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Radiation Management for Breast Cancer After Neoadjuvant Therapy

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Abstract

Purpose of Review Neoadjuvant chemotherapy (NAC) utilization is an important part of breast cancer therapy. Recent advances call into question the optimal role of radiotherapy after NAC, as many radiation studies were performed without NAC. This review was conducted to understand the current data, outstanding questions and ongoing trials related to radiotherapy after NAC.

Recent Findings Response to NAC is associated with promising clinical outcomes, particularly in triple-negative and HER2+ breast cancer. Retrospective data suggest that modification of radiotherapy based on tumor response to NAC may be appropriate, though caution is advised without prospective randomized evidence. NSABP B-51 and Alliance A011202 will investigate the management of nodal disease in this setting. Future trials will examine the optimal sequencing of treatments.

Summary The personalization of adjuvant radiotherapy based on response to neoadjuvant chemotherapy is an attractive goal that is currently being evaluated in multiple clinical trials, including NSABP B-51.

Keywords Neoadjuvant chemotherapy · Breast cancer · Radiation · Regional nodal irradiation · Radiation omission

Introduction

The use of neoadjuvant chemotherapy (NAC) for breast cancer is growing. First utilized in the 1970s [1], NAC is now utilized in over 20% of breast cancer cases, particularly in the setting of a large primary tumor or clinically positive lymph nodes (cN+) [2]. Potential benefits of NAC include improved operability [3] (downstaging of breast and axillary disease leading to de-escalation of surgery), improved cosmesis [4] (decreased size of necessary surgical resection), acquisition of valuable prognostic information based on response status, avoidance of axillary lymph node dissection (ALND), and the ability to personalize adjuvant systemic therapy [5, 6]. Patients with tumors that respond well to NAC—particularly those with triple-negative breast cancer (TNBC) or HER2+ disease—have improved clinical outcomes compared to those who do not respond [1, 7, 8]. The reasons for the proliferation of NAC include the progressive recognition of these benefits, improvements in up-front staging techniques, improvement in molecular stratification, and development of targeted therapies that improve NAC efficacy.

The incorporation of NAC calls into question many existing treatment paradigms. The benefit of radiotherapy (RT) after breast cancer surgery has been well-established in the adjuvant setting [9–11], but the utilization of NAC has led to many unanswered questions. In particular, the role of RT in the setting of clinical or pathologic complete

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response (cCR or pCR) after NAC is debated. This review seeks to summarize the current body of evidence surrounding NAC and RT and highlight the open questions that are currently under study.

Rationale for Neoadjuvant Systemic Therapy

The benefits of NAC have been studied in many trials. NSABP B-18 and B-27 examined the sequencing of systemic therapy and surgery [12, 13]. These trials are useful for the study of RT after NAC because of the uniformity of RT use; lumpectomy patients were given adjuvant whole breast irradiation (WBI), mastectomy patients did not receive any adjuvant RT, and regional nodal irradiation (RNI) was not permitted. B-18 randomized 1,523 patients with operable breast cancer to pre-operative or post-operative chemotherapy [12]. After 9 years of follow up, there was no statistically significant difference in ipsilateral breast tumor recurrence (IBTR), overall survival (OS), or disease-free survival (DFS), although there was a trend for improved survival in favor of younger patients who received NAC [3]. The NAC group had more lumpectomies than the adjuvant chemotherapy group (67.8% vs 59.8, statistical significance not reported), emphasizing the ability of NAC to downstage the extent of disease and allow for breast conservation. Patients with a clinical or pathologic response after NAC had significantly improved survival outcomes compared to those without a response.

