Translating new breast ultrasound techniques into clinical practice: evaluating their intended uses and describing other unexpected uses for them

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Abstract: Several new ultrasound tools have been developed to further evaluate breast lesions detected on B-mode ultrasound. Strain elastography (SRE) was developed to assess the likelihood of malignancy of lesions based on their stiffness. This has been incorporated into the latest edition of the American College of Radiology (ACR) Breast Imaging Reporting and Data System (BI-RADS) lexicon and atlas. However, no agreed cut-off stiffness values have been established to distinguish benign from malignant lesions making the translation into routine clinical practice difficult. Superb microvascular imaging (SMI) was developed to better evaluate the vascularity within sonographic lesions and assess their likelihood of malignancy. However, there is also no agreed cut-off value for vascular index (VI) to distinguish between benign and malignant lesions. MicroPure was developed to better visualize and evaluate calcifications seen on ultrasound. Its effective use in breast screening and evaluating the calcifications detected for likelihood of malignancy have not been established. This article describes the original intended uses of these applications and reviews the studies evaluating them, showing the varying success of the translation of these tools into routine clinical practice. Also described are some other uses of these tools for which they were not originally intended. This illustrates the importance of being perceptive to alternative uses of imaging tools in their translation from bench to bedside.

Keywords: Breast ultrasound; strain elastography (SRE); MicroPure imaging (MP); superb microvascular imaging (SMI)

Introduction

Background

Conventional B-mode ultrasound has been used detect and differentiate breast lesions (1,2).

New ultrasound tools have been developed to further evaluate breast lesions. These include strain elastography (SRE), MicroPure Imaging (MP) and superb microvascular imaging (SMI).

Rationale and knowledge gap

These techniques have had varying success in their translation into clinical practice. SRE findings was not previously incorporated into the American College of Radiology (ACR) Breast Imaging Reporting and Data System (BI-RADS) atlas and lexicon but was included in the latest 2013 5th edition. Although calcifications and vascularity are included in the BI-RADS ultrasound
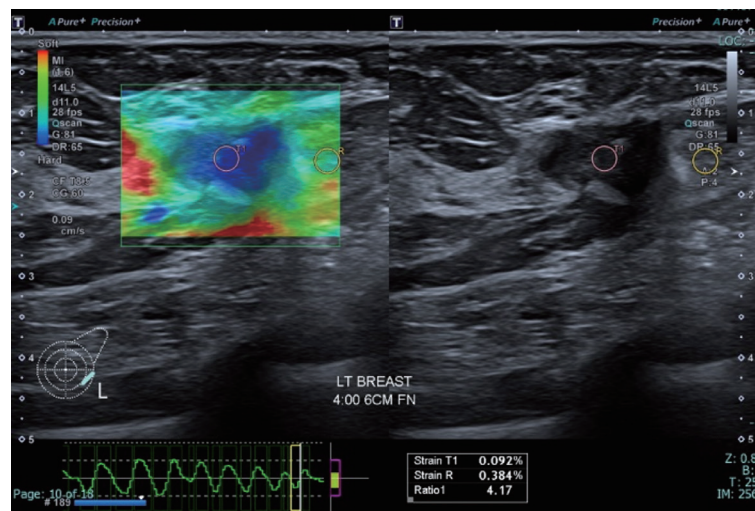
Figure 1 Ultrasound strain elastography showing lesion with strain ratio of 4.17. Histopathology showed invasive ductal carcinoma grade 2.

assessment, specific use of MP and SMI and examples of their use are not in the latest edition of the atlas.

Objective

This article describes the intended uses of these applications, reviews the studies evaluating them and discusses some uses of these tools for which they were not originally intended.

Three newer ultrasound tools

SRE

Ultrasound elastography is a technique that provides information on tissue elasticity and stiffness. It is based on the fact that tissue elasticity can be a predictor of malignancy with benign lesions being more elastic and malignant lesions being stiffer. SRE is a semiquantitative technique with displacement of the tissue from manual compression with the ultrasound transducer or from the patient's cardiac and respiratory movements. The results may be reported as a score based on a colour map scheme, or as a strain ratio (SR) or fat-lesion ratio (FLR) (*Figure 1*).

