

Clinical Radiology

Does preoperative axillary staging lead to overtreatment of women with screen detected breast cancer?

--Manuscript Draft--

Manuscript Number:	CRAD-D-17-00618R1
Full Title:	Does preoperative axillary staging lead to overtreatment of women with screen detected breast cancer?
Article Type:	Original Paper
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Abstract:	<p>Aim To determine the impact of pre-operative axillary ultrasound staging in a screen detected breast cancer population</p> <p>Materials and Method Ultrasound and needle biopsy staging results alongside reference standard sentinel lymph node biopsy and axillary lymph node dissection were retrospectively extracted from the unit's computer records between 01/04/2008 and 31/03/2015. Axillary staging was compared with final pathology and treatment.</p> <p>Results Of the 215,661 screening examinations performed, 780 invasive cancers were diagnosed which had pre-operative axillary staging data, of which 162 (20.7%) were node positive. 36 (4.6%) had a heavy nodal burden (3 or more nodes). 90 (11.5%) had an abnormal axillary ultrasound and axillary biopsy of which 54 were positive for cancer (33.3% of the node positive cases) and triaged to axillary lymph node dissection avoiding a sentinel lymph node biopsy. Of these 22 (40.7%) had neoadjuvant treatment, and 32 (59.3%) proceeded directly to axillary lymph node dissection. The sensitivity of axillary ultrasound and biopsy to detect women with a heavy nodal burden (3 or more nodes) was 41.7% (15 of 36). However, 17 (53%) of the 32 women with a positive axillary biopsy had a low burden of axillary disease (≤ 2 positive nodes) at axillary lymph node dissection, the mean number of nodes obtained was 14.6.</p> <p>Conclusion Significant numbers of women are being potentially overtreated or denied entry into Positive Sentinel Node: adjuvant therapy only vs adjuvant therapy and clearance or axillary radiotherapy (POSNO) because of routine pre-operative axillary staging.</p>

Does preoperative axillary staging lead to overtreatment of women with screen detected breast cancer?

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Acknowledgements

Sian Taylor-Phillips is supported by the NIHR CLAHRC West Midlands initiative. The views expressed in this publication are those of the authors and not necessarily those of the NHS, the National Institute for Health Research, or the Department of Health.

All staff in the Cambridge Breast Unit who performed axillary ultrasound and biopsies and entered data to NBSS

Conflicts of interest: none

	MGW	FKT	STP
Guarantor of integrity of the entire study	Yes	N	N
Study concepts and design	Y	Y	Y
Literature research	Y	N	N
Clinical studies	Y	Y	N
Experimental studies/data analysis	Y	N	Y
Statistical analysis	N	N	Y
Manuscript preparation	Y	Y	Y
Manuscript editing	Y	Y	Y

Dear Dr Wallis

RE: CRAD-D-17-00618: Does preoperative axillary staging lead to overtreatment of women with screen detected breast cancer?

Thank you for your careful, helpful and interesting comments

REVIEWERS' COMMENTS:

Reviewer #1:

In the discussion, I am a bit confused about line 123. Does the author mean, comparison with the other UK breast screening centres? The text is less well written from here on in.

This section has been rephrased and now reads

*It is not easy to directly compare our results with the **rest of the UK breast screening programme as the ~~results of axillary staging have been reported in different ways in the NHSBSP and ABS audits of screen detected cancers over the period of this audit does not report in a comparable ways~~***

Reviewer #2:

I think there should be more acknowledgement in the Discussion and Limitations sections that, particularly given the relatively small number of heavily node positive women in this cohort, the fact that the pre-treatment nodal status of the 22 women with a positive axillary US biopsy receiving preoperative NAC is unknown means that there is potential for the actual accuracy of preoperative axillary assessment for heavy nodal disease to be markedly underestimated. There is no description of the differences in disease burden between those receiving NAC and those treated with primary surgery; it seems likely that in general the former had a heavier burden of disease and likelihood of heavier nodal positivity.

