Do not underestimate anterior prostate cancer

Sarka Kudlackova[a], Daniela Kurfurstova[b], Milan Kral[a], Frantisek Hruska[a], Ales Vidlar[a], Vladimir Student[a]

Aims. With the introduction of magnetic resonance imaging in the diagnosis of prostate cancer and its use in targeted prostate biopsy, an increased incidence of anterior-predominant prostate cancer (APC) has been observed.
Methods. We enrolled 200 patients who underwent radical prostatectomy at our department between 12/2017 and 04/2019. We evaluated tumour location in the individual segments of the prostate, index tumour location and volume, and compared the postoperative stage, Gleason score, grade group (GG), and the presence of extraprostatic extension (EPE) in APC and posterior prostate cancer (PPC). We assessed the rate of MRI scans prior to prostate surgery as well as the influence of family history and PSA on the presence of APC.
Results. We found a significantly higher rate of anterior tumours than previously reported (37%) and confirmed that these tumours are diagnosed with a significantly larger index tumour volume (P=0.003). We also showed that a mere 6.76% of APCs were low-risk tumours not requiring radical treatment. Furthermore, anterior tumours were found significantly more often (P=0.001) in patients who underwent preoperative MRI.
No differences were observed between PSA values, family history, presence of EPE, or locally advanced disease in APC vs. PPC.
Conclusions. The frequency of anterior tumours is higher than previously thought, and they include tumours requiring radical treatment. When these tumours are neglected, it may lead to patient undertreatment with impact on their life prognosis. Thus, we consider the use of MRI-targeted prostate biopsy to be a necessity both for ruling out APC in the case of repeatedly negative prostate biopsies and, in particular, before patient inclusion in active surveillance.

Key words: anterior prostate cancer, prostate biopsy, MRI, targeted biopsy

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[a]Department of Urology, Faculty of Medicine and Dentistry, Palacky University Olomouc and University Hospital Olomouc, Czech Republic
[b]Department of Clinical and Molecular Pathology, Faculty of Medicine and Dentistry, Palacky University Olomouc, Czech Republic
Corresponding author: Daniela Kurfurstova, e-mail: daniela.kurfurstova@seznam.cz

INTRODUCTION

Generally, the predominant location of prostate cancer in the peripheral zone (PPC – posterior prostate cancer) is well known. Anterior prostate cancer (APC) is defined as a tumour located above the urethra and it contains periurethral tissues, anterior horns of the peripheral zone (APZ), transition zone (TZ), and anterior fibromuscular stroma (AFMS) (Fig. 1). McNeal cited Lowsley's 1912 observation that prostate cancers arose from the peripheral part of the gland[1]. Some 15-25% of cases are reported to occur in the anterior part of the prostate, but the diagnosis is difficult[1-7]. Furthermore, anterior tumours have been reported to be less aggressive and less often spread beyond the prostate[8]. With the introduction of new imaging techniques (MRI, PET CT), it is becoming evident that anterior tumours are more frequent and that they include ones that are clinically significant and tend to be diagnosed with delay. Since the introduction of new imaging techniques and the use of targeted biopsy even in the transition zone and anterior fibromuscular area (TZ and AFMS), the number of patients diagnosed with a tumour with a predilection in the anterior zone has been increasing. This results in an increasing number of these tumours in radical prostatectomy specimens. As radical prostatectomy is indicated only in patients with a histologically confirmed carcinoma, it necessarily results in selection bias as those with an anterior tumour may not be diagnosed in this manner[9]. In other words, patients with an anterior tumour do not undergo radical prostatectomy and, thus, these prostates are not examined and included in the cohort evaluated for tumour location. Data on tumour location in the individual segments of the prostate obtained from radical prostatectomies are then necessarily influenced by this fact.

MATERIAL AND METHODS

Study cohort

Between 12/2017 and 04/2019, a cohort of 200 consecutive patients were evaluated who underwent robotic-assisted radical prostatectomy at our department and whose histological specimens were assessed by a single pathologist. Of these, 67.5% were referred from another institution and 32.5% were diagnosed at our department. Magnetic resonance imaging prior to surgery was performed in 24.5% of the patients. The mean age of the patients was 65 years, the mean PSA was 8.12 ng/mL, and the mean prostate size was 50 mL. A positive family history was found in 10.5% of the patients. Characteristics of the study cohort are listed in Table 1.

