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Quantitative transrectal shear wave elastography undergoing salvage extraperitoneal laparoscopic radical prostatectomy following failed radiotherapy

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Short title: Shear wave elastography in radioresistant prostate cancers

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Abstract:

Background: To evaluate pre-surgical quantitative transrectal shear wave elastography (SWE) in the detection and characterisation of radioresistant prostate cancer.

Methods: 12 men with recurrent prostate cancer following external beam radiotherapy were included in a prospective protocol driven study. All underwent MR imaging and quantitative shear wave elastographic assessment of recurrent disease prior to salvage laparoscopic radical prostatectomy procedures. Images were used to construct 3-D mold printing and histopathological processing of surgical specimen. Statistical analyses including ROC were generated using software programmes.

Results: There were 48 cancer foci identified on final histopathology using patient specific mold based approach in 12 patients. Mean number of lesion was 3.4 (range 2 to 4). Quantitative transrectal SWE showed a sensitivity and specificity 0.77 (95% CI 0.627 - 0.880) and 0.82 (95% CI 0.642 - 0.942) respectively. The diagnostic accuracy increased with increasing size of the lesions with overall AUC of 0.89.

Conclusions: In our series quantitative transrectal SWE showed a good **diagnostic accuracy** in the detection and characterisation of recurrent prostate cancer following failed radiotherapy treatment. These findings may help in targeting biopsies or future focal treatment options.

Key words: Elastography, radiotherapy, prostate cancer, ultrasound, surgery

1. Introduction

Salvage treatment options vary for radical radiotherapy (external beam or brachytherapy) failure in men with continued organ confined prostate cancer disease on clinical imaging. These include surgery, cryotherapy, photodynamic treatment, high focused ultrasound treatment and hormonal treatment, however decision making is often challenging, both for patients and physicians **{** ADDIN EN.CITE **{** ADDIN EN.CITE.DATA **}}**. Morbidity of these procedures must be balanced against modest gains in terms of cancer control. With the introduction of minimally invasive surgery (with or without robotic assistance), there appears to be an improved safety range of this option **{** ADDIN EN.CITE **{** ADDIN EN.CITE.DATA **}}**. Previous studies have shown a clear improved survival following salvage surgical treatment, although with a high incidence of functional side effects including urinary incontinence and erectile dysfunction **{** ADDIN EN.CITE **{** ADDIN EN.CITE.DATA **}}**. Weighing morbidity against possibility of cure or significant survival advantage often suggests that salvage surgery offer may best be offered to men with organ-confined disease with PSA less than 10 and Gleason score of 7 or less**{** ADDIN EN.CITE **{** ADDIN EN.CITE.DATA **}}**. Prediction of outcomes remains key to the outcomes of any salvage treatment options. Recruitment of patients to trials, in order to obtain best evidence in these areas, has shown some disappointing results **{** ADDIN EN.CITE **{** ADDIN EN.CITE.DATA **}}** and hence careful recorded cohort studies are crucial to inform clinical practice.

