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Advances in Localized Prostate Cancer Management

Lead Guest Editor: David B. Samadi
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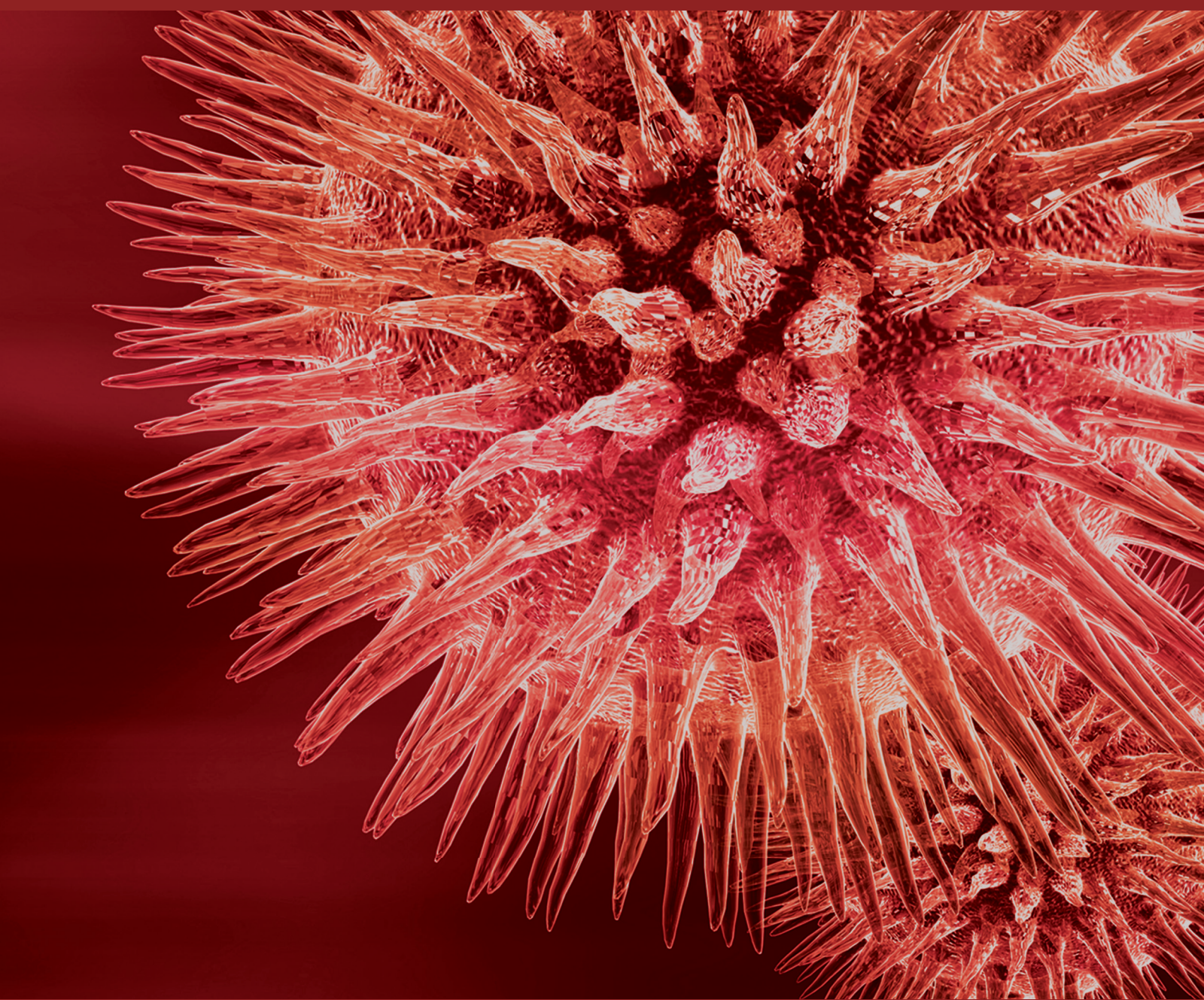

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Editorial

Advances in Localized Prostate Cancer Management

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Advances in technology, including new imaging modalities, genomic tests, and biomarkers, have introduced practice-changing opportunities for the treatment of localized prostate cancer. These advances will allow us to better determine which patients are appropriate candidates for active surveillance and when to offer patients curative treatment. With the rising use of MRI-guided biopsy, further questions about when, and on whom, to use MRI-guided biopsy have been raised. In a quest to highlight best practices for achieving best cancer detection rates for patients with previous negative biopsies, C.-H. Chang et al. compared the prostate cancer detection rates of targeted biopsy and saturation biopsy in patients with previous negative biopsy and the accuracy of these biopsies retrospectively stratified by different serum prostate-specific antigen (PSA) levels. Of the 185 patients enrolled in the study, they found that combining target biopsy (TB) and saturation biopsy (SB) achieved the best cancer detection rate. Furthermore, the accuracy of TB was better than that of SB in patients with serum PSA > 10 ng/mL. More work is needed to evaluate different biopsy strategies in patients with varying PSA levels. Using a recently released robot guided, software based transperineal approach, M. Kroenig et al. compared prostate cancer detection rates between MRI-TRUS fusion targeted and systematic biopsies. 52 patients with elevated PSA levels, clinical suspicion for prostate cancer, and prior negative 12-core transrectal ultrasound guided biopsy received MRI/TRUST fusion biopsy at the University of Freiburg Medical Centre. This group was unable to exhibit an advantage in the overall detection rate of clinically significant prostate cancer using the MRI/TRUS fusion biopsy. This study highlights the potential to improve the radiological PI-RADSv2 classification scheme in order to reduce sensitivity issues.

Is it safe to offer young patients active surveillance? What are the long-term side-effects of treatment that young men might face? In this special issue, D. Milonas et al. report long-term outcomes of young men treated with radical prostatectomy. They compared long-term outcomes of 277 men aged ≤55 years after radical prostatectomy (RP) with an older cohort. Pathological tumor characteristics, biochemical recurrence rates (BCR), and disease progression rates were compared between the two groups. This group found that the younger cohort had superior outcomes especially when their Gleason score, lymph-nodes, and surgical margins status were lower, and the two cohorts had similar BCR. This study highlights the excellent results that RP has for younger men (≤55 years) with localized prostate cancer.

Treatment advances will also aid in a personalized approach to treatment, giving patients more information about their cancer and expected cancer and side-effects of any given treatment. E. Reamer et al. discuss the role of social support and personality differences in men when it comes to prostate cancer treatment selection. In their report, E. Reamer et al. analyzed social influences on the treatment decision-making process of 559 men ≤ 75 years old newly diagnosed with localized prostate cancer. A population-based sample was surveyed cross-sectionally from Detroit, Michigan, and cases were identified by the Metropolitan Detroit Cancer Surveillance System (MDCSS). They evaluated treatment choice, reason for the choice, decision-making difficulty,

satisfaction, and regret. They found that, in addition to seeing a specialist, consulting friends increased men's likelihood of choosing curative treatment and that consulting family or friends increased decision-making difficulty. With a racially diverse cohort, this study highlights the importance of social networks during a patient's treatment decision-making process, and it has implications for how physicians should develop realistic expectations of treatments across communities.

And in an effort to increase awareness about the developments in definitive radiotherapy and compare its outcomes to radical prostatectomy, B. G. L. Vanneste et al. wrote a narrative review on a number of publications regarding definitive treatments for prostate cancer. The current literature did not reveal significant difference between conventional, definitive treatment modalities in cure rates, but in toxicity patterns. The paper focuses its conclusions on patient-specific treatment and recommending different treatment types based on their own advantages and side-effects in correspondence to the specific needs and concerns of individual patients.

Acknowledgments

The editors thank the authors for their efforts and time spent for each manuscript. The lead editor would like to thank all editors for the time spent in reviewing, assigning reviewers, and commenting on submitted manuscripts. The editors hope that this special issue will prove useful to investigators, urologists, oncologists, and radiation oncologists involved in the care of men diagnosed with prostate cancer.

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Research Article

The Influence of Serum Prostate-Specific Antigen on the Accuracy of Magnetic Resonance Imaging Targeted Biopsy versus Saturation Biopsy in Patients with Previous Negative Biopsy

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Objective. We compared the prostate cancer (PCa) detection rates of targeted biopsy (TB) and saturation biopsy (SB) in patients with previous negative biopsy and the accuracy of TB and SB stratified by different serum prostate-specific antigen (PSA) levels. *Materials and Methods*. Overall 185 patients were enrolled. In the magnetic resonance imaging (MRI) group, 65 men underwent TB and SB. In the control group, 120 men underwent SB alone. The primary outcome was the difference in PCa detection rate between the MRI group and control group. The secondary outcome was the difference in accuracy between TB and SB in detecting clinically significant PCa by stratifying the patients in the MRI group into those with PSA < 10 ng/ml and PSA ≥ 10 ng/ml. *Results*. The detection rates for overall and clinically significant PCa were higher in the MRI group than in the control group (46.2% versus 20.9% and 43.1% versus 16.7%, both $p < 0.001$). In the MRI group, the accuracy of TB was higher than SB (94.7% versus 84.2%, $p = 0.001$) for the patients with PSA ≥ 10 ng/mL. *Conclusions*. Combining TB and SB achieved the best cancer detection rate. The accuracy of TB was better than SB in the patients with serum PSA ≥ 10 ng/mL.

1. Introduction

According to European Association of Urology (EAU) guidelines on prostate cancer (PCa), the standard method of diagnosing PCa is ultrasound-guided transrectal (TRUS) or transperineal laterally directed biopsy of the prostate with 10–12 cores [1]. However, on average, less than 0.05% of prostatic tissue is sampled in each biopsy session, and more than 30% of cancers are located in the anterior horn, apex, or transitional zone where transrectal biopsy cores are usually missed [2, 3]. Therefore, a 12-core TRUS biopsy of the prostate carries a false negative rate of up to 20% [4]. In patients with a persistently elevated level of serum prostate-specific antigen (PSA) after an initially negative prostate biopsy, saturation biopsy (SB) with more than 20 cores of prostatic tissue performed in a systemic fashion has traditionally been suggested to improve the diagnostic accuracy [5–7]. However, by increasing the number of biopsy cores, SB may induce more pain and even transient erectile dysfunction [8]. The issue of the overdiagnosis of low-risk cancers caused by SB can also increase the complexity of treatment [9].

With significant advances in the techniques and interpretation of prostate multiparametric magnetic resonance imaging (mpMRI) in recent years, the role of MRI-targeted

biopsy (TB) has been established in the repeated biopsy setting to improve the detection rate of clinically significant PCa [10, 11]. Nevertheless, around 10% of cancers are missed with TB alone [12, 13]. In order to achieve a maximal PCa detection rate, some reports have advocated the combination of TB and SB [14–16]. In this study, we investigated the overall and clinically significant PCa detection rates of TB and SB in patients with previous negative biopsy and compared the accuracy of TB and SB stratified by different serum PSA levels.

2. Materials and Methods

2.1. Study Population. From March 2012 to December 2014, 185 consecutive patients with prior negative biopsy, persistently elevated serum PSA level, and normal digital rectal examinations underwent repeated prostate biopsies in a tertiary referral center. After institutional review board approval, the patients' clinical characteristics and biopsy results were retrospectively recorded and analyzed. Two of the patients had atypical small acinar proliferation (ASAP) or high-grade prostatic intraepithelial neoplasia (HGPIN) on prior biopsy. MRI was arranged before repeated biopsies according to the physicians' clinical considerations, and the patients were divided into an MRI group ($n = 65$) and control group ($n = 120$). We used the Standards of Reporting for MRI-Targeted Biopsy Studies (START) to report the MRI and the biopsy results [17].

2.2. Magnetic Resonance Imaging and Analysis. MRI was performed on a 3-T MRI scanner (Signa HDxt, GE Healthcare, Milwaukee, WI) with an eight-channel high definition (HD) cardiac array coil. The scanning protocol included T2-weighted imaging (T2WI), diffusion-weighted imaging (DWI), and dynamic contrast enhanced (DCE) MRI. DWI was acquired with b-values of 0 and 1000 s/mm^2, and an apparent diffusion coefficient (ADC) map was also generated.

Two radiologists (W. C. L. and T. L. H.) with 4 and 11 years of experience, respectively, in mpMRI reviewed the images (March 2012 to June 2014 by W. C. L., July 2014 to December 2014 by T. L. H.) and identified all suspicious cancerous lesions. Each lesion was assigned a score using the European Society of Urogenital Radiology (ESUR) Prostate Imaging-Reporting and Data System (PI-RADS) [18]. First, an individual score for each sequence (T2WI, DWI, and DCE) was given, and then a sum score was calculated. A lesion with a sum score of more than 10 was taken to indicate a suspicious lesion, and it was marked on a picture archiving and communication system workstation (Infinitt Healthcare, Phillipsburg, NJ).

2.3. Biopsy Protocol. In the MRI group, 65 men underwent prostate mpMRI. After interpreting the mpMRI findings and identifying the most suspicious lesions as the target lesions (maximum three target lesions per patient), a urologist (P. F. H.) performed cognitive registration TB, followed by SB, using a biplane TRUS probe (BK Medical, Transducer 8818). At least two cores were sampled from each target lesion, and at least 16 cores were sampled systemically from the peripheral zone and transition zone. In the control group, 120 men underwent transrectal SB alone by the same urologist with at least 16 cores sampled.

2.4. Histopathology. The biopsy specimens were interpreted by an experienced uropathologist (H. C.). We used the Epstein criteria to define clinically significant PCa as Gleason score (GS) $\geq 3 + 4$, two or more cores positive for cancer, or cancer involving more than 50% of one core [19]. The maximal cancer core length was also recorded.

2.5. Statistical Analysis. We converted the overall ESUR PI-RADS score (3–15 points) to PI-RADS version 2 score (1–5 points) [20] by checking each individual score for further comparison with other studies. The primary outcome was the difference in detection rates for overall and clinically significant PCa between the MRI group and control group. The secondary outcome was the difference in accuracy between TB and SB in detecting clinically significant PCa by stratifying the patients as those with a serum PSA level < 10 ng/ml and those with a PSA level ≥ 10 ng/ml in the MRI group. The chi-square test and Student's t-test were used to analyze categorical and continuous variables between the MRI group and control group, respectively. The McNemar test was used to compare the performance of different biopsy methods in the MRI group. All clinical data analyses were performed using SPSS version 21 (IBM Corp, Armonk, NY, USA).

3. Results

Table 1 lists the characteristics of the study population. There were no significant differences in age, PSA level, and prostate volume between the MRI group and control group. Suspicious lesions with a PIRADS score ≥ 3 were identified in 43 patients (66.2%) in the MRI group.

The overall detection rates for PCa were higher in the MRI group than in the control group (46.2% versus 20.9%, $p < 0.001$). The detection rate for clinically significant PCa was also higher in the MRI group than in the control group (43.1% versus 16.7%, $p < 0.001$). In addition, the maximal cancer core length was longer in the MRI group than in the control group (2.6 mm versus 0.8 mm, $p < 0.001$) (Table 2).

In the MRI group, TB detected 28 cancers (43.1%), of which 25 were clinically significant, whereas SB detected 22 cancers (33.8%), of which 21 were clinically significant. The detection rates for overcall PCa and clinically significant PCa were comparable between TB and SB (43.1% versus 33.8%, $p = 0.11$, and 38.5% versus 32.3%, $p = 0.34$, resp.). There were three clinically significant cancers detected by SB but missed by TB, including two with GS 4 + 3 and one with GS 3 + 4. On the other hand, seven clinically significant cancers were detected by TB but missed by SB, including one with GS 5 + 4, one GS 4 + 5, one GS 4 + 4, two GS 4 + 3, and two GS 3 + 4 (Table 3).

Of the patients with a PSA level < 10 ng/mL, the accuracy of TB and SB was identical in detecting clinically significant

Table 1: Patient characteristics.

	MRI group	Control group	p value
Number of men	65	120	
Age, years, median (IQR)	64 (7.5)	66 (14)	0.19
PSA level, ng/mL, median (IQR)	10.9 (7.5)	8.1 (5.7)	0.17
Prostate volume, mL, median (IQR)	48 (29)	53.5 (24.7)	0.09
PIRADS score, number (%)			
3	9 (13.8%)	Nil	
4	16 (24.6%)	Nil	
5	18 (29.2%)	Nil	

Table 2: Comparison of biopsy results between the MRI group and control group.

	MRI group (TB plus SB)	Control group (SB only)	p value
Total number of cores, median (IQR)	20 (4)	18 (3.5)	0.017
Number of cores with any cancer, mean ± SD	2.03 ± 3.33	0.74 ± 1.84	<0.001
Gleason score, number (%)			<0.001
≦3 + 3	6 (9.2%)	8 (6.7%)	
3 + 4	9 (13.8%)	8 (6.7%)	
4 + 3	10 (15.4%)	6 (5%)	
≧4 + 4	5 (7.7%)	3 (2.5%)	
Maximum cancer core length, mm, mean ± SD	2.6 ± 3.9 (TB)	0.8 ± 2.3	<0.001
Cancer detection, number (%)			<0.001
No cancer	35 (53.8%)	95 (79.2%)	
Clinically insignificant cancer	2 (3.1%)	5 (4.1%)	
Clinically significant cancer	28 (43.1%)	20 (16.7%)	

SB: saturation biopsy; TB: target biopsy.

