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Are the Recommended Criteria for Clinically Insignificant Prostate Cancer Applicable to 12-core Prostate Biopsy Scheme? A Multicentre Study of Urooncology Association, Turkey

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Abstract

Objective: The aim of this study is to investigate the relevance of the Epstein criteria for the 12-core transrectal prostate biopsy (TRUS-Bx) scheme with the evaluation of clinicopathologic data recorded in the Urologic Cancer Database - Prostate (UroCaD-P), Urooncology Association, Turkey (UOAT).

Materials and Methods: Patients with detailed pathological 12-core TRUS-Bx data for each biopsy core and who underwent RP due to PCa were included in this study. A total of 1167 patients from seven different centres were analysed. TRUS-Bx pathological findings were separately evaluated in the areas matching the sextant biopsy (6-core paramedian-lateral) scheme and in all 12-core biopsy areas (12-core biopsy scheme). Overall detection rates of PCa and ratios of clinically significant (sPCa) and insignificant PCa (insPCa) after RP were defined and compared between the biopsy schemes. Biopsy findings, according to the Epstein criteria, were also compared between the two schemes. A model for each biopsy scheme was created, including the Epstein criteria and additional biopsy findings using logistic regression analysis to predict clinically sPCa after RP.

Results: There was a high correlation for the prediction of clinically insPCa between the two biopsy schemes in the same population. However, 7.3% of PCa could not be diagnosed in the 6-core TRUS-Bx scheme. Also, 69.4% of these had clinically sPCa according to the Epstein criteria in 12-core TRUS-Bx scheme and 51.8% of these were clinically sPCa after RP. The presence of perineural invasion (PNI) in 12-core biopsy was also significant regarding predicting sPCa ($p<0.001$).

Conclusion: The Epstein criteria in 12-core prostate biopsy provide a better prediction of clinically sPCa than the 6-core biopsy scheme. Biopsy PNI findings appeared to improve the effectiveness of 12-core prostate biopsy, in addition to the Epstein criteria.

Keywords: Prostate cancer, radical prostatectomy, clinically insignificant prostate cancer, Epstein criteria, 12-core prostate biopsy scheme

Introduction

Prostate cancer (PCa) is the most common cancer in men (1). Currently, diagnosis is via TRUS-guided biopsy (TRUS-Bx) based on prostate-specific antigen (PSA) level and digital rectal examination. However, not all forms of PCa will progress, and detection of clinically insignificant PCa (insPCa) may cause over-treatment in some patients. Although active surveillance

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is an increasingly adopted management approach preventing unnecessary treatment in this patient category (very low-risk localised PCa), a substantial number of patients are still subjected to surgical or radiation-based interventions (2). Therefore, accurate identification of the clinical significance of tumours is crucial in avoiding unnecessary treatment with potential side effects or delay of curative therapy for whom it is required.

Initial attempts for a valid definition of clinical significance were based on tumour volume in 1993 by Stamey et al. (3). Later, preoperative criteria for the prediction of insPCa were defined in 1994 by Epstein et al. (4). Based on sextant biopsy findings, it was defined as a tumour <0.2 mL, organ-confined disease and a Gleason score (GS) <7. This comprised 16% of all PCa in their series (4). The initial report's positive and negative predictive values were 95% and 66%, respectively, for insPCa (4). Subsequently, the Epstein criteria began to be used to predict insPCa to categorise patients for surveillance. However, diverse concordance ratios (37%-96.9%) were reported for the predictive ability of the Epstein criteria in various studies over time (5). During the same period, optimisation studies of TRUS biopsy schemes resulted in a general acceptance of obtaining 12 cores for biopsy. Although the Epstein criteria are assumed to be valid for 12-core biopsies, very scarce information is available in the current literature to support this view.

Therefore, we investigated the validity of the Epstein criteria, as defined according to the sextant biopsy scheme, for the currently utilised 12-core prostate biopsy protocol by analysing the clinicopathologic data recorded in the Urologic Cancer Database - Prostate (UroCaD-P), Urooncology Association, Turkey (UOAT).

