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Radiotherapy in Early Breast Cancer: Optimizing Patient Selection from Trials and Guidelines

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Abstract

Background: Adjuvant radiotherapy (RT) after breast-conserving surgery (BCS) reduces ipsilateral breast tumor recurrence (IBTR), but the absolute benefit varies with baseline risk. With modern systemic therapy and molecular profiling, a subset of patients has sufficiently low local-recurrence risk to consider RT de-escalation or omission.

Methods: We analyzed evidence from randomized trials in older, hormone-receptor–positive (HR+) early breast cancer, prospective cohort studies and current guidelines. Key outcomes were IBTR, distant relapse, overall survival (OS), and toxicity/quality-of-life (QoL).

Results: Two randomized trials validate RT omission in elderly, low-risk HR+ disease receiving endocrine therapy. CALGB 9343 (age ≥70, T1N0, ER+) showed higher 10-year IBTR with omission (≈10% compared with 2% with RT) without OS difference. PRIME II trial (age ≥65, ER+, ≤3 cm, N0) confirmed as a 9–10% absolute increase in 10-year IBTR without OS loss. Biologically selected cohorts suggest omission can transcend age criteria. For women ≥55 years with luminal A tumors (ER+, HER2–, grade 1–2, Ki-67 ≤13.25%) who are treated with endocrine therapy alone in the LUMINA trial, 5-year locoregional recurrence was ~2–3% with great distant control without RT. On-going randomized trials as PRECISION and EXPERT are comparing genomic testing such as Oncotype DX, Prosigna/PAM50 to guide RT omission.

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Randomized and prospective data support RT in most DCIS, yet small, low-grade, wide-margin screen-detected lesions of low risk could be suitable for surveillance or surgery alone. Active-surveillance trials are also underway on this topic. On the other hand, de-escalation alternatives like ultra-hypo fractionated whole-breast RT and partial-breast irradiation have local control with reduced burden of treatment.

Conclusions: RT omission is safe for carefully selected elderly patients with small, node-negative, ER+ tumors on endocrine therapy, with no OS penalty. Biology and genomics can further help in patients' selection. Shared decision-making, adherence to endocrine therapy and multidisciplinary review are essential.

Keywords: radiotherapy, early breast cancer, guidelines

INTRODUCTION

Adjuvant radiotherapy (RT) following breast-conserving surgery (BCS) has long been a cornerstone in the management of early-stage breast cancer, significantly reducing the risk of ipsilateral breast tumor recurrence and improving long-term local control. Landmark randomized trials and meta-analyses, most notably the Early Breast Cancer Trialists' Collaborative Group (EBCTCG), have demonstrated that RT halves the risk of local recurrence and confers a modest but significant reduction in breast cancer–specific mortality (1). However, the absolute benefit of RT varies substantially among patients, depending on age, tumor characteristics, and baseline recurrence risk.

With advances in systemic therapy, endocrine treatment, and surgical techniques, the risk of local recurrence in selected patient populations has declined considerably. This has prompted increasing interest in treatment de-escalation strategies aimed at minimizing overtreatment and reducing the long-term toxicities, treatment burden, and impact on quality of life associated with radiotherapy.

Older patients with hormone receptor–positive, node-negative disease treated with endocrine therapy represent a particularly important subgroup in whom the benefit of RT may be limited. Randomized trials such as CALGB 9343 and PRIME II have demonstrated that omission of RT in carefully selected older women results in higher local recurrence rates but no difference in distant recurrence or overall survival (2,3).

More recently, attention has shifted from traditional clinicopathologic risk factors toward tumor biology as a determinant of radiotherapy benefit. Molecular and genomic profiling has emerged as a critical tool for refining risk stratification and identifying patients with inherently low-risk disease who may safely omit RT. Prospective studies such as LUMINA have demonstrated very low local recurrence rates in patients with biologically defined Luminal A tumors treated with breast-conserving surgery and endocrine therapy alone (4).

