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FULL PAPER

Shear-wave elastography and greyscale assessment of palpable probably benign masses: is biopsy always required?

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Objective: To establish if palpable breast masses with benign greyscale ultrasound features that are soft on shear-wave elastography (SWE) (mean stiffness <50 kPa) have a low enough likelihood of malignancy to negate the need for biopsy or follow-up.

Methods: The study group comprised 694 lesions in 682 females (age range 17–95 years, mean age 56 years) presenting consecutively to our institution with palpable lesions corresponding to discrete masses at ultrasound. All underwent ultrasound, SWE and needle core biopsy. Static greyscale images were retrospectively assigned Breast Imaging Reporting and Data System (BI-RADS) scores by two readers blinded to the SWE and pathology findings, but aware of the patient's age. A mean stiffness of 50 kPa was used as the SWE cut-off for calling a lesion soft or stiff. Histological findings were used to establish ground truth.

Results: No cancer had benign characteristics on both modalities. 466 (99.8%) of the 467 cancers were classified BI-RADS 4a or above. The one malignant lesion classified as BI-RADS 3 was stiff on SWE. 446 (96%) of the 467 malignancies were stiff on SWE. No cancer in females under 40 years had benign SWE features. 74 (32.6%) of the 227 benign lesions were BI-RADS 3 and soft on SWE; so, biopsy could potentially have been avoided in this group.

Conclusion: Lesions which appear benign on greyscale ultrasound and SWE do not require percutaneous biopsy or short-term follow-up, particularly in females under 40 years.

Advances in knowledge: None of the cancers had benign characteristics on both greyscale ultrasound and SWE, and 32% of benign lesions were BI-RADS 3 and soft on SWE; lesions that are benign on both ultrasound and SWE may not require percutaneous biopsy or short-term follow-up.

INTRODUCTION

Shear-wave elastography (SWE) allows quantitative and reproducible measurements of lesion stiffness in kilopascals and can be performed quickly during routine breast ultrasound examinations. It has been shown to yield accurate information with regard to benign/malignant differentiation of solid breast masses.[1–3] SWE allows measurement of the propagation speed of shear waves within the tissue, to locally quantify its stiffness in kilopascals or metre per second. A variety of quantitative measures can be obtained with SWE, including the mean, maximum and "standard deviation" from a user-defined region of interest (ROI). Qualitative assessments have also been found to be useful (shape at SWE, pattern of stiffness and heterogeneity of stiffness).[1–5] Several large studies have shown that the addition of SWE to greyscale ultrasound improves the performance of ultrasound in differentiating benign from malignant breast masses.[1,3,6] Notably, the combination of benign SWE and greyscale ultrasound findings has been shown to be highly specific, and malignancy is extremely unlikely, with a negative-predictive value for the combination of 100%.[6] The SWE parameter of mean stiffness is highly accurate in differentiating between benign and malignant solid breast masses and has performance parameters at least as good as the Breast Imaging Reporting and Data System (BI-RADS) evaluation of greyscale images.[6] Cancers classified as benign by quantitative SWE are uncommon and are more often small (≤10 mm), low grade or pure ductal carcinoma *in situ* (DCIS).[7] Since such tumours are more frequently detected at screening, SWE has been found to have superior performance in females who are symptomatic compared with females with screen-detected abnormalities (SWE sensitivity has been found to be 99% in symptomatic patient and 87% in screening patient).[7]

Because of the very low incidence of malignancy in young females, there has been a tendency not to biopsy or even follow-up females under 25 years with solid breast masses with benign features on greyscale ultrasound.[8] This has been possible because of the accuracy of modern greyscale ultrasound in differentiating benign from malignant breast masses.[9–12] Indeed, in some units in the UK, this arbitrary age cut-off for biopsy or follow-up has been safely increased to 30 years.[13]

We hypothesize that palpable breast masses having both benign greyscale (BI-RADS Category 3)[14] and SWE features have a very low chance of being malignant and biopsy or follow-up may not be required. We have therefore reviewed a prospectively collected consecutive series of palpable breast masses, visible on ultrasound, with both SWE and BI-RADS classification, to assess the malignancy rate in females with masses that have benign greyscale and SWE features.