In B-27, 2411 patients with operable breast cancer were assigned to three treatment groups, all of which featured doxorubicin (Adriamycin) and cyclophosphamide (AC). One treatment arm received docetaxel in addition to AC, which resulted in a significantly increased cCR rate (40.1% vs 63.6%, $p < 0.001$) and pCR (13.7% vs 26.1%), but not DFS [14]. Similar to B-18, pCR was predictive of OS (HR = 0.36, $p < 0.001$) [15]. A combined analysis of all patients who received NAC in these trials demonstrated a 10-year locoregional recurrence (LRR) of 11.1% [16]. Factors associated with increased risk of LRR were age ≥ 50, tumor size > 5 cm, cN+ prior to NAC, lack of pCR, and pathologically involved lymph nodes after NAC (ypN+). For cN+ patients who underwent breast conserving therapy (BCT)—consisting of lumpectomy and ALND followed by WBI—and achieved a pathologic complete response in the breast and axillary lymph nodes, the 10-year risks of IBTR was 6.8%, and regional nodal recurrence was 1.1%. Overall, the risk of LRR was significantly decreased with increasing response to NAC. A 2018 meta-analysis that included 10 randomized trials (including B-18) compared patients who received NAC with adjuvant chemotherapy [1]. The results demonstrated that NAC was associated with a 28% cCR, an increased frequency of BCT compared to adjuvant chemotherapy group (65% vs 49%), and an increased risk of local recurrence (21.4% vs 15.9%, $p < 0.001$). There was no increased risk of distant metastasis (DM) or breast-cancer mortality (BCM). A complete response to NAC was associated with a lower risk of DM and BCM. The authors surmised that the increased risk of local recurrence may have been due to inappropriate selection for BCT or differences in axillary staging and RT. Despite this cautionary finding, these trials support that NAC can lead to an increased frequency of lumpectomies and provide valuable prognostic information regarding local recurrence and survival. In some cases, this information leads to personalization of adjuvant systemic therapies, which can be associated with improved outcomes, including DFS and OS [5, 6]. Current national guidelines support the use of NAC in patients with inoperable disease, bulky lymphadenopathy, large primary tumors, a likely delay in surgery, and most TNBC and HER2+ disease ≥ cT1cN0 [17].

Rationale for Adjuvant Radiotherapy

Decades of data have demonstrated that BCT is a safe alternative to mastectomy in early stage breast cancer [10, 18, 19]. Though dosing and fractionation continue to evolve, the standard of care adjuvant RT regimen following lumpectomy is WBI (or accelerated partial breast irradiation [APBI] in select situations). Post-mastectomy radiotherapy (PMRT) includes irradiation of the chest wall and regional lymph node basins after mastectomy. The decision to prescribe adjuvant RT is based on a variety of factors, including risk for recurrence, performance status, type of axillary management (ALND vs SLNB), reconstruction plan, financial toxicity, and distance from care. In general, WBI with RNI and PMRT are recommended after their respective surgeries if lymph nodes are positive for disease prior to surgery or were involved on final pathology. This has been shown to reduce the risk of regional recurrence, DM, and BCM [20, 21]. Patients without clinical, radiographic, or pathologic evidence of lymph node involvement are typically not offered RT regimens that cover nodal regions. With the improvement and proliferation of NAC, however, the field is evaluating the value and sequencing of adjuvant RT in the setting of clinical and pathologic response.

Nodal Irradiation

The National Comprehensive Cancer Network (NCCN) guidelines currently recommend adjuvant WBI and a strong consideration of RNI in the setting of cN+ disease

prior to any therapies. This recommendation is likely influenced by multiple large trials such as MA.20 and EORTC 22922/10925, which demonstrated improved rates of local recurrence and breast cancer mortality with RNI [20, 21]. However, the strength of the recommendation for RNI in the setting of complete pathologic lymph node response after NAC (ypN0) is controversial [17, 22••]. Although this question has not been answered directly by a randomized clinical trial, several trials can give insight into modern rates of pathologic response to NAC and evolving practice patterns.

The NSABP B-40 and B-41 trials examined the efficacy of bevacizumab (anti-VEGF) and lapatinib (anti-HER2), respectively, as part of an NAC regimen [23, 24]. Although adjuvant WBI was mandated after lumpectomy, RNI and PMRT were prescribed based on physician discretion. Both trials included patients with T2-T3, N0-N2a disease (B-40 also included T1c). In an analysis that combined results from both trials, RNI was found to have been performed in 50.8% of patients, including 64.2% of patients with cN+ disease and 37.9% of patients with cN0 disease. Multivariable analysis confirmed that patients with cN+ disease, lack of axillary pCR, non-Hispanic ethnicity, TNBC, and HER2+ disease were more likely to receive RNI [25]. B-40 reported a 30.8% pCR rate in the breast [23, 25]. B-41 reported rates of pCR in the breast and nodes as 49.4% (trastuzumab alone), 47.4% (lapatinib alone), and 60.2% (trastuzumab and lapatinib). Among patients with cN+, ypN0 disease, the risk of 5-year LRR was 1.47% in B-40 and 0.0% in B-41, compared to cN+, ypN+ patients with a 2.5% and 1.3% 5-year LRR, respectively [25]. Subgroup analyses demonstrated that RNI improved LRR for women with HR+ ypN+ disease on B-40 and improved OS for women with ypN+ disease on B-41, but for the entire cohort, RNI was not associated with improvements in LRR, DM, DFS, or OS.

