

The pathological and clinical features of anterior lesions of prostate cancer: Evaluation in a single cohort of patients

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Summary *Introduction.* The aim of our work is to evaluate the principal differences of the pathological features in prostate cancer (PCa) lesions comparing those in the anterior region of the gland (APCa) to those in the posterior zone (PPCa) among patients who underwent to robotic-assisted radical prostatectomy (RP).

Material and methods. A total of 85 consecutive patients (mean age 66; IQR 62-71) with clinically suspected PCa were studied with multiparametric magnetic resonance of prostate before prostate biopsies. The prostate biopsies were RM-guided (60 in-bore biopsy (MR-GB) and 25 Fusion-biopsy (FB)). A total of 72 cases were eligible for robotic RP. An experienced genitourinary pathologist reviewed the histopathology of the tissue specimens of the patients after RP. The exclusion criteria were as follows: previous hormonotherapy, radiotherapy and chemotherapy for others cancers.

Results. Based on the histological diagnosis, after RP, 68 anterior prostate cancer, and 107 posterior lesions were found. We further subcategorized lesions into peripheral and central zones for each the anterior and posterior lesions. The specific distribution of lesions by pathologic stage was: T2 = 74 (42.3%), T3a = 87 (49.7%), T3b = 12 (6.9%), T4 = 2 (1.1%) cases. Tumor volume of posterior neoplasms ranged from 0.04 to 20.35 cm³, with a median of 3.39 cm³. Anterior tumor volume ranged from 0.17 to 15 cm³, with a median volume of 2.54 cm³. PPCa were larger than APCa but the difference in size was not significant. The prostate cancer grade group (GG) I was distributed as 16.6% and 36% in anterior and posterior lesions cases. GG II and III was 43.8% and 31.5% in anterior and posterior cases, respectively. Comparatively, GG IV-V showed 39.6% and 32.5% for anterior and posterior lesions respectively ($p < 0.001$).

Extraprostatic extension of neoplasm (EPE) was found more frequently in anterior cases (31.4%) than in posterior cases (25.1%), but without significant difference. Lymphovascular invasion was similar in both the groups: 24% and 28.6% in anterior and posterior group, respectively. Anterior lesions showed a significantly higher rate of lymph node metastasis (9.3%) than posterior lesions (3.4%) ($p < 0.005$).

Conclusion. In our study, we have found EPE, often associated with worse prognosis, more frequently (but not significantly) present in anterior lesions among PCa patients. Although posterior lesions are often related to pT3b stage, in our findings, anterior lesions were more often associated with a more aggressive neoplasm with more frequent nodal involvements.

KEY WORDS: Prostate cancer; Anterior lesion; Multiparametric magnetic resonance.

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INTRODUCTION

Prostate cancer (PCa) is the second most frequently diagnosed tumor in males globally (1). Many national and international efforts are ongoing to improve PCa diagnosis, treatment, and, ultimately, the quality of life of patients (2). The majority of tumors have an indolent clinical course, although some cancers have an aggressive and potentially lethal evolution, if they are not promptly treated. PCa is often found in the peripheral area of the prostate gland, although histopathological studies from radical prostatectomy (RP) samples have shown that up to 30% of clinically significant neoplasms (csPCa) can be located in the anterior portion of the gland (APCa), and these are increasing in prevalence (3, 4). Cancers that arise in the anterior zone may be difficult to palpate by digital rectal examination (DRE), and are often missed (5). Moreover, transrectal ultrasound (TRUS)-guided prostate biopsy fails to accurately assess the anterior zone of the prostate, where cancers may not be sampled.

Various studies have shown that targeted MRI/ultrasound fusion biopsy (TB), compared with standard biopsy (SB), is associated with increased detection of high-risk prostate cancer and decreased detection of low-risk prostate cancer (6-8).

