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ROLE OF POSTMASTECTOMY RADIATION THERAPY AFTER NEOADJUVANT CHEMOTHERAPY IN LOCALLY ADVANCED BREAST CANCER

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Neoadjuvant chemotherapy for primary breast cancer is the gold standard in the treatment of locally advanced, inoperable breast cancer, and also based on a large body of evidence has become a standard treatment option for patients with operable disease, who are clear candidates for adjuvant chemotherapy. There are several advantages of administering neoadjuvant chemotherapy: tumor downstaging, improving the chance of breast conserving surgery, *in vivo* assessment of tumor sensitivity to the chosen therapeutic regimen, and early control of micro-metastatic disease. However there are substantially less data to aid in determining which patients treated with neo-adjuvant chemotherapy warrant postmastectomy radiotherapy. According to the recent literature, patients who require mastectomy after systemic therapy should receive postmastectomy radiotherapy.
***Key Words*: breast cancer, locally advanced, neoadjuvant chemotherapy, radiotherapy.**

INTRODUCTION

Postmastectomy radiotherapy (PMRT) has been a subject of considerable study over the past several decades. Consensus and/or expert opinion clinical practice guidelines for PMRT in the adjuvant setting have been studied by numerous groups [1–6] and it was shown that PMRT have overall survival benefit in patients with locally advanced breast cancer (LABC). While PMRT is an integral component of the treatment of LABC, its role in women with LABC undergo neoadjuvant chemotherapy is less well defined. Established guidelines for PMRT in the adjuvant setting are based on the pathologic extent of disease at the time of initial surgery. These guidelines may not be directly transferable to the neoadjuvant setting. Neoadjuvant chemotherapy may result in a decrease in the extent of the disease, both in the breast and the axilla. This observation makes the decision-making process more difficult in the absence of pathologic findings following initial mastectomy [7].

Primary neoadjuvant chemotherapy is now considered current practice and the standard of care for premenopausal patients with LABC [8] and it has also become an option in primary operable disease for patients who are candidates for adjuvant systemic chemotherapy. Antracycline and taxane based chemotherapy regimens are currently the most effective induction agents for women with locally advanced and operable breast cancer. Most patients will have objective clinical response to therapy; however, approximately 10–20% will experience a complete clinical response [3].

There are several advantages of administering neoadjuvant chemotherapy in LABC: tumor downstaging, improving the chance of breast conserving surgery, *in vivo* assessment of tumor sensitivity to the chosen therapeutic regimen, and early control of micro-metastatic disease. On the other hand, the rate of tumor response can be used as a surrogate prognostic marker and for rapid screening of efficiency of new drugs. The use of neoadjuvant chemotherapy has several potential advantages over the traditional sequence of surgery followed by adjuvant chemotherapy, but it also carries some disadvantages (Table 1).

Table 1. Considerations regarding the sequencing of surgery and chemotherapy for patients with operable LABC [9]

Advantages of performing surgery first	Advantages of neoadjuvant chemotherapy
Removes the source of distant metastases	May allow breast conservation after effecting a disease response
Reduces the interval between diagnosis and effective treatment for patients with disease that is resistant to chemotherapy	Allows an in vivo assessment of sensitivity to a chemotherapy regimen
Provides clear information concerning the original extent of disease	Allows chemotherapy to be changed if the disease proves resistant
Provides clear prognostic information concerning the risk of recurrence after mastectomy and therefore the indications for using postmastectomy radiation	Permits an assessment of pathological disease response, which allows for the further stratification of an individual patient's prognosis
	Allows direct comparison of different treatment regimens in clinical trials with a short-term study end point (pathological complete response)
	Allows serial biopsies and images of tumor to be obtained during treatment to gain insight into the molecular mechanisms of tumor sensitivity and resistance

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Abbreviations used: AC – doxorubicin and cyclophosphamide; ASCO – American Society of Clinical Oncology; DFS – disease-free survival; ECE – extracapsular extension; FNA – fine-needle aspirate; LABC – locally advanced breast cancer; LRF – locoregional failure; LVI – lymphovascular invasion; NCI – National Cancer Institute; NSABP – National Surgical Adjuvant Breast and Bowel Project; OS – overall survival; pCR – pathologic complete response; PMRT – postmastectomy radiotherapy; T – docetaxel.

The indications for radiation after mastectomy and for radiation of undissected lymphatic regions have traditionally been based on the pathologic extent of disease. Given that preoperative chemotherapy achieves a disease response in up to 80% of patients, these indications need to be changed for patients treated with this approach. There are substantially less data to aid in determining which patients treated with neoadjuvant chemotherapy warrant PMRT. Appropriate patient selection for PMRT after neoadjuvant chemotherapy is complicated. Because randomized trial data of PMRT in the neo-adjuvant setting are lacking, there exist no established indications to offer guidance with these decisions [7].