Materials and Methods

In this study, we retrospectively reviewed the data of 3,300 patients in the UroCaD-P, UOAT between 2007 and 2019. Data were anonymised entirely in compliance with the local regulations at the source centre before being recorded in the UroCaD-P. Patients who had detailed 12-core TRUS-Bx pathologic data for each biopsy core and subsequently underwent radical prostatectomy (RP) (open, laparoscopic or robotic) due to PCa were included in the study. Patients with incomplete data for TRUS-Bx and/or RP were excluded. As a result, 1,167 patients from 7 different centres were evaluated in the study. Pathological findings were separately evaluated in the areas matching the sextant biopsy (6 cores paramedian-lateral) scheme and all 12-core biopsy areas (6 cores paramedian-lateral and 6 cores far-lateral) and were separately entered into the database for each patient. Detection rates of PCa and ratios of clinically significant (sPCa) and insPCa after RP were separately evaluated and compared between the biopsy schemes. Prediction levels of clinically insPCa were defined according to the Epstein criteria. Also, true clinically insPCa was defined according to the final pathology report after RP (organ-confined PCa and no GS 4 or 5) (4). Proportions of patients who met the Epstein criteria (clinical stage T1c, PSA density ≤0.15 ng/mL/cm^3, ≤6 GS (or Gleason grade group 1), ≤2 positive biopsy cores and ≤50% percentage of tumour in positive biopsy core) were compared between the biopsy schemes. Accordingly, GS (according to 2005 modified Gleason grading system), the number of positive cores and percentage of tumour in positive cores were compared between the sextant and 12-core TRUS-Bx schemes. In addition, PSA, PSA density, age and RP pathological findings of all patients were evaluated.

Two different models were created for each biopsy scheme based on the Epstein criteria alone and additional biopsy findings to predict the clinical significance of the tumours after RP.

Statistical Analysis

The non-parametric paired Wilcoxon test and chi-square test were used to analyse the relationships between categorical and independent variables. Also, the chi-square test, McNamer test and correlation analysis were used for the analysis of categorical variables and p-value, estimated risks (OR), Kappa score, Pearson's R correlation coefficient (R) and confidence intervals (CI), positive predictive values (PPV) and accuracy rates were given. The ability of the two different biopsy schemes to predict clinically insPCa after RP was evaluated using a logistic regression model. The Statistical Package for the Social Sciences version 22.0 was used for all statistical analysis. P-values less than 0.05 were considered statistically significant.

Results

A total of 1,167 patients with a median age of 63 years and a PSA level of 7.5 ng/mL were investigated in the study. The patients' demographic data, 12-core biopsy pathologic data and RP pathologic data are given in Table 1. Among patients, 767 (65.7%) had clinically sPCa, and 400 (34.3%) had clinically insPCa after RP. According to the prediction of the Epstein criteria, there were 143 patients with clinically insPCa after the evaluation of the 6-core TRUS-Bx scheme. In contrast, there were 111 patients, according to the 12-core TRUS-Bx scheme (Table 2). In evaluating 143 clinically insPCa patients who were predicted with the 6-core TRUS-Bx scheme, 33 of these patients were predicted as clinically sPCa according to the 12-core TRUS-Bx scheme. In addition, although PCa was diagnosed in the 12-core TRUS-Bx scheme, 85 (7.3%) patients had no cancer according to the 6-core TRUS-Bx scheme. Also, 59 (69.4%) of these 85 patients were predicted as clinically sPCa according to the Epstein criteria in the 12-core TRUS-Bx scheme, and 44 (51.8%) of them were found to have clinically sPCa after RP. The results of predicting clinically sPCa and insPCa according to the Epstein criteria and analysis of additional pathological findings in the 6- and 12-core TRUS-Bx schemes are given in Table 3. The sensitivity, specificity, PPV and negative predictive values (NPV) of the sextant TRUS-Bx scheme for true clinically sPCa after RP was 94.9%, 26%, 71.1% and 72.7%, respectively (p<0.001, OR: 6.559 CI: 4.43-9.71). The sensitivity, specificity, PPV and NPV of the 12-core TRUS-Bx scheme for the true clinically sPCa after RP were 97%, 22%, 70.5% and 79.3%, respectively (p<0.001, OR: 9,124 CI: 5,65-14,71). There was a high correlation between the two biopsy schemes (p<0.001; Pearson's R: 0.859). The model results for both 6-core and 12-core TRUS-Bx schemes according to the Epstein criteria and the model results of additional pathological findings added to the nomograms as predictive

