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Tissue characterisation in prostate cancer using a novel ultrasound approach

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Introduction

Our approach to prostate cancer diagnosis is at odds with almost every other solid tumour. The prostate is one of the last organs in the body that we biopsy blindly, without the aid of an imaging platform that allows us to actually visualise areas suspicious of cancer. Systematic prostate biopsy relies on probability alone to detect cancer though this can be influenced by judicious placement of the needles (peripheral zone, lateral and parasagittal areas) and by varying the sampling intensity [1]. The reason that imaging is not used to direct biopsies is that, to date, our ability to discriminate cancer from non-cancer has been modest at best [2]. However, there is some sign that this position may soon be challenged. This paper reviews the status of imaging platforms most likely to succeed in helping us discriminate the cancer lesion from the heterogeneous histological background of the prostate.

Characterisation by multi-sequence MRI

MRI has been conventionally used for local staging of prostate cancer. Prostate cancer appears as low signal compared to the high signal intensity of the surrounding normal peripheral zone on T2 weighted sequences, but is not particularly helpful as documented sensitivity varies from 60% to 96% [3]. The benign pathologies of prostatitis and benign prostatic hyperplasia account for the poor specificity [4]. It is particularly unhelpful in the post-biopsy setting as haemorrhage very often appears as low signal similar to tumour on T2 weighted sequences. T1-weighted images can show this as high signal and to a varying degree overcome this inaccurate interpretation. However, as the biopsy artefact can last for up to 6 months even the combination of using T1-weighted and T2-weighted images has limited promise. Nonetheless, newer MR imaging sequences have shown potential in improving the accuracy of MR imaging of the prostate.

Dynamic contrast enhanced MRI (DCE-MRI)

Angiogenesis and increased microvessel density (MVD) noted in prostate cancer have been correlated with metastasis [5], pathological stage [6] and disease specific survival [7]. DCE-MRI enables non-invasive imaging of this abnormal tissue vascularity. A rapid injection of paramagnetic low molecular weight contrast agent, usually gadolinium, with rapid scanning every 2–5s through the prostate demonstrates early enhancement and

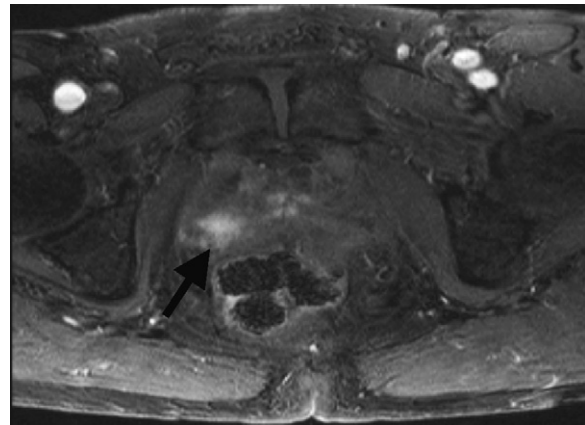


Figure 1 Dynamic contrast enhanced MRI in T1 weighted image shows an early enhancement (arrow) in the right peripheral zone a minute after gadolinium contrast injection.

early washout of signal intensity typical of malignant tissue (Fig. 1). This functional dynamic imaging has been shown to have a sensitivity of 73% and specificity of 80% in localising cancer [8]. Similarly, in a small study comparing T2 weighted and DCE-MRI sequence with radical prostatectomy whole-mount specimens, DCE-MRI increased the area under the receiver operating characteristic curve (ROC) from 0.68 to 0.91 [9]. Villers et al. demonstrated that DCE-MRI can detect small tumour foci with greater accuracy, when compared to radical whole mount specimens. They demonstrated sensitivity, specificity, positive and negative predictive value of 77%, 91%, 86% and 85% for tumour foci $>0.2\text{ cm}^3$ whilst the same parameters for tumour foci $>0.5\text{ cm}^3$ was 90%, 88%, 77% and 95%, respectively [10]. This extraordinary finding is almost certainly related to the use of DCE-MRI prior to diagnostic prostate biopsies which therefore overcame biopsy artefact (Fig. 2).

