HHS Public Access

Author manuscript

Semin Radiat Oncol. Author manuscript; available in PMC 2017 January 01.

Published in final edited form as:

Semin Radiat Oncol. 2016 January ; 26(1): 51–58. doi:10.1016/j.semradonc.2015.08.001.

The Role of Postmastectomy Radiation Therapy in Patients with Breast Cancer Responding to Neoadjuvant Chemotherapy

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Abstract

When surgery is the first line of breast cancer treatment, numerous randomized clinical trials and meta analyses have demonstrated that postmastectomy radiation therapy (PMRT) improves locoregional control and survival for many women with axillary lymph-node positive disease. In contrast, there are no randomized data regarding the use of PMRT in women who receive neoadjuvant chemotherapy (NAC) first followed by mastectomy. This has led to controversy regarding which breast cancer patients benefit from PMRT after NAC, particularly in women with clinically node-positive (cN+) axillary disease that responds well and is down-staged to pathologically negative at surgery (ypN0). Here, we review the current evidence on this topic, which forms the underlying basis for the ongoing phase III clinical trial (NSABP B51/RTOG 1304) that is examining the role of regional nodal irradiation in patients with clinical N1 disease that respond to NAC and become ypN0 at surgery.

Keywords

postmastectomy radiation therapy; neoadjuvant chemotherapy

INTRODUCTION

Neoadjuvant chemotherapy (NAC) for breast cancer is increasingly used in women with operable breast cancer in addition to its established role for inoperable locally advanced or inflammatory breast cancer. The response to NAC can permit inoperable (clinical stage IIIB-C) to become operable but offers numerous advantages when used for operable breast cancer as well. NAC provides an in vivo assessment of the tumor's response to chemotherapy agents and is an avenue to test the efficacy of new systemic agents in clinical trial settings[1]. Achieving a pathologic complete response [pCR], defined as eradication of all invasive disease in the breast and in the lymph nodes, is prognostic for survival – the magnitude of this benefit is strongest in women with triple-negative and HER2- positive/hormone receptor

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Conflict of Interest Notification: None

negative breast cancers[2]. In addition, NAC improves breast conservation rates and can decrease the extent of resection in women with operable breast cancer[3, 4] Nonetheless, many women still undergo mastectomy after completion of NAC.

One of the most challenging problems facing breast cancer radiation oncologists today is deciding which breast cancer patients treated with NAC followed by mastectomy will benefit from postmastectomy radiation therapy (PMRT). This has led to debate regarding the indications for PMRT in the setting of NAC. Lately, several influences have converged to fuel this debate. First, recent publications support expansion of the indications for PMRT when surgery is first line of treatment in low volume axillary node positive (1–3 nodes positive) breast cancer[5–7] raising questions about the applicability of these findings post-NAC. Second, numerous clinical trials evaluating different systemic therapy drugs, particularly those targeted for specific breast cancer subtypes, have yielded increasingly higher rates of complete pathologic response making this question applicable to larger numbers of patients[8]. Third, complete pathologic response induced by NAC has been demonstrated to be prognostic for improved survival[2], and lastly, axillary nodal response to ypN0 post-NAC has been demonstrated to yield low loco-regional recurrence (LRR) rates without the use of PMRT[9] supporting the hypothesis that NAC response selects a lower risk group that will not receive benefit from the addition of PMRT.. Examination of each of these important influences is essential to understanding the current status of PMRT post NAC and emphasizes the need for clinical trial data to clarify treatment indications.

