New Strategies for Prostate Cancer Management

White Paper

Profound Medical and Siemens have a strategic partnership to further the development of prostate cancer care.

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Prostate cancer management The process of transition

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Despite high-profile technical developments that have undoubtedly refined the process of surgery and radio-therapy as treatments for prostate cancer, the underlying principles of care have not really changed since the two approaches to treatment were first developed. Both aim to eradicate all prostate tissue – one by complete removal, the other by exposure to ionizing radiation. Indeed, a recent randomized trial of robotic assisted versus traditional prostatectomy demonstrated that the two approaches to care resulted in very similar outcomes [1]. While principals of care have not changed, the advent of modern imaging and genomic technologies has opened the door to an era of precision diagnosis, ultimately enabling a paradigm shift to individualized and personalized treatments.

Switching our therapeutic target from the host organ to the cancer within it represents the first real departure from standard care since Hugh Hampton-Young undertook the first prostatectomy at Johns Hopkins over 100 years ago. It is this advancement in modern imaging enabling a transition from traditional whole organ treatment to a targeted one based on the clinical significance of the diagnosis and that aims to preserve healthy tissue and patient quality of life, that is the subject of this white paper.

The timing of this white paper is important. It comes very soon after the publication of a landmark study demon-strating that our traditional risk-stratification methods – prostate biopsy that is blind to tumor location – are wanting and that modern magnetic resonance imaging (MRI) doubles the accuracy of diagnosis [2]. MRI provides the ability to 'see' prostate cancer and therefore derive its volume and location – two attributes that have so far evaded us – and thus permitted the departure from the conventional whole gland therapies. It is important to indicate why this departure from our traditional approach to therapy is needed. There are two principal reasons.

First, is the need to reduce the harms associated with treatments. The discovery that treatments preserving at least 50% of the prostate tissue as part of a prostate cancer treatment have hardly any measurable impact on genito-urinary function has been one of the big discoveries of the last decade [3]. Second, is the need to reduce the burden on the already stretched modern health services. These focally applied tissue-preserving approaches tend to be done as day-case procedures as a 'one-off', sometimes outside the traditional surgical operating theater. These aspects contribute to mitigating the future economic burden of prostate cancer care as the population of men ages and therefore become more at risk.

It is important to note that these tissue-preserving approaches cannot and will not be delivered in isolation. Because they are all predicated on state-of-the-art imaging they will need to be delivered as part of a multi-disciplinary care team comprising urologists, oncologist, radiologist, and application specialists. Moreover, it should be noted that despite the novelty and potential benefit that should result from implementing this new system of care, traditional approaches to treatment – active surveillance for low risk disease – and multi-modality treatment (surgery, radiotherapy, systemic agents) for higher risk disease will still be needed. Finding the exact place for each of these approaches will take us some time, but will be simplified now that the accuracy of risk-stratification has improved by the introduction of MR imaging.

In this white paper, experts from around the world expand and develop some of these issues in order to provide the reader with a succinct but informative state-of-the-art account of where we are in this process of transition.

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Multiparametric prostate MRI for prostate cancer diagnosis

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Introduction

The diagnosis of prostate cancer differs from that in other solid organ cancers, where imaging is used to identify patients who require biopsies and the lesions that need to be targeted. Instead the standard prostate cancer diagnostic pathway offers transrectal ultrasound guided (TRUS) biopsies with multiple needles, sampling the entire prostate gland, without regard to the likely location of lesions that can cause patient harms. Patients chosen for this approach include biopsy naive men with elevated serum prostate specific antigen (PSA) levels and/or abnormal digital rectal examinations (DRE), those who are deemed to be at persistent elevated risk of harboring significant cancers despite prior negative TRUS biopsies, and those with low-risk prostate cancer (based on TRUS biopsies) undergoing active surveillance (AS), needing repeated biopsies for disease monitoring.

The non-cancer specific causes of elevated PSA levels, the semi-randomness of the TRUS biopsy procedure, the variable prevalence of prostate cancer in the population at risk [1], and the wide range of genomic diversity and prognosis of prostate cancer, lead to three important consequences:

1. many men without clinically important cancers undergo unnecessary biopsies with the attendant morbidities [2];

2. over-diagnosis of clinically unimportant cancers occurs [3], contributing to over-treatments; and

3. under-diagnosis and under-treatment of clinically important cancers occurs, due to poor tissue sampling and risk-stratification errors.

The PROTECT study, published in 2016, was a critical landmark in showing that the over-diagnosis and over-treatment of low risk disease, resulting from the TRUS biopsy approach, has minimal patient survival benefits [4]. In this study, men diagnosed with prostate cancer using PSA screening and TRUS biopsy were randomly assigned to active monitoring (not as in the way we practise today), radical prostatectomy, or radical radiotherapy. The results showed no cancer-specific survival differences after 10 years of follow-up, but active treatments did reduce the time to metastases. Over three-quarters of men enrolled in the PROTECT study had low-risk disease (the rest were mostly at intermediate risk), emphasizing the need to avoid biopsy and over-treatment in low-risk men, whilst improving the detection of cancers that do require active treatment, to decrease metastasis rates.

Clinical needs in prostate cancer diagnosis

Multiple clinical needs can be identified for men who are at elevated risk of developing harms from prostate cancer, if left undiagnosed and untreated. These include

1. determining the causes of the elevated PSA levels, and whether the elevated PSA can be ascribed to the presence of significant cancers;

2. reducing the number of investigations, including biopsies, needed to determine the cause(s) of the elevated PSA levels, whilst at the same time reducing the number of men over-diagnosed with low-risk disease;

3. improving the detection and anatomic localization of clinically significant prostate cancer (csPCa), to enable appropriate, directed biopsy with a view to improving the risk stratification of diagnosed patients with cancer; and

4. minimizing the time taken to arrive at final diagnoses and to start risk appropriate treatment(s).

All these needs should be met at reasonable costs.

Many tools are being developed to meet the clinical needs for more accurate prostate diagnoses. The emerging clinical paradigm is to use advances in imaging and molecular pathology [5]. The latter include the robust detection of transcriptomic, proteomic, and genomic biomarkers in the serum, urine and tissues of patients. These molecular assays include urine RNA, the detection of circulating tumor cells and serum tumor DNA. The developing idea is that the combined use of PSA isoforms, patient risk calculators, as well as advanced molecular diagnostics, can help identify patients who are likely to benefit from imaging detection and image guided biopsy. Central to these developments are the emerging roles of multiparametric MRI (mpMRI) and MR-guided biopsy (MRGB) for prostate cancer diagnosis and treatment selection.

