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Review Article

PMRT After Neoadjuvant Therapy in ypN0/pCR Breast Cancer: Do We Still Need It?

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ABSTRACT

Background: Modern neoadjuvant systemic therapy yields high pCR rates—especially in HER2-positive and triple-negative disease—raising whether PMRT (and broader regional nodal irradiation, RNI) remains necessary when axillary nodes convert to ypN0. pCR is prognostic, yet historical PMRT data predate today's regimens.

Methods: Narrative synthesis emphasizing contemporary randomized and meta-analytic evidence; subgroup considerations (subtype, initial clinical stage), and toxicity/quality-of-life.

Results: The phase III **NRG/NSABP B-51/RTOG 1304** trial randomized patients who were cN+ at diagnosis and converted to ypN0 after neoadjuvant therapy to **RNI vs no RNI** (with breast/chest-wall irradiation per surgery type). At ~5 years, RNI **did not** improve invasive breast cancer recurrence-free interval or overall survival; absolute event rates were low in both arms. These peer-reviewed results (NEJM, June 2025) support **omission of RNI** in responders (including the mastectomy subgroup). NRG OncologyAdventHealth

Recent meta-analyses in ypN0 populations show **lower locoregional recurrence** with PMRT in selected higher-risk groups (e.g., residual disease, LVI-positive) but **no consistent survival advantage**, underscoring heterogeneity and the need for prospective selection. Lippincott JournalsPMC Meanwhile, pCR rates with contemporary HER2-targeted regimens are frequently **>50–60%** (even higher in ER-negative subsets), increasing the number of potential candidates for de-escalation. PMCASC Publications

Conclusions: For patients initially cN+ who convert to **ypN0**, high-level evidence supports **omitting RNI** (and, by extension, avoiding PMRT solely for regional control) with excellent outcomes at 5 years. PMRT/RNI should be **individualized** for patients with residual disease, adverse biology, or other high-risk features. Longer follow-up and biology-integrated selection (e.g., ctDNA) are priorities.

Keywords*: Postmastectomy radiotherapy (PMRT); Regional nodal irradiation (RNI); Neoadjuvant therapy*

Background:

Clinical Backdrop

The role of postmastectomy radiotherapy (PMRT) in breast cancer has historically been defined by **pathologic stage after upfront surgery**. Randomized trials and meta-analyses established a survival benefit for patients with **≥4 positive axillary nodes** and consistent reductions in locoregional recurrence (LRR) for those with one to three nodes involved. These data, however, predated the widespread adoption of **neoadjuvant systemic therapy (NAC)**, which is now routinely used in HER2-positive and triple-negative subtypes, and increasingly in hormone receptor–positive disease to facilitate downstaging and breast conservation.

NAC introduces a fundamental shift in decision-making. Patients may present with **clinically node-positive disease (cN1–3)** but achieve **pathologic complete response (pCR)** at surgery, converting to **ypN0**. pCR, defined as the absence of invasive carcinoma in the breast and lymph nodes (ypT0/is ypN0), has emerged as a powerful surrogate of long-term

outcome, particularly in triple-negative and HER2-positive cancers. Conversely, the presence of residual disease is strongly prognostic for recurrence and guides systemic escalation strategies such as adjuvant capecitabine or trastuzumab-emtansine.

This staging migration creates a clinical dilemma: should PMRT decisions be based on **initial clinical stage**, reflecting disease burden at presentation, or on **post-treatment pathologic stage**, reflecting response to therapy? The answer has profound implications. With modern HER2-targeted regimens, pCR rates now exceed **50–60% overall**, reaching **70–80% in ER-negative HER2-positive disease**, and similar improvements are observed in triple-negative breast cancer with optimized chemotherapy. As a growing proportion of patients achieve pCR, the absolute risk of locoregional recurrence after mastectomy becomes very low. At the same time, PMRT carries **non-trivial long-term toxicities** including lymphedema, brachial plexopathy, cardiopulmonary injury, and adverse effects on breast reconstruction. Thus, the benefit–risk balance of routine PMRT in ypN0 responders is increasingly questioned.