Shear wave elastography (SWE) is an ultrasound technique which is not dependant on compression/release technique of strain elastography method and hence elastography produced is an improved reflection of tissue stiffness. It has recently been introduced into clinical practice including early detection of cancers. Bercoff et al **{** ADDIN EN.CITE **{** ADDIN EN.CITE.DATA **}}** were first to report measurement of tissue stiffness based on measurement of shear wave speed propagating through the tissues. A combination of acoustic radiation force impulse generation and ultra-fast imaging forms the basis of this multi-wave imaging technique. **The ultrasound systems designed for shear wave elastography generate acoustic radiation force which induces mechanical vibrations in the focus. These vibrations displace tissues and produce shear waves. Depending on the viscoelastic properties of the tissue, speed of shear waves varies. An ultra-fast ultrasound acquisition system (>20,000 frames per second) is used through same probe to capture these shear waves from the tissues { ADDIN EN.CITE <EndNote><Cite><Author>Bercoff</Author><Year>2003</Year><RecNum>4512</RecNum><DisplayText>[12]</DisplayText><record><rec-number>4512</rec-number><foreign-keys><key app="EN" db-id="dr95wrtar2dsxmesffnpxe2qzserx02d0dxt" timestamp="1520331330">4512</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Bercoff, J.</author><author>Chaffai, S.</author><author>Tanter, M.</author><author>Sandrin, L.</author><author>Catheline, S.</author><author>Fink, M.</author><author>Gennisson, J. L.</author><author>Meunier, M.</author></authors></contributors><auth-address>Laboratoire Ondes et Acoustique, ESPCI, Universite Paris VII, UMR 7587 CNRS 1503, Paris, France.</auth-address><titles><title>In vivo breast tumor detection using transient elastography</title><secondary-title>Ultrasound Med Biol</secondary-title></titles><periodical><full-title>Ultrasound Med Biol</full-title></periodical><pages>1387-96</pages><volume>29</volume><number>10</number><edition>2003/11/05</edition><keywords><keyword>Adenocarcinoma/*diagnostic imaging</keyword><keyword>Adult</keyword><keyword>Aged</keyword><keyword>Aged, 80 and over</keyword><keyword>Algorithms</keyword><keyword>Breast Neoplasms/*diagnostic imaging</keyword><keyword>Elasticity</keyword><keyword>Electronics, Medical/instrumentation</keyword><keyword>Female</keyword><keyword>Humans</keyword><keyword>Middle Aged</keyword><keyword>Models, Biological</keyword><keyword>Ultrasonography, Mammary/instrumentation/*methods</keyword><keyword>Vibration</keyword></keywords><dates><year>2003</year><pub-dates><date>Oct</date></pub-dates></dates><isbn>0301-5629 (Print)
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num><language>eng</language></record></Cite></EndNote>}. The elasticity value of the tissue is measured in kilopascals (kPa) and quantitative stiffness is depicted by Young Modulus as $E = \rho v^2/3$(v is velocity of the shear wave (m/s); ρ is density of local tissue(kg/m^3)){ ADDIN EN.CITE <EndNote><Cite><Author>Athanasiou</Author><Year>2010</Year><RecNum>4511</RecNum><DisplayText>[13]</DisplayText><record><rec-number>4511</rec-number><foreign-keys><key app="EN" db-id="dr95wrtar2dsxmesffnpxe2qzserx02d0dxt" timestamp="1520331127">4511</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Athanasiou, A.</author><author>Tardivon, A.</author><author>Tanter, M.</author><author>Sigal-Zafrani, B.</author><author>Bercoff, J.</author><author>Deffieux, T.</author><author>Gennisson, J. L.</author><author>Fink, M.</author><author>Neuenschwander, S.</author></authors></contributors><auth-address>Department of Radiology, Institut Curie, 26 rue d'Ulm, Paris Cedex 05, France. alexandra.athanasiou@curie.net</auth-address><titles><title>Breast lesions: quantitative elastography with supersonic shear imaging--preliminary results</title><secondary-title>Radiology</secondary-title></titles><periodical><full-title>Radiology</full-title></periodical><pages>297-303</pages><volume>256</volume><number>1</number><edition>2010/05/28</edition><keywords><keyword>Adult</keyword><keyword>Aged</keyword><keyword>Area Under Curve</keyword><keyword>Breast Neoplasms/*diagnostic imaging</keyword><keyword>Diagnosis, Differential</keyword><keyword>Elasticity Imaging Techniques/*methods</keyword><keyword>Female</keyword><keyword>Humans</keyword><keyword>Image Interpretation, Computer-Assisted/methods</keyword><keyword>Middle Aged</keyword><keyword>ROC Curve</keyword><keyword>Sensitivity and Specificity</keyword></keywords><dates><year>2010</year><pub-dates><date>Jul</date></pub-dates></dates><isbn>1527-1315 (Electronic)
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10.1148/radiol.10090385</electronic-resource-num><language>eng</language></record></Cite></EndNote>}. **Measurement of shear wave speed provides a map of local tissue stiffness as colour-coded image on screen (elastogram).** The underlying principle is that speed of the shear wave depicts the stiffness properties of the medium in which it propagates. Our group and others have published results of quantitative shear wave elastography in the detection of prostate cancer using endocavitary transrectal transducers **{** ADDIN EN.CITE **{** ADDIN EN.CITE.DATA **}}**. The shear wave images representing shear wave speed (in m/s) or the Young's modulus (in kPa) are colour coded for each pixel. It is real time and displayed on screens as overlay on the B mode images.

Prostate imaging, especially MRI has evolved dramatically over the past decades, however a reliable matching between what is seen on imaging and what is shown in histopathology (especially whole mount organs such as prostate) may not be accurate or reliably matched (supplementary Figure 1). This is due to a gap in processing methodology in particular slicing of organ being different on imaging and histopathology. With advancements in 3-D visualisation, multiplanar reformation and printing technology, it has been possible to improve orientation between imaging and histopathology. We and others have used a recently published a method of rapid prototyping and 3D-printing of prostate MRI images into molds to guide slicing of prostate glands after radical prostatectomy by histopathologists{ ADDIN EN.CITE { ADDIN EN.CITE.DATA }}. The process from acquiring MR images to 3D prototype mold printing was applied to all the participants in this study to achieve reliable results from transrectal SWE (index test) and histopathology of whole mount prostate (reference standard).

The present study was designed as a feasibility phase to assess diagnosis accuracy of transrectal SWE in the detection and characterisation of clinically localised radioresistant prostate cancer.

