Prostate cancer: state of the art imaging and focal treatment

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In 2016, it is estimated 180,890 men are newly diagnosed with prostate cancer and 3,306,760 men live with prostate cancer in the United States. The introduction of multiparametric (mp) magnetic resonance imaging (MRI) of the prostate, standardised interpretation guidelines such as Prostate Imaging Reporting and Data System (PI-RADS version 2), and MRI-based targeted biopsy has improved detection of clinically significant prostate cancer. Accurate risk stratification (Gleason grade/score and tumour stage) using imaging and image-guided targeted biopsy has become critical for the management of patients with prostate cancer. Recent advances in MRI-guided minimally invasive ablative treatment (MIAT) utilising cryoablation, laser ablation, high-intensity focused ultrasound ablation, have allowed accurate focal or regional delivery of optimal thermal energy to the biopsy proven, MRI-detected tumour, under real-time or near simultaneous MRI monitoring of the ablation zone. A contemporary review on prostate mpMRI, MRI-based targeted biopsy, and MRI-guided ablation techniques is presented.

Introduction

The American Cancer Society (ACS) estimates that there are 3,306,760 people living with prostate cancer in the United States and 180,890 new cases of prostate cancer will be diagnosed.1 In 2016 prostate cancer was the most commonly diagnosed non-cutaneous cancer and second-leading cause of death in men.2 With the dramatic increase in good-quality diagnostic multiparametric (mp) magnetic resonance imaging (MRI), organ-confined prostate cancer is increasingly visible, targetable, and potentially treatable with focal ablative technologies.1,3,4

Unfortunately, the timeline and variability of prostate cancer progression from organ-confined disease to extraprostatic spread is unknown; however, it seems intuitive that early detection and proper characterisation may play a role in preventing the development of metastatic disease.5 In view of the significant disparity on recommendations for early detection and prostate cancer screening among various scientific organisations (American Urological Association, American Society of Clinical Oncology, National Comprehensive Cancer Network, American Cancer Society, US Preventative Task Force and the European Association of Urology), and the uncertainty of the harm versus benefit of screening, this review will not delve into this controversy. Our focus will be on the current state of the art of prostate imaging, biopsy, and ablation techniques.
detection and subsequent aggressive treatment of intermediate and high-risk prostate cancer. Therefore, accurate ascription of cancer risk (i.e., grade and stage) using imaging and biopsy is critical. Advances in prostate treatment have become integrated with imaging, image identification, and image guided biopsy, and therapy propelling prostate treatment solutions forward faster than ever.

**Importance of MRI for prostate imaging**

**Native prostate cancer**

Prostate cancer has traditionally been diagnosed by prostate-specific antigen (PSA) screening and digital rectal examination (DRE) followed by DRE-directed biopsy. Use of ultrasound imaging has helped direct the biopsies further but has fallen short of being sensitive enough to find all the prostate cancer within the gland. Furthermore, systematic (non-targeted) sampling the entire organ has provided some answers but may also miss or under-sample small volume, but clinically significant disease, which may result in delayed diagnosis and treatment.

MRI is the best imaging method of the prostate and periprostatic structures because MRI provides superior soft-tissue contrast resolution, high spatial resolution, multiplanar imaging capabilities, and a field of view larger than transrectal ultrasound. The use of integrated endorectal and pelvic phased-array coils has led to improved visualisation of the prostatic fossa. T2-weighted imaging (WI) is sensitive in depicting prostate cancer; however, decreased T2 signal intensity is not specific for prostate cancer and can be seen in benign conditions. Functional parametric imaging including dynamic contrast-enhanced imaging (DCEI), diffusion-weighted imaging (DWI), and MRI spectroscopic imaging (MRSI) complement morphological MRI by reflecting perfusion characteristics, Brownian motion of water molecules, and metabolic profiles, respectively. Significant inverse correlation was shown between the apparent diffusion coefficient (ADC) value and Gleason score/highest grade. A combination of T2WI, DWI and DCEI with or without MRSI, is referred to as mpMRI. The introduction and maturation of mpMRI now allows for imaging-based identification of prostate cancer, which may improve diagnostic accuracy for higher-risk tumours.

In 2015, a consensus panel agreed to Prostate Imaging—Reporting and Data System (PI-RADS) version 2, which promoted standardised MRI acquisition and interpretation to improve detection, localisation, characterisation, and risk stratification of clinically significant prostate cancer in treatment naive prostate glands. Targeted biopsy of suspected cancer lesions detected by MRI is associated with increased detection of high-risk prostate cancer and decreased detection of low-risk prostate cancer particularly with the aid of MRI/ultrasound fusion platforms. The use of mpMRI has expanded beyond staging to detection, characterisation, monitoring for active surveillance, and cases of suspected recurrence after failed definitive therapy (Fig 1a–d).

