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Research article

Comparison of PSA-density of the transition zone and whole gland for risk stratification of men with suspected prostate cancer: A retrospective MRI-cohort study

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ABSTRACT

Purpose: To compare the correlation of transition zone prostate-specific antigen density (TZPSAD) versus whole gland (WG) density (PSAD) with Gleason score.

Methods: In this single-center, retrospective cohort study, men undergoing MRI of the prostate in 2015 and 2016 who had a transperineal template saturation biopsy within 6 months of MRI were included (n = 178; median age 64 y, interquartile range [IQR] 58–68 y; PSA 6.6 ng/ml, 4.6–9.7 ng/ml). The WG and TZ were segmented voxel-wise on T2-weighted transverse planes. The volumes and corresponding PSA-densities were calculated. Correlations with the Gleason score were assessed with Spearman's rho. Optimal thresholds of the PSA densities were computed using the Youden Index of the receiver-operating-characteristics curve. A p-value of ≤ 0.05 was considered statistically significant.

Results: Median WG volume was 45 ml (IQR: 33.9–58.7 ml, range: 17.2–165.3 ml), median volume of the TZ was 27.3 ml (IQR: 19.2–39.3 ml, range: 9.0–141.1 ml). Both PSA density values, PSAD and TZPSAD, correlated significantly with the Gleason score: The PSAD (rho = 0.39) showed significantly weaker correlation than the TZPSAD (rho = 0.44, p = 0.05). ROC analysis revealed an ideal cut-off of 0.15 ng/ml^2 for PSAD (95%-CI: 0.09–0.16 ng/ml^2) and 0.22 ng/ml^2 for the TZPSAD (0.15-0.32 ng/ml^2) for discrimination between Gleason 3 + 4 and 4 + 3.

Conclusion: The TZPSAD exhibited a stronger correlation with cancer dedifferentiation than PSAD and may thus be a better surrogate marker for cancer aggressiveness than PSAD. Moreover, the TZPSAD threshold of 0.22 ng/ml^2 may help in risk stratification of men with suspected PCa.

1. Introduction

Magnetic resonance imaging (MRI) has become an integral part in the workup of men with suspected prostate cancer (PCa). Since the negative predictive value of MRI to exclude clinically significant cancer (Gleason score ≥ 7) is estimated around 90%, meaning that an unsuspicious MRI alone is not enough to rule out PCa [1], it is usually combined with other clinical information for PCa risk estimation, such as the serum prostate-specific antigen (PSA).

PSA is produced either mainly in the transition zone (TZ) by epithelial cells of normal or benign hyperplastic prostatic tissue, or anywhere in the body by malignant PCa tissue. It is therefore *tissue specific* but not *cancer specific* [2]. The absolute blood PSA-level has low specificity and poor discriminatory power between malignant (PCa) and benign causes such as benign prostatic hyperplasia (BPH) [3]. Thus, it has been shown repeatedly that PSA in relationship to the prostatic volume, the so-called PSA density (PSAD), can improve risk classification and has a higher positive predictive value in detection of PCa than the PSA-value alone [4–10]. However, BPH occurs nearly exclusively in the transition zone (TZ) and, therefore, PSA changes from BPH are

Abbreviations: BPH, benign prostate hyperplasia; IQR, interquartile range; MRI, magnetic resonance imaging; PCa, prostate cancer; PSAD, whole gland prostate-specific antigen density; ROC, receiver operating characteristics; TTSB, transperineal template saturation biopsy; TZPSAD, transition zone prostate-specific antigen density

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mainly related to an increase in TZ volume [11]. Hence, it was our hypothesis that matching PSA to the TZ (TZPSAD) in MRI may result in a better discrimination between benign (BPH) and malignant (PCa) origin of the PSA elevation [12], i.e. superior risk stratification of men with suspected PCa.

