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Woodrum-MR-guided focal therapy for native and recurrent prostate cancer

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ABSTRACT

This manuscript presents a current review of the importance of MR imaging, biopsy and ablation for treatment of prostate cancer either early native disease or recurrent prostate cancer after surgery or radiation. Prostate cancer is the most common cancer diagnosis for men, with approximately 35,000 men dying from it each year in the United States[1]. Many men with prostate cancer are often managed with aggressive therapy including radiotherapy or surgery. No matter how expertly done, these therapies carry significant risk and morbidity to the patient's health-related quality of life with impact on sexual, urinary, and bowel function[2]. Furthermore, screening programs using prostatic specific antigen (PSA) and transrectal ultrasound (TRUS) guided systematic biopsy have increasingly identified patients earlier, in the low-risk, low-grade "localized" prostate cancer categories. The indolent nature of many prostate cancers presents a difficult decision of when to intervene given the possible comorbidities and side effects of aggressive treatment. Active surveillance has been increasingly instituted to balance cancer control versus treatment side effects[3]. Although active debate continues on the suitability of focal or regional therapy for these low- or intermediate-risk prostate cancer patients, many unresolved issues remain which complicate this approach of management. Some of the largest unresolved issues are: prostate cancer multifocality, limitations of current biopsy strategies, suboptimal staging by accepted imaging modalities, less than robust prediction models for indolent prostate cancers, and whether established curative therapies can be safely and effectively used following focal therapy for prostate cancer. Despite these restrictions, focal therapy continues to confront the current paradigm of therapy for low- and even intermediate-risk disease[4]. Therefore, accurate assessment of cancer risk (i.e. grade and stage) using imaging and targeted biopsy is critical. Advances in prostate imaging with MRI have been accompanied with advances in MR-guided therapy, propelling prostate treatment solutions forward faster than ever. The following manuscript reviews the current state of MR imaging, biopsy and MR-guided prostate ablations for native and recurrent prostate cancer using laser ablation, cryoablation, and focused ultrasound.

Introduction

The American Cancer Society (ACS) estimates 299,010 new cases of prostate cancer in 2024 and 35,250 deaths secondary to prostate cancer[1,5]. In 2024 prostate cancer is the most commonly diagnosed noncutaneous cancer and second-leading cause of death in men[6]. With the dramatic increase in good quality diagnostic mpMRI, organ confined prostate cancer is increasingly visible, targetable and potentially treatable with focal ablative technologies[2,5,7].

Unfortunately, the time line and variability of prostate cancer progression from organ confined disease to extra-prostatic spread is unknown. However, it seems intuitive that early detection and proper characterization may play a role in preventing the development of metastatic disease[4]. In view of the significant disparity on recommendations for early detection and prostate cancer screening among various scientific organizations (i.e. 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/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 for early native prostate cancer and prostate cancer recurrence after surgery or radiation.

The significance of precise image identification and biopsy is further amplified by Level 1 evidence supporting detection and subsequent aggressive treatment of intermediate and high-risk prostate cancer[8]. 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.

1. Primary Prostate Cancer

CANCER WORK-UP

The historical workup for prostate cancer has been a combination of prostate-specific antigen (PSA) screening and digital rectal exam (DRE) followed by DRE-directed biopsy. More recently, the use of ultrasound (US) imaging has helped direct biopsies toward suspicious lesions and systematically sample the prostate; however, US imaging alone is not sensitive enough to find all the prostate cancer within the gland, despite advanced US modalities (i.e. color/power doppler, elastography and bubble contrast agents). Furthermore, while systematic (non-targeted) sampling of the entire organ has provided some answers, it runs the risk of under-sampling small-volume, high-grade but clinically-significant disease or over-sampling indolent, low-grade disease, potentially resulting in delayed diagnosis or overtreatment.

Magnetic resonance imaging (MRI) is the superior imaging modality for prostate and associated structures due to its exceptional soft tissue conspicuity, high-level spatial resolution, and cross-sectional imaging. Utilization of integrated endorectal and pelvic phased-array coils has led to continued improvement in prostatic fossa visualization. High resolution T2-weighted imaging is sensitive in depicting prostate cancer especially within the transition zone of the prostate; however, decreased T2 signal intensity is not specific for prostate cancer, especially within the peripheral zone where benign conditions can lead to imaging changes. Functional parametric imaging, including dynamic contrast-enhanced imaging (DCEI), diffusion-weighted imaging (DWI), and MR spectroscopic imaging (MRSI), complement morphologic MRI by reflecting perfusion characteristics, Brownian motion of water molecules, and metabolic profiles, respectively. Significant inverse correlation was shown between ADC value and Gleason score/highest grade[9].

In 2013, a consensus panel endorsed utilization of mpMRI to identify patients for focal therapy[10]. Multiparametric MRI is capable of localizing small

tumors for focal therapy. In 2015, a consensus panel agreed to Prostate Imaging Reporting and Data System (PI-RADS) version 2, which promoted standardized MR acquisition and interpretation to improve detection, localization, characterization, and risk stratification of clinically significant prostate cancer in treatment naïve prostate glands[11]. 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[12]. The use of mpMRI has expanded beyond staging to detection, characterization, monitoring for active surveillance and cases of suspected local recurrence after failed definitive therapy. Though interest in the usefulness of biomarkers used in combination with mpMRI remains, emerging evidence supports its adoption as a standard of care tool in prostate cancer diagnosis at the confirmatory stage[13,14].

While mpMRI plays an established, critical role in primary and recurrent prostate cancer, functional and metabolic imaging are playing an expanding role with a host of new agents being developed. Established positron emission tomography (PET) tracers for imaging of prostate cancer include^{11}C and^{18}F choline[18], F fluciclovine[68], Ga prostate-specific membrane antigen (PSMA), and^{11}C-acetate[11]. C-choline PET/CT has an advantage to reveal both local recurrent and distant metastatic prostate cancers[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 postsurgical patients[15]. In a study of post-prostatectomy patients with rising PSA, mpMRI is superior for the detection of local recurrence[11], C-choline PET/CT is superior for pelvic nodal metastasis, and both are equally excellent for pelvic bone metastasis[11]. C-choline PET/CT and mp-MR imaging are complementary for restaging prostatectomy patients with suspected recurrent disease and exhibit diverse patterns of recurrence with implications for optimal salvage treatment strategies[16,17 68].Ga-PSMA is a promising PET tracer and indicates favorable sensitivity and specificity profiles compared to choline-based PET imaging techniques[18]. A recent publication demonstrated that late 3 hour imaging of^{68}Ga-PSMA helped to clarify activity within the prostate due to decreased activity within the bladder at this time point[19]. Early work with simultaneous MRI/PET imaging shows promise in capitalizing both the functional aspects of PET with the superb anatomic capabilities of MRI[20]. Compared to mpMRI, PSMA-imaging techniques, including^{68}Ga-PSMA-PET/MRI[18], F-PSMA-PET/CT, and^{68}Ga-PSMA-PET/CT, have demonstrated improved detection of dominant intraprostatic lesions[21].