The use of MRI for recurrent prostate cancer continues to evolve and has potential to evaluate both local recurrence and distant bony and nodal metastases. In 2013, a consensus panel chaired by Professor Michael Marberger endorsed utilisation mpMRI to identify patients for focal therapy. mpMRI is capable of localising small tumours for focal therapy. Although mpMRI plays an established, critical role in native and recurrent prostate cancer imaging, functional, metabolic imaging for prostate cancer is in its formative years. 

**Recurrent prostate cancer**

After a definitive radical prostatectomy, patients are followed at periodic intervals with measurement of serum PSA and DRE; however, DRE is frequently unreliable in evaluating local recurrent disease after radical prostatectomy. Following radical prostatectomy, PSA levels are expected to be undetectable within several weeks of surgery. If there is a rise in a previously undetectable or stable postoperative PSA level (biochemical failure), a prompt search for persistent, recurrent, or metastatic disease should be pursued; however, PSA alone does not differentiate local from distant disease recurrence. There are three main categories of recurrence after radical prostatectomy for prostate cancer: (1) local recurrence in the prostatic bed, (2) distant metastasis (e.g., bone, lymph node), and (3) a combination of local recurrence and distant metastasis. Therefore, the major objective of diagnostic imaging studies
is to assess patients for the presence of distant metastatic
disease or local recurrent disease, each requiring different
forms of systemic or local therapy. Local recurrence may be
amenable to salvage therapy. Systemic recurrence may be
an indication for systemic treatment including androgen-
deprivation therapy or chemotherapy.

Transrectal ultrasound (TRUS) has been used for the
evaluation of local recurrence with mixed results. The
altered anatomy from surgery or radiation, the develop-
ment of fibrotic tissue, the fact that 30% of recurrent tu-
mours may be isoechoic and that some lesions are distant
from the ultrasound transducer or extend along the bladder
wall influence the accuracy of this technique.

The use of CT or TRUS biopsy has been questioned in the
face of a rising PSA level, as negative results are unreliable
and elevated PSA levels usually precede clinical evidence of
local recurrence by ≥1 years. Furthermore, CT imaging is
even less sensitive depicting local recurrences of ≥2 cm³.¹⁸
Repeat TRUS with vesico-urethral anastomosis (VUA) nee-
dle biopsy may be necessary to document local recurrence
in one-third of cases.¹⁹ Only approximately 25% of men with
post-prostatectomy PSA levels of <1 ng/ml have histological

Figure 1 A 62-year-old man with a history of adenocarcinoma, low-volume Gleason score 3+3, diagnosed a year earlier, presented with elevated
PSA to 9.6 from 4.9 (ng/ml). mpMRI at 3 T with an endorectal coil was performed for further characterisation. (a) Axial and (b) sagittal T2-
weighted images demonstrate an area of decreased signal intensity in the left anterior prostate at the mid-gland (arrow). (c) The corre-
sponding axial ADC map demonstrates restricted diffusion (arrow). (d) The corresponding axial DCE image demonstrates hyperenhancement
(arrow). The lesion was considered to be PI-RADS score 4. MRI/ultrasound fusion-guided, targeted biopsy revealed Gleason score 4+3=7 disease,
involving 40% of the specimen. Subsequently in-bore MRI-guided cryoablation via a transperineal approach was performed. (e) Axial and (f)
sagittal T2-weighted images demonstrate an area of signal void (arrow), indicative of ice ball, which encompasses the MRI-detected left anterior
prostate cancer.
confirmation of local recurrence after biopsy of the prostatic fossa. In a more contemporary series with biochemical recurrence (BCR) in post-surgical patients, mpMRI can aid in the targeting of TRUS biopsies with 65% of biopsies being positive with a mean PSA of 0.58 ng/ml.

$^{11}$C-choline PET/CT has an advantage to reveal both local recurrent and distant metastatic cancerous lesions. $^{11}$C-choline PET/CT had a sensitivity of 73%, a specificity of 88%, a positive predictive value (PPV) of 92%, a negative predictive value (NPV) of 61%, and an accuracy of 78% for the detection of clinically suspected recurrent prostate cancer in post-surgical patients; however, $^{11}$C-choline PET/CT is not widely available (Fig 2a–d).

With the limitations of ultrasound and CT, MRI has been shown to be quite useful in the detection and staging of recurrent prostate tumours. The use of integrated endorectal and pelvic phased-array coils has led to improved visualisation of the prostatic fossa. The addition of DCE MRI to conventional T2-weighted MRI improves the detection of small local recurrent tumours.