The following paragraph has been added to limitations

We can never accurately know the nodal burden of the 22 women with a positive core biopsy who received neo-adjuvant chemotherapy so our sensitivity and specificity for high nodal burden could be an under estimate, but this is true for all other papers who exclude neo-adjuvant chemo therapy from their calculations. ^{13,14,16,17}

Re your last sentence regarding how ideally we would be able to predict which women would benefit from preoperative axillary staging: were you able to extract any trends from your data regarding this, e.g. relationship of tumour size to degree of nodal positivity in your patient cohort?

We have not explored this as we are currently bidding to Breast Care Now for money to clean and interrogate the whole ABS/NHSBSP surgical audit data set to answer this very question.

A minor Discussion point is re comparison of your results with NHSBSP national results, there is also a lack of homogeneity of definitions of sonographic criteria for an abnormal node (i.e. threshold for cortical thickness) used by different screening centres.

'and there is no national agreement on what cortical thickness justifies a needle biopsy.' Has been added

I also wonder whether you could expand your discussion slightly to frame your results in light of some of the other ongoing relevant research on this topic, rather than focusing purely on the potential for denying enrolment to POSNOC. The vast majority of patients enrolled into POSNOC will have had standard care including preoperative axillary ultrasound staging; not performing axillary US routinely would not improve recruitment into POSNOC because this would lead to excessive protocol deviations.

Thank you for suggesting this additional item for discussion we have added the following from old line 151 and two additional references

The possibility of identifying a group of very low risk women who need no axillary surgery is also being considered. The SOUND trial is currently randomising women with small invasive breast cancers with normal axillary ultrasound to SLNB or monitoring²⁶. Nielsen Moody raises the possibility of using ultrasound micro-bubbles to identify the sentinel node and avoid the need for surgery.²⁷

26. Gentilini O, Veronesi U. Abandoning sentinel lymph node biopsy in early breast cancer? A new trial in progress at the European Institute of Oncology of Milan (SOUND: Sentinel node vs Observation after axillary UltraSouND) The Breast 2012;21:678-681

27. Nielsen Moody A, Bull J, Culpan A-M, et al. Preoperative sentinel lymph node identification, biopsy and localisation using contrast enhanced ultrasound (CEUS) in patients with breast cancer: a systematic review and meta-analysis. Clin Rad 2017;72:959-971

In light of your comment we have re worded the final sentence adding.

'A much larger data set is required to confirm this, and to look for additional features that might predict which women would benefit from pre-operative axillary staging or in whom ALND should not be the initial surgical treatment.'

We hope this makes it clear we are not advocating stopping pre-operative staging of the axilla. Other trials underway and in planning might answer this but the ABS/NHSBSP audit data set might help to identify biological features where any axillary intervention could be avoided rather than the crude size criteria currently used by SOUND

Minor typographical points:

- Line 20 of abstract should read 'nodes' not node
- I think references to preoperative NAC changing nodal status (e.g. lines 68, 172) should read 'has potential to change' rather than 'would change'
- line 78 has missing full stop after 'biopsy'
- line 83 could do with a comma after '(figure 1)'
- line 86 could do with a comma after 'biopsy' and another after 'ALND'
- line 88 also missing full stop after '(table 1)'

Several other lines in the results section could do with some commas!
-the paragraph starting at line 146 has no punctuation so is an overly long sentence.

Thank you. All these comments have been addressed and in line 156 I have deleted an extra 'the'

1 Abstract

2 Aim

3 To determine the impact of pre-operative axillary ultrasound staging in a screen detected breast
4 cancer population

5 Materials and Method

6 Ultrasound and needle biopsy staging results alongside reference standard sentinel lymph node
7 biopsy and axillary lymph node dissection were retrospectively extracted from the unit's computer
8 records between 01/04/2008 and 31/03/2015. Axillary staging was compared with final pathology
9 and treatment.

