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The role of imaging in the diagnosis of primary prostate cancer

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Abstract

Ultrasound and magnetic resonance imaging (MRI) are key imaging modalities in prostate cancer diagnosis. MRI offers a range of intrinsic contrast mechanisms (T2, diffusion-weighted imaging (DWI), MR spectroscopy (MRS)) and extrinsic contrast-generating options based on tumour vascular state following injection of weakly paramagnetic agents such as gadolinium. Together these parameters are referred to as multiparametric (mp)MRI and are used for detecting and guiding biopsy and staging prostate cancer. Although sensitivity of mpMRI is <75% for disease detection, specificity is >90% and a standardised reporting system together with MR-guided targeted biopsy is the optimal diagnostic pathway. Shear wave ultrasound elastography is a new technique which also holds promise for future studies. This article describes the developments in imaging the primary site of prostate cancer and reviews their current and future utility for screening, diagnosis and T-staging the disease.

Keywords

Prostate cancer, MRI, ultrasound, biopsy, MR guidance, diffusion, contrast-enhanced, spectroscopy, elastography

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Introduction

Imaging, both qualitative and quantitative, is crucially important in the diagnosis and staging of cancers. The key characteristics of an imaging technique that determines its worth are spatial and contrast resolution. The voxel size of the technique used (spatial resolution) determines the size of lesion that can be discriminated, while contrast resolution determines whether the technique is able to distinguish tumour from surrounding normal tissue based on differences in measured characteristics such as density, stiffness, vascularity, cellularity and metabolic profile. Ultrasound has traditionally been used to assess the prostate and perform systematic non-targeted biopsy, but techniques based on tissue echogenicity alone lack contrast resolution to distinguish tumour. Magnetic resonance imaging (MRI) has revolutionised the diagnostic pathway in prostate cancer, and offers a range of intrinsic contrast mechanisms (T2, diffusion-weighted imaging (DWI), MR spectroscopy (MRS)) and extrinsic contrast-generating options based on tumour vascular state following injection of weakly paramagnetic agents such as gadolinium. The latter generate semi-quantitative and quantitative parameters relating to tissue perfusion and permeability from dynamic contrast-enhanced (DCE) techniques. This article describes the developments in imaging the primary site of prostate cancer and reviews their current and future utility for screening, diagnosis and T-staging the disease.

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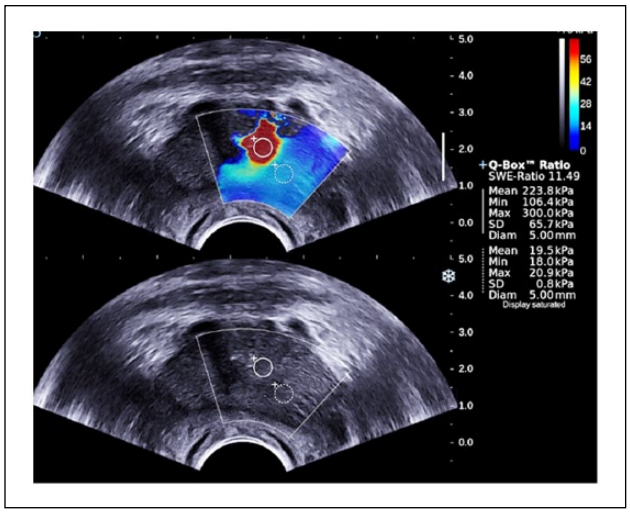

Figure 1. Quantitative measurement of tissue stiffness using shear wave elastography.
Conventional B-mode ultrasound image of the prostate gland (bottom) and an elastographic colour map superposed on the B-mode image (top) visually demonstrate tissue stiffness. Five mm circular regions of interest manually placed over the transitional zone (solid line) and peripheral zone (dotted line) give a calculated mean stiffness of 223.8 kPa and 19.5 kPa, respectively, indicating a stiffer transitional zone.

