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Does shear wave ultrasound independently predict axillary lymph node metastasis in women with invasive breast cancer?

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Abstract Shear wave elastography (SWE) shows promise as an adjunct to greyscale ultrasound examination in assessing breast masses. In breast cancer, higher lesion stiffness on SWE has been shown to be associated with features of poor prognosis. The purpose of this study was to assess whether lesion stiffness at SWE is an independent predictor of lymph node involvement. Patients with invasive breast cancer treated by primary surgery, who had undergone SWE examination were eligible. Data were retrospectively analysed from 396 consecutive patients. The mean stiffness values were obtained using the Aixplorer[®] ultrasound machine from SuperSonic Imagine Ltd. Measurements were taken from a region of interest positioned over the stiffest part of the abnormality. The average of the mean stiffness value obtained from each of two orthogonal image planes was used for analysis. Associations between lymph node involvement and mean lesion stiffness, invasive cancer size, histologic grade, tumour type, ER expression, HER-2 status and vascular invasion were assessed using univariate and multivariate logistic regression. At univariate analysis, invasive size, histologic grade, HER-2 status, vascular invasion, tumour type and mean stiffness were significantly associated with nodal involvement. Nodal involvement rates ranged from 7 % for tumours with mean stiffness <50 kPa to 41 % for tumours

with a mean stiffness of >150 kPa. At multivariate analysis, invasive size, tumour type, vascular invasion, and mean stiffness maintained independent significance. Mean stiffness at SWE is an independent predictor of lymph node metastasis and thus can confer prognostic information additional to that provided by conventional preoperative tumour assessment and staging.

Keywords Breast cancer · Prognosis · Elastography · Metastasis

Introduction

Several large studies have shown that the addition of shear wave elastography (SWE) to greyscale ultrasound improves the performance of ultrasound examination in differentiating benign from malignant breast masses [1–3]. SWE is quantitative and highly reproducible, in contrast to static elastography [3–6]. The combination of SWE and greyscale ultrasound has been shown to be highly sensitive; that is, if both are negative, malignancy is extremely unlikely (no false-negative cases in a series of 111 published in 2012) [3]. It is therefore likely that SWE will be increasingly used in routine clinical practise.

It has been shown that large invasive size, high histological grade and vascular invasion are independently associated with increased stiffness at SWE [7, 8]. These studies did not show lesion stiffness to be an independent predictor of nodal status but given the relatively small numbers, they may have been underpowered for this outcome. Lymph node status is the most powerful prognostic indicator in breast cancer [9] and knowledge of lymph node status influences both surgical management and the use of systemic therapy (adjuvant and neoadjuvant).

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More accurate identification of likely lymph node metastases at diagnosis could minimise the need for a subsequent surgical procedure to clear the axilla following initial surgery and sentinel node biopsy. A second operation carries costs and risks, in addition to an inevitable delay in time to initiation of adjuvant chemotherapy, which should be given in a timely fashion to optimise long-term patient outcome [10].

The aim of this study was to determine, in a large series of patients with primary invasive breast cancer treated initially by surgery, whether SWE findings could independently predict lymph node status when taking known predictors of nodal status such as invasive size, histological grade and vascular invasion status [11, 12] into account. If SWE finding are predictive of lymph node involvement this may be clinically useful in selecting patients for neo-adjuvant chemotherapy (NACT), as the established predictors of nodal involvement are only definitively available post operatively, and ultrasound guided percutaneous biopsy of nodes with abnormal ultrasound morphology only establishes a diagnosis of nodal metastases in around 50 % of cases shown to be positive at surgery [13].

Patients and methods

SWE has been part of routine breast ultrasound examinations at our institution since November 2009. In accordance with the applicable UK National Research Ethics Service guidance [14], ethical approval for the study was not required. Consecutive patients with invasive breast cancer identified during ultrasound scans using the Aixplorer[®] ultrasound system (SuperSonic Imagine, Aix en Provence, France) between 19/04/2010 and 12/12/2012 and treated by primary surgery were included in this study.