METHODS AND MATERIALS

SWE has been part of the routine breast ultrasound examination of solid breast masses at our institution since November 2009. In accordance with the applicable National Research Ethics Service guidance, ethical approval for the study was not required (National Research Ethics Service, 2008). However, written informed consent to use images was obtained, according to routine practice in our institution.

All consecutive patients with palpable mass were scanned using the Aixplorer ultrasound system® (SuperSonic Imagine, Aix en Provence, France) between 29 December 2010 and 4 April 2014. Those patients with discrete masses on greyscale ultrasound, subjected to core needle biopsy and/or surgical biopsy according to standard clinical protocols were included in this study.

32 females who did not have a discrete lump at ultrasound imaging were excluded. Images from a further six patients were not available, and these were excluded. Thus, the final cohort for this study included 682 patients with 694 lesions.

All females were scanned and biopsied with ultrasound guidance by one of five breast radiologists (AE, SV, KT, DM, GE) or an advanced radiography practitioner trained to perform and interpret breast ultrasound. These practitioners had between 7 and 22 years' experience in breast ultrasound and had a minimum of 3 months' experience of performing SWE of solid breast lesions. Greyscale and elastography images were obtained during the standard ultrasound appointment. Acquisition of the elastography images added 1–2 min to the examination time. The elastography colour map findings were taken into account in the diagnostic management of the patients, but the quantitative measurements were produced and analyzed *post hoc* to minimize impact on workflow. Extracting the quantitative data at the end of the clinic took 1–2 min for each lesion. The ROI utilized in all cases was 2 mm in diameter. As the ROI is moved by the operator, the figures change in real time so that the stiffest ROI can be identified. A cut-off value for mean elasticity of the ROI of 50 kPa was used for benign/malignant differentiation, as this level has been validated in previous studies.[2,6,15]

Static greyscale images underwent retrospective standard BI-RADS classification by a breast radiologist and a breast radiology trainee, both blinded to the elastography and pathology findings but aware of the patient's age (Category 3: probably benign, Category 4a: low suspicion, Category 4b: intermediate suspicion, Category 4c: moderate suspicion and Category 5: highly suggestive of malignancy).[16] BI-RADS Categories 1–3 were taken as negative, since the American College of Radiology guidelines state that such lesions can be managed without immediate biopsy. BI-RADS scores of 4 or 5 were taken as positive.[17] Differences between the readers were resolved by consensus.

Core biopsies were performed using a 14-g automated gun under ultrasound guidance. When repeat biopsies, vacuum-assisted biopsies/removals or surgery were performed, the final histological diagnosis was used for analysis. The proportion of malignancies in lesions with BI-RADS 3 classification and average mean stiffness <50 kPa was obtained.

Statistical analyses

For the purposes of this analysis, continuous variables were dichotomized (for example, lesion size was dichotomized into $>$ or <10 mm). The significance of differences in categorical variables between groups was assessed using χ^2 and Fisher's exact tests, and p-values of ≤ 0.05 were taken to indicate statistical significance. Analyses were performed using IBM SPSS® v. 21 (IBM, Portsmouth, UK).

RESULTS

694 lesions in 682 patients (age range 17–95 years, mean age 56 years) were included in the study. 227 (32.7%) lesions were benign (age range 19–91 years, mean age 42 years) and 467 (67.3%) lesions were malignant (age range 24–95 years, mean age 63 years).