10 Results

11 Of the 215,661 screening examinations performed, 780 invasive cancers were diagnosed which had
12 pre-operative axillary staging data, of which 162 (20.7%) were node positive. 36 (4.6%) had a heavy
13 nodal burden (3 or more nodes). 90 (11.5%) had an abnormal axillary ultrasound and axillary biopsy
14 of which 54 were positive for cancer (33.3% of the node positive cases) and triaged to axillary lymph
15 node dissection avoiding a sentinel lymph node biopsy. Of these 22 (40.7%) had neoadjuvant
16 treatment, and 32 (59.3%) proceeded directly to axillary lymph node dissection. The sensitivity of
17 axillary ultrasound and biopsy to detect women with a heavy nodal burden (3 or more nodes) was
18 41.7% (15 of 36). However, 17 (53%) of the 32 women with a positive axillary biopsy had a low
19 burden of axillary disease (≤ 2 positive nodes) at axillary lymph node dissection, the mean number of
20 nodes obtained was 14.6.

21 Conclusion

22 Significant numbers of women are being potentially overtreated or denied entry into Positive
23 Sentinel Node: adjuvant therapy only vs adjuvant therapy and clearance or axillary radiotherapy
24 (POSNOC) because of routine pre-operative axillary staging.

1 Introduction

2 Axillary lymph node involvement has historically been considered the most important
3 prognostic factor with respect to survival in women with breast cancer. Removal of all
4 axillary nodes via axillary lymph node dissection (ALND) was considered to be standard
5 treatment^{1,2,3} but is associated with significant morbidity^{4,5}. This underpins the drive to
6 establish a good diagnostic test to determine axillary node status prior to treatment, to
7 avoid overtreatment in women who were lymph node negative. Less invasive axillary
8 lymph node sampling, whereby just a few suspicious nodes are removed, was subsequently
9 replaced by Sentinel Lymph Node Biopsy (SLNB)^{6,7,8} which has a specificity in the region of
10 96% when compared with ALND.^{6,8} Both axillary node sampling and SLNB are performed at
11 the time of surgical treatment of the primary breast cancer, so if positive require a second
12 operation, and general anaesthetic, to complete surgical treatment.

13 Multiple imaging modalities have been used to determine axillary status pre-operatively⁹
14 but only axillary ultrasound with selective needle biopsy of morphologically abnormal nodes
15 {which has a specificity approaching 100%} is used routinely in clinical practice.^{10,11} The main
16 limitation of axillary ultrasound and needle biopsy is the relatively low sensitivity, which
17 varies widely according to the underlying prevalence of node positivity in the population
18 studied.^{12,13,14} Additionally the more involved nodes an individual has at diagnosis the more
19 likely it is that the ultrasound needle biopsy will correctly make the diagnosis.^{12,13,14} The
20 traditional paradigm of care has changed in the advent of the ACOSOG Z0011¹⁵ which
21 indicates that there is no difference in survival and regional control in women with small (T1
22 – T2) breast cancers and ≤ 2 nodes positive randomised to either ALND or SLNB alone. This

23 suggests that patients with a low axillary burden of disease may not require formal axillary
24 treatment with either complete axillary lymph node dissection or radiotherapy.

25 The current literature is now divided with estimations of 38%¹⁶ and 47%¹⁷ of women with a
26 positive axillary ultrasound and needle biopsy undergoing unnecessary ALND. Some centres
27 such as Memorial Slone Kettering Hospital have abandoned pre-operative axillary
28 ultrasound to avoid triaging all women with positive pre-operative axillary biopsy directly to
29 ALND, but others^{18,19} emphasise that axillary ultrasound preferentially identifies women
30 with high risk disease who benefit from surgical treatment of the axilla. These differing
31 results and approaches might well be due to widely varying underlying disease prevalence.
32 Despite this debate current UK guidelines mandate preoperative axillary ultrasound with
33 needle biopsy of morphologically abnormal nodes.²⁰ This policy might also be reducing
34 recruitment into the POSNOC trial,²¹ a randomised control trial for women with unifocal or
35 multi-focal invasive tumour with a lesion ≤ 5 cm in its largest dimension, 1 or 2 sentinel
36 nodes with macro-metastases at sentinel node biopsy who are randomised to either
37 adjuvant therapy but no treatment to their axilla after surgery or adjuvant therapy plus
38 treatment to their axilla after surgery.

