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The prognostic value of zonal origin and extraprostatic extension of prostate cancer for biochemical recurrence after radical prostatectomy

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Abstract

Objective: To investigate the influence of the zonal origin of prostate cancer and extraprostatic extension on biochemical recurrence (BCR).

Patients and methods: We included 638 consecutive patients undergoing radical prostatectomy between 2005 and 2015 who did not receive neoadjuvant/adjuvant therapy. The largest lesion was defined as the index tumor. We categorized each patient into the transition zone (TZ) or peripheral zone (PZ) group based on the lesion where the index tumor existed. Differences in the BCR defined as increasing prostate-specific antigen rate between groups were examined by Kaplan-Meier analysis and the Cox proportional hazards model.

Results: There were 293 (46%) patients with TZ cancer and 345 (54%) with PZ cancer. TZ cancer was significantly associated with a higher prostate-specific antigen (P = 0.012), lower biopsy positive core rate (P = 0.020), lower pathological Gleason score (P = 0.017), lower pathological stage (P = 0.002), and lower rate of seminal vesicle invasion (P = 0.002). During a median follow-up period of 59 months, 79 patients (12%) developed BCR. In the entire cohort, the PZ origin (hazard ratio: 1.68, P = 0.033) and extraprostatic extension were independent risk factors for BCR. The 3-, 5-, and 7-year BCR-free survival rates of patients with pT3a TZ cancer were 89%, 88%, and 86%, respectively, which were significantly better than those of patients with pT3a PZ cancer (80%, 74%, and 62%, P = 0.012), but were similar to those of the pT2 cancer cohort (92%, 91%, and 90%, P = 0.376).

Conclusion: TZ cancer had more favorable pathological characteristics and oncological outcome than PZ cancer especially in pT3a cases.

Keywords: Radical prostatectomy; Prostate-specific antigen; Prostatic-neoplasm; Neoplasm staging; Biochemical recurrence

1. Introduction

Prostatic glands can be divided into 3 differential anatomical areas: the transition zone (TZ), peripheral zone (PZ), and central zone, as reported by McNeal et al. [1] Among all prostate cancer, the TZ comprises approximately 20% [2]. Prior reports suggested that TZ cancer is more difficult to diagnose by digital rectal examination and transrectal biopsies, and thus, TZ cancer was reported to have a higher prostate-specific antigen (PSA) and larger tumor volume than PZ cancer [2–4]. However, TZ cancer was also reported to be associated with a lower Gleason score (GS) and lower pathological stage. Genetic differences may be 1 reason for the lower recurrence risk of TZ cancer. By molecular investigation, TMPRSS2-ERG gene rearrangement and the expression of Ki-67, MMP-2, MMP-9, p53, and Bcl-2 were less observed in TZ cancer [5].

Extraprostatic extension (EPE, pathological T3a) is one of the most important risk factors for disease recurrence. Although more than 30% of prostate cancer patients with EPE develop subsequent biochemical recurrence (BCR) 7

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to 10 years after radical prostatectomy (RP) [6], the difference in impact of zonal origin on BCR between patients with non-EPE (pT2) and EPE (pT3a) is still unknown. Therefore, in this study we investigated the influence of the zonal origin on BCR in each subgroup of pT2 and pT3a and evaluated the differences.

2. Patients and methods

We reviewed 955 patients undergoing RP with curative intent at our institution for clinical T1-3 (cT1-3) prostate cancers between 2005 and 2015. We excluded 309 patients who received neoadjuvant/adjuvant treatment, including androgen deprivation therapy and radiotherapy, and 8 patients because of data lacking. A total of 638 patients were included in this study (Fig. 1). This study was approved by the Keio University Research Ethics Committee and was in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Prostate cancer was histologically diagnosed before the operation by transrectal ultrasonography guided needle biopsy.