2. Materials and Methods

a) Study Cohort

The feasibility phase of this study is a part of a large Shear Prostate Study with ethics and institutional approval (**East of Scotland Research Ethics Committee, ethical approval number 13/ES/0099 and Caldicott institutional approval number CSAppGN021211**) aimed at diagnostic accuracy of Transrectal SWE in the detection and characterisation of prostate cancer. The study design is shown Figure 1. We recruited 12 men with failed radical external beam radiotherapy for prostate cancer out of 170 patients who had laparoscopic radical prostatectomy (LRP) between Nov 2013 and Feb 2016 after discussions and consensus in multidisciplinary meeting (supplementary figure 2). **All patients signed informed consent forms to participate in the study.** These patients refused or were not suitable for salvage cryotherapy or any other forms of local treatment options. Option of long-term hormonal treatment was also discussed. All the participants had radioresistant disease following failed external beam radiotherapy treatment. **We used RTOG-ASTRO Phoenix Consensus Conference definition for biochemical failure and radioresistant cancer as described earlier {** ADDIN EN.CITE **{** ADDIN EN.CITE.DATA **}}**. All men had pre-surgery transrectal shear wave elastography using protocol described below. The images were saved for further analyses. The primary study outcome measure was diagnostic accuracy of SWE in the detection and characterisation of prostate cancer. Secondary outcome measures, related to salvage extraperitoneal LRP, were 1) clinical efficacy (biochemical disease control by serial prostate-specific antigen measurements) 2) urinary incontinence using validated questionnaires at 3, 6 and 12 months, then annually thereafter 3) readmission to hospital and complications as assessed using Clavian-Dindo classification.

b) Imaging protocol

All images were obtained using transrectal endocavitary transducer (SuperSonic Imagine, Aix en Provence, France) with patient being in lithotomy or lateral position. B Mode images were obtained and prostate glands were measured in volume. SWE mode was then activated and prostate gland elastography was obtained from cranial to caudal direction for each lobe of the prostate. All the regions were scanned as described in our protocol previously **{** ADDIN EN.CITE **{** ADDIN EN.CITE.DATA **}}**. Each of the twelve regions of glands was recorded in Pseudo-colour images and stored for further analysis. When a large positive lesion was seen crossing the arbitrary regions, it was counted for each of those regions and size measured. During scanning minimum pre-load (manual compression) was ensured and images were recorded after a minimum wait of 15 seconds. Shear wave speed or Young's modulus in kPa was measured using cursor on both suspected cancers (red) and benign areas (blue) as shown in Figure 2. Suspected areas were imaged by rotating probe in different direction to confirm abnormalities and to measure their size. Measurement of stiffness of red and blue areas were used to obtain ratio between abnormal and normal areas.

Just before radical prostatectomy, transrectal transducer was positioned to image apical areas of prostate and periurethral stiffness of urethra measured at the point of entry into prostate. In order to delineate this area better, 20-25ml instillagel (FARCO-PHARMA GmbH, 50670 Cologne, Germany) was instilled into urethral and penile clamp applied.

50 ml normal saline was injected between rectum and prostate (outside the Denovillier fascia) under ultrasound guidance to hydro dissect this area and facilitate subsequent dissection. This method is also used to prevent rectal injury during LRP.

All men had MRI scans prior to the salvage using 1.5T or 3T scanner as described in our previous reports{ ADDIN EN.CITE { ADDIN EN.CITE.DATA }}. Briefly, MR imaging in the participating men was carried out on 1.5 T scanners (Siemens Medical Solutions), equipped with surface phased pelvic array (Body Matrix, Siemens Medical Solutions). Anatomical details of the prostatic gland were obtained by acquiring turbo spin-echo (TSE) T2-weighted sequences in the axial, sagittal and coronal planes, with the use of optimized parameters for a better spatial resolution. All patients underwent diffusion-weighted imaging (DWI), (2D echo-planar imaging spin-echo, with at least three b-values and calculated ADC map) in addition to anatomical T2WI.

c) Patient-specific 3D printing of prostate molds

For men opting for salvage radical prostatectomy, we obtained pre-surgical transrectal SWE and MR images. 3-D images of prostate gland were reconstructed using MIMICS (Materialise NV, Leuven, Belgium). The reconstructed images were imported into SolidWorks (Dassault Systemes S.A., U.S.A). Depending on size of prostate on imaging, cavities were generated matching the prostate gland in contour.

The molds were manufactured using Acrylonitrile butadiene styrene (ABS) and 3D printer Replicator 5th (Makerbot Industries, Brooklyn NY 11201 USA). Molten plastic extruding from printer in strands of 0.3 mm size is rapidly cooled to make desired mold in layer wise. Complete printing was achieved under the supervision via built-in camera and molds were delivered to pathology grossing room for further processing of radical prostatectomy specimen in advance.The images in Figure 1a&c described the methods of 3D modelling and mold fabrication. After careful segmentation and photographing from both B-mode and SWE data, each suspicious cancerous area was manually marked on each slide and fused into a 3D model (Figure 2-a). Lesions were distinguished from normal tissue of prostate gland in pseudo-colour image with different quantitative data (Figure 2-b). The advantages of this technique were to provide a better visualised and comprehensive analysis for the characterisation of prostate cancer.

d) Radical prostatectomy specimen processing

Radical prostatectomy specimens were fixed in formalin (40% buffered) immediately after surgical excision and transported to the pathology laboratory. For all patients, a patient-specific customized 3D molds (Figure 1-c) were used as described by us and others **{** ADDIN EN.CITE **{** ADDIN EN.CITE.DATA **}}**. Briefly, fabrication of molds was achieved using 3D printing based on MR/SWE images of prostate gland as described above. This approach ensured a correct alignment and orientation between imaging and histology. Detailed pathology reports were produced for each regions and sizes of the lesions were measured by an experienced uro-pathologist (SL) and all the cancer foci were characterised for Gleason grade. Pathologists were not aware of the imaging results.

e) Statistical analysis

Diagnostic accuracy (sensitivity, specificity, positive and negative likelihood ratios) were calculated based on number of lesions and Gleason grade for SWE. Histopathology of main specimen was the

reference standard. In addition, we analysed correlation between mean stiffness of the tumour and Gleason grade on final histopathology. Staging and margin status, especially for apical area were correlated with SWE imaging.