ROLE OF POSTMASTECTOMY RADIATION THERAPY IN PATIENS WHO RECEIVED NEOADJUVANT CHEMOTHERAPY

There have been no prospective, randomized trials or meta-analyses regarding to role of PMRT in the neoadjuvant setting yet. Therefore treatment recommendations for radiation therapy after neoadjuvant chemotherapy and mastectomy are under considerable debate. The role of PMRT in LABC patients after neoadjuvant chemotherapy is addressed by 16 peer-reviewed articles [10–25] and 3 review articles [7, 26, 27] in the literature. All the studies were single-institution; retrospective reviews, except for the National Surgical Adjuvant Breast and Bowel Project (NSABP) B18 and B27 randomized trials.

In March 2007, the National Cancer Institute (NCI) organized a state-of-the science symposium with faculty from multiple disciplines involved in the care of breast cancer patients. In this symposium PMRT was suggested in patients with clinical stage III disease and patients who have histologically positive lymph nodes after preoperative chemotherapy [27]. Since the NCI symposium, the updated experience of single institutions and an analysis of locoregional failure (LRF) patterns of patients in two prospective trials (NSABP B18 and B27) of neoadjuvant chemotherapy have been published.

NSABP Protocol B-18 was designed to determine whether 4 cycles of doxorubicin and cyclophosphamide (AC) administered preoperatively improved breast cancer disease-free survival (DFS) and overall survival (OS) compared with AC administered postoperatively. Protocol B-27 was designed to determine the effect of adding docetaxel (T) to preoperative AC on tumor response rates, DFS, and OS [28]. Secondary aims were to evaluate the response of the primary breast tumor and involved lymph nodes to preoperative chemotherapy, to correlate the response with outcomes, and to determine whether preoperative chemotherapy increased use of breast-conserving surgery and decreased rates of ipsilateral breast tumor recurrence. Both studies included patients with operable, palpable breast cancer (T1–3, N0–1, M0 for B-18 and T1c-3, N0–1, M0 or T1–3, N1, M0 for B-27) diagnosed by core needle biopsy or fine-needle aspirate (FNA). Results from B-18 show no statistically significant differences in DFS and OS between the two groups. Protocol B-27 results demonstrated that the addition of T to AC did not significantly impact DFS or OS. Preoperative T added to AC significantly increased the proportion of patients having pathologic complete responses (pCRs) compared with preoperative AC alone (26% *vs.* 13%, respectively; $p < 0.0001$). In both studies, patients who achieved a pCR continue to have significantly superior DFS and OS outcomes compared with patients who did not [28]. Although there were no significant differences in OS or DFS overall in Protocol B-18, women < 50 years old seemed to benefit from preoperative *versus* postoperative chemotherapy. In contrast, women ⩾50 years old had better outcomes with postoperative chemotherapy.

Buchholz and colleagues from M.D. Anderson Cancer Center investigated the role of neoadjuvant chemotherapy and mastectomy without PMRT in 150 breast cancer patients [13]. The 5- and 10-year actuarial rates of LRF were both found as 27%. They reported that advanced clinical stage at presentation, pathologic involvement of four or more lymph nodes at surgery, and lack of tamoxifen use independently predicted for an increased risk of LRF. The authors concluded that, advanced disease at presentation and positive lymph nodes after chemotherapy predict for clinically significant rates of LRF and achievement of pCR does not preclude the need for postmastectomy radiation if warranted by the pretreatment stage of the disease. The second study from M.D. Anderson Cancer Center with 542 patients treated with neoadjuvant chemotherapy, mastectomy, and PMRT demonstrated that adding PMRT reduced the absolute risk of LRF from 22 to 11% [16]. PMRT was found to enhance locoregional control in patients presenting with Stage IIB or greater disease (American Joint Committee on Cancer 1988 staging system), pathologic residual tumor size >2 cm, and 4 or more nodes positive at surgery. Investigators updated this study in 2005 and they reported the same series of 542 patients in order to identify the clinical and pathologic factors predictive of LRF after neoadjuvant chemotherapy, mastectomy, and radiotherapy [17]. The authors remarked on the importance of disease staging both before and after neoadjuvant chemotherapy because several risk factors were associated with either the pretreatment or post treatment extent of disease. The clinical factors associated with LRF included combined clinical stage, clinical T stage, ipsilateral supraclavicular nodal disease, chemotherapy response, physical examination size after chemotherapy, and no tamoxifen use ($p = 0.04$ for all factors). The pathologic predictors of LRF included the number of positive nodes, dissection of < 10 nodes, multifocal/multicentric disease, lymphovascular space invasion, extracapsular extension (ECE), skin/nipple involvement, and estrogen receptor-negative disease ($p = 0.05$ for all factors). On post-neoadjuvant chemotherapy assessment, evidence of skin or nipple involvement and extracapsular invasion were also

