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Original Article

Combined mpMRI/US fusion targeted and concurrent standard biopsies in the detection of prostate cancer: a retrospective study

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Abstract: In this retrospective study we compared the PCa detection rates between combined (combined MRI/US fusion targeted biopsy with concurrent standard biopsy) and standard systemic, combined and targeted (component), and targeted (component) and concurrent standard (component) biopsies. Design: Two cohorts, totaling 735 cases, were selected from the University of Wisconsin Pathology archive. 390 cases (cohort 1) were combined biopsies from 2017-2020 and 345 cases (cohort 2) were part of the standard US-guided systematic biopsies from the same period. PCa was stratified into three categories: low, intermediate, and high risks. Results: We found that combined biopsy was significantly better than the standard biopsy in detection of PCa (65.4% vs. 51.6%, P<0.01) and intermediate-risk PCa (18.7% vs. 10.4%, P=0.05) but only slightly better at detecting high-risk PCa (26.7% vs. 23.5%, P=0.32). Further examining the biopsy results in cohort 1, we found that combined biopsy was superior to targeted biopsy (65.4% vs. 56.9%, P=0.02) or concurrent standard biopsy (65.4% vs. 52.1%, P=0.0002) in PCa detection. Combined biopsy detected significantly more high-risk PCa than concurrent standard biopsy (26.7% vs. 17.4, P=0.002), but the difference in detecting high-risk PCa between combined and targeted biopsies was not significant (26.7% vs. 22.1%, P=0.133). Similarly, the differences in detecting PCa and high-risk PCa between targeted and concurrent standard biopsies were not significant (56.9% vs. 52.1%, P=0.172 and 22.1% vs. 17.4, P=0.133, respectively). Both targeted and concurrent standard biopsies missed PCa of each risk level. Conclusion: Combined MRI/US fusion targeted plus standard prostate biopsy is a superior technique for the detection of PCa and clinically significant PCa.

Keywords: Prostate cancer, mpMRI/US fusion targeted biopsy, standard US-guided systematic biopsy

Introduction

Transrectal, ultrasound-guided biopsy is the most used technique for prostate cancer (PCa) detection since the 1990s. This technique has limited specificity [1, 2] and is associated with over diagnosing clinically insignificant PCa and missing clinically significant PCa [3-5], especially PCa located in the anterior aspect of the prostate [6].

The advent of multiparametric magnetic resonance imaging (mpMRI) enables imaging-based identification of prostate cancer (PCa). This has led to the development of mpMRI/ultrasound (US) fusion biopsy (targeted biopsy) platforms in recent years. Studies suggested that targeted biopsy combined with concurrent standard biopsy (combined biopsy, hereafter) is superior to standard US-guided biopsy in detecting clinically significant PCa [7-9], especially high-risk PCa [4, 10-15]. This has led to targeted biopsy increasingly being used clinically. Some studies also suggested that targeted biopsy alone was more cost-effective in detecting clinically significant PCa [16, 17]. Therefore, questions were raised about the necessity of performing concurrent standard biopsy if targeted biopsy was also performed. In this study, we examined our data from combined biopsy and compared with standard systemic biopsy and targeted biopsy alone.

Materials and methods

Two cohorts, a total of 735 prostate biopsies, collected from 2017 to 2020 (protocol approved by the UW IRB) were included for the present

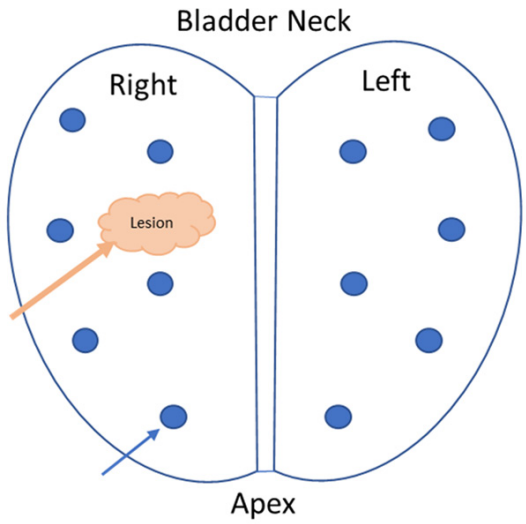

Figure 1. A diagram of combined targeted and concurrent standard biopsy of prostate. Blue dots and arrow indicate the standard 12-core biopsy, while orange colored arrow indicates targeted (lesion) biopsy.

