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Original Research / Özgün Araştırma

Systematic versus cognitive targeted biopsy: evaluation of parameters related to clinically significant prostate cancer and comparison of detection rates

Sistematik ve kognitif hedefe yönelik biyopsi: klinik olarak anlamlı prostat kanseri ile ilgili parametrelerinin değerlendirilmesi ve tespit oranlarının karşılaştırılması

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Özet

Amaç: Bu çalışmanın amacı, kognitif hedefe yönelik biyopsi (KHB) ve sistematik biyopsinin (SB) klinik anlamlı prostat kanseri (kaPKa) tespit oranlarını karşılaştırmak ve kaPKa tespit oranlarını etkileyen faktörleri ortaya çıkarmaktır.

Gereç ve Yöntemler: 2016-2019 yılları arasında lokalize prostat kanseri tanısı alan hastalar retrospektif olarak değerlendirildi. KHB ve SB yapılan hastalar kaydedildi. İndeks lezyondan alınan KHB kor sayısı, yaş, prostat spesifik antijen (PSA) seviyesi, gleason skoru, ISUP (International Society of Urological Pathology) derecesi, PIRADS (Prostate Imaging and Data Reporting System) skoru, indeks lezyonun büyüklüğü ve parmakla rektal muayene (PRM) bulguları kaydedildi. Ayrıca lezyonun magnetik rezonans görüntüleme (MRG)' deki lokalizasyonu ile PRM ile tespit edilen nodülün lokalizasyonu arasında bir uyum olup olmadığı da araştırıldı.

Bulgular: Seksen hasta çalışmaya dahil edildi. SB'li 55 (%68.7) hastada kaPKa saptanırken, tek başına KHB ile 35 (%43.7) hastada kaPKa saptandı (p<0.01). SB ile 2 kaPKa hastası atlanmasına karşın KHB ile kaPKa hastaların % 35'ine tanı konulamadı. SB ve KHB'de kaPKa tespit oranları, PRM ve mpMRG arasında bir uyum olan hastalarda anlamlı olarak daha yüksekti (sırasıyla p= 0.012 ve p<0.01). KHB'de kaPKa saptanan hastalarda ortalama yaş, prostat hacmi, PSA, lezyon çapı, kor sayısı ve (PGVRS) skoru açısından anlamlı farklılıklar saptandı (sırasıyla p=0.005, p=0.02, p=0.005, p=0.003, p=0.017 ve p=0.002).

Sonuç: SB, kaPKa tanısında önemini korumaktadır. Daha büyük lezyonları olan hastalarda KHB tercih edilebilir.

Anahtar Kelimeler: prostat kanseri, prostat biyopsisi, manyetik rezonans görüntüleme, hedefe yönelik biyopsi

Abstract

Objective: This study aims to compare the clinically significant prostate cancer (csPCa) detection rates of cognitive targeted biopsy (CTB) and systematic biopsy (SB) and to reveal the factors affecting csPCa detection rates.

Material and Methods: Patients diagnosed with localized prostate cancer between 2016-2019 were evaluated retrospectively. Patients who underwent SB and concomitant CTB were recorded. The number of cores taken from the index lesion in CTB, age, prostate-specific antigen (PSA) level, Gleason score, International Society of Urological Pathology (ISUP) grade, Prostate Imaging and Data Reporting System (PI-RADS) score, the diameter of index lesion, and digital rectal examination (DRE) findings was recorded. We also studied whether there was a concordance between the localization of the lesion on MRI (magnetic resonance imaging) and the localization of the nodule detected on DRE.