Methodologies for imaging the prostate

Ultrasound shear wave elastography (SWE)

Cancer tissue is stiffer and less 'elastic' than normal tissue. Tissue stiffness is semi-quantitatively measured using Young's Modulus, which describes it in units of pressure (kilopascal (kPa)) based on the applied stress and the resultant tissue deformation or strain. It was recognised more than a decade ago that interfering shear waves, generated using a pair of mechanical sources vibrating at very slightly different frequencies, could produce slowly propagating interference patterns with a velocity proportional to the underlying true shear velocity of the interrogated medium.[1] The calculated Young's Modulus can be colour mapped per pixel to real-time B-mode imaging (Figure 1) using new ultra-fast ultrasound (US) techniques, at up to 10,000 frames per second.[2–4] Limitations of SWE include a low penetration depth of 3–4 cm meaning a lack of reliable assessment of the anterior gland, and artefacts from calcifications.

Initial studies have demonstrated a sensitivity and specificity of SWE for detecting tumour of up to 93% each in patients with a prostate-specific antigen (PSA) >20 µg/l; a possible correlation of stiffness with Gleason grade has also been postulated.[5,6] Quoted cut-off values for differentiating benign from malignant lesions are in the range of 35 to 43.9 kPa,[6–8] and in a recent study comparing SWE findings to prostatectomy samples in 60 men, a discriminant cut-off value of 50 kPa gave a sensitivity and specificity of 81% and 69%.[9] Reproducibility of SWE remains to be determined but the technique, although not widely available, is showing promise.[10]

Multiparametric MRI

Subjective assessment of the prostate is performed qualitatively with T2-weighted (T2-W) imaging (Figure 2(a)); however, collecting the signals at a range of echo times (TEs) enables the rate of decay (or T2 relaxation time) to be calculated to produce a quantitative T2 map. Multiparametric (mp)MRI combines T2-W with DWI, DCE imaging and where available MRS so exploiting image contrast between tumour and normal tissues from a range of differing functional properties. DWI relies on the difference in motion of water molecules between tissues, DCE-MRI demonstrates the presence of angiogenesis and abnormal blood flow within the tumour while MRS obtains a metabolite 'fingerprint' of MR-visible atoms that are recognised by the molecular environment (chemical bonds) in which they exist.

To acquire DWI data, additional magnetic field gradients are applied during image acquisition to sensitise the signal read-out to the motion of water within the tissue. This motion arises largely in the extracellular space and is reduced in cancer where cells are more tightly packed. Using a number of diffusion weightings (b-values) in incremental steps allows the change in signal of each voxel in the image with increasing diffusion-weighting to be calculated as an apparent diffusion coefficient (ADC). ADC values are low in tumours because of their decreased water diffusion properties compared to normal tissues (Figure 2(b)). They appear dark on ADC parameter maps. A meta-analysis of 19 publications consisting of a total of 5892 prostate tumours demonstrated a sensitivity and specificity for DWI alone for detecting tumour of 69% and 89%, respectively.[11]

DCE-MRI exploits the presence of angiogenesis and abnormal blood flow within a tumour. It may be used semi-quantitatively, by plotting the temporal uptake and wash-out of contrast within tissue. Prostate cancer shows a brisk contrast uptake, peaking at 60 secs after administration of the bolus and a sharp wash-out (Type 3 curve, Figure 2(c)). Using pharmacokinetic modelling, it is possible to fully quantify the imaging changes in tissues following contrast injection. Movement of contrast over time between the extravascular, intravascular and intracellular spaces[12] can be represented by K^{trans} (transfer constant between the vascular and intracellular space, a measure of vascular permeability), K_{ep} (diffusion of contrast back into the vascular space) and V_e (the movement of contrast into the extravascular space during the first pass through the tissues). When used in conjunction with morphological T1-W and T2-W sequences, DCE-MRI has a sensitivity for tumour detection of between 43% and 53% and specificity of 83%.[13,14]