Multiparametric prostate MRI

Multiparametric MRI of the prostate combines the use of anatomical T2-weighted images with two functional imaging techniques: dynamic contrast-enhancement (DCE) and diffusion-weighted imaging (DWI), the latter includes the calculation of apparent diffusion coefficient (ADC) maps. MR spectroscopic imaging (MRSI) for the diagnosis of prostate cancer is no longer considered a component of routine prostate mpMRI because it is technically challenging and time consuming to perform correctly, requires significant post-processing expertise for clinical implementation, and is not widely available. A large body of research and clinical experience has accrued to support the value of mpMRI for the non-invasive detection and localization of clinically significant prostate cancers via MRGB [6–8], demonstrating its ability to decrease the detection of insignificant disease [9], and to improve the risk stratification of diagnosed patients. mpMRI has also been shown to be of value in directing the management of known prostate cancer, for example in the selection of men suited for AS [10], clinical staging [11], for depicting the site of biochemical recurrence [12], and surgical planning [13].

There are challenges in implementing prostate mpMRI in clinical practice, including heterogeneity of image quality between centers, and consequently variations in the diagnostic performance for prostate cancer detection. The causes for variable quality and results are multifactorial, being dependent on the MRI equipment capabilities (including equipment vendor, magnet field strength, coils employed, software level, sequence parameter choices), patient factors (motion, metal work, rectal gas), prostate gland (size, coincidental benign conditions, tumor size and grade, tumor sparsity including multifocality, biopsy-related hemorrhage, prior therapies effects) and the radiologic interpretation of images (learning curve effects, subjectivity of observations, inter-observer variations and reporting styles). To address these challenges, it has become necessary to develop imaging, quality and reporting standards for prostate mpMRI.

Prostate imaging and reporting and data system (PI-RADS)

To promote standardization for both clinical use and research, in 2010 the AdMeTech Foundation (Boston, MA, USA) International Prostate MRI Working Group recommended the development of consensus guidelines for prostate mpMRI. Called the Prostate Imaging and Reporting and Data System (PI-RADS), the European Society of Urogenital Radiology (ESUR) published the first version in 2012 [14]. To update and improve upon the first version, and to establish a single international standard, a joint steering committee of the American College of Radiology (ACR), ESUR and the AdMeTech

Foundation developed PI-RADS version 2 (PI-RADS v2), which was released in 2015 and published several months later [15].

PI-RADS v2 aims were to simplify and standardize the terminology and content of mpMRI reports, develop 'assessment categories' that summarize levels of suspicion to assist the selection of patients for biopsies and management, establish acceptable technical parameters for mpMRI, and reduce variability in imaging interpretations. PI-RADS v2 has rapidly become the global standard for the acquisition, interpretation, and reporting of prostate mpMRI and has helped to fuel its unprecedented clinical uptake [16].

Although PI-RADS v2 is built on the foundation of PI-RADS v1, there are important differences between the two systems [17]. For PI-RADS v1, the focus was on the full range of clinical applications of prostate mpMRI, patient management, and assessment of extraprostatic extension/staging. PI-RADS v2 instead focuses on lesion detection and characterization (including benign findings), as well as interpretation and reporting. PI-RADS v2 includes detailed explanations, caveats, and explicit instructions on measuring and mapping prostate lesions. It also includes images that illustrate assessment criteria, and an extensive lexicon of the relevant terminology.

There are also important differences in sequential use of imaging criteria for interpretation and assessment category allocations. For example, PI-RADS v2 does not include MRSI, DCE-MRI is relegated to a clarification role for peripheral zone (PZ) assessments, and instead DWI has been given increased emphasis for evaluation of the PZ, and given less emphasis in transition zone (TZ) assessments.

PI-RADS assessment uses a 5-point Assessment Category scale based on the likelihood that a combination of defined mpMRI features on T2w imaging, DWI and DCE imaging indicate the likely presence of a clinically significant cancer, for any detected lesion in the prostate gland:

PIRADS 1 – Very low (clinically significant cancer is highly unlikely to be present)

PIRADS 2 – Low (clinically significant cancer is unlikely to be present)

PIRADS 3 – Intermediate (the presence of clinically significant cancer is equivocal)

PIRADS 4 – High (clinically significant cancer is likely to be present)

PIRADS 5 – Very high (clinically significant cancer is highly likely to be present).

To arrive at PI-RADS v2 assessment category for each suspicious finding in the prostate, T2w and DWI are initially assessed using pre-specified imaging features

(sequence specific 5-point scale), and DCE is classified as either positive or negative. Then, using the appropriate PI-RADS v2 classifier table for the lesion location (PZ or TZ), these three parameters (T2w, DWI, and sometimes DCE) are integrated, to yield for each lesion, a final PI-RADS v2 assessment category (PIRADS 1–5), that indicates the likelihood that it represents a clinically significant cancer.

It is important to note that there is a range of both malignant and benign pathologies in the prostate gland, and overlaps in their mpMRI characteristics. Therefore, a low PIRADS assessment category of 2 does not completely exclude the possibility of clinically significant cancer. Rather, it simply indicates that it is unlikely. Similarly, assessment category 5 does not provide proof that a lesion is a clinically significant cancer, but rather indicates that it is highly likely.

Assignment to a specific PI-RADS v2 assessment category is based solely on mpMRI findings. It does not consider other factors, such as PSA levels, prostate gland volume, DRE findings, patient/family history, or likely manage-ment choices. The Likert assessments of PI-RADS v1 which were meant to take these additional clinical factors into account have been removed because of the confusion on their use in the PI-RADS v1 literature. Instead, these additional factors, along with local multi-disciplinary discussions, experience, clinical history and PI-RADS v2 assessment categories determine recommendations on patient management, including the need for and most appropriate method for biopsy.

