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Mri-Ultrasound Fusion Targeted Biopsy In Men With Prior Negative Prostate Biopsy For Prostate Cancer

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MRI-Ultrasound Fusion Targeted Biopsy in Men with Prior Negative Prostate Biopsy for Prostate Cancer

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by

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Abstract

A particularly challenging subpopulation of prostate cancer patients are those who present with a persistently elevated PSA and suspicion of prostate cancer despite having had one or more prior negative prostate biopsies. These patients may benefit from the improvements made in prostate imaging through multiparametric MRI (mpMRI) and MRI-guided prostate biopsy techniques. In this study, we evaluate mpMRI and MRI-US fusion biopsy as a means of detecting clinically significant cancer as well as a potential indicator for avoiding repeat biopsies. We performed a retrospective study of 374 men seen between 12/2012 and 06/2015. All patients underwent pre-biopsy mpMRI to identify regions of interest (ROIs) within the prostate and each was assigned an MRI suspicion score. All patients then underwent a 12-core standard trans-rectal mapping biopsy, and all patients with ROIs identified on mpMRI underwent MRI-US fusion targeted biopsy. We defined cancer as any Gleason score ≥ 6, and we defined clinically significant cancer as Gleason score ≥ 3+4. Statistical analysis was performed using chi squared, Fisher's exact, student's t-test, one-way ANOVA, and multivariate logistic regression. All test results were considered statistically significant if $p < 0.05$. 143 patients were included in our analysis. Overall cancer detection rate was 42.66%, and the clinically significant cancer detection rate was 27.27%. For standard 12-core mapping biopsy, the cancer detection rate was 34.97%, and the clinically significant cancer detection rate was 18.18%. For men who underwent targeted biopsies, the cancer detection rate of the targeted biopsies was 40.5%, and the clinically significant cancer detection rate was 27.27%. In total, 21.50% of patients were upgraded by inclusion of targeted biopsy. For the 72 patients with no cancer on targeted biopsy, only 2 were found to have clinically significant cancer on mapping biopsy. A total of 213 ROIs were identified following mpMRI. Cancer was found in 32.86% of the ROIs and clinically significant cancer was found in 22.54%. For the 22 patients with no target identified on MRI, none were found to have clinically significant cancer. Age, PSA, MRI suspicion score, and PSA density were correlated with clinically significant. Anterior location of ROI was significantly correlated with presence of cancer and higher grade cancer, particularly on targeted biopsy. For clinically significant cancer detected on targeted biopsy, multivariate logistic regression revealed that the only significant independent predictor of disease was the presence of an anteriorly located ROI on mpMRI (OR 4.50, $p < 0.01$). In men with one or more previous negative biopsies and continued suspicion for prostate cancer, mpMRI and MRI-US fusion targeted biopsy provide greater detection rate of clinically significant disease compared to standard 12-core TRUS biopsy. Men with negative MRI findings may be able to avoid or delay biopsy. Patients with high MRI suspicion score lesions and those with anterior lesions are at increased risk for significant disease and should be treated with the necessary diligence.

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Introduction

Prostate Cancer

Prostate cancer is the most commonly diagnosed cancer in males in the United States, with an estimated 181,000 new cases and 26,000 deaths in 2016. Currently, the estimated lifetime risk of developing prostate cancer is approximately one in seven [1]. Annual rates of prostate cancer detection have varied over the years. With the advent of PSA testing in the late 1980s, the prostate cancer incidence rose dramatically, peaking in the early 1990s [2]. Rates of detection have since declined as the focus has shifted away from widespread PSA screening in order to minimize over-detection of clinically insignificant tumors [3]. Meanwhile, rates of death from prostate cancer have declined steadily. Currently, lifetime risk of death from prostate cancer is less than 3%, and the 5-year survival rate for a new diagnosis of prostate cancer is greater than 99%. Furthermore, the majority of prostate cancer deaths occur after the age of 75 [1,3].

Though prostate cancer incidence has fluctuated over the past few decades as screening guidelines and practices have changed, the true prevalence of the disease remains difficult to measure. Prostate cancer is rarely diagnosed as a result of clinical symptoms, with physicians relying on screening exams and subsequent biopsies to drive the detection of the disease. This is illustrated well in studies that compared histological examination of autopsy specimens from men who died with no clinical evidence of prostate disease, where the prevalence of malignancy is much higher than the corresponding age-adjusted incidence [4]. A recent systematic review of autopsy studies spanning the

1940s to the 2010s demonstrated varying prevalence of prostate cancer. Across different age groups, cancer prevalence on autopsy ranged from 0% for patients younger than 30 years old to more than 70% for patients greater than 70 years old [5].

Risk Factors

Several risk factors have been identified that are associated with being diagnosed with prostate cancer. The three primary risk factors associated with the disease are age, race or ethnicity, and family history of the disease [6]. Age has the strongest association with the development of prostate cancer and has been identified as a possible predictive factor, with an odds ratio of 1.71 per decade identified by investigators in the systematic review of autopsy studies [5]. Race has been identified as a significant prostate cancer risk factor, with Black or African-American men at a 1.6 times higher risk of diagnosis and a 2.5 times higher risk of death than Caucasian men. African-American and Jamaican men have been shown to have the highest rates of prostate cancer, while Asian men have a lower rate than that of Caucasians. Interestingly, minority groups such as Asians, Hispanics, and Native Americans have lower rates of disease than White Americans, but are thought to be at higher risk as they are more assimilated into American society. Investigations into possible environmental drivers of racial disparity such as diet and obesity rates have not yielded convincing results, though literacy and education have been correlated with increased stage at presentation and greater risk of prostate cancer death, respectively [6].

Finally, prostate cancer has been known to demonstrate clustering within families, with 10-15% of patients having at least one other family member afflicted by the disease. Studies have demonstrated at least a two-fold increase in risk in patients with one affected first degree relative such as a father or brother [7]. A Swedish study from 2010 analyzed over 3.9 million men and included over 25,000 cases of prostate cancer. Hazard ratios were reported for men with increasing number of family members affected by the disease. The hazard ratios were lowest at 1.8 for men with a father diagnosed later in his life and highest at 23 for men with three affected brothers diagnosed at a younger age. Generally, hazard ratios increased with decreasing age at diagnosis of the affected family members [8]. Another large Scandinavian study examined cohorts of twin pairs, concluding that prostate cancer demonstrated higher concordance for cancer in identical twins than breast or colorectal cancer and suggesting that up to 42% of prostate cancer risk can be attributed to heritable factors [9]. Genomic studies have revealed the complex nature of prostate cancer genetics, with many SNPs identified as independently associated with the disease [10]. Other studies have emphasized the importance of BRCA1 and BRCA2 mutations on prostate cancer diagnosis and mortality, as well as increased risk related to HOXB13 germline mutations [11,12].

