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Axillary tumour burden in women with one abnormal node on ultrasound scan compared to women with multiple abnormal nodes

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ABSTRACT

Background:The trial aim was to determine if for women with needle biopsy proven positive node on preoperative axillary ultrasound(AUS), the number of abnormal nodes seen on AUS is a predictor of number of positive nodes at histology.

Methods:This prospective multicentre cohort study included consecutive patients with early breast cancer who had needle biopsy proven positive node on AUS and underwent ALND between October 2015 and July 2016. The number of abnormal nodes at preoperative AUS was recorded by breast radiologists or radiographers.

Results:123 patients were included in the study. Median age of the women was 62(range 30 to 93) years. 54 of 123(44%) women had one abnormal node while 69(56%) had multiple abnormal nodes on AUS. 40 of 123(33%) women had two or less nodes with metastases at histology after ALND. Tumours 20 mm or less($P < 0.001$) and one abnormal node on AUS($P < 0.001$) were associated with two or less nodes with metastases at ALND. Both remained significant in logistic regression analysis. The likelihood of at least three metastases based on the combination of these two factors had 95% sensitivity(79 of 83), 35% specificity(14 of 40), negative predictive value of 78%(14 of 18) and positive predictive value of 75%(79 of 105).

Conclusion:Among women with needle biopsy proven positive nodes, around 3 in 4 women(78%) with invasive tumour size 2 cm or less and one abnormal node on AUS have 2 or less positive nodes at ALND. These women are overtreated by upfront ALND and can be offered SNB.

Introduction

Preoperative axillary ultrasound (AUS) is performed routinely in many centres to stage the axilla and abnormal nodes are subjected to fine needle aspiration cytology (FNA) or core biopsy{ ADDIN REFMGR.CITE <Refman><Cite><Year>2009</Year><RecNum>260</RecNum><IDText>Breast cancer (early & locally advanced): diagnosis and treatment</IDText><MDL Ref_Type="Journal"><Ref_Type>Journal</Ref_Type><Ref_ID>260</Ref_ID><Title_Primary>Breast cancer (early & locally advanced): diagnosis and treatment</Title_Primary><Date_Primary>2009</Date_Primary><Keywords>Breast </Keywords><Keywords>diagnosis</Keywords><Reprint>Not in File</Reprint><Periodical>http://guidance.nice.org.uk/CG80</Periodical><ZZ_JournalStdAbbrev><f

name="System">http://guidance.nice.org.uk/CG80</f></ZZ_JournalStdAbbrev><ZZ_WorkformID>1</ZZ_WorkformID></MDL></Cite></Refman>}. Generally, women with needle biopsy proven positive nodes proceed to axillary lymph node dissection (ALND) as ultrasound detected nodal disease (FNA or core biopsy positive) has higher tumour burden compared with sentinel node biopsy (SNB) detected nodal metastases{ ADDIN REFMGR.CITE { ADDIN EN.CITE.DATA }}. However, around 40 per cent of women with ultrasound detected nodal disease (FNA or core biopsy positive) are found to have two or less nodes with macrometastases at ALND{ ADDIN REFMGR.CITE { ADDIN EN.CITE.DATA }}. ALND is often associated with debilitating side effects such as arm swelling, numbness, shoulder function impairment and reduced quality of life compared with sentinel node biopsy (SNB){ ADDIN REFMGR.CITE { ADDIN EN.CITE.DATA }}.These women are overtreated by ALND as the 1 or 2 nodes with macrometastases are likely to be removed at the time of sentinel node biopsy and the role of further axillary treatment in this subgroup has been challenged by ACOSOG Z0011{ ADDIN REFMGR.CITE { ADDIN EN.CITE.DATA }} and is being questioned by POSNOC{ ADDIN REFMGR.CITE

