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Axillary Clearance Following Positive Sentinel Lymph Node Biopsy in Symptomatic Breast Cancer

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Abstract. *Background/Aim: Symptomatic cancers display a different biological behaviour from screen-detected cancers, which may impact the management of axillary metastases. We aimed to determine the role of unselected axillary nodal clearance (ANC) in symptomatic patients with positive sentinel node biopsies (SNBs). Patients and Methods: A case-note review was performed on 95 symptomatic breast cancer patients who underwent ANC following positive SNB. Results: Thirty-eight (40%) patients were treated with a mastectomy and 57 (60%) with breast-conserving surgery. At ANC, 25 patients (26.3%) showed evidence of further lymph node metastases, with 15 (60%) having two or fewer macrometastases. The presence of more than 2 SNB macrometastases was associated with further ANC metastases (p<0.001). The presence of further metastases at ANC was not associated with either reduced overall survival or disease-free survival. Conclusion: A number of symptomatic breast cancer patients with positive SNBs may be overtreated. Ongoing trials examining the management of low volume SNB macrometastases need to consider the symptomatic subgroup in their conclusions.*

Sentinel lymph node biopsy (SNB) has replaced axillary lymph node clearance (ANC) as the surgical option of choice to stage the axilla in clinically node negative breast cancer patients. SNB is as reliable as ANC in staging patients without the associated increased morbidity of ANC (1). Traditionally, ANC was reserved for patients with evidence of metastases at SNB. However, because of the morbidity of axillary clearance and the fact that the majority of patients with positive SNBs do not have additional involved nodes, there has been an increasing move towards a more conservative management of these patients (2).

In addition, tumour-specific biology (*e.g.* cancer phenotype, genomic profiling) is playing an increasingly important role in determining the benefits of adjuvant therapy even in the presence of axillary metastases (3). For example, some cancer patients with favourable gene expression profiles may be spared chemotherapy despite having node-positive disease (4). To determine the risk or adverse effects of adjuvant chemotherapy may no longer be based on axillary staging alone, thus, it may be possible to reduce the need for automatic progression to axillary clearance in the presence of positive nodes in low-risk tumours. Although there is general consensus that ANC is not necessary in almost any patient with SNB-detected micrometastases (foci of tumour >0.2 mm and <2 mm) or isolated tumour cells (<0.2 mm) (5), persistent clinical equipoise remains about the correct management of SNBs with positive macrometastases (defined as foci of >2 mm) (6-9).

Currently, patients with macrometastases still undergo axillary clearance or axillary radiotherapy, with the latter, however, shown to be non-inferior for selected patients with regards to local recurrence and possibly survival (10, 11). The ZO11 trial (12) attempted to answer specifically whether patients with one or two sentinel macrometastatic nodes at SNB could be safely treated without further ANC. In patients undergoing breast-conserving surgery and receiving whole breast radiotherapy, it was concluded that there was no difference in axillary recurrence, disease-free and overall survival between having an ANC and not having one (at 6.3 years follow-up). There were concerns, however, about the documentation of radiotherapy tangential fields, protocol deviations and early accrual closure (13) as well as whether these results could be applied to mastectomy patients not undergoing radiotherapy. This matter was brought up to the European Society of Medical Oncology (14) and the UK's National Institute for Health and Care Excellence (NICE) (15), who advised that Z011s findings should be confirmed by further trials. Several international trials, therefore, have intended to validate Z011 or answer the question regarding

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the management of SNB macrometastases in the wider population (*e.g.* mastectomy patients), such as POSNOC in the UK (16) and SENOMAC in Sweden (6).

Most completed and ongoing trials have recruited predominantly screen-detected cancers with symptomatic cancers forming a smaller portion in their cohort. Symptomatic cancer patients tend to be younger, more likely ER-negative and with worse survival compared to screen-detected cancers that may not be explained by lead-time bias alone (17), suggesting that symptomatic cancers behave differently. In addition, earlier cancer dissemination to the axilla is more likely in symptomatic cancers, with one study showing a five-fold increased risk of non-sentinel nodes at ANC in symptomatic compared to screen-detected cancers (18).