Even with improvements in US and PET/CT imaging, MRI remains preeminent for detection and staging of prostate tumors within the pelvis. MRI/PET may ultimately provide the optimal combination of diagnostic resolution in the pelvis coupled with the whole-body screening functionality of PET imaging to provide the single platform for detection and localization.

BIOPSY METHODS

Prostate Biopsy Techniques

Ultrasound guided biopsies: The transrectal ultrasound-guided (TRUS) prostate biopsy has remained the cornerstone for prostate cancer tissue diagnosis dating back to the systematic 'sextant' biopsy protocol with 3 cores per side[22]. 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[23]. Using this systematic 12 core TRUS sampling for men undergoing initial biopsy with elevated PSA yields cancer detection rates between 30-55%[24]. The false negative rate for this 12-core schema is on the order of 20-24% and repeated 12 core or saturation biopsies show detection rates of 11-47%[25,26]. This is particularly true for men with anteriorly located and apex tumors[27]. To improve the accuracy of the sampling, some experts advocate the use of template,

transperineal-mapping (TPP) biopsies to systematically sample all quadrants of the prostate[28]. This has been criticized for oversampling of insignificant tumors with risk of additional morbidity and need for general anesthesia. While the comparative costs and benefits of TPP-biopsy remain under debate, a growing body of evidence suggests it offers high sensitivity of clinically significant cancer detection and more accurate anterior prostate gland sampling[29,30].

MR-based biopsy techniques

Increasingly, evidence supports the use of pre-biopsy mpMRI for identification of clinically significant disease. The hope is to identify the significant lesions for targeted biopsy while not oversampling otherwise normal regions[28,31,32]. Emerging research suggests pre-biopsy mpMRI can reduce unnecessary biopsies; however, underdetection rates associated with pre-biopsy mpMRI suggest TRUS biopsies may be necessary even if pre-biopsy mpMRI results are negative[33,34]. There are three main MR-based biopsy technical approaches.

Cognitive/Visual - directed MRI Targeted Biopsy: Overall, cognitive fusion (or visually directed) biopsy techniques demonstrate the most variability between operators due to the reliance on spatial orientation of the lesion from the MR which is used to direct the US and biopsy needle by the operator. With appropriate experience, this can be readily implemented but can be very difficult with small lesions or targets well away from the US transducer, such as with anterior tumors in large glands. Although MR-directed cognitive fusion biopsy of the prostatectomy bed is still useful for the evaluation of patients with biochemical failure after surgery, no dedicated MR-TRUS fusion software biopsy system is currently available for this application. The cognitive/fusion method is prone to error in reliably mapping the MRI suspicious lesion on real time TRUS and the confirmation of TRUS guided targeted biopsy needle location over the MRI suspicious lesion is not feasible, except when needle tracks are visible. 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[35]. 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 tumors. Valerio et al compared cognitive fusion 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% vs. 44.3%, $p = 0.24$)[36]. The current diagnostic ability of visually/cognitively targeted and software-based biopsies seem to be nearly comparable with experienced operators. A recent meta-analysis found high variability between studies comparing cognitive-fusion versus image-guided fusion prostate biopsies, highlighting the need for thoughtful consideration of operator familiarity and experience when selecting a biopsy strategy[37].

Software-based Ultrasound – MRI fusion Targeted Biopsy[38,39]: Software-based MRI/TRUS fusion-guided biopsy platforms seek to combine the advantage of lesion visualization from the MRI with the ease and availability of US based biopsy platforms for real-time imaging. There are three key tracking methods including 1) image organ-based tracking, 2) electromagnetic sensor-based tracking, and 3) mechanical arm, sensor-based tracking[40].

Image organ (prostate) - based tracking method fuses prior MRI with real-time 3D US using a surface-based registration and elastic organ-based deformation algorithm (Urostation, Koelis, Meylan, France). MRI-identified suspicious lesions are loaded into the system which then projects the target into the biopsy aiming mechanism on the US probe. This is relatively inexpensive and allows systematic biopsy. However, confirmation of targeted needle biopsy tracts is retrospective[41].

Additional systems utilize electromagnetic sensor-based tracking using a non-rigid registration algorithm. The advantage with this approach is that it allows real-time spatial tracking of targets and needle location and is less operator-dependent allowing free hand scanning during procedures (UroNav, InVivo, Inc., Gainsville, FL, USA; Real-time Virtual Sonography [RVS], Hitachi-Aloka, Tokyo, Japan and BK Fusion, BK Medical ApS, Herlev, Denmark). Published in 2016, a prospective study of 1003 men undergoing a MR/ultrasound fusion targeted biopsy and concurrent standard biopsy found that targeted MR/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)[42].

A similar but slightly different approach uses a mechanical arm, sensor-based tracking system where the tracking arm is attached to a conventional US probe. Again, this allows real-time spatial tracking of targets and needle location (Artemis, Eigen Inc., Grass Valley, CA, USA). This system is also less operator-dependent but relatively expensive. In a 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 vs. 121; $p < 0.001$) and more Gleason score ≥7 prostate cancers (158 vs. 117; $p < 0.001$) when compared with systemic biopsy[43]. In a 2012 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[44]. A recent study further confirmed that MR/ultrasound fusion targeted biopsy had higher sensitivity, detecting clinically significant disease with less oversampling.