Many authors (4, 5) report that there is no difference in terms of Gleason grade (GG) IV or V rate between patients with APCa or posterior (P)PCa, although APCa has smaller tumor volume and shows a higher rate of positive surgical margins after RP when compared with PPCa (5, 9). Additionally, anterior cancers tend to be more aggressive than posterior ones, so early detection of anterior prostate cancer is clinically important (9-11). The aim of the present study is to compare the detection of anterior and posterior PCa in a contemporary cohort of Caucasian patients, admitted to the hospital for suspected PCa diagnosis and to evaluate clinical and pathological features between APCa and PPCa. The investigation was prompted by the finding that, in our practice of RP specimens, tumor volume is lower and GG is higher in a majority of cases, when the index tumor is predominantly located in the anterior region of the gland, compared to the posterior zone.

No conflict of interest declared.

MATERIALS AND METHODS

A total of 85 consecutive patients (mean age 66; IQR 62-71) with clinically suspected PCa were enrolled at our institution between January 2016 and January 2019. All enrolled patients had been studied with *multiparametric magnetic resonance* (mpMRI) of prostate before prostate biopsies. We identified 386 suspected lesions at mpMRI (excluding the lesion of transitional zone we included in the evaluation 229 lesions of posterior region and 157 in anterior region of prostate). The demographics and radiological details of cohort are summarized in Table 1. The prostate biopsies were all RM-guided, in-bore biopsy (MR-GB) and *Fusion-biopsy* (FB). According to the risk category, patients were offered *active surveillance* (AS), robot assisted *radical prostatectomy* (RARP), or *radiation therapy* (RT). All details are clarified in Table 2. A total of 72 cases were eligible for robotic RP. The study was a retrospective analysis with the approval by the *Ethics Committee Institutional Review Board of Abano Policlinic* and signed informed consent was provided by all patients. An experienced genitourinary pathologist reviewed the histopathology of the tissue specimens of the patients after RP. The pathologist, reviewing all prostatectomy tissue sections, identified PCa foci larger than 5 mm in diameter. The exclusion criteria were as follows: previous hormone therapy and radiotherapy, chemotherapy

Table 1. Overall and stratified according to bioptic status clinical and radiologic features of patients undergoing target biopsy of prostatic anterior lesion identified at mpMRI.

	Overall (n = 386)	Posterior lesions (n = 229)	Anterior lesions (n = 157)	p-value
Age				
Median	66	67	66	0.7
IQR	62-71	61-72	63-71	
PSA (ng/ml)				
Median	7	6.7	7.7	0.02
IQR	5-9.2	4.8-9.1	5.2-10.1	
Prostate volume (ml)				
Median	53.7	55	51.2	0.5
IQR	42-69.1	43-69.7	38.1-67.8	
PSA density				
Median	0.12	0.12	0.15	< 0.001
IQR	0.09-0.18	0.09-0.16	0.09-0.23	
DRE (%)				
Negative	260 (67.4)	161 (70.3)	106 (67.5)	0.5
Positive	126 (32.6)	77 (33.6)	47 (29.9)	
Previous TRUS-GB (%)	141 (36.6)	69 (30.1)	72 (45.9)	0.002
PIRADS score (%)				
3	145 (37.6)	105 (45.9)	40 (25.5)	< 0.001
4	136 (35.2)	83 (36.2)	53 (33.8)	
5	105 (27.2)	41 (17.9)	64 (40.8)	
Index kesion diameter (mm)				
Median	14	13	16	< 0.001
IQR	11-19	9-17	12-23	
Index kesion site (%)				
Peripheral	277 (71.8)	183 (79.9)	94 (59.9)	< 0.001
Central	109 (28.2)	46 (20.1)	63 (40.1)	

IQR: interquartile range; TRUS-GB: transrectal ultrasound-guided biopsy; PSA: prostatic specific antigen; DRE: digito-rectal examination.

Table 2.

Overall and stratified according to Fusion and In-bore biopsy bioptic outcomes of patients undergoing target biopsy of prostatic anterior lesion identified at mpMRI.