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**Figure 2** A 60-year-old man with a history of proton beam therapy for prostate cancer presents with BCR of PSA 7.8 ng/ml. His PSA nadir was around 2.5 after radiation. mpMRI at 3 T with an endorectal coil was performed for further evaluation. (a) Axial T2-weighted images demonstrate an area of hypointensity in the left lateral peripheral zone at the apex (arrow). (b) The corresponding DCE image demonstrates hyperenhancement (arrow). (c) The corresponding ADC map demonstrates hypointensity (arrow), indicative of restricted diffusion. (d) The corresponding C-11 choline PET/CT image demonstrates choline avidity (arrow). Findings were consistent with recurrent prostate cancer in the left peripheral apex. Subsequent transperineal needle biopsy revealed adenocarcinoma, Gleason score 4+3 in the left peripheral zone at the apex, as well as a small focus of Gleason 4+3 just to the right of the patient’s midline. MRI-guided cryoablation via transperineal approach was performed. (e) Axial and (f) sagittal T2-weighted images demonstrate a hockey-stick-shaped area of ice ball (arrow), which encompasses the foci of biopsy-proven prostate cancer.
Prostate biopsy techniques

Ultrasound-guided biopsies

The TRUS prostate biopsy has remained the cornerstone of prostate cancer diagnosis dating back to the systematic "sextant" biopsy protocol with three cores per side.\textsuperscript{24} A meta-analysis of 68 studies led to a recommendation of a more laterally directed schema with 12 cores improving prostate cancer detection rates by a factor of 1.3.\textsuperscript{25} Using this systematic 12 core TRUS sampling for men undergoing initial biopsy with elevated PSA yields cancer detection rates between 30–55%.\textsuperscript{26} The false-negative rate for this 12 core schema is of the order of 20–24%\textsuperscript{27} and repeated 12 core or saturation biopsies show detection rates of 11–47%.\textsuperscript{28} This is particularly true for men with anteriorly located tumours.\textsuperscript{29} To improve the accuracy of the sampling, some experts advocate the use of template, transperineal-mapping biopsies to systematically sample all quadrants of the prostate.\textsuperscript{30} This has been criticised for oversampling of insignificant tumours with risk of additional morbidity and need for general anaesthesia.

MRI-based biopsy techniques

In the last decade, increasing evidence supports the use of pre-biopsy mpMRI for significant disease localisation, with intent of addressing the limitations of the systematic biopsy, reducing the detection of low-risk cancers, and improving the detection of clinically significant prostate cancer.\textsuperscript{30–32} There are three MRI-based biopsy technical approaches.

Cognitive/visual-directed MRI targeted biopsy

During TRUS-guided biopsy procedures the operator can estimate the location of MRI suspicious lesions based on prior review of prostate MRI. With appropriate experience, this is straightforward and easy to implement without an upfront equipment investment; however, this cognitive fusion (or visual estimation) based targeted biopsy method is highly operator dependent. This method is prone to error in reliably mapping the MRI suspicious lesion on real-time TRUS and the confirmation of TRUS-directed targeted biopsy needle location over the MRI suspicious lesion is not feasible. In a study of 555 patients by systematic biopsy as well as cognitive fusion-guided targeted biopsy, overall 54% (302/555) of patients were found to have cancer; 82% of them were clinically significant. Systematic biopsy and cognitive fusion-guided targeted biopsy detected 88% and 98% of clinically significant cancers, respectively.\textsuperscript{33} Cognitive fusion targeted biopsy showed 16% more high-grade cancers and higher mean cancer core lengths than standard systematic biopsy. Cognitive targeted biopsy would only avoid 13% of insignificant tumours. Using a similar visually directed approach for the trans-perineal biopsy, Valerio et al.\textsuperscript{34} compare this to a software-based targeted biopsy. The software-based, targeted transperineal approach found more clinically significant disease than visually directed biopsy, although this was not statistically significant (51.9% versus 44.3%, p=0.24)\textsuperscript{34} The current diagnostic ability of visually/cognitively targeted and software-based biopsies seem to be nearly comparable. Ongoing prospective trials hope to confirm these findings, albeit based on those with significant operator experience.

Software-based ultrasound: MRI fusion targeted biopsy

Software-based MRI/TRUS fusion-guided biopsy enables the combination of the advantages of real-time TRUS providing better temporal resolution and cost effectiveness, with those of MRI providing better spatial resolution and more accurate cancer detection, and has the potential to improve the detection of clinically significant cancers and for re-biopsy of patients with elevated PSA despite prior benign biopsy results. There are three key tracking methods including (1) image organ-based tracking, (2) electromagnetic sensor-based tracking, and (3) mechanical arm, sensor-based tracking.