Recent advances in MRI have demonstrated the value and importance of good prostate imaging. These advances are actively changing the way prostate cancer is diagnosed and treated. However, even with these advances it is critical to understand that MRI still has its limitations and needs further development. A recent study of 125 surgical prostatectomy patients studied the accuracy of the pre-surgical biopsy where there had been a pre-biopsy mpMRI with subsequent MR-US fusion biopsy. They found that there was a 4% (5 of 123) MR miss rate on surgical pathologic analysis[45]. Another study of 1042 men examined mpMRI targeted biopsies versus systematic biopsies. They found that the addition of systematic biopsy to targeted biopsy found 7% (60/825) more clinically significant cancers[46]. These lesions would have been underdiagnosed if mpMR suspected lesions only were targeted. Supporting these findings, a recent review found that systematic biopsies should be used in combination with targeted biopsies to ensure the most robust assessment of the prostate gland in at-risk patients[47]. In a recent study in 100 patients who underwent mpMRI, 162 clinically important malignant lesions were present after subsequent prostatectomy. On a per patient basis, mpMRI depicted clinically important prostate cancer in 99 (99%) of the 100 patients. However, at least one clinically important tumor was missed in 26 (26%) patients[48]. Considering the state of evidence, a recent review article recommended mpMRI as the initial step in the workup of men with suspected cancer[49].

In-Bore Direct MRI Targeted Biopsy: There are two main in-bore direct MRI targeted biopsy approaches including robot assisted, transrectal biopsy (DynaTRIM, InVivo) or a transperineal approach via template. In-bore MRI-guided biopsies have the advantage of real-time MR imaging to confirm biopsy acquisition position, thereby improving sampling accuracy. Using the direct in-bore biopsy technique one eliminates the issues of mis-registration, organ deformation and organ movement which continue to plague software-based US-fusion imaging. Additionally, transperineal biopsies using a template reduce or nearly eliminate the bacterial infection risk seen in transrectal biopsies. A study of 265 patients with

rising PSA and negative TRUS biopsy found that performance of MR-guided robot-assisted transrectal biopsy (DynaTRIM, InVivo) in this population produced a detection rate of 41% (108/265) for prostate cancer and 87% (94/108) for clinically significant cancer[44]. Penszkofer et al showed in a prospective clinical study, that in-bore prostate biopsies with at least one MRI detected lesion in men on active surveillance monitoring and in men with suspected recurrent cancer following treatment, detected cancer in 72% under active surveillance and detected recurrent cancer in 72% with possible recurrence[50,51]. The accuracy of the transperineal in-bore biopsy appears acceptable as demonstrated by analysis of biopsy and post-prostatectomy histopathology[52]. MRI-detected targets located in the anterior gland had the highest cancer yield (62.5%). In a retrospective study of 223 patients, Del Monte et al found MRI in-bore targeted biopsy showed higher malignant cell percentages per-core; however, no statistically significant difference in detection rate between in-bore biopsy and MRI-TRUS fusion biopsy was found[53]. These results were supported by Ramos et al's study (n = 280), finding that in-bore biopsy was associated with higher detection rates of clinically significant cancer in targeted cores only[54]. Exclusive to PI-RADS category 4 or 5 lesions, a recent retrospective study (n = 286) found that in-bore MRI-targeted biopsy demonstrated higher specificity compared to fusion biopsy[55]. Although these advantages are attractive, this technique is underutilized due to specialized MRI compatible tools, relative cost disadvantage, difficulty obtaining access to MRI, and need for coordination between Urology and Radiology.

TREATMENTS FOR PRIMARY PROSTATE CANCER

Once prostate cancer is identified from imaging and/or biopsy, a treatment plan must be formulated for the patient. The traditional therapy options for clinically localized prostate cancer with intent for cure have been either surgical resection or radiotherapy[56]. A recent meta-analysis of 19 studies suggests that surgery offers a benefit in overall and prostate cancer-specific survival compared with radiotherapy[57]. This is further supported by the results of a randomized phase III trial which found that, among patients who develop metastases within 10 years of treatment, those who received prostatectomy had a lower mortality rate[58]. For patients with localized high-risk prostate cancer, recent reviews suggest a benefit in radical prostatectomy over radiotherapy for overall and prostate cancer specific mortality[59,60]. Roughly about half of patients choose surgery and half choose radiotherapy[61].

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[62]. A recent meta-analysis reported that differences in quality-of-life outcomes, such as urinary, bowel, and sexual function, between surgery and radiotherapy recipients diminished over time[63]. Active screening programs for prostate cancer have enabled earlier identification of low-risk prostate cancer, but due to related morbidity from standard therapies, many choose active surveillance to delay treatment until cancer progression[3].

EVOLVING FOCAL AND PARTIAL GLAND THERAPY TREATMENT OPTIONS

For men with newly diagnosed prostate cancer and with a life expectancy >10 years, radical prostatectomy and radiation therapy remain preferred definitive therapy of choice[64-66]. However, patients are increasingly interested in less radical, more focal, methodologies for treatment, especially in the active surveillance population. For this population of low- and intermediate-risk prostate cancer patients, they also may be uncomfortable remaining on active surveillance but don't want surgery or radiation. This patient-driven interest for a more minimally invasive approach is driving focal therapies for prostate carcinoma in low-risk patients[67]. As a result, several minimally invasive thermal ablation methods under direct MR guidance, most prominently cryotherapy, laser ablation, and high-intensity focused ultrasound (HIFU), have been developed and are currently being evaluated[68-70]. Despite this, focal therapy is still controversial due to the potential for multifocality of prostate cancer,

limitations of current biopsy strategies, variation in quality MR imaging and less than robust prediction models for indolent prostate cancers. Furthermore, prostate cancer recurrence rates after established forms of therapy range from 20-60%[71]. Although emerging research suggests that partial gland ablation recipients suffer fewer side effects compared to those who receive surgery or radiotherapy, little is known about long-term outcomes associated with thermal and non-thermal focal treatment options[72].

Patient Selection for Focal and Partial Gland Therapy

Selecting the appropriate patient for focal/partial gland therapy as a primary treatment for prostate cancer is the most important element of a successful outcome. Accurately staging the prostate cancer is critical not only for the highest grade of prostate cancer but also understanding the extent of low-grade (i.e. Gleason 6) disease as well. With low-risk disease, there is level 1 evidence that implies a lack of benefit from radical/nonconservative therapy[73-75]. Patients are many times initially targeted for cancer workup due to rising PSA or nodule on digital rectal exam. These patients may undergo further workup with mapping biopsy and/or mpMRI with targeted biopsy. Patients are then classified to have low, intermediate, or high-risk disease. For consideration of focal therapy, the patient needs to have low or intermediate risk disease with a focal positive index lesion on mpMRI, Gleason ≤4+3, and PSA <20ng/mL. The target lesion should be confined to one lobe of the prostate[74]. Furthermore, the target should be visible with the imaging modality which will be used to guide the focal ablation treatment. With MRI having exceptional soft tissue conspicuity, high spatial resolution, and multi-planar imaging capacity, this approach has clear advantage over transrectal ultrasound as an imaging guidance platform.

