Axillary lymph node clearance in patients with positive sentinel lymph node biopsy

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ABSTRACT

INTRODUCTION The use of adjuvant radiotherapy is standard practice following breast conserving surgery and mastectomy in selected patients. Prospective clinical trials are currently being designed to assess the effect of omitting axillary lymph node clearance (ALNC) in selected patients. The aim of this study was to identify the percentage of patients understaged and not considered for postmastectomy radiotherapy (PMRT) and/or supraclavicular fossa radiotherapy (SCFRT) with positive sentinel lymph node (SLN) macrometastasis if the proposed prospective trial inclusion/exclusion protocols are followed.

METHODS A total of 38 women who were found negative for axillary metastases preoperatively but positive at SLN biopsy and who had ALNC were analysed. PMRT or SCFRT was offered to patients if ≥ 4 positive lymph nodes (including sentinel nodes) were positive for macrometastasis and/or a tumour size of ≥ 5 cm was detected. Fisher's exact test was used to determine the statistical significance of omitting ALNC.

RESULTS The mean age of the 38 patients was 55 years. A fifth (21.1%) of patients had T1, 76.3% had T2 and 2.6% had T3 disease. The percentage of positive SLNs was 52.6% (1 node), 34.2% (2 nodes) and 13.1% (3 nodes). The number of positive nodes at clearance was 0–3. If the inclusion criteria for trials that consider omitting ALNC are followed (eg POSNOC trial), 23.7% of patients ($p=0.0001$) with ≥ 4 positive nodes (including SLNs) would not be offered SCFRT and PMRT. Similarly, if multicentric disease were to be excluded from the trial criteria, the proportion of undertreated patients would reduce by 15.7%.

CONCLUSIONS Our study has shown a significant risk of missing patients for PMRT or SCFRT if no ALNC is offered in the presence of SLN macrometastasis. Tumour multicentricity is an important factor in predicting high axillary nodal involvement. Consequently, exclusion of T2 tumours with multicentric involvement in trials considering omitting ALNC may be more appropriate.

KEYWORDS

Radiotherapy – Mastectomy – Sentinel node – Axillary clearance

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Adjuvant radiotherapy to the breast following breast conserving surgery has become standard for breast cancer patients. It helps achieve local disease control and is offered routinely across all subgroups of invasive breast cancers as well as certain types of ductal in situ disease. In contrast, adjuvant radiotherapy to the chest wall following mastectomy (postmastectomy radiotherapy [PMRT]) and/or supraclavicular fossa radiotherapy (SCFRT) is offered selectively across the patient groups.

The clinical indications for PMRT and/or SCFRT usually relate to the number of involved axillary nodes and the tumour size. With the results of the American College of Surgeons Oncology Group phase 3 randomised controlled Z0011 trial questioning the need for axillary lymph node clearance (ALNC) in patients with macrometastasis in one or two positive sentinel lymph nodes (SLNs) in early stage

breast cancer following breast conserving surgery and whole breast radiation, axillary understaging affecting the indications for adjuvant PMRT and SCFRT has emerged as a potential risk. Our study aimed to identify the percentage of patients with positive SLNs who would be understaged and therefore not considered for PMRT or SCFRT if no further axillary dissection were offered.

Methods

A total of 38 women who were assessed initially as negative for axillary metastases with ultrasonography and fine needle aspiration (FNA) but found positive at SLN biopsy and who had ALNC were identified. Patient data were collected retrospectively from prospectively recorded patient information from the medical notes. The data were taken

Table 1 T-stage data of the study cohort	
T-stage	Patients
T1	8 (21%)
T2	29 (76%)
T3	1 (3%)

from a single breast unit for patients who attended between January 2011 and March 2012.

All patients in the study had axillary SLNs identified using a dual agent injection technique (patent blue dye and radioactive technetium-99 colloid) as part of our standard clinical practice. SLNs were assessed for macrometastasis using haematoxylin and eosin staining, and patients with nodes positive for macrometastasis were offered delayed completion axillary dissection. Furthermore, as standard practice, patients with locally advanced tumours (≥ 5 cm and/or positive axillary lymph nodes) received neoadjuvant chemotherapy consisting of four cycles of epirubicin ($90\text{mg}/\text{m}^2$) with cyclophosphamide ($600\text{mg}/\text{m}^2$) followed by four cycles of docetaxel ($100\text{mg}/\text{m}^2$), given at three-weekly intervals. All 38 patients had oestrogen and progesterone receptor positive tumours. Nine underwent a mastectomy with initial SLN biopsy and twenty-nine had breast conserving surgery. The absolute indication for SCFRT with/without PMRT in our study included ≥ 4 nodes with macrometastasis and a tumour size of ≥ 5 cm.

A two-tailed Fischer’s exact test was performed to assess the statistical significance of omitting PMRT and/or SCFRT if ALNC was to be omitted. A p -value of <0.05 was considered significant.

Results

The mean patient age was 55 years (range: 35–76 years). The majority of patients (29/38, 76%) had T2 disease. Eight patients (21%) had T1 disease and one patient (3%) had T3 disease (Table 1).

