# International multidisciplinary consensus on the integration of radiotherapy with new systemic treatments for breast cancer: European Society for Radiotherapy and Oncology (ESTRO)-endorsed recommendations

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**Novel systemic therapies for breast cancer are being rapidly implemented into clinical practice. These drugs often have different mechanisms of action and side-effect profiles compared with traditional chemotherapy. Underpinning practice-changing clinical trials focused on the systemic therapies under investigation, thus there are sparse data available on radiotherapy. Integration of these new systemic therapies with radiotherapy is therefore challenging. Given this rapid, transformative change in breast cancer multimodal management, the multidisciplinary community must unite to ensure optimal, safe, and equitable treatment for all patients. The aim of this collaborative group of radiation, clinical, and medical oncologists, basic and translational scientists, and patient advocates was to: scope, synthesise, and summarise the literature on integrating novel drugs with radiotherapy for breast cancer; produce consensus statements on drug–radiotherapy integration, where specific evidence is lacking; and make best-practice recommendations for recording of radiotherapy data and quality assurance for subsequent studies testing novel drugs.**

*Lancet Oncol* 2024; 25: e73–83

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## Introduction

In the last 15 years, there have been substantial advances in the treatment of patients with breast cancer, with the introduction of novel anticancer drugs and other anticancer drugs in late stages of clinical development.[1–4] Targeted therapies in particular, such as antibody–drug conjugates and immunotherapy agents, have shown positive results within clinical trials and are now becoming a standard of care in breast cancer management globally.[3,4] The use of innovative preclinical models has been instrumental in identifying tumour targets and expediting the development of effective anticancer drugs. These preclinical models have led to a reduced time lag between preclinical discoveries and their clinical application, allowing for immediate relevance and applicability in breast cancer care. The availability of new systemic therapies has sparked an important discussion on how to effectively and safely integrate targeted drugs with local treatments, especially radiotherapy, in both curative and advanced breast cancer settings.[5,6]

Targeted drugs have a profound impact on various aspects of tumour biology, the tumour microenvironment, and cellular energetics, which can influence treatment outcomes following radiotherapy.[7] Although the potential for a synergistic effect exists, understanding the mechanistic effects, biodistribution, and pharmacokinetics of these new drugs is essential for optimising their combination with radiotherapy and establishing the most effective and safe approaches. One of the main challenges in extracting meaningful insights from current clinical data is the heterogeneity in radiotherapy target, dose, and fractionation prescriptions, particularly in the context of advanced disease. Furthermore, pivotal registration trials to evaluate new drugs often have little or no comprehensive quality assurance in radiotherapy and properly reported dosimetry data. In many cases, concurrent radiotherapy with targeted drugs is an exclusion criterion during trial therapy.[5]

The objective of this consensus is to present a comprehensive assessment of preclinical and clinical evidence regarding the integration of targeted drugs with radiotherapy for the optimal treatment of patients with breast cancer. The consensus recommendations, endorsed by the European Society for Radiotherapy and Oncology (ESTRO), aim to facilitate the widespread adoption of high-quality breast radiotherapy in clinical settings.

## Methods

### Consensus development process

The consensus statements were developed by a multidisciplinary writing committee (appendix pp 3–4), consisting of a core group and an expert panel of healthcare professionals from various fields (such as radiation and clinical oncologists, medical oncologists, radiobiologists, and translational researchers), a patient advocate, and representatives from the ESTRO guidelines committee. The writing committee conducted meetings via webinars and communicated through emails to carefully assess the available evidence and contribute to consensus development. The core group oversaw the preparatory and finalisation work, including key-topics identification, methodology, definition of critical or systematic literature needs, work-group identification, acquisition of level of evidence, identification of key statements, and the establishment of a (modified) Delphi consensus procedure.[8] The expert panel were selected and approved by the project coordinators and the ESTRO

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guidelines committee to ensure appropriate gender, profession, and country balance. The expert panel participated in the consensus-defining panel meeting, voting, and finalising and approving of the statements.

### Modified Delphi process

The consensus statements were collected in a dedicated survey and presented using the online survey tool, Google Form. The survey ensured participant anonymity, allowing for confidential responses. A 5-point Likert scale was used, ranging from very low (1) to very high (5), to gauge participant agreement with each statement.[8] To achieve consensus, a threshold offset of at least 75% agreement was required. Consensus was categorised as: 100%, unanimous support; 90–99%, strong support; and 75–89%, support. Statements that achieved consensus (at least 75% support) in the first voting round (Delphi round 1) were excluded from further consideration. After considering suggestions provided by the panel, participants then voted again on the items that did not reach at least 75% agreement (Delphi round 2). Any statement that still did not reach a consensus after the second voting round was excluded. The consensus was established by combining all the statements that received support throughout first and second rounds of the survey process. During this phase of first and second voting rounds, only minor modifications to grammar and wording were accepted. The consensus-based guidance workflow is summarised in the figure.

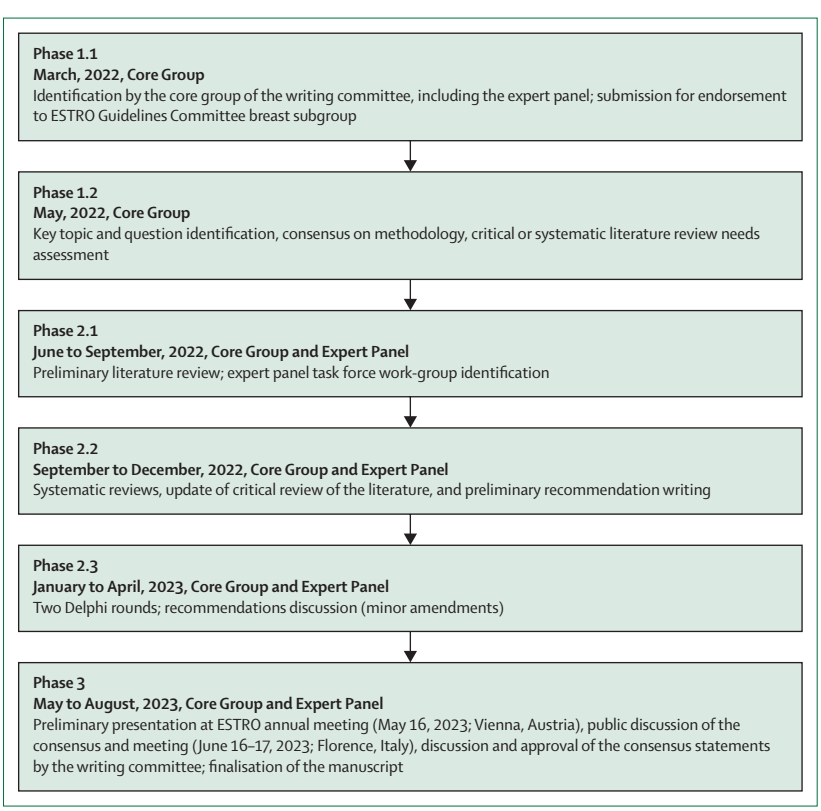


***Figure:*** **Consensus-based guidance workflow based on the modified Delphi process**
The writing committee included Core Group and Expert Panel members. ESTRO=European Society for Radiotherapy and Oncology

### Search strategy and selection criteria

A previously published critical review provided a comprehensive evaluation of the existing preclinical and clinical evidence on the combination of radiotherapy and targeted drugs for breast cancer.[8] This review served as the foundation for the development of this consensus recommendation project. The literature search for this systematic review was conducted in three phases. In the first phase, a comprehensive search was performed in PubMed and EMBASE databases for each drug category, including CDK4 and CDK6 inhibitors, PI3K ormTOR inhibitors, anti-HER2 drugs (non-antibody–drug conjugates), antibody–drug conjugate drugs, PARP inhibitors, and immunotherapies. The search followed the PRISMA guidelines, and all relevant systematic reviews within each subgroup were analysed.[9] The quality of the included systematic reviews was assessed using the AMSTAR2 tool to evaluate the risk of bias.[10] Additionally, the preclinical working group screened a series of integrative studies on the combinatory administration of radiotherapy with targeted drugs (appendix pp 5–9). In the second phase, the search results were presented to the expert panel to determine whether there was a need for additional systematic reviews on any missing topics. Finally, in the third phase, two identified new systematic reviews were conducted and published specifically focusing on CDK4/6 inhibitors[11] and the antibody–drug conjugate trastuzumab emtansine (T-DM1)[12] in combination with radiotherapy. The search strategy was implemented in accordance with PRISMA to search PubMed, MEDLINE, Embase, and Cochrane literature databases, and restricted to English language publications. For the T-DM1 systematic review, between January, 2010, and September, 2022, a specific research string based on the following keywords was developed: “breast” or “mammary” or “breast cancer” or “breast neoplas*”, “radiotherapy”, “irradiation”, “radiation”, “radio-therapy”, “concurrent*”, “concomitant*”, “combin*”, “associat*”, “simultaneous*”, “trastuzumab DM1”, “T-DM1”, “trastuzumab emtansine”, “trastuzumab-DM1”, “huN901-DM1”, “huN901 DM1”, and “huN901DM1”. For the CDK4/6 inhibitors systematic review, between Jan 1, 2000, and Nov 1, 2022, a specific research string based on the following keywords was developed: “breast” or “mammary” or “breast cancer” or “breast neoplas*”, “radiotherapy”, “irradiation”, “radiation”, “radio-therapy”, “concurrent*”, “concomitant*”, “combin*”, “associat*”, “simultaneous*”, “cyclin-dependent kinase 4/6 inhibitor”, “palbociclib”, “ribociclib”, and “abemaciclib”. Keywords used were “breast cancer”, “radiotherapy”, “concurrent”, “cyclin-dependent kinase 4/6 inhibitor”, “palbociclib”, “ribociclib”, and “abemaciclib”.

### Key topics and voting rounds

The core group and expert panel were requested to assess the level of evidence for key topics in the consensus recommendations. These topics included: key question 1—what are the minimum requirements for reporting radiotherapy parameters in a clinical trial to evaluate the safety of combining a targeted systemic treatment with radiotherapy for breast cancer; and key question 2—based on the current evidence, what is the safety profile of a specific new systemic treatment when used in combination with ablative or palliative radiotherapy for intracranial or extracranial sites of disease in metastatic and curative settings. The level of evidence and grade of recommendations are provided in the appendix (p 10).[13]

## Results

Key question 1 is represented within a case report form (appendix pp 11–15) which focused on establishing the minimum requirements for reporting radiotherapy parameters in both early and metastatic breast cancer trials. The consensus recommendations on key quware presented in panel 1.

Key question 2 addressed the consensus recommendations on the integration of main targeted drugs with radiotherapy for breast cancer treatment (panel 2). These recommendations encompass both early and metastatic breast cancer settings, including intracranial and extracranial disease.

After the initial voting round, consensus was reached among all 40 panellists for both of the two statements pertaining to key question 1, and 14 of the 17 statements pertaining to key question 2. Following panel discussions, two additional statements were introduced for key question 1, and adjustments were made to nine of the key question 2 statements, based on suggestions from the panellists, in the lead-up to the second voting round. In the second voting round, all 40 panellists responded and consensus was achieved for all consensus recommendations. The Delphi voting agreement results, stratified by voting rounds 1 and 2, are summarised in the appendix (pp 16–18).

### *Panel 1:* Final consensus statements on key question 1—minimum requirements of reporting radiotherapy parameters in clinical trials assessing new systemic treatments for breast cancer

1a) Long-term safety data are needed for combining new biological drugs with radiotherapy for patients with early breast cancer [V, A]
- Strong consensus (95%)

1b) When combining new systemic treatments and radiotherapy, reporting of radiotherapy parameters and toxicity is mandatory when reporting safety data in both early and advanced disease settings [V, A]
- Unanimous consensus (100%)

1c) There are few or no high-quality clinical data concerning the combination of radiotherapy and new systemic treatments for breast cancer: prospective research studies are strongly recommended to strengthen the available evidence [V, A]
- Unanimous consensus (100%)

1d) The potential risks, benefits, and uncertainties regarding the combination of radiotherapy and new systemic treatments for breast cancer should be fully discussed with the patient [V, A]
- Unanimous consensus (100%)

Levels of evidence (I–V) and grades of recommendation (A–E) have been applied using the system shown in the appendix (p 10).

## Discussion: minimum requirements of reporting radiotherapy parameters in clinical trials assessing new systemic treatments for breast cancer

Radiotherapy plays a crucial role in the treatment of patients with breast cancer. In cases of non-metastatic breast cancer, radiotherapy is typically included as part of the breast conservation approach, known as breast-conserving therapy.[14] The use of radiotherapy after mastectomy is on the rise, primarily due to its proven benefits in terms of local control and breast cancer mortality, both in cases of patients who are node-positive and patients who are node-negative.[15] Additionally, there is a growing trend towards de-escalating axillary surgery by replacing it with axillary radiotherapy in some cases.[16] In instances where patients have a local recurrence following breast-conserving surgery or mastectomy, re-irradiation can be considered as a treatment option.[17]

In the early-stage setting, it is essential to establish whether radiotherapy should be administered concurrently or sequentially with each drug or strategy, exploring the potential advantages and disadvantages of each approach. Future trials should consider evaluating the timing of radiotherapy and study drugs as a preplanned exploratory endpoint, a step that will accelerate and enhance our knowledge about the process of integrating therapies.