Results: Eighty patients were included in the study. csPCa was detected in 55 (68.7%) patients with SB, whereas CTB alone detected csPCa in 35 (43.7%) patients (p<0,01). SB missed 2 patients with csPCa, but 35% of the men with csPCa would be missed by CTB. Detection rates of csPCa in SB and CTB were significantly higher in patients with a concordance between DRE and mpMRI (p= 0.012 and p<0.01, respectively). In patients who had csPCa in CTB, significant differences were detected in the mean age, prostate volume, PSA, lesion diameter, number of cores, and PI-RADS score (p=0.005, p=0.02, p=0.005, p=0.003, p=0.017, and p=0.002, respectively)

Conclusion: SB maintains its importance in the diagnosis of csPCa. CTB can be preferred in patients with larger lesions.

Keywords: prostate cancer, prostate biopsy, magnetic resonance imaging, targeted biopsy

The study was approved by Bezmialem Vakıf University Hospital Ethic Committee (Approval No: 2021/184, Date: 2021/06/22). All research was performed in accordance with relevant guidelines/regulations, and informed consent was obtained from all participants.

INTRODUCTION

Prostate cancer (PCa) is mens second most commonly observed malignancy, and it forms approximately 15% of all malignancies (1). After the widespread use of prostate-specific antigen (PSA), there has been a significant elevation in PCa incidence (2). In patients with increased PSA or suspicious digital rectal examination (DRE), the standard method for the diagnosis of PCa is a transperineal or transrectal ultrasound-guided biopsy (TRUS-BX) (3). It is carried out randomly, as ultrasound cannot differentiate benign prostatic tissue from the foci of PCa, and typically, 12 cores are obtained from the peripheral zone (4). Widespread use of PSA and TRUS-BX has increased the number of patients diagnosed at an earlier stage. However, the rate of clinically insignificant prostate cancer (ciPCa) has also been observed (5).

Recently, there have been significant improvements in prostate MR imaging techniques. Multiparametric MRI (mpMRI) has led to significant advances in the assessment of PCa before biopsy (6,7). Lesions detected on mpMRI are reported following the Prostate Imaging and Data Reporting System (PIRADS) version 2 document and classified on a scale from 1 to 5 (8). Systematic transrectal ultrasound-guided biopsy (SB) may miss clinically significant prostate cancer (csPCa), leading to recurrent biopsies; it may also diagnose insignificant cancer and may result in unnecessary treatment (9,10). The sensitivity of mpMRI in detecting PCa with the International Society of Urological Pathology (ISUP) grade > 2 is very high, but the sensitivity for ISUP grade 1 is very low (11,12). The potential of detecting csPCa with fewer biopsy cores and avoiding ciPCa has led to the idea of targeting only the suspicious areas on mpMRI.

Targeted prostate biopsy by using mpMRI images is performed in 3 ways: (1) in-bore targeted biopsy carried out with MRI guidance; (2) fusion targeted biopsy, in which with the help of software, mpMRI images are combined with real-time transrectal ultrasound imaging; and (3) cognitive targeted biopsy (CTB), in which the operator evaluates the localization of suspicious lesions on mpMRI before biopsy and combines MRI and TRUS images in his mind during biopsy procedure (10,13,14). In-bore MRI targeted, and fusion biopsies are expensive and require special equipment, whereas CTB is cost-effective, easy to perform, and does not need special equipment (10,15). The main disadvantage of CTB is that it is highly operator-dependent (13,16). There is controversy about the superiority of these techniques over each other and whether they eliminate the need for systematic biopsy. Current guidelines recommend having a mpMRI prior to biopsy and combining targeted and systematic biopsies in cases with a PIRADS ≥ 3 lesions (3).

It was aimed to compare csPCa detection rates of CTB and SB in patients with PCa and to reveal the factors that affect the csPCa detection rates in this study.

