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ORIGINAL ARTICLE

The increase of stage, grading, and metastases in patients undergoing radical prostatectomy during the last decade

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Abstract

Purpose To investigate changes in clinical data and pathological features of prostatectomy specimens of prostate cancer (PCa) patients in a large tertiary care center over the last 12 years as potential consequence of reduced acceptance of prostate-specific antigen (PSA)-based screening and implementation of active surveillance as a therapeutic option in PCa.

Methods We retrospectively identified all patients with PCa who underwent radical prostatectomy at our institution between 2004 and 2016 from our clinical database. We reviewed clinical and pathological data including patient age, PSA level, number of positive cores and Gleason score in prostate biopsy, and pathologic N- and T-stage, and Gleason score in radical prostatectomy specimen.

Results Data of 5497 consecutive patients were analyzed. Median PSA increased from 7 (IQR 4.8–10.5) to 9 ng/ml (IQR 5.8–16.1; $p < 0.001$), and median number of positive biopsy cores increased from 3 (IQR 2–5) to 5 (IQR 3–7; $p < 0.001$). The proportion of patients with Gleason score ≥ 7 in biopsy and prostatectomy specimens increased from 40 to 78% and 49 to 89% ($p < 0.001$), respectively. The rate of locally advanced ($\geq$ pT3a) and lymph node-positive tumors increased from 28 to 43% and 5 to 16% ($p < 0.001$), respectively.

Conclusions We observed a significant change in clinical and pathological findings in our prostatectomy series with a significantly higher proportion of aggressive and locally advanced PCa in recent years. These findings may be related to a reduced acceptance of PSA-based screening and the use of active surveillance as management strategy and have significant impact on daily patient care.

Keywords Prostate cancer · Screening · Radical prostatectomy · Stage migration

Introduction

The widespread use of prostate-specific antigen (PSA) as a tool in prostate cancer (PCa) screening has led to a changing epidemiology of this malignancy. Since the introduction of PSA screening, a significant increase in the detection of PCa could be observed, with rising numbers of patients undergoing definitive treatment, such as radical prostatectomy.

In large prostatectomy series in the 1980s, there was a notable trend toward low-risk and low-stage tumors in newly diagnosed diseases [5, 11, 29], attributable to a more timely PCa diagnosis due to the implementation of PSA testing. Consequently, PSA screening resulted in a decline in PCa mortality rates—a finding that was confirmed by the "European Randomized Study of Screening for Prostate Cancer" (ERSPC) trial [28]. However, there is also evidence of an increased risk of overtreatment in patients with low-risk disease. In the latest update of the ERSPC trial, the authors estimated a number needed to detect of 27 and a number to be invited to screening of 781 to prevent one cancer-related death [28].

This overtreatment may lead to preventable long-term therapy-related morbidities and quality-of-life impairments in this PSA-screened population. Instead, active surveillance

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has proven to be a feasible and safe management strategy in low-risk PCa patients to avoid overtreatment [18].

In contrast, a series of recommendations exist that argue against PSA-based screening programs. They are supported by findings of different studies on PSA-based screening [1, 19, 26] that denied an effect of PSA testing on PCa-related mortality. Although these data should be interpreted with caution, they may lead to a loss of acceptance of PSA screening programs and subsequently to a more restricted use of PSA testing [10]. After all, there is evidence that a decreased use of PSA testing may lead to a "reverse stage migration". In an analysis from the "Pennsylvania Cancer Registry", the authors reported a shift toward more advanced disease at diagnosis and proposed a causal connection between "reverse stage migration" and the decreased use of PSA-based screening [24]. Additionally, the incidence of PCa is decreasing in the USA and in Europe in the last years, most probably caused by the reduced use of PSA-based screening [8, 32]. A former analysis focusing on the changes in PCa characteristics using a large prostatectomy series had been published in the first decade of the twenty-first century [4], indicating an inverse stage migration trend in those patients treated with radical prostatectomy.

In the present study, we aimed to investigate whether clinical data and tumor characteristics of prostatectomy specimens of PSA-screened PCa patients in a single large tertiary care center have still changed over the last decade.

