Annals of Oncology 26: 1043–1044, 2015
doi:10.1093/annonc/mdv162
Published online 7 April 2015

Determining the indications for post mastectomy radiotherapy: moving from 20th century clinical staging to 21st century biological criteria

In the era of effective systemic therapy, the decision on whether or not to recommend post-operative adjuvant radiotherapy for intermediate risk breast cancer remains a point of discussion in many multidisciplinary tumour board meetings. Variations in advice regarding post-mastectomy radiotherapy have been demonstrated within the context of guideline-based practice [1]. A recent survey of nodal irradiation policy in European Organisation for Research and Treatment of Cancer (EORTC) centres also demonstrated a wide variation in practice [2].

On the one hand, there is level 1 evidence for a significant survival benefit from the addition of post mastectomy radiotherapy, including the chest wall from the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) overview for patients with nodal metastases, including low-volume N1 disease [3]. There is also increasing evidence for the addition of peripheral nodal irradiation in early breast cancer from two recently reported trials. One is the EORTC internal mammary chain and medial supraclavicular radiation (IM-MS) trial, reported by Poortmans et al. and the other is the National Cancer Institute of Canada Clinical Trials Group NCIC CTG M.20 trial of comprehensive regional nodal irradiation in patients treated with breast conserving therapy (Whelan et al, both papers currently in press in the *New England Journal of Medicine*). On the other hand, the increasing use of effective systemic therapy, often not available or applied to the patients included in the aforementioned trials, has improved the overall survival in patients with pN1 disease, i.e. one to three nodal metastases. The EBCTCG overview is dominated by the data from the Danish Breast Cancer Cooperative Group trials (1441 of 2801 patients with one to three positive nodes). Even in the subgroup analysis of the DBCG 82b and 82c trials in which at least eight nodes were removed from the axilla, the locoregional recurrence rate was very high (27%) in the non-irradiated group [4]. In addition, the adjuvant chemotherapy regime of cyclophosphamide, methotrexate and 5-FU (CMF) used in the 82b trial is currently considered suboptimal. Anthracycline-based chemotherapy with or without taxanes has replaced CMF as the current standard for women with one to three positive nodes and confers a significant survival advantage over CMF [5]. Five years of Tamoxifen or longer has been shown to improve survival compared with shorter treatment duration [6, 7], and Her-2 neu inhibition was not available at the time of the trials included in the overview. Therefore, although the relative risk reduction from radiotherapy might be significant, the absolute gains may only be modest.

Punglia et al. [8] have suggested a bell-shaped curve to describe the effect of improving local control with local therapy in relation to the effectiveness of systemic therapy, a concept adapted by Poortmans [9]. The basic concept is that with increasing effectiveness of systemic therapy, the survival gain from improving local control with radiotherapy improves as the metastatic risk decreases, but only up to a certain level, and beyond that it lowers again. Furthermore, any benefits have to be weighed against potential long-term toxicity of the treatment. As a result, many national evidence-based guidelines set caveats in their advice regarding adjuvant post mastectomy radiotherapy, or radiotherapy to the regional lymph nodes, or do not advise it at all [10, 11].

The article by Nordenskjöld et al. 'No clear effect of post-operative radiotherapy on survival of breast cancer patients with 1–3 positive nodes' in this issue is very relevant to the current debate, as the results described are non-concordant with the results of the EBCTCG overview, and the recently published nodal radiotherapy trials. This epidemiological study describes a population-based analysis of 4448 patients treated in the years 1989–2006 in two Swedish regions, with/without adjuvant chest wall or regional nodal radiotherapy. Apart from the radiotherapy policy, the treatment protocol of these two regions was identical. Patients with one to three positive nodes on axillary dissection all received optimal systemic therapy, based on the St Gallen breast cancer panel recommendations at the time. The relative survival analysis demonstrated no difference in survival between the two regions related to addition or omission of post mastectomy radiotherapy, or regional nodal radiotherapy. This is contradictory to the overview results, and the authors suggest that the use of modern systemic therapy may, in part, explain these results.

We hope that some of the issues raised will be resolved with data from the BIG 02-04 MRC EORTC SUPREMO trial, which recruited >1600 patients between April 2007 and May 2013 [12]. This trial included patients with intermediate risk stage II breast cancer after mastectomy who also received modern systemic therapy. Patients were prospectively randomized to receive chest wall radiotherapy or not. However, the final results of this trial are expected in 2023 at the earliest.

In the meantime, the policy regarding adjuvant radiotherapy for intermediate risk breast cancer is becoming more difficult to extrapolate from trials such as those included in the overview, all of which included some degree of axillary dissection. The staging axillary dissection is increasingly being replaced by the sentinel node procedure. The results of the recent EORTC AMAROS trial [13] will probably lead to an increased use of primary axillary radiotherapy for patients with a positive sentinel node, instead of axillary clearance.

In addition, neoadjuvant systemic therapy is increasingly used for stage II disease, making decisions based on the post (chemo-)therapy staging complex. Should we determine radiotherapy indications based on pre-treatment TNM classification, or should we adapt radiotherapy policy based on the down-staging achieved with neoadjuvant systemic treatment? In the SUPREMO trial, patients with neoadjuvant and post-operative adjuvant systemic therapy were both included in the randomisation, so the results will hopefully be relevant for future treatment scenarios as well.