MATERIAL AND METHODS

Patients diagnosed as localized PCa by TRUS-BX between 2016 and 2019 were evaluated retrospectively, and patients who underwent SB and concomitant CTB were recorded. All patients had an elevated PSA and/or suspicious DRE and a discrete index lesion of PIRADS ≥ 3 on mpMRI. Patients with a PIRADS score ≤2, PSA >20 ng/ml, a history of PCa or previous prostate biopsy, and patients with the suspicion of metastatic disease were excluded. All patients underwent standard 12-core SB, and additional cognitive targeted biopsies were carried out at the same session. The number of cores obtained from the index lesion in CTB was noted. Patient age, PSA level, Gleason score, ISUP score, PIRADS score, the maximum diameter of the index lesion, and DRE findings were recorded. We also evaluated whether there was a concordance between the localization of the lesion detected on MRI and the localization of the nodule detected in DRE. Clinically significant PCa was defined as Gleason grade ≥7. Ethical approval was obtained from the Institutional Ethics Committee (2021/184).

mpMRI

Patients had a 1.5 T mpMRI scan before the biopsy. Imaging protocol includes T2 weighted multiplanar, diffusion-weighted, dynamic contrast-enhanced, and T1 weighted images with fat suppression obtained in accordance with the standards defined by guidelines (17,18). Lesions on the MRI were categorized and scored following the PIRADS version 2 document by a

radiologist who has been interpreting multiparametric prostate MRI images for more than 4 years. Patients with PIRADS score 3 (presence of csPCa is equivocal), PIRADS score 4 (csPCa presence is probable), and PIRADS score 5 (presence of csPCa is highly probable) lesions on MRI underwent CTB. A single index lesion was biopsied in each patient. In men with more than one lesion on MRI, the biopsy was performed from the lesion with the higher score.

Biopsy Technique

Prostate biopsies were performed by 3 colleagues with more than 10 years of experience in TRUS-BX procedures performed prostate biopsies. In SB, 12 cores were randomly obtained from the peripheral zone, including the bilateral base, midgland, and apex transrectally. CTB was carried out under TRUS guidance in the axial scan. Lesions detected in MRI were aimed at ultrasonography according to the zonal anatomy of the prostate and anatomical structures such as nodules and cysts.

Statistical Analysis

Statistical analyses were conducted using the SPSS 17.0 statistical program (SPSS Inc., Chicago, IL, USA). While evaluating the study data, the Pearson Chi-Square test was used to compare qualitative data according to groups and descriptive statistical methods (Mean, Standard Deviation, Frequency, and Ratio). Skewness and kurtosis values were used to decide whether the distribution was normal or not. The cut-off points of the kurtosis and skewness values should be within 3 as the absolute value for the skewness and 10 as the absolute value for the kurtosis (19). Analysis showed that all our data had a normal distribution. An Independent Sample T test was used to compare the quantitative data showing normal distribution according to the groups. Statistical significance was defined as a P value < 0.05.

RESULTS

Patient characteristics are given in Table 1. Eighty patients were included in the study. Fifty-seven

Table 1. Characteristics of the patients

Number of patients	80
Age, years	65.6 ±7.24
PSA, ng/ml	8.53±4.64
Prostate volume, ml	47.86±19.41
Lesion diameter, mm	12.02±5.34
Total Number of patients with clinically significant prostate cancer	57 (71.25)
Number of patients with clinically significant cancer in standard biopsy (%)	55 (68.75)
Number of Patients with clinically significant cancer in cognitive biopsy (%)	35 (43.75)
Patients with positive DRE (%)	64 (80)
PIRADS Score	
3 (%)	14 (17.5)
4 (%)	44 (55)
5 (%)	22 (27.5)
ISUP Score	
1(%)	23 (28.8)
2(%)	24 (30)
3(%)	24 (30)
4(%)	5(6.2)
5(%)	4(5)

PSA: Prostate specific antigen; **PIRADS:** Prostate Imaging and Data Reporting System;
ISUP: International Society of Urological Pathology.

(71.2%) patients were diagnosed as csPCa. MRI scan revealed that 14 (17.5%) patients had a PIRADS score of 3 lesions, 44 (55%) patients had a PIRADS score of 4 lesions, and 22 (27.5%) patients had a PIRADS score of 5 lesions. The mean number of cores per lesion was 2.07±1.1 in CTB.

