VOLUME 32 · NUMBER 6 · FEBRUARY 20 2014

JOURNAL OF CLINICAL ONCOLOGY

COMMENTS AND CONTROVERSIES

Locoregional Radiotherapy in Patients With Breast Cancer Responding to Neoadjuvant Chemotherapy: A Paradigm for Treatment Individualization

Julia White, *The Ohio State University Comprehensive Cancer Center, Columbus, OH*
Eleftherios Mamounas, *MD Anderson Cancer Center Orlando, Orlando, FL*

See accompanying article on page 491

The increasing use of neoadjuvant chemotherapy for patients with breast cancer with axillary nodal metastases has created debate among multidisciplinary tumor boards centered on the optimal use of locoregional radiotherapy. Clinical decision making regarding the use of postmastectomy and regional nodal radiotherapy has been built on evidence from numerous randomized clinical trials where pathologic staging from upfront surgery was the determinant of receiving treatment after adjuvant chemotherapy.[1] It is generally recommended that patients who have axillary nodal metastases receive radiotherapy to the chest wall and regional nodes after mastectomy or to breast and regional nodes after lumpectomy. Conversely, in patients with negative axillary nodes, radiotherapy is not typically recommended after mastectomy and is confined to the breast alone after lumpectomy. The absence of similar evidence in the setting of neoadjuvant chemotherapy has led to conflicting opinions about the key factors that should drive the clinical decision to administer locoregional radiotherapy. The thoughtful concepts of Marks and Prosnitz[2] endorse the concept that the prechemotherapy-positive axillary nodal metastases are the key factor and caution that reducing radiotherapy based on chemotherapy response places women at risk for worse breast cancer mortality. Conversely, others have supported the idea that pathologic nodal status postchemotherapy is the important factor and argued that for patients who become pathologically node negative after neoadjuvant chemotherapy, radiotherapy may not offer significant benefit.[3] It is clear that the absence of evidence permits the generation of disparate treatment recommendations for the same clinical scenario, placing women at risk for either over- or undertreatment.

As stated by Marks and Prosnitz,[2] the critical threat of suboptimal locoregional cancer treatment is that it will result in worse breast cancer survival. Significant evidence exists that the addition of locoregional radiotherapy after upfront surgery and adjuvant chemotherapy can improve breast cancer survival in addition to providing large gains in locoregional cancer control.[1,4,5] The Early Breast Cancer Trialists Collaborative Group (EBCTCG) 2005 meta-analysis studied the effect of radiotherapy on locoregional recurrence at 5 years and breast cancer mortality at 15 years. This demonstrated that the absolute benefit in reducing breast cancer mortality resulting from radiotherapy was related to the magnitude of locoregional risk in the nonirradiated patients. However, an analysis that divided absolute locoregional recurrence risk reduction after lumpectomy or mastectomy by 5 years into three categories of $< 10\%$, 10% to 20%, or $> 20\%$ demonstrated that for those with $< 10\%$ absolute reduction in local recurrence resulting from radiotherapy by 5 years, there was no improvement in breast cancer mortality by 15 years.[1] Similarly, the EBCTCG 2011 meta-analysis demonstrated that the reductions gained in 10-year overall breast cancer recurrence rate (local, regional, and distant) by postlumpectomy breast radiotherapy resulted in improvement in 15-year breast cancer mortality rate.[6] An analysis that stratified the predicted absolute reduction in 10-year overall breast cancer recurrence risk from radiotherapy into groups of low ($< 10\%$), intermediate (10% to 19%), and large ($> 20\%$) found in the low-risk group an absolute reduction of 6.9% with radiotherapy (18.9% without *v* 12% with radiotherapy), corresponding to a negligible absolute reduction in 15-year risk of death resulting from breast cancer of 0.1% (-7.5% to 7.7%). Collectively these analyses support that the survival benefit from radiotherapy after upfront surgery and chemotherapy is related to an individual patient's risk of any recurrence based on clinical and pathologic features. It is recognized that the extent of response to neoadjuvant chemotherapy is associated with prognosis, with the best relative disease-free survival occurring in those who achieve a complete pathologic response.[7] Therefore, it is logical that if upfront chemotherapy can place a patient in a sufficiently low risk category for locoregional recurrence after surgery, then adding radiotherapy will not significantly reduce the risk of breast cancer mortality.