3. Results

a) Patient cohort

Baseline characteristics of the cohort are shown in Table 1. A large number of men were not suitable for radical surgery at the time of initial decision and most of them had neo/adjuvant hormonal treatment for atleast two years. The disease showed biochemical recurrence within a range of 3 to 10 years after initial radical radiotherapy treatment. The overall median pre-treatment PSA level and Gleason score sum of the cohort were 9.57 ng/mL (range: 2.6–20 ng/mL) and 8 (range: 7–10), respectively. All men had histologically proven adenocarcinoma. All men had extended lymph node dissection and one of the participants showed metastatic disease. Despite negative surgical margins and negative lymph nodes, three men had persistent high PSA and required hormonal treatment. Two men had progression of disease and needed Docetaxol chemotherapy.

b) Quantitative transrectal shear wave elastography

- detection

Overall sensitivity and specificity of SWE in the detection of prostate cancer for various sizes of the lesions was 0.77 (95% CI 0.627 - 0.880) and 0.82 (95% CI 0.642 - 0.942) respectively. The diagnostic accuracy increased with increasing size of the lesions with overall AUC of 0.89 (Figure 3-a). **Figure 3-**b shows diagnostic accuracy of SWE for various Gleason score disease with AUC 0.89 with significant increase for intermediate and higher score disease. There were 48 cancer foci identified on final histopathology using patient specific mold based approach (Table 2). Mean number of lesion was 3.4 (range 2 to 4).

- Characterisation:

Most of lesions (37/48; 77%) were seen using transrectal SWE and were 3+4 or more. Mean stiffness between different Gleason scores showed significant differences (Figure 5, $p<0.05$).

- Staging

Figure 4-a shows a small focus (4mm, red circle) of disease with mean stiffness of 64.7kPa in one patient who had complete excision for localised. Three patients had positive surgical margins, two could be reliably predicted using SWE. Figure 4-b shows higher peri-urethral stiffness of 180.1kPa (red circle) and histopathology confirmed positive surgical margins (Figure 4-c). MRI in Figure 4-d and 4-e in red circles show localised disease only, however SWE correctly identified extracapsular extension.

c) Comparison with MRI

Table 3 shows comparison of performance of quantitative shear wave elastography and MRI (anatomical sequences and DWI) for different sizes of the lesions based histopathology of radical prostatectomy as reference standard. The performance of MRI and SWE is comparable and both were poor in smaller (<5mm). In three patients SWE correctly identified extracapsular extension of cancer and none of these were reported on MRI. There were not many lesions in the anterior zone of the prostate and hence performance of both imaging modalities in this area would need further study.

Performance of SWE was particularly promising for measuring periurethral stiffness in the apical region of the prostate. In seven men, SWE could reliably predict status of apical margin using mean periurethral stiffness as a marker of disease. It was false positive and false negative in two cases respectively. 3D reconstructed images (**Figure 2-a**) clearly show disease in apical area and could be helpful in guiding surgical technique.

d) Complications and oncological outcome

There was one rectal injury repaired intraoperatively. Two patients developed bladder neck stenosis and needed laser bladder incision (in 1 case the procedure needed to be repeated). Three patients were readmitted for urinary tract infections and treated conservatively. One patient required artificial urinary sphincter placement for intractable urinary incontinence.

Four patients need intermittent/long-term hormonal treatment and rest of them have undetectable PSA at various points in their follow-up.

