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ORIGINAL ARTICLE

Comparison of Post Biopsy Pathology and Post Radical Prostatectomy Pathology in Patients with Prostate Cancer Detected After Fusion Biopsy

Füzyon Biyopsi Sonrası Prostat Kanseri Saptanan Hastalarda Biyopsi Sonrası Patoloji ile Radikal Prostatektomi Sonrası Patolojinin Karşılaştırılması

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ABSTRACT

Aims: To compare the post-radical prostatectomy (RP) final pathologies and post-biopsy pathologies of the patients diagnosed with prostate cancer (PCa) after fusion biopsy according to the International Society of Urological Pathology (ISUP) grading system.
Material and Methods: In this retrospective study, data of 182 patients who underwent fusion biopsy and concomitant systematic biopsy between January 2020 and August 2022 was reviewed. All these patients were biopsy naive with PIRADS-3 lesions according to the multiparametric MRI (mp-MRI) imaging. A total of 89 patients with PCa detected by biopsy were included in the study. Age, PSA, PSA density, and lesion grades according to PI-RADS were analyzed. The post-biopsy (fusion and systematic biopsy) pathology results of 60 patients who underwent RP were compared with the final pathology results after RP.
Results: Pathological results after fusion biopsy and RP were compared. The individual agreement between RP and fusion biopsy for each ISUP grade was moderate to almost excellent (0.558 to 0.848). When the overall agreement between RP and fusion biopsy was evaluated, the weighted kappa was calculated as 0.721 (95% CI: 0.577 to 0.865), which was determined as substantial significant agreement. On the other hand, the overall agreement between systematic biopsy and pathology results after RP was calculated as weighted kappa 0.544 (95% CI: 0.405 to 0.683) and this agreement was determined as moderate agreement.
Conclusion: Our study showed that the concordance between the pathology result after fusion biopsy and the final pathology after RP was higher than the standard TRUS prostate biopsy. We think this compliance is crucial in the regulation and follow-up of the treatment of the patients.

Keywords: Prostate cancer, mp-MRG, fusion biopsy, ISUP grade

ÖZ

Amaç: Füzyon biyopsisi sonrası prostat kanseri (PCa) saptanan hastaların radikal prostatektomi (RP) sonrası final patolojileri ile biyopsi sonrası patolojilerini Uluslararası Ürolojik Patoloji Derneği (ISUP) derecelendirme sistemine göre karşılaştırmak.
Gereç ve Yöntem: Bu retrospektif çalışmada Ocak 2020-Ağustos 2022 yılları arasında füzyon biyopsi ve beraberinde sistematik biyopsi yapılan 182 hastanın verileri tarandı. Bu hastaların tümü multiparametrik MRG (mp-MRG) görüntülemesi yapılan PIRADS-3 lezyonu olan ve biyopsi naiv hastalardı. Biyopsi sonucunda PCa saptanan 89 hasta çalışmaya dahil edildi. Hastaların yaş, PSA, PSA dansitesi, PI-RADS'a göre lezyon dereceleri incelendi. Bu hastalardan RP yapılan 60 hastanın biyopsi sonrası (füzyon ve sistematik biyopsi) patoloji sonuçlarıyla RP sonrası final patoloji sonuçları karşılaştırıldı.
Bulgular: Füzyon biyopsisi ve RP sonrası patolojik sonuçlar karşılaştırıldı. Her bir ISUP derecesi için RP ve füzyon biyopsisi arasındaki bireysel uyum orta ila neredeyse mükemmeldi (0,558 ila 0,848). RP ve füzyon biyopsisi arasındaki genel uyum değerlendirildiğinde, ağırlıklı kappa 0,721 (%95 CI: 0,577 ila 0,865) olarak hesaplandı ve bu uyum önemli uyum olarak belirlendi. Diğer yandan, RP sonrası sistematik biyopsi ve patoloji sonuçları arasındaki genel uyum ağırlıklı kappa 0,544 (%95 GA: 0,405 ila 0,683) olarak hesaplanmış ve bu uyum orta düzeyde uyum olarak belirlenmiştir.
Sonuç: Çalışmamızda füzyon biyopsi sonrası patoloji sonucuyla RP sonrası final patoloji arasındaki uyumun standart TRUS prostat biyopsisine göre daha yüksek oranda olduğunu gösterdik. Bu uyumun hastaların tedavisinin düzenlenmesinde ve takibinde önemli olduğunu düşünüyoruz.