There is supporting evidence that neoadjuvant chemotherapy response is linked to lower rates of subsequent locoregional recurrence risk in the absence of radiotherapy. Mamounas et al[8] analyzed locoregional recurrence rates in approximately 3,000 women enrolled onto two National Surgical Adjuvant Breast and Bowel Project (NSABP) clinical trials evaluating neoadjuvant chemotherapy (NSABP B-18 and NSABP B-27). Both protocols specified that patients treated with lumpectomy were required to receive breast radiotherapy only, and patients treated with mastectomy were not allowed to receive any radiotherapy. The combined analysis of these two trials provides important information on the rates, patterns, and independent predictors of locoregional recurrence after neoadjuvant chemotherapy. The 10-year cumulative incidence of locoregional recurrence was 12.3% for patients who underwent mastectomy (local, 8.9%; regional, 3.4%)

and 10.3% for patients who underwent lumpectomy and received breast radiotherapy (local, 8.1%; regional, 2.2%). Independent predictors of locoregional recurrence in patients undergoing lumpectomy were age, clinical nodal status, and pathologic nodal status/pathologic breast response; for those undergoing mastectomy, they were clinical tumor size, clinical nodal status, and pathologic nodal status/pathologic breast response. In particular, women who had clinically involved nodes before chemotherapy who were pathologically node negative at surgery (with or without pathologic complete response in the breast) had lower locoregional recurrence than those who were found to have persistent nodal metastases pathologically. More specifically, in 224 patients who underwent breast-conservation therapy with clinically positive nodes before neoadjuvant chemotherapy and pathologically negative nodes afterward, the risk of regional nodal recurrence was low, between 0% and 2.4%, and the risk of local recurrence in the breast was 7% to 10% at 10 years. Similarly, in 102 patients undergoing mastectomy with clinically positive nodes before neoadjuvant chemotherapy and pathologically negative nodes afterward, the risk of chest wall and regional nodal recurrence was between 0% and 10.8%. These locoregional recurrence rates fit into a low-risk category of patients who are unlikely to experience improved overall survival from radiotherapy. It is important to emphasize that the results of the combined analysis of NSABP B-18 and B-27 are primarily applicable to patients with clinical stage I to II disease; 55% of the patients presented with cT1-2N0 disease, 20% with cT1-2N1 disease, and 16% with cT3N0 disease. Only 9% of the patients presented with cT3N1 disease.

Higher rates of locoregional recurrence have been demonstrated in patients who present with clinical stage $\geq$ III disease, even if they achieve a pathologic complete response after neoadjuvant chemotherapy. McGuire et al[9] reported locoregional recurrences in a group of 106 women achieving a pathologic complete response from neoadjuvant chemotherapy, 74 of whom initially had clinical stage IIIA, B, or C disease. For those who initially presented with stage III disease, locoregional recurrence at 10 years was 33.3% without radiotherapy versus 7.3% with radiotherapy ($P = .040$); howevefr, similar locoregional recurrence rates were seen with or without radiotherapy in the group that presented with clinical stage I or II disease before chemotherapy.