PCa. However, of the patients with a PSA level ≥ 10 ng/mL, the accuracy of TB in detecting clinically significant PCa was higher than SB (94.7% versus 84.2%, $p = 0.001$, chi-square test) (Table 4).

4. Discussion

The incidence of infectious complications significantly increases with every prostate biopsy taken [21]. Therefore, every effort should be made to increase the cancer detection rate of prostate biopsy, especially in patients with previous negative biopsy and clinically suspected PCa. In this study, we demonstrated that the cancer detection rate was higher using a combination of TB and SB than SB alone in patients with previous negative biopsy. In addition, for the patients with PSA ≥ 10 ng/mL, the accuracy of TB was better than SB in detecting clinically significant PCa.

Previous studies have indicated the importance of combining TB and SB. Using radical prostatectomy specimens as the reference standard, Radtke et al. reported that a combination of TB and SB could detect 97% of significant PCa, which was significantly better than mpMRI (85%), TB (79%), and SB (88%) alone ($p < 0.001$ each) [22]. Hansen et al. prospectively evaluated the combination of transperineal TB and SB in patients with previously negative biopsy, and they found that, in patients with high probability MRI lesions (PIRADS 5), a combination of TB and SB could achieve the highest detection rates of PCa with GS ≧ 3 + 4 [15]. Pepe et al. reported that transperineal SB missed 9% of cancers, all of which were in the anterior zone, and that TB improved the accuracy in diagnosing significant anterior PCa [16]. Consistent with previous literature, we used an MRI group and a control group to show that the detection rate for clinically significant PCa was higher with a combination of TB and SB than with SB alone (43.1% versus 16.7%, $p < 0.001$). Combining TB and SB also achieved a higher detection rate of clinically significant PCa than SB alone in the MRI group (43.1% versus 32.3%, $p = 0.02$). Nevertheless, in the MRI group, TB and SB missed three and seven clinically significant cancers, respectively. Therefore, combining TB and SB should yield the highest cancer detection rate.

Li et al. reported the impact of serum PSA level on the detection rate of transrectal biopsy in the initial biopsy setting [23]. They found that, in men with PSA > 10 ng/mL, SB would not improve the cancer detection rate. In our MRI group, there was no significant difference in the detection rate of clinically significant cancer by TB and SB (38.5% versus 32.3%, $p = 0.34$). The accuracy between TB and SB was also comparable for the patients with PSA < 10 ng/mL ($p = 1$). However, for those with PSA ≥ 10 ng/mL, the accuracy of TB was higher than that of SB (94.7% versus 84.2%, $p = 0.001$) in detecting clinically significant PCa. Serum PSA level has been correlated with the aggressiveness of PCa [24], and PCa with PSA ≥ 10 ng/mL is categorized as intermediate or high risk, possibly implying a higher Gleason grade or more often clinically significant cancer compared

Table 3: Comparison of TB and SB in the MRI group.

		SB	
	No cancer	Clinically insignificant cancer	Clinically significant cancer
No MRI target	22 (33.8%)	0	1 (1.5%)
TB			
No cancer	13 (20%)	0	1 (1.5%)
Clinically insignificant cancer	1 (1.5%)	1 (1.5%)	1 (1.5%)
Clinically significant cancer	7 (10.8%)	0	18 (27.7%)

Data are shown as number (percentage). SB: saturation biopsy; TB: target biopsy.

Table 4: Performance of TB and SB in the detection of clinically significant cancer with different PSA levels.

	PSA < 10 ng/mL			PSA ≥ 10 ng/mL		
	TB	SB	p value	TB	SB	p value
Sensitivity	88.9%	88.9%	1	89.5%	68.4%	0.03
NPV	94.7%	94.7%	1	90.5%	76%	<0.001
Accuracy	96.3%	96.3%	1	94.7%	84.2%	0.001

NPV: negative predictive value, SB: saturation biopsy, and TB: target biopsy.

to those with PSA < 10 ng/mL. In a prospective analysis using whole-mount section slides, Junker et al. demonstrated that tumor aggressiveness was correlated with PIRADS score [25]. In addition, the diagnostic accuracy of the PIRADS scoring system was better for those with high-grade PCa [18]. Therefore, the accuracy of MRI-guided TB may be better for patients with higher PSA or aggressive PCa. In other words, MRI is even more important in patients with a serum PSA level ≥ 10 ng/mL, and it should never be omitted in these patients. In addition, a combination of SB and TB is recommended to overcome the minor false negative rate of TB.

Pepe et al. reported that about 70% of clinically significant PCa in the anterior zone was diagnosed on repeat biopsy [26]. In addition, TB was shown to improve the detection rate, volume, and grade of anterior PCa compared with systematic biopsies [27]. In our series, we did not include the anterior zone in SB cores. Therefore, some clinically significant cancers would have been missed with a possible subsequent decrease in accuracy of SB. On the other hand, Cerantola et al. demonstrated that TB with cognitive MRI-US registration allowed for an accuracy of 82% in achieving the correct target, but that anterior tumors were less likely to be successfully targeted [28]. Due to the limited number of lesions in the anterior zone on MRI, we did not evaluate the role of TB in detecting tumors in this region. The issue of detecting anterior tumors by different biopsy methods should be evaluated in future studies.

In our series, TB was performed with cognitive registration. Theoretically TB with software registration is less operator-dependent and offers more objective results. In a prospective study, Wysock et al. demonstrated that although TB with software registration was more histologically informative than TB with cognitive registration, the detection rates for Gleason sum ≥ 7 were similar [29]. Another comparison between software and cognitive fusion did not show any advantage of one fusion method over the other [30]. The American Urological Association (AUA) and Society of Abdominal Radiology (SAR) consensus statements stated that in the absence of image fusion platforms, cognitive targeting remains a reasonable approach in skilled hands [31].

There are several limitations to this study. First, this is a retrospective study with a limited number of cases. Second, the definition of clinically significant cancer followed the Epstein criteria. However, it is debatable whether the Epstein criteria are feasible in the era of TB [32]. Third, we performed SB transrectally instead of transperineally, so it was difficult to sample prostatic tissue in the anterior zone or apex. We used biopsy results as the reference test, but both SB and TB could have false negative results [33]. Ideally, radical prostatectomy should be the best reference test; however it is not practical and may carry positive selection bias. Fourth, the operator performing SB was not blinded to the MRI reports, and the radiologist was not blinded to the clinical data. However, our data represent real clinical practice. Finally, we only included patients with previous negative biopsy, so the results cannot be applied to those undergoing an initial biopsy.

5. Conclusion

Our findings highlight the importance of combining TB and SB to achieve the best cancer detection rate for patients with previous negative biopsy. In addition, we found that the accuracy of TB was better than that of SB in patients with serum PSA ≥ 10 ng/mL. Further studies are needed to evaluate the impact of different biopsy strategies in patients with various PSA levels.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

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Research Article

Influence of Men's Personality and Social Support on Treatment Decision-Making for Localized Prostate Cancer

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Background. Optimal treatment for localized prostate cancer (LPC) is controversial. We assessed the effects of personality, specialists seen, and involvement of spouse, family, or friends on treatment decision/decision-making qualities. *Methods*. We surveyed a population-based sample of men ≤ 75 years with newly diagnosed LPC about treatment choice, reasons for the choice, decision-making difficulty, satisfaction, and regret. *Results*. Of 160 men (71 black, 89 white), with a mean age of 61 (±7.3) years, 59% chose surgery, 31% chose radiation, and 10% chose active surveillance (AS)/watchful waiting (WW). Adjusting for age, race, comorbidity, tumor risk level, and treatment status, men who consulted friends during decision-making were more likely to choose curative treatment (radiation or surgery) than WW/AS (OR = 11.1, $p < 0.01$; 8.7, $p < 0.01$). Men who saw a radiation oncologist in addition to a urologist were more likely to choose radiation than surgery (OR = 6.0, $p = 0.04$). Men who consulted family or friends (OR = 2.6, $p < 0.01$; 3.7, $p < 0.01$) experienced greater decision-making difficulty. No personality traits (pessimism, optimism, or faith) were associated with treatment choice/decision-making quality measures. *Conclusions*. In addition to specialist seen, consulting friends increased men's likelihood of choosing curative treatment. Consulting family or friends increased decision-making difficulty.

1. Introduction

Approximately 13% of men in the US will be diagnosed with prostate cancer at some point in their lifetime [1]. Over 80% of prostate cancers are diagnosed at the local stage [2]. The 5-year survival for localized prostate cancer (LPC) is 99% [1]. Three main options are generally available for the treatment of LPC: active surveillance/watchful waiting (AS/WW), surgery (radical prostatectomy), and radiation (internal or external radiation) [3]. Since mortality is essentially the same for each treatment [4], experts recommend that treatment choice should be responsive to patient preferences [5]. These personal preferences have been shown to be shaped by a patient's own beliefs, personality traits [6–8], and the people that he interacts with during the decision-making process [7, 9–20], though many of these studies were performed in majority white populations. Understanding how men's personality traits and social influences impact the treatment decision-making process in a diverse population is important for physicians and other healthcare professionals to provide the best support possible for individual patients as they choose the best treatment for their unique circumstances.

Social influences on decision-making studied previously include consulting friends and family in addition to healthcare providers. Partners and spouses often are involved in discussions about LPC treatment choices with both patients and providers and in choosing the final LPC treatment option [9–11]. Being married or cohabitating was reported to be associated with less decisional conflict and less decision-making difficulty [7]. Being married was also found to be positively associated with choosing curative treatment for LPC, specifically prostatectomy [12], and negatively associated with choosing AS/WW [13]. Family and friends were reported to often urge curative treatment as well [14]. Several studies have found that physician recommendation is the most important factor in a patient's treatment choice [17–19]. However, additional, systematic research examining all the social influences and their impact not only on treatment

choice but also on the treatment decision-making process is needed.

Our study sought to further evaluate the important associations between personality traits, social influences, and the LPC treatment decision-making process in a population-based, racially diverse sample. Specifically, we evaluated the effect of personality traits (optimism, pessimism, and faith), physician specialty, and social support consulted (family, friends, and spouse/partner) on patients' LPC treatment choice and qualities of the treatment decision-making process (i.e., decision-making difficulty, satisfaction, and regret).

2. Materials and Methods

We conducted a population-based cross-sectional survey of black and white men living in the Metropolitan Detroit area aged 75 years or less and newly diagnosed with LPC between 2009 and 2010. A detailed description of the study method, sampling, and survey instrument has been previously reported [19]. Briefly, new LPC cases were identified by Rapid Case Ascertainment (RCA) in the Metropolitan Detroit Cancer Surveillance System (MDCSS), a population-based cancer registry that is part of the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program. If the patient's physician stated that the patient was healthy enough to participate, the eligible case was mailed a self-administered survey with a small ($10) monetary incentive. The content and design of the surveys were developed based on thorough literature review and refined by the findings of qualitative studies [21, 22]. The Dillman method was used to encourage survey response [23]. To reduce the participant burden, the survey was divided into 2 parts and mailed to participants approximately one month apart. The first part of the survey asked men to report their treatment choice, reasons for the choice, type of specialists seen, and what treatment options were offered and recommended by their physicians [19]. The second half of the survey asked about personality traits (e.g., optimism, pessimism, and faith), who the patient consulted besides physicians, including spouse/partner, other family members, and friends, and decision-making experiences (i.e., decision-making difficulty, satisfaction, and regret) [23, 24]. LPC was defined as T1 to T2 tumors based on American Joint Committee on Cancer (AJCC) stage criteria. The study received approval from the institutional review board at Wayne State University.

2.1. Sampling. During the study period, a total of 874 potentially eligible LPC cases were identified. To achieve similar numbers of white and black men, white men were sampled at a ratio of 1 : 3, leaving a total of 559 men sampled for study contact. After initial physician and patient contact, 168 total patients were excluded from the study (118 because their physicians did not approve their participation and 50 because they did not meet all study inclusion criteria), resulting in 391 eligible cases to be surveyed [19]. Of them, 266 men completed the first part of the survey, resulting in a response rate of 68%. 22 men declined the invitation to participate in the second part of the survey. Therefore, a total of 244 men were mailed a second survey, and 201 men completed it with response rate of 82%. Among the 201 men who responded to both surveys, 10 men were excluded from the analysis due to insufficient clinical information (i.e., inability to assess their tumor risk level due to a missing PSA level or Gleason score). Another 9 were excluded due to extensive missing data (missing > 10% of data on both surveys), and another 22 were excluded due to having chosen a treatment option other than surgery, radiation, or WW/AS (Figure 1). A final sample of 160 participants was included in the data analyses for this report. 86% of the 160 participants completed the first survey within six months of diagnosis (mean: 119 days, SD: 54 days); 72% completed the second survey within six months of diagnosis (mean: 158 days, SD: 63 days).

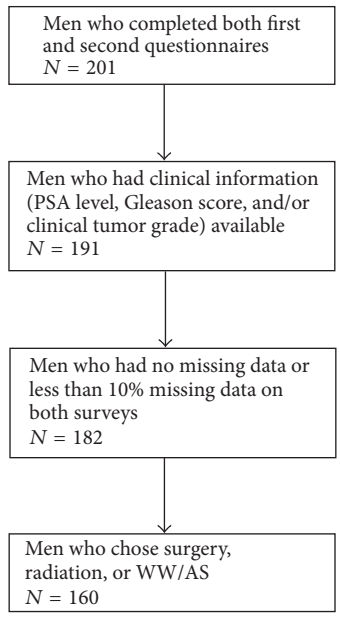

Figure 1: Flowchart of participants included in final analysis.

2.2. Instruments and Measures. The primary outcome variables were treatment choice and qualities of the treatment decision-making process. Treatment choice was self-reported and included WW/AS, surgery, and radiation. The treatment decision-making qualities (i.e., decision-making difficulty, satisfaction, and regret) were based on existing scales (α = 0.87, α = 0.86, and α = 0.81–0.92, resp.) modified for our study [6, 24–26], with a Cronbach's alpha value of 0.77, 0.75, and 0.74, respectively, in our study. All were measured as 5-point Likert-type responses ranging from "strongly disagree" to "strongly agree." Higher scores represent more decision-making difficulty, satisfaction, or regret.

Predictor variables included age, self-reported race (black or white), self-reported number of comorbidities, tumor characteristics, education level, presence of a spouse/partner, whether family, friends, or spouse/partner were consulted about the patient's treatment decision, types of physicians seen (urologist, urologist and primary care physician (PCP), and radiation oncologist with or without urologist/PCP), and personality traits (optimism, pessimism, and faith). PSA,

Gleason scores, and tumor clinical stage were used to define the tumor risk level according to the American Urological Association-endorsed D'Amico criteria. Self-reported PSA and Gleason scores were used when available and supplemented by MDCSS. The personality trait scale was modified from two preexisting validated scales ($\alpha = 0.78$ and $\alpha = 0.67$–0.86) [27, 28]. Respondents ranked how well each statement matched their personal beliefs using a 5-point Likert-type response format ranging from "not at all true" to "completely true." Higher scores represented stronger match of each statement to the respondent's beliefs. Factor analysis identified 3 well-defined, meaningful subthemes in the personality trait subscale, optimism, pessimism, and faith score, with a Cronbach alpha of 0.90, 0.69, and 0.76, respectively.

2.3. Statistical Analysis. The distribution of demographic characteristics (age, race, marital status, and education), clinical characteristics (PSA level, Gleason score, and number of comorbidities), social influence sources consulted, physicians seen, and personality trait variables was described. Racial differences in the distribution of these variables and their unadjusted effects on treatment choice were examined using chi-square test or Fisher's exact test for dichotomous variables and t-tests or ANOVA for continuous variables. Multinomial logistic regression models were performed to examine the effect of each significant predictor in bivariate analysis on treatment choice while adjusting for age, race, tumor risk level, number of comorbidities, and whether treatment had been started or received at the time of survey. Due to the lack of variability in the Likert scale responses for decisional satisfaction and regret, linear regression was not feasible. Instead, the decision-making quality measures were dichotomized with the median as the cutoff. Logistic regression models were then performed to examine the effects of social sources consulted, personality traits, and types of physicians seen on decision-making quality measures (i.e., decision-making difficulty, satisfaction, and regret) while adjusting for age, race, tumor risk level, number of comorbidities, and treatment status. All analyses were computed using R version 3.1.2 (R Development Core Team, Vienna, Austria) with a p value < 0.05 being significant.