Histological processing

Following radical prostatectomy, the prostate tissue was fixed in 10% formalin for 24 h and subsequently processed completely using the method of whole-mount sections. Tissue sections with a thickness of 3 μm were stained with haematoxylin-eosin and evaluated by a single pathologist with extensive experience in diagnosing prostate cancer. All carcinoma foci were labelled on the specimens. The three largest of them were measured and drawn in a diagram used in the PIRADS v2 classification, with the largest focus labelled as index tumour.

Statistics (data analysis)

In this study, clinical and pathologic features were presented as quantiles (median, range) or frequencies. Continuous variables were compared by the Mann-Whitney test. Categorical variables were tested for independence by Fisher's exact test. A boxplot and/or a barplot were used for graphic presentation. The level of significance was set at 5% for all statistical tests. All analyses were performed using the statistical software STATISTICA, version 13 (Statsoft, Inc., USA).

We assessed the location of 1-3 largest foci and whether there was a single focus or the tumours were multifocal. We mapped all tumour foci from 200 serially sectioned radical prostatectomy specimens. The volume and anatomic location of each tumour focus were determined. Cancer locations were reported according to an adapted scheme as described by Barentz (Synopsis of PIRADS2). We determined the proportion of individual prostate segments involved by tumour. Subsequently, index tumour location, i.e. the largest focus (anterior vs. posterior), was assessed only. A tumour was labelled as anterior when it was completely or largely in the portion of the prostate located anterior to the urethra. For the largest focus, its volume was calculated from three dimensions using rotational ellipsoid formula. The volumes of anterior and posterior index tumours were compared. For the largest focus, the Gleason score and ISUP grade group were determined[10]. We compared anterior prostate cancer and posterior prostate cancer stratified into three risk groups according to D'Amico risk criteria[11]. We also evaluated the occurrence of anterior tumours in patients who had undergone preoperative MRI as well as the effect of family history and PSA levels on the presence of anterior tumour of the prostate.

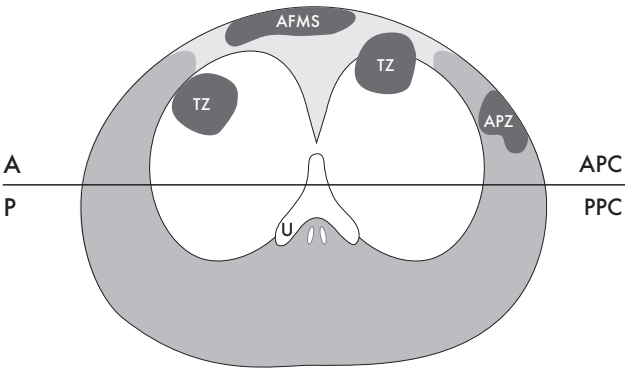

Fig. 1. Anterior part is defined as area anterior to prostatic urethra.
APC – anterior prostate cancer, AFMS – anterior fibromuscular stroma, PPC – posterior prostate cancer, TZ – transition zone, APZ – anterior horns of the peripheral zone.

RESULTS

A single-focus tumour was identified in 25% and a multifocal tumour was found in 75%. When the presence of all tumour foci in the individual segments of the prostate was assessed, there was no difference between anterior and posterior tumours. In fact, the tumour rate was higher in the anterior segments: 52.5% vs. 47.5% (Fig. 2).

Anterior index tumour and posterior index tumour were found in 74 (37%) and 126 (63%) of 200 patients, respectively (Fig. 3). Anterior index tumours were shown to have significantly larger volumes than posterior ones (P=0.003).

When comparing the postoperative stage according to ISUP GG, no difference was shown between anterior and posterior tumours in the low- and moderate-risk groups. In the high-risk group, there were significantly more posterior tumours (P=0.004). In the patients who underwent MRI, anterior tumours were more frequent (37.84% vs. 16.67%, P=0.001).