<Refman><Cite><Author>Goyal</Author><Year>2015</Year><RecNum>428</RecNum><IDText>POSNOC: A Randomised Trial Looking at Axillary Treatment in Women with One or Two Sentinel Nodes with Macrometastases</IDText><MDL Ref_Type="Journal"><Ref_Type>Journal</Ref_Type><Ref_ID>428</Ref_ID><Titl

e_Primary>POSNOC: A Randomised Trial Looking at Axillary Treatment in Women with One or Two Sentinel Nodes with Macrometastases</Title_Primary><Authors_Primary>Goyal,A.</Authors_Primary><Authors_Primary>Dodwell,D.</Authors_Primary><Date_Primary>2015/12</Date_Primary><Keywords>WOMEN</Keywords><Reprint>Not in File</Reprint><Start_Page>692</Start_Page><End_Page>695</End_Page><Periodical>Clin.Oncol.(R.Coll.Radiol.)</Periodical><Volume>27</Volume><Issue>12</Issue><Misc_3>S0936-6555(15)00312-X [pii];10.1016/j.clon.2015.07.005 [doi]</Misc_3><Address>Royal Derby Hospital, Derby, UK. Electronic address: amit.goyal@nhs.net
St James Hospital, Leeds, UK</Address><Web_URL>PM:26254841</Web_URL><ZZ_JournalFull><fname="System">Clin.Oncol.(R.Coll.Radiol.)</f></ZZ_JournalFull><ZZ_WorkformID>1</ZZ_WorkformID></MDL></Cite></Refman>}. The challenge is to reliably identify this subgroup that can proceed to sentinel node biopsy rather than ALND.

In patients with AUS detected nodal metastasis (FNA or core biopsy positive), we previously showed that tumour size is a strong predictor and tumour histology a weak predictor of number of nodes with macrometastases at ALND{ ADDIN REF MGR.CITE { ADDIN EN.CITE.DATA }}. Together, the predictive ability is low and needs to be improved to reliably select patients who can proceed to SNB instead of ALND. Two retrospective studies have shown that for FNA or core biopsy proven node positive patients, the number of abnormal nodes on preoperative AUS is associated with the extent of nodal disease at histology after ALND{ ADDIN REF MGR.CITE { ADDIN EN.CITE.DATA }}.The aim of the present prospective study was to determine if the number of abnormal nodes seen on preoperative AUS in combination with tumour characteristics reliably predicts the number of positive nodes at histology after ALND and whether this information can be used in clinical practice to identify patients with two or less positive nodes who may be offered SNB rather than ALND.

Methods

A mix of screening and symptomatic women with FNA or core biopsy proven positive node on axillary ultrasound (AUS positive) who subsequently underwent ALND between October 2015 and July 2016 were included in this prospective audit

from six centres (Derby, Leeds, Leicester, Kettering, Cambridge and Dundee). Axillary ultrasound was performed by breast radiologists or radiographers. A node was considered abnormal if there was cortical thickening, loss or displacement of fatty hilum or round shape. The number of abnormal nodes at pre-operative ultrasound examination was recorded. Patient demographics, tumour size, tumour grade, tumour histology, receptor status, number of nodes removed, number of positive nodes and presence or absence of extranodal invasion were recorded. Women who received neoadjuvant chemotherapy or did not undergo surgery were excluded. The study was registered and approved as a multicentre audit locally.

Statistical analysis

Tumour size had a substantially skewed distribution and was analysed using the Mann–Whitney U test. The χ^2 test was used for evaluation of tumour pathology and all binary variables. Tumour grade and number of abnormal nodes on ultrasound scan are an ordinal scale, for which the Mann–Whitney U test was used. Multiple logistic regression analysis was performed to identify significant predictors, for which sensitivity, specificity, and negative and positive predictive values were calculated. $P < 0.050$ was considered statistically significant.

Results

A total of 123 women who had a needle biopsy proven positive node on preoperative AUS were eligible for inclusion in the study. All women underwent breast surgery (breast-conserving surgery or mastectomy) and ALND. The median age of the women was 62 (range 30 to 93) years. Patient demographics, number of abnormal nodes on preoperative AUS, tumour characteristics and findings at ALND are shown in *Table 1.54* of 123 (44%) women had one abnormal node while 69 (56%) had two or more abnormal nodes on preoperative AUS. 40 of 123 (33%) women had two or less nodes with metastases at histology after ALND. Nodes with extranodal invasion were present in 75 of 123 patients (61 per cent).