INDICATIONS FOR PMRT AFTER UPFRONT SURGERY ARE EXPANDING

The modern approach to PMRT was founded largely by the Danish Breast Cancer Cooperative Group (DBCG) 82b and c[10, 11] and British Columbia[12] clinical trials that enrolled over 3500 women from 1979–1990 who were randomized to PMRT or observation post surgery and systemic therapy. Systemic therapy on these trials included either cyclophosphamide/methotrexate/5-fluorouracil or tamoxifen. More than 90% of women in these studies had lymph-node positive (pN+) disease. These trials demonstrated substantial reductions in long-term LRR which translated into improved breast-cancer specific and overall survival (OS). Based principally on these results, numerous consensus groups have recommended PMRT for patients with ≥4 pathologically involved lymph nodes and/or patients with pathologic stage III disease[13–15]. However, no consensus has been reached regarding women with earlier stage, node positive disease (T1–2 tumors with 1–3 pathologically involved nodes). This relationship of gains in local regional control from PMRT and improvements in breast cancer survival was further studied and corroborated by the 2005 Early Breast Cancer Trialists' Collaborative Group (EBCTG) meta-analysis. In this meta-analysis[16], the 5-year LRR rate for women with pN+ disease was 22.8% without PMRT and 5.8% with PMRT. This 17% absolute reduction in 5-year LRR translated into a 5.4% reduction in breast-cancer mortality with PMRT (60.1% vs. 54.7%). However, women with pathologically node negative (pN0) disease had smaller absolute rates of 5 year LRR (6.3% no PMRT vs. 2.3% with PMRT) and there was no significant difference in breast cancer mortality (BCM) with the use of PMRT in these women (27.7% vs. 31.3%). In addition, this meta-analysis demonstrated that patients who had an absolute reduction of 10-year LRR risk by >10% had a lower risk of 15-year BCM[16]. Despite this, debate persisted

about the benefit of PMRT in patients with 1–3 axillary nodal metastases when surgery is the first line of treatment.

The EBCTCG meta-analysis regarding PMRT was recently updated with specific focus on the 1–3 axillary node positive group. This meta-analysis included individual patient data on more than 8,000 women from 22 randomized trials[5]. Overall, for women with pN+ disease, the 5-year and 10-year risks of LRR were significantly improved with PMRT: 6.6% vs. 21.3% and 8.1% vs. 26.0% ($p<0.00001$). Breast cancer mortality was reduced by 8.1% with the addition of PMRT: 58.3% vs. 66.4% ($p=0.001$). Similar results were seen when examining the subgroup of women with 1–3 positive axillary lymph nodes in which PMRT decreased the 10-year risk of LRR by 16.5% (3.8% vs. 20.3%, $p=0.00001$) and reduced BCM by 7.9% (42.3% vs. 50.2%, $p=0.01$). In addition, data was available on 318 women with only 1 positive lymph node, 145 of whom were randomly assigned to PMRT and 173 were observed after surgery and systemic therapy. The 10-year risk of LRR was significantly decreased with PMRT: 2.3% vs. 17.8% ($p=0.00001$) but a statistically non-significant 6.5% improvement in BCM (31.7% vs. 38.2%) was seen. The updated meta-analysis again clearly demonstrates that PMRT is not indicated for pN0 disease: 5-year and 10-year risks of LRR with and without PMRT were 1.9% vs. 1.2% and 3.0% vs. 1.6% ($p=0.1$) in women with pN0 disease with no reduction in BCM.

Two recent randomized trials support the use of regional nodal irradiation (RNI) in women with 1–3 pathologically involved lymph nodes that also will likely influence PMRT use[6, 7]. EORTC 22922/10925 randomized 4,004 patients with pathologic stage I-III (pN+ or pN0/ medial tumors) to radiotherapy to the internal mammary nodes/medial supraclavicular fossa (IM-MS) or no IM-MS irradiation after breast-conserving surgery (76%) or mastectomy (24%)[6]. Approximately 87% of the patients were pN0 or pN1. The primary endpoint was OS. Radiotherapy to the IM-MS improved disease-free survival from 69.1% to 72.1% ($p=0.04$), distant-metastasis-free survival from 75% to 78% ($p=0.02$) and OS from 80.7% to 82.3% ($p=0.056$). Lastly, the NCIC MA.20 trial randomized women with 1–3 involved lymph nodes or high-risk node negative disease treated with breast conserving surgery to whole breast irradiation or whole breast irradiation+RNI[7].The addition of RNI decreased LRR from 5.2% to 3.2% ($p=0.02$) and improved disease-free survival from 84% to 89.7% ($p=0.003$) with a trend towards improved OS (90.7% to 92.7%, $p=0.07$).