A meta-analysis (3) in 2012 of nine studies of the accuracy of quantitative ultrasound elastography for differentiation of malignant and benign breast abnormalities showed overall sensitivity and specificity of 88% but found a wide range of cut-off values from 0.5 to 4.5.

The World Federation for Ultrasound in Medicine and Biology (WFUMB) published guidelines in 2015 for breast elastography (4,5). These guidelines acknowledged also the marked variance in SR cut off values used in differentiating benign from malignant lesions.

A subsequent meta-analysis (6) in 2022 reviewed 65 studies. This found that despite the WFUMB guidelines, breast SR measurement was still laden with multiple heterogeneities. These lie within the whole range of assessments involving the patient selection, index test, reference standard and flow and timing.

In discussion of the possibility that manufacturer models may influence SR values, the review found that most of the same model subgroups did not reproduce the same favourable threshold effects and having a machine predetermined cut-off value at this stage would require more robust evidence than currently available. The review also concluded that currently the optimal breast SR cut-off point or value remains unresolved.

One common finding on elastography is the artefact seen with breast cysts. These have two characteristic appearances (7,8), the bullseye artefact or the blue-green-red (BGR) trilaminar artefact with blue being the superficial colour and red the deep one (*Figure 2*).

While most simple cysts show typical sonographic features of circumscribed margins, anechoic content with posterior acoustic shadowing, there are instances where inspissated contents may make the diagnosis less
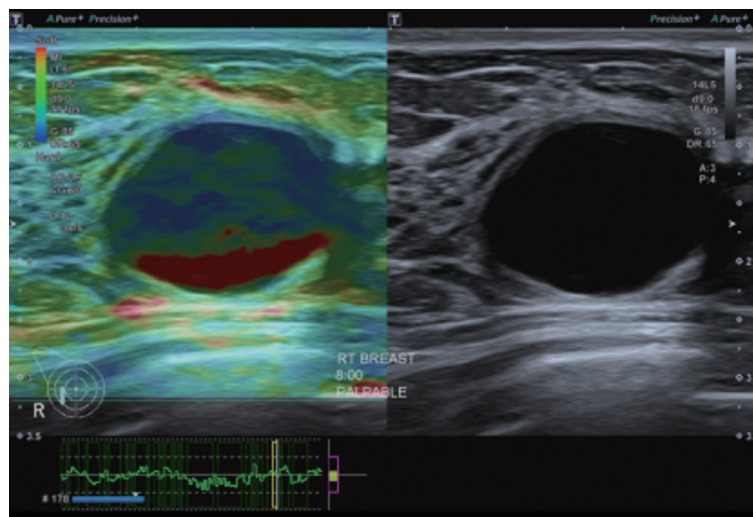
Figure 2 Breast cyst showing BGR trilaminar artifact. BGR, blue-green red.
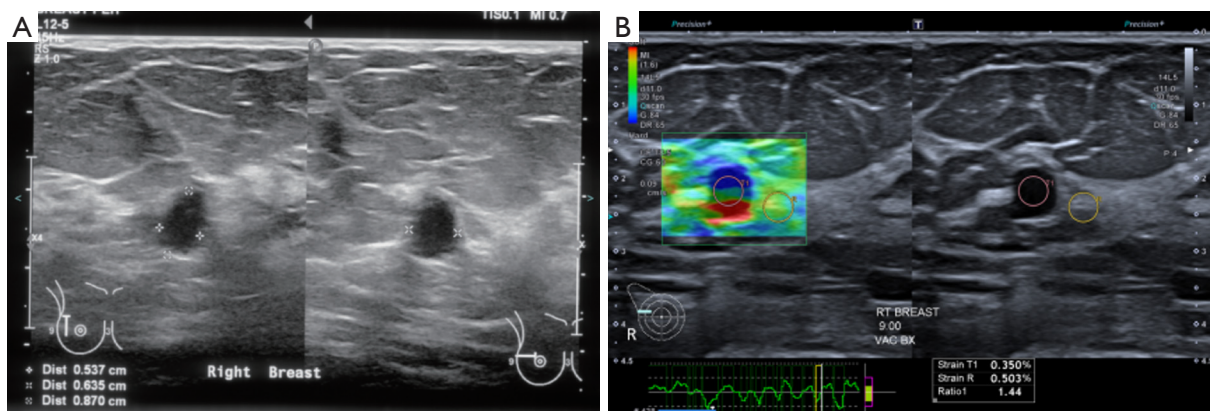
Figure 3 Elastography for cystic lesion. (A) Right breast lesion on initial ultrasound. The lesion shows irregular margins, appears taller than wide and shows hypoechoeic content. This was categorised as BI-RADS 4 and referred for biopsy. (B) Same lesion showing trilaminar artefact on elastography. Vacuum biopsy was performed and histology was that of an apocrine cyst. BI-RADS, Breast Imaging Reporting and Data System.

