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Prostate Imaging Reporting and Data System score (PI-RADS) and Glutathione S-transferase P1 methylation status (GST-P1) in the diagnosis of prostate cancer patients with borderline PSA values

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ABSTRACT

Objectives. The objective of this study was to evaluate the potential use of Prostate Imaging – Reporting and Data System version 2 (PI-RADS) in combination with Glutathione S-transferase P1 (GST-P1) expression for an improved diagnosis of prostate cancer, in patients with inconclusive values of prostate-specific antigen (PSA). *Materials and Methods*. The study was conducted on 80 patients for whom PSA values were evaluated and were found to be inconclusive (4-10 ng/ml). These patients underwent imagistic evaluation (PI-RADS), followed by transurethral prostate biopsy, with the evaluation of GST-P1 expression and histopathological examination (for diagnosis confirmation). *Results*. By combining the results of PI-RADS and GST-P1 the capacity of the tests to correctly identify healthy subjects, with an area under curve of 0,832 (95% CI 0.732–0.907), with a sensitivity of 73,25% and a specificity of 77,78%. *Conclusions*. PI-RADS lesions and GST-P1 methylation testing when PSA levels are in a "grey zone", provide a better specificity and sensitivity by comparison through single testing. Testing patients with inconclusive PSA levels allows for a more accurate diagnosis and less over-diagnosis by non-invasive procedures, such as repeated biopsies.

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Introduction

Neoplastic diseases play an important role in the mortality, combined representing the second biggest cause of death worldwide [1]. In addition to being a major cause of death, neoplastic diseases also have a major impact on quality of life. This is affected by the evolution of the disease, the treatment regimens that are required [2,3], or the difficulties related to the nutritional needs of cancer patients and the prevention of cachexia [4-6]. According to the data of World Health Organization, the most frequent cancers in male patients are prostate, colorectal and lung cancers and the incidence of these disease in on an increasing trend [7,8]. While one of the causes is aging of population, screening programs, based on less invasive tests can lead to early diagnosis and increased chance for survival [8,9]. Prostate cancer, despite having one of the highest incidences of cancers in male population [10-12], also has a high five years survival rate when diagnosed in early stages [13]. Social disparities, with difficult access to medical services for patients within rural areas [14] or possible disabilities [15] influences the time to diagnosis and the evolution of the disease [16,17], especially in developing regions, an aspect that was also observed and analyzed in other pathologies [18,19]. Moreover, recently, several studies raised awareness upon neglecting cancer patients during the Covid-19 pandemic [20,21].

Current medical development introduced new diagnosis procedures, mainly through the usage of imaging methods, such as Prostate Imaging Reporting and Data

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System version 2 (PI-RADS) [22] or, as in the case of other cancers [23], the development of tests that target genetic biomarkers [24-26]. There are multiple studies that evaluate the role of combining the PI-RADS with other diagnosis methods in order to increase the accuracy of prostate cancer diagnosis [27-29].

The results of all these efforts to clarify the status of the patient dramatically increases the survival rate through better and timely diagnosis [30] associated with modern systemic therapies, such as immunotherapies [31].

In this study we evaluate the potential use of PI-RADS in combination with Glutathione S-transferase P1 (GST-P1) expression in the diagnosis of prostate cancer patients with inconclusive (borderline) values of prostate specific antigen (PSA).

Materials and Methods

The study was an observational one, conducted on 80 consecutive patients (between January 2018 and January 2020) that presented either for control examination or due to lower urinary tract symptoms at the Urology clinic of County Hospital of Constanta. All those patients met the inclusion criteria of having an inconclusive PSA value between 4 and 10 ng/ml; PSA was evaluated by using the ECLIA method.

All patients included in the study underwent PI-RADS evaluation and prostate biopsy with histopathological examination and GST-P1 methylation testing. The histopathological examination was considered as being the golden standard for prostate cancer diagnosis. Possible results were prostate cancer or benign prostate hyperplasia.

We ran a binomial logistic regression procedure using the two variables (PI-RADS and GST-P1) as independent variables and the histopathological test as dichotomous dependent variable. The area under curve (AUC) was calculated and used to determine the performance of the variables in diagnosing prostate cancer, the best one being considered the one with the largest AUC.

