Abstract

Prostate cancer of transition zone origin or anterior location has been recognized as infrequent, smaller in size and indolent. Whereas, our previously report showed that transition zone/anterior cancer was frequently experienced in Japanese men. The current study was conducted to show clinicopathological characteristics of transition zone/anterior cancer. A total of 201 radical prostatectomy specimens were categorized as cancer of anterior, posterior under the criteria as more than 2/3 of the tumor's existence in the certain area. Clinicopathological characteristics including Gleason score, pathological stage, lymph node metastasis, extraprostatic extension, surgical incision into the prostate (shown as pT2+), and surgical margin status were compared between anterior and posterior cases. Cases were divided as 83, 73, and 45 of anterior, posterior cancer, and no dominancy, respectively. Anterior cancers included significant numbers of high grade tumors (13/83 cases: 15.7%), although the incidence was less than posterior cancers (28.8%: 21/73). The cases in pT2+ were significantly frequent in anterior cases than posterior ones (22.9% vs. 4.1%). No seminal vesicle invasion was shown in anterior cases. Thus, although anterior cancers are less aggressive than posterior cancers, a significant numbers of clinically important cancers were located in the anterior portion in Japanese men.

Key words:

Gleason score, prostate cancer, surgical pathology, transition zone, tumor location

Introduction

Prostate cancer is the second most common malignancy and fifth leading cause of cancer death among men worldwide in 2013[1]. Incidence rate of prostate cancer varies extremely among regions and countries. For example, the incidence rate is 25 times higher in Australia and New Zealand when compared to South-Central Asia. Eastern Asia, including Japan, is the second lowest region of the incidence, although the number of patients has risen rapidly and continuously. The incidence rate of prostate cancer among Japanese men drastically increased to 37.9/1,000,000 in 2010 from 4.6/1,000,000 in 1975[1, 2].

It is crucial to recognize cancer location in the prostate when determining treatment strategy. Thought to be common knowledge, we have understood that prostate cancer arises in the peripheral zone in a majority of the cases; while the incidence of the cancer at the transition zone is rather low[3, 4]. Accordingly, the trans-rectal approach has been a common method for prostate biopsy in current practice for patient care.

Prostate cancer of transition zone origin or anterior location has been investigated and the data mostly originates from Western countries. According to these studies, the anterior cancer constituted only 10 to 30% of all prostate cancer[5-9]. Transition zone cancer has been shown to be relatively small and has a low Gleason grade[3, 4, 10].

In Japan, we encounter many cases where the index tumor is located predominantly at the transition zone/anterior region in our daily pathological practice when dealing with patients. In a majority of these cases, tumor volume and Gleason grade look similar when compared to peripheral/posterior zone predominant tumors in our impression. To prove this hypothesis, we have compared the zonal difference of prostate cancer between American and Japanese men. We have found a significantly higher proportion of solely transition zone located cancer in Japanese men than in American, namely 35.3% and 0.6%, respectively[11].

In the current study, we categorized Japanese prostate cancer cases into two groups, with main tumor location as anterior or posterior predominant cancers. Subsequently, we examined clinicopathological differences between the two groups to demonstrate whether the hypothesis held true or not.

Materials and Methods

Cases

A total of 201 consecutive prostate cancer cases which underwent radical prostatectomy at the Jikei University School of Medicine Hospital between 2010 and 2012 were used with approval by the Ethics Committee Institutional Review Board. Information of preoperative biopsy method was available for 134 patients. 125 patients underwent trans-rectal biopsy and 8 patients underwent trans-perineal biopsy as initial biopsy. In one patient, cancer was detected by transurethral resection for dysuria.

Routine procedure

All radical prostatectomy specimens were surface-inked, serially sliced by 4mm in thickness, put side by side and photographed. The slices were totally embedded, sectioned by 3um, and stained by H.E. (hematoxylin and eosin). The areas of the tumor was drawn by the closed circles on the glass slides under the microscope, then precise tumor mapping was constructed by transferring the circles onto the printout of the photographs in all cases (Fig. 1a).