Image organ (prostate)-based tracking methods fuse prior MRI with real-time ultrasound using a surface-based registration and elastic organ-based deformation algorithm (Urostation, Koelis). MRI suspicious lesions will be brought into the aiming mechanism of the biopsy gun attached to the ultrasound probe. This is relatively inexpensive and allows systemic biopsy; however, confirmation of targeted needle biopsy tracts is retrospective.\textsuperscript{35}

Electromagnetic sensor-based tracking using non-rigid registration algorithm allows real-time spatial tracking of targets and needle location. This system is less operator-dependent and allows a free-hand scanning during procedures (UroNav, InVivo; Real-time Virtual Sonography [RVS], Hitachi-Aloka). In a recent prospective study of 1,003 men undergoing a MRI/ultrasound fusion targeted biopsy and concurrent standard biopsy, targeted MRI/ultrasound fusion biopsy was shown to diagnose 30% more high-risk prostate cancer (defined as Gleason score 4 + 3 or greater) while a combination of standard and targeted biopsies revealed 22% more prostate cancer, mostly (83%) low-risk prostate cancer (defined as Gleason score 3 + 3 and low volume 3 + 4).\textsuperscript{36}

A sensor-based tracking system, in which a mechanical tracking arm is attached to a conventional ultrasound probe, allows real-time spatial tracking of targets and needle location (Artemis, Eigen). This system is less operator-dependent, but relatively expensive. In a recent retrospective review of 601 men who underwent both MRI/ultrasound fusion targeted biopsy and systematic biopsy, targeted MRI/ultrasound fusion biopsy detected fewer Gleason score 6 prostate cancers (75 versus 121; p<0.001) and more Gleason score ≥7 prostate cancers (158 versus 117; p<0.001) when compared with systemic biopsy.\textsuperscript{37} In a review of 105 patients with prior negative biopsies and elevated PSA, MRI/ultrasound fusion targeted biopsy improved detection of clinically significant prostate cancer when compared with systemic biopsy.\textsuperscript{38}

In a recent study of 1,042 men who underwent mpMRI and targeted and systemic biopsies, the addition of systemic...
biopsy to targeted biopsy found 7% (60/825) additional clinically significant cancer. These lesions would have been underdiagnosed if mpMRI suspected lesions only were targeted.

In a study of 125 consecutive patients who had pre-biopsy mpMRI, subsequent MRI/ultrasound fusion biopsy, and subsequently underwent radical prostatectomy, 4% (five of 123) MRI-detected clinically significant prostate cancers were missed at MRI/ultrasound fusion targeted biopsy. In a prospective study of 116 MRI-detected lesions in 62 patients who underwent pre-biopsy mpMRI and targeted and systematic biopsies, the highest cancer-detection rates were found for PI-RADS score 5 with a detection rate of 81%. In contrast, PI-RADS score 4 had low to moderate cancer-detection rates. Further refinement of PI-RADS scoring criteria may still be necessary to enhance true positives and reduce false positives.

**In-bore direct MRI targeted biopsy**

There are two in-bore direct MRI targeted biopsy approaches including robot assisted, transrectal biopsy (DynaTRIM, InVivo) and transperineal biopsy using a brachytherapy template. The advantage of direct in-bore MRI-guided biopsy is imaging confirmation of targeting of MRI-detected lesions without the need for sophisticated image registration and fusion with live ultrasound images. Transperineal biopsy using a brachytherapy template may reduce the bacterial transmission risk of a transrectal approach for biopsy. In a study of 265 patients with rising PSA despite prior negative TRUS-guided biopsies utilising a robot-assisted transrectal biopsy device (DynaTRIM, InVivo), a detection rate of overall prostate cancer and clinically significant prostate cancer per patient was 41% (108/265) and 87% (94/108), respectively. Reporting results from a prospective clinical observational study, Penszkofer et al. showed the utility of in-bore prostate biopsies with at least one MRI detected lesion in men with no prior prostate cancer, those undergoing active surveillance monitoring and in men with suspected recurrent cancer following treatment. Overall cancer was detected in 56.7% with 48.1% with no prior cancer, 72% of those under active surveillance and 72% of those in whom recurrence was expected. The accuracy of the transperineal in-bore biopsy appears good as demonstrated by analysis of biopsy and post-prostatectomy histopathology. MRI-detected targets located in the anterior gland had the highest cancer yield (62.5%). Although these advantages are attractive, this approach is not widely used because it requires upfront investment including MRI compatible equipment, use of scanner time for a longer procedure, higher costs per procedure, and collaboration with the urologist, radiologist, and anaesthesiologist.

**Focal thermal ablative therapy options**

Once prostate cancer is found, localised, and imaged, it is necessary to determine a potential treatment plan. Standard therapies include radiotherapy, surgery, or androgen deprivation; however, these therapies have significant risk and morbidity to the patient’s health-related quality of life with potential impact on sexual, urinary, and bowel function. Active screening programmes for prostate cancer have enabled earlier identification of low-risk prostate cancer because of related morbidity from standard therapies and are using active surveillance to delay treatment until cancer progression. Due to the morbidities of standard therapies, patients and physicians are beginning to examine focal therapies for early treatment. Although focal therapy is still controversial due to the potential multifocality of prostate cancer, limitations of current biopsy strategies, suboptimal staging by accepted imaging modalities, and less than robust prediction models for indolent prostate cancers. In spite of these restrictions focal therapy continues to confront the current paradigm of therapy for low-risk disease. Furthermore, prostate cancer recurrence rates after established forms of therapy range from 20–60%. In this review, we describe some of the recent advances in focal therapy for native prostate cancer and recurrent prostate cancer where MRI imaging is used to direct focal therapy.