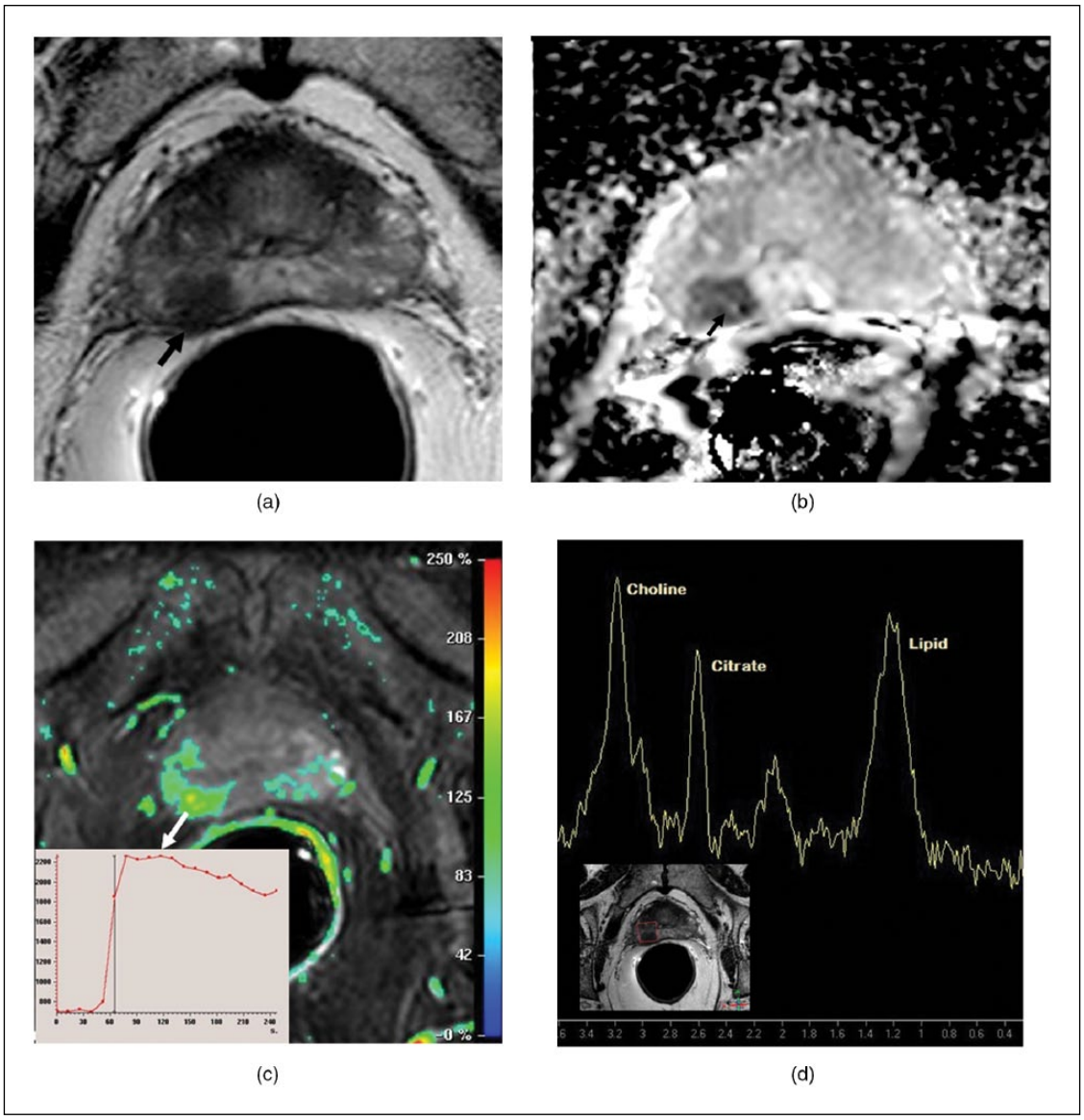

Figure 2. Multiparametric MRI in a patient with a right mid-gland peripheral zone tumour.
Transverse T2-W image through the mid-prostate (a) shows a well-defined, low-signal intensity lesion (arrow) with restricted diffusion on the ADC map ((b), arrow). A dynamic contrast-enhanced-derived relative enhancement colour overlay on a T1-W image with contrast uptake and washout shows a Type 3 curve of brisk uptake and washout (c). Single-voxel MRS demonstrates a reversal in choline to citrate ratio, with a prominent choline and a relatively reduced citrate peak (d).
MRI: magnetic resonance imaging; T2-W: T2-weighted; ADC: apparent diffusion coefficient; T1-W: T1-weighted; MRS: magnetic resonance spectroscopy.