All RP specimens were fixed in formalin for 24 hours and covered with ink. The specimen was cut in 4-mm sections perpendicular to the urethra from the apex to the base after removing seminal vesicle. Apical and bladder neck sections were cut radially. The slides were stained with hematoxylin and eosin. Each section was examined for cancer location and EPE. EPE was diagnosed when cancer cells were observed in the adipose tissue layer around the prostate "capsule." We regarded tumor at an inked margin as a positive surgical margin. In addition to standard evaluation of the pathological diagnosis, we defined the index tumor as the largest cancer when there were several masses, and the zonal origin (TZ or PZ) of prostate cancer was defined according to the zone containing more than half of the index tumor [5,7]. All patients were assessed by serum PSA after RP. BCR was defined as elevation of PSA to >0.2 ng/ml. In our cohort, 16 patients had a nadir PSA of greater than 0.2 ng/ml after RP, and we considered their BCR at the timing of RP in this study.

Clinical parameters, including age, body mass index (BMI), serum PSA level, biopsy positive core rate, biopsy GS, and cT stage, and pathological parameters, including prostate volume, maximum tumor diameter, pathological GS, pathological T (pT) stage, surgical margin status, and zonal origin of prostate cancer, were assessed.

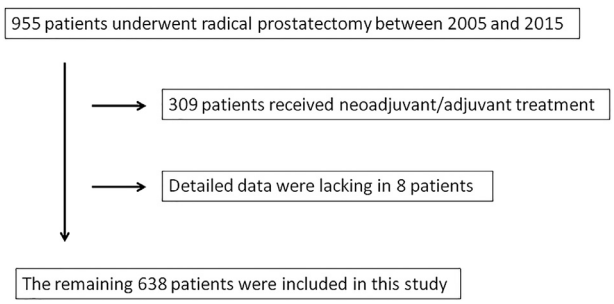

Figure 1. After excluding those who did not fulfill the inclusion criteria, 638 patients were eligible for this study.

Differences between groups were evaluated using the *t* test and X^2-test for categorical indices. The Kaplan-Meier method was used to estimate the BCR, and the log-rank test was used to assess significance. Cox proportional hazard regression models were used for univariate and multivariate analyses to clarify the risk factor for BCR. For statistical analysis, these indices were divided into 2 groups: age (<70 and ≥70 years), BMI (<25 and ≥25 kg/m^2), GS (≤3 + 4 and ≥4 + 3 including the presence of pattern 5), serum PSA level (<10 and ≥10 ng/ml), prostate volume (<30 and ≥30 cm^3), and maximum tumor diameter (<1.4 and ≥1.4 cm). Statistical analysis was performed by SPSS version 25.0 (IBM-SPSS Inc., Tokyo, japan) and *P* values less than 0.05 were judged as significant.

3. Results

3.1. Clinicopathological comparison between TZ and PZ cancer

Of the 638 specimens, the median follow-up was 59 (6−123) months and the median age was 65 years old. In total, 351 (55%) patients underwent lymph node dissection, and the median number of nodes resected was 7 (range: 1−24). A total of 293 (46%) patients had TZ origin tumor. On comparison of tumor origin groups (TZ vs. PZ), there was no significant difference in age, BMI, biopsy GS, or clinical T stage.

Regarding pathological features, patients with TZ cancer had a lower GS (GS 3 + 4 or lower: 51% vs. 41%, $P = 0.017$) and a larger index tumor (1.4 cm or greater: 61% vs. 49%, $P = 0.007$) than patients with PZ cancer. Furthermore, patients with TZ cancer had a lower pT stage than those with PZ cancer ($P = 0.002$). As expected, the TZ cancer group had a lower rate of seminal vesicle invasion than the PZ cancer group (2% vs. 7%, $P = 0.002$). In the TZ cancer group, all seminal vesicle invasions were observed in different lesions from the index TZ tumor. There were no significant differences in the multiplicity of tumors (54% vs. 61%, $P = 0.921$), the proportion of positive lymph nodes (1% vs. 3%, $P = 0.168$), and surgical margin status (37% vs. 42%, $P = 0.218$) between TZ and PZ groups (Table 1).

