Single Positive Core Prostate Cancer at Biopsy: Clinicopathological Implications and Risk Factors for Adverse Pathological Outcomes

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Abstract

It is common for prostate cancer to be diagnosed by one single positive core in prostate biopsy, while the clinical significance remains unclear. In this study, we included 293 patients with single positive core prostate cancer and investigate the final pathological outcomes on radical prostatectomy. The results indicated that the single positive core prostate cancer should not be considered a low-risk disease.

Background: Whether one positive core prostate cancer (PCa) is a low-risk disease remains to be determined. We investigated the pathological results of radical prostatectomy specimens diagnosed on single core positive prostate biopsy. **Methods:** Between January 2013 and December 2019, A total of 3441 consecutive patients treated with radical prostatectomy in our institution were examined. Among them, 293 patients were diagnosed with single positive core PCa on biopsy, and the clinical parameters and pathological findings of their radical prostatectomy specimens were analyzed. **Results:** Of the 293 patients, 108 (36.9%) had undergraded Gleason Scores (GS) based on the biopsy. Positive surgical margins (PSMs), perineural invasion (PNI), extracapsular extension (ECE, pT3a) and seminal vesicle invasion (SVI, pT3b) were found in 16.4%, 15.0%, 3.4% and 2.4% of patients, respectively. In the multivariate analysis, we found that preoperative PSA level predict a significant increased risk of upgraded GS and PSMs, and biopsy GS was is a strong predictor of PNI, upgraded GS, tumor stage pT3 at radical prostatectomy. **Conclusions:** Single positive core PCa have clinically significance in the radical prostatectomy specimens, with considerable rates of undergrading for the GS, PNI, PSMs, ECE and SVI. For patients with single positive core PCa, other prognostic factors must be considered in the treatment plan.

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Keywords: Prostatic neoplasms, Prostate biopsy, Radical prostatectomy, Gleason score

Background

Prostate cancer (PCa) is one of the most common male malignancies worldwide, with an estimated 1,276,106 new cases and 358,989 deaths in 2018.[1] The widespread use of PSA screening has resulted in a steady increase in PCa diagnoses and stage migration over the past few decades, although its value remains controversial.[2] The treatment of localized PCa, including active surveillance (AS), radical prostatectomy (RP), or radiotherapy, is based on several clinicopathological factors such as patients age, PSA levels, preoperative MRI, Gleason score (GS) and clinical stage.[3]

Various studies have indicated that the percentage of positive biopsy cores in prostate biopsy was a powerful predictor of adverse clinical outcomes after RP.[4,5] It is common for tumors to be diagnosed by a single positive core in systemic biopsy and these patients are generally considered to have favorable clinical outcomes or even 'insignificant cancer', making them candidates for AS. However, several studies in Western countries have found that a single positive core cannot predict a small volume of tumor, and there may be more extensive disease in the final pathological evaluation of the RP specimens.[6,7] It is well known that the biological characteristics of PCa between Chinese and men from Western countries are different.[8] In view of the lack of consensus, we evaluate the pathologic results of RP in patients detected on a single positive biopsy, and identified preoperative clinical factors that could predict adverse pathological outcomes.

Methods

The study was a retrospective analysis and approved by the Clinical Research Ethics Committee of the First Affiliated Hospital,

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College of Medicine, Zhejiang University. All methods were carried out in accordance with relevant guidelines and regulations. We reviewed all patients who underwent RP at our institution from January 2013 to December 2019. A database of 3441 patients was screened for patients diagnosed with a single positive core in the prostate biopsy. The patients who received neoadjuvant hormonal therapy or radiotherapy or patients with stage pT0 cancer were excluded.

A total of 293 patients were included in the analysis. All men underwent transperineal systematic prostate biopsy with ten cores and were treat with open retropubic, laparoscopic (LRP), or robot-assisted laparoscopic radical prostatectomy by different surgeons. Lymph node dissection was selectively performed depending on the surgeon's discretion. The preoperative parameters including the patients' age, preoperative PSA level, clinical stage, biopsy GS, and the pathological data from the RP specimens including GS, surgical margin status, perineural invasion (PNI), extracapsular extension (ECE, pT3a) and seminal vesicle involvement (SVI, pT3b) were retrieved.

