Leading article

Axillary conservation in early breast cancer

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Management of the axilla is controversial. There has never been a widely agreed means of balancing an understanding of nodal status as prognostic information, the need to prevent axillary recurrence and the wish to avoid treatment-related morbidity, particularly arm lymphoedema.

Balancing these conflicting requirements is difficult, particularly as the results of previous trials of locoregional therapy in early breast cancer are less relevant in these days of earlier (commonly screen-detected) presentation, more detailed pathological assessment, improved systemic therapies, and better surgery and radiotherapy. Improved outcomes and a reduced risk of locoregional recurrence are welcome, but make it difficult to conduct contemporary clinical trials, particularly those that attempt to reduce the intensity of treatment in an effort to reduce morbidity. Recent developments and clinical research concerning axillary management need to be appreciated in this context.

The routine use of axillary node clearance (ANC) or axillary radiotherapy (ART) for the clinically node-negative axilla was replaced by the use of image-guided biopsy to confirm nodal involvement before axillary treatment, and more recently by sentinel lymph node biopsy (SLNB) to establish nodal status.

The avoidance of ANC and the lymphoedema it so commonly causes in node-negative early breast cancer following the introduction of SLNB represents one of the most significant advances in early breast cancer management over the past 15 years.

Since the widespread adoption of SLNB and the refinement of histopathological methods to quantify the degree of involvement of positive nodes, there have been further efforts to define the best local treatment for the sentinel node-positive patient. It is now clear that patients with isolated tumour cells (ITCs) or micrometastases (deposits of 2 mm or less in diameter) in these nodes do not require further intervention to the axilla, as the risk of axillary recurrence is very low and not influenced by further surgery or radiotherapy[1].

Until recently, the majority of patients with macrometastases (deposits larger than 2 mm) in the sentinel lymph node were routinely treated with ANC or ART. The publication of the American College of Surgeons Oncology Group Z0011 (Alliance) trial in 2010 challenged this practice[2].

The Z0011 trialists planned to recruit 1900 patients with T1–2 breast cancer and one or two involved sentinel lymph nodes treated with breast-conserving surgery. Patients were randomized to completion ANC or no further axillary surgery over a 4-year recruitment period. All patients were required to have whole-breast radiotherapy without any additional radiation to the axilla or supraclavicular regions. Systemic therapy was given at the discretion of the investigators.

Overall, disease-free and locoregional recurrence-free survival were no different between groups, but surgical morbidities including lymphoedema were significantly lower in the SLNB-only group.

The need for routine axillary therapy in this patient group came under question, and a more conservative approach to the axilla was rapidly adopted in the USA following the publication of the results of Z0011[2]. The American Society of Clinical Oncology has advised that ANC/ART can be avoided in patients with node-positive early breast cancer if their circumstances reflect the Z0011 eligibility criteria[3].

There are, however, many concerns about this trial that limit the interpretation and application of its results. Recruitment was less than 50 per cent of predicted, and involved 115 centres. Around 20 per cent of patients were lost to follow-up, information on nodal status was missing in 11 per cent of patients, there was no surgical quality assurance, and overall survival rather than axillary recurrence was chosen as the primary endpoint. Additionally, around half of the patients had micrometastatic disease (for which avoidance of further axillary therapy is routine), leaving 430 patients with axillary nodal macrometastases.

Perhaps the most significant concern related to the lack of prospective quality control for radiotherapy; this allowed the possibility that radiation oncologists, aware of the type of axillary surgery performed, may have introduced bias by adjusting radiotherapy to treat the axilla in those patients treated by SLNB alone[4].

The concerns about radiotherapy prompted an evaluation of this treatment within the trial, revealing an inconsistent practice with

a significant proportion of major protocol violations[5].

Modern locoregional management of breast cancer requires the careful integration of surgery and radiotherapy. This principle was not reflected in the conduct of the Z0011 trial, and this serious flaw invalidates the conclusion that patients with macrometastatic disease in sentinel lymph nodes do not require further axillary intervention.

Paradoxically, recent trials designed to assess the influence of regional radiotherapy have demonstrated improved outcomes following the addition of regional radiotherapy[6]. The National Cancer Institute of Canada Clinical Trials Group (an intergroup trial of regional nodal irradiation in early breast cancer) and European Organization for Research and Treatment of Cancer (EORTC radiation oncology and breast cancer groups phase III trial 22922–10925) trials assessed the impact of radiation to the internal mammary and medial supraclavicular nodes, and the French randomized trial of irradiation of internal mammary nodes after mastectomy was designed to assess the impact of internal mammary node irradiation alone[6].

Overall, disease-free and metastasis-free survival were all improved by the addition of regional radiotherapy. These trials did not directly study outcomes in the context of specific axillary management, but do suggest that treatment of nodal draining areas improves outcome even without any effect on the risk of locoregional recurrence.

In further support of the benefits of regional radiotherapy, the Early Breast Cancer Trialists' Collaborative Group recently published an overview of the older trials of postmastectomy radiotherapy and axillary surgery[7]. Regional radiotherapy was administered in the majority of the trials. After mastectomy and axillary dissection, radiotherapy reduced both recurrence and breast cancer mortality in women with positive lymph nodes, even when systemic therapy was given.

Knowledge of the extent of nodal involvement is required for oncological decision-making in contemporary practice. The most important prognostic factor for locoregional recurrence, and the most influential in terms of decisions concerning postmastectomy radiotherapy, is the extent of nodal involvement[7].

In addition, although decisions concerning systemic therapies are increasingly influenced by pathological/molecular phenotype, stage-dependent factors – particularly the extent, and not just the presence, of nodal involvement – are widely used and critical in the use of available prognostic and predictive models including Adjuvant! Online, Predict, LifeMath and the Nottingham Prognostic Index.

The undoubted benefits of systemic therapies in reducing locoregional as well as systemic recurrence[8], and the earlier stage of disease that is now more commonly encountered, mean that efforts to reduce the morbidity associated with locoregional treatment are a priority, but caution and carefully designed prospective trials are needed. The UK POSNOC (POsitive Sentinel NOde: adjuvant therapy alone *versus* adjuvant therapy plus Clearance or axillary radiotherapy) trial[9] will help to define further the role of axillary treatment in patients with macrometastatically positive sentinel lymph nodes. The UK Association of Breast Surgeons is also formulating a cautious multidisciplinary consensus guideline in this difficult area[10].

One of the greatest advances in the management of early breast cancer over the past two to three decades is the profound reduction in uncontrolled locoregional failure. The laudable desire to reduce morbidity must not come at the cost of poorer outcomes in terms of locoregional recurrence or survival.

Recent trials of regional therapy in early breast cancer have provided conflicting results, and acceptance of a practice of routinely avoiding further axillary treatment to the macrometastatically node-positive axilla on the basis of current evidence is premature.

Disclosure

A.G. is Chief Investigator for the POSNOC trial, and D.D. is a member of the trial management group. The authors declare no conflict of interest.

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