Ultrasound and Elastography

Andy Evans
Dundee
Recent advances in the use of US in breast disease

**New technologies**

- Contrast enhanced ultrasound
- Superb Microvascular Imaging
- Automated whole breast ultrasound
- Shear wave elastography

**New use of conventional ultrasound**

- Predicting axillary nodal burden
- Predicting the prognosis of breast cancer pre-operatively
Contrast enhanced Ultrasound

Recent systematic review and meta-analysis
5 studies, 992 patients

<table>
<thead>
<tr>
<th></th>
<th>sens</th>
<th>spec</th>
<th>AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>conventional US</td>
<td>0.87</td>
<td>0.80</td>
<td>0.90</td>
</tr>
<tr>
<td>CEUS-registered US</td>
<td>0.93</td>
<td>0.87</td>
<td>0.95</td>
</tr>
</tbody>
</table>

Wubuliasimu M et al Clin Radiol 2018;73:936-943
CEUS and elastography for monitoring NACT

End of treatment assessment

<table>
<thead>
<tr>
<th></th>
<th>AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>US</td>
<td>0.86</td>
</tr>
<tr>
<td>CEUS</td>
<td>0.72</td>
</tr>
<tr>
<td>US and CEUS</td>
<td>0.91</td>
</tr>
</tbody>
</table>

Superb Microvascular Imaging

- Similar images to CEUS but no injection
- May be usefully combined with SWE to improve B/M differentiation

Automatic Breast Volume Scanner versus Handheld Ultrasound in Differentiation of Benign and Malignant Breast Lesions: A Systematic Review and Meta-analysis

• 9 studies
• 1985 patients
• 628 cancers

**AUC**

• ABVS 0.93
• HHUS 0.94

the axillary goal posts have moved!
Surgeons only want us to pre-operatively diagnoses high volume disease

• Low volume disease is effectively treated by RT with less side effects compared to axillary clearance
• Maybe low volume disease doesn’t need local treatment if patient is receiving systemic therapy
• Low volume disease axilla patients could usefully go into POSNOC
Predicting nodal burden pre-operatively

• 1,298 patients

**Indicators of high nodal burden (HNB)**
• breast tumour size
• number of abnormal LNs
• cortical thickness
• effacement of the fatty hilum
• tumour grade
• HER-2

Predicting nodal burden pre-operatively

• On MVA number of abnormal LNs was the sole independent predictor of HNB (p < 0.0001, area under the curve = 0.774)
• The positive predictive value of HNB in patients with ≥ 4 abnormal LNs was 93%

Predicting nodal burden pre-operatively

- Study of 312 patients

**Independent predictors of HNB**

- higher (≥2) T stage
- Number of abnormal nodes
- Cortical thickness

Dundee Data

115 patients

Factors associated with a low nodal burden

• Screen detection
• HER2 negative disease
• Small US tumour size
• thinner cortical thickness
Significant categorical variables

Chart Title

- screen detected: 62 (1-2 nodes), 38 (3 or more nodes)
- symptomatic: 30 (1-2 nodes), 70 (3 or more nodes)
- HER-2 pos: 15 (1-2 nodes), 85 (3 or more nodes)
- Her-2 neg: 42 (1-2 nodes), 58 (3 or more nodes)
- US skin thickening: 13 (1-2 nodes), 87 (3 or more nodes)
- US normal skin: 41 (1-2 nodes), 59 (3 or more nodes)

Legend: 1-2 nodes, 3 or more nodes
Significant continuous variables

<table>
<thead>
<tr>
<th>Imaging Factors</th>
<th>Group A (1-2 node(s)) (n = 43)</th>
<th>Group B (≥ 3 nodes) (n = 72)</th>
<th>Univariate OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>USS tumour size (mm)</td>
<td>Median (IQR)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>19 (14-25)</td>
<td>24 (17-35)</td>
<td>1.06 (1.01 – 1.10)</td>
<td>0.009</td>
</tr>
<tr>
<td>USS cortical thickness</td>
<td>Median (IQR)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4.00 (3.45-5.40)</td>
<td>5.30 (4.10-8.15)</td>
<td>1.37 (1.13 – 1.67)</td>
<td>0.002</td>
</tr>
</tbody>
</table>
Final predictive model
AUC 0.77

- route of referral
- US tumour size
- US node cortical thickness
- US skin thickening
How should our practice change?