Tailoring adjuvant RT to patient risk status was studied in the RAPCHEM trial. This trial was a prospective registry study assessing adjuvant RT de-escalation for lower risk patients that stratified patients with cT1-2N1 breast cancer after NAC and surgery by risk for LRR [26•]. For low-risk patients, defined as ypN0, the recommendation was for omission of RNI after lumpectomy and omission of PMRT after mastectomy. Axillary lymph node dissection (ALND) was performed in 81% of the study cohort. For the entire cohort, 5-year LRR was 2.2%. This rate was not significantly different between the risk groups (2.1% low risk, 2.2% intermediate risk, 2.3% high risk). Though approximately 37% of low-risk patients received more RT than specified by the study guidelines, this did not significantly alter the 5-year LRR rates.

An additional study analyzed RT patterns on ACOSOG Z1071, which examined the role of SNLB after NAC in patients with cN+ disease [27••, 28]. After multivariate analysis, RNI/PMRT was associated with improved 5-year LRR (HR 2.35, $p = 0.018$), but no improvement in OS, DFS, or BCSS in patients with residual nodal disease after neoadjuvant chemotherapy. The subset of patients with ypN0 disease did not experience this benefit. In this group, omission of PMRT for mastectomy patients was not associated with a statistically significant detriment in 5-year LRR (100% PMRT vs 96.2% no PMRT, p value not reported). Omission of RNI after lumpectomy had a similar LRR (90.1% RNI vs 94.6% no RNI, $p = 0.51$). Patients with TNBC who underwent mastectomy (13.6% of the entire cohort) had higher numerical 5-year LRR when nodal irradiation was omitted (100% +RNI vs 90.4% − RNI), though this did not reach statistical significance.

As discussed by Marks et al., caution must be taken with de-escalation in this setting [22••]. A subgroup analysis of the Danish DBCG82 b&c trials demonstrated that those at the lowest risk for metastatic spread were actually the ones with the largest DFS and OS benefit from PMRT [29]. In a series from MD Anderson, 1289 women with stage II–III breast cancer received NAC followed by BCS/mastectomy and ALND +/- adjuvant radiotherapy. Among the 28.5% of ypN0 patients, RNI was not associated with an improvement in any disease recurrence (20.3% no RNI vs 15.9% for RNI, $p = 0.25$), indicating that RNI could possibly be omitted in this population. However, on multivariate analysis for the entire cohort, there was a 10-year LRR and DM benefit with RNI (LRR HR 0.497, 95% CI 0.279–0.884; DM HR 0.731, 95% CI 0.541–0.988) [30]. With such a strong HR indicating benefit of RNI in the whole population, subgroup analyses must be validated with prospective randomized trials before definitive conclusions can be drawn.

Two ongoing trials will provide high-level evidence regarding nodal management after NAC. The first, NSABP B-51, is a de-escalation study designed to evaluate the efficacy of nodal irradiation (PMRT after mastectomy and RNI after lumpectomy) in reducing the risk of recurrence in patients with cT1-3N1 disease who undergo NAC and are found to be ypN0 [31••]. Patients who undergo mastectomy are randomized to PMRT vs no PMRT and lumpectomy patients are randomized to WBI + RNI vs WBI alone. The primary study endpoint is invasive breast cancer recurrence-free interval (IBC-RFI). Secondary endpoints include OS, locoregional recurrence-free interval, distant recurrence-free interval, toxicity, and quality of life outcomes. This is a superiority trial, with nodal irradiation as the experimental arm. The results of this trial will provide level I evidence for or against the utility of nodal irradiation in patients with cN1, ypN0 disease. The second trial, Alliance A011202, was designed to answer a slightly different question [32••]. A similar population of patients with cT1-3N1 disease who undergo NAC will be evaluated, but only those who have a positive SLNB will be included. The randomization is to completion ALND + WBI + RNI vs WBI + RNI. As most historical RNI trials

were done in the setting of ALND, this trial is important for assessing the role of RNI in the setting of axillary staging de-escalation. The primary outcome is invasive breast cancer RFI. Secondary outcomes include OS, lymphedema, and residual cancer burden (RCB). This non-inferiority trial will help us understand whether patients with cN1 disease who have a positive SLNB can undergo RT alone and omit completion ALND without compromising their risk of recurrence.