What Changed

Until recently, the evidence base for PMRT after NAC was limited to retrospective series and pooled analyses. These studies suggested that PMRT might modestly reduce LRR even in ypN0 patients, but they consistently failed to demonstrate a survival advantage, and the results were confounded by heterogeneous systemic therapy and surgical practices. The absence of prospective randomized data perpetuated a conservative approach: many guidelines continued to recommend PMRT for all patients who were node-positive at presentation, regardless of treatment response.

This paradigm shifted with the results of the **NRG/NSABP B-51/RTOG 1304 trial**, published in *The New England Journal of Medicine* in 2025. B-51 enrolled patients with biopsy-proven cN1 disease who converted to ypN0 following NAC and randomized them to receive **regional nodal irradiation (RNI)** or **no RNI** (with chest wall or breast irradiation provided per surgical procedure). At a median follow-up of 59 months, the trial demonstrated **no significant difference** in invasive breast cancer recurrence–free interval, disease-free survival, or overall survival. The five-year invasive recurrence-free survival was **92.7% with RNI versus 91.8% without** (hazard ratio 0.88, 95% CI 0.60–1.28). Locoregional recurrence-free survival was ~99% in both arms, underscoring the already excellent outcomes of ypN0 patients in the modern era. Importantly, results were consistent across key subgroups, including type of surgery (mastectomy vs breast-conserving surgery) and receptor subtype.

These findings contrast with earlier meta-analyses, which had suggested a possible LRR benefit from PMRT in ypN0 patients, particularly when other high-risk features such as lymphovascular invasion were present. Taken together, the data indicate that for patients who achieve nodal pCR, the **absolute risk of recurrence is already so low that additional regional radiation confers no measurable benefit**—at least in the first five years.

The **rise in pCR rates with contemporary systemic therapy** provides the biological explanation for this shift. In HER2-positive breast cancer treated with dual HER2 blockade, and in triple-negative disease with optimized chemotherapy, durable pCR is common. As systemic therapy continues to improve, the incremental contribution of PMRT to locoregional control in ypN0 patients diminishes further.

Thus, clinical practice is now moving from a **stage-based paradigm**—where all patients with initial cN+ disease received PMRT—to a **response-adapted paradigm**, in which PMRT may be safely omitted in patients who achieve ypN0 after NAC. This shift is supported by high-level evidence and is poised to reshape guideline recommendations worldwide, while ongoing follow-up and biomarker-driven strategies (e.g., circulating tumor DNA) aim to refine selection even further.

3. Randomized Evidence

For decades, the role of PMRT was guided almost entirely by **trials conducted in the adjuvant setting**. The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analyses demonstrated significant reductions in locoregional recurrence and breast cancer mortality with PMRT in patients with ≥4 positive nodes, and consistent benefit for one to three nodes. However, these studies preceded the widespread use of neoadjuvant systemic therapy (NAC), and their applicability to patients achieving pathologic complete response (pCR) after NAC remained uncertain.

The NRG/NSABP B-51/RTOG 1304 trial

The pivotal evidence came from the **NRG/NSABP B-51/RTOG 1304** trial, reported in *NEJM* in 2025. This phase III trial enrolled patients with biopsy-proven **cN1 disease at diagnosis** who converted to **ypN0 after NAC**. Patients undergoing mastectomy were randomized to **PMRT including regional nodal irradiation (RNI)** or **no radiation**, while those undergoing breast-conserving surgery were randomized to **whole-breast irradiation with or without RNI**.

At a median follow-up of nearly 5 years, the trial demonstrated **no significant benefit** from adding RNI in this setting. The five-year invasive breast cancer recurrence–free survival was **92.7% with RNI versus 91.8% without** (hazard ratio 0.88, 95% CI 0.60–1.28). Locoregional recurrence rates were exceptionally low in both groups (~1%), and no differences were

observed in disease-free survival or overall survival. Importantly, outcomes were consistent across subgroups defined by type of surgery, hormone receptor status, and HER2 status.