3. Results

Among the 160 men eligible for this study, 59% chose surgery, 31% chose radiation, and 10% chose AS/WW. 103 (64%) of respondents had started or received treatment at the time of survey. Among these men, the mean time between diagnosis and treatment was 57 (±SD 39) days. Significant differences existed between white men and black men in univariate analysis. Compared to white men, black men were more likely to consult their family for treatment decision (66% versus 43%; $p < 0.01$), be unmarried/not partnered (31% versus 10%; $p < 0.01$), have no more than a high school education (76% versus 53%; $p < 0.01$), and report a higher faith score (mean: 3.9 versus 3.1 on a 5-point scale; $p < 0.01$) (Table 1). Overall, men in our sample were highly satisfied (median score: 5.0 on a 5-point scale, SD: 0.4) and had little regret (median score: 1.0 on a 5-point scale, SD: 0.8) with their treatment decision-making process. Men experienced a moderate level of decision-making difficulty (median score: 2.2 on a 5-point scale, SD: 1.0). Using multinomial logistic regression adjusting for age, race, comorbidities, tumor risk level, and treatment status, men who consulted friends regarding their treatment decision were more likely to choose curative treatment (radiation or surgery) compared to WW/AS (radiation [OR = 11.1, $p < 0.01$] or surgery [OR = 8.7, $p < 0.01$]) (Table 2). In addition, when comparing men who saw only a urologist, men who saw a radiation oncologist in addition to a urologist and/or a PCP were more likely to choose radiation compared to surgery (OR = 6.0, $p = 0.04$) (Table 2). Men who consulted family or friends experienced higher decision-making difficulty than men who did not (OR = 2.6, $p < 0.01$, and OR = 3.7, $p < 0.01$, resp.) (Table 3). Consulting one's spouse/partner did not affect decision-making difficulty, satisfaction, or regret (Table 3). Personality traits (optimism, pessimism, and faith) were not associated with treatment choice or with qualities of the treatment decision-making process.

4. Discussion

This population-based study evaluated the impact of both social and personality factors on treatment choices and decision-making qualities. We found that social, but not personality, factors predicted treatment choice and decision-making difficulty. These findings underscore the importance of providing decision support not just to patients but also to members of their social support system, including friends, family, and spouse/partner. The previously identified importance of physicians taking patient preferences into account [29] should be expanded to include the opinions and preferences of patient's friends and family members in helping patients make an informed treatment decision for LPC.

An interesting finding of our study was that consultation with friends during decision-making increased men's likelihood of choosing curative treatment compared to WW/AS after adjusting for age, race, comorbidities, tumor risk level, and treatment status. This suggests that friends may encourage patients to choose more aggressive treatment. This broader understanding of the influence of members from the patient's social support networks, while understudied, is consistent with previous findings. Earlier interviews of prostate cancer patients in the UK found that men often felt considerable pressure from family, as well as from doctors and support groups, to pursue curative treatment [14]. A recent focus group study of physicians found that, even with the increase in recommendations of AS/WW as a treatment strategy, most family members and spouses were more often in support of active treatment and opposed to AS [20]. Our recent focus group study found that men and their partners often felt it was necessary to justify their AS decision to their social support, particularly to alleviate the fears of family and friends about their untreated cancer [11]. Of particular importance is the influence of friends or family members who were previously diagnosed with prostate cancer [21, 22]. One

Table 1: Differences in demographic, clinical, and personality characteristics by race and treatment choice.

Variable	Total	By race			By treatment choice			
	$n = 160$ (%)	White $n = 89$ (%)	Black $n = 71$ (%)	p-value*	WW/AS $n = 16$ (%)	Radiation $n = 50$ (%)	Surgery $n = 94$ (%)	p-value*
Age								
Mean (SD)	61.0 (7.3)	61.8 (6.5)	60.1 (8.2)	0.14	64.6 (7.4)	63.0 (6.9)	59.4 (7.1)	<**0.01**
Less than 65	102 (63.8)	55 (61.8)	47 (66.2)	0.68	8 (50.0)	28 (56.0)	66 (70.2)	0.12
65 and greater	58 (36.3)	34 (38.2)	24 (33.8)		8 (50.0)	22 (44.0)	28 (29.8)	
# of comorbidities								
0	34 (21.3)	22 (24.7)	12 (16.9)	0.42	3 (18.8)	4 (8.0)	27 (28.7)	**0.02**
1	60 (37.5)	31 (34.8)	29 (40.8)		4 (25.0)	21 (42.0)	35 (37.2)	
2	38 (23.8)	23 (25.8)	15 (21.1)		6 (37.5)	11 (22.0)	21 (22.3)	
≥3	28 (17.5)	13 (14.6)	15 (21.1)		3 (18.8)	14 (28.0)	11 (11.7)	
PSA level								
≤4	66 (42.0)	39 (44.3)	27 (39.1)	0.59	4 (26.7)	23 (46.0)	39 (42.4)	0.61
5–9	70 (44.6)	40 (45.5)	30 (43.5)		7 (46.7)	21 (42.0)	42 (45.7)	
10–19	8 (5.1)	3 (3.4)	5 (7.2)		2 (13.3)	2 (4.0)	4 (4.3)	
≥20	13 (8.3)	6 (6.8)	7 (10.1)		2 (13.3)	4 (8.0)	7 (7.6)	
Gleason score								
≤6	80 (50.0)	50 (56.2)	30 (42.3)	0.16	8 (50.0)	30 (60.0)	42 (44.7)	**0.04**
7	65 (40.6)	33 (37.1)	32 (45.1)		4 (25.0)	15 (30.0)	46 (48.9)	
8–10	15 (9.4)	6 (6.7)	9 (12.7)		4 (25.0)	5 (10.0)	6 (6.4)	
Tumor risk Level†								
Low	28 (18.3)	17 (19.5)	11 (16.7)	0.79	5 (33.3)	19 (42.2)	4 (4.3)	<**0.01**
Intermediate	44 (28.8)	26 (29.9)	18 (27.3)		8 (53.3)	15 (33.3)	21 (22.6)	
High	81 (52.9)	44 (50.6)	37 (56.1)		2 (13.3)	11 (24.4)	68 (73.1)	
Treatment started/received by survey								
Yes	103 (64.4)	63 (70.8)	40 (56.3)	0.08	5 (31.3)	35 (70.0)	63 (67.0)	**0.02**
No	57 (35.6)	26 (29.2)	31 (43.7)		11 (68.8)	15 (30.0)	31 (33.0)	
Education								
≤High school	101 (63.5)	47 (53.4)	54 (76.1)	<**0.01**	11 (68.8)	35 (70.0)	55 (59.1)	0.40
>High school	58 (36.5)	41 (46.6)	17 (23.9)		5 (31.3)	15 (30.0)	38 (40.9)	
Married/partnered								
Yes	127 (80.4)	79 (89.8)	48 (68.6)	<**0.01**	12 (75.0)	40 (81.6)	75 (80.6)	0.84
No	31 (19.6)	9 (10.2)	22 (31.4)		4 (25.0)	9 (18.4)	18 (19.4)	
Consulted family								
Yes	85 (53.5)	38 (43.2)	47 (66.2)	<**0.01**	6 (37.5)	28 (56.0)	51 (54.8)	0.42
No	74 (46.5)	50 (56.8)	24 (33.8)		10 (62.5)	22 (44.0)	42 (45.2)	
Consulted friends								
Yes	85 (53.5)	48 (54.5)	37 (52.1)	0.88	3 (18.8)	31 (62.0)	42 (45.2)	<**0.01**
No	74 (46.5)	40 (45.5)	34 (47.9)		13 (81.3)	19 (38.0)	51 (54.8)	
Consulted spouse/partner								
Yes	120 (76.9)	65 (74.7)	55 (79.7)	0.59	8 (57.1)	38 (77.6)	74 (79.6)	0.20
No	36 (23.1)	22 (25.3)	14 (20.3)		6 (42.9)	11 (22.4)	19 (20.4)	
Physician seen								
Urologist only	15 (9.2)	11 (13.3)	4 (6.8)	0.47	3 (18.8)	2 (4.3)	10 (12.3)	<**0.01**
Urologist/PCP only	59 (41.5)	33 (37.3)	26 (44.1)		7 (43.8)	5 (10.6)	47 (58.0)	
Rad. onc. ± urologist/PCP	70 (49.3)	41 (49.4)	29 (49.2)		6 (37.5)	40 (85.1)	24 (29.6)	

Table 1: Continued.

Variable	Total	By race			By treatment choice			
	$n = 160$ (%)	White $n = 89$ (%)	Black $n = 71$ (%)	p-value*	WW/AS $n = 16$ (%)	Radiation $n = 50$ (%)	Surgery $n = 94$ (%)	p-value*
Optimism‡								
Mean (SD)	4.0 (0.8)	3.9 (0.7)	4.0 (0.9)	0.44	4.1 (0.6)	4.2 (0.5)	3.9 (0.9)	0.09
Pessimism‡								
Mean (SD)	2.0 (0.8)	1.9 (0.7)	2.0 (0.9)	0.42	1.8 (0.7)	1.9 (0.7)	2.0 (0.8)	0.24
Faith score‡								
Mean (SD)	3.5 (1.1)	3.1 (1.1)	3.9 (1.1)	<**0.01**	3.3 (1.2)	3.6 (1.1)	3.4 (1.2)	0.97

* p values were calculated using chi-square test or Fisher's exact test for dichotomous data and t-tests or ANOVA for continuous outcomes. †Tumor risk level categorized using the American Urological Association endorsed D'Amico criteria: low indicates PSA level < 10, Gleason score ≤ 6, and clinical stage T1-2a; intermediate indicates PSA of 10–20, Gleason score of 7, and clinical stage T2b; high indicates PSA > 20, Gleason score ≥ 8, and clinical stage T2c-3a. ‡Measured on a scale of 1 to 5: 1, not at all true, and 5, completely true.

Table 2: Factors associated with treatment choice.

Variable	Radiation versus WW/AS		Surgery versus WW/AS		Surgery versus radiation	
	OR (95% CI)*	p-value†	OR (95% CI)*	p-value†	OR (95% CI)*	p-value†
Consulted friends	11.07 (2.21 to 55.3)	<**0.01**	8.67 (1.73 to 43.6)	<**0.01**	0.78 (0.31 to 1.99)	0.61
Physician seen						
Urologist only (ref.)						
Urologist/PCP	0.29 (0.02 to 3.79)	0.35	1.20 (0.18 to 8.17)	0.86	4.12 (0.45 to 3.78)	0.21
Rad. onc. ± urologist/PCP	6.06 (0.74 to 49.4)	0.09	1.01 (0.15 to 6.65)	0.99	0.17 (0.03 to 0.94)	**0.04**

* Adjusted for age, comorbidities, tumor risk level, race, and treatment status. † Calculated using multinomial logistic regression.

study showed LPC patients who consulted other patients to be half as likely to choose AS/WW as those who did not [13]. We have shown that this cohort of patients underestimates their life expectancy without treatment and overestimates their gain in life expectancy with curative treatments [30]. This bias may be shared or influenced by similar misconceptions among family and friends. The recent physician focus group study argued that, even with an increase in patients and physicians willing to choose AS in recent years, patients' family and friends may lack understanding about AS and be more anxious about the untreated cancer than the patient himself [20]. Further educational intervention about LPC treatment choices, particularly about AS, which includes family and friends in addition to patients and their spouses/partners may be needed.

A novel finding of our study was that consulting friends and family was associated with greater difficulty in making a treatment decision. In this study, family did not include patient's spouse/partner. We cannot be certain whether this association occurred because men who are having difficulty making a treatment decision were more likely to turn to their family and friends for advice or because consulting friends and family caused increased decision-making difficulty. Part of the greater decision-making difficulty may be due, in part, to conflicting opinions and preferences among family and friends involved in the decision-making process. The potential for positive social support during this difficult time, however, remains high. A previous study found that discussing treatment options with family or friends, prior to beginning treatment for prostate cancer, significantly improved patients' general happiness at 1 and 6 months following treatment [16]. Some evidence exists to support the use of decision aids among family and friends as a possible solution to ameliorate potential misconceptions held by family and friends. In particular, decision aids with expressed probabilities and explicit values clarifications helped people to have more accurate risk perceptions and to choose a treatment most congruent with their personal beliefs [31]. While these findings come from studies focused on patients, future research should expand the subject population to include patients' family and friends.

Our study did not find a significant association between a man consulting his spouse/partner and treatment choice or qualities of the treatment decision-making process. Previous research has demonstrated that spouses/partners often are involved in discussions about LPC. Frequent roles of spouses/partners are to provide emotional support, discuss treatment options with the patient, go to doctor appointments with the patient and be involved with conversations with the providers, gather information for the patient, aid in sharing information about the diagnosis with family members and friends, and help the patient decide on a treatment choice [9–11]. However, although spouses/partners are often actively involved in the treatment decision-making process, some research argues that they ultimately support or are satisfied with whatever treatment decision the LPC patient makes [10, 11]. Perhaps this may help explain why consulting a spouse is not significantly associated with the

Table 3: Factors associated with treatment decisional quality outcomes.

Variable	Decisional satisfaction		Decision-making difficulty		Decisional regret	
	OR (95% CI)*	p-value†	OR (95% CI)*	p-value†	OR (95% CI)*	p-value†
Consulted family	0.65 (0.32 to 1.29)	0.22	2.59 (1.29 to 5.35)	**<0.01**	1.60 (0.81 to 3.19)	0.18
Consulted friends	0.98 (0.50 to 1.91)	0.94	3.70 (1.86 to 7.66)	**<0.01**	1.79 (0.92 to 3.54)	0.09
Consulted spouse/partner	0.69 (0.29 to 1.57)	0.39	2.23 (0.96 to 5.48)	0.07	1.05 (0.47 to 2.38)	0.91
Optimism	1.36 (0.87 to 2.27)	0.19	0.94 (0.59 to 1.47)	0.77	0.82 (0.51 to 1.28)	0.40
Pessimism	0.79 (0.50 to 1.25)	0.31	1.19 (0.75 to 1.89)	0.46	1.25 (0.79 to 1.98)	0.34
Faith score	1.34 (0.98 to 1.88)	0.08	1.56 (0.85 to 1.58)	0.36	0.97 (0.71 to 1.32)	0.84
Physician seen						
Urologist only (ref.)						
Urologist/PCP	1.74 (0.53 to 5.89)	0.36	0.79 (0.24 to 2.67)	0.69	0.49 (0.14 to 1.62)	0.25
Rad. onc. ± urologist/PCP	1.99 (0.62 to 6.52)	0.24	1.21 (0.38 to 3.98)	0.75	0.39 (0.11 to 1.25)	0.12

*Adjusted for age, comorbidities, tumor risk level, race, and treatment status. †Calculated using logistic regression. ‡Rad. onc.: radiation oncologist.

final treatment decision. It is also possible that only certain roles that a spouse/partner fills during the LPC treatment decision-making process influence qualities of the treatment decision-making process or final treatment choice.

Consistent with literature, we also found that physician specialty affected treatment choice. Men who saw a radiation oncologist in addition to a urologist and/or a PCP were more likely to choose radiation as compared to surgery after adjusting for age, race, comorbidities, tumor risk level, and treatment status. Such an association is not unexpected, as there are recognized preferences held by each physician specialty. Urologists often recommend surgery [32] or, increasingly recently, AS/WW [33] as the optimal treatment strategy, while radiation oncologists prefer radiation therapy [32]. Jang et al. [34] examined the association between provider visits and treatment choice in 85,088 men with newly diagnosed early-stage prostate cancer. There was a strong association between the type of specialist seen and primary therapy received. A study of 167 LPC patients by Sommers et al. concluded that it is likely that the association between physician specialty and LPC treatment choice reflects both patient preferences and physician bias toward the treatment options offered by their specialty [35]. Two more recent studies confirmed that physician recommendation influenced treatment choice [36, 37]. In addition, it was found that men expressing a preference for AS were more likely to have received a physician recommendation for AS and less likely to have received a recommendation for active therapy [37]. Our finding, which reinforces the association between physician specialty and LPC treatment choice, is important as it stresses the highly influential role that physicians have in patients' treatment decision-making process. Optimal decision-making therefore must openly address physician preferences and biases.

Contradictory to previous literature, we found that faith score was not significantly associated with treatment choice or qualities of the treatment decision-making process. Two reports based on a sample of a LPC patient cohort found that increased spirituality was associated with greater decisional satisfaction, less decisional conflict, less decision-making difficulty, and less decisional regret [7, 8]. In addition, increased spirituality was shown to be associated with increased physical and mental health of men with prostate cancer, including improvement in emotional well-being and decrease in symptom distress and anxiety [38]. These studies measured spirituality using the Functional Assessment of Chronic Illness Therapy-Spirituality Well-Being Scale (FACIT-Sp), which includes two subscales: peace/meaning (capturing a sense of purpose and meaning in life) and faith (spiritual beliefs) [7, 8, 38]. Mollica et al. found that increased scores on both subscales were associated with decisional qualities [7, 8]. In Krupski et al.'s study, the higher peace/meaning subscale was associated with decisional qualities, while the faith subscale was not [38]. Perhaps the faith score that we measured in this study did not fully capture the specific factors of spirituality that impact the treatment decision-making process. It could also be that the use of religious coping as a resource to handle a prostate cancer diagnosis and the stressful decision-making process differs among different groups of men. For example, a study of men with prostate cancer in Georgia demonstrated that black men and those with lower education, lower income, and more comorbidity reported significantly higher levels of religious coping than other groups [39]. Further studies of the impact of faith on men's treatment decision and the treatment decision-making process are needed.

