Predictive Clinicopathologic Features and Prognostic assessment of pT0 prostate cancer: a case control study

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Abstract

Background: pT0 prostate cancer is relatively rare. We wanted to share and explore the predictive clinicopathological features and prognosis of biopsy-proven pT0 prostate cancer in Chinese population.

Methods: We retrospectively analyzed the clinicopathological and prognostic data of 8 patients with pT0 prostate cancer who received radical prostatectomy (RP) at our institution between 2006 and 2019. pT0 group was compared with a control group of 96 patients who underwent RP during the same period. Exclusion criteria included patients undergoing neoadjuvant hormone therapy or transurethral resection of the prostate (TURP) before the operation

Results: There were significant differences in the exposure rates of six clinicopathological features between two groups. Apart from finasteride use, the other five items were particularly frequent in the pT0 group: prostate-specific antigen (PSA) <10 ng/ml (7/8), one positive biopsy core only (7/8), biopsy Gleason score <7 (8/8), and prostate volume>40ml (7/8), length of biopsy positive for cancer≤2mm. When these five parameters were combined as predictive model, the sensitivity was 75%, the specificity was 99%. The 8 patients were followed up for an average of 67 months without biochemical recurrence or progression.

Conclusions: Preoperative PSA, number of positive biopsy core, Gleason score, prostate volume, and the length of cancer can help predict pT0 stage of prostate cancer. Patients with pT0 stage had a relatively favorable prognosis.

Background

The Prostate cancer is the most common malignancy in men, and radical prostatectomy(RP) is the standard surgical procedure[1]. In rare cases, patients diagnosed with prostate cancer by the histopathological examination of the previous biopsy have no tumor tissue in the specimens obtained at RP[2]. This phenomenon was defined as pT0 prostate cancer, with a prevalence of 0.2%-0.8%, which was first reported by Goldstein et al[3–5]. This is more common in patients who have received neoadjuvant endocrine therapy or transurethral resection of the prostate(TURP) before RP, but it can occur in addition to the above[2]. The absence of prostate cancer tissue in RP specimens presents challenges for clinicians and patients. Many studies[4–10] have described the clinicopathological features and prognosis of pT0 prostate cancer, and some studies[11–13] have proposed effective models for preoperative prediction of pT0 prostate cancer. However, these studies are all based on European and American populations, and there are no relevant reports based on Chinese or even Asian populations. Because the clinicopathological and epidemiological characteristics of prostate cancer patients in China are very different from those in Europe and the United States, the data on pT0 prostate cancer provided by existing studies cannot be extended to the Chinese population[14]. To compensate for this deficiency, we conducted this study to share and explore the clinicopathological features and prognosis of stage pT0 prostate cancer in the Chinese population and to propose a preoperative prediction model that can be used in the Chinese population.

Methods

Selection and inclusion of research objects

We selected 8 patients with pT0 prostate cancer in our hospital from 2006 to 2019 as the experimental group, and 96 patients with complete clinicopathological and prognostic data during the same period of surgery as the control group. All patients underwent RP and those who had received neoadjuvant endocrine therapy or TURP before surgery were excluded from the study. All patients were followed up regularly after RP surgery, and prognostic data were recorded. Biochemical recurrence was defined as two consecutive >0.2ng/ml.All patients received transrectal prostate ultrasound to measure prostate volume before prostate biopsy, and the calculation formula was : 0.52 × upper and lower diameter × anteroposterior diameter ×left and right diameter. All patients underwent transrectal ultrasound-guided prostate biopsy, which was performed by experienced ultrasonologists in our institution. Standard 12-needle needle biopsy was performed, and 1-3 more needles were added if patients had prostate nodules. Location of the puncture site was accurately recorded by the operator and fixed with 10% formaldehyde solution. All specimens were diagnosed by two pathologists and reviewed by each other.

Pathological section making and pathological diagnosis process

The RP specimen was fixed with 10% formaldehyde solution, the upper and lower broken end of the prostate was removed within 10mm, and the prostate tissue was removed layer by layer from the tip perpendicular to the urethra, with a thickness of 3mm. All sections were stained with Hematein Eosin(HE). The RP specimen was analyzed and pathologically diagnosed by two experienced pathologists. If the diagnosis is difficult, immunohistochemical analysis is performed. When no tumor tissue was found, the specimens were sectioned into thinner layers, and the corresponding biopsy specimens were re-analyzed to determine the preoperative pathological diagnosis. When the first pathologist diagnosed a specimen as pT0 prostate cancer, the second pathologist was required to confirm, and the pT0 prostate cancer specimen should be examined by at least two pathologists.