**Focal therapy treatments for native prostate cancer**

Although radical prostatectomy and radiation therapy remain the preferred definitive therapy of choice for men with newly diagnosed prostate cancer and with a life expectancy >10 years, there is increasing interest in less radical focal methodologies for treatment especially in the watchful waiting population. For this population of low- and intermediate-risk prostate cancer patients, active surveillance may be undesirable from the patient standpoint, yet the complications and co-morbidities associated with standard therapies may seem too great for the patient. This patient-driven interest for a more minimally invasive approach is driving focal therapies for prostate carcinoma in low-risk patients. As a result, several minimally invasive thermal ablation methods under direct MRI guidance, most prominently cryotherapy, laser ablation, and high-intensity focused ultrasound (HIFU), have been developed and are currently being evaluated.

**Selection of patients with native prostate cancer for MRI-guided focal therapy**

In selecting the appropriate patient for focal therapy of the native prostate gland, it is critical to determine that the patient has localised low-risk disease. With low-risk disease, there is level 1 evidence that implies a lack of benefit from radical therapy. Patients are targeted for cancer work-up due to rising PSA or nodule on DRE. Patients are further evaluated with a mapping biopsy and/or mpMRI with targeted biopsy. Patients are classified to have low or intermediate prostate cancer with a focal positive lesion on mpMRI, Gleason ≤4+3, and PSA <20 ng/ml. To be considered for focal therapy, the target lesion should be confined to one lobe of the prostate. Furthermore, the target should
be visible with the imaging technique that will be used to guide the focal ablation treatment.

MRI-guided cryoablation

MRI-guided percutaneous cryoablation combines excellent soft-tissue resolution and ice ball monitoring. Early experience combining cryoablation with MRI has shown a high degree of accuracy in defining normal and frozen tissue on all MRI sequences. There are few data using MRI-guided cryoablation within the native prostate. Two published canine studies demonstrated feasibility and overall safety. These studies did highlight one limitation of cryoablation, which is that the visualised edge of the ice (0°C) does not represent the ablation margin. The actual ablation margin is best demonstrated with contrast enhancement post-procedure and is actually at the −20°C isotherm, which is just inside the edge of the ice ball. There are two published reports of MRI-guided cryoablation in native prostate glands, each with relatively small numbers. Gangi et al. performed MRI-guided prostate cryoablation in 11 patients using 1.5 T MRI. They had some minor complications of haematuria, dysuria, and urine retention. Additionally, they had one major complication of rectal fistula with spontaneous closure after 3 months. The other study examined 18 patients with two slightly different methodologies. The group treated with a more aggressive freezing regimen had better results over time. These studies confirm that MRI-guided cryoablation is technically feasible with relative safety; however, more short- and long-term data are needed to assess overall efficacy.

MRI thermometry for thermal ablation

One of the major advantages associated with MRI guidance of thermal ablations is the MRI thermometry and subsequent dose estimations, which are performed in near real-time and allow for adjustments of treatment parameters and tumour targeting. The thermometry to monitor local temperatures most commonly is accomplished using the known linear dependence of proton resonance frequency (PRF) as a function of temperature. During delivery of ablative energy (generated by ultrasound transducer or laser applicator) a series of two-dimensional (2D) phase-sensitive T1-weighted fast spoiled gradient-recalled echo MRI images are acquired. Based on temperature changes, a thermal dose can be calculated to predict a tissue lethal dose.

MRI-guided laser ablation

Laser-induced interstitial thermal therapy (LIITT) uses a locally placed laser fibre to deliver targeted thermal ablation. LIITT is inherently MRI compatible making it an obvious choice of ablation technologies to couple with MRI imaging. MRI-based temperature monitoring allows real-time feedback during LIITT treatment as both deposition of light energy and MRI signal acquisition can be performed simultaneously without degradation in the MRI image. Performance of the ablation within the MRI allows the use of post-treatment imaging to verify treatment delivery. Because MRI images clearly depict the prostate anatomy and the surrounding critical structures, MRI is critical for monitoring ablation growth to prevent encroachment onto adjacent critical structures.

Two publications also demonstrated feasibility in the canine prostate. These were beneficial due to showing technical feasibility but also demonstrated correlation of the MRI temperature map with contrast-enhanced T1-weighted images. A subsequent study in cadavers demonstrated technical feasibility in the human prostate using 3 T MRI (Fig 3). Lee et al. published early results on 23 patients treated with focal laser ablation demonstrating promising results. Raz et al. described using laser ablation for treatment of two prostate cancer patients at 1.5 T with discharge 3 hours after the procedure. These studies demonstrate the potential utility of laser ablation in the prostate; however, more data are needed to determine short- and long-term effects.