Definition of anterior/posterior portion and the criteria for anterior/posterior cancer

In each slice on the printout for mapping, a line was drawn to connect anterior and posterior edges (line A: sagittal axis), then a perpendicular line (B: frontal axis) was drawn as to connect

the right and left lateral edges with the center of line A. The anterior and posterior portions were designated by line B (Fig. 1b). Line B was drawn on each slice of the mapped pictures, then each case was designated as anterior or posterior cancer according to the criteria as more than 2/3 of the tumor existence in the portion (Fig. 1c). Cases which do not fit in this criterion were categorized as cancer with no dominancy.

The cases were also divided into two groups of transition zone (TZ) cancer or peripheral zone (PZ) cancer with more than 2/3 of the tumor existence in each zone as described previously[11].

Clinicopathological comparison by tumor locations

Clinical parameters such as patient age, serum prostate specific antigen (PSA) level, and pathological parameters such as tumor volume, Gleason score (GS), extraprostatic extension (EPE), lymphovascular invasion, pathological T stage (pT), pathological lymph node metastasis and surgical margin status were compared between the two groups, and of the two differing categories (anterior vs. posterior; transition zone vs. peripheral zone). The tumor volume was estimated by $4/3\,\pi \times (L/2) \times (W/2) \times (H/2)$ which is the measurement of a scalene ellipsoid. Tumors indefinite for extraprostatic extension because of surgical incision into the tumor were classified as pT2+/EPEx as described in the WHO classification[12]. The cases with no locational dominancy were eliminated from the analysis. The pathological findings and assessment were performed and reviewed by single genitourinary pathologist (H.T.) throughout the study.

Statistical analysis

Statistical analysis was performed using StatView 5.0 (SAS institute Inc. Cary, NC). The chi-square test or Mann-Whitney U-test was utilized.

Results

Tumor location (Table 1)

A total of 201 cases were divided into 83 cases (41.3%), 73 (36.3%), and 45 (22.3%) as anterior, posterior, and no-dominancy category, respectively. Similarly, the cases were subcategorized as 85 cases (42.3%) of transition zone cancer, 115 (57.2%) of peripheral zone cancer, and one (0.5%) of no dominancy.

Comparison of clinical backgrounds (Table 2)

Median age was 64 and 65 in anterior and posterior cases; 64 and 66 in transition zone and peripheral zone cases, respectively (P=0.5838). Serum PSA level distributed from 4.10 to 43.76ng/ml with average of 10.47 and median of 7.70 in anterior cases; from 3.70 to 47.09ng/ml, with an average of 12.14ng/ml and a median of 8.66ng/ml in posterior cases (P=0.1271). Serum PSA level distributed from 4.10 to 43.76ng/ml with average of 10.55 and median of 7.66 in transition zone cases; from 1.52 to 47.09ng/ml, with an average of 11.47ng/ml and a median of 8.63ng/ml in peripheral zone cases (P=0.3302).

Comparison of pathological features (Table 3)

Tumor volume

Tumor volume of anterior cases distributed from 0.0041 to 22.4 cm^3, with an average of 3.81cm^3 and a median volume of 2.74cm^3, and that of posterior cases distributed from 0.0026 to 26.8 cm^3, with an average of 5.34cm^3 and a median of 3.74cm^3. The posterior cases tend to be larger than anterior cases, although there was no statistical significance (P=0.0508). Tumor volume of transition zone cases distributed from 0.0041 to 22.4 cm^3, with an average of 4.10cm^3 and a median volume of 2.93cm^3, and that of peripheral zone cases distributed from 0.0026 to 26.8 cm^3, with an average of 5.33cm^3 and a median of 3.27cm^3(P=0.5318).

Gleason score

The GS6, 7, and 8-10 distributed as 15.7% (13/83 cases), 68.7% (57/83 cases) and 15.7% (13/83 cases) in anterior cases; and 8.2% (6/73 cases), 63.0% (46/73 cases) and 28.8% (21/73 cases) in posterior cases, showing statistical significance (P=0.0258). The GS6, 7, and 8-10 distributed as 15.3% (13/85 cases), 67.1% (57/85 cases) and 17.6% (15/85 cases) in transition zone cases; and 10.4% (12/115 cases), 66.1% (76/115 cases) and 23.5% (27/115 cases) in peripheral zone cases (P=0.1951).

