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Original Research Article

GLEASON SCORE CONCORDANCE IN SINGLE CORE PROSTATE CANCER PATIENTS IS INFLUENCED BY THE NUMBER OF FRAGMENTS SAMPLED AT BIOPSY

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Introduction

Prostate cancer (PCa) is the most common male malignancy in western countries and the second leading cause of cancer death in men (1). The disseminated use of serum prostate-specific antigen (PSA)-based screening for PCa has led to an increase in the proportion of patients with low-stage and low-volume PCa (2,3). As a result, the prevalence of single positive core disease appears to have significantly increased. Single core PCa is expected to be clinically insignificant, indolent and to have lower positive surgical margins (PSM) (4). Systematic reviews have provided inadequate information for assessing the comparative effectiveness of the treatments and any associated harms (5). The risk of dying from PCa is approximately 3%, suggesting that conservative management may be appropriate for many men (6,7). These recent changes may explain the renewed interest in active surveillance (AS) with delayed therapy for highly select patients, particularly those diagnosed with well-differentiated tumors (Gleason < 6) and a low volume. Most single positive core PCa are included in this group (8). Studies comparing the entry criteria for AS protocols, especially in terms of the biopsy parameters, are needed to clarify the best candidates for AS. The Gleason score (GS) is an important parameter in the treatment of PCa when combined with the PSA, clinical stage and prostate size (9,10). Therefore, the accurate determination of the GS on the diagnostic needle biopsy is a crucial component of the algorithm for treatment selection (9). The Gleason grading system has consistently been shown to predict the outcome in patients with PCa. Because a transrectal ultrasonographic prostate biopsy may provide only a sampling of the cancer, the potential exists for a discrepancy between the patient biopsy and pathological GS (11).

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Single core PCa is one of the most important criteria for AS as it should behave like an indolent disease; however, can single core PCa actually be considered to be an indolent tumor? Studies have shown that using more biopsy cores may minimize discrepancies with the GS (12). Because the number of cores sampled may help improve the selection criteria for AS, we analyzed the relationship between the number of cores sampled with the concordance and discrepancy in the GS in a single core group.

The aim of our study was to compare the clinical and pathological findings of PCa patients diagnosed by a single positive core or by multiple positive cores at biopsy who underwent a radical retropubic prostatectomy (RRP). We also evaluated the influence of the number of sampled cores at biopsy in these two groups.

Material and Methods

This study was an observational and retrospective analysis that was submitted to and approved by the ethics committee of HCFMUSP under the number 12/9201. We retrospectively reviewed the patient records for all RRPs performed at São Paulo's State Cancer Institute (ICESP) between January 1, 2006 and November 30, 2011. We found 249 patients who underwent RRP for localized PCa and whose tumors were diagnosed by a single positive core biopsy (group 1). As the control group (group 2), we selected all consecutive PCa patients who underwent RRP from January 1 to November 30, 2011 (462 cases). Single positive core cases were excluded from this second group (86). The remaining 376 patients, who had > 1 positive biopsy core, were matched with the patients in group 1 according to age, prostate weight, PSA level and clinical stage to avoid selection bias. There were 250 patients with PCa diagnosed by multiple positive cores who were similar to the patients in group 1 (249). Men who had received prior hormonal treatment, radiotherapy or any other ablative treatment before the RRP; patients for whom the data were incomplete or missing; and patients with pT0 tumors were excluded from the study (17 patients in group 1 and 48 in group 2).

We employed the Gleason grading system to analyze all biopsies and prostatectomy specimens. The RRP specimens were submitted for histopathological examination by a group of experienced uropathologists at our institution. The 2005 TNM classification system was used to stage the PCa. We evaluated the preoperative data, including the epidemiological characteristics, biopsy data, clinical stage and PSA level, and the pathological data for the RRP specimens, including the frequencies of PSM, extraprostatic extension (EPE) and seminal vesicle invasion (SVI).

We analyzed the concordance and discrepancy of the pre- and postoperative GS. The difference in the accuracy was classified into undergrading and overgrading and was quantified according to the GS difference of one point or more than one point. The pathological data for the single positive core patients (group 1) were compared with the data for the patients with multiple positive cores (group 2). Continuous variables, such as age, PSA level, clinical stage, prostate weight and GS, were analyzed by the Mann-Whitney test. The relationships between the biopsy and RRP specimens were analyzed by the chi-square test. In this study, statistical significance was set at $p<0.05$. The analysis was performed using SPSS ver. 17.0.

Results

No significant differences were found in terms of the patient's age, PSA level, prostate weight and clinical stage between groups 1 and

2, thus confirming the similarity of the two groups (Table 1).