Prostate MRI performance

Radiologic-pathologic correlations
Detailed mpMRI-prostatectomy histologic correlation studies have shown improved visibility of larger [18–21], higher grade lesions [18, 20, 21], the latter applying mostly to index lesions [18, 22, 23]. As a guide, solid growth pattern GS = 6 lesions need to have a volume of ≥ 0.5 mL (approximately 9–10 mm diameter sphere) to be detected. Index lesions with primary GS ≥ 4 pattern with a volume ≥ 0.2 mL (approximately 7–8 mm diameter sphere) can be also identifiable in some studies at high field strength [19, 22, 23]. However, it should be noted that although most index lesions are detected [18], non-index lesions are often over-looked even if they are high-grade, which has important implications for focal therapies that are undertaken after confirmatory targeted biopsies alone [18]. In the absence of additional systematic whole-gland template biopsy sampling, it is possible to leave behind untreated, smaller volume, high-grade disease, which may partly account for focal therapy failures [24].

mpMRI interpretation using the PI-RADS v2 system does not aim to detect all prostate tumors, having by design a poorer sensitivity for low volume, sparse GS = 6 disease that is unlikely to cause patient harms (very-low-risk

prostate cancer). This is intentional, because of the concerns of 'over-diagnosis' and over-treatment discussed above, and to reduce the number of men undergoing AS. Indeed, a negative mpMRI (PIRADS 1 and 2 categories) in the context of selecting patients for AS, is a good prognostic finding for patient suitability [10]. In so doing, a negative mpMRI assessed with PI-RADS v2 is predictor of downgrading in biopsy-proven GS 3+4 PCa to GS 3+3 disease at prostatectomy pathology [27]. As expected, the larger a tumor and the higher its grade, the more likely it is to be detected and to have a higher PI-RADS v2 assessment category (PIRADS 4 and 5) [25, 26]. These radiologic-pathologic correlation studies do show that smaller, non-index, csPCa foci are undetected using PI-RADS v2 assessment criteria.

PI-RADS v2 test-performance
Multiple studies have now shown that the PI-RADS v2 assessment categories are effective in cancer detection in the PZ and TZ, with increases in the predictive value for each increment in PIRADS assessment category for all cancers and for csPCa. In a large retrospective analysis of in-bore targeted biopsies in 1057 patients, csPCa (GS ≥ 7) was found in 17%, 34%, and 67% of patients with PIRADS 3, 4, and 5 lesions, respectively [8]. Another study in 339 patients employing transrectal US targeting and 12 core systematic biopsy found csPCa (GS ≥ 7) disease in 0%, 10%, 12%, 22% and 72% for PIRADS 1–5 assessment categories respectively [6]. These studies reflect the combined performance of PI-RADS v2 and MRGB, including their respective limitations. To minimize the limitations of MRGB to diagnosis, Greer et al. in a retrospective study, assessed the lesions detected using PI-RADS v2 criteria on mpMRI in 163 patients by 9 readers [28]. 654 lesions (including 420 PZ lesions) were compared with whole-mount prostatectomy findings (in 110 patients) and systematic biopsies (in 50 patients). The probability of cancer detection for PI-RADS v2 assessment categories 2, 3, 4, and 5 lesions incrementally increased (16%, 33%, 71%, and 91%, respectively). This study also confirmed the dominant sequence concept for the PZ location of lesions, but not for T2-weighted imaging over DWI in the TZ, using the PI-RADS v2 descriptive criteria. Greer et al. also documented meaningful contributions by DCE-MRI to diagnostic yields in the PZ for assessment categories 2–4.

PI-RADS v2 performance data from the single centers mentioned above have been confirmed by meta-analyses [29, 30] including an analysis of 3,857 patients where PI-RADS v2 had a pooled sensitivity of 0.89 (95% confi-dence interval [CI] 0.86–0.92) with specificity of 0.73 (95% CI 0.60–0.83) for prostate cancer detection [29]. Comparative data show improved performance of PI-RADS v2 compared to PI-RADS v1 [31]. The consistent high sensitivity and more variable specificity, indicate that 'rule-out' clinically significant disease performance for PI-RADS v2 is better than its 'rule-in' ability, meaning that

biopsies are required for positive mpMRI scans, reported using the PI-RADS v2 system. Heterogeneity of results appears to be related to multiple factors, including the csPCa prevalence, reference standard, radiologic experience and the variations in technical performance of the mpMRI examination itself [29, 30]. The cancer prevalence has been shown to have a dominant effect on the negative predictive value (NPV) of mpMRI (*vide infra*).

A degree of caution is needed when attempting to apply the results of published data, including meta-analyses to clinical practice. Most of the reported studies are retrospective in nature, wherein sub-optimal image datasets are often excluded from analyses. Furthermore, many studies use histologic verification in prostatectomy specimens and thus suffer from surgical selection bias, while other studies use the MRGB itself as its own reference standard. In addition, studies are often performed in expert centers with the advantages of state-of-the-art equipment, optimized protocols, and with highly experienced sub-specialized radiologists, thus reducing the generalizability of results.

Supportive data
Attempting to minimize multiple selection biases, the Prostate MRI Imaging Study (PROMIS) prospectively benchmarked the diagnostic accuracy of mpMRI before a first prostate biopsy in daily clinical practice [32]. PROMIS assessed the normal range of presenting patients, examined them in available MRI scanners, with mpMRI reporting by non-specialist but trained radiologists. PROMIS evaluated the accuracy of mpMRI for detecting clinically significant cancer in comparison to the current standard of TRUS biopsy. Men eligible for the PROMIS study included those with a clinical suspicion due to a raised PSA (up to ≤ 15 ng/mL), ethnicity or a previous family history of prostate cancer in a first-degree relative. 576 men from 11 hospitals in England had three tests, (1) a PI-RADS compliant mpMRI using 1.5T systems (without an endorectal coil), with image interpretation being undertaken by a variety of trained radiologists who did not explicitly use either of the PI-RADS systems (instead using Likert impressions), (2) standard TRUS biopsies, and (3) Template Prostate Mapping (TPM) biopsies. The blinding of the three tests to each other allowed the results of mpMRI to TRUS biopsy to be compared in a paired fashion, with a high level of confidence for assessing relative diagnostic accuracy.

On TPM-biopsy, 408 (71%) of 576 men had cancer with 230 (40%) patients having clinically significant cancers (using the primary definition of GS ≥ 4+3 and/or any cancer with a maximum cancer core length (CCL) of ≥ 6 mm). mpMRI was more sensitive (93%, 95% CI 88–96%) than TRUS-biopsy (48%, 42–55%) but less specific (41%, 36–46% for MP-MRI vs 96%, 94–98% for TRUS-biopsy). Since there are differing views on how to define csPCa on TPM-biopsy, the results of other pathologic

definitions were included in the study results including GS ≥ 3+4 and/or any cancer with a maximum CCL of ≥ 4 mm, and GS ≥ 7. Regardless of the definition used, mpMRI continued to have significantly better sensitivity and negative predictive value than TRUS biopsies, and worse specificity and positive predictive value, again indicating that biopsies were required for positive mpMRI to confirm the presence of clinically significant cancers.