Predictors of number of nodes with metastases at ALND

Tumours 20 mm or less ($P < 0.001$) and one abnormal node on preoperative AUS ($P < 0.001$) were associated with two or less nodes with metastases at ALND (*Table 2*). 30

of 54 women (55.6 per cent) with one abnormal node on preoperative AUS, and 17 of 29 women with T1 tumour (58.6 per cent) had two or less nodes with metastases at ALND (*Table 2*).

In a logistic regression analysis with two categorical factors (*Table 3*), tumour size (grouped) (χ^2 test $p=0.018$) and number of abnormal nodes on preoperative AUS (χ^2 test $p=0.001$), both contribute significantly to the predictive model but the evidence is stronger for the number of abnormal nodes on preoperative AUS. *Table 4* summarizes the degree of prediction of the likelihood of at least three metastases based on these two factors. This combination had 95 per cent sensitivity (79 of 83), 35 per cent specificity (14 of 40), a negative predictive value of 78 per cent (14 of 18) and positive predictive value of 75 per cent (79 of 105) for heavy nodal burden (≥ 3 positive nodes).

Discussion

Our study shows that among women with needle biopsy proven positive nodes, the combination of number of abnormal nodes on AUS and tumour size can reliably identify patients who may be offered SNB thus less risk of arm morbidity compared with ALND{ ADDIN REFMGR.CITE { ADDIN EN.CITE.DATA }}. Our study shows that less than 1 in 4 women (22 per cent) with invasive tumour size 2 cm or less and one abnormal node on preoperative AUS are found to have more than two positive nodes at histology after ALND, and thus are likely to need a second operation (completion ALND) after initial SNB. The majority of these women (78 per cent) in our study were found to have two or less positive nodes at histology after ALND. The role of further axillary treatment in women with two or less positive nodes at SNB was challenged by ACOSOG Z0011{ ADDIN REFMGR.CITE { ADDIN EN.CITE.DATA }}. American Society of Clinical Oncology guidelines were updated to recommend omission of ALND in women with one to two metastatic sentinel nodes who undergo breast-conserving surgery with whole-breast radiotherapy{ ADDIN REFMGR.CITE <Refman><Cite><Author>Lyman</Author><Year>2016</Year><RecNum>468</RecNum><IDText>Sentinel Lymph Node Biopsy for Patients With Early-Stage Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update

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Ref_Type="Journal"><Ref_Type>Journal</Ref_Type><Ref_ID>468</Ref_ID><Title_Primary><f name="Times New Roman">Sentinel Lymph Node Biopsy for Patients With Early-Stage Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update</f></Title_Primary><Authors_Primary>Lyman,G.H.</Authors_Primary><Authors_Primary>Sommerfield,M.R.</Authors_Primary><Authors_Primary>Bosserman,L.D.</Authors_Primary><Authors_Primary>Perkins,C.L.</Authors_Primary><Authors_Primary>Weaver,D.L.</Authors_Primary><Authors_Primary>Giuliano,A.E.</Authors_Primary><Date_Primary>2016/12/12</Date_Primary><Keywords>Sentinel lymph node</Keywords><Keywords>Sentinel Lymph Node Biopsy</Keywords><Keywords>Biopsy</Keywords><Keywords>Breast</Keywords><Keywords>Breast cancer</Keywords><Reprint>Not in File</Reprint><Start_Page>561</Start_Page><End_Page>564</End_Page><Periodical>J Clin Oncol</Periodical><Volume>35</Volume><Issue>5</Issue><ZZ_JournalFull><f name="System">J Clin Oncol</f></ZZ_JournalFull><ZZ_WorkformID>1</ZZ_WorkformID></MDL></Cite></Refman>}. However, a recent survey shows that radiation oncologists in the US

treat the undissected axilla with radiotherapy rather than omitting axillary treatment{
ADDIN REFMGR.CITE

