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1   **Introduction**

2   Breast lesions yielding an image guided biopsy diagnosis of Ductal Carcinoma in Situ (DCIS) may contain

3   invasive foci when the entire lesion is removed at surgery. Such an upgrade may lead to further surgery,

4   especially to the axilla (1). Predicting the likelihood of upgrade to invasion is useful as it may change

5   options for initial surgery, particularly with regard to sentinel node biopsy. Factors predicting upgrade

6   of DCIS lesions diagnosed with stereotactic biopsy have been well established in the literature and

7   include mammographic extent, palpability and grade of DCIS diagnosed on percutaneous biopsy (2-4).

8   However, factors predicting upgrade following an US guided biopsy of DCIS have not been well

9   established and only two previous studies have studied shear wave elastography (SWE) in this context

10   (5-8). A number of reports of SWE of the breast have shown that DCIS lesions are less stiff than invasive

11   cancers (9, 10). These findings suggest that SWE may be useful in predicting the presence of invasion.

12   The aim of this study is to establish the role of mammographic, ultrasound, SWE and other pre-operative

13   features in predicting invasion at surgical excision in lesions yielding an US guided 14g core biopsy

14   diagnosis of DCIS.

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16 **Methods**

17 SWE has been part of the routine breast ultrasound examination at our centre since November 2009.

18 Quantitative data are routinely extracted prospectively within a few days of the examination and before

19 biopsy results were known. In accordance with the applicable National Research Ethics Service guidance,

20 ethical approval for this retrospective study of prospectively acquired anonymised data was not

21 required (National Research Ethics Service, 2008(11)). However, written informed consent to use images

22 was obtained, according to routine practice.

23 All patients with US visible lesions were scanned using the Aixplorer ultrasound system (SuperSonic

24 Imagine™, Aix en Provence, France) between December 2010 and December 2015 Those patients with

25 lesions visible on greyscale US and subjected to ultrasound guided 14g needle core biopsy yielding a

26 biopsy diagnosis of DCIS were included in this study. Patients with biopsies from elsewhere in the

27 ipsilateral breast showing invasive disease were excluded.

28 All patients were scanned and biopsied with ultrasound guidance by one of five breast radiologists or an

29 advanced radiography practitioner trained to perform and interpret breast ultrasound. These

30 practitioners had between 7 and 22 years of breast ultrasound experience and had at least 3 months

31 experience of performing SWE of solid breast lesions prior to the commencement of the study.

32 Greyscale and SWE images were obtained during the standard ultrasound appointment. Four SWE

33 images in two orthogonal planes were obtained. The region of interest (ROI) utilised in all cases was

34 2mm in diameter. A threshold value of 50 kilopascals (kPa) was used for mean elasticity (Emean) to

35 dichotomise the elasticity data. This threshold has been validated in previous studies using SWE to

36 differentiate between benign and malignant masses (12, 13). The average of the 4 values from the 4

37 images was used for analysis. Additionally the mean SWE value across the entire study group was also

38 used as a possible cut off value.

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39   The size and BIRADS classification of the greyscale US abnormalities were recorded as was the presence

40   or absence of an US visible mass or calcification (some lesions were visible as textural change with or

41   without US visible calcifications). The dominant mammographic feature was also recorded as was the

42   BIRADS classification of any mammographic abnormality.

43   The source of the patient from either mammographic screening or the symptomatic referral service was

44   noted as was the palpability of the lesion. The histological grade of DCIS present on the US guided 14g

45   core biopsy was recorded. Regarding subsequent surgical excisions, micro-invasion was included in the

46   DCIS group as such lesions do not routinely warrant an axillary nodal procedure. The size, grade,

47   vascular invasion and nodal status of any invasive foci were collected from the surgical pathology report.

48   The significance of differences between groups was established using the chi-square test with $p < 0.05$

49   taken to indicate statistically significant differences.

