ORIGINAL RESEARCH
Urooncology

Doi: 10.4274/jus.galenos.2025.2025-2-9
J Urol Surg

Optimizing Prostate Cancer Diagnosis: A Prospective, Randomized Comparison of 12-core vs. 20-core Biopsy for Detection Accuracy and Upgrading Risk

Dursun Baba[1], Soner Çoban[2], Ahmet Çalışkan[3], Yusuf Şenoğlu[4], Muhammet Ali Kayıkçı[1], Ali Tekin[5]

[1]Düzce University Faculty of Medicine, Department of Urology, Düzce, Turkiye
[2]University of Health Sciences Turkiye, Yüksek İhtisas Training and Research Hospital, Clinic of Urology, Bursa, Turkiye
[3]Akçakoca State Hospital, Clinic of Urology, Düzce, Turkiye
[4]Marmara University Faculty of Medicine, Department of Urology, İstanbul, Turkiye
[5]Acıbadem University Atakent Hospital, Clinic of Urology, İstanbul, Turkiye

What's known on the subject? and What does the study add?

Transrectal ultrasound guided systematic prostate biopsy is widely regarded as the gold standard for diagnosing prostate cancer. Although the traditional 12-core biopsy protocol is extensively utilized, its capacity to detect clinically significant cancers is constrained due to the heterogeneous distribution of tumors. Multiparametric magnetic resonance imaging and targeted biopsies have emerged as significant components in the diagnostic process. However, their extensive use is impeded by high cost, limited accessibility, and technical challenges. Consequently, systematic biopsy techniques maintain their importance due to their cost-effectiveness and accessibility, despite the ongoing controversy regarding the efficacy of standard biopsy protocols and the potential benefit of extended biopsy schemes in improving diagnostic accuracy. The present study aims to compare the efficacy of 12 and 20 core biopsy protocols in the diagnosis of prostate cancer.

Abstract

Objective: This study compares the diagnostic efficacy of 12-core and 20-core transrectal ultrasound (TRUS)-guided prostate biopsy protocols in detecting prostate cancer (PCa) and evaluates the clinical significance of extended biopsy protocols.

Materials and Methods: A prospective, randomized, single-center study was conducted with 511 patients who underwent TRUS-guided prostate biopsy for suspected PCa. Patients were randomly assigned to either a 12-core biopsy group (n=248) or a 20-core biopsy group (n=263). The primary endpoint was the cancer detection rate, while secondary endpoints included clinically significant cancer detection [International Association of Urological Pathology (ISUP) grade ≥2], biopsy-pathology correlation, upgrade rates, and complication assessment.

Results: The 20-core biopsy group had a significantly higher cancer detection rate (39.2%) compared to the 12-core group (28.6%). However, clinically significant cancer detection rates were similar between the groups. The 20-core protocol reduced the likelihood of ISUP grade 1 cancer being upgraded after radical prostatectomy, improving diagnostic accuracy. A strong correlation was observed between tumor burden in biopsy and radical prostatectomy specimens. Prostate-specific antigen density analysis identified an optimal cutoff value of 0.1058, providing 66.1% diagnostic accuracy. Complication rates were comparable between the protocols [5.65% (n=14), 6.46% (n=17)].

Conclusion: The 20-core biopsy protocol enhances overall cancer detection and reduces unnecessary upgrading in low-risk PCa cases, improving diagnostic precision. While multiparametric magnetic resonance imaging (MRI)-guided fusion biopsy offers high accuracy, its limited availability makes extended biopsy protocols a viable alternative, particularly in centers without MRI-based targeting methods. Further multicenter studies are needed to refine biopsy strategies for clinical practice.