Taken together the data from the EBCTCG meta-analyses as well as the EORTC 22922 and NCIC MA20 clinical trials support the expanding role for PMRT/locoregional radiotherapy in many women with 1–3 positive axillary nodes in addition to the established indication for those with 4 or more positive nodes. Equally important is the finding from the EBCTCG meta-analyses is that PMRT did not benefit women with pN0 disease.

NEOADJUVANT CHEMOTHERAPY COMPLICATES CLINICAL DECISION-MAKING REGARDING USE OF PMRT

The use of NAC prior to mastectomy has created substantial controversy regarding identifying the subgroups of women that would benefit from PMRT. The first complicating matter is that women who receive NAC today represent a heterogeneous group ranging from

locally advanced and even inoperable disease to operable, early-stage disease. Therefore, it is difficult to generalize treatment recommendations across such broad stages of disease presentation. In addition, unlike the data reviewed regarding PMRT when mastectomy is used in the upfront setting in which there are numerous randomized trials and meta-analyses to guide decision-making, the current literature on PMRT after NAC is solely retrospective. While these studies overall are well executed and have provided important observations regarding PMRT use after NAC, the results are subject to the pitfalls inherent to retrospective research including selection bias, variation in data quality, etc. Further, the retrospective data are largely from single-institutions and include patients studied over a long period of time during which significant changes occurred in NAC delivery and higher rates of pCR were achieved.

One of the most important considerations is that use of NAC modifies the pathologic extent of disease at the time of surgery. It is therefore not clear which factor is most important in terms of a patients' individual LRR risk: the clinical stage at the time of presentation before initiation of NAC or the residual pathologic disease burden at surgery after NAC, which is a measure of the response of the disease to NAC. The group of women that remain at the center of the PMRT after NAC debate are those that present with clinically lymph-node positive (cN+) axillary disease before initiation of NAC. One argument for recommending PMRT for all women with cN+ disease before initiation of NAC, regardless of the pathologic nodal status at the time of surgery, is that the meta-analysis data have demonstrated reduced BCM in women with pN+ disease with PMRT use – therefore, omission of radiotherapy in these women potentially places them at increased risk of death from breast cancer[17]. Conversely, for women who are cN+ at presentation and have an excellent response to NAC such that they are pathologically node negative at surgery (ypN0), the meta analysis data could similarly be invoked to indicate that PMRT in pathologically node negative disease places these patients at increased risk of toxicity including potentially serious cardiac events without the benefit of reducing LRR or BCM[18]. It is clear that on either side of the debate, the main argument for or against PMRT stems from a desire to minimize harm to the patient. In this section, we will review the current literature regarding the role of PMRT in women who receive NAC.

PMRT Use in Patients Receiving NAC: MD Anderson Cancer Center

The majority of clinical data regarding PMRT use after NAC comes from a series of publications from the University of Texas MD Anderson Cancer Center (MDACC). The women reported in these series were treated on various prospective institutional protocols evaluating the role of NAC for non-metastatic, noninflammatory breast cancer patients. The decision to undergo PMRT was determined by the patient and her physicians, and was not a randomized treatment. Huang et al.[19] reported the results of one of the earliest and largest series in which the outcomes of 542 patients treated with NAC, mastectomy and PMRT were compared to those from 134 women treated in a similar fashion but without PMRT (Table 1). These women were enrolled from 1974–2000 and the median follow-up was 69 months.

In the PMRT cohort, 83% of women had stage IIIA-IV disease compared to 50% of women in the cohort that did not receive PMRT. The complete response rate from NAC was 14% in those receiving PMRT versus 6% in those not receiving PMRT. Overall, the 10-year LRR rate was 11% in the women who received PMRT compared to 22% in those who did not (p=0.0001) and OS was also improved with PMRT. In a subgroup of 46 women with clinical stage III-IV disease (35 received PMRT, 11 no PMRT) who achieved a pCR with NAC, the 10-year LRR was 3% with PMRT compared to 33% without PMRT (p=0.006).