Table 1. Patient characteristics

	Group 1 (%)	Group 2 (%)	p
No. of patients	249	250	-
Mean age (SD)	65.5 (6.4)	64.4 (5.9)	0.083[a]
Mean ng/ml PSA (SD)	9.76 (7.1)	10.73 (7.9)	0.128[a]
PSA < 10 (No. of patients / %)	166 (66.7)	159 (63.6)	0.472[b]
PSA ≥10 (No. of patients / %)	83 (33.3)	91 (36.4)	
Mean weight g prostate (SD)	55.7 (26.7)	51.4 (22.4)	0.102[a]
Prostate < 50 g (No. of patients / %)	127 (51.0)	143 (57.2)	0.165[b]
Prostate ≥ 50 g (No. of patients / %)	122 (49.0)	107 (42.8)	
Clinical Stage			
cT1	186 (74.7)	167 (66.8)	0.153[b]
cT2	60 (24.1)	79 (31.6)	
cT3	3 (1.2)	4 (1.4)	

SD: standard deviation, PSA: prostate specific antigen, Group 1: positive single core, Group 2: multiple positive core, [a]: Mann-Whitney test; [b]: chi-square test.

Table 2 shows that most cases underwent a sextant with 12 or more cores from the transrectal biopsy, including 186 (74.7%) patients in group 1 and 200 patients (80%) in group 2. Table 2 also shows that the biopsies with 12 or more cores had higher rates of concordance between the Gleason pre- and postoperative scores in both groups when compared with those with fewer than 12 fragments (59.7 x 41.3% in group 1 and 47.5 x 36.0% in group 2). This difference was significant in group 1 (p=0.010) but not in group 2 (p=0.133). Only a small number of patients had a GS difference greater than two or more points in both groups (6.8% in group 1 and 8.8% in group 2), but this difference is more evident when we analyze the single core group with fewer than 12 cores (11.1%).

Table 2: Coincidence and discrepancies in groups 1 and 2 according to the number of fragments

	No. of fragments at biopsy	Gleason						Total	
		Coincident		difference of 1 point		difference of > 1 point			
		n	%	n	%	n	%	n	%
Group 1	**<12**	26	41.3	30	47.6	7	11.1	63	100
	>12	111	59.7	65	34.9	10	5.4	186	100
	Total	137	55.0	95	38.2	17	6.8	249	100
Group 2	**<12**	18	36.0	30	60.0	2	4.0	50	100
	>12	95	47.5	85	47.5	20	10.0	200	100
	Total	113	45.2	115	46.0	22	8.8	250	100

Coincidents: Biopsy GS equal to RRP specimens GS.

We found that the GS at biopsy was identical to the GS in the surgical specimen in 55% in group 1 and 45.2% in group 2 (p=0.028). The GS was undergraded in 34.9% and 50.4% and overgraded in 10.1% and 4.4% in groups 1 and 2, respectively. Among all GS discrepancies, the most frequent difference occurred between the cases differing by just one point in the GS

(Table 2) and was due to undergrading (Table 3). In group 1, patients with a biopsy sampling fewer than 12 cores had a significantly higher proportion of undergrading (p=0.007) and a significantly lower proportion of coincident GS (p = 0.010). In group 2, we found no significant differences between concordance, undergrading and overgrading according to the number of cores (p=0.161). The rate of overgrading also did not change according to the number of fragments in group 1 (p=0.873).

Table 3: Coincidence and types of discrepancy in groups 1 and 2 according to the number of fragments

	No. of fragments at biopsy	Gleason						Total	
		Undergrading		Coincidents		Overgrading			
		n	%	n	%	n	%	n	%
Group 1	<12	31	49.2	26	41.3	6	9.5	63	100
	>12	56	30.1	111	59.7	19	10.2	186	100
	Total	87	34.9	137	55.0	25	10.1	249	100
Group 2	<12	31	62.0	18	36.0	1	2.0	50	100
	>12	95	47.5	95	47.5	10	5.0	200	100
	Total	126	50.4	113	45.2	11	4.4	250	100

Undergrading: Biopsy GS less than RRP specimen GS. Coincidents: Biopsy GS equal to RRP specimens. Overgrading: Biopsy GS greater than RRP specimen GS.

As shown in Table 4, group 1 had 20.9% PSM, and group 2 had 37.6%; this difference was significant (p<0.001). We found no difference in the PSM rates according to the number of fragments biopsied in group 2 (p=0.695). However, Table 4 shows that biopsies with fewer than 12 cores had more PSM (36.5%) than the cases with more than 12 cores (15.6%) in group 1; these values were significantly different (p<0.001). No significant difference was observed when the number of biopsy cores was analyzed with respect to the presence of EPE (group 1, p=0.075 and group 2, p=0.280) or SVI (group 1, p=0.467 and group 2, p=0.779).

Table 4: Positive surgical margin in groups 1 and 2 according to the number of fragments

	No. of fragments at biopsy	Surgical positive margin				Total	
		No		Yes			
		n	%	n	%	n	%
Group 1	<12	40	63.5	23	36.5	63	100
	>12	157	84.4	29	15.6	186	100
	Total	197	79.1	52	20.9	249	100
Group 2	<12	30	60	20	40	50	100
	>12	126	63	74	37	200	100
	Total	156	62.4	94	37.6	250	100

Discussion

AS is a treatment option for selected patients with low-risk PCa, and single positive core PCa is one of the well-established criteria. However, the existence of discrepancies between the patient biopsy and pathological GS is common. We have shown that using more biopsy cores may increase the concordance in

the GS in this single core group, which may help improve the selection criteria for AS. None of the previous studies incorporated a review of two matched and similar populations (single core vs. multiple positive cores PCa) according to age, prostate weight, PSA and clinical stage to avoid selection bias.

