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Oncological outcomes in robot-assisted radical prostatectomy: the value of PSA density as a preoperative predictive factor

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Abstract

Background: Pretreatment assessment of patients diagnosed with localized prostate cancer (PCa) is essential for therapeutic decision-making. Currently available staging systems based on prostate-specific antigen (PSA), Gleason score, and clinical stage allow for determining the prognostic characteristics of these patients. Several studies have evaluated the preoperative use of prostate-specific antigen density (PSAD) as a prognostic factor for further risk stratification. To date, the role of PSAD in this setting is still an object of debate.

Objectives: The present analysis aimed to assess the predictive potential of PSAD for adverse oncological outcomes after robot-assisted radical prostatectomy (RARP) and to compare its accuracy to preoperative PSA (pPSA).

Design and methods: We retrospectively reviewed 427 patients diagnosed with localized PCa who underwent RARP at a single institution between January 2015 and January 2020. Generating receiver operator characteristic (ROC) curves, calculating areas under the curves (AUCs), and using a linear regression model, we analyzed the association of PSAD and pPSA with postoperative positive surgical margins (PSM), Gleason score ≥ 7, persistent PSA, and biochemical recurrence (BCR), with a median follow-up of 47 months.

Results: PSAD showed a significant association with PSM ($p < 0.0001$), PSA persistence ($p < 0.0001$), and Gleason ≥ 7 ($p < 0.0001$), without being statistically significant in predicting BCR ($p = 0.098$). The predictive value of PSAD was comparable to pPSA for outcomes of PSA persistence (AUC 0.727 *versus* 0.771) and Gleason ≥ 7 (AUC 0.683 *versus* 0.649).

Conclusion: PSAD is a predictive factor for postoperative oncological outcomes of PSM, Gleason score ≥ 7, and persistence of PSA. Despite the need for further studies, PSAD could be useful as a prognostic parameter in conjunction with established staging systems.

Plain language summary

Oncological outcomes in robot-assisted radical prostatectomy: the value of PSA density as a preoperative predictive factor

Prostate-specific antigen density (PSAD) has an established role in the diagnostic process of prostate cancer (PCa). However, controversy remains on the assessment of its value as a pretreatment prognostic factor. The aim of our study was to evaluate the predictive ability of PSAD for oncological outcomes in PCa patients treated with robot-assisted radical prostatectomy (RARP) and to compare with the value of preoperative PSA (pPSA). The present analysis showed a significant association of PSAD with positive surgical

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margins (PSM), Gleason Score >=7 and prostate-specific antigen (PSA) persistence after RARP. Moreover, PSAD demonstrated to perform comparably to pPSA in predicting the outcomes of clinically significant PCa (csPCa) and post-RARP PSA persistence. Therefore, PSAD is considered a preoperative predictive factor potentially useful in conjunction with other previously established prognostic criteria and clinical features.

Keywords: oncological outcomes, prostate cancer, prostate-specific antigen, prostate-specific antigen density, robot-assisted radical prostatectomy

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Introduction

Prostate cancer (PCa) is the second most diagnosed cancer in men, with nearly 1.4 million cases reported in 2020 worldwide, representing the sixth leading cause of cancer death in the male population.[1–3] Radical prostatectomy (RP) is one of the mainstays of treatment for localized PCa, and the robot-assisted procedure has been adopted as the preferred surgical approach during the last decade.[4,5] In this setting, entering the era of precision surgery and individualized medicine,[6,7] pretreatment assessment of the clinical and pathological features of patients with localized PCa is of paramount importance to determine their prognosis and design the most optimal and individualized therapeutic strategy. The current established risk stratification system based on serum prostate-specific antigen (PSA) level, biopsy Gleason score, and clinical tumor stage identifies patients with unfavorable preoperative pathological factors and classifies them in low-, intermediate,- and high-risk groups according to pretreatment risk of recurrence.[3,8] However, PCa patients constitute a heterogeneous population regarding oncological outcomes.[8,9] Therefore, improved tools and additional preoperative parameters are needed to predict postoperative outcomes and individual patients' prognoses more accurately.