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Results

Analysis of 1954 US visible masses with histological correlation yielded 57(3%) patients with an US 14g
core biopsy diagnosis of DCIS who had subsequent surgical excision. The mean age of the patients was
60 yrs (range 23 -82 yrs). 33(58%) lesions were screen-detected while 24(42%) resulted from
investigation of symptoms. At surgical excision 24(42%) patients had invasive foci while 33 had DCIS
only. The features of the 24 invasive cancers are shown in Table 1. 12 of 24 (50%) invasive foci were
less than 10mm in diameter and 2 of 24 (8%) were node positive. The mean histological whole tumour
size (i.e. extent including DCIS) was 28mm for the pure DCIS lesions and 53 mm for those containing an
invasive focus.

The relationship between pre-operative factors and presence of invasion are shown in Tables 2 to 4.
Patients presenting with symptoms were more likely to have invasive foci than patients presenting
through screening (58% [14 of 24] vs. 30% [10 of 33], p=0.03). Patients whose lesions had a mean
stiffness at SWE of > 50kPa were more likely to have an invasive focus then women with lesions whose
mean stiffness was <50kPa (51% [20 of 39] vs. 22% [4 of 18], p=0.04). The mean stiffness value in the
entire study group was 84kPa. Using this as a cut off value did not aid the identification of those women
with invasive foci. The mean stiffness values for women with and without invasion were 89 kPa and
78kPa respectively, while the median values were 74 kPa and 56 kPa. Trends towards younger women
and women with high greyscale US suspicion scores (BI-RADS) did not achieve statistical significance.

Patient age, core biopsy DCIS grade, US lesion size (mean size was 17mm), mammographic features and
mammography BI-RADS score showed no significant relationship with the presence of invasion at
excision. The presence of an ultrasound visible mass or calcification likewise did not have an association
with invasion. Palpability of the lesion did not have a statistically significant relationship with invasion as
10 of 18 (55%) of palpable lesions were invasive compared to 14 of 39(36%) impalpable lesions (p=0.16).

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75   Combining the two significant predictors of invasion further improves risk stratification (Table 5) with

76   symptomatic and stiff lesions having a risk of invasion of 67% (12 of 18) while soft lesions presenting at

77   screening had only a 17% (2 of 12) risk of invasion (p=0.02).

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Discussion

We have shown that the stiffness of lesions yielding a core biopsy diagnosis of DCIS has a significant relationship with the risk of occult invasion at excision. We have also found that occult invasion is commoner in women whose lesions are symptomatic compared to women presenting through mammographic screening. The combination of these two factors allows a high risk group of women with stiff lesions that are symptomatic to be identified. This group has a risk of invasion of 67% and it contains half the women in the study group with invasion. Thus, this is a group where sentinel lymph node biopsy (SNB) may be justified or, alternatively, another approach such as re-biopsing these women using a large volume vacuum-assisted biopsy (VAB) technique to try and confirm the presence of invasion could be considered. Women whose lesions are not symptomatic or stiff have a low risk of invasion (17%) and neither repeat biopsy nor SNB would seem justified. The two intermediate groups (screen detected and stiff, or symptomatic but soft) also have a relatively low risk of invasion and SNB or further biopsy is probably not required in these patients either. It should also be noted that the nodal positivity rate in those women with invasion in this study was very low (8%).

A number of previous studies have shown that invasive cancers tend to be stiffer than DCIS lesions (9, 10) while two previous studies have shown that stiffness is associated with upgrade following an ultrasound guided biopsy with a DCIS diagnosis (5,8). Neither of these studies combined the significant factors to provide the risk stratification shown in table 5 which may aid clinical management.