The histological characteristics of the benign lesion are shown in Table 1; the commonest benign lesion was fibroadenoma. Of the 467 malignant lesions, 459 (98.2%) lesions were invasive carcinoma. The commonest invasive cancer was grade 3 ductal carcinoma of no special type, which was >15 mm. There were 4 (0.8%) DCIS masses, 1 (0.2%) metastasis from melanoma, 2 (0.4%) lymphomas and 1 (0.2%) plasmacytoma. The characteristics of the lesions according to age are shown in Table 2. The

Table 1. Benign lesion characteristics

Characteristics	Number of lesions (%)
Fibroadenoma	141 (62.1)
Fibrocystic change	26 (11.5)
Inflammation	10 (4.4)
Papilloma	8 (3.5)
Lobular carcinoma *in situ*	4 (1.8)
Fat necrosis	9 (3.9)
Others	29 (12.8)
Total	227 (100)

Table 2. Number and characteristics of lesions according to age

Patient age (years)	Number of patients	Number of cancers (%)
<30	46	3 (6.5)
30–39.99	87	21 (24.1)
40–49.99	183	110 (60.1)
50–59.99	98	74 (75.5)
60–69.99	95	85 (89.5)
70–79.99	91	87 (95.6)
≥80	94	87 (92.5)

mean ultrasound size of lesions in the study was 19.4 mm (benign lesions, 17 mm; malignant lesions, 21 mm).

223 (32.1%) of the 694 lesions were assigned different BI-RADS scores by the two readers; 13 (1.8%) lesions were classified as BI-RADS 3 by one reader but as BI-RADs 4a by the other reader. There were no cases where a lesion was classified as BI-RADS 3 by one reader and BI-RADS 4b, 4c or 5 by the other.

466 (99.8%) of the 467 cancers were classified BI-RADS 4a or above; the BI-RADS scores of the cancers are shown in Table 3. Only one cancer was classified as BI-RADS 3; the one (0.2%) malignant lesion classified as BI-RADS 3 by both readers was a 12-mm lesion in a 72-year-old patient, which was stiff on SWE (mean stiffness 119 kPa) and occult on mammography (Figures 1 and 2). It was a grade 2 invasive ductal carcinoma of no special type measuring 32 mm at final pathology.

21 (4.5%) of the 467 cancers were soft on SWE (mean stiffness of <50 kPa). 10 (47.6%) of these were <10 mm on greyscale ultrasound size and 15 (71.4%) cancers were <15 mm. 2 (9.5%) cancers were pure DCIS, 2 (9.5%) cancers were lymphoma and 1 (4.8%) cancer was a plasmacytoma. The remaining 16 (76.2%) cancers were invasive cancers (age range 40–68 years, mean age 60 years), with histological characteristics shown in Table 4. Thus, 3.5% of invasive breast cancers were classified as benign on SWE.

No malignancies in females aged under 40 years had benign shear-wave values. Of the 21 soft malignancies, 6 (28.6%) malignancies occurred in females aged 40–50 years, 5 (23.8%) malignancies in females aged 50–60 years, 4 (19.0%) malignancies between 60–70 years and 6 (28.6%) malignancies over 70 years.

Benign lesions
Of the 227 benign lesions, 83 (36.6%) lesions were classified as BI-RADS 3 on greyscale ultrasound, 79 (34.8%) lesions as BI-RADS 4a, 46 (20.3%) lesions as BI-RADS 4b, 12 (5.3%) lesions as BI-RADS 4c and 7 (3%) lesions as BI-RADS 5. 149 (65.6%) lesions were soft on SWE and 78 (34.4%) lesions were stiff. 73 (32.2%) lesions were correctly classified as benign by both SWE and greyscale ultrasound.

Of the lesions classified as BI-RADS 4a on greyscale that were soft on SWE, 54 (91.5%) lesions were benign; only 5 (8.5%) lesions were cancers.

The positive-predictive value of BI-RADS classification was 18.5% for BI-RADS 4a, 61% for BI-RADS 4b, 92.8% for BI-RADS 4c and 96.9% for BI-RADS 5. The negative-predictive value of the BI-RADS classification was 98.8% for BI-RADS 3.