<Refman><Cite><Author>Azghadi</Author><Year>2016</Year><RecNum>436</RecNum><IDText>Practice Patterns of Radiation Field Design for Sentinel Lymph Node-Positive Early-Stage Breast Cancer</IDText><MDL

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8209(16)30105-7 [pii];10.1016/j.clbc.2016.05.009
[doi]</Misc_3><Address>Department of Radiation Oncology, University of
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jyoti.mayadev@ucdmc.ucdavis.edu</Address><Web_URL>PM:27266803</Web_U
RL><ZZ_JournalFull><f name="System">Clin.Breast
Cancer</f></ZZ_JournalFull><ZZ_WorkformID>1</ZZ_WorkformID></MDL></C
ite></Refman>}. The ACOSOG Z0011 study had various limitations, as a result
clinical practice has not changed in most centres in the UK, Australia and New
Zealand. Women with 1 or 2 nodes with macrometastases at SNB in these centres are
either offered participation in the POSNOC study{ ADDIN REFMGR.CITE
<Refman><Cite><Author>Goyal</Author><Year>2015</Year><RecNum>428</Re
cNum><IDText>POSNOC: A Randomised Trial Looking at Axillary Treatment in
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name="System">Clin.Oncol.(R.Coll.Radiol.)</f></ZZ_JournalFull><ZZ_WorkformID>1</ZZ_WorkformID></MDL></Cite></Refman>} that is evaluating the role of further axillary treatment in these patients or outside the study may be offered axillary radiotherapy that has less functional sequelae than ALND{ ADDIN REFMGR.CITE { ADDIN EN.CITE.DATA }}.

This multicentre prospective study validates our previous findings from a retrospective single centre study{ ADDIN REFMGR.CITE { ADDIN EN.CITE.DATA }}. Tumour size remained a significant predictor, while tumour histology lost its weak predictive ability for more than two positive nodes at ALND in the present study. The number of abnormal nodes on preoperative AUS emerged as the strongest predictor.

Similar to our study, Hieken et al.{ ADDIN REFMGR.CITE <Refman><Cite><Author>Hieken</Author><Year>2013</Year><RecNum>449</RecNum><IDText>Preoperative axillary imaging with percutaneous lymph node biopsy is valuable in the contemporary management of patients with breast cancer</IDText><MDL

Ref_Type="Journal"><Ref_Type>Journal</Ref_Type><Ref_ID>449</Ref_ID><Title_Primary>Preoperative axillary imaging with percutaneous lymph node biopsy is valuable in the contemporary management of patients with breast cancer</Title_Primary><Authors_Primary>Hieken,T.J.</Authors_Primary><Authors_Primary>Trull,B.C.</Authors_Primary><Authors_Primary>Boughey,J.C.</Authors_Primary><Authors_Primary>Jones,K.N.</Authors_Primary><Authors_Primary>Reynolds,C.A.</Authors_Primary><Authors_Primary>Shah,S.S.</Authors_Primary><Authors_Primary>Glazebrook,K.N.</Authors_Primary><Date_Primary>2013/10</Date_Primary><Keywords>Adult</Keywords><Keywords>Aged</Keywords><Keywords>Aged,80 and over</Keywords><Keywords>Axilla</Keywords><Keywords>Axillary dissection</Keywords><Keywords>Biopsy</Keywords><Keywords>Biopsy,Needle</Keywords><Keywords>Breast</Keywords><Keywords>Breast cancer</Keywords><Keywords>Breast Neoplasms</Keywords><Keywords>Female</Keywords><Keywords>Humans</Keywords><Keywords>Lymph Nodes</Keywords><Keywords>Lymphatic Metastasis</Keywords><Keywords>Magnetic Resonance

