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Research Article

The role of prostate-specific antigen density in men with low-risk prostate cancer suitable for active surveillance: results of a prospective observational study

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ABSTRACT

Background: Low-risk prostate cancer (PCa) is currently managed also with active surveillance (AS). However, up to 40% of patients in AS may require radical treatment at a long-term follow-up. The aim of our study is to further investigate the role of prostate-specific antigen (PSA) density in AS.
Methods: A prospective observational study on PCa naïve patients with PSA<20 ng/ml submitted to prostate biopsy was conducted. Data on family history of PCa, PSA at biopsy, and digitorectal examination were collected. Prostate volume was calculated during TRUS. Bioptic cores number, Gleason Score, and International Society of Urological Pathology (ISUP) Grade Group were recorded. Patients who subsequently underwent radical prostatectomy (RP) were selected and stratified in low, intermediate, and high Risk based on the D'Amico risk classification at biopsy and after RP.
Results: A total of 746 patients were enrolled. PCa was found in 320 patients (42.9%), of whom 252 underwent RP (78.8% of positive biopsies). At biopsy, patients were stratified based on the D'Amico risk classification in low, intermediate, and high risk and were 20.6%, 66.7%, and 12.7%, respectively. Definitive pathology after RP showed PCa change in the risk group in 52.4% of patients (n = 132) and PCa upgrading in 46.8% of patients (n = 118). At Student *t* test and logistic regression, PSA density was significantly correlated with change in the risk group and upgrading in low-risk PCa (p = 0.024) with an age adjusted odds ratio of 10.01 and 7.53, respectively.
Conclusion: PSA density is a strong instrument in AS to decide whether to treat. However, further larger studies are needed to strongly assess this correlation.

1. Introduction

Prostate Cancer (PCa) is the most common male malignant tumor. Nevertheless, PCa mortality is low, and many patients might avoid radical treatment as active surveillance (AS) for low-risk tumor appears to be a safe clinical option with no increased mortality. Thus, prostate-specific antigen (PSA) screening requires a high number of treated patients to reduce mortality and often determine higher comorbidities [1,2]. However, 43%–47% of classified International Society of Urological Pathology (ISUP) Grade Group (GG) 1 cancer are reported to be a more aggressive disease at definitive pathology, with a subsequent risk group change according to the D'Amico risk classification that occurs in more than 10% of the patients that undergo radical prostatectomy (RP) [3–7]. Also, in AS protocols, at long-term follow-up, 30%–40% of the patient require radical treatment as intermediate-risk PCa has a greater PCa-specific mortality, and accurate initial management may improve overall survival [8,9]. PSA density should be evaluated in many AS protocols as it seems to be accurate enough to correctly assign the patient to AS [10]. Our aim is to further inquire the role of PSA density in AS to decide whether or not to start a radical treatment.

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2. Materials and methods

A prospective observational clinical study on patients who were candidate to transrectal ultrasound (US)-guided prostate biopsy in our department started in June 2016.

2.1. Ethics

The study underwent institutional review board approval. The study protocol was conformed to the provision of the Declaration of Helsinki. We acquired a written informed consensus for every patient enrolled.

2.2. Population

Inclusion criteria were age younger than 70 years, PSA comprised between 3 and 20 ng/ml, and no previous diagnosis of PCa. We collected data on family history of PCa, PSA at biopsy and digitorectal examination (DRE). Prostate volume was calculated during transrectal US. Bioptic cores number, Gleason Score, and ISUP GG were recorded. Patients who subsequently accepted RP were selected and stratified in low, intermediate and high risk according to D'Amico risk classification at biopsy and after RP. Patients were divided in groups based on the changes in risk class as per the D'Amico risk classification, tumor node metastasis (TNM) classification and ISUP GG discrepancy between biopsy and definitive histology. Local clinical tumor stage was evaluated with PCa-positive core number and side plus DRE, and multiparametric magnetic resonance imaging while available.

2.3. Statistical analysis

Patient characteristics were compared between groups using independent sample t-test for continuous variables and Pearson chi-square for categorical variables. Age-adjusted logistic regression was used to evaluate associations between groups characteristics to search for predictors of change in risk group; p-value was set as <0.05, and confidence interval (CI), at 95%. A receiver-operating characteristic (ROC) curve was calculated for PSA density in low-risk and in GG 1 patients for changes in the risk group and upgrading.

