Regional nodal irradiation cuts breast cancer recurrence

Adding regional nodal irradiation to whole-breast irradiation significantly improved disease-free survival in women at high risk of recurrence following breast-conserving surgery and adjuvant therapy.

Whole-breast irradiation (WBI) plus regional nodal irradiation (RNI) significantly improved disease-free survival, but not overall survival, in a randomized, multicenter phase III trial of women with node-positive or high-risk node-negative disease who were treated with breast-conserving surgery and adjuvant therapy.

An interim analysis of 1,832 women with breast cancer found that after a median follow-up of 62 months (between March 2000 and March 2007), WBI plus RNI significantly reduced the risk of locoregional recurrence from 5.5% to 3.2% (hazard ratio [HR], 0.58; P = 0.02) and distant recurrence from 13.0% to 7.6% (HR, 0.64; P = 0.002), according to the lead investigator, Dr. Timothy Whelan, head of radiation oncology at McMaster University and the Juravinski Cancer Centre, Hamilton, Ontario, Canada.

As a result, disease-free survival rate improved from 84.0% for WBI to 89.7% for WBI plus RNI (HR, 0.67; P = 0.003). Overall survival in the intergroup trial was 90.7% with WBI, compared with 92.3% with the combined radiation regimen, but the difference did not reach statistical significance (HR, 0.76; P = 0.07).

In view of the positive findings from the National Cancer Institute of Canada Clinical Trials Group MA.20 study, the data safety monitoring committee recommended that the results be released. The data were presented by Dr. Whelan at the 2011 annual meeting of the American Society of Clinical Oncology (ASCO).[1]

What's new, what's important

For patients who are treated with breast-conserving surgery (BCS), the most common site of local recurrence is the ipsilateral breast itself. The risk of recurrence can be as high as 20% or more, even in node-negative women. Whole-breast irradiation (WBI) after BCS is the standard approach.

The clinical trial discussed in this report is the first study to examine the role of regional nodal radiation (RNI) in addition to WBI in patients who underwent lumpectomy. It is very interesting to see that the addition of RNI to WBI resulted in a 42% reduction in locoregional recurrence and 36% reduction in distant recurrence in this patient population. Moreover, disease-free survival at 5 years after radiation therapy increased 33% if RNI was also done (P = 0.003).

Patients received 50 Gy in 25 fractions with or without a 10-Gy boost or 50 Gy in 25 fractions with or without a 10-Gy boost plus RNI of 45 Gy in 25 fractions.

It is interesting to see this study, when the radiation oncology field is moving more into brachytherapy. However, WBI + RNI may be a reasonable approach for patients with early-stage disease who are at a high risk for recurrence, as defined in this study. Nonetheless, as Drs. Duggan and Julian emphasize in their commentary, it is important to consider the side effects of RNI and select patients appropriately.

—Jame Abraham, MD, *Editor*

ASCO and the American Society for Therapeutic Radiology and Oncology guidelines recommend locoregional irradiation after mastectomy for tumors > 5 cm or with more than three positive axillary nodes. Of the 1,832 women (mean age, 53.3 years) in the current study, 85% had one to three positive lymph nodes; 10% had high-risk, node-negative breast cancer; and 5% had more than four positive nodes. All of the women were treated with breast-conserving surgery plus adjuvant chemotherapy (91%) or endocrine therapy (71%).

The addition of RNI to WBI significantly increased the rates of grade 2 or higher dermatitis from 40% to 50% (P < 0.001), pneumonitis from 0.2% to 1.3% (P = 0.01), and lymphedema from 4% to 7% (P = 0.004). The lymphedema was primarily grade 2.

Adverse cosmetic outcome, a potential indicator of late-radiation morbidity, increased over time in the combination radiation and WBI treatment groups, from 29% and 26%, respectively, at 3 years (P = 0.22) to 36% and 29%, respectively, at 5 years, which was a statistically significant difference (P = 0.047). The investigators observed no increase in cardiac events or second cancers.

Radiation dosages for WBI were 50 Gy in 25 fractions plus a boost at the discretion of the cancer center of 10 Gy in 5 fractions and 45 Gy in 25 fractions for WBI plus RNI. The irradiation was applied to the internal mammary, supraclavicular, and high axillary lymph nodes. WBI and RNI were delivered concurrently, so that the added therapy would not re-

Report prepared by Patrice Wendling.

Commun Oncol 2011;8:544–546

quire additional office visits for the patients.

MA.20 was sponsored by the Canadian Cancer Society Research Institute, National Cancer Institute/Cancer Therapy Evaluation Program, and Canadian Breast Cancer Research Alliance. Dr. Whelan and his coinvestigators disclosed no conflicts of interest.