Extraprostatic extension (EPE)

Status of EPE distributed as 45.8% (38/83 cases) of EPE0, 31.3% (26/83 cases) of EPE1, and

22.9% (19/83 cases) of EPEx in anterior cases, 31.5% (23/73 cases) of EPE0, 64.4% (47/73 cases) of EPE1, and 4.1% (3/73 cases) of EPEx in posterior cases, respectively. The anterior cases showed significantly less frequency of EPE1 and more frequency of EPEx than posterior cases ($P<0.0001$ and $P=0.0017$, respectively). Status of EPE distributed as 43.5% (37/85 cases) of EPE0, 36.5% (31/85 cases) of EPE1, and 20.0% (17/85 cases) of EPEx in transition zone cases, 37.4% (43/115 cases) of EPE0, 51.3% (59/115 cases) of EPE1, and 11.3% (13/115 cases) of EPEx in peripheral zone cases, respectively. The transition zone cases showed significantly less frequency of EPE1 ($P=0.0444$), although no significant difference was shown in the frequency of EPEx ($P=0.1095$).

Statuses of pathological T and surgical margin

The pT stage distributed as 45.8% (38/83 cases) of pT2, 22.9% (19/83 cases) of pT2+, 31.3% of pT3a (26/83 cases), and 0% (0/83 cases) of pT3b in anterior cases; 31.5% (23/73 cases) of pT2, 4.1% of pT2+ (3/73 cases), 38.4% (28/73 cases) of pT3a, and 26.0% (19/73 cases) of pT3b in posterior cases, respectively. The pT stage distributed as 43.5% (37/85 cases) of pT2, 20.0% (17/85 cases) of pT2+, 34.1% of pT3a (29/85 cases) and 2.4% (2/85 cases) of pT3b in transition zone cases; 37.4% (43/115 cases) of pT2, 11.3% of pT2+ (13/115 cases), 32.2% (37/115 cases) of pT3a, and 19.1% (22/115 cases) of pT3b in peripheral zone cases, respectively. In a comparison of the anterior and posterior cases, the anterior cases revealed the statistically significant

numbers of pT2+/EPEx cases (22.9%: 19/83 cases) than the posterior cases (4.1%: 3/73 cases), and the posterior cases indicated the significant number of pT3b/seminal vesicle invasion (26.0%: 19/73 cases) than the anterior cases (0%: 0/83 cases). No significant difference was shown with regard to surgical margin status between the anterior and posterior cases as 38.6% (32/83 cases) vs 34.2% (25/73 cases); between transition zone and peripheral zone cases as 37.6 (32/85 cases) vs 36.5 (42/115 cases), respectively.

Lymphovascular invasion and lymph node metastasis

The posterior cases showed significantly higher incidence of lymphovascular invasion as 37.0% (27/73 cases) than the anterior cases as 8.4% (7/83 cases). Similar tendency was shown between transition zone and peripheral zone cases: 11.8% (10/85 cases) in transition zone cases and 32.2% (37/115 cases) in peripheral zone cases, respectively. The posterior cases included a higher number of lymph node metastasis (12.3%: 9/73 cases) than the anterior cases (3.6%: 3/83 cases), although the statistical significance was not apparent (P=0.0670). Similar tendency was shown between transition zone and peripheral zone cases: 3.5% (3/85 cases) in transition zone cases and 10.4% (12/115 cases) in peripheral zone cases, respectively (P=0.1274).

Discussion

In the management of prostate cancer, location of the tumor is extremely important for diagnosis and treatment of disease. The tumor location should essentially be defined by anatomical portions such as peripheral, transition, and central zones. Of particular importance for the most practical management of the tumor is the anterior or posterior location since anterior cancer is less likely to be detectable by digital rectal exam and trans-rectal biopsy than the posterior tumor. Accordingly, we thoroughly investigated the differences between anterior and posterior tumors rather than those by anatomical zones. From many analyses and textbooks, the location of most prostate cancers in Western men has been shown as peripheral/posterior zone; 70 to 90% of all cases[5-9]. Recent studies from Japan, including our data, have indicated that approximately half of prostate cancers are located in the anterior area[11, 13, 14]. Thus, the tumor location seems to be rather different between races and/or geographic locations. It is essential for urologists to recognize this fact.