On multivariate analysis of factors associated with LRR, the most significant factor was omission of PMRT (hazards ratio=4.7, 95% confidence interval 2.7–8.1). Others included ≥20% pathologically involved nodes after NAC, clinical stage≥IIIB, no tamoxifen use, and estrogen-receptor (ER) negative disease. Overall, cancer-specific survival at 10 years was similar in each treatment group; 58% *versus* 55% respectively for those that did or did not receive PMRT (*P* =.85). However, on univariate analysis cause-specific survival was improved for certain subgroups of women receiving PMRT including those with ≥clinical stage IIIB disease, cN2-N3 disease, and ≥4 pathologically involved nodes.

In another influential publication from the MDACC, McGuire et al.[20] reported the outcomes of a group of 106 women with clinical stage II-III disease treated from 1982–2002 with NAC and mastectomy who achieved a pCR at the time of surgery (Table 1). Median follow-up was 62 months. The majority of women had stage III disease (66%) and 72 women received PMRT, whereas 34 did not. Overall, the 10-year LRR rate did not differ between the PMRT and no PMRT groups (5% vs. 10%, p=0.40) most likely influenced by the 0% 10-year LRR for the 32 patients with clinical stage I-II disease. However, PMRT significantly decreased the 10-year LRR for the 74 patients presenting with clinical stage III disease (7% vs. 33%, p=0.04). OS was also significantly improved for patients with clinical stage III disease who received PMRT (77.3% vs. 33.3%, p=0.002). As a result, the authors concluded that PMRT is warranted in patients who present with clinical stage III disease and achieve a pCR after NAC.

Several specific subgroups of women in this database have also been retrospectively examined by investigators at the MDACC. Garg et al. analyzed the impact of radiotherapy in 107 young women (age<35 yrs old) with Stage IIAIIIC disease treated with NAC and mastectomy with PMRT (n=80) or without PMRT (n=20) from 1975 through 2005 (Table 1)[21]. Clinical stage III patients comprised 84% of those receiving PMRT and 42% of those who did not. The complete response rate was 19% in those receiving PMRT versus 15 % in those who did not undergo PMRT. As seen in the earlier analysis (Huang et al), PMRT significantly improved locoregional control (88% vs. 63%) and OS (67% vs. 48%) in this group of young women. PMRT reduced LRR in patients with clinical stage IIB disease (0% vs. 44%, p=0.03) and stage III disease (15% vs. 36%, p=0.02). Nagar et al. reported outcomes of 162 women with clinical T3N0 disease treated from 1985–2004 with NAC followed by mastectomy and PMRT (n=119) or no PMRT (n=43) [Table 1][22]. The 5-year LRR rate was 9% but was significantly higher in patients who did not receive PMRT (24% vs. 4%, p<0.001). In the 89 patients who were ypN0 at surgery, the difference in LRR between patients who did and did not receive PMRT was no longer statistically different (2% with PMRT vs. 14% without PMRT, p=0.06). Patients in the non-irradiated group that

were found to have ypN+ disease had a 5-year LRR of 53% compared to 5% in the group that received PMRT.

In summary, the MDACC database has been an early and important source of data on outcomes for PMRT use in women who receive NAC. Based on these studies women at the highest risk of LRR after NAC and mastectomy are those who present with advanced clinical stage III disease (especially cN2-N3 involvement) and those women who have residual pathologically involved nodes (ypN+) at the time of surgery. PMRT is not routinely recommended for patients who present with clinical T3N0 disease and are found to have ypN0 disease.

PMRT in Women With Clinical Stage II-III Disease Down-staged by NAC to Pathologically Negative Lymph Nodes

Patients with clinical stage II and early stage III (T3N1) disease who receive NAC and have an excellent response to treatment continue to challenge clinicians in terms of the role of PMRT. Two retrospective studies have explored these patient populations in more detail. Le Scodan et al.[23] analyzed the outcomes of 134 women with clinical stage II-III disease who were treated with NAC followed by mastectomy with ypN0 disease (Table 1). The majority (63%) had clinical stage II disease at presentation. Of these, 78 received PMRT and 56 did not. The 5-year and 10- year LRR-free survival rates were high with or without PMRT: 96.2% vs. 92.5% and 96.2% vs. 86.8% (p=not significant). Likewise, 10-year OS did not statistically differ between the 2 groups (77.2% with PMRT vs. 87.7% without PMRT). The authors conclude that omission of PMRT in women who achieve ypN0 status does not increase the risk of LRR or death.