For reference, using TMB for verification, increases in the predictive value for each increment in Likert score for csPCa (primary definition) was found in 3%, 12%, 21%, 58% and 81% for Likert 1–5 scores in the PROMIS study. However, it remains indeterminate whether explicit PI-RADS v2 image based reporting would have similar performance in the same cohort of patients. Never-the-less, these figures are the most robust mpMRI performance data in the literature; which should serve as a benchmark of what can be achievable in clinical practice, using the combination of mpMRI features and clinical information on modern 1.5T systems.

Conclusions

There is no longer a question as to whether mpMRI can detect and localize most csPCa. An abundance of research and clinical practice data has confirmed its clinical utility. In comparison to the standard of care TRUS biopsy, in most studies, MRGB finds more clinically significant prostate cancers and fewer low-risk ones. Widespread implementation of PI-RADS v2 has facilitated the standardization of mpMRI acquisitions, interpretations and reporting, and mpMRI utilization for the diagnosis and management of prostate cancer continues to accelerate. Multiple analyses have shown the potential for mpMRI and mpMRI-direct biopsy to promote the effectiveness of prostate cancer diagnosis pathway [33–37]. As a result, mpMRI has been incorporated into multiple clinical care guidelines in the clinical setting of prior negative biopsy [38, 39]. Many advantages have also been promoted for patient diagnosis prior to first biopsy, including a greater precision in determining tumor grade and volume, thereby positively contributing to patient risk stratification and patient management plans [9, 32, 36, 37]. However, the latter indication has yet to appear in international care guidelines.

However, mpMRI and MRGB also miss some csPCa, and PI-RADS v2 has some important limitations for interpretation. Thus, while mpMRI is a major advance and will likely play a central role in the emerging paradigm of high-precision prostate cancer diagnosis, there is additional work that needs to be done before we know exactly where and how PI-RADS will impact on prostate cancer pathways. Based on ongoing research and accrued clinical experience, revisions of PI-RADS v2 are envisaged; none of which are anticipated to change the overall assessment scheme nor its test-performance. It is hoped

that PI-RADS v2.1 will improve the mpMRI reading performance and decrease inter-reader variability. Looking to the not-too-distant future, efforts are already underway to expand and adapt PI-RADS to meet a variety of needs in the evolving paradigms of prostate cancer care. The latter will be PI-RADS v3, and it is anticipated that this will be a multi-year endeavor requiring additional research data on PI-RADS clinical usage to emerge.

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MR-targeted biopsies: The role and application of prostate mpMRI as part of the urological assessment

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MR imaging has become the center-piece of prostate cancer assessment. We have established negative predictive values of around 90% for normal MRI predicting absence of significant disease in biopsies, and positive predictive values (PPV) of 60–90% for MRI lesions converting into biopsy-proven significant cancer diagnosis. The MRI has become the gold standard to compare any test against.

In assessing naïve patients or in active surveillance it is used in combination with other patient individual criteria for triaging patients to various types of further assessment: Avoiding biopsies, minimizing the number of biopsy cores taken to diagnose significant disease, minimizing the number of repeat biopsies to finally diagnose disease, and optimizing the accuracy of tissue diagnosis guiding the choice of treatment and therefore treatment outcomes.

There are now several publications which leave no doubt that the above vision for optimizing the diagnostic pathway is the right approach [1, 2]. The PROMIS study was the first study with blinded data on the diagnostic accuracy of both multiparametric (mp) MRI and TRUS biopsy against an accurate reference test in biopsy-naïve men. It is the largest multi-center trial to date of the population at risk, in which the conduct and reporting of each test was standardized and done blind to other test results (level 1b evidence for diagnostic accuracy).

Main findings suggest that TRUS-biopsy performs poorly as a diagnostic test for clinically significant prostate cancer.

If mpMRI was used as a triage test, 30% of men might safely avoid a biopsy. mpMRI has high sensitivity and negative predictive value (NPV): a negative MRI implies a high probability of no clinically significant cancer, detection of clinically significant cancer improves, and over-diagnosis of insignificant cancers reduces. mpMRI has low specificity and PPV: a biopsy is still needed in men with suspicious MRI findings, focusing on the suspicious area. Outcomes of each respective item above not only benefit patients but also make sense health economically [3].

With a new diagnostic tool available, how do we as urologists use it in day-to-day life? We do have some guidance from our existing practice to allow us to gain comfort with the values prostate mpMRI provides:

There is sufficient high-level evidence and guidelines about screening for prostate cancer [4, 5]. The normal ranges for PSA still bear a remaining risk of finding prostate cancer or significant prostate cancer of up to 30% and 10% respectively [6]. Health systems across the world have agreed that this is an acceptable remaining risk.

We know that after a normal TRUS biopsy the chance of finding prostate cancer in a subsequent second one is at least 10% [7, 8] and that the long-term risk of dying from prostate cancer after a normal prostate biopsy is between 0.03 and 2% [9, 10]. On that basis for years we have discharged patients after a normal prostate biopsy.

We can therefore conclude that a remaining risk of 10% after a normal mpMRI is certainly acceptable in all modern societies and health systems.

The MRI can be applied as part of multiple processes. The approach for biopsy can be transrectal or transperineal, the MRI can be a visual or cognitive aide or fused onto the live ultrasound image, fusion can be rigid or elastic, and biopsy core distribution may aim for the target only or also include systematic biopsies.

Comparing transrectal and transperineal approaches, the urological service provision in office or secondary care matters as transperineal approaches in the majority of techniques still need a general anesthesia. Local anesthetic techniques are described but not broadly established. Rising antibiotic resistance has increased the infection and sepsis rate of transrectal biopsies in particular in first world countries and large cities with populations with ethnically diverse background. Transperineal biopsy has a sepsis rate of no more than 1 in 500. Without MRI support transperineal biopsies have a detection rate in biopsy-naïve patients of around 55% vs. reported 40–45% in TRUS [11, 12]. With MRI support this rises for positive MRI to 71% and about 60–65% respectively [1, 2, 13].

Targeting an existing MRI lesion clearly increases the detection rates of both transrectal and transperineal biopsy techniques. Transperineal biopsy techniques historically prescribe larger numbers of cores and allow access to the anterior prostate which may explain a higher detection rate. If we should biopsy the target only may depend on the clinical scenario. In second/repeat biopsies the current publications clearly suggest that target or systematic biopsies alone do not yield the significant cancer of both combined [14]. Although the current evidence suggests the same for patients undergoing their first biopsy, work is in progress using models which target the lesion and an area around. In repeat active surveillance biopsies target biopsies alone may very well suffice. The presentation of preliminary results suggests that such a model may achieve detection rates close to the combined approach but using less biopsy cores.