straightforward. SRE may be useful in these circumstances. SRE may also be useful in demonstrating the cystic component of a complex solid-cystic lesion. This may help target the solid component for histological correlation (*Figures 3,4*).

SMI

Doppler ultrasound (including colour and power Doppler) has been used to evaluate the internal vascularity in solid breast lesions. They supplement B-mode imaging by additionally demonstrating features suggestive of malignancy including the presence of both peripheral and central vascularity, penetrating vessels, and branching vessels (9-11).

However, these Doppler technologies remove clutter by suppressing low velocity components. This suppression results in a loss of data, and subsequent loss of visibility of flow in smaller vessels <0.1 mm in diameter including micro-vessels in breast cancer (12). This loss of Doppler signals from intra-tumoral micro-vessels in breast cancer may result in poorer correlation between the vascular
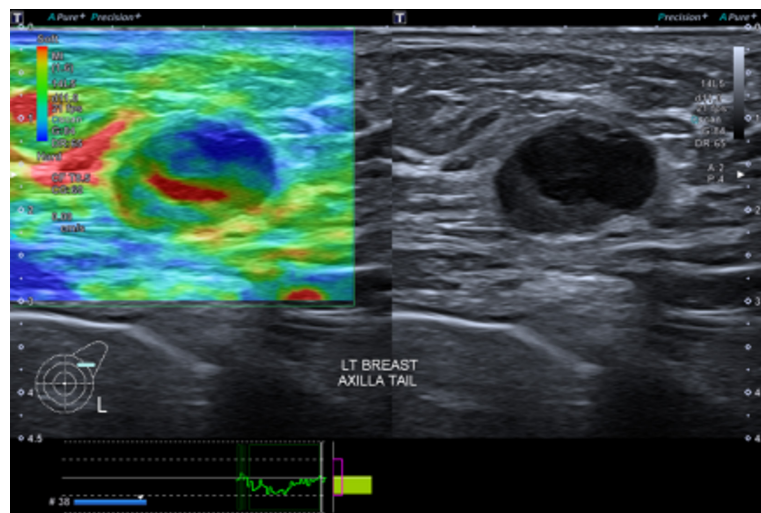
Figure 4 Complex solid-cystic lesion with only the cystic part showing the trilaminar artefact. Histology was encapsulated papillary lesion with ductal carcinoma *in situ*.
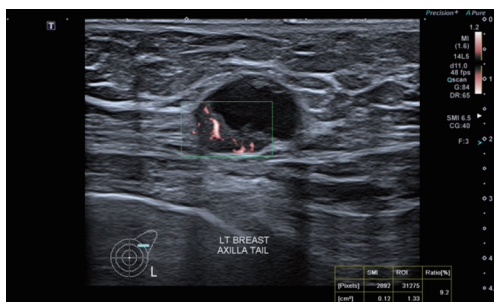
Figure 5 Complex solid-cystic lesion showing micro-vascularity on SMI within the solid component. Histology from ultrasound-guided vacuum biopsy showed low-grade papillary ductal carcinoma *in situ*. SMI, superb microvascular imaging.

features seen on ultrasound and micro-vessel density on pathological examination (12,13).

Instead of suppressing these low flow signals, SMI analyses clutter motion and uses an adaptive algorithm to identify and separate these flow signals from overlaying tissue motion artifacts. This results in a high resolution ultrasound image in which minute vessels and low velocity flow can be demonstrated. All this can also be done at high frame rates. As a result, SMI can provide more detailed microvascular information about breast tumours (*Figures 5,6*).

Comparative studies of the performance of B-mode versus B-mode with SMI have been published. These show improved diagnostic capability in distinguishing benign and malignant lesions (particularly in the BI-RADS 4 category) using vascular quality, morphology and distribution characteristics (14,15).