Table 1. Demographic data, 12-core biopsy pathologic data and RP pathologic data of the patients		
Data, mean ± standard deviation (minimum-maximum)		**n=1167**
Age (years)		62.7±6.5 (42-86)
BMI (kg/m^2)		26.7±3.1 (18.5-34.9)
PSA (ng/mL)		10.5±11.5 (1-125.7)
fPSA (ng/mL)		1.31±2.06 (0.1-24.67)
PV (cm^3)		52.1±27.2 (14-200)
PSA density (ng/mL/cm^3)		0.23±0.23 (0.01-1.88)
Clinical T stage, n (%) (n=1123)	T1c	265 (22.7)
	T2a	212 (18.2)
	T2b	37 (3.2)
	T2c–T3	609 (52.2)
GS of 12-core prostate biopsy		6.65±0.83 (4-10)
ISUP grade of 12-core prostate biopsy, n (%)	1	591 (50.7)
	2	334 (28.6)
	3	115 (9.9)
	4	68 (5.8)
	5	59 (5.1)
PNI presence of 12-core prostate biopsy, n (%) (n=1096)		319 (29.1)
LVI presence of 12-core prostate biopsy, n (%) (n=1074)		92 (8.6)
HGPIN presence of 12-core prostate biopsy, n (%) (n=1048)		254 (24.2)
RP pathological T stage, n (%) (n=1166)	pT2	777 (66.6)
	pT3a	234 (20.1)
	pT3b	151 (12.9)
	pT4	4 (0.3)
GS of RP specimen		6.81±0.85 (4-10)
ISUP grade of RP specimen, n (%)	1	437 (37.4)
	2	437 (37.4)
	3	148 (12.7)
	4	65 (5.6)
	5	80 (6.9)
True clinically sPCa after RP, n (%)		767 (65.7)
True clinically insPCa after RP, n (%)		400 (34.3)

BMI: Body mass index, PSA: Prostate-specific antigen, fPSA: Free PSA, PV: Prostate volume, GS: Gleason score, ISUP: International society of urological pathology, PNI: Perineural invasion, LVI: Lymphovascular invasion, HGPIN: High grade prostatic intraepithelial hyperplasia, RP: Radical prostatectomy, sPCa: Significant prostate cancer, insPCa: Insignificant prostate cancer

Table 2. Pathological findings and data of clinically sPCa/insPCa according to the Epstein Criteria in 6- and 12-core biopsy schemes, separately				
Biopsy results		**12-core TRUS-Bx scheme group (n=1167)**	**6-core TRUS-Bx scheme group (n=1167)**	**p***
Diagnosis, n (%)	Benign pathology	0 (0)	85 (7.3)	-
	PCa	1167 (100)	1082 (92.7)	
	Clinically insPCa according to the Epstein criteria	111 (9.5)	143 (12.3)	
	Clinically sPCa according to the Epstein criteria	1056 (90.5)	1024 (87.7)	
Percentage of tumour in positive biopsy core		50.5±31.7 (1-100)	44.8±32.6 (0-100)	<0.001
Number of positive biopsy core		3.34±2.45 (1-12)	2.32±1.6 (0-6)	<0.001

PCa: Prostate cancer, insPCa: Insignificant PCa, sPCa: Significant PCa, TRUS-Bx: Transrectal prostate biopsy
*Paired t-test

