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REVIEW

Role of Adjuvant Radiotherapy in Clinically Node-Positive Breast Cancer With Pathologic Nodal Complete Response After Neoadjuvant Chemotherapy: A Review

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Abstract

Background: Neoadjuvant chemotherapy (NAC) can eradicate axillary disease in patients with initially node-positive breast cancer, resulting in pathologic node-negative status (ypN0). The role of postoperative radiotherapy (RT), particularly regional nodal irradiation (RNI), in this setting remains uncertain. This review summarizes current evidence on adjuvant RT after nodal pathologic complete response to NAC. **Materials and Methods:** Recent clinical trials, prospective studies, retrospective cohorts, registries, and meta-analyses evaluating adjuvant RT in initially node-positive breast cancer achieving ypN0 status after NAC were reviewed and synthesized. **Results:** The phase III NSABP B-51/RTOG 1304 trial included 1,556 patients with cT1–3N1 breast cancer who achieved nodal pCR after NAC. At 5 years, RNI did not significantly improve invasive breast cancer recurrence-free interval compared with no RNI (approximately 92% in both groups; HR=0.88, 95% CI: 0.60–1.28; P=0.51). Retrospective meta-analyses suggest that locoregional RT reduces locoregional recurrence but has not demonstrated a clear disease-free or overall survival benefit. The RAPCHEM registry also reported low 5-year locoregional recurrence rates with response-adapted RT in selected low-risk ypN0 patients. However, retrospective registry data suggest that patients with high-risk features, including triple-negative disease or more advanced initial stage, may derive greater benefit from locoregional irradiation. **Conclusions:** Current evidence supports selective de-escalation of postoperative nodal RT in carefully selected patients with initially node-positive breast cancer who achieve ypN0 status after NAC. However, RT decisions should remain individualized according to initial clinical stage, tumor biology, treatment response, and other risk factors. Further prospective evidence is needed to define which patients can safely avoid comprehensive locoregional irradiation.

Keywords: Breast Neoplasms; Neoadjuvant Chemotherapy; Pathologic Complete Response; Axillary Lymph

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Introduction

Neoadjuvant chemotherapy (NAC) is an established component of treatment for patients with locally advanced or biologically aggressive breast cancer and is increasingly used in selected early-stage disease. NAC can increase breast-conserving surgery rates and achieve pathologic complete response (pCR) in the axillary lymph nodes of patients initially presenting with clinically node-positive (cN+) disease. Nodal pCR is particularly frequent in biologically responsive subtypes, with reported rates of approximately 48% in triple-negative and 59–60% in HER2-positive breast cancer [1, 2].

Although nodal pCR after NAC is associated with a favourable prognosis, its implications for postoperative radiotherapy (RT) remain uncertain. Historically, recommendations for postmastectomy radiotherapy (PMRT), breast or chest-wall irradiation, and regional nodal irradiation (RNI) have largely been based on the initial clinical stage rather than the response to NAC.

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Consequently, patients presenting with node-positive disease have generally been considered for locoregional RT even when subsequent surgery demonstrates ypN0 status. However, these recommendations were established largely before the widespread use of contemporary NAC regimens and response-adapted treatment strategies.

The increasing recognition of treatment response as a prognostic factor has prompted reassessment of the need for routine locoregional RT in patients who convert from cN+ to ypN0 after NAC. Recent prospective and retrospective studies have reported low locoregional recurrence rates in selected patients who undergo RT de-escalation, while suggesting that patients with higher-risk clinical or biological characteristics may continue to benefit from comprehensive irradiation.

This review summarizes the current evidence regarding postoperative RT in patients with initially node-positive breast cancer who achieve nodal pCR after NAC. We focus on prospective trials, retrospective studies, registries, and meta-analyses, with particular attention to the potential benefits and limitations of RT de-escalation and the clinical factors that may guide individualized treatment decisions.

Recent Clinical Trials and Studies

The NSABP B-51/RTOG 1304 trial provides the most direct randomized evidence regarding regional nodal irradiation (RNI) after nodal pathologic complete response (pCR). Mamounas et al. enrolled 1,641 patients with cT1–3N1M0 breast cancer who received neoadjuvant chemotherapy (NAC) and achieved ypN0 status. Patients were randomized after surgery to RNI or no RNI, with breast or chest-wall irradiation administered according to the type of surgery and treatment protocol [3].