Keywords: Prostate biopsy, prostate cancer, PSA density, radical prostatectomy

Correspondence: Dursun Baba MD, Düzce University Faculty of Medicine, Department of Urology, Düzce, Turkiye
E-mail: drbaba28@hotmail.com **ORCID-ID:** orcid.org/0000-0002-4779-6777
Received: 24.02.2025 **Accepted:** 05.04.2025 **Epub:** 18.04.2025

Cite this article as: Baba D, Çoban S, Çalışkan A, Şenoğlu Y, Kayıkçı MA, Tekin A. Optimizing prostate cancer diagnosis: a prospective, randomized comparison of 12-core vs. 20-core biopsy for detection accuracy and upgrading risk. J Urol Surg. [Epub Ahead of Print]

Introduction

Prostate cancer (PCa) is one of the most frequently diagnosed malignancies in men worldwide and ranks second in cancer-related mortality (1,2). While strategies aimed at early diagnosis of clinically significant cancer have been implemented, continuous improvements in diagnostic strategies remain necessary (3). Although biochemical markers and imaging techniques play a crucial role in PCa diagnosis, histopathological confirmation is still required for a definitive diagnosis (4).

Transrectal ultrasound (TRUS)-guided systematic prostate biopsy has long been considered the gold standard for diagnosing PCa (5). The traditional 12-core biopsy protocol is widely used; however, its limited sensitivity to the heterogeneous distribution of tumors has raised concerns about its ability to detect clinically significant cancers effectively (6). Consequently, expanded biopsy protocols with more cores have been proposed to improve diagnostic accuracy, particularly in high-risk cases.

In recent years, multiparametric magnetic resonance imaging (mpMRI) and targeted fusion biopsies have gained prominence in diagnostic workflows, enhancing detection rates for clinically significant PCa (7,8). mpMRI-guided biopsies have demonstrated superior sensitivity in identifying clinically relevant tumors compared to systematic biopsies (9). However, the high cost, limited accessibility, and technical challenges of advanced imaging techniques restrict their widespread application in all patients.

Given these constraints, traditional systematic biopsy techniques remain crucial due to their cost-effectiveness and widespread availability. Standard biopsy protocols continue to play a pivotal role, particularly in cases where imaging fails to identify suspicious lesions and biopsy remains necessary (10). However, there is ongoing debate regarding the effectiveness and necessity of standard biopsy protocols and whether more extended biopsy schemes provide superior diagnostic accuracy, and should be integrated into routine clinical practice (11,12).

This study aims to compare the diagnostic efficacy of 12-core and 20-core prostate biopsy protocols in detecting prostate cancer. Specifically, the study evaluates cancer detection rates, identification of clinically significant cancers, upgrade rates after biopsy, and complication profiles. Furthermore, the potential impact of extended biopsy protocols on clinical practice will be discussed in the light of the current literature.

Materials and Methods

Study Design and Ethical Approval

This study is a prospective, randomized, single-center trial conducted between January 2011 and January 2014 to compare the diagnostic efficacy of 12-core and 20-core biopsy protocols in patients undergoing their first TRUS-guided prostate biopsy due to suspected prostate cancer. The study was approved by the Clinical Research Ethics Committee of Düzce University Faculty of Medicine (decision no: 2010/101, date: 30.12.2010), and written informed consent was obtained from all participants prior to their inclusion in the study.

Study Population and Inclusion Criteria

The study included patients who presented to the urology outpatient clinic with lower urinary tract symptoms and required evaluation for suspected prostate cancer. The inclusion criteria were a total prostate-specific antigen (tPSA) level between 2.5 and 10 ng/mL, suspicious digital rectal examination (DRE), and eligibility for the first TRUS-guided prostate biopsy. Patients were excluded if they had an active urinary tract infection, were had undergone urethral catheterization within the past two weeks, had a tPSA level exceeding 10 ng/mL, were using 5-alpha reductase inhibitors or phytotherapeutic agents, or had previously undergone transurethral prostate surgery.

Randomization and Study Groups

This study adheres to the CONSORT guidelines for randomized clinical trials. A total of 511 patients who met the inclusion criteria were randomly assigned to one of the two groups by computer-assisted block randomisation using the unequal allocation method with variable block sizes: the 12-core biopsy group (12PB, n=248) and the 20-core biopsy group (20PB, n=263). The randomisation process was performed using the Mersenne Twister algorithm, a high-quality pseudorandom number generator known for its long period and reliability in random sequence generation. Sample size determination was conducted through a power analysis to establish the minimum number of participants required for the study. Demographic characteristics, tPSA and free PSA (fPSA) levels, DRE findings, prostate volumes, and biopsy pathology results were evaluated for all patients. The CONSORT flow diagram for patient allocation and study progression is provided in Figure 1.