While the published data on the usefulness of TZPSAD are equivocal [10,13], it is important to note that the volumetric parameters in these studies were derived from transrectal ultrasound imaging. Ultrasound as a modality is profoundly operator dependent [14,15] and has inferior soft-tissue contrast to magnetic resonance imaging (MRI) [14]. The latter yields immutable, volumetric datasets with excellent soft-tissue contrast between the anatomical zones of the prostate. To date, no study has evaluated the correlation of MRI-derived TZPSAD with PCa aggressiveness.

Therefore, the purpose of this retrospective MRI cohort study was to compare the correlation of TZPSAD versus whole gland PSAD with the histological PCa Gleason score.

2. Materials and methods

This retrospective study was approved by the local ethics committee, who waived the need for study-specific informed consent. Absence of patient's general informed consent for research was an exclusion criterion.

2.1. Patient cohort

We evaluated 473 patients at our institution who were referred for a multiparametric MRI (mpMRI) of the prostate at 3 T in the years 2015 and 2016. We included only patients with complete MRI data and without prior surgical, radiation or pharmacological treatment. In total, n = 182 had received a transperineal template saturation biopsy (TTSB) within ≤ 6 months from MRI examination. Of these, four had to be excluded post-hoc due to unavailable or unsuitable axial T2 series for segmentation. Hence, the final study cohort consisted of n = 178 patients. This patient selection process is summarized in the flowchart in Fig. 1.

2.2. Reference standard

All patients had undergone TTSB within ≤ 6 months after the MR scan, performed by board-certified urologists. TTSB was performed under general anesthesia using a 5-mm brachytherapy template grid as reported before [16]. Histopathology specimens were evaluated by dedicated genitourinary pathologists. An example of a histopathology template map and the corresponding MRI slice is shown in Fig. 2.

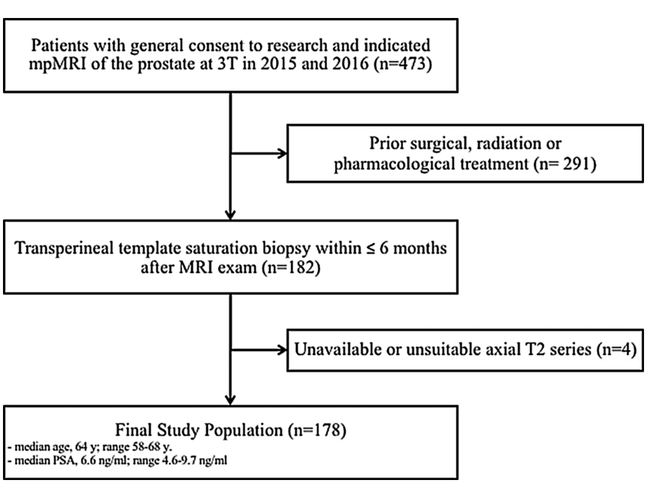

Fig. 1. Flowchart of the patient selection process.

2.3. MR imaging protocol

All patients were examined with a 3 T MRI system (Skyra, SIEMENS Healthcare®, Erlangen, Germany) with two independent transmit channels (TimTX TrueShape, Siemens Healthcare, Erlangen, Germany). The reception coils were composed of an 18-channel phased-array receiver and, for some patients, a balloon covered, expandable endorectal coil. The axial T2 sequence used for segmentation had an in-plane resolution of 0.27 × 0.27 mm and a slice thickness of 3 mm. Our clinical imaging protocol was established in line with the latest guidelines [17] analogous to [16].

2.4. De-identification and segmentation

Prior to segmentation, all personal data were removed from the DICOM metadata and a random study-ID was assigned. Thus, the reader was blinded to the clinical information. Using the transverse T2w sequence of the mpMRI scans, the whole prostate and transition zone were segmented voxel-wise on every plane. Segmentations were checked by a second, independent reader for correctness. We used the freely available, open-source application ITK-SNAP 3.6.0 for this purpose (http://www.itksnap.org). Fig. 3 depicts a single slice as well as a 3D-rendering of a representative segmentation example. By using the metadata in the DICOM header, segmented volumes of the whole gland as well as the transition zone only were calculated. PSA-density was computed for both volumes separately. Lastly, we calculated the volumes of the whole gland and the transition zone by means of 3-axis measurements and the bullet formula (cylinder + half ellipsoid = length * width * height * 5Π/24) as proposed by MacMahon et al. [18]. We compared the computed and the segmented volume estimates as well as the derived PSAD values.