In the case of metastatic disease, the landscape of radiotherapy has undergone substantial changes. Patients with metastatic breast cancer now have prolonged survival rates, primarily due to advancements in systemic therapies. Also, the introduction of robust and adaptive (image-guided) radiotherapy treatment planning, along with the availability of innovative radiotherapy techniques, has revolutionised the approach to treating patients with metastatic disease. Traditional palliative radiotherapy for symptom control is no longer the only option. Instead, patients with few metastases, also known as oligometastatic patients, are often treated with high-dose per fraction radiotherapy using stereotactic ablative body radiotherapy (SABR) to effectively control the metastatic lesion. These patients

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See Online for appendix

***Panel 2:*** **Final consensus statements on key question 2—current evidence regarding the safety profile of a specific new systemic treatment when used in combination with ablative or palliative radiotherapy for intracranial or extracranial sites of disease in the metastatic and locoregional settings**

**1) CDK4 or CDK6 inhibitors**

1a) CDK4 or CDK6 inhibitors and concomitant radiotherapy during adjuvant locoregional radiotherapy for breast cancer should be investigated in the context of clinical trials or prospective registration cohorts [V, A]*

- Unanimous consensus (100%)

1b) CDK4 or CDK6 inhibitors and concomitant radiotherapy during whole-brain radiotherapy or intracranial stereotactic radiotherapy should be investigated in the context of clinical trials or prospective registration cohorts [IV, A]

- Strong consensus (92·5%)

1c) CDK4 or CDK6 inhibitors and concomitant radiotherapy could be offered during palliative and ablative extracranial radiotherapy [IV, B]

- Strong consensus (90%)

**2) PIK3 inhibitors**

2a) PIK3 inhibitors and concomitant radiotherapy should not be offered [V, D]†

- Strong consensus (90%)

**3) mTOR inhibitors**

3a) mTOR inhibitors and concomitant radiotherapy should not be offered [V, C]†

- Strong consensus (95%)

**4) Anti-HER-2 drugs (non-antibody–drug conjugates)**

4a) Trastuzumab or pertuzumab and concomitant radiotherapy could be offered during locoregional radiotherapy for breast cancer [I, A]

- Unanimous consensus (100%)

4b) Trastuzumab or pertuzumab and concomitant radiotherapy could be offered during whole brain and ablative intracranial stereotactic radiotherapy [IV, B]

- Strong consensus (97·5%)

4c) Lapatinib and concomitant radiotherapy during locoregional radiotherapy for breast cancer is safe [II, B]‡

- Consensus (85%)

4d) Lapatinib and concomitant radiotherapy could be offered during whole brain and ablative intracranial stereotactic radiotherapy [II, B]

- Consensus (87·5%)

4e) Newer tyrosine kinase inhibitors (ie, neratinib, tucatinib) and concomitant radiotherapy should be investigated in the context of clinical trials or prospective registration cohorts [V, C]†

- Strong consensus (97·5%)

**5) Antibody–drug conjugates**

5a) Trastuzumab emtansine (T-DM1) and concomitant radiotherapy might be considered during adjuvant locoregional radiotherapy for breast cancer [II, B]

- Strong consensus (92·5%)

5b) T-DM1 and concomitant radiotherapy should not be offered for whole-brain and ablative intracranial stereotactic radiotherapy [IV, D]

- Strong consensus (90%)

5c) Newer antibody–drug-conjugates (ie, trastuzumab deruxtecan) and concomitant radiotherapy should be investigated in the context of clinical trials or prospective registration cohorts [V, C]†

- Unanimous consensus (100%)

**6) PARP inhibitors**

6a) PARP inhibitors and concomitant radiotherapy for primary, adjuvant, and metastatic breast cancer settings should be investigated in the context of clinical trials or prospective registration cohorts [II, A]

- Strong consensus (97·5%)

6b) PARP inhibitors and concomitant radiotherapy should not be offered for advanced breast cancer outside clinical trials [II, D]§

- Consensus (80%)

**7) Immunotherapy**

7a) Immunotherapy and concomitant radiotherapy could be considered during locoregional radiotherapy for breast cancer [II, B]

- Strong consensus (95%)

7b) Immunotherapy and concomitant radiotherapy including ultra hypofractionated regimens used for stereotactic radiotherapy could be offered for advanced breast cancer [II, B]¶

- Strong consensus (92·5%)

Levels of evidence (I–V) and grades of recommendation (A–E) have been applied using the system shown in the appendix (p 10). *No safety report for concomitant CDK4 or CDK6 inhibitors with postoperative locoregional radiotherapy for breast cancer; data derived from metastatic setting. †Currently, there is no clear evidence on the safety of combined treatment with these inhibitors in both metastatic and non-metastatic settings. ‡Lapatinib is not approved in the early breast cancer setting. §Safety data for PARP inhibitors and concomitant radiotherapy are scarce; few data are available in the metastatic setting. ¶Data derived from other solid organ tumours.

are often treated with curative intent, since they have the potential for improved survival, even in cases of brain metastases.[18,19]

Given the evolving landscape of systemic therapy for breast cancer, it is essential to prioritise proper documentation of radiotherapy, including accurate target volumes delineation and reporting on radiotherapy planning and outcomes, using a well defined, internationally recognised format.[20] With the introduction of new systemic therapies, the possibility of different types of toxicity when combined with radiotherapy might lead to the discontinuation of systemic therapy during

radiotherapy, potentially lowering the systemic control or the adaptive and synergistic effects on local control (appendix pp 19–20). Most pivotal trials that are testing new systemic therapies have adopted a conservative approach, avoiding concomitant treatment with radiotherapy. However, we recommend that, in cases with a strong biological and therapeutic rationale, studies involving combinations with radiotherapy should be considered as part of the design for early-phase studies in patients.

The half-life model is based on theoretical pharmacokinetic parameters. Particularly in situations involving drug toxicity, it can be challenging to implement this model in practice and use it as a tool for clinical decision making.[21] Approximately 94–97% of a drug is eliminated after four to five half-lives. Consequently, beyond this time frame, the plasma concentration of a given drug would fall below a clinically relevant concentration and be considered eliminated.[22] The plasma elimination half-lives of the main new systemic therapies for breast cancer treatment and the minimum wash out drug interval adopted in main pivotal trials are summarised in the appendix (p 21). We strongly recommend that trials evaluating new targeted drugs include radiotherapy quality assurance data in their reporting to enable further analysis of potential toxicity resulting from the interaction between the radiotherapy and systemic treatment modalities. Careful collection of granular data on radiotherapy doses, fractions, durations, and sites, patient characteristics, and immediate and delayed side-effects of the treatment combination is of utmost importance.

## Discussion: safety profiles of drugs in combination with radiotherapy

### CDK4/6 inhibitors with radiotherapy

CDK4/6 inhibitors have become the standard of care for first-line or second-line treatment in patients with hormone receptor positive or HER2 (also known as ERBB2)-negative metastatic breast cancer, showing improved efficacy compared with endocrine therapy alone.[23] Furthermore, both abemaciclib and ribociclib have shown a significant improvement in invasive disease-free survival among patients with early-stage high-risk disease.[24,25]

Unfortunately, we found no information regarding concurrent radiotherapy in the adjuvant setting; in all the published phase 3 trials, adjuvant radiotherapy should have been completed before patients entered the study, and if a patient required radiotherapy during the active treatment phase they were discontinued from the treatment and entered the follow-up phase.[24–27] A short-term follow-up analysis of patient-reported outcomes from the MonarchE trial found a similar rate of radiation pneumonitis in patients previously treated with radiotherapy in the two treatment arms.[28] Concurrent administration of radiotherapy with adjuvant CDK4/6 inhibitors might be an option in the future, but requires further investigation. In advanced disease, the combination of palliative radiotherapy and CDK4/6 inhibitors has only been specifically addressed in the PALOMA trials (NCT01942135 and NCT01740427, using palbociclib), in which it was recommended to temporarily suspend palbociclib for 7 days before the radiotherapy course.[29,30]

In the MONALEESA trials (NCT01958021, NCT02422615, and NCT02278120, using ribociclib), palliative radiotherapy was permitted solely for relieving bone pain, and in the MONARCH trials (NCT02107703 and NCT02246621, using abemaciclib), all patients with metastases requiring radiotherapy had to permanently discontinue therapy and undergo tumour assessment before receiving radiotherapy. Consequently, there is a shortage of information available on concomitant treatment from pivotal randomised trials.

To better understand the safety profile of combining CDK4/6 inhibitors with palliative and ablative radiotherapy for both metastatic and early breast cancer, we conducted and published a systematic review and meta-analysis of the existing literature published in English.[11] The review included 11 retrospective studies, all of which focused on the metastatic setting (appendix p 22). Most of the included studies had small sample sizes; however, the meta-analysis revealed that the side-effect profiles of drugs administered concurrently with radiotherapy is similar to those seen in the larger randomised controlled trials of CDK4/6 inhibitors in advanced breast cancer treated using sequential adjuvant radiotherapy.[29,30] The pooled proportion (weighed on a total of 382 patients) of grade 3 or worse (serious adverse event severity, NCI CTCAE version 5) haematological toxicities was 14% (95% CI 0·03–0·30), whereas the pooled proportion of grade 3 or worse non-haematological toxicities was 3% (95% CI 0·01–0·05). There is no evidence of an increased risk of interstitial lung disease. These findings suggest that the simultaneous administration of CDK4/6 inhibitors and radiotherapy is generally well tolerated, with predominantly haematological grade 3 or worse adverse events. In the European Organisation for Research and Treatment of Cancer (EORTC)-ESTRO OligoCare consortium recommendations, it was unanimously agreed that SABR should be performed for all treated organs without CDK4/6 inhibitor dose reduction, and without increasing the number of SABR fractions compared with SABR without concomitant systemic therapy.[6] Results from several ongoing trials evaluating the combination of CDK4/6 inhibitors and radiotherapy for breast cancer are expected to provide additional evidence regarding their safety (appendix p 23).

### PI3K inhibitors and radiotherapy

In the clinical setting, there are few data available on the efficacy and safety of combining PI3K–AKT or mTOR signalling pathway-targeting drugs with radiotherapy, particularly in advanced breast cancer (appendix p 24). In the phase 3, randomised SOLAR-1 trial, which compared alpelisib plus fulvestrant with placebo plus fulvestrant in

patients with advanced breast cancer previously treated with endocrine therapy, the exclusion criteria included receiving radiotherapy within 4 weeks or limited-field radiotherapy for palliation within 2 weeks before randomisation.[31] Also, in the BYLieve phase 2 study, evaluating alpelisib plus fulvestrant in advanced breast cancer after a CDK4/6 inhibitor, radiotherapy within 4 weeks before randomisation was an exclusion criterion.[32]

Capivasertib, a new oral selective AKT1–3 inhibitor, combined with fulvestrant resulted in significantly longer progression-free survival than treatment with fulvestrant alone among patients with hormone receptor-positive advanced breast cancer whose disease had progressed during or after previous aromatase inhibitor therapy with or without a CDK4/6 inhibitor.[33] Radiotherapy with a wide field of radiation within 4 weeks before study treatment initiation was a main exclusion criterion for trial participation.[33] Currently, there is insufficient clear evidence regarding the safety of combining radiotherapy with PI3K–AKT inhibitors. Further studies are required to determine the optimum dosing of these drugs in combination with radiotherapy for maximum tumour response while minimising toxicity.

### mTOR inhibitors and radiotherapy

Although mTOR inhibitors have demonstrated anticancer activity in various types of cancer, there is little information regarding their efficacy and safety when combined with radiotherapy, particularly in advanced breast cancer (appendix p 25). The BOLERO-2 trial, for instance, excluded patients who had received radiotherapy within 4 weeks before randomisation, except in cases where localised radiotherapy was administered for analgesic purposes or for osteolytic lesions at risk of fracture, provided it was completed within 2 weeks before randomisation.[34] Currently, there is insufficient evidence to support the safe combination of radiotherapy and mTOR inhibitors. Therefore, it is advisable to administer radiotherapy and mTOR inhibitors sequentially.

### Anti-HER2 drugs (non-antibody–drug conjugates) and radiotherapy

Anti-HER2 therapies have profoundly transformed the treatment landscape for patients with HER2-positive breast cancer, leading to improved survival outcomes in both the adjuvant and metastatic settings.[5,35,36] The concomitant use of trastuzumab and postoperative breast cancer radiotherapy, both of which have the potential for cardiac toxic effects, has been studied in several retrospective cohorts in the adjuvant setting. Overall, the combination of trastuzumab and postoperative radiotherapy has shown good tolerability, with no apparent increase in acute or late cardiac toxic effects. Additionally, acute side-effects affecting the skin and oesophagus were minimal and reversible.[37–39] Prospective studies where trastuzumab might be given with radiotherapy have yielded similar results.[40–43] In the ATEMPT trial, concomitant administration of trastuzumab with postoperative whole-breast irradiation showed a low risk of pneumonitis (approximately 1% in both study groups) and generally low skin toxicity (no grade 3 or worse toxic effects in the trastuzumab group).[42] Analysis of cardiac function in the HERA trial, where trastuzumab was administered concomitantly with left-sided radiotherapy (n=1270), right-sided radiotherapy (n=1271), or no radiotherapy (n=780), revealed that radiotherapy did not significantly affect left ventricular ejection fraction or cardiovascular events at a median follow-up of 11 years.[43] In the APHINITY trial, which showed the benefit of adding pertuzumab to trastuzumab in the adjuvant setting, radiotherapy was administered concomitantly; although adverse events were not specifically analysed in relation to radiotherapy, no specific warnings or indications of increased cardiac toxic effects were reported.[44] Retrospective studies involving small cohorts have also indicated that the combination of pertuzumab and trastuzumab is safe.[45,46] For patients undergoing whole-brain radiotherapy or stereotactic radiotherapy for brain metastases, the concurrent use of trastuzumab, pertuzumab, or both has been well tolerated, with no increased risk of adverse events.[47,48] The recently published EORTC-ESTRO OligoCare recommendations on the use of targeted drugs in combination with SABR present a consensus that trastuzumab and pertuzumab can be administered concomitantly with radiotherapy, without the need for dose reduction.[6]

In the ALLTO and NeoALLTO trials, postoperative locoregional radiotherapy was administered concurrently with lapatinib tosilate, trastuzumab, or both. Although skin toxic effects were more prevalent in the lapatinib-containing treatment arms, this might not necessarily be attributable to concomitant radiotherapy, as rash is a common side-effect of lapatinib treatment, even in the absence of irradiation.[49,50] A systematic review based on retrospective studies showed that the combination of lapatinib with stereotactic radiotherapy improved local control and survival with a reduced risk of radiation-induced necrosis compared with stereotactic radiotherapy alone.[51] Scarce evidence is currently available regarding the concurrent use of other tyrosine kinase inhibitors, such as tucatinib, with radiotherapy. In the HER2 CLIMB trial,[52] in case of isolated intracranial progression without extracranial disease progression, patients were eligible to continue treatment with study drugs after completion of local treatment of brain metastases to allow for clinical benefit—however, tucatinib was to be withheld for 1 week before radiotherapy, and re-initiated 7 days or more after completion of stereotactic radiotherapy, and 21 days or more after whole brain radiotherapy. Further prospective evaluation of potential synergistic effects is warranted.

### Antibody–drug conjugates and radiotherapy

The phase 3 KAITLIN study allowed the use of trastuzumab emtansine (T-DM1) with pertuzumab in combination with postoperative breast radiotherapy, although specific radiotherapy-related toxic effects were not reported.[53] No excess pulmonary toxic effects were observed, and patient-reported outcomes were similar to the trastuzumab plus pertuzumab group without radiotherapy. In the KATHERINE trial, the incidences of acute skin toxic effects and radiation pneumonitis were low for both T-DM1 and trastuzumab, although numerical values suggested a potential increase in radiation pneumonitis with T-DM1 (1·5% [11 of 740 cases] compared with 0·7% [five of 720 cases]).[54] In the ATEMPT trial (a small, non-randomised study treating 383 of 497 enrolled patients with T-DM1), a non-significant increase in grade 2 or worse skin toxic effects was observed with concurrent T-DM1 plus radiotherapy, compared with trastuzumab plus radiotherapy, and the rate of pneumonitis was similar.[42] Other smaller trials have shown consistent results, indicating that the use of T-DM1 is relatively safe during adjuvant breast radiotherapy.[55,56]

T-DM1 has been shown to cross the blood–brain barrier and to have clinical efficacy against brain metastases. However, combining T-DM1 with stereotactic radiotherapy substantially increases the risk of later symptomatic radiation-induced necrosis compared with radiotherapy alone.[57–59] The mechanism underlying these intracranial toxic effects is currently speculative, but T-DM1 targeting of reactive astrocytes might play a role.[59] There are insufficient data to evaluate the safety of whole-brain radiotherapy or extracranial palliative radiotherapy or stereotactic radiotherapy when combined with T-DM1.