Recently, in an attempt to improve existing predictive models, some authors analyzed the impact of pathological findings of prostate biopsy on oncological outcomes.[9] In this context, the National Cancer Center Network Guidelines included a sub-stratification of the intermediate-risk group into favorable intermediate-risk group and unfavorable intermediate-risk group [which includes patients with International Society of Urological Pathology (ISUP) 3, and/or >50% positive biopsy cores and/or ⩾2 intermediate-risk factors].[10] Furthermore, several studies evaluated the pretreatment use of prostate-specific antigen density (PSAD) as a predictor of oncological outcomes. Although PSAD has a significant and established role in PCa diagnosis,[11] its value as a predictive prognostic factor remains a subject of debate. Some studies demonstrated a valuable role of PSAD in predicting adverse pathological findings or biochemical recurrence (BCR) after surgical treatment[9,12–17] but contradictory results were also reported.[18–20]

The present study aimed to assess PSAD as a potential predictor of oncological outcomes in patients undergoing robot-assisted radical prostatectomy (RARP) for clinically localized PCa. Moreover, a comparison between PSAD and preoperative PSA level (pPSA) was performed to determine their predictive strength.

Materials and methods

Patients and methods

The study population consisted of 427 consecutive patients who underwent RARP for clinically localized PCa between January 2015 and January 2020 at a single institution. The Institutional Review Board committee approved the study design, and all included patients signed the informed consent prior to surgery.

We retrospectively reviewed the recorded clinical, pathological, and radiological data. The data presented in our study were collected in compliance with the latest version of the World Health Organization Declaration of Helsinki and extracted from databases appropriately anonymized and de-identified before being

released. Moreover, the reporting of this study conforms to the Strengthening the Reporting of Observational Studies in Epidemiology statement.[21] PSA was performed between 4 and 6 weeks pre-biopsy and was confirmed with a second PSA value. PSAD was determined as a pre-biopsy PSA value divided by transrectal ultrasound (TRUS)-estimated prostate volume. Systematic prostate biopsy was performed through a transrectal ultrasound-guided approach, and Gleason scoring was defined according to the 2014 ISUP grading system.[22] The clinical stage was determined by pre-biopsy digital rectal examination, following Tumor, Node, Metastasis (TNM) classification.[3,23]

RARP was performed by four surgeons, using an anterior intraperitoneal approach. None of the patients received prior androgen-deprivation therapy and cases of salvage RARP following radiation treatment were excluded. A routine pathological assessment was performed to analyze prostatectomy specimens. Two specialists of urologic pathology evaluated the histopathology reporting on histopathological type, Gleason score according to ISUP grade,[22] tumor volume, presence of cribriform and/or intraductal carcinoma, surgical margin status, extraprostatic extension (location and extent), and tumor staging.

We analyzed the association of PSAD and pPSA with post-surgical oncological outcomes in terms of persistence of PSA after RARP (PSA $\geq$ 0.1 ng/ml), the presence of postoperative positive surgical margins (PSM), clinically significant PCa (Gleason score $\geq$ 7), and BCR (PSA $\geq$ 0.2 ng/ml).

Statistical analyses

Statistical analysis was performed using SPSS version 26.0 (IBM SPSS Statistics). Data on continuous variables are presented as medians with their respective ranges and analyzed using a Mann–Whitney *U* test. Data on qualitative variables are presented as the absolute value and proportion and analyzed with a chi-squared test.

The performance of PSAD and pPSA in predicting oncological outcomes was determined by generating receiver-operating characteristic (ROC) curves and calculating areas under the curves (AUCs). A comparison between the predictive value of PSAD and pPSA was performed. Subsequently, linear regression models were generated to assess the predictive value of PSAD and pPSA for oncological outcomes of PSM, PSA persistence, Gleason score $\geq$ 7, and BCR. All statistical tests were two-sided with p values < 0.05 considered statistically significant.

