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The value of MR textural analysis in prostate cancer: a review

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Introduction

In current practice, men with potential prostate cancer are screened with serum prostate specific antigen (PSA); raised levels and/or a suspicious digital rectal exam (DRE), are investigated with prostatic biopsies and magnetic resonance imaging (MRI). The PSA test is not recommended as a population screening test, as it is deemed not to be sufficiently specific or sensitive for the detection of clinically significant prostate cancer.[1] However updated guidance by the US Preventative Service Task Force, which is based on level C evidence, recommends that men aged 55 to 69 years, can make an informed decision as to whether or not to undergo PSA-based screening.[2]

Trans-rectal ultrasound (TRUS) biopsy has traditionally been the most widely used biopsy method but has a number of limitations including risk of infection and bleeding, and challenges in accessing the anterior gland particularly in large prostates. Prostate cancer can be defined as clinically significant when at least a single biopsy core of Gleason score 3+4 (ISUP Grade 2) or greater is found; clinically insignificant cancer is defined as presence of only low volume Gleason 3+3 (ISUP Grade 1) [3, 4]. TRUS biopsy has been shown to both miss clinically significant prostate cancer and detect clinically insignificant prostate cancer.[5, 6]

Recent studies have shown the potential value of using pre-biopsy multi-parametric MRI (mpMRI) to improve detection and characterisation of clinically significant prostate cancer. Pre-biopsy mpMRI has been shown to increase the detection rate of clinically significant prostate cancer from 26% to 38% when compared to TRUS guided biopsies in the multi-centre randomised PRECISION clinical trial.[4] The PROMIS study demonstrated the potential for mpMRI to be used as a triage test before prostate biopsy. The results from this UK multi-centre study showed a quarter of men had normal mpMRI and could potentially avoid an unnecessary biopsy if mpMRI was performed first.[3] Around a third of UK centres have now adopted pre-biopsy mpMRI as a standard of care.

The prostate imaging reporting and data system (PI-RADSv2) produced through an international collaboration between the American College of Radiology and the European Society of Uroradiology (ESUR) has been developed to reduce variation in scan acquisition and to standardise interpretation of prostate mpMRI and is now in routine clinical use.[7] This has helped to further strengthen the case for mpMRI as a triage tool in routine care. This has partially resolved the previous unmet clinical need but there are some challenges remaining including MRI "missing" 10% of Gleason 3+4 tumours, detection of tumours at the prostatic apex and accurate risk stratification.[8]

With clinical practice moving towards pre-biopsy mpMRI as a standard of care there is increasing interest in the potential to use radiomics to increase the overall accuracy of mpMRI and in an attempt to tackle some of the remaining issues mentioned above and/or resolving mismatches between MRI and biopsy. Radiomics refers to the extraction of large amounts of "invisible" quantitative imaging features from medical images which can be analysed to provide predictive and prognostic information about patients.[9] These quantitative metrics can provide important insights into prostate cancer phenotype and may potentially aid diagnosis, improve assessment of treatment response and better predict patient outcome.[10] Textural analysis, a method of radiomics, assesses the structural heterogeneity and spatial organisation of different tissues.[11] By addressing challenges to the more widespread adoption of this technique, which include the need for standardisation of imaging protocols and segmentation methods, future work may provide additional information to guide the non-invasive characterisation of prostate cancer.[12]

This review focuses on the potential value of using magnetic resonance textural analysis (MRTA) in the assessment of prostate cancer. Initially a brief overview of pathological grading and relevant aspects of mpMRI for current characterisation of prostate cancer will be provided. This will be followed by review of the evidence-base on MRTA in prostate cancers and a discussion of whether this emerging technique could be implemented into the clinical pathway as a standardised tool for use in prostate cancer assessment.