MODALITIES USED TO ABLATE PRIMARY PROSTATE CANCER:

MR-guided Cryoablation

MR guided percutaneous cryoablation combines excellent soft tissue resolution and ice ball monitoring without the use of MRI thermometry. Early experience combining cryoablation with MRI has shown a high degree of accuracy in defining normal and frozen tissue on all MR imaging sequences[76,77]. There is limited data using MR guided cryoablation for primary treatment of prostate cancer. Two published canine studies demonstrated feasibility and overall safety[78,79]. These studies did expose one limitation of cryoablation which is that the visualized 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. There are two published reports of MR guided cryoablation in native prostate glands, each with relatively small numbers (Fig. 1)[80,81]. Gangi et al. performed MRI guided prostate cryoablation in eleven patients on 1.5T MRI with minor complications of hematuria, dysuria, and urine retention and one major complication of rectal fistula with spontaneous closure after 3 months[80]. These studies confirm that MR-guided cryoablation is technically feasible with relative safety, however, more intermediate and long-term outcome data is needed to assess overall efficacy. A recent literature review on MR-guided cryoablation found that focal or whole gland cryoablation may be appropriate for low- and intermediate-risk cases wherein surgery is not recommended or gland salvage is required[82].

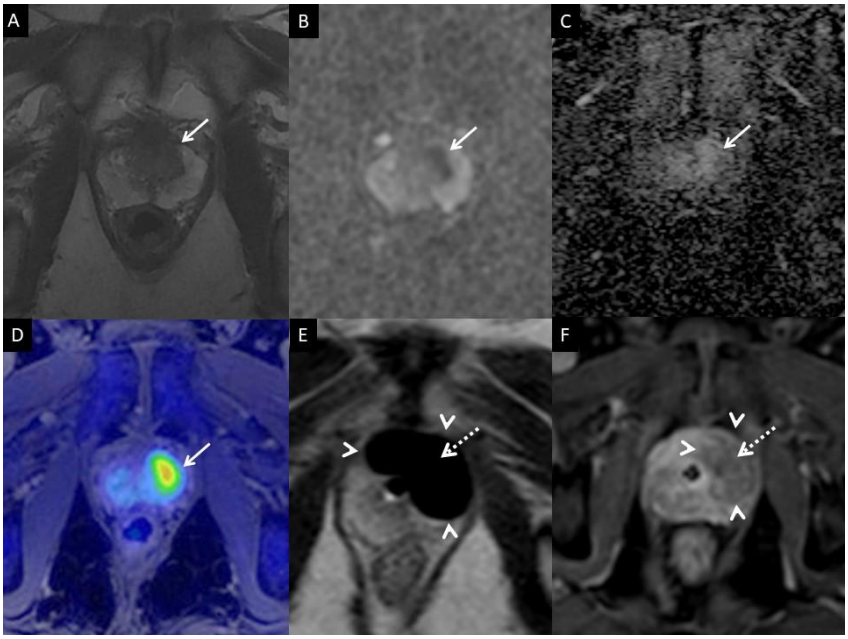

Figure 1 (Cryoablation): 70-year-old male presents with Gleason 3+3 adenocarcinoma of the left anterior prostate with a PSA of 6.2 ng/mL. Multiparametric MRI at 3 Tesla demonstrated an area of decreased signal intensity in the left anterolateral peripheral zone at the prostatic midgland (Panel A, arrow) with corresponding hypointensity on ADC map (Panel B, arrow), and early hyperenhancement (Panel C, arrow). Using a 1.5T MRI, three IceRod cryoneedles were placed via the transperineal approach into the left anterior prostate and freezing was performed under imaging guidance with three freeze-thaw cycles. An iceball is clearly visible on axial T2-weighted image during the freezing phase (Panel D,/ tumor arrow, iceball arrowheads, urethra dashed arrow).Subsequent post-ablation dynamic gadolinium enhanced series demonstrates the corresponding ablation zone to encompass the previously demonstrated cancerous lesion (Panel E, arrow).

MR thermometry for thermal ablation

One major advantage of MR guidance for heating thermal ablations is ablation monitoring using MRI thermometry where subsequent dose estimations can be applied. The MR thermometry typically performed is a near real-time proton resonance frequency (PRF) sequence which demonstrates signaling change as a function of temperature[83]. During delivery of ablative energy (generated by ultrasound transducer or laser applicator a series of 2D phase sensitive T1-weighted fast spoiled gradient-recalled echo MR images are acquired on MRI scanner[84-86]. Based on temperature changes, a thermal dose can be calculated to predict a real-time tissue lethal dose[87]. However, the two major limitations with this sequence are the inaccuracy in fat tissue and susceptibility to motion artifact. Additionally, PRF only measures temperature change relative to an established reference temperature[88].

MR-guided Laser Ablation

Laser-induced interstitial thermal therapy (LITT) uses a locally placed laser fiber probe to deliver targeted thermal ablation under MR guidance. LITT is inherently magnetic resonance (MR) compatible. MR guidance for laser applicator placement and ablative monitoring provides the imaging to prevent encroachment onto adjacent critical structures. Two early publications demonstrated technical feasibility of laser ablation monitoring in canine prostate and demonstrated correlation of the MR temperature map with contrast enhanced T1-weighted images[89,90]. A subsequent study in cadavers demonstrated technical feasibility in the human prostate within a 3T MRI scanner[91]. Lee et al. examined 23 patients treated with focal laser ablation demonstrating promising results[69]. Raz et al. described using laser ablation for treatment of 2 prostate cancer patients at 1.5T with discharge 3 hours after the procedure[92]. A recent phase I trial (n = 8) found that laser ablation, though safe and feasible, may require broader treatment margins to effectively destroy tumors[93]. These studies demonstrate the potential utility of laser ablation in the prostate. However, more clinical data is needed to determine short- and long-term efficacy.