Table 3. Prediction of clinically sPCa and insPCa after RP according to the Epstein criteria and analysis of additional pathological findings in the 6- and 12-core biopsy schemes

	All patients (n=1167)	Patients with true clinically sPCa after RP (n=767)	Patients with true clinically insPCa after RP (n=400)	p*
Prediction of the Epstein criteria in 6-core TRUS-Bx scheme				p<0.001 OR: 6.559 (CI: 4.43-9.71) Pearson's R: 0.303 Kappa: 0.247 McNemar <0.001
• Clinically insPCa, n (%)	143 (12.3)	39 (5.1)	104 (26)	
• Clinically sPCa, n (%)	1024 (87.7)	728 (94.9)	296 (74)	
Prediction of the Epstein criteria in 12-core TRUS-Bx scheme				p<0.001 OR: 9.124 (CI: 5.65-14.7) Pearson's R: 0.307 Kappa: 0.230 McNemar <0.001
• Clinically insPCa, n (%)	111 (9.5)	23 (3)	88 (22)	
• Clinically sPCa, n (%)	1056 (90.5)	744 (97)	312 (78)	
PNI presence in 12-core biopsy, n (%) (n=1096)	319 (29.1)	263 (36.5)	56 (14.9)	p<0.001 OR: 3.3 (CI:2.38-4.54) Pearson's R: 0.226
LVI presence in 12-core biopsy, n (%) (n=1074)	92 (8.6)	79 (11.2)	13 (3.5)	p<0.001 OR: 3.5 (CI: 1.91-6.36) Pearson's R: 0.131
HGPIN presence in 12-core biopsy, n (%) (n=1048)	254 (24.2)	175 (25.7)	13 (21.5)	p=0.133 OR: 1.3 (CI: 0.93-1.71) Pearson's R: 0.046

RP: Radical prostatectomy, PCa: Prostate cancer, insPCa: Insignificant PCa, sPCa: Significant PCa, ISUP: International society of urological pathology, PNI: Perineural invasion, LVI: Lymphovascular invasion, HGPIN: High grade prostatic intraepithelial hyperplasia, OR: Odds ratio, CI: Confidence interval
*chi-square test, McNemar test and Correlation were used. Estimated risk are given as odds ratio and Correlation is given as Pearson's R

Table 4. In the same patients, created model results of predicting clinically sPCa and insPCa after RP according to the Epstein criteria and additional pathological findings in both 6- and 12-core biopsy schemes

	p-value	Exp (B)	CI
Predictive model of the Epstein criteria in 6-core TRUS-Bx scheme (Model p<0.001)			
• PSA	0.383	1.055	0.935-1.191
• PSA density	**0.008**	0.383	0.188-0.777
• Clinical T Stage	**0.028**	0.234	0.064-0.856
• Biopsy GS	<**0.001**	0.015	0.003-0.073
• Tumour percentage of positive core	**0.014**	0.346	0.149-0.804
• Number of positive cores	0.976	0.988	0.442-2.207
Predictive model of the Epstein criteria in 12-core TRUS-Bx scheme (Model p<0.001)			
• PSA	0.413	1.052	0.932-1.118
• PSA density	**0.013**	0.401	0.196-0.822
• Clinical T Stage	**0.032**	0.238	0.064-0.884
• Biopsy GS	<**0.001**	0.017	0.004-0.078
• Tumour percentage of positive core	**0.002**	0.259	0.110-0.612
• Number of positive cores	0.565	1.268	0.565-2.847
New modelling of findings in 12 core prostate biopsy (Model p<0.001)			
• Epstein criteria	<**0.001**	7.379	4.447-12.242
• PNI presence in prostate biopsy	<**0.001**	2.514	1.771-3.568
• LVI presence in prostate biopsy	0.093	1.734	0.913-3.296

PSA: Prostate-specific antigen, GS: Gleason score, PNI: Perineural invasion, LVI: Lymphovascular invasion, RP: Radical prostatectomy, PCa: Prostate cancer, CI: Confidence interval
*Analysis results are given with creation of Logistic regression models

factors for the sextant and 12-core TRUS-Bx scheme are given in Table 4. Analysis of data revealed the presence of perineural invasion (PNI) in the 12-core biopsy scheme as a significant predictor in both univariate and multivariate analyses in terms of sPCa (p<0.001; OR: 3.3 CI: 2.38-4.54; Pearson's R: 0.226).