Current Diagnostic Methods

Pathological grading

The majority of textural analysis validation studies in prostate cancer have used the traditional Gleason system as a histological comparison. This system is based on five basic grade patterns of the histological arrangement of carcinoma cells and the uniformity of the glands on a prostatic tissue section.[13] The Gleason sum score (GS) is currently assigned by combining the highest-grade score with the most common grade.[14]

The International Society of Urological Pathology (ISUP) 2014 Gleason grading compresses the old Gleason system and simplifies it into more accurate prognostic groups (**Table 1**). The biggest changes being the compression of GS ≤6 to ISUP grade 1 and the split of GS 7 cancers into two distinct prognostic groups: ISUP 2 and 3.[15] Future validation studies should compare textural results against pathology with ISUP grades.

mpMRI

Multiparametric MRI is becoming a more widely used non-invasive alternative to biopsy in the characterisation and diagnosis of prostate cancer. There are four main parameters used in detecting prostate cancer: T2-weighted MRI (T2w-MRI), diffusion weighted imaging (DW-MRI), dynamic contrast enhanced imaging (DCE-MRI) and MRI spectroscopy (MRI-S).[16] MRI-S has fallen out of favour since it was first reported.

T2w-MRI

T2w-MRI provides a three dimensional (3D) map of prostatic anatomy and can indicate the size of a cancer and its aggressiveness.[17] It differentiates the internal zonal anatomy of the prostate. If the peripheral zone (PZ) contains cancerous tissue, it would be visualised as round or ill-defined and of low T2w signal intensity.[18] The main limitation for the detection of

PZ cancers with T2w-MRI, is that low signal intensity can also be seen in benign abnormalities such as prostatitis, fibrosis and post-biopsy haemorrhage (which can be assessed for on T1w imaging).[19] If significant haemorrhage is seen it is recommended to repeat the mpMRI three to four weeks later.

The degree of decrease in signal intensity on T2w-MRI has been shown to correlate with an increase in GS of tumours within the PZ.[20] Using T2w-MRI to differentiate between benign and cancerous tissue in the transition zone (TZ) is unreliable.[18] TZ cancer is often seen as a homogenous signal mass with indistinct margins, this is referred to as the 'erased charcoal sign'.[21] T2w-MRI is easier to acquire and less prone to artefacts compared to functional (non-anatomical) sequences.[22]

DCE-MRI

DCE-MRI uses T1 weighted (T1w) sequences with an intravenously administered gadolinium based contrast agent to assess tumour vascularity.[19] T1w-sequences are obtained before, during and after intravenous (IV) contrast administration. Neovascular vessels in cancerous tissues are more disordered and the vessel walls are more permeable. As a result there is greater extravasation of contrast through vessel walls in tumours.[18]

Quantitative metrics can be extracted from DCE-MRI by using pharmacokinetics, which yield the volume transfer coefficient (K_{trans}) and the extracellular volume ratio (V_e) values. K_{trans} describes the microvascular permeability and blood flow, while V_e describes the leakage space.[19] K_{trans} is elevated in many prostate cancers, due to factors influenced by neoangiogenesis, combining to cause a significant increase in vascular permeability when compared to normal tissues.[23] Tumours demonstrate early and high amplitude enhancement and in some cases, this is followed by rapid contrast washout.

Like T2w-MRI, there is an overlap with benign conditions (prostatitis, vascular nodules of benign prostatic hypertrophy), therefore DCE-MRI is used as an adjunct sequence for

assessment in prostate cancer. Studies have shown that these various kinetic parameters poorly correlate with GS. However it has been shown to be one of the more useful sequences used in detecting residual or recurrent tumour following radiotherapy or prostatectomy.[19]

DW-MRI

DW-MRI measures the thermally induced random molecular displacement of water molecules within tissues.[24] This measurement provides information about water diffusion within tissues as well as perfusion of blood in the capillary network. To combine these measurements an apparent diffusion coefficient (ADC) value is calculated.[25] To calculate an ADC, several acquisitions are needed with different magnetic field gradient durations and amplitudes (b values).[19] Studies have shown a significant but inconsistent inverse relationship between ADC and GS in PZ prostate cancer.[26, 27] Prostate cancer shows low signal intensity on ADC maps and high signal intensity on high b-value DW-MRI images at high b-values. DW-MRI is considered to be an important parameter in mpMRI due to its superior accuracy in distinguishing between benign and malignant abnormalities in the PZ.[19, 28] Therefore, when performing prostate mpMRI for cancer detection both DW-MRI and T2w-MRI should be the minimum dataset used.

Value of mpMRI

The PROMIS study showed that mpMRI was more sensitive for the detection of significant cancers than biopsy, but less specific.[3] One of the main limitations of prostate MRI is variations in imaging quality between centres. Although PI-RADSv2 has helped to standardise interpretation and reporting of mpMRI, it has been less successful in ensuring accuracy and reproducibility of data acquisition.[10, 12] This is similar to the problem that is faced with textural analysis software.