In the DESTINY-BREAST03 trial, palliative radiotherapy (excluding lung area) was allowed concurrently with trastuzumab deruxtecan, but no adverse events related to concomitant radiotherapy (including increased risk of interstitial lung disease) were reported.[60] The ASCENT trial did not include information on radiotherapy (although restricted sequential palliative radiotherapy was allowed); thus, there is currently a shortage of safety data on the use of sacituzumab govitecan in relation to radiotherapy.[61]

### PARP inhibitors and radiotherapy

In the context of non-metastatic settings, the TBCRC 024 multicentre, phase 1 trial aimed to determine the maximum tolerated dose of veliparib in combination with postoperative chest wall and regional nodal radiotherapy in women with inflammatory or locally-recurrent breast cancer after surgery. The incidence of grade 3 toxic effects increased over time, with severe late toxic effect rates observed, particularly in terms of fibrosis in the radiotherapy field (40% [five of 15 cases] at 3 years).[62] The RADIOPARP phase 1 trial focused on determining the maximum tolerated dose of olaparib concurrently with radiotherapy in patients with triple-negative breast cancer who had residual tumour or inoperable disease after neoadjuvant chemotherapy.[63] At 2-year follow-up, no grade 3 or worse treatment-related toxic effects or cardiac, pulmonary, or gastrointestinal adverse events were reported, indicating a favourable safety profile. Late presenting grade 3–4 events were rare, with one patient having grade 4 thrombocytopenia at 1 year follow-up while receiving further cytotoxic therapy for metastatic disease. These findings suggest that the concurrent use of veliparib or olaparib with radiotherapy is generally well tolerated, but that long-term monitoring is necessary to assess and manage potential late toxic effects. Data from the last few years have shown the effectiveness of olaparib in the high-risk early breast cancer setting as an adjuvant treatment following standard chemotherapy. The OlympiA phase 3 trial investigated the use of olaparib in the adjuvant setting after completion of local treatment and neoadjuvant or adjuvant chemotherapy; it was required that patients had completed the course of radiotherapy between 2 weeks and 12 weeks before enrolling in the trial.[64]

In patients with breast cancer with germline pathogenic variants in the *BRCA1* or *BRCA2* genes, PARP inhibitors as single agents are the standard of care in the metastatic setting.[65,66] A phase 1 study evaluated the concurrent use of veliparib with whole brain radiotherapy in patients with brain metastases, including patients with breast cancer.[67] Overall, the addition of veliparib to whole brain radiotherapy did not reveal unexpected toxic effects compared with radiotherapy alone.

Although no serious additional acute toxicity has been reported thus far from combining PARP inhibitors with radiotherapy, available data on this combination in breast cancer are scarce. Furthermore, there is a shortage of long-term safety data for this combination in breast cancer and there is little evidence demonstrating a clinically significant benefit. Similarly, there are insufficient safety and efficacy data for combining PARP inhibitors with radiotherapy in other solid organ malignancies. Considering these factors, it remains preferable to not use radiotherapy concurrently with PARP inhibitors until further research provides more comprehensive safety and efficacy data for this combination therapy. The main ongoing trials investigating PARP inhibitors and radiotherapy combinatory strategy are summarised in the appendix (p 26).

### Immunotherapy and radiotherapy

Immunotherapy has emerged as a key treatment option in triple negative breast cancer, both in the neoadjuvant setting and as first-line therapy for PD-L1 positive tumours. The use of immunotherapy in triple negative breast cancer is supported by major clinical trials, such as KEYNOTE-522,[68] IMPASSION-130,[69] and KEYNOTE-355.[70] In the neoadjuvant KEYNOTE-522 trial, pembrolizumab was initially not allowed during

postoperative radiotherapy. However, an amendment based on safety data was made, allowing concurrent administration of pembrolizumab and radiotherapy.[68] An event-free survival benefit was observed in patients who received pembrolizumab with either concurrent or sequential adjuvant radiotherapy. The combination of pembrolizumab and radiotherapy appears to be well tolerated and does not seem to be associated with additional risks.[71] In the recently published event-free survival analysis, slightly higher rates of pneumonitis (grade 3 or worse 0·9% [seven of 783 cases] *vs* 0·5% [two of 389 cases]) and skin toxicity (grade 3 or worse 4·7% [37 of 783 cases] *vs* 0·3% [one of 389 cases]) were reported compared with the placebo group, who also received radiotherapy.[72]

The IMPASSION-130 trial allowed palliative radiotherapy before randomisation, but specific efficacy and toxicity data for this subgroup of patients are not reported.[69] In the KEYNOTE 355 trial, patients treated with radiotherapy were eligible for enrolment if at least 2 weeks had passed since the last dose of radiotherapy.[70] Pooled data from 68 prospective trials involving immune checkpoint inhibitors in 16 835 patients indicated that administering these drugs within 90 days following radiotherapy did not appear to increase the risk of serious adverse events.[73] Several small studies have investigated the effect of checkpoint inhibition with radiotherapy in the palliative setting. Overall, these studies indicate that the combination of immune checkpoint inhibitors and radiotherapy is safe and well tolerated.[74,75]

Clinical data on the combination of immunotherapy and radiotherapy in breast cancer remain scarce. Ongoing trials aiming to determine the optimal dose and timing of radiotherapy in combination with immunotherapy in breast cancer are shown in the appendix (pp 27–29). Although safety data for the combination of immunotherapy and radiotherapy in breast cancer are insufficient, evidence from other solid organ malignancies suggests that radiotherapy can be considered safe when given concurrently with immunotherapy. Nonetheless, certain aspects, such as patient selection, total dose, and dose per fraction, remain open for debate to achieve the best therapeutic outcomes.

## Conclusions

These consensus statements emphasise the importance of considering radiotherapy parameters and comprehensive quality assurance in clinical trials assessing novel systemic therapies for breast cancer. Collection and timely reporting of long-term safety data is crucial when combining new biological drugs with radiotherapy, especially for patients with early breast cancer, for both sequential and concurrent therapy.

For specific targeted drugs, recommendations vary. Although CDK4/6 and PARP inhibitors with concomitant radiotherapy have shown promising safety data, further investigation within clinical trials or prospective cohort studies is warranted. PI3K–AKT and mTOR inhibitors showed safety signals warranting caution, discouraging their combination with radiotherapy. Immunotherapy agents and non-antibody–drug conjugate anti-HER2 drugs, such as trastuzumab, pertuzumab, and lapatinib, can be administered alongside radiotherapy safely, whether in adjuvant or metastatic settings. The antibody–drug conjugate T-DM1 appears to be safe for adjuvant radiotherapy, but prudence dictates avoiding its concurrent use with intracranial radiotherapy. The use of emerging tyrosine kinase inhibitors and antibody–drug conjugates concurrently with radiotherapy requires further investigation.

There is a crucial need for thoughtful and harmonious integration of radiotherapy into clinical trials for emerging breast cancer treatments. The main challenges include identifying the potential interactions between new systemic therapies and radiotherapy in both early and metastatic settings, and exploring the evolving possibilities presented by advanced radiotherapy techniques. Recognising the importance of considering the interplay between both systemic and locoregional therapies for optimising patient care is essential to obtain a comprehensive understanding of expected clinical outcomes. The creation of a research environment that accommodates these challenges and provides comprehensive guidance for the appropriate use of radiotherapy across various clinical scenarios is needed to ensure a synergistic approach that optimises both patient outcomes and the use of resources. Engaging in a comprehensive discussion with patients about the potential risks, benefits, and uncertainties associated with this therapeutic combination is an essential aspect of care.

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All authors contributed to conceptualisation, data curation and analysis, investigation, methodology, supervision, validation, writing of the original draft, and review and editing of the manuscript. Authors were not precluded from accessing data in the study, and they accept responsibility to submit for publication.

#### Declaration of interests

IMe declares participation in advisory boards supported by Eli Lilly, Novartis, Pfizer, Pierre Fabre, SeaGen, Daiichi Sankyo, and AstraZeneca. CB declares honoraria from Eli Lilly, and participation in advisory boards supported by Eli Lilly, Novartis, Pfizer, and Amgen. ML received honoraria from or participated in advisory boards for Roche, Novartis, Eli Lilly, Pfizer, AstraZeneca, Daiichi Sankyo, Gilead, SeaGen, Merck Sharp and Dohme, Exact Sciences, Takeda, Ipsen, Sandoz, Libbs, and Knight; received a travel grant from Gilead; and received research support for their institution from Gilead. EdA declares honoraria from or participation in advisory boards for Roche, Genentech, Novartis, SeaGen, Zodiac, Libbs, Pierre Fabre, Eli Lilly, and AstraZeneca. JC declares consulting or advisor roles supported by Roche, Celgene, Cellestia, AstraZeneca, SeaGen, Daiichi Sankyo, Erytech, Athenex, Polyphor, Eli Lilly, Merck Sharp and Dohme, GSK, Leuko, Bioasis, Clovis Oncology, Boehringer Ingelheim, Ellipses, Hibercell, BioInvent, Gemoab, Gilead, Menarini, Zymeworks, Reveal Genomics, and Expres2ion Biotechnologies. NH declares honoraria for lectures or consulting from AstraZeneca, Daiichi Sankyo, Gilead, Eli Lilly, Merck Sharp and Dohme, Novartis, Pierre Fabre, Pfizer, Roche, Sanofi, Sandoz, and SeaGen. HSR declares institutional research support from Astellas Pharma, AstraZeneca, Daiichi Sankyo, F Hoffmann-La Roche, Genentech, Gilead Sciences, GSK, Eli Lilly, Merck & Co, Novartis Pharmaceuticals Corporation, OBI Pharma, Pfizer, Pionyr Immunotherapeutics, Sermonix Pharmaceuticals, Taiho Oncology, and Veru. GC reports personal fees for consulting, advisory roles, and speakers' bureau from Roche, Genentech, Novartis, Pfizer, Eli Lilly, Foundation Medicine, Samsung, and Daiichi Sankyo; honoraria from Ellipses Pharma; and fees for travel and accommodations from Roche, Genentech, and Pfizer. LV declares participation in advisory boards from Daiichi Sankyo and Pfizer. ME declares participation in advisory boards supported by Pfizer and Novartis, and lecture fees supported by AstraZeneca. TS declares participation in advisory boards supported by Bristol Myers Squibb, Merck Sharp and Dohme, Novartis, and Pierre Fabre; and lecture fees supported by Astellas, AstraZeneca, and Bristol Myers Squibb. GM declares consultancy honoraria from Roche, Novartis, AstraZeneca, Pfizer, Jensen, Eli Lilly, and Sanofi. LDM declares consulting fees from Roche, Novartis, Eli Lilly, Merck Sharp and Dohme, Daiichi Sankyo, SeaGen, Gilead, Eisai, Pierre Fabre, AstraZeneca, Stemline Menarini, Exact Sciences, Agendia, GSK, and Pfizer. MM declares consulting fees from Cedilla Therapeutics and PharmEnable, and research support from PharmaMar, Eli Lilly, Pfizer, and Circle Pharma. SP-S declares consulting fees from Pfizer, Novartis, Eli Lilly, AstraZeneca, Gilead, Merck, Sharp and Dohme, and Roche. BP declares consulting fees from Astra Zeneca, SeaGen, Gilead, Eli Lilly, Merck Sharp and Dohme, Daiichi Sankyo, and Pierre Fabre. CS declares consulting fees from AstraZeneca, Daiichi Sankyo, Eisai Europe, Gilead, Novartis, Pharmalex, Pfizer, Phillips Health Works, Pierre Fabre, PintPharma, Puma Biotechnology, Roche Farma, SeaGen, Solti, Synthon Biopharmaceuticals, and Zymeworks. All other authors declare no competing interests.

#### Acknowledgments

Our sincere gratitude goes to Marco Banini, Marianna Valzano, and Pietro Garlatti from the University of Florence (Florence, Italy). We would also like to express our appreciation to Frank Vicini, Saverio Cinieri, Asal Rahimi, Maryam Garousi, Marta Perachino, Paola Francica, Chelain Goodman, Fatjona Kraja, and Alizee Camps Malea for their valuable contributions. CEC is funded by the National Institute of Health and Care Research (NIHR) and supported by the NIHR Cambridge Biomedical Research Centre. The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care. We extend our thanks to Fondazione Radioterapia Oncologica non-profit organisation and all who have provided essential support for scientific research. We also acknowledge the unconditional support of all the companies involved in the implementation of scientific research and studies, including IFCA Spa, Fondazione Cassa di Risparmio di Pistoia e Pescia, Conad Società Cooperativa, Fabiani Gioiellerie, Permira, Rinascente, and Giorgio Tesi Group. During the preparation of this work the authors used ChatGPT to improve readability and language of the work. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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# Postmastectomy Radiation Therapy: An ASTRO-ASCO-SSO Clinical Practice Guideline

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DOI https://doi.org/10.1200/JCO-25-01747


## ABSTRACT

*ASCO Guidelines provide recommendations with comprehensive review and analyses of the relevant literature for each recommendation, following the guideline development process as outlined in the ASCO Guidelines Methodology Manual. ASCO Guidelines follow the ASCO Conflict of Interest Policy for Clinical Practice Guidelines.*

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**PURPOSE** This guideline provides recommendations on use of postmastectomy radiation therapy (PMRT) in breast cancer treatment. 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** A multidisciplinary American Society for Radiation Oncology–ASCO–Society of Surgical Oncology task force addressed four key radiation therapy (RT) questions in patients with breast cancer who undergo mastectomy: (1) indications for PMRT after upfront surgery, (2) indications for PMRT after neoadjuvant systemic therapy followed by surgery, (3) appropriate PMRT volumes and dose-fractionation regimens, and (4) treatment techniques. Recommendations were based on a systematic review and created using a predefined consensus-building methodology for quality of evidence grading and strength of recommendation.

**RECOMMENDATIONS** 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 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 or 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 three-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, use of a bolus is recommended, but routine use of tissue-equivalent bolus is not recommended.

Additional information is available at www.asco.org/breast-cancer-guidelines.


