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CLINICAL TRIAL

The clinical utility of assessment of the axilla in women with suspicious screen detected breast lesions in the post Z0011 era

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Abstract Axillary ultrasound (AUS) and biopsy are now part of the preoperative assessment of breast cancer based on the assumption that any nodal disease is an indication for axillary clearance (AC). The Z0011 trial erodes this assumption. We applied Z0011 eligibility criteria to patients with screen detected cancers and positive axillary assessment to determine the relevance of AUS to contemporary practice. Women screened between 1/1/2012 and 30/6/2013 and assessed for lesions with highly suspicious imaging features are included. We analysed demographic and assessment data and ascertained the final histopathology with particular reference to axillary nodal status. Among 449 lesions, AUS was recorded in 303 lesions (67.5 %). 290 (96 %) were carcinomas, 30.3 % with nodal disease. AUS was abnormal in 46 (15.9 %). AUS had a sensitivity of 39.8 %, specificity 94.6 %, positive predictive value (PPV) 79.2 % and negative predictive value (NPV) 78.1 %. Axillary FNAB was positive in 27 women, suspicious in two, benign in 16 and not performed in one. In one FNA positive case, the lesion was a nodular breast primary in the axillary tail in a multifocal breast cancer. Combining AUS and FNAB, the sensitivity was 76.5 %, specificity 90.9 %, PPV 96.3 % and NPV 55.6 %. Applying the Z0011 inclusion criteria, 24 of the 27 (88.9 %) women with abnormal AUS and positive FNA were ineligible for Z0011-based management. Of three women eligible for Z0011, one proceeded to AC after SN biopsy, leaving only two women (7.4 %) who might have been considered for SN only management had it not been for the results of the axillary assessment. Among women with negative AUS, nodal metastasis was demonstrated in 21.7 %, 86.8 % of these women having only 1–2 positive nodes. Abnormal AUS and FNA preferentially identify candidates for AC. Negative AUS predicts negative or low nodal burden. Axillary assessment streamlines care.

Keywords Axilla · Biopsy · Breast neoplasms · Sentinel node biopsy · Screening · Ultrasound

Introduction

Over the last decade, ultrasound assessment of the axilla with needle biopsy of abnormal nodes has been incorporated into the pre-operative evaluation of women with breast cancer because it accurately identifies a significant proportion of women with nodal disease. The clinical utility of AUS is based on the premise that women with established nodal metastases should forgo sentinel node mapping and biopsy and proceed directly to axillary clearance (AC). Economic evaluation of AUS has found it to be cost-effective [1] and the practice has been endorsed by professional bodies as standard of care for preoperative nodal staging [2].

The publication of the results of the ACOZOG Z0011 trial in 2011 questioned the assumption that all sentinel

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node positive patients should have AC [3]. This study randomized women with early stage breast cancer and less than three positive nodes, being treated with breast conserving surgery, whole-breast irradiation and adjuvant systemic therapy (hormonal or chemotherapy at the discretion of the treating team), to AC or no further axillary surgery. The finding of equivalent and low locoregional recurrence rates, as well as similar 6-year survival figures between the two groups casts doubt on the value of routine AC for all node positive women. The 2014 guidelines from the American College of Surgical Oncology are aligned with the Z0011 trial results in not recommending axillary lymph node dissection for women with early stage breast cancer who have one or two sentinel lymph node metastases and will receive breast-conserving surgery with conventionally fractionated whole-breast radiotherapy [4]. In the context of these developments, the role of preoperative AUS may no longer be assumed for all breast cancer patients. However, no study has evaluated the clinical utility of AUS in the context of the post Z0011 patterns of practice. We are also unaware of any prior evaluation of AUS focused on a breast cancer screening program, where early stage breast cancers with low nodal burden are typically diagnosed.

In this study, our aims were twofold: firstly to evaluate the performance indices for AUS and biopsy of the axilla in the setting of a population-based breast cancer mammography screening program, and then to apply the eligibility criteria for Z0011 study to determine the clinical utility of the information provided by AUS.

This study will enable us to establish evidence-based guidelines for axillary assessment reflective of contemporary practice.

Consent

This study was conducted with approval from the RAH Human Research Ethics Committee, protocol number 131112.