Patients aged under 40 years
Of the 131 lesions in patients under 40 years, 107 (81.7%) lesions were benign and 24 (18.3%) lesions were malignant. All 24 cancers were stiff on SWE; and none were classified as BI-RADS 3 on greyscale ultrasound. 3 (12.5%) cancers were classified as BI-RADS 4a, 10 (41.7%) cancers as BI-RADS 4c and 11 (45.8%) cancers as BI-RADS 5. Of the 107 benign lesions, 43 (40.2%) lesions were correctly classified as benign by both SWE and BI-RADS.

Patients aged under 50 years
Of the 314 lesions in patients aged under 50 years, 180 (57.3%) lesions were benign and 134 (42.7%) lesions were malignant. Of the 134 cancers, 6 (4.5%) cancers were soft on SWE; none were BI-RADS 3 on greyscale ultrasound. 6 (4.5%) cancers were classified as BI-RADS 4a, 16 (11.9%) cancers as BI-RADS 4b, 51 (38.1%) cancers as BI-RADS 4c and 61 (45.5%) cancers as BI-RADS 5.

Of the 180 benign lesions, 126 (70%) lesions were soft on SWE and 67 (37.2%) lesions were correctly classified as benign by SWE and BI-RADS.

Table 3. Malignant lesions Breast Imaging Reporting and Data System (BI-RADS) classifications

BI-RADS classification	Number of lesions (%)
BI-RADS 3	1 (0.2)
BI-RADS 4a	18 (3.9)
BI-RADS 4b	72 (15.4)
BI-RADS 4c	157 (33.6)
BI-RADS 5	219 (46.9)

Figure 1. Greyscale ultrasound image of a solid lesion classified as Breast Imaging Reporting and Data System 3 by both readers.
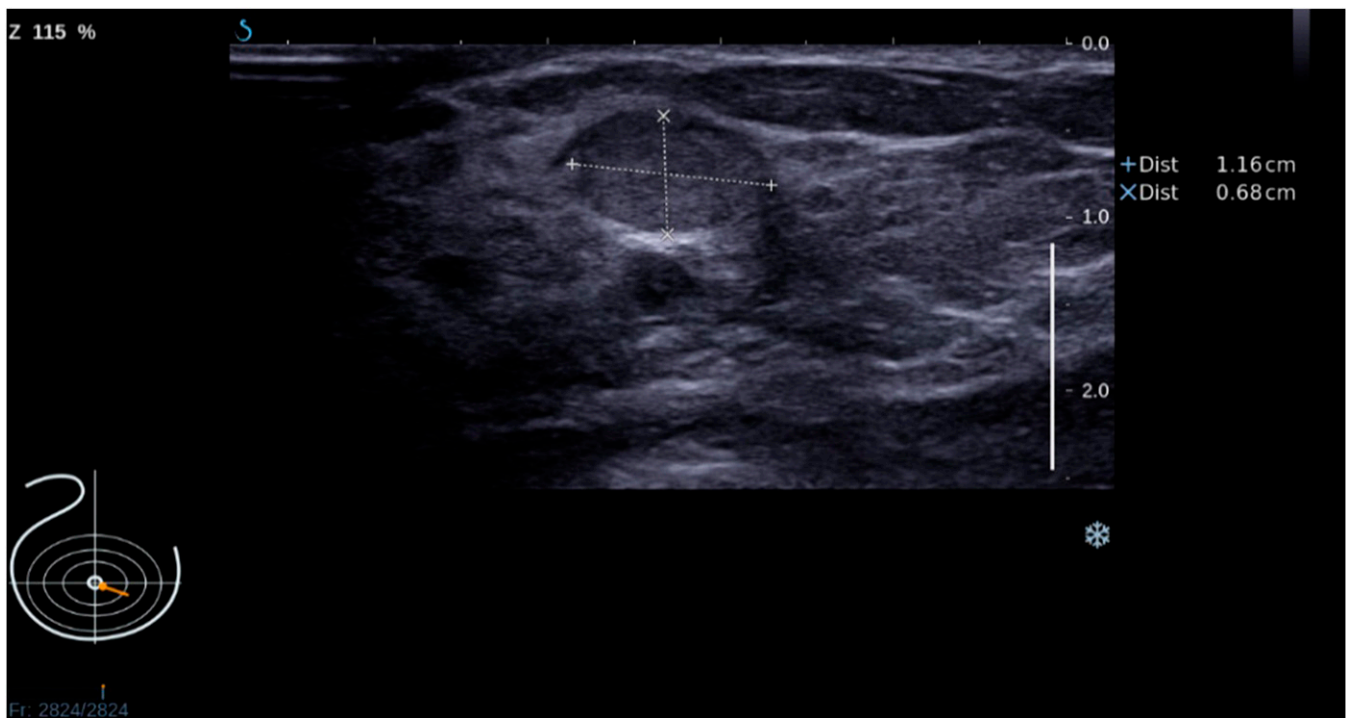
DISCUSSION