Anahtar Kelimeler: Prostat kanseri, mp-MRG, füzyon biyopsi, ISUP derecesi

Introduction

Prostate adenocarcinoma (PCa) is one of the most common cancers in men, with an annual incidence of more than one million cases worldwide and a mortality rate of more than three hundred thousand.(1) PCa has long been diagnosed by the standard transrectal ultrasonography (TRUS)-guided biopsy performed as a result of elevated prostate-specific antigen (PSA) and/or abnormal digital rectal examination (DRE). (2) Although the TRUS prostate biopsy method has been used as the gold standard for years, the 12-14 core biopsies have been performed blindly.(3) The main reason for blind biopsy is the inability to clearly distinguish suspicious lesions on the TRUS imaging.(3) Therefore, the sensitivity of PCa detection in prostate biopsy with the standard TRUS is as low as 27%-40%. In addition, 10-20% of TRUS biopsy may fail to detect possible cancer.(4) As a result, the diagnosis of PCa may require two or more repeat biopsies in 50% of patients.(4) In recent years, technological advances have brought the multiparametric magnetic resonance imaging (mp-MRI) to the forefront in prostate imaging. The use of mp-MRI in the pre-biopsy evaluation has

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significantly increased the ability to detect clinically significant PCa,(5, 6) thus, reducing the overtreatment risk.(7) As a result of the widespread use of the Mp-MRI, the Prostate Imaging, Reporting and Data System (PI-RADS) were developed in 2012 (8) and this data system (PI-RADS version 2.1) was updated in 2015. (9) Currently, the European Association of Urology (EAU) guidelines strongly recommend mp-MRI before prostate biopsy.(10) The guideline recommends fusion biopsy+systematic biopsy in patients with PI-RADS≥3 lesions and no prior biopsy.(10) The EAU guidelines also recommend targeted biopsy in patients with previously negative biopsy results if PI-RADS≥3 lesions are detected after mp-MRI imaging.(10)

In patients undergoing TRUS prostate biopsy, discrepancies between the pathologies after needle biopsy and radical prostatectomy may be high. (11, 12) In a study of 1363 patients examining the concordance between ISUP grade after standard TRUS biopsy and ISUP grade after radical prostatectomy (RP) in pathologic evaluations, it was observed that 32% of the cases had a lower grade on TRUS biopsy while 9% had a higher grade.(13) In another study, it was found that 41.9% of the cases were graded lower in the final pathology after RP and 8.3% were graded higher in the evaluation according to ISUP.(14)

Targeted biopsy has increased the accuracy rates in diagnosis and staging and the discordance rate between biopsy and final pathology has started to decrease.(15) Although there are many studies examining the concordance between pathology after standard TRUS biopsy and pathology after RP, there are very few studies on fusion biopsy. In the light of this background information and knowledge gap, we aimed to examine the concordance of ISUP grade between biopsy and final pathology of our PCa patients with fusion biopsy and consequent RP.

Materials and Methods

This retrospective study received ethics committee approval from the Local Ethics Committee of Selcuk University Faculty of Medicine on 12.10.2022 with decision number 2022/433. We retrospectively analyzed the data of 182 patients who underwent mp-MRI between January 2020 and August 2022 due to an elevated PSA value (threshold ≥4 ng/dL) and/or suspicion of PCa on digital rectal examination (DRE) and had PI-RADS (version 2.1) ≥3 lesions. All of these patients were biopsy naive. A total of 89 patients with pathology results reported as PCa were included in the study. Age, PSA, prostate volume, PSA density, lesion classification according to PI-RADS, and number of lesions were recorded.

All patients underwent mp-MRI with a 3-Tesla MRI system (Siemens, Magnetom Area). The mp-MRI images were evaluated according to PI-RADS version 2.1 by a single radiologist with five years of experience in this field. LOQIC S8 (GE Healthcare/ S.Korea) ultrasonography device with rigid fusion software was used during fusion biopsy. Fusion biopsies of patients with PI-RADS 3 or more lesions were performed by a single urologist with at least 15 years of experience and a radiologist interpreting mp-MRI scans. In biopsy naive patients, 14 quadrant systematic biopsies were performed, including at least 3 from each index lesion. In some cases, more biopsies were taken from the suspicious lesion according to the decision of the radiologist. All pathologic evaluations were performed by a pathologist experienced in uropathology. The ISUP grading system was used for pathologic evaluation in 2014.(16) The ISUP grading system consists of 5 grades according to Gleason score (GS); ISUP grade 1 (GS 6≤), ISUP grade 2 (GS 3+4), ISUP grade 3 (GS 4+3), ISUP grade 4 (GS 4+4/ GS 3+5/ GS 5+3) and ISUP grade 5 (GS 4+5/ GS 5+4/ GS 5+5). The final ISUP grades of 60 patients who underwent RP with ISUP grades as a result of pathology evaluation after biopsy were evaluated in detail.