Screening for Prostate Cancer

While prostate cancer survival rates are excellent overall, there is a significant discrepancy between five-year survival rates for patients diagnosed with locally

or regionally contained disease and disease with distant metastases at the time of diagnosis. With the presence of distant metastases at the time of diagnosis, the five-year survival rate falls from 100% to a mere 28.2% [13]. It is clear that prostate cancer is a disease with a broad range of lethality, considering the disparity in mortality between locally contained and disseminated disease, as well as the prevalence of incidental disease found on autopsy. In response, physicians have attempted to optimize population screening guidelines in order to prevent life-threatening cases while avoiding overdiagnosis of nonlethal disease.

The oldest screening test for prostate cancer is the digital rectal examination, or DRE. It has been performed to detect nodules, asymmetry, or induration that may suggest the presence of tumors in the posterior and lateral aspects of the gland. Unfortunately, not all tumors arise in these locations [14]. Furthermore, the effectiveness of the DRE as an exam has been called into question given the subjective nature of the test and the fair, but not great level of interrater agreement [15]. A metaanalysis of DRE performance suggested a sensitivity of 59%, specificity of 94%, and a positive predictive value of only 28% [16].

Screening for prostate cancer with PSA testing began in the late 1980s, and in 1992 the American Cancer Society recommended annual screening with DRE and PSA for men over the age of 50 [17]. PSA is a glycoprotein produced specifically by prostate epithelial cells and has a half life of 2.2 days. Early analysis of PSA found a correlation between PSA levels and increasing clinical

stage, as well as cancer volume. Investigators noted, however the wide range of PSA levels in patients with locally confined disease and the elevation of PSA associated with benign prostatic hypertrophy. PSA was identified as an excellent tool for surveillance and detection of recurrent disease following surgical intervention or radiation therapy [18]. Other studies have concluded that PSA elevations can precede detection of prostate cancer by five to ten years [19]. However, reliability of PSA screening has been a topic of significant debate. PSA can be affected by a range of benign conditions, including ejaculation, acute urinary retention, inflammation or prostatitis, digital rectal exam, transrectal ultransonography, or prostate biopsy [20–22]. Medications, especially five-alpha reductase inhibitors such as finasteride and dutasteride, may reduce PSA levels by as much as 50% [23,24].

Evaluating the effectiveness of PSA has been challenging for a number of reasons. First, most men with normal PSA values do not undergo confirmatory biopsy, leading to a verification bias that overestimates sensitivity and underestimates specificity [25]. Furthermore, PSA is usually compared to results of prostate biopsy, which in itself is an imperfect and evolving test [26]. Nevertheless, the American Cancer Society performed a systematic review in 2009 to evaluate PSA screening. The investigators estimated that PSA screening with a cutoff of 4.0 ng/mL led to a sensitivity of 21 percent for detecting any cancer and 51 percent for detecting high grade disease, as well as a specificity of 91% [27]. The positive predictive value of PSA screening has been best studied, with a multicenter clinical trial of over 6,000 men finding a positive predictive value of

32% for PSA over 4.0 ng/mL, but only 25% for men with PSA between 4.0 and 10.0 ng/mL [28]. Another large trial, the Prostate Cancer Prevention Trial, estimated negative predictive value of PSA under 4.0 ng/mL to be 85% after studying biopsies of men with normal PSA values [29].

Multiple strategies have been proposed to attempt to increase the accuracy of PSA testing to improve detection of high risk disease. These include age- and race-specific cutoff values, measuring PSA values over time (PSA velocity) or with respect to prostate size (PSA density), and relative levels of free versus complexed PSA [30]. Unfortunately, none of these methods has significantly improved the diagnostic accuracy of PSA [31–33]. In 2012, after performing a review of the evidence regarding the efficacy of PSA screening, the USPSTF published new prostate cancer screening guidelines, giving PSA screening a D rating and recommending against its use [34,35]. This recommendation was met with controversy, as some groups felt as though the USPSTF underestimated the benefits of screening while overstating the harms [36]. The American Urological Association subsequently published a new recommendation encouraging providers to engage in shared decision making with patients and to explain the risks and benefits of PSA screening, especially to those at higher risk, such as African American men, and men with a life expectancy greater than 10 years [37].

Diagnosis of Prostate Cancer

Despite the controversy over screening and early detection of prostate cancer, many men continue to be referred to a urologist for evaluation following an

elevated PSA or abnormal DRE. Diagnosis of prostate cancer is performed through clinical examination combined with histological assessment of tissue obtained via prostate biopsy. Prostate biopsy is primarily performed via one of two anatomical approaches. The first and most common approach is the transrectal ultrasonography (TRUS)-guided prostate biopsy, a technique that was developed in the late 1980 and was formalized with the introduction of the TRUS-guided systematic sextant biopsy protocol by Hodge in 1989 [14]. This procedure is commonly done in the office setting with local anesthesia, and involves a transrectal ultrasound probe through which spring-loaded needles may be inserted and guided into the different regions of the prostate [38]. These regions include the anterior fibromuscular stroma, transition zone (TZ), central zone (CZ), periurethral zone, and peripheral zone (PZ). TRUS-guided biopsy assists the operator in obtaining samples from various regions of the prostate and at times the seminal vesicles, which are located posteriorly at the base of the gland.

The number and distribution of sample cores taken has evolved over time. The original scheme included six cores – one from the base, mid, and apex of the gland on each side. This sextant protocol improved upon the previous standard, where samples were digitally directed [39]. Subsequent pathological studies of radical prostatectomy specimens demonstrated that the majority of disease arises in the posterolateral PZ, and modifications to the sextant scheme were introduced to focus on sampling the lateral areas of the gland [40]. The current method endorsed by the American Urological Association is the extended 12-core systematic biopsy that includes apical and far-lateral cores [41]. A

saturation biopsy with an increase in the number of cores to 18 or more on initial biopsy has not demonstrated the same benefit as the increase from six to 12, though studies have shown an decrease in clinically significant cancer detected on repeat biopsy after initial saturation biopsy [42].

The transperineal prostate biopsy has typically been used as an alternative approach for patients who are unable to undergo a transrectal procedure. A 2008 prospective randomized trial compared the transperineal and transrectal approache and found no significant difference in cancer detection rates and complications between the two approaches [43]. The authors concluded that the transrectal approach is preferred as it can be performed with local anesthesia, as opposed to the transperineal approach, which requires spinal or more generalized anesthesia. Recent reviews of the evidence, however, have argued for a larger role for transperineal biopsy, citing improved sampling of the anterior and apical sides of the prostate with lower false negative rate and reduced risk of underestimating disease grade [44]. The authors argue that transperineal biopsy, though more costly than transrectal biopsy, may be especially useful for patients with a previous negative transrectal biopsy.

With both types of biopsy method, there are risks and complications of the procedure. Prostate biopsy is generally well tolerated and considered a safe procedure, with less than 1% of patients suffering serious complications requiring hospitalization. The most common post-biopsy complications include infection, ranging from UTI and low-grade fever to sepsis, and bleeding. These risks are

mitigated through prophylactic antibiotic administration and periprocedural management of the minor complications that may arise [14].