Materials and methods

The design of our breast cancer screening program

BreastScreen South Australia is part of a national breast cancer-screening program, accredited to provide this service since 1991, after a pilot in 1989. The design of this program has been described previously [5]. In brief, asymptomatic women aged 50–69 years are invited to participate at 1 or 2 yearly intervals, depending on family history and prior high risk lesions. Two radiologists read two view screening mammograms independently. A third reader arbitrates discordant results. A 5-tier grading scheme is applied [6] grade 1, normal; grade 2, benign; grade 3, indeterminate/equivocal; grade 4, suspicious for malignancy and grade 5, radiologically malignant. Women with grade 1 or 2 lesions are "cleared" to return for rescreening in 1–2 years. The remaining lesions are recalled for further assessment. Based on work up mammography and, in most cases, ultrasound examination, the lesion is regraded. Some lesions are cleared, while biopsy is performed for those with imaging grades of 3 and above.

Lesions with malignant biopsy findings are referred for treatment. Diagnostic open biopsy is used when the imaging and needle biopsy findings are discordant or inconclusive. For lesions undergoing surgery, all final pathology and treatment data are audited and are entered prospectively into an electronic database. Clients not referred for surgery are tracked through their subsequent screening visits and also via the State Cancer Registry, which is required to notify BreastScreen South Australia of cancers diagnosed within 27 months of a cleared screen (interval cancers) [7].

Study design

For women screened between 1/1/2012 and 30/6/2013 and assessed at our clinic for grade 5 mass lesions, we prospectively recorded whether ipsilateral axillary ultrasound (AUS) was performed and the results of this assessment.

Clinical examination of the breast and ipsilateral axilla are routinely carried out for women undergoing biopsy. During the study period, AUS was not mandatory at our Program. It took place at the discretion of the assessment radiologist, who proceeded to axillary fine needle aspiration biopsy (FNAB) when the AUS was abnormal. Although standardised protocols for AUS, or a prescribed system of classifying the AUS findings were not in place, our radiologists were familiar with the interpretation of AUS and reported using it routinely during their clinical work outside of our service. Informally, morphology and cortical thickness >4 mm were mentioned often in the radiology reports of abnormal AUS.

At our service, pathologists provide rapid, on site evaluation of all FNA samples, including those from sonographically abnormal axillary nodes.

For each lesion, we tabulated patient demographics, imaging grade, mammographic size, biopsy methods, and final outcome. We correlated the assessment data with the final surgical histopathology, with particular reference to the nodal status. For women with abnormal AUS and positive axillary FNA, we applied the inclusion criteria of the Z0011 trial to determine eligibility for Z0011-based management.

Table 1 Final diagnosis in grade 5 mass lesions undergoing AUS

Diagnosis	*N* (%)
Invasive cancer	290 (96.0 %)
Mammary angiosarcoma	1 (0.3 %)
DCIS	2 (0.7 %)
Radial scar	3 (1.0%)
Phyllodes tumour, benign	2 (0.7%)
Fat necrosis	1 (0.3 %)
Fibroadenoma	1 (0.3 %)
Fibrocystic change, ADH	1 (0.3 %)
Adenosis	1 (0.3 %)
Benign	1 (0.3 %)
Total	303

Results

During the 18 months timeframe, 449 women with grade 5 lesions other than calcifications were assessed. Twelve of these women had multifocal lesions.

AUS was recorded in 303 women (67.5 %) but not in 146 women (32.5 %). Table 1 lists the final diagnosis of the 303 grade 5 mass lesions assessed by AUS. Invasive carcinoma comprised 290 (96.0 %) cases. Other malignancies and a range of benign diagnoses accounted for the remaining lesions.

There were 290 invasive cancers found in 287 women, three having synchronous, bilateral cancers. The mean patient age at screening was 61.7 years (standard deviation 8.6 years, range 43–84 years). A strong family history of breast cancer was documented in 27 women (9.3 %). The left breast was affected in 47.2 % and the right breast in 52.8 %. The mean size of the tumours at diagnosis was 17.3 mm and the median size was 14 mm.

Axillary nodal metastases were ultimately documented in 88 cases (30.3 %). The remaining 202 invasive cancers (69.7 %) were node negative after final histologic evaluation.