strongly correlated with locoregional recurrence. The lack of tamoxifen use postoperatively was also associated with increased locoregional recurrence. In this study authors concluded that after neoadjuvant chemotherapy and mastectomy, comprehensive radiation was beneficial in both local control and survival for patients with clinical T3 tumors or stage III–IV disease and for patients with four or more positive nodes [17].

After these two studies investigators reported their updated institutional experience that included additional patients and evaluates both locoregional control and survival outcomes [18]. They included 106 stages II, IIIA and IIIB (American Joint Committee on Cancer 2003 staging system) patients who achieved a pathologic complete response (pCR) at surgery after receiving neoadjuvant chemotherapy. After 62 months of follow-up they reported that use of radiation therapy did not affect the 10-year rates of LRF for patients with Stage I or II disease (the 10-year LRR rates were 0% for both groups). However, the 10-year LRF rate for patients with Stage III disease was significantly improved with radiation therapy (33,3% *vs.* 7,3%; p = 0.040). Within this cohort, use of radiation therapy was also associated with improved OS (the 10-year OS rate was 77.3% the irradiated patients and 33.3% for the non-irradiated patients (p = 0.0016)). Investigators concluded that; PMRT provides a significant clinical benefit for breast cancer patients who present with clinical Stage III disease and achieve a pCR after neoadjuvant chemotherapy.

Table 2 presents the summary of selected literature. A statistically significant survival benefit with PMRT was reported in clinical stage III disease, those with >4 positive nodes or lymphovascular invasion (LVI), and in women <35 years [7].

Table 2. Summary of the selected literature regarding to role of PMRT in patients who received neoadjuvant chemotherapy

Institution	Stage	№ of patients		OS		Median follow-up (years)	p
		RT-	RT+	RT-	RT+		
MDACC	I–IV	134	542	47	54	10	0.063
	Path N0	60	141	67	81	10	0.271
	Path 1–3	40	185	70	56	10	0.179
	Path ⩾4	32	211	18	44	10	0.005
University of Miami	III	13	42	46	69	3.9	0.003
Emory	II–III pCR	10	22	78	100	3–5	0.08
MDACC	III pCR	12	62	33	77	10	0.0017
MDACC	Age <35	27	80	48	67	5	0.03
	IIA–III	33	24	56	67	5	0.076
	Path N0	41	28	47	86	5	0.435
	Path 1–3	6	38	48	67	5	0.031
	Path ⩾4	9	39	57	83	5	0.01

Abbreviations: MDACC – M.D. Anderson Cancer Center; Path – pathologic; pCR – pathologic complete response; RT – radiotherapy.

Finally Fowble and colleagues investigated the role of PMRT after neoadjuvant chemotherapy in stage II–III breast cancer patients in their review [7]. In this study 14 hypothetical clinical scenarios of patients undergoing neoadjuvant chemotherapy followed by mastectomy were created by seven breast cancer physician. The cases were designed to assess the impact of the following factors on the decision for PMRT: age, initial stage, BRCA status, histology, grade, LVI, receptor status, residual disease, number of axillary nodes examined, size and number of positive nodes, ECE, conversion of N1 disease to pathologic N0, and the use of sentinel node biopsy only in clinical N0 and clinical N1 (fine needle aspiration positive) disease. The authors did not include the cases with inflammatory breast cancer, those with close or positive mastectomy margins, and those with 4 or more positive axillary nodes because PMRT would be considered the standard of care in these patients. The authors identified, reviewed and abstracted the available literature (MEDLINE and Cochrane databases), and formulated evidence tables with endpoints of LRF, DFS, and OS. Their findings demonstrated that Clinical stage II (T1–2N0–1) patients, aged >40 years, estrogen receptor-positive subtype, with pathologic complete response or 0–3 positive nodes without LVI or ECE, were identified as having ⩽10% risk of LRF without radiation. Limited data support stage IIIA patients with pathologic complete response as being low risk.