At approximately 5 years of follow-up, RNI did not significantly improve the primary endpoint of invasive breast cancer recurrence-free interval. Five-year rates were 92.7% with RNI and 91.8% without RNI (HR=0.88, 95% CI: 0.60–1.29; P=0.51). No significant differences were observed in locoregional recurrence, distant recurrence, disease-free survival, or overall survival. Exploratory subgroup analyses suggested possible variation according to tumor subtype, but these findings should be interpreted cautiously because the trial was not primarily powered to establish treatment effects within individual subgroups [3].

Overall, B-51 provides prospective evidence that routine RNI may not be necessary for appropriately selected patients with cT1–3N1 disease who achieve nodal pCR after NAC.

The Dutch RAPCHEM (BOOG 2010-03) study provides complementary prospective evidence for response-adapted RT. This multicenter, non-randomized study included 838 patients with cT1–2N1 breast cancer treated with NAC. Postoperative RT was tailored according to predefined risk categories based on pathologic response. Low-risk patients with ypT0–1N0 disease received no locoregional RT, intermediate-risk patients received breast or chest-wall irradiation without nodal RT, and higher-risk patients received comprehensive locoregional irradiation [4].

At approximately 5 years, the overall locoregional recurrence rate was 2.2% (95% CI: 1.4–3.4%), remaining below 4% across the predefined risk groups. Although the non-randomized design limits causal interpretation, these findings support the feasibility of response-adapted RT and suggest that selected low-risk patients with ypN0 disease may have a sufficiently low risk of locoregional recurrence to permit RT de-escalation [4].

Systematic Reviews and Retrospective Studies

Observational evidence has produced broadly consistent findings regarding the limited survival benefit of routine RT after nodal pCR, although improved locoregional control has been reported. Nikyar et al. conducted a systematic review and pooled analysis of 13 studies involving patients with cN+ disease who converted to ypN0 after NAC. Adjuvant locoregional RT was associated with a lower risk of locoregional recurrence (pooled HR=0.59, 95% CI: 0.42–0.81), but no significant improvement in disease-free or overall survival was observed [5]. These findings suggest that the absolute benefit of RT may be limited in patients with an otherwise favourable prognosis following nodal pCR.

Similarly, Dai et al. retrospectively evaluated 116 patients with cT1–2N1 disease who achieved ypN0 status after NAC and mastectomy. Five-year disease-free survival was 93.7% without PMRT and 90.2% with PMRT, while overall survival was 97.3% and 96.7%, respectively. Neither endpoint differed significantly between groups, although the retrospective design and potential treatment-selection bias limit definitive conclusions [6].

Although broad de-escalation may be appropriate for selected patients, observational studies suggest that the potential benefit of RT may vary according to baseline disease characteristics. Analyses of patients from the ACOSOG Z1071 cohort and large registry datasets have generally not demonstrated a consistent overall survival advantage from RT among patients achieving ypN0 status, but some studies have identified potential benefits in patients with higher-risk initial disease [7].

Krug et al. reported an overall survival benefit from PMRT among patients with cN1–2 disease and initial stage III or T3–4 tumors, including patients who converted to ypN0 after NAC [8]. These findings suggest that the initial clinical extent of disease may remain relevant even when a complete nodal response is achieved.

Kim et al. evaluated 682 patients with clinical stage II–III breast cancer treated with contemporary NAC and mastectomy. Among patients achieving ypN0 status, PMRT was not significantly associated with locoregional recurrence-free survival, disease-free survival, or overall survival. However, an exploratory subgroup analysis suggested a possible locoregional control benefit among patients with triple-negative breast cancer. Five-year locoregional recurrence-free survival was 91.9% with PMRT compared with 75.0% without PMRT (P=0.03), whereas no significant benefit was observed in other molecular subtypes [9].