When the absolute PSA level was compared, no difference was found between these two groups of tumours (median 6.09 ng/mL in anterior vs. 5.94 ng/mL in posterior ones). Furthermore, no effect of a positive family history on tumour location (12.1% in anterior vs. 9.5% in posterior ones, P=0.64) and no difference between the occurrence of extraprostatic extension or PSM in APC vs. PPC was shown (Table 1).

DISCUSSION

The diagnosis of prostate cancer is still based only on histological examination of prostate biopsy samples, transurethral resection samples or radical prostatectomy specimens. Over the years, the protocol of prostate biopsy has changed with an aim to increase the detection rate of prostate cancer and reduce the morbidity rate associated with the procedure. The originally used sextant biopsy was modified, based on systematic reviews, into multiple systematic biopsy with needle biopsies directed at the peripheral zone and more laterally, so that the maximum core length would be from this part[12-14]. This resulted in an increase in detection rate to 29-56% (ref.[14]). These studies then led to the conclusion that the carcinoma occurred with a predilection in the peripheral zone and, if found in the anterior part, the tumour was insignificant. Anterior prostate is routinely undersampled by standard TRUS-guided biopsy because anterior biopsies are excluded from standard 12-core template biopsy. If saturation biopsy (more than 18 samples) is performed as part of rebiopsy, the transition zone and anterior part of the prostate are not examined sufficiently[14-15]. The overwhelming majority