	Overall (n = 386)	Posterior lesions (n = 229)	Anterior lesions (n = 157)	p-value
Targeted biopsy technique (%)				
MR-GB	217 (56.2)	118 (51.5)	99 (63.1)	0.3
Fusion	169 (43.8)	111 (49.5)	58 (36.9)	
Number of cores taken				
Median	12	12	12	0.09
IQR	2-14	2-14	2-14	
Positive cores *				
Median	1	1	2	< 0.001
IQR	0-3	0-2	1-3	
Gleason grade (%)				
Negative	138 (35.8)	102 (44.5)	36 (22.9)	
1	64 (16.6)	38 (16.6)	26 (16.6)	< 0.001
2	90 (23.3)	37 (16.2)	53 (33.8)	
3	65 (16.8)	35 (15.3)	30 (19.1)	
4	26 (6.7)	15 (6.6)	11 (7)	
5	3 (0.8)	2 (0.9)	1 (0.6)	
Indication (%)				
No treatment	138 (35.8)	102 (44.5)	36 (22.9)	< 0.001
Active surveillance	43 (11.1)	32 (14)	11 (7)	
RP	175 (45.3)	72 (31.4)	103 (65.6)	
RT	23 (6)	18 (7.9)	5 (3.2)	
ADT	7 (1.8)	5 (2.2)	2 (1.3)	

MR-GB: Magnetic Resonance-Guided Biopsy; ADT: androgen deprivation therapy; RT: radiotherapy; RP: radical prostatectomy.

for others cancers. Based on the histological diagnosis, 68 anterior and 107 posterior lesions were found. We also subcategorized the lesions into peripheral and central zones for each anterior and posterior group. The specific distribution of lesions by pathologic stage was: T2 = 74 (42.3%), T3a = 87 (49.7%), T3b = 12 (6.9%), T4 = 2 (1.1%) cases (ref Table 3).

Pathology protocol

The radical prostatectomy specimens were fixed in 10% formalin and cut into approximately 5 mm sections by hand as follows: apex and base in coronal plane, seminal vesicles in sagittal plane, and mid-gland in transverse plane, perpendicular to the long axis of the urethra. The 5-mm paraffin-embedded slices blocks were sectioned into 5- μ m-thick sections and stained with *hematoxylin and eosin* (H&E). Dedicated pathologists examined surgical specimens, which were processed according to the Stanford protocol (30). ISUP grade group system was applied to classify tumors (31). Surgical margins were reported positive when cancer invaded the inked surface of the specimen. Lymph nodes were assessed for histopathology after hematoxylin and eosin staining. Immuno-histochemical staining was performed when appropriate. In each case, the number of removed lymph nodes and LNI was reported. Prostate and nodal specimens were then staged according to the 2010 AJCC staging system for PCa (18).

Perioperative-features

In each case, clinical pelvic lymph node staging (cN) was

Table 3.
Overall pathologic outcomes of patients who underwent radical prostatectomy (n = 72).

	Overall
Pathologic stage (%)	
T2	74 (42.3)
T3a	87 (49.7)
T3b	12 (6.9)
T4	2 (1.1)
Pathologic ISUP grade (%)	
1	10 (5.7)
2	70 (40)
3	56 (32)
4	34 (19.4)
5	5 (2.9)
Pathologic nodal status (%)	
N0	113 (64.6)
N1	10 (5.7)
Nx	52 (29.7)
Positive surgical margins (%)	11 (6.3)
Pathologic index lesion (%)	
Anterior	68 (39.9)
Posterior	107 (61.1)

mpMRI: multiparametric Magnetic Resonance Imaging; ADT: androgen deprivation therapy; RT: radiotherapy; RP: radical prostatectomy; * among those with positive biopsies.

performed by axial imaging modalities (computed tomography CT or MRI). Enlarged pelvic nodes larger than one centimeter in diameter were staged as cN1 disease. The metastatic status was investigated by both axial imaging and total bone scan modalities. Patients were staged according to 2010 American Joint Committee on Cancer (AJCC) staging system for PCa (7th edition) (18). PCa patients were divided into low, intermediate and high risk, according to the D'Amico risk classification (19). In high risk patients in the RARP group, *extend pelvic lymph node dissection* (ePLND) was performed (20, 21). In intermediate risk patients, the decision to perform an extended lymph node dissection was mainly based on

Table 4.
Uni- and multivariate analysis model predicting features of patients who underwent.