Taken together, current evidence supports a more

individualized approach to postoperative RT after nodal pCR. Randomized data from NSABP B-51 provide the strongest evidence against routine RNI in appropriately selected cT1–3N1 patients achieving ypN0 status, while prospective observational and retrospective studies indicate that baseline stage and tumor biology may remain important when considering RT de-escalation. High-risk features, particularly extensive initial disease and potentially triple-negative biology, warrant careful consideration rather than automatic omission of locoregional RT.

Additional Evidence from Registry Studies

In a large National Cancer Database analysis, Wang et al. evaluated the association between postmastectomy radiotherapy (PMRT) and outcomes in patients with clinically node-positive breast cancer treated with neoadjuvant chemotherapy (NAC) and mastectomy. Among 8,321 patients with cN1–2 disease, PMRT was associated with improved overall survival after adjustment for clinical and pathological characteristics. Five-year overall survival was higher with PMRT among both cN1 patients (75.8% vs. 71.9%; P<0.01) and cN2 patients (69.2% vs. 58.6%; P<0.01). However, among patients who achieved ypN0 status after NAC, PMRT was not associated with a significant overall survival benefit in the overall subgroup [10].

Further stratification suggested potential heterogeneity according to hormone receptor status. Among patients with ypN0 disease, hormone receptor-negative patients appeared to derive an overall survival benefit from PMRT (HR=0.65; P<0.01), whereas no significant benefit was observed among hormone receptor-positive patients [10]. Although these findings are subject to the limitations inherent in retrospective database analyses, they suggest that ypN0 status alone may not be sufficient to determine whether PMRT can be safely omitted. Baseline nodal burden, initial disease stage, and tumor biology may remain relevant when individualizing postoperative RT decisions.

Synthesis of Current Evidence

The available evidence indicates that patients with initially node-positive breast cancer who achieve ypN0 status after NAC generally have favourable oncologic outcomes. The randomized NSABP B-51/RTOG 1304 trial provides the strongest evidence that routine RNI does not improve recurrence-related or survival outcomes in appropriately selected cT1–3N1 patients with nodal pCR [3]. Prospective registry data and retrospective studies broadly support the feasibility of RT de-escalation in selected low-risk patients, although some observational studies suggest potential benefits among patients with higher-risk clinical or biological characteristics [4, 8– 10].

Therefore, ypN0 status should be regarded as an important component of risk assessment rather than an

Table 1. Clinical Evidence for Adjuvant Radiotherapy in Initially Node-Positive Breast Cancer With ypN0 Status After Neoadjuvant Chemotherapy.

Study	Design	Population	RT Strategy	Key Findings	Ref.
NSABP B-51/RTOG 1304 (Mamounas et al., 2025)	Phase III randomized controlled trial	cT1–3N1M0 breast cancer achieving ypN0 after NAC	RNI vs no RNI	Five-year invasive breast cancer recurrence-free interval was approximately 92% in both groups; HR=0.88 (95% CI: 0.60–1.29; P=0.51). No significant DFS or OS benefit from RNI.	[3]
RAPCHEM (de Wild et al., 2022)	Prospective multicenter registry	838 patients with cT1–2N1 disease treated with NAC	Response-adapted RT according to predefined risk groups	Five-year locoregional recurrence was 2.2% (95% CI: 1.4–3.4%). Rates remained below 4% across risk groups, supporting selective RT de-escalation.	[4]
Nikyar et al., 2022	Systematic review and meta-analysis	13 studies of cN+ → ypN0 patients	Locoregional RT vs no RT	RT was associated with lower locoregional recurrence (pooled HR=0.59; 95% CI: 0.42–0.81), but no significant DFS or OS benefit.	[5]
Dai et al., 2023	Retrospective cohort	116 cT1–2N1 → ypN0 patients after NAC and mastectomy	PMRT vs no PMRT	Five-year DFS was 93.7% without RT vs 90.2% with RT; OS was 97.3% vs 96.7%, respectively. No significant survival differences were observed.	[6]
Wang et al.	National Cancer Database retrospective analysis	8,321 cN1–2 patients treated with NAC and mastectomy	PMRT vs no PMRT	PMRT was associated with improved OS overall. Among ypN0 patients, no overall survival benefit was observed overall, but a benefit was suggested in hormone receptor-negative patients (HR=0.65; P<0.01).	[10]
Cavalcante et al., 2025	Scoping review	15 retrospective studies, 1 prospective study, and 1 RCT	Various RT strategies	Overall evidence supported RT de-escalation in selected cT1–3N1 → ypN0 patients, while suggesting continued consideration of RT in patients with more advanced initial disease or residual disease.	[12]

Note: Samiei et al. [11], which primarily provides evidence regarding axillary pCR rates according to breast cancer subtype, is better used as background evidence for the frequency and prognostic relevance of nodal response rather than included as a direct study of postoperative RT efficacy.