Discussion

The widespread use of PSA testing has led to over-diagnosis because of increased prostate biopsy rates and increased number of cores in each biopsy (6,7). At the same time, over-treatment rate of RP also increased over time. After the published reports about RP series, 26-33% of RP specimens were clinically insPCa (organ-confined PCa, tumour volume less than 0.2 cc, and no Gleason pattern 4 or 5) (4,8). Our series found that 34.3% of patients had clinically insPCa after RP, consistent with the literature. Therefore, it is becoming more important to distinguish the clinically significant disease from clinically insPCa in the decision-making process before treatment to avoid unnecessary treatment interventions. Therefore, identification of insPCa for active surveillance became a major topic of interest. The Epstein criteria have been widely used for that purpose in clinical practice despite some deficiencies (9). Based on the final pathology results, predictive variables were suggested as ≤0.15 ng/mL/cm^3 PSA density, T1c clinical stage and favourable features on 6-core prostate biopsy [≤6 GS (Gleason grade group 1), ≤2 positive biopsy cores and ≤50% percentage of tumour in positive biopsy core] (4,10).

When we look at each predictive factor evaluated in the Epstein criteria, PSA density was previously found to be useful to differentiate more aggressive PCa (11). It was also used as an inclusion criterion for AS (12,13). Cut-off values of PSA density were defined as 0.15 ng/mL/cm^3 and 0.2 ng/mL/cm^3 in previous studies. In our evaluation and validation of the Epstein criteria with the 12-core biopsy scheme, the threshold of PSA density was taken at the level of 0.15 ng/mL/cm^3, like the original study, to predict clinically insPCa. The clinical stage T1c is a main factor for the Epstein criteria because it predicts about 30% of clinically insPCa after RP (4,8).

One of the questions we aimed to answer is the optimal number and percentage of positive biopsy cores from a 12-core biopsy to predict a significant tumour at RP. In this context, some protocols recommend the threshold as the percentage of positive cores (14). In such protocols Dall'Era et al. (15) recommended the presence of <6 total GS, <10 ng/mL PSA level, ≤33% positive cores and tumour presence in ≤50% of each positive core as indicators of insPCa. Similarly, van AS et al. (16), included clinical stage T1-2a, ≤7 total GS (3+4) or ≤ International Society of Urological Pathology grade 2, <15 ng/mL PSA level and <50% positive biopsy cores. In summary, the primary purpose of all these criteria is to predict clinically insPCa and to avoid over-treatment in eligible patients. Many publications suggested that a low number of positive cores was associated with favourable pathological findings at RP specimens (17,18,19). However, there are important studies questioning the role of a number of positive cores on biopsy as a predictive factor for insPCa (18,19). In the current study, we found that the average number of positive biopsy cores was higher in the 12-core biopsy scheme than the 6-core biopsy scheme (3.34 vs 2.32, p<0.001). In the regression model for our population, the ≤2 positive biopsy core finding was not a predictive factor for clinically insPCa in both 6- and 12-core biopsy schemes within the context of the Epstein criteria.