Results

Table 1 summarizes the clinical and pathological data of patients included in the study. Prior to surgery, the median (range) PSA level was 5.82 (0.47–50) ng/ml with a median PSAD of 0.15 (0.01–1.24) ng/ml. Postoperatively, 346 patients (81%) presented a Gleason score of $\geq$ 7 with non-clinically significant PCa accounting for 19% of the entire cohort. The Gleason score upstaging rate was 26.7% (114 patients). The median weight of the surgical specimen was 43 (16–122) g. Persistence of PSA post-RARP was identified in 29 patients (7.9%), PSM was described in 185 cases (43.3%) and 41 patients (10.7%) presented BCR, with a median follow-up of 47 months (IQR 22.7–56.2).

To analyze the overall performance of PSAD, we generated ROC curves according to oncological outcomes of PSA persistence, BCR, PSM, and Gleason score $\geq$ 7, and calculated the AUCs. PSAD showed a significant predictive value for PSM (AUC 0.614; 95% CI 0.561–0.667, $p < 0.0001$), PSA persistence (AUC 0.727; 95% CI 0.627–0.827, $p < 0.0001$), and Gleason score $\geq$ 7 (AUC 0.683; 95% CI 0.623–0.743, $p < 0.0001$), without being statistically significant in predicting BCR (AUC 0.588; 95% CI 0.496–0.681, $p = 0.064$). Subsequently, the same analysis was conducted with pPSA. Preoperative PSA was found to have significant predictive value for postoperative PSA persistence (AUC 0.771; 95% CI 0.680–0.862, $p < 0.0001$), Gleason score $\geq$ 7 (AUC 0.649; 95% CI 0.582–0.716, $p < 0.0001$), and BCR (AUC 0.615; 95% CI 0.532–0.698, $p = 0.016$). No statistically significant results were obtained when predicting PSM (AUC 0.548; 95% CI 0.439–0.604, $p = 0.087$). As shown in Figure 1(a) and (b), the analysis of the AUCs found the predictive value of PSAD to be comparable to pPSA for outcomes of PSA persistence (AUC 0.727 *versus* 0.771) and Gleason score $\geq$ 7 (AUC 0.683 *versus* 0.649).

To extend these findings, linear regression models were generated to assess the ability of PSAD and pPSA to independently predict the reported oncological outcomes. PSAD showed a

Table 1. Clinical and pathological characteristics of the study cohort.

Variable	Value
N	427
Median (range):	
Age (years)	63.8 (45.12–78.39)
PSA level (ng/ml)	5.82 (0.47–50)
TRUS-prostate volume (cc)	37 (12–185)
PSAD (ng/ml/ml)	0.15 (0.01–1.24)
Clinical stage (*n*, %):	
T1	344 (80.5)
T2	79 (18.5)
T3	4 (1)
Biopsy Gleason score (*n*, %):	
6	173 (40.5)
7	161 (37.7)
8	48 (11.3)
9	45 (10.5)
Pathological Gleason score (*n*, %):	
6	81 (18.9)
7	259 (60.6)
8	20 (4.9)
9	67 (15.6)
Nerve-sparing surgery (*n*, %):	
No	110 (25.7)
Yes	317 (74.3)
Extraprostatic extension (*n*, %):	
No	289 (67.7)
Yes	138 (32.3)
Surgical margins (*n*, %):	
No	242 (56.7)
Yes	185 (43.3)
Seminal vesicle invasion (*n*, %):	
No	389 (91.3)
Yes	37 (8.7)
Persistence of PSA (*n* = 366) (*n*, %):	
No	337 (92.1)
Yes	29 (7.9)
Biochemical recurrence (*n* = 384) (*n*, %):	
No	343 (89.3)
Yes	41 (10.7)

PSA, prostate-specific antigen; PSAD, prostate-specific antigen density; TRUS, transrectal ultrasound.