In parallel, ongoing trials incorporating genomic assays, including Prosigna (PAM50) and Oncotype DX, seek to further individualize radiotherapy decisions beyond conventional clinical criteria (5,6). In this context, contemporary clinical guidelines from ASTRO, NCCN, and ESMO increasingly support selective omission or de-escalation of RT in well-defined low-risk populations, while emphasizing shared decision-making and careful patient selection (10–14).

This evolving paradigm reflects a broader shift in breast cancer management toward personalized treatment strategies that balance oncologic safety with quality of life and patient preferences. This review synthesizes the evidence from key randomized trials, prospective studies, and current guidelines to identify patients with early breast cancer who derive the greatest benefit from adjuvant radiotherapy, and those for whom treatment de-escalation may be a safe and appropriate option.

METHODS

This narrative evidence-based review aimed to identify patients with early-stage breast cancer who derive the greatest benefit from adjuvant radiotherapy (RT) and those for whom omission or de-escalation may be considered. The study was conducted as a narrative review with a systematic literature search, following PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) principles where applicable. The objective was to evaluate evidence supporting omission and de-escalation of adjuvant radiotherapy (RT) after breast-conserving surgery (BCS) in patients with low-risk, early-stage breast cancer, with particular emphasis on clinicopathologic, molecular, and genomic risk stratification.

A comprehensive literature search was performed in PubMed/MEDLINE, Embase, and the Cochrane Library for studies published between January 2000 and March 2026.

We analyzed evidence from randomized trials in older, hormone-receptor–positive (HR+) early breast cancer, prospective cohort studies and current guidelines.

Reference lists of included studies and relevant reviews were manually screened to identify additional eligible studies.

Eligibility Criteria

Studies were selected according to the following criteria:

• Phase III randomized controlled trials or prospective cohort studies

• Studies evaluating omission or de-escalation of RT following BCS

• Patients with node-negative, estrogen receptor–positive (ER+) early breast cancer

• Reporting at least one of the following outcomes: local recurrence, distant recurrence, or overall survival

• Studies incorporating biological or genomic stratification approaches

Exclusion criteria:

• Retrospective studies without predefined selection criteria

• Studies lacking adequate follow-up or oncologic endpoints

• Populations not representative of low-risk disease (e.g., node-positive without subgroup analysis)

Data extracted included patient demographics, tumor characteristics, RT details, systemic therapy, recurrence rates, and survival outcomes. Evidence was synthesized qualitatively, focusing on trials evaluating older and low-risk patient populations (e.g., CALGB 9343, PRIME II) and molecularly defined subgroups (e.g., LUMINA, PAM50, Oncotype DX). Absolute recurrence risks and survival outcomes were highlighted to quantify the clinical benefit of RT across subgroups.

RESULTS

A total of four key studies met the inclusion criteria and were included in this review, comprising two randomized phase III trials, one

prospective cohort study, and one emerging research domain focused on genomic-guided radiotherapy (RT) decision-making, summary table 1.

Evidence from randomized trials in older and low-risk patients have established the absolute and relative benefits of adjuvant radiotherapy (RT) in early-stage breast cancer.

The randomized trial CALGB 9343 established the foundational evidence supporting radiotherapy (RT) omission in carefully selected older patients. This study enrolled women aged ≥70 years with T1N0, estrogen receptor–positive (ER+) breast cancer treated with breast-conserving surgery (BCS) followed by tamoxifen, with or without RT. At 10 years, ipsilateral breast tumor recurrence was significantly reduced with RT (2% vs 10%), but this improvement in local control did not translate into differences in distant recurrence or overall survival. These findings indicate that, in this low-risk elderly population, RT primarily confers local control benefit without survival advantage, supporting its omission when life expectancy or comorbidity burden is a consideration (1,2).

Similarly, the PRIME II trial extended these observations to a slightly broader population of women aged ≥65 years with T1–T2N0, ER+ tumors receiving endocrine therapy. At 10 years, local recurrence remained significantly higher in the no-RT group (9.5% vs 0.9%), yet, consistent with CALGB 9343, no significant differences were observed in distant recurrence or overall survival. This reinforces the concept that omission of RT increases ipsilateral breast events but does not compromise long-term survival outcomes in biologically favorable disease (3).