2.5. Statistical analysis

Statistical analysis was performed with R 3.4.4 (R Foundation for Statistical Computing, Vienna, Austria). Since normality could not be assumed for any of the parameters in our population, continuous variables were summarized as median and (interquartile) range, ordinals as counts and/or percentages. Calculated and segmented volume estimates were compared with Bland-Altman plots/statistics. Correlation of PSA density with Gleason score was tested with Spearman's *rho* for the whole gland and transition zone. The difference of the two correlations were tested for significance by conversion to z-scores using Fisher's transform (function *paired.r* of the package *psych 1.8.4)*. Lastly, patients were dichotomized into no or intermediate risk (max. Gleason score ≤ 3 + 4; ≤ ISUP grade group 2) vs. high risk (max. Gleason score ≥ 4 + 3, ≥ ISUP grade group 3) and the optimal threshold (Youden index) PSA density was computed using receiver operating characteristics (ROC) curve analysis. 95%-confidence intervals of the thresholds were obtained by bootstrapping with 2000 replicates. Area under the ROC curves were compared with DeLong's test for paired curves. All p-values ≤ 0.05 were considered statistically significant.

3. Results

3.1. Patient demographics

Median age of our cohort was 64 y, interquartile range [IQR] was 58–68 y. The median PSA was 6.6 ng/ml (IQR: 4.6–9.7 ng/ml). Time interval between PSA measurement and MRI examination was 30 days (IQR: 13–63 d). All men had undergone TTS biopsy within ≤ 6 months from MRI examination (median: 22.5 d, IQR: 12–42 d). Median prostate volume was 45 ml (IQR: 33.9–58.7 ml, range: 17.2–165.3 ml), median volume of the transition zone was 27.3 ml (IQR: 19.2–39.3 ml, range: 9.0–141.1 ml), representing 61.3% of the whole gland volume (IQR:

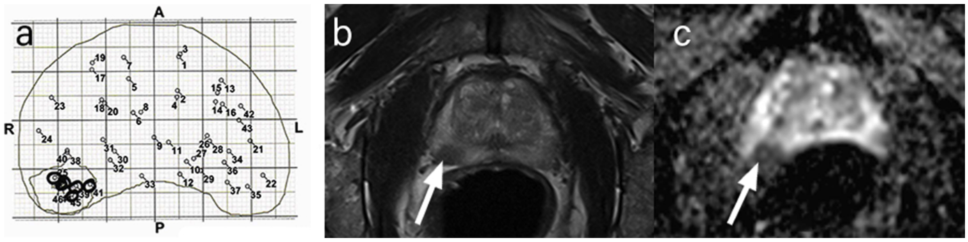

Fig. 2. An Example of histopathology template map (a) and the corresponding MRI slice. Clinically significant PCa (Gleason score 3 + 4) in the right PZ of a 77-year-old patient (white arrow). The tumor seen in the T2w image (b) shows a clear diffusion restriction (c).

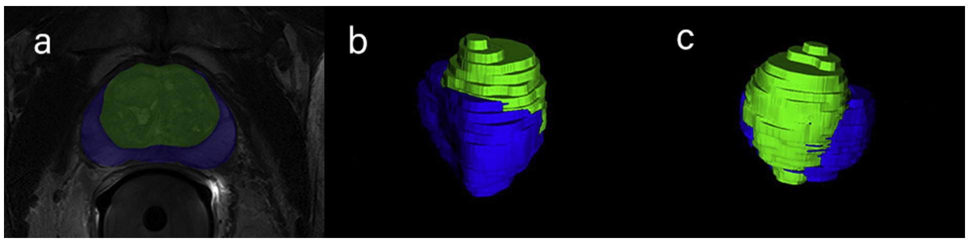

Fig. 3. a) Screenshot of a representative segmentation (axial plane) b,c) 3D-Rendering of the segmentation from an oblique back and front view, respectively. The peripheral zone is colored in blue, the transition zone in green.