Ultrasound- and MRI-guided focused ultrasound ablation

Treatment of the prostate with focused ultrasound ablation is not new although the MRI-guided version of the procedure has not, as of yet, been approved by Food and Drug Administration (FDA) in the United States. This treatment modality has been performed with TRUS imaging guidance with success in Europe for many years; however, a major limitation of ultrasound imaging guidance is the difficulty in visualising the focus of cancer, especially if the focus is small. Therefore, the treatment strategy used with ultrasound-guided HIFU is to ablate the entire prostate or relatively large region where the site of biopsy-proven cancer was found using a mapping biopsy and/or mpMRI. This often results in inadequate tumour control or over-ablation of unnecessary normal/neural tissue with potential subsequent morbidity. An early study, using HIFU ablation in prostate by Gelet et al. treated 82 patients who were subsequently followed up for 24-months. These patients also received subsequent radiation treatment. Among these patients, 68% were cancer free at the time of follow-up. Due to the relatively high complication rates, the treatment device underwent multiple iterations and improvements. A subsequent study, by Gelet et al., demonstrated incontinence and impotency rates around 14% and 61% respectively at 19 months post-treatment. In both studies, major limitations were identified as total procedure time due to a need to cover the entire prostate and inability to monitor temperature elevations or ablation zone expansion. MRI thermal monitoring and localisation of lesions/zones within the prostate should allow optimisation of ablation treatment zone while ablation temperature monitoring should allow improved safety margin in regard to vital adjacent tissues. Currently, there are two MRI-integrated systems using transrectal (Exablate, InSightec, D.A. Woodrum et al. / Clinical Radiology xxx (2017) 1–15

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Focal therapy treatments for recurrent prostate cancer

Recurrences after surgical resection can range from 25–40%, which is usually manifested by rising serum level of PSA. Approximately 30,000 men will develop BCR with rising PSA after radical prostatectomy each year in the USA. A study by Sella et al. utilising MRI performed with an endorectal coil examined the location of recurrences and found 81% occurred as local prostate bed recurrence. For those patients who undergo radiotherapy, BCR can range widely between 33 and 63% over 10 years, and contributes another 45,000 men/year with post-radiotherapy recurrent cancer in the USA alone. Salvage treatments currently available for recurrent prostate cancer include: salvage radical prostatectomy, salvage radiotherapy, salvage ultrasound-guided HIFU, salvage ultrasound-guided cryoablation, and newly described salvage MRI-guided laser and cryoablation.

Selection of patients with localised recurrent prostate cancer for MRI-guided focal therapy

The first issue is to determine whether the rising PSA represents local recurrence, systemic recurrence, or both. The second issue in managing patients with BCR of prostate cancer is assessing the risk of cancer treatment versus the risk of further intervention. Overall, rapid PSA rise, short-disease free interval, and high-grade disease are all poor prognostic indicators with a higher likelihood of systemic recurrence, while slow PSA rise, long disease-free interval, and low-grade disease are better prognostic indicators with a higher likelihood of local recurrence.

Suggested criteria for MRI-guided focal ablative treatment in recurrent prostate cancer are as follows: (1) biopsy-proven local recurrent tumour that can be visualised by MRI, (2) absence of distant metastasis confirmed with chest, abdomen, pelvis CT and/or MRI plus bone scintigraphy and/or $^{11}$C-choline PET/CT. Although these selection criteria are
Ultrasound-guided cryotherapy for recurrent prostate cancer

Ultrasound-guided cryotherapy is currently being used for primary prostate cancer treatment as well as salvage treatment after primary radiotherapy failure. Due to the relative recent development as a treatment modality, there are limited studies on its efficacy. Chin et al. reported on 118 patients treated with salvage ultrasound cryotherapy after radiotherapy failure. This study showed a negative biopsy rate of 87% with a median follow-up of 18.6 months. Siddiqui et al. presented 15 patients with salvage ultrasound-guided cryotherapy after radical retropubic prostatectomy. Their findings demonstrated a 40% biochemical disease free state (bDFS) at a mean follow-up of 20 months. As cryotherapy devices have evolved with mixed gas technology, smaller cryoprobes, and improved urethral preservation with warmers, better imaging, and increased operator experience, the success rates have improved and complication rates decreased. A recent large study from the COLD cryo on-line data registry reported the 5-year bDFS to be 58.9% by the ASTRO definition of BCR and 54.5% by the Phoenix definition of BCR. For patients treated with salvage ultrasound-guided cryotherapy after primary radiotherapy failure, the most recent reported complication rates are perineal pain (4–14%), mild-moderate incontinence (6–13%), severe incontinence (2–4%), and urethrorectal fistula (1–2%). With the use of urethral warming catheter, the rate of sloughing and urethral stricture has been reduced to near zero. Erectile dysfunction (ED) is still high with rates of 69–86%.

