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ORIGINAL ARTICLE

Prostate Cancer

Gleason score and tumor laterality in radical prostatectomy and transrectal ultrasound-guided biopsy of the prostate: a comparative study

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We aimed to compare Gleason score and tumor laterality between transrectal ultrasound-guided biopsy of the prostate (TRUSBX) and radical prostatectomy (RP). Some factors that could cause a discrepancy in results between these two procedures were also evaluated. Among the 318 cases reviewed, 191 cases were selected for inclusion in this comparative study. We divided the patients into two groups using the Gleason score: an intermediate/high-grade group (≥ 7) and a low-grade group (< 6). Exploratory analyses were conducted for comparisons between groups. We also performed comparisons between TRUSBX and RP for tumor laterality. TRUSBX overestimated 6% and underestimated 24% cases in comparison with RP for Gleason score, and overestimated 2.6% and underestimated 46% cases compared with RP for tumor laterality. Biopsy specimens were slightly smaller in TRUSBX cases with underestimated tumor laterality ($P < 0.05$), and no relationship between the biopsy specimen size and underestimated Gleason score in TRUSBX was found. Prostatic volume showed no statistical correlation with the likelihood of under or overestimation ($P > 0.05$). Thus, our study showed that TRUSBX has a high likelihood of underestimating both the Gleason score and tumor laterality in prostate cancer (PCa). The size of the fragment appears to be an important factor influencing the likelihood of laterality underestimation and Gleason score overestimation via TRUSBX. Due to the high likelihood of underestimation of the Gleason score and tumor laterality by 12-core prostate biopsy, we conclude that this type of biopsy should not be used alone to guide therapy in PCa.

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INTRODUCTION

Prostate cancer (PCa) is the most common malignant tumor in men older than 50 years¹ and its diagnosis is made by: digital rectal examination, prostate-specific antigen (PSA) test, and transrectal ultrasound-guided biopsy of the prostate (TRUSBX). In addition to diagnostic information, TRUSBX provides other tumor data that can guide the therapeutic approach, such as Gleason score and tumor laterality.^{2–4}

The Gleason score is the most commonly accepted and widely used parameter for the prediction of tumor biology and treatment outcome. Hence, accurate diagnosis of the Gleason score by TRUSBX is a pivotal element of the algorithm for treatment. However, compared with radical prostatectomy (RP), TRUSBX generally underestimates the Gleason score. TRUSBX may underestimate the Gleason score in more than 50% of cases and studies have demonstrated about 40% of men diagnosed with low-grade PCa by TRUSBX actually have high-grade tumors.^{3–8}

Actually, RP is considered the best treatment for localized PCa.^{9,10} However, RP has a significant incidence of urologic complications, such as urinary incontinence and sexual impotency, which often significantly diminish the patients' quality of life.¹¹ To decrease these complications,

hemi-ablation of the prostate gland has been suggested as an alternative therapy in unilateral tumors.¹² Thus, correctly identifying tumor laterality (uni or bilaterality) via TRUSBX is an important factor in determining the selection of hemi-ablation, although recent studies also suggest that TRUSBX tends to underestimate tumor laterality.^{12,13}

As a result of these discrepancies findings, we compared the Gleason score and tumor laterality determined from RP and TRUSBX. Some factors that could cause a discrepancy in results between the two procedures were also evaluated. This study is also particularly important because it includes a population (Brazilian men) that is typically understudied.

MATERIALS AND METHODS

Clinical and pathological studies

From 2005 to 2010, we reviewed 318 consecutive cases of PCa treated by RP. The biopsies and RP specimens were obtained from the files of the Department of Pathology, Medical School of Ribeirao Preto, Brazil. All cases were reviewed by two pathologists to confirm a diagnosis of PCa and other histologic features were assessed. The following preoperative clinical variables were collected: age at diagnosis, preoperative PSA

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level, transrectal ultrasound prostate volume and clinical stage. We also collected pathological findings from biopsy specimens: the tumor laterality (right or left side, or both), Gleason sum and score (including presence of a tertiary grade), and the number of cores in the biopsy, the number of cores involved with cancer and percentage of the tissue involved with cancer. The length of positive and negative fragments was also acquired. Biopsy specimens from each site were processed separately. Each core was fixed in 10% formalin, embedded in paraffin, sectioned longitudinally, stained with hematoxylin and eosin, and examined. To confirm the cancer diagnosis, immunohistochemical study using 34 β E12 and p63 was done in some cases. After the diagnosis of cancer, a conventional RP was performed. The histological processing was the same as previously described for biopsy specimens. From the RP specimens, the following data was collected: the tumor laterality (right or left, or both), Gleason sum and score (including the presence of a tertiary grade) and pathologic stage.