53.4–69.1%, range: 18.9–93.0%). Occurrence of maximum Gleason scores are summarized in Table 1; patient demographics are summarized in Table 2. In 94 patients, the tumor was located in the peripheral zone (PZ), and in 12 patients in the TZ, respectively. One patient had a large tumor involving both zones.

3.2. Comparison of calculated and segmented volume estimates

Segmentation was successfully performed in all patients, none of the subjects exhibited artifacts which would have rendered segmentation unreliable. The calculated volume estimates of TZ and whole gland showed a systematic overestimation when compared with the segmented volumes: The mean difference in the TZ was 19.5 ml (95%-CI: −0.4–39.4 ml, $p < 0.001$) and in the whole gland 26.5 ml (1.3–51.7 ml; $p < 0.001$). The error was higher in larger prostates, as can be appreciated in the Bland-Altman plots in Supplemental Fig. 1.

Table 1
Prevalence of Gleason scores. Summary table of Gleason score prevalence (highest score per patient) in our cohort.

Gleason score	Count (n)
No cancer	65
3 + 3	22
3 + 4	57
4 + 3	21
4 + 4	3
4 + 5	8
5 + 4	1
5 + 5	1

Table 2
Patient Demographics. Summary of demographic information of our cohort (n = 178). Continuous variables were summarized as median, interquartile range given in parentheses.

Age [y]	64 (58–68)
PSA [ng/ml]	6.6 (4.6–9.7)
Time interval between MRI and PSA [d]	30 (13–63)
Time interval between MRI and biopsy [d]	22 (2–144)
Median prostate volume [ml]	45 (17.2–165.3)
Median volume of the transition zone [ml]	27.3 (9.0–141.1)

Continuous variables were summarized as median; interquartile range given in parentheses.

3.3. Comparison of PSA density values

Both PSA density values derived from the segmentations correlated significantly with Gleason scores: Spearman's rho PSAD for the whole gland (PSAD) was $rho = 0.39$, $p < 0.001$ and for transition zone (TZPSAD) was $rho = 0.44$, $p < 0.001$ (Fig. 4). The difference between the two correlations was statistically significant ($p = 0.05$). Two representative cases illustrating the superior correlation of the TZPSAD are depicted in Fig. 5.

The PSA density values derived from the calculated whole gland and TZ volumes correlated with the Gleason scores as well with $rho = 0.37$, $p < 0.001$ and 0.40, $p < 0.001$, respectively. However, the difference between these two correlations was not significant ($p = 0.18$).

Subgroup analysis revealed improved correlation for the TZPSAD in both cases with TZ and PZ tumors, with *rho* improving from 0.27 to 0.31 and from 0.38 to 0.42, respectively. The difference between the two was, however, not significant ($p = 0.34$ and 0.07), which may in part be attributable to the low number of TZ tumors (n = 12).

ROC analysis revealed an ideal cut-off of 0.15 ng/ml^2 for the whole gland density (95%-CI: 0.09–0.16 ng/ml^2) and 0.22 ng/ml^2 for the transition zone density (95%-CI: 0.15–0.32 ng/ml^2) for the discrimination between Gleason scores 3 + 4 and 4 + 3. The difference between the AUCs (0.69 vs. 0.72, Fig. 6), however, was not significant ($p = 0.059$).