• Minimum cortical thickness for biopsy 3mm
• Either don’t look or don’t look very hard in women with small screen detected cancer
Pre-operative Prediction of the Prognosis of Invasive Breast Cancer

Andy Evans
Dundee
Pre-operative Prediction of the Prognosis of Invasive Breast Cancer

• More women are now being treated with systemic therapy prior to surgery
• Such a method could aid selection of neo-adjuvant therapy
Results

• 1082 patients with invasive cancer Jan 2010-November 2014
• 411 Screening 671 symptomatic
• Mean follow-up 5.1 yrs
• 103 breast cancer deaths
Survival by US size

p < 0.0001

Survival probability (%)

cause of death

Time

Survival probability (%)

Time

Number at risk
Group: 1
272 261 198 69 3 0
Group: 2
461 434 316 110 2 0
Group: 3
355 317 208 73 2 0

US size group
1
2
3

+Dist 3.73 cm
Survival by US distal effect

\[ p = 0.004 \]
Survival by US skin involvement
p<0.0001
Breast cancer mortality by type of skin involvement

1=skin thickening
2=skin invasion
3=both
US skin involvement and clinical features

• Only 25% of those with ultrasound detected skin thickening had clinical skin involvement

• 77% of breast cancer deaths in those with ultrasound visible skin involvement occurred in the sub-group of patients without clinical skin involvement
We hypothesize that skin involvement on US results in invasion of the cutaneous lymphovascular plexus
Survival according to stiffness at SWE

$P < 0.001$

<table>
<thead>
<tr>
<th>Number at risk</th>
<th>Group: 1</th>
<th>Group: 2</th>
<th>Group: 3</th>
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<tr>
<td></td>
<td>360</td>
<td>367</td>
<td>361</td>
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<td></td>
<td>339</td>
<td>345</td>
<td>328</td>
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<td>240</td>
<td>256</td>
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<td></td>
<td>82</td>
<td>95</td>
<td>75</td>
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<tr>
<td></td>
<td>2</td>
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<td>2</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>0</td>
<td>0</td>
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</tbody>
</table>
Survival by pre-op diagnosis of nodal metastasis $p<0.0001$
Breast cancer mortality by nodal mets and method of mets diagnosis

1 = surgically node negative
2 = US negative, positive sentinel node
3 = pre-op diagnosis of nodal mets

Number at risk
Group: 1
660 636 488 224 30 0
Group: 2
136 132 111 39 10 0
Group: 3
195 171 118 43 7 0
Survival according to method of presentation

\[ p < 0.0001 \]

![Survival probability graph with source legend: screening (blue), sympto (green).](image)

<table>
<thead>
<tr>
<th>Time</th>
<th>Number at risk Group: screening</th>
<th>Number at risk Group: sympto</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>413</td>
<td>675</td>
</tr>
<tr>
<td>2</td>
<td>405</td>
<td>607</td>
</tr>
<tr>
<td>4</td>
<td>308</td>
<td>415</td>
</tr>
<tr>
<td>6</td>
<td>109</td>
<td>143</td>
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<tr>
<td>8</td>
<td>3</td>
<td>4</td>
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<tr>
<td>10</td>
<td>0</td>
<td>0</td>
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</table>
Survival by core biopsy grade

\( p < 0.0001 \)
Survival according to HER-2 status

$p=0.0004$
Survival by ER status

$\text{p}<0.001$

Number at risk

<table>
<thead>
<tr>
<th>Group</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>Total</th>
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<tbody>
<tr>
<td>Group 0</td>
<td>182</td>
<td>158</td>
<td>104</td>
<td>37</td>
<td>0</td>
<td>0</td>
<td>905</td>
</tr>
<tr>
<td>Group 1</td>
<td>905</td>
<td>853</td>
<td>618</td>
<td>214</td>
<td>7</td>
<td>0</td>
<td>905</td>
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</tbody>
</table>

cause of death

Survival probability (%)
Cox regression analysis

<table>
<thead>
<tr>
<th>Covariate</th>
<th>b</th>
<th>SE</th>
<th>Wald</th>
<th>P</th>
<th>Exp(b)</th>
<th>95% CI of Exp(b)</th>
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<tbody>
<tr>
<td>core_grade</td>
<td>0.5041</td>
<td>0.2405</td>
<td>4.3930</td>
<td>0.0361</td>
<td>1.6555</td>
<td>1.0332 to 2.6525</td>
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<tr>
<td>skin_changes</td>
<td>0.9774</td>
<td>0.2292</td>
<td>18.1801</td>
<td>&lt;0.0001</td>
<td>2.6574</td>
<td>1.6957 to 4.1647</td>
</tr>
<tr>
<td>US_size</td>
<td>0.02138</td>
<td>0.01045</td>
<td>4.1832</td>
<td>0.0408</td>
<td>1.0216</td>
<td>1.0009 to 1.0428</td>
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<tr>
<td>preop_nodal_mets</td>
<td>1.1343</td>
<td>0.2217</td>
<td>26.1781</td>
<td>&lt;0.0001</td>
<td>3.1089</td>
<td>2.0133 to 4.8008</td>
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<tr>
<td>source</td>
<td>1.0504</td>
<td>0.3626</td>
<td>8.3901</td>
<td>0.0038</td>
<td>2.8588</td>
<td>1.4044 to 5.8192</td>
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<tr>
<td>ER</td>
<td>-0.8613</td>
<td>0.2416</td>
<td>12.7129</td>
<td>0.0004</td>
<td>0.4226</td>
<td>0.2632 to 0.6785</td>
</tr>
</tbody>
</table>
ROC curve for a pre-operative index