## ACCOMPANYING CONTENT

Listen to the podcast by Brittany Harvey, Dr Kathleen Horst, Dr Rachel Jimenez, and Dr Yara Abdou at https://ascopubs.org/do/postmastectomy-radiation-therapy-astro-asco-sso-guideline

Appendix

Data Supplement

Accepted July 30, 2025
Published September 16, 2025

ASTRO Board of Directors approval: May 23, 2025
ASCO Evidence Based Medicine Committee approval: May 27, 2025
SSO Executive Committee approval: June 2, 2025

J Clin Oncol 43:3292-3311


View Online Article

## TARGET POPULATION AND AUDIENCE

**Target Population**

Adults (age ≥18 years) who received a diagnosis of breast cancer and underwent mastectomy.

**Target Audience**

Radiation oncologists, surgical oncologists, medical oncologists, oncology nurses, patients, radiologists, and other relevant oncologic professionals.

## INTRODUCTION

According to the WHO, in 2022, breast cancer was the second most common cancer and the fourth leading cause of cancer mortality worldwide.[1] 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.[2] 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.

The American Society for Radiation Oncology (ASTRO), 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[3] 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.

## GUIDELINE QUESTIONS

This clinical practice guideline addresses four overarching clinical questions: (1) What are the indications for PMRT in patients who receive mastectomy as their initial treatment for breast cancer? (2) What are the indications for PMRT in patients who receive neoadjuvant systemic therapy before mastectomy? (3) What are the appropriate treatment volumes (eg, chest wall or reconstructed breast, regional nodes, boost) and dose-fractionation regimens for patients who receive PMRT? (4) What are the appropriate techniques (eg, 3-dimensional conformal radiation therapy [3-D CRT], intensity-modulated radiation therapy [IMRT], protons, breath hold, bolus) for treating patients who receive PMRT?

## METHODS

### Guideline Development Process

This systematic review–based guideline product was developed by an ASTRO-ASCO-SSO joint task force that consisted of a multidisciplinary team of radiation, medical, and surgical oncologists; a radiation oncology resident; a medical physicist; a patient representative, and an ASTRO guidelines staff member with health research methodology expertise (Appendix Table A1, online only). This guideline was also developed in collaboration with the European Society for Radiotherapy and Oncology, which provided representatives and peer reviewers. This work was funded by ASTRO.

The joint task force used evidence-based methodologies to develop guideline recommendations in accordance with the National Academy of Medicine standards.[4,5] The evidence identified from key questions (KQs) is assessed using the Population, Intervention, Comparator, Outcome, Timing, Setting (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 Data Supplement 1 (online only) 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 five-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.

### 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 adoption of biologically tailored neoadjuvant systemic therapy and the de-escalation of axillary surgery with the use of sentinel lymph node biopsy or targeted axillary dissection, this guideline seeks to

**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.<br>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.<br>Most informed people would choose the recommended course of action, but a substantial number would not.<br>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 | Two 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 | One well-conducted and highly generalizable RCT or a meta-analysis including such a trial **OR**<br>Two or more RCTs with some weaknesses of procedure or generalizability **OR**<br>Two 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 | One RCT with some weaknesses of procedure or generalizability **OR**<br>One or more RCTs with serious deficiencies of procedure or generalizability or extremely small sample sizes **OR**<br>Two 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[a] | 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. |

NOTE. 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.

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

[a]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.



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, supraclavicular or infraclavicular, and internal mammary nodes (IMN). Specific situations where treatment volumes may be less comprehensive are noted in the text.

## Evidence Review: KQs, Key Outcomes, and Inclusion and Exclusion Criteria

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.

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

**TABLE 2.** Key Questions in PICO Format

| KQ | Population | Intervention | Comparator | Outcome |
|---|---|---|---|---|
| 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<br>Regional recurrence<br>Locoregional recurrence<br>Disease-free survival<br>Breast cancer mortality<br>Distant metastasis-free survival<br>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<br>Regional recurrence<br>Locoregional recurrence<br>Disease-free survival<br>Breast cancer mortality<br>Distant metastasis-free survival<br>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<br>Chest wall/reconstructed breast without RNI<br>RNI including IMNs<br>Boost | Conventional fractionation<br>Chest wall/reconstructed breast with RNI<br>RNI without IMNs<br>No boost | Local recurrence<br>Regional recurrence<br>Locoregional recurrence<br>Disease-free survival<br>Breast cancer mortality<br>Distant metastasis-free survival<br>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)<br>Electrons<br>Protons<br>Set-up verification, image guidance/surface guidance<br>Respiratory management, gating, breath hold<br>Bolus | 3-D CRT<br>PMRT with photons<br>No bolus | Local recurrence<br>Regional recurrence<br>Locoregional recurrence<br>Disease-free survival<br>Breast cancer mortality<br>Distant metastasis-free survival<br>Toxicity and adverse effects |

Abbreviations: 3-DCRT, 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.



oligometastatic or palliative disease, phyllodes tumors, or sarcomas of the breast.

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; and study types such as dosimetric or contouring studies, health economics or 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[6,7] flow diagram showing the number of articles screened, excluded, and included in the evidence review, and Data Supplement 2 for the literature search strategy, which includes the evidence search parameters and inclusion and exclusion criteria).

## Guideline Review and Approval

The guideline was reviewed by 17 official peer reviewers (Data Supplement 3) 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, the 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.

### Guideline Updating

Based on periodic formal review of the emerging literature, the respective organizations will determine the need to update. The ASCO Guidelines Methodology Manual (available at www.asco.org/guideline-methodology) provides additional information about the guideline update process. This is the most recent information as of the publication date.

## RESULTS

The data used by the task force to formulate recommendations are summarized in evidence tables available in Data Supplement 4. 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.

## KQs AND RECOMMENDATIONS

### KQ1: Indications for PMRT With Mastectomy as Initial Treatment (Table 3)

See evidence tables in Data Supplement 4 for the data supporting the recommendations for KQ1, and Figure 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.[2,8-10,15-17] Support for the use of PMRT in patients with nodal involvement comes from the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis.[2,11] 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.[2,11] 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 1-3 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,[2,18] 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.[8,10,17] In this context, the benefit of PMRT for low-volume, node-positive disease (pN1) has been questioned. The Selective Use of Postoperative Radiotherapy after Mastectomy

**TABLE 3.** Indications for PMRT With Mastectomy as Initial Treatment

| KQ1 Recommendation | Strength of Recommendation | Quality of Evidence (refs) |
|---|---|---|
| 1. For patients with node-positive (pN+) breast cancer, PMRT is recommended<br>*Implementation remarks:*<br>Omission of PMRT may be appropriate for select patients with pN1mic or low nodal burden pN1a disease following ALND who have favorable clinicopathologic features.<br>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[2,8-12] |
| 2. For patients with any pT4 breast cancer, PMRT is recommended even in the absence of any other risk factors. | Strong | High[2,8] |
| 3. For patients with pT3N0 breast cancer, PMRT is conditionally recommended.<br>*Implementation remark:* PMRT may be omitted or treatment volumes reduced (eg, chest wall alone) for patients with favorable clinicopathologic features including low-to-intermediate grade, HR-positive/HER2-negative subtype, postmenopausal status, absence of LVI, and a low 21-gene recurrence score. | Conditional | High[2,8,10] |
| 4. For patients with pT1-2N0 breast cancer, PMRT is **not** recommended.<br>*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[2,13,14] |
| 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.

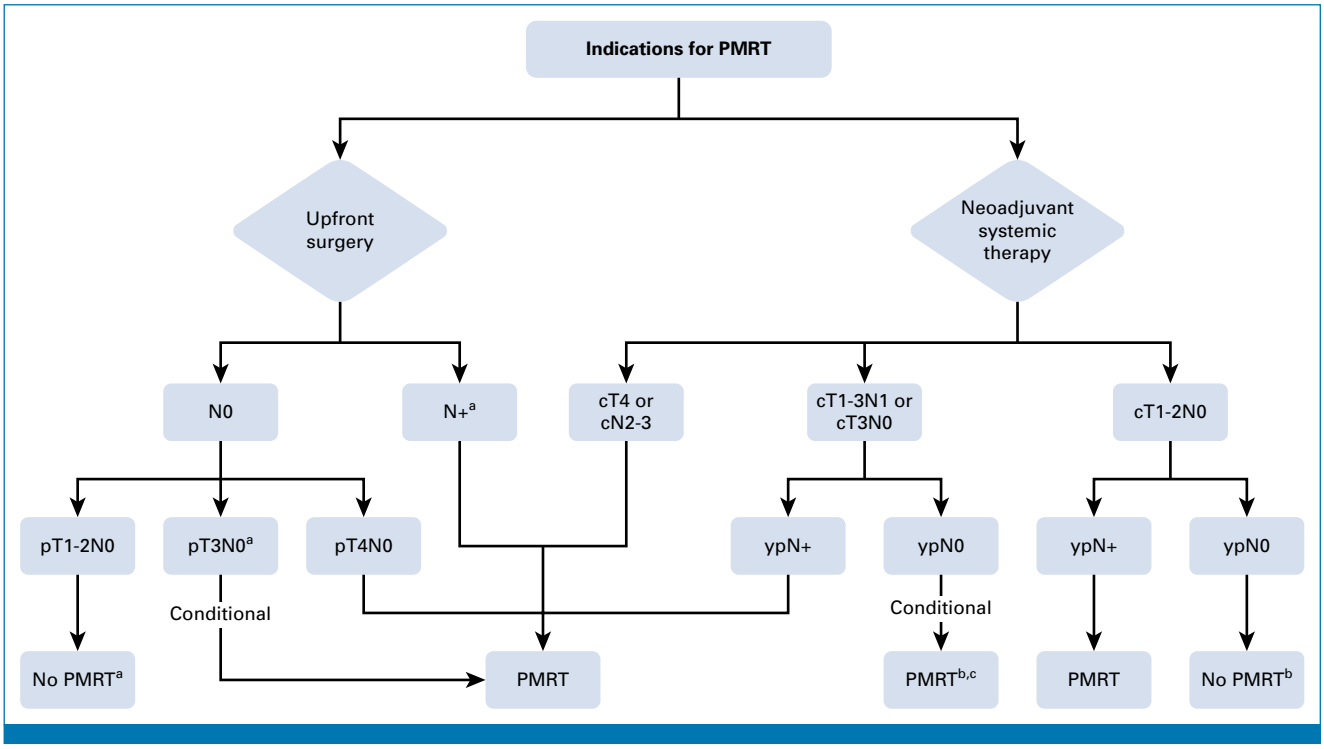



**FIG 1.** Indications for PMRT. [a]See implementation remarks in Table 3 for details. [b]See implementation remarks in Table 4 for details. [c]PMRT may be omitted in the setting of complete pathological response in the breast and lymph nodes (ypT0N0). PMRT, postmastectomy radiation therapy.



(SUPREMO; ClinicalTrials.gov identifier: NCT00966888) trial 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 eight lymph nodes removed. Final results from this study will provide additional insights regarding the value of PMRT in this favorable-risk population.[19] 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, ClinicalTrials.gov identifier: 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 end point 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 two positive lymph nodes present if sentinel lymph node biopsy alone is performed.[20] 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,[21] largely due to the competing risk for distant failure. Therefore, while LRR is an important end point, 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.[17,22,23] 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.[2,8–10,24,25] 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.[24,25] For patients with pT3N0 breast cancer, who were included in these RCTs, there was a >50% reduction in LRR with PMRT.[24,25] 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.[26] 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.[27-29] Patients with pT3N0 disease were included in the European Organisation 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. 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.[2,8] 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 (ClinicalTrials.gov identifier: NCT00966888) and the TAILOR-RT (ClinicalTrials.gov identifier: 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.[13] 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.[13] 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.[13] 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, although mastectomy patients comprised only approximately 25% of participants.[14] 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%.[2,30] 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.[30]

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.[31] 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.[8] 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 Data Supplement 4 for the data supporting the recommendations for KQ2 and Figure 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

**TABLE 4.** Indications for PMRT With Neoadjuvant Systemic Therapy

| KQ2 Recommendation | 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[32-36] |
| 2. For patients with positive lymph nodes after neoadjuvant systemic therapy (ypN+), PMRT is recommended. | Strong | Moderate[37-41] |
| 3. For patients with cT1-3N1 or cT3N0 breast cancer with pathologic negative nodes after neoadjuvant systemic therapy (ypN0), PMRT is conditionally recommended<br>*Implementation remarks:*<br>Patients with high-risk features (eg, young age, LVI, high residual cancer burden in the breast) may derive a greater benefit from PMRT.<br>PMRT may be omitted in the setting of complete pathologic response in the breast and lymph nodes (ypT0N0). | Conditional | Moderate[37,38,40-50] |
| 4. For patients with cT1-2N0 breast cancer with pathologic negative nodes after neoadjuvant systemic therapy (ypN0), PMRT is not recommended.<br>*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[37,38,43-45,47-49] |
| 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.

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.[42,51] 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.[32-36] Some studies have also shown an improvement in OS, but these were small retrospective evaluations.[32,33] 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.[32-36] In addition, several studies have demonstrated that residual nodal disease after neoadjuvant systemic therapy (ypN+) is associated with an increased risk of LRR.[37-39]

The extent of axillary nodal disease after neoadjuvant systemic therapy (ie, ypN1 *v* ypN2-3) is also an important risk factor.[37,40] 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.[39,40] An OS benefit for PMRT has been reported for patients with ypN2-3 disease.[40] 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 (ClinicalTrials.gov identifier: NCT01901094), evaluating whether RT to the undissected axilla and other regional lymph nodes after sentinel lymph node 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 (ClinicalTrials.gov identifier: NCT01872975), which randomly assigned 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, magnetic resonance imaging, positron emission tomography (PET) scan, or PET/CT scan, and patients with N2-3 disease detected clinically or by imaging were ineligible.[52] 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.[53] 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,[43,44] 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.[35] 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.[33,37,38,43,45,46,54] 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.[37,40,41,44,45,47,48,55,56]

The benefits of PMRT may be higher in younger women compared with older women.[32,43,57] 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.[32] This finding is consistent with a study from Korea that found age ≤40 years to be an independent predictor of LRR.[43] 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.[58-60]

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.[37,38,43-45,47-49]

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,[31] 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 Data Supplement 4 for the data supporting the recommendations for KQ3.