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name="System">Surgery</f></ZZ_JournalFull><ZZ_WorkformID>1</ZZ_Workfor
mID></MDL></Cite></Refman>} found that the number of abnormal nodes on
ultrasound scan (one vs. multiple) predicted the extent of nodal tumour burden at
ALND. Among needle biopsy positive women, 2 in 3 women with one abnormal node
on AUS had two or less positive nodes at ALND. Likewise Farrell et al.{ ADDIN
REFMGR.CITE { ADDIN EN.CITE.DATA }} reported increasing tumour burden
with the multiple abnormal nodes on preoperative AUS. The median number of nodes
with cancer on ALND was 3 (range 1-21), 5 (range 1-28) and 7 (range 1-41) for
patients with one, two and more than two abnormal nodes on preoperative AUS.

It may be argued that needle biopsy is not needed in women with invasive tumour 2
cm or less and one abnormal node on preoperative AUS and they can proceed to SNB.
The concern is that the biopsied node with metastases may be left in the axilla at
SNB. Nathanson et al.{ ADDIN REFMGR.CITE
<Refman><Cite><Author>Nathanson</Author><Year>2007</Year><RecNum>451
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e_Primary>Preoperative identification of the sentinel lymph node in breast
cancer</Title_Primary><Authors_Primary>Nathanson,S.D.</Authors_Primary><Aut
hors_Primary>Burke,M.</Authors_Primary><Authors_Primary>Slater,R.</Authors_
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 dnathan1@hfhs.org</Address><Web_URL>PM:17661149</Web_URL><ZZ_Journa
 lFull><f name="System">Ann.Surg
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 te></Refman>} reported a 78 per cent concordance between the biopsied node and
 sentinel node. Therefore, a clip can be placed in the needle biopsy positive node and a
 x-ray of the specimen should be performed at SNB to ensure that the clipped node is
 removed. The problem is to successfully localise the clipped node intra-operatively.
 Z1071 shows that in patients with 3 sentinel nodes identified, the clipped node is the
 sentinel node in 78 per cent cases{ ADDIN REFMGR.CITE { ADDIN
 EN.CITE.DATA }}. Alternative strategies are to mark the clipped node using a wire,
 sterile black carbon suspension (SpotTM){ ADDIN REFMGR.CITE { ADDIN
 EN.CITE.DATA }}or radioactive iodine seed(I¹²⁵){ ADDIN REFMGR.CITE {
 ADDIN EN.CITE.DATA }}. If the clipped node is not retrieved, patients should
 undergo ALND.

The simple and less expensive technique of tattooing the positive node at the time of needle biopsy is attractive but remains to be standardised and tested in further studies. The dye may be used both to mark the malignant node and visualise the node intra-operatively{ ADDIN REFMGR.CITE { ADDIN EN.CITE.DATA }}.

Our study is notable as this is a prospective study and the first UK data to allow selection of patients who can be offered SNB. There is a potential to improve the predictive tool as around half of the women with 2 or less positive nodes at ALND do not meet the criteria (tumour size 2 cm or less and one abnormal node on AUS) and will be offered upfront ALND. This study may be criticised as there may be inter-operator and inter-site variability in defining an ‘abnormal node’ at preoperative AUS. However, our study reflects what is happening in the real world and this allows the results to be generalised to other centres. Additionally, the variability is unlikely to affect the results as the entry point is women with a needle biopsy proven positive node rather than an ‘abnormal node’.

To conclude, among women with needle biopsy proven positive nodes, the present study shows that around 3 in 4 patients with invasive tumour size 2 cm or less and one abnormal node on preoperative AUS have 2 or less positive nodes at ALND. These women are overtreated by upfront ALND and can be offered SNB.