	Univariate analysis		Multi-variate analysis	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Age (yrs)	1.09 (1.05-1.12)	< 0.001	1.07 (1.03-1.12)	0.002
PSA (ng/ml)	1.12 (1.06-1.17)	< 0.001	1.15 (1.06-1.24)	0.001
Prostate volume (ml)	0.98 (0.97-0.99)	< 0.001	0.97 (0.95-0.98)	< 0.001
Recto-rectal examination	5.99 (3.69-9.71)	< 0.001	7.03 (3.76-13.16)	< 0.001
Previous TRUS-GB	1.55 (1.02-2.35)	0.04	1.03 (0.59-1.8)	0.9
N of bioptic cores	1.02 (0.99-1.06)	0.3	-	-
PIRADS score				
3	Ref.		Ref.	
4	5.63 (3.27-9.68)	< 0.001	4.08 (2.17-7.67)	< 0.001
5	17.27 (9.17-32.53)	< 0.001	9.6 (3.77-24.45)	< 0.001
Index lesion diameter (mm)	1.08 (1.05-1.12)	< 0.001	0.98 (0.92-1.03)	0.7
mpMRI index lesion location				
Posterior	Ref.	< 0.001	Ref.	0.01
Anterior	2.41 (1.59-3.65)		2.09 (1.19-3.68)	

targeted biopsy with clinical csPCa (GS ≥ 7)
csPCa: clinically significant prostate cancer; PSA: prostate specific antigen; TRUS-GB: transrectal ultrasound-guided biopsy; mpMRI: multi-parametric magnetic resonance imaging.

pre-operative nomograms showing a risk of lymph node invasion greater than 5% (22). In low risk patients, the decision to perform an ePLND was based on clinical factors indicating increased risk of tumor upgrading and lymph node invasion in the surgical specimen (23). Skilled and experienced surgeons performed RARP with ePLND using the *da Vinci Robot Surgical System* (Intuitive Surgical, Inc, Sunnyvale, CA, USA). All procedures were performed through a trans-peritoneal approach with anterograde prostatic dissection (24). Urethro-vesical anastomosis was performed using barbed sutures as previously described (25-26). The lymph node dissection template included bilateral external iliac lymph nodes until the crossing of the ureter and the external iliac artery.

Statistical analysis

Continuous variables were expressed as median and interquartile range (IQR) whereas categorical variables were expressed as frequencies with percentages. The independent-samples T-test and Chi-Square test were used to compare means and frequencies between the two groups, respectively. All data were statistically analyzed using SPSS v 21 for Macintosh.

RESULTS

Median age was 66 (IQR 63-71) and 67 (range 61-72) years among anterior and posterior lesions cases, respectively. Mean serum PSA level was 7.7 ng/mL (IQR 5.2-10.1) in anterior cases and 6.7 ng/mL (IQR 4.8-9.1) in posterior cases.

Tumor volume of posterior neoplasms ranged from 0.04 to 20.35 cm³, with a median of 3.39 cm³. Tumor volume of anterior cases ranged from 0.17 to 15 cm³, with a median volume of 2.54 cm³. This difference in size was not statistically significant (p > 0.05).

The GG I was distributed as 16.6% and 36% in anterior and posterior lesions cases, respectively. GGII and III was 43.8% and 31.5% in anterior and posterior cases, respectively. GG IV-V was 39.6% and 32.5% for anterior and posterior lesions, respectively (p < 0.001).

Extraprostatic extension of neoplasm (EPE) was found more frequently in anterior cases (31.4%) than in posterior cases (25.1%), but without significant difference (p > 0.05). Pathologic stages among patients with primary posterior lesions were as follows: 42.3% in pT2, 49.7% in pT3a, 6.9% in pT3b, and 1.1% in T4. Among patients with anterior primary lesions, in 38.0% were in pT2 stage, 5.3% were in pT3a, 5.6% were in pT3b, and 11.1% in T4. Lymphovascular invasion was similar in both the groups: 24% and 28.6% in anterior and posterior group respectively. Anterior lesions showed a significantly higher rate of lymph node metastasis (9.3%) than in posterior lesions (3.4%) (p < 0.005).