Statistical analysis

All statistical analysis was performed using R statistical language software (version 4.1.2; The R Foundation for Statistical Computing, Vienna, Austria; https://www.r-project.org). The weighted kappa (κ) value with linear weights was used to assess the agreement between the reference standard grades (RP pathology) and fusion, and systematic grading systems. The weights to the disagreement were assigned according to the method of the equally spaced. The Cohen's kappa was used to examine the individual agreement of grades. The weighted kappa and Cohen's kappa values were interpreted as follows: slight agreement (0 – 0.20); fair agreement (0.21 – 0.40), moderate agreement (0.41 – 0.60), substantial agreement (0.61 – 0.80), and almost perfect agreement (0.81 – 1.00). (17) The Cohen and weighted kappa values were calculated with 95% confidence intervals. A p-value <.05 was considered statistically significant.

Results

The records of 89 patients who underwent fusion biopsy and were found to have PCa were retrospectively analyzed. Among these patients, data from 60 patients who underwent RP after biopsy were analyzed separately. The mean age of the patients who underwent fusion biopsy was 66 (50-82), PSA values were 13 ng/dl (4.16-100), prostate volumes were 53 cc (20-182) and PSA density was 0.27 (0.04-1.53). The number of PI-RADS≥3 lesions was 133. Of these lesions, 41 (31%) were PI-RADS 3, 48 (36%) PI-RADS 4, and 44 (33%) were PI-RADS 5 lesions. The mean number of index lesions per patient was 1.52 (1-5). The characteristics of the patients who underwent RP and the index lesions are given in Table 1.

When the post-biopsy ISUP grades of the patients who underwent fusion biopsy and were found to have PCa were analyzed, ASAP was observed in 6 (6%) patients, ISUP grade 1 in 29 (32%) patients, ISUP grade 2 in 16 (18%) patients, ISUP grade 3 in 16 (18%) patients, ISUP grade 4 in 9 (11%) patients, and ISUP grade 5 PCa in 13 (15%) patients. ISUP grades and treatment modalities of the patients are given in Table 2. When the pathology results after RP were analyzed, 17 patients had ISUP

grade 1 (28.3%), 18 patients had ISUP grade 2 (30%), 19 patients had ISUP grade 3 (31.7%), 3 patients had ISUP grade 4 (5%) and 3 patients had ISUP grade 5 (5%). The agreement between ISUP grades after fusion biopsy and RP was 88.2% (Cohen's κ=0.727) in ISUP grade 1, 83.3% (Cohen's κ=0. 798) in ISUP grade 2, 63.2% (Cohen's κ=0.558) in ISUP grade 3, 100% (Cohen's κ=0.848) in ISUP grade 4 and 66.7% (Cohen's κ=0.649) in ISUP grade 5. The overall ISUP grade agreement rate after fusion biopsy and RP was 78.3%, which was statistically significant (Weighted κ (95% CI) = 0.721 (0.577 to 0.865). Upgrade was observed in 6 patients and downgrade was observed in 6 patients according to ISUP grade after fusion biopsy. The highest discordance between RP and fusion biopsy was observed in ISUP grade 3. While 12 patients with ISUP grade 3 were in agreement with RP pathology, 5 patients had downgraded and 2 patients had upgraded. The results of agreement, disagreement/discrepancy, downgrade, or upgrade ISUP grade according to fusion biopsy are given in Table 3 and Figure 1.