4. Discussion

The American Society for Therapeutic Radiology and Oncology (ASTRO) recommends new definition of biochemical failure following radical treatment of prostate using external beam radiation therapy with or without androgen deprivation therapy. An increase in PSA of 2ng/ml or more above the nadir level is a consensus definition of biochemical failure **{** ADDIN EN.CITE **{** ADDIN EN.CITE.DATA **}}**. Therapeutic options after failure of radical radiotherapy for prostate cancer disease are associated with higher rate of morbidity compared to those used as first-line **{** ADDIN EN.CITE <EndNote><Cite><Author>Heidenreich</Author><Year>2012</Year><RecNum>316</RecNum><DisplayText>[8]</DisplayText><record><rec-number>316</rec-number><foreign-keys><key app="EN" db-id="25wzas2vpxaezoeevt1xes9pspsfev9tt2vx">316</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Heidenreich, A.</author><author>Porres-Knoblauch, D.</author><author>Epplen, R.</author><author>Piper, C.</author><author>Pfister, D. J.</author><author>Euro Prostate Center Aachen</author></authors></contributors><auth-address>RWTH Aachen University, Aachen, Germany; RWTH University, Aachen, Germany.</auth-address><titles><title>Radical salvage prostatectomy for locally recurrent prostate cancer after radiation therapy</title><secondary-title>J Clin Oncol</secondary-title><alt-title>Journal of clinical oncology : official journal of the American Society of Clinical Oncology</alt-title></titles><periodical><full-title>J Clin Oncol</full-title><abbr-1>Journal of clinical oncology : official journal of the American Society of Clinical Oncology</abbr-1></periodical><alt-periodical><full-title>J Clin Oncol</full-title><abbr-1>Journal of clinical oncology : official journal of the American Society of Clinical Oncology</abbr-1></alt-periodical><pages>47</pages><volume>30</volume><number>5_suppl</number><dates><year>2012</year><pub-dates><date>Feb 10</date></pub-dates></dates><isbn>1527-7755 (Electronic)
0732-183X (Linking)</isbn><accession-num>27967872</accession-num><urls><related-urls><url>http://www.ncbi.nlm.nih.gov/pubmed/27967872</url></related-urls></urls></record></Cite></EndNote>**}**. Defining extent of disease and precise localisation on imaging becomes a crucial step in the work-up of these patients as this will inform future management of these cases including discussions on long-term prognosis **{** ADDIN EN.CITE <EndNote><Cite><Author>Pokala</Author><Year>2016</Year><RecNum>321</RecNum><DisplayText>[28]</DisplayText><record><rec-number>321</rec-number><foreign-keys><key app="EN" db-id="25wzas2vpxaezoeevt1xes9pspsfev9tt2vx">321</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Pokala, N.</author><author>Huynh, D. L.</author><author>Henderson, A. A.</author><author>Johans, C.</author></authors></contributors><auth-address>Division of Urology, University of Missouri School of Medicine, Columbia, MO. Electronic address: pokalan@health.missouri.edu.
Division of Urology, University of Missouri School of Medicine, Columbia, MO.</auth-address><titles><title>Survival Outcomes in Men Undergoing Radical Prostatectomy After Primary Radiation Treatment for Adenocarcinoma of the Prostate</title><secondary-title>Clin Genitourin Cancer</secondary-title><alt-title>Clinical genitourinary cancer</alt-title></titles><periodical><full-title>Clin Genitourin Cancer</full-title><abbr-1>Clinical genitourinary cancer</abbr-1></periodical><alt-periodical><full-title>Clin Genitourin Cancer</full-title><abbr-1>Clinical genitourinary cancer</abbr-1></alt-periodical><pages>218-25</pages><volume>14</volume><number>3</number><dates><year>2016</year><pub-dates><date>Jun</date></pub-dates></dates><isbn>1938-0682 (Electronic)
1558-7673 (Linking)</isbn><accession-num>26774347</accession-num><urls><related-

urls><url>http://www.ncbi.nlm.nih.gov/pubmed/26774347</url></related-urls></urls><electronic-resource-num>10.1016/j.clgc.2015.12.010</electronic-resource-num></record></Cite></EndNote>}. The results of present study show that transrectal SWE is a novel non-invasive imaging technique with good diagnostic accuracy especially for larger sizes of lesions and those with higher grade of disease. The results are significant and suggest that the benefits of SWE are maintained in post-radiated prostates and even in those who had androgen deprivation therapy. To our knowledge, no researchers have published prior studies on this topic. Our preliminary study results add and inform diagnostic approach to men with biochemical relapse following radiation failure.