Prostate Cancer Clinical Staging

The clinical staging of prostate cancer takes into account multiple pretreatment parameters to predict the extent of the disease. This allows for an assessment of prognosis and helps providers and patients to select the best option for initial management. The parameters that are considered for clinical staging are DRE, PSA and related blood tests, tissue histology on needle biopsy, and results of imaging [14]. The current system of clinical staging is based on the tumor, node, metastasis (TNM) classification system first adopted by the American Joint Committee on Cancer (AJCC) in 1975 and modified for prostate cancer in 1992 [45]. The latest version from the AJCC combines TNM stage with PSA value and histological grade to categorize patients into one of four prognostic groups [46].

Histologic grading of tissue obtained through prostate biopsy is performed using the Gleason grading system [47]. The system involves taking the sum of the predominant grade at low-power magnification and the grade of the second most common pattern in the sample to yield a score from 2 to 10. More recent research and discussion regarding Gleason scores has focused on the effect that tertiary Gleason patterns may have, especially when they are grade 5. Furthermore, Gleason 6 scores have been identified to be of low risk, and stratification between Gleason 3+4 and 4+3 tumors has been suggested [14]. Higher Gleason score is associated with worse prognosis, but other factors such

as PSA level, number of positive cores, percentage of positive cores, and presence of perineural invasion are taken into account when performing risk-stratification [48]. Risk nomograms that predict pre-operative extent of disease have been developed from institutional experience, and other validated classification schemes such as the Cancer of the Prostate Risk Assesment (CAPRA) score have been developed to help predict longer term outcomes following treatment [49,50].

Initial Management of Prostate Cancer

Following prostate cancer tissue diagnosis from biopsy, initial staging should be completed for patients with Gleason 7 or greater with a radionuclide bone scan and abdominal-pelvic CT or MRI scan in order to best direct initial management. Depending on the prognostic risk group that the patient falls into, there are many different options available for initial disease management. The most conservative of these are watchful waiting and active surveillance. Watchful waiting typically refers to the observation of a patient who will develop metastases and then require palliative care, while active surveillance, also known as expectant management, allows for the delay of primary treatment until there is biochemical or histological evidence of cancer progression. Active surveillance is typically reserved for patients with low-risk disease (Gleason score < 6, PSA < 10 and clinical stage < T2a), though it may have some benefit for patients with Gleason 7 (3 + 4) tumors [51]. It has typically been used for men with a life expectancy < 10 years, although rates of active surveillance are increasing and include younger

men [52]. Because delaying treatment may lead to cancer progression and loss of curative potential, these initial management decisions must be carefully considered [53]. Investigators have constructed statistical models to predict which tumors are likely to progress and which are likely to remain indolent. The Epstein criteria, established in 1994, identified factors such as tumor volume < 0.2 cm^3 and Gleason score < 7 that predict the presence of "clinically insignificant" disease, as evaluated on pathological staging [54]. These criteria were updated in 1998 to include a free/total PSA ratio (0.15 or greater) and other favorable needle biopsy findings (fewer than three cores involved and < 50% of any one core) to attain a positive predictive value of 95% and a negative predictive value of 77.2% for "insignificant" tumors [55].

While active surveillance may be the optimal choice for patients with low risk disease, patients with clinically significant tumors require interventional treatment. The primary categories of established treatments include radiation therapy and radical prostatectomy. Hormone therapy with androgen deprivation is most often used in conjunction with radiation therapy as a primary treatment option. Androgen deprivation therapy (ADT) is generally recommended for unfavorable intermediate-risk, localized high-risk, and locally advanced prostate cancer based on results of clinical trials involving patients with locally advanced prostate cancer [56]. ADT has also been employed in the salvage setting, and was previously used for primary therapy as a palliative care for men with shorter life expectancy who did not wish to seek more aggressive treatment [14]. However, a recent trial comparing 15,000 men who received ADT with no other treatment

showed no mortality benefit [57]. Meanwhile, the risks of associated with ADT have been well described and include increased risk of diabetes and cardiovascular disease [58]. ADT is still being evaluated in clinical trials as an adjunct to salvage radiotherapy.

Radiation therapy and radical prostatectomy are typically considered the two primary options to provide biochemical control over prostate cancer. There are two main categories of radiotherapy, external beam radiation therapy, and brachytherapy. External beam radiation therapy includes intensity-modulated radiation therapy (IMRT), stereotactic body radiation therapy, and heavy-particle radiotherapy. IMRT is a sophisticated form of 3D conformal radiotherapy that utilizes computers to focus the photon radiation dose to the prostate in an effort to deliver maximum effect while minimizing radiation of adjacent structures [59]. Stereotactic body radiation therapy, also known as Cyberknife, delivers higher doses of radiation over much smaller periods of time, a process known as hyperfractionation. The cost is less than that of IMRT and initial results show similar treatment efficacy, though longer term results are not yet available [60]. Heavy-particle radiotherapy utilizes proton or neutron beams and has the potential for even more focused radiation delivery, though at increased cost [14]. Early results suggest that heavy-particle radiotherapy is comparable to IMRT in clinical and quality of life measures [61,62]. Brachytherapy involves the implantation of radioactive seeds or needles into the prostate gland to deliver a high dose of radiation and has been shown to be effective in patients with low- and intermediate-risk localized disease [63]. While radiotherapy can deliver targeted

treatment, side effects including gastrointestinal and urinary morbidity and erectile dysfunction [61].

Radical prostatectomy was the first treatment developed for prostate cancer, with earliest reports dating back to Kuchler in 1866 and Young in 1905 at Johns Hopkins [14]. Despite its complexity and considerable risks of side effects, the procedure remains the gold standard in attempting a curative intervention. Radical prostatectomy may be performed through one of a few different approaches, including perineal, open retropubic, laparoscopic, and robotic. There has been debate regarding the optimal approach, especially in context of the rise in popularity of robotic prostatectomy since its introduction in 2000 with the da Vinci Surgical System. Studies comparing the robotic approach to the open retropubic approach have concluded that the two methods are comparable on functional and oncologic outcomes, while other studies have demonstrated more favorable rates of side effects for each [64–66]. The primary advantage of the radical prostatectomy over other forms of treatment is its potential for cure with minimal collateral damage when correctly and skillfully performed [67]. Additionally, more accurate tumor staging may be performed upon pathological examination of the surgical specimen, and treatment failure is more easily identified, allowing for timely initiation of salvage therapy [14]. Disadvantages of radical prostatectomy include the necessary hospitalization and postoperative recovery, possibility of incomplete resection, and risk of erectile dysfunction and urinary incontinence. The “trifecta” of priorities for radical prostatectomy include cancer control, preservation of continence, and preservation of potency [68]. Generally, younger,

healthier men with life expectancy of at least ten years are the best candidates for radical prostatectomy.