significant association with PSM (coefficient B 0.059, 95% CI 0.089–0.029; $p < 0.0001$), PSA persistence (B 0.187, 95% CI 0.126–0.248; $p < 0.0001$), and Gleason score ≥ 7 (B 0.083, 95% CI 0.045–0.121; $p < 0.0001$). Subsequently, we analyzed the predictive performance of pPSA, showing a significant association of this preoperative factor with PSM (B 1.363, 95% CI 2.227–0.499; $p = 0.002$), PSA persistence (B 5.359, 95% CI 3.633–7.104; $p < 0.0001$), and Gleason score ≥ 7 (B 1.896, 95% CI 0.886–2.907; $p < 0.0001$). No significant association of either PSAD or pPSA with BCR was demonstrated (B 0.046, 95% CI 0.1–0.008; $p = 0.098$ and B 0.818, 95% CI 2.297–0.660; $p = 0.277$).

The results of analyses for the association between the value of PSAD and pPSA and postoperative oncological results are provided in Tables 2 and 3.

Discussion

Pretreatment risk assessment in patients diagnosed with localized PCa is of key importance for therapeutic decision-making. Defining the treatment strategy is based on staging systems consisting of clinical and pathological factors.[3,24] Based on this system, adverse features post-surgery and PSA recurrence rates can be predicted. Therefore, identifying additional prognostic parameters to enhance the currently established stratification systems would allow for better patient selection and treatment individualization.

In this setting, pretreatment PSAD has been proposed as a potential predictor factor of oncological outcomes after surgical treatment of PCa. Initially, PSAD was introduced by Benson *et al.*[11] in 1992, to improve the accuracy of PSA in the diagnosis of PCa by distinguishing PCa from benign prostatic hypertrophy. The cutoff level of PSAD for the diagnosis of presumptive PCa was set at 0.15,[25] remaining to date the most widely accepted value for differentiating clinically significant from non-clinically significant PCa.[26] Since that time, PSAD has been extensively evaluated as a prognostic factor for oncological outcomes after RP.

Several studies have identified PSAD as a predictor of adverse pathological features in PCa patients undergoing surgical treatment. Freedland *et al.*[12] described PSAD as a strong independent predictor of PSM, seminal vesicle invasion, non-organ

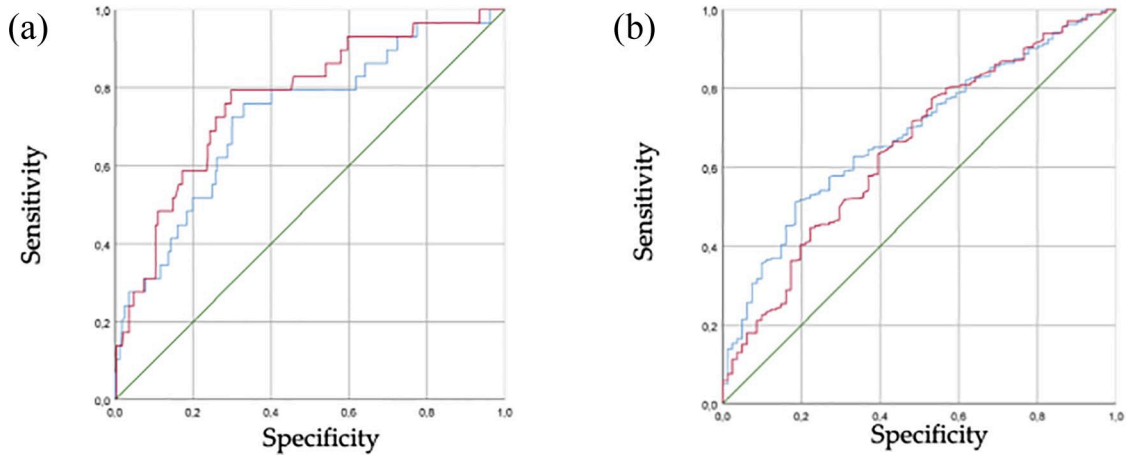

Figure 1. ROC curves and AUC show the performance of PSAD and pPSA in predicting postoperative outcomes. (a) Comparison of ROC curves and AUC of PSAD (blue line; AUC 0.727) and pPSA (red line; AUC 0.771) for prediction of PSA persistence and (b) comparison of ROC curves and AUC of PSAD (blue line; AUC 0.683) and pPSA (red line; AUC 0.649) for prediction of Gleason score ⩾ 7.
AUC, area under the curve; pPSA, preoperative PSA; PSA, prostate-specific antigen; PSAD, prostate-specific antigen density; ROC, receiver operator characteristic.

