

Breast cancer

BENEFITS OF LOCOREGIONAL IRRADIATION ADDED TO WHOLE BREAST IRRADIATION

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TRIAL SUMMARY: Regional nodal irradiation improves survival for high-risk disease post breast-conserving surgery

Whelan TJ, Olivetto I, Ackerman I, NCIC-CTG. MA.20: An Intergroup trial of regional nodal irradiation in early breast cancer. ASCO 2011. *J Clin Oncol* 2011;29(suppl):Abstract LBA1003.

In this trial, women with high-risk node-negative (N0) or node-positive (N+) breast cancer treated with breast-conserving surgery (BCS) + adjuvant chemotherapy and/or endocrine therapy were stratified by positive nodes, axillary nodes removed, chemotherapy and endocrine therapy, and randomized to whole-breast irradiation (WBI; 50 Gy in 25 fractions +/- boost irradiation) or WBI + regional nodal irradiation (RNI; 45 Gy in 25 fractions) to the internal mammary, supraclavicular and high axillary lymph nodes. Characteristics of the study population were: mean age 53.3 years; 10% N0; 85% 1–3 positive nodes; 5% >4 positive nodes; 91% adjuvant chemotherapy; and 71% adjuvant endocrine therapy. Between 2000 and 2007, 1832 women were randomly assigned to WBI + RNI or WBI. The primary outcome was overall survival (OS).

COMMENTARY: Trials published in the 1990s from Scandinavia^{1,2} and British Columbia³ showed a reduced risk of recurrence and survival benefits for women treated with systemic therapy by adding locoregional radiation after mastectomy. Based on this information, both the 1999 American Society for Radiation Oncology (ASTRO) and the 2001 American Society of Clinical Oncology (ASCO) guidelines have recommended locoregional radiation for tumours greater than 5 cm or with 4 or more positive lymph nodes. There was little evidence at that time to guide the management of women who received BCS. This well-designed, international, multicentre clinical trial is one of the first to address this question, particularly relevant since most women in North America now receive BCS. The trial also evaluates RNI in the era of more effective systemic therapy, which provides more effective locoregional control than older systemic treatments.

The study compared the effectiveness of RNI to the internal mammary, supraclavicular and high axillary nodes in addition to WBI after BCS for node-positive (N+) and high-risk N0 breast cancer treated with systemic therapy. High-risk N0 was defined as tumour size ≥ 5 cm, or ≥ 2 cm and <10 axillary nodes removed with either estrogen receptor-negative (ER-), lymphovascular invasion-positive (LVI+) or Grade 3 features. This study includes centres from Canada, the US and Australia with well-defined endpoints. Of note,

TABLE 1. WBI + RNI vs WBI: DFS, HR and OS at median followup (62 months)

DFS, HR and OS	WBI + RNI (n=916)	WBI (n=916)
Isolated locoregional DFS (HR=0.59, p=0.02, 5-year risk)	96.8%	94.5%
Distant DFS (HR=0.64, p=0.002, 5-year risk)	92.4%	87.0%
DFS (HR=0.68, p=0.003, 5-year risk)	89.7%	84.0%
OS (HR=0.76, p=0.07, 5-year risk)	92.3%	90.7%

DFS= disease-free survival HR=hazard ratio OS=overall survival
WBI=whole-breast irradiation RNI=regional nodal irradiation

WBI + RNI vs WBI was associated with an increase in \geq Grade 2 pneumonitis (1.3% and 0.2%, respectively; p=0.01) and lymphedema (7.3% and 4.1%, respectively; p=0.004). Trial results demonstrate that additional RNI reduces the risk of locoregional and distant recurrence and improves disease-free survival (DFS) with a trend toward improved OS (see **Table 1**).

WBI included the lower axillary nodes, and all sentinel N+ patients were treated with completion axillary lymph node dissection (ALND). All patients were included in this intention-to-treat analysis. Adjuvant chemotherapy consisted of anthracyclines in 90% and taxanes in one-third of patients; adjuvant endocrine therapy included aromatase inhibitors in two-thirds of patients. Thus, this trial reflects much more closely the current standard of practice for systemic therapy, although only those accrued in the last 2 years received trastuzumab for human epidermal growth factor receptor (HER2)-positive disease.

This first report provides a comprehensive 5-year outcomes analysis. Pneumonitis, lymphedema (mainly Grade 2) and fair-to-poor cosmetic outcome were slightly increased in the RNI group. There was no increase in cardiac events or second cancers. Although there is no statistically significant survival benefit, there is a strong trend in overall survival. Distant DFS was significantly improved with an early separation of Kaplan-Meier curves and the Oxford overview has already demonstrated a relationship between locoregional control and survival.⁴ This study reaffirms the locoregional benefits of radiation and extends the indications for RNI to all women with positive lymph nodes receiving full ALND.

The study does not directly answer the question of how to manage women who have positive sentinel lymph nodes with micrometastases that are more likely to be detected by

more careful examination of 1–2 lymph nodes. In addition, it does not incorporate changes of practice influenced by the American College of Surgeons Oncology Group (ACOSOG) Z0011 trial that showed no difference in local control, distant metastases or survival for no further ALND vs completion ALND.⁵

At this time, our institution is taking a pragmatic approach. We feel that, pending confirmation of the ACOSOG trial results (a German trial is underway), a full ALND is the acceptable standard of care. Patients with any nodal macro-metastases should be considered for locoregional radiation. All patients with pathology showing 1–2 nodes positive for micrometastases regardless of further surgery are referred to radiation and medical oncology and discussed at a tumour board. Consideration should be given to nodal radiation for any high-risk features (high grade, LVI+, ER/ progesterone receptor [PR]–, triple negative or age <50 years). We still require more information on managing patients treated with neoadjuvant therapy, so those with clinically or pathologically positive nodes before systemic therapy should be considered for locoregional radiation. If there is a pathologic complete response, individual discussion is warranted.

References

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IN BRIEF

Already known

- Trials published in the 1990s from Scandinavia and British Columbia showed a reduced risk of recurrence and survival benefits for women treated with systemic therapy by adding locoregional radiation after mastectomy.

What this study showed

- This study confirms the benefits of locoregional radiation in the era of more effective systemic therapies and extends the indications for treatment to women with 1–3 positive lymph nodes.
- Even though women undergoing WBI receive treatment to the lower axilla, it confirms the additional benefit of aggressive locoregional radiation to this group.
- Distant DFS is significantly improved with regional nodal irradiation and likely outweighs demonstrated toxicities of pneumonitis, lymphedema and altered cosmesis.

Next steps

- Longer-term followup and further information on the impact of micrometastases are required.
- A German trial is underway to validate the results of ACOSOG Z0011, which showed no difference in local control, distant metastases or survival for no further ALND vs completion ALND.

Disclosure:

The author reports no conflicts of interest relevant to this article.