Another factor to consider is the reading performance of the local radiologist; one should always consider systematic biopsies early in the learning curve of the team. If focal therapy is a treatment option, systematic biopsies should also be performed to establish presence of multifocal disease.

There are several devices and techniques available which either allow to perform a biopsy directly in the MRI scanner or to fuse the MRI with the live transrectal ultrasound image and thereby support precise targeting. Tracking of the fusion may be by direct mechanical recording of the ultrasound probe or by use of an electromagnetic field. The latter allows more flexibility for the operator. Precision is likely to be equal. It is debatable if fusion technology is needed. Several publications have found equal results for visual/cognitive targeting and fusion supported biopsies [15, NICE guidance]. All evidence comes from high-tech research centres with specialist expertise in reading MRIs, technical biopsy skills and histology reporting. The fusion softwares allow standardization of biopsy techniques and in services with a high turnover of trainees it is preferable to use fusion to minimize variation of biopsy performance.

Conclusion

Multiparametric MRI of the prostate is established as the superior diagnostic tool in assessment of prostate cancer. Immediate patient and health economic benefits are proven and longer term benefits are obvious. A team-based approach between urologists, radiologists and pathologists is advisable to optimize the quality of the use of mpMRI. Different techniques and technology will be required for the most common clinical scenarios. Technology and software supported processes will minimize variation in particular in high volume centers or broad application in office urology.

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Cost-effectiveness of MR imaging-guided strategies for detection of prostate cancer in biopsy-naïve men

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The overdiagnosis and overtreatment of clinically indolent prostate cancer has been repeatedly criticized due to significant adverse effects on the quality of life for patients, and contribution to escalating health care costs [1, 2]. However, aggressive prostate cancer continues to cause significant morbidity and death. Hence, there is urgent need to develop better diagnostic pathways for detection of clinically significant cancer [3]. Magnetic resonance (MR) imaging and MR imaging-guided biopsy strategies are important technologies for the detection of clinically significant prostate cancer [4–7] but there is a reluctance to incorporate MR imaging into practice guidelines for prostate cancer detection because MR Imaging is perceived to be an expensive technology.

Escalating costs in the management of prostate cancer are related to inefficient diagnostic pathways that frequently place patients in incorrect treatment groups. Current estimates place prostate cancer care costs in the United States at over $10 billion annually [8]. Rather than looking at imaging costs in isolation, the cost effectiveness of using imaging in outcome based paradigms for detection of clinically significant prostate cancer needs to be evaluated. If we can maximize the accuracy of identifying clinically significant lesions, the costs of overtreatment can be reduced while improving quality of life for the patients.

To test the assumption whether MRI is truly too expensive for routine insertion into prostate cancer diagnostic pathways prior to biopsy, we created a decision analysis model to compare the cost-effectiveness of different diagnostic strategies without and with the use of multi-parametric MRI in the detection of clinically significant

prostate cancer [9]. The base case in the model was a biopsy-naïve man for whom prostate biopsy has been recommended on the basis of abnormal digital rectal examination results or elevated prostate-specific antigen levels. The model was further tested in three age groups which are most affected by morbidity and mortality due to prostate cancer based on life expectancy: 41–50 years, 51–60 years, and 61–70 years. Strategies with and without contrast administration for diagnostic MRI exam were evaluated, each further evaluated for a diagnostic pathway using:

a) cognitively guided biopsy;
b) MRI-ultrasound fusion biopsy;
c) in-gantry MRI guided biopsy.

These were compared with the standard clinical paradigm of a 12-quadrant transrectal ultrasound guided biopsy. An abbreviated model is depicted in Figure 1.

Model parameters as disease prevalence, sensitivity and specificity of each technique, were derived from literature. Costs of the techniques were derived from from the physician fee schedule at www.CMS.gov; costs of patients losing a day of work were derived from the Bureau of Labor Statistics.

The primary outcome measure was net health benefit, which was measured as quality-adjusted life years gained or lost by investing resources in a new strategy compared with a standard strategy at a willingness-to-pay threshold of $50,000 per quality adjusted life year gained. In other words, society is assumed to be willing to pay $50,000 for each quality adjusted life year, and strategies meeting this threshold are considered cost effective. One way sensitivity

analysis was performed on the parameters input into the model. Probabilistic sensitivity analysis was performed by using Monte Carlo simulations, and the proportion of samples for each strategy that were cost-effective was then calculated.

We found that diagnostic MR imaging examinations followed by targeted MR-guided biopsy methods are cost-effective compared with the standard transrectal US-guided biopsy strategy for detection of clinically significant prostate cancer, in over 94% of the simulations. All strategies that employ diagnostic MR imaging followed by MR-guided biopsy of only suspicious lesions yielded additional net health benefits for all age groups, higher than the standard biopsy strategy. The analysis also revealed that, non-contrast diagnostic MR examinations

followed by cognitively guided biopsy and foregoing standard biopsy in the case of a negative MR examination was the most cost-effective strategy. Maximal net health benefits were provided through in-Gantry biopsy, and the additional QALY gained by this strategy over the cognitive biopsy strategy was also cost-effective.