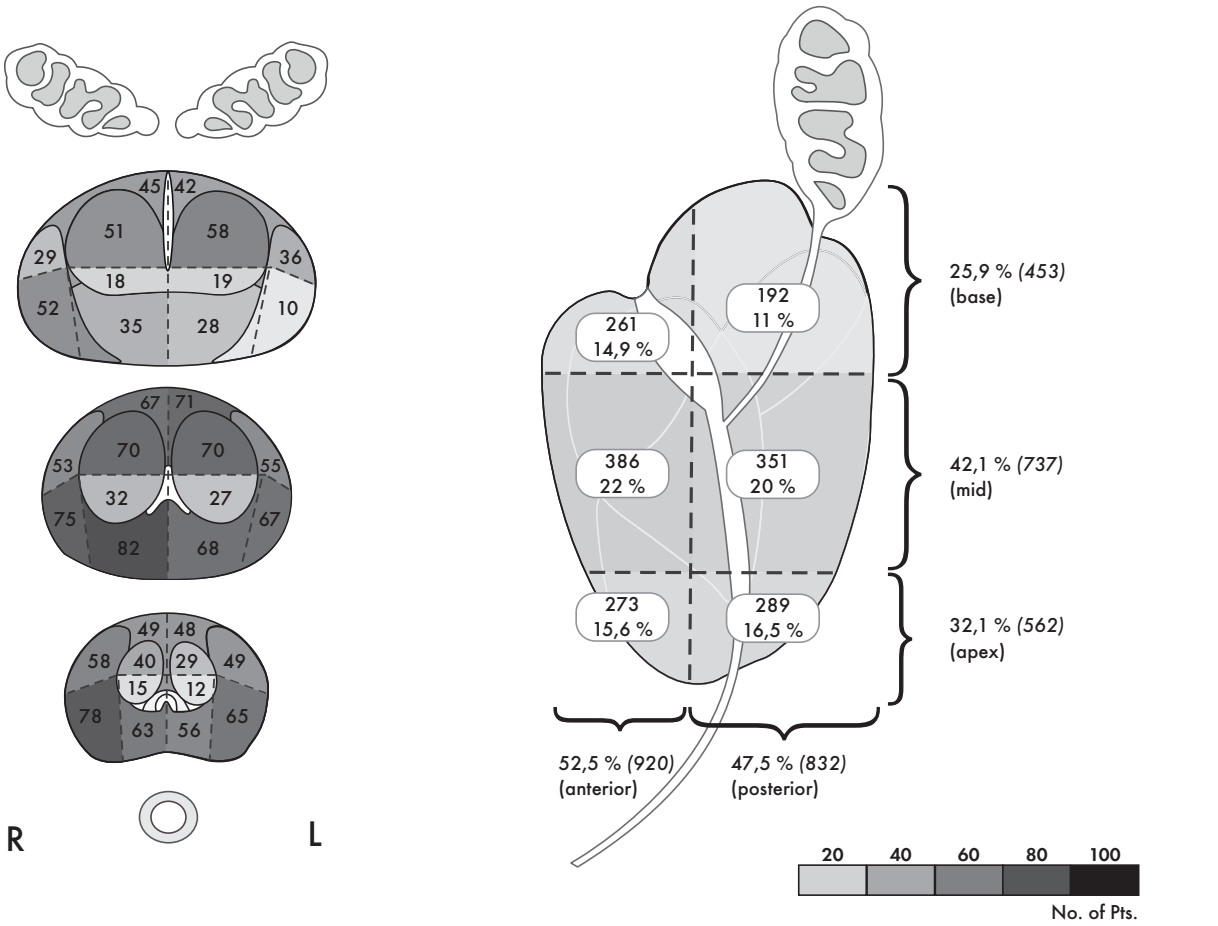

Fig. 2. Number of tumour involvement in the individual segments . According to PIRADS v.2.

of studies on tumour location, including McNeal studies, have been conducted on material obtained from radical prostatectomies[2]. Moreover, these tumours were largely diagnosed with biopsy of the peripheral zone, which meant that only peripheral zone tumours, a certain proportion of transition zone tumours, and anterior tumours with a large volume were thus detected. Only a few studies evaluated tumour location from autopsies or radical cystoprostatectomy material. The ones that did, reported nearly identical occurrence in the anterior vs. peripheral zones. Because of the study design, the majority of findings were tumours with a small volume[16-17].

With the advent of multiparametric MRI in the diagnosis of prostate cancer, an increased tumour occurrence in the anterior zone has been observed. We have confirmed this finding by evaluating our cohort. With respect to the conclusions of previous publications, we addressed several questions.

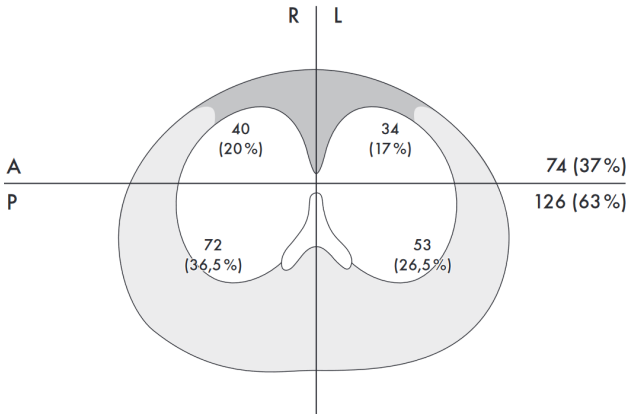

Fig. 3. Location of index tumour in individual quadrates.
A – anterior P – posterior.

1. Does it still hold true that anterior tumours are less frequent? In our cohort, we failed to show a significantly higher occurrence of tumours in the peripheral zone compared to those in the anterior zone. In other words, we can say that anterior tumours are equally frequent.
2. Anterior tumours are diagnosed with a larger tumour volume. Yes, it is true. This suggests that these tumours are diagnosed later than those in the peripheral zone.
3. Anterior tumours are diagnosed at a higher PSA level. We failed to confirm the assumption that anterior tumours are mostly diagnosed at higher PSA levels. We believe that this has been contributed to by the introduction of magnetic resonance imaging in the rebiopsy strategy, particularly with higher PSA levels[18].
4. Anterior tumours are less aggressive. This statement may be accepted with regard to the significantly more

Table 1. Demographic and clinicopathological comparison of anterior vs posterior tumor locations.