A comparison was made between the Gleason scores and tumor laterality of the needle biopsy and RP specimens. The definitive tumor laterality of the PCa was defined at prostatectomy specimens. Tumor laterality was scored as unilateral (tumor affecting only one side of the prostate), and bilateral (tumor affecting both sides of the prostate). When at least 1 biopsy revealed adenocarcinoma only in the same lobe (ipsilateral) of prostatectomy specimen, the biopsy was designated as unilateral. Likewise, when at least 1 biopsy showed adenocarcinoma in each lobe, the biopsy was designated as bilateral. For statically analysis, the Gleason scores were divided into two different prognostic groups: low-grade (≤ 6) and intermediate/high-grade (≥ 7). Gleason score was based on the final radical RP specimens. We have named the underestimation of the laterality any case with incorrect estimation of the bilateral disease in RP as unilateral disease in biopsy; while overestimation of the laterality occurs when a patient showed bilateral disease in the biopsy, but unilateral in the RP.

The transrectal ultrasound-derived prostate volume was invariably calculated using the prostate ellipse formula ($0.52 \times \text{length} \times \text{width} \times \text{height}$). Clinical and pathological stages were assigned based on the 2002 tumor node metastasis (TNM) system. The Gleason grading was based on the recommendations of the 2005 international society of urological pathology consensus conference. TRUSBX were performed using an 18-gauge needle and a 12-core biopsy technique (sextant biopsy + lateral base, lateral mid-zone, lateral apex, bilaterally). Many cases were excluded from this study due to the lack of information on PSA or transrectal ultrasound prostate volume, incomplete data on clinical and pathological stage, PCa diagnosed from transurethral resection or outside of our institution and biopsy core number of < 12 . After exclusion criteria had been applied, 191 cases were selected for inclusion in the comparative study between TRUSBX and RP. The research protocol was approved by the Ethics Committee of our hospital, and informed consent was waived.

Statistical analysis

To perform the analyses, we divided the patients into two groups using the Gleason score: an intermediate/high-grade group (Gleason score, >7) and a low-grade group (Gleason score, <6). Descriptive statistics was used for the demographic, clinical, and pathological variables. Exploratory analyses were conducted for comparisons between groups of patients according to medical features of interest. The Chi-squared test was used to compare the frequency of categorical variables between groups and the Mann-Whitney test was used to compare continuous variables with nonnormal distributions. ANOVA testing was used to analyze the differences between group means and their associated procedures.

For comparison of the two procedures, we used the linear-mixed effect model (MIXED). Significance was set at $P < 0.05$. Data analysis was conducted using SAS[®]9.0 software (SAS Institute, Inc., Cary, NC, USA).

RESULTS

The mean age of the 191 patients was 64 (± 6.5) years, and the mean preoperative total PSA level was 8.18 (± 6.12) ng ml⁻¹. The Gleason score ranged from 5 to 10. Seventy-five patients (39.3%) had a Gleason score < 6 , 104 patients (54.4%) had a Gleason score of 7, and 12 patients (3.3%) had a Gleason score ≥ 8 (Table 1). The predominant TNM stage was pT2c (58.1%); 81.2% of patients were white males. There was no significance association between Gleason score and age, but there was a significant positive correlation between Gleason score and enlargement of seminal vesicles, ejaculatory duct, and urethral canal ($P < 0.05$) and also tumor capsular invasion ($P < 0.05$).