Transrectal SWE is a novel imaging method and focus of our study. Grey-scale B modal ultrasound images based on brightness of image representing structural image of tissue had shown poor performance in the detection or characterisation of prostate cancer. It is used to guide biopsy sampling from different regions of prostate, however. SWE relies on the generation of shear waves within the target tissue by acoustic radiation force impulse (ultrasound beam produced by the transducer into the tissues). The generated shear waves travel laterally between 1 to 10m/s and attenuated by the tissues. The velocity of waves is determined by the stiffness of the tissue or what is also known as shear modulus of the tissue { ADDIN EN.CITE <EndNote><Cite><Author>Sarvazyan</Author><Year>2011</Year><RecNum>801</RecNum><DisplayText>[29]</DisplayText><record><rec-number>801</rec-number><foreign-keys><key app="EN" db-id="25wzas2vpxaezoeevt1xes9pspsfev9tt2vx">801</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Sarvazyan, A.</author><author>Hall, T. J.</author><author>Urban, M. W.</author><author>Fatemi, M.</author><author>Aglyamov, S. R.</author><author>Garra, B. S.</author></authors></contributors><auth-address>Artann Laboratories, Trenton, NJ 08618 USA.</auth-address><titles><title>An Overview of Elastography - an Emerging Branch of Medical Imaging</title><secondary-title>Curr Med Imaging Rev</secondary-title><alt-title>Current medical imaging reviews</alt-title></titles><periodical><full-title>Curr Med Imaging Rev</full-title><abbr-1>Current medical imaging reviews</abbr-1></periodical><alt-periodical><full-title>Curr Med Imaging Rev</full-title><abbr-1>Current medical imaging reviews</abbr-1></alt-periodical><pages>255-282</pages><volume>7</volume><number>4</number><dates><year>2011</year><pub-dates><date>Nov</date></pub-dates></dates><isbn>1573-4056 (Print)
1573-4056 (Linking)</isbn><accession-num>22308105</accession-num><urls><related-urls><url>http://www.ncbi.nlm.nih.gov/pubmed/22308105</url></related-urls></urls><custom2>3269947</custom2></record></Cite></EndNote> } and is expressed in kilopascals using Young's Modulus. Shear modulus of the tissue is extremely sensitive to physiological or pathological changes and hence its measurement can be used as a marker of disease { ADDIN EN.CITE <EndNote><Cite><Author>Garra</Author><Year>2007</Year><RecNum>809</RecNum><DisplayText>[30]</DisplayText><record><rec-number>809</rec-number><foreign-keys><key app="EN" db-id="25wzas2vpxaezoeevt1xes9pspsfev9tt2vx">809</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Garra, B. S.</author></authors></contributors><auth-address>Department of Radiology, University of Vermont College of Medicine, Fletcher Allen Health Care, Burlington, VT 05401, USA. bgarra@uvm.edu</auth-address><titles><title>Imaging and estimation of tissue elasticity by ultrasound</title><secondary-title>Ultrasound Q</secondary-title><alt-title>Ultrasound quarterly</alt-title></titles><periodical><full-title>Ultrasound Q</full-title><abbr-1>Ultrasound quarterly</abbr-1></periodical><alt-periodical><full-title>Ultrasound Q</full-title><abbr-

1>Ultrasound quarterly</abbr-1></alt-periodical><pages>255-68</pages><volume>23</volume><number>4</number><keywords><keyword>Biomechanical Phenomena</keyword><keyword>Echocardiography/methods</keyword><keyword>Elasticity</keyword><keyword>Elasticity Imaging Techniques/classification/*methods</keyword><keyword>Female</keyword><keyword>Humans</keyword><keyword>Male</keyword><keyword>Prostate/diagnostic imaging</keyword><keyword>Stress, Mechanical</keyword><keyword>Ultrasonography, Doppler/methods</keyword><keyword>Ultrasonography, Mammary/methods</keyword></keywords><dates><year>2007</year><pub-dates><date>Dec</date></pub-dates></dates><isbn>0894-8771 (Print)
0894-8771 (Linking)</isbn><accession-num>18090836</accession-num><urls><related-urls><url>http://www.ncbi.nlm.nih.gov/pubmed/18090836</url></related-urls></urls><electronic-resource-num>10.1097/ruq.0b013e31815b7ed6</electronic-resource-num></record></Cite></EndNote>**}**. Ultrafast imaging technology based on improved software processing (Supersonic Shear Imaging also known as SSI) has made it possible to image these waves. The stiffness is colour-coded on screen and this relates to the speed of the shear waves. The vertical bar on the left side of image represents velocity range (in kilopascals) with range from dark blue (soft tissues) to red (stiff tissues) **{** ADDIN EN.CITE <EndNote><Cite><Author>Cao</Author><Year>2013</Year><RecNum>814</RecNum><DisplayText>[31]</DisplayText><record><rec-number>814</rec-number><foreign-keys><key app="EN" db-id="25wzas2vpxaezoeevt1xes9pspsfev9tt2vx">814</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Cao, R.</author><author>Huang, Z.</author><author>Varghese, T.</author><author>Nabi, G.</author></authors></contributors><auth-address>School of Engineering, Physics, and Mathematics, University of Dundee, Dundee DD1 4HN, UK.</auth-address><titles><title>Tissue mimicking materials for the detection of prostate cancer using shear wave elastography: a validation study</title><secondary-title>Med Phys</secondary-title><alt-title>Medical physics</alt-title></titles><periodical><full-title>Med Phys</full-title><abbr-1>Medical physics</abbr-1></periodical><alt-periodical><full-title>Med Phys</full-title><abbr-1>Medical physics</abbr-1></alt-periodical><pages>022903</pages><volume>40</volume><number>2</number><keywords><keyword>Elasticity Imaging Techniques/*instrumentation</keyword><keyword>Humans</keyword><keyword>Male</keyword><keyword>*Mechanical Phenomena</keyword><keyword>*Phantoms, Imaging</keyword><keyword>Prostate/diagnostic imaging</keyword><keyword>Prostatic Neoplasms/*diagnostic imaging</keyword></keywords><dates><year>2013</year><pub-dates><date>Feb</date></pub-dates></dates><isbn>0094-2405 (Print)
0094-2405 (Linking)</isbn><accession-num>23387774</accession-num><urls><related-urls><url>http://www.ncbi.nlm.nih.gov/pubmed/23387774</url></related-urls></urls><custom2>3562344</custom2><electronic-resource-num>10.1118/1.4773315</electronic-resource-num></record></Cite></EndNote>**}**.