As a large non-screening United Kingdom National Health Service (NHS) unit, we sought to determine the outcome of ANC in our symptomatic patients who had a positive SNB at primary surgery. This was to examine the portion of patients who had further non-sentinel nodes involved and to examine our population in light of other studies, examining the issue of managing SNB metastases in clinically node-negative patients.

Patients and Methods

The study was a retrospective quality assurance assessment and required no approval from the ethical committee. Also, it was not registered on a clinical trials database.

The study population was identified from a prospectively maintained operating theatre database at the Pennines Acute Hospital NHS Trust, a non-screening breast surgery unit in Manchester, United Kingdom. All patients were women over the age of 18 diagnosed with invasive breast cancer (T1-3), who underwent sentinel node biopsy that was found to be positive (micro or micrometastases) and subsequently underwent axillary node clearance. The patients were treated between January 2008 and December 2017.

Data collection. Electronic patient records were accessed to obtain clinicopathological data including: i) age at surgery, ii) date of surgery, iii) histology, iv) pathological tumour category, v) number of positive lymph nodes, vi) oestrogen, receptor (ER) and progesterone receptor (PR) status, vii) human epidermal growth factor receptor 2 (HER2) status, viii) nuclear grade and ix) proliferation index (as measured by Ki-67 immunostaining). Micrometastases were defined as foci of tumour between 0.2 mm and 2 mm and macrometastases were defined as foci greater than 2 mm in size.

Treatment. At diagnosis, all patients underwent diagnostic mammography combined with breast and axillary lymph node ultrasound imaging. All patients had clinically and radiologically negative axillae and thus underwent a sentinel lymph node biopsy using combined radioisotope and blue dye. Patients who underwent any primary breast procedure with or without immediate reconstruction were included.

Up until 2014, all patients who had micro or macrometastatic disease at SNB underwent an axillary lymph node clearance after passing through the multi-disciplinary team meeting. After 2014, only patients with at least one lymph node with positive macrometastatic disease were recommended for lymph node clearance. After completion of surgical and adjuvant therapy patients were followed up on an annual basis for a total of 5 years and had mammography with or without breast ultrasonography every year.

Statistical analysis. Student's *t*-test and analysis of variance (ANOVA) was used to compare continuous variables. Relationships between categorical variables were compared using *Chi*-squared test. Recurrence-free and overall survival were graphically presented using Kaplan-Meier survival curves. The association between survival and clinicopathological variables was initially assessed using univariate Cox proportional hazards model. Statistical tests were performed using SPSS 22.0 for windows (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY, USA). Values of $p<0.05$ were considered statistically significant. All reported *p*-Values are two-sided.

Results

Ninety-nine patients were identified. Four patients were excluded as they had been referred from breast cancer screening units and opted to have their treatments at our unit. This left 95 symptomatic patients with positive SNBs who subsequently had ANCs. The median age was 50 years (range=32-78). Mean tumour size was 24.0 mm (range=2-70 mm). Thirty-eight (40%) patients were treated with a mastectomy and 57 (60%) with breast-conserving surgery; either a wide-local excision or therapeutic mammoplasty. Four patients (4.3%) had neoadjuvant chemotherapy and 71 patients (75.5%) had adjuvant chemotherapy. Nine patients (9.6%) had adjuvant chemotherapy after their SNB but before their ANC. Clinicopathological details and oncological therapy are summarised in Table I.

At primary axillary surgery, a median of 3 axillary lymph nodes (range=1-12) were removed. A median of 1 positive (micro- or macrometastases) SNB node was identified with a range of 1 to 7 positive lymph nodes. Sixty-three SNBs (66.3%) had macrometastases (+/– micrometastases) and 32 (33.7%) had micrometastases alone.