We then compared the Gleason score and tumor laterality between TRUSBX and RP in 191 cases, as shown in Table 2. Of the 76 cases

Table 1: Descriptive epidemiology

Data	n=191	Percentage
Age (year)		
≤49	3	1.6
50-59	55	28.7
60-69	96	50.3
≥70	37	19.4
PSA (ng ml ⁻¹)		
<4.0	27	14.1
4.0-9.9	94	49.2
10.0-19.9	54	28.3
≥20.0	16	8.4
Gleason score		
≤6	75	39.3
7	104	54.4
≥8	12	6.3
TNM		
pT1a	8	4.2
pT1c	2	1
pT2a	23	12.1
pT2b	8	4.2
pT2c	111	58.1
pT3a	17	8.9
pT3b	22	11.5
Ethnicity		
White	155	81.2
Black	23	12
Mulatto*	13	6.8

*Mulatto is the term used in Brazil to name the offspring result from the union of white and black people. PSA: prostate-specific antigen; TNM: tumor node metastasis

Table 2: Sensitivity and specificity of TRUSBX in relation to RP to detection tumor laterality and high-grade PCa

RP	TRUSBX			RP	TRUSBX		
	Low-grade	High-grade	Total		Unilateral	Bilateral	Total
Low-grade	65	11*	76	Unilateral	40	5 [†]	45
High-grade	46**	69	115	Bilateral	91 [‡]	55	146
Total	111	80	191	Total	129	62	191

*Overestimated cases for Gleason score; **Underestimated cases for Gleason score; [†]Overestimated cases for tumor laterality; [‡]Underestimated cases of tumor laterality. TRUSBX: transrectal ultrasound guided prostate biopsy; RP: radical prostatectomy; PCa: prostate cancer

classified as low-grade by RP (40%), 65 were in agreement with TRUSBX findings (34%), whereas 11 cases were overestimated by TRUSBX (6%). Of the 115 cases classified as high-grade by RP (60%), 69 were in agreement with TRUSBX findings (36%), and 46 were underestimated by TRUSBX (24%). In the assessment of tumor laterality, TRUSBX overestimated the laterality in 5 cases (2.6%). TRUSBX incorrectly diagnosed 91 cases (46%) as unilateral tumors, whereas RP showed that both sides of the gland were affected in these cases.

To determine the factors causing discordance between the results of TRUSBX and RP, we first evaluated if prostate volume was associated with laterality and Gleason score discordance. To do so, we separate cases into two groups by prostate volume (greater than or < 60 cm³). The 91 cases where tumor laterality was underestimated by TRUSBX, the mean prostatic volume was 74.9 cm³; of these, 39 cases showed prostatic volume was < 60 cm³ (42.8%), and in 52 cases, prostatic volume was > 60 cm³ (57.2%). Prostatic volume showed no statistical correlation with the likelihood of under or overestimation ($P > 0.05$).

We also evaluated whether the size of the biopsy specimens affects the diagnosis of tumor laterality and grading. There was no relationship between the biopsy specimen size and underestimated Gleason score in TRUSBX. However, biopsy specimens were smaller in TRUSBX

cases with overestimated Gleason scores compared TRUSBX cases with underestimated Gleason scores, as well as compared to TRUSBX cases with the same Gleason score by RP ($P < 0.05$, **Table 3** and **Figure 1**). Biopsy specimens were slightly smaller in TRUSBX cases with underestimated tumor laterality than in TRUSBX cases with the same tumor laterality by RP ($P < 0.05$, **Table 4** and **Figure 2**).

DISCUSSION

The mean age, race, and preoperative PSA level of our patients were in agreement with those reported in previous studies.^{1,4,14} The TNM tumor stage was in agreement with that of a recent study by Nassif *et al.* (65% of patients were pT2c); however, the average tumor stage of patients in this study was different from that of recent international reports.¹⁴ For instance, a study on 369 patients by Freedland *et al.* in the United States reported that the predominant TNM tumor stage was pT2a (34% of patients).⁹ Another study performed in United States by Makarov *et al.* reported the predominant stage of 5730 patients as pT1c (77% of patients).¹⁵ Considering that our patients were presenting to a public health care institution, the discrepancy between our results and those of the international studies may be explained by a recent Brazilian study performed by Nardi *et al.* That study showed that