What is unclear is whether the increased stiffness in the upgrade group is because the invasive focus itself was imaged but not biopsied or whether increased stiffness identifies DCIS lesions at particular risk of invasion. The stiffness of invasive cancers is usually most marked at the lesional/stromal boundary and is thought to be due in part, to the stiffness of the extracellular matrix (ECM) produced by cancer associated fibroblasts (CAFs). CAFs are important in tumour progression, invasion and metastasis (14-

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102   16) and this is likely to be the reason why stiffness at SWE has been shown to be an independent

103   predictor of nodal metastasis (17). Similarly the stiffness detected in DCIS lesions is likely to be due to

104   the stiffness of the extracellular matrix produced by CAFs, which are also present within DCIS lesions.

105   Stromal influences are known to be important in initiating invasion within DCIS lesions (14-16). It is

106   therefore possible that the increased stiffness seen with DCIS lesions with occult invasion is due to stiff

107   stroma produced by activated CAFs which also initiate invasion, in contrast to less stiff stroma in DCIS

108   lesions with lower invasive potential.

109   We have also found that occult invasion is commoner in women whose lesions were symptomatic

110   compared to women presenting through mammographic screening.   It has been noted in previous

111   studies that palpability is associated with upgrade following a biopsy diagnosis of DCIS (2-4). Not all

112   patients with symptoms have a palpable lesion (some may have presented with nipple discharge) and

113   some screen detected lesions are palpable. We found palpability less predictive than the source of

114   referral.

115   A number of previous studies have studied the greyscale US features of lesions yielding an US guided

116   core biopsy diagnosis of DCIS and upgrade to invasive cancer. The results of these studies have been

117   inconsistent. Some have found abnormal axillary lymph nodes and large lesion size to be associated

118   with higher rates of upgrade to invasive cancer (6, 7). In our study, we did not find US lesion size a

119   useful predictor of invasion. We did not assess the value of abnormal axillary lymph nodes in our study

120   as the node positivity rate was so low.

121   Studies looking at upgrade following stereotactic biopsy of malignant calcifications have found that DCIS

122   grade of the biopsy and calcification extent are predictors of occult invasion (2-4). Neither of these

123   factors was significant in the present study. The reason why grade of DCIS does not predict invasion in

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124   the current study is not clear. There is not a hint of a difference so the small numbers in the current

125   study does not appear to be the reason for this finding.

126   There are a number of limitations in the current study. The study was carried out in a single centre and

127   has a relatively small numbers of patients. The centre has a special interest in SWE so whether the

128   results are generalizable is open to question. However the results are consistent with the two other

129   study examining the role of SWE in predicting invasion after an US guided core biopsy result of DCIS

130   (5,8).

131   In conclusion, we have found that stiffness on SWE and the referral source of the patient are predictors

132   of occult invasion in women with an US guided core biopsy diagnosis of DCIS and that the combination

133   of these factors allows stratification of invasion risk which might be used to guide future patient

134   management.

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136   **References**

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138   1. O'Flynn EA, Currie RJ, Mohammed K, Allen SD, Michell MJ. Pre-operative factors indicating risk of

139   multiple operations versus a single operation in women undergoing surgery for screen detected breast

140   cancer. Breast. 2013 Feb;22(1):78-82.

141   2. Lee SK, Yang JH, Woo SY, Lee JE, Nam SJ. Nomogram for predicting invasion in patients with a

142   preoperative diagnosis of ductal carcinoma in situ of the breast. Br J Surg. 2013 Dec;100(13):1756-63.

143   3. Kim J, Han W, Lee JW, You JM, Shin HC, Ahn SK, Moon HG, Cho N, Moon WK, Park IA, Noh DY. Factors

144   associated with upstaging from ductal carcinoma in situ following core needle biopsy to invasive cancer

145   in subsequent surgical excision. Breast. 2012 Oct;21(5):641-5.