3.2. The clinical impact of the location of the index tumor on BCR

During the follow-up, 26 patients (9%) in TZ cancer group and 53 patients (15%) in the PZ cancer group developed BCR. The median times to BCR were 1.7 years (1.0−2.5), and 1.1 years (0.4−1.9) in the TZ and PZ groups, respectively. The Kaplan-Meier curve demonstrated that

Table 1
Clinicopathological features of 638 patients with transition zone vs. peripheral zone origin tumors

No. of patients (%)	Whole cohort 638	TZ origin tumor 293 (46)	PZ origin tumor 345 (54)	*P* value (Pz vs. Tz)
Preoperative characteristics				
Age, median (range)	65 (43−78)	66 (48−75)	65 (43−78)	0.591[a]
BMI, median (range)	23.3 (15.2−37.7)	23.5 (13.2−37.7)	23.2 (14.5−31.1)	0.282[a]
Preoperative PSA (ng/ml), median (range) (%)	6.7 (1.5−29.5)	7.0 (3.0−29.5)	6.5 (1.5−24.1)	0.012[a]
>10	513 (80)	221 (75)	292 (84)	0.004
≥10	125 (20)	72 (25)	53 (15)	
Number of biopsy cores, median (range)	10 (6−30)	10 (6−30)	10 (6−22)	0.355[a]
Biopsy positive core rate (%), mean (s.d.)	25.8 (18)	23.4 (18)	27.8 (18)	0.020[a]
Biopsy Gleason score (%)				0.266[b]
≤6	235 (37)	126 (43)	109 (32)	
3 + 4	206 (32)	83 (28)	123 (36)	
4 + 3	134 (21)	65 (22)	69 (20)	
≥8	63 (10)	19 (7)	44 (13)	
Clinical T stage (%)				0.170[c]
cT1c	178 (28)	74 (25)	104 (30)	
cT2	447 (70)	214 (73)	233 (68)	
cT3	13 (2)	5 (2)	8 (2)	
Pathological features				
Prostate volume, mean, ml (range)	32.2 (7−106)	33.7 (7−101)	30.9 (12−106)	0.724[a]
Index tumor diameter, mean, cm (range) (%)	1.4 (0.1−3.8)	1.6 (0.2−3.7)	1.3 (0.1−3.8)	0.358[a]
>1.4	348 (54)	177 (61)	171 (49)	0.007
≤1.4	290 (46)	116 (39)	174 (51)	
Number or tumors				0.921
solitary	268 (42)	134 (46)	134 (39)	
multiple	370 (54)	159 (54)	211 (61)	
Pathological Gleason score (%)				0.017[b]
≤6	71 (11)	40 (14)	31 (9)	
3 + 4	218 (34)	108 (37)	110 (32)	
4 + 3	253 (40)	115 (39)	138 (40)	
≥8	96 (15)	30 (10)	66 (19)	
Pathological T stage				0.002[d]
T2	434 (68)	219 (75)	215 (62)	
T3a	180 (28)	68 (23)	112 (33)	
T3b	23 (4)	5 (2)	18 (5)	
T4	1 (0)	0 (0)	1 (0)	
Seminal vesicle invasion	29 (5)	5 (2)	24 (7)	0.002
Lymph nodes				0.168[e]
positive	13 (2)	3 (1)	10 (3)	
negative	338 (53)	146 (50)	192 (56)	
not determined	287 (45)	144 (49)	143 (41)	
Positive surgical margin	252 (40)	107 (37)	145 (42)	0.218

BMI = body mass index; EPE = extraprostatic extension; PSA = prostate-specific antigen; PZ = peripheral zone; TZ = transition zone.
[a] student's *t* test.
[b] 4 + 3 and more vs. 3 + 4 and less.
[c] cT2 and 3 vs. cT1c.
[d] pT3 and 4 vs. pT2.
[e] positive vs. negative.

the TZ cancer group had a significantly higher BCR-free survival rate than the PZ cancer group (P = 0.017), as shown in Fig. 2. The 3-, 5-, and 7-year BCR-free survival rates were 92%, 91%, and 88%, respectively, in the TZ cancer group, and 88%, 84%, and 80%, respectively, in the PZ cancer group. Univariate analysis indicated that a higher PSA at diagnosis ($P < 0.001$), higher pT stage ($P < 0.001$), higher pathological GS ($P < 0.001$), and PZ origin ($P = 0.012$) were related to BCR. Multivariate analysis revealed that a higher PSA (hazard ratio (HR): 2.56, $P = 0.001$), pT3 (HR: 1.82, $P = 0.010$), GS 4 + 3 or more (HR: 3.03, $P < 0.001$), and PZ origin (HR: 1.68, $P = 0.033$) were independent prognostic factors for BCR (Table 2).