For the PCa treatment, the clinical, laboratory and pathological data are essential. The GS is one of the most important prognostic factors for PCa. GS undergrading on the biopsy is the most common cause of a discrepancy between the pre-operatory and RRP specimens (13, 14). Several explanations exist for such discrepancies, including pathology error, borderline grades and sampling errors (14). The most common sampling error occurs when a higher grade component in the RRP is missed on the needle biopsy(15). The International Society of Urological Pathology (ISUP) proposed changes to the GS in 2005 with the aim of improving the agreement of the grading system. After the implementation of this new system, the correlation scores increased from 58% to 72% (16). All pathological analyses were performed according to the new classification as this study began in 2006. This study did not include GS 2-4 (17). Regarding sampling errors, we analyzed the influence and implication of the number of biopsy cores in the RPP specimens.

Single core PCa patients are expected to have a low tumor volume and, therefore, a potentially curable disease. However, their PCa could also be considered an indolent tumor, for which immediate treatment may be not only unnecessary but also harmful (4). In this case, AS with a late intervention appears to be a viable option that does not pose major risks to the patient (18). Otherwise, repeating the biopsy with more than 12 cores is important to monitor the patients for changes in tumor histology over time. Up to 30% of patients receive a secondary therapy after a median of approximately 2.5 years of surveillance. Most are treated for histologic reclassification (27-100%) or PSA doubling time <3 years (13-48%), whereas 7-13% are treated with no evidence of progression (19). However, the biopsy and pathological analysis of PCa fragments can result in frequent errors (8). When extended biopsies were performed, we found an improved concordance of the GS between the biopsy and RRP specimens (9). The concordance between the biopsy and RRP GS was the most frequent result (55% in group 1 and 45.2% in group 2), which is in agreement with the studies of King et al (20) and Fukagai et al (21), who found 60% and 45.7% concordance, respectively. In group 1, more than 12 cores being biopsied increased the concordance with the GS significantly (p=0028). In group 2, we observed the same trend, but it was not significant (p=0.12). Separating the discrepancies between GS into undergrading and overgrading, we noticed that undergrading was responsible for this significant difference (34.9%, p=0.07), and these data corroborate the Lattouf reports that found 38.2% undergrading (22). Even when the prostatectomy specimens from a single neoplastic microfocus in saturation biopsies were analyzed by Pepe et al., 87.3% of the patients had significant cancer, with the presence of EPE in 27.3% and PSM in 14.5% (23).

The rate of PSM was higher in group 2 (37.6% vs. 20.9%, p=0.031), which may confirm the possibility of the single positive core group being formed by smaller and indolent tumors. Analyzing only group 1, the patients with >12 cores had less PSM than those with <12 cores. We can assume that a single core tumor diagnosed by >12 fragments is actually a smaller tumor due to the smaller number of PSM. However, the single core cases diagnosed by <12 fragments exhibit substantial discrepancy with the GS, which suggests that the biopsy was not representative of the correct tumor sample. In fact, many of these cases do not actually have a small tumor, which explains why they had more positive margins; if an extended biopsy was performed, these cases would not be considered to have real single core tumors.

Why is a biopsy not as good at predicting the outcome of the surgical pathology? One of the biggest reasons for this variability in the results is the biopsy sampling (24). Stanford showed that when <18 fragments were biopsied in single positive core PCa, there

was a concordance of only 57%, confirming that extended sampling is necessary to ensure that a single core patient has an insignificant cancer. This finding suggests that other methods are necessary to predict biochemical failure or minimize differences in the pathological analysis of RRP specimens (25). In fact, relying on the GS of a single core PCa is not a good practice because we observed a concordance of only 55%. Moreover, when considering those diagnoses performed with a biopsy with <12 cores, this percentage decreased to 41.3%.

The retrospective nature is a limitation of our study, and therefore, further large-scale, prospective, multi-institutional trials are necessary for the verification of the clinical and pathological characteristics of the patients diagnosed with a single positive core PCa (4).

Conclusion

Single positive core disease tends to be a clinically significant cancer, with a considerable discrepancy rate between the pre- and postoperative GS. Although this difference was smaller in the single core group, it still remains considerable (44.9% discrepancy). Single positive core disease has a high potential for upgrading after a prostatectomy. These characteristics, including margin positivity, suggest that single positive core PCa should be analyzed individually and may be considered for treaty in the same manner as multiple positive core PCa, mainly when the biopsy included more than 12 cores.

Performing a biopsy with more than 12 cores significantly increased the concordance of the GS in those patients with a single positive core. Analyzing only the single core group, those patients with >12 cores has less positive surgical margins than those with <12 cores.

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