The limitation of this research is that the cohort consists of radical prostatectomy cases with some inclusion of referrals from community hospitals. Therefore, information of preoperative biopsy was not available in several cases and biopsy methods and numbers of the repeat are variable among cases. On the other hand, it is almost impossible to resolve this problem. To reduce these biases, we selected consecutive cases as much as possible from the single

institution. The basic strategies for the selection to radical prostatectomy are unified. The operative procedures are identical with limited numbers of operators. All of the cases are diagnosed by single genitourinary pathologist [H. T.].

Several studies from the United States have shown that anterior cancers are smaller and lower in GS than posterior cancers and suggested better prognosis[5, 7, 8]. In the current study, the anterior cases showed significant tumor volume as much as the posterior ones with no statistical differences. The distributions of GS were different between anterior and posterior cancers with significantly higher proportion of GS8-10 in posterior tumors (28.8%: 21/73 cases), although a considerable proportion (15.7%: 13/83 cases) of anterior cases showed high GS. From these results, the anterior cancer seems to be similar in size and grade to posterior cancer, suggesting similar clinicopathological characteristics. Needless to say, we have to interpret these results with deep caution because anterior cancers include both transition zone and anterolateral peripheral zone cancers. McNeal and his colleagues have identified definite histologic features of transition zone cancer in the past[15]. They defined transition zone-look feature as well differentiated cancer of variable gland size, composed of uniform tall columnar cell with pale to clear cytoplasm and basally located nuclei. On the other hand, Garcia et al have demonstrated that transition zone-look feature was also shown in some peripheral zone cancer[16]. From our current study, this subject cannot be confirmed well. Further examinations including

molecular pathological studies should be performed to figure out the difference(s) between transition zone and peripheral zone cancers.

An assessment of surgical margin after operative procedure is crucial for better patient care. In this study, there was no significant difference in the frequency of positive surgical margin between anterior and posterior cases, whereas anterior cancer showed a higher number of pT2+/EPEx than posterior cancer. With regards to the surgical margin, some reports have indicated higher positive surgical margin rate in anterior cancers, while other studies have shown no significant difference[5, 7, 8]. Hossac et al indicated less frequency of EPE positive in anterior cases, yet similar frequency of positive surgical margin in comparison of anterior and posterior cancers. Another report from Japan has shown a significantly higher number of surgical margin positive cases in apex-anterior cancers in pT2 /pT2+ categories[13]. As a result of the findings, at least, the Japanese urologists should recognize that certain amount/grade of cancer may be located in the anterior portion of the prostate and take extra care for resecting the anterior area in surgical procedure. This kind of study need to be performed in other countries or regions worldwide and same prudence may be required if similar results were obtained.

In the comparison of anterior and posterior tumors, our study also highlighted characteristics

of the posterior tumors. Rates of both EPE positive and seminal vesicle invasion (=pT3b) were significantly higher in the posterior cancer than in the anterior cancer. Accordingly, a significant difference in pT stage distribution was shown between anterior and posterior cases, supported by the previous studies from the U.S[5, 7]. Higher frequency of seminal vesicle invasion in the posterior cases should be correlated to the anatomical location of the seminal vesicle. In our study using a strictly Asian population, the total frequency of seminal vesicle invasion was 11.9% (24/201 cases). The frequency of seminal vesicle invasion has been shown as only 4.5% (482/10748 cases) from a major medical institute in the U.S.[17] Whereas, Yamoah et al. have shown that seminal vesicle invasion after prostatectomy was a predictor for biochemical recurrence in the African-American male[18]. Thus, the frequency and importance of seminal vesicle invasion is variable among races/regions. Our data indicated that seminal vesicle invasion was related to the cases of cancer location at the posterior portion of the prostate, although further study should be performed to elucidate clinicopathological implications of seminal vesicle invasion between races.

