Chapter 12
Radiotherapy Following Neoadjuvant Chemotherapy in Locally Advanced Breast Cancer

Nisha Ohri and Alice Ho

Abstract Neoadjuvant chemotherapy (NAC) is commonly used in patients with locally advanced breast cancer. Several challenges faced by radiation oncologists in treating these patients include the lack of an accurate pathologic stage to guide management and determining how response to NAC should affect further local therapy. In the postmastectomy setting, the available data demonstrates that both initial clinical stage and final pathologic stage independently predict for locoregional recurrence (LRR). Postmastectomy radiation therapy (PMRT) improves local control in patients with locally advanced clinical stage III disease, regardless of response to NAC, and in those with residual pathologic nodal disease. Patients with early-stage disease who respond well to NAC are at low risk for LRR. Within the intermediate risk groups, additional factors such as molecular subtype and presence of a complete pathologic response, both of which have been shown to predict for LRR, may help guide further management decisions. With regard to breast-conserving therapy after NAC, the available data demonstrates this is a safe and effective option in patients with minimal up-front nodal disease and small residual tumors after NAC. Additional contraindications for lumpectomy in any setting should also be considered. The role of regional nodal irradiation in patients who have received NAC is controversial, particularly among pathologically node-negative patients. There are two ongoing randomized trials open for accrual in the USA that aim to evaluate the benefits of adjuvant radiation therapy, including regional nodal irradiation, after NAC.

Keywords Breast cancer • Neoadjuvant chemotherapy • Postmastectomy radiation therapy • Pathologic complete response • Regional nodal irradiation

N. Ohri
Department of Radiation Oncology, Mount Sinai Hospital, 1184 Fifth Avenue, New York, NY 10029, USA

A. Ho (✉)
Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, 1250 First Avenue, SM-07, New York, NY 10011, USA
e-mail: HoA1234@mskcc.org

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12.1 Introduction

Neoadjuvant chemotherapy (NAC) is a common treatment modality for patients with locally advanced breast cancer. It can be used to facilitate surgery when up-front surgical resection is not feasible or to avoid mastectomy in cases where up-front breast conservation surgery may result in poor cosmetic outcome [1, 2]. Delivering preoperative systemic therapy may also treat micrometastatic disease and avoid delays due to postoperative healing issues after surgery.

The benefits of radiation therapy (RT) after breast conservation surgery with or without adjuvant chemotherapy have been well-established by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis [3]. Similarly, multiple randomized trials have demonstrated locoregional recurrence (LRR) and breast cancer survival benefits with postmastectomy radiation therapy (PMRT) in appropriately selected patients [4, 5]. The use of PMRT in general will likely increase, given that the most recent update of the EBCTCG meta-analysis showed significantly lower 10-year recurrence and 20-year breast cancer mortality rates with the addition of PMRT in patients with only one to three positive lymph nodes [6].

These trials included in the EBCTCG meta-analysis, however, did not enroll patients who received NAC. Neoadjuvant chemotherapy has been shown to change the extent of disease in 80–90 % of cases [2]. As a result, the pathologic indications for adjuvant radiation therapy after up-front surgical resection may be different in the setting of preoperative systemic therapy. Several common challenges faced by radiation oncologists when treating patients who have undergone NAC include the lack of an accurate pathologic stage to guide treatment decisions, assessing how the response to NAC should affect further local therapy, and formulating new treatment strategies for patients who demonstrate a poor response to NAC. To date, there is limited data from randomized trials to help answer these questions. This chapter will review the evolution of the role of radiation therapy in optimizing locoregional control in breast cancer patients who receive NAC.

12.2 LRR After NAC and Mastectomy Without PMRT

Available data from randomized studies comes from the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-18 and B-27 trials. Mamounas et al. performed a retrospective combined analysis of these two trials to examine the rates and patterns of LRR after NAC as well as identify independent predictors of local failure. These trials were conducted in the late 1980s and 1990s before the benefits of PMRT were established [4, 5]. At that time, clinical trials did not allow postmastectomy chest wall or regional nodal RT, allowing the group to study LRR rates after NAC and mastectomy in patients who did not receive adjuvant radiation.

The NSABP B-18 trial randomly assigned 1523 patients with operable and palpable T1-3 and N0-1 breast cancer to receive either four cycles of neoadjuvant doxorubicin and cyclophosphamide (AC) or four cycles of adjuvant AC. Patients aged 50 or greater received hormonal therapy with tamoxifen for 5 years regardless of receptor status. The NSABP B-27 trial had similar enrollment criteria and randomly assigned 2411 patients to receive either four cycles of neoadjuvant AC or four cycles of neoadjuvant AC followed by four cycles of either neoadjuvant or adjuvant docetaxel. All patients received hormonal therapy with tamoxifen for 5 years regardless of age or receptor status. In both studies, patients who underwent breast conservation surgery received adjuvant radiation therapy. Patients who underwent mastectomy did not receive PMRT. The combined data set included 742 patients from the neoadjuvant AC arm of B-18 and 2346 patients from all three arms of B-27.