MR spectroscopy (MRS)

One of the drawbacks of MR imaging has been the lack of specificity. Recent studies seem to indicate that MRS could add specificity to MR imaging. MRS is a molecular imaging technique which exploits the abnormal tumour metabolism seen in prostate cancer tissue – increased phospholipid turnover resulting in a high choline concentration compared to citrate levels. MRS evaluates this increased choline to citrate ratio level. MRS combined with anatomical imaging provided by T2-weighted images can significantly improve the characterisation of cancer location and volume within prostate [11–15], extracapsular extension [16,17] and cancer aggressiveness [18,19]. There is

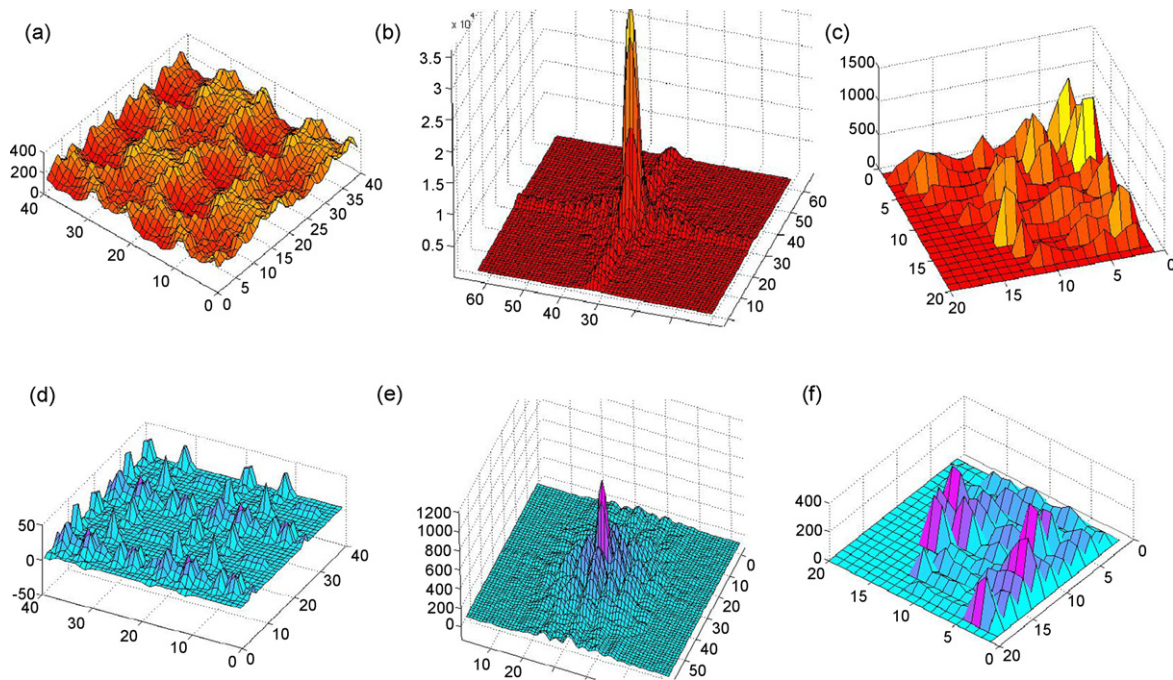


Figure 2 Graphical representation of the results of the three characterisation algorithms for malignant and Non-malignant areas. Graphs (a–c) represent a malignant lesion and (d–f) represent a non-malignant area. Note the obvious difference in the y-axis value between (a) and (d), (b) and (e), (c) and (f).

evidence that tumour detection by MRS is dependent on Gleason grade. In other words, the accuracy of MRS increased from 44% for Gleason score 6 tumours to 90% for Gleason score 8 and 9 [19].

Diffusion weighted imaging (DWI)

Prostate cancer exhibits decreased water diffusivity due to the increased cell density typically seen in cancer. DWI determines these water diffusion characteristics across cell membranes. This is substantially affected by change in cell density, vascularity, viscosity of extracellular fluid, membrane permeability, active transport and directionality all of which impede water mobility. This is calculated as an 'apparent diffusion co-efficient' with prostate cancer scoring a low ADC value [20]. There is some evidence to show DWI could further risk stratify patients based on the ADC values [21].