MRS examines the relative reduction in citrate and increase in choline that occurs in prostate tumours (Figure 2(d)). This metabolic signature is characteristic but the inherent signals are low. Taken together T2-W+DWI+DCE+MRS are referred to as mpMRI and used in combination they improve sensitivity and specificity for discriminating tumours.[15]

To facilitate standardisation and consistency, the European Society of Urogenital Radiology (ESUR) in 2012 established clinical guidelines for the acquisition, interpretation and reporting of mpMRI of the prostate.[16] These recommendations, referred to as Prostate Imaging-Reporting and Data System (PI-RADS), were based on literature evidence and consensus expert opinion. PI-RADS v1 recommended the combination of high-resolution T2-W imaging, and at least two functional MRI techniques, either DWI, DCE-MRI, or MRS. In v2,[17] MRS is no longer recommended, with mpMRI consisting of anatomical imaging, DWI, and DCE-MRI alone. Often, for simplicity T2-W and DWI imaging alone are used; as the T2-W data are morphological and not parametric, the use of the term mpMRI in this setting is a misnomer.

Unlike PI-RADS 1, which suggested both 'minimal' and 'optimal' requirements, v2 aims only to establish minimal technical parameters for an acceptable mpMRI examination. PI-RADS guidelines are not recommended in the setting of suspected post-therapy recurrent prostate cancer, nor progression during surveillance. Factors such as PSA, clinical history, or previous biopsy results are not reflected in a PI-RADS score and require a Likert scale (based on a 5-point score) of probability of prostate cancer. An initial study comparing the PI-RADS and Likert scales for tumour localisation prior to biopsy indicated that although radiologists performed well with both, in the transitional zone (TZ), performance was better with the Likert than the PI-RADS scale.[18]

Imaging in the screening setting

MRI is a relatively expensive technique, and is resource limited, so is not cost effective for population screening. In selected patients stratified by risk, however, it may have potential to contribute. In a pilot study of 51 men with a family history of prostate cancer in whom biopsies indicated cancer in 28 sextants in 13/51, 32 had twice the population risk based on 71 single nucleotide polymorphism profiling. T2-W+DWI endorectal MRI at 3.0T performed prior to biopsy showed a sensitivity/specificity per-patient for high-risk patients of 90.0%/86.4% vs. low-risk individuals of 66.7%/100% respectively for a skilled observer.[19] These results indicate that with an endorectal technique at 3.0T, T2-W+DWI may be worthwhile in men with a family history of prostate cancer and increased genetic risk. Refinements in patient stratification through improved genetic profiling and biochemical and clinical markers may well further improve the utility of MRI for screening specialist patient groups.

A more realistic screening tool would be the use of SWE which could be potentially accessible in primary care. Initially, however, validation of the technique against histology and correlation of findings with current gold-standard imaging (mpMRI) is needed to prove its utility.

Imaging men with raised PSA

Traditionally the diagnostic pathway involves transrectal ultrasound biopsy (TRUS) followed by mpMRI. As imaging post-biopsy is less accurate,[20] a recent National Institute for Health and Care Excellence (NICE) guideline has proposed imaging prior to biopsy. This is ideal but imposes an additional burden on imaging resource where a raised PSA may be related to gland size and/or inflammation. Typically, an overall PI-RADS score of 4 or 5 means a biopsy is recommended.

A prospective study of mpMRI in 178 patients with elevated serum PSA (>4.0 ng/ml) before systematic needle biopsy by two radiologists independently evaluating the right and left prostate lobes and the peripheral zone (PZ) and TZ separately, where prostate cancer was detected in 72 (40.4%), indicated that the diagnostic performance of DWI (Az = 0.848) and T2-W+DWI (Az = 0.845) were significantly ($p < 0.001$) more accurate than that of DCE-MRI (Az = 0.746) with greater sensitivity (DWI 74.8%, T2-W+DWI 72.9%, DCE-MRI 52.8%).[14] Another prospective study focusing on 50 men with 'grey-zone' PSA of 4–10 ng/ml who underwent mpMRI prior to biopsy showed that on an octant basis, the sensitivity/specificity of tumour detection was similar among the three techniques (36%/97% for T2-W MRI, 38%/96% for DWI, 43%/95% for DCE-MRI). Combining the techniques gave a sensitivity and specificity of 53% and 93% respectively, which was significantly higher than the individual methods ($p < 0.001$).[13] Unfortunately, cancer in the TZ remains difficult to detect, even with mpMRI, which has been shown to be no better than T2-W imaging alone.[21] Even MRS, despite its difficulties in implementation and requirement for specialist expertise, though it proved promising in initial single-centre studies,[22] did not prove worthwhile in a multicentre setting.[23] For initial diagnosis, there is an increasing trend to perform T2-W+DWI alone because of simplicity and resources, although it is important to be mindful that a very significant proportion of up to 25% of dominant lesions and 50% of non-dominant tumours will be missed.