Five patients (13.2%) were found to have three positive SLNs, thirteen (34.2%) had two positive SLNs and twenty (52.6%) had one positive SLN (Table 2). Nine patients (23.7%) were found to have further positive lymph nodes at completion axillary dissection. The number of additional positive nodes at ALNC in the whole cohort ranged from 0 to 3 except for 1 patient in whom all 13 axillary nodes were positive. Eight of the nine patients with additional positive

Table 2 Patient data with positive sentinel lymph nodes	
Positive sentinel nodes	Patients
1 node	20 (53%)
2 nodes	13 (34%)
3 nodes	5 (13%)

Table 3 Clinical data from the axillary lymph node clearance positive patients	
	Number
Patients with positive nodes	9 (23.7%)
T1	1
T2	7
T3	1
Grade 1	0
Grade 2	7
Grade 3	2
2 positive SLNs	9
Plus 2 or 3 additional positive nodes at ALNC	8
Plus >3 additional positive nodes at ALNC	1
Total patients with ≥ 4 positive nodes including SLNs	9 (23.7%)
ALNC = axillary lymph node clearance; SLN = sentinel lymph node	

nodes at ALNC were found to have a further two or three positive nodes and only one patient had >3 positive nodes (Table 3). Almost a quarter of patients from the total study cohort (9/38, 23.6%; $p=0.0001$) were found to have ≥ 4 positive nodes (including SLNs). Six patients (6/38, 15.8%) had multicentric disease.

Discussion

In 2010 the results of the American College of Surgeons Oncology Group Z0011 trial were published.¹ This trial evaluated 891 women with clinical T1–T2 invasive breast cancer with no palpable adenopathy and macrometastasis in either 1 or 2 SLNs randomised to undergo only SLN biopsy or SLN biopsy with ALNC. The findings showed no significant difference in the five-year overall survival (91.8% [95% confidence interval (CI): 89.1–94.5%] vs 92.5% [95% CI: 90.0–95.1%]) or disease free survival (82.2% vs 85.9%) after ALNC and after SLN biopsy only. It was concluded that ALNC did not alter survival in women with limited SLN metastatic breast cancer who underwent breast conservation and received adjuvant systemic cytotoxic and whole breast radiotherapy.

Further to this, a prospective clinical trial, the POSNOC (Positive Sentinel lymph Node: Observation vs Clearance) trial, is being designed in the UK to assess the effect of omitting ALNC in a selected patient group. The inclusion criteria are shown in Table 4. The trial includes: patients of any age group; T1–T2 disease; and clinically, radiologically (axillary ultrasonography) and pathologically (FNA/core biopsy) assessed negative axillary status with multifocal disease.²

Currently, clinical indications to offer adjuvant PMRT and SCFRT to patients with varying risk factors can be categorised into absolute and relative indications. According to the 2012 National Comprehensive Cancer Network

Table 4 POSNOC trial inclusion criteria ²
• Any age
• T1–T2 tumours
• Clinically, radiologically (ultrasonography of the axilla) and pathologically (fine needle aspiration/core biopsy) negative axillary status
• MO
• Multicentric tumours

breast cancer guidelines, absolute indication to offer PMRT and SCFRT includes macrometastasis in ≥ 4 lymph nodes (including SLNs) and/or a tumour size of ≥ 50 mm or a $\geq 20\%$ ten-year risk of locoregional recurrence.^{3–5} Other relative risks such as positivity in 1–3 nodes, lymphovascular invasion, grade 3 disease and age ≤ 35 years are currently being investigated in the ongoing SUPREMO (Selective Use of Postoperative Radiotherapy after Mastectomy) trial (<http://www.supremo-trial.com/>).

We sought to evaluate the potential risks of implementing the Z0011 trial findings in our study cohort and to assess the POSNOC trial protocol. The Hull and East Yorkshire Hospitals NHS Trust treats approximately 500 new breast cancer patients per year. For our study, patient selection was carried out strictly on the basis of axillary assessments that were clinically and radiologically negative as well as being negative according to initial pathology reports. Consequently, only those patients who were found to be clinically node negative but who were later found to have a positive SLN biopsy were included in the study.

Of the 500 new patients attending in the study period, 38 (7.6%) were suitable for analysis, in keeping with the local false negative axillary rates of axillary ultrasonography. The results from our study showed that 23.6% of patients ($p=0.0001$) with ≥ 4 positive nodes would miss PMRT and SCFRT if ALNC were to be omitted. Furthermore, if cases of multifocal tumours were to be excluded from trials considering omitting ALNC, the proportion of undertreated patients who would otherwise have been offered PMRT and/or SCFRT in our study group would reduce by 15.7%.

Although the study has limitations (analysis of mixed groups [patients with and without neoadjuvant therapy], smaller patient numbers, inclusion of patients with ≥ 3 positive SLNs undergoing mastectomy), we conclude that omitting ALNC in patients with positive SLNs can result in an inherent loss of axillary staging information, thereby possibly leading to undertreatment. Moreover, ALNC provides

important information concerning the risk of supraclavicular involvement and influences the design of radiotherapy fields.⁶ Within limitations, the probability of having ≥ 4 axillary lymph nodes involved in patients with positive SLN biopsy can be predicted using known pathological features with nomograms.^{7,8} However, to offer patients PMRT and/or SCFRT in strict accordance with the absolute indications, full axillary staging either on imaging and/or ALNC is an essential prerequisite. With the preoperative staging modalities used currently (eg axillary ultrasonography and FNA) showing a variable rate of diagnostic sensitivities,^{9,10} ALNC for axillary staging continues to remain the gold standard.

Conclusions

Our study has shown a significant risk of missing patients for PMRT and/or SCFRT if the ‘no further axillary treatment’ approach is practised in patients with positive SLN biopsies. Tumour multifocality was found to be an important factor in predicting additional axillary nodal involvement. Based on the study findings, we suggest that exclusion of T2 and above tumours with multifocal involvement in trials considering omitting ALNC may be more appropriate.

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