The AUS was classified as abnormal in 46 (15.9 %) cases and normal in 84.1 %. The final status of the axillary nodes by the AUS classification is shown in Table 2. Nodal metastatic disease was confirmed in 35 of 46 cancers with abnormal AUS, giving a positive predictive value (PPV) of 76.1 %. The negative predictive value (NPV) of a normal AUS in this setting was 191 of 244 (78.3 %).

FNA biopsy was indicated when the AUS was abnormal. The axillary FNAB was classified as positive for malignancy in 27 (58.7 %), benign in 16 (34.8 %), suspicious in 2 (4.3 %) and was not performed in one case.

Table 3 presents the correlation of the axillary FNA with the final axillary staging data. In 26 of 27 cases with positive axillary FNA, nodal disease was confirmed, leading to a PPV of 96.3 %. One case had malignant cells on the FNA smear of the axillary mass; however, all nine axillary nodes removed were uninvolved. Review confirmed a positive smear. Further evaluation of the mastectomy specimen revealed a multifocal carcinoma, including one circumscribed tumour in the upper outer quadrant which had features of a needle track associated with it. This may have been the site of the mass seen on AUS and assumed to be an axillary node.

Among the subset of cases with abnormal AUS but without a positive FNA, 8 of 18 cases (44.4 %) ultimately had nodal disease confirmed, amounting to a false negative rate of 44.4 % and a negative predictive value of 10 of 18 (55.5 %) for axillary FNA.

Table 2 Predictive value of axillary ultrasound findings in invasive breast cancers

	N	Nodal disease confirmed	No nodal disease
AX ultrasound abnormal	46 (15.9 %)	35 PPV (76.1 %)	11 FPR (23.9 %)
AX ultrasound normal	244 (84.1 %)	53 FNR (21.7 %)	191 NPV (78.3 %)
Total	290	88	202

Table 3 Predictive value of axillary FNA for invasive cancers with abnormal axillary ultrasound

	Total	Nodal disease confirmed	No nodal disease
FNA positive	27	26 PPV (96.3 %)	1 (FPR 3.7 %)
FNA not positive	18	8 (FNR 44.4 %)	10 NPV (55.5 %)
Total	46	34	11

One case with abnormal AUS and positive axillary FNA was a multifocal invasive carcinoma with tumours measuring 14, 10, 10 and 6 mm, and with extensive DCIS. All nine axillary nodes examined were uninvolved. One circumscribed tumour in the upper outer quadrant of the breast had a needle track in it. This may have been the site of the mass seen on AUS and assumed to be an axillary lymph node

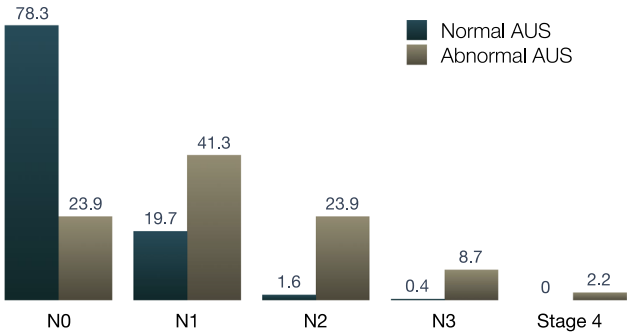

Fig. 1 Nodal stage by AUS results

Nodal burden

After final histopathologic examination, 55 (19.0 %) cancers were T1a, 91 (31.4 %) T1b, 60 (20.7 %) T1c, 76 (26.2 %) T2, 4 (1.4 %) T3 and 1 (0.3 %) T4. Extent was not established histologically in 3 (1 %) patients as they were unfit for surgery or had disseminated disease.

The cancers were grade 1 in 69 (24.1 %), grade 2 in 141 (49.3 %), grade 3 in 74 (25.9 %) and of unknown grade in 6 (2.1 %).

The final nodal stage was as follows: N0 in 202 (69.7 %), N1 in 67 (23.1 %), N2 in 15 (5.2 %), N3 in 5 (1.7 %) and not established in one patient (0.3 %) with disseminated disease.

Figure 1 shows the nodal stage among patients with abnormal AUS versus those with normal AUS. Focusing on patients with more than two positive nodes, among the 27 women with abnormal AUS and positive axillary FNA, 14 (51.9 %) had more than two positive nodes or stage 4 disease, while only seven of 244 (2.9 %) women with normal AUS had more than two positive nodes.