RP specimens were submitted for histopathological examination by two experienced pathologists at our institution. The Gleason score was determined according to the International Society of Urological Pathology 2014 consensus guidelines[9] and categorized into a five-grade group: grade group 1 (Gleason score = 6), grade group 2 (Gleason score 3 + 4 = 7), grade group 3 (Gleason score 4 + 3 = 7), grade group 4 (Gleason score 8), and grade group 5 (Gleason score 9-10). The discrepancy between the GSs from biopsy and RP specimens was analyzed and divided into undergrading (upgraded) and overgrading (downgraded) categories. The 2002 TNM classification system was used for staging PCa.[10]

The patients' characteristics are presented as frequencies (%) and means ± SD. The rates of concordance and discrepancy between the preoperative and postoperative GSs were evaluated with the kappa coefficient of agreement. Multivariate logistic regression model was constructed to determine whether patient age, preoperative PSA, biopsy GS and clinical stage were predictive of adverse pathological outcomes, including PNI, upgraded GS, PSMs and tumor stage ≥ pT3 in this study. All statistical analyses were performed using SPSS, version 24 (SPSS, Chicago, IL), with significance defined as $P < .05$.

Results

The characteristics of the 293 patients are presented in Table 1. Only two patients adopt an active surveillance strategy before surgery. It was noted that 17 patients (6.8%) had extraprostatic involvement, and 48 (16.4%) had positive margins even in the patients with one single positive core. No lymph node metastasis was observed. For the concordance between biopsy and RP specimen GSs, an exact match was observed for 49.4% of patients (n = 145); while 108 patients (36.9%) had an undergraded GS at biopsy; 40 (13.7%) had overgraded GS. The kappa-statistic measure of agreement between biopsy and RP specimens was poor (K = 0.247) (Figure 1).

Multivariate logistic regression model was used to analyzed the preoperative factors associated with adverse pathological factors. As shown in Table 2, preoperative serum PSA levels were positively associated with upgraded GS and PSMs, and increasing biopsy GS were associated with increased risk of PNI, extraprostatic involvement and decreased risk of upgraded GS in the RP specimen; Neither age nor clinical stage was predictive of adverse pathological outcomes.

Table 1 Characteristics of the Study Population

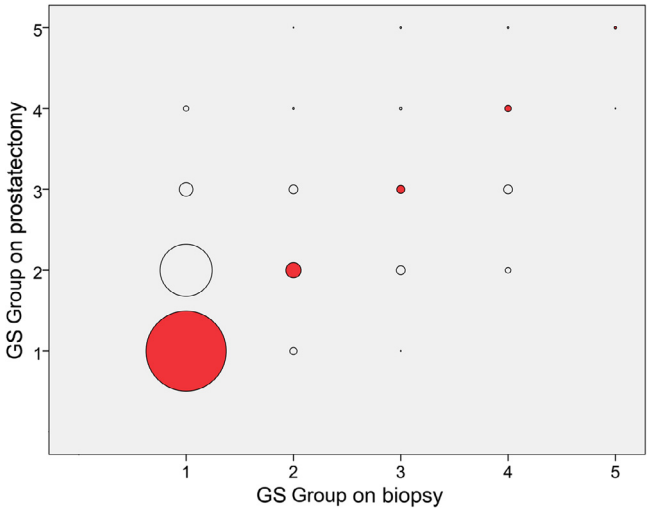
Variable	N (%)
Age (Mean ± SD, range)	66.7 ±7.2 (44-85)
PSA (Mean ± SD, range)	12.21 ± 9.43 (0.66-71.82)
Biopsy GS	
6	192 (65.5)
3 + 4 = 7	42 (14.3)
4 + 3 = 7	27 (9.2)
8	28 (9.6)
9	4 (1.4)
Clinical stage	
cT1	112 (38.2)
cT2	181 (61.8)
Surgical approach	
Open	85 (29.0)
LRP	81 (27.6)
Robotic-assisted LRP	127 (43.4)
RP specimens GS	
6	115 (39.2)
3+4=7	102 (34.8)
4+3=7	49 (16.7)
8	19 (6.5)
9	8 (2.7)
Pathological stage	
T2a-b	255 (87.0)
T2c	21 (7.2)
T3a	10 (3.4)
T3b	7 (2.4)
Positive margin	
Yes	48 (16.4)
No	245 (83.6)
Perineural invasion	
Yes	44 (15.0)
No	249 (85.0)
Comparison between GS of biopsy and RP specimen	
Upgrading	108 (36.9)
Concordant	145 (49.4)
Downgrading	40 (13.7)