There are several published reports showing benefits of SWE in the detection and characterisation of prostate cancer **{** ADDIN EN.CITE **{** ADDIN EN.CITE.DATA **}}**, however the technology has not been evaluated in radiation failure patients. This is particularly challenging area as fibrosis distorts the interpretation of images and quality of imaging modality is compromised. In the present study, SWE using endocavitary transrectal transducer has shown reliable results. The performance of this

imaging modality was particularly good in larger lesions and those situated close to apex of the prostate. Periurethral stiffness seen in the present could be a potential marker of risk of positive surgical margins and can guide surgery in this area in the future. Real time imaging with ability to obtain superimposed B-mode and SWE images simultaneously on screen is an added advantage. Apical area of prostate is particularly difficult to image using conventional techniques and our experience using SWE in this study has been encouraging. SWE performed better than MRI, although numbers are small and further studies are needed exploring this further.

Diagnostic imaging aimed at the detection of recurrence of disease in radiated prostate has been a challenge. Studies have shown that results of MRI using T2-weightedimaging perform poorly for detecting local recurrence due to the fact that the glands become atrophic and scarred giving a diffuse low signal intensity. Magnetic resonance imaging shows a loss of differentiation between peripheral and central zone with changes due to post-irradiation fibrosis. Diagnostic accuracy of spectroscopy, particular reappearance of choline peaks has been reported to be useful **{** ADDIN EN.CITE **{** ADDIN EN.CITE.DATA **}}**. Haider et al **{** ADDIN EN.CITE **{** ADDIN EN.CITE.DATA **}}**using transrectal biopsies as reference standard showed a good diagnostic accuracy of dynamic MRI in radiation failure patients. Similar results have been reported by others (**{** ADDIN EN.CITE <EndNote><Cite><Author>Rouviere</Author><Year>2004</Year><RecNum>875</RecNum><DisplayText>[37]</DisplayText><record><rec-number>875</rec-number><foreign-keys><key app="EN" db-id="25wzas2vpxaezoeevt1xes9pspsfev9tt2vx">875</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Rouviere, O.</author><author>Valette, O.</author><author>Grivolat, S.</author><author>Colin-Pangaud, C.</author><author>Bouvier, R.</author><author>Chapelon, J. Y.</author><author>Gelet, A.</author><author>Lyonnet, D.</author></authors></contributors><auth-address>Department of Genitourinary Radiology, Hopital E. Herriot, Lyon, France.</auth-address><titles><title>Recurrent prostate cancer after external beam radiotherapy: value of contrast-enhanced dynamic MRI in localizing intraprostatic tumor--correlation with biopsy findings</title><secondary-title>Urology</secondary-title><alt-title>Urology</alt-title></titles><periodical><full-title>Urology</full-title><abbr-1>Urology</abbr-1></periodical><alt-periodical><full-title>Urology</full-title><abbr-1>Urology</abbr-1></alt-periodical><pages>922-7</pages><volume>63</volume><number>5</number><keywords><keyword>Aged</keyword><keyword>Biopsy/methods</keyword><keyword>Humans</keyword><keyword>Magnetic Resonance Imaging/*methods</keyword><keyword>Male</keyword><keyword>Middle Aged</keyword><keyword>Neoplasm Recurrence, Local/*pathology</keyword><keyword>Observer Variation</keyword><keyword>Prostate/*pathology</keyword><keyword>Prostatic Neoplasms/*pathology/radiotherapy</keyword><keyword>Ultrasonography, Interventional</keyword></keywords><dates><year>2004</year><pub-dates><date>May</date></pub-dates></dates><isbn>1527-9995 (Electronic)
0090-4295 (Linking)</isbn><accession-num>15134982</accession-num><urls><related-urls><url>http://www.ncbi.nlm.nih.gov/pubmed/15134982</url></related-urls></urls><electronic-resource-num>10.1016/j.urology.2003.12.017</electronic-resource-num></record></Cite></EndNote> **}** . Arumainayagam et al. **{** ADDIN EN.CITE <EndNote><Cite><Author>Arumainayagam</Author><Year>2010</Year><RecNum>1019</RecNum><DisplayText>[38]</DisplayText><record><rec-number>1019</rec-number><foreign-keys><key app="EN" db-id="25wzas2vpxaezoeevt1xes9pspsfev9tt2vx">1019</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Arumainayagam, N.</author><author>Kumaar, S.</author><author>Ahmed, H. U.</author><author>Moore, C.