Surgical management of the axilla

In our series, one woman had bony metastases at diagnosis and was managed with hormonal therapies, while the remaining 26 of 27 women with abnormal AUS and positive axillary FNA underwent surgery. The first axillary staging procedure was sentinel node biopsy in one of the 26 women, the remaining 25 had AC without SN biopsy.

Eligibility for Z0011 trial-based management

We applied the eligibility criteria for the Z0011 trial to women with abnormal AUS and positive FNA results. As shown in Table 4, 24 of 27 (88.9 %) of women with abnormal AUS and positive axillary FNA were ineligible for Z0011-based management. This was due to palpable breast mass or axillary adenopathy in 19 women (including one with distant metastasis), mastectomy in four and soft tissue induration and swelling of the ipsilateral axilla due to a heavy nodal burden (all 16 nodes with ECS) in one case. One other woman had extra-capsular spread of nodal deposits into fat. While this is not an exclusion criterion for Z0011 per se, recent data suggest it portends a higher likelihood of non-sentinel node involvement [8].

Discussion

The American College of Surgeons Oncology Group Z0011 trial showed that for carefully selected subsets of patients with positive sentinel nodes, there is no outcome advantage in proceeding to AC. This finding has two implications; it shows that the more extensive surgical procedure of AC is not therapeutic per se, and also that the information gained from this procedure does not lead to management decisions that alter survival. In this same vein, the AMOROS trial had previously illustrated that once the presence of nodal disease is established, the extent of nodal involvement did not impact the choice of therapy [9]. The failure to meets its accrual targets (due to slow recruitment), limited follow up and non-standardised radiation therapy to the axilla are some of the controversial aspects of the Z0011 study, causing some to question the application of its recommendations into routine clinical practice [3, 10, 11]. The POSNOC trial is currently being implemented in the UK, in an attempt to provide further evidence for the safety and efficacy of avoiding AC in subsets of women with early breast cancer http://www.controlled-trials.com/ISRCTN54765244/. However, evidence shows that the Z0011 results are changing practice patterns. Since the presentation of the Z0011 trial results in June 2010 a 20 % reduction in the rate of AC for patients with sentinel node macrometastases has been observed [12]. The proportion of women eligible for Z0011-based management is small. SEER data on women older than 66 years, reported that 4.4 % of these women would fulfil the Z0011 inclusion criteria [13]. A large study from Australia and New Zealand found that 6.9 % of women with breast cancer would meet Z0011 eligibility criteria [14].

While palpable axillary adenopathy was an exclusion criterion for the Z0011 study, abnormal AUS with positive axillary biopsy was not addressed specifically in the Z0011 design. Several studies report that the establishment of nodal disease by preoperative needle biopsy is being treated as equivalent to clinically positive adenopathy and thus an indication for AC [15–17]. In our study, all but one woman with a positive axillary FNA following an abnormal AUS proceeded directly to AC.

Our study aimed to address two separate issues: (1) How effective is axillary assessment in identifying women with nodal disease? and (2) What proportion of women with

Table 4 Eligibility for Z0011-based management in women with abnormal AUS & positive axillary FNA