The sample included women with symptoms and women with screen-detected abnormalities. All women were scanned and biopsied by one of three breast radiologists or an advanced radiography practitioner trained to perform and interpret breast ultrasonography. These practitioners had between 5 and 20 years of breast ultrasound experience and had at least 3 months experience of performing SWE of solid breast lesions.

Greyscale and elastography images were obtained during the standard ultrasound appointment. The elastography colour map findings were taken into account in the diagnostic management of the patients but the quantitative measurements were produced and analysed later to minimise impact on workflow. The elasticity values were obtained by moving a delineated region of interest (ROI) over the colour map. As the ROI moves, the readings change in real time so the ROI can be positioned over the part of the image showing the stiffest tissue.

Four elastography images—in each of two orthogonal planes—were taken of each lesion. The transducer was held still over the lesion for about 10 s to allow the shear wave image to build up. If the patient was breathing heavily, she was asked to hold her breath during acquisition. Mean ROI stiffness values (kPa) from the four images were used for analysis.

Analysis was based on histological data points from pathological examination of the resected specimen: histological grade, tumour type, invasive size, vascular invasion, ER, HER-2 status and lymph node stage. These were assessed according to UK national guidelines [15, 16]. Macro-metastases were counted as node positive while micro-metastases and isolated tumour cells were counted as node negative. Univariate and multivariate logistic regression were used to establish the significance of associations of histological and shear wave findings with lymph node status.

Results

The sample comprised 396 patients; 217 presented with symptoms, whereas 179 had cancers detected by mammographic screening. The patients' ages ranged from 31 to 92 years with a median of 62 years. The histological characteristics of the study group are shown in Table 1. The median invasive tumour size was 19 mm, 28 % of patients had lymph node metastases and 27 % had vascular invasion. The tumour stiffness values according to nodal status are shown in Table 2. Nodal status according to range of mean stiffness values is shown in Table 3. Nodal metastasis rates ranged from 7 % for tumours with mean stiffness <50 kPa to 41 % for tumours with a mean stiffness of >150 kPa.

At univariate analysis, invasive size, histological grade, HER-2 status, vascular invasion, tumour type and mean

Table 1 Histological features of the 396 invasive cancers in the study group

Histological feature	Number (%)
Grade 1	55 (14)
Grade 2	167 (42)
Grade 3	174 (44)
Node positive	112 (28)
Vascular invasion	105 (27)
HER 2 positive ^a	36 (9)
ER positive	330 (83)
PR positive	271 (68)
Invasive size <15 mm	131 (33)

^a 6 patients had unknown HER 2 status

Table 2 Mean stiffness (kPa) values of 396 breast cancers by nodal status

	Range of mean stiffness values (kPa)	Mean of mean stiffness values (kPa)	Median of mean stiffness values (kPa)
Node negative (<i>n</i> = 284)	14–281	114	105
1–3 nodes positive (<i>n</i> = 78)	31–281	141	130
4 or more nodes positive (<i>n</i> = 34)	77–265	156	149

Table 3 Nodal status according to mean stiffness value (range)

Mean stiffness range (kPa)	Node negative <i>n</i> (%)	Node positive <i>n</i> (%)
<50	27 (93)	2 (7)
50–99	101 (78)	28 (22)
100–149	83 (72)	32 (28)
>150	73 (59)	50 (41)

stiffness were significantly associated with nodal involvement while ER, PR and age were not (Table 4). At multivariate analysis, invasive size, tumour type, vascular invasion and mean stiffness maintained independent significance in predicting nodal involvement while ER, PR, HER-2, age and histological grade did not (Table 5).

Discussion

We have found that mean stiffness as measured by SWE is an independent predictor for nodal involvement in breast cancer in addition to well-established predictors such as invasive size and vascular invasion status. In contrast to previous studies, [11, 12] histological grade was not an independent predictor of nodal involvement on multivariate analysis. This may be because stiffness on SWE is associated with histological grade [7, 8].