In the current study, clinicopathological similarities and differences between the anterior and posterior prostate cancer were indicated in Japanese men. From this study, it is impossible to explain the definitive reasons to make clinicopathological differences between anterior and posterior cancers. One of the possible answers could be genetic differences between cancer

locations. Although no molecular pathological study was performed in our study, a previous report has shown that ERG expression was observed at 8.0% and 50% in anterior and posterior cancers, respectively[8]. Similar results were shown as higher ERG expression rate in peripheral zone cancers than in transition zone cancers in both American and Japanese men[19-21]. Other data have suggested that frequency of some important genomic alteration was different among races such as lower frequencies in TMPRESS2-ERG fusion and PTEN deletion in the Asian prostate cancer cases[22-25]. This evidence suggests molecular pathological differences exist between anterior and posterior cancers and among races. Similar results should be expected in a variety of the races.

Disclosure Statement

None declared.

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Tables

Table 1: Distributions of the dominant tumor location

Location	Anterior	Posterior	No dominancy	Total
Number	83 (41.3%)	73 (36.3%)	45 (22.3%)	201 (100%)

Location	Transition zone	Peripheral zone	Other	Total
Number	85 (42.3%)	115 (57.2%)	1 (0.5%)	201 (100%)

Table 2: Clinical backgrounds by dominant tumor locations

	Anterior	Posterior	p-value
Age (median)	64	65	0.5838
Serum PSA (median: ng/ml)	7.7	8.66	0.1271

	Transition zone	Peripheral zone	p-value
Age (median)	64	66	0.6694
Serum PSA (median: ng/ml)	7.66	8.63	0.3302

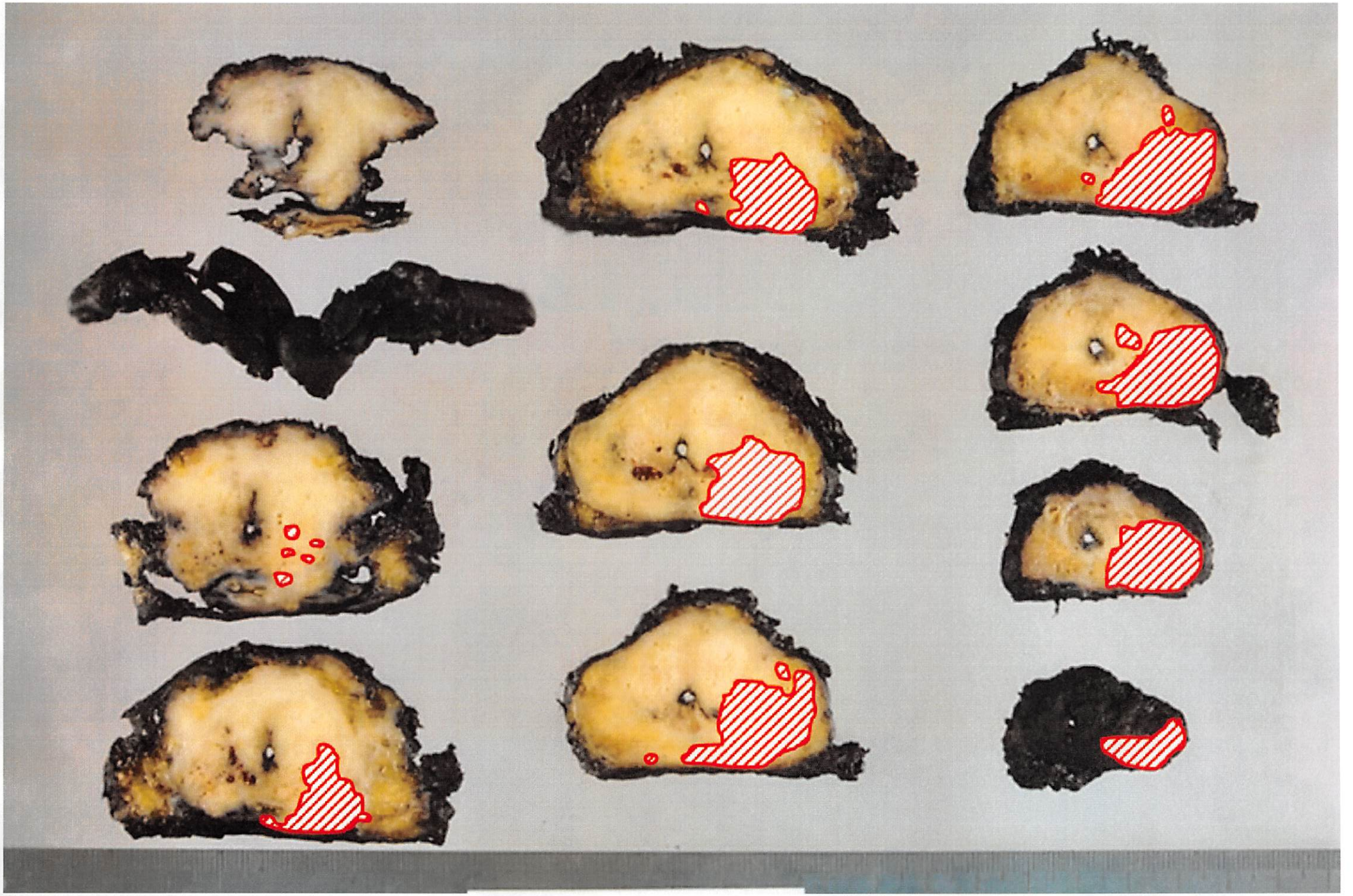
Table 3: Pathological Features by dominant tumor locations