MRI disproportionately misses low grade tumors, and microscopic tumors (also less likely to be aggressive), both of which are often detected on an ultrasound guided biopsy, while yielding better performance for higher risk disease. These characteristics may result in avoiding unnecessary associated complications and overtreatment that may occur after diagnosis. MR imaging-guided pathways have been shown to reduce the detection of low risk cancers by 89.4% and reduced the overall need
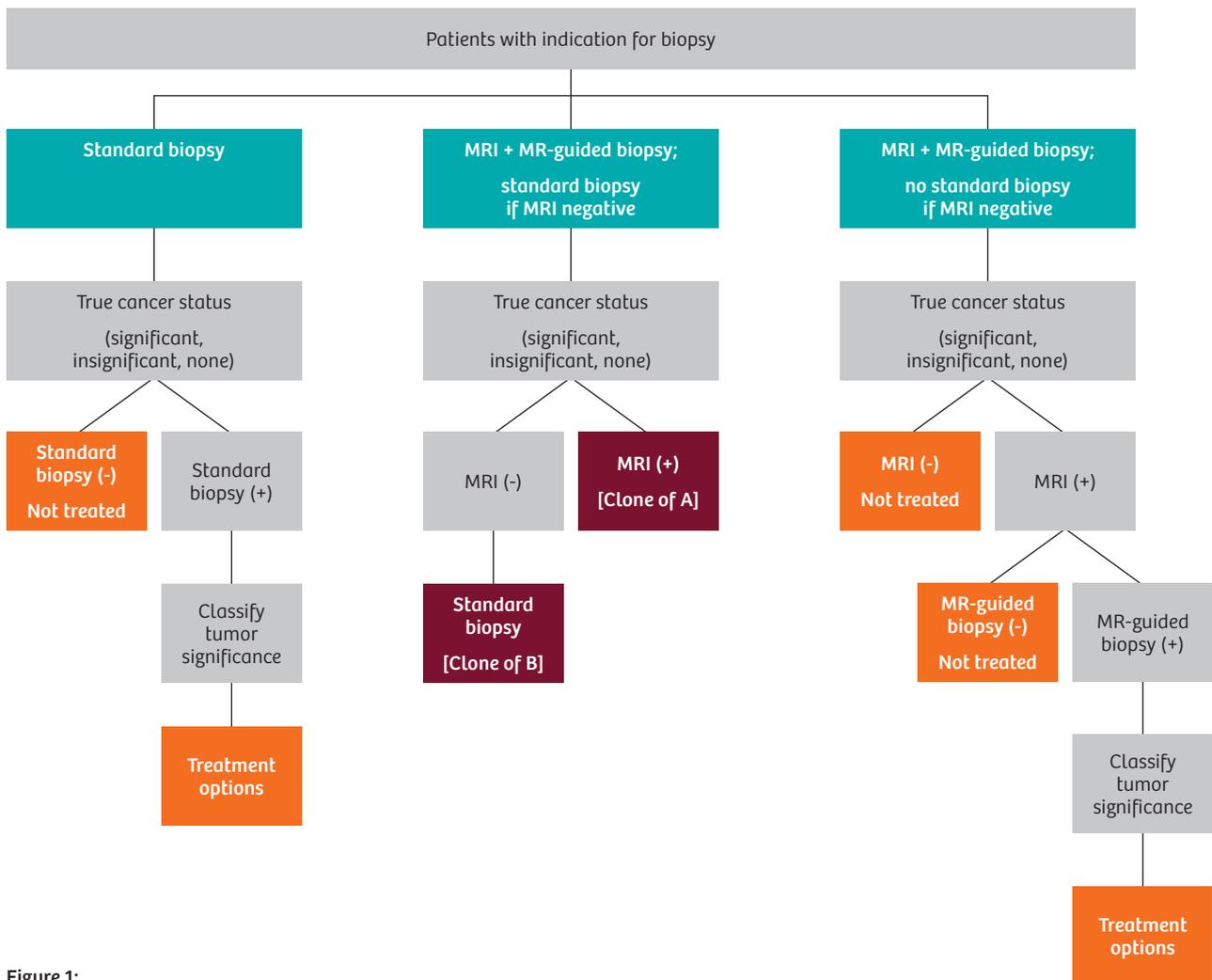

Figure 1:
Decision-tree model. The model compared MR imaging–guided strategies with standard transrectal US-guided biopsy for the detection of prostate cancer. Each box = a point along the decision model.
Figure reprinted with permission from Radiology 2017;285:157-166.

for biopsy by 51% [8]. A meta-analysis [10] revealed that the sensitivity of transrectal US biopsy in the detection of clinically insignificant cancers was approximately 83%, whereas that for MR imaging-guided methods was approximately 44% [10]. Furthermore, for intermediate/high-risk cancers, the negative predictive value of a negative MR imaging examination was 96.9% whereas that of a standard biopsy was 71.9% [8]. These are some factors that likely accounted for the improved cost-effectiveness of MRI-guided strategies seen in the present study.

Thus we found in this study that contrary to the common assumptions (indeed contrary to our own assumptions prior to initiating the study), MRI guided strategies are cost effective for detection of clinically significant prostate cancer. This work may provide cost-effectiveness based impetus for exploring the incorporation of MRI guided strategies for the diagnosis of prostate cancer.

Please Note: The above is summarized from work presented in greater detail in our previous publication [9].

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An approach to the management of localized prostate cancer and low risk disease

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A dramatic shift in clinical practice has occurred over the last decade, from the radical treatment of virtually all newly diagnosed prostate cancer patients, to a much more selective approach, incorporating expectant management, or active surveillance, for the roughly 40% of patients with low risk disease. By now, the safety of this approach has been demonstrated in several large long-term prospective cohorts published over the last few years. Indeed, the USPSTF (U.S. Preventive Services Task Force) has recently revised its position on PSA testing from 'D', unequivocally opposed to PSA screening in all circumstances, to a 'C', or neutral recommendation, largely on evidence that conservative management has become widely adopted in the US for low risk prostate cancer, thereby diminishing the overtreatment of this disease substantially.

The advent of MRI used widely to assess extent of disease in men with localized prostate cancer has also been a game changer. Further, the incorporation of molecular biomarkers has enhanced the accuracy of risk prediction.

'Grey zone' patients

While the option of surveillance represents a huge step forward for patients with low risk disease, the dichotomy between surveillance and radical treatment is still too wide for many patients. Similarly, with over 50% of active surveillance patients progressing to treatment within five years, the jump to conventional whole-gland therapies is often not warranted [1]. The unmet need currently is the patient in the 'grey zone' between these two poles. Such patients include the following:

1. Men with Gleason 3+4=7 with less than 10% pattern 4. Many of these patients are artifactually upgraded by tangential cut of a Gleason 3 acinus by the biopsy needle. Of those who are accurately graded, many have indolent disease and don't require treatment, despite the presence of small amounts of Gleason pattern 4 cancer.

2. Men who are diagnosed with Gleason 7 cancer based on a targeted biopsy of a small, focal, solitary lesion seen on MRI, in whom the remainder of the biopsies are negative or show only microfocal Gleason 6. Many of these patients may be cured by treatment of the index lesion only. In particular, in patients such as these with a favorable genetic score (Prolaris, Oncotype, etc.) radical treatment may be excessive.

3. Young men with extensive Gleason 6 cancer. (This is fortunately not common). While these patients can be reassured that their Gleason 6 cancer will not metastasize in the foreseeable future, surveillance data beyond 15–20 years does not yet exist, and therefore there is some uncertainty about the outcome in those with a long life expectancy > 20 years.

4. Men with Gleason 6 cancer with a high Oncotype Dx, Prolaris, Confirm MDx, or other genetic test of their pathology, suggesting they may have more aggressive disease than otherwise anticipated. (These patients are also uncommon). Such patients are understandably anxious about the safety of active surveillance.

Treatment decisions

These patients are in the grey zone, where provider preference may exert an undue influence on treatment decisions.