For the entire cohort, the 10-year cumulative incidence of LRR was 11.1 %. Among 1947 patients who underwent mastectomy, 12.6 % had a LRR (9.0 % local, 3.6 % regional). Several independent predictors of LRR were identified for all patients: age $\geq$50 years at randomization, clinical tumor size $>$5 cm before NAC, clinical nodal involvement before NAC, pathologic breast tumor response, and nodal status at surgery. For patients who underwent mastectomy, all factors except age remained significant on multivariate analysis. When LRR rates were examined according to the number of pathologically involved nodes at surgery, rates were higher with four or more positive lymph nodes than with one to three positive lymph nodes. However, LRR rates were above 10 % for all subsets of pathologically node-positive patients, indicating that residual nodal disease following NAC is an important negative prognostic factor for locoregional recurrence [7].

A series of retrospective reviews from the MD Anderson Cancer Center (MDACC) has also helped identify clinical and pathologic factors that predict for LRR after NAC and mastectomy without adjuvant radiation. The first study, published in 2002, analyzed outcomes from 150 breast cancer patients with early-stage to locally advanced disease treated on prospective institutional trials. With a median follow-up of 4.1 years, the 5- and 10-year actuarial rates of LRR were 27 %. Three factors independently predicted for LRR: (1) clinical stage IIIB or greater disease, (2) four or more positive lymph nodes, and (3) lack of tamoxifen. The pathologic complete response (pCR) rate was 10 % at the time of mastectomy. However, the LRR rate among those patients who achieved a pCR remained high at about 20 %, with pretreatment clinical stage ranging from IIA to IIIB. Patients who did not achieve a pCR had a similar rate of LRR (28 %). These results suggested that PMRT should be considered in patients who present with clinical stage III disease, even in the setting of a pCR. Clinical stage II disease is associated with a lower baseline risk of LRR, suggesting that the local control benefit of PMRT is also smaller [8].

To further study these lower-risk patients who undergo NAC and mastectomy, Garg et al. similarly analyzed a cohort of stage I and II patients from the same data set. The study included 132 patients, with 95 % of patients presenting with clinical stage II disease. All patients received either an anthracycline-based neoadjuvant

regimen or single-agent paclitaxel followed by modified radical mastectomy. Nineteen percent of patients had no residual invasive disease at the primary site, 43 % had residual tumors $\leq$2 cm, and 26 % had residual tumors >2 cm. Among patients who presented with clinically involved lymph nodes, 36 % were pathologically node negative. The overall 5- and 10-year LRR rates were 10 %. Several factors associated with increased LRR were identified: (1) clinical stage T3N0 at presentation, (2) four or more positive lymph nodes at surgery, (3) age $\leq$40 at diagnosis, and (4) lack of tamoxifen. The 5-year LRR rate for patients with clinical T1-2 disease and one to three nodes positive at surgery was very low (5 %). This led investigators to conclude that among patients presenting with clinical stage II disease, PMRT is indicated for those who are young (defined as $\leq$40 years old), have T3 tumors, or have four or more positive lymph nodes at surgery. Conversely, patients with initial clinical T1-2 disease and one to three positive lymph nodes at surgery may have too low a risk of LRR to benefit from PMRT [9].

12.3 The Role of PMRT in Minimizing LRR After NAC and Mastectomy

Another series of retrospective studies from the MDACC investigated the role of PMRT in locally advanced breast cancer patients treated with NAC and mastectomy. In 2004, Huang et al. published a study including 676 patients treated from 1974 to 1998 with doxorubicin-based NAC and mastectomy $\pm$ PMRT. Ninety-five percent of patients also received adjuvant chemotherapy. Radiation therapy included 50 Gy to the chest wall and regional lymph nodes with an additional 10 Gy boost to the chest wall. About 30 % of patients received adjuvant hormonal therapy with tamoxifen.