Similarly, Shim et al. identified 151 patients with clinical stage II (60%) and III (40%) breast cancer treated with NAC and mastectomy who had ypN0 disease (Table 1)[24]. PMRT was delivered to 105 patients. The 5-year LRRfree survival was 98.1% with PMRT and 92.3% without PMRT and 5-year OS was similar at 93.3% vs. 89.9%. On multivariate analysis of risk factors for LRR and disease-free survival, PMRT was not a prognostic factor. Given these findings, the authors suggest that PMRT may not be necessary for women who have ypN0 disease at surgery.

Taken together, the studies by Le Scodan et al. and Shim et al. emphasize that patients who present with clinical stage II-III disease and achieve ypN0 status after NAC may not be at higher risk of failure without the use of PMRT. This finding underscores the importance of NAC response, particularly in the axillary nodes, as an important factor to consider in PMRT decision-making after NAC.

DISEASE RESPONSE TO NAC DRIVES CLINICAL OUTCOMES

Recently, Cortazar et al.[2] performed a pooled analysis of nearly 12,000 patients enrolled on international neoadjuvant trials from the Collaborative Trials in Neoadjuvant Breast Cancer (CTNeoBC) working group. The main goals of this analysis were to establish the association between pCR and event-free survival (EFS) and OS; to establish the definition of pCR that best correlates with EFS/OS; to identify breast cancer subtypes in which pCR is best

correlated with EFS/OS; and to test whether an increase in frequency of pCR between treatment groups improves EFS/OS. The analysis found that the best definition of pCR is the absence of invasive disease in the breast and in the lymph nodes (ypT0/ypTis ypN0). Using this definition, achieving a pCR resulted in a 64% reduction in risk of death (hazard ratio, HR for OS=0.36) and 52% reduction in relapse or death (HR=0.52 for EFS). These reductions were greatest for patients with triple-negative breast cancer (HR=0.16 for OS; HR=0.24 for EFS) and in those with HER2-positive/hormone-receptor negative disease treated with trastuzamab (HR=0.08 for OS; HR=0.15 for EFS). These results clearly demonstrate that achieving a pCR is an important prognosticator and can select patient who are expected to have improved survival outcomes.

There is also compelling evidence that response to NAC as measured by downstaging the axilla influences LRR. Mamounas et al.[9] performed a combined analysis LRR rates in women enrolled on 2 NSABP NAC trials - NSABP B18 and NSABP B27. It is important to note that the majority of the patients on these trials had clinical stage II disease: 55% cT1-2N0, 20% cT1-2N1, 16% cT3N0 and 9% T3N1 (Table 2). Patients who underwent mastectomy (n=1,071) on these 2 trials were not allowed to undergo PMRT providing an opportunity to evaluate patterns of local regional failure based on NAC and mastectomy alone. Independent predictors of LRR on multivariate analysis included clinical tumor size >5 cm, cN+ disease, and pathologic nodal status/pathologic breast tumor response. In patients with pCR in the breast, those with ypN+ had higher risk of LRR compared to those who became ypN0. In a small subset of patients (n=32) who had cN+ disease prior to NAC and converted to ypN0 and pCR in the breast at the time of surgery, no LRR events were seen. In the 121 patients with cN+ who became ypN0 by NAC but had residual breast disease, 10-year LRR rates were modest at 10.8% for tumors that at clinical presentation were ≤5cm and 9.2% for clinical tumor size >5cm. However, patients with cN+ disease that remained ypN+ had higher rates of 10-year LRR (17% for clinical tumor size ≤5cm and 22.4% for clinical tumor size >5cm).