3.3. The impact of the zonal origin of prostate cancer on BCR in the pT3a subgroup

Next, we performed subgroup analyses for pT2 and pT3a. In the pT3a subgroup, patients with TZ cancer had significantly larger tumors ($P = 0.004$) of a higher

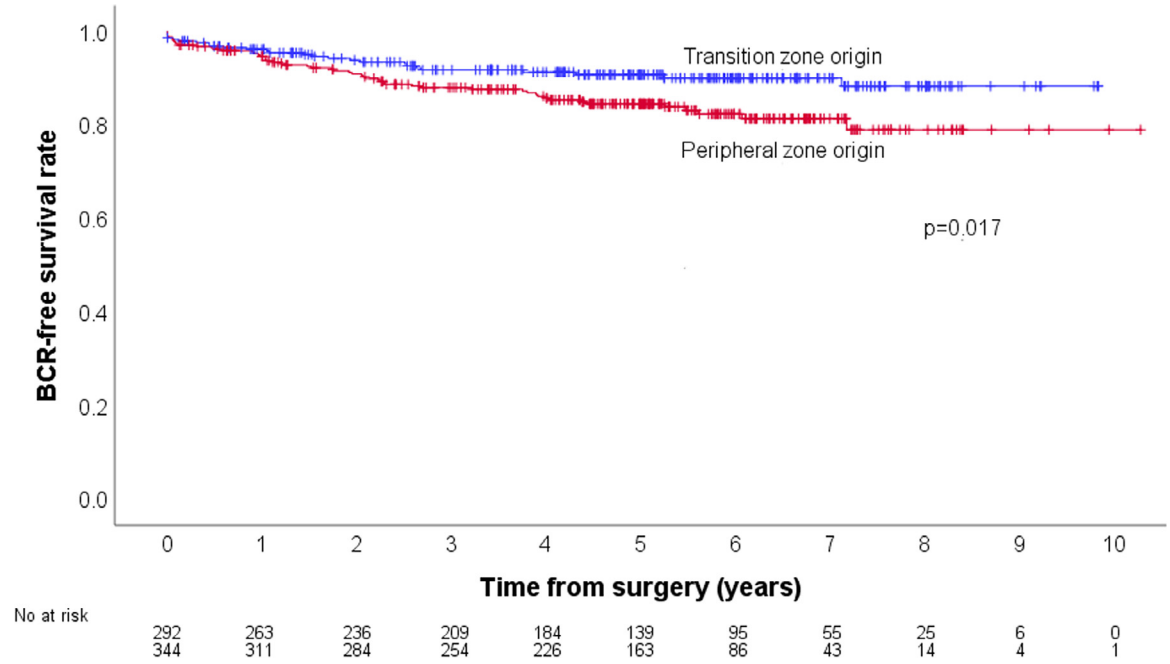

Figure 2. Kaplan-Meier analysis of the biochemical recurrence-free survival of patients who received radical prostatectomy divided by the zonal origin of the index tumor. The biochemical recurrence-free survival rate was significantly higher in the TZ cancer group than in the PZ cancer group.

pathological grade ($P = 0.017$; Table 3). However, patients in the pT3a TZ cancer group had a better BCR-free survival rate than those with pT3a PZ cancer ($P = 0.012$; Fig. 3). On the other hand, in the pT2 subgroup, no differences in BCR were observed between the TZ and PZ cancer groups ($P = 0.702$).

In the pT3a subgroup, a higher initial PSA ($P < 0.001$), higher pathological GS ($P = 0.009$), positive surgical margin ($P < 0.001$), and PZ origin ($P = 0.028$) were found to be associated with BCR on univariate analysis. Multivariate analysis revealed that a higher initial PSA (HR: 2.32, $P < 0.001$), higher pathological GS (HR: 2.61, $P = 0.033$), and PZ origin (HR: 2.57, $P = 0.028$) were independent predictive factors for BCR (Table 4).