DISCUSSION

In the literature, the imaging techniques for prostate cancer are in constantly evolving, and several different examination techniques play a fundamental role in the diagnosis, staging (27), and choice of therapeutic approach (28). In particular, the localization of prostate cancer foci with

mpMRI is crucial in the planning the best diagnostic plane and surgical approach, for example, in robotic surgery (29-31). The pathological and biological features of prostate cancer lesion have been analyzed by numerous studies. The anatomical and biological behavior of APCa are unique, and the definition varies. In the study by Villers and colleagues, they defined the anterior borders of the prostate as the region of parenchyma at least 2.1 cm anterior to the posterior capsule which is an area that the transrectal biopsy needle characteristically fails to reach (32). Anatomically, this is a portion of the prostate anterior to the urethra which includes areas of McNeal's transition zone, the anterior fibromuscular stroma and the anterior horns of the peripheral zone. These features make the use of MRI-guided prostate biopsy techniques indispensable to obtain a correct therapeutic approach; late identification of anterior lesions significantly affects disease prognosis and surgical outcomes (extra-prostatic extension and positive surgical margins).

Here, we have studied the differences between neoplasms arising from anterior and posterior gland. In retrospective studies of RP, it is reported that over 50% of tumors are located in anterior prostate (33-34). In agreement with the literature, we found 40% of lesions were located in anterior gland. At the time of diagnosis, anterior lesions were bigger than posterior ones, because APCa are commonly more advanced and have *positive surgical margins* (PSM) on RP specimens so therefore they can carry more risk for the patient (35). However, the findings from the present investigation do not support the observed trend from the literature, that anterior lesions have a lower GG than posterior (36-37).

We found that anterior lesions have a higher GG than posterior lesions ($p < 0.005$) and a more advanced local stage at the time of detection, even in presence of a smaller volume of neoplasm.

Anatomy of the anterior extraprostatic space which spans across the apex through the base, is unique in that the capsule is vaguely defined and is covered with fibromuscular shielding (*anterior fibromuscular stroma*) AFMS (8). Not only does the lack of capsular structure makes it difficult to define EPE and PSM in these regions, but the particular histological structure may provide an alternative route through which malignant cells can spread and gain access to the lymphatic drainage system. In most studies in literature, APCa are reported to be associated with lower rate of EPE while PSM rate was higher compared to posterior cancers.

Differences in EPE between anterior and posterior lesions result from mechanical/anatomical distinctions, rather than biological differences (38), though we have found that EPE was slightly more common in anterior lesions, but not statistical so. To better clarify this discrepancy, further anatomopathological studies must be carried out. In accordance with the literature, the present study has found higher rates of seminal vesicles invasion (pT3b) in the posterior lesions than in the anterior lesions, probably correlated to the anatomical location of the seminal vesicle (39). Certainly, an interesting aspect is represented by lymph node diffusion. In our cohort, more lymph nodal involvement has been found in anterior lesions than in posterior ones.

This study has some limitations predominantly related to the retrospective design and the small size of the cohort. Additionally, selection bias may be due to patients who underwent MRI and fusion prostate biopsy were not all patients with a clinical suspect of PCa. Clinicians were used to suggest MRI (+/- biopsy) in more challenging clinical scenario. Moreover, the patients who underwent RP could be a selected subgroup of patients with a longer life expectancy and/or with a more aggressive PCa since low-risk PCa might have been managed expectantly with active surveillance. Certainly, a prospective evaluation of pathological and clinical features and long term follow-up of APCa with a major number of cases will be useful to better investigate the real impact of PCa location within the gland.

CONCLUSIONS

Our anatomo-topographic study shows that the anterior prostatic lesions, although smaller than posterior tends to have a higher pathological grade. In contrast with others, we have found EPE, often associated at a worse prognosis, more likely present in anterior lesions. Although, posterior lesions are often related to pT3b stage, in our findings, anterior lesions are associated to a more aggressive neoplasm with more frequent nodal involvements.

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