In summary, response to NAC drives long-term patient outcomes[2]. Also, the data from NSABP B18/B27 support the hypothesis that, in patient with cN+ axillary nodes that becomes ypN0 after NAC, the LRR risk may be modified to a low enough risk that PMRT can be safely omitted. Prospective data are needed to assess the safety of this approach.

SPECIAL SITUATIONS: SENTINEL LYMPH NODE BIOPSY AFTER NAC AND NEOADJUVANT ANTI-ENDOCRINE THERAPY

In addition to the complexity of PMRT decision-making after NAC due to the lack of prospective, randomized data, changes in the surgical management of the axilla and the increasing use of neoadjuvant anti-endocrine therapy (NET) in postmenopausal women with estrogen-recepor (ER+) or progesterone-receptor (PR+) positive disease complicate matters further. Here, we briefly review these trends and assess the impact on PMRT use.

Surgical Management of the Axilla After NAC

In the upfront surgical setting, sentinel lymph node biopsy (SNB) has replaced axillary lymph node dissection (ALND) for women with clinically negative axilla (cN0) without sentinel lymph node (SLN) metastases[25] and for women with early stage breast cancer with involvement of 1–2 SLN[26]. Most women who present with cN+ axilla and receive NAC will undergo ALND. However, the role of SNB after NAC continues to evolve in these women and in women who present with cN0 axilla. The concern with SNB after NAC is that this approach may result in higher false-negative rates (FNR) than those seen with SNB in the upfront setting. The Sentinal Neoadjuvant (SENTINA) trial[27] and ACOSOG Z1071[28] trials both demonstrated that SNB technique is critical in achieving low FNR. In the group of patients on the SENTINA trial that presented with cN+ disease that became ypN0 after SNB and ALND, the FNR of the SNB was 24% if only 1 SLN was removed and 18% if only 2 SLNs were removed. However, the FNR was <5% with removal of 3 SLNs and <10% with use of a dual tracer technique. Similarly, the ACOSOG Z1071 study found that the FNR of SNB in women who present with cN+ disease is ≤10% with removal of >2 SLNs or with use of dual tracer.

Neoadjuvant Anti-Endocrine Therapy

Due to lower rates of pCR seen after NAC in women with ER+/PR+ disease compared to women with triple-negative or HER2+/ER-/PR- disease, several trials have investigated the role of NET in these women[29–31]. Pathologic complete response rates with NET are low at ≤1%, so other endpoints of tumor response are often reported. In the major randomized trials, the endpoints reported have included clinical response rates on exam, radiological response rates and rates of breast conserving surgery. However, a more consistent secondary endpoint measured has been Ki67 response. On multivariate analysis of the P024 trial (compared 4 months of neoadjuvant letrozole versus tamoxifen)[29], Ki67 response, pathological tumor size (T1–2 vs. T3–4), pathological nodal status, and ER status of the tumor were prognostic for relapse and death after relapse[30]. This led to the development of the preoperative endocrine prognostic index (PEPI). The PEPI score has been validated in the IMPACT trial[30]. In an analysis of patients on the P024 trial, no relapses were seen in the 29 patients that fell into the PEPI 0 category [pT1–2, pN0, Ki67≤2.7%, and maintained ER expression]. The authors conclude that for breast cancer patients with pathological stage 1 or 0 disease after NET and a PEPI score 0, the risk of relapse is extremely low, and are therefore unlikely to benefit from adjuvant chemotherapy[30]. This patient population is also likely to have no benefit from PMRT. Future prospective PMRT trials after NET should focus on the safety of the omission of PMRT in women the pathologic T1–2, node-negative tumors with PEPI score 0. The validation of the modified PEPI score 0 (all factors with the exception of ER status) as a marker for low risk of recurrence is one of the primary endpoints of the ongoing phase III trial Alliance A011106 (Alternate approaches for clinical stage II or III estrogen receptor positive breast cancer neoadjuvant treatment in postmenopausal women) [NCT01953588][32]. This trial is evaluating the role of neoadjuvant fulvestrant, letrozole or both in the neoadjuvant setting with a required biopsy at week 4 and optional biopsy at week 12 to test for endocrine resistance (Ki67>10%).