The agreement between ISUP grades after systematic biopsy and RP was 85.7% (Cohen's κ=0.457) in ISUP grade 1, 35.3% (Cohen's κ=0. 180), 44.4% in ISUP grade 3 (Cohen's κ=0.404), 33.3% in ISUP grade 4 (Cohen's κ=0.295) and 33.3% in ISUP grade 5 (Cohen's κ=0.238). The overall ISUP grade agreement rate after systematic biopsy and RP was 50.9% (Weighted κ (95% CI) =0.544 (0.405 to 0.683). According to ISUP grade after systematic biopsy, a downgrade was observed in 19 patients and an upgrade was observed in 8 patients. Discordance between RP and systematic biopsy was mostly observed in ISUP grade 2 (9 downgrades and 2 upgrades) and ISUP grade 3 (8 downgrades and 2 upgrades). (Table 3)

Table 1: Characteristics of PCa patients underwent fusion biopsy and index lesions

	Patients undergoing RP after fusion biopsy (n=60)	Patients with PCa after fusion biopsy (n=89)
Age	62 (50-74)	67 (50-82)
PSA (ng/ml)	12,6 (4,16-61,2)	13 (4,16-100)
Prostate Volume (cc)	50 (22-92)	53 (20-182)
PSA Density	0,26 (0,07-0,94)	0,27 (0,04-1,53)
According to mp-MRG PI-RADS lesion classification	PI-RADS 3 = 26(%33)	PI-RADS 3 = 41(%31)
	PI-RADS 4 = 25(%32)	PI-RADS 4 = 48(%36)
	PI-RADS 5 = 27(%35)	PI-RADS 5 = 44(%33)
Number of lesions (mean)	1,30 (1-3)	1,52 (1-5)

RP: Radical Prostatectomy, **PCa**: Prostate Cancer, **PSA:** Prostat Specific Antigen, **mp-MRG:** Multiparametrik MRG, **PI-RADS:** Prostate Imaging Reporting and Data System

Table 2: ISUP grades and treatment modalities of patients underwent fusion biopsy

Fusion biopsy ISUP grade	Pathology Result	n=89 (100%)
	ASAP	6 (%6)
	ISUP Grade 1	29 (%32)
	ISUP Grade 2	16 (%18)
	ISUP Grade 3	16 (%18)
	ISUP Grade 4	9 (%11)
	ISUP Grade 5	13 (%15)
Treatment modality	**Treatment Modality**	n=89(100%)
	Active Surveillance	5
	RP	60
	Radiotherapy	6
	Radiotherapy +MAB	13
	MAB	4
	Chemotherapy	1

ISUP: International Society of Urological Pathology , **ASAP:** Atypical small acinar proliferation, **RP:** Radical Prostatectomy **MAB:** Maximal Androgen Blockade

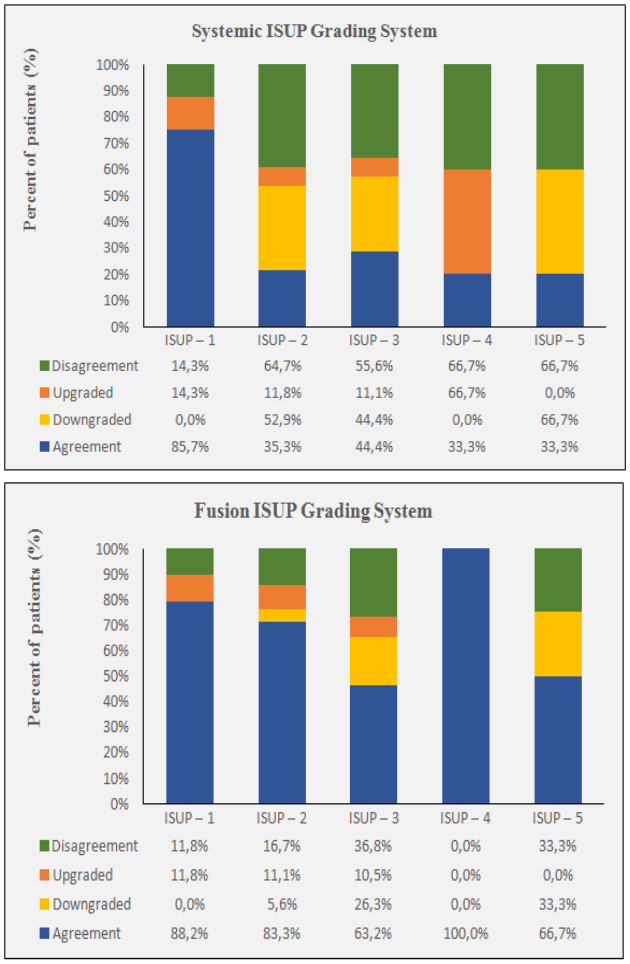

Figure 1: Comparison of fusion and systematic biopsy ISUP grades with ISUP grades after RP

SUP: International Society of Urological Pathology, **RP:** Radical Prostatectomy