US- and MR-guided High-intensity Focused Ultrasound (HIFU) Ablation

Treatment of the prostate with focused ultrasound ablation is not new, although MRI guided version of procedure has not, as of yet, been approved by FDA in the United States. HIFU achieves cellular death by rising the cellular temperature >60°C causing cellular necrosis. HIFU ablation technique does not require placement of a needle probe in a targeted prostate tumor via the rectum or skin (perineum) to deliver thermal energy and destroy cancerous tissue. This treatment modality has been performed with transrectal ultrasound (US) imaging guidance with success in Europe for many years[68,94]. The major limitation of US imaging guidance for prostate ablation is that ultrasound cannot precisely visualize the focus of cancer and therefore the target of therapy. Therefore, the initial treatment strategy used with US-guided high intensity focused ultrasound (HIFU) was to ablate the entire prostate, or a relatively large region where the site of biopsy-proven cancer was found using a mapping biopsy and/or mpMRI. This often resulted in inadequate tumor 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-month duration. These patients also received subsequent radiation treatment[95]. Among these patients, 68% were cancer free at the time of follow-up. Due to 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[96]. Current generation US guided HIFU has evolved into more robust treatment platforms with motion detection, improved planning modules and capacity to perform focal and partial gland therapy using US/MRI fusion[97]. The largest prospective single arm study with 1,002 patients demonstrated that whole gland ablation could be performed with severe incontinence rates from 3-6% and urethral stricture rates of 6-35%[98]. The 8-year biochemical free survival rates were 76% for low risk, 63% for intermediate risk, and 57% for high risk[98]. A subsequent single arm prospective clinical trial of HIFU hemiablation in 50 patients with unilateral, low-intermediate risk disease and 39.5 month followup demonstrated biochemical recurrence rate of 28-36% with 6% incontinence rate and 20% impotence rate[99]. As the ultrasound guided technology has improved so have the results[97]. A 2-year follow-up of 928 patients treated with 3 sequential versions of Sonablate devices demonstrated a corresponding 5 year biochemical disease free rate of 48.3%, 62.3%, and 82% respectively[97]. At the current time, ultrasound guidance is challenged with the inability to see the tissue heating produced by the focused ultrasound such that there is no real-time feedback. This is one of the advantages of real-time MR imaging which does in fact see and measure the tissue heating in a real-time quantitative manner.

To address the issue of visualization and temperature monitoring, two different MR guided focused ultrasound systems were developed. With MR thermal monitoring and localization of lesions/zones within prostate, focused ultrasound could be performed with smaller treatment zones presumably resulting in improved treatment margins with decreased morbidity. Currently, there are two MRI-integrated systems using transrectal (Exablate, InSightec, Haifa, Israel) (Fig2) or transurethral (Profound Medical Inc., Toronto, Canada) transmission routes for treatment of prostate lesions with focused ultrasound technology. The system is fully integrated with the MRI console with temperature feedback control to adjust power, frequency, and rotation rate. Following the publication of results from the TULSA-PRO Ablation Clinical Trial (n = 115), which found a 93% reduction in median PSA and 96% of patients presenting with > 75% PSA reduction,

Profound Medical Inc.'s TULSA system received FDA approval in August 2019[100,101]. A recent systematic review found that Profound Medical Inc.'s TULSA system was effective at prostate cancer ablation and reducing urinary symptoms[102]. The results of a phase II trial (n = 101) evaluating the Exablate approach suggest that MR-guided US ablation is effective for treating grades 2 and 3 prostate cancer without causing side effects. Specifically, in 88% of patients, no intermediate- or high-risk cancer remained in the treated area at 6 and 24 months.[102] Exablate Prostate received FDA approval in December 2021[103].

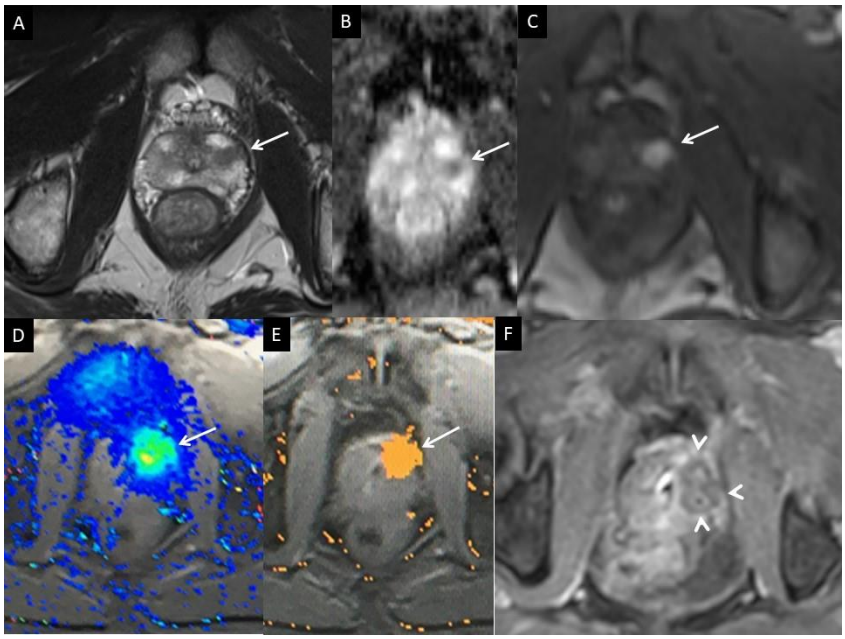

Figure 2 (Laser ablation): 67-year-old male presents with Gleason 3 + 4 prostate adenocarcinoma in left lateral peripheral zone at the apex. During MR guided laser ablation, axial T1-weighted images demonstrate a small hypointensity in left lateral peripheral zone within the lesion (Panel A, arrow) which corresponds to the change in temperature seen on phase imaging (Panel B, arrow) and calculated ablation zone on the damage map (Panel C, arrow).