Interpretation
B-51 provides the first level I evidence supporting **omission of PMRT/RNI in patients with initial cN+ disease who achieve ypN0 after NAC**. The low recurrence rates in both arms highlight that systemic therapy advances—particularly HER2-targeted agents and optimized chemotherapy—have dramatically improved local control in responders.

Other randomized datasets
- **MA.20 and EORTC 22922/10925 trials** examined the role of RNI in node-positive or high-risk node-negative patients, but these were conducted in the adjuvant setting with few neoadjuvant-treated patients. They established that RNI improves disease-free survival, but the benefit was driven by patients with residual nodal disease and cannot be directly extrapolated to the ypN0 population.
- Trials of **accelerated partial breast irradiation (APBI)** and **hypofractionation** inform technique and fractionation choices but are less directly relevant to the specific PMRT de-escalation question in the neoadjuvant era.

Bottom line
Randomized evidence now supports a **response-adapted paradigm**: for patients presenting with cN+ disease who achieve nodal pCR, PMRT/RNI can be safely omitted without compromising early oncologic outcomes. This represents a major departure from historical practice, shifting decision-making from initial stage–based to biology- and response-driven selection. Longer follow-up from B-51 will clarify whether late recurrences emerge, but for now, the data strongly endorse de-escalation in this well-defined group.

4. Observational and Meta-Analytic Evidence
Before the availability of **B-51**, practice was largely informed by retrospective studies and meta-analyses of patients treated with neoadjuvant therapy. These analyses provided heterogeneous but important signals about the role of PMRT in ypN0 populations.

Retrospective series
Several large institutional cohorts (MD Anderson, Korean, Chinese, and European datasets) examined outcomes in patients converting to ypN0 after NAC. Consistently, they demonstrated that **locoregional recurrence (LRR) rates were low** in ypN0 patients, often <5% at 5 years, regardless of whether PMRT was given. However, certain subgroups appeared to derive relative benefit from PMRT:
- **Young age (<40 years)**
- **Triple-negative breast cancer (TNBC)** or biologically aggressive subtypes
- **Lymphovascular invasion (LVI+)** or high-grade tumors
- **Initially heavy nodal burden (cN2–3)**, even if downstaged to ypN0

In these higher-risk groups, omission of PMRT was sometimes associated with increased LRR, though the absolute excess risk remained modest compared to historical controls.

Meta-analyses
Pooled analyses up to 2024 synthesized thousands of patients across observational datasets. The key themes include:
- **LRR reduction with PMRT:** In ypN0 patients overall, PMRT was associated with a relative reduction in LRR of ~30–40%, but the **absolute risk difference was often <5%** at 5 years.
- **No consistent overall survival (OS) benefit:** Across studies, improvements in LRR rarely translated into significant survival differences, underscoring the already favorable prognosis of ypN0 responders.
- **Residual disease matters:** The clearest survival benefit from PMRT was seen in ypN+ cohorts or ypN0 patients with other adverse factors (e.g., LVI, high grade).
- **Subtype heterogeneity:** Some analyses suggested TNBC patients might retain a measurable LRR risk even after pCR, though numbers were small and confidence intervals wide.

Reconciling with B-51
The meta-analyses raised caution that **not all ypN0 patients are equal**: while most enjoy very low recurrence risk, a subset with aggressive biology or residual microscopic risk features may still benefit from PMRT. By contrast, **B-51** demonstrated that in an unselected ypN0 group, the population-level absolute benefit of RNI is negligible. Together, these data argue for a **risk-adapted strategy**: omit PMRT in the majority of ypN0 patients, but consider it in selected high-risk subsets until further biomarker-integrated evidence emerges.

Clinical message

Observational and pooled evidence support the safety of omitting PMRT in most ypN0 patients, while highlighting subgroups—**young age, TNBC, LVI+, or initial cN2–3**—where individualized consideration is prudent. These signals should guide multidisciplinary discussion and patient counseling in contexts where strict adherence to B-51 criteria may not fully capture risk.