Breast Irradiation

The value of adjuvant RT to the breast after lumpectomy was quantified in a 2011 EBCTCG meta-analysis, which demonstrated a long-term relative LRR benefit of approximately 50% [33]. A strong benefit from WBI was observed across many subgroups based on age, tumor grade, receptor status, and nodal status. Mortality benefits were also observed. The study concluded that for every four recurrences avoided at 5 years, one breast cancer death would be prevented at 15 years. Even though patients from this meta-analysis were treated prior to 2000, the paradigm is generally unchanged. However, current improvements in NAC, including targeted therapies such as anti-HER2 agents, have caused investigators to consider the omission of RT to the breast after NAC and lumpectomy in initially clinically node-negative patients with pCR for certain low-risk groups. To this end, NRG BR008 is a multi-institutional effort to study omission of WBI in a specific population of low risk, HER2+ breast cancer patients. This subset of patients, some of whom will undergo NAC with chemotherapy and anti-HER2 agents, will be randomized to adjuvant WBI or omission of adjuvant WBI. The primary outcome of the study is RFI. By demonstrating the non-inferiority of RT omission in this setting, patients could experience significant improvements in long-term side effects, cosmesis, and financial toxicity.

Sequencing of Radiotherapy and Other Adjuvant Therapies After NAC

As the appropriate subset of patients for whom NAC should be utilized continues to be refined, there has been development of additional adjuvant therapies. Several trials in the last decade have demonstrated benefits from adjuvant therapies after NAC and definitive therapy [6, 34, 35]. With multiple effective adjuvant treatments, including RT and various systemic agents, optimal sequencing is important. Relative safety of concurrent RT and endocrine therapy has previously been demonstrated [36], but the safety profiles of newer therapies in conjunction with RT are still being evaluated. One of these treatments is trastuzumab emtansine (T-DM1), which was studied in the phase III KATHERINE trial [35]. Patients with early stage, HER2+ breast cancer who underwent NAC and were found to have residual disease in the breast or axilla were randomized to receive 14 cycles of trastuzumab vs T-DM1. RT was recommended per study protocol to start within 60 days of surgery and be given concurrently with T-DM1. In terms of toxicity, radiation pneumonitis was observed in 1.5% of patients in the T-DM1 arm compared to 0.7% in the trastuzumab arm. A radiation-related skin injury occurred in 1.4% of the T-DM1 arm compared to 1.0% of the trastuzumab arm. These numbers are small and appear to suggest that concurrent RT and T-DM1 should be acceptable. However, a case report based on clinical experiences from the Mayo Clinic raised a concern that concurrent T-DM1 may have contributed to more radiation dermatitis than documented on study [37]. The authors note that low overall rates of any-grade radiation dermatitis (< 30% in both arms) indicate that skin toxicities may not have been appropriately graded, as higher rates of low-grade skin toxicity would be expected for patients undergoing adjuvant RT. They hypothesized from their own clinical experience that the conjugated component of T-DM1, emtansine (a microtubule inhibitor), may cause more radiosensitization than previously thought. Similarly, a small case series from France found that concurrent T-DM1 and stereotactic radiosurgery for metastatic breast cancer increased rates of radiation necrosis from 28.6 to 50%, compared to sequential treatment [38]. Concurrent T-DM1 and RT are likely safe for patients based on randomized data, but more follow-up is warranted to accurately classify the risk of toxicity.

The CREATE-X trial studied a similar use of adjuvant capecitabine in patients with HER2-negative disease with residual tumor found after NAC [6]. In patients with TNBC, capecitabine was found to increase DFS and OS compared to standard treatment without capecitabine. There was no recommendation for timing of adjuvant RT on trial; it could be given before or after randomization. In practice, timing is based on institutional preference. Safety concerns are one of the main drivers behind recommendations of treatment sequencing, but clinical efficacy is another. Multiple studies suggest that concurrent capecitabine with RT can be delivered without additional severe toxicities [39, 40], and preclinical evidence suggests that capecitabine may be more effective if given with or after adjuvant RT [41]. Clinical trials are needed to evaluate safety and efficacy of various treatment sequences.

Another recent addition to the armamentarium of systemic therapy is pembrolizumab from Keynote-522 [34]. In this phase III trial, patients with triple-negative breast cancer received NAC (including pembrolizumab vs placebo), definitive surgery, and then adjuvant pembrolizumab or placebo for up to nine cycles. This adjuvant systemic therapy could be started concurrently with RT or two weeks after completion of RT [42]. Radiation dermatitis was not a measurable endpoint in this study, but severe skin reaction was measured. A grade ≥ 3 severe skin reaction was present

in the pembrolizumab group in 4.7% of cases compared to 0.3% of cases in the placebo group, though most of these reactions occurred in the neoadjuvant phase and thus cannot be attributed to the deleterious effects of concurrent therapy. One grade 5 pneumonitis event was reported in the pembrolizumab group, though an increased risk of severe pneumonitis with neoadjuvant chemotherapy-immunotherapy has not been convincingly demonstrated [43]. As more patients are treated with this regimen, institutional experiences on toxicity will be important to understand the rare toxicities of combination therapy.