The vascular index (VI) is a parameter that is determined by SMI to quantify flow signals as the ratio of colour pixels to all pixels within the mass. Studies have shown good interobserver reproducibility of VI (16,17). There is also improved diagnostic performance in distinguishing benign from malignant lesions with malignant lesions showing a significantly higher VI. However, different cut off values (2.95–4) were determined or used in each study.

One study (18) also showed improvement in BI-RADS categorization based on VI compared to B-mode imaging.

Apart from solid masses, SMI may also demonstrate micro-vascularity within the solid component of complex solid-cystic lesions (*Figure 5*). This may be useful in distinguishing these complex lesions from complicated cysts with echogenic inspissated content and simple cysts with some reverberation artefact posterior to the superficial cyst wall. The vascular solid component would require histological evaluation to exclude malignancy (*Figure 7A,7B*).

MP

MP is an ultrasound processing technique to highlight microcalcifications. This combines tissue harmonic imaging (which allows improvement of spatial resolution to aid
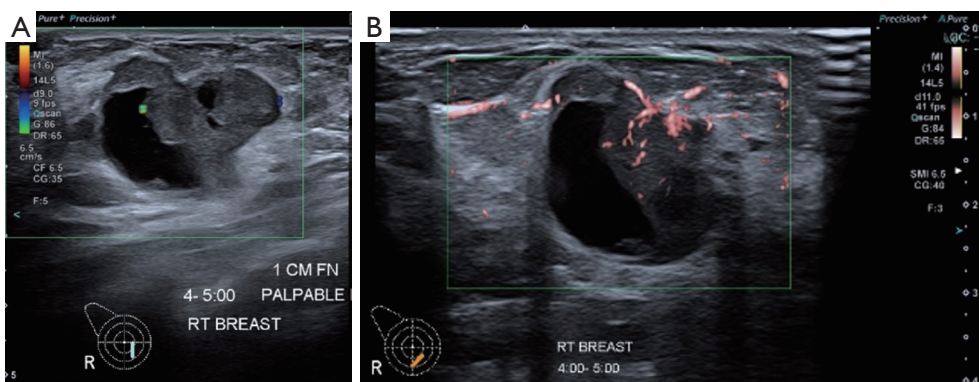
Figure 6 SMI used in complex solid-cystic lesion. (A,B) Complex solid-cystic lesion with minimal internal vascularity seen on colour Doppler (A) and prominent micro-vascularity seen on SMI (B). Core needle biopsy showed histology of invasive ductal carcinoma grade 1 ER/PR positive, HER-2 negative. SMI, superb microvascular imaging; ER, estrogen receptor; PR, progesterone receptor; HER-2, human epidermal growth factor receptor 2.
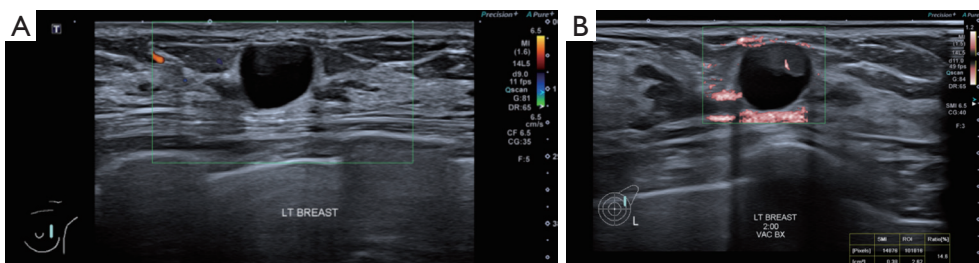
Figure 7 Vascular assessment of solid component in complex solid-cystic lesion. (A) Colour Doppler shows no internal vascularity and possible reverberation artefact. (B) SMI showing micro-vessel in the hypoechoeic part of the lesion showing that this is a solid component. Ultrasound-guided vacuum biopsy showed histology of intraductal papilloma with florid usual ductal hyperplasia and small focus of atypical ductal hyperplasia. SMI, superb microvascular imaging.

detection) with speckle suppression using a constant false alarm rate filter. This filter suppresses visualisation of fat, mammary gland borders and chest wall musculature and reduces echogenic areas from the structures which may mimic microcalcifications. It also extracts only isolated high-brightness echoes against the heterogeneous background (19,20). By comparing the average brightness within a small area to that of the central pixel and calculating the difference, these brighter areas representing microcalcification are prominently displayed as white spots superimposed on a blue background.