We did not find that men's personality traits of pessimism or optimism had significant associations with either treatment choice or qualities of the treatment decision-making process, which contradicts one study of 125 LPC patients which found that men with lower optimism were at greater risk for treatment decision-making difficulty and lack of decisional satisfaction [6]. This study found that self-efficacy partially mediated the effect of optimism on treatment decisional quality [6]. Although we used a similar scale to measure optimism, we did not assess self-efficacy in our study. The time point at which the participants in our study were surveyed differed from the previous study, when men were surveyed after choosing but before receiving treatment [6], while we surveyed men who had been diagnosed about 6 months previously regardless of whether they had started their treatment. Furthermore, we had a higher

percentage of black men compared to the previous study, which could also contribute to the difference in findings. The complex relationship of personal beliefs, personality traits, and religion/faith and their influence on decision-making needs further investigation.

This is one of few population-based studies that examined the effects of physician specialty, patient personality traits, and social influences on LPC treatment choice and decisional quality outcomes. Despite the novel nature of this study's topic of investigation, there are several limitations to this study. First, as with any survey study, there is potential for recall bias. However, we assessed the degree of accuracy among patient self-reported data by comparing patient-reported tumor characteristics with tumor characteristics from our tumor registry (MDCSS). These two sets of data were highly correlated ($\rho > 0.7$, data not shown) [19]. Any bias resulting from misclassification of some variables due to self-reporting would not likely have differed significantly between the different demographic groups within our study. Second, we oversampled black men to achieve a more racially diverse study sample. It is possible that our study design may have contributed to potential selection bias. Third, our sample was gathered from the Metropolitan Detroit area, so the findings of our study may not be applicable to areas with different populations. However, our study sample was more racially diverse than many other studies examining the treatment decision-making process of LPC patients. Fourth, our study's relatively small sample size limited our ability to perform race-stratified data analysis. Larger, racially diverse studies are needed to confirm our study findings. Our study also had a lower number of men ($n = 16/160$) who chose AS/WW. Larger studies are needed to confirm our findings for men who chose AS/WW, particularly since the number of men being recommended and choosing AS/WW as a treatment for LPC has increased in recent years [34]. We also did not differentiate watchful waiting from active surveillance in this study due to the small sample size and because these terms are often used interchangeably by physicians and patients. As this survey was done during the period from 2009 to 2010, it likely underrepresents AS in present practice. However, the main treatment options and their possible benefits and harms as well as the controversies surrounding the best treatment for individuals are not changed. Finally, our data were skewed toward high satisfaction and low regret with treatment decision with little variability. This may limit our ability in delineating any associations between personality traits or social influences consulted and decisional satisfaction or regret. This may also be due to the short time interval between making a treatment choice and completing our survey. Longer-term studies with larger populations are needed to further explore these associations.

5. Conclusion

This population-based study of a racially diverse cohort highlights the important effect of social influences during the patient's treatment decision-making process, including patient's personality traits, family, friends, and physicians, on his treatment choice and decisional quality outcomes. Consulting with friends increased men's odds of choosing curative treatment, and consulting with family and/or friends was associated with an increase in men's difficulty in making a treatment decision. Men who saw a radiation oncologist were more likely to choose radiation than surgery. These findings demonstrate the importance of an informed treatment decision-making process that should include both the patient and their family and friends to align preferences, provide education, and reduce decision-making difficulty. These findings also suggest expanded use of decision aids and other educational interventions to recognize and include family and friends in the shared decision-making process. Developing realistic expectations of treatments across communities of influence may help guide patients to make the treatment choice that best fits their own goals and preferences.

Disclosure

Part of the results were presented at 2015 Annual Michigan Family Medicine Research Day, May 2015, Howell, Michigan, and at 2015 AACR Conference on the Science of Cancer Health Disparities in Racial/Ethnic Minorities and the Medically Underserved, November 2015, Atlanta, GA.

Conflicts of Interest

All authors report that they do not have any financial conflicts of interest.

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Research Article

Long-Term Oncological Outcomes for Young Men Undergoing Radical Prostatectomy for Localized Prostate Cancer

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Aim. The aim of this study was to describe PCa characteristics and long-term outcomes in young men aged ≤55 years after radical prostatectomy (RP) and to compare them with older men cohort. *Methods*. Among 2,200 patients who underwent RP for clinically localized PCa at our centre between 2001 and 2015, 277 (10.3%) men aged ≤55 years were identified. All preoperative and pathological parameters were compared between groups. Biochemical progression free survival (BPFS) and disease progression free survival (DPFS) were assessed at 5 and 10 years. *Results*. Men aged ≤55 years had similar pathological tumor characteristics and biochemical recurrence rate (BCR) compared to their older counterparts. Disease progression rate 2.5% versus 0.4% was higher in older patients ($p = 0.026$). BPFS rate was not different in both study groups. Estimated 10-year DPFS was 98.8% in younger men compared to 89.2% in their older counterparts ($p = 0.031$). Multivariate Cox regression showed that Gleason score lymph-nodes and surgical margins status were significant predictors for disease progression. *Conclusions*. In our cohort, men aged ≤55 years had similar pathological PCa characteristics and BCR rate in comparison with older men. RP can be performed with excellent long-term DPFS results in men with localized PCa at ≤55 years of age.

1. Introduction

Prostate cancer (PCa) is a disease of the elderly with 80% of men diagnosed at the age ≥65 [1]. However, PCa diagnosis is not uncommon in younger men, and the proportion of patients with PCa aged <50 years has increased from 1% in the 1970s to 5% in the PSA era [2]. Different autopsy studies show high rates of latent PCa in the fourth and fifth decades of age. The prevalence of latent PCa in younger men varies markedly among different autopsy series from 2.6% in Greek series [3] to a much higher 27% prevalence in Hungary [4] and up to 34% in USA [5]. Altogether, the study shows that about 20%–30% of 40–50-year-old men would harbor a PCa [6]. The increase of PCa diagnosis at young age raises a number of important questions about their biology and treatment modalities. A 60-year-old patient with a low risk and Gleason score 6 PCa is a suitable candidate for active surveillance. However, a similar scenario in men aged 45–55 might prompt immediate intervention in majority of cases, because of opinion that PCa detected in young age might behave more aggressively [7] and because young men are more likely to undergo RP [8]. Data about young age men with PCa treatment outcomes are controversial. According to the pre-PSA era studies, younger men are likely to have a more aggressive disease and carry a worse prognosis [9, 10]. However, more recent studies suggest high rates of indolent PCa with more favorable outcomes in young men after radical prostatectomy (RP) compared to their older counterparts

[11–13]. A common limitation of these studies was prostate specific antigen (PSA) relapse used as endpoint of oncological outcomes, whereas disease progression or cancer related death should be the optimal endpoint in order to provide more generalizing conclusions.

The twofold aim of our study was to determine whether younger men had more favorable pathological findings and oncological outcomes (biochemical recurrence rate (BCR) and disease progression) in comparison with older counterparts and to evaluate prognostic risk factors for disease progression after RP.

2. Patients and Methods

Between 2001 and 2015, 2,200 men were treated with RP for clinically localized PCa at a single university hospital centre. We identified 277 men aged ≤55 years at time of RP. Clinical characteristics such as PSA level, clinical stage, and biopsy Gleason score were reported before RP. Pathological parameters (pathological stage, Gleason score, surgical margin status, and lymph nodes status) were collected after surgery. PSA testing after RP was performed every three months in the first year, biannually in the second and third year, and once a year thereafter. BCR was identified as a PSA value of >0.2 ng/ml in two consequent measurements. Disease progression was identified upon skeletal lesions confirmation by bone scan, CT, or MRI using RECIST criteria. Local recurrence was confirmed by histological investigation after surgery or biopsy. Pathological stage was assessed using 2002 TNM system, and tumor grading was classified using the Gleason grading system (2001–2005) and the revised 2005 Gleason grading system afterwards. Histopathological investigation in the majority of cases was performed by one uropathologist I.G. Adjuvant therapy (radiation therapy (RT) alone or RT + androgen deprivation therapy) was performed depending on the pathological characteristics of PCa within four months after RP, and salvage therapy (radiation therapy (RT) alone or RT + androgen deprivation therapy) was applied after detecting BCR. Prospective collection of data was approved by the university's ethical committee, and all patients signed a consent form provided before RP.

Clinical, pathological, and follow-up data (time to BCR, time to detected metastasis, or local recurrence) were compared between men aged ≤55 years at time of RP and older patients. The chi-square test for nominal variables and the t-test for continuous variables were used to compare baseline clinical and pathological characteristics. BPFS and DPFS rates for each study group were estimated using Kaplan-Meier analysis. The long-rank test was used to compare survival of younger versus older men. Men who underwent adjuvant therapy without BCR were excluded from BPFS analyses. The impact of baseline parameters on disease progression was assessed by bivariate and multivariate Cox regression analyses adjusted for clinical stage, preoperative PSA level, biopsy Gleason score, pathological stage, pathological Gleason score, lymph nodes, and surgical margins status. For this analysis PSA value was categorized to ≤4.0 versus 4.1–10 versus 10.1–20.0 versus >20.0 ng/ml.

3. Results

The number of men aged ≤55 years treated by RP in our centre increased significantly from 2.8% in 2003 to 15.5% in 2015. Within presented study cohort (Table 1), younger men aged ≤55 years were more likely to present with low PSA level ($p = 0.038$), clinically organ confined disease ($p < 0.001$), and less aggressive tumor according to biopsy Gleason score ($p = 0.046$). Pathological PCa stage ($p = 0.1$), grade ($p = 0.37$), and positive lymph nodes rate ($p = 0.85$) were not different comparing young men with older counterparts. BCR was similar between groups and reached 29% during median 50 months overall follow-up; metastases were detected at significantly higher rate in older men ($p = 0.026$). Skeletal disease progression lesions were detected in 40 of 50 (80%) cases, and in 10 (20%) cases local metastatic process was confirmed histologically after salvage surgery or biopsy. The median time to disease progression was 43 months in men aged >55 years versus 54 months in younger men.

The Kaplan-Meier analysis showed similar BPFS rate (Figure 1) for men aged ≤55 years and older patients (2-, 5-, and 8-year BPFS was 85.9%, 77.9%, and 72.4% versus 82.8%, 73.7% and 63.7%, resp.; log rank $p = 0.57$); therefore different estimated DPFS rate (Figure 2) was detected between study groups (5- and 10-year DPFS was 98.8% and 98.8% versus 96.9% and 89.2% resp.; log rank $p = 0.031$).

Bivariate regression analysis revealed that almost all pre- and postoperative parameters, except patients' age and PSA below 20 ng/ml, are predictors for disease progression and Gleason score was most significant of them (Table 2). Multivariate Cox regression analysis shows that pathological Gleason score, positive surgical margins, and lymph nodes were mostly significant predictors of disease progression (Table 3). Patients' age (≤55 versus >55 years of age) failed to reach significant predictor status.

4. Discussion

Age at the detection of cancer is a well-recognized prognostic factor in a patient with majority localizations of malignancy. Although few studies demonstrated an association of a young age and high stage of PCa with worse prognosis [9, 10], data from recent studies have shown that earlier diagnosis of PCa in young men is associated with low grade and stage disease or even with superior outcome [11–13].

Becker et al. presented data of more than 13 thousand men who underwent RP at a single centre [13]. The authors compared men aged <50 and ≥50 years and detected a significant difference in pathological grade and stage between groups favorable to younger patients. Similar findings were presented by some other authors [11, 12]. Twiss et al. demonstrated opposite results in their analysis of 790 men after RP. These authors did not detect difference in preoperative and pathologic predictors of organ-confined disease and BCR between men aged <50 years and older [14]. Our data also showed that the proportion between organ-confined (70.4% versus 65.5%), locally advanced (29.6% versus 34.5%), low grade (Gleason score ≤ 3 + 4, 83.4% versus 80.6%), and high

Table 1: Clinical and pathologic features of men undergoing prostatectomy.

Parameter	Age ≤ 55 (n = 277)	Age > 55 (n = 1.923)	p
Follow-up (mo), median (quartiles)	48.5 (24.0–77.3)	50.0 (24.0–79.3)	0.8
PSA (ng/mL), median (quartiles)	5.8 (4.5–9.0)	6.36 (4.8–9.5)	0.038
Clinical stage, n (%)			
cT1	104 (37.5)	565 (29.4)	
cT2	154 (55.6)	1098 (57.1)	0.001
cT3	19 (6.9)	260 (13.5)	
Pathological stage, n (%)			
pT2	195 (70.4)	1260 (65.5)	
pT3a	70 (25.3)	519 (27.0)	0.1
pT3b	12 (4.3)	144 (7.5)	
Biopsy GS, n (%)			
3 + 3	183 (66.1)	1,125 (58.5)	
3 + 4	77 (27.8)	597 (31.0)	
4 + 3	10 (3.6)	75 (3.9)	0.046
8	5 (1.8)	87 (4.5)	
9-10	2 (0.7)	39 (2.0)	
Pathological GS, n (%)			
3 + 3	78 (28.2)	539 (28.0)	
3 + 4	153 (55.2)	1,011 (52.6)	
4 + 3	28 (10.1)	183 (9.5)	0.37
8	11 (4.0)	89 (4.6)	
9-10	7 (2.5)	101 (5.3)	
Pathological nodal status, n (%)			
N0	65 (23.5)	619 (32.2)	
N1	7 (2.5)	62 (3.2)	0.85
Surgical margins status, n (%)			
R0	214 (80.5)	1482 (80.1)	
R1	52 (19.5)	368 (19.9)	0.92
PSA relapse, n (%)	79 (28.5)	544 (28.3)	0.9
Disease progression, n (%)	1 (0.4)	49 (2.5)	0.026

PSA: prostate specific antigen, GS: Gleason score.

grade (Gleason score ≥ 4 + 3, 17.6% versus 19.4%) disease was similar when comparing young men and older counterparts, respectively. This suggests that data regarding pathological findings after RP in young men are still controversial. Therefore, data from recent studies confirm that pathological PCa characteristics in young men are not more aggressive than in older men.

Long-term BFSR for young men cohort presented in various studies is high. Becker et al. reported 80.7% and 63.0% estimated 5- and 10-year BFSR for men aged <50 years, and it was significantly higher ($p = 0.006$) compared to the older counterparts [13]. Freedland et al. presented 6-year BFSR data according to the decade of life in 1,753 men after RP and showed that men younger than 50 years of age had significantly higher BFSR compared to other groups [11]. Parker et al. also detected significantly lower BCR rate and highest BPFS among men aged <50 years versus all other age groups in their analysis of 5,195 men after RP [12]. In our study, 5- and 8-year BFSR was 77.9% and 72.4%, respectively, for young men, but the difference compared to men aged >55 years was not significant ($p = 0.57$). Looking at the data of all mentioned publications, we would like to emphasize that age at the time of surgery failed to achieve independent predictor status in multivariable analysis in most studies.

PSA relapse is not always associated with disease progression; therefore, behaviour of cancer could be estimated by disease progression or cancer related death. In present study, only one case (0.4%) of metastatic disease was detected in men aged ≤55 year compared to 49 cases (2.5%) in older men ($p = 0.026$). In presented cohort bivariate Cox proportional hazards model showed that clinical stage and biopsy Gleason score are significant predictors for disease progression, and the highest hazard ratio was detected for very poorly differentiated cancer (Gleason score 9-10). Preoperative PSA only at value >20 ng/ml could influence PCa progression. Younger patients age ≤55 years did not reach substantial level as independent parameter ($p = 0.07$). All pathological parameters in bivariate analysis were detected as highly significant predictors for disease progression ($p = 0.001$). Multivariate analysis shows that only some pathological

Table 2: Bivariate Cox proportional hazards analysis of factors predicting time to disease progression after radical prostatectomy.

Parameter	Hazard ratio	CI 95%	p
Clinical stage (cT):			
cT2 versus cT1	3.2	1.8–7.6	0.011
cT3 versus cT1	6.8	2.4–9.6	0.001
Pathological stage (pT):			
pT3a versus pT2	3.7	1.7–8.1	0.001
pT3b versus pT2	17.5	8.3–36.8	<0.001
PSA (ng/ml)			
4.1–10 versus ≤4	1.3	0.4–3.7	0.7
10.1–20 versus ≤4	2.1	0.7–6.4	0.2
>20 versus ≤4	5.3	1.6–16.9	0.005
Biopsy GS:			
3 + 4 versus 3 + 3	3.8	1.9–7.9	<0.001
4 + 3 versus 3 + 3	7.7	2.5–23.7	<0.001
4 + 4 versus 3 + 3	6.8	2.4–19.1	<0.001
≥4 + 5 versus 3 + 3	52.9	19.8–141.1	<0.001
Pathological GS:			
3 + 4 versus 3 + 3	N.D	N.D	N.D
4 + 3 versus 3 + 3	16.8	4.1–68.7	<0.001
4 + 4 versus 3 + 3	24.6	6.6–92.1	<0.001
≥4 + 5 versus 3 + 3	114.0	30.9–421.6	<0.001
Lymph nodes status (pN):			
N1 versus N0	4.5	2.0–9.9	0.001
Surgical margins:			
R1 versus R0	5.6	2.9–10.9	<0.001
Age, years			
≤55 versus >55	6.4	0.9–46.3	0.07

PSA: prostate specific antigen, GS: Gleason score.