Textural analysis

Radiomics is an emerging field which involves conversion of digital medical images into mineable high-dimensional data which can be used to extract quantitative image features on the basis of intensity, shape, volume and texture features.[29, 30] Radiomic textural analysis allows assessment of the spatial inter-relationships of pixel intensities and can be used to quantify lesion heterogeneity, consequently it has been an area of rapid growth in cancer imaging research recently because of the potential to extract additional quantitative data from standard-of-care medical imaging which could help improve diagnostic accuracy and clinical decision making.[31] The technique uses mathematical methods to evaluate the grey level intensity and position of pixels within an image.[32] The goal of radiomics is to convert images into mineable data, with high fidelity and high throughput which incorporates five processes: image acquisition and reconstruction; image segmentation and rendering; feature extraction and qualification; databases and case sharing; ad hoc informatics analysis.[33]

First order texture analysis, otherwise known as histogram analysis, extracts pixel intensity values within a region of interest which are then displayed graphically.[32] The more simplistic textural analysis involves an initial filtration setup by applying fine, medium and coarse filters to imaging data which allow features within the image which are not perceptible to the naked eye to be extracted and quantified in terms of heterogeneity, irregularity and brightness. The fine filter enhances tissues while the medium and coarse filters enhance underlying vasculature and other discriminatory features.[34] An example histogram produced by first order textural analysis software is shown in **Figure 3.** As there is no comparison between pixel relationships in histogram analysis, it does not convey spatial information. Metrics are calculated from the histogram, including uniformity, spread, symmetry and randomness of pixel intensity values within the ROI.[11] The common histogram features quoted in the published literature are mean, standard deviation (SD), skewness, kurtosis, $entropy_{HIST}$ and $energy_{HIST}$. **Table 2a** defines and indicates the impact of these histogram features.

More complex computation (radiomic) analysis of image features explores relationships between pixels within the ROI.[35] Additional information can be extracted regarding local variability in pixel intensities with smoother or more homogeneous areas having smaller textural variability; rougher or more heterogeneous areas having greater textural variability. Second order statistics, also referred to as Haralick features, compare the relationship between two pixels whereas higher order textural analysis compare the relationship between more than two pixels. These forms of textural analysis are referred to as matrices. These more complex statistical analyses allow the conveyance of spatial information. Second order features provide information on a more localised level than histogram features and are based on grey-level dependence matrices (GLCM). Simplistically, they describe how often a grey tone in an image will appear in a spatial relationship to another grey tone.[36] Higher order features are based on neighbourhood grey-tone difference matrices (NGTDM) or grey-level run-length matrices (GLRLM).[32]

GLCM indicates the spatial relationship between 3D pixels (voxels) in a specific direction while also indicating the properties of homogeneity, randomness, uniformity and linear dependency of an image. The NGTDM is based on differences between voxels and neighbouring voxels. This can indicate coarseness and complexity within an image, similar to perception of images by the human eye.[37] There are thousands of features which can be extracted using second order analysis, the most commonly encountered in the published literature include $energy_{GLCM}$, homogeneity, contrast, $entropy_{GLCM}$ and correlation.[11] These features are further defined in **Table 2b.**

Machine learning

Machine learning techniques have been integrated into the radiomic workflow in some more recent studies. Firstly, this technique can be used for tumour auto-segmentation into regions or volumes of interest which may reduce the likelihood of normal tissue inclusion. Another

use which requires further validation, is in the production of a classification model to stratify patients into various risk categories. In a cohort of 147 patients with prostate cancer, Fehr et al studied different classifiers which could be used to stratify patients with prostate cancer.[38]

There is currently great interest in the use of artificial intelligence and machine learning in medical imaging.[39] At present there is a lack of evidence to support routine clinical use but these techniques have the potential to improve the translation of radiomic workflows into prostate cancer management pathways. The combination of textural analysis of mpMRI with machine learning classification may facilitate more informed clinical decision making in the future.

Clinical implementation

Figure 1 illustrates a simplified workflow demonstrating a pathway of how textural analysis could be implemented into clinical practice. This entails several key steps which explained are detailed below.