At a median follow-up of 5.7 years, patients who received PMRT had a significantly lower 10-year rate of LRR compared to patients who did not (11 % vs. 22 %, $p = 0.0001$). Patients presenting with clinical stage I-IIA disease had similar rates of LRR with and without radiation, while those with stage IIB disease or greater had significantly lower rates of LRR with PMRT (11 % vs. 26 %, $p < 0.0001$). Stratifying by clinical T-stage and N-stage, patients with T3-4 tumors or N2-3 nodal disease benefited significantly from PMRT. Looking at posttreatment pathology, LRR rates were lower with PMRT for residual tumors >2 cm or with four or more positive lymph nodes ($p < 0.001$ for both parameters). In a subset of patients with clinical stage II disease and one to three positive lymph nodes after NAC, there was no difference in LRR rate with PMRT. Among patients who achieved a pCR, 10-year LRR rates were similar for patients with clinical stage I or II disease ($p = 0.22$) but were significantly improved with the addition of PMRT in patients with clinical stage III disease (33 % vs. 3 %, $p = 0.006$). PMRT significantly improved cause-specific survival (CSS) in patients with clinical stage IIIB disease or greater (44 % vs. 22 %, $p = 0.002$), clinical T4 tumors at presentation (45 %

vs. 24 %, $p = 0.007$), and four or more positive lymph nodes (45 % vs. 18 %, $p = 0.005$). Similar to prior studies, this review identified multiple pretreatment clinical factors and posttreatment pathologic factors that predicted for LRR after NAC and mastectomy. PMRT was highly effective in patients with significant residual disease burden after NAC and in patients who presented with locally advanced disease, even in the setting of a pCR [10].

A follow-up study analyzing clinical and pathologic predictors of LRR in the same cohort of 542 patients, all of whom received NAC, mastectomy, and PMRT, was subsequently published 1 year later. Over 70 % of the cohort had clinical stage IIIA or stage IIIB disease. Median follow-up was 70 months. The 5-year rate of LRR was 9 %, and the 10-year rate was 11 %. Over 60 % of failures occurred in the chest wall, and about 30 % occurred in the supraclavicular lymph nodes. On multivariate analysis, five factors were independently associated with LRR: (1) skin/nipple involvement, (2) supraclavicular lymph node involvement, (3) extracapsular extension, (4) estrogen-receptor-negative disease, and (5) lack of tamoxifen use. The 10-year LRR rate for patients with one or none of these factors was only 4 % compared to 8 % with two factors and 28 % with three or more factors ($p < 0.0001$). This data provided compelling evidence for the benefit of PMRT in patients receiving NAC with multiple high-risk features and also illuminated the need for alternative treatment strategies in such patients [11].

12.4 PMRT Following NAC for T3N0 Breast Cancer

The role of PMRT in patients with clinical T3N0 disease treated with NAC and mastectomy is controversial given the absence of nodal involvement upon disease presentation. An MDACC study specifically examined this question in a large retrospective series of 162 patients with cT3N0 breast cancer who received NAC followed by mastectomy. A substantial proportion of patients ($n = 119$; 73 %) received PMRT, which targeted the chest wall, high axilla, and supraclavicular fossa ± internal mammary node irradiation. The 5-year LRR rate for the irradiated group was 4 % compared to 24 % in the non-irradiated group ($p < 0.001$). However, more patients in the irradiated group had pathologically involved lymph nodes at surgery (52 % vs. 26 %, $p = 0.003$), which previous studies identified as a negative prognostic factor for LRR. Among all patients with pathologically involved lymph nodes, the 5-year LRR rate was lower with PMRT (5 % vs. 53 %, $p < 0.001$). Among pathologically node-negative patients, there was a trend toward improved 5-year LRR rate with PMRT (2 % vs. 14 %, $p = 0.06$). In the subset of patients who achieved a pCR ($n = 13$; 8 %), there were no locoregional recurrences. However, it is difficult to interpret these results given the limitations of a very small sample size. This study demonstrated a significant locoregional control benefit with PMRT after NAC and mastectomy in patients presenting with clinical T3N0 breast cancer who have pathologically involved lymph nodes. Even in

patients who are pathologically node negative at surgery, the risk of LRR may be high enough to warrant consideration of PMRT [12].

12.5 Posttreatment Pathology and LRR

One of the biggest challenges in assessing patients who have received NAC is the lack of an accurate pathologic stage, as many patients are downstaged after treatment. From the NSABP B-18 trial, clinical breast tumor size was reduced in 80 % of patients ($n = 693$), and clinical nodal response was observed in 89 % of node-positive patients ($n = 185$) [2].

To explore how posttreatment pathology impacts LRR rate, Buchholz et al. from the MDACC performed a retrospective study of mastectomy patients treated with neoadjuvant vs. adjuvant chemotherapy without PMRT. The analysis included 1031 patients who received adjuvant chemotherapy and 150 patients treated with NAC. Most patients received a doxorubicin-containing regimen. Ninety-two percent of patients in the neoadjuvant group received additional chemotherapy after mastectomy. About 30 % of patients in both groups received tamoxifen.