At ANC, 25 patients (26.3%) showed evidence of further non-sentinel lymph node metastases with 70 patients (73.7%) having no evidence of further axillary metastases. Of these 25 patients, 4 patients (16%) had micrometastases alone and 12 (40%) had 1 or 2 further macrometastases at ANC. The total axillary burden of macrometastases (SNB+ANC) was calculated for all patients who had macrometastases at SNB. Out of 63 patients, 46 (73%) patients had 1 or 2 macrometastases in total.

As patients with 1 or 2 nodes with macrometastases were considered to be low risk for further metastases at ANC [as per Z0011 (12) and ongoing POSNOC trial criteria (19)] we explored this subgroup further. At SNB, 52 patients (82.5%) had 1 or 2 macrometastases at SNB. Of these, 12 (23.1%) patients had further non-sentinel nodes at ANC and 40 (76.9%) had none, even though one presented with micrometastases

Table I. *Baseline clinical-pathological characteristics and oncological treatments of patients who underwent axillary clearance after positive sentinel node biopsies.*

Clinico-pathological characteristics	n (%)*	Oncological treatments	n (%)*
Median age, years (range)	50 (26 to 91)	Primary breast operation	
Mean invasive tumour size, mm (95%CI)	24 (2-70)	Breast conserving surgery	57 (60)
Tumour pathological T Stage		Mastectomy	38 (40)
T1	48 (50.5)	Neoadjuvant chemotherapy	
T2	43 (45.0)	Yes	91 (90.5)
T3	3 (4.2)	No	4 (4.2)
Invasive grade		Adjuvant chemotherapy	
1	13 (13.7)	Yes	72 (75.8)
2	44 (46.3)	No	23 (24.2)
3	38 (40)	Adjuvant chemotherapy received between SNB and completion ANC	
Oestrogen receptor (ER) status		Yes	9 (9.5)
Negative	14 (14.7)	No	86 (90.5)
Positive	81 (85.3)	Adjuvant radiotherapy	
HER2 receptor status		Yes	68 (71.6)
Negative	77 (81.1)	No	27 (28.4)
Positive	18 (18.9)	Adjuvant endocrine therapy	
Ki-67		Yes	81 (85.3)
Low (<20%)	48 (51.1)	No	14 (14.7)
High (>20%)	47 (48.9)	Adjuvant Herceptin therapy	
		Yes	18 (18.9)
		No	77 (81.1)

*Unless otherwise stated. SNB: Sentinel node biopsy; ANC: axillary node clearance; HER2: human epidermal growth factor receptor 2; ER: oestrogen receptor.

alone. When considering the total axillary burden in this subgroup (SNB+ANC), 33 patients (63.5%) had 1 macrometastatic node in total (*i.e.* had micrometastases at either SNB or ANC), 13 (25%) had 2 macrometastases and the remainder (11.5%) had 3 macrometastases or more. Further details of SNB and ANC findings are detailed in Table II.

The association between clinicopathological factors at SNB and the likelihood of involved non-sentinel metastases was examined. The presence of further metastases at ANC (*versus* negative ANC) correlated with tumour size (p=0.02). When the four T3 tumours were excluded, the association between tumour size and likelihood of further non-sentinel nodes was p=0.007. There was no association between invasive grade, Ki67, ER or HER2 status and the likelihood of identifying involved non-sentinel nodes. The presence of more than 2 macrometastases at SNB was also significantly associated with an increased likelihood of further metastases at ANC (p<0.001). There was no statistically significant association between the presence of macrometastases at SNB *vs*. micrometastases alone at SNB and the likelihood of ANC metastases, however, this may be due to the low number of patients with micrometastases at SNB that had further non-sentinel nodes. An association between clinicopathological characteristics and the likelihood of further non-sentinel nodes is shown in Table III.

During a median follow-up time of 79.8 months (range=7.2-110.9 months), 11 patients (11.6%) died, giving a median overall survival of 73.6 months (range=7.2-110.9 months).