A particular advantage of performing imaging prior to biopsy is that the mpMRI can also be used for guiding prostate biopsy, thus ensuring that the most significant visible lesion is targeted, which significantly improves detection rates.[24,25] In particular, it has been shown to be invaluable in identifying anterior lesions, often missed on TRUS. In 162 patients with a total of 241 anterior lesions on mpMRI, prostate cancer was confirmed in 121 (50.2%), of whom 97 (40.2%) required targeted biopsies. Positive targeted biopsies also contained a significantly longer length of tumour, indicating a greater tumour burden when considering management options.[26] A sensitivity of mpMRI of <75%, however, means that targeted biopsy based on mpMRI must always be additional to or part of a scheme of systematic biopsy. Biopsy should always be considered for men with a progressively rising PSA despite 'normal' mpMRI findings.

Current available biopsy techniques include standard 12 core TRUS, 'cognitive fusion' biopsy, MR-fusion biopsy, MR-guided biopsy and template biopsy. Targeted techniques demonstrate better localisation and sampling of mpMRI-defined tumours and have the potential to minimise the sampling error that comes with conventional systematic techniques,[27,28] and are recommended where available. There are no guidelines on which biopsy system is considered best practice: local expertise and availability of facilities currently drives the decision between a template biopsy or 12-core TRUS biopsies supplemented by targeted sampling using either image fusion through co-registration or cognitive fusion.

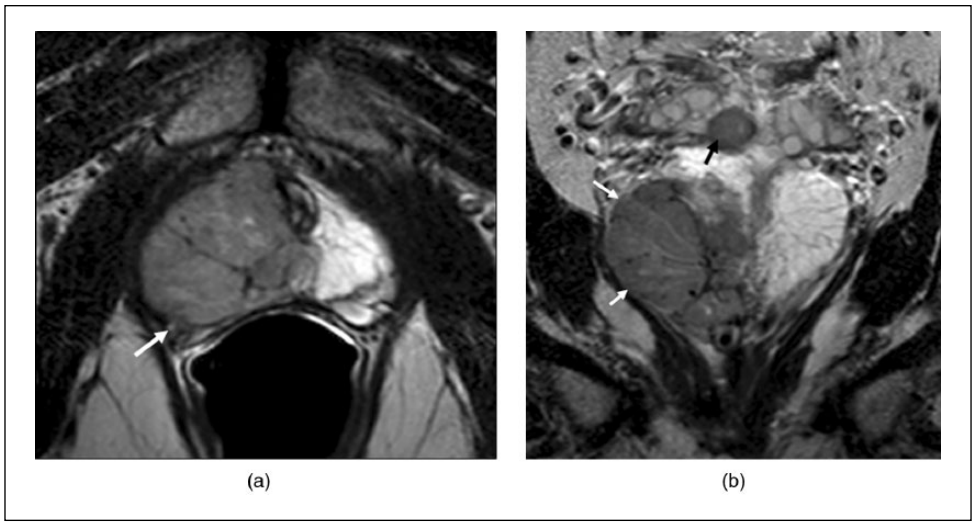

Figure 3. Extracapsular extension and seminal vesicle invasion of prostate cancer.
T2-W transverse T2-W image through the prostate apex using an endorectal coil at 3T (a) shows an intermediate signal intensity lobulated mass within the prostate on the right with extracapsular breach (arrow). The coronal image (b) confirms the extent of the tumour (white arrows) and indicates a well-defined focus of intermediate signal intensity tumour within the right seminal vesicle (black arrow).
T2-W: T2-weighted.

