Sarah Schellhorn (ASCO representative)**: ASCO (education committee chair), Breast Cancer Connect (meeting faculty), Cardinal Health (advisory board), Eisai (consultant), *Journal of Clinical Oncology* (editor), Seagen (meeting faculty-ended 12/2022); **Deborah Schofield**: American Association of Physicists in Medicine (technical exhibits chair), American College of Radiology (consultant); **Kekoa Taparra**: American Association for Cancer Research (meeting faculty, travel expenses), American Society of Hematology (meeting faculty, travel expenses), ASTRO (meeting faculty, travel expenses), University of Texas MD Anderson Cancer Center and Stanford CARE (consultant-ended 3/2023); **Jean Wright**: ASTRO (advisory board, APEx surveyor), ASTRO Clinical Affairs and Quality Committee (chair), Oncospace (research-site PI), Physicians' Education Resource (consultant, travel expenses), Prostate Cancer Foundation (research-site PI), *International Journal of Radiation Oncology Biology and Physics* (breast section editor), UpToDate (royalties-*family member*); **Richard Zellars**: Abbvie (research-PI). **Penny Anderson, Lisa Bradfield, Kathleen Horst (chair), Iman Washington**, and **Youssef Zeidan** reported no disclosures.

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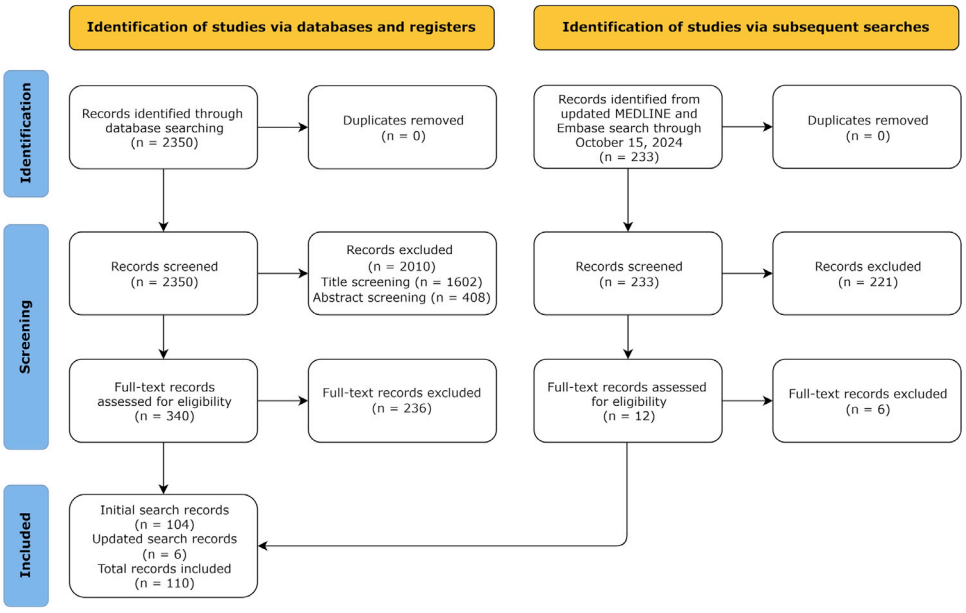
Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.prro.2025.05.001.



PRISMA 2020 study selection diagram.[159,160]
Abbreviation: PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

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