Table 3: Multivariate Cox proportional hazards analysis of factors predicting time to disease progression after radical prostatectomy.

Parameter	Hazard ratio	CI 95%	p
Clinical stage	1.1	0.6–1.5	0.1
Pathological stage	1.2	0.7–2.0	0.6
PSA (ng/ml)	1.0	0.7–1.5	0.9
Biopsy GS	1.1	0.8–1.4	0.6
Pathological GS	2.4	1.7–3.1	<0.0001
Lymph nodes status			
N1 versus N0	0.39	0.15–0.65	0.002
Surgical margins			
R1 versus R0	4.1	1.8–9.4	0.001
Age, years			
≤55 versus >55	0.15	0.02–1.1	0.06

PSA: prostate specific antigen, GS: Gleason score.

parameters such as positive lymph nodes (HR 0.39, $p = 0.002$), positive surgical margins (HR 4.1, $p = 0.001$), and Gleason score (HR 2.4, $p < 0.0001$) are important for disease progression. These findings are in concordance with various other studies' data [15–20]. Interestingly enough, no

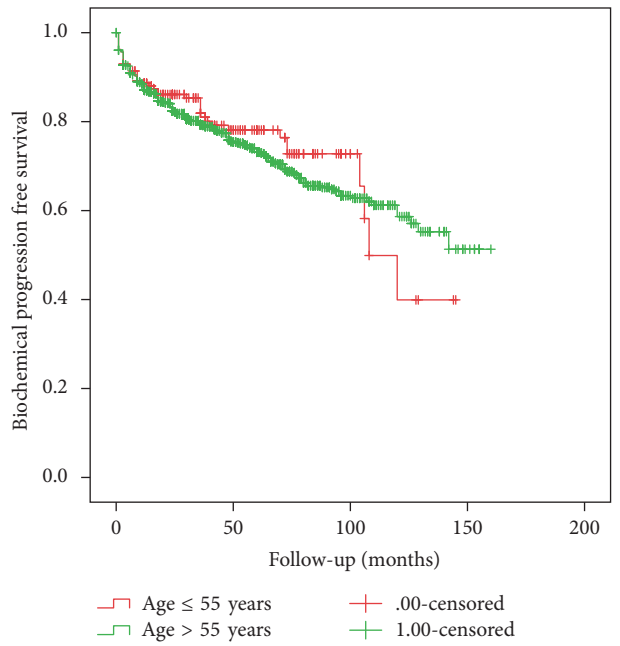

Figure 1: Comparison of Kaplan Meier biochemical progression free survival between study groups (log rank $p = 0.57$).

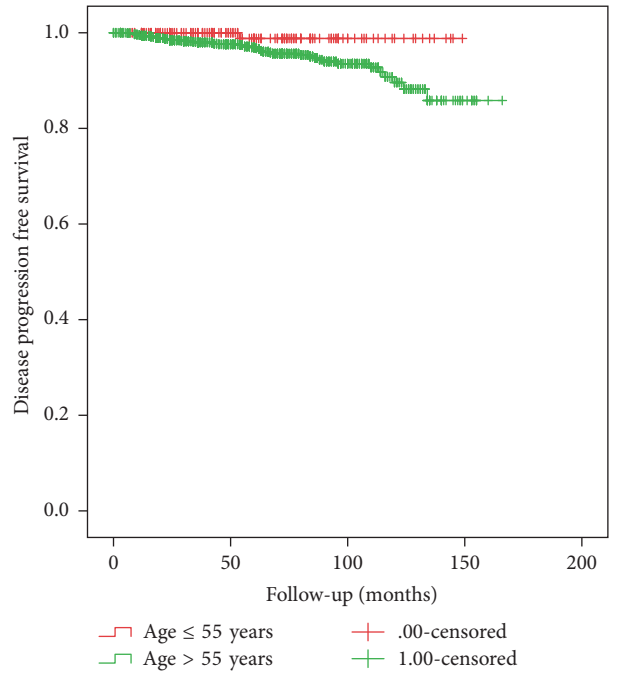

Figure 2: Comparison of Kaplan Meier disease progression free survival between study groups (log rank $p = 0.031$).

difference was detected comparing these parameters between men aged ≤55 years versus >55 years in our cohort. Estimated 10-year DPFS was 98.8% versus 89.2% ($p = 0.031$) in favor of men aged ≤55 years. Presented data show that older men are more likely to progress to metastatic disease after a definitive treatment of BCR. More aggressive behavior of

cancer in older men is unclear and needs more intensive multi-institutional research.

Two possible hypotheses arise trying to explain our study findings. The first one is that older men potentially have a more aggressive disease. Several studies comparing oncological outcomes after RP in young and older men supported such a conclusion [11–14]. In their review of young-age prostate cancer, Hussein et al. noticed that young-age PCa has several biological and genetic features that are distinct from elderly-onset cancer, but in the majority of cases young men tend to have low grade and stage disease. On the other hand, the authors pay attention that early-onset PCa could represent a subset of young-age and familial PCa with more aggressive disease and higher prostate-cancer-specific death rate [6]. Until now, only two factors (family history and race) are confirmed to have close relationship with the detection of PCa in young men [21, 22], but the data about its aggressiveness is controversial. We did not find more aggressive disease characteristics in younger men while comparing postoperative data, but higher disease progression rate in elderly patients directly supports the hypothesis that we have raised. The pathomechanism of such behavior is unclear and needs further research. Our second hypothesis is biologically age-related decreasing possibilities against disease progression and lower response of older patients to additional treatment after PSA relapse. No difference in grade, stage, lymph nodes involvement, and BCR rate logically suggests that additional conditions play an important role in disease progression. More long-term clinical data are needed to confirm our findings. In general, the results of present study regarding oncological outcomes indicate that young men with PCa could be suitable candidates for all treatment modalities.

The choice of treatment strategy depends not only on oncological outcomes, but also on the quality of life after definitive treatment. Continence and erectile function are most important parameters that concern men after the treatment they underwent. ProtectT trial regarding these two parameters shows significant inferiority of RP when compared to radiation therapy and active surveillance [23], and we should agree that RP harbors increasing risk of functional adverse events. Therefore, if we look at the data analyzing young men's population, continence end erectile function recovery rate is very high and reaches 95% and 80%, respectively, that is a significantly higher rate in comparison with older counterparts [13, 14]. The most important predictor for preservation of erectile function is nerve-sparing procedure [13, 14] that is strongly recommended in cases of young age and organ confided disease. So, we can conclude that men in young age with localized PCa are suitable candidates for surgical treatment with good DP control and low functional adverse events rate after RP.

The present study is not devoid of limitations. A relatively short follow-up is one of them. The absence of other treatment modality group and direct comparison of results is another limitation of our study. Although disease progression, not death from cancer, was chosen as the end point of this study, looking at our results we hope that the analysis of cancer specific mortality would show similar tendencies.

The strength of the present study is prospectively collected data, pathological investigation by one experienced pathologist in majority of cases, standard evaluation of disease progression, and treatment of BCR. To our knowledge, this study is the first one to describe disease progression free survival as end point in young patients cohort after RP.

5. Conclusions

The presented analysis of a large, single centre's cohort of men after RP indicates that young patients aged ≤55 years have similar histopathology and BCR rate after surgery for localized PCa compared to older counterparts. However, young patients have a significantly lower risk for disease progression in long-term follow-up and men aged ≤55 years with localized PCa should not be discouraged from radical treatment.

Competing Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Review Article

Prostate Cancer Radiation Therapy: What Do Clinicians Have to Know?

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Radiotherapy (RT) for prostate cancer (PC) has steadily evolved over the last decades, with improving biochemical disease-free survival. Recently population based research also revealed an association between overall survival and doses ≥ 75.6 Gray (Gy) in men with intermediate- and high-risk PC. Examples of improved RT techniques are image-guided RT, intensity-modulated RT, volumetric modulated arc therapy, and stereotactic ablative body RT, which could facilitate further dose escalation. Brachytherapy is an internal form of RT that also developed substantially. New devices such as rectum spacers and balloons have been developed to spare rectal structures. Newer techniques like protons and carbon ions have the intrinsic characteristics maximising the dose on the tumour while minimising the effect on the surrounding healthy tissue, but clinical data are needed for confirmation in randomised phase III trials. Furthermore, it provides an overview of an important discussion issue in PC treatment between urologists and radiation oncologists: the comparison between radical prostatectomy and RT. Current literature reveals that all possible treatment modalities have the same cure rate, but a different toxicity pattern. We recommend proposing the possible different treatment modalities with their own advantages and side-effects to the individual patient. Clinicians and patients should make treatment decisions together (*shared decision-making*) while using patient decision aids.

1. Introduction

Prostate cancer (PC) is the most common cancer among males in the Western world, with more than 1.11 million new cases diagnosed in 2012 and 307,000 deaths [1, 2]. The lifetime risk of developing PC is 1 in 8 [3]. It is expected that the incidence will substantially increase in the coming decades due to the aging population, which makes it a huge health care problem. The total economic costs of PC in Europe are estimated to exceed €8.43 billion [4]. One of the biggest challenges in the 21st century will be to offer the best individualised treatment at reasonable costs.

External-beam radiotherapy (EBRT) and brachytherapy (BT) are potentially curative therapies for PC. RT has undergone tremendous improvements in the last decades. Dose escalation in prostate EBRT leads to improved locoregional control, biochemical disease-free survival (bDFS), distant metastasis-free survival, PC specific mortality, and even overall survival in intermediate- and high-risk PC [5–11]. However, dose escalation is limited by toxicity of surrounding healthy tissues, and therefore improved tumour control is expected to come at the cost of higher toxicity, greatly impacting patients' quality of life [12–14]. However, dose escalation is possible due to advances in different RT techniques, sophisticated computer-based treatment planning, and/or development of extra devices, avoiding increased dose delivery to the surrounding healthy tissue. The purpose of this article is to provide insight into the enormous improvements in RT techniques to practicing clinicians and primary care doctors and to develop a greater comfort level when referring patients to a radiation oncologist. Furthermore, it provides an overview of an important discussion issue concerning

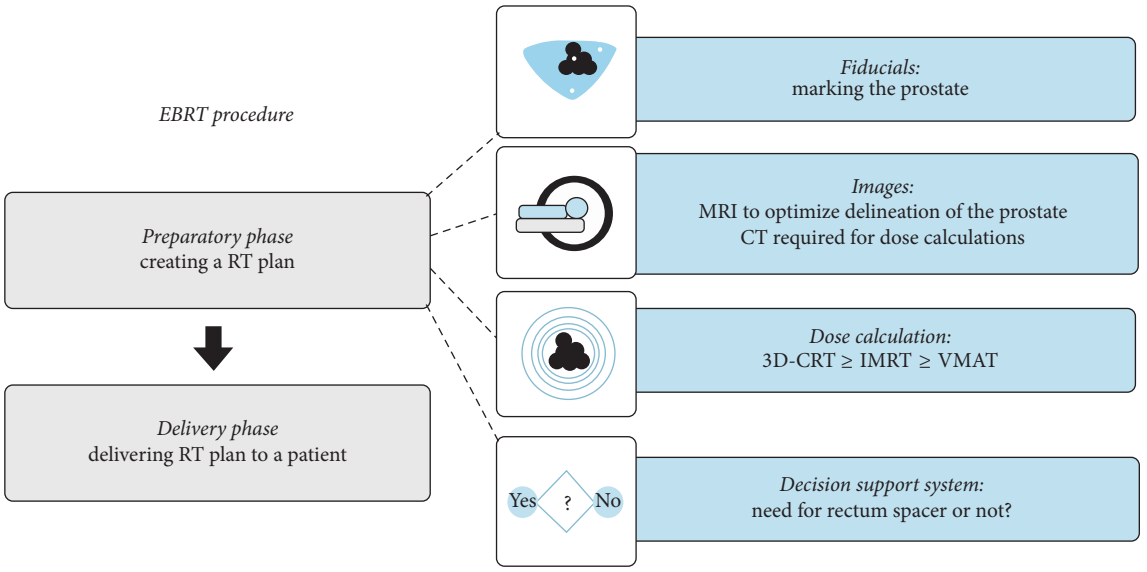


Figure 1: Overview of an EBRT procedure.

RT from a clinician's perspective: the comparison between operation and RT.

2. Overview of External Beam Radiation Treatments

In EBRT a dose of ionising radiation is generated by an external X-ray source. In the past this was a cobalt-60 source machine, but nowadays a high-tech tele-therapy unit is used for this purpose [15, 16]. Linear accelerators are the source of electronic induced irradiation. The radiation beam leaves the linear accelerator by a gantry. Different options of machines are commercially available: a traditional linear accelerator where the gantry can rotate around the patient (Arc therapy). Other possibilities are tomotherapy (=helical therapy) where the radiation dose is delivered slice-by-slice [17], or cyberknife (=a robotic radiosurgery system) where the location of the prostate is identified during treatment and active corrections are made for movements of the prostate during treatment delivery [18]. Evolving radiation techniques as protons and carbon ions are also introduced and are discussed below. Over the last 20 years the methods of delivering a dose of ionising radiation to a target area have changed incrementally.

An EBRT procedure consists of 2 main parts (Figure 1).

First, in a preparatory phase an RT plan needs to be created. This process is referred to as RT planning. Secondly, the linear accelerator requires delivering this plan to a patient in an appropriate fashion: the RT dose delivery.

In the preparatory phase, images of the patient are acquired. On these scans the clinical target area is delineated to which the radiotherapy dose is prescribed. In the 90s this area was delineated on conventional planar 2D X-rays, on which the target area (the prostate and seminal vesicles) could only be assumed. Later, CT based planning was introduced [19]. On the latter the target areas are visualised and can be delineated directly leading to up to one-third less geographical miss of the target [20]. Another advantage of CT based planning was that also critical structures like rectal wall and bladder around the target could be visualised and subsequently spared from radiation, by avoiding the X-ray beams to pass through them. Currently an MRI is being integrated more broadly into the planning process. MRI allows us to delineate the prostate more precisely from the pelvic diaphragm, and the base of the prostate can be differentiated more precisely from the seminal vesicles [21, 22]. An additional MRI changes the delineation of the clinical target volume in 18% to 20% of cases compared to CT based planning [23, 24]. Moreover, tumour extension in and outside of the prostate and invasion in the seminal vesicles are better visible on MRI and therefore more often included in the target volumes [24, 25]. Chang and colleagues reported significant volume changes with MRI delineation: extracapsular extension was significantly more incorporated into target volumes with the addition of MRI (40%) in comparison with CT (32%). The seminal vesicles are also more often included: 18% versus 3%, respectively. In addition, CT scans overestimate prostate volume by 10% to 45% [21, 22, 26–32]. Furthermore, an MRI revealed an important decrease of the interobserver delineation variation, especially at the prostatic apex [33]. We expect that a correct delineation of the target volume will result in better treatment outcome, with less toxicity, but until now this is not proven yet.