Biopsy Procedure

All biopsies were performed under local anesthesia (1% lidocaine) and with the prophylactic administration of 500 mg ciprofloxacin, using an 18-gauge biopsy needle and an automatic biopsy gun, via the transrectal route under TRUS guidance. The 12-core biopsy protocol was based on the standard sextant biopsy scheme. In this scheme, samples were obtained from the lower, middle, and upper regions of both prostate lobes, and these cores were symmetrically extended to obtain a total of 12 biopsy samples. In the extended 20-core biopsy protocol, additional samples were taken from the anterior and lateral prostate regions, expanding the biopsy coverage (13).

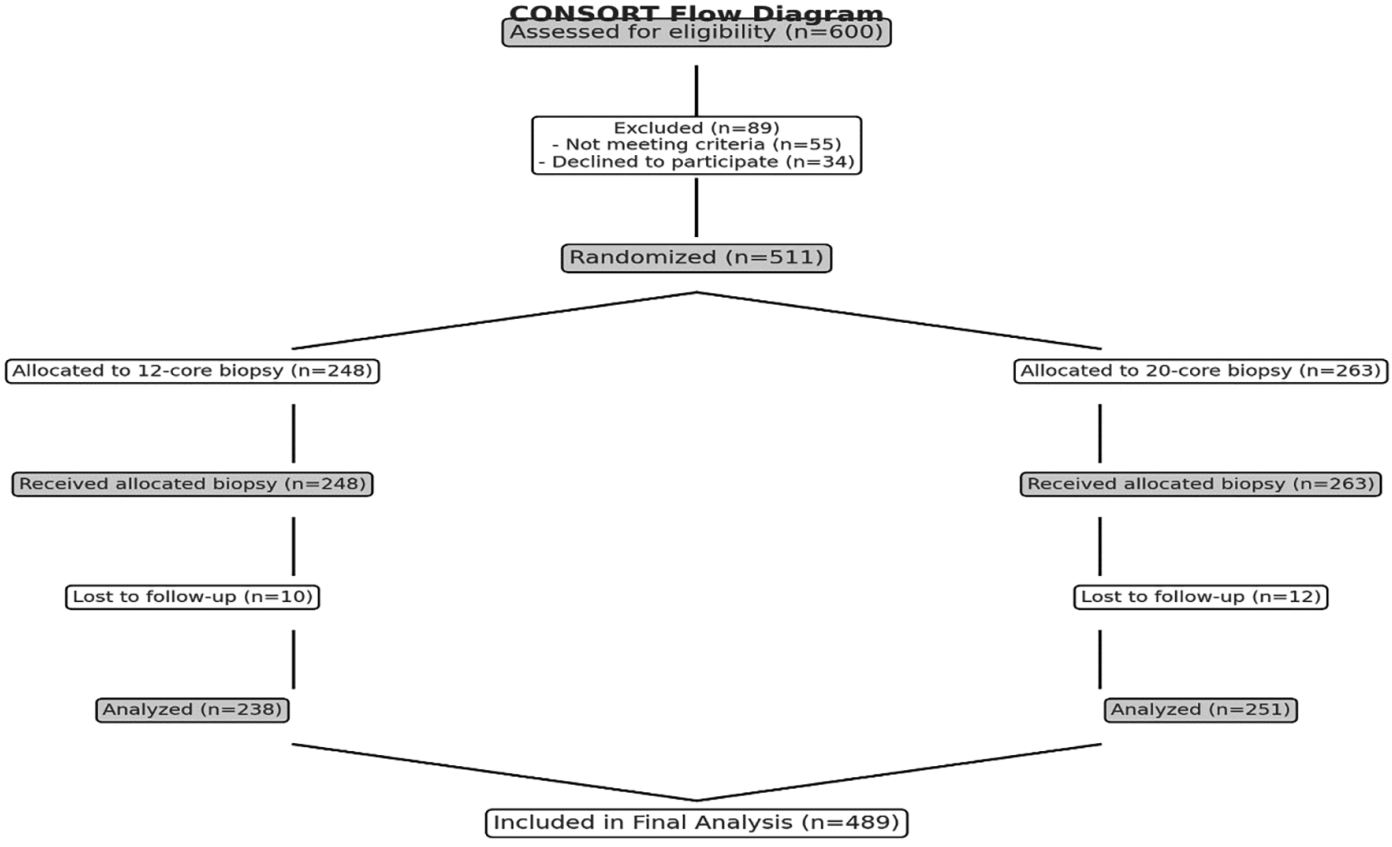

Figure 1. The flow diagram for patient allocation and study

Endpoints

The primary endpoint of the study was the cancer detection rate for each biopsy protocol. Secondary endpoints included the detection of clinically significant cancers [International Association of Urological Pathology (ISUP) grade ≥2], correlation between biopsy findings and radical prostatectomy specimens, staging discrepancies (upgrade and downgrade rates), and post-procedural complication rates.

Complication Monitoring

All patients were assessed before the procedure and again two weeks after the biopsy for potential complications, including urinary symptoms, fever, dysuria, hematuria, hematospermia, and rectal bleeding. Complications were classified using the Clavien-Dindo grading system, as recommended by the European Association of Urology, and statistical comparisons between the groups were performed.

Statistical Analysis

Data analysis was performed using the Statistical Package for the Social Sciences (SPSS). Descriptive statistics were presented as mean ± standard deviation, minimum-maximum values, and percentage distributions. The Fisher-Freeman-Halton exact test was used to analyze categorical variables, while independent t-tests and one-way analysis of variance (ANOVA) were applied for continuous variables. The relationship between the tumor proportion detected in biopsy specimens and that in radical prostatectomy specimens was assessed using Pearson's correlation analysis. The diagnostic value of PSA density was evaluated using receiver operating characteristic (ROC) curve analysis to determine the optimal cut-off value. A p-value of <0.05 was considered statistically significant.