A few studies have demonstrated superior detection of larger numbers of microcalcifications with MicroPure ultrasound imaging than with B-mode ultrasound (19-22).

However, using MP to detect calcifications in a breast screening setting has been deemed inappropriate. Although a study found that evaluations of the presence or absence of

microcalcifications did not significantly differ from those of mammography, accuracy was low overall with mean values of 52% (23).

Another study (24) found that malignant cases were seen to have significantly more microcalcifications than benign cases and MP can be used to identify areas with breast microcalcifications but cannot effectively characterize such areas as benign or malignant.

Studies have also suggested that MP may be used to target areas with calcifications for biopsy (22,24).

Some clinical scenarios where this may be helpful would include:

Firstly, cases with mammographically indeterminate or suspicious calcifications and a hypoechoeic lesion on ultrasound with possible calcifications. MP may demonstrate calcifications in the lesion which correlate with those on mammography. This would suggest a single lesion
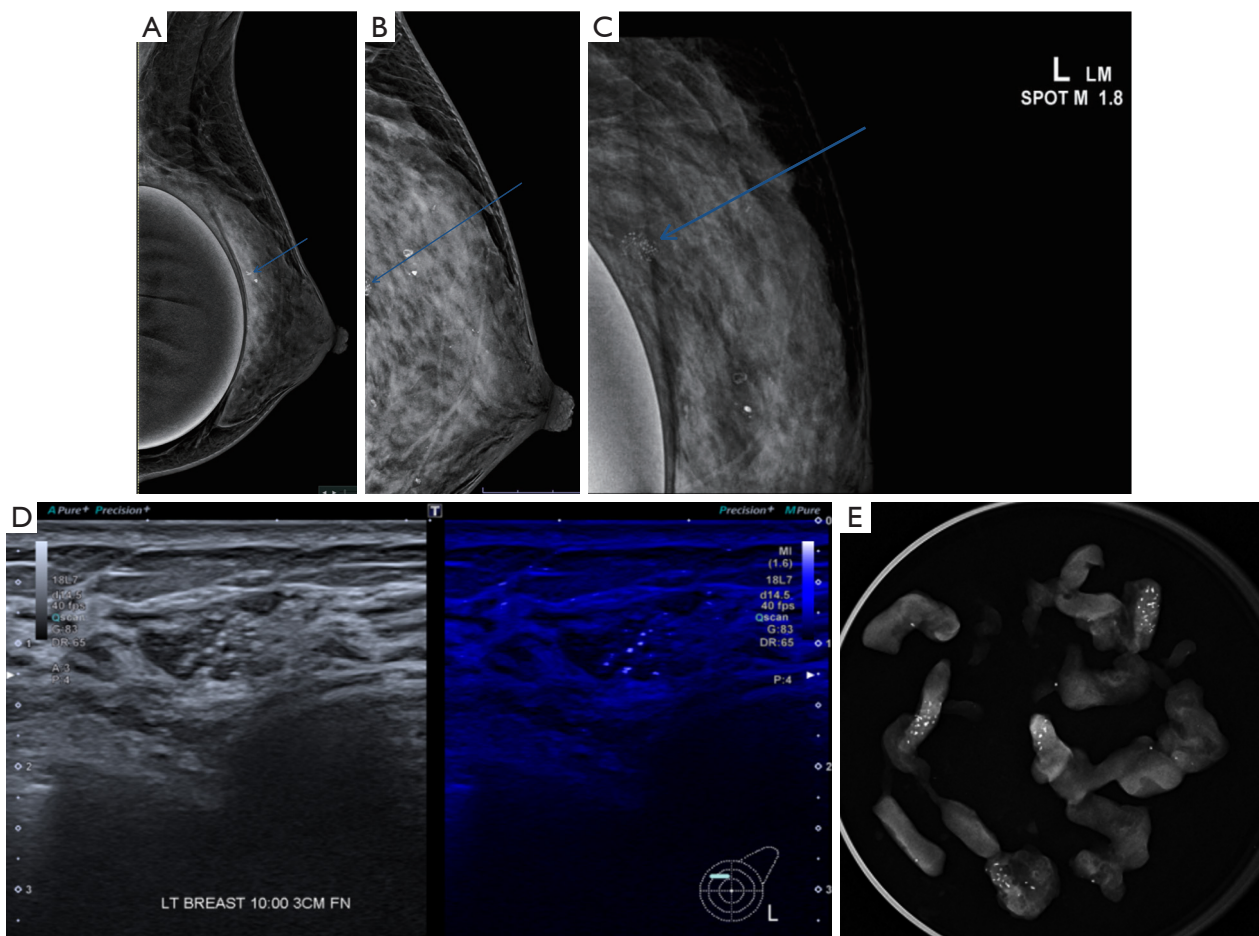
Figure 8 MicroPure used to guide vacuum biopsy of breast calcifications in a patient with breast implant. (A) Left mediolateral oblique mammographic view showing implant and some benign calcifications (arrow). (B) Implant displaced view showing posterior superior tight cluster of suspicious calcifications (arrow). (C) Spot magnification view showing suspicious cluster of calcifications (arrow) close to the fibrous external capsule of the implant. (D) B-mode and MicroPure imaging showing clustered calcifications. (E) Specimen radiograph from ultrasound guided vacuum biopsy showing the suspicious calcifications within the cores. Histology showed a fibroadenoma and ductal carcinoma *in situ*.