Importance of Representative Tissue Sampling

The choice of optimal therapy depends greatly upon the patient's risk group and life expectancy [14]. In turn, the risk group is heavily influenced by clinical stage. A continued concern with current prostate biopsy methods is the risk for non-representative tissue sampling. Patients who are categorized as low-risk following prostate biopsy that demonstrated Gleason 6 disease may enter an active surveillance protocol only to find that higher grade disease was present in their prostate but did not happen to be detected by one of the 12 cores. In a 2012 systematic review, investigators found that 42% of men who would have fallen into the D'Amico low-risk group were found to have an increase in Gleason score following rebiopsy or pathological analysis of radical prostatectomy specimen. When using Epstein criteria, an increase in risk group was found in 34% of patients [69]. A 2010 study found that 47% of active surveillance patients undergoing radical prostatectomy were found to have Gleason 7 or greater disease [70]. In a recent Swedish study of men with very low risk prostate cancer (T1c, PSA concentration less than 10 ng/ml, PSA density < 0.15 ng/ml^2, Gleason 6 in up to 4 positive biopsy cores with a total biopsy cancer length of ≤ 8 mm) who underwent radical prostatectomy, 34% had upgrading to stage pT3 or Gleason 7 or higher [71]. Another study that used modified Epstein criteria (PSA < 10 ng/ml, positive biopsy cores ≤ 3, and maximum involvement of any single core

≤ 50%) found that in men who were considering active surveillance and had a rebiopsy within three months of initial biopsy, 27% were upgraded or upstaged on repeat biopsy. These men were also significantly less likely to have organ confined disease or Gleason 6 or lower disease upon prostatectomy [72]. On the other side, we would prefer to detect fewer indolent tumors that are truly clinically insignificant in order to avoid overdiagnosis and the accompanying increases in costs and morbidity.

Use of MRI in Prostate Cancer Diagnosis

As discussed above, introduction of TRUS significantly increased the cancer detection rate of transrectal prostate biopsy [39]. However, TRUS imaging has been unable to reliably identify and localize tumors within the prostate [73]. In fact, TRUS was shown to be no better than DRE in predicting disease outcome [74]. Another imaging modality, MRI, has also long been investigated for its ability to assist with clinical staging. For many years, however, MRI did not demonstrate consistency in localizing tumors within the gland [75]. However, recent advances in MRI imaging have allowed for reevaluation of the utility of MRI in prostate cancer diagnosis. Multiparametric MRI (mpMRI) is a type of study that involves multiple MRI sequences including T2-weighted imaging, diffusion weighted imaging, and perfusion imaging and presents the individual sequences in an integrated manner [76]. Studies have demonstrated that mpMRI is the most accurate noninvasive technique to localize prostate cancer and can assist in risk stratification [77]. A study by Rosenkrantz et al evaluated the ability of mpMRI to

localize index lesions later identified on pathological specimen. Across six different MRI readers, the investigators found an average sensitivity of 60.2% with positive predictive value of 65.3% for an exact match, and an average sensitivity of 75.9% with positive predictive value of 82.6% for an approximate match [78]. MpMRI has also been shown to have high negative predictive value for the presence of extracapsular extension in low risk patients and high positive predictive value for local disease advancement in high risk patients [79]. With the success of mpMRI in identifying prostate lesions, scoring systems have been adopted, including a three or five point Likert scale based on impression and the PI-RADS classification system based on fixed criteria [80,81]. These MRI suspicion scores have been demonstrated to be strongly correlated with higher grade disease, and are thought to be a clinically useful parameter to help characterize prostate cancer [82,83].

MRI-Guided Biopsy Techniques

With better localization of tumors in the gland through mpMRI, new biopsy techniques have been developed to attempt to target the suspicious region of interest (ROI) identified on imaging studies. These MRI-guided targeted TRUS biopsies include visual estimation or cognitive fusion biopsy, in-bore biopsy, and software co-registered fusion biopsy. Visual estimation, also known as MRI cognitive fusion, is the least costly MRI-guided biopsy technique but lacks real time feedback and carries significant interoperator variability and learning curve. Some studies have found a lower cancer detection rate with visual estimation

than systematic or template biopsy, while others have found significantly higher rates of cancer detection with MRI-guided visual estimation [76]. In-bore MRI-guided biopsy involves performing prostate biopsy while the patient remains inside the MRI unit. Due to the vast increase in cost compared to TRUS-guided biopsy, in-bore MRI-guided biopsy has generally been reserved for patients who have had a prior negative biopsy with continued suspicion for prostate malignancy. Many studies have demonstrated a cancer detection rate above 40% with 80-90% of tumors being clinically significant [84].

Software co-registered MRI-guided biopsy is typically achieved through co-registration of the MRI image with a series of TRUS images that are taken at the time of the biopsy. The software then constructs a three-dimensional rendering of the prostate gland and aligns the biopsy with the co-registered image of the ROIs seen on mpMRI. These MRI-US fusion biopsy devices are manufactured by various companies and involve a high up-front investment as well as a learning curve for its utilization [76]. MRI-US fusion biopsy has demonstrated to be more likely to detect cancer than standard 12-core TRUS biopsy, detect more cancer per core, upgrade Gleason scores when compared to 12-core biopsy, and detect more high-risk prostate cancer while detecting less low-risk prostate cancer [85–88]. In a recent meta-analysis of studies evaluating MRI-guided biopsy techniques, investigators did not find a difference in overall cancer detection rate, but did observe a higher rate of detection of clinically significant disease and a lower rate of detection of clinically insignificant disease [89].

Men with Prior Negative Biopsy

A particularly challenging subpopulation of prostate cancer patients are those who present with a persistently elevated PSA and suspicion of prostate cancer despite having had one or more prior negative prostate biopsies. Following a negative prostate biopsy, the information provided by serial serum PSA and PSA kinetics is limited, and many patients ultimately undergo repeated biopsy procedures in search of a histological answer for persistently elevated serum PSA. These repeat biopsies may be unnecessary, and, furthermore, may lead to overdiagnosis of clinically insignificant prostate cancer and subsequent overtreatment. The risk of missing clinically significant disease, especially in the context of the imperfect sampling methods of standard TRUS-guided 12-core biopsy, has prompted some men to receive as many as 10 prostate biopsies [90].

For patients with at least one negative prostate biopsy, previous studies have described cancer detection rates on subsequent biopsies. Overall, cancer detection rates on repeat biopsies are significantly lower than on an initial biopsy with the standard TRUS-guided 12-core approach [91]. In a retrospective study of 2,500 men who underwent up to 10 repeat biopsies, Roehl et al. found that the serial cancer detection rates were 29%, 17%, 14%, 11%, 9% and 7%, on the first six successive biopsies [90]. Low diagnostic yield was also found when men with prior negative biopsies underwent saturation biopsy to attempt to detect significant disease [92]. Contrarily, a recent study found a CDR of 25% on the fourth biopsy in a cohort of 255 men with initial negative biopsy [93].