Statistical method

We used Stata software to statistically analyze the clinicopathological data and prognostic data of the two groups. In order to compare pT0 group with control group, we used chi-square test, Mann-Whitney test and student t test to conduct statistical analysis on qualitative, sequential and quantitative variables. P <0.05 was considered statistically significant. We developed a predictive model and verified its diagnostic efficacy by calculating sensitivity and specificity, positive predictive value and negative predictive value.

Results

Clinicopathological data of PT0 group

A total of 8 patients diagnosed with prostate cancer by preoperative prostate biopsy but no tumor tissue was found in the RP specimen were included in the pT0 group. Table 1 summarizes their clinicopathological features and prognostic data in detail. The mean age of the 8 patients at the time of RP was 69.1 year (range: 63–73). The clinical staging of the 7 patients was T1c, only 1 was T2a, the mean total PSA was 5.9 ng/ml (range: 2.7–11.4), and the mean prostate volume obtained by preoperative transrectal prostate ultrasound was 54.2 ml (range: 35.9–74.8). Gleason score of prostate biopsy was 5 in 1 case and 6 in others. Except for the presence of prostate nodules in 1 case, two needle biopsies were added, and the remaining 7 cases were standard 12-needle biopsy. The number of positive biopsy cores were 2 in only one patient, and 1 in all the other patients. The positive length of tumor biopsy in all patients was less than 2 mm. It is worth noting that half of the patients had been taking finasteride for a long time (More than three months) before the RP due to lower urinary tract symptoms.

Table 1
Clinicopathological features and follow-up data of 8 pT0 patients

Clinical data						**biopsies data**				**RP specimen data**	**Fo pr**
Patient	Age	Preoperative Finasteride(Y/N)	Clinical stage	tPSA	Prostate volume(ml)	Gleason score	P/T	Length of cancer(mm)	Location	HGPIN/ASAP	Fo up
1	69	Yes	T2a	11.4	68.9	6	2/14	1&1	Apical& nodule	ASAP&HGPIN	14
2	70	Yes	T1c	4.5	57.4	6	1/12	1	Middle	HGPIN	12
3	63	No	T1c	4.1	41.2	6	1/12	1	Apical	ASAP	11
4	72	No	T1c	4.2	43.2	6	1/12	1	Apical	HGPIN	82
5	70	Yes	T1c	2.7	74.8	6	1/12	1	unknown	BPH	66
6	64	No	T1c	4.3	35.9	5	1/12	1	Apical	ASAP	46
7	73	No	T1c	9.8	66.4	6	1/12	1	Posterolateral	HGPIN	38
8	72	Yes	T1c	6.6	45.7	6	1/12	2	left basal part	HGPIN	19

ASAP: atypical small acinar proliferation; HGPIN: high-grade prostatic intraepithelial neoplasia; BPH: benign prostate hyperplasia; P/T: number of positive bic number of biopsy cores; RP: radical prostatectomy.

All prostate biopsies corresponding to pT0 specimens were reviewed by a second pathologist, and all cases were reconfirmed with prostate cancer. RP specimens from these 8 patients were evaluated by more than two pathologists, with 5 diagnosed as high-grade prostatic intraepithelial neoplasia (HGPIN), 3 diagnosed as atypical small acinar proliferation (ASAP), and 1 diagnosed as benign prostatic hyperplasia (BPH). The 8 patients were followed up for an average of 67 months(range:16–143), and all survived without biochemical recurrence or progression.

Comparison of data between groups

A total of 96 patients with complete clinicopathological features and prognostic data were included in the control group for comparison with the pT0 group. Table 2 describes the comparison of clinicopathological data between pT0 group and control group. There was no significant difference in age (P = 0.76, Student t test) and positive rate of digital rectal examination (DRE) (P = 0.431, chi-square test) between the two groups. Notably, there was a statistically significant difference in the long-term use of finasteride between the two groups (50% vs 12.5%, P = 0.018, chi-square test). In the pT0 group, the median number of positive biopsy cores was significantly lower than the control group (1 vs 3, p = 0.027, Mann-Whitney test), and the cancer length of biopsy was also significantly lower than the control group (1.3 vs 6.2 mm, p = 0.014, Student t test). The mean preoperative PSA of the pT0 group was significantly lower than that of the control group (5.9 vs 14.3, P = 0.039, Student t test), Gleason score also tended to be lower(p = 0.012, Mann-Whitney test), but the mean preoperative prostate volumewas significantly larger than that of the control group(54.2 vs 29.2, P < 0.01, Student t test).

