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

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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 patient with breast cancer will benefit from PMRT after NAC, particularly in women with clinically node-positive axillary disease that responds well and is down staged to pathologically negative disease at surgery (ypN0). We review the current evidence on this topic, which forms the underlying basis for the ongoing phase III clinical trial—National Surgical Adjuvant Breast and Bowel Project (NSABP) B51/RTOG 1304—that is examining the role of regional nodal irradiation in patients with clinical N1 disease that responds to NAC and becomes ypN0 at surgery.
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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 cases (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-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 patient with breast cancer 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. Firstly, recent publications support expansion of the indications for PMRT when surgery is the first line of treatment in low-volume axillary node–positive (1-3 nodes positive) breast cancer,[5-7] thus raising questions about the applicability of these findings post-NAC. Secondly, 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]Thirdly, complete pathologic response induced by NAC has been demonstrated to be prognostic for improved survival.[2] Lastly, axillary nodal response to ypN0 post-NAC has been demonstrated to yield low locoregional recurrence (LRR) rates without the use of PMRT[9]; thus supporting the hypothesis that NAC response selects a lower risk group that does not receive benefit from the addition of PMRT.

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Examination of each of these important influences is essential to understand the status of PMRT post-NAC and emphasizes the need for clinical trial data to clarify treatment indications.

Indications for PMRT After Up-Front Surgery are Expanding

The modern approach to PMRT was founded largely by the Danish Breast Cancer Cooperative Group 82b and c [10, 11] and British Columbia [12] clinical trials that enrolled more than 3500 women from 1979-1990 who were randomized to PMRT or observation after surgery and systemic therapy. Systemic therapy in 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 rates, which translated into improved breast cancer–specific survival and overall survival (OS). Based principally on these results, numerous consensus groups have recommended PMRT for patients with ≥4 pathologically involved lymph nodes and patients with pathologic stage III disease.[13-15] However, no consensus has been reached regarding women with earlier-stage, node-positive disease (T1-T2 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 meta-analysis by the 2005 Early Breast Cancer Trialists' Collaborative Group (EBCTG). 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 the 5-year LRR rate translated into a 5.4% reduction in breast cancer mortality rate 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% without PMRT vs 2.3% with PMRT), and there was no significant difference in the breast cancer mortality (BCM) rate with 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 rate 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 8000 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% ($P < 0.00001$). The BCM rate 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 were 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 nonsignificant 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%, respectively ($P = 0.1$), in women with pN0 disease with no reduction in BCM.

There are 2 recent randomized trials that support the use of regional nodal irradiation (RNI) in women with 1-3 pathologically involved lymph nodes that also would likely influence PMRT use.[6,7] European Organisation for Research and Treatment of Cancer (EORTC) 22922/10925 randomized 4,004 patients with pathologic stage I-III (pN+ or pN0/medial tumors) to radiotherapy to the internal mammary nodes or medial supraclavicular (SCL) fossa (IM-MS) or no IM-MS irradiation after breast-conserving surgery (76%) or mastectomy (24%).[6] Approximately 87% of the patients had pN0 or pN1 disease. The primary end point was OS. Radiotherapy to the IM-MS improved the disease-free survival rate from 69.1%-72.1% ($P = 0.04$), the distant metastasis–free survival rate from 75%-78% ($P = 0.02$), and the OS rate from 80.7%-82.3% ($P = 0.056$). Lastly, the National Cancer Institute of Canada (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 the LRR rate from 5.2%-3.2% ($P = 0.02$) and improved the disease-free survival rate from 84%-89.7% ($P = 0.003$), with a trend toward improved OS rate (90.7%-92.7%, $P = 0.07$).

Taken together, the data from the EBCTCG meta-analyses as well as the EORTC 22922 and NCIC MA.20 clinical trials support the expanding role for PMRT or 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 that PMRT did not benefit women with pN0 disease.

NAC Complicates Clinical Decision Making Regarding Use of PMRT

The use of NAC before 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 up-front setting in which there are numerous randomized trials