Each of these techniques or sequences has its own merits and they are complimentary to each other. Arguably, incorporating all the sequences in one patient, so-called multi-sequence or multi-parametric MRI, should increase the overall accuracy. It is hoped that the current limitations on spatial resolution will be improved by higher magnetic strength 3 tesla scanners. However, this advantage is likely to be limited to DCE-MRI and DWI [22,17], and requires careful evaluation.

Characterisation by ultrasound techniques

In the field of ultrasound, notable diagnostic techniques are contrast-enhanced ultrasound, real time elastography and the tissue characterisation techniques utilising raw radiofrequency data (e.g. Prostate HistoScanningTM).

Contrast enhanced ultrasound (CEUS)

Increased MVD is also the basis for CEUS. The advent of gas microbubbles [23] as an ultrasonic contrast agent has enabled improved detection of low volume blood flow through these microvessels by increasing the signal to noise ratio [24]. These microbubbles also generate vibrations at higher harmonics compared to surrounding tissue [24] thereby improving detection. Mitterberger et al. [25] compared CEUS targeted biopsies with the systematic TRUS biopsies on a PSA screened population of 690 men. Cancer detection rate was 26% with targeted biopsies and 24% with systematic biopsies, but interestingly they noted the mean Gleason score of targeted biopsies was higher (6.8 vs 5.4) compared to systematic biopsy. Although CEUS has not been shown to improve the overall detection rate, it can reduce the number of cores needed (4–5) to diagnose cancer. These findings were con-

firmed in several smaller studies. Pre-procedure 5 alpha reductase inhibitors to reduce flow abnormalities in prostatitis and BPH have been proposed to increase the specificity of CEUS [26], although this may in itself affect the cancer tissue characteristics and detection. Other modifications of CEUS are Continuous Harmonic Imaging (CHI), Intermitent Harmonic Imaging (IHI) and Cadence contrast Pulse Sequence (CPS) which all require validation in large studies.

Real time elastography (RTE)

Cancer tissue also exhibits increased cell density and therefore a change in tissue elasticity. Ophir et al. [27] exploited this to develop a technique called strain imaging which is capable of detecting the displacement of echo signals when the tissue in question is compressed and decompressed to a very small degree (around 2%). With the development of computational efficiency, this was further developed into real time elastography [28].

In a prospective evaluation of 230 patients the cancer detection rate by RTE targeted biopsies was 30% compared to 25% for systematic biopsies [29]. Although the overall detection rate was not statistically significant ($p=0.134$), it was shown that 12.7% of RTE-targeted cores were positive compared to 5.6% of systematic biopsy cores ($p<0.001$). Thus, the yield of useful information that can be used accurately to risk stratify men who eventually have diagnosis of prostate cancer (percentage cores involved, volume of cancer) seems to be better. Whether this correlates to better treatment outcomes is yet to be proven. Similar findings were shown by Nelson et al. [30] where elastography targeted biopsies returned more positive biopsies with an odds ratio of 2.53 ($p=0.007$). In a recent study of 100 men with confirmed prostate cancer, preoperative RTE findings were compared with radical prostatectomy whole-mount specimens. The sensitivity and specificity of RTE in localising the tumour focus was 75% and 76%, respectively [31]. The sensitivity for left sided tumours was slightly less (68–72%) compared to right sided tumours (75–84%) and likewise, the ability to detect basal tumours was much lower (75%) compared to apical tumours (90%). The authors commented that this discrepancy might be due to the left lateral position during scanning compressing the prostate on that side and the increased tissue mass from the apex to the base. There are a couple of limitations to this technology. First, the inter-observer variability in compressing the prostate can influence ultimate detection as it is difficult to standard-

ise this. Several methods are being investigated in order to overcome this variability, such as a visual indicator on the screen to indicate the force of compression as well as semi-quantitative methods, for example the strain ratio, to establish the elasticity quotient between two different areas [32]. Second, BPH and atrophic prostatitis can give rise to similar RTE tissue characteristics to cancer, resulting in false positive findings [33].