Thirteen patients (13.7%) developed distant cancer recurrence and 2 of these patients also developed local recurrence in the ipsilateral breast. Sixteen patients (16.8%) developed lymphoedema during the follow-up period.

To examine whether there was a difference in survival between patients who had further axillary metastases at ANC and survival we used a cox proportional hazards model. Following univariate Cox proportional hazards analysis, invasive tumour grade (but not tumour size, receptor status or Ki67) was associated with reduced overall and disease-free survival (p=0.01 for both). There was no association between the presence of further metastases at ANC (*vs*. tumour-free ANC) and reduced overall or disease-free survival, suggesting no difference between patients with negative and those with further axillary nodes involved (Figure 1).

Discussion

The management of the axilla in breast cancer remains a controversial topic with benefits of locoregional control balanced against the morbidity of performing a potentially

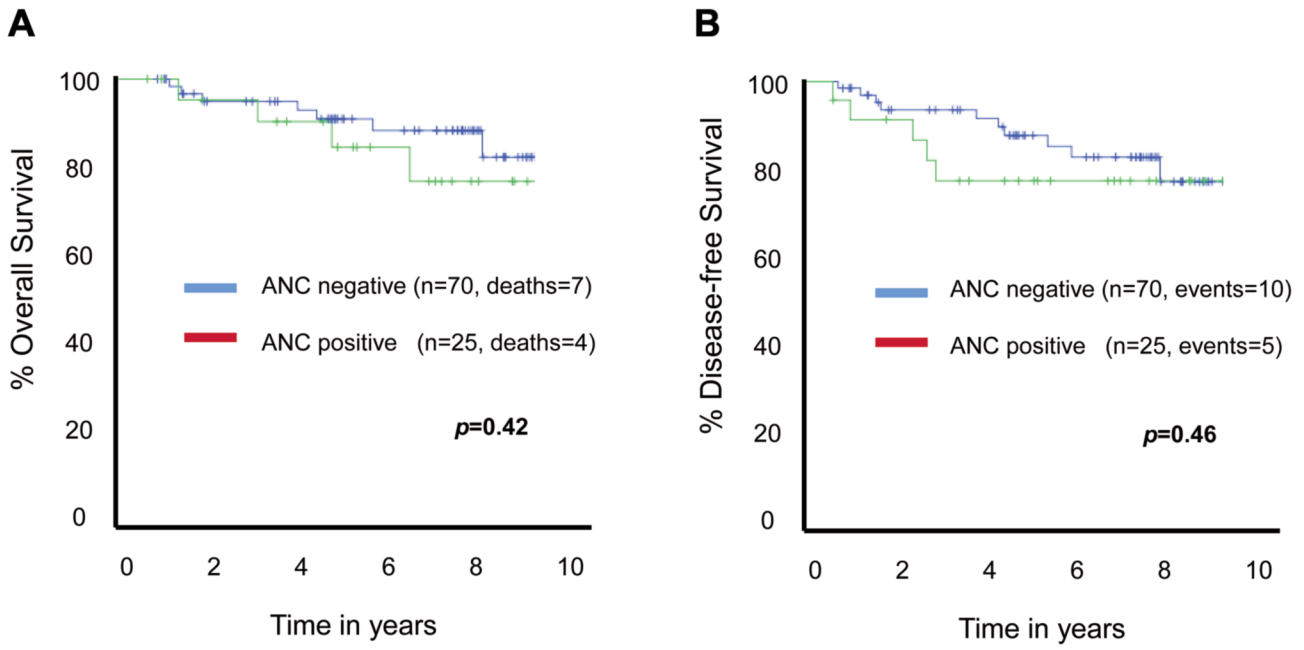

Figure 1. *Kaplan-Meier survival curves for overall survival and disease-free survival. Association between presence (positive) and absence (negative) of further non-sentinel nodes at axillary nodal clearance (ANC) and overall survival (A) and disease-free survival (B).*

Table II. *Details of lymph node pathology at sentinel node biopsy and subsequent axillary node clearance ANC.*