39 We sought to audit the impact of routine axillary ultrasound and selective needle biopsy
40 from one UK breast screening service and thus identify the risks and benefits of
41 preoperative axillary staging in a low risk screen-detected population.

42

43 Materials and Method

44 This was a retrospective audit registered by our institution. All women recalled to
45 assessment that are considered to have findings suspicious for breast malignancy on
46 ultrasound have an axillary ultrasound performed at the same time. If the axillary node or
47 nodes are considered to be morphologically abnormal (axillary cortical thickening of more
48 than 3 mm, eccentric cortical thickening or complete nodal replacement)²² then the
49 patient proceeds to ultrasound guided biopsy of the most suspicious node with either a 14
50 or 16-gauge automated biopsy needle (Achieve, Carefusion, Vernon Hills IL, USA) with two
51 passes. Those women who have an unexpected invasive cancer identified either on US
52 biopsy or 9G Vacuum assisted biopsy (VAB) will have axillary ultrasound +/- needle biopsy
53 when they attend the results clinic.²³ Morphologically normal nodes were not biopsied.

54 All assessment data and subsequent pathology and treatment data is prospectively
55 recorded on National Breast Screening Computer System (NBSS) [Hitachi Consulting, Lisbon
56 Spain]. Data were retrospectively extracted from NBSS using a standard report, BASOX BASO
57 extract designed for the Association of Breast Surgeons and NHS breast screening
58 programme annual audit of screen detected breast cancers.²⁴

59 The accuracy of the axillary ultrasound and needle biopsy test was calculated using results
60 of SLNB and ALND as the reference standard, with 3 or more nodes involved classed as
61 positive, and 2 or fewer classed as negative. This was chosen because the test is used to
62 determine whether women receive SLNB or ALND, and previous research indicates
63 advantages of progressing directly to ALND for 3 or more nodes. Sensitivity, specificity,
64 positive and negative predictive values were calculated along with their corresponding
65 confidence intervals using the exact binomial based method (Stata version 13.1; Stata Corp
66 LP, College Station, Tx, USA). Cases where the woman had neoadjuvant chemotherapy

67 (NAC) between the axillary ultrasound and needle biopsy (the index test) and the SLNB or
68 ALND were excluded because this treatment **has the potential to** change the nodal status.
69 Cases where nodal status was unknown were also excluded from these calculations. All
70 excluded cases which received the index test are shown as an extra column in the 2x2 table.

71 Results

72 Between April 2008 and March 2015, we performed 215,661 screening examinations at one
73 UK breast screening centre and 997 (7.93 per 1,000 screened) cancers were diagnosed, of
74 which 780 (6.23 per 1,000 screened) were invasive. 4 were excluded (3 were considered too
75 unwell for axillary ultrasound and were treated with hormonal therapy and one was lost to
76 follow up opting to be treated abroad), giving a total of 776 invasive cancers with pre-
77 operative axillary staging data. Figure 1 shows that 34 women were treated with NAC, 22 of
78 whom had a positive axillary ultrasound and core biopsy. These all had ALND as part of their
79 post NAC surgery. The 12 patients who had a normal axillary ultrasound have uncertain
80 nodal status as we were not performing SLNB prior to NAC.

81

82 162 (20.7%) of the 764 invasive cancers with known nodal status were node positive (figure
83 1), of these 36 (4.6%) had a heavy nodal burden (3 or more nodes) (table 1). 90 (11.5%) had
84 an abnormal axillary ultrasound and axillary biopsy of which 54 (60%) were positive for
85 cancer (33.3% of the node positive cases). Of these 54 women with a malignant axillary core
86 biopsy, 22 (40.7%) had neoadjuvant treatment followed by surgery to the breast and ALND,
87 and 32 (59.3%) proceeded directly to ALND. 15 (47%) of these women had more than 3
88 nodes positive (table 1). In other words, 54 (7.1%) of 764 women with invasive cancer
89 were triaged to ALND avoiding a SLNB.