Results

According to Table 1, a total of 511 patients were included in the study, with 248 undergoing a 12-core biopsy and 263 undergoing a 20-core biopsy. The mean age of patients in the 12-core biopsy group was 63.25±6.78 (44-78) years, while in the 20-core biopsy group, it was 62.14±7.56 (39-79) years (p=0.079). The mean PSA levels, ratio of free to total PSA levels and the prostate volumes were also similar, between the two groups. The rate of suspicious DRE was slightly higher in the 20-core biopsy group (31.78%) compared to the 12-core biopsy group (28.74%), but this difference was not statistically significant (p=0.518).

Table 1. Baseline characteristics and pathology results

Variable/pathology	12-core biopsy (mean ± SD)	12-core biopsy (minimum-maximum)	20-core biopsy (mean ± SD)	20-core biopsy (minimum-maximum)	p-value
Age (years)	63.25±6.78	44-78	62.14±7.56	39-79	0.079
PSA (ng/mL)	5.88±1.95	0.04-10.0	5.92±2.06	0.70-10.02	0.810
Free PSA (ng/mL)	1.33±0.945	0.03-6.90	1.23±0.798	0.07-5.60	0.387
PSA ratio	0.227±0.117	0.008-0.69	0.207±0.092	0.011-0.56	0.148
Prostate volume (mL)	60.09±31.94	13-184	60.55±34.12	11-243	0.882
Abnormal DRE (%)	28.74%	N/A	31.78%	N/A	0.518
BPH	166 (66.9%)	N/A	151 (57.4%)	N/A	N/A
Prostate cancer	71 (28.6%)	N/A	103 (39.2%)	N/A	0.024
ASAP	9 (3.6%)	N/A	4 (1.5%)	N/A	N/A
HGPIN	2 (0.8%)	N/A	5 (1.9%)	N/A	N/A

PSA: Prostate-specific antigen, DRE: Digital rectal examination, BPH: Benign prostatic hyperplasia, ASAP: Atypical small acinar proliferation, HGPIN: High-grade prostatic intraepithelial neoplasia, SD: Standard deviation

Histopathological evaluation demonstrated that the overall cancer detection rate was significantly higher in the 20-core biopsy group (39.2%) compared to the 12-core biopsy group (28.6%) (p=0.024). The rates of atypical small acinar proliferation and high-grade prostatic intraepithelial neoplasia were low and comparable between the two groups.