We have found that the combination of greyscale ultrasound and SWE is very sensitive for the diagnosis of malignancy in females with symptomatic breast masses. None of the 467 palpable cancers had benign characteristics on both ultrasound modalities.

UK breast radiologists use the Royal College of Radiologist five-point classification system which differs from BI-RADS, as it does not specify the percentage of likelihood of malignancy associated with each category. So, whereas BI-RADS 3 represents probably benign and short-term follow-up is required, UK Royal College of Radiologist 3 represents probably benign/indeterminate and further investigations are warranted.[18] In the UK, it is usual practice for a benign diagnosis to be made on the basis of clinical and ultrasound findings without immediate biopsy in young females under 25 years.[8–10] Conversely, it is standard policy in most breast units to perform percutaneous biopsy (or short-term follow-up) on solid benign masses presenting over the age of 25 years.[8] Some units have safely changed their policy and have extended the age below which they do not perform biopsy to 30 years through strict adherence to BI-RADS criteria for a benign solid breast mass, without any instances of missed breast cancers.[13]

In our study, 33.4% of cases were assigned different BI-RADS scores by the two readers, and these differences were resolved by consensus. There are few studies evaluating the observer agreement of the BI-RADS lexicon for ultrasound, despite its introduction in 2003. These studies show a higher level of intraobserver agreement than interobserver agreement. In these studies, the intraobserver agreement varied between substantial

and almost perfect, while the interobserver agreement for sonographic descriptors varied between fair and substantial. The highest agreement was found for mass orientation and the lowest for margin assessment, with an interobserver agreement for BI-RADS final category that was moderate. The low levels are owing to subcategorizing of BI-RADS 4 into 4a, 4b and 4c; and these results are similar to our study.[19] The boundary between BI-RADS 3 and 4a and above is important because management may change as a consequence. Disparity between the two assessors in this study crossed this boundary in only <2% of cases. This suggests that the BI-RADS assessment used in this study should be highly reproducible.

The accuracy of SWE in benign and malignant differentiation, when added to greyscale ultrasound and clinical findings, is likely to lead to an increase in the number of benign lesions that can be accepted as such, without requiring percutaneous biopsy.[1,6,20] The findings of this study suggest that lesions which appear benign on both greyscale ultrasound and SWE do not require percutaneous biopsy or short-term follow-up. In this study, application of these criteria could have obviated the need for biopsy in 32.6% of benign lesions. Adding SWE findings to BI-RADS features for Category 3 and 4a lesions has been shown to improve specificity, without loss of sensitivity.[1] These authors also found that stiffness on SWE examination helped identify the few malignancies that would otherwise have been assessed as BI-RADS Category 3.[1]

Studies of cancers misclassified as benign by greyscale ultrasound and SWE suggest that greyscale ultrasound and SWE may be complimentary modalities. Greyscale ultrasound tends to