The stiff tissue associated with invasive breast cancer is usually seen at the periphery of the tumour, extending into the peri-tumoural stroma. Often, the tumour itself is less stiff than the surrounding stroma. Although not proven, it is likely that the stiffness represents abnormal tumour-associated collagen, which has been shown to exhibit increased collagen crosslinking and abnormal alignment. These collagen abnormalities have recently been shown to have independent prognostic significance [17, 18]. In recent years, stromal gene signatures, and components such as

Table 4 Univariate logistic regression

Dependent parameter	Independent parameter	<i>p</i> value
Nodal Involvement (yes/no)	Age (years)	0.6083
	ER (binary)	0.1739
	HER2 status	0.0408
	Invasive size (mm)	<0.0001
	PR (binary)	0.0930
	Stiffness reading	<0.0001
	Tumour grade	<0.0001
	Tumour type (classified)	0.0020
	Vascular invasion	<0.0001

Table 5 Multivariate logistic regression

Dependent parameter	Independent parameter	<i>p</i> value
Nodal involvement (yes/no)	Age (years)	0.7655
	ER (binary)	0.4626
	HER2 status	0.4570
	Invasive size (mm)	<0.0001
	PR (binary)	0.3698
	Stiffness reading	0.0350
	Tumour grade	0.6300
	Tumour type (classified)	0.0104
	Vascular invasion	0.0027

Caveolin 1 and LOX 2, have been shown to be important prognostic and predictive indicators in breast cancer [19–22]. It is possible that the peri-tumoural stromal stiffness represents an imaging surrogate for some of these stromal processes. As these stromal prognostic indicators are not measured by the conventional predictors of nodal involvement, such as invasive size and histological grade, it is not surprising that stromal stiffness has independent predictive significance. Vascular invasion, another well-established predictive factor for axillary lymph node metastasis in breast cancer, has been shown to have a strong relationship with stromal stiffness on SWE [7, 8]. Like SWE stiffness, vascular invasion is also most commonly seen at the tumour–stromal interface [23]. The independence of vascular invasion and stromal stiffness as predictors of nodal metastasis suggests that the predictive power of stromal stiffness is mediated by other factors in addition to vascular invasion.

Previous SWE studies have found that increased stiffness is associated with nodal metastases on univariate analysis [7, 8]. However, these studies did not show SWE stiffness to be an independent predictor of lymph node metastasis on multivariate analysis. This difference in findings compared to the current study may reflect insufficient statistical power resulting from the lower participant

numbers (166 and 100, compared to 396 in this study). The larger of the previous studies took only one shear wave measurement from each tumour while the current study took four, further increasing the statistical power of our study.

The main weakness of the current study is that it is from a single centre with a special interest in SWE. We do not know whether such results are reproducible in other clinical centres. Although the analysis was retrospective, the SWE data were acquired prospectively as part of our routine clinical practise, and recorded before core biopsy results or surgical pathology were known.

In current practise, ultrasound guided needle biopsy of axillary lymph nodes with abnormal cortical morphology allows pre-operative diagnosis of axillary metastases in only around 50 % of women [13]. Preoperative diagnosis of nodal metastases is valuable as, when added to tumour size estimation on imaging and histological grading on core biopsy, it refines preoperative prognostication [24, 25]. This can facilitate the use of NACT to down-stage tumours prior to surgery, or to identify more accurately at diagnosis the most appropriate axillary surgery for patients following NACT. There remains some debate regarding the optimal timing of sentinel lymph node biopsy (SLNB) in patients receiving NACT [26], and the false negative rate of SLNB after neoadjuvant chemotherapy may be higher than would be deemed acceptable [27]; consequently, any tool to help facilitate more accurate staging of the axilla at diagnosis would be valuable. Our findings suggest that SWE has the potential to refine preoperative prognostication, and thus help improve decision making with regard to neo-adjuvant chemotherapy and management of the axilla.

In conclusion, mean stiffness at SWE is an independent predictor of lymph node metastasis in women with invasive breast cancer and thus can contribute additional, non-invasive prognostic information compared to conventional preoperative tumour assessment and staging.

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Conflict of interest The authors declare no other potential conflict of interest.

Ethical Standards In accordance with the applicable UK National Research Ethics Service guidance [14], ethical approval for the study was not required.

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