3. Results

Since June 2016, a total of 746 patients were enrolled into the study. All of them respected the eligibility criteria. Only 5 patients refused to participate. The median age was 63 years (inter quartile range (IQR): 58–68); median biopsy core number, 14 (IQR: 14–16); median PSA, 6.39 ng/ml (IQR: 4.78–8.79); median prostate volume, 35 ml (IQR: 22–51); and median PSA density, 0.28 (IQR: 0.20–0.38). Family history of PCa was present in 156 patients (20.9%), whereas 114 (15.3%) had a prior negative biopsy. DRE was negative, suspect, and positive in 224 (30.0%), 296 (39.7%), and 226 (30.3%) patients, respectively. PCa-positive biopsies were found in 320 (42.9%) patients. Patients were treated as per the current guidelines, and 252 (78.8%) patients underwent RP. The patients who chose surgery were stratified in groups according to the D'Amico risk classification before and after RP. Risk classification was low, intermediate, and high Risk in 20.6%, 66.7%, and 12.7%, respectively, while ISUP GG was 1, 2, 3, 4, or 5 in 30.2, 38.9, 18.3, 7.9, and 4.8% of patients, respectively. GG discrepancy rate in definitive histology was 46.8%, whereas changes in the risk group rate was 54.7%. Only 2 patients had downgrading that comprised both risk group and Gleason score (GS) and were excluded from the analysis. Results for each risk class change are reassumed in Table 1. Table 2 shows the TNM classification before and after RP for each risk class. Student *t* test on continuous variable demonstrated a statistically significant correlation for PSA density ($p = 0.004$) and PSA ($p = 0.042$) in low-risk patients for risk group changes. In low-risk PCa, upgrading occurred in 36 cases (69.2%). In intermediate-risk patients, PSA and PSA density values were higher than those in low and high risk but were not associated with risk class changes at statistical analysis ($p > 0,05$). High-risk patients in our study had higher mean PSA values than other categories but lower PSA density values. On categorical variables, DRE and family history of PCa were not associated to risk class changes and upgrading in any risk class on Pearson's chi-square and Fisher's exact tests ($p > 0.05$). Results are reassumed in Table 3. Logistic regression demonstrated that PSA density was a statistically significant predictor of risk class changes and upgrading in low-risk patients with odds ratio (OR) 10.01, 95% CI 5.06–15.60, and $p = 0.024$, whereas PSA at biopsy was not a predictor of risk class changes with OR 1.30, 95% CI 0.42–4.16, and $p = 0.643$. Logistic regressions are reassumed in Table 4. ROC curves in Fig. 1 were calculated for PSA density to define risk class changes; in the low-risk group, risk class changes had an area of 0.899 ± 0.068 (95% CI: 0.766–1.000) for a PSA density of 0.185.

4. Discussion

Clinically significant PCa is often underestimated in the current clinical practice, as demonstrated with the actual AS protocols [3,4,8,9]. In our study, we evaluated PSA density efficacy to

Table 1
Patients who experienced PCa risk class changes based on the D'Amico Risk Class, excluding downstaging (n = 248)

Risk class		Low risk (n = 52)		Intermediate risk (n = 166)		High risk (n = 30)
Change in risk class		No	Yes	No	Yes	No
		16 (30.8%)	36 (69.2%)	70 (42.2%)	96 (57.8%)	30 (100%)
PSA (ng/ml)		4.92 (1.19)	6.05 (1.14) *	8.58 (4.03)	7.85 (3.95)	9.46 (3.92)
PSA density		0.16 (0.05)	0.29 (0.16) *	0.38 (0.26)	0.34 (0.23)	0.29 (0.12)
Core number		15 (3)	14 (2)	16 (3)	15 (2)	14 (2)
PCa positive core number		2 (1)	3 (2)	4 (3)	5 (3)	6 (4)
Positive core number %		13.3 (6.9%)	18.8 (14.3)	28.2 (19.2)	32.9 (21.2)	43.2 (29.3)
Age (years)		64 (4)	61 (4)	63 (5)	65 (6)	65 (3)
PS-DRE	Negative	6 (37.5%)	8 (22.2%)	16 (22.9%)	16 (16.7%)	2 (6,7%)
	Suspect	8 (50.0%)	20 (55.6%)	30 (42.9%)	40 (41.7%)	10 (33,3%)
	Positive	2 (12.5%)	8 (22.2%)	24 (34.3%)	40 (41.7%)	18 (60,0%)
Family history of PCa		0 (0.0%)	8 (22.2%)	16 (22.9%)	14 (14.6%)	2 (6.7%)

All continuous variables are expressed as mean (standard deviation). Categorical variables are expressed as n (%). Student *t* test for an independent sample was used for continuous variables, and Fisher's exact test, in categorical variables.
PSA, prostate-specific antigen; PCa = prostate cancer; PS-DRE, positive digitorectal examination.
* = $p < 0.05$.