Advanced clinical stage at presentation was significantly more common in the neoadjuvant group (55 % with clinical stage IIIA disease or greater vs. 9 %, $p < 0.001$). However, the pathologic size of primary tumor and nodal involvement was significantly less in the neoadjuvant group, suggesting favorable response to treatment. Fifty-six percent of patients had residual tumors measuring less than 2 cm, and 46 % were pathologically node negative (28 % presented as clinically node negative). The overall 5-year rate of LRR was higher in the neoadjuvant group (27 % vs. 15 %, $p = 0.001$). When stratified by primary tumor size (0–2 cm, 2.1–5.0 cm, >5.0 cm), the 5-year LRR rate remained significantly higher in the neoadjuvant group for each subset. Based on lymph node status, a significantly higher rate of LRR was seen in patients with four or more positive lymph nodes after NAC. For pathologically node-negative patients or those with one to three involved lymph nodes, the LRR rates were similar between both groups. While patients with T1N1 disease had similar rates of LRR (both <20 %), patients with T2N1 disease had higher rates of LRR with neoadjuvant chemotherapy (30 % vs. 15 %, $p = 0.016$). The group concluded that PMRT should be offered to all patients with pathologic N2 or T3 disease or clinical stage IIIA disease, regardless of preoperative or postoperative chemotherapy. There was insufficient information to assess LRR in patients with clinical stage II disease who received NAC, particularly in those with residual nodal involvement [13].

12.6 LRR After a Pathologic Complete Response

Previous retrospective series demonstrated that LRR rates in patients with locally advanced disease at presentation who achieved a pCR after NAC in the breast and axilla remained relatively high and were significantly reduced with the addition of PMRT [10]. As systemic therapy regimens continue to improve, the rate of pCR after neoadjuvant chemotherapy is expected to increase.

McGuire et al. from the MDACC performed a retrospective review specifically evaluating the outcomes of patients with locally advanced breast cancer who achieved a pCR after NAC. The study included 106 patients, with about 70 % presenting with clinical stage III disease. Over 90 % of patients received an anthracycline-based chemotherapy regimen before modified radical mastectomy. Seventy-two patients (68 %) received PMRT, which consisted of 50 Gy in 25 fractions to the chest wall and regional lymph nodes and an additional 10 Gy boost to the chest wall. The supraclavicular fossa and axillary apex were treated with a photon field, and the internal mammary nodes and medial chest wall were treated with an electron field.

Median follow-up was 5 years. While the irradiated group had a significantly higher proportion of patients who presented with advanced clinical stage (81 % vs. 35 % stage III, $p < 0.001$), the 10-year rates of LRR remained similar between the irradiated and non-irradiated groups (5 % vs. 10 %, respectively; $p = 0.40$). Stratifying by presenting clinical stage, there were no locoregional recurrences among patients with stage I or II disease, regardless of PMRT. Conversely, among patients with stage III disease, the use of PMRT was associated with a significantly lower 10-year LRR rate (7.3 % vs. 33.3 %, $p = 0.040$). No additional predictors of LRR were identified. Irradiated patients had significantly higher rates of 10-year distant metastasis-free survival (88 % vs. 41 %, $p = 0.0006$), CSS (87 % vs. 40 %, $p = 0.0014$), and OS (77 % vs. 33 %, $p = 0.0016$). This study confirmed that in locally advanced breast cancer patients who achieve a pCR after NAC, PMRT improves both local control and survival, again highlighting the significant impact of high disease burden at presentation [14].

12.7 Biology Subtype, pCR Rates, and Long-Term Outcomes

Over the past decade, multiple studies have determined that the likelihood of achieving a pathologic complete response (pCR) is associated with breast cancer subtype, with triple-negative (TN) and trastuzumab-treated Her2+ patients demonstrating a greater proclivity toward pCR compared to hormone-receptor-positive patients. Several studies have also demonstrated that a pathologic complete response to NAC can predict for improved long-term outcomes in breast cancer patients. A retrospective review by Kuerer et al. of 372 patients with locally

advanced breast cancer treated on two prospective trials with anthracycline-based NAC examined pCR rates and survival outcomes. All patients underwent total mastectomy or segmental mastectomy with axillary dissection, additional adjuvant chemotherapy, and adjuvant radiation therapy. The pCR rate was 12 %. The 5-year OS and DFS rates were significantly higher in patients who achieved a pCR (89 % and 87 %, respectively) compared to the rest of the cohort (64 % and 58 %, respectively) [15].

More recently, von Minckwitz et al. from the German Breast Group performed a larger pooled analysis of 6377 patients from seven prospective neoadjuvant chemotherapy clinical trials. The group aimed to precisely define a pathologic complete response and determine its prognostic impact on long-term survival outcomes based on molecular subtype of breast cancer. All patients received neoadjuvant anthracycline-taxane-based chemotherapy. The median tumor size was 4.0 cm, and 12 % of patients presented with locally advanced disease. At a median follow-up of 46.3 months, there were 1466 relapses (23 %) and 775 deaths (12.2 %).