Abbreviations: GS = Gleason score; LPR = laparoscopic radical prostatectomy; PSA = prostate-specific antigen

Discussion

The incidence of single positive core PCa seems to be increasing in the era of PSA screening,[11] however, the clinical significance

Figure 1 Concordance of Gleason scores (GS) between biopsy and radical prostatectomy (RP) specimen. Red filled circles represent concordant scores between biopsy and RP specimen; empty circles represent discordant scores. The size is proportional to the number of cases falling in each combination.



of this disease is still in debate. The single positive core PCa was initially considered to be low-risk disease, while several studies had shown that not all of these patients had clinically insignificant cancer in the final pathological evaluation of RP.[12-14] In a study by Thong et al,[14] 192 patients of PCa with a single minute focus (5% or less) of biopsy GS 6 were included, while 22% of the patients had adverse pathological outcomes (including upgrading in 18% and upstaging in 8%) after surgery. Another analysis of 503 Japanese patients with single positive core PCa showed that 258 (51.3%) had ≥ pT2c disease and 160 (32%) had an upgraded GS on their final pathology.[13] Our results also suggested that the patients with single positive core may not be ideal candidates for AS, as 36.9% had undergraded GSs, 16.4% had PSMs, 15.0% had PNI, 3.4% had ECE and 2.4% had SVI.

Previous studies have found that GS determined by the biopsy was upgraded on the pathologic specimen in 19% to 57% of patients.[15-17] The significant discrepancies of the GS between the biopsy and RP specimens might attribute to several factors, such as interobserver variability, the biopsy technique, and the number of biopsy cores. Considering that the GS is one of the most important prognostic factors for PCa, the frequency of GS upgrading has a significant impact on treatment options between AS and curative therapy, especially for the patients with well-differentiated adenocarcinoma diagnosed with single positive core PCa. Our results showed that 36.9% of cases were upgraded after prostatectomy, which was consistent with those published studies. In the multivariate analysis, serum PSA levels were positively associated with GS upgrading, indicating that the higher concordance between biopsy and RP analysis occurred when the patient had a low PSA level. While biopsy GS was a negative predictor of GS upgrading, which supported a cautious approach to categorizing single core positive PCa of GS 6 as insignificant cancer since these patients have a higher risk of higher-grade disease than suggested on initial biopsy.

ECE and SVI are associated with an increased risk of biochemical recurrence (BR) and PCa-specific death[18], and probably need for salvage therapy.[19] Previous studies have reported that upstaging can occur after RP even in single focus cancer.[14,20,21] Yamamoto et al[13] observed that of the 503 patients with a single positive core PCa, 159 (32%) had pathological findings ≥ pT3. Interestingly, this pT3 rate was significantly higher than that in the multiple positive core group (27%). In the present study, 7.2% of the patients became bilateral tumors, 6.8% upstaged to T3 stage, which is much lower than that reported previously. Despite the significant discordance of GS between the biopsy and RP specimens, higher biopsy GS predicted an increased risk of pT3 stage in the multivariate model. Chaux et al[22] also found that the single core biopsy GS ≥8 significantly increased the rate of ECE, PSMs, and SVI.

The presence of PSMs in RP specimen is considered a poor prognostic factor associated with biochemical recurrence-free survival[23], but its impact on overall survival is still controversial[24]. The rate of PSMs in patients with microfocal PCa ranged from 5% to 29%.[22,25] We similarly observed a positivity of 16.4% in our patients. In the multivariate model, preoperative PSA was the only independent predictor of PSMs in single positive core patients. However, the RP was performed by several surgeons, using open, laparoscopic or robotic surgical techniques, and the impact of surgeon variability on the incidence of PSMs should not be ignored,[26] which was not considered in the present study.