Table 3. Comparison of fusion and systematic biopsy ISUP grade and ISUP grade after RP

	ISUP RP Pathology (Gold standard)						
	ISUP – 1	ISUP – 2	ISUP – 3	ISUP – 4	ISUP – 5	Total	**Cohen's** κ (95% CI)
Fusion ISUP							
ISUP – 1	15 (88.2)	1 (5.6)	4 (21.1)	0 (0)	0 (0)	20 (33.3)	0.727 (0.539 to 0.914)
ISUP – 2	1 (5.9)	15 (83.3)	1 (5.3)	0 (0)	0 (0)	17 (28.3)	0.798 (0.629 to 0.966)
ISUP – 3	1 (5.9)	2 (11.1)	12 (63.2)	0 (0)	1 (33.3)	16 (26.7)	0.558 (0.327 to 0.787)
ISUP – 4	0 (0)	0 (0)	1 (5.3)	3 (100)	0 (0)	4 (6.7)	0.848 (0.557 to 1.000)
ISUP – 5	0 (0)	0 (0)	1 (5.3)	0 (0)	2 (66.7)	3 (5)	0.649 (0.196 to 1.000)
Total	17 (28.3)	18 (30)	19 (31.7)	3 (5)	3 (5)	60	
Agreement	15 (88.2)	15 (83.3)	12 (63.2)	3 (100)	2 (66.7)	47 (78.3)	
Disagree-ment	2 (11.8)	3 (16.7)	7 (36.8)	0 (0)	1 (33.3)		
Downgra-ded	0 (0)	1 (5.6)	5 (26.3)	0 (0)	1 (33.3)		
Upgraded	2 (11.8)	2 (11.1)	2 (10.5)	0 (0)	0 (0)		
Weighted κ (95% CI) =0.721 (0.577 to 0.865); Percent agreement=78.3%							
Systematic ISUP							
ISUP – 1	12 (85.7)	9 (52.9)	3 (16.7)	0 (0)	0 (0)	24 (43.6)	0.457 (0.232 to 0.681)
ISUP – 2	2 (14.3)	6 (35.3)	5 (27.8)	0 (0)	0 (0)	13 (23.6)	0.180 (–0.093 to 0.453)
ISUP – 3	0 (0)	2 (11.8)	8 (44.4)	0 (0)	1 (33.3)	11 (20)	0.404 (0.145 to 0.661)
ISUP – 4	0 (0)	0 (0)	1 (5.6)	1 (33.3)	1 (33.3)	3 (5.5)	0.295 (–0.209 to 0.799)
ISUP – 5	0 (0)	0 (0)	1 (5.6)	2 (66.7)	1 (33.3)	4 (7.3)	0.238 (–0.216 to 0.693)
Total	14 (25.5)	17 (30.9)	18 (32.7)	3 (5.5)	3 (5.5)	55	
Agreement	12 (85.7)	6 (35.3)	8 (44.4)	1 (33.3)	1 (33.3)	28 (50.9)	
Disagree-ment	2 (14.3)	11 (64.7)	10 (55.6)	2 (66.7)	2 (66.7)		
Downgra-ded	0 (0)	9 (52.9)	8 (44.4)	0 (0)	2 (66.7)		
Upgraded	2 (14.3)	2 (11.8)	2 (11.1)	2 (66.7)	0 (0)		
Weighted κ (95% CI) =0.544 (0.405 to 0.683); Percent agreement=50.9%							

ISUP: International Society of Urological Pathology, **RP:** Radical Prostatectomy

Discussion

GS has been used as a grading system for histologic grading of PCa for years. However, the ISUP grading system which is defined in 2014 is widely accepted instead of GS. GS is one of the most important parameters in determining the prognosis and treatment decision of PCa.(16, 18) There may be discrepancies between standard TRUS biopsy and final pathology after RP. Therefore, there are many studies examining the concordance of GS in patients with PCa after biopsy and GS in the final pathology after RP.(19, 20) In studies, the discordance of GS between TRUS prostate biopsy and pathologic evaluation after RP can be more than 50%. (21-23) In our study, ISUP grade concordance after systematic biopsy and RP was 50.9% and was consistent with the literature. In the comparison of systematic biopsy and ISUP grade after RP, the downgrade rate was 35% and the upgrade rate was 14%.