AUC=0.81, p<0.001
Survival according to pre-op prognosis group quartiles

<table>
<thead>
<tr>
<th>pre_op_index_group</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
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<tbody>
<tr>
<td>255</td>
<td>246</td>
<td>188</td>
<td>52</td>
<td>2</td>
</tr>
<tr>
<td>282</td>
<td>269</td>
<td>200</td>
<td>70</td>
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<tr>
<td>266</td>
<td>250</td>
<td>181</td>
<td>68</td>
<td>2</td>
</tr>
<tr>
<td>282</td>
<td>246</td>
<td>163</td>
<td>67</td>
<td>1</td>
</tr>
</tbody>
</table>
Post operative Predict! score in those treated by immediate surgery AUC 0.86
Shear Wave Elastography (SWE)

• Strain is produced by the Ultrasound probe (shear waves)
• Ultrafast sequence catches in real time the propagation of the shear waves
Elastic heterogeneity is also a useful SWE parameter

<table>
<thead>
<tr>
<th>SWE parameter</th>
<th>Area under the curve</th>
</tr>
</thead>
<tbody>
<tr>
<td>Max stiffness</td>
<td>0.95</td>
</tr>
<tr>
<td>Mean stiffness</td>
<td>0.95</td>
</tr>
<tr>
<td>Elastic heterogeneity</td>
<td>0.96</td>
</tr>
</tbody>
</table>

Qualitative SWE “ring sign”
Normal
Fibroadenoma
Invasive Cancer
Invasive Cancer
Greyscale Benign, Suspicious Elastography, Invasive Cancer
Greyscale Suspicious, Elastography and Histology
Benign
Average Mean Stiffness on Four Images vs. Average Mean Stiffness on Four Images Taken by a Second Operator

Intraclass correlation coefficient=0.87
Collagen Axial Structure

Tropocollagen

Secreted from cell

Proteolytic cleavage
Procollagen N protease
Procollagen C protease

Cross links involve lysyl oxidase

Overlap
Gap
Overlap
Gap
Overlap
Gap

1.5 nm
10.4 nm
300 nm

67 nm
Collagen EM Pictures

Normal Tissue

Cancer Tissue
Benign/Malignant differentiation

- Over 30 studies, many from South Korea
- Two large multicentre studies
- All show SWE has similar performance as grey scale US
- Improved performance when SWE and US combined
- As stiffness at SWE is continuous variable it can be used to improve specificity or sensitivity by varying the cut off value
BIRADS vs. Mean stiffness for 175 Solid Masses

p<0.03 sensitivity
Conclusion

• Shear wave elastography gives quantitative and reproducible information on solid breast masses with diagnostic accuracy at least as good as BI-RADS classification of greyscale ultrasound imaging.
• BIRADS and shearwave combined gives very high sensitivity and NPV
• Can we biopsy less benign breast masses?
Which cancers are missed by SWE?

• Small
• Low grade
• DCIS
• Screen detected
Median stiffness by type

P<0.001
SWE and diagnosing lobular cancers in symptomatic women

4 (8%) of lobular cancers (ILC) were benign/normal on both mammography and greyscale ultrasound, but suspicious on SWE. The incremental gain in sensitivity by using SWE in ILC was statistically significant compared to ductal cancers (p=0.01).

YT Sim et al Clinical Radiology 2016
None of the 467 cancers had benign characteristics on both grey scale US and SWE.

No malignancies in women aged under 40 had benign shear-wave values.

The one malignant lesion classified as BI-RADS 3 was stiff on SWE.

32% of benign lesions were BIRADS category 3 and soft on SWE, so biopsy could potentially be avoided.

Gianotti E et al BJR 2016
The one malignant lesion classified as BIRADS 3 was from a 72 year old patient with a 32mm Grade 2 invasive ductal carcinoma of no special type.
Unit change in policy

- We no longer biopsy or follow up women under 40 with symptomatic clinically benign masses which are:
  - Soft on SWE
  - BIRADS 3 on grey scale
- No missed cancers over 2 yrs
- Plan to extend age range to 50 yrs
Other uses of SWE

• Monitoring NACT
• Predicting upgrade after an US guided biopsy yielding DCIS
• Predicting prognosis
Interim assessment NACT

Parameters

• % reduction in US diameter
• % reduction in stiffness
• % reduction in MRI diameter

Evans et al Eur J US 2017
MRI

% change in MRI diameter

Sensitivity

100-Specificity

AUC 0.68
US

AUC 0.67
Change in Stiffness

AUC 0.82
Thank you!

Thanks to
Sarah Vinnicombe
Shelley Henderson
Brooke Lawson