which may be targeted on ultrasound.

Secondly, cases with calcifications on mammography but patient unable to tolerate mammographically guided biopsy. Demonstration of the calcifications on ultrasound would allow ultrasound biopsy under sedation or anaesthesia without the need for mammographic guidance or breast compression.

Thirdly, cases where calcifications on mammography are at a difficult location for mammographically guided biopsy such as in the posterior aspect of the breast or close to an implant. Ultrasound guided biopsy with MP can be more readily performed (*Figure 8A-8E*).

The following case is one such example. A 30-year-old female with prior breast implants is on follow up for bilateral nodules. Mammography detected a tight cluster of calcifications in the posterior superior aspect of the left breast. These could not be visualised on the craniocaudal view. There are also other calcifications within the same breast with a mammographically benign appearance. Ultrasound showed a possible correlative finding in the upper inner quadrant and MP shows this is likely to be the cluster seen on mammography. Ultrasound guided vacuum biopsy was then performed and specimen radiograph confirmed the suspicious cluster of calcifications within the cores. Histology showed a fibroadenoma and ductal carcinoma *in situ*.

Discussion

SRE, SMI and MP are three techniques which supplement B-mode and Doppler imaging of the breasts.

SRE has been shown to increase the sensitivity of detecting malignant lesions when added to B-mode imaging although the cut off for the SR for malignant lesions varies greatly between studies and a standardised cut off value has yet to be determined.

It is also useful in demonstrating a unique trilaminar artefact in cystic lesions as well as the cystic component of complex solid-cystic lesions.

SMI (with VI) has been shown to be helpful in distinguishing benign from malignant lesions.

It is also useful in demonstrating small vessels with slow flow in the solid component of solid-cystic lesions which should be further targeted for histological correlation. These may not be visualised on colour Doppler imaging.

MP has not been shown to be an effective replacement for mammography in screening for breast calcifications which may indicate underlying malignancy. It is also not effective in determining if a lesion is benign or malignant based on the appearance of the calcifications seen on ultrasound. However, in cases with mammographic calcifications and a sonographic lesion, demonstrating calcification within the lesion on ultrasound would increase confidence of correlating the two lesions as one. It may also provide real-time guidance for targeting these calcifications sonographically during biopsy.

Conclusions

The above scenarios illustrate the fact that in translating newly developed tools into clinical practice, there are often mixed results. Some of these tools do not fulfil the purpose for which they were initially developed. They are sadly "lost in translation" so to speak. However, in applying these tools, there may be valuable unexpected uses for which they were not initially developed. It is hoped that these may be incorporated into clinical practice guidelines and references atlases in future. These scenarios are a reminder for their users to remain open and perceptive to the potentially useful applications which may be "found in translation".

Acknowledgments

Footnote

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