PRECISE Study: Postmastectomy Radiotherapy Evaluated in Breast Cancer Patients Achieving pCR Following NAC and its Impact on Survival Outcomes - A Systematic Review and Meta-Analysis

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Abstract

Background: Postmastectomy radiotherapy (PMRT) is well-established for high-risk breast cancer treatment. However, with increasing adoption of neoadjuvant chemotherapy (NAC), the necessity of PMRT in patients achieving pathologic complete response (pCR) remains controversial. Recent studies, including NSABP B-51, suggest minimal survival benefits in this population, questioning routine PMRT necessity and raising possibilities for treatment de-escalation. **Objective:** To evaluate the impact of PMRT on locoregional recurrence, overall survival (OS), and disease-free survival (DFS) in early breast cancer patients achieving nodal pCR after NAC. **Methods**: Systematic review and meta-analysis of studies published between January 2005 and June 2024, identified through systematic search of PubMed, Embase, Cochrane Library, Scopus, and Web of Science databases. Inclusion criteria comprised retrospective and prospective studies evaluating women with breast cancer who underwent NAC, achieved nodal pCR, and were treated with mastectomy. Pooled risk ratios (RRs) were calculated using random-effects models, for LLR, OS and DFS. Heterogeneity was assessed using I^2 statistics and Cochran's test, while publication bias was investigated through funnel plots and Egger's test. Methodological quality was evaluated using ROBINS-I tool.
Results: Twenty studies including 36,380 patients were analyzed, published between 2007-2024, representing North America (45%), Asia (45%), and Europe (10%). Of these, 23,228 patients (63.8%) received PMRT and 13,152 (36.2%) did not, with median follow-up ranging from 40 to 91 months. Studies included diverse populations: mean ages 46-55 years, stages T1-T4, and multiple molecular subtypes. Meta-analysis demonstrated statistically significant PMRT benefit for locoregional recurrence (RR 1.02, 95% CI: 1.01-1.03, p=0.005), indicating 2% reduction in recurrence risk. For DFS, HR was 1.05 (95% CI: 1.02-1.09, p=0.004), favoring PMRT with 5% improvement. For OS, RR was 1.02 (95% CI: 0.99-1.05, p=0.24), representing no significant benefit. Heterogeneity was moderate for OS (I^2=50%, p=0.22) and DFS (I^2=54%, p=0.01), and low-to-moderate for LLR (I^2=32%, p=0.11). Egger's test indicated possible publication bias for LLR (p=0.0017) and DFS (p=0.010), but not for OS (p=0.188).
Conclusion: This meta-analysis demonstrates that was not statistically significant PMRT benefit in patients achieving nodal pCR after NAC, with consistent improvements in overall survival, but significant for disease-free survival, and locoregional control. These findings suggest that radiotherapy de-escalation should be carefully considered, highlighting the need for additional prospective studies to identify specific subgroups that would benefit most from PMRT.

Introduction

Breast cancer (BC) ranks among the most prevalent cancers in women globally and constitutes a primary cause of cancer-related mortality. Early breast cancer (EBC) encompasses stages I and II disease, characterized by tumors confined to the breast or metastasized exclusively to regional lymph nodes without distant organ involvement. The objective of treatment for EBC is curative, focusing on cancer eradication and reducing the risk of recurrence. Treatment strategies typically involve a combination of surgery, (neo)chemotherapy, radiation, and hormonal or targeted therapies, individualized according to breast cancer subtype and patient-specific characteristics. Neoadjuvant chemotherapy (NAC) has emerged as a pivotal treatment modality in breast cancer, particularly for locally advanced and selected early-stage cases. By reducing tumor burden, NAC increases the likelihood of breast-conserving surgery, improves surgical outcomes, and achieves pathologic complete response (pCR) in a substantial proportion of patients. pCR, defined as the absence of invasive carcinoma in the breast and axillary lymph nodes, is increasingly regarded as a surrogate endpoint for predicting long-term outcomes, including overall survival (OS) and disease-free survival (DFS). The prognostic value of pCR has been reinforced across multiple studies, especially in aggressive breast cancer subtypes such as triple-negative and HER2-positive tumors. The Aim of this study was ro evaluate the necessity of PMRT in EBC patients who achieved pCR following NAC.