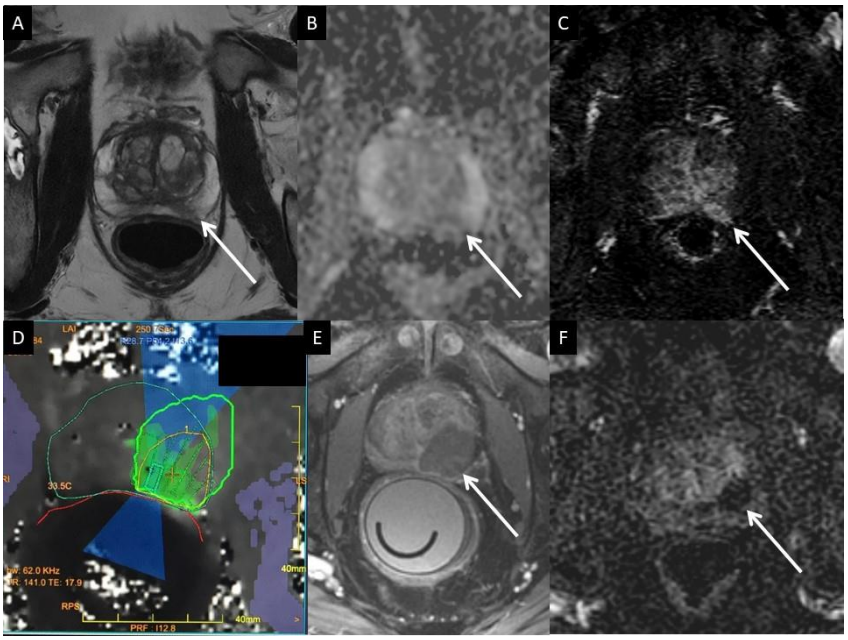

Figure 3 (InSightec):65-year-old male presents with Gleason 3+4 prostatic adenocarcinoma of the left peripheral prostate. Multiparametric MRI at 3 Tesla demonstrated an area of decreased signal intensity in the left lateral peripheral zone at the prostatic midgland (Panel A, arrow) with corresponding hypointensity on ADC map (Panel B, arrow), and early subtle hyperenhancement (Panel C, arrow). InSightec ultrasound transducer was placed in the rectum and treatment plan created (Panel D). Post-ablation dynamic gadolinium enhanced series demonstrates the corresponding ablation zone to encompass the previously demonstrated cancerous lesion (axial Panel E, arrow and sagittal, Panel F).

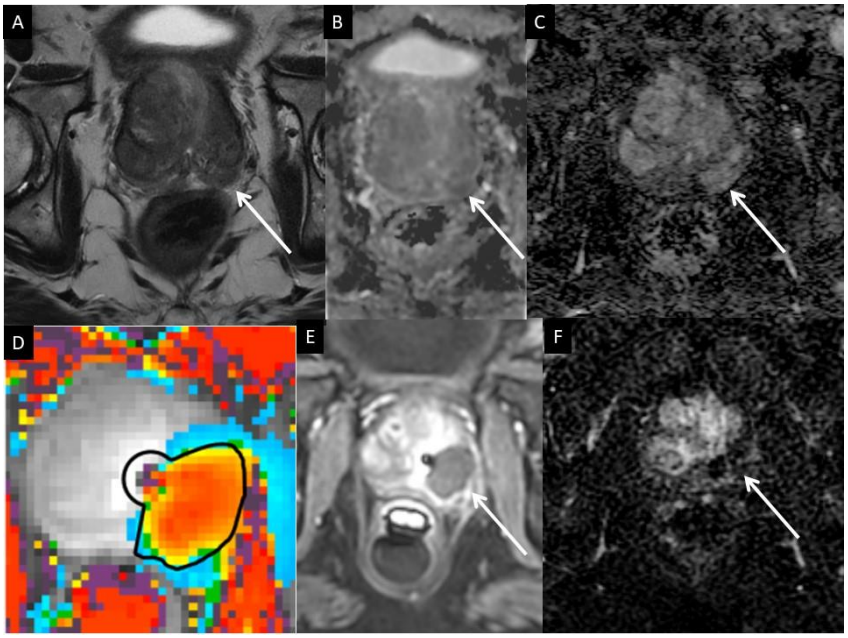

Figure 4 (TULSA): 75-year-old male with history of refractory prostate cancer status post external beam radiation therapy with subsequent salvage prostatectomy and lymphadenectomy. PSA was undetectable but started rising. Pelvic MRI demonstrated a hyperenhancing recurrence posterior to the vesicourethral (VU) anastomosis. TRUS-guided biopsy revealed Gleason 4 + 4. Axial T2-weighted images demonstrate a soft tissue nodule with hypointensity posterior to VU anastomosis (Panel A, arrows). Corresponding ADC map demonstrates restricted diffusion (Panel B, arrows). Corresponding DCE image demonstrates hyperenhancement (Panel C, arrows). CT/PET choline imaging demonstrates corresponding increased activity in the hyperenhancing nodule (Panel D, dashed arrow). Using a 1.5T MRI, six IceRod cryoneedles were placed via the transperineal approach posterior to the vesicourethral anastomosis. An iceball is clearly visible on axial T2-weighted image during the freezing phase (Panel E, iceball arrowheads).Subsequent post-ablation dynamic gadolinium enhanced series demonstrates the corresponding ablation zone to encompass the previously demonstrated cancerous lesion (Panel F, arrowheads).

Recurrent Prostate Cancer

Recurrent prostate cancer after surgery can range from 25 to 40% manifesting as a rise in PSA[104-106]. Up to one-third of all men with prostate cancer will develop biochemical recurrence (BCR) with rising PSA after radical prostatectomy[104]. Approximately 81% of prostate cancer recurrences occur locally in the prostate bed and can be visualized with multiparametric MRI[107]. With radiation treatment, biochemical recurrence can range widely between 33 and 63% over 10 years, and this contributes another 45,000 men/year with post-radiotherapy recurrent cancer in the USA alone[108,109]. Salvage treatments currently available for recurrent prostate cancer include salvage radical prostatectomy, salvage radiotherapy, salvage ultrasound (U/S)-guided high-intensity focused ultrasound, salvage U/S-guided cryoablation, and newly described salvage MRI-guided laser and cryoablation.

MRI FOR RECURRENT PROSTATE CANCER

After a definitive radical prostatectomy or radiation therapy, patients are followed at periodic intervals with measurement of PSA levels and DRE. However, DRE is frequently unreliable in evaluating local recurrent disease after radical prostatectomy. Following a 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, including 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 the 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 and/or chemotherapy.

Transrectal ultrasound (TRUS) has been used for the evaluation of local recurrence. However, the altered anatomy of the region, the development of fibrotic tissue, the fact that 30% of recurrent tumors may be isoechoic and that some lesions are in an anterior position or extend along the bladder wall influence the accuracy of this modality. Furthermore, CT imaging can depict only local recurrences of greater than or equal to 2 cc[110].

The use of biopsy has been questioned in the face of a rising PSA level, since the negative results are unreliable and elevated PSA levels usually precede clinical evidence of local recurrence by one or more years. Repeat TRUS with vesicourethral anastomosis (VUA) needle biopsy may be necessary to document local recurrence in one-third of cases[111]. About 25% of men with post-prostatectomy PSA levels of less than 1 ng/ml have histologic confirmation of local recurrence after biopsy of the prostatic fossa[112]. In a more contemporary study, MRI directed biopsies in 132 post-prostatectomy patients using cognitive /visual registration and TRUS guided biopsies, with a median PSA of 0.59 ng/ml and a median lesion size on MRI of 1cm yielding a positive predictive value of 85% with positive biopsy rates of 74% with lesion sizes between 1-2cm[113].