CURRENT CLINICAL TRIALS OF LOCOREGIONAL RADIOTHERAPY IN WOMEN RECEIVING NAC

Prospective, randomized data are needed to optimize locoregional therapy in women who present with cN+ disease and receive NAC. This group of women is the subject of two ongoing cooperative group trials addressing locoregional management based on pathologic response in the lymph nodes. The NSABP B51/Radiation Therapy Oncology Group (RTOG) 1304 phase III clinical trial (NCT01872975)[33] is designed to test whether RNI improves the breast cancer recurrence-free interval rate (local, regional, and distant recurrences and deaths resulting from breast cancer) in women with clinical T1–3 N1 disease (N1 status documented by fine-needle aspirate or core needle biopsy) before NAC and then become pathologically-node negative at the time of surgery. Women who undergo mastectomy are randomly assigned to observation or chestwall and RNI (undissected axilla, internal mammary nodes in the first 3 intercostal spaces, and ipsilateral supraclavicular fossa) whereas women who undergo breast-conserving surgery are randomized to adjuvant whole breast irradiation versus whole breast irradiation and RNI. The ALLIANCE A011202 (NCT01901094)[34] trial has the same enrollment criteria as NSABP B51/RTOG 1304 but requires SNB at the time of surgery. Women who are ypN+ on SNB are randomized to completion ALND+RNI versus RNI alone. In addition, women on the Alliance A011106 trial who develop endocrine resistance at week 4 or week 12 (Ki67>10%) will go on to receive preoperative chemotherapy. Those women with cN+ disease that convert to ypN0 will also be eligible for NSABP B51/RTOG 1304.

RADIOTHERAPY TECHNIQUE

At our institution, all patients undergo computed tomography(CT)-based simulation. Patients with right-sided breast cancers undergo a single free-breathing CT scan. For patients with left-sided cancers we obtain an additional deep-inspiration breath hold (DIBH) to enable respiratory gating if necessary to meet normal tissue constraints. Target volumes are contoured using the guidelines and recommendations from the RTOG Breast Contouring Atlas and the RTOG 1304/NSABP B51 protocol[35]. Clinical target volumes (CTV) created include: chestwall CTV, mastectomy scar CTV, axilla CTV, supraclavicular (SCL) CTV, and internal mammary chain (IMC) CTV. Margins are then added to create the appropriate planning target volumes (PTV). In select cases (for example, patients presenting with gross IMC involvement), a nodal boost CTV/PTV is also created. For each case, the following normal tissues are also routinely contoured: heart, ipsilateral lung, contralateral lung, and contralateral breast and thyroid.

3D conformal (3DCRT) radiation plans are then created to meet dose goals to the target PTVs and normal tissues constraints. In most cases this can be achieved using a mono-isocentric technique. The breast/chestwall and IMC PTV are most commonly treated with 2–6 tangential fields using mixed energies with field-in-field technique in combination with beam modifiers (dynamic wedges, compensation) to meet planning goals for target coverage and dose homogeneity. However, the ultimate method used for PMRT is driven by evaluation of dose volume analysis. Therefore other methods such as di-centric matching photon fields, matching photon and medial electron fields, hybrid 3DCRT and intensity

modulated radiation therapy (IMRT) approaches are used as necessary to meet the dose to targets and constraints to OAR. The SCL PTV/axilla PTV are most often treated with mixed photon energies, differentially weighted, 2–4 oblique fields with field-in-field technique in combination with beam modifiers (typically dynamic wedges) to meet planning goals for target coverage and dose homogeneity. In cases in which a 3D conformal radiotherapy plan either results in inadequate dose to the PTVs or in excess dose to normal structures, inverse-planned IMRT plans are then created. In these cases, all PTVs are generally treated in a single plan using 5–9 beams.

The prescription dose is 50 Gy in 25 fractions. Use of a mastectomy scar boost is not routinely delivered but is strongly considered for women with a large amount of residual disease after completion of NAC. In plan evaluation, we aim to achieve the planning objectives set forth in the RTOG 1304/NSABP B51 protocol (Table 3). An institutional study of 124 patients in a routine clinical practice demonstrates that these objectives are met in >80% of PMRT or whole breast+RNI treatment plans and >90% in the 108 women treated with 3DCRT (as opposed to IMRT) suggesting that achieving these constraints on women enrolled on trial should be very feasible[36].