M.</author><author>Payne, H.</author><author>Freeman, A.</author><author>Allen, C.</author><author>Kirkham, A.</author><author>Emberton, M.</author></authors></contributors><auth-address>Division of Surgery and Interventional Sciences, University College Hospital, London, UK. nim.arum@ucl.ac.uk</auth-address><titles><title>Accuracy of multiparametric magnetic resonance imaging in detecting recurrent prostate cancer after radiotherapy</title><secondary-title>BJU Int</secondary-title><alt-title>BJU international</alt-title></titles><periodical><full-title>BJU Int</full-title><abbr-1>BJU international</abbr-1></periodical><alt-periodical><full-title>BJU Int</full-title><abbr-1>BJU international</abbr-1></alt-periodical><pages>991-7</pages><volume>106</volume><number>7</number><keywords><keyword>Aged</keyword><keyword>Humans</keyword><keyword>Magnetic Resonance Imaging/methods/*standards</keyword><keyword>Male</keyword><keyword>Middle Aged</keyword><keyword>Neoplasm Recurrence, Local/*diagnosis</keyword><keyword>Prostate/*pathology</keyword><keyword>Prostatic Neoplasms/*diagnosis/radiotherapy</keyword><keyword>Reference Standards</keyword><keyword>Retrospective Studies</keyword></keywords><dates><year>2010</year><pub-dates><date>Oct</date></pub-dates></dates><isbn>1464-410X (Electronic)
1464-4096 (Linking)</isbn><accession-num>20230392</accession-num><urls><related-urls><url>http://www.ncbi.nlm.nih.gov/pubmed/20230392</url></related-urls></urls><electronic-resource-num>10.1111/j.1464-410X.2010.09291.x</electronic-resource-num></record></Cite></EndNote>**}** reported excellent correlation between multiparametric MRI (using T weighted images and dynamic data) and saturation biopsies. All of these published reports have used transrectal ultrasound guided biopsies as reference standard and this certainly introduces a detection bias of variable degree. In the present study, we used histopathology using patient-specific mold based processing. Our study has not used dynamic contrast enhanced imaging or spectroscopy as this was not the intended outcome of the study, however there are reports that combination of MR techniques (T2-weighted MR, MR spectroscopic, dynamic contrast-enhanced MR, and diffusion-weighted MR imaging) commonly termed as multiparametric MR imaging has potential of improving detection and perhaps characterisation of recurrent disease. Interobserver variations, reproducibility of technique, protocols and reference standards are some of areas of future studies.

There are several strengths of this feasibility study such as prospective design, using radical prostatectomy specimen histology in a patient-specific processing as reference standard, detailed pathological analysis and reporting. **Patient-specific molds fabricated using rapid-prototyping from pre-surgical images of prostate helped in achieving a better correlation between imaging and histopathology of prostate cancer foci. In a heterogenous and multifocal disease like prostate cancer, it is difficult to assign a correct correlation between imaging and pathology without an orientation methodology.** The study is, however limited by small numbers but comparable to many reports of imaging modalities in radiation failure prostate cancer patients **{** ADDIN EN.CITE **{** ADDIN EN.CITE.DATA **}}**. It is a single institutional study and all the SWE images were acquired by a single operator, so interobserver agreement was not established to assess reproducibility. Further studies are needed to assess performance in multi-institutional settings with assessment of inter-reader agreement.

Transrectal SWE imaging significantly improves detection and characterisation of radioresistant prostate cancer after radical external beam radiotherapy. The information from this study may form the basis for subsequent clinical evaluation of patients with recurrent prostate cancer including directing biopsies or focal treatment. The SWE technology can quantitatively assess the disease

which may help in risk stratification to different salvage treatment options. A particular helpfully promising role of this technology is the assessment of the apical area is emerging to guide surgery with aim to reduce positive surgical margins, however this needs future studies with larger number of patients.

Disclosure section

Cheng Wei has no conflicts of interest or financial ties to disclose.

Magda Szewczyk-Bieda has no conflicts of interest or financial ties to disclose.

Paddy Nibblock has no conflicts of interest or financial ties to disclose.

Emma Brown has no conflicts of interest or financial ties to disclose.

Stephen Lang has no conflicts of interest or financial ties to disclose.

Ghulam Nabi has no conflicts of interest or financial ties to disclose.

Reference

{ ADDIN EN.REFLIST }

Legends for figures

1. **Figure 1**: The flow chart of the study. a: T2-Weighted MR images and 3D modelling (two of the prostate lesions shown in red mass area); b: shear wave elastography images and corresponding 3D modelling (lesions shown in red circles); c: prostatectomy specimen slices; and d: histology photos and corresponding 3D modelling (lesions shown yellow mass areas).
2. **Figure 2**: 3D measurement of SWE with quantitative data. Suspicious cancer area: 147.1 kPa; normal tissue: 19.1 kPa.
3. **Figure 3** a: diagnostic SWE accuracy for overall lesions with different size; b: diagnostic accuracy of SWE for different Gleason grade diseases.
4. **Figure 4** a: Small focus of suspicious lesion shown in apex with mean stiffness 64.7kPa (red mass) compare to normal prostate organ with mean stiffness 27.3kPa; b: Peri-urethral cancer focus with mean stiffness 180.1kPa (red mass) compared to normal prostate organ with stiffness 25.0kPa; c: Extraprostatic extension (EPE) of prostatic carcinoma; d: MRI ADC map; e: Axial T2WI MRI slice with confirmation of localised cancer only.
5. **Figure 5:** Whisker plot showing relationship of Young's modulus (in kPa) with benign and malignant regions
6. **Supplementary Figure 1:** Imaging-histology correlation in prostate cancer surgery. Left: customised image-based mold for sectioning; right: conventional sectioning of prostate specimens.
7. **Supplementary Figure 2:** Consort criteria and diagram