90 Of the 36 women with an abnormal axillary ultrasound but a negative core biopsy 9 (25%)
91 were node positive at SLNB and proceeded to ALND (figure 1). 2 (22.1%) of these women
92 had more than 3 nodes positive(table1)

93 Of the 686 women with a normal axillary ultrasound and no axillary biopsy 12 were treated
94 with NAC so their initial nodal status is unknown. Of the remaining 674, 99 (14.7%) were
95 node positive at SLNB and proceeded to ALND (figure1). 19 (19.2%) of these women had
96 more than 3 nodes positive (table2).

97 After excluding all women who were treated with NAC the sensitivity for diagnosing a node
98 positive woman was 22.9% (32 of 140).

99 Table 1 shows the detailed nodal burden of the 142 women with positive nodes treated by
100 primary surgery by method of diagnosis.

101 As a test to detect women with 3 or more involved nodes axillary ultrasound and needle
102 biopsy has a sensitivity of 41.7% (95%CI 25.5%-59.2%) and specificity of 97.7% (95%CI
103 96.3%-98.6%), with positive predictive value 46.9% (95% CI 29.1%-65.3%) and negative
104 predictive value 97.2% (95.7%-98.2%) at 5% prevalence (table 2).

105 After excluding all women who were treated with NAC the sensitivity of diagnosis of women
106 with a low axillary disease burden (2 or less nodes) was only 17.3% (17 of 98). These 17
107 women (53% of the 32 women with a positive axillary core biopsy) had a low burden of
108 axillary disease. The mean number of nodes obtained at ALND was 14.6. On review of their
109 clinical and imaging findings they would have all been eligible for ASCSOG Z00011 which
110 means that their positive pre-operative axillary staging resulted in potentially unnecessary
111 axillary nodal surgery and in more recent years denied them access to the POSNOC trial.

112

113 Discussion

114 This is the first paper that specifically documents the advantages and disadvantages of
115 routine pre-operative staging of the axilla in a low risk population derived exclusively from a
116 screening population. In this cohort 54 (7.1%) were triaged to NAC or direct ALND as a result
117 of pre-operative staging but more than half (53%) of women with positive axillary core
118 biopsy had a low burden of axillary disease (≤ 2 positive nodes) at ALND compared to 77.7%
119 of the women with a negative axillary core biopsy and the 74.7% with normal axillary nodes.
120 The group with a positive axillary core biopsy group may have been overtreated with
121 unnecessary ALND, an intervention which can result in long term morbidity such as
122 lymphedema.

123 It is not easy to directly compare our results with the **rest of the** UK breast screening
124 programme as the **results of axillary staging have been reported in different ways in the**
125 NHSBSP and ABS audits of screen detected cancers over the period of this audit **does not**
126 **report in a comparable way. Additionally,** in the early years of the audit national data
127 completeness was not good **and there is no national agreement on what cortical thickness**
128 **justifies a needle biopsy.** However, our node positive rate ~~of~~ (20.7%) is similar to the
129 national node positive rate, which has been stable in the region of 22% for the period 2008
130 to 2015. ²⁰ Using the 2013-14 audit which has the most complete raw data set to enable a
131 national comparison, 21% (668 of 3116) surgically node positive patients had a malignant
132 axillary core biopsy and an additional 206 women with a positive axillary core biopsy
133 proceeded to neo adjuvant chemotherapy raising the percentage of node positive women
134 identified to 27% (688+206/ 3116+206) which compares to our own audit of 32.9%.

135 Comparison to international series is equally problematic because of differences in
136 underlying prevalence of node positivity and how each paper manages patients undergoing
137 NAC. The 3 meta-analyses^{12, 13, 14} quote pooled sensitivities for ultrasound guided axillary
138 biopsy of about 50% compared to our 33% but the median prevalence of nodal metastases
139 of 43.2% across the 35 studies in Houssami's more recent paper¹³ was almost double ours at
140 21.7%. Our 'clinical utility' or ability to triage patients with axillary nodal disease directly to
141 ALND rather than SLNB at 7.1% is lower than Houssami at 19.8% (11.6 – 28.1%).