In addition to improved radiotherapy planning, developments were introduced to verify correct dose delivery during the whole course of RT over the several fractions delivered according to the radiotherapy plan. In earlier times patients were positioned on a linear accelerator using surrogate reference points: external reference points like skin lines or tattoo points or using bony landmarks visualised by conventional plain X-ray photographs taken on the linear accelerator. However, as it is known that the prostate and the seminal

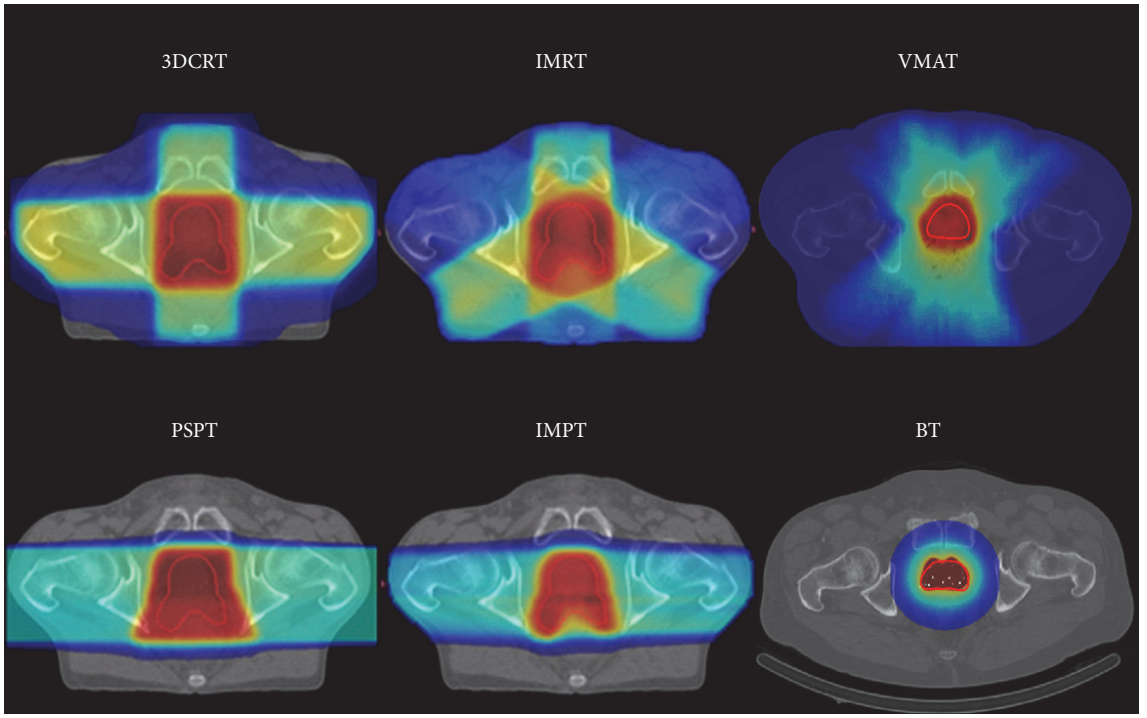


Figure 2: Examples of dose distribution of a 3DCRT, IMRT-5, VMAT, PSPT, IMPT, and a BT treatment plan calculated on the same patient. The red surface represents the high-dose regions, the yellow surface the intermediate-high-dose regions, the dark blue surface the low-dose regions, and the azure blue surface the intermediate-dose regions. 3D-CRT: 3-dimensional conformal radiotherapy; IMRT: intensity modulated radiotherapy; VMAT: volumetric modulated arc therapy; PSPT: passively scattered proton therapy; IMPT: intensity modulated proton therapy; BT: brachytherapy.

vesicles can move independently from these reference points this can be problematic because it could lead to off-target dose delivery, which in turn compromises tumour cure [34, 35]. In earlier times this problem was compensated by expanding the margins of the RT field to minimise the chance of a geographical miss. The downside of this approach was however that this approach leads to a higher volume of irradiation to the surrounding healthy tissues and critical structures. More recently, this problem is tackled by the placement of fiducials (markers) into the prostate before the RT treatment [36–38]. In this way the movement of the prostate can be monitored during treatment, and field setups can be adjusted in case of movement of the prostate ensuring correct dose delivery, even with small safety margins. A comparable methodology is implantation of electromagnetic transponders (Calypso®) [39]. Other image guidance strategies are used but are focused on visualisation of the prostate itself instead of a surrogate (marker): cone-beam computed tomography [40], MRI [41], and ultrasound imaging [42]. The most popular strategy is the use of fiducials because of the easy and quick performance. Disadvantages of the image guidance strategy directly focused on the organ are poor image quality (cone-beam computed tomography, ultrasound) and high costs (MRI). All this leads to the development of dose volume constraints to diminish the chance on rectal and urinary toxicity [13, 43].

As delineation became more accurate and precise, consequently the necessity emerged for better shaping the dose around the target and avoiding the critical structures. In earlier techniques, like 3D-conformal RT, beams were shaped around the tumour contours with a collimator blocking gamma rays out of unwanted areas (i.e., healthy organs). The tumour was irradiated mostly using 4 fields opposed to each other (anteroposterior and lateral opposing fields). The result was a high-dose "box" in the overlap zone of the four bundles. Later, intensity-modulated radiotherapy (IMRT) techniques were introduced. Here the tumour was approached from additional angles, using mobile computer-controlled collimators, creating additional degrees of freedom to shape the high-dose region around the target.

Volumetric modulated arc therapy (VMAT) or rapid arc therapy is a relatively novel radiation technique. It is an advanced form of IMRT that delivers a 3D-dose distribution with a 360-degree rotation of the gantry in a single or multiarc treatment. This results in an improved target volume coverage and sparing of normal tissues compared with less modern techniques (Figure 2). VMAT has the advantage of favourable dose distributions. Furthermore, it reduced the monitor units required compared with IMRT and reduced treatment delivery time [44, 45].

These improvements in delineation and more conformal RT technique but also treatment delivery verifications allowed for further dose escalation resulting in higher cure rates with similar or slightly higher toxicity [8, 46–53]. Standard RT uses a daily dose of 1.8 to 2.0 Gy for 39–45 fractions. The updated published randomised phase III trials of dose

Table 1: Updated phase III randomised trials on dose escalation for prostate cancer. All results are statistically significant, except those marked with n.s.

	N	Median FU (yrs)	Dose (Gy)	Benefit bDFS (%)	Toxicity GI (%)	Toxicity GU (%)
MD Anderson						
Kuban et al. 2008	301	8.7	70 versus 78	59 versus 78	13 versus 26	13 versus 8$^{n.s.}$
MGH						
Michalski et al. 2015	1499	7	70.2 versus 79.2	57 versus 74	16 versus 22	10 versus 15
Dutch trial						
Heemsbergen et al. 2014	669	9.1	68 versus 78	61 versus 69	25 versus 35	40 versus 41$^{n.s.}$
Royal Masden						
Dearnaley et al. 2014	843	10	64 versus 74	43 versus 55	24 versus 33	8 versus 11$^{n.s.}$
GETUG						
Beckendorf et al. 2011	306	5.1	70 versus 80	68 versus 76.5	14 versus 19.5	10 versus 17.5

bDFS: biochemical disease-free survival. n.s.: not significant.

Table 2: Updated phase III randomised trials on hypofractionation for prostate cancer. All results are statistically significant, except those marked with n.s.

	N	Median FU (yrs)	Dose (Gy) per fraction	Benefit bDFS (%)	Toxicity Gr2 GI (%)	Toxicity Gr2 GU (%)
Dutch trial						
Aluwini et al. 2015	820	5	39 × 2 versus 19 × 3.4	77 versus 80$^{n.s.}$	Equal; 13	22 versus 23
RTOG 0415						
Lee et al. 2016	1092	5.8	41 × 1.8 versus 28 × 2.5	85.3 versus 86.3	11.4 versus 18.3	20.5 versus 26.2
CHHiP						
Dearnaley et al. 2016	3163	5.1	37 × 2 versus 20 × 3 versus 19 × 3	88.3 versus 90.6 versus 85.9	Equal; 2$^{n.s.}$	11 versus 13$^{n.s.}$

bDFS: biochemical disease-free survival; CHHiP: conventional or hypofractionated high dose intensity modulated radiotherapy in prostate cancer; n.s.: not significant; Gr2: grade 2 or more toxicity.

escalation are summarised in Table 1. The dose escalations revealed a 10 to 20% increase of bDFS. This advantage, however, did not translate into an improvement of overall survival. Besides, Kalbasi and colleagues demonstrated in a huge cohort of patients (42,481) of the National Cancer Data base that dose escalation up to ≥75.6 Gy is associated with improved overall survival in men with intermediate- and high-risk prostate cancer [11].

2.1. Hypofractionation. A total dose cannot be delivered in one fraction, since this would produce serious adverse reactions. Therefore, the total dose needs to be split into fractions. Healthy cells can recover themselves from the RT during the interfraction periods, whereas tumour cells are damaged. Hypofractionated (HF) EBRT means a larger dose per fraction with less fractionations, mainly given over a shorter time period, with a lower total dose. This lower total dose has a comparable effect with a higher standard dose in fractions of 2 Gy [54]. The damage is greater in larger fractionations and the total dose is lower for the same effect. To easily compare the different RT schemas all RT schedules are recalculated in standard 2 Gy fractions. Several tools are available to calculate different RT schedules with each other, for example, http://rotoolbox.com/calculators/eqd2/.

HF for PC is traditionally performed in 19 to 28 fractions of 2.5 Gy to 3.4 Gy per fraction. HF has earned increasing attention as it has a higher therapeutic ratio (=the difference between treatment benefits and morbidity) than standard fractionated IMRT, which may theoretically lead to greater local cancer control [55, 56]. Furthermore, HF EBRT ameliorates logistical inconveniences for both patients and their providers. It is particularly useful for patients who benefit logistically from a shortened HF course like patients living at long distance from an RT centre or who have a poor support system [57, 58]. The results of three recently published phase III trials are summarised in Table 2 [59–61]. These trials revealed that HF is well tolerated, albeit with a slight increase in toxicity rates when compared to conventional schedules. No improvement on bDFS has been noticed; however, the follow-up period is possibly insufficient. Further evaluations and reports are expected in the coming years.

2.2. Stereotactic Body Radiotherapy. Stereotactic body radiotherapy (SBRT) is an extreme form of HF. Stereotaxy refers to a precise method of target localisation using three-dimensional coordinates derived from medical imaging. SBRT for PC is traditionally performed in 3–7 fractions of 6 Gy to 10 Gy per fraction. SBRT is delivered with even

higher than standard precision procedures, for example, a customised body pillow formed by vacuum suction [62]. Just like in conventional EBRT there is an evolution with more dose guidance and higher precision (see above). The available literature consists mainly of several nonrandomised phase II trials. Recently, a large multi-institutional trial of 1100 patients was reported. Separate prospective phase 2 protocols of localised PC patients from different institutes treated between 2003 and 2011 were pooled for analysis [63]. With a median follow-up of 36 months, the five-year bDFS rate was 93%. As this series mostly consisted of low- and intermediate-risk patients and follow-up is still limited, this treatment is only recommended for selected low- and intermediate-risk patients with localised PC. That the *acute* urogenital toxicity seemed higher than conventional EBRT [64] might pose a disadvantage. On the other hand, low *late* urinary and rectal toxicities after median follow-up of three years were reported [65]. Data from published prostate SBRT trials have shown late grade 3 GI and GU toxicities within the 3%. However, this data is preliminary and prospective randomised phase III trials and additional follow-up are required to further clarify the relative differences between both treatment modalities.

3. Brachytherapy

BT is an internal RT, where radiation comes from an implanted source, such as seeds or capsules. BT permits an extreme dose escalation far exceeding other RT modalities. Furthermore, no extra treatment margin is necessary for set-up errors. In general, two types of BT are clinically used: low-dose rate (LDR) and high-dose rate (HDR). In LDR radioactive sources are permanently implanted in the prostate, whereas at HDR temporary needles are placed in the prostate in which a radioactive source irradiates the prostate temporarily. Both modalities can be used either as a monotherapy or as a boost with EBRT. Monotherapies are generally used for low- and intermediate-risk PC, whereas combined therapy usually is used for intermediate- and high-risk PC [66]. The logistics are the main advantage of LDR: you can implant it with small shields, whereas HDR is applied in a specialised shielded room for radioprotection issue. LDR has the disadvantage that some extensions are difficult to cover, for example, seminal vesicle extension and extra capsular extension, which can be adequately covered by HDR.

3.1. Low-Dose Rate. Permanent seed implantation involves injecting approximately 50–125 radioactive seeds into the prostate depending on the volume [67]. General or spinal anaesthesia is required. The seed implantation is performed under TRUS guidance via the transperineal approach, with the patient placed in dorsal lithotomy position. LDR is accomplished in an outpatient single visit setting. Individual (loose) seeds or stranded seeds (seeds linked together in dissolvable suture material) are used in LDR [66]. Stranded seeds minimise seed migration and improve dose delivery [68, 69]. The planned RT dose is emitted over several months with an average dose rate of 0.1 Gy/h, depending on the specific isotope [70]. Iodine-125 (I-125) and palladium-103 (Pd-103) are mostly used. Pd-103 has a higher dose rate and is more frequently used in the United States. The prescription dose varies from 145 Gy for I-125 to 120 Gy for Pd-103. The BT alone is an option for patients with low- and intermediate-risk disease when there are only limited features, such as a serum PSA between 10 and 20 ng/mL or small volume Gleason score 7 [68, 70].

Grimm et al. conducted a comprehensive literature review to identify over 18,000 papers involving treatment of localised PC published during 2000–2010 [71]. Selection criteria were made based on the following criteria: median follow-up of at least five years (which is still short for PC); patient stratification into pretreatment risk; both clinical and pathological staging; accepted standard definitions for PSA failure; minimum patients number for each risk group which was accepted as 100 for low- and intermediate- and 50 for high-risk group; and results published in peer-review journals only. All the study outcomes were calculated for each risk group and suggested that BT alone, particularly seed implant, provides superior bDFS in low-risk patients. For the intermediate-risk group, combination RT (EBRT + BT) seems to be equal to BT alone. For high-risk patients combination RT with or without androgen deprivation therapy seems to be superior. Furthermore, in a recently reported randomised trial (ASCENDE-RT, NCT00175396), a LDR boost was demonstrated to be much more effective than an EBRT boost in high-risk prostate cancer patients: a 9-year BRFS of 83% versus 63% [72]. However, these results should be interpreted with some caution because this is only published in an abstract form: no mention of image guidance or quality assurance is made, yet. Toxicity rates are also not clearly mentioned in this abstract. Although these results encourage choosing BT as an element of management, it should be remembered that selection bias may play a main role.

3.2. High-Dose Rate. With HDR BT, transperineal catheters are first inserted in the prostate under general or spinal anaesthesia. The hollow catheters are connected to an HDR "afterloader" with an isotope, mostly iridium-192 (Ir-192). The dose rate is at least 12 Gy/h. The afterloader machine loads the hollow catheters while the BT team is outside the shielded room for radioprotection issues. This machine pushes a wire connected to the radioactive source into each of the different catheters, one by one under computer-control, utilising stop positions and dwell times according to the plan. After treatment, the afterloader withdraws the sources. After the BT treatment the catheters are removed. No radioactive seeds are left in the body.

HDR is often used in a combination therapy with EBRT. Outcomes are superior to those achieved with EBRT alone [73–77]. One phase III trial is reported by Mount Vernon Hospital where they compared EBRT (55 Gy, 20x) with EBRT (37.5 Gy, 13x) and HDR boost (17 Gy, 2x) [73]. Hoskin et al. demonstrated a 7-year BRFS rate of 75% compared with 61%, respectively, with similar incidence of severe late urinary and rectal morbidity. An ongoing randomised trial (PROBACH, NTR3897) will further evaluate the value of HDR as a boost therapy in intermediate- and high-risk PC.

Another older phase III trial is reported by Sathya and colleagues [78]. They proved that the combination of HDR

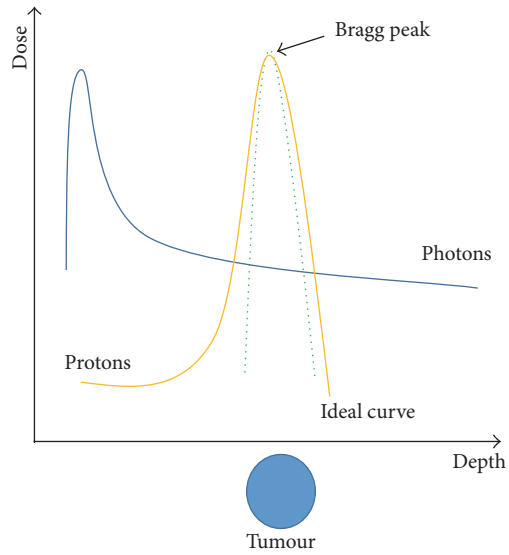


Figure 3: The Bragg peak demonstrating the plots energy loss of ionising radiation during its travel through the body. Maximum energy deposition at the target area (tumour) without energy loss after the target (healthy organs).

plus EBRT was superior to EBRT alone for a 5 years BRFS of 71% compared with 39%. This is logic when comparing the total dose schedules to the prostate: the combination therapy was superior with 75 to 80 Gy (comparable with nowadays EBRT schedules) in comparison with EBRT only where the given dose was inferior with 66 Gy and with 2 cm safety margins.

Although the interest in monotherapy HDR is growing, no phase III trials are conducted. Several nonrandomised series are reported on the results of monotherapy HDR in multiple and in single fractions, which are promising.

4. New Techniques: Proton Therapy, Carbon Ion

Newer RT techniques which utilise heavy particles such as protons and carbon ions have a potential dosimetric benefit of the so-called "Bragg" peak (Figure 3). This means that the maximum dose delivery occurs immediately before the particles come to rest. This means that the maximum effect on the tumour can be determined while minimising the impact on the surrounding healthy tissue. These approaches are currently in development [79–81].

Zietman et al. published the only randomised series currently available, comparing a high- to a low-proton boost, resulting in a significant increase in bDFS in the high-dose arm [8].

Carbon ions seem more efficient than protons which can be explained by the fact that carbon ion beams are twice to three times more effective than protons or photons [82, 83]. Habl and colleagues published an HF schedule using either carbon ions or protons resulting in comparable acute toxicities [84]. Long-term outcome data on these treatments are not yet available. However, until now, no evidence is shown to support the use of protons in preference to conventional RT for patients with prostate cancer; neither technique had been shown to give improved results over the others with respect to disease control or toxicity [85].