study. Cohort 1 consisted of 395 combined biopsy cases (**Figure 1**), which were identified as having at least one lesion classified by the Prostate Imaging Reporting and Data System version 2.1 (PI-RADS) of 3 or greater. Target lesions were localized via prostate mpMRI by radiologists utilizing T2-weighted images (T2WI), dynamic contrast enhancement (DCE), and diffusion weighted imaging (DWI). mpMRI findings were categorized according to PI-RADS version 2.1 by abdominal radiologists experienced in prostate MRI. Lesions (PI-RADS 3-5) were contoured on commercially available software (DynaCAD, Philips, Eindhoven, Netherlands) (**Figure 2**) and imported to an ultrasound equipped with fusion hardware/software (UroNav, Philips,). MRI/US-fusion assisted targeted and systematic biopsy was performed by urologists with both targeted and conventional systemic prostate biopsy. A second review of the mpMRI with PI-RADS v2.1 score for 105 of the 390 combined biopsy cases was conducted by an experienced abdominal radiologist (SAW) blind to the diagnosis at the time of this study. Cohort 2 consisted of 345 cases, which were chronologically selected standard systematic US guided biopsies in the same period (**Table 1**).

Biopsy-proven PCa cases were categorized by risk: low, intermediate, and high [18]. Low risk PCa was defined by a Gleason score of 6 or low volume of Gleason score 3+4. For this study, low volume was categorized by <50% of any core containing cancer and <33% of all biopsy cores positive for cancer. Intermediate risk was defined as Gleason score 3+4 with 50% or more of any core positive for cancer or 33% or more of all biopsy cores positive for cancer. High-risk tumors were Gleason score 4+3 or greater [18].

The rates of PCa detection were compared between combined (cohort 1) and the standard (cohort 2), combined and targeted (cohort 1), and targeted and concurrent standard (cohort 1) biopsies. The two sets of PI-RADS scores (original and second review) from the 105 cases were also compared using Pearson's correlation coefficient. Chi-square tests were performed to determine significance.

Results

Examining the biopsy results from cohort 1 and cohort 2, we found that combined biopsy was significantly better than standard biopsy in detecting PCa (65.4% vs. 51.6%, P<0.01, **Table 2**) and intermediate-risk PCa (18.7% vs. 10.4%, P=0.02) but only slightly better in detecting high risk PCa (26.7% vs. 23.5%, P=0.32, **Table 3**).

Further examining the biopsy results from cohort 1 (combined biopsy cases), we found that combined biopsy was superior to both targeted biopsy (65.4% vs. 56.9%, P=0.02) and concurrent standard biopsy (65.4% vs. 52.1%, P=0.0002, **Table 4**) in PCa detection. Significantly more high-risk PCa was detected by combined biopsy than concurrent standard biopsy (26.7% vs. 17.4, P=0.002, **Table 4**), but the difference in detecting high-risk PCa between combined and targeted biopsies was not significant (26.7% vs. 22.1%, P=0.133, **Table 4**). Compared to concurrent standard biopsy, targeted biopsy detected significantly more PCa of intermediate risk (17.9% vs. 9.7%, P=0.0005) and significantly less PCa of low risk (16.9% vs. 24.9%, **Table 4**). The differences in detecting PCa and high-risk PCa between targeted and concurrent standard biopsies were not significant (56.9% vs. 52.1%, P=0.172 and 22.1% vs. 17.4%, P=0.105, respectively, **Table 4**).