PNI is a very common pathological entity in RP specimen and an important mechanism of tumor progression through the prostatic capsule. The prognostic significance of PNI remains controversial. Some studies have shown that PNI does not predict BR,[27,28] while

Table 2 Multivariate Analysis of Potential Predictors of Adverse Pathological Outcomes

Risk factors	PNI		Upgraded GS		Positive margins		≥ pT3	
	OR (95%CI)	*P* value	OR (95%CI)	*P* value	OR (95%CI)	*P* value	OR (95%CI)	*P* value
Age (Continuous)	0.992 (0.948-1.038)	0.724	1.009 (0.975-1.045)	0.596	1.007 (0.963-1.052)	.769	0.955 (0.891-1.024)	.194
PSA (Continuous)	1.006 (0.973-1.040)	0.719	1.036 (1.006-1.066)	0.016	1.037 (1.009-1.066)	.010	1.015 (0.968-1.063)	.543
Biopsy GS (Categorical)	1.418 (1.087-1.850)	0.010	0.468 (0.338-0.648)	< 0.001	1.125 (0.854-1.483)	.403	1.731 (1.193-2.512)	.004
cT stage (Categorical)	1.530 (0.766-3.054)	0.228	1.340 (0.802-2.240)	0.264	1.184 (0.620-2.262)	.609	1.444 (0.491-4.248)	.505

Note: The Biopsy GS was categorized into a five-grade group: grade group 1 (Gleason score = 6), grade group 2 (Gleason score 3 + 4 = 7), grade group 3 (Gleason score 4 + 3 = 7), grade group 4 (Gleason score 8), and grade group 5 (Gleason score 9-10); the cT stage was categorized into cT1 and cT2.
Abbreviations: GS = Gleason score; LPR = laparoscopic radical prostatectomy; OR = odds ratio, PNI = Perineural invasion; PSA = prostate-specific antigen.

others showed that PNI is associated with an increased risk of BR in patients treated by RP.[29,30] In the literature, PNI has been observed in 31% to 74% of RP specimens,[31,32] while no study has reported the incidence of PNI in patients with single positive core. PNI was found in 15% of our cases, which is much lower than that of patients with multifocal PCa. Understandably, high biopsy GS was associated with a significantly increased risk of PNI in our study.

One strength of our study is the relatively large number of patients included. On the other hand, the main limitation is that the biopsy and RP specimens were examined by two pathologists in our institute, which may lead to interobserver variability, which is common in GS interpretation. In addition, the use of diagnostic multiparametric MRI, such as MRI-TRUS fusion biopsy and direct MRI-guided biopsy, has increased the detection rate of clinically significant PCa.[33] However, this technique, which may affect the results of the present study, is not available in our hospital. Finally, limited follow-up prevented a thorough examination of biochemical outcomes in patients who experienced upgrading and/or upstaging.

Conclusions

In conclusion, our results show that single positive core PCa should not considered as indolent disease as a certain proportion of them has malignant potential after prostatectomy. Further analysis is required to verify the clinical and pathological characteristics of patients diagnosed with single positive core and develop a nomogram to predict the probability of insignificant PCa.

Clinical Practice Points

- The widespread use of PSA screening has resulted in a steady increase in the overall proportion of patients diagnosed with single-core positivity on prostate biopsy, but the clinical significance hasn't yet been determined in Chinese men with PCa.
- We found that there was a greater than 1/3 risk of pathological upgrading in single positive core PCa, and it did not guarantee a favorable pathological outcome after RP.
- Patients with single positive core PCa may harbor more aggressive disease, and this information may prove valuable when counseling patients regarding outcomes and determining the necessity of definite treatment.

Disclosure

The authors declare no conflicts of interest in the publication of this study

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CRediT authorship contribution statement

Qiqi Mao: Conceptualization, Methodology, Investigation, Writing – original draft, Writing – review & editing. **Yiwei Lin:** Investigation, Writing – review & editing. **Dan Xia:** Formal analysis, Writing – review & editing. **Shuo Wang:** Writing – review & editing. **Hai Jiang:** Conceptualization, Methodology, Writing – review & editing.

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