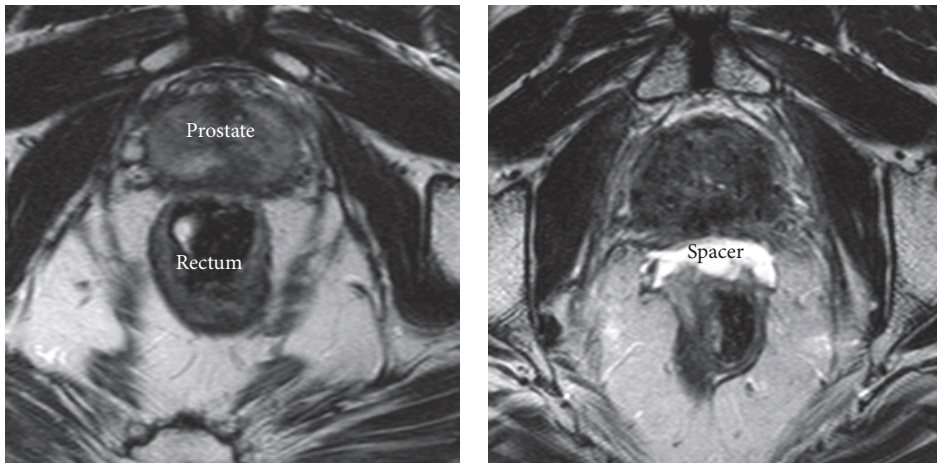
An ongoing multi-institutional phase III-randomised trial (PARTIQoL, NCT01617161) evaluates the value of protons in low- and intermediate-risk PC in comparison with IMRT. This trial will probably shed light on the additional value of protons in comparison with conventional IMRT for PC. In any event, we believe the future lies in multifactorial decision support systems calculating for each individual patient the outcome and the cost-effectiveness of the various treatments [86, 87].

5. New Devices: Balloon/Spacer

Another way to reduce toxicity is to physically create some space between the healthy organ (rectum) and the targeted area (prostate). As ionising radiation decreases by the inverse square law, even a few millimetres of increased separation can lead to sparing the healthy organ for high doses of radiation.

To spare rectal structures several spacer devices are developed [88]. These can be divided into endorectal balloons and relatively novel rectum spacers. Endorectal balloons are placed into the rectum for each daily treatment. Although the ventral anorectal wall is pushed towards the prostate, the distance from the posterior rectal wall to the prostate is increased with an overall effect proved to be beneficial in RT [89].

Rectum spacers are implanted as a tissue filler into the anterior perirectal fat to separate the rectum from the prostate (Figure 4). Increasing the prostate-rectum distance displaces the rectal wall away from the prostate and out of the high-dose RT regions. The overall effect is a reduction in the total volume of irradiated rectum and the maximum dose to the rectum. The implantation of such rectum spacers is performed transperineally under real-time TRUS guidance. The insertion procedure can be performed under local, spinal, or general anaesthesia [90]. The implanted rectum spacer remains in place over the course of the RT treatment and the spacer biodegrades naturally within six months after implantation [91]. Different types of rectum spacers have been developed: an absorbable hydrogel, a hyaluronic acid, a collagen, and a saline-filled balloon [91, 92]. Although several studies are available on the acute outcome, dosimetry, and cost-effectiveness of a rectum spacer, the long-term outcomes are not yet clear [93–103]. If the spacer is combined with HF, BT, SBRT, or proton therapy, the reduction of toxicity could be even more expected. Very recently, decision rules based on clinical risk factors solely are identified for which patients a spacer implantation is predicted to be beneficial [104]. However, further research is needed to assess the predictive performance of these decision rules and to generate adequate decision support systems. The available results are encouraging for the design of further clinical trials.



(a) (b)

Figure 4: Axial T2-weighted magnetic resonance images of a patient with a hydrogel spacer before injection (a) and after injection (b).

6. RT Compared to Surgery

The results of a well-balanced randomised phase III trial comparing RT with RP and active monitoring are very recently reported (PROTECT, NCT02044172) [105, 106]. Hamdy and colleagues compared all those treatments for low-risk localised prostate cancer with a median follow-up of 10 years (1643 patients). Only 17 prostate-cancer-specific mortalities were observed: 8 patients in the active-monitoring group, 5 men in the RP group, and 4 patients in the EBRT group. The differences among the groups were not significant. RP and EBRT were associated with lower incidences of disease progression than active monitoring, respectively, 46 incidences for active therapies compared with 112 man for active-monitoring ($p < 0.001$). Also metastases rates developed more in the active-monitoring group: 33 men in comparison with 13 and 16 for RP and EBRT, respectively ($p = 0.004$). Patient-reported outcomes are also reported: RP had the greatest negative effect on sexual function and urinary continence. EBRT had little effect on urinary continence (urinary voiding and nocturia); however, bowel function was worse. In the active-monitoring group sexual and urinary function declined gradually over years.

All treatments provide an extremely high cure rate. Recently, Lennernäs et al. published the first randomised trial comparing RP with EBRT + HDR [107]. Due to insufficient power and small series (89 patients) no conclusion could be drawn about the efficacy. Nonetheless, some observational data suggest that outcomes with RP lead to better overall and cancer-specific survival than RT [108–112]. Wallis and colleagues recently published a meta-analysis comparing RP with EBRT or BT [108]. They pooled 118,830 patients from 19 studies and concluded that overall and prostate cancer-specific mortality were higher for patients treated with RT compared with RP. Subgroup analyses by risk group, radiation regimen, time period, and follow-up length did not alter the results.

However, all those comparison trials have several limitations. First, patients with greater comorbidity tend to be treated with RT [113]. In addition, comorbidities that have been shown a major impact on survival are not always mentioned [114]. Further, some RT schedules in those trials are using inferior low-dose [115]. Also, a potential bias exists for unaccounted differences between risk groups [116]. Next, baseline characteristics are often different and have a profound impact as differences in the percentage of positive biopsies or Gleason 4 + 3 versus 3 + 4 tumours [116–118]. Furthermore, big meta-analyses are being criticised as the studies synthesised in such analyses do not all pose level 3 evidence [119, 120].

Other data suggest that even either EBRT or BT using adequate dosing schedules and conformal techniques are similar to RP when men with clinically localised PC are stratified based upon clinical tumour stage, pretreatment serum Prostate Specific Antigen, and Gleason score [121, 122]. Kim et al. concluded that outcomes are not inferior to those of RP despite the fact that the EBRT group included more high-risk patients [122]. Grimm et al. conducted a comprehensive literature review to identify all studies involving treatment of localised PC. They even concluded that BT provides superior outcome in patients with low-risk and intermediate-risk disease. High-risk disease revealed the best outcome with combination therapy of EBRT and BT [71]. However, like all comparison trials those have several limitations [123]. First, the endpoint of bDFS is not fair because the definition is different for RP and RT. Further, it is difficult to determine bDFS as a surrogate of cancer-specific survival. Moreover, in the comprehensive literature review of Grimm many RP studies are excluded because they are based on pathology report after RP, which is not possible with RT. Next, many surgical factors can influence oncological outcome and are not reported as innovations in RP (robotic-assisted RP) and caseload volume per institute. Finally, the risk stratification (intermediate-risk group) was more varied amongst articles,

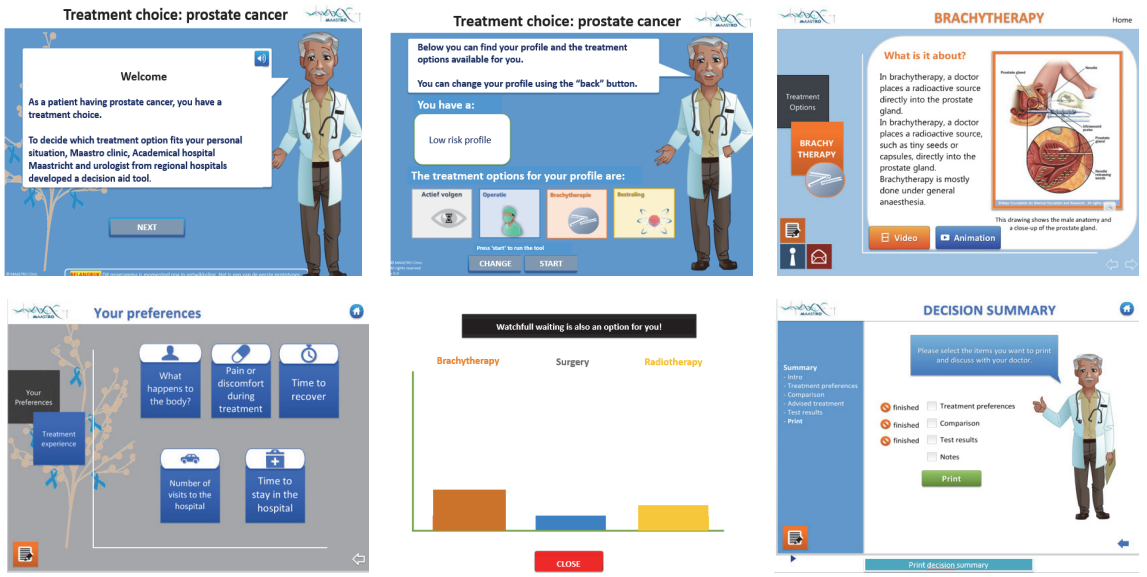


FIGURE 5: A summary of some screen shots of an interactive PDA for PC (http://www.treatmentchoice.info/). The PDA provides information to the patient of the characteristics of his disease, the available treatments for his own situation, his individual preferences, and a comparison of the possible treatments. It offers a summarised advice based upon the information provided by the patient. The purpose of this is to inform the patient; a final decision is always taken together with the clinician.

thus reflected in significant differences in baseline risk for PSA failure between the treatment methods.

To conclude, one well-controlled randomised phase III trial (PROTECT) randomly assigned men with localised PC to active monitoring, RT, or RP. This trial revealed comparable outcomes for each treatment, but with a different toxicity pattern.

Our belief is that a paradigm shift from current population-based medicine to personalised and participative medicine is underway. This transition is being supported by the development of multifactorial clinical decision support systems based on prediction models of treatment outcome and constantly reevaluated in different patient datasets in order to refine and reoptimise the models, ensuring the continuous utility of the models.

Nowadays, decisions on the most appropriate treatment for each patient are dependent on unique personal patient characteristics and preferences, clinician judgment, and resource availability. Therefore, to achieve the right treatment for each individual, we believe patients and clinicians should make decisions together: shared decision-making (SDM) [124, 125] to embrace truly participative medicine. SDM is an interactive process in which patients and clinicians collaborate in choosing health care, based upon the best available evidence [126–128]. Several studies have reported that patients involved in SDM experience less decisional conflict, improved compliance with treatment, and a greater quality of life with less comorbidities such as anxiety, fatigue, and depression [129]. This has been confirmed in a Cochrane study by Stacey and colleagues [130]. The health care system benefits, also in terms of reduced costs and fewer unnecessary/unwanted procedures [131]. However, the implementation of SDM remains a challenge in health care systems due to numerous barriers [132–134]. These barriers can be divided into patient, clinician, and organisational barriers. Patient barriers include age and attitudes. Older patients tend to prefer a paternalistic model in which treatment decisions are made by the doctor [132]. Of course, a significant part of patients opt for this model while the doctor chooses the ideal treatment for the particular patient. There are also barriers from the health care provider side, such as the perception that SDM is too time-consuming or complicated to pursue [133, 134]. Furthermore, clinicians often unintentionally use jargon. Finally, organisational factors such as a lack of support, time, and resources are also commonly described barriers [133].

Patient decision aids (PDAs) have been developed to overcome these challenges [135]. PDAs supply patients with treatment options, treatment-specific information, and treatment comparison to help patients discover their personal preferences [136] (Figure 5, http://www.treatmentchoice.info/decision-aid-tools.html). PDAs are not developed to promote one option over another or to replace clinician consultation. Instead, they prepare patients to make informed, values-based individual decisions with clinicians (http://ipdas.ohri.ca/) [130, 137].

7. Conclusion

During the past 20 years, RT in PC has improved significantly in all areas, including treatment technique, planning, and quality control. Examples of improved RT techniques are image-guided RT, IMRT, VMAT, SBRT, LDR-HDR BT, and protons. Rectum spacers and balloons have been developed to diminish rectal toxicities. Further research is needed to define the value of all these promising new techniques. With

those technical implementations the long-term bDFS are improved. We recommend dose escalation up to ≥75.6 Gy (calculated as standard fractionations of 2 Gy). Doses up to 75.6 Gy is associated with improved overall survival in men with intermediate- and high-risk prostate cancer. HF is an attractive therapeutic option, and the randomised phase III trials revealed a slight increase of toxicity rates in comparison to conventional schedules.

An important discussion issue between urologists and radiation oncologists is summarised: the comparison between RP and RT. The results of a well-balanced randomised phase III trial comparing RT with RP and active monitoring are very recently reported. The outcomes of RP and RT are similar, but they differ significantly in terms of the side-effects. We recommend proposing different treatment modalities to the individual patient characteristics and preferences. For each individual, we recommend that clinicians and patients should make decisions together, shared decision-making, while using patient decision aids.

Competing Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Research Article

Diagnostic Accuracy of Robot-Guided, Software Based Transperineal MRI/TRUS Fusion Biopsy of the Prostate in a High Risk Population of Previously Biopsy Negative Men

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Objective. In this study, we compared prostate cancer detection rates between MRI-TRUS fusion targeted and systematic biopsies using a robot-guided, software based transperineal approach. *Methods and Patients*. 52 patients received a MRIT/TRUS fusion followed by a systematic volume adapted biopsy using the same robot-guided transperineal approach. The primary outcome was the detection rate of clinically significant disease (Gleason grade ≥ 4). Secondary outcomes were detection rate of all cancers, sampling efficiency and utility, and serious adverse event rate. Patients received no antibiotic prophylaxis. *Results*. From 52 patients, 519 targeted biopsies from 135 lesions and 1561 random biopsies were generated (total $n = 2080$). Overall detection rate of clinically significant PCa was 44.2% (23/52) and 50.0% (26/52) for target and random biopsy, respectively. Sampling efficiency as the median number of cores needed to detect clinically significant prostate cancer was 9 for target (IQR: 6–14.0) and 32 (IQR: 24–32) for random biopsy. The utility as the number of additionally detected clinically significant PCa cases by either strategy was 0% (0/52) for target and 3.9% (2/52) for random biopsy. *Conclusions*. MRI/TRUS fusion based target biopsy did not show an advantage in the overall detection rate of clinically significant prostate cancer.

1. Introduction

Prostate cancer (PCa) is the second most common cancer and third most leading cause of death of men in the western world [1]. Correct risk stratification and early detection of PCa are crucial for optimal treatment of high risk patients and to avoid overtreatment in low risk patients. Risk stratification is based on histologic analysis of invasive prostate biopsies, which are indicated by elevated prostate specific antigen (PSA) levels. Low specificity (6–66%) [2] of PSA tests and low detection rates (27%–43%) [3] of transrectal ultrasound (TRUS) guided 12-core biopsies hamper detection rates and cause unwanted side effects such as infections.

Introducing a transperineal approach for biopsy, significantly lowered complication rates, however, required general anesthesia instead [4, 5]. Detection rates were reported comparable to the transrectal approach [6, 7]. The introduction of multiparametric magnetic resonance imaging (mpMRI) for planning biopsies further increased biopsy efficiency [8, 9]. Particularly, MRI/TRUS fusion biopsy improved detection rates of clinically significant prostate cancer with fewer biopsies necessary as reported by several reviews [8,

10, 11]. Individual studies, however, showed heterogeneous results. Several studies report no clear advantage of men mpMRI/TRUS-guided targeted biopsy and recommend the combination of targeted and systematic biopsies for the detection of prostate cancer [12].

The recently released platform (iSR'obot Mona Lisa) by Biobot surgical LTD combines several technical aspects to further refine the mpMRI/TRUS fusion approach. The system uses an "elastic" fusion algorithm to account for deformations from transrectal TRUS imaging compared to undeformed MRI imaging. It also uses a robotic arm, which allows all biopsies to be taken from the same two perineal 1 mm incisions and also defines the penetration depth automatically. This allows for a short procedure time and user friendly handling. In our study, we employed this system to evaluate the detection rate of clinically significant disease (Gleason grade ≥ 4) as primary outcome detection rate of all cancers, sampling efficiency and utility, and serious adverse event rate as secondary outcomes. Transperineal targeted biopsies were compared to volume adapted transperineal systematic random biopsies according to the Ginsburg study scheme [13].

2. Patients and Methods

2.1. Patients. Between 10/2015 and 05/2016, 52 patients (median age of 66, interquartile range (IQR): 60–71.75) with elevated PSA (median 8.75 ng/ml, IQR: 5.86–13.04) or clinical suspicion for PCa and prior negative 12-core transrectal ultrasound guided biopsy received MRI/TRUS fusion biopsy of the prostate in our institution. For our retrospective analysis, primary outcome was the detection rate of clinically significant disease (Gleason grade ≥ 4). Secondary outcomes were detection rate of all cancers, sampling efficiency and utility, and serious adverse event rate. Patients received no antibiotic prophylaxis.

2.2. Multiparametric Magnetic Resonance Imaging (mpMRI). Each patient received a multiparametric MRI of the prostate prior to MRI/TRUS fusion biopsy using surface coils only. In each patient, triplanar T2-weighted turbo spin-echo MR imaging, axial unenhanced T1-weighted MR imaging, and diffusion weighted imaging sequences with ADC (apparent diffusion coefficient) maps were acquired. Contrast agent was applied when evaluated as necessary based on the current PI-RADS version 2 lexicon. The current PI-RADSv2 lexicon describes lesion in the transitional zone primarily on T2 weighted images and refers to DWI in cases of PI-RADS 3 to decide whether to upgrade to PI-RADS 4. Contrast agent is not a feature to describe (or detect) transitional zone lesions. In the peripheral zone, the lexicon primarily relies on DWI. Contrast agent only is administered in cases of PI-RADS 3 (i.e., moderately low ADC value with no hyperintense signal in the corresponding high b-value image).