5. Toxicity, Patient-Reported Outcomes, and Survivorship Considerations

The rationale for omitting PMRT in carefully selected ypN0 patients is not solely oncologic; it is equally rooted in minimizing treatment-related morbidity and improving survivorship outcomes.

Acute and late toxicities

PMRT, particularly when delivered with **regional nodal irradiation (RNI)**, exposes critical normal tissues:

- **Skin and soft tissue:** Dermatitis, fibrosis, and chest wall tightness are common acute and late events.
- **Lymphedema:** Axillary irradiation adds substantially to the risk, particularly in patients who have undergone axillary dissection. Prospective series report rates of 10–25% at 5 years.
- **Cardiopulmonary toxicity:** Despite advances in planning (deep inspiration breath-hold, IMRT, proton therapy), RNI still increases mean heart and lung dose. Long-term sequelae include coronary artery disease, heart failure, and secondary lung cancers.
- **Brachial plexopathy and shoulder dysfunction:** Particularly relevant in patients receiving supraclavicular fields.

Impact on reconstruction

In the modern era, many mastectomy patients undergo **immediate breast reconstruction**. PMRT is consistently associated with higher rates of:

- Capsular contracture and implant loss in implant-based reconstruction
- Fibrosis and cosmetic compromise in autologous reconstruction
- Higher rates of revision surgeries and patient dissatisfaction

This makes radiation de-escalation especially meaningful for women seeking durable reconstructive outcomes.

Patient-reported outcomes (PROs)

Emerging PRO studies, including embedded analyses within randomized trials, highlight that PMRT/RNI is associated with:

- **Worse arm and shoulder function**
- **Increased fatigue and pain**
- **Lower body image and cosmetic satisfaction** (particularly after reconstruction)
- **Psychosocial distress** from fear of long-term toxicity

These impacts persist beyond the acute phase and can meaningfully affect quality of life, even in survivors with excellent cancer control.

Survivorship lens

In the context of ypN0 patients after NAC, where baseline recurrence risk is already low, the **absolute therapeutic gain from PMRT is marginal**. Thus, the proportional weight of toxicity, PROs, and survivorship considerations becomes magnified. Shared decision-making, incorporating not only recurrence risk but also survivorship priorities (fertility, reconstruction, physical functioning, cardiopulmonary health), is critical.

Take-home message:

In ypN0 patients, the toxicity and survivorship burden of PMRT/RNI may outweigh its modest oncologic benefit. Avoiding unnecessary radiation can spare patients long-term morbidity, preserve reconstruction outcomes, and improve quality of survivorship.

6. Emerging Biomarkers and Ongoing Trials

While **B-51** establishes that routine PMRT/RNI can be safely omitted in unselected ypN0 patients after NAC, ongoing research seeks to identify **biomarker-defined subgroups** who may still benefit — or who may be spared even more confidently.

Molecular and genomic predictors

- **Intrinsic subtype:** TNBC and HER2+ cancers have higher baseline recurrence risk, but those achieving pCR often have excellent prognosis. Work is ongoing to determine whether molecular features within these groups (e.g., residual immune infiltration, proliferation markers) refine PMRT need.
- **Gene-expression signatures:** Genomic assays like **Oncotype DX, MammaPrint, Prosigna**, and newer panels are being explored not just for systemic therapy guidance but also for predicting locoregional recurrence risk. Small retrospective studies suggest low-risk signatures correlate with negligible LRR even without PMRT.

- **Radiogenomics:** Integration of imaging-derived features (MRI, PET) with molecular data is being investigated to non-invasively stratify recurrence risk after NAC.

Circulating biomarkers

- **Circulating tumor DNA (ctDNA):** Persistent ctDNA after NAC strongly predicts systemic relapse. Trials are exploring whether **ctDNA-negative** patients can be safely de-escalated from PMRT, while **ctDNA-positive** patients may benefit from intensified local or systemic therapy.
- **Circulating tumor cells (CTCs):** Similar efforts are ongoing but less mature than ctDNA.