Age	Imaging size mm	Reason for recall	Palpable?	Surgery	Size-histology mm	Subtype	Grade	VI	Biomarkers	Z11 eligible	Final nodal status
73	11	Breast lesion & node	NAD	WLE, AC	12	Ductal	2	Y	E+, P+, HER2−	ECS into fat	2 of 8, ECS to fat
58	6	Breast lesion & node	NAD	WLE, SNB	6, 5	Ductal	2	N	E+, P−, HER2−	Y	SN1:2, ITC; AC:1:7
70	19	Breast lesion & node	NAD	WLE, AC	25	Ductal	2	Y	E+, P+, HER2−	Y	1 of 13
66	23	Two breast lesions	NAD	M, AC	50	Ductal	2	Y	E+, P+, HER2−	Mastectomy	8 of 14
61	45	Multiple breast lesions	Breast nodularity	M, AC	14, 10, 10, 6	Ductal	1	N	E+, P+, HER2−	Mastectomy	0 of 9
71	13	Breast lesions & nodes	NAD	M, AC	24, 8	Ductal	3	N	E+, P+, HER2−	Mastectomy	2 of 14, ECS
74	47	Breast, AUS: L1–3 nodes	NAD	M, AC	40	Pleo-lobular	3	N	E+, P+, HER2−	Mastectomy	9 of 11
70	41	Breast lesion & node	Palpable adenopathy	WLE, AC	18	Ductal	3	Susp	E+, P+, HER2+	Palpable nodes	1 of 14
68	NA	Enlarged axillary nodes	Palpable adenopathy	AC only	NA	Ductal	3	N	E−, P−, HER2−	Palpable nodes	1 of 16
62	28	Enlarged axillary nodes	Palpable adenopathy	WLE, AC	22	Ductal	3	N	E+, P+, HER2−	Palpable nodes	1 of 15
75	23	Breast lesion	Breast & adenopathy	M, AC	18	Ductal	3	Y	E+, P−, HER2−	Palpable breast & node	1 of 26
64	19	Breast & axillary tail	Breast & adenopathy	M, AC	15	Ductal	2	Y	E−, P−, HER2−	Palpable breast & node	8 of 14, ECS
67	37	Breast lesion & nodes	Palpable adenopathy	M, AC	37	Ductal	3	Y	E−, PR−, HER2−	Palpable breast & node	3 of 21
56	29	Breast lesion	Breast & adenopathy	M, AC	30	Ductal	3	N	E+, P−, HER2+	Palpable breast & node	27 of 36
56	52	Breast lesions	Breast & adenopathy	M, AC	30, 10, 8	Ductal	3	Y	E+, P−, HER2−	Palpable breast & node	2 of 10
52	21	Breast lesion	Breast & adenopathy	WLE, AC	48	Mixed	2	Y	E+, P+, HER2−	Palpable breast & node	2 of 11
50	39	Enlarged axillary node	Breast & adenopathy	M, AC	60	Ductal	3	Y	E−, P+, HER2+	Palpable breast & node	5 of 14, ECS
52	48	Breast lesion & node	Breast & adenopathy	No surgery	NA	Lobular	2	NA	E+, P+, HER2−	Palpable breast & node	NA
54	42	Breast lesion & node	Breast & adenopathy	M, AC	30	Basal	3	Y	E−, P−, HER2−	Palpable breast & node	9 of 11, ECS
62	22	Breast lesion & node	Breast & adenopathy	WLE, AC	23	Ductal	2	Y	E+, P+, HER2−	Palpable breast & node	1 of 8

Table 4 continued

Age	Imaging size mm	Reason for recall	Palpable?	Surgery	Size-histology mm	Subtype	Grade	VI	Biomarkers	Z11 eligible	Final nodal status
64	30, 19	Multiple breast lesions	Breast & adenopathy	WLE, AC	20, 3	Ductal	2	Y	E+, P+, HER2−	Palpable breast & node	4 of 15, ECS
54	50	Breast lesion	Breast, skin dimpling	M, AC	60	Lobular	2	N	E+, P+, HER2−	Palpable, large breast lesion	21 of 22, ECS
67	17	Breast lesion & node	Breast mass	M, AC	21, 17, 5	Lobular	2	Y	E+, P+, HER2−	Palpable breast mass, ECS	12 of 16, ECS
73	16	Enlarged axillary nodes	Breast mass	WLE, AC	18	Lobular	2	N	E+, P+, HER2−	Palpable breast mass	4 of 28
64	18	Breast lesion & node	NAD		36	Ductal	2	Y	E+, P+, HER2−	Palpable breast mass	5 of 10
56	25	Breast lesions	Breast, skin dimpling	WLE, AC	29, 4, 3	Ductal	3	N	E+, P+, HER2−	Palpable breast mass	2 of 17
60	14	Breast lesion	NAD	WLE, AC	12	Pleomorphic-lobular	3	Y	E−, P−, HER2−	Indurated axilla	16 of 16, ECS

nodal disease identified by AUS/FNA fall outside of the Z0011 criteria and are candidates for ALND?