Prostate HistoScanning™

HistoScanning is an ultrasound-based computer aided diagnostic technique that has been developed to characterise tissue as malignant or benign. The interaction of sound waves with tissue results in the alteration of physical properties of the reflected echoes, the so-called backscatter. In malignancy, the altered tissue characteristics of density, elasticity and texture manifest as changes in the backscatter signal. In a standard B-mode ultrasound the backscatter is essentially a radiofrequency signal which undergoes multilevel processing to produce greyscale images for visualisation. It has been recognised that the radiofrequency data carries much more information, most of which is either discarded or distorted during image processing. Prostate HistoScanning utilises this backscattered raw radiofrequency data which seems to contain numerous statistical parameters that differ between malignant and benign tissue. Analysis of these parameters in three specifically developed statistical models or 'Tissue Characterisation Algorithms' forms the core of Prostate HistoScanning. The tissue characterisation algorithms can be applied in discrete regions of interest throughout the prostate gland, so that the presence or absence of cancer can be ascertained within a small discrete volume of 0.04 cm^3 . These small volumes or subunits have no cross-correlation with adjacent subunits and hence the adding up of adjacent cancer positive subunits accurately estimates the volume of tumour foci and also enables the spatial orientation and precise location of the tumour within the gland.

Prostate HistoScanning system comprises of a standard ultrasound scanner with a radiofrequency output terminal and a high processor speed computer. The transrectal ultrasound (TRUS) is performed with the patient in the left lateral position and uniform data acquisition is done in both sagittal and transverse planes with the help of a handheld motor. The radiofrequency output from the scanner is then fed into a separate central processing unit with the HistoScanning algorithms, which in turn

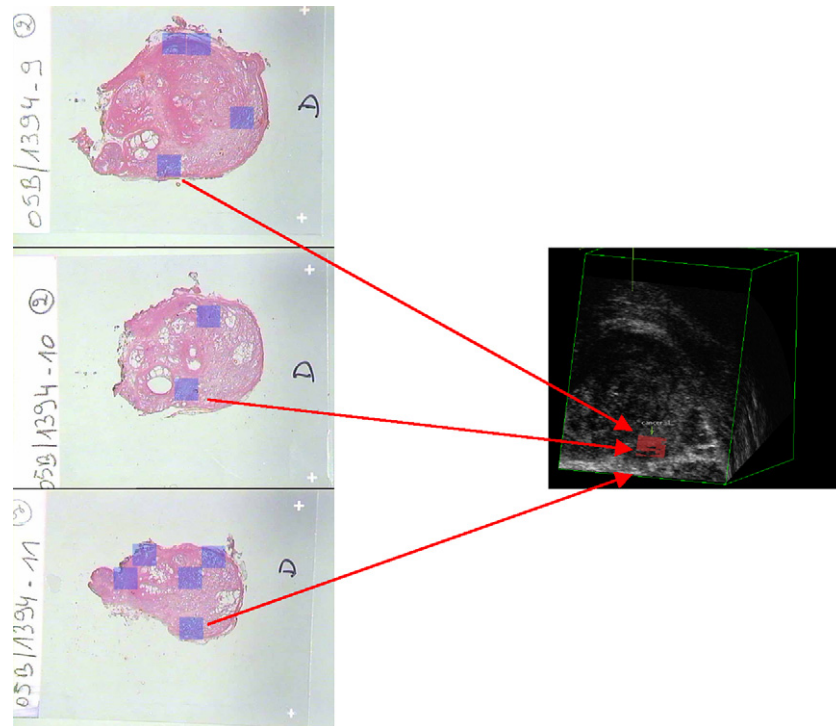


Figure 3 An example of correlation of tumour foci between step sectioned histological specimens (areas shaded in blue) and prostate HistoScanning (area denoted by red).

analyses the data and depicts the suspicious tumour foci graphically in a three-dimensional model.

To date there has been one series evaluating the role of Prostate HistoScanning. Twenty-nine patients with biopsy proven prostate cancer had Prostate HistoScanning prior to surgery and the findings were compared with histological 5 mm step sectioning of radical prostatectomy specimens [34]. The study was done in 2 phases. 15 of 29 patients formed the training test allowing for calibration and refinement of the three characterisation algorithms. In the second phase, in 14 out of 29 patients the algorithms were validated. This was carried out by initially, in a blinded fashion, analysing the Prostate HistoScanning data without knowledge of the histology. These results were subsequently correlated to whole-mount histology in order to determine diagnostic accuracy. Since the study population were known to have prostate cancer, it could be argued that there was still an inherent bias. In a study of this type, though such a bias is unavoidable, the authors have also looked at key features of cancer such as tumour localisation, maximum diameter of index lesion, multifocality, laterality of disease and extraprostatic extension – all of which are unlikely to be influenced by the known cancer status.