According to The American Society of Clinical Oncology (ASCO) guidelines about PMRT; there is insufficient evidence to make recommendations or suggestions on whether all patients initially treated with preoperative systemic therapy should be given PMRT after surgery [30]. However ASCO recommended, in general, patients who require mastectomy after systemic therapy should receive PMRT. The rationale for this is based on the inability to accurately know initial pathologic stage including tumor size and axillary lymph node status.

ROLE OF REGIONAL LYMPH NODE IRRADIATION IN PATIENTS WITH NEGATIVE PATHOLOGIC NODE STATUS AFTER NEOADJUVANT CHEMOTHERAPY

Neoadjuvant chemotherapy generally induces significant changes in the pathologic extend of the disease. It is clear from NSABP B-18 and B-27 trials that neoadjuvant chemotherapy leads to complete eradication of disease within lymph nodes in 20–40% of patients [31–33]. The rate of regional node failures in these trials for patients undergoing mastectomy without radiation was <5% [26]. Daveau and colleagues analyzed 248 patients with clinical N0–2 lymph node status at diagnosis and pN0 status after neoadjuvant chemotherapy [20]. All 248 patients underwent breast irradiation and 158 of them also received irradiation to regional lymph node. The result of this retrospective study suggested that cN0 and cN1 to cN2 breast cancer patients with pathologically negative lymph node status after neoadjuvant chemotherapy and surgery have favorable outcomes and a low risk of locoregional relapse, and that adjuvant breast irradiation alone is not associated with a higher risk of LRR or death relative to combined breast and local node irradiation. Buchholz and colleagues also showed that omission of regional node irradiation in patients, who were clinically and pathologically node

negative, did not result in an increased risk of regional failure or a decreased DFS or OS [27]. Specifically, patients with clinical stage III disease at diagnosis had a 5-year risk of locoregional recurrence of 20% even after an excellent response to systemic treatment (defined as residual primary size <5 cm and 0 to 3 involved lymph nodes) [16]. The pathologic extent of disease after chemotherapy also needs to be considered when assessing the risk of locoregional recurrence after mastectomy. Data from NSABP B-18 and B-27 suggest that patients with lymph node positive disease after preoperative chemotherapy also have a clinically relevant rate of locoregional recurrence [26]. Specifically, the 8-year risk of locoregional recurrence after mastectomy was 15% for 447 patients who had residual positive lymph nodes after preoperative chemotherapy. In contrast, both NSABP B-18/B-27 and the retrospective M.D. Anderson data suggest that patients with clinical stage II disease who have negative lymph nodes after preoperative chemotherapy have an 8-year risk of locoregional recurrence after mastectomy that is less than 10% [27]. The most important predictor of long-term outcome in breast cancer is the absence of residual tumor in the breast and axillary lymph nodes after neoadjuvant chemotherapy. The 5 year DFS and OS rates approach 85 to 90% in breast cancer patients with pCR after neoadjuvant chemotherapy [20, 32, 34, 35].

Regarding to PMRT series in the literature, the treatment fields remain poorly defined in patients with <4 positive axillary nodes, with the exception of radiation to the chest wall in all patients because this is the most common site of recurrence [26]. Axillary and internal mammary node recurrences were infrequent in the neoadjuvant chemotherapy series in which sites of regional node failure were reported [10, 15, 17]. On the other hand irradiation of radiographically suspicious internal mammary nodes that were not resected after neoadjuvant chemotherapy has resulted in internal mammary nodes control rates of 89% in one study [23]. It should also be noted that chest wall and comprehensive nodal radiation were routinely used in the series from MDACC.

CONCLUSION

There are substantially less data to aid in determining which patients treated with neoadjuvant chemotherapy warrant PMRT. Moreover, determining the appropriate selection criteria is more complicated in this group of patients than in those initially treated with surgery. This is because the majority of patients treated with neoadjuvant chemotherapy have a significant change in their disease resulting from the chemotherapy. Therefore, the pathological factors that historically have been used to identify subgroups of patients with clinically relevant risk of locoregional recurrence after mastectomy are less certain.

There is insufficient data with respect to role of regional lymph node irradiation in patients with negative pathologic node status after neoadjuvant chemotherapy. Whether the omission of lymph node irradiation is allowed for these patients should be prospectively addressed.

In conclusion, PMRT plays an important role in the management of patients receiving neoadjuvant chemotherapy and mastectomy for LABC. Radiation was found to benefit both local control and survival in patients presenting with clinical T3 tumors or stage III to stage IV disease, and in patients with 4 or more positive nodes after neoadjuvant chemotherapy. PMRT should be considered for these patients regardless of their response to the neoadjuvant chemotherapy.

CONFLICT OF INTEREST

There is no conflict of interest.

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