Materials and methods

Study design

We retrospectively identified all patients with biopsy-proven PCa who underwent radical prostatectomy at our institution between April 2004 and September 2016 from our clinical database. We reviewed clinical and pathological data including patient age, PSA level, number of positive cores and Gleason score in preoperative prostate biopsy, and pathologic N- and T-stage, and Gleason score in postoperative radical prostatectomy specimen.

Surgical procedure and histopathological evaluation

Radical prostatectomy was performed using an open retropubic or a robot-assisted minimally invasive approach as previously described [3]. The decision to perform pelvic lymph node dissection was based on the individual patient's risk group. Pathological features were assessed using the AJCC (American Joint Cancer Committee) 2002 staging system and tumor grade was classified using the Gleason grading system [13].

Statistical analysis

To evaluate changes over time, clinicopathological data were collected, summarized, and compared in biannual time periods. Univariate analysis was performed by Kruskal–Wallis–ANOVA test and post hoc tests for continuous variables and Chi square test for categorical variables. A p value < 0.05 was considered to be statistically significant. All calculations were carried out using STATISTICA 13 (Dell Statistica, Tulsa, OK, USA).

Results

A total of 5497 consecutive patients were identified. Basic characteristics of these patients are demonstrated in Table 1. Median patient age at diagnosis was 64 years (IQR 61–69) at the beginning of the time period in the years 2004/05 vs. 66 years (IQR 61–72) at the end of it in 2016 ($p = 0.002$). Median PSA of all patients increased from 7 ng/ml (2004/05, IQR 4.8–10.5) at the beginning of the time period to 9 ng/ml at the end of it (2016, IQR 5.8–16.1; $p < 0.001$; Fig. 1). The median number of positive biopsy cores increased significantly from 3 (IQR 2–5) to 5 (IQR 3–7; $p < 0.001$; Fig. 2). The proportion of patients with Gleason score ≥ 7 in biopsy and prostatectomy specimens almost doubled from

Table 1 Patient characteristics

Parameter	Value
Age at RP (years)	Median 66, IQR 61–71
Preoperative PSA (ng/ml)	Median 7.5, IQR 5.2–11.8
Number of positive biopsy cores	Median 4, IQR 2–6
Gleason score (biopsy)	
Gleason ≤ 6	42.8%
Gleason 7a	27.2%
Gleason 7b	11.9%
Gleason 8–10	18.0%
Tumor classification	
pT2	65.4%
pT3	33.7%
pT4	0.8%
Lymph node status	
pN0	69.9%
pN+	8.5%
pNX	21.6%
Gleason score (prostatectomy)	
Gleason ≤ 6	30.6%
Gleason 7a	32.6%
Gleason 7b	15.3%
Gleason 8–10	21.5%