Pathological characteristics at sentinel node biopsy	n (%)*	Pathological characteristics at axillary node clearance	n (%)*
Total number of SNB nodes removed, median (range)	3 (1 to 12)	Total number of nodes removed, median (range)	22 (5-63)
Number of SNB positive		Involved non-sentinel nodes at ANC	
Micrometastases alone	32 (33.7)	None	70 (73.7)
1 macrometastasis	43 (45.3)	Micrometastases alone	4 (4.2)
2 macrometastases	9 (9.5)	Macrometastases	21 (22.1)
>2 macrometastasis	11 (11.1)	Extracapsular spread	
Extracapsular spread		Yes	3 (3.2)
Yes	15 (15.8)	No	92 (96.8)
No	80 (84.2)		

*Unless otherwise stated. SNB: Sentinel node biopsy; ANC: axillary node clearance.

unnecessary ANC. There is currently a treatment paradigm shift towards a more conservative approach to the management of positive axillary lymph nodes with a general decline in the number of patients receiving ANC after positive SNBs in the last decade (20).

However, there still remains debate about the safety of avoiding ANC in patients with macrometastases. Despite concerns about the generalisability of the Z011 results (13), some institutions in the USA have managed patients who meet the Z0011 criteria with conservative management alone (21), but this has not been in the case in Europe. Multiple ongoing trials are attempting to address this question (6).

In this single-centre study, we reviewed our heterogenous cohort of symptomatic patients who had undergone an ANC following positive SNB. We included patients who had undergone breast-conserving surgery or mastectomy. We found that just over 24% of patients had further non-sentinel node metastases at ANC. In patients who had only 1 or 2 macrometastases, only 17.5% of patients had further nodes involved. These numbers suggest that we are potentially over-treating 80% of our patients with unnecessary axillary node clearance. In addition, at least 16.8% of our patients developed lymphoedema during the follow-up period and this portion has to be considered in the context of the percentage of T1-2

Table III. *Univariate analysis comparing patients who had further involved non-sentinel nodes to those who had no further metastases at ANC.*

Pathological characteristics	No involved sentinel nodes at ANC, n=70 n (%)*	Involved sentinel nodes at ANC, n=25 n (%)*	*p*-Value
Mean age at diagnosis Years (range)	52.4 (26-91)	49.7 (32-78)	0.54
Mean pathological tumour size mm (range)	22.3 (2-56)	28.7 (5-70)	0.02
ER status			0.55
Negative	11 (15.7)	3 (12)	
Positive	59 (84.3)	22 (88)	
HER2 Status			0.12
Negative	58 (82.9)	19 (76)	
Positive	12 (17.1)	6 (24)	
Invasive tumour grade			0.24
1	11 (15.7)	2 (8)	
2	29 (41.4)	16 (64)	
3	31 (42.8)	7 (28)	
Ki67			0.24
Low (<20%)	33 (68.8)	15 (31.3)	
High (>20%)	39 (80.4)	7 (19.6)	
Number of nodes removed at ANC			
Median (range)	21 (5-55)	23 (9-63)	0.28
Metastases at SNB			0.14
Micrometastases alone	27 (84.4)	5 (15.6)	
Macrometastases	43 (69.3)	20 (31.7)	
Macrometastases at SNB			0.003
1 or 2 macrometatases	40 (76.9)	12 (23.1)	
>2 macrometstases	3 (27.3)	8 (72.7)	
Extracapsular spread**			0.21
Yes	35 (72.9)	13 (27.1)	
No	8 (53.3)	7 (46.7)	

*Unless otherwise stated. **In subgroup with macrometastases at SNB. SNB: Sentinel node biopsy; ANC: axillary node clearance; HER2: human epidermal growth factor receptor 2; ER: oestrogen receptor.

patients (18%) who had 2 or fewer macrometastases at ANC.