4. Discussion

In this retrospective cohort study, we investigated whether the PSA density by transition zone volume (TZPSAD) correlates better with the histological Gleason score than the PSA density computed for the whole gland volume (PSAD). We could confirm that the TZPSAD exhibited a stronger correlation with cancer aggressiveness than PSAD and may thus be a better surrogate marker for risk stratification. Furthermore, our optimal cut-off for the PSAD of 0.15 ng/ml^2 is in line with the published literature [19], as is our threshold of 0.22 ng/ml^2 for the TZPSAD [20]. Our data and analysis hence confirmed our hypothesis that TZPSAD is superior to the PSAD for risk stratification of men with

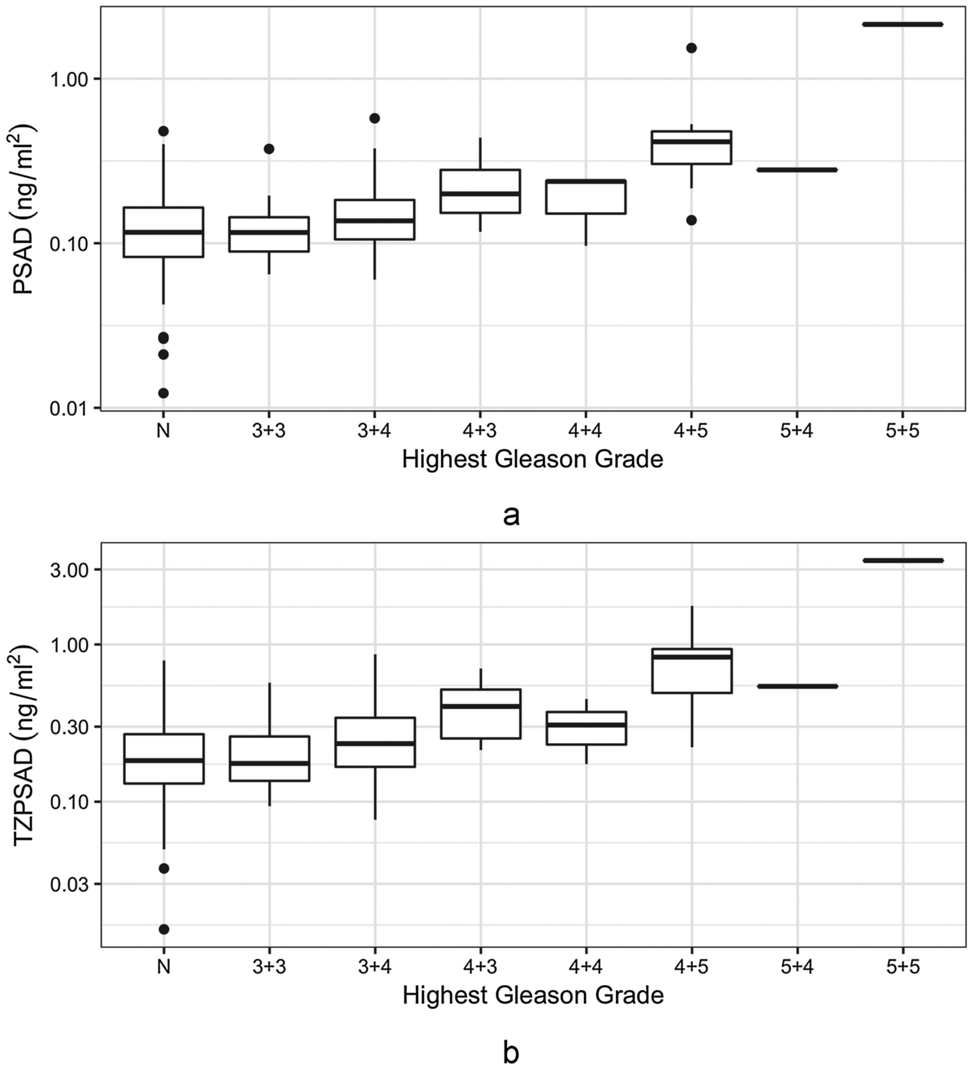

Fig. 4. Boxplot depicting the PSA density distribution in the respective Gleason score categories. The middle line represents the median, the top and bottom of the box the interquartile range, and the whiskers mark the 95%-confidence intervals. Outliers (outside of the CI) are marked with points. A positive correlation in both cases can be appreciated qualitatively, the Spearman correlation coefficient was PSAD*rho* = 0.39, and significantly higher for the TZPSAD*rho* = 0.44, respectively (p = 0.05).

suspected PCa.