Immunologic and microenvironmental factors

Pathologic immune response (e.g., tumor-infiltrating lymphocytes, TILs) and residual tumor bed biology may act as surrogates for local control. High TILs correlate with improved response and lower recurrence, raising the possibility of integrating immune signatures into PMRT decision-making.

Ongoing trials

- **NSABP B-51/RTOG 1304 – long-term follow-up:** Continued surveillance will determine whether the lack of benefit from RNI persists beyond 10 years, and whether late failures emerge.
- **Alliance A011202:** Testing axillary surgery vs axillary + RNI in patients with residual nodal disease (ypN+). This trial will clarify the role of PMRT in the *opposite* setting — patients with residual high-risk disease.
- **Biomarker-driven cohorts:** Multiple prospective registries (e.g., NRG, TBCRC) are embedding tissue, blood, and imaging biomarker collection alongside PMRT outcomes to refine predictive models.
- **Adaptive radiotherapy trials:** Some groups are piloting **response-adapted RT** guided by imaging or biomarkers, with the goal of tailoring dose, volume, and even omission in near real time.

Future paradigm

The trajectory of evidence is clear: PMRT decision-making is moving away from **static stage-based algorithms** toward a **dynamic, biology- and response-adapted model**. Molecular assays, ctDNA, and integrated imaging biomarkers may eventually allow true personalization — selecting only the patients who stand to benefit while sparing the rest.

Take-home message:

Emerging biomarkers and ongoing trials promise to sharpen PMRT decisions beyond B-51, transforming practice from stage-driven to biology-driven. In the future, a combination of **clinical response + molecular profiling + ctDNA status** may provide the most precise framework for PMRT use.

7. Practical Recommendations and Future Directions

Current clinical practice

Based on the totality of evidence:

- **Patients with initial cN+ disease who achieve ypN0 after NAC:**
  - The **B-51 trial** provides level I evidence that PMRT/RNI can be safely omitted in this setting, with locoregional recurrence rates <2% and no survival difference.
  - PMRT should not be considered standard of care for this group, though shared decision-making remains important.
- **Patients with residual nodal disease (ypN+):**
  - Remain at elevated risk; PMRT/RNI continues to be strongly recommended, consistent with historical data and ongoing **Alliance A011202**.
- **High-risk ypN0 subsets (e.g., young age, TNBC, LVI+, initial cN2–3):**
  - Evidence from observational and meta-analytic studies suggests these patients may still harbor residual risk. Until biomarker-directed guidance matures, individualized consideration of PMRT may be appropriate.

Patient-centered decision-making

- Integrating **toxicity, reconstruction impact, and quality of life** is critical in counseling.
- For ypN0 patients, where absolute oncologic benefit of PMRT is minimal, **survivorship priorities** (cosmesis, function, cardiopulmonary health) often weigh more heavily.
- **Multidisciplinary discussion** (surgical, medical, and radiation oncology) ensures balanced recommendations.

Future directions

1. **Biomarker integration:**
   - Molecular signatures, immune profiling, and ctDNA hold promise in refining PMRT selection.
   - Prospective validation is needed before routine clinical use.
2. **Adaptive trial designs:**

- Ongoing and future studies will test **real-time stratification** (imaging, ctDNA) to guide radiation volume and dose.

3. **Long-term follow-up of B-51:**
   - Essential to confirm whether omission remains safe at 10+ years.
4. **Global implementation:**
   - As NAC use expands worldwide, consensus guidelines will need to adapt, balancing evidence from high-resource and low-resource settings.

Bottom line:
PMRT in the neoadjuvant era is shifting from a **stage-driven** to a **response- and biology-driven** paradigm. For ypN0 patients, omission of PMRT is now evidence-based, sparing thousands of women unnecessary toxicity. The future lies in refining risk further with **biomarkers and adaptive trials**, ensuring PMRT is reserved only for those who stand to benefit.

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