Table 2
Comparison between the pT0 group and the control group

	Mean value or rate (range and SD)		P value
	pT0 group (n = 8)	Control group (n = 96)	
Patient age (yr)	69.1(63–73, SD = 3.7)	68.3(54–82, SD = 6.8)	0.76
Abnormal DRE rate	12.5%	31.25%	0.431
PSA	5.9(2.7–11.4, SD = 3.1)	14.3(2.7–56.5, SD = 11.3)	0.039
Prostate volume(ml)	54.2(35.9–74.8, SD = 14.6)	29.2(12.1–74.8, SD = 12.3)	< 0.01
Long-term use finasteride	50%	12.5%	0.018
Gleason score on biopsy < 7/ = 7/>7	100%/0%/0%	52%/25%/23%	0.012
Median no. of positive cores	1(1–2)	3(1–12)	0.027
Length of biopsy positive for cancer(mm)	1.3(1–2, SD = 0.5)	6.2(1–34, SD = 5.6)	0.014
DRE: digital rectal examination; PSA, prostate-specific antigen.			

Predictive model and prognostic assessments

Apart from finasteride use, the other five items were particularly frequent in the pT0 group (Table 2). we defined a cutoff that was predictive of pT0 prostate cancer : prostate-specific antigen (PSA) < 10 ng/ml, one positive biopsy core only, biopsy Gleason score < 7, and prostate volume > 40 ml, length of biopsy positive for cancer ≤ 2 mm. When these five parameters were combined as a predictive model, only 2 of the 8 pT0 prostate cancer patients were misdiagnosed, and only 1 of the 97 control patients was misdiagnosed as pT0 prostate cancer, with a sensitivity of 75%, specificity of 99%, positive predictive value of 86%, and negative predictive value of 98% (Table 3).

Table 3
The predictive power of pT0 prostate cancer based on these five characteristics

	pT0 group	Control group	Total
5 characteristics combined	6	1	7
5 characteristics not combined	2	95	97
Total	8	96	104
Sensitivity:75% (2/8)	Specificity:99% (95/96)		
Positive predictive value:86% (6/7)	Negative predictive value:98% (95/97)		

The survival curve provided by kaplan-meier analysis showed that the pT0 group had better overall survival than the control group of 50 patients with Gleason score less than 7, although it was not statistically significant (Fig. 1, P = 0.091).

Discussion

Innovation and clinical application value

To our knowledge, this study is the first to report the clinicopathological characteristics and prognostic data of pT0 prostate cancer patients in a Chinese population and to propose an effective predictive model. Compared with previous study based on the French population, we found that in addition to the number of positive biopsy cores (P = 0.027), the length of biopsy positive for cancer (P = 0.014) and Gleason score on biopsy (P = 0.012), there were also statistically significant differences in preoperative PSA (P = 0.039), prostate volume (P < 0.01) and the long-term use of finasteride (P = 0.018) between the pT0 group and the control group based on the Chinese population[13]. Based on the above characteristics, we can define some predictive factors: prostate-specific antigen (PSA) < 10 ng/ml, one positive biopsy core only, biopsy Gleason score < 7, and prostate volume > 40 ml, length of biopsy positive for cancer ≤ 2 mm. When these parameters are combined, the sensitivity is 75%, the specificity is 99%, the positive predictive value is 86%, and the negative predictive value is 98%, which means that at least 4/5 of the patients who meet all the five parameters have stage pT0 prostate cancer, and the patients who do not meet all the five parameters almost never have pT0 prostate cancer. Combined with the high specificity of the model, the risk of missing out on high-risk prostate cancer would be small if the model was used for prediction. Several current studies have also found that pT0 prostate cancer has a good prognosis, and although the small risk of recurrence and progression cannot be ignored, it is superior to some low-risk prostate cancers that can be recommended for active surveillance[6, 13]. Some scholars have also pointed out that the emergence of pT0 prostate cancer may be an overtreatment[15, 16]. Our predictive model may play a role in reducing excessive care when it is validated in large sample studies.