The results of the combined analysis of NSABP B-18 and B-27 clearly demonstrate that in addition to age and clinical stage before neoadjuvant chemotherapy,[8] pathologic response in the breast and axillary nodes has a major impact on the rate of locoregional recurrence and in fact seemingly minimizes the effects of age, clinical tumor size, and nodal status before neoadjuvant chemotherapy. Specifically, in patients who have positive nodes before neoadjuvant chemotherapy, the rate of locoregional recurrence can be modified downward if the nodes become pathologically node negative after neoadjuvant chemotherapy (particularly if there is also pathologic complete response in the breast). The NSABP B51/RTOG (Radiation Therapy Oncology Group) 1304 phase III clinical trial (NCT01872975) is designed to answer whether regional radiotherapy improves the invasive breast cancer recurrence–free interval rate (local, regional, and distant recurrences and deaths resulting from breast cancer) in women who present with clinical N1 axillary nodal disease (documented pathologically by needle biopsy) before neoadjuvant chemotherapy and then become pathologically node negative at time of surgery. After mastectomy, patients are randomly assigned to no radiotherapy versus chest wall and regional nodal radiotherapy, and after lumpectomy, random assignment is to breast radiotherapy alone versus breast and regional lymph node radiotherapy. Patients with high-risk breast cancer at presentation, clinical stage N2 to 3 disease, or stage IIIB or C disease are not eligible. The results of this clinical trial have the potential to produce a major paradigm shift in the locoregional management of early-stage breast cancer, namely by providing evidence for presence or absence of benefit from regional radiotherapy when pathologic downstaging of the axillary nodes by neoadjuvant chemotherapy occurs.

For women who receive neoadjuvant chemotherapy and whose lymph nodes remain pathologically positive after surgery, regional radiotherapy is indicated. However, these women can be enrolled onto the ALLIANCE (Alliance for Clinical Trials in Oncology) A011202 phase III clinical trial (NCT01901094) that is designed to answer whether axillary node dissection improves the rate of breast cancer recurrence over that seen with sentinel node biopsy alone when regional radiotherapy is delivered. Together, these trials will potentially allow us to fulfill our commitment to patients with breast cancer who receive neoadjuvant chemotherapy—to achieve maximal breast cancer survival while tailoring locoregional treatment to best fit their disease.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Manuscript writing: All authors
Final approval of manuscript: All authors

REFERENCES

1. Clarke M, Collins R, Darby S, et al: Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: An overview of the randomised trials. Lancet 366:2087-2106, 2005
2. Marks LB, Prosnitz LR: Reducing local therapy in patients responding to preoperative systemic therapy: Are we outsmarting ourselves? J Clin Oncol 32:491-493, 2014
3. Fowble BL, Einck JP, Kim DN, et al: Role of postmastectomy radiation after neoadjuvant dhemotherapy in stage II-III breast cancer. Int J Radiat Oncol Biol Phys 83:494-503, 2012
4. Overgaard M, Nielsen HM, Overgaard J: Is the benefit of postmastectomy irradiation limited to patients with four or more positive nodes, as recommended in international consensus reports? A subgroup analysis of the DBCG 82 B & C randomized trials. Radiother Oncol 82:247-253, 2007
5. Ragaz J, Olivotto IA, Spinelli JJ, et al: Locoregional radiation therapy in patients with high-risk breast cancer receiving adjuvant chemotherapy: 20-year results of the British Columbia randomized trial. J Natl Cancer Inst 97:116-126, 2005
6. Darby S, McGale P, Correa C, et al: Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: Meta-analysis of individual patient data for 10,801 women in 17 randomized trials. Lancet 378:1707-1716, 2011
7. Rastogi P, Anderson SJ, Bear HD, et al: Preoperative chemotherapy: Updates of National Surgical Adjuvant Breast and Bowel Project Protocols B-18 and B-27. J Clin Oncol 26:778-785, 2008
8. Mamounas EP, Anderson SJ, Dignam JJ, et al: Predictors of locoregional recurrence after neoadjuvant chemotherapy: Results from combined analysis of National Surgical Adjuvant Breast and Bowel Project B-18 and B-27. J Clin Oncol 30:3960-3966, 2012
9. McGuire SE, Gonzales-Angulo AM, Huang EH, et al: Postmastectomy radiation improves the outcome of patients with locally advanced breast cancer who achieve a pathologically complete response to neoadjuvant chemotherapy. Int J Radiat Oncol Biol Phys 68:1004-1009, 2007

DOI: 10.1200/JCO.2013.53.4974; published online ahead of print at www.jco.org on December 30, 2013