142 Even though we have a low risk population our ability to preferentially detect women with a
143 heavy disease burden is very similar to Van Wely's meta-analysis.¹⁴ 47% of our core biopsy
144 positive patients had 3 or more nodes compared to Van Wely 52%. 22.1% of our core biopsy
145 negative patients and 19.2% of our normal axillary node patients were heavily node positive
146 compared to 22% and 33.8% respectively presumably again reflecting the differences in
147 underlying nodal prevalence.

148 Even though, like other studies, we are successfully identifying women with positive nodes
149 and preferentially detecting those with a heavy disease burden. This is at a cost to those
150 women with less than 3 nodes. Because, despite controversy about recruitment and
151 radiotherapy¹⁸ the ACOSOG Z0011 trial,¹⁵ which suggests that these patients with a low
152 axillary burden of disease do not require formal axillary treatment, has certainly changed
153 treatment in the United States¹⁸ and led to the initiation of POSNOC in the UK.²⁵ The
154 possibility of identifying a group of very low risk women who need no axillary surgery is also
155 being considered. The SOUND trial is currently randomising women with small invasive
156 breast cancers with normal axillary ultrasound to SLNB or monitoring²⁶. Nielsen Moody raises

157 the possibility of using ultrasound micro-bubbles to identify the sentinel node and avoid the need for
158 surgery.²⁷

159 Unlike the two other published studies who set out to retrospectively identify a population
160 of women specifically deemed eligible for ACOSOG Z0011 trial^{16,17} we have audited all the
161 ~~the~~ screen detected cancers over seven years from one centre and identified that 53% of
162 the patients with a positive axillary biopsy have been potentially over treated or denied
163 entry into a trial, as opposed to 38% of women from Ireland¹⁶ and 46% of women from
164 Memorial Sloane Kettering¹⁷, suggesting that the risks are higher in a low risk screening
165 group.

166 Our study has limitations; We can never accurately know the nodal burden of the 22 women
167 with a positive core biopsy who received neo-adjuvant chemotherapy so our sensitivity and
168 specificity for high nodal burden could be an under estimate, but this is true for all other
169 papers who exclude neo-adjuvant chemo therapy from their calculations.^{13,14,16,17} It is from
170 a single centre and although we performed over 215,000 screening examinations over a
171 seven-year period we only identified 164 women with node positive invasive cancer and
172 only 17 women were potentially over treated. However, if our results were to be
173 reproduced across England Wales and Northern Ireland based on the 2013/14 data²⁴
174 possibly as many as 390 women of the 668 with a positive axillary core biopsy would be
175 similarly over treated every year. Between 10%¹⁵ and 30%²⁸ will suffer debilitating
176 lymphedema.

177

178 In conclusion, our study demonstrates that in a low risk screening population, a significant
179 percentage of women are being potentially overtreated with respect to axillary surgery,

180 with the subsequent morbidity associated with this. A much larger data set is required to
181 confirm this, and to look for additional features that might predict which women would benefit
182 from pre-operative axillary staging or in whom ALND should not be the initial surgical
183 treatment.

184

185 Figure 1. Flow of women through the study. Neo-adjuvant chemotherapy (NAC) will change
186 nodal status so these patients were not followed up further.

187

188 Table 1. Final nodal status of women with positive results from Sentinel Lymph Node Biopsy
189 (SLNB) and/or Axillary Lymph Node Dissection (ALND) after negative axillary ultrasound,
190 positive ultrasound but negative needle biopsy, and after positive ultrasound and needle
191 biopsy.

192

193 Table 2 Test accuracy of Axillary ultrasound and needle biopsy, with reference standard Sentinel
194 Lymph Node Biopsy (SLNB) or Axillary Lymph Node Dissection (ALND). PPV denotes positive
195 predictive value and NPV negative predictive value. Brackets indicate 95% confidence intervals.

- 196 A. with 3 or more nodes involved classed as positive, and 2 or fewer classed as negative.
197 B. any involved nodes classed as positive. Excluded cases 34 received neo-adjuvant therapy so
198 nodal status would have changed between index test and reference standard, and 6 ultrasound
199 negative but SLNB positive cases did not have nodal status recorded.