Possible mechanism of PT0 prostate cancer

The absence of prostate cancer tissue in the RP specimen was more common in patients who had received neoadjuvant endocrine therapy before surgery and who had been diagnosed with prostate cancer by TURP. Previous literature has reported that after neoadjuvant endocrine therapy, 2.5–24.2% of patients had no prostate cancer in postoperative specimens[17–19]. This condition may be caused by the effect of neoadjuvant endocrine therapy or by the removal of tumor tissue by TURP[19]. In addition to the above two cases, there are still cases where prostate cancer tissues cannot be found in the tissue samples obtained by RP, which is defined as pT0[2]. In order to explore the clinicopathological features of pT0 stage prostate cancer, all patients involved in this study had not received neoadjuvant endocrine therapy or TURP before RP, thus ensuring the reliability of the results.

After the exclusion of relevant therapeutic factors, four mechanisms have been proposed to explain the occurrence of pT0 prostate cancer. The first mechanism is that the prostate cancer lesion is removed from the prostate as a whole during the biopsy. The second mechanism is the false positive in the preoperative prostate biopsy, which may be caused by the pathologist's misdiagnosis. In our study, this mechanism has been largely disproved, as each RP specimen diagnosed with pT0 had a prostate biopsy specimen repeatedly confirmed by another experienced pathologist. The third mechanism is also the most widely recognized at present, that is, there is a possibility of false negative in the pathological diagnosis of postoperative prostate tissue, which is related to the interval between sections and the influence of inflammatory reaction on the diagnosis. The study of Kollermann et al.[16] found that prostate cancer foci less than 0.2 mm were found in 13 cases after thinner slice of pathological specimens of 20 patients initially diagnosed with pT0. Bream et al.[20] also reported that tumor tissue was found in two of the four patients previously diagnosed with pT0 after re-examination by experienced pathologists. In our study, 8 samples with no tumor tissue were confirmed by supplementary sections at intervals of 1 mm and cross-checked by two pathologists. The last mechanism proposed the possibility that biopsy tissue and pathological tissue could not be the same patient in theory. Some scholars proposed that before the diagnosis of pT0 prostate cancer, tissue DNA should be compared to confirm that the specimen originated from the same patient[21]. In addition, the prostate volume of the pT0 group was significantly larger than that of the control group in our study, and it may be that the large prostate volume is one of the factors that increase the difficulty in finding prostate cancer tissues. Finally, it is worth noting that half of the patients in the pT0 group were taking finasteride for a long period of time before surgery. Although studies have suggested that finasteride has a chemoprevention effect on low-grade prostate cancer, the association with the presence of stage pT0 prostate cancer is unknown[22].

Prognosis assessment and outlook

In our study, 8 patients with stage pT0 prostate cancer showed good prognosis at a mean follow-up of 67 months, with no progression or biochemical recurrence. Although some scholars pointed out that the risk of recurrence and progression should not be ignored, but with the improvement of prediction model and the collection of large sample survival data, preoperative prediction and active monitoring of pT0 prostate cancer may be a good direction to reduce overtreatment[2].

Conclusions

According to our experience, preoperative PSA, number of positive biopsy core, Gleason score, prostate volume, and the length of cancer can help predict pT0 stage of prostate cancer in the Chinese population. Patients with pT0 stage had a relatively favorable prognosis.

Abbreviations

RP: radical prostatectomy; TURP: transurethral resection of the prostate; HE: hematein eosin; HGPIN: high-grade prostatic intraepithelial neoplasia; ASAP: atypical small acinar proliferation; BPH: benign prostatic hyperplasia; DRE: digital rectal examination

Declarations

Ethics approval and consent to participate

Our study was approved by Medical Ethics Committee of the First Affiliated Hospital of Soochow University. The ethics examination and approval number is 2020 Ethics Batch Number 117. All participants in this study signed a consent form in person or by a close relative, agreeing in writing to use their clinicopathological data for this study.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

JX participated in study design, data collection, statistical analysis and as a major contributor completed the writing and submission of papers. CW participated in the study design, data statistics and the writing and polishing of the article with the first author. CW has made the same contribution as JX as co-first author. JO and JZ proposed the research hypothesis, provided the clinical data needed for the study, and coordinated the overall situation. ZX participated in data collection and was responsible for docking with professors of pathology.