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Commentary

Select patients carefully for regional nodal irradiation

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Breast-conserving surgery (BCS) continues to be a significant option for women with early-stage breast cancer. With this, the need for regional control becomes increasingly important in high-risk patients with early-stage breast cancer. The addition of regional nodal irradiation (RNI) to whole breast irradiation (WBI) may be one means for providing further "protection" from distant and locoregional recurrence. As demonstrated by the NCIC-CTG MA.20 trial, the addition of RNI to WBI after BCS in women with node-positive or high-risk node-negative breast cancer treated with adjuvant systemic therapy improves disease-free survival (DFS) with a trend toward improvement in overall survival (OS) as well.[1] Node-negative women were considered to be at high risk if their tumor was ≥ 5 cm or if it was ≥ 2 cm and fewer than 10 axillary nodes had been removed, with either estrogen receptor negativity, nuclear grade 3, or presence of lymphovascular invasion.[1]

From March 2000 to March 2007, 1,832 women were randomized to receive WBI or WBI + RNI. RNI included the internal mammary, supraclavicular, and high axillary nodes. When comparing WBI + RNI with WBI alone, a reduction in both locoregional (96.8% vs 94.5%, respectively) and distant (92.4% vs 87%) recurrence was seen, as well as improvements in DFS (89.7% vs 90.7%) and OS (92.3% vs 90.7%).[1] Adverse outcomes included an increased risk of radiation pneumonitis and lymphedema.[1]

Although the results of the MA.20 trial are significant and indicate the need to include RNI in guideline recommendations for the treatment of early-stage breast cancer, there is no true consensus among breast-care specialists in its implementation. For instance, in a study reported by Clavel et al,[2] 67 radiation oncologists were surveyed to document the use of RNI after BCS and to identify the factors that influenced their clinical decisions. Most of them indicated that the number of positive lymph nodes, nodal ratio, number of lymph nodes removed, and the presence of extracapsular extension were the primary factors that directed the decision to offer RNI, and few included the internal mammary chain in their treatment plan. Despite these similarities, the survey revealed a range of practices among the radiation oncologists, thus supporting the need for treatment guidelines when choosing to implement RNI.

Perhaps the variation in treatment with RNI reported by Clavel and colleagues is justified in the MA.20 trial itself. When taking cofactors into consideration, data from the trial suggest that not all patients with node-positive disease have the same risk of residual regional disease. For instance, patients with three positive lymph nodes had a locoregional recurrence (LRR) risk of 10%, compared with 2% for patients with two positive lymph nodes.[1] Similarly, extracapsular extension, lymphovascular invasion, larger primary tumor size, and larger metastatic burden were all associated with a higher risk of LRR.[1] These findings suggest that RNI should be tailored to the patient after proper assessment of tumor characteristics has taken place.

Furthermore, the LRR data reported in the MA.20 trial is somewhat predictable. Of 77 total LRRs

Manuscript received November 16, 2011; accepted November 17, 2011.

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Disclosures: Dr. Duggal, a Breast Surgical Fellow, is funded by the Pittsburgh Affiliate of Susan G. Komen for the Cure. Dr. Julian has nothing to disclose.

reported, 48 occurred in patients in the WBI treatment arm and 29 in the WBI + RNI arm.[1] This difference translates into an absolute reduction in the rate of LRR of 2.3%, which can be reasonably expected. What is of further interest is that 67% of regional recurrences were in the axilla, supporting the need to tailor RNI not only to tumor characteristics but also to the region in which LRR is most likely.[1] In other words, perhaps RNI of the supraclavicular and internal mammary nodes should not be emphasized as highly as RNI to the high axillary nodes.

The benefits of RNI need to be carefully balanced against its risks. Those risks include (but are not limited to) pain, lymphedema, pneumonitis, brachial plexus neuropathy, shoulder range of motion, malignancy, radiation dermatitis, and poor cosmetic outcome. In a 5-year follow-up of the START trial,[3] 40% of women reported at least moderate changes to the breast after WBI, and 30% reported arm and shoulder pain. Concerns for body image reduced over time.[3] Women who were treated with hypofractionated radiotherapy experienced fewer adverse effects than those who received standard radiotherapy.[3] The results of this survey and the frequency of adverse events following RNI in the MA.20 trial (radiation dermatitis, 50%; lymphedema, 7%) suggest that WBI + RNI may pose an even greater risk of adverse events than WBI alone.[1] This further supports the fact that RNI should be carefully selected for and applied in the treatment of early-stage breast cancer.

Treatment with RNI for selected patients should be based on biological risk factors, molecular markers, and tumor genetics. This is an area that needs further study. Validation of the MA.20 trial results and further research should precede the implementation of RNI as a standard-of-care guideline in the treatment of high-risk early-stage breast cancer.

How we treat breast cancer

The treatment of breast cancer at the Allegheny Cancer Center at Allegheny General Hospital centers around a multidisciplinary approach. Women undergoing breast-conserving surgery (BCS) with node-positive breast cancer, as determined from preoperative ultrasound-guided axillary node biopsy or sentinel lymph node resection, generally undergo completion axillary lymph node dissection (ALND). Treatment with ALND, however, is based on multiple factors, including patient age and comorbidities, tumor biology, number of positive sentinel nodes, and tumor volume of the sentinel lymph node.

After undergoing ALND, patients are referred to the radiation oncology department. The implementation of regional nodal irradiation (RNI) is based on whether or not the patient has had ALND, the number of positive lymph nodes, and the nodal ratio. In the event that ALND is not performed, further treatment takes on a multidisciplinary effort that is guided by recommendations from the radiation oncologist, medical oncologist, and surgical oncologist.

The criteria used to define high-risk breast cancer at our institution are similar to those used in the MA.20 trial: tumor size > 3 cm, estrogen receptor negativity, HER2/*neu* positivity, or lymphovascular invasion. High-risk node-negative breast cancer is treated with whole-breast irradiation after BCS. Regional irradiation is generally not recommended for high-risk node-negative breast cancer at our institution.

—Shivani Duggal, DO, and Thomas B. Julian, MD, FACS

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