^{11}C-choline PET/CT has an advantage to reveal both locally recurrent and distant metastatic malignant 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 postsurgical patients[15]. A recent meta-analysis of 18 studies (n = 2,126) found a pooled detection rate of 62% for recurrent prostate cancer. However[11], C-choline PET/CT is not widely available.

With the limitations of US and CT imaging, MRI has been shown to be quite useful in detection and staging of recurrent prostate tumors[114-116]. MRI provides superior soft tissue contrast resolution, high spatial resolution, multiplanar imaging capabilities, and a large field of view. The use of integrated endorectal and pelvic phased-array coils has led to improved visualization of the prostatic fossa. The use of mpMRI for recurrent prostate cancer continues to evolve and has potential to evaluate both local recurrence and distant bony and nodal metastase[16]. Functional information from MR spectroscopic imaging and diffusion-weighted imaging may complement morphologic MRI by reflecting tissue biochemistry and Brownian motion of water molecules, respectively. These functional imaging techniques may be used to supplement conventional MR imaging in diagnostic clinical studies.

2. Salvage Therapies for Prostate Cancer

A. SURGERY

Salvage radical prostatectomy (sRP) after radiotherapy is more difficult because of local fibrosis and tissue plane changes secondary to the radiation. From this standpoint only a few centers take on these cases. However, sRP has the longest follow-up period for any of the salvage therapies with follow-up greater than 10 years. The biochemical disease-free survival (bDFS) at 10 years was 30-43% based on aggregated data from four institutions. The 10 year cancer-specific survival rates were 70-77%[117,118]. More recently, salvage robotic radical prostatectomy has been reported with some small patient studies demonstrating more promising results, but it is premature to report on long term follow up[119]. Due to the difficulties posed after primary radiation treatment failure, the complication rates for sRP have been higher than primary surgery with incontinence rates of 58% and major complication rates of 33%[120]. The largest series to date is a multi-institutional collaboration study which reviewed 404 patients with a median follow up of 4.4 years and freedom from clinical metastasis of >75% at 10 years from surgery. This study also identified the most favorable groups to undergo sRP were in men

with a PSA < 4 ng/ml and post radiation prostate biopsy Gleason score of ≤ 7[121]. In a recent retrospective study in patients with local recurrence after primary treatment (n = 106), functional outcomes were inferior compared to those from primary robot assisted radical prostatectomy[122].

B. RADIATION

Salvage radiotherapy can be used for BCR following surgery or primary radiotherapy failures. Frequently, salvage brachytherapy (BT) is performed for primary radiotherapy failures. In a large study out of Mayo Clinic, 49 patients with primary external beam radiotherapy (EBRT) failure were treated with salvage low dose rate BT. They demonstrated a 3-year biochemical disease free survival (bDFS) of 48% and a 5-year bDFS of 34%[123]. Multiple other studies demonstrate a slightly better bDFS, but neoadjuvant androgen treatment was also used in conjunction with the radiation confounding the results. Overall, the 5-year bDFS for salvage BT after primary radiotherapy is approximately 20-70%. Complications for salvage BT were either genitourinary (GU) or gastrointestinal (GI). Grade 3-4 GU toxicity was 17% as a late complication and grade 3-4 GI toxicity was around 5.6%[120,123,124]. In a more contemporary series of 98 patients, the 3-year bDFS was 60.1%, and there was no difference between low-dose rate BT and high-dose rate BT. On multivariate analysis, only the prostate specific antigen doubling time (PSADT) < 12 months was significantly associated with PSA relapse[125]. The results of a recent follow-up study (n = 89) found 5- and 8-year survival rates (95% CI) for salvage radiotherapy were 90.2% (78.9-95.6%) and 69.8% (46.4-84.4%), respectively. Additionally, the 5-year bDFS survival rate was 50.8% (36.7-63.3%)[126].

C. HIGH INTENSITY FOCUSED ULTRASOUND (HIFU)

Salvage high intensity focused ultrasound (HIFU) which targets focused ultrasound energy to a specific area has been used for primary prostate cancer treatment and for salvage therapy. Salvage HIFU is a relatively recent treatment modality with a growing number of studies on its efficacy. Three different studies have been published with a 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%)[120,127-129]. In the largest multi-institutional pooled series of 418 patients treated with whole gland HIFU after failed radiotherapy, the 7-year cancer specific survival and metastasis free survival of >80% were attained at the price of significant morbidity. According to this study, salvage HIFU should be initiated early following radiation failure and by centers with significant experience[130]. In a recent systematic review (n = 1,241), Maestroni et al found that salvage HIFU was effective at treating radiorecurrent prostate cancer, yielding an 85.2% 5-year survival rate[131].

D. ULTRASOUND-GUIDED CRYOABLATION

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 US cryotherapy after radiotherapy failure[132]. This study showed a negative biopsy rate of 87% with a median follow up of 18.6 months. Siddiqul et. al presented 15 patients with salvage ultrasound guided cryotherapy after radical retropubic prostatectomy[133]. Their findings demonstrated a 40% bDFS at a mean follow up of 20 months. As cryotherapy devices have evolved with mixed gas technology, smaller cryoprobe size, 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 a 5-year bDFS to be 58.9% by the ASTRO definition of BCR and 54.5% by the

Phoenix definition of BCR[134]. For patients treated with salvage US 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%.96 In a pooled study of 396 patients who underwent salvage cryosurgery for radiation failure with a medial follow up of 47.8 months, had respective 5- and 10-year DFS of 63% and 35% with disease specific survivals of 91% and 79% respectively[135]. A 2022 systematic review (n = 11,228), with a follow-up period between 9.0 and 297.6 months, reported a disease-specific survival rate of 65.5-100.0% with a biochemical recurrence rate of 15.4-62.0%[136].

Selection of Patients for Focal Therapy

One of the most important aspects of assessing recurrent prostate cancer is determination of whether the recurrence is localized or metastatic[105]. 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[65,137].