confined disease, and BCR after RP. Horiguchi *et al.*[27] found that PSAD was the most valuable predictor among the PSA-based parameters for determining the presence of extraprostatic disease. Similarly, Kundu *et al.*[15] showed a correlation between PSAD and higher pathological stage and tumor aggressiveness, in terms of decreased progression-free survival rate. Moreover, Sfoungaristos and Perimenis[17] retrospectively analyzed 285 PCa patients who underwent RP, showing that PSAD was a significant predictor of PSM, seminal vesicle invasion, lymph node involvement, and extracapsular disease.

Furthermore, the value of PSAD predicting PSA recurrence was assessed. Multiple retrospective studies[14,15,18,28–30] demonstrated an association between preoperative PSAD and BCR. Brassell *et al.*[18] described PSAD as a predictor of BCR, whether calculated preoperatively (using TRUS-estimated prostate volume) or postoperatively (using pathological prostate volume or weight). PSAD was also found to be an independent predictor of BCR in the study of Radwan *et al.*,[16] who reviewed 1327 PCa patients treated with RP. Moreover, studies conducted by Koie *et al.*[29] and Yashi *et al.*[9] showed that PSAD is a strong predictor of BCR in patients diagnosed with high-risk PCa. More recently, however, Tzeng *et al.*[20] analyzed a large series of 11,725 patients showing a lack of association between PSAD and BCR. Finally, the only prospective study conducted in this area was presented by Sfoungaristos and Perimenis[31] in 2013, including 244 patients diagnosed with localized PCa who underwent RP. The authors demonstrated an association between

Table 2. Analysis of PSAD predictive performance using a linear regression model.

Postoperative oncological outcomes	Coefficient B	95% CI	*p* Value
PSA persistence	0.187	0.126–0.248	<**0.0001**
Positive surgical margins	0.059	0.089–0.029	<**0.0001**
Pathological Gleason score ⩾ 7	0.083	0.045–0.121	<**0.0001**
Biochemical recurrence	0.046	0.1–0.008	0.098

PSA, prostate-specific antigen; PSAD, prostate-specific antigen density.
Statistically significant *p* value <0.05.

Table 3. Analysis of pPSA predictive performance using a linear regression model.

Postoperative oncological outcomes	Coefficient B	95% CI	*p* Value
PSA persistence	5.359	3.633–7.104	<**0.0001**
Positive surgical margins	1.363	2.227–0.499	**0.002**
Pathological Gleason score ⩾7	1.896	0.886–2.907	<**0.0001**
Biochemical recurrence	0.818	2.297–0.660	0.277

pPSA, preoperative PSA; PSA, prostate-specific antigen.
Statistically significant p value <0.05.

PSAD and adverse pathological findings and identified PSAD as a significant predictor of BCR ($p = 0.009$).

Nevertheless, in the scenario of comparing pPSA with PSAD as predictors of oncological outcomes following RP, different studies have shown inconsistent findings. Freedland *et al.*[12] in 2002, found that PSAD was superior to PSA in determining BCR. However, in a later publication in 2003,[13] the authors reported no clinically significant difference between the two predictor factors. Similarly, Radwan *et al.*[16] determined the superiority of PSAD in predicting BCR, although this difference was not statistically significant. However, PSAD correlated more strongly than pPSA with extracapsular disease, PSM, and seminal vesicle invasion. Conversely, Brassell *et al.*[18] identified pPSA as the strongest predictor of BCR, being comparable to PSAD in predicting surgical margin status and extracapsular extension.