Figure 2. Shear-wave elastography (SWE) image showing high peritumoral stiffness (mean stiffness 119 kPa). Percutaneous core biopsy and subsequent surgery confirmed the presence of a grade 2 invasive ductal carcinoma of no special type.
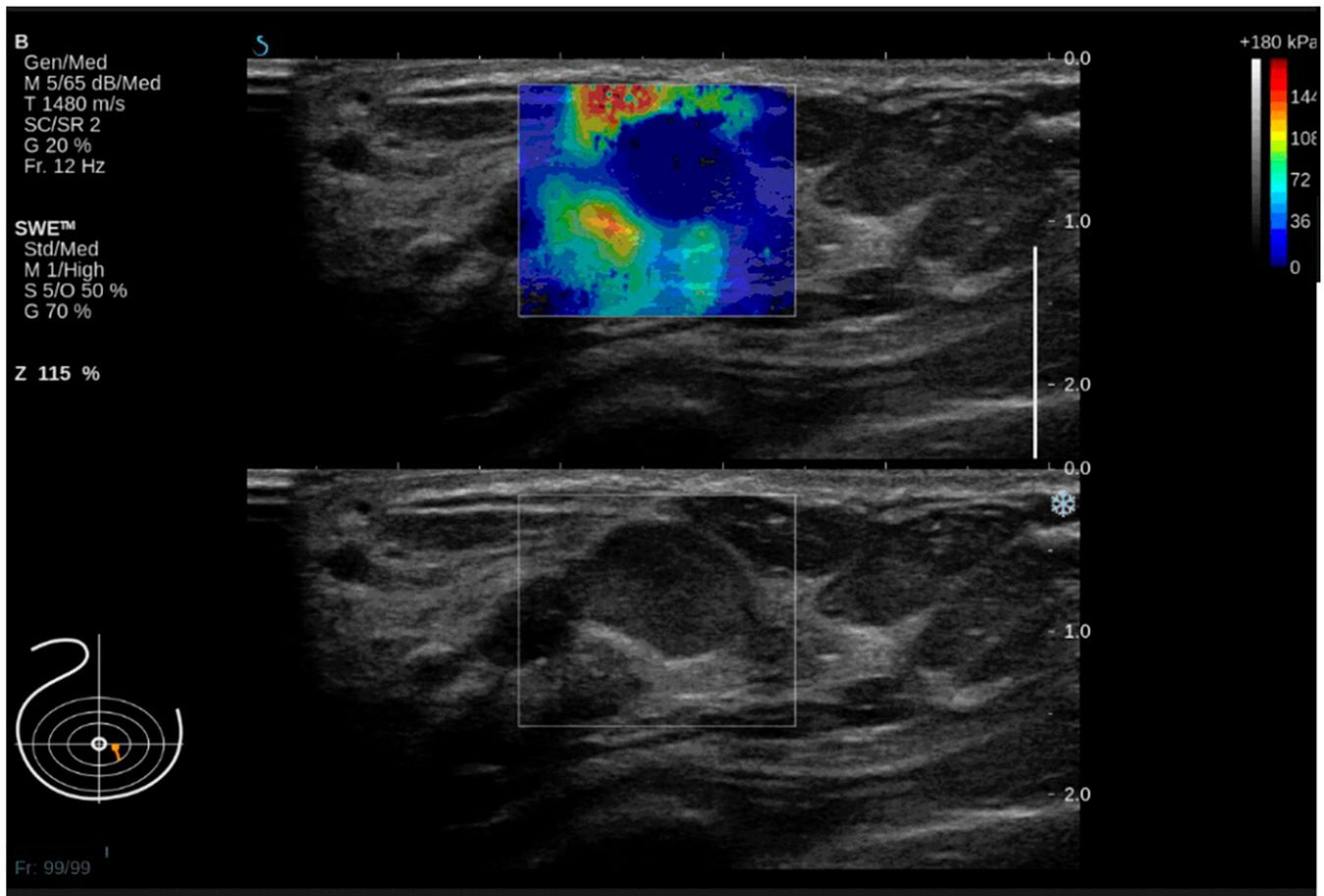
misclassify high-grade, triple-negative breast cancers as benign, as such cancers can have well-defined margins and often lack the distal acoustic shadowing seen in lower grade luminal cancers.[20–22] By contrast, SWE tends to misclassify low-grade cancers, particularly tubular cancers, as benign.[7] SWE has the additional advantage of being equally sensitive for the detection of lobular cancers and ductal cancers, in contrast to greyscale ultrasound.[23] These data suggest that the rate of cancers having negative findings on both greyscale ultrasound and SWE will be lower than the false-negative rates of each modality alone. The practical clinical implications of our findings are substantial, for the patient and the wider National Health Service. Discharge of patients from symptomatic clinics with breast masses that have benign greyscale ultrasound and SWE characteristics would be beneficial, as they would not undergo the trauma of core biopsy nor the anxiety of waiting for results. It would greatly benefit underresourced breast radiologists and ultrasound practitioners, who would not have to perform as many biopsies, and it would decrease the burden on histopathology services and shorten multidisciplinary breast team meetings.