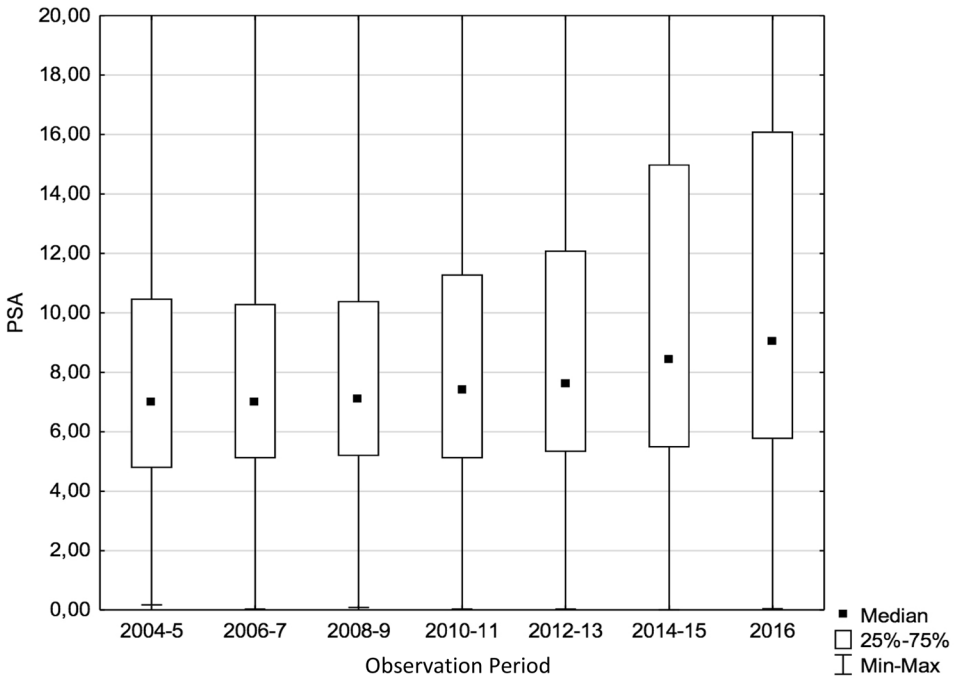

Fig. 1 Preoperative PSA during observation period

2004/5 vs. 2016 p<0,001

2004/5: mean 11, median 7
2016: mean 18, median 9

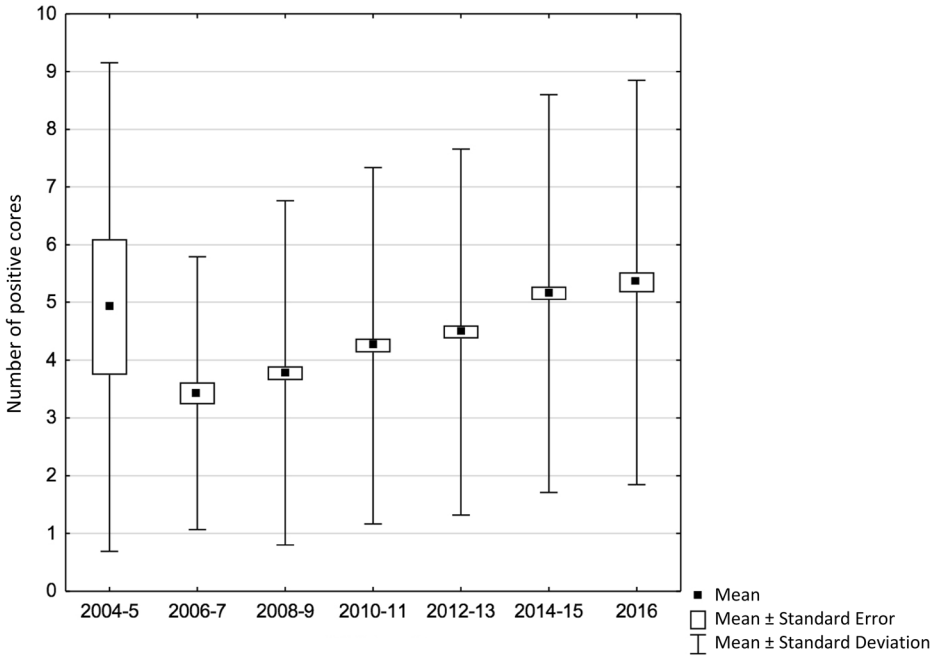

Fig. 2 Number of positive cores in preoperative biopsy during observation period

2004/5 vs. 2016 p<0,001

Fig. 3 **a** Proportion of patients with Gleason sum ≥ 7 in preoperative biopsy ($p < 0.001$). **b** Proportion of patients with Gleason sum ≥ 7 in prostatectomy specimen ($p < 0.001$)

40 and 49% up to 78 and 89% ($p < 0.001$, Fig. 3a, b). The rate of locally advanced (≥ pT3a) and lymph node-positive tumors increased from 28 to 43% and 5 to 16%, respectively ($p < 0.001$, Fig. 4a, b).

Discussion

In the present study, we observed a significant stage migration between 2004 and 2016 both in clinical characteristics (higher preoperative PSA level, higher number of positive biopsy cores, and higher proportion of Gleason score > 7 in prostate biopsy) and postoperative pathological features (higher rates of extraprostatic disease, Gleason score of ≥ 7 and lymph node metastases in prostatectomy specimen).

One decade earlier two precedent studies could demonstrate a similar trend toward more advanced and aggressive disease in the USA and in Europe [4, 12]. The authors found an increase in the number of patients with nonorgan-confined PCa and lymph node metastases from 19 to 33% and from 1.2 to 5.6% within 6 years [4].