Segmentation and co-registration

Accurate tumour segmentation is a crucial initial workflow step. Features from histogram and matrices analyses have all been shown to be affected by segmentation method.[11] Inclusion of normal tissues within the segmented ROI can influence the results of textural analysis. Prostate cancer, like any other tumour can have poorly defined margins which may make manual segmentation challenging. Most of the published studies evaluating MR textural analysis in prostate can have used similar methodology with manual segmentation on a single axial image demonstrating the largest cross-sectional area of tumour. An improvement on this, would be to segment the whole tumour volume.[21]

Another important consideration is the methodology used for comparison of pathological and imaging data, which may be challenging if only using a single imaging slice for radiomic analysis. Retrospective studies have generally either employed cognitive co-registration using visual cues such as the prostatic urethra as indicated by **Figure 2** or in a few studies digital co-registration. It is also important to ensure all the mpMRI sequences are co-registered.

A small study by Parmar et al in 20 patients with lung cancer compared semi-automated segmentation with manual segmentation, showing reduced inter-observer variability and delineation for radiomic analysis.[40] There is a paucity of evidence on the value of automated segmentation methods for whole tumour evaluation in prostate cancer and this warrants evaluation in future prospective studies to determine if it is beneficial.

Software packages

A variety of different software packages, both open-source and commercial based are available to be used for textural analysis of imaging data. A recent review by Larue et al, provides a detailed overview of various different software packages, including information regarding types of imaging modality supported, image pre-processing steps and features extraction.[37] Recently a new open-source software package (LIFEx, www.lifexsoft.org) has been developed and made freely available in an attempt to standardise further research.[41] This software permits multi-modality radiomic analysis of medical imaging. The two main commercial software packages, TexRAD and RADIOMICS use a Laplacian of Gaussian (LoG) filter as part of image and feature pre-processing. The Gaussian filter reduces image noise allowing the subsequent Laplacian filter to detect regions of rapid intensity change.[42] Pre-processing is essential as it allows the correction of magnetic field inhomogeneities and intensity normalisation across subject acquisition both in study and between studies.[37] Researchers should ensure any package used has adequate pre-processing before

commencing with their studies. Currently there is a paucity of data to recommend using one software package over any other.

Texture analysis in the diagnosis of PZ cancer

At the time of writing there are 10 articles in the published literature evaluating the potential role of MRTA in prostate cancer which are summarised in **Table 3** and reviewed in more detail in subsequent sections.

The largest patient cohort studied to date (n = 147) assessed the potential value of MRTA for differentiating clinically significant prostate cancer in the PZ from non-significant/benign prostatic tissue was evaluated in two separate papers. Fehr et al used the same set of patients as Wibmer et al but increased the proportion of TZ samples and the textural features extracted.[36, 38]

$Entropy_{GLCM}$ and correlation extracted from T2w-MRI showed significant differences between benign and malignant cases in both studies. Fehr et al additionally found mean pixel intensity to be a useful discriminatory feature for differentiating clinically significant tissue. All features extracted from DW-MRI showed a high significance level leading to their recommendation to use first and second order features extracted primarily from DW-MRI for diagnosis of clinically significant PZ cancer.[36, 38]

Texture analysis in the diagnosis of TZ cancer

Conversely, multiple studies have reported conflicting results for MRTA use in the diagnosis of clinically significant TZ cancers. Wibmer et al showed no significant difference in textural features extracted from DW-MRI between PZ and TZ cancers. At T2w-MRI only correlation and contrast were significant features in both TZ and PZ textural analysis.[36]

Sidhu et al also evaluated the utility of textural features for detection of clinically significant TZ cancer in a study of 26 patients and found kurtosis and $entropy_{HIST}$ extracted from DW-MRI and T1w sequences to be significant predictors.[43] Kurtosis became insignificant following removal of the tumour from the slice. Two small pilot studies (n = 8 and n = 18) also looked at the diagnostic accuracy of MRTA for TZ cancers but these studies were under-powered, so the results are inconclusive.[44, 45]

Texture analysis in the characterisation of clinically significant prostate cancer

