This study by Marhin and colleagues showed no difference in cardiac toxicity by fractionation scheme over this relatively narrow dose range.

One source of hesitation affecting the routine use of hypofractionation in the majority of patients has been the lack of data regarding cardiac toxicity when using higher-than-conventional doses per fraction and the lack of guidelines for cardiac dose constraints at fractional doses greater than 2 Gy. Experimental studies have suggested that doses per fraction greater than 2 Gy are pro-inflammatory, increasing the risk of atherosclerotic plaque formation.6

The American Society for Radiation Oncology has published a guideline on whole-breast fractionation that notes that the existing studies have not raised any specific concerns about increased cardiac toxicity when using hypofractionation and breast tangents, with follow-up of up to 12 years.7 The task force noted, however, that the survival curves from the study by Marhin and colleagues5 suggest that there may be a higher risk of cardiac toxicity from the hypofractionation regimens 10 or more years after treatment. The American Society for Radiation Oncology task force therefore concluded that, at this time, hypofractionation should be used in patients in whom the heart can largely be eliminated from the treatment fields while maintaining target volume coverage. It is important to routinely employ 3-dimensional conformal planning techniques with close attention to target volume coverage and doses to the heart, minimizing the dose to cardiac structures, especially when contemplating hypofractionation regimens.

E. E. R. Harris, MD

References


The Role of Postmastectomy Radiation Therapy After Neoadjuvant Chemotherapy in Clinical Stage II-III Breast Cancer Patients With pN0: A Multicenter, Retrospective Study (KROG 12-05)

Shim SJ, Park W, Huh SJ, et al (Eulji Univ, Seoul, Republic of Korea; Sungkyunkwan Univ School of Medicine, Seoul, Republic of Korea; et al)

Purpose.—The purpose of this study was to investigate the role of postmastectomy radiation therapy (PMRT) after neoadjuvant chemotherapy (NAC) in clinical stage II-III breast cancer patients with pN0.

Methods and Materials.—We retrospectively identified 417 clinical stage II-III breast cancer patients who achieved an ypN0 at surgery after receiving NAC between 1998 and 2009. Of these, 151 patients underwent mastectomy after NAC. The effect of PMRT on disease-free survival (DFS), locoregional recurrence-free survival (LRRFS), and overall survival (OS) was evaluated by multivariate analysis including known prognostic factors using the Kaplan-Meier method and compared using the log—rank test and Cox proportional regression analysis.

Results.—Of the 151 patients who underwent mastectomy, 105 (69.5%) received PMRT and 46 patients (30.5%)
did not. At a median follow-up of 59 months, 5 patients (3.3%) developed LRR (8 sites of recurrence) and 14 patients (9.3%) developed distant metastasis. The 5-year DFS, LRRFS, and OS rates were 91.2, 98.1, and 93.3% with PMRT and 83.0%, 92.3%, and 89.9% without PMRT, respectively (all P values not significant). By univariate analysis, only age (≤40 vs >40 years) was significantly associated with decreased DFS (P = .027). By multivariate analysis, age (≤40 vs >40 years) and pathologic T stage (0-1 vs 1 vs 2-4) were significant prognostic factors affecting DFS (hazard ratio [HR] 0.353, 95% confidence interval [CI] 0.135-0.928, P = .035; HR 2.223, 95% CI 1.074-4.604, P = .031, respectively). PMRT showed no correlation with a difference in DFS, LRRFS, or OS by multivariate analysis.

Conclusions.—PMRT might not be necessary for pN0 patients after NAC, regardless of clinical stage. Prospective randomized clinical trial data are needed to assess whether PMRT can be safely omitted in pN0 patients after NAC and mastectomy for clinical stage II-III breast cancer.

This study by Shim and colleagues is a retrospective review of 151 patients with stage II-III breast cancer who were found to have pathologically negative lymph nodes after NAC, 105 (69.5%) of whom received PMRT and 46 (30.5%) of whom did not. At a median follow-up of 57 months, the 5-year LRRFS rate was 98.1% versus 92.3%, the 5-year DFS rate was 91.2% versus 83.0%, and the 5-year OS rate was 93.3% versus 89.9%, all favoring the PMRT group, although none of these differences was statistically significant. The authors concluded that PMRT may not provide benefit in this setting regardless of the clinical stage at presentation.

With the more widespread adoption of neoadjuvant systemic therapy, decisions regarding the use of PMRT in this clinical scenario are an increasingly common challenge for the radiation oncologist, and there is a paucity of data to guide decision making. The only other single-institution studies specifically addressing this question have emerged from 1 institution, The University of Texas MD Anderson Cancer Center,1,2 and the pooled analysis of the National Adjuvant Breast and Bowel Project (NSABP) B-18 and B-27 randomized trials includes very few patients in the subgroup who had pN0 disease and then underwent mastectomy.3 These previously published data suggest that those who present with clinical stage II disease and attain a pathologic complete response (pCR) can likely safely omit PMRT, whereas those who present with stage III disease are likely to benefit from PMRT, even in the setting of pCR.