Table 2
Clinical and pathological PCa staging according to risk class

Risk class		cTNM, n (%)		pTNM, n (%)	
PCa risk class	Low risk (n = 52)	cT2a	52 (100%)	pT2a	16 (30.8%)
				pT2b	10 (19.2%)
				pT2c	8 (15.4%)
				pT3a	16 (30.8%)
				pT3b	2 (3.8%)
	Intermediate risk (n = 166)	cT2a N0	106 (63.9%)	pT2a Nx	8 (4.8%)
				pT2b Nx	50 (30.2%)
				pT2b N0	33 (19.9%)
				pT2c Nx	10 (6.0%)
				pT2c N0	14 (8.4%)
		cT2b N0	60 (36.1%)	pT3a Nx	16 (9.7%)
				pT3a N0	13 (7.8%)
				pT3a N1	2 (1.2%)
				pT3b Nx	6 (3.6%)
				pT3b N0	8 (4.8%)
				pT3b N1	6 (3.6%)
	High risk (n = 30)	cT2a N0	2 (6.6%)	pT2c N0	2 (6.6%)
		cT2b N0	2 (6.6%)	pT3a N0	5 (16.7%)
				pT3a N1	4 (13.3%)
		cT2c N0	26 (86.8%)	pT3b N0	5 (16.7%)
				pT3b N1	14 (46.7%)

PCa, prostate cancer.

discriminate whether to use AS in low-risk PCa and avoid over-treatment and unnecessary treatment.

In the enrolled population, we failed to find predictors for risk class changes in both intermediate- and high-risk patients. In low-risk patients, PSA density was a valuable predictor of risk class changes.

Interestingly, in a subgroup analysis, in patients who respected eligibility criteria for AS protocols with age younger than 70 years, PSA density confirmed as a predictor of risk class changes to intermediate- or high-risk PCa. The importance of these findings is that they confirm that PSA density should be considered as a requirement in AS protocols to avoid underdiagnosis and understaging. PSA at biopsy is indeed another necessary inclusion criterion, as it is related to risk class changes in the low-risk group.

Furthermore, ROC curve estimates that a PSA density cutoff of 0.185 may be adequate to correctly discriminate between low-risk and higher risk PCa, thus becoming a relevant inclusion criterion in AS protocols.

As PSA density increase with higher PSA and lower prostate volumes, current literature with Dong *et al.* [11] further underline this aspect, as they report a correlation in GS 6 patients with volume and tumor upgrading, as patient with small prostate with high PSA value are more likely to harbor a more aggressive disease. These findings support our results, as lower prostate volumes are usually associated to higher PSA density values. Their results were further confirmed in other studies that showed the importance of prostate volume as a predictor of upgrading [12,13]. Hence, PSA density is related both to PSA levels and prostate volume, and it increases with higher PSA levels and with lower volumes, thus becoming a more precise instrument to predict PCa upgrading. In fact, Kundu *et al.* [14] showed that PSA density was increased in more aggressive PCa, thus being a potential instrument to determine the tumor aggressiveness. In our study, we founded further evidences as, at multivariate logistic regression, higher PSA density values in low-risk PCa had a ten-fold risk of risk class changes, thus confirming its value in AS setting to discriminate between true low-risk PCa and more aggressive disease. Also, Sfoungaristos *et al.* [15], in a large prospective series, found that PSA density was the only predictor of GS upgrading at definitive pathology, although the number of cores and the percentage of PCa positive material in the whole biopsy tissue were not. This evidence is supported in our study as we did not find any association between positive core numbers and risk class changes or upgrading. Therefore, results were confirmed by Magheli *et al.* in a large single-center study as they found a strong correlation between PSA density and upgrading in 6 GS patients [16]. However, none of this study classified the patients based on their risk class, except a study by Sfoungaristos *et al.* [15] that had inclusion criteria selective for low-risk patients, and their results may have been influenced.

Corcoran *et al.* showed that the ability of PSA density to predict upgrading diminishes as the GS increase because less differentiated tumors produce less PSA for unit. However, PSA density values were higher in GS > 6, and their results confirmed that, in the low-risk setting, it is a useful predictive tool [17]. According to these findings, in our study, in intermediate- and high-risk PCa, PSA density lost its predictive value of upgrading and risk class changes.