Few studies have explored the potential value of MRTA for non-invasive grading of prostate malignancy. A small number have reported that textural features accurately correlate with GS on pathological material obtained at TTMB or radical prostatectomy. The textural features of contrast and homogeneity showed most promise. Vignati et al found that second order features of contrast and homogeneity significantly correlated with GS in a study of 45 patients.[46] Gnep et al corroborated these findings in a larger study of 74 patients and reported that contrast extracted from DW-MRI significantly correlated with GS.[47] Wibmer et al have conflicting results, reporting that contrast and homogeneity extracted from DW-MRI were not significant features in their larger patient cohort (n = 147). Fehr et al indicated that $entropy_{GLCM}$ and $energy_{GLCM}$ extracted from DW-MRI were useful but could only reliably differentiate GS 6 from GS 7 and not GS (4+3) from GS (3+4).[38] These initial results suggest that textural features may only be able to characterise broad groups of cancer grade, rather than more precise ones.

Various groups have evaluated textural features extracted from T2w MRI, providing a general consensus that homogeneity correlates with GS.[22, 36, 46] Wibmer et al suggested that homogeneity may be plausible for differentiating GS 6 from GS>7 and in differentiating GS (4+3) from GS (3+4) but not between GS 6 and GS 7. In two of three studies, contrast extracted from T2w MRI also correlated with GS.[36, 46]

Texture analysis summary

Evidence on the utility of MRTA in prostate imaging is limited, although initial studies are encouraging and indicate that radiomics might improve diagnostics and reduce the need for invasive procedures. A future role in differentiating significant from non-significant cancer in the PZ shows promise as does the ability to predict GS. Further work is required on the utility of TZ textural features. Many of the research studies have used 3T MRI and there is limited evidence on data acquired using 1.5T MRI scanners. This again highlights the gap between research potential and translation to clinical practice. More studies need to be conducted on 1.5T systems with a minimum of 16 pelvic phased array coils as per ESUR guidelines, to determine whether the prevalent MRI hardware in the United Kingdom is suitable.

The small cohort size and retrospective nature of most published studies makes it difficult to gauge how reliable and reproducible the reported findings are. **Table 4** summarises the MR textural features which show most promise and warrant further evaluation in further well designed, prospective studies with larger patient cohorts.

Current limitations

Retrospective studies

Retrospective studies are more prone to bias and confounding variables which can affect the significance of the results and introduce decision errors into the interpretation of the results, leading to wrongly drawn conclusions. Study heterogeneity makes it difficult to ensure reproducibility, hence large datasets are needed to help overcome this problem. Sala et al recommend using shared informatics databases across sites to ensure large sample sizes.[10] In practice, this can be a difficult to achieve due to data protection laws and infrastructure costs. Most of studies conducted so far are single centre pilot studies with small sample sizes and differing methodologies, this makes it hard to compare results and explains the lack of reproducibility.

Exclusion criteria

Incomplete data is an example of an exclusion criterion used for some of the published studies listed in **Table 3**. Removing patients from a study detracts from the power of the study. If patients were selected using a randomised method, exclusion may also reduce how accurately the study represents the general population. Other common exclusion criteria used in these studies are: treatment prior to MRI, imaging artefacts making cancer segmentation impossible, small tumours (<0.5ml) and/or location precluding segmentation of benign prostatic tissue.[36]

Selection bias

Most of the studies published so far suffer from selection bias. As a result, their findings may not be generalisable to the wider population of patients with prostate cancer. Some studies only investigated patients with clinically significant cancer of GS 7 or greater, providing no information on the utility of MRTA in less aggressive cancers. Other studies chose to focus on TZ cancers, due to the lack of data in other studies. Lastly, some studies focused on patients who had undergone radical prostatectomy allowing histopathologic comparison, thereby selectively choosing patients who have undergone surgery following a TRUS biopsy. The value of MRTA in diagnosing and characterising prostate cancers in those who are missed by TRUS biopsy remains uncertain. Some studies performed TRUS biopsy to avoid selection bias, but as mentioned before, this pathology is not as accurate.[44, 48] TTMB/TPM is defined by some studies as gold standard and the recommended pathological comparison tool as it is highly accurate.[43]

Over testing the data

More significant issues common to some of the studies is potential bias due to oversampling i.e. extraction of more features than there are participants. Testing many features requires a statistical correction to remove Type 1 (false-discovery) error. The use of complex regression models to find significant features, increases the risk of overfitting the data.[48, 49] Regression models may show effective results in one study yet are unlikely to be reproducible in other studies. Using only one textural feature per 10 patients in a multiple regression model would reduce the risk of overfitting in future trial designs.