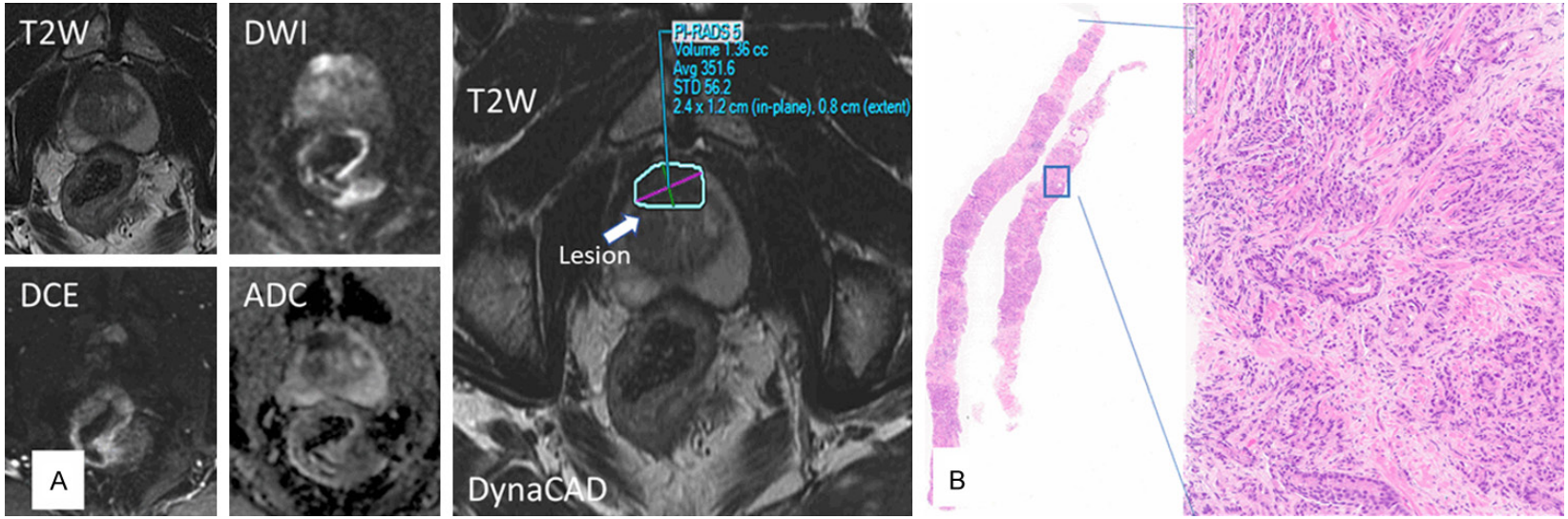

Figure 2. Targeted biopsy. A. A target lesion was localized via prostate mpMRI utilizing T2-weighted images (T2WI), dynamic contrast enhancement (DCE), and diffusion weighted imaging (DWI). mpMRI findings were categorized according to PI-RADS version 2.1 by abdominal radiologists experienced in prostate MRI. A lesion of PI-RADS 5 was contoured on commercially available software (DynaCAD, Philips, Eindhoven, Netherlands). B. Biopsy cores from the lesion showing prostatic adenocarcinoma, Gleason score 4+5, occupying 90% of the tissue (hematoxylin and eosin stained, far right panel showing cancer at 10×10 magnification).

Table 1. Patients' Demographic and Pathological Information

Cohort	Dx	GGG	N	Age	Risk	Positive Cores (n)	Total Cores (n)	Max Inv. of Single Core	Total Tumor Volume (%)
1	BPT	0	135	63.59	0.00	0.00	17.50	0.00%	0.00%
	PCa	1	37	65.31	1.00	2.22	17.27	23.57%	1.63%
		2	114	66.50	1.64	4.84	17.48	56.92%	9.79%
		3	43	68.79	3.00	6.58	17.14	71.74%	17.44%
		4	34	68.59	3.00	6.00	16.71	74.71%	17.13%
		5	27	67.29	3.00	9.07	17.04	77.96%	30.14%
		Total	390						
2	BPT	0	167	65.18	0	0	13.17	0	0
	PCa	1	32	67.19	1.00	2.28	12.63	18.94	2.69
		2	66	65.37	1.56	4.00	12.68	51.53	11.19
		3	23	68.20	3.00	5.74	12.26	59.61	16.50
		4	25	67.18	3.00	6.20	12.16	73.60	30.78
		5	32	69.85	3.00	8.31	12.09	84.38	50.55
		Total	345						

BPT: benign prostate tissue; Cohort 1: combined biopsy; Cohort 2: standard biopsy; Dx: diagnosis; GGG: Gleason Grade Group; PCa: prostate cancer; Risk: PCa was classified into low (1), intermediate (2) and high (3) risks.