### *What Are the Appropriate Treatment Volumes (eg, chest wall or reconstructed breast, regional nodes, boost) and Dose-Fractionation Regimens for Patients Who Receive PMRT?*

In the EBCTCG meta-analysis of 8,135 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.[2] The meta-analysis also included eight 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%-80% of all local recurrences identified in RCTs were located in the chest wall,[9,17] 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.[14,61,76] 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.[61] 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 recurrence with the addition of IMN or supraclavicular irradiation in patients with stage I to III breast cancer.[14] 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.[76] 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

**TABLE 5.** PMRT Treatment Volumes and Dose-Fractionation Regimens

| KQ3 Recommendation | 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.<br>*Implementation remarks:*<br>Treatment to the chest wall/reconstructed breast alone may be used in select patients (eg, pT3N0).<br>Coverage of the IMNs may be individually determined based on tumor location (medial/central), tumor size, and extent of nodal involvement. | Strong | High[2,12,61-65] |
| 2. For patients *without* breast reconstruction receiving PMRT, moderate hypofractionation is recommended.<br>*Implementation remarks:*<br>Moderate hypofractionation is preferred, given equivalent oncologic outcomes and reduced toxicity.<br>Conventional fractionation may be an option in rare circumstances. | Strong | High[66-73] |
| 3. For patients *with* breast reconstruction receiving PMRT, moderate hypofractionation (preferred) or conventional fractionation is recommended. | Strong | Moderate[65,74] (moderate hypofx)<br>High[14,61,62,66,67,71-73,75] (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[66,67,74,76-80] |
| 5. For patients with nodal disease not surgically addressed and at risk of harboring residual disease, a nodal boost is recommended. | Strong | Expert opinion |

NOTE. Moderate hypofractionation is most frequently defined as 266 to 267 cGy per fraction for 15-16 fractions. Conventional fractionation is most frequently defined as 180 to 200 cGy per fraction for 25 to 28 fractions.[66-73]
Abbreviations: fx, fractionation; hypofx, hypofractionation; IMNs, internal mammary nodes; KQ, key question; PMRT, postmastectomy radiation therapy.

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.[2,10,81] Additionally, among patients who undergo an inadequate axillary dissection or whose pathological specimens demonstrate tumor deposits and/or 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.[2,17]

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.[14,76] 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.[62-64] 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.[63,82] 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.[64] 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.[64] Finally, the Korean Radiation Oncology Group 08-06 trial randomly assigned 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.[61-64,76]

Most of the studies evaluating PMRT have used conventional fractionation with doses approximating 5,000 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.[66,67,74,83-85] There is also precedent from RCTs to support the use of moderately hypofractionated regimens. In the landmark British Columbia study, 3,750 cGy in 16 fractions was used to deliver PMRT.[12] In the United Kingdom Standardization of Breast Radiotherapy A trial, enrolling 2,236 women with breast cancer, 15% underwent PMRT, and hypofractionated schedules resulted in similar locoregional failure rates, and lower adverse events, compared with conventional fractionation.[68] Additionally, the United Kingdom Standardization of Breast Radiotherapy B trial involved 2,215 women with breast cancer, with approximately 8% receiving PMRT.[69] At a median follow-up of 10 years, they found that 4,005 cGy in 15 daily fractions yielded comparable outcomes to 5,000 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.[69] In China, a noninferiority study randomly assigned 820 patients with at least four positive axillary nodes or T3-4 disease, excluding those with internal mammary or supraclavicular nodal involvement, to moderate hypofractionation (4,350 cGy in 15 fractions) or conventional fractionation (5,000 cGy in 25 fractions). At a median follow-up of 58.4 months, locoregional failure was deemed noninferior between arms (8.3% hypofractionation *v* 8.1% conventional fractionation), and there was a lower rate of grade 3 skin toxicity in the hypofractionation arm.[70] An additional RCT confirmed that there were no discernible differences in toxicities, LRR, distant failure rate, or DFS between PMRT regimens of 4,005 cGy in 15 fractions and 5,000 cGy in 25 fractions.[71] 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.[74,83] The phase III Fractionation on Patient Outcomes After Breast

REConstruction trial randomly assigned 400 patients with stage 0-III breast cancer, excluding T4 disease, after mastectomy with implant-based reconstruction to hypofractionated RT (4,256 cGy in 16 fractions) or conventional RT (5,000 cGy in 25 fractions).[65] The primary end point 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% *v* 7.7%). There was no difference in chest wall toxicity between the two groups at a median follow-up of 40.4 months.[65,86] Based on these data, the use of moderate hypofractionation is recommended as the preferred PMRT approach in the setting of implant-based reconstruction.[65]

Another completed RCT, Alliance A221505 (RT CHARM: Hypofractionated Post Mastectomy Radiation with Breast Reconstruction; ClinicalTrials.gov identifier: NCT03414970)[87] randomly assigned nearly 900 patients with T1-3N1-2 or T3N0 disease undergoing mastectomy with immediate or delayed reconstruction (implant-based or autologous) to hypofractionated PMRT (4,256 cGy in 16 fractions) or conventional PMRT (5,000 cGy in 25 fractions) with a primary end point of reconstruction complication rate. In this trial, patients with T4 and N3 disease, including IMN involvement, were excluded.[87] Final published results from this study will provide additional data on the clinical outcomes and toxicity of hypofractionated PMRT with reconstruction.[87] 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 previously mentioned trials,[65,70,72,86,87] 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.[88,89] 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.[90,91]

Finally, there is increasing interest in the use of ultrahypofractionated treatment regimens (ie, 2,600 cGy in five 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,[92] and additional trials are underway to further evaluate these abbreviated treatment regimens for patients requiring PMRT.[93,94]

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,[9] only retrospective studies have examined the use of chest wall boosts for high-risk patients and have provided some support for doses up to 6,600 cGy using conventional fractionation.[95-98] 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.[99] 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.[100] 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.[63,64] 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.[101,102] However, if adding a boost to an undissected node, doses of 6,000 cGy EQD2 should be considered for microscopic disease and at least 6,600 cGy EQD2 for gross or residual disease.

### KQ4: Appropriate PMRT Delivery Techniques (Table 6)

See evidence tables in Data Supplement 4 for the data supporting the recommendations for KQ4.

**TABLE 6.** Appropriate PMRT Delivery Techniques

| KQ4 Recommendation | 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[14,62-64,82,103-105] |
| 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).<br>*Implementation remark:* Use of IMRT (including VMAT) may increase OAR low-dose exposure compared with 3-D CRT. | Strong | Moderate[106-110] |
| 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.<br>*Implementation remarks:*<br>Other normal tissue sparing techniques may be used.<br>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[109,111,112] |
| 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[113] |
| 5. For patients with cT1-3 breast cancer receiving PMRT, the routine use of tissue-equivalent bolus is not recommended.<br>*Implementation remark:* Bolus may be used in circumstances where improved dosimetric coverage of the skin is needed. | Strong | Moderate[114-119] |
| 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.



### *What Are the Appropriate Techniques (eg, 3-D CRT, 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.[8,12,14,62-64,82,103,120] 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 and/or right coronary artery, bilateral lungs, contralateral breast, spinal cord, thyroid, esophagus, humeral head, stomach, liver, and/or brachial plexus).[121,122] Use of contouring guidelines, such as those provided by the Radiation Therapy Oncology Group atlas, RADCOMP (Radiotherapy Comparative Effectiveness),[121] and European atlases,[122,123] 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, 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).[14,62-64,82,103-105] 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.[124] 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.[125,126] Studies comparing various techniques have shown low LRR rates regardless of technique.[66,103,105,106]

Treatment with inverse planned IMRT can decrease the high-dose exposure of OARs compared with 3-DCRT, and in some cases decrease the risk of toxicity.[66,107,108,127] 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.[66] Another study

**TABLE 7.** Guidance on Target Coverage

| Structure | Goal | 5,000-5,040 cGy in 25-28 fx | 4,000-4,256 cGy in 15-16 fx |
|---|---|---|---|
| Ipsilateral chest wall[52,87] | Ideal | D95 ≥95% PTV | D95 ≥95% PTV |
| | Acceptable | D90 ≥90% PTV | D90 ≥90% PTV |
| | Ideal | D0.1 cc ≤110% | D0.1 cc ≤107%[b] |
| | Acceptable | D0.1 cc ≤115%Rx | D0.1 cc 115% Rx |
| Axilla[a,42,79] | 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[b] |
| | Acceptable | D0.1 cc ≤115%Rx | D0.1 cc 115% Rx |
| Supraclavicular fossa[52,87] | 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[b] |
| | Acceptable | D0.1 cc ≤120%Rx | D0.1 cc 115% Rx |
| Internal mammary nodes[52,87] | Ideal | D95 ≥90% PTV | D95 ≥90% PTV |
| | Acceptable | D90 ≥80% PTV | D90 ≥80% PTV |

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



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% *v* 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.[127] One tradeoff of reduced high-dose exposure to OARs with IMRT 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,[128] 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.[134,135] Although a dose-dependent relationship between cardiac exposure to RT and heart disease has been demonstrated in several landmark studies,[136-140] 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 should be given to minimizing RT exposure to the heart for patients with preexisting 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.[141,142]

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.[111,112] Among patients for whom DIBH can be successfully implemented, cardiopulmonary dose can be reduced compared with a free-breathing 3-D CRT technique.[111,143] 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.[139,144] 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.[109] Although there was no difference in single-photon emission CT perfusion defects in the LAD territory or lung perfusion or 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.[109] 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.[109,111]

The use of proton therapy remains under investigation at the time of guideline development. Single-institution series,

**TABLE 8.** Guidance on Organs at Risk

| Structure | Goal | 5,000-5,040 cGy in 25-28 fx | 4,000-4,256 cGy in 15-16 fx |
|---|---|---|---|
| Ipsilateral lung[52,87] | | V5 Gy ≤75% | V4 Gy ≤65%[b] |
| | Ideal | V10 Gy ≤65% | V8 Gy ≤55%[b] |
| | | V20 Gy ≤35%[a] | V17 Gy ≤25%[b] |
| | Acceptable | V20 Gy ≤40% | V17 Gy ≤35% |
| Contralateral lung[87] | Ideal | V5 Gy ≤10% | V4 Gy ≤10%[b] |
| | Acceptable | V5 Gy ≤15% | V4 Gy ≤15%[b] |
| Heart[c,87] | Ideal (left-sided) | Dmean ≤3 Gy | Dmean ≤2.4 Gy[b] |
| | Acceptable (left-sided) | Dmean ≤5 Gy | Dmean ≤4Gy[b] |
| | Ideal (right-sided) | Dmean <2 Gy | Dmean ≤1.6 Gy[b] |
| | Acceptable (right-sided) | Dmean ≤3 Gy | Dmean ≤2.4 Gy[b] |
| Contralateral breast/chest wall[52,87] | Ideal | V3 Gy ≤10% | V3 Gy ≤10% |
| | Acceptable | V5 Gy ≤10% | V5 Gy ≤10% |
| Additional considerations | | | |
| Brachial plexus[92] | Suggested | D0.1cc ≤105%Rx | D0.1 cc ≤105% Rx |
| Esophagus | Suggested | V10 Gy <30%/V20 Gy <15%[129] | V8 Gy <30%/V17 Gy <15%[b,130] |
| Left ventricle[131] | Suggested | V2 Gy <36% | V1.6 Gy <36%[b] |
| Spinal cord[a] | Suggested | D0.1 cc 45 Gy | D0.1 cc 38.54 Gy |
| Thyroid[132,133] | 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 |

NOTE. Where dose constraints differed by protocol, the more conservative guidelines were used. 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.
Abbreviations: Dmean, mean dose received by an organ; HYPOG-1, Hypofractionated Radiotherapy for Breast Cancer Nodal Irradiation-1; Rx, prescription dose.
[a]Based on the HYPOG-1 trial protocol (ClinicalTrials.gov identifier: NCT03127995).
[b]Extrapolated from conventionally fractionated data.
[c]Cardiac dose should be constrained as low as reasonably achievable.



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.[145-149] The RAD-COMP 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.[121,130]

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 [CBCT], SGRT), is recommended for patient localization for complex planning and multifield techniques, such as IMRT (including VMAT).[150,151] Volumetric imaging (eg, CBCT) is valuable under these conditions to assess for evolving anatomic changes or setup variability that may adversely affect treatment accuracy. However, the planning target volume margins should account for setup variability and the type and frequency of image guidance used during treatment.[152]

Alternatively, SGRT using the patient's external surface and nonionizing radiation can assist in PMRT patient setup,[111,153] monitor intrafraction motion,[154,155] and verify breath hold position.[112,153] However, in addition to training and workflow issues,[155] significant tissue deformations and limitations in the technology to detect darker skin tones have been identified as potential drawbacks.[156] 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 setup verification. Guidance for the use of SGRT with image guidance, including common challenges and potential errors, has been published.[155]

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,[52,86,157] 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.[114-118,158] At the same time, despite the historical assumption of benefit, the impact of bolus on local control has been questioned, including three small retrospective studies that did not identify a local control benefit with bolus.[116-118] 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.[114] 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.[117,118] 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, although no studies to date have specifically evaluated the impact of bolus across different skin tones.[90,91] 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.[114]

## 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 [ClinicalTrials.gov identifier: NCT03488693]), hypofractionation (RT CHARM [ClinicalTrials.gov identifier: NCT03414970],[87] HYPOG-01 [ClinicalTrials.gov identifier: NCT03127995], FAST FORWARD nodal substudy,[92] HYPORT-Adjuvant study[159]), PMRT after neoadjuvant chemotherapy (NSABP B-51 [ClinicalTrials.gov identifier: NCT01872975]),[52] particle therapy (RADCOMP [ClinicalTrials.gov identifier: NCT02603341], PARABLE (United Kingdom),[130] Danish Breast Proton Trial [ClinicalTrials.gov identifier: NCT04291378]),[160] and the role of axillary surgery (Alliance A011202 [ClinicalTrials.gov identifier: NCT01901094]) that will impact clinical decision making and future clinical practice.

**ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care, and that all patients should have the opportunity to participate.**

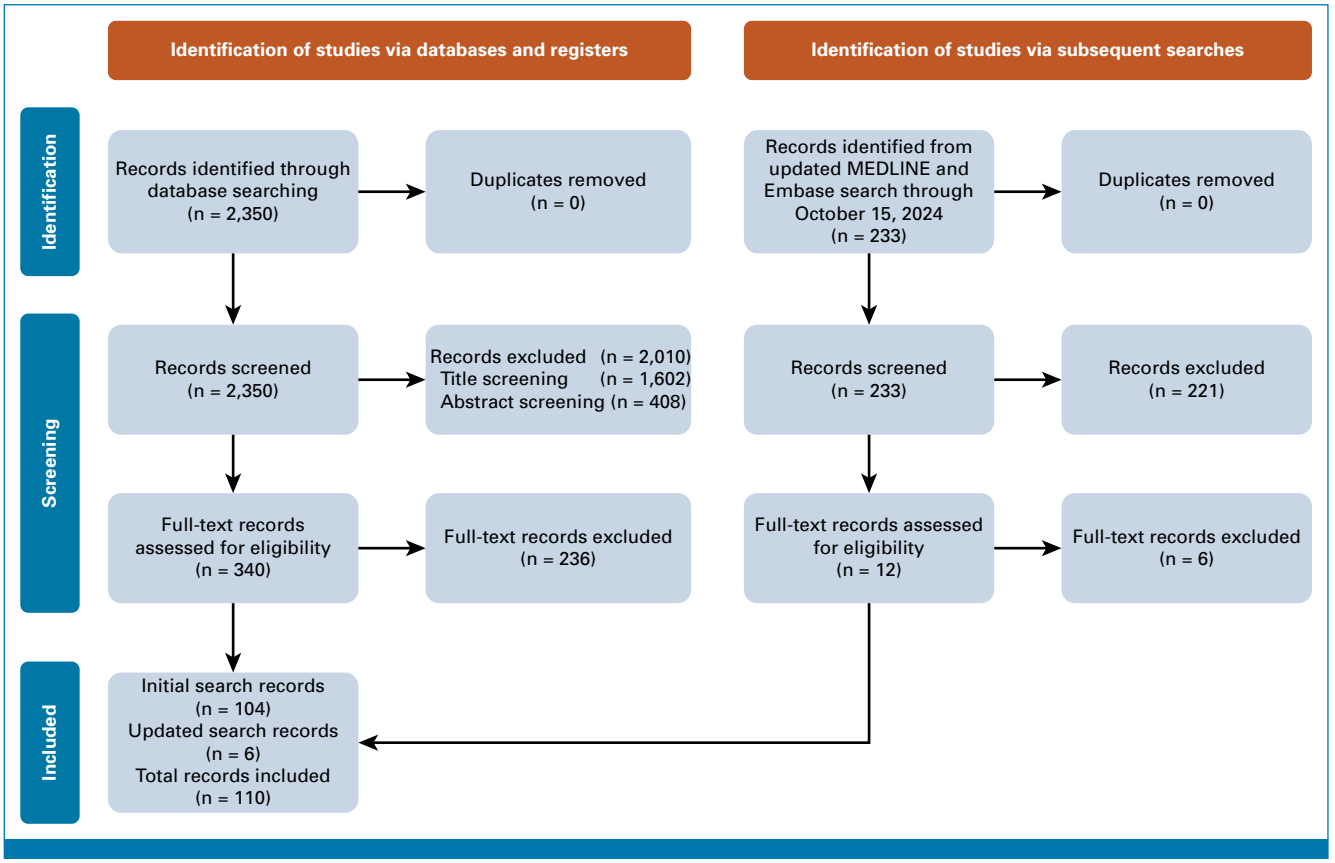
## ADDITIONAL RESOURCES

For current information, including selected updates, supplements, and clinical tools and resources, visit www.asco.org/breast-cancer-guidelines. The Data Supplement for this guideline includes a list of abbreviations used in the guideline, the PICOTS and literature search strategies, a list of guideline peer reviewers, and data supporting the recommendations. Guideline recommendations are also available in the free ASCO Guidelines app (available for download in the Apple App Store and Google Play Store). Listen to key recommendations and insights from panel members on the ASCO Guidelines podcast. The Methodology Manual (available at www.asco.org/guideline-methodology) provides additional information about the methods used to develop this guideline. Patient information is available at www.cancer.org.

The task force welcomes your comments on this guideline, including implementation challenges, new evidence, and how this guideline impacts you. To provide feedback, contact us at guidelines@asco.org. Comments may be incorporated into a future guideline update. To submit new evidence or suggest a topic for guideline development, complete the form available at www.asco.org/guidelines.

## INCLUSIVE LANGUAGE

ASCO is committed to promoting the health and well-being of all patients. ASCO guidelines are intended to apply to, and be discussed clearly and compassionately with, all patients. For this reason, guideline authors use appropriately inclusive language. In instances in which the guideline draws upon data based on research in a specified population (eg, studies regarding women with ovarian cancer), the guideline authors describe the characteristics and results of the research as reported.




PRISMA 2020 study selection diagram. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.



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## EDITOR'S NOTE

This ASCO Clinical Practice Guideline provides recommendations, with comprehensive review and analyses of the relevant literature for each recommendation. Additional information, including a supplement with additional evidence tables, clinical tools and resources, and links to patient information at www.cancer.org, is available at www.asco.org/breast-cancer-guidelines. These evidence-based recommendations guide clinical practice on the use of PMRT in patients with breast cancer.

## EQUAL CONTRIBUTION

R.B.J. and K.C.H. were Expert Panel vice chair and chair, respectively.

## SUPPORT

Supported by the American Society for Radiation Oncology.

## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/JCO-25-01747.

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## ACKNOWLEDGMENT

ASCO wishes to thank Tiffinay Traina, MD, Rachel Yung, MD, and the Evidence Based Medicine Committee for their thoughtful reviews and insightful comments on this guideline. The task force thanks the National Institutes of Health (NIH) Library biomedical librarians, Tracy C. Shields, MSIS, and Alicia A. Livinski, MPH, MA, for conducting the literature searches for this guideline; and Kekoa Taparra, MD, PhD, MPH (lead resident), Claire Baniel, MD, Katie Hwang, MD, Osagie Igiebor, MD, and Kaidi Wang, MD, for literature review assistance. The task force also thanks the peer reviewers for their comments and time spent reviewing the guideline. See Data Supplement for their names and disclosures. The authors also thank task force participant Angel Montero, MD, PhD, for serving as ESTRO's representative but who withdrew from authorship.

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## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

**Postmastectomy Radiation Therapy: An ASTRO-ASCO-SSO Clinical Practice Guideline**

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Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

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No other potential conflicts of interest were reported.

# APPENDIX 1

## ASCO GUIDELINE DISCLAIMER

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The Expert Panel was assembled in accordance with ASCO's Conflict of Interest Policy Implementation for Clinical Practice Guidelines ("Policy," found at www.asco.org/guideline-methodology). All members of the Expert Panel completed ASCO's disclosure form, which requires disclosure of financial and other interests, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as a result of promulgation of the guideline. Categories for disclosure include employment; leadership; stock or other ownership; honoraria, consulting or advisory role; speaker's bureau; research funding; patents, royalties, other intellectual property; expert testimony; travel, accommodations, expenses; and other relationships. In accordance with the Policy, the majority of the members of the Expert Panel did not disclose any relationships constituting a conflict under the Policy.

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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.

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 (Data Supplement). 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.

**TABLE A1.** ASTRO-ASCO-SSO Joint PMRT Task Force Membership

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Abbreviations: ASTRO, American Society for Radiation Oncology; SSO, Society of Surgical Oncology.

ROJ Radiation Oncology Journal

Original Article

pISSN 2234-1900 · eISSN 2234-3156
Radiat Oncol J 2024;42(4):308-318
https://doi.org/10.3857/roj.2024.00248

# Radiation therapy volumes after primary systemic therapy in breast cancer patients: an international EUBREAST survey

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Received: April 2, 2024
Revised: May 25, 2024
Accepted: May 28, 2024

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**Purpose:** After primary systemic therapy (PST), agreement on the extent of locoregional therapy is lacking in breast cancer patients who convert from a node-positive to a node-negative status. The aim of this survey was to investigate radiation therapy approaches after PST according to different axillary surgical strategies and disease responses.

**Materials and Methods:** The European Breast Cancer Research Association of Surgical Trialists developed a web-based survey containing 39 questions on locoregional management based on clinical scenarios in initially node positive breast cancer patients undergoing PST. Twelve international breast cancer societies distributed the link to breast surgeons and radiation oncologists.

**Results:** Responses from 349 breast specialists were recorded, 72 of whom (20.6%) were radiation oncologists from 17 countries. Nodal status at diagnosis informed the decision for postoperative regional nodal irradiation (RNI) for 44/72 (61.1%) responders. RNI in node positive patients having undergone axillary lymph node dissection (ALND) is delivered in selected cases by 30/72 (41.7%) responders and systemically recommended by 26/72 (36.1%) responders. In case of macrometastases found on ALND, 43/72 (59.7%) responders always deliver RNI. In case of micrometastases in the sentinel lymph node(s) or targeted lymph node(s), 45/72 (62.5%) responders prefer RNI to completion ALND. A majority of responders (59.7%) determine the target volume for RNI according to European Society for Radiotherapy and Oncology guidelines. Significant heterogeneity was observed regarding nodal basins and volumes of interest for dose coverage by RNI.

**Conclusions:** There is significant heterogeneity in radiation-therapy delivered to the axilla after PST. A more standardized approach engaging both radiation oncologists and breast surgeons will help to optimize the harm-benefit equilibrium of axillary surgery and RNI.

**Keywords:** Axillary lymph node dissection, Primary systemic therapy, Sentinel lymph node biopsy, Regional nodal irradiation

## Introduction

Breast cancer therapy has evolved significantly in the past decades. Early detection and tumor biology-driven systemic therapy has led to improvement in disease control and individualization of locoregional therapies (i.e., surgery and/or radiation therapy) [1,2]. Primary systemic therapy (PST), as opposed to postoperative (i.e., adjuvant) therapy, is recommended to down-stage the in-breast and axillary tumor load to perform less extensive surgery, and to tailor subsequent treatments based on the evaluation of tumor response. For patients with residual disease after PST, new postoperative treatment options emerge, making PST the preferred approach for an increasing number of breast cancer patients [3,4]. Current guidelines recommend PST in subtypes that are highly sensitive to chemotherapy (e.g., highly proliferative, triple negative or human epidermal growth factor receptor 2-positive disease) and in patients with a high tumor load, who might become candidates for de-escalation of surgery [5-7]. However, post-PST locoregional radiation therapy (RT) guidelines are mostly relying on pre-PST disease stage, while meanwhile de-escalation of locoregional therapy upon response is evaluated in clinical trials [1,8]. Even though there is no long-term data from randomized trials, many centers already adopt locoregional therapy to the individual response to PST [8]. The non-for-profit organization, European Breast Cancer Research Association of Surgical Trialists (EUBREAST), has initiated the AXSANA study (EUBREAST03) which aims to evaluate the outcomes of different types of axillary surgery after PST [2]. As part of the EUBREAST effort to improve locoregional therapy for breast cancer, an international survey regarding locoregional treatment approaches after PST was conducted. Since axillary surgery and regional nodal irradiation (RNI) are interchangeable in some cases (as shown in the AMAROS [9] and OTOSOAR [10] trial) or complementary [11], this work aims to explore current practices after PST. In a previous report about surgical management of the axilla, significant heterogeneity in surgical approaches after PST was observed [12]. In this report, survey results regarding RNI practices after PST are summarized and discussed. The clinical scenarios that were described in the survey do not necessarily reflect the recommended standard of care—e.g., sentinel lymph node (SLN) biopsy or targeted axillary dissection (TAD) in case of residual nodal disease at the final histology analysis (ypN+) [6]. Thereby, it aims to demonstrate which nodal basins are targeted for RT according to the type of surgery in real-life circumstances.

## Materials and Methods

The survey was designed by a panel of EUBREAST breast cancer experts, comprising two radiation oncologists who serve as faculty of the European Society for Radiotherapy and Oncology (ESTRO) breast cancer course (P.P., O.K.P.), two gynaecologists/breast surgeons (M.L.G., T.K.) one of whom is also on the faculty of the same ESTRO course (T.K.), and two breast surgeons (J.D.B., O.D.G.). The survey was distributed through the networks of 13 international breast cancer societies supporting the initiative (Supplementary Table S1) and was launched online through a Google Form on April 20, 2021 and closed on October 6, 2021. This study does not need an institutional review board review due to the nature of the survey.

Each responding healthcare professional agreed explicitly to participate in the study before submitting their form. Participants completed the questionnaire anonymously. No specific requirements were set for physicians participating in the survey. They were asked to complete the questions based on the standard of care at their center. Survey data were collected in a secure and anonymous central database for analysis and reported in aggregate form. For each question, participants selected one or more answers from a list of options.

The survey comprised three sections: a general section directed to all responders regardless of their specialty, one directed to breast surgeons, and one directed to radiation oncologists. The results from the second section have been published before [12]. The list of questions concerning radiation oncology is available in Supplementary Table S2. Statistical analysis was performed with Microsoft Office Excel 365, version 2020 (Microsoft, Redmond, WA, USA) and GraphPad Prism version 6.0 (GraphPad Software, San Diego, CA, USA).

## Results

A total of 349 breast surgeons and radiation oncologists completed the survey. Of these respondents, 72/349 (20.6%) were radiation oncologists from 17 countries, listed in Supplementary Table S3. Among these, 44/72 (61.1%) worked in university hospitals or hospitals affiliated to universities. The annual hospital caseload exceeded 200 new primary breast cancer patients in the centers of 52/72 (72.2%) responders. A total of 21/72 (29.1%) of responders worked at centers participating in the EUBREAST03/AXSANA study, and 27/72 (37.5%) worked in centers participating in other clinical trials evaluating axillary management after PST.

### 1. Nodal positive definition

Of all radiation oncologists, 53/72 (73.6%) indicated that histopathological or cytological confirmation was required to classify a patient as nodal positive prior to PST (cN+). Another 17/72 (23.6%) asked for such confirmation only in selected cases, and 2/72 (2.7%)

classify cN+ patients based on clinical and/or radiological suspicion alone. Among those respondents requiring biopsy confirmation, a core needle biopsy was preferred by 30.0% (21/70) and a fine needle aspiration by 22.8% (16/70). For the remainder, it was dependent on the individual case.

### 2. Influence of nodal status at diagnosis on postoperative RNI

Nodal status at diagnosis informed the decision for postoperative RNI for 44/72 (61.1%) responders, whereas 28/72 (38.8%) responders based RNI on combined pre- and/or post-PST assessment.

### 3. Post-PST nodal radiation therapy in case of residual disease

RNI in ypN+ patients undergoing axillary lymph node dissection (ALND) is delivered in selected cases by 30/72 (41.7%) responders; systemically recommended by 26/72 (36.1%) responders and not recommended at all by 16/72 (22.2%) responders (Fig. 1A). A majority of responders (43/72; 59.7%) determine the target volume for RNI according to ESTRO guidelines [13], while 24/72 (33.3%) use Radiation Therapy Oncology Group (RTOG) guidelines [14] and another 5/72 (6.9%) do not delineate nodal volumes but use field-based RT (Fig. 1B).

In case of ALND in patients who presented with macrometastases at either upfront staging or upon completion surgery after RNI, 43/72 (59.7%) responders would deliver RNI regardless of the number of macrometastases, 26/72 (36.1%) responders offer RNI in case of >3 macrometastases, and 3/72 (4.1%) responders would not consider RNI in such cases (Fig. 2A).

In case of micrometastases (ypN1mic) in the lymph node(s) retrieved via SLN biopsy or TAD, 45/72 (62.5%) responders prefer RNI rather than completion ALND (Fig. 2B). In case of isolated tumor cells (ypN0(i+)) in the SLNs or targeted lymph nodes, 47/72 (65.3%) responders recommended RNI rather than ALND (Fig. 2C).