The sensitivity of the BI-RADS classification of greyscale images in this study is particularly high. A number of factors may be responsible for this. Firstly, this study included only symptomatic masses; small screen-detected lesions which are more difficult to characterize were not included. Secondly, the age of the patient was known; so, this may have influenced the readers. Thirdly, the classification was performed by two readers and a consensus reached. This would exclude any obvious errors from being made.

There are a number of limitations to this study. Although the study contains a large number of cancers, it was performed at a single centre with a special interest in SWE. It is not known whether the results of this study are applicable to other centres. SWE is not a difficult technique to learn and it has been found to be highly reproducible; so, it is likely that similar results would be obtained in other centres. However, SWE is available from a number of manufacturers and there are technical differences between the systems. Therefore, results from one SWE system may not be applicable to systems from other manufacturers and it would be essential to carry out similar studies using other manufacturer equipment.

If the results can be replicated by other investigators, then the use of SWE imaging in combination with greyscale ultrasound could greatly simplify the management of BI-RADS Category 3 benign breast masses, by obviating the need for biopsy or follow-up, especially in females under 40 years, in whom there are no soft cancers. SWE is available as an add on to an increasing

Table 4. Invasive primary breast cancers classified as benign by shear-wave elastography ($n = 21$)

Characteristics	Number of lesions (%)
Grade 1	3 (14.3)
Grade 2	6 (28.6)
Grade 3	7 (33.3)
<15 mm	10 (47.6)
Ductal no special type	9 (42.8)
Lobular carcinoma	3 (14.3)
Tubular carcinoma	1 (4.8)
Papillary carcinoma	1 (4.8)
Node positive	2 (9.5)
Vascular invasion	2 (9.5)
Her 2+	2 (9.5)
ER+	15 (71.4)
PR+	12 (57.1)
BI-RADS classification 4a	5 (24)
BI-RADS classification 4b	5 (24)
BI-RADS classification 4c	8 (38)
BI-RADS classification 5	3 (14)

BI-RADS, Breast Imaging Reporting and Data System; ER, oestrogen receptor; HER, human oestrogen receptor; PR, progesterone receptor.

number of ultrasound machines; so, the cost of implementing SWE is small. The introduction of a policy of not biopsying lesions with both benign greyscale and SWE characteristics is therefore likely to lead to significant cost savings for healthcare providers as detailed above, as well as provide a quicker yet safe service to patients. This study has not included findings of clinical examination; physical examination findings in clinical practice would provide a further safeguard against the discharge of females from the clinic without biopsy, in whom there is a breast cancer.

CONCLUSION

This study has shown that the combination of greyscale ultrasound and SWE is very sensitive for the diagnosis of malignancy in females with symptomatic breast lumps. Our findings suggest that lesions which appear benign on greyscale ultrasound that are soft on SWE do not require percutaneous biopsy or short-term follow-up. The introduction of a policy of not biopsying benign lesions with benign greyscale and soft SWE characteristics would benefit patients, clinicians and healthcare providers alike. Nonetheless, further studies with larger populations, using equipment from different manufacturers, are needed to validate our results.

ACKNOWLEDGMENTS

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