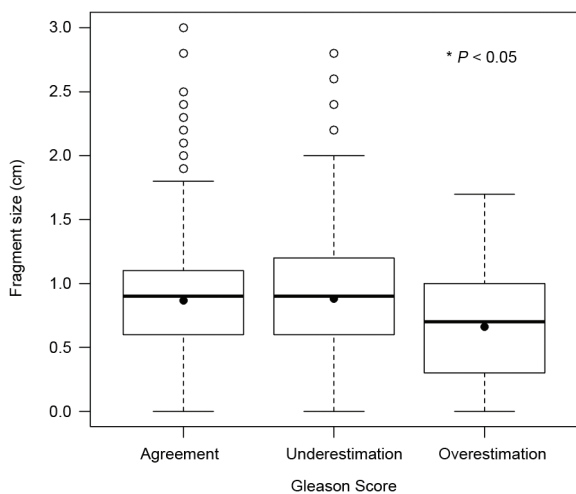


Figure 1: Distribution of fragment size in Gleason score groups after comparing biopsy with prostatectomy results.

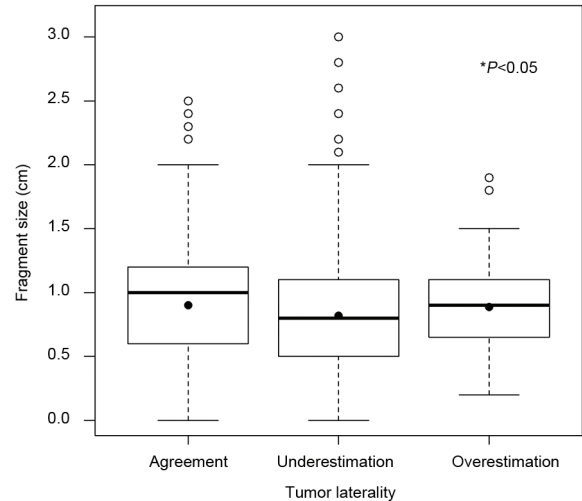


Figure 2: Distribution of fragment size in laterality groups after comparing biopsy with prostatectomy results.

Table 3: Sizes of biopsy in agreement, underestimation and overestimation groups for gleason score when results of biopsy was compared with prostatectomy

Gleason	NF	Biopsy size (cm)							
		Mean	Minimum	CI	1 st quartile	Median	3 rd quartile	Maximum	
Agreement	1637	0.87	0	0.85	0.89	0.6	0.9	1.1	3.0
Underestimation	564	0.88	0	0.85	0.92	0.6	0.9	1.2	2.8
Overestimation	132	0.66*	0	0.58	0.74	0.3	0.7	1	1.7

* $P < 0.05$. NF: number of fragments; CI: confidence interval

Table 4: Sizes of biopsy in agreement, underestimation and overestimation groups for laterality when results of biopsy was compared with prostatectomy

Laterality	NF	Biopsy sizes (cm)							
		Mean	Minimum	CI	1 st quartile	Median	3 rd quartile	Maximum	
Agreement	1146	0.9	0	0.88	0.93	0.6	1	1.2	2.5
Underestimation	1102	0.82*	0	0.79	0.85	0.5	0.8	1.1	3
Overestimation	87	0.89	0.2	0.81	0.96	0.6	0.9	1.1	1.9

* $P < 0.05$. NF: number of fragments; CI: confidence interval



PCa patients at public institutions have higher PSA and an increased likelihood of metastatic disease, likely indicating that they present with more advanced disease.¹⁶