However, in the present study we could confirm that this development is still an ongoing process, resulting in a rate of locally advanced (≥ pT3a) and lymph node-positive tumors of 43% and 16%, respectively. Recently published multi-institutional data have shown a rising number of lymph node metastases accordingly. The authors could show an increase in the rate of lymph node involvement from 2.5% in 2004 to 6.6% in 2014 [23]. The difference between the percentage in this multi-institutional data from the US and our local findings suggests a variety of causes that may have led to these findings and that may differ in their local significance. Accordingly, Gallina et al. found that stage and grade migration affected the USA and Europe in the past to different extents [12].

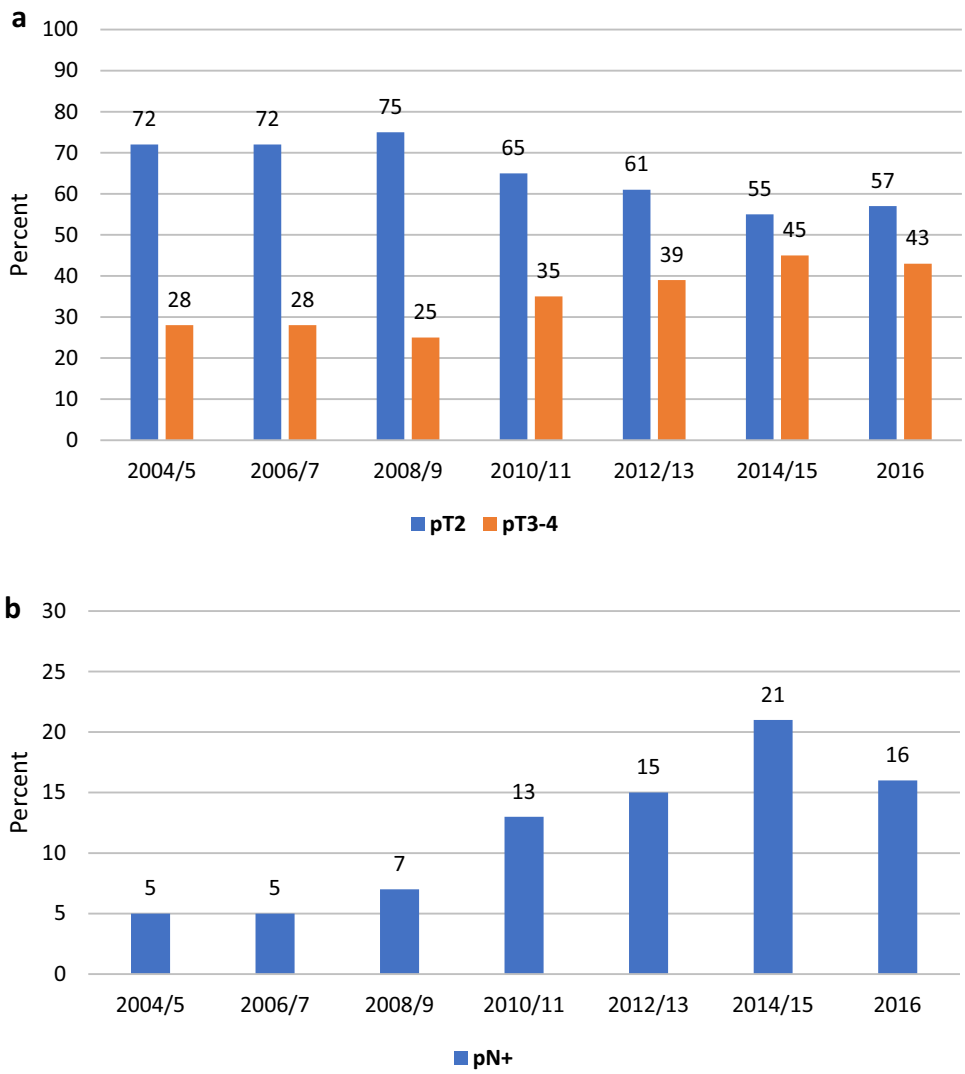

Fig. 4 **a** Proportion of pT2 and ≥pT3 tumors in prostatectomy specimens ($p < 0.001$). **b** Proportion of lymph node-positive specimens ($p < 0.001$)

On one hand, our results may be explained by a reduced acceptance of PSA-based screening programs, resulting in a real "reverse stage migration". Data from the Pennsylvania Registry support this idea: the authors could show a relationship in time between publication of US Preventive Services Task Force (USPSTF) recommendations against PSA-based early detection and screening practices, and the decreasing incidence of low-stage prostate cancer. In contrast, the incidence of regional and metastatic disease remained stable [24]. Earlier studies had described a decrease in PSA screening rates in the USA following the publication of the USPSTF recommendations [25, 31, 35], which makes a relationship between decreasing PSA-screening rates and lower incidence of low-risk PCa plausible. However, similar European data demonstrating any changes in PSA-screening rates over the years are lacking, so a relationship between the utilization of PSA screening and the results of the present study can just be hypothesized.

