

Breast cancer

IMPACT OF INTERNAL MAMMARY NODE IRRADIATION IN HIGH-RISK PATIENTS

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TRIAL SUMMARY: No benefit with internal mammary node inclusion in locoregional radiotherapy

Olson R, Woods R, Lau J et al. Impact of internal mammary node inclusion in the radiation treatment volume on the outcomes of breast cancer patients treated with loco-regional radiation after 6 years follow-up. CARO 2011. Abstract 78.

This large retrospective review includes 2,413 women with high-risk (lymph node-positive or Stage T3/T4 node-negative) breast cancer referred to a provincial radiotherapy program from 2001 to 2006 for adjuvant therapy. The following endpoints were compared between women who received internal mammary node (IMN) radiotherapy and those who did not: breast cancer-specific survival (BCSS), relapse-free survival (RFS) and overall survival (OS).

Of the 2,413 women, 999 (41.4%) had IMN radiation vs 1,414 who did not. **Table 2** summarizes the 5-year BCSS, RFS and OS for the 2 groups, with a median followup of 6.2 years.

COMMENTARY: A number of randomized controlled trials and a large meta-analysis have established the benefit of adjuvant locoregional radiotherapy for high-risk breast cancer patients. However, there is ongoing controversy over the therapeutic benefit of including IMN irradiation in these patients. The IMN chain is a first-echelon drainage site, similar to the axillary nodes. Historic surgical series have demonstrated that 44% to 65% of patients with medial tumours and positive axillary lymph nodes have IMN involvement. Even in patients with lateral tumours and negative axillary nodes, 4% to 13% can have IMN involvement.¹ Therefore, irradiation of this nodal region would potentially contribute to the eradication of microscopic disease and the therapeutic benefit of adjuvant radiotherapy. Due to the anatomic location, however, surgical accessibility is more difficult and radiation-related toxicity is potentially greater than for the axilla.

In the postmastectomy setting, several large randomized trials have demonstrated a 9–10% survival benefit at 10 years, in addition to a substantial locoregional control benefit.²⁻⁴ The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis of 78 randomized trials has confirmed this improvement in survival and locoregional control from locoregional radiotherapy. Specifically, from analysis of 25 trials of adjuvant radiotherapy following mastectomy and axillary clearance, the 5-year local recurrence risk was reduced from 23% to 6% compared with no radiation therapy, and the 15-year breast cancer mortality risk was reduced from 60.1% to 54.7% ($p=0.0002$).⁵ This year, the early results of the NCIC CTG MA.20 study demonstrated improvements in locoregional control and distant RFS, and suggested a

TABLE 2. Five-year BCSS, RFS and OS outcomes for inclusion vs exclusion of IMN radiation

| 5-year endpoints | IMN included | IMN excluded | HR (95% CI) |
|------------------|--------------|--------------|-------------------------------|
| BCSS | 84.8% | 82.9% | 0.93 (0.76–1.14); $p=0.51$ |
| RFS | 87.4% | 86.9% | 0.99 (0.83–1.19); $p=0.94$ |
| OS | 84.8% | 82.9% | 0.84 (0.70–1.01); $p=0.06$ |

IMN=internal mammary nodes
BCSS=breast cancer-specific survival

HR=hazard ratio
RFS=relapse-free survival

CI=confidence interval
OS=overall survival

The authors concluded that no benefit could be demonstrated with inclusion of IMN radiation in locoregional radiotherapy for high-risk breast cancer, after adjusting for other potentially confounding prognostic and radiotherapy-related variables.

trend toward OS with locoregional radiotherapy for women with limited nodal involvement (1–3 lymph nodes) following breast-conserving surgery. In all but one study included in the EBCTCG meta-analysis, the adjuvant locoregional radiotherapy volume included the IMN site.

Inclusion of the IMN results in increased radiation to the heart, particularly for left-sided tumours. The Stockholm group has reported higher risks of ischemic heart disease following high doses of radiation to the myocardium. When cardiac morbidity was compared between left- and right-sided breast cancers following surgery and adjuvant radiotherapy, a 0.4% absolute increase in risk of acute myocardial infarction was observed.⁶ As irradiation of the IMN chain is associated with higher radiation doses to the heart, the relative benefit of irradiating this regional site needs to be balanced with the relative increase in toxicity. With newer techniques of radiotherapy delivery, it may be feasible to reduce the dose delivered to heart while treating the IMN chain.