MRI-guided cryoablation for recurrent prostate cancer

MRI-guided cryoablation for recurrent prostate cancer has also been shown feasible and successful in a number of small limited studies. Woodrum et al. published a study of 18 patients treated with MRI-guided cryoablation for locally recurrent prostate cancer. The cohort was broken into two groups of nine patients with alteration of the cryoablation technique between the groups. The study demonstrated that a tight (5 mm) spacing of cryoneedles, three freeze-thaw cycles, and sometimes decreasing the urethral warmer temperature produced better short-term recurrence-free intervals. Additionally, Gangi et al. demonstrated successful MRI-guided cryoablation treatment of several patients with recurrent prostate cancer as well. This
technique offers the advantage that it is not appreciably limited by the prior surgical or radiation treatment to the targeted area.\textsuperscript{62,63} Using MRI guidance, cryoablation treatment can be tailored to the desired area (Figs 2e–f; 5–6).

**MRI-guided laser interstitial therapy (LITT) for recurrent prostate cancer**

Using LITT for recurrent prostate cancer is a relatively recent development. A feasibility study and a case report using 3 T MRI with the Visualase 980 nm diode laser system (Medtronic, Minneapolis, MN, USA) to treat a prostate cancer.\textsuperscript{88} A small case series was also presented by the same group, which demonstrated the feasibility of treating recurrent prostate cancer with laser ablation (Fig 7).\textsuperscript{88} One complicating factor with MRI-guided laser ablation in patients with prior surgical resection is the presence of surgical clips, which cause susceptibility artefacts and degrade the MRI-based temperature mapping. Therefore, recurrences within the surgical clips present would be a relative contraindication for this method of treatment.

**HIFU for recurrent prostate cancer**

Salvage HIFU, which targets focused ultrasound energy to a specific area has been used for primary prostate cancer treatment and for salvage therapy. HIFU achieves cellular death by rising the cellular temperature >60°C causing cellular necrosis. Salvage HIFU is relatively recent treatment modality with limited studies on its efficacy. Three different studies have been published with relatively short follow-up period of 7.4–18.1 months. These studies demonstrated a highly variable bDFS of 25–71%, which was confounded by variable definitions of PSA failure and variable use of hormonal therapy before treatment. The most commonly reported complications are incontinence (10–49.5%), urethral stricture with retention (17–17.6%), erectile dysfunction (66.2–100%), and recto-urethral fistula (3–16%).\textsuperscript{87,89–91}

**Follow-up imaging**

After MRI-guided salvage thermal ablation, the best way to monitor the patient is by measuring serum PSA. PSA levels are expected to be undetectable within several weeks of salvage procedure. Detectable levels of PSA after salvage treatment indicate residual or untreated cancerous lesions. A rise in a previously undetectable or stable postoperative PSA levels during post-treatment follow-up indicate recurrent or possibly metastatic disease.

Follow-up imaging is performed at 6 months post-procedure. Laser ablation can leave heat fixation artefacts

![Figure 5](image-url) MRI-guided cryoablation for recurrent prostate cancer performed on a 69-year-old man with rising PSA after prior brachytherapy treatment 7 years prior. mpMRI at 3 T with an endorectal coil was performed for further evaluation. (a) Axial T2-weighted image demonstrates an indistinct hypointense lesion in the right lateral peripheral zone (arrow). Multiple interstitial brachytherapy seeds are present within the prostate gland bilaterally. (b) The corresponding DCE image demonstrates no abnormal tumour enhancement. Note the patient had been on Lupron for 3 months, which likely decreased the sensitivity. Intraprocedural MRI/ultrasound fusion guided, targeted biopsy from the right peripheral mid-gland was positive for Gleason 4 + 4 low volume cancer (see Fig. 1a). (c) Axial and (d) sagittal T2-weighted images demonstrate ice ball coverage of the prostate cancer located in the posterior right prostate (arrow).
post-ablation, which can make early post-procedural imaging difficult to interpret. Cryoablation has been shown to have some residual ablation zone contrast enhancement when imaging <6 months post-ablation, which resolves at 6 months after imaging. Endorectal coil MRI with DCE and DWI is useful for the assessment of prostatic fossa, iliac lymph nodes, and pelvic bones. Mild inflammatory enhancement about the ablation zone without a discrete mass is a common finding after procedure and usually resolves within 3 months after procedure. Persistent or new discrete enhancing nodules on MRI are suspicious for residual or recurrent cancerous lesions. These enhancing nodules, if still confined in the prostatic bed, may be amenable for repeated MRI-guided salvage ablation.