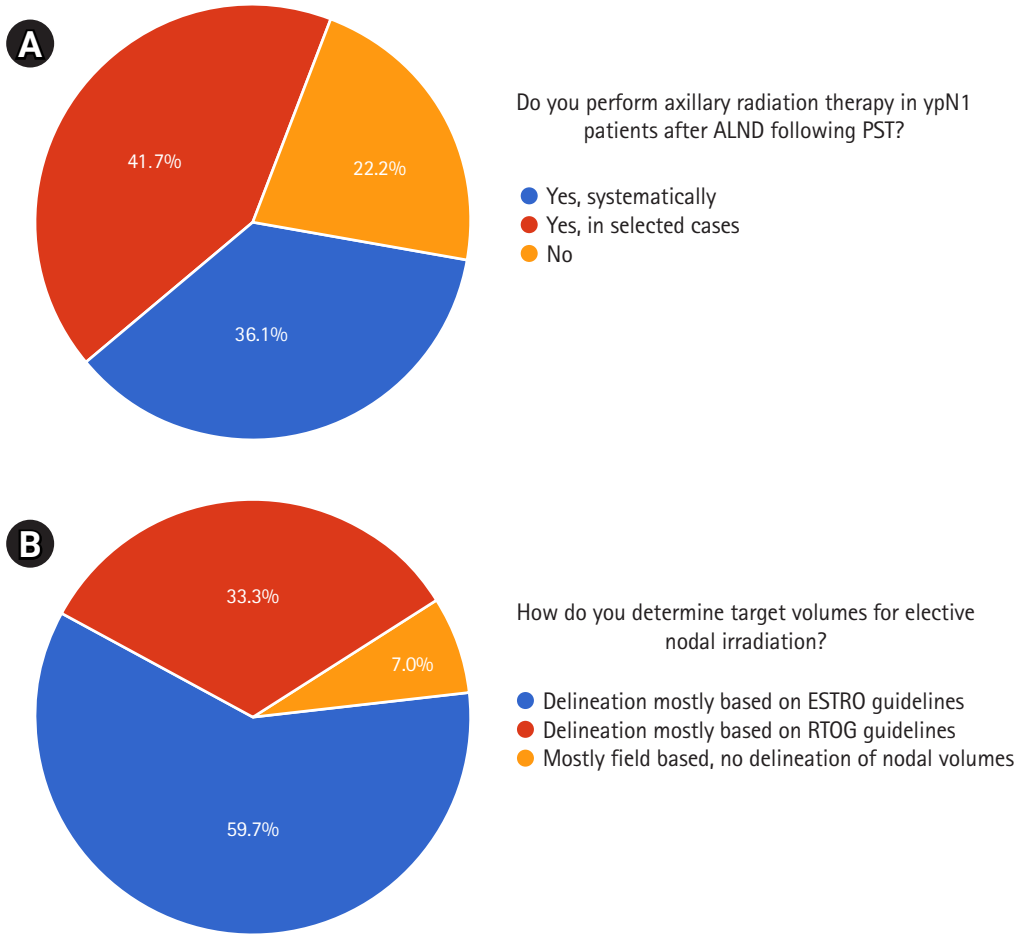


**Fig. 1.** Regional nodal irradiation after primary systemic treatment (PST); in case of breast cancer patients with positive nodes at final histology (A) and target volumes (B). ALND, axillary lymph node dissection; ESTRO, European Society for Radiotherapy and Oncology; RTOG, Radiation Therapy Oncology Group.


https://doi.org/10.3857/roj.2024.00248

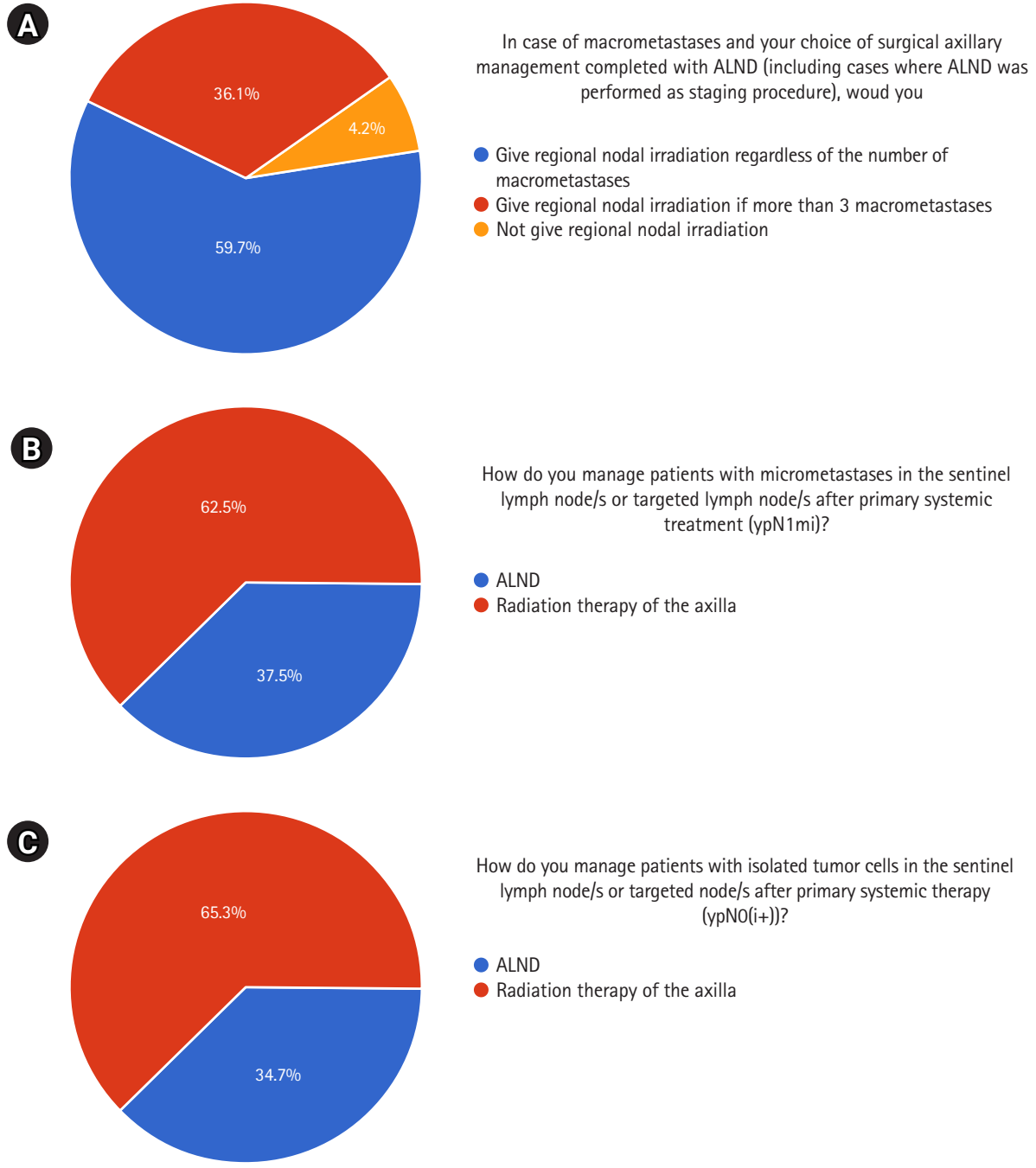


**Fig. 2.** Regional nodal irradiation and residual disease in the axillary lymph-node(s). Macro-metastases after ALND (A); micro-metastases after SLNB/TAD (B); isolated tumor cells after SLNB/TAD (C). ALND, axillary lymph node dissection; SLNB, sentinel lymph node biopsy; TAD, targeted axillary dissection.

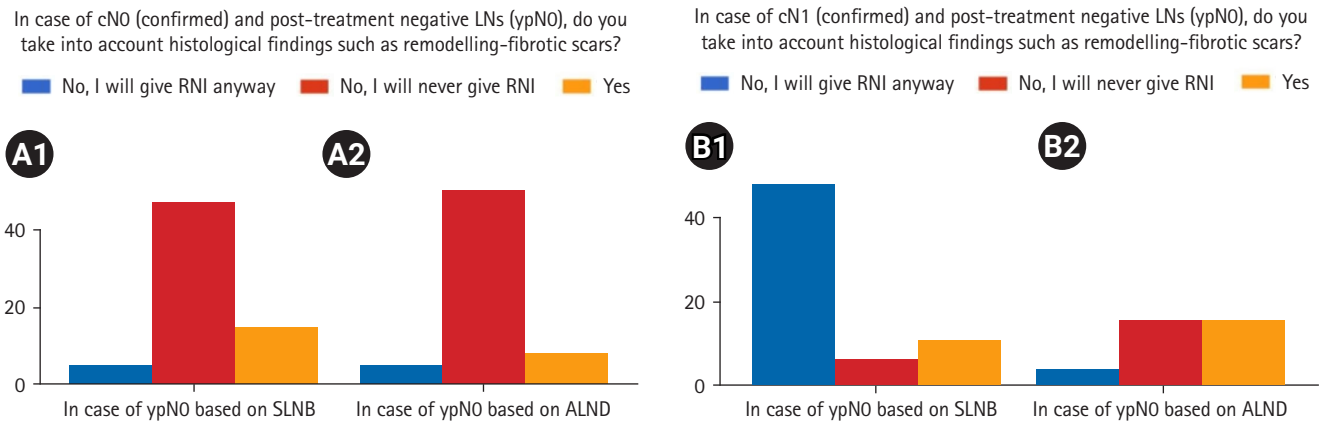


**Fig. 3.** RNI and remodelling-fibrotic scars: in nodal negative (clinically and pathologically) breast cancer patients after SLNB (A1); in nodal negative (clinically and pathologically) breast cancer patients after ALND (A2); in clinically nodal positive breast cancer patients converted to negative nodal status after primary systemic treatment after SLNB (B1); in clinically nodal positive breast cancer patients converted to negative nodal status after primary systemic treatment after ALND (B2). RNI, regional nodal irradiation; ALND, axillary lymph node dissection; SLNB, sentinel lymph node biopsy.

**Table 1.** LN basins of postoperative irradiation in primary nodal positive breast cancer patients undergoing sentinel lymph node biopsy or targeted axillary lymph node dissection

| | Level 1-4<br>Level 1-4<br>Level 3-4 | Level 3-4 | IMC Level 3-4<br>IMC | IMC Level 1-4<br>Level 1-4<br>Level 3-4<br>IMC | Unoperated levels (1-4) upwards[a]<br>Unoperated levels (1-4) upwards[a]<br>Level 1-4<br>Unoperated levels (1-4) upwards[a]<br>Level 1-4 Level 3-4<br>Unoperated levels (1-4) upwards[a]<br>Level 3-4 | Unoperated levels (1-4) upwards[a]<br>IMC<br>Unoperated levels (1-4) upwards[a]<br>Level 1-4<br>IMC<br>Unoperated levels (1-4) upwards[a]<br>Level 3-4<br>IMC<br>Unoperated levels (1-4) upwards[a]<br>Level 1-4 Level 3-4<br>IMC |
|---|---|---|---|---|---|---|
| ypN0 | 29 (40) | 18 (25) | 5 (7) | 6 (8) | 12 (17) | 2 (3) |
| ypN0(i+) | 32 (44) | 17 (24) | 5 (7) | 7 (10) | 10 (14) | 1 (1) |
| ypN1(mi) | 30 (42) | 18 (25) | 5 (7) | 8 (11) | 9 (13) | 2 (3) |
| ypN1 | 31 (43) | 10 (14) | 4 (6) | 14 (19) | 11 (15) | 2 (3) |
| ypN2 | 24 (33) | 5 (7) | 3 (4) | 29 (40) | 6 (8) | 6 (8) |
| ypN3 | 18 (25) | 5 (7) | 2 (3) | 36 (50) | 4 (6) | 7 (10) |
| ypN+ inner and central tumors | 5 (7) | 4 (6) | 12 (17) | 37 (51) | 7 (10) | 9 (13) |
| ypN+, ECE, < 2 mm | 28 (39) | 7 (10) | 4 (6) | 19 (26) | 9 (13) | 6 (8) |
| ypN+, ECE, > 2 mm | 29 (40) | 7 (10) | 5 (7) | 2 (3) | 7 (10) | 20 (28) |
| ypN+, tumor fat deposit, intramammary + LN | 16 (22) | 2 (3) | 4 (6) | 35 (49) | 9 (13) | 5 (7) |
| cN0 and ypN0 in axilla but internal mammary node avid on PET/CT pre-PST | 2 (3) | 2 (3) | 29 (40) | 25 (35) | 10 (14) | 4 (6) |

Values are presented as number (%).
LN, lymph node; ypN, pathology staging after primary systemic therapy; ECE, extracapsular extension; IMC, internal mammary chain, axilla level 1,2,3,4 per European Society for Radiotherapy and Oncology lymph node atlas for breast delineation; PET/CT, positron emission tomography/computed tomography; PST, primary systemic therapy.
[a]Where the axillary surgical changes end on CT-sim, the axillary nodal volume may include all or part of a basin level (example only the upper part of level 1, all level 2, rotter, level 3 & 4).


https://doi.org/10.3857/roj.2024.00248

**Table 2.** LN basins of postoperative irradiation in primary nodal positive breast cancer patients undergoing axillary lymph node dissection after PST

| | Level 1-4<br>Level 1-4 Level 3-4 | Level 3-4 | IMC Level 3-4<br>IMC | IMC Level 1-4<br>Level 1-4 Level 3-4<br>IMC | Unoperated levels (1-4) upwards[a]<br>Unoperated levels (1-4) upwards[a]<br>Level 1-4<br>Unoperated levels (1-4) upwards[a]<br>Level 1-4 Level 3-4<br>Unoperated levels (1-4) upwards[a]<br>Level 3-4 | Unoperated levels (1-4) upwards[a]<br>IMC<br>Unoperated levels (1-4) upwards[a]<br>Level 1-4<br>IMC<br>Unoperated levels (1-4) upwards[a]<br>Level 3-4<br>IMC<br>Unoperated levels (1-4) upwards[a]<br>Level 1-4 Level 3-4<br>IMC |
|---|---|---|---|---|---|---|
| ypN0 | 2 (3) | 33 (46) | 9 (13) | 1 (1) | 16 (22) | 3 (4) |
| ypN0(i+) | 10 (14) | 33 (46) | 9 (13) | 1 (1) | 16 (22) | 3 (4) |
| ypN1(mi) | 11 (15) | 32 (44) | 9 (13) | 1 (1) | 15 (21) | 4 (6) |
| ypN1 | 12 (17) | 29 (40) | 9 (13) | 1 (1) | 13 (18) | 8 (11) |
| ypN2 | 15 (21) | 13 (18) | 17 (24) | 6 (8) | 7 (10) | 14 (19) |
| ypN3 | 12 (17) | 7 (10) | 18 (25) | 15 (21) | 6 (8) | 14 (19) |
| ypN+ inner and central tumors | 6 (8) | 3 (4) | 29 (40) | 14 (19) | 7 (10) | 13 (18) |
| ypN+, ECE, < 2 mm | 1419) | 19 (26) | 12 (17) | 7 (10) | 11 (15) | 9 (13) |
| ypN+, ECE, > 2 mm | 18 (25) | 14 (19) | 13 (18) | 10 (14) | 11 (15) | 6 (8) |
| ypN+, tumor fat deposit, intramammary + LN | 10 (14) | 6 (8) | 20 (28) | 16 (22) | 8 (11) | 9 (13) |
| cN0 and ypN0 in axilla but internal mammary node avid on PET/CT pre-PST | 3 (4) | 1 (1) | 41 (57) | 10 (14) | 8 (11) | 9 (13) |

Values are presented as number (%).
LN, lymph node; ypN, pathology staging after primary systemic therapy; ECE, extracapsular extension; IMC, internal mammary chain, axilla level 1,2,3,4 per European Society for Radiotherapy and Oncology lymph node atlas for breast delineation; PET/CT, positron emission tomography/computed tomography; PST, primary systemic therapy.
[a]Where the axillary surgical changes end on CT-sim, the axillary nodal volume may include all or part of a basin level (example only the upper part of level 1, all level 2, rotter, level 3 & 4).