The correlation co-efficient between Prostate HistoScanning and histology in determining the

maximum cross-sectional diameter of the index tumour was $r=0.95$ ($p<0.001$). Likewise, the investigators found a 100% concordance in the attribution of multifocality and laterality of disease between Histoscanning and histology (Fig. 3). In a subsequent analysis, the performance of Prostate HistoScanning in predicting the volume of all tumour foci within the prostate was assessed [35]. The authors used a cut-off threshold volume of $>0.5\text{ cm}^3$, the typical threshold used for attribution of significant foci of prostate cancer [36]. Although it is arguable whether this volume represents significant disease it has an advantage in that it corresponds to a tumour cross-sectional diameter of 9–10 mm, assuming the tumour foci is spherical in shape. Such a length in a trans-rectal biopsy core of 20 mm would be attributed as significant cancer, since 50% of the tissue in the core is involved [37]. Indeed, the recent prostate cancer guidelines released by the UK National Institute of Clinical Excellence have recommended that 10 mm involvement of any core is the maximum allowable length for management using active surveillance [38]. Based on this cut off value, Prostate HistoScanning detected all 12 lesions above 0.5 cm^3 . Likewise, it also predicted the volume of all 28 lesions above $>0.1\text{ cm}^3$ with close correlation with the histological volume estimation (Pearson co-efficient $r=0.99$, $p<0.0001$) (Fig. 4). This in turn

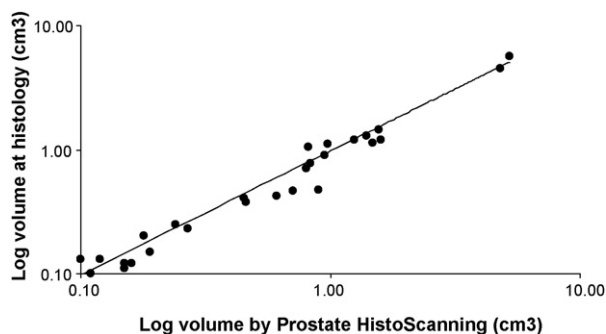


Figure 4 Degree of Correlation between Prostate HistoScanning and histology in estimating the volume of 28 cancer lesions in 13 patients (Pearson co-efficient $r = 0.99$, $p < 0.0001$).

translated to a significant correlation between total cancer volume on Prostate HistoScanning and histology (Pearson co-efficient $r = 0.97$, $p < 0.0001$).

Future research strategy

Clearly, this is the first clinical series of HistoScanning in the detection of prostate cancer and it is important to comment on a number of methodological issues concerning the study. Besides the small number of patients (14 out of 29) who had blinded evaluation, there might have been bias in the case selection towards those who had large volumes of prostate cancer on biopsies, as all of these men underwent surgery. Also, the histological step sectioning was done in the sagittal plane rather than the standard apex to base transverse step sectioning as per the Stanford protocol [39]. This was because the Prostate HistoScanning itself took sagittal images and therefore the step-sectioning needed to reflect this. With these limitations in mind, we outline the steps needed in order to evaluate this new technology in a robust and objective manner:

- (1) In the first instance, there is a need for well controlled multi-centre studies to replicate the above results and establish the accuracy of this relatively inexpensive, non-invasive test to characterise prostate cancer, allowing for reproducibility and an opportunity to address the limitations raised in the previous study.
- (2) To be clinically meaningful, Prostate HistoScanning technology has to be evaluated in clinical settings where it is more likely to make an impact in the management of prostate cancer. If such a test can prove a high level cancer detection, then the most obvious and desirable clinical application would be 'triaging' men with high age-specific serum PSA values or other risk factors for harbouring prostate cancer, rather than resorting to biopsies in all men [40]. In other words, it can act as a test to determine who those from this population requires biopsy and those who do not, returning to PSA surveillance. Indeed, MRI could hold similar potential as shown in a follow-up study involving 36 men with PSA between 4 and 10 ng/ml, a negative MR spectroscopy could potentially be helpful in deferring prostate biopsy [41]. However, this is clearly more costly. To use Prostate HistoScanning as a triage test and reassure men with a raised PSA that they require no biopsy, a negative predictive value for Prostate HistoScanning should be more than 90% to exclude significant prostate cancer. In order to validate Prostate HistoScanning in this scenario and for this objective, TRUS guided biopsies would be a poor reference test for a number of reasons. TRUS biopsies have been shown to have a high false negative rate in the range of 20–30% [42] because they systematically under-sample the anterior, midline and apical regions of the gland. In addition, the deployment of the biopsy needle is tangential which makes it difficult to attribute any one sample to a particular location. Hence, a better reference test that closely meets the required specification of a gold standard for such a PSA screened population is transperineal prostate biopsies at 5 mm intervals, or so-called prostate mapping biopsies, using a brachytherapy-type grid or template to guide the biopsy needle [43]. This technique has been shown to hold accuracy rates for detection of significant foci in the order of 95%, whilst also giving accurate information on location of each biopsy using the grid coordinates. Thorough biopsy in such a manner would ensure true validation of sensitivity, specificity and negative predictive value determination of Prostate HistoScanning.
- (3) Similar to the development of other ultrasound-based technologies, the most obvious clinical evaluation and application would be using this technology to target abnormal areas seen on Prostate HistoScanning and compare to the standard sextant or extended 12 core transrectal biopsies. This would allow evaluation of whether Prostate HistoScanning improves the cancer detection rates and reduces the false negative biopsy results.
- (4) Next in the development phase is the potential application of Prostate HistoScanning in the monitoring of the treated gland after interventions such as radiotherapy, brachytherapy, hormonal therapy or one of the minimally inva-

sive modalities, such as high intensity focused ultrasound (HIFU), cryotherapy, photodynamic therapy (PDT) or radiofrequency ablation (RFA). Imaging has an important role to play in the follow-up of minimally invasive treatments as the conventional PSA nadir estimation may not be entirely applicable. Studies should evaluate Prostate HistoScanning as a tool for verification of treatment effect and residual disease and in the surveillance of possible recurrence in the medium to long term.

- (5) Most of the current active surveillance regimens have protocol biopsies repeated at year 1 and then at regular intervals of 2–3 yrs [44]. This represents a significant burden for healthcare systems and men undergoing active surveillance. Prostate HistoScanning could possibly be incorporated into these active surveillance protocols and fill the existing gap in assessing these low risk tumours over long periods of time.
- (6) Recently, there has been much focus on focal therapies for prostate cancer [45,46] which work on an ultrasound platform. Furthermore, at present the best available imaging for prostate cancer is multi-sequence MRI [10]. This has created the need for an image registration process [47] to allow real time fusion of MR images with treatment ultrasound images, in order to treat in a true focal manner. This area is currently undergoing much research. However, if there were an ultrasound-based technology such as Prostate HistoScanning that was proven to be better, or at least equivalent in imaging capability to MRI, this opens the possibility of targeting the tumour in a focal manner without the need for image-registration.

Summary

With the requirement to accurately risk stratify men in order to prioritise their treatment allocation (active surveillance vs radical therapy) the questions that we ask of our staging investigations are different from those that we have traditionally posed. Less important is the question, 'Is cancer present?'. More and more important becomes the question, 'Is this cancer important?'. The current interest in focal therapies requires us to ask even more novel questions such as: 'What are the limits of the cancer?'; 'How many lesions are present?'; 'What is the relationship between index and satellite lesions?' All these questions require precise imaging of the tumour at low threshold volumes,

probably at the 0.2 cm³ or 0.1 cm³ level, something that until very recently was beyond the specification of imaging platforms. Developments in MRI and in the rapidly evolving field of tissue characterisation will hopefully provide the inputs that modern management of prostate cancer requires.

Conflict of interest

Senthil Govindaraju receives funding from Advanced Medical Diagnostics, the developers of HistoScanning whilst Mark Emberton is a paid medical consultant for this company in running phase II clinical trials at this centre. Hashim Uddin Ahmed and Mahua Sahu have no conflict of interests.

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