Pathology results of systematic and cognitive biopsies are shown in Table 2. Clinically significant PCa was detected in 55 (68.7%) patients with SB, whereas CTB alone detected csPCa only in 35 (43.7%) patients. This difference was significant (p<0.01). SB missed only 2 patients with csPCa, and additional CTB diagnosed these patients. Thirty-five percent of the men with csPCa would be missed by CTB but diagnosed by SB. In CTB samples, 29 (36.2%) patients were reported as having benign prostatic hyperplasia, but in 12 of these patients, csPCa was detected with SB. Also, 16 (20%) patients had ciPCa according to CTB samples, but in 10 patients, csPCa was detected with SB.

In 24 (30%) patients, there was a concordance between DRE and mpMRI; that is to say, the localization of the lesion detected on MRI was the same as the localization of the nodule palpated in DRE. There was no such concordance in 56 (70%) patients; either there was no nodule in DRE, or the localization of the nodule was different from the localization of the lesion. csPCa detection rates in SB and CTB were significantly higher in men with a concordance between DRE and mpMRI (p= 0.012 and p<0.01, respectively). Of the 24 patients who had a concordance between MRI and DRE, 21 (87.5%) had csPCa detected with SB, and 20 (83.3%) had csPCa detected in the CTB. In 56 patients with no concordance between DRE and MRI, only 15 (26.7%) patients had csPCa in CTB, and 33 (58%) patients had csPCa in SB.

A nodule was palpated with DRE in 64 (80%) patients. When SB results were evaluated, 44 (68.7%) of the 64 patients had csPCa, and 20 (31.3%) patients had ciPCa. Sixteen patients had normal DRE; 11 (68.7%) of the 16 patients had csPCa, and 5 (31.2%) had ciPCa. There was no statistically significant relationship between DRE and the presence of csPCa (P=0.905). According to the CTB samples, 31 (48.4%) patients with a palpable nodule had clinically significant, and 33 (51.6%) had clinically insignificant PCa. In 16 patients with normal DRE, 4 (25%) had clinically significant, and 12 (75%) had clinically insignificant PCa. No statistically significant relationship between DRE and csPCa was detected (p=0.091). Table 3 shows the comparison of csPCa presence with the PIRADS score. Results of this study showed that the csPCa detection rate increased with the increasing PIRADS score for both STB and CTB (p=0.02 and p=0.003, respectively).

When SB samples were evaluated, no differences were observed between patients with csPCa and ciPCa in age and prostate volume (p=0.499 and p=0.097, respectively). Table 4 reports that mean PSA, lesion diameter, and PIRADS score were significantly greater in patients with csPCa (p=0.001, p=0.014, and p=0.02, respectively). As shown in Table 5, in patients who had csPCa in the CTB samples, significant differences were detected in the mean age, prostate volume, PSA, lesion diameter, number of cores, and the PIRADS score (p=0.005, p=0.02, p=0.005, p=0.003, p=0.017 and p= 0.002 respectively).

Table 2. Pathology results of the systematic and cognitive biopsies

	Systematic Biopsy (n=80)	**Cognitive Biopsy (n=80)**
BPH (%)	1 (1.25)	29 (36.25)
ISUP 1 (%)	24 (30)	16 (20)
ISUP 2 (%)	24 (30)	20 (25)
ISUP 3 (%)	22 (27,5)	12 (15)
ISUP 4 (%)	7 (8,75)	0
ISUP 5 (%)	2 (2.5)	3 (3.75)

BPH: Benign prostatic hyperplasia; **ISUP:** International Society of Urological Pathology

Table 3. Comparison of clinically significant prostate cancer presence with PI-RADS score

	PIRADS 3 (n=14)	PIRADS 4 (n=44)	PIRADS 5 (n=22)	p
No. of patients with clinically significant Pca in standard biopsy (%)	7 (50)	30 (68.1)	18 (81.8)	0.02
No. of patients with clinically significant Pca in cognitive biopsy (%)	2 (14.2)	17 (38.6)	16 (72.7)	0.003

PIRADS: Prostate Imaging and Data Reporting System; **Pca:** Prostate cancer

Table 4. Baseline characteristics of the patients with clinically significant and insignificant prostate cancer in systematic biopsy.