With the improvements made in prostate imaging through mpMRI and the development of new MRI-guided prostate biopsy techniques, patients with prior negative biopsies may benefit from these advances. Many studies have demonstrated the utility of mpMRI and MRI-guided biopsy for these patients. Cancer detection rates superior to standard TRUS biopsy have been described, as well as a greater proportion of clinically significant disease among detected cancers [94,95]. Another recent study found an increased cancer detection rate as well as improved risk stratification with repeat biopsies using mpMRI and MRI-US fusion biopsy [96]. This value of mpMRI has also been well documented, and MRI suspicion scores have been shown to be a strong predictor of significant cancer detection on subsequent MRI-guided biopsy [97–99]. Furthermore, a systematic review demonstrated that in men with at least one negative prior biopsy, the two-thirds (328 of 479) with an MRI abnormality led to a positive biopsy rate of 70% (229 of 328) when rebiopsied using an MRI-guided procedure [100]. This has led some investigators to suggest using mpMRI as a screening tool to help reduce the number of unnecessary biopsies in men with prior negative biopsy results [101]. In this paper, we evaluate mpMRI and MRI-US fusion biopsy as a means of detecting clinically significant cancer as well as a potential indicator for avoiding repeat biopsies.

Methods

We performed a retrospective study utilizing data collected from clinical encounters between 12/2012 and 06/2015. During this period, 374 men with an indication for prostate biopsy presented to our institution. All patients underwent pre-biopsy mpMRI which was subsequently read by experienced radiologists who identified any region of interest (ROI) and assigned a MRI suspicion score based on either a 3-point Likert scale or the PI-RADS classification system. All patients then underwent a 12-core standard trans-rectal mapping biopsy, and all patients with ROIs identified on mpMRI underwent MRI-US fusion targeted biopsy of those lesions with at least one biopsy core taken per target. All targeted biopsies were performed using the Artemis/Pro-Fuse™ system (Eigen, Grass Valley, California).

Other members of the prostate cancer research group led by Dr. Preston Sprenkle created a secure database of patient information stored on a secure Yale server. The data entered in the database was retrospectively encoded from information found in the patient electronic medical record, including procedure notes and pathology reports. This data was then downloaded and transferred in deidentified form.

From among this set, only men with at least one previous biopsy and no diagnosis of prostate cancer were included in our analysis. Variables included in the data analysis consist of the following: patient age, serum PSA level at time of biopsy, number of previous biopsies, prostate volume measured on MRI, prostate volume measured on TRUS, MRI result, MRI suspicion scores for each

ROI, location for each ROI, clinical stage, and information for each biopsy core taken including location, primary Gleason pattern, secondary Gleason pattern, percent of core occupied by cancer, length of cancer in each core, and qualitative description of histology. Maximum Gleason score was then assigned on a per-patient basis based on the highest Gleason score found on any mapping biopsy or targeted biopsy core.

The author proceeded to process this data set and encode it to allow for data analysis. PSA density was calculated twice by dividing serum PSA level by prostate volume on TRUS and MRI. Location of ROI was encoded into four variables differentiating between left and right; anterior and postieror; base, mid-gland, and apex; and McNeal zone of the gland. Because some patients had MRI suspicion score reported on a three point Likert scale while others were graded according to PI-RADS, we combined the MRI suspicion score into a single variable by translating PI-RADS scores to the three point Likert scale. Patients were then evaluated for the detection of cancer through each biopsy method. We defined cancer as any Gleason score ≥ 6, and we defined clinically significant cancer as Gleason score ≥ 3+4.

Statistical analysis was performed by the author using Stata 13 software (Statacorp, College Station, Texas). Summary statistics included mean, standard deviation, median, minimum, and maximum. Comparative statistics between groups of patients were performed using chi squared, Fisher's exact, student's t-test, and one-way ANOVA. Multivariate logistic regression was performed to

evaluate predictive qualities of patient characteristics. All test results were considered statistically significant if $p < 0.05$.

Results

Upon analysis of the available data, 143 of the 374 patients met inclusion criteria. Analysis was performed at the patient level and the ROI level.

Patient Characteristics

The overall mean age of men included was 64.1 years with a minimum of 47 years and a maximum of 82 years. Mean PSA at time of biopsy was 11.59 ng/mL with a minimum of 0.4 ng/mL and a maximum of 96.90 ng/mL. On average, men in this cohort had received 1.8 previous negative biopsies with the greatest number being 5. Mean MRI-measured prostate volume was 68.52 mL (16.5 – 309) and mean TRUS-measured prostate volume was 67.67 mL (8.81 – 243). Mean PSA density was 0.20 ng/mL^2 (0.01 – 1.82) when calculated with TRUS volume and 0.21 ng/mL^2 (0.01 – 1.45) when calculated with MRI volume. Of the 143 men, 139 (97.2%) successfully completed the pre-biopsy multiparametric MRI, while the remaining 4 were unable to tolerate a complete exam.

MRI Results

Twenty-two patients (15.38%) had no suspicious lesions seen on MRI. Two of the patients with an incomplete exam did not have suspicious lesions reported during the part of the exam that was completed. Of the patients with suspicious lesions identified on MRI, 24 patients (16.78%) had only low suspicion lesions, 40 patients (27.97%) had at least one moderate suspicion lesion with no high suspicion lesions, and 55 patients (38.46%) had one or more high suspicion

lesion. Of patients with ROIs on mpMRI, 61 (50.41%) had at least one anteriorly located ROI.

A total of 213 ROIs were identified following mpMRI. Of these 213, 47.89% (102) were located on the left lobe of the gland and 51.64% (110) were located on the right lobe of the gland. There was no left vs right sided information for 1 ROI. Between anterior and posterior location within the gland, 33.33% (71) were located in the anterior portion while 64.79% (138) were located in the posterior portion of the gland. There was no anterior vs posterior information for 4 of the ROIs. Among base, mid, and apex regions of the gland, 24.41% (52) were located in the base of the gland, 49.30% (105) were located mid-gland, and 25.35% (54) were located in the apex of the gland. There was no information in this dimension for 2 of the ROIs. Regarding McNeal zone of the prostate gland, 75.12% (160) were located in the peripheral zone, 18.78% (40) were located in the central or transitional zone, 3.29% (7) were located in the anterior stroma, and 0.47% (1) were located in the seminal vesicles. There was no McNeal zone information for 5 of the ROIs. The MRI suspicion scores of these ROIs were distributed as follows: 20.66 % (44) were low suspicion, 37.55% (80) were moderate suspicion, and 39.44% (84) were high suspicion. There was no MRI suspicion score reported for 5 of the ROIs.