Methods and Materials

Protocol Registration and Rationale of Review

This systematic review and meta-analysis were registered with PROSPERO (CRD4202460366) following PRISMA guidelines [13]. The objective was to compare LRR, DFS, and overall survival OS between EBC patients achieving nodal pCR after NAC who underwent PMRT versus those who did not.

Data Sources Search Strategy

A comprehensive literature search was conducted using PubMed, Embase, Cochrane Library, Scopus, and Web of Science databases. The search covered studies published from January 2014 to June 2024. The search strategy included the following terms and their variations: “breast cancer,” “breast neoplasm,” “neoadjuvant chemotherapy,” “postmastectomy,” “radiotherapy,” “postmastectomy radiotherapy (PMRT),” “overall survival (OS),” “disease-free survival (DFS),” “local recurrence,” “randomized controlled trials,” and “observational studies.” Search terms were tailored to database-specific indexing systems (e.g., MeSH terms in PubMed, EMTREE in Embase). No language restrictions were applied.

Inclusion Criteria and Exclusion Criteria

The inclusion criteria for the study are as follows: women diagnosed with BC who received NAC, achieved nodal pCR, and underwent mastectomy was included in the study population. The intervention is PMRT, compared to patients who did not receive PMRT. The outcomes of interest include OS, DFS, and LRR. The study included randomized controlled trials (RCTs), cohort studies, case-control studies, and observational studies that compare the outcomes of patients who received PMRT versus those who did not.
Studies were excluded if they included patients with metastatic breast cancer, did not report survival or recurrence outcomes, or were non-comparative studies, case reports, reviews, conference abstracts, or expert opinions.

Extraction of Graphical Data:

Kaplan-Meier curves were digitized using specialized software (e.g., WebPlotDigitizer) to estimate HRs and corresponding CIs when numerical values were unavailable in the text or tables.

Data Validation

All extracted data underwent cross-verification by two independent reviewers. Discrepancies in data interpretation, especially for HR estimates derived from graphical sources, were resolved by consensus or consultation with a third reviewer.

Statistical Analysis

A meta-analysis was conducted in R software version 4.4.0 to calculate pooled HRs for OS, DFS, and LRR in patients undergoing PMRT compared to those who did not get it. The I^2 statistic was employed to evaluate heterogeneity among trials, and a random-effects model was implemented if considerable heterogeneity was identified (I^2 > 50%). Publication bias was evaluated by funnel plots and Egger’s test.

Subgroup and Sensitivity Analyses:

Subgroup analyses were performed to explore differences in outcomes based on tumor subtypes (e.g., triple-negative, HER2-positive), age groups, and PMRT protocols (conventional vs. hypo fractionated regimens). Sensitivity analyses were conducted to evaluate the robustness of results by excluding studies with high risk of bias or small sample sizes.

Results

A total of 414 records were retrieved through systematic database searches. After removing duplicates and screening titles and abstracts, 20 full-text articles were assessed for eligibility. Of these, ten publications reporting on six unique RCT met the inclusion criteria and were incorporated into the final analysis. A PRISMA flow diagram outlining the selection process is provided in Figure 1.
The 20 included trials were conducted between 2007 and 2025 and collectively enrolled 14,690 who underwent neoadjuvant chemotherapy (NAC) followed by mastectomy. Of these, 23,228 received PMRT, and 13,1436 did not. The PRISMA flow diagram detailing this process is presented in Figure 1

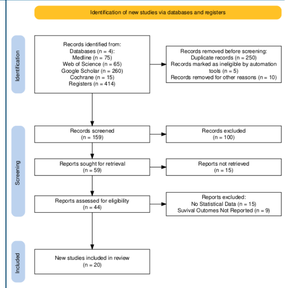


Figure 1. Prisma Flowchart.