Conclusion

In summary, identifying women who are at high risk of LRR after NAC and mastectomy is challenging due to the lack of prospective, randomized data. Review of the best available evidence suggests that PMRT should be recommended for women with residual nodal disease at the time of surgery (ypN+) and women who present with clinical stage III disease. Women with clinically node negative and pathologically node negative disease are at low risk of LRR. For women who present with clinically lymph node positive disease that is clinical stage II-IIIa and that convert to pathologically node negative post NAC, we strongly recommend enrollment on RTOG 1304/NSABP B51. Outside of participation in this trial, PMRT decision-making has to be individualized for these patients based on clinicopathologic characteristics and patient preference. Women who remain ypN+ on SNB should receive RNI (with or without ALND) on ALLIANCE A011202.

Acknowledgment

Grants/Funding: None related to this work

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Table 1

Summary of key retrospective studies evaluating role of postmastectomy radiation therapy after neoadjuvant chemotherapy.

	No. of Patients	Follow up mo	% Clinical Stage	% Complete Response rate	% LRR		p-value
					PMRT	No PMRT	
Huang[19], 1974–2000	676	67	I–II 30 III 70	14.3	11	22	0.0001
McGuire[20], 1985–2004	106	62	I–II 33 III 67	100	5	10	0.40
Garg[21], 1975–2005 (age<35 years)	107	72	II 27 III 73	17.7	12	37	0.001
Nagar[22], 1985–2004	162	-	cT3N0	8	4	24	<0.001
Le Scodan[23], 1990–2004	134	91	II 63% III 37%	100% ypN0	4	12	0.12
Shim[24], 1998–2009	151	57	II 60% III 40%	100% ypN0	2	8	0.15

* Legend: LRR=locoregional recurrence; PMRT=postmastectomy radiation therapy

Table 2

Summary of the NSABP B18/B27 combined analysis for patients treated with mastectomy.

	No. of Patients	Clinical Stage[+]	10 yr LRR cN0 patients			10 yr LRR cN+ Patients		
Mamounas, 1988–2000	M, 1071	T1–2N0, 55%		cT1–2	cT3		cT1–2	cT3
		T1–2N1, 20%	ypN0/breast pCR	6.5%	6.2%	ypN0/breast pCR	0%	0%
		T3N0, 16%	ypN0/no breast pCR	6.3%	11.8%	ypN0/no breast pCR	10.8%	9.2%
		T3N1, 9%	ypN+	11.2%	14.6%	ypN+	17%	22.4%

[+]Distribution for all patients (lumpectomy and mastectomy) on the 2 trials;

LRR=locoregional recurrence; cN0=clinically negative nodes; cN+=clinically involved axillary nodes; M=mastectomy, pCR=pathologic complete response

Table 3

Planning objectives on NSABP B51/RTOG 1304

	Per Protocol	**Acceptable**
Chestwall	≥95% receives 47.5 Gy	≥90% receives 45 Gy
Axilla	≥95% receives 47.5 Gy	≥90% receives 45 Gy
Supraclavicular Fossa	≥95% receives 47.5 Gy	≥90% receives 45 Gy
Internal Mammary Nodes	≥90% receives 45 Gy	≥90% receives 40 Gy
Heart		
Mean dose	≤4 Gy	≤5 Gy
Volumetric constraints (left)	V25Gy≤5%; V15Gy≤30%	V30Gy≤5%; V15Gy≤35%
Volumetric constraints (right)	V25Gy≤0%; V15Gy≤10%	V30Gy≤05; V15Gy≤15%
Ipsilateral Lung	V20Gy≤30%	V20Gy≤35%
	V10Gy≤50%	V10Gy≤60%
	V5Gy≤65%	V5Gy≤70%
Contralateral Lung	V5Gy≤10%	V5Gy≤15%
Contralateral Breast	V3Gy<5%	V4.1Gy<5%