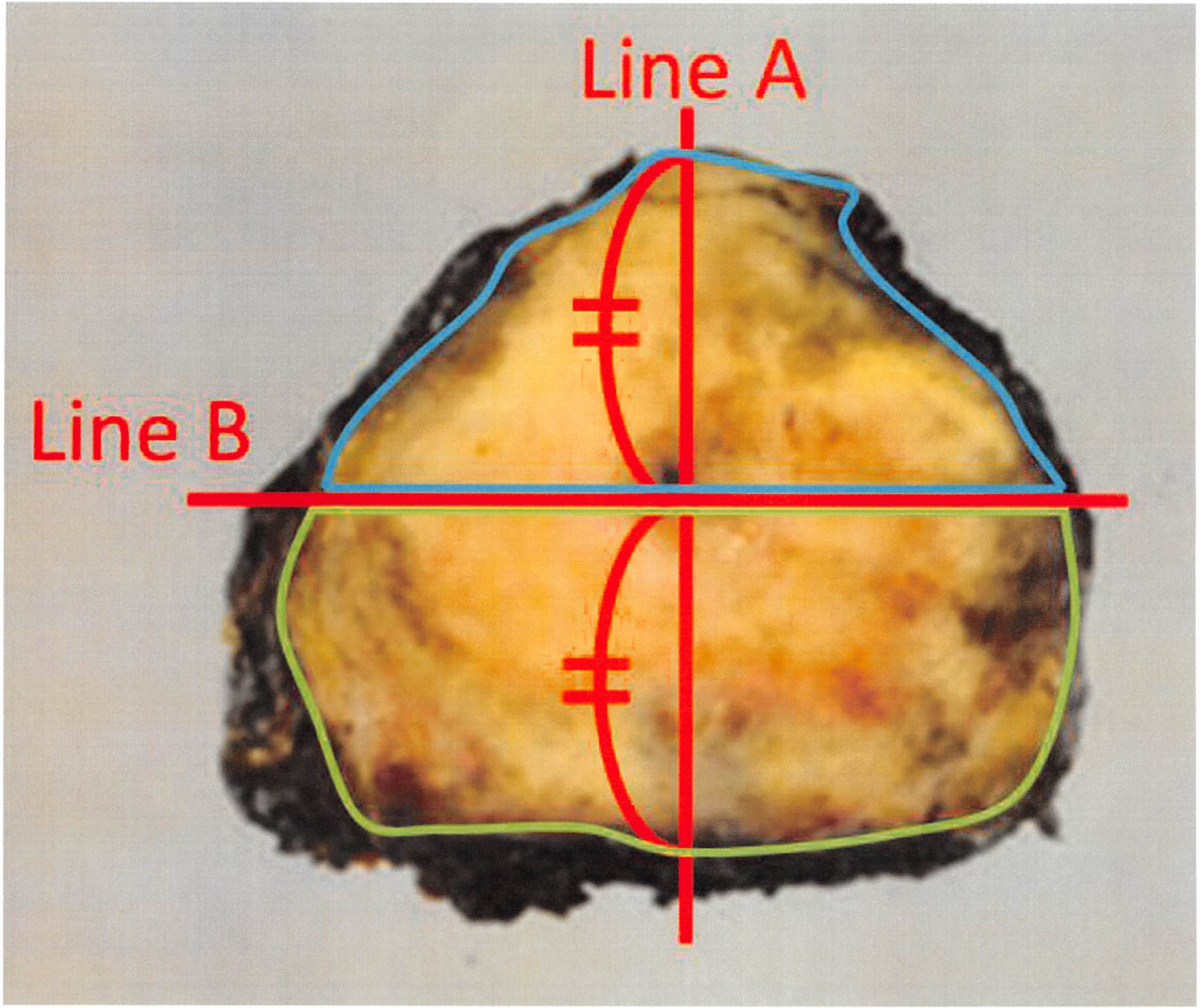
	Anterior	Posterior	*P*value	Transition zone	Peripheral zone	*P*value
Tumor volume (median: cm^3)	2.74	3.737	0.0508	2.93	3.27	0.5318
Gleason Score						
GS 6	13/83 (15.7%)	6/73 (8.2%)		13/85 (15.3%)	12/115 (10.4%)	
GS 7	57/83 (68.7%)	46/73 (63.0%)	0.0258	57/85 (67.1%)	76/115 (66.1%)	0.1951
GS 8-10	13/83 (15.7%)	21/73 (28.8%)		15/85 (17.6%)	27/115 (23.5%)	
Extraprostatic extension						
EPE0	38/83 (45.8%)	23/73 (31.5%)		37/85 (43.5%)	43/115 (37.4%)	
EPE1	26/83 (31.3%)	47/73 (64.4%)	<0.0001	31/85 (36.5%)	59/115 (51.3%)	0.0444
EPEx	19/83 (22.9%)	3/73 (4.1%)	0.0017	17/85 (20.0%)	13/115 (11.3%)	0.1095
Lymphovascular invasion						
Negative	76/83 (91.6%)	46/73 (63.0%)	<0.0001	75/85 (88.2%)	78/115 (67.8%)	0.0007
Positive	7/83 (8.4%)	27/73 (37.0%)		10/85 (11.8%)	37/115 (32.2%)	
Pathological T stage						
pT2	38/83 (45.8%)	23/73 (31.5%)		37/85 (43.5%)	43/115 (37.4%)	
pT2+	19/83 (22.9%)	3/73 (4.1%)	<0.0001	17/85 (20.0%)	13/115 (11.3%)	0.0212
pT3a	26/83 (31.3%)	28/73 (38.4%)		29/85 (34.1%)	37/115 (32.2%)	
pT3b	0/83 (0%)	19/73 (26.0%)		2/85 (2.4%)	22/115 (19.1%)	
Lymph node metastasis						
Negative	77/83 (92.8%)	61/73 (83.6%)	0.067	78/85 (91.8%)	100/115 (87.0%)	0.1274
Positive	3/83 (3.6%)	9/73 (12.3%)		3/85 (3.5%)	12/115 (10.4%)	
Not examined	3/83 (3.6%)	3/73 (4.1%)		4/85 (4.7%)	3/115 (2.6%)	
Surgical margin status						
Negative	51/83 (61.4%)	48/73 (65.8%)	0.6196	53/85 (61.4%)	73/115 (63.5%)	0.8832
Positive	32/83 (38.6%)	25/73 (34.2%)		32/85 (37.6%)	42/115 (36.5%)	

Figure Legend

Figure 1

a: Routine procedure The areas of the tumor was drawn by the closed circles on the glass slides under the microscope (not shown in the figure), then precise tumor mapping was constructed by transferring the circles onto the printout of the photographs in all cases (Left and Right) b: Definition of anterior and posterior portion in this study. A line was drawn to connect anterior and posterior edges (line A: sagittal axis), then a perpendicular line (B: frontal axis) was drawn as to connect the right and left lateral edges with the center of line A. The anterior and posterior portions were designated by line B. c: Decision of anterior/posterior cancer Line B was drawn on each slice of the mapped pictures, then each case was determined as anterior or posterior cancer according to the criteria as more than 2/3 of the tumor existence in the certain portion (Left: anterior cancer; Right: posterior cancer)

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