200

201

202

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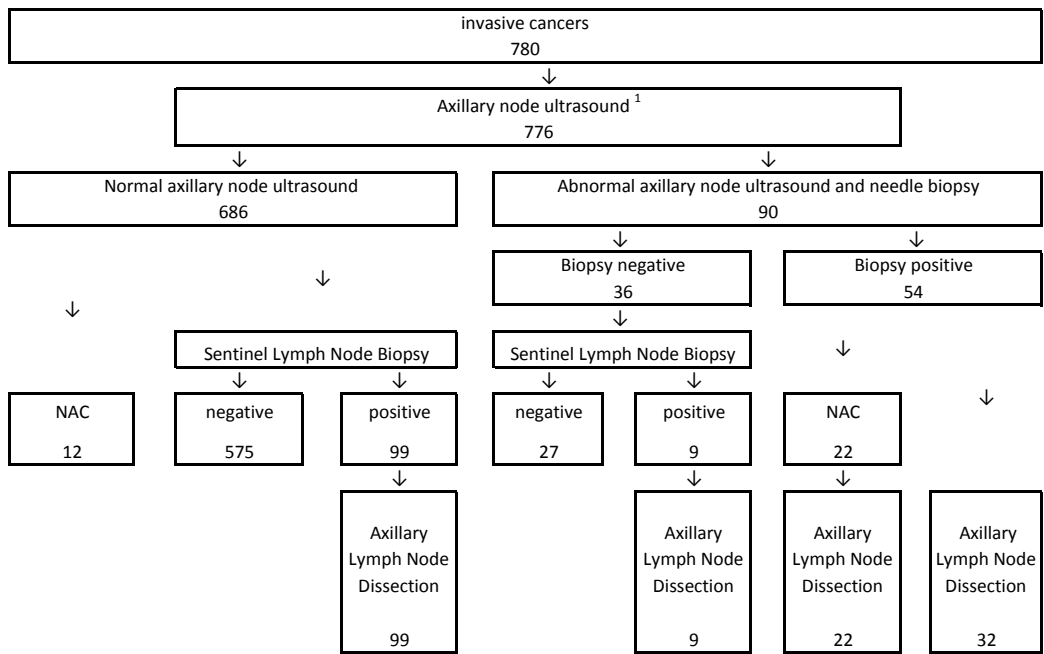
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Figure 1

Figure 1



¹ 4 excluded due to ill health or no follow up

Table 1

Surgical nodal burden	Ultrasound Negative	Needle biopsy Negative	Needle biopsy Positive	Total
	SLNB Positive	SLNB Positive	ALND Positive	
1	50 (50.5%)	4 (44.4%)	9 (28.1%)	63 (45.0%)
2	24 (24.2%)	3 (33.3%)	8 (25.0%)	35 (25.0%)
3	8 (8.1%)	1 (11.1%)	3 (9.4%)	12 (8.6%)
4+	11 (11.1%)	1 (11.1%)	12 (37.5%)	24 (17.1%)
N/K	6 (6%)	0	0	6 (4.3%)
	99 (100%)	9 (100%)	32 (100%)	140 (100%)

Table 2

A.		SLNB/ALND			
Ultrasound and needle biopsy	3+ nodes	<=2 nodes	Excluded		
Positive	15	17	22	PPV=	46.8% (29.1%-65.3%)
Negative	21	716	19	NPV=	97.2% (95.7%-98.2%)
	Sensitivity = 41.7% (25.5%-59.2%)		Specificity = 97.6% (96.3%-98.6%)		
B.		SLNB/ALND			
Ultrasound and needle biopsy	1+ nodes	<1 nodes	Excluded		
Positive	32	0	22	PPV=	100% (89.1%-100%)
Negative	102	635	19	NPV=	86.2% (83.5%-88.6%)
	Sensitivity = 23.9% (16.9%-32.0%)		Specificity =100% (99.4%-100.0%)		

Highlights

1. Less than 5% of screen detected cancers are heavily node positive (3 or more nodes).
2. Pre-operative axillary staging preferentially selects women with a heavy nodal burden.
3. Over half of women with a positive axillary node biopsy are potentially over treated.