What is the basis for accurate and rational treatment decisions in these patients? There are a number of clear guideposts. Most men with Gleason 6 cancer do not require any treatment. These patients should be managed with surveillance, and re-biopsied and or re-imaged every 3–5 years after the initial confirmatory biopsy. At the other end of the disease spectrum, men with high grade cancer (Gleason 8 or higher), or multifocal or extensive Gleason 7 cancer, should be treated radically, either with surgery or radiation.

The remainder, about 30% of the population, fall into this equivocal 'grey zone'. Many have indolent disease, but some have aggressive cancer. For these patients, many treatment options involving important tradeoffs of quality and quantity of life exist.

1. For patients with Gleason 3+4 where the percent Gleason 4 is low, and MRI shows no evidence of a large high grade cancer, active surveillance or function sparing minimally invasive procedures are reasonable options. Genetic biomarker analysis can provide further confidence in the indolent nature of the disease. Older men (> age 75, i.e. 10 year median life expectancy or less) and those with significant co-morbidity should also be offered conservative management or function sparing minimally invasive procedures.

2. For patients with a solitary lesion on MRI that is confirmed as Gleason 7 cancer, without any other evidence of significant cancer on systematic biopsy, the option of focal therapy is compelling. The quality of life benefits of focal therapy are incontrovertible. The trifecta of preservation of erectile function, continence, and disease control are reported as high as 85%.

3. Young men with extensive Gleason 6 cancer could also benefit from function sparing minimally invasive procedures.

4. In addition to those men with high volume Gleason 6 cancer, those who have Gleason 6 with a high Oncotype Dx, Prolaris, Confirm MDx, or other genetic test of their pathology might also benefit from a function sparing minimally invasive approach.

These recommendations emphasize how dramatically the management of localized prostate cancer has evolved over the last decade. Ten years ago, active surveillance was criticized as failing some curable patients whose occult high grade cancers were undiagnosed, untreated, and led to preventable cancer deaths. The estimate from prospective series is that this represented between 2 and 4% of active surveillance candidates. While this percentage was small, each preventable cancer death represents a personal tragedy for the individual and his family. Today, the advent of multiparametric MRI in the assessment of these men means that most low risk surveillance candidates who harbor higher grade occult cancer are identified early and treated appropriately. This will likely reduce the already low rate of preventable deaths to less than 1%. Many of these upgraded patients will have solitary intermediate grade lesions and be candidates for focal therapy. Further, in the 1% who may suffer a preventable cancer death despite all efforts, death from prostate cancer usually comes 15–20 years after diagnosis of early localized disease. Thus the number of life years lost is expected to be small.

Thus, in the modern era, many strategies exist to personalize treatment based on contemporary imaging with multiparametric MRI, and selective use of genetic biomarkers to predict disease biology. Individual patient preferences and trade-offs abound. Clearly, however, most patients will fall into one of the 3 groups described above; those who are candidates for active surveillance, those who warrant radical treatment, and those who are candidates for a function sparing minimally invasive procedures, delivered near whole gland or focally in order to preserve quality of life.

Targeted tissue-sparing or focal therapy can be delivered in many ways, which differ in ease of administration, cost, precision, and side effects. An incomplete list includes high-intensity focal ultrasound (HIFU), transurethral MR-guided ultrasound ablation (TULSA), cryosurgical ablation, electroporation, and brachytherapy. All of these technologies offer the ability to treat a defined portion of the prostate with reasonable effectiveness and low morbidity. Some are likely more effective for certain locations than others; for example, anterior cancers may be better treated with a percutaneous or transurethral approach, and posterior cancers with a transrectal approach. However, differences in oncologic success and functional outcome will require comparative trials or long term registries before definitive statements can be made about relative effectiveness.

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Focal therapy:
Clinical value and patient selection

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We have not yet managed to fully agree on the term that describes an approach to care that aims to preserve tissue, but it looks as though the term 'focal therapy' has stuck. The term is useful in that it serves to distinguish this intervention from traditional whole gland therapies as well as the process of active surveillance – a method of care that is designed to tell us when to intervene, not how to intervene.

Having said this, active surveillance and focal therapy do share common ground. They both require a pre-set threshold of risk that if exceeded results in a treatment recommendation. Conversely, if the risk remains sub-threshold, treatment is averted. In active surveillance this process of care is applied at the patient level and re-applied at set intervals. In contrast, focal therapy applies this process of care to the prostate itself. Volumes of the prostate that contain malignant tissue exceeding the risk threshold are treated, together with a margin [1]. Anything below the threshold is preserved, but as in active surveillance, will be subject to monitoring.

The principal debate in focal therapy arises on the level of this threshold; at the time of writing, no consensus has been agreed [2]. In general, volume and tumor grade have provided the main inputs. Volume thresholds of 0.2 and 0.5 ml have been proposed and/or the presence of Gleason pattern 4 in both its primary and secondary forms.

Having agreed that there is no absolute consensus on where this threshold should lie, it is possible to agree on the attributes that describe the 'ideal' patient. Most experts would agree that the following should be fulfilled.

Patient characteristics

- The prostate should harbor a discrete lesion on MRI that should have definable margins

- The MRI-derived lesion needs to be associated with clinically significant prostate cancer

- The lesion can be treated and a margin applied to it

- The remaining parts of the prostate need to return normal signal on MRI and/or prove negative for clinically significant disease on biopsy

- The individual should place high utility on preserving genito-urinary function

In addition to the above conditions, clear communication to the patient which not only covers all the usual aspects of consent, but also explicitly the areas where evidence is lacking (long term oncological outcomes) and what salvage options would be possible should the treatment fail. Finally, men treated in a tissue preserving manner need to be aware that they will need life-long surveillance and ideally should commit to formal review (registry) or the participation in a clinical trial.

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Focal therapy of prostate cancer: Modalities

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The concept of focal therapy (partial organ ablation) is well-established in many neoplasms, perhaps best exemplified in breast cancer. Breast cancer focal therapy was first reported ~80 years ago, with randomized trials confirming treatment efficacy in the 1980's. Consequently, 80% of women with breast cancer currently undergo lumpectomy (up from 10% prior to the randomized trials). In prostate cancer, focal therapy is still relatively nascent with mostly early feasibility studies and small case series populating the literature. The initial report of prostate cancer focal therapy was approximately 20 years ago [1], and the first randomized clinical trial was published earlier this year [2]. There are many different modalities that have been evaluated, including cryotherapy, high-intensity focused ultrasound (HIFU), transurethral ultrasound ablation (TULSA), brachytherapy, laser interstitial thermal therapy, irreversible electroporation, and photodynamic therapy [3].