Imaging for T-staging

T2-W images form the mainstay of staging where in addition to detecting tumour they can be used to document its extent, volume, multifocality, capsular and seminal vesicle involvement (Figure 3). T2-W imaging is also important for documenting features that would determine the best management pathway or surgical approach such as effacement of the rectoprostatic angles. Several studies have addressed methods for optimising sensitivity and specificity of MRI in T-staging tumours– the use of field strength (1.5T vs 3T), endorectal vs. external pelvic array receiver, different sequence combinations (T2, DWI, DCE, MRS) and reporting systems have been compared. Data generally show that 3T acquisition is better than 1.5T[29,30] and that an endorectal technique is superior[31] although use of higher field strengths and resource implications mean that this is a topic of much debate.[32] A large recent meta-analysis that included data from 75 studies (9796 patients) with pooled data for extracapsular extension (45 studies, 5681 patients), seminal vesicle invasion (34 studies, 5677 patients), and overall stage T3 detection (38 studies, 4001 patients) showed sensitivity and specificity of 0.57 (95% confidence interval (CI) 0.49–0.64) and 0.91 (95% CI 0.88–0.93), 0.58 (95% CI 0.47–0.68) for extracapsular extension and 0.96 (95% CI 0.95–0.97) for seminal vesicle invasion, and 0.61 (95% CI 0.54–0.67) and 0.88 (95% CI 0.85–0.91) for stage T3 detection, respectively. Therefore, although addition of functional imaging to T2-W and use of higher field strengths (3T) improves sensitivity for extracapsular extension and seminal vesicle invasion, MRI has a heterogeneous and poor sensitivity for prostate cancer staging although specificity remains high.[33]

Use of the standardised reporting system is able to influence staging sensitivity in trainee radiologists, so its use is strongly advocated in training. A study of 145 consecutive patients who underwent radical prostatectomy and mp (T2W + DWI + DCE) MRI were staged either without (n = 80) or with (n = 65) use of the PI-RADS system. Extraprostatic extension was present in 66.3% and 64.6% of each group. In trainee radiologists, the PI-RADS criteria for extraprostatic extension improved sensitivity from 24% to 68% without reducing specificity (68%).[34] To summarise, using high-quality mpMRI sequences at high field strength, even using endorectal techniques where available, and a consensus reporting system, the sensitivity for recognising T3 disease is at best 70%. Encouragingly, specificity is high and false positives are rare. Once diagnosis and stage has been established and management plan decided, mpMRI may be used for follow-up of patients selected for active surveillance[35] or for detecting post-radiation recurrence.[36]

Forward look

To improve sensitivity for prostate cancer detection and staging, improved contrast resolution will be necessary. It is likely that combination imaging techniques such as positron-emission tomography (PET)-MR may provide solutions. An area of growing interest is in imaging prostate-specific membrane antigen (PSMA), a type 2 transmembrane glycoprotein expressed in prostate epithelial cells and highly expressed in prostate cancer in a disease progression-dependent manner. Recently, radiolabelled ligands (^{68}Ga-PSMA) have been introduced. A template-based analysis of 130 patients prior to prostatectomy

showed a sensitivity, specificity and accuracy for ^{68}Ga-PSMA-PET of 68.3%, 99.1% and 95.2% compared to 27.3%, 97.1% and 87.6% for morphological imaging.[37] Another advance is the development of radiomics, which undertakes a complex analysis of first- and second-order statistical features within the signal-intensity data of the mpMRI. This generates textural maps of tumours and allows construction of optimal texture feature models.[38] Preliminary experimental results indicate that these optimised models outperform each of their constituent feature groups in diagnostic accuracy,[39] but the technique is in its infancy and requires significant further work. It is clear, however, that the role of MRI in prostate cancer in unlikely to be usurped, rather it will be expanded by more intensive analytical techniques or use of adjunctive imaging technologies such as PET or quantitative ultrasound.

Conflicting interests

Professor deSouza is an employee of The Institute of Cancer Research. Professor deSouza has received grants from Cancer Research UK (CRUK), National Institute for Health Research (NIHR) and the European Union (EU).

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Ethical approval

Not applicable.

Informed consent

Not applicable.

Guarantor

NS.

Contributorship

HH and NS researched literature and conceived the study. HH and NS wrote and approved the final version of the manuscript.

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