Variable	Overall	Tumor location		*P*
		Posterior	Anterior	
	n = 200	n = 126	n = 74	
Age at surgery (year)				
Mean (s.d.)	65 (7)	65 (7)	66 (7)	0.62
Median (range)	65 (60–70)	65 (60–70)	66 (60–70)	
Pretreatment PSA(ng/Ml)				
Mean (s.d.)	8.13 (7.22)	7.40 (5.41)	9.36 (9.46)	0.74
Median (range)	6.03 (4.61–8.90)	6.09 (4.80–8.30)	5.94 (4.50–10.00)	
Tumor volume (cc)				
Mean (s.d.)	1.610 (2.08)	1.281 (1.759)	2.170 (2.452)	0.003
Median (range)	0.794 (0.352–1.809)	0.679 (0.283–1.649)	1.102 (0.545–2.884)	
MRI before treatment				
Yes	49 (24.50%)	21 (16.67%)	28 (37.84%)	0.001
No	151 (75.50%)	105 (83.33%)	46 (62.16%)	
CaP family history				
Yes	21 (10.50%)	12 (9.52%)	9 (12.16%)	0.56
No	179 (89.50%)	114 (90.48%)	65 (87.84%)	
Pathological T stage				
pT2	142 (71.00%)	83 (65.87%)	59 (79.73%)	0.037
pT3	58 (29.00%)	43 (34.13%)	15 (20.27%)	
EAU risk group before operation				
Low	110 (55.00%)	65 (51.59%)	45 (60.81%)	0.22
Intermediate	76 (38.00%)	52 (41.27%)	24 (32.43%)	
High	14 (7.00%)	9 (7.14%)	5 (6.76%)	
EAU risk group after operation				
Low	12 (6.00%)	7 (5.56%)	5 (6.76%)	0.004
Intermediate	165 (82.50%)	100 (79.37%)	65 (87.84%)	
High	23 (11.50%)	19 (15.08%)	4 (5.41%)	
PSA group (ng/Ml)				
0-4	32 (16.00%)	19 (15.08%)	13 (17.57%)	
4-10	132 (66%)	89 (70.63%)	43 (58.11%)	0.11
10-20	26 (13.00%)	15 (11.90%)	11 (14.86%)	
>20	10 (5.00%)	3 (2.38%)	7 (9.46%)	
Surgical margin status				
Positive	37 (18.50%)	23 (18.25%)	14 (18.92%)	1.00
Negative	163 (81.50%)	103 (81.75%)	60 (81.08%)	
Primary diagnosis				
In our institution	65 (32.50%)	23 (28.57%)	14 (39.19%)	0.16
Referred to our institution	135 (67.50%)	90 (71.43%)	45 (60.81%)	

Continuous variables were compared with the Wilcoxon rank sum test. Categorical variables were compared using the Fisher exact test.

frequent occurrence of high-risk carcinoma in PPC (15.8% vs. 5.41%). On the other hand, only 6.76% of APCs were low-risk tumours not requiring active therapy. Anterior tumours thus deserve the same attention as posterior ones.

Since the introduction of new imaging techniques and targeted biopsies even into the transition and anterior zones, the number of patients diagnosed with a tumour in these locations has been increasing[18-21] and, as a result the number of anterior prostate cancers in radical prostatectomy specimens has been increasing, too. We can assume that it is selection bias that causes this difference[9]. Previous series have suggested that anterior tumours are not significant and that, in the vast majority of cases, the index tumour is located in the peripheral zone[4-19]. Our results, however, show that there are large tumours that are found in the anterior zone only and, thus, are missed with standard biopsy. As our results suggest, the frequency of anterior tumours is significantly higher compared with the literature (37% vs. 24.9%) (ref.[18]). Contrary to previous expectations, however, they are not merely insignificant carcinomas that would not require radical treatment (only 6.76% of APCs were low-risk tumours). In the past, these patients underwent repeated biopsies, and a proportion of them were diagnosed at a time when their disease was

advanced or generalized and they could not be offered radical treatment with a curative intent. Referring to our results, we recommend inclusion of targeted prostate biopsy in the standard diagnostic protocol for prostate cancer. Particularly in cases when patient inclusion in an active surveillance protocol is considered, we find it crucial to rule out anterior tumour by MRI-targeted biopsy[22]. Consequently, if a significant anterior tumour is not ruled out, patient undertreatment may occur during active surveillance[23-25].

CONCLUSION

With the introduction of MRI-targeted prostate biopsy in the standard diagnostic protocol, an increased occurrence of anterior prostate cancers has been observed. But they are not merely insignificant carcinomas that would not require radical treatment. Our results are of such significance and have such an important impact on the diagnosis and treatment that we consider it necessary to include MRI-targeted prostate biopsy in the standard diagnostic protocol. Anterior tumours should be considered especially in the case of repeatedly negative prostate biopsies and, in particular, before including a patient in active surveillance.

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