Various definitions of pCR were studied, including ypT0 ypN0 (15.0 %), ypTis ypN0 (4.8 %), and ypT0/is ypN+ (2.9 %). DFS was highest among patients with no residual invasive or in situ disease in the breast or lymph nodes or ypT0 ypN0, followed by ypTis ypN0, and finally ypT0/is ypN+ ($p < 0.001$). Patients were then stratified by the following molecular subtypes: luminal A, luminal B/Her2−, luminal B/Her2+, Her2+, and triple negative. Pathologic complete response rates ranged from 9 % (luminal A) to 50 % (Her2+ with trastuzumab). Both DFS and OS were significantly correlated with pCR only for the Her2+ (with and without trastuzumab) and triple-negative subtypes ($p < 0.001$). While DFS and OS rates were favorable for low-proliferating luminal A-like tumors, pCR was not predictive of survival outcomes in this molecular subtype. A mixed pattern was seen for luminal B-like tumors, with pCR appearing prognostic for Her2− tumors but not Her2+ tumors. This study demonstrated that to achieve the greatest prognostic value, pCR should be defined as no residual invasive or in situ disease in the breast or axilla. Additionally, pCR can serve as a surrogate marker for long-term outcomes in patients with Her2+, triple-negative, and luminal B/Her2− disease and may help guide treatment decisions for patients in whom the role of further local therapy remains unclear [16].

While pCR can be a reliable surrogate for DFS in certain patients, its relationship to LRR outcomes is less clearly defined. To address this question, another study from the MDACC by Caudle et al. aimed to identify patients at high risk for LRR after NAC and breast-conserving therapy based on response to NAC and molecular subtype. This study included 595 patients for analysis and used the following subtypes: ER+ or PR+ (HR+) and Her2−, HR+/Her2+, HR−/Her2+, and HR−/Her2−. All patients underwent lumpectomy with axillary node evaluation. Clinically node-negative patients underwent sentinel lymph node biopsy with completion axillary dissection if positive. Clinically node-positive patients underwent axillary dissection. Radiation therapy included 50 Gy in 25 fractions to the breast with an additional 10 Gy boost to the tumor bed. Regional nodal irradiation was delivered per physician discretion. Because this study was conducted before the

routine use of neoadjuvant trastuzumab, patients who received trastuzumab were excluded.

Patients with HR− tumors had the greatest response to NAC. Pathologic complete response rates were lower in the HR+/Her2− (9 %) and HR+/Her2+ (18 %) subsets than in the HR−/Her2+ (36 %) and HR−/Her2− (38 %) subsets ($p < 0.001$). Additionally, HR− tumors had smaller pathologic tumor sizes and less residual nodal disease burden. However, 5-year LRR-free survival and OS rates were significantly higher for HR+/Her2− (97.0 % and 92.5 %, respectively) and HR+/Her2+ patients (95.9 % and 85.8 %, respectively) than for HR−/Her2+ (86.5 % and 84.4 %, respectively) and HR−/Her2− patients (89.5 % and 83.0 %, respectively). Among patients who did not achieve a pCR, those who were HR− had decreased 5-year LRR-free survival, while HR+ patients maintained high rates of LRR-free survival. While this study was limited by the lack of trastuzumab use in the neoadjuvant setting, it demonstrated high rates of local control in the HR+/Her2− and HR+/Her2+ subtypes, regardless of response to NAC. Although there are currently no alternative treatment strategies to improve locoregional control in patients with HR– subtypes who do not achieve a pCR after NAC, improving the efficacy of locoregional treatment in this subset of patients who are at high risk for LRR is an important research endeavor [17].

The most compelling evidence for the significance of a pathologic complete response and biologic subtype as independent predictors for LRR in patients receiving NAC comes from the pooled analysis of the CTNeoBC (Collaborative Trials in Neoadjuvant Breast Cancer) trials. In the final analysis, 5694 patients with data on biologic subtype and all covariates included in the multivariable analysis model were studied. Thirty-six percent of patients were HR+/grade 1, 11 % HR+/grade 3, 14 % HR−/Her2+, 18 % HR+/Her2+, and 21 % TN. The overall rate of LRR at 5 years was low (6.8 %). Biologic subtype (TN vs. HR+/grade 1: HR of 4.09 [3.01–5.55]) and pCR (ypN+ vs. pT0/isN0: HR 2.36 [1.62–4.34]) were the strongest predictors of LRR, with an overall LRR rate of 12.2 % in TN patients and 11.8 % in patients with residual positive lymph nodes following NAC. These results provided further evidence for the impact of biologic subtype and response to NAC on LRR risk [18].