Overall Biopsy Results

Including both 12-core mapping biopsy and targeted biopsy, the overall cancer detection rate was 42.66% (61 of 143 patients), and the clinically significant

cancer detection rate was 27.27% (39 of 143 patients). Of these men with cancer detected on mapping biopsy or targeted biopsy, 36.07% (22) had Gleason 3+3 disease, 29.5% (18) had Gleason 3+4 disease, and 34.43% (21) had Gleason 4+3 or greater disease. Between men with and without cancer found on mapping biopsy or targeted biopsy, there was no statistically significant difference in mean age (64.71 vs 63.68, $p = 0.39$), PSA (13.33 vs 10.29, $p = 0.09$), or number of previous biopsies (1.74 vs 1.89, $p = 0.43$). There was a difference in mean prostate volume as measured on MRI (50.62 vs 82.0, $p < 0.01$) and mean PSA density (0.29 vs 0.14, $p < 0.01$). Between men with and without clinically significant cancer found on mapping biopsy or targeted biopsy, there was no significant difference in mean number of previous biopsies (1.85 vs 1.82, $p = 0.89$). There was a statistically significant difference in mean age (66.02 vs 63.4, $p = 0.05$), PSA (15.61 vs 10.08, $p < 0.01$), prostate volume on MRI (51.71 vs 74.88, $p < 0.01$), and PSA density (0.34 vs 0.16, $p < 0.01$). Having an anteriorly located ROI was significantly correlated with detection of cancer (65.57% vs 30.00%, $p < 0.01$) and detection of clinically significant cancer (44.26% vs 10.00%, $p < 0.01$).

Mapping Biopsy Results

For standard 12-core mapping biopsy, the overall cancer detection rate was 34.97% (50 of 143 patients), and the clinically significant cancer detection rate was 18.18% (26 of 143 patients). Of the men with cancer detected on mapping biopsy, 48.0% (24) had Gleason 3+3 disease, 22.0% (11) had Gleason 3+4

disease, and 30.0% (15) had Gleason 4+3 or greater disease. Between men with and without cancer found on mapping biopsy, there was no statistically significant difference in mean age (65.04 vs 63.6, p = 0.24) or number of previous biopsies (1.68 vs 1.90, p = 0.26). There was a significant difference in mean PSA (14.04 vs 10.27, p = 0.04), prostate volume on MRI (50.62 vs 78.24, p < 0.01), and PSA density (0.31 vs 0.15, p < 0.01). Between men with and without clinically significant cancer found on mapping biopsy, there was no significant difference in mean number of previous biopsies (1.92 vs 1.80, p = 0.63). There was a statistically significant difference in mean age (67.77 vs 63.28, p < 0.01), PSA (18.43 vs 10.07, p < 0.01), prostate volume on MRI (50.82 vs 72.49, p = 0.03), and PSA density (0.41 vs 0.16, p < 0.01). For mapping biopsy, having an anteriorly located ROI was significantly correlated with detection of cancer (49.18% vs 28.33%, p = 0.02) but not correlated with detection of clinically significant cancer (26.23% vs 16.67%, p = 0.20).

Targeted Biopsy Results

For men who underwent targeted biopsies, the overall cancer detection rate of the targeted biopsies was 40.5% (49 of 121 patients), and the clinically significant cancer detection rate was 27.27% (33 of 121 patients). Of the men with cancer detected on targeted biopsy, 32.65% (16) had Gleason 3+3 disease, 28.57% (14) had Gleason 3+4 disease, and 38.78% (19) had Gleason 4+3 or greater disease. Between men with and without cancer found on targeted biopsy, there was no statistically significant difference in mean age (65.51 vs 63.51, p = 0.14) or

number of previous biopsies (1.88 vs 1.82, p = 0.79). There was a difference in mean PSA (14.00 vs 10.39, p = 0.05), prostate volume on MRI (51.84 vs 76.13, p < 0.01), and PSA density (0.31 vs 0.16, p < 0.01). Between men with and without clinically significant cancer found on targeted biopsy, there was again no significant difference in mean age (66.16 vs 63.61, p = 0.09) and number of previous biopsies (1.88 vs 1.83, p = 0.84). There was a statistically significant difference in mean PSA (16.87 vs 10.20, p < 0.01) prostate volume on MRI (52.03 vs 71.64, p = 0.02), and PSA density (0.35 vs 0.17, p < 0.01). For targeted biopsy, having an anteriorly located ROI was significantly correlated with detection of cancer (59.02% vs 21.67%, p < 0.01) and detection of clinically significant cancer (42.62% vs 11.67%, p < 0.01).

Mapping Biopsy vs Targeted Biopsy

In comparing the results of mapping biopsy and targeted biopsy for each patient, 11 of the 93 patients (11.83%) who did not cancer found on mapping biopsy were found to have cancer on targeted biopsy. Of these 11, 6 were Gleason 3+3, 3 were Gleason 3+4, and 2 were Gleason 4+3 or greater. Of the 24 patients who were found to have Gleason 3+3 disease on mapping biopsy, 5 (20.83%) were upgraded to Gleason 3+4 following targeted biopsy, and 3 (12.5%) were upgraded to Gleason 4+3 or greater. Only 1 of the 11 patients (9.09%) with Gleason 3+4 disease on mapping biopsy was found to have Gleason 4+3 disease on targeted biopsy. In total, 21.50% (20 of 93) of patients were upgraded by inclusion of targeted biopsy. For the 72 patients found to have no cancer on

targeted biopsy, only 9 (12.5%) were found to have cancer on mapping biopsy. Seven of these were Gleason 3+3 disease, and the remaining 2 had Gleason 4+3 or greater disease. Sixteen patients were found to have Gleason 3+3 disease on targeted biopsy, and 4 of these 16 (25%) were found to have Gleason 3+4 disease and none were found to have Gleason 4+3 or greater disease. Of the 14 patients with Gleason 3+4 disease on targeted biopsy, none were found to have Gleason 4+3 or greater disease on mapping biopsy. For the 22 patients with no target identified on MRI, 3 (13.64%) were found to have Gleason 3+3 disease on mapping biopsy, and none were found to have any clinically significant cancer. Overall, 14 of 143 patients (9.79%) were upstaged in clinically significant risk category when targeted biopsy was added to mapping biopsy, while 6 (4.2%) were upstaged in clinically significant risk category when mapping biopsy was added to targeted biopsy.