Limitations of MRTA

Textural feature extraction, like mpMRI, currently suffers from a lack of standardisation. Grey level discretization, isotropic resampling of the image, non-standardised nomenclature, directionality in texture matrices and multiple textural packages all affect feature computation.[11]

Textural feature computation requires grey level discretisation into an appropriate number of bins to analyse an image. There are two methods which can be used to achieve this: using a fixed number of bins or a fixed bin width. Bins refer to class intervals which are used to divide up pixel intensity data. Using a fixed number of bins will result in dividing the image into equally spaced intervals with varying bin sizes. Using a fixed bin width based on units of image intensity, will result in a constant intensity resolution.[50] The literature recommends, if using a fixed number of bins, to have a minimum of 32 bins, although anything over 64 bins adds little prognostic value.[11, 51, 52] Due to limited work there is no definitive answer as to whether bin width or bin interval size is more important.

The evidence available suggests that three dimensional (3D) textural analysis outperforms two dimensional (2D) textural analysis, with multiple prostate MRTA studies commenting on

2D textural analysis being a limitation.[22, 46, 49] An isotropic resampling of the image is recommended for 3D textural analysis, particularly in higher order statistics.[11]

This review has used Hatt et al's proposed nomenclature to differentiate between the two levels of entropy and energy by using subscripts.[11, 53] 'HIST' indicates histogram and first order textures ($entropy_{HIST}$); 'GLCM' indicates the GLCM matrix and second order textures ($entropy_{GLCM}$). There is a lack of clarity in some studies over which version is used, hence all future studies should include this or a similar method.

There is no recommended directionality of textural matrices in second and higher order textures. Some studies have calculated GLCMs as an average of all directions or separately for each direction. This further contributes to MRTA heterogeneity between centres. Although undefined the most commonly used distance in a GLCM between voxels is one voxel.[11]

It is also worth highlighting that to date there is a paucity of data on the role of MRTA in follow-up assessment of prostate carcinoma unlike with other tumour types (where margins are often easier to distinguish). The focus of research in prostate cancer due to clinical need is more to identify or stratify tumours and this is potentially more challenging.

Future perspectives

Radiomics is a relatively new field and is not yet ready for routine clinical implementation. MRTA is more complicated than radiomics using CT and PET datasets in part because standardisation and calibration of MRI is intrinsically more complex than techniques based on photon detection.[54] Other factors which increase the complexity of MRI textural analysis compared to CT and PET include variability in acquisition protocols and spatial resolution. It has been reported that the effects of different MRI scanning protocols can be negated by post-processing brain MR data acquired on different scanners to erase inter-patient differences in intensity range, and resampling to a uniform matrix size, but there is no comparable data for mpMRI of the prostate.[55] Initial studies have indicated its potential

value, but there are challenges ranging from image acquisition and textural feature estimation which need to be overcome. The problems posed by these challenges contribute to the heterogeneity of MRTA imaging quality between centres.

There is a need for well-designed, prospective multi-centre studies to clarify more definitively whether MR textural analysis could have a valuable role in prostate cancer in the clinical routine. To maximise the validity of future research, it is important that all centres follow strict methodological guidelines similar to established standards for reporting of diagnostic accuracy studies (STARD) and standards for reporting of MRI-targeted biopsy studies (START) of the prostate.[56, 57] Currently there are is no consensus agreement on this aspect but recent work by Lambin et al introduces the concept of a radiomics quality scoring system, encompassing all aspects of trial design and workflow steps to try and improve the robustness of future textural analysis studies.[58]

The value of second order and higher order texture needs to be determined before it can be used. Studies in the immediate future should concentrate on using histogram features, across all three mpMRI sequences on a prospective cohort of patients with suspected prostate cancer. Continuing work should also be performed on incorporating machine learning into methods, especially with regard to automatic segmentation and classification models. The use of regression models in future studies is not recommended until much larger datasets are used. MRTA can also be used as prognostic factor for determining recurrence of disease as shown by Gnep et al.[47]

Conclusions

Currently diagnosis of prostate cancer is based on a combination of histological and imaging findings. MRTA offers the potential for objective, non-invasive patient stratification in terms of potential treatment options. At present the evidence on the utility of MRTA in prostate imaging is limited. Roles in differentiating significant from non-significant cancer in the PZ

and prediction of GS show promise. Future larger prospective studies are required to validate textural features indicated to have potential in characterisation and/or diagnosis of prostate cancer before translation into routine clinical practice.