Table 2. Comparison of combined biopsy (CB) with standard biopsy (SB) in detecting PCa

Dx	CB (Cohort 1) n (%)	SB (cohort 2) n (%)	**P*-value
PCa	255 (65.4)	178 (51.6)	0.00015
Neg	135 (34.6)	167 (48.4)	
total	390	345	

Combined biopsy: combined targeted biopsy with concurrent standard biopsy, *Chi-squared test.

Table 3. Comparison of combined biopsy (CB) with standard biopsy (SB) in detecting higher risk PCa

PCa risk	CB (cohort 1) n (%)	SB (cohort 2) n (%)	**P*-value
Low	78 (20)	61 (17.7)	P=0.42
Intermediate	73 (18.7)	36 (10.4)	P=0.02
High	104 (26.7)	81 (23.5)	P=0.32
Total	390	345	

Combined biopsy: combined targeted biopsy with concurrent standard biopsy; *Chi-squared test.

While both targeted and concurrent standard biopsies missed PCa, targeted biopsy alone missed significantly less PCa cases (12.9% vs. 20.4%, P=0.02), especially intermediate/high risk PCa (2.4% vs. 13.7%, P<0.01), compared to concurrent standard biopsy (**Table 4**, cells highlighted in green and blue, respectively).

Examining the 170 of 255 PCa cases detected by both targeted and concurrent standard biopsies in cohort 1, targeted biopsy detected significantly more PCa of higher risk than concurrent standard biopsy (15.9% vs. 9.4%, P=0.04, **Table 5**, cells highlighted in yellow).

We also compared the original PI-RADS scores with the scores generated by the reviewing radiologist for the 105 of 390 cases from cohort 1. Only 75 of the 105 (71.4%) cases were scored ≥3 by the reviewing radiologist (SW), with exact agreement of PI-RADS scores in 42 of the 105 (40%) cases (**Table 6**). There was a moderate correlation between the two sets of PI-RADS scores (Pearson's r=0.48).

Discussion

Our data between cohorts show that the combined biopsy is a superior technique to the standard systematic biopsy for detecting PCa, especially PCa of intermediate risk; these results support prior published research [18-22]. Unlike past findings, comparing combined biopsy (cohort 1) to standard systemic biopsy (cohort 2) did not show that the combined biopsy detected high-risk PCa at a significantly higher rate.

Likewise, combined biopsy identified high-risk PCa with only a slightly higher rate than the tar-

Table 4. Comparison of PCa detection rate between targeted biopsy (TB), concurrent standard biopsy (CSB) and combined biopsy (CB) in 390 cases with initial PI-RADS score ≥3 (Cohort 1) with risk stratifications

		CB n (%)	TB n (%)	CSB n (%)	*p-value		
					CB vs. TB	CB vs. CSB	TB vs. CSB
PCa		255 (65.4)	222 (56.9)	203 (52.1)	0.015	0.0002	0.172
Risk	H	104 (26.7)	86 (22.1)	68 (17.4)	0.133	0.002	0.105
	I	73 (18.7)	70 (17.9)	38 (9.7)	0.780	0.0003	0.0005
	L	78 (20)	66 (16.9)	97 (24.9)	0.268	0.103	0.006
Neg		135	168	187			
Total		390	390	390			

CB: combined biopsy, TB: targeted biopsy, CSB: concurrent standard biopsy, H: high, I: intermediate, L: low, *Chi-squared test.