ROI-Level Results

Cancer was found in 32.86% (70 of 213) of the ROIs. Clinically significant cancer was found in 22.54% (48 of 213) of the ROIs. Of the ROIs with cancer detected on targeted biopsy, 31.43% (22) had Gleason 3+3 disease, 28.57% (20) had Gleason 3+4 disease, and 40.00% (28) had Gleason 4+3 or greater disease. There was a strong correlation between MRI suspicion scores and presence of cancer, with cancer found in 47.62% of high suspicion ROIs, 26.25% of moderate suspicion ROIs, and 13.64% of low suspicion ROIs ($p < 0.01$). This relationship was also demonstrated for clinically significant cancer, with Gleason 3+4 or

greater disease found in 38.10% of high suspicion ROIs, 15.00% of moderate suspicion ROIs, and 6.82% of low suspicion ROIs. Between ROIs with and without cancer found on targeted biopsy, there was no significant correlation in location in terms of left vs right ($p = 0.41$) and base vs mid-gland vs apex ($p = 0.47$). There was a statistically significant correlation regarding anterior vs posterior location ($p < 0.01$) and McNeal zone ($p = 0.04$). There was cancer found in 50.70% of anterior ROIs compared to 23.19% of posterior ROIs. Regarding McNeal zone, there was cancer found in 28.12% of ROIs in the peripheral zone, 40.00% of ROIs in the central or transitional zone, 71.43% of ROIs in the anterior stroma, and 0.00% of ROIs in the seminal vesicles. Between ROIs with and without clinically significant cancer found on targeted biopsy, there was again no correlation in terms of left vs right ($p = 0.53$) and base vs mid-gland vs apex ($p = 0.21$). There was a statistically significant correlation regarding anterior vs posterior location ($p < 0.01$) and McNeal zone ($p < 0.01$). There was clinically significant cancer found in 38.03% of anterior ROIs compared to 15.22% of posterior ROIs. Regarding McNeal zone, there was cancer found in 18.75% of ROIs in the peripheral zone, 27.50 % of ROIs in the central or transitional zone, 71.43% of ROIs in the anterior stroma, and 0.00% of ROIs in the seminal vesicles.

Predicting Biopsy Results

As discussed above, multiple factors were correlated with presence of clinically significant disease across biopsy methods in univariate analysis. Age, PSA, MRI

suspicion score, and PSA density were correlated with clinically significant disease in both mapping biopsy and targeted biopsy conditions. Anterior location of ROI was a particularly interesting factor, as it was significantly correlated with presence of cancer and higher grade cancer, particularly on targeted biopsy. In multivariate logistic regression with independent variables Age, PSA, PSA density, prostate volume on MRI, number of previous biopsies, MRI suspicion score, and presence of anteriorly located ROI, only high suspicion score (OR 5.36, $p = 0.02$) and PSA density (OR 1.09 per 0.01 ng/mL^2, $p = 0.03$) were significant independent predictors of clinically significant disease found on mapping or targeted biopsy. Presence of an anteriorly located ROI approached significance with odds ratio 2.56 ($p = 0.07$). For clinically significant cancer detected on mapping biopsy, multivariate logistic regression demonstrated that Age (OR 1.11, $p = 0.03$) and PSA density (OR 1.13 per 0.01 ng/mL^2, $p < 0.01$) were significant independent predictors of disease. For clinically significant cancer detected on targeted biopsy, multivariate logistic regression revealed that the only significant independent predictor of disease was the presence of an anteriorly located ROI on mpMRI (OR 4.50, $p < 0.01$). High MRI suspicion score approached statistical significance with OR 3.88 ($p = 0.10$). Interestingly, PSA density was not a significant independent predictor of clinically significant disease found on targeted biopsy ($p = 0.57$).

Discussion

Patients who present with a persistently elevated PSA and one or more prior negative prostate biopsies present a common management dilemma. Consensus guidelines for rebiopsy have not been determined, and the optimal method of rebiopsy continues to be investigated. An ideal approach would detect patients with clinically significant prostate cancer while avoiding morbidity related to excessive biopsies and the identification of low risk disease. In turn, this necessitates improved screening to better identify high risk patients within this population. It is common for men with continued suspicion for disease to undergo as many as 10 repeat biopsies [90]. With advances in MRI technology and the development of MRI-US fusion biopsy, investigators have explored the utility of these advances for this population of patients. The results of our analysis contribute to this discussion.

Multiple authors have compared the performance of MRI-targeted biopsy with both MRI in-bore and MRI-US fusion approaches to standard TRUS biopsy for patients with previous negative TRUS biopsies. Hambrock et al first described significantly higher cancer detection rates of 59% following MRI in-bore targeted biopsy, as compared to cancer detection rate of 15% in a matched cohort who received only TRUS biopsy. In the men who were found to have cancer, 48% were found to have Gleason ≥ 7 disease [94]. Continuing this methodology, Hoeks et al reported a 41% cancer detection rate of in-bore MRI-guided targeted biopsies in a series of 265 men with elevated PSA and previous negative systematic TRUS biopsies [95]. Meanwhile, other authors have described the

effectiveness of MRI-US fusion targeted biopsies in these patients. Utilization of the MRI-US fusion biopsy technology allowed for direct comparison of standard 12-core biopsy cores with targeted biopsy cores in terms of cancer detection. Vourganti et al reported a targeted biopsy detection rate of 28.72% compared to 23.08% for mapping biopsy in a population of 195 men. Of patients with cancer found on targeted biopsy, 71.42% were Gleason ≥ 7. Targeted biopsy was found to upgrade disease in 38.36% of the men with cancer found by either method, while missing only 5 cases of Gleason 7 disease [97]. Sonn et al reported similar rates of cancer detection [98]. Efforts to compare the two targeted biopsy methods have shown no difference between the two [102]. Our findings are consistent with these rates, with overall cancer detection rate of 42.66%. Targeted biopsy had a cancer detection rate of 40.5% (67.35% Gleason ≥ 7) compared to 34.97% (52% Gleason ≥ 7) for mapping biopsy. Targeted biopsy upgraded 21.50% of patients with cancer found by either method, while missing only 6 cases of Gleason ≥ 7 disease. As with other studies, we did not find any correlation between cancer detection rate and number of previous biopsies. Our data support the value of MRI-US fusion biopsy for patients with prior negative TRUS biopsies.

In our analysis, no patients with a negative MRI were found to have Gleason ≥ 7 disease on standard biopsy. Increased MRI suspicion score was also correlated with higher grade disease and higher cancer detection rate on biopsy. Other studies have discussed this relationship between MRI suspicion score and predicted disease. Utilizing a 5-point Likert scale, Mendhiratta et al reported that MRI suspicion score < 4 carried a negative predictive value of 96%

for Gleason ≥ 7 disease. MRI suspicion score ≥ 4 was present in 22 of 26 men with Gleason ≥ 7, and MRI-US fusion targeted biopsy detected all 22 cases [101]. In our analysis, 25 of the 38 men with Gleason ≥ 7 disease had a high MRI suspicion score. Though our negative predictive value of low or medium MRI suspicion score of 85% is not as high as that reported by Mendhiratta et al, we did have a 100% negative predictive value for negative MRI. Another recent cohort matched study by Abdi et al utilizing PI-RADS classification found that PI-RADS score > 3 was associated with an odds ratio of 15.68 in predicting presence of Gleason ≥ 7 disease [99]. On multivariate regression, we found an odds ratio of 5.36 for high MRI suspicion score in predicting Gleason ≥ 7 disease. While this is generally consistent with the findings from Abdi et al, we also found that high MRI suspicion score lost significance as an independent predictor when the analysis was divided into presence of significant disease found on each biopsy method. Our results support the notion that mpMRI has utility in predicting the presence of clinically significant disease and may even serve as a screening tool to risk-stratify men in this population.