In recent years, the widespread use of fusion biopsy as a result of the increasing adoption of mp-MRI has facilitated the detection of high-grade cancer (≥ISUP grade 2) on biopsy compared to systematic biopsy alone.(24) Especially the ability to obtain direct biopsies from index lesions is crucial for the diagnosis of PCa. On the other hand, fusion biopsies performed with mp-MRI may increase the rate of detection of clinically insignificant cancer while detecting high-grade cancer.(24) In addition to increasing the rate of cancer detection, a more important issue is the extent to which the ISUP grade in pathologic evaluation can be matched in the final pathology after RP. In a 2020 meta-analysis, post-biopsy pathologies of patients with PCa detected by fusion biopsy and systematic biopsy were compared with final pathologies after RP.(19) Targeted fusion biopsy showed 23.3% stage elevation compared to 42.7% in systematic biopsy.(19) In our study, the ISUP grade concordance rate after RP with fusion biopsy was 78.3%. When the literature was reviewed, it was observed that the concordance rate was higher in our study. Regarding ISUP grade discordance, the downgrade rate was 11.6% and the upgrade rate was 10%. ISUP grade discrepancy (21.6%) after fusion biopsy and RP was less in our study then the literature rates. Of the 13 patients with ISUP grade discrepancy, 10 patients were ISUP grade 2 (three patients) and ISUP grade 3 (seven patients). We think that the high rate of ISUP grade concordance between fusion biopsy and RP in our study may due to the multidisciplinary work of the experienced urologist, radiologist and pathologist.

Biopsy is essential in the diagnosis and treatment management of patients with suspected PCa. This is because a biopsy from the right area provides a clear diagnosis, and with the appropriate definition of the ISUP grade, treatment planning is made in accordance with the patient's risk classification. The main aim of biopsy in patients with suspected PCa is to capture the tumor area.(25) In standard TRUS biopsy, it is difficult to accurately identify the tumor area. This is because it is not targeted and only the peripheral margin of the prostate is biopsied.(25) Because of these disadvantages, clinically significant PCa may be overlooked with standard biopsy. In some studies, it was reported that the ISUP grade increased by 25% to 40% in the final pathology compared to RP.(26) In addition to these disadvantages of standard biopsy, there may be inconsistencies in pathology due to the multifocal nature of PCa, the limited area covered by the biopsy, and the planning of the sample size. Some studies in the literature have reported that ISUP grade can be evaluated more accurately after RP by increasing the number of cores taken in biopsy. (27) However, taking more core biopsies may increase complications.(28) In the fusion biopsy procedure, since targeted biopsy is performed with fewer cores, the rate of clinically

significant cancer is increased, fewer complications are seen, and the agreement between the ISUP grade after biopsy and the ISUP grade in the final pathology is increased.(28) In a study examining the errors in the pathologic evaluation of cases with PCa after standard TRUS biopsy, it was reported that high grading was more common in ISUP grade 4 and 5 cases while low grading was more common in ISUP grade 1 and 2 cases. (13) In our study, the highest grade discordance was observed in ISUP grade 3. Upgrade was observed in five patients with ISUP grade 3 and downgrade in two patients with fusion biopsy pathology result. Five of the patients who underwent fusion biopsy actually had clinically insignificant PCa (ISUP grade 1), but these patients had an upgrade on fusion biopsy. In the remaining 55 patients, clinically significant PCa was detected on fusion biopsy and confirmed by RP. In our study, the rate of detection of clinically significant PCa on fusion biopsy was consistent with the studies in the literature. In our study, the compliance after RP was 100% in three patients with ISUP grade 4. This result may probably be due to the low number of patients with ISUP grade 4 and 5.

It is clear that our study has some limitations. First of all, being a retrospective study is the most important limitation. On the other hand, since the number of patients who underwent RP is relatively small and the number of patients with ISUP grade 4 and 5 is small, the comparison of pathology results covers a smaller sample. The strength of our study is that the same urologist and radiologist performed the biopsy and interpreted mp-MRI who are experienced in the PCa and the results were evaluated by the same pathologist.

Conclusions

In recent years, with the increasing use of mp-MRI and fusion biopsy procedure in the diagnosis of PCa, the rate of clinically significant cancer detection has increased and the ISUP grade agreement between post-biopsy pathology and final pathology after RP has become higher than standard biopsy. In our study, we demonstrated the agreement of fusion biopsy with the final pathology after RP. We believe that this agreement will be demonstrated more clearly in future larger series, prospective and comparative studies.

Conflict of Interest: There is no conflict of interest between the authors.

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