Contrast agent was applied when a PI-RADS 3 lesion was observed in the peripheral zone. A board-certified radiologist decided about contrast agent administration. Our study reports on the diagnostic accuracy of PI-RADSv2. We therefore suppose that the applied decision scheme to administer i.v. contrast reflects the PI-RADSv2 diagnostic accuracy.

Lesions were classified by a board-certified radiologist according to the PI-RADS version 2 lexicon into categories 2 to 5 (category 1 denoting "no tumor"). For a workflow description of the diagnostic process, refer to [14]. Before the MRI/TRUS fusion biopsy, lesions were segmented manually in the Biobot software environment by a radiologist trained in prostate MRI evaluation.

2.3. iSR'obot MonaLisa (Biobot). The MonaLisa system uses a software controlled robotic arm, which is mounted to the operation table. The system utilizes two software components: UroFusion for preparation of the mpMRI images and the registration of suspected cancer lesions. UroBiopsy is used to generate the TRUS based model, fuse mpMRI, and TRUS model and perform the biopsy.

T2 weighted mpMRI images were uploaded into UroFusion. A team of experienced radiologists (Matthias Benndorf, Philipp Lenz, Tobias Krauss, Mathias Langer) manually contoured the prostate and a 3D model was generated. Tumor volumes were contoured within the T2 weighted images only but were defined using T2, DWI, and DCE-MRI from the original mpMRI dataset according to the recommendation of PiRADS version 2 classification.

When the patient was under general anesthesia, he was put in lithotomy position. Antiseptic washing was performed. No local anesthesia or antibiotic prophylaxis was given.

The MonaLisa system was connected to a BK3000 ultrasound machine with a transrectal probe. The transrectal probe was mounted onto the robotic arm of the system and covered by a rigid plastic sheath to allow the probe to be automatically moved tension-free within the sheath. The sheath was prefilled with Instillagel® to avoid air bubbles and allow for optimal contact of the probe with the sheath and consequently with the tissue. The sheath was then inserted into the rectum in a position to allow for optimal coverage of the prostate within a 133 mm scanning range and optimal image quality. When start and end points for the scanning process were defined within the UroBiopsy software, transversal images were recorded every 0.5 mm. From this dataset, a 3D model was generated. The mpMRI 3D model was uploaded into the software and coregistered to the ultrasound model. To account for prostate deformation due to the transrectal ultrasound probe, the software calculates an algorithm, which fits the mpMRI model onto the TRUS model. The same algorithm is then applied to the cancer lesions. The final model shows the TRUS based outline of the prostate and the defined tumor volumes from the mpMRI. Target and random biopsies were then planned. We used the volume adapted Ginsburg study group scheme for planning the random biopsies [13]. All biopsies were taken from only two 1 mm incisions. The robot arm contains a sterile needle guide where the biopsy needle was inserted. The whole robotic arm was covered with a sterile cover to prevent contamination. A software controlled stop bar defines the penetration depth individually for each biopsy position. We used a reusable biopsy gun (Uromed REF6020) with trocar shaped biopsy needles (Uromed REF 6025.10). Biopsy cores

were collected in formalin. When the robot arm had defined the penetration angle and the penetration depth, the needle was inserted and the biopsy gun was released. Incisions were covered with a small plaster. Every patient received a transurethral catheter overnight.

2.4. Histopathologic Analysis. Each formalin-fixed biopsy was macroscopically measured in 2 dimensions and put in a tissue cassette separately for further tissue processing and paraffin-embedding. Eight H&E stained tissue sections of each paraffin block were histologically evaluated by a urological pathologist. For each tumor, positive biopsy percentage of tumor, tumor type (almost exclusively "conventional" acinar adenocarcinoma), and Gleason Patterns integrated in ISUP-Grade Groups [15] were documented in a standard histopathologic report as well as histologic description of the other tumor negative biopsies. In case of suspect findings, immunohistochemistry was performed to rule out or confirm invasive PC or to determine special cancer subtypes/differentiation.

2.5. Statistical Analysis. Descriptive statistics were done by calculating mean ± standard deviation (SD), median and interquartile range (IQR), and p value using SPSS© software (SPSS statistics 22, IBM).

3. Results

52 patients (median age 66 years, interquartile range (IQR): 60–71.75) with elevated PSA (median 8.75 ng/ml, IQR: 5.86–13.04) or clinical suspicion for PCa and prior negative 12-core TRUS-guided biopsy were included into the study. From 52 patients, 519 targeted biopsies from 135 lesions and 1561 random biopsies were generated (total $n = 2080$). 8.9% (12/135), 29.6% (40/135), 40.7% (55/135), 11.9% (16/135), and 8.9% (12/135) lesions were classified as PiRADSv2 5,4,3, and 2 and unclassified, respectively.

The median target volume was 0.31 ml (IQR: 0.17–0.59) with median 3 (IQR: 2–5) biopsies per target, which corresponds to a biopsy density of 10.26/ml (IQR: 6.45–15.79). The median prostate volume was 49.3 ml (IQR: 37.82–73.32) (Table 1).

Overall detection of any PCa was 50.0 (26/52) for target and 59.6 (31/52) for random biopsy. The rate of clinically significant PCa was 44.23% (23/52) and 50.0% (26/52) for target and random biopsy, respectively (Table 2).

The subgroup analysis for specific PI-RADS classes with respect to the detection rates for any or clinically significant PCa is shown in Table 3. Detection rate for PI-RADS score 4 and 5 lesions only for all tumors and significant tumors dropped from 50.0% (26/52) to 44.0% (21/52) and from 44.23% (23/52) to 40.0% (21/52), respectively (Table 3).

The detection rate on a lesion based scale was 29.60% (40/135) and 22.96% (31/135) for overall and clinically significant PCa, respectively. Detection rate for peripheral versus central lesions was significantly higher for any and significant cancer (39.0% (29/75) versus 22.0% (13/60); $p = 0.0233$ and 32.0% (24/75) versus 15.0% (9/60); $p = 0.0342$) (Table 4).

Table 1: Patient characteristics at MonaLisa biopsy ($n = 52$ patients, $n = 135$ MRI lesions).

	Mean/±SD/median/IQR
Age (years)	65.8/7.3/66.0/60.0–71.8
PSA (ng/ml)	9.9/5.9/8.8/5.7–13.04
MRI prostate volume (ml)	57.6/26.6/49.3/37.8–73.3
Number of lesions/patient (n)	2.6/1.5/2.0/1.0–4.0
MRI lesion volume (ml)	0.6/0.7/0.3/0.2–0.6
Number of biopsies (total)/patient (n)	39.8/40.0/36.3–43.0
Number of target biopsies/patient	10.2/4.8/9.0/6.0–14.0
Target biopsy density (n/ml lesion volume)	12.4/8.9/10.3/6.5–15.8
Number of random biopsies/patient	30.0/5.6/32.0/24.0–32.0

PSA: prostate specific antigen; MRI: magnetic resonance imaging.

Table 2: Detection rate of prostate cancer of target versus random biopsy.

	Any cancer* % (n/n)	Significant cancer** % (n/n)
Overall	59.6 (31/52)	51.9 (27/52)
Target biopsy	50.0 (26/52)	44.2 (23/52)
Random biopsy	59.6 (31/52)	50.0 (26/52)

*: prostate cancer with any Gleason grade; **: prostate cancer with Gleason grade ≥ 4.

Table 3: MRI lesion-based detection rate of target biopsies ($n = 135$).

	Any cancer* % (n/n)	Significant cancer** % (n/n)
PiRADS score		
5	83.0 (10/12)	75.0 (9/12)
4	45.0 (18/40)	35.0 (14/40)
3	18.0 (10/55)	13.0 (7/55)
2	6.0 (1/16)	6.0 (1/16)
Unclassified	25.0 (3/12)	17.0 (2/12)

PiRADS: Prostate imaging Reporting and Detection System.
*: prostate cancer with any Gleason grade; **: prostate cancer with Gleason grade ≥ 4.

We could not detect a volume dependent bias affecting the detection rate. There was no statistical difference in tumor detection rate between higher and lower target volumes (30.88% (21/68) versus 28.36% (19/67), $p = 0.9$). Even the lower interquartile 25% with volumes 0.17–0.31 ml showed no decreased rate of 35.29% (12/34/). In a logistic regression analysis, tumor volume ($p = 0.192$; OR = 1.005) and biopsy density (number of biopsies per ml tumor volume) ($p = 0.029$; OR = 1.001) did also not show statistically significant risk bias for detecting PCa.

The distribution of different Gleason scores from detected PCa according to target biopsy or random biopsy is shown

Table 4: Detection rate of prostate cancer in peripheral versus central target biopsy.

	Any cancer*			Significant cancer**		
	Peripheral% (n/n)	Central% (n/n)	p value	Peripheral% (n/n)	Central% (n/n)	p value
Overall	39.0 (29/75)	22.0 (13/60)	0.0223	32.0 (24/75)	15.0 (9/60)	0.0342
PiRADS score						
5	75.0 (6/8)	100.0 (4/4)	0.32	75.0 (6/8)	75.0 (3/4)	0.99
4	56.0 (14/25)	25.0 (4/16)	0.052	44.0 (11/25)	19.0 (3/16)	0.10
3	27.0 (6/22)	12.0 (4/34)	0.14	23.0 (5/22)	6.0 (2/34)	0.065
2	9.0 (1/1)	0.0 (0/5)	—	9.0 (1/1)	0.0 (0/5)	—
Unclassified	22.0 (2/9)	100.0 (1/1)	—	11.0 (1/9)	100.0 (1/1)	—

PiRADS: Prostate imaging Reporting and Detection System.
*: prostate cancer with any Gleason grade; **: prostate cancer with Gleason grade ≥ 4.

Table 5: Tumor characteristics.

	Target biopsy only	Random biopsy	p value
Gleason score% (n/n)			
6	12.0 (3/26)	16.0 (5/31)	0.63
7	15.0 (4/26)	32.0 (10/31)	0.15
8–10	73.0 (19/26)	52.0 (16/31)	0.0017
Upgrading* % (n/n)	23.1 (6/26)	11.5 (3/26)	0.28
Bilateral tumor			
Mean (±SD; n/n)	32.26 (0.48; 10/31)	70.97 (0.46; 22/31)	0.002

*: specific Gleason upgrading (biopsy versus radical prostatectomy), defined as an increase in either the primary or the secondary pattern.

in Table 5. A significantly higher rate of bilateral tumors (p = 0.002) was detected in random biopsy compared to target biopsy (mean: 70.97 (±0.46; 22/31) versus mean: 32.26 (±0.48; 10/31); Table 5).

Specific Gleason upgrading (biopsy versus radical prostatectomy), defined as an increase in either the primary or the secondary pattern, was detected in 23.06% (6/26) and 11.54% (3/26) for target and random biopsy (p = 0.28; Table 5). Target biopsy detected significantly higher rates of Gleason 8–10 tumors (p = 0.0017; Table 5). No statistical difference was detected between detection rates for Gleason grades 6 and 7 (Table 5).

Sampling efficiency as the median number of cores needed to detect clinically significant PCa was 9 for target only (IQR: 6–14.0) and 32 (IQR: 24–32) for random biopsy. The utility as the number of additionally detected clinically significant PCa cases by either strategy was 0% (0/52) and 3.85% (2/52) for target and random biopsy.

Adverse events were reported in two patients: temporary bleeding and a rectum perforation. No infectious complications were reported.

4. Discussion

Previous studies regarding the detection rate of MRI/TRUS fusion biopsy of the prostate were summarized in the four recent systematic reviews by Robertson et al. 2013 [16], Marks et al. 2013 [17], Valerio et al. 2015 [11] (23.6% (range: 4.8–52%) for standard biopsy and 33.3% (range: 13.2–50%) for target biopsy), and Gayet et al. 2016 [10]. All reviews report a moderate advantage for the MRI/TRUS fusion target biopsy in the detection rate of clinically significant prostate cancer with fewer numbers of biopsies necessary.

Valerio et al. report an overall cancer detection rate of clinically significant prostate cancer with Gleason grading greater than or equal to 4 to be 33.3% (range: 13.2–50%) and 23.6% (range: 4.8–52%) for MRI/TRUS target biopsy and 12-core TRUS-guided transrectal biopsy as standard test. No overall statistically significant difference was detected. However, results from individual studies were heterogeneous with higher detection rates for either approach. Especially in the setting of repeat biopsy in men with persistent PSA elevation and prior negative 12-core transrectal biopsy, the MRI/TRUS fusion biopsy has shown superior results in detecting clinically significant prostate cancer [10, 18] and has been recommended in the European guideline for prostate cancer [19].

The systematic review by Gayet et al. [10] focused on different technical platform to perform mpMRI/TRUS fusion biopsies and their performance in detecting clinically significant prostate cancer. Detection rates for significant prostate cancer ranged between 35.7–43.4% and 28.5–36.8% for targeted and systematic random biopsy [10].

However, several other studies report no clear advantage of mpMRI/TRUS-guided targeted biopsy and recommend the combination of targeted and systematic biopsies for the detection of prostate cancer [12].

In this study, we report a series of 52 patients with suspected prostate cancer in a repeat biopsy situation with MRI/TRUS fusion target and random biopsy of the prostate using the novel MonaLisa system (Biobot surgical). All patients had received a previously negative 12-core transrectal TRUS-guided biopsy.

Almost all reported studies were tested against the standard 12-core transrectal biopsy. The strongpoint of our study clearly is the stringent use of a systematic volume adapted perineal random biopsy with high sampling density as control. Only by applying the same robot-guided perineal technique in either target or random mode, the true value of the MRI guided target biopsy can be evaluated.

In our series, we report a high detection rate in both biopsy modes comparable to the literature [10, 11, 16, 17]. Even small volumes were targeted correctly. A moderate advantage could be detected for cancer detection rate in random biopsy with 44.23% (23/52) and 50.0% (26/52) for target and random biopsy, respectively. Some of the reported studies in the reviews above have also reported higher detection rates for random biopsies [11]. The number of bilateral tumors was also approximately twice as high in random compared to target biopsy. We also detected a higher rate of Gleason Grade upgrading in target biopsy. However, approximately 4 times the number of biopsies were needed (32 (random) versus 9 (target)) to reach the same or improved detection rate.

The lesion based analysis showed low overall detection rates of 31.1% and 24.4% for any and significant cancer in our dataset. The latest (153 patients and 287 lesions) series published by Kesch et al. 2016 [20] using the same technique as we did shows similar detection rate of 34.8% and 29.9% for any and significant cancer, respectively. Another series (62 patients and 116 lesions) by Mertan et al. 2016 [21] and Cash et al. 2016 [22] (408 patients) reported similar results as well. The latest data including ours underline the poor performance of the PI-RADS scoring systems on a lesion based analysis.

The number of adverse events was acceptable. The reported rectum perforation occurred in a patient with the highest prostate volume of 141.9 ml of the series. It occurred early when adjusting the TRUS probe inside the rectum and did not happen due to high sampling number. The patient received immediate endorectal clipping of the lesion and fully recovered without further complications. Few case reports exist on this complications [23]. It might be underestimated complications because late onset of the symptoms might occur and most of the complications regarding transrectal ultrasound and/or biopsy of the prostate are reported within 24 h [6]. Therefore, high volume prostates will have to be treated with special caution, even though higher numbers of such patients will have to be analyzed in the future.

The value of the MRI/TRUS target biopsy using the technique described in our series provides heterogeneous results. On the one hand, we do not see an advantage in the detection rate of clinically significant tumors and understage tumor volume. On the other hand, we needed 4 times the number of biopsies to reach the detection rate with random biopsies. Economic implications are generated for target as well as for random biopsy. For target biopsy, a mpMRI and subsequent evaluation by a radiologist is needed for each patient. The low number of biopsies needed is clearly in favor of the workload by the pathologist for evaluating the biopsies histopathologically. On the other hand, random biopsy could spare the mpMRI and possible bias from the software based fusion process to the TRUS image. The workload for the pathologist, however, would be 4 times higher. The most important implication for a patient with suspected prostate cancer but previous negative 12-core transrectal biopsy is a high level of security regarding the status of the prostate. High numbers of biopsies do not present an increased infectious risk in the transperineal approach. General anesthesia is required in the transperineal setting to allow for precise planning and execution of the biopsies and optimal pain management.

5. Conclusions

The important strongpoint of our approach is the transperineal approach itself with excellent access to all areas of the prostate and the easy and quick planning of the biopsy positions, which allows optimal coverage of the high risk areas especially the apex and the anterior zone [13]. The most precise characterization of the tumor in our series is provided by the combination of the two methods. Our data suggests that there is potential to improve the radiological PI-RADS version 2 classification scheme in order to avoid future false positive findings and further reduce the number of false negatives. We hope that combination of target and random biopsies will enable us in the future to develop feedback correlations from target and random biopsies to the original MRI data to improve radiological classification.

Competing Interests

All authors declare no conflict of interests.

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