In the pT3a subgroup, the 3-, 5-, and 7-year BCR-free survival rates in patients with TZ cancer were 89%, 88%, and 86%, respectively, which were significantly better than those of patients with PZ cancer (80%, 74%, and 62%, $P = 0.012$), but were similar to rates of the pT2 cancer cohort (92%, 91%, and 90%, $P = 0.376$; Fig. 3).

4. Discussion

The definition of the tumor location in the prostate is not uniform. In this study, we followed previous reports that proposed the definition of TZ tumors as more than 50% of the "index tumor," which is the largest of several lesions, existing in the TZ [7,8]. In our cohort, 293 consecutive patients (46%) had TZ index tumors. In general, anterior or TZ prostate cancer in Western men comprises 10% to 20% [1,2,7,9]. On the other hand, recent studies from Japan reported that almost half of prostate cancers are located in the TZ [4,10], although it is unknown whether this reflects a difference in geographic prevalence or in the background

Table 2
Univariate and multivariable Cox regression analyses of clinicopathological indices in 638 patients for biochemical recurrence

	Univariate	Multivariate		
	P value	HR	95% CI	*P* value
Age (≥70 vs. <70 years)	0.786			
BMI (≥25 vs. <25 kg/m^2)	0.241			
PSA at diagnosis (≥10 vs. <10 ng/ml)	**<0.001**	**2.56**	**1.60** **4.08**	**<0.001**
Maximum tumor diameter (≥1.4 vs. <1.4 cm)	0.409			
Pathological T stage (pT3 vs. pT2)	**<0.001**	**1.82**	**1.16** **2.85**	**0.010**
Pathological Gleason's score (≥4 + 3 vs. ≤3 + 4)	**<0.001**	**3.03**	**1.73** **5.30**	**<0.001**
Positive lymph node (positive vs. negative)	0.631			
Location of the index tumor (Pz vs. Tz)	**0.012**	**1.68**	**1.04** **2.71**	**0.033**

BMI = body mass index; CI = confidence interval; HR = hazard ratio; PSA = prostate-specific antigen; PZ = peripheral zone; TZ = transition zone.

Table 3
Clinicopathological features of pT3a patients with transition zone vs. peripheral zone origin tumors

No. of patients (%)	Whole cohort 180	TZ origin tumor 68 (38)	PZ origin tumor 112 (62)	*P* value (Pz vs. Tz)
Preoperative characteristics				
Age, median (range)	66 (43−76)	66 (50−75)	67 (43−76)	0.618[a]
BMI, median (range)	23.3 (13.2−30.9)	23.7 (13.2−30.9)	23.2 (14.5−30.1)	0.067[a]
Preoperative PSA (ng/ml), median (range) (%)	7.14 (0.5−29.5)	7.42 (4.2−29.5)	7.02 (0.5−24.1)	0.847[a]
>10	37 (21)	17 (25)	20 (18)	0.228
≤10	143 (79)	51 (75)	92 (82)	
Number of biopsy cores, median (range)	10 (6−22)	10 (6−20)	10 (6−22)	0.185[a]
Biopsy positive core rate (%), mean (s.d.)	33.3 (18)	33.3 (23)	35.1 (19)	0.926[a]
Biopsy Gleason score (%)				0.450[b]
≤6	54 (30)	22 (32)	32 (29)	
3 + 4	64 (36)	25 (37)	39 (35)	
4 + 3	39 (22)	15 (22)	24 (21)	
≥8	23 (13)	6 (9)	17 (15)	
Clinical T stage (%)				0.371[c]
cT1c	46 (26)	15 (22)	31 (28)	
cT2	124 (69)	49 (72)	75 (67)	
cT3	10 (6)	4 (6)	6 (5)	
Pathological features				
Prostate volume, mean, ml (range)	33.9 (7−106)	32.3 (7−101)	30.4 (12−106)	0.892[a]
Index tumor diameter, mean, cm (range) (%)	1.6 (0.1−3.8)	1.8 (0.2−3.7)	1.5 (0.1−3.8)	0.004[a]
>1.4	138 (77)	58 (85)	80 (71)	0.051
≤1.4	42 (23)	10 (15)	32 (29)	
Number or tumors				0.150
solitary	61 (34)	28 (41)	33 (29.5)	
multiple	119 (66)	40 (59)	79 (70.5)	
Pathological Gleason score (%)				0.017[b]
≤6	8 (4)	1 (2)	7 (6)	
3 + 4	46 (26)	16 (24)	30 (27)	
4 + 3	94 (52)	41 (60)	53 (47)	
≥8	32 (18)	10 (15)	22 (20)	
Lymph nodes				0.699[d]
positive	3 (2)	2 (3)	1 (1)	
negative	101 (56)	37 (54)	64 (57)	
not determined	76 (42)	29 (43)	47 (42)	
Positive lymph nodes (%)	3 (2)	2 (1)	1 (1)	0.681
Positive surgical margin (%)	150 (83)	58 (85)	92 (82)	0.439