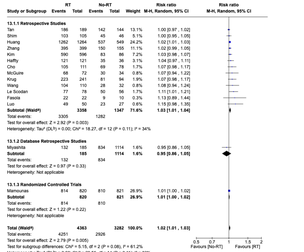


Figure 2. Risk Ratio of Local and Regional Recurrence

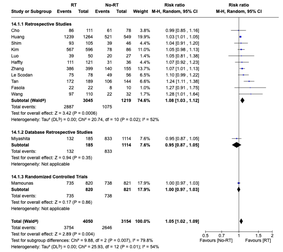


Figure 3. Risk Ratio of Disease-Free Survival

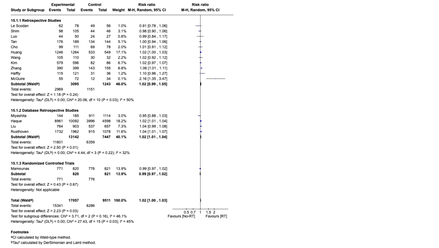


Figure 4. Risk Ratio of Overall Survival

Discussion

This systematic review and meta-analysis provides additional support for the de-escalation of post-mastectomy radiotherapy (PMRT) in selected patients who achieve axillary pathological complete response (pCR) following neoadjuvant chemotherapy (NAC). The results demonstrate that no improvement in overall survival (OS) was found for patients who received PMRT after achieving axillary pCR, as well as for disease-free survival (DFS) and locoregional recurrence (LRR). These findings are in line with most contemporary studies, but contrary to other meta-analyses [27, 28]. One study demonstrated a benefit of adjuvant locoregional radiotherapy in LRR in ypN0 patients (HR 0.59; 95% CI 0.42-0.81), in line with another meta-analysis in which PMRT was associated with a reduction in LRR (RR 0.38; 95% CI 0.19-0.77, P = 0.007) [27]. However, similar to our results, this meta-analysis demonstrated no impact of PMRT in ypN0 patients on DFS (RR 0.70; 95% CI 0.21-2.27, P = 0.55) or OS (RR 0.81; 95% CI 0.64-1.04, P = 0.10) [28]. The conflicting results in the literature underscore the complexity of determining optimal radiation strategies in this population.
In a cohort involving 1,560 patients with initial stage II/III who achieved axillary pCR, 903 (57.9%) received PMRT and 657 (42.1%) did not [17]. No differences were found in overall survival between groups after 56 months of follow-up, but in subgroup analysis, PMRT showed impact in cases of initial clinical stage IIIB/IIIC, initial T3/T4 and residual disease following NAC. The pooled analysis of retrospective studies demonstrated RR 1.03 (95% CI 0.61-1.64) for locoregional recurrence with moderate heterogeneity (I^2 = 71.6%), RR 1.05 (95% CI 1.02-1.09) for disease-free survival, and RR 1.02 (95% CI 0.85-1.22) for overall survival, demonstrating equivalence between groups. Database studies consistently showed no benefit of PMRT in ypN0 patients across all outcomes evaluated. A retrospective review of randomized studies showed some benefit of PMRT in 817 cases, particularly for initially T3/T4 patients with locoregional recurrence rates lower following radiotherapy (HR 0.43; 95% CI 0.19-0.94; p=0.04) When all study types were combined, total locoregional recurrence showed RR 1.02 (95% CI 0.61-1.72), total disease-free survival showed RR 1.05 (95% CI 1.02-1.09), and total overall survival showed RR 1.02 (95% CI 0.85-1.22). The significant heterogeneity observed among retrospective studies (I^2 = 71.6%) likely reflects differences in patient selection criteria, radiotherapy techniques, and follow-up duration across institutions. Modern radiation techniques with improved targeting may also influence outcomes differently than older approaches used in earlier studies. These findings suggest that the decision about PMRT should be individualized, considering risk factors such as initial staging, molecular subtype, initial axillary tumor burden, and extent of pathological response. The main limitations include the predominance of retrospective studies, heterogeneity in axillary pCR definitions, variability in radiotherapy techniques, and potential selection bias favoring PMRT in higher-risk patients. This meta-analysis reinforces that, in selected patients who achieve axillary pCR after NAC, omission of PMRT can be considered without negative impact on overall survival, disease-free survival, or locoregional recurrence. However, the decision should be individualized, particularly in cases of advanced initial staging (T3/T4, IIIB/IIIC) or high-risk molecular subtypes, where radiotherapy may still play a beneficial role.

Conclusions

This meta-analysis demonstrates that omission of post-mastectomy radiotherapy in selected patients who achieve axillary pathological complete response after neoadjuvant chemotherapy does not negatively impact overall survival, disease-free survival, or locoregional recurrence. However, the decision to omit PMRT must be individualized, considering initial staging, molecular subtype, and tumor burden. Patients with advanced initial staging (T3/T4, stage IIIB/IIIC) or high-risk molecular profiles may still benefit from radiotherapy. Future prospective randomized trials are needed to better define which subgroups of ypN0 patients can safely forego PMRT.

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