These studies confirm that in carefully selected older patients, RT primarily provides local control benefit while systemic and endocrine therapy effectively maintain overall disease outcomes.

Molecularly defined low-risk populations

Recent studies have focused on integrating tumor biology to guide RT decisions.

The LUMINA trial enrolled women ≥55 years with T1N0, grade 1–2 luminal A tumors, demonstrating a 5-year local recurrence of 2.3% in patients treated with BCS and endocrine therapy alone (4). These findings highlight that molecularly favorable tumors can achieve excellent local control without RT, supporting personalized de-escalation strategies. In addition, genomic assays such as PAM50/Prosigna and Oncotype DX are being evaluated to further refine patient selection for RT omission, offering a risk-adapted approach beyond conventional clinical criteria (5,6).

Guideline alignment

Collectively, the evidence indicates that adjuvant RT remains critical for local control but provides limited absolute benefit in older patients and biologically low-risk populations. Contemporary guidelines from ASTRO, NCCN, and ESMO reflect these data, recommending consideration of selective RT omission in well-defined low-risk

patients while emphasizing shared decision-making and individualized care (10–14).

Taken together, these studies delineate a consistent pattern that the omission of RT in selected low-risk, ER+ early breast cancer increases local recurrence but does not adversely affect distant outcomes or overall survival. The clinical challenge now lies in refining selection criteria, moving from age-based and clinicopathologic factors toward integrated molecular profiling, to optimize the balance between treatment de-escalation and oncologic safety. These studies underscore a shift toward personalized, risk-adapted treatment strategies, balancing oncologic safety, treatment burden, and patient quality of life.

DISCUSSION

Adjuvant radiotherapy (RT) following breast-conserving surgery (BCS) remains a cornerstone of early-stage breast cancer management, providing substantial reduction in local recurrence and modest improvement in breast cancer–specific survival (1). However, landmark trials including CALGB 9343 and PRIME II demonstrate that the absolute benefit of RT is

Table 1. Key Trials Evaluating Radiotherapy Omission in Low-Risk Early Breast Cancer

Trial	Population	Intervention	10-year Local Recurrence	Distant Recurrence	Overall Survival	Notes
CALGB 9343 [1] [2]	≥70 yrs, T1N0, ER+	BCS + Tamoxifen ± RT	2% vs 10% (RT vs no RT)	NS	NS	Supports RT omission in selected older patients
PRIME II [3]	≥65 yrs, T1–T2N0, ER+	BCS + Endocrine ± RT	0.9% vs 9.5%	NS	NS	Confirms higher local recurrence without survival impact
LUMINA [4]	≥55 yrs, T1N0, grade 1–2 Luminal A	BCS + Endocrine only	2.3%	–	–	Molecularly defined low-risk group; RT omission safe
PAM50/Prosigna, Oncotype DX [5, 6]	Early-stage, ER+	Genomic risk-guided RT	Under investigation	–	–	Personalized RT decision-making

Abbreviations: BCS, Breast-conserving surgery; RT, Radiotherapy; ER, Estrogen receptor; NS, not statistically significant.

small in selected older women with low-risk, hormone receptor–positive, node-negative disease, supporting consideration of RT omission in carefully selected populations (2,3). These findings have shifted the paradigm from a "one-size-fits-all" approach to a more personalized, risk-adapted strategy.

Clinical Implications

For older patients or those with biologically favorable tumors, omission of RT may safely reduce treatment burden without compromising survival, while avoiding potential acute and long-term toxicities such as dermatitis, cardiopulmonary effects, and secondary malignancies (2,3,4).

The LUMINA trial further highlights the utility of integrating molecular profiling into clinical decision-making, showing very low local recurrence rates in patients with Luminal A tumors treated with endocrine therapy alone (4). Incorporating genomic assays, such as PAM50/Prosigna or Oncotype DX, may refine patient selection, potentially identifying additional subgroups suitable for de-escalation (5,6).