All authors read and approved the final manuscript

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Figures

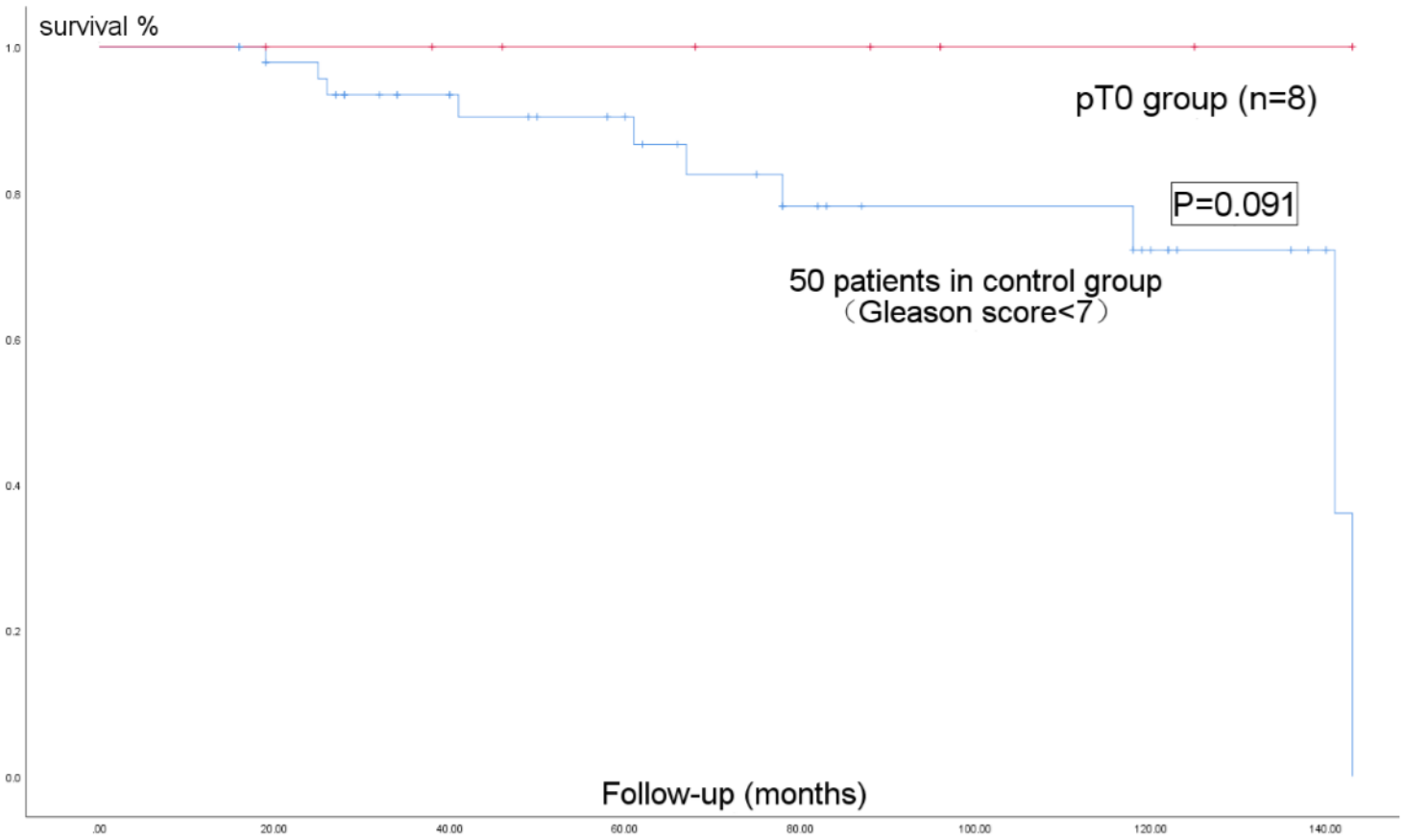

Figure 1

Kaplan-Meir plot for comparing the total survival of pT0 group (n = 8) and that of patients with Gleason score <7 in the control group (n=50)