Ideal characteristics of focal therapy modality

The ideal modality for prostate cancer focal therapy would have the following attributes:

- Provides consistent and complete destruction of the intended focus of prostate cancer, with histological evidence of cytocidal effect.

- Capable of ablating various-sized lesions, at various locations in the prostate, with treatment plans ranging from near whole-gland to targeted or focal.

- Technically reliable, ensuring the intended treatment is delivered consistently.

- Easy to learn.

- Provides image-guided ablation feedback during treatment, to monitor the extent of ablation and confirm adequate dosing of the target tissue.

- Cost-effective, quick to administer and with short treatment times.

- Reproducible and scalable, with consistent results across cases and centers.

- Repeatable while still allowing for conventional salvage treatments (if needed).

Currently, there are a number of modalities utilized for focal therapy, each meeting these criteria to varying degrees. The aforementioned modalities are in various stages of development and attainment of clinical data, ranging from proof-of-principle to Phase III data.

Potential benefits of MR-guided treatments

Multiparametric MR imaging is currently the best imaging modality for the diagnosis and characterization of localized prostate cancer and its accuracy for the detection of index tumors is estimated to be around 90% [4]. Targeted or focal therapy aims to eradicate the prostate cancer while minimizing the damage to the surrounding organs and nerves and hence minimize potential complications. MR images can be used to guide focal therapy, both for pre-treatment planning and real-time imaging during treatment. MR imaging is the ideal modality for guidance during focal therapy enabling excellent visualization of the targeted cancer(s) and surrounding anatomy. Real-time temperature information from the target tissue can be obtained during ablation with MR thermometry, ensuring therapeutic temperatures are reached in the target zone. Real-time temperature monitoring can also be utilized to decrease the risk of overtreatment and unnecessary damage to the surrounding organs [5–9]. Another important advantage of performing the ablation under MR guidance is the ability to obtain immediate post-procedure, contrast-enhanced MR images, providing accurate information regarding the ablation zone and technical success of the procedure. In summary, MR guidance during targeted ablation of prostate cancer is feasible and intends to improve the accuracy and effectiveness of the therapy while sparing important surrounding structures and hopefully optimizing sexual, urinary and bowel-related outcomes.

Case presentation

A 62-year-old male presenting with elevated serum PSA of 8.95 ng/mL underwent TRUS guided random and MR-targeted biopsy (total of 14 cores), showing three positive cores with Gleason 6 in the left base peripheral zone. Patient's biopsy-proven cancer can be visualized on multiparametric MRI (Fig. 1). Following informed consent, the patient underwent tailored whole gland ablation using
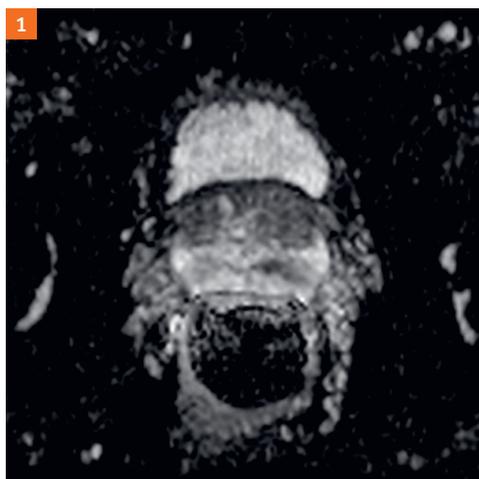
Figure 1:
Axial ADC map through the prostate base shows the dark signal in the left peripheral zone consistent with patient's known prostate cancer.

Figure 2:
High-resolution T2-weighted image demonstrating the prostate with ultrasound applicator in the urethra.
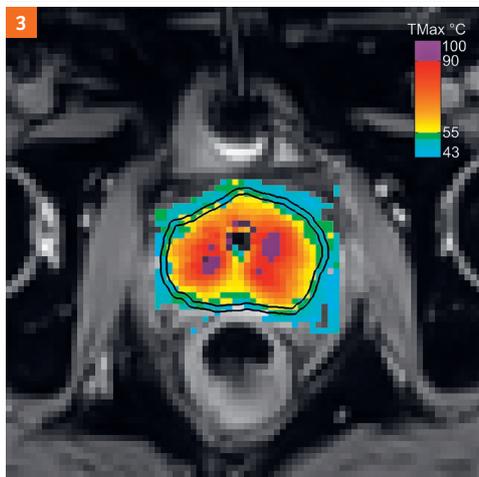
Figure 3:
Real time MR thermometry images obtained during ablation show increased temperature in the left base of the prostate during ablation.

Figure 4:
Immediate post-ablation, contrast enhanced MR image shows the non-enhancing prostate.

Figure 5:
TULSA-PRO® system: The ultrasound applicator and robotic positioning system are inside the scanning room on the MRI bed.

the MRI-guided TULSA-PRO device (Profound Medical Inc., Toronto, Canada; CE marked in Europe and investigational in the US), as part of the TACT pivotal study. The procedure was performed under general anesthesia followed by insertion of a suprapubic catheter and transurethrally inserted nitinol guidewire. A rigid ultrasound applicator incorporating a linear array of ten independent ultrasound transducers that emit directional high-intensity ultrasound energy directly into the adjacent prostate was inserted into the urethra over this guidewire. A treatment delivery console with customized software was used to outline the target prostate boundary during planning, monitor the thermal therapy delivery in real time during treatment, and implement the proprietary temperature feedback control algorithm.

Under MRI guidance, the ultrasound applicator was positioned precisely within the prostatic urethra with a 3-mm safety margin between the ultrasound transducers

and sphincter plane at the prostate apex. High-resolution prostate MR images were then acquired for treatment planning (Fig. 2). The attending urologist and radiologist traced the outer prostate boundary in consensus. The target prostate volume was heated to ≥ 55°C representative of complete acute thermal coagulation. Real-time MRI thermometry images were acquired every six seconds, providing continuous assessment of a three-dimensional temperature volume during treatment (Fig. 3). After treatment, contrast-enhanced MRI was acquired to assess the non-perfused volume (Fig. 4). The patient was discharged on the same day without any perioperative complications. The suprapubic catheter was left in place for two weeks. There was no short-term urinary or sexual morbidity. The patient will continue to be followed regularly for five years within the TULSA-PRO pivotal TACT clinical trial, and subsequently after the trial period is completed.

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Profound Medical and Siemens have entered into a strategic agreement to further the development of prostate cancer care. The development of this white paper was supported by Siemens Healthcare GmbH and Profound Medical.