The prostate cancer research international active surveillance (PRIAS) protocol for AS has a PSA density cutoff of 0.20 as one of the inclusion criteria [18]. In a recent article, Gandaglia *et al.* [19] found out that the PRIAS protocol is one of the AS protocols with the lowest rate of misclassification at definitive histology (13%), thus confirming the importance of maintaining PSA density as a necessary threshold in patient's selection for AS. In particular, the median PSA density value associated with unfavorable pathology was 0.19, similar to the 0.185 PSA density cutoff found in our ROC curve associated with a 0.899 AUC of risk class changes.

The strength of the study is its prospective nature. In addition, all the samples were analyzed by a single pathologist, increasing

Table 3
Statistical analysis of low-risk patients submitted to radical prostatectomy (n = 52)

Variable	Modification in risk class		
	No (n = 16, 30.8%)	Yes (n = 36, 69.2%)	p value
PSA (ng/ml)	4.92 (1.19)	6.05 (1.14) *	0.042
PSA density	0.16 (0.05)	0.29 (0.16) *	0.004
P-DRE	1 (12.5%)	4 (22.2%)	0.676
Age (years)	64 (4)	61 (4)	0.109
Family history of PCa	0 (0.0%)	4 (22.2%)	0.147

All continuous variables are expressed as mean (standard deviation). Categorical variables are expressed as n (%). Student *t* test for independent sample was used for continuous variables, and Fisher's exact test, in categorical variables.
PSA, prostate-specific antigen; PCa, prostate cancer; PS-DRE, positive digitorectal examination.
* = $p < 0.05$.

Table 4
Logistic regression of low-risk patients submitted to radical prostatectomy with risk class change (n = 36)

Covariates	Odds Ratio (95% CI)	p value
PSA density	10.01 (5.06-15.6) *	p = 0.024
PSA (ng/ml)	1.30 (0.42-4.16)	p = 0.643
Age (years)	0.92 (0.66-1.28)	p = 0.521

PSA, prostate-specific antigen; PCa, prostate cancer; CI, confidence interval.
* = p < 0.05

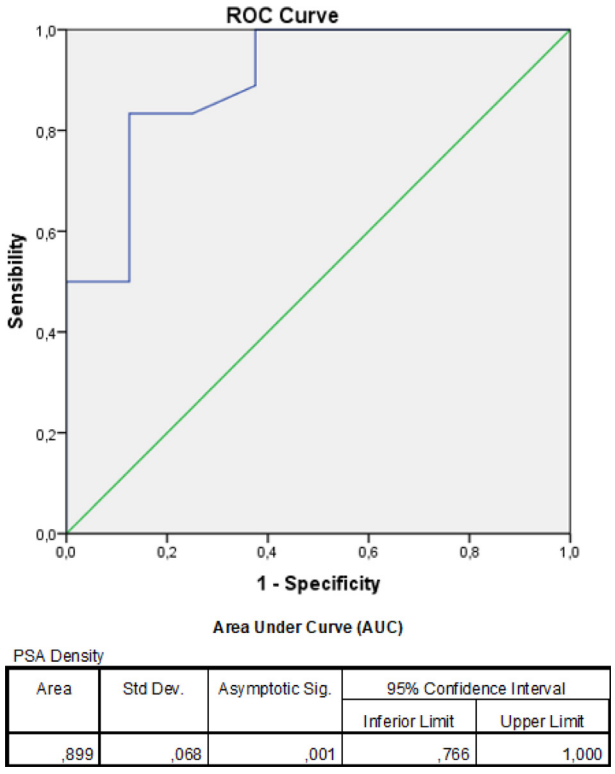

Fig. 1. ROC curve relating PSA density and upstaging in low risk Prostate Cancer group. Area is 0.899 for a PSA density of 0.185. PSA, prostate-specific antigen; ROC, receiver-operating characteristic.

the accuracy of the study. The high OR, found for PSA density in the prediction of PCa risk class changes, underlines its potential benefit in the low-risk setting of patients. The chance to further discriminate clinically significant PCa will be helpful to make a more and more accurate choice for patients' treatment and to reduce the overtreated or underdiagnosed patients.

Limitations of the study are the small number of patients enrolled that is associated with a lower statistical value of the findings, as only few low-risk PCa were effectively enrolled. Furthermore, US evaluation of prostate volume at biopsy is prone to sampling error and is operator dependent. However, enrollment and prostate biopsy were performed by four expert urologists, thus reducing the potential bias of volume calculation.

In conclusion, PSA density values confirm to be a useful criterion to help specialists to decide whether to treat low-risk PCa at biopsy.

However, the number of enrolled cases represents a limitation of this study to draw definitive conclusions that need to be confirmed in larger multicentric studies.

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Conflicts of interest

All authors have no conflict of interest to declare.

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