In relation to the first aim, we established that the combination of AUS/FNA is highly accurate in establishing nodal disease. Addressing the second aim, when we applied the Z0011 eligibility criteria retrospectively to our patients with positive axillary FNA, 24 of 27 were ineligible for Z0011-based management, principally because of large tumour size and a heavy nodal burden. Our experience shows that the combination of abnormal AUS and positive axillary FNA was highly predictive of a significant nodal burden and preferentially identified women who would be candidates for AC according to the Z0011 study. Our observations are concordant with those of Abe and colleagues who found 28 % of AUS positive patients to have pN2 or pN3 disease versus 3 % of those with negative AUS [18]. Recently Verheuvel reported larger tumour size, mastectomy rates, tumour grade, HER2 positivity rates, hormone negativity, macrometastases, extracapsular spread and Level III extension in patients with node positive disease established after AUS guided biopsy versus after SNB [19].

By contrast, for the far larger proportion of patients with negative AUS, our analysis indicates that even though 21.7 % of these women ultimately had nodal disease, they typically have a low nodal burden and can be managed with sentinel node biopsy. We found the incidence of pN2 or pN3 disease among women with negative AUS to be 2 %. Schipper found this rate to be 4.4 % [16], Choi reported 3.7 % [20], while Ibrahim-Zada found a 13 % rate of nodal involvement in patients with negative AUS with or without axillary FNA, and the nodal burden in this group proved low, with 81 % having no further nodal involvement [21].

The results of the Z0011 and the IBCSG studies show that histopathology and immunohistochemistry, designed to find metastases as small as single cells, lack sufficient specificity for identifying clinically relevant sentinel node metastases [3, 22]. Since it can most reliably detect bulky nodal disease, the combination of abnormal AUS and positive axillary biopsy is well suited for identifying women eligible for one-stage AC, while AUS negative women will proceed with sentinel node biopsy, with only a minority requiring completion AC.

Prior to AUS, imprint cytology and frozen section examination were used commonly as rapid methods for establishing the status of the sentinel nodes intra-operatively. These two tests have similar results, each proving effective for finding larger nodal deposits, but have a 50 % false negative rate in detecting micrometastases [23]. One-step nucleic acid amplification is another technique introduced recently (OSNA, Sysmex Corporation, Kobe, Japan). This automated assay is based on measuring copies of

cytokeratin 19 mRNA in portions of sentinel nodes [24]. One of the advantages of AUS is that if the involvement of the sentinel node can be established prior to surgery, the more time sensitive and resource intensive intraoperative evaluations become redundant for those patients. This procedure enables informed consultation with the patient and one stage surgery for most patients. It obviates the economic costs and utilization of resources involved in intraoperative examination, sentinel node mapping and biopsy, as well as the second operations needed to clear the axilla after sentinel node metastases are identified.

Over the last decade, several studies have confirmed preoperative AUS to be effective in identifying most women with nodal involvement of breast cancer without requiring the removal of any nodes. Meta-analyses indicate that over 70 % of cases with nodal disease are identified correctly [25, 26]. To our knowledge, this study is the first to address the efficacy of AUS in the setting of population-based mammographic screening. The smaller size of screen detected breast cancers is associated with lower stage disease at diagnosis, including lower rates of nodal involvement. Diepstraten's meta-analysis showed significantly reduced sensitivity of AUS in the setting of low prevalence of axillary involvement [25]. Their pooled sensitivity of AUS for studies with <40 % prevalence of axillary involvement was 38, versus 62 % for studies with higher prevalence [25]. While AUS has been adopted into practice in screening programs by extension from the symptomatic setting, the clinical utility of axillary assessment has not been evaluated specifically in this low prevalence setting to ensure optimal resource utilisation. In Houssami's 2011 meta-analysis, the pooled estimate for sensitivity was 75.0 %. Our sensitivity of 76.5 % compares favourably with that figure, even though the prevalence of nodal disease was only 30.3 % in our screen detected cancers, versus 47.2 % in their meta-analysis. The pooled specificity figure was 98.5 versus 90.9 % in our series and the PPV 98.3 % in the meta-analysis versus 96.3 % in our series. With an overall 30.3 % rate of nodal disease, our study fits into the low prevalence band for Diepstraten's meta-analysis. While their pooled sensitivity of AUS for studies with <40 % prevalence of axillary involvement was 38 %, we found the sensitivity of AUS to be 55.6 % in our series which was closer to the 62 % rate for their studies with higher prevalence. The quality of the AUS, the skills of the operators, including sonographers and radiologists and the imaging criteria used to designate abnormal axillary nodes are all likely to be important contributors to this result. Lee's review of AUS morphologic lymph node features in 224 cancers identified the absence of a hyperechoic hilum ($p = 0.003$) and increased cortical thickness ($p = 0.03$) as the most predictive of nodal involvement [27]. Similarly, Britton found the absence of a fatty hilum and cortical thickness greater than 4 mm to constitute the AUS morphologic features most predictive of nodal metastases; however, 30 % of patients with normal AUS had nodal disease [28]. In our study, AUS took place at the discretion of the assessment team, without standardised reporting protocols among the eleven reporting radiologists. While our results are reflective of contemporary, routine clinical practice, further evaluation of the morphologic criteria used by the radiologists is not possible at this stage.