In our study, TRUSBX showed a high likelihood of underestimating and a low likelihood of overestimating the Gleason score. A study by Cookson *et al.* in 226 patients showed that TRUSBX underestimated the Gleason score in 54% of cases,⁵ and other studies have reported similar findings.^{2,3} Although an upgraded Gleason score after RP is most common, 7.4% to 30% of the Gleason score 7 (3 + 4) biopsies were shown to be downgraded to Gleason score 6 (3 + 3) or lower at RP.¹⁷ In our study, when we compared the Gleason score between TRUSBX and RP, 11 (6%) cases were overestimated by TRUSBX. Freedland *et al.*¹⁸ described 123 (11%) downgrading cases (lower RP grade than biopsy grade) among 1113 men treated with RP. Therefore, the rate of the downgrading in RP in our study is consistent with the literature. Biopsies and corresponding prostatectomy specimens of our downgraded cases were reviewed, and RP revealed the presence of a tertiary grade in eight cases (72%). For other three cases, multiple factors are to be considered when assessing the cause of the downgraded RP phenomenon. It is conceivable that distinguishing ill-formed (grade 3) and small-fused glands (grade 4) could potentially result in an overestimation of the biopsy Gleason score.¹⁹ In addition to the intra-observer variation inherent to any morphological grading system, sampling bias in the RP could play a role, since only a very small percentage of the whole prostate is presented to the pathologist.

Similarly, our study demonstrated that in the assessment of tumor laterality, TRUSBX has a high likelihood of underestimation and a low likelihood of overestimation, as compared to RP. In line with this find, a study of 316 patients by Jeong *et al.* reported that approximately 65% of patients initially diagnosed with unilateral tumors by TRUSBX or magnetic resonance (or both together) actually had bilateral tumors at final diagnosis.¹³ This discrepancy may be related to increased prostatic volume, because in our study, over half (57.2%) of the cases of underestimation of tumor laterality had a prostatic volume > 60 cm³. However, there is no relation between increased prostatic volume and the likelihood of underestimation or overestimation Gleason score or tumor laterality. It is noteworthy that 5 (2.6%) out of a total of 191 cases were found to be unilateral on prostatectomy and bilateral tumors on biopsy (overestimated cases). Some factors can explain this fact: presence of “vanishing phenomena” or “minimal-volume PCa” in one of the lobes of the prostate. It is interesting that 4 of our 5 cases fulfill criteria of Epstein *et al.* for small-volume PCa.²⁰

There is no clear recommendation about the ideal size of a TRUSBX specimen. Empirically, the Brazilian Pathology Society has indicated that the ideal fragments for histological analysis of prostatic tissue should be > 1 cm. Fragments between 0.5 and 0.9 cm are considered marginal, and fragments < 0.4 cm are considered inadequate for a reliable histological examination.²¹ Furthermore, multiple techniques for quantifying the amount of cancer on needle biopsy have been developed, including measurement of the number of positive cores, total millimeters of cancer among all cores, percentage of each core occupied by cancer and total percentage of cancer in the whole specimen.²²

Our results indicated that biopsy specimens were smaller in cases where TRUSBX overestimated the Gleason score, suggesting that using larger fragments for TRUSBX can decrease the chance of false-positive results. However, similar analyses of the underestimation of Gleason scores did not suggest that biopsy specimen size is the causative factor. Other factors may be involved, for instance, the fact that the method for determining Gleason score differs between TRUSBX and RP.²³

Moreover, the subjective nature of Gleason score patterns or even human error by the pathologist could result in underestimation.²⁴

The preservation of the contralateral lobe of the prostate has been cited as potentially therapeutic in PCa as well as a procedure that increases postoperative quality of life. Onik *et al.* first described focal hemi-ablation therapy for prostate tumors in a pilot study of nine patients with a mean follow-up of 3 years; seven patients showed stable PSA levels and remission of the tumor on biopsy.^{12,25} Furthermore, Lambert *et al.* showed that 95% of men recover sexual potency and normal genitourinary activity within 3 months after focal hemi-ablation.²⁸ Recent research has suggested that if TRUSBX detects PCa in only 1 lobe of the prostate, these patients are good candidates for focal hemi-ablation; therefore, hemi-ablation is being used more frequently for such patients.²⁷⁻²⁹ Because TRUSBX plays an important role in determining the choice of treatment for PCa, the underestimation of tumor laterality we demonstrate here is of critical importance. In fact, as will be further discussed below, two techniques have should be used for selection of the patients eligible for the hemi-ablation therapy: multiparametric magnetic resonance imaging (mpMRI) and transperineal template biopsies.