According to Table 2, the distributions of ISUP grade groups (BxISUPG) showed no statistically significant difference (p=0.503). However, when ISUP grades from radical prostatectomy specimens (RpISUPG) were analysed, significant differences were found: in the 12-core biopsy group, ISUP grade 2 biopsy cases comprised 45.83%, and in the 20-core biopsy group, 20.29% (p=0.0061).

According to Table 3, a significant positive correlation (r=0.510, p<0.001) was found between the tumor percentage detected in the biopsy samples and the tumor percentage observed in the radical prostatectomy specimens. Regarding staging discrepancies, the overall upgrade rate was 41.03%, while the downgrade rate was 7.69%. Although the upgrade rate was higher in the 12-core biopsy group (47.92%) compared to the 20-core biopsy group (36.23%) (p=0.089), this difference did not reach statistical significance. Similarly, the downgrade rates were comparable between the two groups (8.33% *vs.* 7.25%, p=0.729). Regarding radical prostatectomy outcomes, the overall prostatectomy rate was higher in the 20-core biopsy group (26.3%) compared to the 12-core biopsy group (19.4%), although this difference was not statistically significant.

However, the percentage of cases where ISUP grade group remained unchanged was slightly higher in the 20-core biopsy group (56.52%) compared to the 12-core biopsy group (43.75%), (p=0.585). These findings suggest that a higher biopsy core count may reduce the likelihood of upgrading but does not significantly affect downgrading rates.

As shown in Figure 2, biopsy tumor burden is strongly correlated with radical prostatectomy tumor burden, supporting the predictive value of biopsy-based assessments.

When patients who met the active surveillance criteria were analyzed, 47 patients were identified in the 12-core biopsy group and 74 patients were identified in the 20-core biopsy group. When the results of the radical prostatectomies performed on these patients were examined, the ISUP grade group 1 upgrade rate was significantly lower in the 20-core biopsy group (35.6%) compared to the 12-core biopsy group (62.5%), (p=0.020) (Table 4). This suggests that a higher biopsy core number increases the

Table 2. ISUP grade biopsy and radical prostatectomy

ISUP grade	12-core biopsy (n, %)	20-core biopsy (n, %)	p-value	RP (12-core)	RP (20-core)	p-value (RP)
1	47 (66.2%)	74 (71.84%)	0.503	29.17%	49.28%	0.047
2	14 (19.72%)	17 (16.5%)	0.688	45.83%	20.29%	0.006
3	8 (11.27%)	7 (6.8%)	0.411	10.42%	17.39%	0.431
4	1 (1.41%)	0 (0.0%)	0.408	6.25%	5.80%	0.874
5	1 (1.41%)	5 (4.85%)	0.403	8.33%	7.25%	1.000
2-5	24 (33.8%)	29 (28.16%)	0.503	70.83%	50.72%	0.0296

ISUP: International Society of Urological Pathology, RP: Radical prostatectomy, BxISUPG: Biopsy ISUP grade, RpISUPG: Radical prostatectomy ISUP grade

Table 3. Biopsy and radical prostatectomy correlation + staging errors			
Metric/category	**12-core biopsy (mean ± SD)**	**20-core biopsy (mean ± SD)**	**p-value**
Pearson correlation (r)	0.510	N/A	N/A
P-value	<0.0001	N/A	N/A
Sample size (N)	117	N/A	N/A
Upgraded	47.92%	36.23%	0.089
Downgraded	8.33%	7.25%	0.729
Unchanged	43.75%	56.52%	0.585
R. Prostatectomy performed	19.4%	26.3%	0.073
SD: Standard deviation			