PSA has widely been used to screen men at risk for PCa for more than three decades now. It is physiologically found in all ductal and acinar cells. Thus, the largest share of the serum PSA level originates from the TZ [21]. BPH exclusively affects the TZ and has a high prevalence in elderly men. Hence, its extent correlates with serum PSA elevation, which may mimic PSA originating from malignant PCa tissue [2]. It follows that serum PSA alone has low specificity, i.e. poor differentiation between malignant and benign processes [3].

The low specificity of PSA can be mitigated when combined with other surrogate markers and/or imaging [9,22]. One of these tools is the PSA density (PSAD) which has first been used by Benson et al [23,24]. The PSAD, calculated as total PSA per prostate volume, is higher in men with PCa than in men with benign hyperplasia (BPH) due to the fact that PCa releases more PSA per volume than BPH [9]. Since 1992, numerous studies proved that the PSA density can improve the accuracy and has a higher positive predictive value than PSA alone [3–10].

Since BPH is essentially a benign overgrowth of the transition zone, preliminary studies found a refinement of the PSAD, the TZPSAD, to be useful when applied to ultrasound examinations [5,12,20,25,26]. However, other authors could not replicate these results [10,13]. This is not surprising, as ultrasound has considerable limitations when it comes to approximating the true prostatic volume: Ultrasound is profoundly operator dependent [14,15,27], has inferior soft-tissue contrast to MRI [14] which does not allow reliable distinction of the zonal anatomy, and generally does not generate 3D volumetric data sets suitable for reproducible and accurate segmentation of the whole gland or the anatomical zones. Hence, 3-axis measurements are used as a surrogate, together with the ellipsoid or bullet formula for a crude estimation of the volume [15,27–30]. Our results show that 3-axis measurement derived volume estimates introduce a bias into the PSA density values which may in turn influence patient management. MRI, however, yields reproducible, high-resolution 3D datasets with high soft-tissue contrast of the different anatomical zones of the prostate, well-suited for anatomical segmentation and more reliable volume estimates. In the near future, this segmentation step may well become automated and thus time-efficient [31]. A first MRI study by Peng et al. on the subject of MR-volume derived PSA markers yielded similar findings [32], though their cohort (TRUS and prostatectomy) and analysis differed slightly from ours, not demonstrating superiority of TZPSAD compared to PSAD. Nevertheless, we expect our results to be more easily reproduced in the future than some of the preceding ultrasound studies.