The current series adds to this small body of literature, reporting an overall low rate of LRR (3.3%) in a cohort of patients with stage II-III disease. The patient population was primarily clinically node positive (81.9% in the PMRT group and 91.3% in the no-PMRT group), but more than half had stage II disease (63% in the PMRT group and 59.1% in the no-PMRT group). As described previously, there was an absolute difference in the PMRT versus no-PMRT groups with respect to LRRFS, DFS, and OS rates, all favoring the PMRT group, but none of these differences was significant. It is important to consider the relatively small number of patients in each subset and the very small number of events, particularly locoregional events. While the low overall risk of LRR is reassuring, the small number of events limits the statistical strength to detect differences between the groups.

Even so, on the reported multivariate analysis, the HR for LRR was 0.198 favoring PMRT, with a P value that trended toward significance at .097.

Using univariate and multivariate analyses, the authors attempted to evaluate the impact of stage, but the analyses included only clinical T and N stage, not the stage group. While the analyses did not demonstrate a difference in outcome with respect to these variables, they did not reveal the impact of stage II versus stage III classification, which is the most important variable reported in the MD Anderson series.

Given the previously published data from MD Anderson regarding patients with stage II disease who attain a pCR and the fact that the majority of patients in this series presented with stage II disease, I feel it is reasonable to consider this series an important addition to the literature supporting the omission of PMRT in the setting of stage II disease with pN0 after neoadjuvant therapy. However, I do not feel this series can be used to draw conclusions regarding the more controversial subset of patients with stage III disease.

Two randomized studies recently opened that will help determine the role of PMRT in patients with pN0 disease after neoadjuvant therapy. In the Radiation Therapy Oncology Group 1304/NSABP B-51 study, patients who present with node-positive disease and become pN0 are randomized to receive PMRT or no PMRT (or regional nodal radiation [RNI] vs no RNI in the setting of breast conservation), and the primary endpoint is invasive breast cancer recurrence-free interval. Alliance A011202 also enrolls node-positive patients who undergo neoadjuvant therapy, and it evaluates the benefit of axillary node dissection as well as the
benefit of PMRT or RNI. In this study, patients undergo breast-conserving surgery or mastectomy with sentinel node biopsy after neoadjuvant systemic therapy. Those with sentinel node-negative disease are randomized to receive PMRT or no PMRT (or RNI vs no RNI in the setting of breast conservation), and those with sentinel node-positive disease are randomized to receive PMRT (or RNI in the setting of breast conservation) or PMRT (or RNI in the setting of breast conservation) plus completion axillary dissection.

Enrollment in these clinical trials should be strongly considered for all patients who fit these criteria, and in time, if these important trials are able to accrue well, we will have critically needed randomized data to guide us in decisions regarding PMRT in this setting.

J. L. Wright, MD

References

Five year outcomes of hypofractionated simultaneous integrated boost irradiation in breast conserving therapy; patterns of recurrence


In 2005, we introduced hypofractionated 3-dimensional conformal radiotherapy with a simultaneous integrated boost (3D-CRT-SIB) technique after breast conserving surgery. In a consecutive series of 752 consecutive female invasive breast cancer patients (stages I-III) the 5-year actuarial rate for local control was 98.9%. This new technique gives excellent 5-year local control.

This article by Bantema-Joppe and colleagues presents a thought-provoking radiotherapy technique and fractionation schedule for breast-conserving therapy in patients with breast cancer. With modern, sophisticated treatment planning software, an SIB can now easily be planned. In the past, concern would have been expressed with regard to safety in terms of cosmetic outcomes (breast fibrosis, shrinkage, edema, and telangiectasia) with the 2.3 Gy per fraction used in the SIB in this study. However, 2 randomized studies (a Canadian trial and the UK Standardisation of Breast Radiotherapy [START] Trial B) comparing hypofractionated whole-breast radiotherapy (delivering 2.65 Gy/fraction and 2.67 Gy/fraction, respectively, to the whole breast) with standard-fractionation whole-breast radiotherapy (2 Gy/fraction) have reported 10-year outcomes suggesting that cosmesis after hypofractionated whole-breast irradiation is at least as good as that after whole-breast irradiation with standard fractionation. The SIB boost study presents a 5-year actuarial local control rate of 98.9%. The Canadian study reported a 10-year local recurrence rate of 6.2% in the hypofractionated arm, with no boost delivered. The UK START Trial B reported a 3.8% local relapse rate at 10 years in the 40-Gy hypofractionated arm, with 43% of patients receiving a boost. Certainly, the treatment planning with the hypofractionated SIB technique reported by Bantema-Joppe and colleagues is intriguing. But with the publication of the Canadian trial and the UK START Trial B in which whole-breast radiotherapy was completed in 3-4 weeks, the question now is whether a 5.5-week (28-fraction) treatment schedule would be indicated in most cases.

E. S. Bloom, MD

References

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