Table 4. ISUP G1 upgrade rate and radical prostatectomy outcomes			
ISUP G1 patients Metric/radical prostatectomy outcome	**12-core biopsy (mean ± SD)**	**20-core biopsy (mean ± SD)**	**p-value**
Total	47	74	N/A
Radical prostatectomy performed	32	45	N/A
Count of ISUP G1 upgrades	22 (62.5%)	16 (35.6%)	0.020
ISUP G1: International Society of Urological Pathology grade 1, SD: Standard deviation			

accuracy of identifying clinically insignificant PCa and decreases the likelihood of upgrading after radical prostatectomy.

Since there was a significant difference between benign prostatic hyperplasia (BPH) and PCa groups in terms of PSA density, a cutoff value that could distinguish these two groups was determined. As a result of the ROC curve analysis, when PCA was diagnosed in patients with a PSA density of 0.1058 and above, the correct diagnosis rate was calculated as 66.1% (Figure 3).

Grade I complications according to the Clavien-Dindo classification were detected in a total of 31 patients. The most common complaints were hematuria and painful urination. 12-core biopsy group 5.65% (14) 20-core biopsy group 6.46% (17). No statistical difference was detected between the two groups (p=0.840).

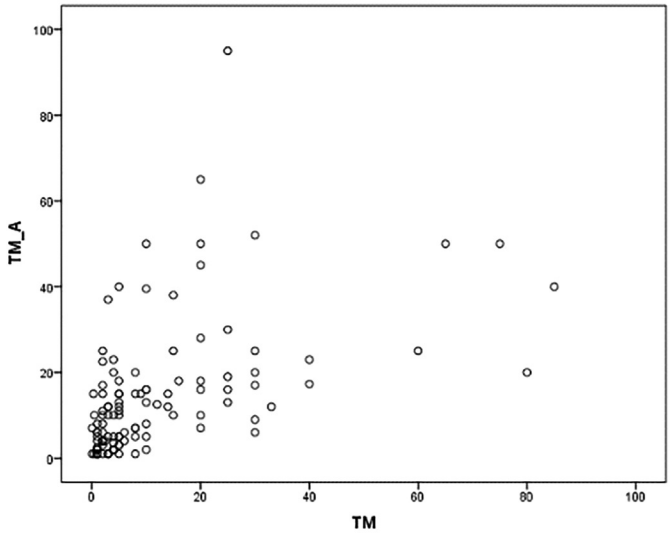

Figure 2. The relationship between the percentage of tumours in the biopsy (TM_A) and the percentage of tumours in the radical prostatectomy specimen (TM)

Discussion

This study evaluates the clinical relevance of extended biopsy protocols by comparing the diagnostic efficacy of 12-core and