Potential criteria for MR guided focal ablative treatment of recurrent prostate cancer are as follows: (1) biopsy proven local recurrent tumor that can be visualized 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 scan[16,66]. Although not perfect, these criteria seek to rule out patients where they have both local and systemic metastases unless local treatment is coupled with systemic treatment strategy for cancer control.

MRI guided Recurrent Prostate Cancer Focal Therapy Options

MR-guided Cryoablation

MR-guided cryoablation for recurrent prostate cancer is technically feasible and been successful in short-term follow-up. Woodrum et al. published on 18 patients treated with MR guided cryoablation for locally recurrent prostate cancer where treatment optimization parameters were assessed for two groups of 9 patients[81]. Ultimately, the study demonstrated that a more aggressive tight (5mm) spacing of cryoneedles, 3 freeze-thaw cycles, and prudent adjustment of the urethral warmer temperature produced better short-term recurrence free intervals. Gangi et al. also demonstrated successful MR-guided cryoablation treatment of several patients with recurrent prostate cancer[80]. This technique offers the advantage that it is not appreciably limited by the prior surgical or radiation treatment to the targeted area[80,81]. Using MR guidance, cryoablation treatment can be tailored to the desired area (Fig 2). In another series, MR-guided cryoablation has been reported to successfully treat select patients with locally recurrent tumors after failed radiation therapy[138]. A recent retrospective analysis (n = 47) of patients who underwent MR-guided cryoablation after primary radiotherapy found that wider ablation margins may be necessary for effective treatment[139].

MR-Guided Laser Interstitial Therapy (LITT)

Using Laser interstitial thermal therapy (LITT) for recurrent prostate cancer has been shown to be feasible with a case report using a 3T MRI with Visualase 980nm diode laser system (Medtronic, Minneapolis, MN, USA)[81]. A small case series was also presented by the same group which demonstrated feasibility of treating recurrent prostate cancer with laser ablation. Difficulties encountered with this ablation technique in these patients were the temperature mapping distortion secondary to the surgical clips from prior surgery. This could also be encountered with brachytherapy seed implantation as well. Therefore, recurrences

within the surgical clips or brachytherapy seeds would represent a relative contraindication for this method of treatment.

MR-Guided Focused Ultrasound Briefly describe the ongoing multicenter prospective US pivotal study for low volume Gleason 7 cancer using MR guided trans-rectal focused US. Final accrual likely to be complete by late in 2018.

Follow-up Imaging

After MR-guided salvage focal ablation, the best way to monitor the patient is by measuring serial serum PSA and MR imaging. PSA levels should decrease soon after ablation and ideally drop to undetectable within several weeks of salvage procedure if there is no remaining prostate tissue. In the setting of prior radiation, the PSA is expected to return to prior baseline PSA levels seen after radiation treatment. In either situation the PSA should decrease to a new plateau level and remain there over time. A rise in a previously undetectable or stable postoperative PSA levels during post-treatment follow up indicates recurrent or possibly metastatic disease warranting a further workup to localize viable disease.

One possible schematic for follow up is PSA every 3 months and MR imaging at 6, 12, 18, 24 months post procedure and then lengthen to yearly after the first two years post-ablation if all is negative. Cryoablation has been shown to have some residual ablation zone contrast enhancement when imaging less than 6 months post ablation which resolves at - month imaging[140]. Multiparametric MRI can assess 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 MR-guided salvage ablation. Post-ablative biopsies should also be entertained at one- and two-years post treatment with particular attention to the margin of the ablation zone.

Challenges of Focal Therapy

LIMITATIONS TO MRI VISUALIZATION OF ICEBALL TEMPERATURE ISOTHERMS

A limitation for MR-guided cryoablation is that the leading edge of the iceball is well visualized due to very rapid T2 relaxation of ice protons, but this corresponds to 0°C and may not be completely lethal. Therefore, it is necessary to carry the edge of the ice beyond the tumor margin by at least 5mm assuming that iceball lethal isotherms of -40°C are less than 5mm from the leading edge of the iceball[141]. Complicating factors to this assumption include heat transfer from adjacent major vessels or urethral warmers[142]. Studies have shown that ultra-short echo times (UTE) can be used to visualize temperature changes within the iceball; however, this technique is yet to be widely applied clinically[143-145]. 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. This small margin of error presents an ongoing challenge of balancing treatment efficacy with morbidity.

LIMITATIONS OF MRI THERMOMETRY

Proton resonance temperature mapping (PRF) capitalizes on the phenomenon of linear change of resonance frequency of water protons with temperature. PRF temperature mapping is a powerful tool, but it has some major limitations such as sensitivity to motion and tissue edge artifacts. PRF relies on a baseline comparison image which all subsequent images are compared. As a consequence, motion is a large problem where the baseline image alignment is disrupted causing phase registration artifacts. A method that has been proposed to alleviate this is reference-less temperature mapping. Another potential issue is the presence of the surgical clips, which can cause metallic artifact resulting in image distortion and signal drop-out, degrading the MR images. In

the native prostate, this is less of an issue, but in the post-surgical prostate bed, surgical clip artifact becomes a real problem for phase change-based temperature imaging. The final major limitation with PRF-based temperature mapping is the problem with tissue/fat interface. The resonance frequency is only dependent on temperature for water protons. The resonance frequency of protons in fat is different, producing artifact and inaccuracy for tissue fat interfaces. Some approaches attempt to resolve this issue by the use of the so-called Dixon technique to separate MRI signals from fat and water, use of the PRF method on the fat-only images, and use of phase changes of the fat signal to correct for non-temperature-dependent phase changes[146]. This technique, however, has only been applied in a limited number of cases, as of yet[147].

Conclusions

Prostate cancer is the most common solid malignancy in men. As the clinical burden is significant, prostate cancer diagnosis and treatment for new or recurrent disease will demand considerable resources and effort for years to come. mpMRI is playing a pivotal role in the diagnosis and management of this disease. MRI and ultrasound fusion for prostate biopsy guidance appear to represent the next step in timely diagnosis and navigation to clinically significant cancers. mpMRI is an effective modality in the depiction of a locally recurrent tumor after failed definitive treatment. While minimally invasive MR-guided focal ablation of native or locally recurrent prostate cancer is feasible and rapidly becoming a viable treatment alternative, there is still continued work needed to determine long term efficacy. To date, all focal therapy treatment series suffer from relatively small patient numbers with short follow-up and need for comparison to established therapies. Additionally, it is critically important that good prospective clinical trials for each treatment modality be performed to assess the advantage of each and to determine long-term efficacy.

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