COLLABORATORS (in alphabetical order)

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Table 1 Characteristics of patients

Characteristic	n = 123
Age y (median[range])	62[30-93]
Presentation of breast cancer	
symptomatic	98 (80%)
screen detected	25 (20%)
Number of abnormal nodes on ultrasound scan	
1	54 (44%)
2	28 (23%)
>2	41 (33%)
Type of surgery	
Wide local excision	46 (37%)
Mastectomy	77 (63%)
Total no. of nodes removed, mean [SD]	19.9 [8.0]
Total number of positive lymph nodes, mean [SD]	6.6 [7.2]
Number of positive lymph nodes	
1	27 (22%)
2	13 (11%)
3	16 (13%)
≥4	67 (54%)
Extranodal invasion	
present	75 (61%)
absent	44 (36%)
not reported or uncertain	4 (3%)
Tumour size	
Up to 20 mm	29 (24%)
20.1–50 mm	72 (59%)

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Over 50 mm	22 (18%)
Multifocality	
Present	97 (81%)
Absent	23 (19%)
Tumour grade	
I	8 (7%)
II	41 (33%)
III	74 (60%)
Tumour pathology	
Invasive ductal	93 (76%)
Invasive lobular	15 (12%)
Other	15 (12%)
Lymphovascular invasion	
present	75 (64%)
absent	43 (36%)
ER status	
positive	93 (76%)
negative	30 (24%)
HER2 status	
positive	96 (79%)
negative	25 (21%)

Table 2 Tumour characteristics and the number of nodes with metastases identified at axillary lymph node dissection (n=123)

Variable	1 to 2 (n = 40)	3 or more (n = 83)	p-value
Type of surgery			
Wide local excision	18 (45%)	28 (34%)	0.23‡
Mastectomy	22 (55%)	55 (66%)	
Number of abnormal nodes on ultrasound scan			
1	30 (75%)	24 (29%)	<0.001¶
2	7 (18%)	21 (25%)	
>2	3 (8%)	38 (46%)	
Tumour size			
Up to 20 mm	17 (43%)	12 (14%)	<0.001¶
20.1–50 mm	22 (55%)	50 (60%)	
Over 50 mm	1 (3%)	21 (25%)	
Multifocality			
Present	30 (79%)	67 (82%)	0.72‡
Absent	8 (21%)	15 (18%)	
Tumour grade			
I	2 (5%)	6 (7%)	0.57¶
II	16 (40%)	25 (30%)	
III	22 (55%)	52 (63%)	
Tumour pathology			
Invasive ductal	35 (88%)	58 (70%)	0.052‡
Invasive lobular	1 (3%)	14 (17%)	
Other	4 (10%)	11 (13%)	
Lymphovascular invasion			
present	21 (54%)	54 (68%)	0.12‡
absent	18 (46%)	25 (32%)	
ER status			
positive	8 (20%)	22 (27%)	0.43‡
negative	32 (80%)	61 (73%)	
HER2 status			
positive	11 (28%)	14 (17%)	0.16‡
negative	28 (72%)	68 (83%)	

‡ χ^2 test and ¶Mann–Whitney *U* test.

Table 3 Logistic regression for two factors, tumour size and number of abnormal lymph nodes on preoperative AUS

	N	Odds ratio	95% confidence limits
Tumour size (mm)			
≥ 50	22	1.0	
21-50	72	0.26	0.055, 1.20
≤ 20	29	0.085	0.022, 0.34
No. of abnormal nodes on AUS			
More than 2	41	1.0	
2	28	0.29	0.032, 2.54
1	54	0.084	0.009, 0.80

Table 4 Predictive value of tumour size and number of abnormal lymph nodes on preoperative AUS

	No. of nodes with metastases		Total
	≤ 2	≥ 3	
Tumour size ≤ 20 mm and 1 abnormal node on AUS	14	4	18
Tumour size > 20 mm or ≥ 2 abnormal nodes on AUS	26	79	105
Total	40	83	123

Summary statistics for heavy nodal burden (≥ 3 positive nodes) as a predictor of presence of 3 or more metastases, with 95% confidence limits:

Sensitivity 95% (88%, 98%)

Specificity 35% (22%, 50%)

Negative predictive value 78% (55%, 91%)

Positive predictive value 75% (66%, 83%).