On the other hand, changes in the management of PCa in the last years may have influenced these findings:

First, we observed a change in treatment strategies for locally advanced high-risk PCa in recent years. Whereas for a long time high-risk PCa had been preferentially treated by radiation therapy, there has been a trend toward surgery as the primary treatment modality in high-risk disease during the last years [15]. This changing trend is supported by the fact that radiation therapy—which was formerly proposed as primary treatment in all cases with a high probability of positive surgical margins—has shown a higher proportion of treatment failure in terms of metastatic progression [34], prostate cancer-specific mortality [2], and all-cause mortality [6, 30] in high-risk disease.

Second, this development is accompanied by a strong trend toward performing prostate surgery in high-volume centers [14]. As functional impairment and oncological failure after surgery are more frequent in men with high-risk

tumors, these cases may be concentrated in specialized centers.

Third, there is evidence that life expectancy of men in their 70s is increasing, and the threshold of 10 years life expectancy already accounts for men at the age of 75 [9]. Thus, radical prostatectomy has become a more accepted treatment option, even in elderly patients. It is well known that elderly patients bear a higher risk of advanced and more aggressive disease [17, 22].

Another explanation is the implementation of active surveillance as a management option for low-risk PCa [18]. A recent Swedish study showed a significant increase in the use of active surveillance from 2009 to 2014 from 40 to 74% of patients with low-risk prostate cancer [20]. These patients do not need to undergo radical prostatectomy, so this trend may contribute to a stage shift in prostatectomy series with a higher number of intermediate- and high-risk PCa patients.

Unfortunately, our data do not investigate the underlying causes being responsible for this changing trend at our institution. Clearly, there is also a need for further investigations using national, multi-institutional data.

However, irrespective of the underlying causes of our findings, our results have a high impact on daily care of these patients. As the incidence of lymph node metastases is rising, a more precise staging may be necessary to provide an individual, risk-adopted treatment strategy. The use of sensitive diagnostic tools like PSMA PET-CT [27] may be useful and increasingly important in this setting. Besides, a higher proportion of unfavorable postoperative histopathologic features may result in a higher rate of patients needing adjuvant or salvage radiotherapy with rising morbidity and cost [7]. Particularly, the incidence and course of postoperative urinary incontinence is dependent on tumor stage [16], adjuvant radiotherapy [33], and age at surgery [21]. Therefore, we may expect a long-term higher need for additional incontinence treatment.

Main limitations of the present study include the single-institution, retrospective review of data, limiting our ability to assess causation. Our cohort comprised of patients seen at a specialty center, which impacts the generalizability of our findings to patients in other community-based centers or in other countries. The trend to concentrate high-risk patients in high-volume centers may be a source of a selection bias with a higher proportion of this risk group in our series.

Conclusions

In this large prostatectomy series, we demonstrated an ongoing trend with significant changes in clinical and pathological characteristics over the last 12 years, with a significantly higher proportion of aggressive and locally advanced PCa in recent years. Further studies are needed to elucidate whether these changes are due to a decreasing acceptance of PSA-based screening, to epidemiological factors (e.g., increasing life expectancy), or to changes in disease management over the last years, such as implementation of active surveillance as management strategy in low-risk PCa. These changing PCa characteristics have a significant impact on daily patient care, because a higher number of patients with advanced disease will require a more precise preoperative assessment, a higher number of adjuvant radiotherapies and a higher number of postoperative incontinence therapies.

Author contributions VB: data collection; BS: data collection; AH: manuscript writing; MA: data collection; AB: data analysis; CG: project development; CS: project development, data analysis; ST: project development, data analysis, manuscript writing.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The work complies completely with the ethical standards of the Helsinki Declaration.

Informed consent Informed consent was obtained from all individual participants included in the study.

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