Presence of tumour in <50% of the positive biopsy core was the best factor correlated with the prediction of insPCa among the Epstein criteria in the literature (17). In a recently published study, very low-risk patients (≤6 GS, ≤2 positive biopsy core and ≤50% of tumour in positive core) and other low-risk patients (≤6 GS, >2 positive core and/or >50% percentage of tumour in positive core) were compared and a risk stratification, including tumour volume on biopsy was recommended for low-risk patients (20). In the current study, we found that the mean percentage of tumour in positive biopsy cores were higher in the 12-core biopsy scheme than in the 6-core biopsy scheme (50.5% vs 44.8%; p<0.001). When we look at the regression model in our study, the presence of ≤50% of tumour in positive biopsy core was an independent predictive factor for clinically insPCa in both 6- and 12-core biopsy schemes, consistent with the literature.

The current study aimed to evaluate the performance of the Epstein criteria for the 12-core prostate biopsy scheme. We also investigated the role of possible additional predictive factors that can be added to the criteria such as prostate biopsy PNI, lymphovascular invasion and others. In our cohort, the Epstein criteria in both 6-core and 12-core biopsy schemes significantly predicted clinically sPCa (or insPCa) and were found to correlate with each other. However, the 12-core biopsy scheme was superior for this prediction. However, despite the better performance of 12-core biopsy, only 88 of 400 (22%) patients with true clinically insPCa at final pathology could be predicted. This finding indicates a major room for improvement. Thus, additional analysis of our data highlighted the presence of PNI at the biopsy specimen as a promising predictive factor. The finding of PNI in biopsy is shown as the extension of PCa cells along the nerve bundle in prostate tissue (21). It is reported in 20% of all biopsies harbouring PCa, which is generally accompanied by high GS and PSA levels (22).

Additionally, a high correlation level was shown between PNI on biopsy and extra prostatic extension and surgical margin positivity after RP (22,23,24,25,26,27). However, PNI on biopsy was not always an independent predictive factor of sPCa (28,29). Nevertheless, prostate biopsy PNI presence was an independent predictive factor for clinically sPCa at RP in our study when we incorporated this variable into the Epstein criteria.

In summary, there was a high correlation for the prediction of clinically sPCa/insPCa between the two biopsy schemes in the same patient population. Nevertheless, 7.3% of patients could not be diagnosed with PCa in 6-core TRUS-Bx scheme. Also, 69.4% of these patients (5.1% of all) were clinically sPCa according to the Epstein criteria in the 12-core TRUS-Bx scheme, and 51.8% of them (3.8% of all) were clinically sPCa after RP. According to our results, using the Epstein criteria with 12-core prostate biopsy provides better results in predicting clinically

sPCa than 6-core biopsy. Furthermore, PNI on biopsy can be a useful predictive factor in addition to the Epstein criteria.

Study Limitations

The major limitations of our study are its retrospective nature and analysis. Therefore, indications for surgery were at the physician's discretion. Another important limitation is that there was no centralised pathological examination and the proposed changes in the Gleason grading system over time. However, multicentric pathological examinations by uropathologists at respective centres and long-term data acquisition may reflect a real-life nationwide picture.

Conclusions

The Epstein criteria in sextant prostate biopsy scheme predicted clinically significant PCa with high sensitivity in our cohort in concordance with the original publication and subsequent literature. The performance of biopsy the Epstein criteria in predicting insPCa at final pathology was better with 12-core prostate biopsy scheme in our cohort. In addition, incorporation of the biopsy PNI finding to the prediction model improved the performance of the Epstein criteria.

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Ethics

Ethics Committee Approval: We investigated the validity of the Epstein criteria, as defined according to the sextant biopsy scheme, for the currently utilised 12-core prostate biopsy protocol by analysing the clinicopathologic data recorded in the Urologic Cancer Database - Prostate (UroCaD-P), Urooncology Association, Turkey (UOAT).

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Authorship Contributions

Concept: S.Ç., F.K., K.Y., F.N., L.T., Design: S.Ç., F.K., K.Y., F.N., L.T., Data Collection or Processing: H.Ö., B.A., V.İ., Y.B., G.A., S.S., S.B., T.M., Analysis or Interpretation: S.Ç., K.Y., L.T., Literature Search: S.Ç., F.K., Writing: S.Ç., K.Y., L.T.

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