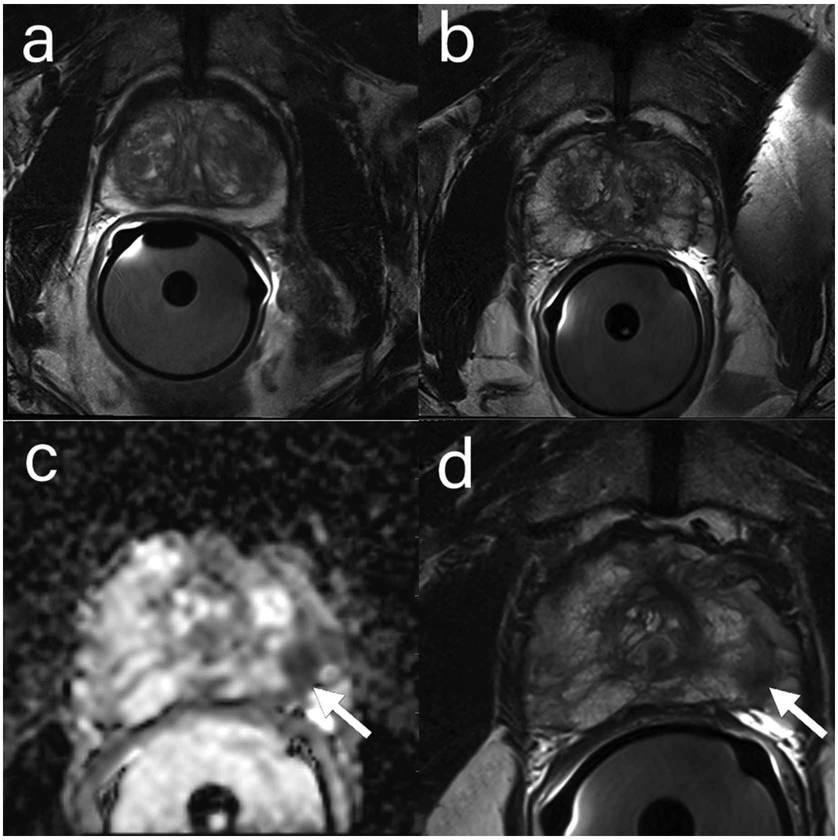

Fig. 5. (a) Example of a patient with high PSA but also large TZ volume and no cancer (Serum PSA = 13.1 ng/ml; PSAD = 0.22 and TZPSAD 0.26 ng/ml^2) (b) midglandular axial T2 section of a 55 year-old patient with serum PSA elevation and a relatively small TZ (Serum PSA 9.16 ng/ml, PSAD: 0.23 and TZPSAD: 0.45 ng/ml^2). The culprit in this patient was an apical tumor (Gl. score 4 + 4) as marked by an arrow in the DWI (c) and an apical T2 slice (d).

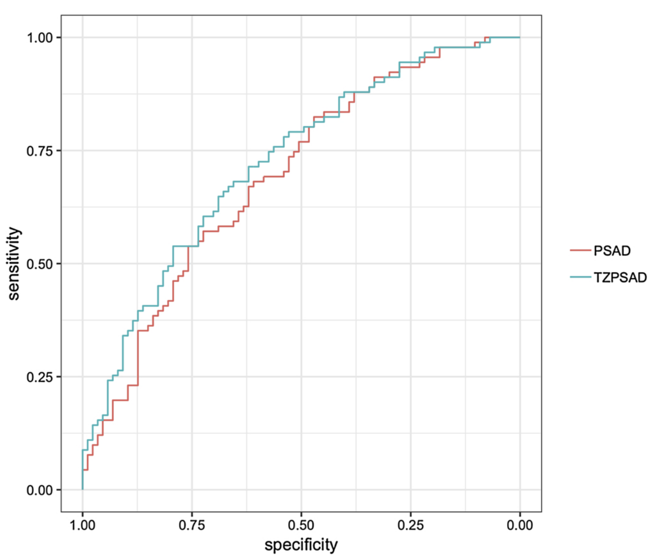

Fig. 6. ROC curves of the two PSA density parameters, showing a non-significant change of discriminatory power between Gleason scores 3 + 4 and 4 + 3 (ISUP grade groups 2 and 3) of the TZPSAD compared to the (whole gland) PSAD (AUC 0.72 vs. 0.69, p = 0.059).

Our study has several limitations that need to be acknowledged. First, the retrospective design inherently entails the risk of various biases, e.g. a selection bias is to be expected. Second, we used TTS biopsy instead of whole mount prostatectomy specimens as standard of reference. This entails the risk of missing some cancers when compared to whole mount prostatectomy. However, choosing the latter as a reference standard introduces a strong bias towards high-grade lesions. Third, we only used the segmentations of one reader. However, we have previously shown in an extensive interreader study in a different cohort from the same institution [manuscript currently under review], that in particular the interreader agreement in segmenation of the TZ is very high. Thus, we believe including more readers would not have added to the results or altered our conclusions.

In conclusion, we found that the TZPSAD exhibited a stronger correlation with cancer dedifferentiation than PSAD and may thus be a better surrogate marker for cancer aggressiveness than PSAD. Moreover, we found that a TZPSAD threshold of 0.22 ng/ml^2 may help in risk stratification of men with suspected prostate cancer.

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Declarations of interest

None.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ejrad.2019.108660.

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