The indications for systemic therapy are increasingly based on biological characteristics of the tumour. It can be anticipated that, in the future, the indications for post mastectomy radiotherapy (and/or regional nodal therapy) may also be increasingly guided by the individual tumour prognostic and predictive scores based on tumour biology, rather than anatomical staging. With regard to prognostic tests for local recurrence, studies of the Oncotype DX® [14] and Mammprint® [15] have demonstrated that gene profiling not only predicts for distant metastases, but also for locoregional recurrence after mastectomy or breast conserving therapy. The study with Oncotype DX® from Manounas et al. only investigated patients with node-negative, ER-positive disease recruited into systemic therapy trials. None of the mastectomy patients received radiotherapy, making the results less applicable to mastectomy patients with N1 disease. In the study of the 70-gene Mammaprint® profile, 298 patients were included after mastectomy, of which about half had received chest wall and/or internal mammary chain irradiation. The stratification into high-risk and low rick Mammaprint® profile improved on the risk estimation based on a model of clinical–pathological risk factors for locoregional recurrence in the irradiated mastectomy patients. However, the profile could not improve the performance of the clinical–pathological model between locoregional recurrence risk in the unirradiated mastectomy patients. More recently, a 4-gene profile was reported to identify patients at very low risk of locoregional recurrence based on a retrospective subset analysis of the Danish breast Cancer Cooperative Group post mastectomy trials 82 band 82c [16]. Unfortunately, these and similar studies do not seem to allow us, as yet, to incorporate gene profiles based on contemporary trials in the decision whether or not to advise local therapy. The studies discussed were retrospective analyses, so with inherent biases regarding for example radiotherapy indication. In the TRANS-SUPREMO sub-study, blood and tumour tissue from mastectomy patients who were entered into the BIG 02-04 MRC EORTC SUPREMO trial was collected at entry into the trial. So far, over a 1000 tumour samples have been stored on tissue microarrays. This will provide an invaluable bio-bank for future studies to address the issue of which biological parameters will help to provide additional discriminatory value to improve how we can individualise treatment policy in the 21st century.

N. S. Russell[1]*, I. H. Kunkler[2] & G. van Tienhoven[3]
[1]Department of Radiotherapy, The Netherlands Cancer Institute–Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands;
[2]Department of Oncology, Western General Hospital, University of Edinburgh, Edinburgh, UK;
[3]Radiation Oncology and Hyperthermia, Academic Medical Center, Amsterdam, The Netherlands
(*E-mail: n.russell@nki.nl)

disclosure

The authors have declared no conflicts of interest.

references

1. Punglia RS, Hughes ME, Edge SB et al. Factors associated with guideline-concordant use of radiotherapy after mastectomy in the national comprehensive cancer network. Int J Radiat Oncol Biol Phys 2008; 72: 1434–1440.
2. Belkacemi Y, Kaidar-Person O, Poortmans P et al. Patterns of practice of regional nodal irradiation in breast cancer: results of the European Organization for Research and Treatment of Cancer (EORTC) NOdal Radiotherapy (NORA) survey. Ann Oncol 2015; 26: 529–535.
3. McGale P, Taylor C, Correa C et al. Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. Lancet 2014; 383: 2127–2135.
4. Overgaard M, Nielsen HM, Overgaard J. Is the benefit of postmastectomy irradiation limited to patients with four or more positive nodes, as recommended in international consensus reports? A subgroup analysis of the DBCG 82 b&c randomized trials. Radiother Oncol 2007; 82: 247–253.
5. Peto R, Davies C, Godwin J et al. Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100,000 women in 123 randomised trials. Lancet 2012; 379: 432–444.
6. Davies C, Godwin J, Gray R et al. Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. Lancet 2011; 378: 771–784.
7. Davies C, Pan H, Godwin J et al. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. Lancet 2013; 381: 805–816.
8. Punglia RS, Morrow M, Winer EP, Harris JR. Local therapy and survival in breast cancer. N Engl J Med 2007; 356: 2399–2405.
9. Poortmans P. Postmastectomy radiation in breast cancer with one to three involved lymph nodes: ending the debate. Lancet 2014; 383: 2104–2106.
10. Harnett A, Smallwood J, Titshall V, Champion A. Diagnosis and treatment of early breast cancer, including locally advanced disease--summary of NICE guidance. BMJ 2009; 338: b438.
11. Recht A, Edge SB, Solin LJ et al. Postmastectomy radiotherapy: clinical practice guidelines of the American Society of Clinical Oncology. J Clin Oncol 2001; 19: 1539–1569.
12. Kunkler IH, Canney P, van Tienhoven G, Russell NS. Elucidating the role of chest wall irradiation in 'intermediate-risk' breast cancer: the MRC/EORTC SUPREMO trial. Clin Oncol (R Coll Radiol) 2008; 20: 31–34.
13. Donker M, van Tienhoven G, Straver ME et al. Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981–22023 AMAROS): a randomised, multicentre, open-label, phase 3 non-inferiority trial. Lancet Oncol 2014; 15: 1303–1310.
14. Mamounas EP, Tang G, Fisher B et al. Association between the 21-gene recurrence score assay and risk of locoregional recurrence in node-negative, estrogen receptor-positive breast cancer: results from NSABP B-14 and NSABP B-20. J Clin Oncol 2010; 28: 1677–1683.
15. Drukker CA, Elias SG, Nijenhuis MV et al. Gene expression profiling to predict the risk of locoregional recurrence in breast cancer: a pooled analysis. Breast Cancer Res Treat 2014; 148: 599–613.
16. Tramm T, Mohammed H, Myhre S et al. Development and validation of a gene profile predicting benefit of postmastectomy radiotherapy in patients with high-risk breast cancer: a study of gene expression in the DBCG82bc cohort. Clin Cancer Res 2014; 20: 5272–5280.