	Patients with clinically significant cancer in standard biopsy (n=55)	**Patients with clinically insignificant cancer/BPH in standard biopsy (n=25)**	**p**
Age, years	64.70±11.31	65.23±7.34	0.499
Prostate volume, ml	45.93±19.3	51±18.22	0.097
PSA, ng/ml	10.03±6.77	6.63±3.76	0.001
Lesion diameter, mm	13.02±5.54	9.96±4.32	0.014
PIRADS score			0.13
3 (%)	7 (12.73)	7 (28)	
4 (%)	30 (54.55)	14 (56)	
5 (%)	18 (32.72)	4 (16)	

PSA: Prostate specific antigen; **PIRADS:** Prostate Imaging and Data Reporting System

Table 5. Baseline characteristics of the patients with clinically significant and insignificant prostate cancer or BPH in cognitive targeted biopsy.

	Patients with clinically significant cancer in cognitive biopsy (n=35)	**Patients with clinically insignificant cancer/BPH in cognitive biopsy (n=45)**	**p**
Age, years	68.37±5.36	63.48±7.19	0.005
Prostate volume, ml	43.26±16.93	51.44±19.28	0,02
PSA, ng/ml	11.21±7.67	7.14±6.10	0.005
Lesion diameter, mm	14.43±5.91	10.15±4.01	0.003
Number of cores	2.20±1.35	1.97±1.13	0.017
PIRADS score			0.002
3 (%)	2 (5.71)	12 (26.67)	
4 (%)	17 (48.57)	27 (60)	
5 (%)	16 (45.72)	6 (13.33)	

PSA: Prostate specific antigen; **PIRADS:** Prostate Imaging and Data Reporting System

DISCUSSION

The results of this study regarding the diagnosis rate of csPCa with cognitive biopsy contradicted the data in the literature. In the majority of the studies, better results were obtained with MRI-targeted biopsies. A meta-analysis reported that the detection of csPCa was significantly higher in MRI-guided biopsies (in-bore, fusion, or cognitive) compared to SB, and only 10% of patients with csPCa cases would be missed without SB (20). Kasivisvanathan et al. stated that MRI-guided biopsies diagnosed more csPCa than SB, and the ratio of csPCa missed by MRI-guided biopsy but diagnosed by additional SB was 13% (21). John et al. performed CTB and concomitant SB in 131 men; 17.6% of the clinically significant cancers were detected with CTB only, and 8.4% were detected with SB only (22). In the current study, the csPCa detection rate was significantly higher in SB compared to CTB; 35% of the significant cancers would be missed without SB. The results of the study conducted by von Below et al. were similar to this study. They performed mpMRI and then CTB in 53 patients with newly diagnosed PCa. Systematic biopsy diagnosed 32 significant cancers, whereas cognitive biopsy diagnosed 20 and missed 17 significant cancers, and only 5 significant cancers were diagnosed with additional cognitive biopsy (23). The different aspect of their study was that lesions with PIRADS scores 1 and 2 were also biopsied.

DRE has a significant role in the clinical diagnosis of PCa. In patients with an abnormal DRE, the risk of detecting PCa increases (24). Omri et al. performed systematic and MRI-fusion biopsies in 47 DRE-negative and 39 DRE-positive patients (25). They reported that in patients with palpable nodules, the detection rate of csPCa per core was significantly higher in targeted biopsy samples compared to patients with normal DRE. In a study of 12-core systematic and concomitant CTB, a 10.1% improvement in cancer detection rate by additional targeted biopsies was reported in patients with normal DRE, and it was concluded that additional targeted biopsies did not increase the detection rate in patients with positive DRE (26). We found no significant relationship between DRE and csPCa. However, when we evaluated the patients who had a concordance between DRE and MRI, we found that csPCa detection rates in standard and cognitive biopsies were significantly higher in this subgroup of patients.