BMI = body mass index; PSA = prostate-specific antigen.
[a] Student's *t* test.
[b] 4 + 3 and more vs. 3 + 4 and less.
[c] cT2 and 3 vs. cT1.
[d] positive vs. negative.

of prostate cancer screening. Consequently, we could investigate the prognostic impact of tumor location on oncological outcome with the largest cohort of TZ cancer in Japan.

There have been several reports on the clinicopathological features of anterior (TZ) tumors, and they noted the potential for delay in diagnosis due to difficulty in detection by transrectal biopsies [2−4,9−15]. We found that the TZ cancer group had a higher initial PSA level and a larger index tumor than the PZ cancer group despite a lower pathological GS and less pT3 disease, which was consistent with previous reports [3,9].

A few previous studies reported that TZ cancer had a better oncological outcome than PZ cancer [5,12,16]. These previous studies demonstrated that cancer originating in the PZ has a 1.6 to 1.7-times higher risk of BCR than that originating in the TZ [5,12,16], which is similar with our results (HR: 1.68). Teloken et al. found that TZ tumor origin independently and positively affects BCR, especially in patients with high-grade cancer [16]. In this study, PZ origin was an independent risk factor for BCR, as well as common prognostic factors, including higher preoperative PSA, higher pathological GS, and positive surgical margin. The new finding of this study is that the zonal origin had a strong prognostic impact on BCR, especially in the pT3a subgroup. The BCR rate in patients with pT3a TZ cancer was similar to that of the pT2 cohort. Therefore, the zonal origin of prostate cancer can be used to divide pT3a patients into 2 subgroups and help predict their prognosis more accurately. These results may aid urologists in providing more correct patient counseling and be used for clinical