12.8 Success of Breast Conservation Therapy After NAC

One significant advantage of NAC is the ability to potentially convert patients who would require up-front mastectomy to breast conservation candidates. The NSABP B-18 and EORTC 10902 trials compared locoregional control rates in patients who had preoperative chemotherapy with patients who had postoperative chemotherapy. Both studies demonstrated higher rates of breast conservation therapy in the preoperative chemotherapy arms [2, 19].

Long-term results of the NSABP B-18 trial showed similar rates of LRR in the preoperative chemotherapy and postoperative chemotherapy groups. For patients

who underwent lumpectomy, the in-breast tumor recurrence (IBTR) rates were 13 % and 10 %, respectively ($p = 0.21$) [20]. Similarly, 10-year OS and LRR rates from the EORTC 10902 trial for patients who underwent breast conservation therapy were similar with preoperative chemotherapy and postoperative chemotherapy [21].

To study the patterns and predictors of local failure after NAC and breast-conserving therapy, Chen et al. from the MDACC performed a retrospective review of 340 patients with stage I–III breast cancer. A majority of patients (96 %) were clinical stage II–III at presentation. Lumpectomy included gross excision of the residual primary tumor with a margin of normal-appearing tissue. Re-excision was performed for positive margins, with 4 % of patients having focally positive final margins. About 80 % of patients underwent axillary level I–II dissection. Adjuvant radiation therapy included 50 Gy in 25 fractions to the whole breast with an additional 10 Gy electron boost to the tumor bed. Regional nodal irradiation was delivered at the discretion of the treating physician.

At a median follow-up of 60 months, 29 (8.5 %) patients developed LRR, and 16 were IBTRs. The 5-year LRR-free survival was 91 %, and the 5-year IBTR-free survival was 95 %. Four factors correlated with increased IBTR and LRR rates: (1) clinical N2 or N3 disease, (2) pathologic residual tumor >2 cm, (3) multifocal pattern of residual disease, and (4) lymphovascular space invasion (LVSI) [22]. The same group subsequently developed the MD Anderson Prognostic Index (MDAPI), which used the presence or absence of these four predictors of recurrence to establish an overall score ranging from 0 to 4. The actuarial 5-year IBTR-free survival rates were 97 % for a score of 0–1 ($n = 276$), 88 % for a score of 2 ($n = 43$), and 82 % for a score of 3–4 ($n = 12$), $p < 0.001$ [23]. These studies demonstrated that breast-conserving therapy after NAC in appropriately selected patients results in low rates of LRR and IBTR. This was confirmed by results from the recent large CTNeoBC pooled analysis (LRR rate of 6.0 % with a pCR after NAC and 6.3 % without a pCR) [18].

The available data demonstrates that breast-conserving therapy after NAC is a safe and effective option in patients with minimal nodal disease at presentation, residual T1 tumors or smaller after NAC without multicentric disease, and without LVSI. The contraindications for lumpectomy in any setting should also be considered, including up-front multicentric disease, diffuse microcalcifications, and persistently positive resection margins following lumpectomy. Finally, all patients should undergo whole-breast irradiation after breast-conserving surgery.

12.9 Regional Nodal Irradiation

The benefits of regional nodal irradiation (RNI) have been studied in both breast-conserved and postmastectomy patients, however in the setting of adjuvant chemotherapy delivery only. The National Cancer Institute of Canada Clinical Trials Group (NCIC-CTG) MA.20 trial was a randomized multicenter trial that included

over 1800 patients with high-risk node-negative or node-positive breast cancer. All patients underwent breast-conserving surgery with axillary level I/II lymph node dissection. Patients were randomized to whole-breast irradiation (WBI) or WBI + RNI. The breast was treated to 50 Gy in 25 fractions with or without a 10 Gy boost to the tumor bed. The axillary apex, supraclavicular fossa, and internal mammary nodes were treated to 45 Gy in 25 fractions. Over 80 % of patients had one to three positive lymph nodes, and over 90 % received adjuvant chemotherapy.

Median follow-up was 62 months. The WBI + RNI group had a higher DFS (89.7 % vs. 84.0 %, $p = 0.003$), locoregional DFS (96.8 % vs. 94.5 %, $p = 0.02$), and distant DFS (92.4 % vs. 87.0 %, $p = 0.002$). There was a trend toward improved 5-year OS with WBI + RNI (92.3 % vs. 90.7 %, $p = 0.07$). While a longer follow-up may be required to establish an OS benefit with RNI, these results suggest that all patients undergoing breast-conserving surgery with node-positive disease should receive RNI in addition to WBI [24]. Coupled with the recent update of the EBCTCG meta-analysis demonstrating improved 10-year recurrence and 20-year breast cancer mortality rates with the addition of PMRT in patients with one to three positive lymph nodes, there appears to be a local control and survival benefit when these patients are treated more aggressively [6].