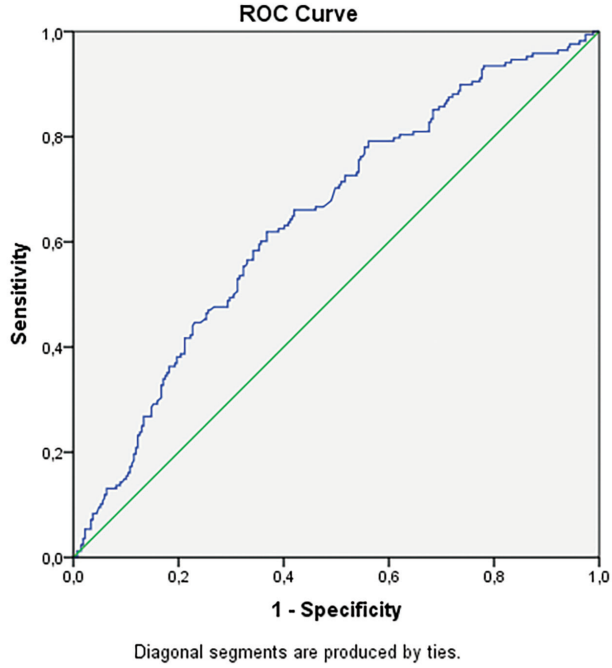

Figure 3. ROC curve analysis of PSA density 0.1058 and prostate ca diagnosis

ROC: Receiver operating characteristic, PSA: Prostate-specific antigen

20-core biopsy protocols in the detection of prostate cancer. The prospective and randomised design increased the reliability and generalisability of the findings. The results showed that the 20-core biopsy protocol increased the overall cancer detection rate and better identified PCa cases suitable for active surveillance when evaluated with radical prostatectomy outcomes. Consequently, the 20-core biopsy is considered a valid alternative for patients with no suspicious lesions detected on mpMRI or in centers where mpMRI is not available, thus contributing significantly to the clinical decision-making process.

The cancer detection rate of the 20-core biopsy protocol was significantly higher than that of the 12-core biopsy in our study (39.2% *vs.* 28.6%, p=0.024). Similarly, many previous studies have demonstrated that extended biopsy protocols improve the accuracy of PCa diagnosis (14-16). The standard 12-core biopsy protocol carries the risk of missing lesions in the lateral zones of the prostate, whereas extended biopsy protocols may better capture tumor heterogeneity, reducing the false-negative rate. However, some studies suggest that extended biopsy protocols may lead to overdiagnosis of clinically insignificant PCa (17-19). Our study demonstrates a lower upgrading rate in cancers detected by the 20-core biopsy, which is an important finding that may enhance diagnostic reliability in patients undergoing biopsy for active surveillance.

A significant proportion of prostate cancers that are initially deemed clinically insignificant based on biopsy findings undergo upgrading after radical prostatectomy. Our findings show that patients undergoing 20-core biopsy in ISUP grade group 1 cases have a significantly lower upgrading rate after radical prostatectomy compared to those undergoing 12-core biopsy (35.6% *vs.* 62.5%). It is thought that 20-core prostate biopsy allows a more precise characterization of this group, especially in patients eligible for active surveillance, and that unnecessary overtreatment may be significantly reduced. In this context, it is anticipated that active surveillance can be implemented more safely and that the need for treatment in patients undergoing 20-core biopsy may be reduced. This suggests that the 20-core biopsy scheme provides a more accurate characterization of low-grade tumors, reducing overtreatment (20). Previous studies have also emphasized that accurate ISUP grading on biopsy is crucial in patients undergoing active surveillance, as misleadingly low biopsy grades may lead to underestimation of aggressive disease (21,22).

A significant positive correlation was found between the percentage of tumor detected in biopsy samples and the tumor percentage observed in radical prostatectomy specimens (r=0.510, p<0.001, Table 3, Figure 2) (23). This suggests that biopsy tumor burden is a strong predictor of tumor extent in surgical specimens. Literature supports that increasing biopsy sampling density strengthens this correlation, reinforcing the prognostic reliability of extended biopsy protocols (24). A high tumour percentage in biopsy samples can provide important information about the extent of cancer in the organ. Accordingly, this ratio can be considered a determining factor in the treatment planning of patients with a high tumour percentage in biopsy material.

Our analysis of the PSA density ROC curve indicated that a PSA density cutoff value of 0.1058 provides a diagnostic accuracy of 66.1% for PCa detection, consistent with the current literature (Figure 3). The diagnostic value of PSA density has been highlighted in previous studies, particularly in differentiating BPH from PCa (25,26). Studies have shown that threshold values for PSA density (e.g., ≥0.10 or ≥0.15) increase clinically significant cancer detection rates and are recommended to be included in clinical decision-making processes to prevent unnecessary biopsies (27). However, PSA density alone may not be sufficient, and it is recommended that it be used in combination with other biomarkers for optimal clinical decision-making (28).