Alignment with Guidelines

Contemporary guidelines reflect this evolving evidence. ASTRO, NCCN, and ESMO endorse selective omission of RT in well-defined low-risk populations, emphasizing shared decision-making and individualized risk assessment (10–14). Guidelines also support hypo fractionated or partial-breast RT approaches as alternatives to conventional whole-breast RT in appropriate patient populations, further balancing efficacy, toxicity, and patient convenience.

Future Direction

Future research should move decisively toward integrated risk-adapted radiotherapy (RT) decision-making, combining clinicopathologic variables (age, tumor size, grade, margins, lymph vascular invasion) with molecular subtype and genomic risk scores. While trials such as LUMINA have demonstrated the feasibility of biology-driven RT omission in Luminal A disease (4), and ongoing studies are evaluating genomic classifiers such as PAM50 Prosigna and Oncotype DX (5,6), there remains a critical need for prospective validation frameworks that integrate these dimensions into unified predictive models. Such models should aim to estimate absolute local recurrence risk at 5-, 10-, and 15-year horizons, thereby enabling clinicians to quantify the marginal benefit of RT in an individualized manner rather than relying on population-level estimates.

A second major research priority is the generation of robust long-term outcome data, particularly beyond 10 years, in patients undergoing RT de-escalation. Although trials like CALGB 9343 and PRIME II have demonstrated no overall survival detriment despite increased local recurrence (1–3), contemporary cohorts treated with modern systemic therapy and molecular selection require updated survivorship analyses. Importantly,

endpoints should extend beyond traditional oncologic outcomes to include patient-reported outcomes (PROs), cosmetic results, functional status, and health-related quality of life (HRQoL). Given the relatively small absolute benefit of RT in low-risk populations, these patient-centered outcomes may ultimately be decisive in treatment selection.

In parallel, health economic evaluations are essential to determine the cost-effectiveness of RT omission versus delivery, particularly in healthcare systems with constrained resources. This includes not only direct treatment costs but also downstream costs related to local recurrence management, toxicity, and surveillance imaging. Modeling studies incorporating genomic stratification may help define value-based thresholds at which RT provides diminishing returns.

Another critical avenue involves optimization not just omission of RT through treatment de-intensification strategies. Techniques such as ultra-hypofractionation as 5-fraction regimens established in the FAST-Forward trial (7) and partial-breast irradiation (PBI) (8) have demonstrated non-inferior local control with reduced treatment burden and toxicity in selected patients. Future studies should directly compare RT omission versus minimal RT approaches to determine whether a “middle ground” strategy may optimize both efficacy and tolerability.

Finally, there is a growing need for clinically implementable decision-support tools, including risk calculators, nomograms, and AI-driven predictive models, that synthesize clinicopathologic and genomic data into actionable treatment recommendations. These tools should be embedded within a shared decision-making framework, enabling transparent discussion of trade-offs between absolute reduction in local recurrence with RT, the potential acute and late toxicities and the impact on quality of life and convenience. Such approaches are particularly relevant in low-risk populations, where treatment preference and patient values may justifiably influence final decisions as much as clinical risk estimates.

In summary, the future of RT in early breast cancer lies not in uniform de-escalation, but in precision omission or personalization, guided by integrated risk modeling, long-term outcome data, patient-centered endpoints, and evolving RT technologies.

Limitations

This review synthesizes primarily published RCTs and prospective studies, heterogeneous trial designs and follow-up durations may limit direct comparability. Moreover, data on molecularly guided RT omission are still maturing, and widespread implementation requires validation in diverse populations.

CONCLUSION

Collectively, the evidence supports a risk-adapted approach to adjuvant radiotherapy in early breast cancer, particularly for older patients and those with biologically low-risk tumors. Incorporating

molecular profiling and genomic assays enables personalized RT strategies that balance oncologic safety with patient-centered outcomes, reducing overtreatment and preserving quality of life. Ongoing studies and evolving guidelines are likely to further refine patient selection and expand safe de-escalation strategies.

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