Clinical Radiology

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

--Manuscript Draft--

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Abstract:	Aim To determine the impact of pre-operative axillary ultrasound staging in a screen detected breast cancer population 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. 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. 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 (POSNOC) because of routine pre-operative axillary staging.

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

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

Conflicts of interest: none

Author Contributions

	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 monitoring [26]. 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
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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'

Abstract

Aim

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

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.

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.

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 (POSNOC) because of routine pre-operative axillary staging.

Introduction

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

Multiple imaging modalities have been used to determine axillary status pre-operatively [9] but only axillary ultrasound with selective needle biopsy of morphologically abnormal nodes {which has a specificity approaching 100%} is used routinely in clinical practice.[10,11] The main limitation of axillary ultrasound and needle biopsy is the relatively low sensitivity, which varies widely according to the underlying prevalence of node positivity in the population studied. [12,13,14] Additionally the more involved nodes an individual has at diagnosis the more likely it is that the ultrasound needle biopsy will correctly make the diagnosis. [12,13,14]The traditional paradigm of care has changed in the advent of the ACOSOG Z0011[15] which indicates that there is no difference in survival and regional control in women with small (T1 – T2) breast cancers and ≤2 nodes positive randomised to either ALND or SLNB alone. This

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

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

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

Materials and Method

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

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

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

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

Results

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

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

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

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

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

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

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

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

Discussion

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

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 way. Additionally, in the early years of the audit national data completeness was not good and there is no national agreement on what cortical thickness justifies a needle biopsy. However, our node positive rate ~~of~~ (20.7%) is similar to the national node positive rate, which has been stable in the region of 22% for the period 2008 to 2015. [20] Using the 2013-14 audit which has the most complete raw data set to enable a national comparison, 21% (668 of 3116) surgically node positive patients had a malignant axillary core biopsy and an additional 206 women with a positive axillary core biopsy proceeded to neo adjuvant chemotherapy raising the percentage of node positive women identified to 27% (688+206/ 3116+206) which compares to our own audit of 32.9%.

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

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

Even though, like other studies, we are successfully identifying women with positive nodes and preferentially detecting those with a heavy disease burden. This is at a cost to those women with less than 3 nodes. Because, despite controversy about recruitment and radiotherapy [18] the ACOSOG Z0011 trial, [15] which suggests that these patients with a low axillary burden of disease do not require formal axillary treatment, has certainly changed treatment in the United States [18] and led to the initiation of POSNOC in the UK. [25] 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 monitoring [26]. Nielsen Moody raises

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

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

Our study has 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] It is from a single centre and although we performed over 215,000 screening examinations over a seven-year period we only identified 164 women with node positive invasive cancer and only 17 women were potentially over treated. However, if our results were to be reproduced across England Wales and Northern Ireland based on the 2013/14 data[24] possibly as many as 390 women of the 668 with a positive axillary core biopsy would be similarly over treated every year. Between 10% [15] and 30% [28] will suffer debilitating lymphedema.

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

with the subsequent morbidity associated with this. 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.

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

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

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

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

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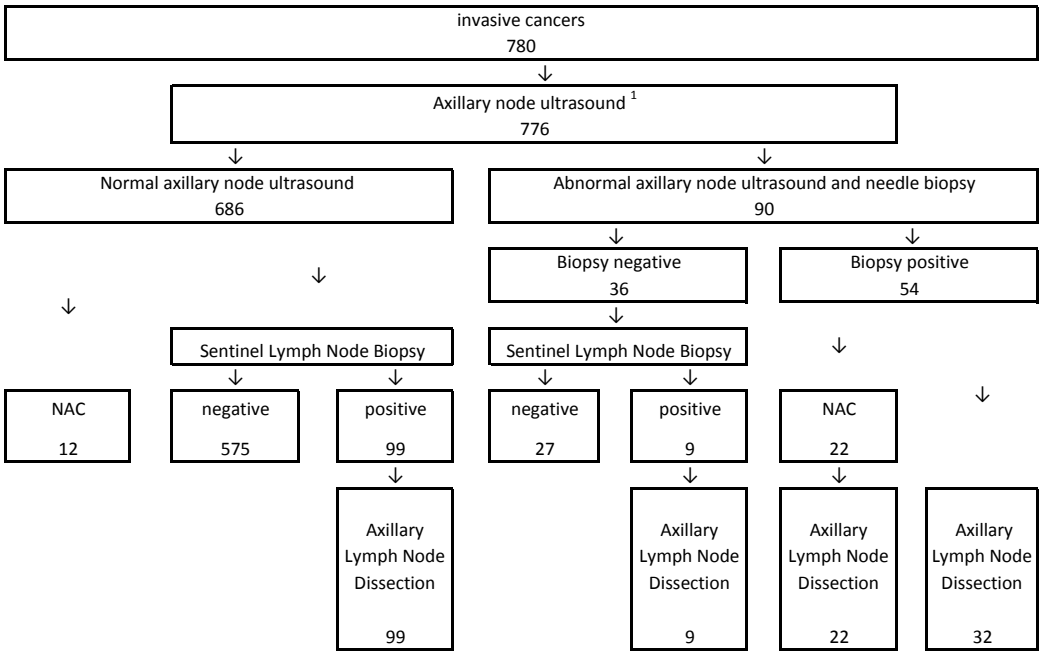
Figure 1



[1] 4 excluded due to ill health or no follow up

Table 1

Surgical nodal burden	Ultrasound Negative SLNB Positive	Needle biopsy Negative SLNB Positive	Needle biopsy Positive ALND Positive	Total
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

Table 2

A.

Ultrasound and needle biospy	SLNB/ALND 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.

Ultrasound and needle biospy	SLNB/ALND 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.