



Axillary conservation in women with 1–2 sentinel node-positive breast cancer: Further research is needed

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The practice of completion axillary dissection after a positive sentinel node biopsy in women with early breast cancer has been declining.¹ The morbidity associated with axillary dissection can be disabling and impair quality of life. Axillary conservation spares patients the common complications of lymphoedema, pain, neuropathy, and restricted shoulder movement.

This change in practice followed the publication of the American College of Surgeons Oncology Group (ACOSOG) Z-11 randomised trial. In this study, 891 patients with 1–2 positive sentinel lymph nodes (SLNs) who underwent breast-conserving surgery for a primary tumour ≤ 5 cm and were clinically node-negative at diagnosis were randomised to axillary dissection or not. Adjuvant whole breast irradiation was mandatory but information on radiation doses and treatment volumes was not available. The majority of patients received adjuvant systemic therapy. In the axillary dissection group, 27% of patients had additional involved lymph nodes. At a median follow-up of nine years, there was no difference in axillary recurrence rates ($\leq 1.1\%$) between the two groups. No difference in local recurrence rates,

disease free survival (DFS) or overall survival was observed.

Two other recent studies indicated that axillary dissection did not improve outcomes. The International Breast Cancer Study Group 23-01 trial of 934 patients investigated the role of axillary dissection or not in patients with a primary tumour ≤ 5 cm who had axillary micrometastases in 1–2 SLNs. In the axillary dissection group 13% had additional involved lymph nodes but there was no difference in local recurrence (2%), regional recurrence ($\leq 1\%$), disease free survival or overall survival at a median follow-up of five years. In the European Organisation for Research and Treatment of Cancer (EORTC) AMAROS trial, 1425 patients with positive SLNs were randomised to axillary dissection or axillary irradiation. In the axillary dissection group, 33% had additional involved lymph nodes. With a median follow-up of five years, there was no difference in axillary recurrence rates ($\leq 1\%$), DFS or overall survival between the two groups. The 5-year rate of lymphoedema was 11% in the axillary radiation arm compared to 23% in the axillary dissection arm.

These studies have led to axillary conservation being increasingly adopted for patients with 1–2 positive SLNs. In many circumstances axillary dissection may now be overtreatment in an era of early detection of breast cancer and effective systemic therapy. For women in whom further axillary management is deemed appropriate, the AMAROS results suggest that axillary radiotherapy may be a justifiable alternative to further surgery.

There is a significant controversy in the adoption of axillary conservation for patients with 1–2 positive SLNs. The controversy may be attributed to conflicting interpretations of the published evidence, discrepancies in treatment guidelines and variability in opinion and practice. There is concern about omitting axillary dissection for all patients who meet the ACOSOG Z-11 trial eligibility criteria and those who are outside the eligibility criteria. It is notable that 38% and 45% of patients in the axillary dissection arm and no dissection arm, respectively, had nodal micrometastases only. There are also concerns regarding the omission of axillary dissection in patients treated with mastectomy or primary systemic therapy, and patients with a primary tumour of unfavourable pathology.

The controversy is compounded by the uncertainty among radiation oncologists concerning the need for axillary radiotherapy in patients with positive SLNs who have not had further axillary surgery. A prospective radiotherapy quality assurance programme was not incorporated in the ACOSOG Z-11 trial. Detailed radiotherapy records were available in 26% of patients. Central review of these records showed that 11% of patients did not receive radiotherapy at all; 50% of patients received whole breast irradiation using high tangents that encompassed level 1 and some of level 2 axillary nodes and 19% of patients received directed regional nodal radiotherapy using a third field.² Although these findings do not indicate that regional nodal irradiation is necessary or beneficial in patients with 1–2 positive SLNs, they suggest that it may be a reasonable option in selected patients.

The controversy surrounding axillary conservation in patients with 1–2 positive SLNs is further intensified by recent studies reporting improved outcomes associated with regional nodal irradiation.³ With a median follow-up of 9.5 years, the National Cancer Institute of Canada Clinical Trials Group MA.20 trial of 1832 patients reported that regional nodal irradiation in addition to whole-breast irradiation after breast-conserving surgery and axillary dissection not only decreased local-regional recurrence but was associated with a statistically significant improvement in DFS with a trend to improved overall survival. Seventy-four percent of study participants had 1–2 positive axillary nodes, and the majority of patients received adjuvant systemic therapy. The regional radiation target volume included the supraclavicular and internal mammary nodes, and in patients with >3 positive nodes or <10 dissected nodes, the axilla. Results of other

studies of regional nodal irradiation including the EORTC 22922-10925 randomised trial and the Danish Breast Cancer Group cohort study also suggest that comprehensive local-regional therapy may contribute to improved overall survival. However, underpinning the controversy of axillary conservation in patients with positive sentinel nodes is that these studies of regional nodal irradiation were not able to distinguish the benefit of axillary dissection or radiotherapy from supraclavicular or internal mammary nodal irradiation.

In 2014, the Early Breast Cancer Trialists Collaborative Group individual patient data meta-analysis of post-mastectomy radiotherapy trials reported improved DFS and breast-cancer-specific survival in patients with node-positive disease, irrespective of the number of involved lymph nodes.⁴ This has led to some centres routinely offering post-mastectomy radiotherapy to all node-positive patients. However, the limitation of the overview is that the women included were treated between 1964–86. It remains unclear if the results are applicable to women treated in the contemporary era.

At present, there are conflicting data and insufficient evidence to support routine omission of completion axillary dissection and radiotherapy in patients with macrometastases in 1–2 SLNs. The pragmatic UK/Australia and New Zealand POSNOC randomised non-inferiority trial offers a carefully designed research platform to further investigate this approach and address deficiencies in the published literature. Patients with a primary tumour ≤5 cm and macrometastases in 1–2 SLNs are randomised to receive adjuvant therapy alone or adjuvant therapy and completion axillary dissection or axillary radiotherapy.⁵ In distinction from ACOSOG Z-11 trial, patients who have undergone mastectomy are included in the POSNOC study. Adjuvant therapy includes systemic therapy for all patients, and ipsilateral breast or chest wall irradiation as per pre-defined local guidelines. In the adjuvant therapy alone arm, axillary irradiation by adjustment of the superior and posterior tangential borders is not permitted. Importantly, integral to POSNOC is a comprehensive radiotherapy quality assurance programme.

In Australia and New Zealand, the POSNOC study is conducted under the auspices of Breast Cancer Trials (<https://www.breastcancertrials.org.au/current-clinical-trials/posnoc>). As of 24 July 2018, 1100 of 1900 women have been randomised to the POSNOC study. The axilla has long been a source of controversy in the management of early breast cancer where opinion and evidence have not always been aligned. Despite the often strongly expressed views, there remains significant uncertainty over optimal axillary management and high-level evidence from robustly designed and conducted randomised trials is necessary to resolve the uncertainty. Strong international efforts to complete recruitment to the POSNOC study is essential for generating the critical data to resolve the recurring debate surrounding axillary

conservation and enable evidence-based, individualised care of patients with macrometastases in 1–2 SLNs.

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