Table 5. Comparison of PCa detection rates between targeted biopsy (TB) and concurrent standard biopsy (CSB) in the 255 positive cases identified by combined biopsy (CB, cohort 1) relative to PCa risk level (TB vs. CSB)

TB		CSB		Overall PCa risk			PCa Risk Level TB vs. CSB	Cases n (%)
Dx	PCa Detection n (%)	Dx	PCa Detection n (%)	Low n (%)	Intermediate n (%)	High n (%)		
PCa	222 (87.1)	Neg	52 (20.4)	17 (7.1)	17 (6.6)^	18 (7.1)*	N/A	52 (20.4)ξ
PCa		PCa	203 (79.6)	0	21 (8.2)	18 (7.1)	TB>CSB	39 (15.3)ξ
PCa		PCa		34 (14.2)	23 (9)	50 (19.6)	TB=CSB	107 (42)
PCa		PCa		0	10 (3.9)	14 (5.5)	TB<CSB	24 (9.4)ξ
Neg	33 (12.9)	PCa		27 (10.6)	2 (0.8)^	4 (1.6)*	N/A	33 (12.9)ξ
Total				78	73	104		255

Combined biopsy: combined targeted biopsy plus concurrent standard biopsy; TB>CSB: PCa risk in the cases detected by TB> in that by CSB; N/A: not applicable, ^P=0.0005, *P=0.002, ξP=0.04 (Chi-squared test).

Table 6. Comparison of the two sets of PI-RADS scores for the 105 randomly selected combined biopsies (Part of Cohort 1)

PCa Risk	PCa Case (n)	Cases (n) with PI-RADS ≥3 in at least one lesion		Cases (n) with PI-RADS changed by R2 in at least one lesion				
		R1	R2	PI-RADS ≥3 to <3	PI-RADS >3 to 3	PIRADS <3 to ≥3	PI-RADS 3 to >3	PI-RADS No change
Benign	37	37	7	30	2	0	1	4
Low	16	16	16	1	3	0	2	10
Intermediate	19	19	19	6	2	0	2	9
High	33	33	33	5	1	2	6	19
Total	105	105	75	42	8	2	11	42

PI-RADS: multiparametric magnetic resonance Imaging; R1: first radiologist(s), R2: 2nd radiologist (SW).

geted biopsy component alone. However, compared to the concurrent standard biopsy component alone, the combined biopsy was able to detect high-risk PCa with a significantly higher rate. These findings are consistent with published studies [19, 23].

Compared to concurrent standard biopsy, targeted biopsy had a higher rate of detecting intermediate/high risk PCa. But the difference was only significant in detecting PCa of intermediate risk, not in detecting high-risk PCa [19]. We found that targeted biopsy alone, like concurrent standard biopsy, also missed intermediate/high risk PCa. Similar findings were also reported by others [23-25].

While confident in our data, we recognize the limitations of this study. First, different from many published studies, the present study is a

retrospective study. Second, the cases in the two cohorts were not well-controlled, with mixed biopsy-naïve and biopsy-veteran cases, and the targeted and concurrent standard biopsy were not done blindly in combined biopsy cohort. Third, MRI/US fusion biopsy was introduced in 2017 at our institution, and we had limited experience in MRI/US fusion biopsy.

As the PI-RADS evolves, there exists more than one version of the guidelines. Using different versions may lead to differences in scoring since factors hold different significance depending on the zone of the prostate [20, 21]. For example, T1-Weighted Image (T1WI) has a more important role in Version 2 than Version 1. Also, Version 1 considers DCE MRI and DWI equally without considering the region of biopsy collection. In Version 2, the role of DCE and DWI is narrowed to specifically influence the score based on the region of extraction (DCE for the peripheral zone while DWI for transitional zone (TZ)). Those differences in addition to the subjective nature of human perception and experience of the readers may have resulted in interobserver variability in scoring the lesions (see **Table 5**), particularly lesions in the TZ, and impacted the biopsy results [22].

While combined biopsies tend to produce better results, their cost-effectiveness has been called into question as the benefits of including standard biopsies may not justify the added expenses. There is compelling evidence that the benefits of a combined biopsy continue to outweigh the additional cost associated with mpMRI [23-25].

In summary, combined biopsy is superior to targeted or standard biopsy alone in detecting PCa including high risk PCa. As we gain more experience in reading mpMRI images and accurately classifying lesions, particularly lesions in the TZ, combined biopsy technique will likely change the landscape of PCa diagnostics.

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Disclosure of conflict of interest

None.

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