The result that the higher PIRADS scores were related to an increased detection rate of csPCa is consistent with the literature. John et al. stated that the csPCa detection rate was significantly greater in score 4 and 5 lesions (22). In a large prospective study, the csPCa detection rate of PIRADS scores 3, 4, and 5 was 23%, 49%, and 77%, respectively (27). A significant association between the PIRADS score and the presence of csPCa was found.

Lesion diameter has an important effect on the PCa detection rate. Ozden et al. performed cognitive and concomitant systematic prostate biopsies in 219 patients with elevated PSA and/or suspicious DRE and lesions on MRI with PIRADS score ≥ 3 and reported that the csPCa detection rate of CTB was significantly higher for lesions ≥ 10 mm (28). Prostate volume was also evaluated in the same study, and it was reported that the clinically significant PCa detection rate of CTB has significantly elevated in men with a prostate volume <30 ml. John et al. found no relationship between lesion diameter and the clinically significant PCa detection rate (22). We found that lesion diameter was significantly larger and prostate volume was significantly smaller in patients with csPCa in both SB and CTB samples compared to patients with insignificant PCa. Patients with larger lesion diameters or smaller prostate volumes have a higher clinically significant cancer detection risk. Studies show that MRI-fusion biopsy is more successful than cognitive biopsy in smaller lesions (20).

Generally, it is recommended to obtain 2-4 cores per lesion in CTB. Sonmez et al. reported that 2-3 biopsy cores are adequate in PIRADS 4 and 5 lesions, but at least a 4-core biopsy should be performed in PIRADS 3 lesions (29). Another study reported that at least 2 cores should be taken to obtain a better pathological result (30). In this study, the mean number of cores per lesion in patients with csPCa, according to cognitive biopsy samples, was 2.2±1.3. It was significantly high-

er compared to the patients with ciPCa. Following the literature, we think at least 2 cores should be taken per lesion in targeted biopsies.

In this study, the success of cognitive biopsy in detecting csPCa was lower than systematic biopsy, which can be due to various reasons. The experience of the operators performing the CTB plays a crucial role in achieving a healthy result. Operators in this study have more than 10 years of experience in SB, but they are less experienced in the cognitive biopsy. Stabile et al. stated that the csPCa detection rate was highly affected by operator experience in targeted biopsy techniques. A greater csPCa detection rate was observed as the number of targeted biopsies performed increased (31). Communication between the operators and radiologists before the biopsy is crucial in determining the exact localizations of suspicious lesions. There may have been a deficiency in this regard in our study. The low number of patients is another limitation. Studies with a larger number of patients may yield different results.

CONCLUSION

In conclusion, we believe SB still maintains its importance in the diagnosis of csPCa. CTB can be preferred in patients with larger lesions and concordance between localization of nodules on DRE and localization of suspicious lesions on mpMRI. In addition to CTB, a concomitant SB should always be performed.

Conflict of Interest

The authors declare to have no conflicts of interest.

Financial Disclosure

The authors declared that this study has received no financial support.

Informed Consent

Informed consent was obtained from all individual participants included in the study.

Ethical Approval

The study was approved by Bezmialem Vakıf University Hospital Ethic Committee (Approval No: 2021/184, Date: 2021/06/22) and written informed consent was received from all participants. The study protocol conformed to the ethical guidelines of the Helsinki Declaration.

Author Contributions

Conception and design; CE, Aİ, Data acquisition; YK, BD, Data analysis and interpretation; CE, HT, Drafting the manuscript; CE, Aİ, Critical revision of the manuscript for scientific and factual content; SK, Statistical analysis; BD, Supervision; CE, HA.

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