146   4. Brennan ME, Turner RM, Ciatto S, Marinovich ML, French JR, Macaskill P, Houssami N. Ductal

147   carcinoma in situ at core-needle biopsy: meta-analysis of underestimation and predictors of invasive

148   breast cancer. Radiology. 2011 Jul;260(1):119-28

149   5. Park AY, Son EJ, Kim JA, Han K, Youk JH. Lesion stiffness measured by shear-wave elastography:

150   Preoperative predictor of the histologic underestimation of US-guided core needle breast biopsy. Eur J

151   Radiol. 2015 Dec;84:2509-14.

152   6. Park SH, Kim MJ, Kim SJ, Kim EK. Ductal carcinoma in situ diagnosed using an ultrasound-guided 14-

153   gauge core needle biopsy of breast masses: can underestimation be predicted preoperatively?

154   Ultrasonography. 2014 Apr;33(2):128-35.

155   7. Park AY, Gweon HM, Son EJ, Yoo M, Kim JA, Youk JH. Ductal carcinoma in situ diagnosed at US-guided

156   14-gauge core-needle biopsy for breast mass: preoperative predictors of invasive breast cancer. Eur J

157   Radiol. 2014 Apr;83(4):654-9.

9

158   8. Bae JS, Chang JM2, Lee SH, Shin SU, Moon WK. Prediction of invasive breast cancer using shear-wave

159   elastography in patients with biopsy-confirmed ductal carcinoma in situ. Eur Radiol. 2016 Apr 16. [Epub

160   ahead of print]

161   9. Vinnicombe SJ, Whelehan P, Thomson K et al. What are the characteristics of breast cancers

162   misclassified as benign by quantitative ultrasound shear wave elastography? Eur Radiol. 2014

163   Apr;24(4):921-6.

164

165   10. Berg WA, Mendelson EB, Cosgrove DO, Doré CJ, Gay J, Henry JP, Cohen-Bacrie C. Quantitative

166   Maximum Shear-Wave Stiffness of Breast Masses as a Predictor of Histopathologic Severity. AJR Am J

167   Roentgenol. 2015 Aug;205(2):448-55

168   11. National Research Ethics Service (2008) Approval for medical devices research: guidance for

169   researchers, manufacturers, research ethics committees and NHS R&D offices (Version 2). London:

170   *National Patient Safety Agency*.

171   12. Evans A, Whelehan P, Thomson K et al Differentiating benign from malignant solid breast masses:

172   value of shear wave elastography according to lesion stiff-ness combined with gray scale ultrasound

173   according to BI-RADS classification. Br J Cancer 2012 107:224–229

174   13. Evans A, Whelehan P, Thomson K, et al. Quantitative shear wave ultrasound elastography: initial

175   experience in solid breast masses. Breast Cancer Research 2010; 12:R1

176   14. Osuala KO, Sameni M, Shah S, Aggarwal N, Simonait ML, Franco OE, Hong Y, Hayward SW, Behbod F,

177   Mattingly RR, Sloane BF.Il-6 signaling between ductal carcinoma in situ cells and carcinoma-associated

178   fibroblasts mediates tumor cell growth and migration. BMC Cancer. 2015 Aug 13;15:584. doi:

179   10.1186/s12885-015-1576-3.

180   15. Martins D1, Beça FF, Sousa B, Baltazar F, Paredes J, Schmitt F. Loss of caveolin-1 and gain of MCT4

181   expression in the tumor stroma: key events in the progression from an in situ to an invasive breast

182   carcinoma. Cell Cycle. 2013 Aug 15;12(16):2684-90.

183   16. Vargas AC, McCart Reed AE, Waddell N, Lane A, Reid LE, Smart CE, Cocciardi S, da Silva L, Song S,

184   Chenevix-Trench G, Simpson PT, Lakhani SR. Gene expression profiling of tumour epithelial and stromal

185   compartments during breast cancer progression. Breast Cancer Res Treat. 2012 Aug;135(1):153-65

186   17. Evans A, Rauchhaus P, Whelehan P, Thomson K, Purdie CA, Jordan LB, Michie CO, Thompson AM,

187   Vinnicombe S. Does shear wave ultrasound independently predict axillary lymph node metastasis in

188   women with invasive breast cancer? Breast cancer research and treatment. 2014;143:153-7

189

190