MpMRI-guided targeted biopsies have become a gold-standard method in PCa diagnosis. Studies have demonstrated that mpMRI-guided biopsies have a higher clinically significant cancer detection rate compared to standard biopsy techniques (8,29). However, mpMRI is not universally accessible, and factors such as high costs, a steep learning curve, and technical requirements limit its widespread use. Our results indicate that since fusion biopsy is not available in every center, extended biopsy protocols remain a valuable alternative for clinical practice. In healthcare settings with limited MRI availability, the 20-core biopsy strategy has been shown to improve diagnostic accuracy compared to standard biopsy methods (30). Recently, the addition of perilesional sampling and standard biopsy to MRI fusion biopsy has also been recommended, while studies have suggested that 20-core biopsy should be performed in patients without suspicious lesions in MRI (14,31,32).

Study Limitations

This study has several limitations. First, it is a single-center study, which limits the generalizability of the findings to different patient populations. Variability in biopsy outcomes across different institutions must be considered when applying these results to broader clinical settings.

This study lacks long-term follow-up data. Specifically, in patients undergoing active surveillance, long-term tumor progression and false-negative biopsy outcomes were not assessed. Further prospective studies are needed to evaluate the long-term impact of extended biopsy protocols on disease progression and clinical outcomes.

The discrepancy between biopsy and radical prostatectomy findings is another important limitation. Biopsy may not fully capture tumor heterogeneity, and even with extended biopsy protocols, some tumor regions may remain unsampled, leading to false-negative results. Although our study demonstrated a significant correlation between biopsy and surgical pathology outcomes, discrepancies may still occur due to sampling errors and tumor heterogeneity.

None of the patients in our study underwent mpMRI, and the lack of fusion biopsy and mpMRI guidance is another limitation. The lack of fusion biopsy and mpMRI guidance in our study is another limitation. While mpMRI-guided biopsies have been shown to improve diagnostic accuracy, this technique is not widely available in all healthcare settings. Therefore, our findings suggest that extended biopsy protocols remain a viable alternative, particularly in centers without access to MRI or fusion biopsy technology.

Post-biopsy complications were not extensively analyzed in this study. While procedural complications were reported using the Clavien-Dindo classification, detailed evaluation of serious complications such as sepsis, hemorrhage, or urinary retention was not performed. Further large-scale studies are needed to assess whether extended biopsy protocols significantly increase procedural risks.

Cost-effectiveness analysis was not conducted. Increasing the number of biopsy cores may prolong the procedure, affect patient comfort, and increase the workload for pathology departments. Future studies should evaluate the financial impact of extended biopsy protocols and determine their cost-effectiveness in different clinical settings.

Conclusion

This study demonstrates that the 20-core biopsy protocol enhances overall cancer detection rates, reduces unnecessary upgrading in low-grade prostate cancer, and strengthens the prognostic reliability of biopsy findings. The results suggest that the 20-core biopsy provides a more accurate risk stratification, particularly in patients undergoing active surveillance, potentially preventing overtreatment.

Although mpMRI-guided fusion biopsy offers high diagnostic accuracy, it is not widely available due to financial and logistical constraints. Our findings support that extended biopsy protocols remain a valuable diagnostic alternative, particularly in healthcare settings with limited MRI access.

Future multicenter, long-term follow-up studies are needed to further evaluate the clinical impact of extended biopsy protocols on patient outcomes. Additionally, cost-effectiveness analyses should be conducted to assess the financial feasibility of implementing extended biopsy strategies in routine clinical practice.

Ethics

Ethics Committee Approval: Approval was received from the Clinical Research Ethics Committee of Düzce University Faculty of Medicine (approval number: 2010/101, date: 30.12.2010).

Informed Consent: Informed consent forms were obtained from all patients.

Footnotes

Authorship Contributions

Surgical and Medical Practices: S.Ç., A.Ç., Y.Ş., A.T., Concept: A.T., Design: A.T., Data Collection or Processing: S.Ç., A.Ç., M.A.K., Analysis or Interpretation: D.B., Y.Ş., M.A.K., A.T., Literature Search: D.B., A.Ç., Writing: D.B., Y.Ş., A.T.

Conflict of Interest: Ali Tekin MD is section editor in Journal of Urological Surgery. He had no involvement in the peer-review of this article and had no access to information regarding its peer-review.

Financial Disclosure: The authors declared that this study received no financial support.

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