Several prior retrospective studies comparing outcomes for patients treated with and without IMN irradiation have failed to demonstrate any improvement in 10-year OS.⁷⁻⁹ However, criticism of these reviews included significant heterogeneity in the patient groups regarding risk of nodal involvement, radiation delivery technique and chemotherapy treatment. This large retrospective review supports that inclusion of the IMN in the adjuvant locoregional radiotherapy volume is not associated with improved outcomes. The main strength of this study is the large number of patients treated within a provincial program with established guidelines for adjuvant therapy. Limitations include the retrospective

nature and relatively short followup to demonstrate a difference in the outcomes of BCSS and OS.

The early results of a prospective Finnish trial comparing adjuvant breast radiotherapy with and without IMN irradiation in women with Stages I and II breast cancer following breast-conserving surgery has reported no difference in lung or skin toxicity after a short median followup of 2.7 years.¹⁰ Breast-cancer specific outcomes and long-term cardiac and lung toxicity endpoints have not yet been reported from this study. Until results from such prospective randomized studies are available, the decision to include the IMN chain in the radiotherapy program will require discussion of the potential benefits and toxicities between the patient and treating physician. Ongoing advances in radiation delivery techniques may improve the therapeutic ratio of adjuvant radiotherapy for breast cancer by allowing for treatment of all areas at risk of microscopic disease, including the internal mammary nodes, while minimizing the dose to normal tissues such as the heart and lungs.

References

1. Caceres E. Incidence of metastasis in the internal mammary chain in operable carcinoma of the breast and 5 year results. *Acta Unio Int Contra Cancrum* 1963;19:1566-9.
2. 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* 2005;97:116-26.
3. Overgaard M, Jensen MB, Overgaard J et al. Postoperative radiotherapy in high-risk postmenopausal breast-cancer patients given adjuvant tamoxifen: Danish Breast Cancer Cooperative Group DBCG 82c randomised trial. *Lancet* 1999;353: 1641-8.
4. Overgaard M, Hansen PS, Overgaard J et al. Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy. Danish Breast Cancer Cooperative Group 82b Trial. *N Engl J Med* 1997;337:949-55.
5. 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* 2005;366:2087-106.
6. Rutqvist LE, Lax I, Fornander T, Johansson H. Cardiovascular mortality in a randomized trial of adjuvant radiation therapy versus surgery alone in primary breast cancer. *Int J Radiat Oncol Biol Phys* 1992;22:887-96.
7. Obedian E, Haffty BG. Internal mammary nodal irradiation in conservatively-

IN BRIEF

Already known

- Adjuvant locoregional radiotherapy to the breast/chest wall and locoregional lymph nodes, including the internal mammary nodes, results in better outcomes in women with node-positive or high-risk node-negative breast cancer.

What this study showed

- With a relatively short median followup of 6.2 years, inclusion of the internal mammary chain did not demonstrate added benefit to irradiation of the breast/chest wall and axillary regional lymph nodes.

Next steps

- Advances in radiation delivery techniques may minimize normal tissue dose when treating the regional lymph nodes and breast/chest wall.
- Prospective studies randomizing patients to locoregional radiotherapy with or without IMN irradiation are needed.
- Advanced staging investigations will improve selection of patients for IMN irradiation.

- managed breast cancer patients: is there a benefit? *Int J Radiat Oncol Biol Phys* 1999;44:997-1003.
8. Arriagada R, Lê MG, Mouriessse H et al. Long-term effect of internal mammary chain treatment. Results of a multivariate analysis of 1195 patients with operable breast cancer and positive axillary nodes. *Radiother Oncol* 1988;11:213-22.
 9. Fowble B, Gray R, Gilchrist K et al. Identification of a subgroup of patients with breast cancer and histologically positive axillary nodes receiving adjuvant chemotherapy who may benefit from postoperative radiotherapy. *J Clin Oncol* 1988; 6:1107-17.
 10. Kaija H, Maunu P. Tangential breast irradiation with or without internal mammary chain irradiation: results of a randomized trial. *Radiother Oncol* 1995; 36:172-6.