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ADVANCES IN RADIOTHERAPY SPECIAL FEATURE: COMMENTARY

Regional radiotherapy in high-risk breast cancer: is the issue solved?

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ABSTRACT

Adjuvant radiotherapy is the treatment standard for breast cancer with lymph node metastases after breast-conserving surgery or mastectomy. The inclusion of regional lymph nodes into the treatment volumes has been a question in recent clinical trials. Their impact on treatment standards and open questions is discussed.

Radiotherapy plays an essential role in adjuvant treatment of breast cancer after breast-conserving surgery and in high-risk patients after mastectomy. However, the indications for inclusion of regional lymph nodes into radiotherapy treatment volumes have changed and are currently not homogeneously applied between countries and often not even between institutions in the same country. This commentary will focus on the indication for radiotherapy in patients with 1–3 lymph node metastases and on the use of regional radiotherapy, including parasternal irradiation in high-risk patients.

Whereas the inclusion of the supra-/infraclavicular and upper axillary regions in high-risk patients with four or more involved lymph nodes is a treatment standard worldwide, the indications for local or locoregional radiotherapy in intermediate-risk patients with 1–3 lymph node metastases has long been a matter of discussion. In previous years, increasing evidence was provided support that post-mastectomy radiotherapy in this patient group is an advantage. In a subgroup analysis of randomized trials of the Danish Breast Cancer Group (DBCG82b/c) on 1152 node-positive patients with at least 8 lymph nodes removed by axillary dissection, radiotherapy to the chest wall, periclavicular, axillary and parasternal lymph nodes significantly reduced the rate of locoregional recurrences in both patients

with 1–3 or with >3 involved lymph nodes compared with those with no radiotherapy. More important, the 15-year survival was also significantly improved in both patient groups.¹ This has been confirmed by a recent meta-analysis of the Early Breast Cancer Trialists' Collaborative Group on the value of post-mastectomy radiotherapy of the chest wall, periclavicular, axillary and parasternal lymph nodes, which included 8135 females treated within 22 randomized trials. This analysis demonstrated that post-mastectomy radiotherapy leads to the same relative benefit in terms of locoregional tumour control as well as overall survival in the patient groups with 1–3 involved nodes as for patients with >3 lymph node metastases.² While these data provide a clear basis for the routine clinical use of post-mastectomy radiotherapy in the group of patients with 1–3 lymph node metastases, they did not answer the question whether local or locoregional radiotherapy should be applied.

This latter question was addressed within the Canadian NCIC-CTG MA20 randomized trial, where 1832 patients with high-risk factors (of those 85% with lymph node metastases) after breast-conserving surgery received radiotherapy to the breast with or without additional regional radiotherapy to level III axillary, periclavicular and parasternal lymph nodes. Preliminary data showed a small but significant improvement of locoregional disease-free and

overall survival by approximately 2% (from 94.5% to 96.8% and from 90.7% to 92.3%, respectively). Interestingly, metastases-free survival was significantly improved by the addition of regional radiotherapy from 87.0% to 92.4%.³ Similar results were obtained within the European Organisation for Research and Treatment of Cancer (EORTC) trial including 4004 patients randomized between inclusion or exclusion of the parasternal and medial supraclavicular nodes into locoregional radiotherapy.⁴

The DBCG IMN study on 3072 patients applied locoregional radiotherapy, including parasternal lymph nodes only in right-sided and without parasternal lymph nodes in patients with left-sided breast cancer after mastectomy or breast-conserving radiotherapy.⁵ Inclusion of parasternal lymph nodes into the treatment volume again significantly improved the overall survival (75% vs 78%). For patients treated in the DBCG IMN study, it was estimated that the number needed to treat with IMN RT to avoid 1 death at 7 years was 33 patients, whilst in the “worst-case” scenario, the number of patients with no heart disease treated at an age of 50 years to cause 1 cardiac death at 10 years after parasternal radiotherapy was 3333.⁶ Only the smallest trial reported so far, the French multi-centre randomized trial including 1334 patients failed to show a survival benefit after addition of parasternal radiotherapy to radiotherapy of the chest wall, axilla and supraclavicular nodes.⁷ In none of the trials was increased cardiac mortality reported after parasternal irradiation after average follow-up times of 10 years, however, final conclusions still need longer follow-up.

In light of the overall conclusive results from the trials performed to date, the indication for adjuvant radiotherapy after mastectomy for patients with 1–3 involved lymph nodes should no longer be a matter of discussion. For the issue of inclusion of regional nodes, specifically parasternal nodes into the treatment volume, of patients with high-risk factors, it has to be concluded that this extension of the radiotherapy treatment volume leads to a small but significant improvement of survival for the average of the patient population, obviously by decreased distant metastases. Some countries (e.g. Denmark) considered this evidence by defining locoregional radiotherapy including parasternal radiotherapy as a treatment standard in all patients with

lymph node metastases as well as in patients with pT3 tumours. Other countries (e.g. Germany) are still more ambiguous and recommend leaving the indication for the inclusion of parasternal lymph nodes to individual decision.⁸ Independent of such national differences in guidelines, the comparably small survival benefit after complete regional radiotherapy (including parasternal irradiation) can easily be outweighed in individual patients if, for example, cardiac sparing is not sufficiently considered. To take advantage of such small benefit, the use of radiotherapy techniques that optimize cardiac sparing is warranted and individual specific anatomical situations that hinder sufficient cardiac sparing should lead to a discussion of omission of parasternal radiotherapy in these patients. Whether longer follow-up or further subgroup analyses of the randomized trials will help to potentially define patients who benefit more from parasternal radiotherapy needs to be awaited.

Another issue is the opposite treatment strategy, that is, treatment de-escalation, for patients with clinically negative but sentinel-node-positive axillary lymph nodes. These patients have been treated with similar success by axillary dissection or by locoregional radiotherapy of the remaining breast or thoracic wall and the axillary and parasternal lymph nodes⁹ or by local radiotherapy of the breast or thoracic wall alone.^{10,11} Specifically, the patient cohorts of the Z0011 trial¹⁰ and the AMAROS trial⁹ show substantial overlap with those who received complete locoregional radiotherapy after surgical axillary treatment within the above-mentioned studies. As the results of these three trials do not contradict each other, it can currently only be concluded that axillary surgery may be omitted in specific groups of patients and that at least some of these patients likely benefit from regional radiotherapy.

For future translational studies, the evaluation of molecular markers or genetic profiling of breast cancer to stratify patients for potential treatment decisions for or against regional radiotherapy will be of utmost importance. On a mid-term scale, such individualized strategies should not only include risk factors given by the tumour disease but also patient-related dose-volume-related risk factors for the development of toxicities.

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