Finally, some recent studies have proposed PSAD as a predictor of Gleason score upgrading after RP. Corcoran *et al.*[32] determined PSAD as the strongest predictor of Gleason score upgrading in patients with ISUP 1 and 2 confirmed on prostate biopsy. Moreover, Oh *et al.*[33] identified PSAD as a more accurate preoperative predictor of Gleason score upgrading than pPSA.

The current study adds to previous publications in the assessment of PSAD as a prognostic factor in PCa. Our analysis demonstrated that preoperative PSAD significantly correlates with adverse pathological features in terms of PSM, PSA persistence, and Gleason score ⩾7. However, the association of preoperative PSAD and BCR post-RP was not statistically significant in the analysis of our series. Furthermore, PSAD was found to be comparable to pPSA in predicting the persistence of PSA and Gleason score ⩾7. These results suggest that PSAD has a role in predicting oncological outcomes of PCa patients treated with RP, appearing to be an inexpensive and widely available tool that can be used in conjunction with the existing risk stratification nomograms, aiming to improve their prognostic ability.

There are several limitations to the present study. First, it is a retrospective study based on a relatively small patient cohort. In addition, the use of magnetic resonance imaging (MRI) in the diagnosis of PCa was introduced at this center in 2019, meaning preoperative MRI was not available for all patients included in the study. Therefore, the prostate volume used to calculate preoperative PSAD was the TRUS-estimated prostate volume. The accuracy of TRUS volumes is known to be user dependent, which interferes with the determination of PSAD as variations in the measurement of prostate volume may influence its value. Nevertheless, some studies reported that prostate volumes estimated by MRI and TRUS showed an excellent agreement between them and with RP specimens.[34] Moreover, the small population size limited the possibility of establishing a conclusive PSAD cutoff level, preventing the generation of a logistic regression model and the development of a multivariate analysis. Finally, the high rate of PSM described in this series is remarkable. The data are potentially related to multiple factors: first, the significant percentage of patients who underwent neurovascular bundle preservation (74.3%). Second, the considerable number of patients presenting extraprostatic involvement in the series (32.2%). Third, the description of the pathology report, which included in several cases minimal intraprostatic incisions performed intraoperatively as PSM. Finally, the experience of the surgeon and the

surgical technique represent key factors related to PSM rate.

In summary, preoperative PSAD value has shown a strong predictive potential in patients diagnosed with PCa undergoing RP. Further studies are needed to assess its application in conjunction with validated risk nomograms, aiming to individualize the management of PCa patients.

Conclusion

Pretreatment risk stratification of PCa patients is a key determinant for therapeutic decision-making. PSAD was demonstrated to have a role in the prognostic assessment of these patients, being a predictor of oncological outcomes in terms of surgical margin status, Gleason score ≥ 7, and persistence of PSA after RP. However, in the current analysis, PSAD was not significantly associated with postoperative BCR.

Despite the need for further studies, we conclude preoperative PSAD could be useful to determine the aggressiveness of PCa and to predict outcomes after RP and might be used in conjunction with established staging systems to improve patient stratification.

Declarations

Ethics approval and consent to participate

Not applicable. We conducted a retrospective and observational study. The data presented were collected in compliance with the latest version of the World Health Organization Declaration of Helsinki. Since the data were extracted from databases appropriately anonymized and de-identified before being released, obtaining patient informed consent was unnecessary.

Consent for publication

Not applicable. We conducted a retrospective and observational study, based on data extracted from databases appropriately anonymized before being released. The data presented in our study were collected in compliance with the World Health Organization Declaration of Helsinki.

Author contributions

Roser Vives Dilme: Conceptualization; Data curation; Methodology; Writing – original draft; Writing – review & editing.

Juan Gómez Rivas: Conceptualization; Methodology; Supervision; Writing – review & editing.

Laura Fernández Hernández: Data curation.

Irene De la Parra Sánchez: Data curation.

Rafael Sánchez del Hoyo: Formal analysis.

María Isabel Galante Romo: Supervision.

Enrique Redondo González: Supervision.

José Luis Senovilla Pérez: Supervision.

Lorena Fernández Montarroso: Supervision.

Jesús Moreno Sierra: Supervision.

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Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

Not applicable.

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