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Table & Figure Legends

Table 1: ISUP grade and Gleason Grade comparison. A table showing how the International Society of Urological Pathology (ISUP) 2014 Gleason grading compresses the old Gleason system and simplifies it into more accurate prognostic groups**.**[15]

Figure 1: Simplified model of radiomics workflow. Model shows the steps that would be involved if suitable for clinical practice. This model is essentially used with a view to be able to replace the role of prostatic biopsies. If on active surveillance the model would perform a perfect circle, with new images acquired every couple of years.

Figure 2: **A picture demonstrating how the pathology is cognitively co-registered to a T2w image.** Cognitive co-registration. A histopathological slice of a radical prostatectomy specimen (left picture) has been cognitively co-registered to a T2w image (right picture) of the same patient. The blue arrow points to the prostatic urethra. The prostatic urethra shape has been used to co-register the images in addition to the shape of the prostate. This allows the best match to the pathology. The tumour regions of interest (ROIs) have been outlined in black.

Figure 3: Histogram of pixel intensities within a region of interest. Pixel intensities from a region of interest that was run through TexRAD was converted into a histogram. From the histogram statistical features would be calculated such as those in **Table 2a**.

Table 2: Definitions and impacts of known textural features. Tables defining histogram and matrix features with impact of feature given for histogram features. **a)** Histogram (first order) texture definitions and impacts. **b)** Matrix (second order) texture definitions. The impact of matrix features has yet to be determined. $Entropy_{HIST}$ and $energy_{HIST}$ refer to the histogram version of this feature. $Entropy_{GLCM}$ and $energy_{GLCM}$ refer to the matrix version of this feature. This table has been adapted from Wibmer A et al 2015 and Miles KA et al 2013.[36, 59]

Table 3: A review table of prostate MRTA studies. A table summarising published literature that explores links between prostate cancer and MR textural analysis. The papers are shown as the first author with the year that the study was published and related reference number in this review. The sample size shown is the final patient number that took part, taking into account exclusion criteria and withdrawals. Textural features show the ones that the study tested. First order features refer to histogram analysis; second order features refer to the GLCM matrix. Entropy and energy are noted with subscripts to indicate if they are second (GLCM) or first order features (HIST), as they can be either. Where no subscript is given, it means that energy and/or entropy were not defined by the paper. MRI equipment is listed with scanner magnet strength first and then subsequent coils and arrays used. The textural segmentation and software column, indicates whether single slice or volume approaches were chosen for tumours and then which textural analysis software was used. The results data was then split up for each of the MRI sequences, to highlight how results differ between different sequences. In the results part, p values are given when present in the data with relevant statistical test. Some features were presented in multiple comparisons such as Gleason score 6 to 7 and Gleason score (3+4) to (4+3), hence it was further analysed to assess if it was significant at all levels. This explains why there are no p values for those results. The limitations refer to the weaknesses of the study, if one is not listed e.g. selection bias, it would indicate that there was none. Abbreviations: (SD: standard deviation, T2w: T2 weighted, DW: diffusion weighted, ADC: apparent diffusion coefficient, T1w: T1 weighted, TZ: transition zone, PZ: peripheral zone, TRUS: transrectal ultrasound, ROI:

region of interest, 2D: two dimensional, AUC: area under the curve, V_e: extracellular volume ratio, PSMA: Prostate specific membrane antigen, GS: Gleason score, MRI: magnetic resonance imaging), RLNU: Run length non-uniformity, ASM: angular second moment, MPP: mean of positive pixel

Table 4: Potential features of interest warranting further study. Summary of potential textural features which may have some value in the diagnosis and/or characterisation of peripheral zone and transition zone cancers. These features are based on early data and are therefore not conclusive. Abbreviations: T2w: T2-weighted, ADC: apparent diffusion coefficient, SD: standard deviation.