In Leenders series, the prevalence of nodal disease was similar to our series at 37.3 %, but AUS was reported as abnormal in twice as many cases (28.4 %) leading to a sensitivity of only 43.8 % but with a specificity of 80.7 %. For cases with abnormal AUS and FNA, their sensitivity was 24.7 % [29]. They also had a false positive case. It is likely that the specific criteria used to designate AUS as abnormal may influence the trade off between sensitivity and specificity of this test. Diepstraten et al. point out that "one in four women with an ultrasound-guided biopsy proven negative axilla has a positive SNB [25]. We found that 21.7 % of women, approximately 1 in 5, with a normal AUS had nodal disease documented subsequently. We reserve axillary biopsy only for cases with abnormal AUS, whereas some centres biopsy visible nodes [26]. When Britton and colleagues used core biopsy for any node with a longitudinal diameter exceeding 5 mm, they found nodal deposits in 12 % of the women with normal AUS [28]. Stachs' multivariate evaluation of predictors of false-negative AUS reported that the size of nodal deposits ≤5 mm was the only predictor of this outcome [30]. Consistent with this limited nodal burden, we found that among the 21.7 % of women found to have positive nodes after normal AUS, 86.8 % had only one or two positive nodes. Sentinel node biopsy is likely to reveal the nodal stage of these women and be the basis for informed discussions about further management. We believe the low prevalence of nodal disease in the screen detected setting, together with the low sensitivity of FNA in detecting small nodal deposits justify triaging the use of axillary biopsy based on abnormal AUS findings.

Abnormal axillary nodes have been assessed by both FNA and core biopsy. When both tests were performed, core biopsy was found to be 8.6 % more sensitive but the difference in the positivity rates did not reach statistical significance and a minority of cases were positive with either one or other test [31]. In our hands the negative predictive value after a non-malignant axillary FNA was 55.6 %, which is lower than the 79 % reported by Fung et al., likely reflecting differences in sonographic criteria for designating a node abnormal [32].

Limitations of this study

Since axillary assessment was not mandatory at the time but was at the discretion of the duty radiologist, AUS was not recorded consistently in all patients. In fact AUS results are only available in 67.5 % of the cases. While the basis for the decision as to whether to assess the axilla is not specified, it must be acknowledged that this variation in practice may introduce a selection bias which could have the effect of making axillary assessment appear more effective than it would be in unselected patients.

While our study demonstrates that a large proportion of our patients with positive AUS/FNA fall outside of the Z0011 criteria and may proceed to ALND, our study does not address the larger questions posed by the Z0011 trial. Specifically (a) for patients who meet the Z0011 selection criteria, the role, if any, of AUS/FNA remains to be established, and (b) for Z0011 eligible patients with positive AUS/FNA the necessity for routine ALND is yet to be determined. These questions may be addressed by trials currently in progress.

Conclusion

AUS appears well suited for the purpose of identifying clinically significant nodal disease, as specified in the Z0011 trial. The results of our study suggest that AUS used in a population-based screening program is able to identify women with a high nodal burden that would justify one-stage AC. The assessment of the axilla does not adversely affect women with histologically negative sentinel nodes or those with a low sentinel node tumour burden that would otherwise be candidates for Z0011-based management.

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Conflict of interest None of the authors has declared a conflict of interest.

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