### 4. Significance of remodelling fibrotic scars after PST

After a negative SLN biopsy, histological findings suggesting a complete response of a previous nodal metastases, such as remodelling-fibrotic scars, are considered by 15/67 (22.3%) responders as an indication to recommend RNI in case of initially node negative status (cN0), and by 11/66 (16.6%) only in case of initially nodal positive status. Among the 52 responders not taking scars into account, 5/52 (9.6%) give RNI anyway in case of initially cN0 and 2/55 (3.6%) in case of cN1. In initially cN0, 47/52 (90.3%) would not recommend RNI despite fibrotic changes, while only 6/55 (10.9%) would abstain RNI in initially nodal positive breast cancer patients (Fig. 3A.1 and 3B.1).

In case of no residual nodal disease (ypN0) after ALND, above-described histological findings are considered by 8/65 (12.3%) responders to recommend RNI in case of cN0 status, and by 16/36 (44.4%) in case of nodal positive breast cancer patients. Among the 57 responders not taking scars it into account, 5/57 (8.7%) give RNI also in case of cN0 and 4/57 (7.0%) only in case of cN+ (Fig. 3A.2 and 3B.2).

### 5. Lymph node basins of RT in selected conditions

The lymph node basins of RNI in primary cN+ breast cancer patients undergoing PST and SLN/TAD or ALND differ according to the residual tumor burden. The responders were given different cases, according to the tumor response to PST, axillary surgery (ALND, TAD, SLN biopsy), the total number of axillary lymph nodes resected, and the patient's arm morbidity. For each case, the responder was allowed to choose several answers, which reflected the nodal basins and volumes of interest for dose coverage by RNI.

The different scenarios and replies are fully represented in the supplement (Supplementary Table S4–S8). A summary of the different selection options from the survey in selected conditions is reported in Tables 1–3.

**Table 3.** LN basins of postoperative irradiation in primary nodal positive breast cancer patients undergoing axillary lymph node dissection after PST, in case of postoperative arm lymphedema

| | Level 1-4<br>Level 1-4 Level 3-4 | Level 3-4 | IMC Level 3-4<br>IMC | IMC Level 1-4<br>Level 1-4 Level 3-4<br>IMC | Unoperated levels (1-4) upwards[a]<br>Unoperated levels (1-4) upwards[a]<br>Level 1-4<br>Unoperated levels (1-4) upwards[a]<br>Level 1-4 Level 3-4<br>Unoperated levels (1-4) upwards[a]<br>Level 3-4 | Unoperated levels (1-4) upwards[a]<br>IMC<br>Unoperated levels (1-4) upwards[a]<br>Level 1-4<br>IMC<br>Unoperated levels (1-4) upwards[a]<br>Level 3-4<br>IMC<br>Unoperated levels (1-4) upwards[a]<br>Level 1-4 Level 3-4<br>IMC |
|---|---|---|---|---|---|---|
| ypN0 | 5 (7) | 39 (54) | 8 (11) | 1 (1) | 16,22) | 3 (4) |
| ypN0(i+) | 5 (7) | 39 (54) | 8 (11) | 1 (1) | 16 (22) | 3 (4) |
| ypN1(mi) | 5 (7) | 38 (53) | 9 (13) | 1 (1) | 16 (22) | 3 (4) |
| ypN1 | 10 (14) | 32 (44) | 11 (15) | 1 (1) | 12 (17) | 6 (8) |
| ypN2 | 13 (18) | 15 (21) | 16 (22) | 7 (10) | 7 (10) | 14 (19) |
| ypN3 | 12 (17) | 9 (13) | 16 (22) | 14 (19) | 6 (8) | 15 (21) |
| ypN+ inner and central tumors | 3 (4) | 5 (7) | 29 (40) | 11 (15) | 9 (13) | 15 (21) |
| ypN+, ECE, < 2 mm | 12 (17) | 24 (33) | 12 (17) | 7 (10) | 9 (13) | 9 (13) |
| ypN+, ECE, > 2 mm | 15 (21) | 18 (25) | 13 (18) | 9 (13) | 9 (13) | 9 (13) |
| ypN+, tumor fat deposit, intramammary + LN | 9 (13) | 11 (15) | 21 (29) | 14 (19) | 7 (10) | 10 (14) |
| cN0 and ypN0 in axilla but internal mammary node avid on PET/CT pre-PST | 4 (6) | 4 (6) | 41 (57) | 7 (10) | 5 (7) | 11 (15) |

Values are presented as number (%).
LN, lymph node; ypN, pathology staging after primary systemic therapy; ECE, extracapsular extension; IMC, internal mammary chain, axilla level 1,2,3,4 per European Society for Radiotherapy and Oncology lymph node atlas for breast delineation; PET/CT, positron emission tomography/computed tomography; PST, primary systemic therapy.
[a]Where the axillary surgical changes end on CT-sim, the axillary nodal volume may include all or part of a basin level (example only the upper part of level 1, all level 2, rotter, level 3 & 4).

## Discussion and Conclusion

Herein we present the results of an international EUBREAST survey exploring RNI practices after PST. Similar to our previous report, reflecting the practices of axillary surgery after PST, our results show that there is some extent of heterogeneity in radiation practices [11]. For the purpose of the discussion, Supplementary Fig. S1 summarizes the different types of axillary procedures to allow a comprehensive understanding of the nodal basins that are treated by surgery.

In our survey, a large fraction of responders would not consider RNI even in case of residual nodal disease after PST if an ALND had been performed. This most probably reflects differences in current practices between centers and countries in upfront surgery as well. The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analyses [15,16] show a clear benefit in disease outcomes when giving RNI after ALND to nodal basins that were not resected during ALND (axilla levels 2–4 and the internal mammary node chain). This benefit was also demonstrated in patients with no or limited nodal involvement (1–3 metastatic nodes and even in high-risk medial/central tumors without axillary nodal involvement) [11,15-17]. Likely, the observed differences in practices reflect poor understanding and lack of acceptance regarding the contribution of RNI on disease outcomes combined with a fear of toxicity reported only in some older trials (initiated before 1989), indicating that radiation resulted in increased morbidity and mortality mostly from cardiac events [18,19]. This is now, based on the most recent EBCTCG publication, clearly related to older treatment regimens and should not further influence contemporary decision-making [16]. Indeed, there is a high level of evidence, even from the two dimensional (2D)-RT era and with long-term follow-up, showing that if RT is applied with appropriate quality assurance measures, the benefit in disease control is indeed significant with limited tox-


https://doi.org/10.3857/roj.2024.00248

icity and without increasing cardiac mortality [20-22]. The reduction in the odds of breast cancer death following RNI appears larger after less extensive surgery (e.g., breast conserving surgery or axillary sampling) [23]. More contemporary radiation techniques allow to further significantly reduce heart and lung doses even in challenging cases [24], thereby sharply reducing risks of RT-related morbidity.

Nowadays, breast cancer patients with a larger tumor burden (e.g., T3, cN+) are often offered PST to downstage the disease, which leads to less extensive surgery. Thus, similar to what was discussed above [23], the nodal basins at risk should be covered to achieve the maximum benefit of therapy.

The majority of responders in the present report recommended pathological confirmation of nodal involvement in patients with clinically suspicious nodes. Suspicious nodes on imaging or palpation are not necessarily truly positive and should be biopsied to guide both systemic and locoregional therapy. In the NSABP-B04 trial, only 75% out of those clinically node-positive on palpation had positive nodes on histopathological evaluation after ALND [25]. Therefore, suspicious nodes should be confirmed by fine needle aspiration or core needle biopsy. While core needle biopsy may provide more detailed information, it is not mandatory if the aim is only to confirm nodal involvement [26-28].

The large majority of responders indicated that the clinical pre-PST stage is important for identification of the nodal volumes to be targeted after PST and a not negligible number of responders take into account the scarring and fibrotic changes for selecting patients to RNI. In case of initial nodal involvement that becomes ypN0 at the SLN biopsy and ALND, RNI is administered by the 16% and 44% of the responders, respectively, based on the scarring and fibrotic changes of the node(s) on final pathology. However, such nodal changes can be noted even in a healthy population, due to chronic disease or as a reaction to nodal clip placement or biopsy of the node [29]. Therefore, such changes are no reliable indicators for previous tumor involvement and should not pose an indication for RNI in the absence of other risk factors.

According to ESTRO breast cancer faculty recommendations [30], the radiation oncologist must review and take into account pre-PST images to plan RT. This allows a comprehensive estimation of the disease extent and volumes that are at high risk of locoregional recurrence. Thus, pre-PST nodal stage and the level of nodal involvement need to be considered for planning RNI to assure that nodal basins at high risk for residual tumor will be covered, especially if nodal basins that might initially have been involved by tumor are not dissected, taking into account the extend of axillary surgery.

A majority of responders indicated that the ESTRO guidelines [31] are used to define nodal volumes while the remainder used RTOG guidelines or indicated that a field-based planning (i.e., similar to 2D era, based on bony landmarks) is performed. It is an important achievement for the radiation oncology community that delineation of nodal basins has been now quite broadly accepted for RNI planning, however, our survey clearly shows we should strive for further implementation of this essential component of anatomy-based RT preparation and delivery. Breast cancer represents approximately 30%–40% of all radiation therapy unit workload [32], and nodal delineation is time consuming and mandates practice. Field-based 2D planning based on bony landmarks has governed breast radiation planning for decades. It is relatively easy and less time consuming, and is in some centers performed by the non-medical radiation planning team. Delineation of nodal basins mandates an understanding of the concept of the nodal atlas and the anatomy shown on the planning computed tomography (CT) scan and requires a lot of practice. Professional courses such as provided by Fellowship in Anatomic Delineation and Contouring (FALCON) [30] are extremely valuable, as is experience and training that allow to identify potential residual disease after PST and axillary surgery [33]. Relying on bony landmarks can result in under-coverage of the levels of the axilla that did not undergo lymphadenectomy, especially as these bony landmarks are based on extensive ALND that include also full dissection of level 2 (behind the pectoralis muscle up to the axillary vessels) which is sometimes not routinely done nowadays (Supplementary Fig. S2).

Surgical changes in the axillary levels such as clips (often applied at the superior border of the dissection), seroma, and inflammatory changes and other post-surgical effects can be noted on the RT planning CT scan. Our survey show that many radiation oncologists take these surgical changes into account for planning RNI, understanding that even if an ALND was performed, such surgical changes may only be observed in level 1 (partial ALND). In such cases, level 2, retropectoral nodes and levels 3–4 should be targeted if RNI is indicated. However, some radiation oncologists stated that only levels 3–4 will be targeted after ALND, suggesting that either they have full confidence in the ALND procedure (which includes levels 1–2) or the volumes are according to the concept of the 2D era [33] where only a medial supra-clavicular field is applied after ALND.

A common quality indicator of ALND used to be the removal of at least 10 lymph nodes [34]. The results show that to some extent, the radiation oncologist decides on the nodal levels to target according to the number of nodes that were examined. In addition, the number of nodes retrieved in the setting of PST is often lower than in the setting of upfront surgery in case of ALND. Surprisingly, the survey shows that not all radiation oncologists consider the type of axillary surgical procedure (e.g., SLN biopsy, TAD, ALND) after PST and pay more attention to the number of nodes to decide

on the RNI volumes, suggesting that in part there might be a lack of familiarity with the differences in these procedures or, alternatively, a lack in confidence with the extent of nowadays ALND. Remarkably, some will not target the lower levels of the axilla in case SLN biopsy or TAD was performed and target levels 3–4 and/or internal mammary chain (IMC) drainage. SLN biopsy or TAD are surgical staging methods to evaluate the lower axillary levels and not anatomic procedures like ALND. Therefore, levels 1–2, Rotter, with/without IMC are considered not covered by the ALND and should be irradiated in case there is an indication for RNI.

Our study holds several limitations. The survey was conducted not to achieve a consensus but to reflect current practices. Therefore, in some of the questions the responders were given different options or could choose several options simultaneously, limiting our ability to inform the reader of a straightforward level of agreement. Moreover, in case of 2D planning, the radiation oncologist might not be familiar with the axillary levels of the delineation atlases, therefore some of the responses might not reflect actual practices.

In conclusion, this survey shows heterogeneity in clinical practices of RNI, but also underlines the tremendous progress made since the 20th century's 2D era. We discuss the use of delineation guidelines for RNI and highlight the importance of understanding new axillary procedures applied after PST, supporting multidisciplinary team efforts such as the Toolbox [8], Oncoplastic Breast Consortium, and EUBREAST initiatives. Surgery and radiation for breast cancer are at times exchangeable and at times complementary. A comprehensive collaboration between disciplines that allows for in-depth mutual understanding will further improve the therapeutic benefit of locoregional therapies.

## Conflict of Interest

No potential conflict of interest relevant to this article was reported.

## Funding

None.

## Author Contributions

Conceptualization, MLG, OKP, ODG, JDB, TK, PP; Investigation and methodology, MLG, OKP, JDB; Writing of the original draft, MLG, OKP, JDB; Writing of the review and editing, TK, PP; Formal analysis, MLG, OKP, JDB; Data curation, MLG, OKP, JDB; Visualization, TK, PP.

## Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

## Acknowledgements

We thank 13 international breast cancer societies for supporting this work: the American Society of Breast Surgeons, Arbeitsgemeinschaft für gynäkologische Onkologie, Associazione Nazionale Italiana Senologi Chirurghi, Collegio Italiano dei Senologi, Deutsche Gesellschaft für Radioonkologie, Deutsche Gesellschaft für Senologie, European Breast Cancer Research Association of Surgical Trialists, Global Breast Hub, Israel Breast Surgeons Society, Israel Radiation Therapy Society, Swiss Society of Senology, Scuola Italiana di Senologia, and Società Polispecialistica Italiana Giovani Chirurghi.

## Supplementary Materials

Supplementary materials can be found via https://doi.org/10.3857/roj.2024.00248.

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 https://doi.org/10.3857/roj.2024.00248