A recent meta-analysis by Budach et al. performed a pooled analysis of three large randomized trials (MA.20, EORTC 22922–10925, and the French trial) to further establish the benefits of regional nodal irradiation. Combining all three trials, there was a significant OS benefit with the addition of medial supraclavicular lymph node irradiation (HR 0.88, 95 % CI 0.80–0.97), with an absolute benefit of 1.6 % at 5 years from the MA.20 trial, 1.6 % at 10 years from the EORTC trial, and 3.3 % at 10 years from the French trial. Looking at the MA.20 and EORTC trials, medial supraclavicular and internal mammary lymph node irradiation was associated with a significant improvement in DFS (HR 0.85, 95 % CI 0.77–0.94) and distant metastasis-free survival (HR 0.82, 95 % CI 0.73–0.92). These combined results again indicate a statistically significant survival benefit with RNI [25].

There is little data to guide treatment decisions regarding regional nodal irradiation after NAC. A study from the Rene Huguenin Cancer Center in France looked specifically at patients who were pathologically node negative after NAC and breast-conserving surgery with axillary lymph node dissection. All patients ($n = 248$) received adjuvant whole-breast irradiation, with 64 % also receiving regional nodal irradiation. The 5-year LRR-free survival and OS rates were similar with regional nodal irradiation (89.4 % and 88.7 %, respectively) and without regional nodal irradiation (86.2 % and 92 %, respectively). However, the targeted lymph nodes varied significantly within the regional nodal irradiation group [26].

Similar results were seen in another retrospective study by the Korean Radiation Oncology Group (KROG 12-05). This study looked at the benefit of elective nodal irradiation in patients with clinical stage II–III breast cancer who received NAC followed by breast-conserving therapy and were pathologically node negative. The overall 5-year LRR-free survival and DFS rates were 95.5 % and 90.5 %, respectively. Elective nodal irradiation did not significantly affect survival outcomes [27].

While the necessity of regional RT or PMRT for ypN0 patients has been studied, data regarding the clinical benefits from treatment is conflicting. Internal mammary lymph node irradiation was not standardized in these studies. It is possible that exclusion of the IMNs from the radiation treatment volumes may have increased the risk of locoregional recurrence, consequently obscuring the benefit of PMRT [26–28].

12.10 Ongoing Trials Investigating the Role of RT After NAC

There are two ongoing randomized NAC trials that are open for accrual in the USA. The NSABP B-51/RTOG 1304 (NRG 9353) trial is enrolling patients with clinical stage II–III breast cancer (T1-3N1M0) with biopsy-proven axillary nodal disease (Fig. 12.1). Patients receive NAC with anti-Her2-targeted therapy if Her2+. Patients who are pathologically node negative at surgery (by axillary dissection or sentinel lymph node biopsy) are randomized to breast RT alone (lumpectomy) or no RT (mastectomy) vs. breast RT with regional nodal irradiation or PMRT with regional nodal irradiation. This study aims to evaluate the benefits of adjuvant radiation therapy, including regional nodal irradiation, in patients who are initially node positive and become node negative after NAC [29].

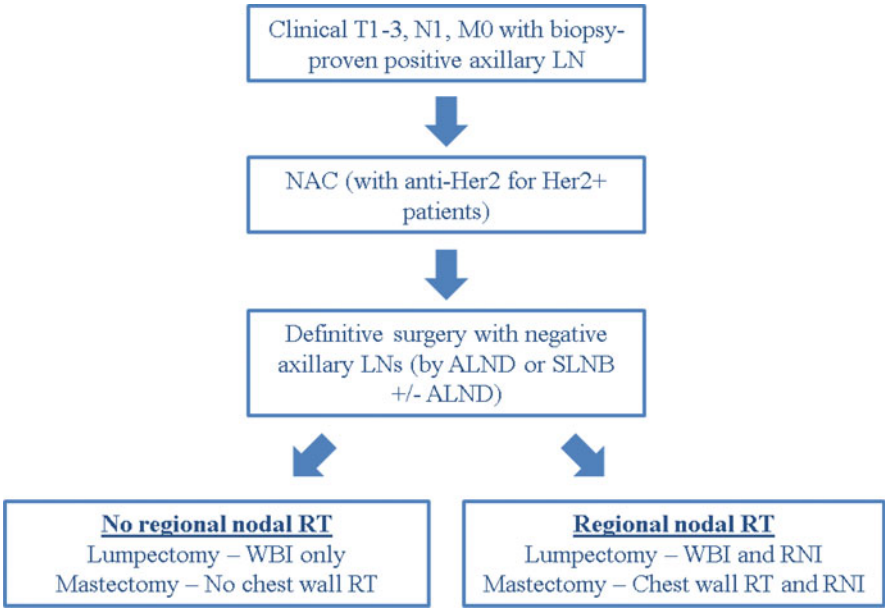

Fig. 12.1 NSABP B-51/RTOG 1304 (NRG 9353) schema. Abbreviations: *NAC* neoadjuvant chemotherapy, *ALND* axillary lymph node dissection, *SLNB* sentinel lymph node biopsy, *WBI* whole-breast irradiation, *RNI* regional nodal irradiation