Epstein *et al.* reported that 44-core needle biopsy increases considerably the specificity (~95%) of TRUSBX to detect tumor and the likelihood of false-negative results decreases.^{30,31} Increasing the number of biopsy fragments assessed in enlarged prostates may avoid underestimation of laterality, thereby providing more reliable guidance for the selection of hemi-ablation. However, increasing the number of biopsy fragments can cause unwanted side-effects such bleeding, infections, and pain. Our study showed that TRUSBX underestimated the laterality more often when the biopsy fragments were smaller. This suggests that increasing the size of the fragments when using TRUSBX may decrease the likelihood of underestimation. This may be a better alternative than increasing the number of biopsied core fragments. Two other factors we did not assess may partly be responsible for the underestimation. First, our patient population had more advanced tumors than those reported in other studies; this may have affected the Gleason score underestimation. Second, we did not assess the quality of the biopsied tissue, nor the quantitative of prostate tissue present in the biopsied fragments and these factors may be important for properly assessing Gleason score and tumor laterality. As this study is currently ongoing, we will attempt to determine if these parameters play a role in underestimation via TRUSBX.

Active surveillance is another growing interest as an alternative to radical treatment, especially the low-risk category (Gleason score of 6 or less, PSA < 10 mg ml⁻¹, clinical stage T1c or T2a). Active surveillance presents several advantages, especially for older men or all those who wish to preserve their quality of life compared with immediate treatment.³² Improving the selection of low-risk PCas is highly relevant due to a significant risk of undergrading of tumor at diagnosis. For men who are found to have PCa progression on active surveillance, focal hemi-ablation therapy may be an attractive option to limit the therapy-associated morbidity. In summary, patients with minimal cancer are amenable to active surveillance or focal therapy active and the decision must be based on accurate staging and grading of the cancer; therefore, imaging technologies and biopsy strategies should be improved.

Recently, MRI as emerged as the main diagnostic method for PCa using a combination of anatomic images and functional techniques, referred as mpMRI with many indications, varying from low- to high-risk lesions. Matsuoka *et al.*³³ have shown that a combination of extended biopsy and mpMRI has a better performance than extended

biopsy alone for predicting lobes without significant cancer. While Margel *et al.*³⁴ reported an excellent diagnostic performance for MRI evaluation of potential candidates for active surveillance, Park *et al.*³⁵ described a rate of 14.3% of missed lesions on MRI exams that had an unfavourable pathology at RP. Stamatakis *et al.*³⁶ have suggested a nomogram using morphological and functional characteristics of mpMRI to minimize these limitations.

An alternative to minimize the high-probability of underestimation of PCa diagnosed by a TRUSBX, is the perineal approach, as described in the transperineal template-guided mapping biopsy (TTMB). This procedure has been shown to be more accurate than conventional, and saturation biopsies guided by transrectal ultrasound, for cancer detection and localization. Recent studies, as the one by Taira *et al.*³⁷ have defined TTMB as best procedure for active surveillance. However, TTMB is significantly more involved and invasive. Also to reduce misclassification on the initial diagnostic biopsy, repeat prostate biopsy have been suggested. In a recent review, Ukimura *et al.*³⁸ concluded that the information from the first biopsy remains the standard for the initial diagnostic evaluation of a suspicious prostate, but for active surveillance and focal therapy protocols will substantially rely on the information from the serial biopsies and MRI-guided biopsies.

CONCLUSION

Our study showed that TRUSBX has a high likelihood of underestimating both the Gleason score and tumor laterality in PCa. The size of the fragment appears to be an important factor influencing the likelihood of laterality underestimation and Gleason score overestimation via TRUSBX.

AUTHOR CONTRIBUTIONS

GEBS, RBR, RCR, JSL and RAP provided study concepts and design. RBR, VFM and RPA provided literature research. RAP and RBR performed the clinical studies. RPA, GEBS, RSC, JSL prepared the manuscript. FFS helped with statistical analysis, interpretation of the data. GEBS and VFM edited the manuscript. All authors read and approved the final manuscript.

COMPETING INTERESTS

All authors declare no competing interests.

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