### Challenges

**Limitations to MRI visualisation of ice ball temperature isotherms**

A major limitation for MRI-guided cryoablation is that the ice ball isotherms are not readily visualised. The leading edge of the ice ball is well visualised due to very rapid T2
relaxation of ice protons, but this corresponds to 0°C and may not be lethal. Therefore, it is necessary to carry the edge of the ice beyond the tumour margin by at least 5 mm; however, this approach assumes that ice ball lethal iso-
therms of −40°C are <5 mm from the leading edge of the ice
ball and in the presence of complicating factors such as
heat transfer from adjacent major vessels or urethral
warmers, this assumption may or may not be true.
Additionally, there are currently no reliable MRI-
compatible temperature-monitoring devices to con
firm lethal temperatures. MRI performed with ultra-short echo
times (UTE) has been demonstrated to be a promising tool
in visualising temperature changes within frozen tissues;
however, the technique is yet to be applied in clinically.
Confounding the need for good margin coverage is the
problem of very restrictive space in and around the prostate
bed with close proximity to the rectum, bladder, and
external striated urethral sphincter with very little margin
for error.

Limitations of MRI thermometry

PRF temperature mapping utilises the phenomenon of
linear change of resonance frequency of water protons with
temperature. It is a powerful tool in MRI, however, there are
certain limitations to the technique due mainly to the fact
that these types of thermometry measure phase changes
between an initial baseline image and all subsequent im-
gages acquired in real time. Ideally, all these images should
be in perfect alignment with no motion between them. As a
consequence, motion is a large problem where the baseline
image alignment is disrupted causing phase registration
artefacts. A method that has been proposed to alleviate this
is the reference-less temperature mapping. Another
potential issue is the presence of the surgical clips, which
can cause metallic artefact resulting in image distortion and
signal drop-out, which can severely degrade MRI images.
In the native prostate, this is less of an issue, but in the post-
surgical prostate bed surgical clip artefact becomes a real
problem for phase change-based temperature imaging. The
final major limitation with PRF-based temperature mapping
is problem with tissue/fat interface. The resonance fre-
cquency is only dependent on temperature for water pro-
tons. Resonance frequency of protons in fat is unaffected by
temperature and therefore the PRF method is much less
sensitive to temperature changes in tissues with high fat
content, as can be the case with glandular tissue. Some
approaches attempt to resolve this issue by the use of the

Figure 7 MRI-guided laser ablation for recurrent prostate cancer in a 65-year-old man with prior radiation therapy. (a) Axial DCE contrast-
enhanced MRI at 3 T demonstrates abnormal enhancement of the left peripheral mid-gland (arrow). (b) T2-weighted images demonstrates
an abnormal contour in the left peripheral zone (arrow). Intraprocedural images of the 15 W laser ablation with double-applicator activation. (c)
A magnitude T1-weighted image demonstrates an area of low T1 signal intensity in the area of the ablation (arrow). (d) Corresponding
temperature-sensitive phase imaging displaying colour-coded temperature changes (arrow). (e) Based on the temperature-dependent phase
image changes, the ablation zone is computed, using the Arrhenius model of thermal tissue damage, and projected back onto the magnitude
image as solid orange (arrow).
so-called Dixon technique to separate MRI signals from fat and water, use of the PRF method on fat-only images and use of phase changes of the fat signal to correct for non-temperature-dependent phase changes. This technique, however, has not, as of yet, been applied clinically.

Limitations of MRI availability

Access to MRI can be problematic due to the increasing demand of diagnostic imaging; however, as an increasing number of MRI-guided or supported procedures develop, there is a shifting paradigm of thinking that MRI is just used for diagnostic imaging. Within neurosurgery there has been an increasing shift to utilise intraoperative MRI to assist with excision. With the prostate, there has been increasing utilisation of MRI for diagnosis as demonstrated with the publication of PIRADS versions 2 where the importance and nuances of prostate MRI have been laid out. From a practical standpoint, this may necessitate working with diagnostic radiology to determine times of decreased demand when MRI-guided procedures can be performed. Initially, it is also important to have a specialised team who are familiar with the MRI environment and the procedure being performed in the MRI until it becomes more routine. All these factors make initiation harder but the imaging guidance and precision that MRI brings to the procedure are significant.

Conclusions

As the most common cancer in men, prostate cancer diagnosis and treatment for new or recurrent disease will demand considerable resources and effort for years to come. MRI plays a seminal role in the management of this disease. MRI and ultrasound fusion for prostate biopsy guidance appears to represent the next step in timely diagnosis and navigation to clinically significant cancers. Although MRI-guided focal ablation of native or recurrent prostate cancer is feasible and rapidly becoming a viable treatment alternative, all focal therapy treatment series suffer from relatively small patient numbers and the need for comparison to established therapies. Additionally, it is critically important that good prospective clinical trials for each be performed to assess the advantage of each treatment modality and to determine the long-term efficacy.

References


30. Salami SS, Ben-Levi E, Yaskiv O, et al. In patients with a previous negative prostate biopsy and a suspicious lesion on magnetic resonance imaging, is a 12-core biopsy still necessary in addition to a targeted biopsy? BJU Int 2015;115:562–70.