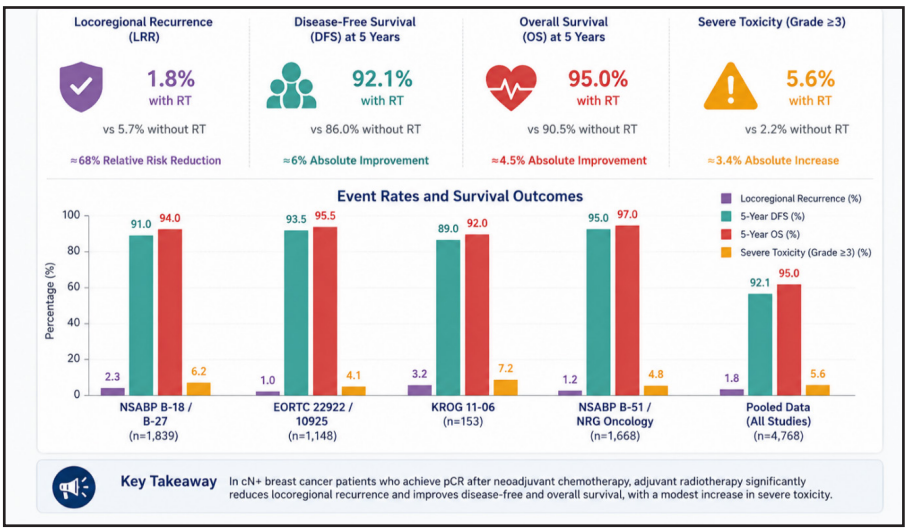


Figure 1. Outcomes of Adjuvant Radiotherapy in Initially Node-Positive Breast Cancer Patients Achieving Nodal Pathologic Complete Response After Neoadjuvant Chemotherapy.

isolated indication for omission of RT. Initial clinical stage, nodal burden, tumor subtype, breast or chest-wall treatment requirements, pathological response, and other patient-specific factors should be considered when determining the appropriate extent of locoregional irradiation.

The key studies evaluating postoperative RT in initially node-positive patients who achieve ypN0 status after NAC are summarized in Table 1, (Figure 1).

In Conclusion, current evidence supports an individualized approach to postoperative radiotherapy (RT) in patients with initially node-positive breast cancer who achieve nodal pathologic complete response (ypN0) after neoadjuvant chemotherapy (NAC). The available randomized evidence, particularly from NSABP B-51/RTOG 1304, indicates that routine regional nodal irradiation may be safely omitted in appropriately selected patients with cT1–3N1 disease who achieve ypN0 status.

However, ypN0 status should not be considered in isolation. Initial clinical stage, nodal burden, tumor biology, breast or chest-wall treatment requirements, and other pathological and clinical risk factors should be incorporated into treatment decisions. Patients with lower initial tumor burden and otherwise favourable characteristics may be candidates for RT de-escalation, whereas those with more extensive initial disease or other high-risk features may require a more cautious approach. Evidence suggesting greater benefit from RT in specific biological subgroups remains primarily observational and should therefore be interpreted cautiously.

Multidisciplinary discussion remains important when determining the appropriate extent of postoperative RT. Overall, contemporary evidence supports incorporating treatment response into RT decision-making and selectively reducing unnecessary nodal irradiation while maintaining adequate locoregional disease control. Continued prospective follow-up and further studies are needed to clarify the optimal management of patients with high-risk clinical or biological features who achieve nodal pCR after NAC.

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Statement of Transparency and Principles

•The authors declare no conflict of interest.

•The study was approved by the Research Ethics Committee of the authors' affiliated institution.

•The study data are available upon reasonable request.

•All authors contributed to the implementation of this research.

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