Beyond MRI suspicion score, our results highlighted the importance of anterior lesions found on mpMRI. Anterior lesions have been shown to represent the majority of tumors missed on standard TRUS biopsy [103]. Vourganti et al noted the frequency of anterior tumors found in men with prior negative TRUS biopsies, diagnosing anterior disease in 33 of the 73 men (45.2%) with cancer [97]. Other authors have investigated this relationship more closely. Volkin et al found a cancer detection rate of 42.4% for targeted biopsy of anterior lesions in patients

with prior negative TRUS biopsy versus a 29.3% detection rate with repeated TRUS biopsy [104]. Our analysis found a cancer detection rate of 50.70% for targeted biopsy of anterior lesions, with 75% of those tumors containing Gleason ≥ 7 disease. This is consistent with the values found by Volkin et al and comparable to those reported by Schouten et al, who utilized MRI in-bore targeted biopsy to achieve an overall cancer detection rate of 73%, with 70% of cancerous lesions located anteriorly and 65% of lesions with Gleason ≥ 7 [105]. We also evaluated the predictive value of having an anterior lesion for cancer detection. While having anterior lesions was not a significant predictor for clinically significant disease on mapping biopsy, it did predict the presence of clinically significant disease on targeted biopsy cores with odds ratio of 4.5. This builds on the idea that some anatomical locations of lesions seen on mpMRI may be more likely to harbor significant disease in men with previous negative biopsies. This region of the prostate is poorly sampled on standard TRUS biopsy, even when repeated multiple times. In this population, men should have some form of MRI-targeted biopsy to characterize lesions and achieve better sampling of those in more difficult anatomic positions.

Further investigation of the relationship between clinically significant disease, MRI suspicion score, and anatomic location of lesions is warranted. Currently, MRI-targeted biopsy still fails to detect all cases of clinically significant cancer, confirming the need for continued mapping biopsy in all patients. With further advances in imaging technology, however, such as the use of contrast-enhanced ultrasound by Jang et al, we may be able to better characterize and

target an even greater proportion of lesions within the gland [106]. Optimal risk stratification of patients with prior negative biopsies will allow for the differentiation of those with indolent or insignificant disease from those with aggressive tumors while minimizing morbidity related to repeated prostate biopsies.

The strengths of this study include the standardized protocol that all patients in the study period followed. MpMRIs were read and lesions were graded by one of a panel of radiologists, supporting the reproducibility of our MRI suspicion score grading system. MRI-US fusion biopsy was performed by a few experienced operators. Limitations of this study include its retrospective design, as our data was limited to the information available in patient charts. Many of our patients are referred from outside providers, and thus we are unable to assume a standardized technique of TRUS biopsy or pathological reading for previous biopsies. The potential for selection bias due to referral patterns to our institution limits the generalizability of our results. Despite these limitations, we believe that this study contributes to the ongoing discussion of the utility of prebiopsy mpMRI and MRI-US fusion targeted biopsy in this group of men with previoius negative biopsies.

Conclusion

In men with one or more previous negative biopsies and continued suspicion for prostate cancer, mpMRI and MRI-US fusion targeted biopsy provide greater detection rate of clinically significant disease compared to standard 12-core TRUS biopsy. Men with negative MRI findings may be able to avoid or delay biopsy. Patients with high MRI suspicion score lesions and those with anterior lesions are at increased risk for significant disease and should be treated with the necessary diligence. Further investigation into the relationship between mpMRI, anatomic location of lesions, and effectiveness of MRI-targeted biopsy is required before broad changes to current practice can be recommended.

List of Tables

Table 1 *Patient Characteristics*

	Total (n = 143)	Cancer (n = 61)	No Cancer (n = 82)	p-value	CS Cancer (n = 39)	No CS Cancer (n = 104)	p-value
Age (mean)	64.11	64.71	63.68	0.386	66.02	63.40	0.046
PSA (mean)	11.59	13.33	10.29	0.086	15.61	10.08	0.005
Previous Biopsies (mean)	1.83	1.74	1.89	0.428	1.85	1.82	0.893
MRI Prostate Volume (mean)	68.52	50.62	82.00	< 0.001	51.71	74.88	0.006
PSA Density (mean)	0.20	0.14	0.29	< 0.001	0.16	0.34	< 0.001
MRIss							
High	55	36 (65.45%)	19 (34.55%)		25 (45.45%)	30 (54.55%)	
Moderate	24	13 (32.50%)	27 (67.50%)		8 (20.00%)	32 (80.00%)	
Low	40	8 (33.33%)	16 (66.66%)		5 (20.83%)	19 (79.17%)	
Negative MRI	22	3 (13.64%)	19 (86.36%)		0 (0.00%)	22 (100.00%)	
	141			< 0.001			< 0.001
Has Anterior ROI	61	40 (65.57%)	21 (25.61%)	< 0.001	27 (69.23%)	34 (32.69%)	< 0.001

Table 2 *Mapping Biopsy vs Targeted Biopsy*

		MRI-US Fusion Targeted Biopsy					
		Gleason ≥ 4+3	Gleason 3+4	Gleason 3+3	No Cancer	No Target	Totals
Standard TRUS Biopsy	Gleason ≥ 4+3	13	0	0	2	0	15
	Gleason 3+4	1	6	4	0	0	11
	Gleason 3+3	3	5	6	7	3	24
	No Cancer	2	3	6	63	19	93
	Totals	19	14	16	72	22	143

Table 3 *MRI Suspicion Score and Biopsy Results*

	MRI SS			
	High	Moderate	Low	Total
Gleason 3+3	11	5	3	19
	19.30%	8.77%	5.26%	33.33%
Gleason 3+4	9	6	3	18
	15.79%	10.53%	5.26%	31.58%
Gleason ≥ 4+3	16	2	2	20
	28.07%	3.51%	3.51%	35.09%
Total	36	13	8	57
	63.16%	22.81%	14.04%	100.00%

Table 4 *Results of Multivariate Logistic Regression*

Predictor of CS Cancer on Targeted Biopsy	Odds Ratio	95% CI
Age	1.06	(0.98,1.16)
PSA	1.02	(0.84, 1.23)
Previous Biopsies	1.29	(0.79, 2.12)
Prostate Volume	0.98	(0.95, 1.01)
PSA Density	1.03	(0.94, 1.12)
High Suspicion Lesion	3.88	(0.78, 19.28)
Moderate Suspicion Lesion	1.36	(0.23, 7.94)
Has Anterior ROI	4.50	(1.48, 13.75)

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