CDK4/6 inhibitors (CDK4/6i) are approved agents for ER+/HER2- locally advanced and metastatic breast cancer. Preclinical studies suggest that CDK4/6i may have radiosensitizing effects [44]. However, clinical toxicity data regarding CDK4/6i and RT are limited to case reports and small retrospective cohorts and appear to show mixed results [45]. Multiple ongoing, prospective clinical trials involving CDK4/6i and RT will provide more insight into efficacy and safety of this novel combination [46, 47].

PARP inhibitors indirectly limit the cell's ability to repair double-strand DNA breaks, including those induced by radiotherapy [48]. In tumor cells with deficient DNA repair mechanisms (common in patients with BRCA mutations and TNBC) [49], this leads to increased radiotherapy efficiency [50]. A phase I trial has demonstrated the safety of RT and concurrent olaparib in TNBC [48]. The phase II TARA trial will evaluate the safety and efficacy of concurrent talazoparib and RT, followed by concurrent atezolizumab and RT in the setting of metastatic TNBC [51]. Southwest Oncology Group (SWOG) S1706 is a phase II clinical trial randomizing patients with inflammatory breast cancer who received NAC and surgery to standard adjuvant RT or standard adjuvant RT with concurrent olaparib [52].

Lessons from these trials, and others, will assist in shaping maximally effective adjuvant therapy sequences. While there does not appear to be immediate toxicity concerns regarding the sequencing of these adjuvant therapies with RT, accurate recording and reporting of toxicities are essential. Novel approaches that can safely enhance synergy between RT and additional adjuvant therapies are needed.

Future Directions

As pCR rates continue to improve and use of NAC continues to expand, an intriguing question arises: will omission of surgery become a feasible option for certain low-risk patients with a suspected complete response to NAC? If possible, this could potentially improve cosmesis, quality of life, sequelae from surgical complications, and financial toxicity [53]. To this end, NRG BR005 was designed [54] to be a two-stage, phase II trial which first sought to assess the accuracy of post-NAC tumor bed biopsies in patients with cCR to assess for residual disease. The prespecified negative predictive value (NPV) threshold for detecting residual disease was > 90%. If feasibility could be proven, the second part of the trial would assess if patients could proceed with definitive RT and avoid surgery. The primary analysis of 98 patients was presented in 2019 and demonstrated a NPV of 77.5%, which was below the threshold value [54]. Only 50% of the patients with residual disease were identified on post-NAC biopsy. The study was terminated, and the efficacy of definitive RT was not evaluated. However, a study from MD Anderson used a combination of fine needle aspiration (FNA) and vacuum-assisted core biopsy (VACB) in a similar setting and found a NPV of 95% [53]. The same group completed a multi-institution, phase II trial for RT alone in patients who received NAC and were found to have a complete response after VACB of the tumor bed [55]. Definitive breast surgery was omitted in these patients, and they proceeded with WBI + boost. After 26.4 months of follow-up, LRR was 0% in 31 patients. Further follow-up is required to accurately gauge the efficacy of this technique. Breast conservation therapy with the omission of surgery is not ready for prime time, but with continued improvements in neoadjuvant agents, imaging, biopsy techniques, and surveillance technologies, further study is merited. Circulating tumor DNA (ctDNA) may also be an important tool in adjuvant treatment decisions. ctDNA levels after NAC appear to be prognostic of recurrence risk and survival and may help identify patients who may or may not benefit from adjuvant RT [56–58]. As technologies and techniques develop, current treatment paradigms will continue to be challenged and improved.

Conclusions

Many breast cancer treatment paradigms have been disrupted with the proliferation of effective NAC and de-escalation of axillary staging. Recommendations for radiotherapy are subsequently evolving. Treatment plans that personalize the sequencing, coverage, dose, and concurrent systemic agents will replace standard adjuvant treatments. RT personalization will be based on factors such as molecular status, response to NAC, and patient preference, among others. It is essential that radiation oncologists work in a multi-disciplinary fashion in each step of clinical trial execution. The results of several ongoing trials, including NSABP B-51 and Alliance A011202, will provide high-quality, sought-after answers to many open questions.

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Data Availability Data is available for use in the public domain as permitted by Journal practices.

Declarations

Ethical Approval This article does not contain any studies with human or animal subjects performed by any of the authors.

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Papers of particular interest, published recently, have been highlighted as:
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