During a median follow-up period of 79.8 months [comparable to other studies (12, 21, 22)] we also showed that there may be no survival advantage in patients who had no further involved non-sentinel nodes compared to those with further metastases. In particular, 44% (11/25) of patients who did have additional non-sentinel nodes bore either only one macrometastasis or micrometastases alone. The additional removal of isolated macrometastases or micrometastases may not confer additional clinical benefit as the majority of these patients also went on to have adjuvant chemotherapy +/– endocrine therapy.

However, it would imply that staging of the axilla is helpful prognostically and should help direct treatment taking also into account the tumour biology. These data point towards the notion that clearance does not add any survival benefit. This is, of course, only based on a single centre and it's difficult to know its relevance until trials, such as POSNOC, have concluded.

As shown in previous studies, tumour size and number of positive macrometastases are the most significant risk factors for further non-sentinel node metastases (12, 22) and this was demonstrated in our cohort, where larger tumours and >2 macrometastases were significant predictors of further non-sentinel nodes.

Z0011 focused only on patients undergoing BCS whilst our cohort also included mastectomy patients (12). When considering only our BCS patients (the majority in our cohort) a similar percentage of non-sentinel nodes was found as in the Z011 cohort (27.3% *vs*. 21.1% in ours), demonstrating similarities in this population in terms of low axillary burden.

Yun *et al*., in a retrospective series, focused on a cohort of 214 patients who had undergone mastectomy and had positive SNBs (17). This group found significantly worse OS in patents who had SNB alone compared to those who had axillary radiation or ANC. Despite this, 23% of patients in the SNB-alone group had T3 or T4 tumours compared to 5.3% in our cohort. POSNOC, amongst other trials, include patients managed by breast-conserving surgery or mastectomy and allow application to a heterogenous group, such as ours.

All patients in our cohort were symptomatic non-screen-detected cancers. Symptomatic cancer is a poor prognostic factor for survival compared to screen-detected cancer (23). Although this has been partially explained by lead-time bias, some researchers have found it to be independent of tumour biology and age (24). In the context of a cohort of patients who are all clinically node-negative but SNB-positive, it could be pertinent that these patients should be considered differently from screen-detected or mixed populations. If screen-detected cancers include a subgroup of clinically insignificant, slower growing cancers, this could indicate a need for a more aggressive axillary treatment in patients with symptomatic cancers or at least a more cautious application of trials, such as Z0011 or POSNOC.

In a large case series of 773 patients with micrometastases, there was no significance in the number of non-sentinel nodes found in symptomatic compared to screen-detected cancers (18.5% *vs*. 17.5%) (25), however, another series of 140 patients have found a five-fold increased risk of non-sentinel node metastases after micrometastases at SNB (18). Farshid *et al*. have, similarly, demonstrated that symptomatic cancers have a greater portion of non-sentinel node metastases, however, this was not significant on multivariate analysis (26).

Another factor that needs to be considered when treating breast cancer patients is differences in pre-operative axillary ultrasound, which was not required in the Z0011 trial (12)

but is a standard practice in the UK (15). The argument for those that advocate selective axillary ultrasound is that some ultrasound-positive patients may have low axillary burden and could be spared an ANC if they instead went to SNB (27). Although the discussion of axillary ultrasound is a separate issue, the UK practice of pre-operative ultrasound may increase the safety of conservative management of SNB-positive patients with low risk tumours as any patients with clinically or radiologically negative axillae would have a lower burden of disease prior to an SNB

Using current guidelines, our data shows that in our cohort of symptomatic cancers with clinically- and ultrasound-negative axillae a large portion of symptomatic breast cancer patients with positive SNBs may be overtreated. Ongoing trials examining the management of low volume SNB macrometastases need to separately consider the symptomatic subgroup for drawing their conclusions.

Conflicts of Interest

None of the Authors have any conflicts of interest to declare.

Authors' Contributions

HS: study design, data collection and analysis, manuscript writing; ZM: data collection, data analysis, manuscript proofreading; GD: concept creation, data analysis, manuscript writing, proofreading, manuscript editing; MA – concept creation, manuscript writing, proofreading, manuscript editing.

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