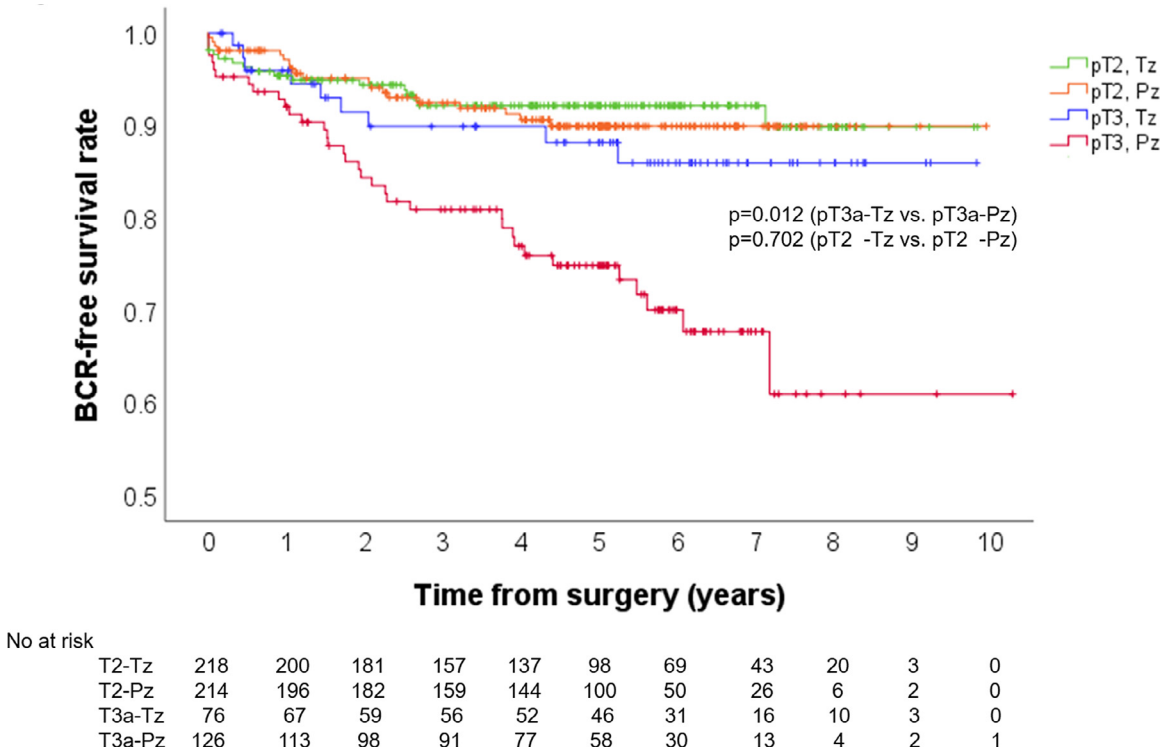

Figure 3. Kaplan-Meier analysis according to the pathological T stage and zonal origin of the index tumor. The biochemical recurrence-free survival in the pT3a TZ cancer group was significantly higher than that in the pT3a PZ group, but was similar to that of pT2 prostate cancer patients.

Table 4
Univariate and multivariable Cox regression analyses of clinicopathological indices in pT3a patients for biochemical recurrence

	Univariate	Multivariate			
	P value	HR	95% CI		*P* value
Age (≥70 vs. <70 years)	0.816				
BMI (≥25 vs. <25 kg/m^2)	0.175				
PSA at diagnosis (≥10 vs. <10 ng/ml)	**<0.001**	**2.32**	**1.13**	**4.78**	**<0.001**
Maximum tumor diameter (≥1.4 vs. <1.4 cm)	0.491				
Pathological Gleason's score (≥4 + 3 vs. ≤3 + 4)	**0.009**	**2.61**	**1.08**	**6.30**	**0.033**
Surgical margin (positive vs. negative)	<0.001		Removed		
Location of the index tumor (Pz vs. Tz)	**0.028**	**2.57**	**1.16**	**5.68**	**0.028**

BMI = body mass index; CI = confidence interval; HR = hazard ratio; PSA = prostate-specific antigen; PZ = peripheral zone; TZ = transition zone.

decision-making when selecting appropriate follow-up schedule and treatment.

We hypothesize 2 reasons for why TZ cancer has less aggressive characteristics. First, the anterior fibromuscular stroma, which can be considered as a thickening of the prostatic "capsule," may act as a barrier to cancer spreading [17]. Another is that PZ cancer can easily invade the perineural space and neurovascular bundle, which have traditionally been regarded as having a low resistance to tumor invasion [18]. Ejaculatory ducts, which are located on the central zone (posterior side), may be another path for PZ tumor invasion into the seminal vesicle and outside the prostate [19].

Limitations of this study include its retrospective setting, patient selection bias, and single institutional bias. We did not examine the extent of EPE, which was reported to be associated with the prognosis of pT3 prostate cancer [20]. External validation with an independent data set consisting of sufficient patients is needed to confirm whether the zonal origin of prostate cancer can be used to predict the prognosis of localized prostate cancer patients.

5. Conclusion

Our results indicate that TZ cancer has more favorable pathological characteristics and oncological outcome than

PZ cancer. The BCR risk in pT3a TZ cancer patients was similar to that in pT2 patients. These results may help urologists provide more correct patient counseling and be used for clinical decision-making when selecting treatment.

Conflict of interests

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.urolonc.2019.03.012.

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