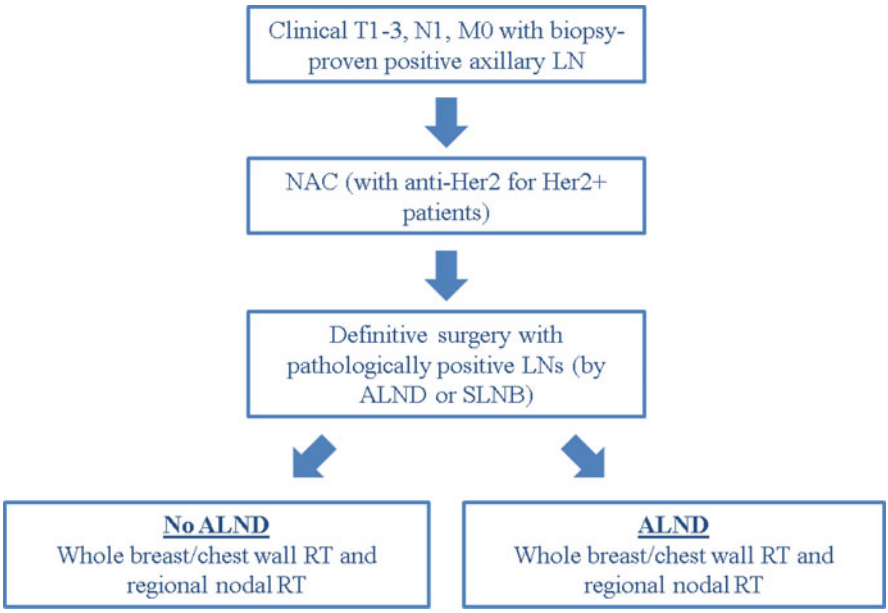

Fig. 12.2 Alliance A11101 schema. Abbreviations: *NAC* neoadjuvant chemotherapy, *ALND* axillary lymph node dissection, *SLNB* sentinel lymph node biopsy

The Alliance A11101 trial (Fig. 12.2) is another randomized trial that is enrolling patients with clinical stage II–III breast cancer (T1-3N1M0). Patients receive NAC with anti-Her2-targeted therapy if Her2+. Patients who are pathologically node positive by sentinel lymph node biopsy after NAC are randomized to breast/chest wall and regional nodal RT vs. axillary lymph node dissection and breast/chest wall and regional nodal RT. This study aims to compare axillary lymph node dissection to axillary radiation therapy in patients who remain node positive after NAC [30].

12.11 Conclusions

While we await the results of ongoing randomized trials, there is a lack of randomized data to guide treatment decisions for local therapy after NAC. Based on the available data, which is mostly retrospective, the initial clinical stage at presentation and the final pathologic stage after NAC both independently predict for LRR. A suggested treatment algorithm for PMRT after NAC is shown in Fig. 12.3. Following NAC, PMRT is indicated for patients who initially present with clinical stage III disease or greater regardless of response to NAC. It is also indicated for patients with residual pathologic nodal disease at the time of mastectomy. Clinical T3N0 disease has been associated with high LRR rates as well,

Pathologic Stage

Clinical Stage: LRR Rates	ypN+	ypN-/no breast pCR	pCR
T1-2 N0	11%	6%	7%
T3 N0	14-53%	13%	0-8%
T1-2 N1	15-27%	11%	0-9%
N2 or T3 N1 or T4 N0-1	16-40%		

Fig. 12.3 Estimated rates of locoregional recurrence in breast cancer patients after neoadjuvant chemotherapy (NAC) and mastectomy based on initial clinical stage and pathologic response to NAC. *Red* – PMRT recommended; *green* – no PMRT; *orange* – consider PMRT. Abbreviations: *LRR* locoregional recurrence, *pCR* pathological complete response

warranting further local therapy in the absence of a pCR. Even with a pCR, PMRT can be considered. Patients who present with early-stage clinically node-negative disease and remain pathologically node negative at the time of surgery do not seem to benefit from PMRT. The remaining groups of patients with clinical stage II disease may not require further therapy, as suggested by the reviewed data. However, this is largely based on results from small retrospective series. Additional factors such as age and molecular subtype can be considered for these patients.

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