Statistical analyses were conducted by using IBM SPSS Statistics version 26, a p value of less than 0.05 was considered statistically significant.

The study received ethical committee approval no 446/30.03.2018 of the Ethical Committee for clinical studies approval of the Emergency County Hospital Constanta. Procedures at all stages of the study were carried out in compliance with the principles of the Declaration of Helsinki. Informed consent forms were received from all participants before the enrolment in the study group.

Results

Patient characteristics are summarized in Table 1. The average age of the patients was 68 years, with an average value of PSA level of 7.1 ng/ml. More than half of the patients presented GST-P1 methylation (42 of 80) and for PI-RADS score, no patient had a score of 5, one patient had a score of 1 and most of the patient (50%) presented with an intermediate score [3]. Around two thirds of the patients were histopathologically diagnosed with prostate cancer.

Table 1. General characteristics of the patients included in the study group

Characteristics	Values
Patients (n=80)	
Age (mean±sd, years)	68.0±9.16
PSA (mean±sd, ng/ml)	7.1±1.82
GST-P1 Methylation	
Negative (n, %)	38 (47.5%)
Positive (n, %)	42 (52.5%)
PI-RAIDS 2	
1 - Very Low (n, %)	1 (1.3%)
2 - Low (n, %)	21 (26.3%)
3 - Intermediate (n, %)	40 (50%)
4 - High (n, %)	18 (22.5%)
5 - Very High (n, %)	0 (0%)
Prostate Cancer	
Positive (n, %)	53 (66.3%)
Negative (n, %)	27 (33.8%)

Footnote. PSA: prostate-specific antigen, GST-P1: Glutathione-S-transferase gene P1, PI-RADS: Prostate Imaging Reporting and Data System scoring system v.2

The sensitivity and specificity of PI-RADS, for diagnosing prostate cancer in patients with borderline values of PSA, when the cut-off value was considered to be 4, were 96.3% (95% CI 81.0% - 99.9%) respectively 32.08% (95% CI 19.9% - 46.3%). Detailed values are in Table 2 for different cut-off points.

Table 2. Diagnostic accuracy of PI-RADS in the study group

Criterion	Sensitivity	95% CI	Specificity	95% CI
≥1	100.00	93.3 - 100.0	0.00	0.0 - 12.8
>1	100.00	93.3 - 100.0	3.70	0.09 - 19.0
>2	83.02	70.2 - 91.9	48.15	28.7 - 68.1
>3	32.08	19.9 - 46.3	96.30	81.0 - 99.9
>4	0.00	0.0 - 6.7	100.00	87.2 - 100.0

We further ran a binomial regression using as predictors the PI-RADS score and GST-P1 methylation. The logistic regression model was statistically significant $\chi2(2) = 27.82$, $p<0.001$. The model explained 40.7% (Nagelkerke R square) of the variance in prostate cancer diagnosis and correctly classified 78.8% of the cases. Sensitivity was 79.25%, specificity was 77.78%, positive predictive value 87.5% and negative predictive value was 65.62%. Of the two predictor variables both were statistically significant (Table 3). Men for whom the GST-P1 was methylated had 7.92 higher odds of having prostate cancer. Increasing value of the PI-RADS score was

associated with an increased likelihood of having prostate cancer, each grade having 3.01 times higher odds for prostate cancer compared to the previous score.

Table 3. Logistic regression predicting likelihood of prostate cancer based on GST-P1 methylation and PI-RADS score

	B	S.E.	Wald	df	p	Odds Ratio	95% C.I. for Odds Ratio	
							Lower	Upper
GST-P1 Methylation (1)	2.07	.61	11.66	1	.001	7.92	2.41	25.95
PI-RADS Stabilization	1.13	.43	6.84	1	.009	3.01	1.33	7.23
Constant	-3.43	1.25	7.46	1	.006	.032		

When combined, the predictive value of the combination of PI-RADS and GST-P1 (AUC 0.832, 95% CI 0.732 – 0.907) was superior in a statistically significant way to each of the two evaluations alone. For GST-P1 the AUC was 0.756, (95% CI 0.644 – 0.869, p= 0.015), and for PI-RADS the AUC was 0.727 (95% CI 0.616 – 0.820, p=0.014).

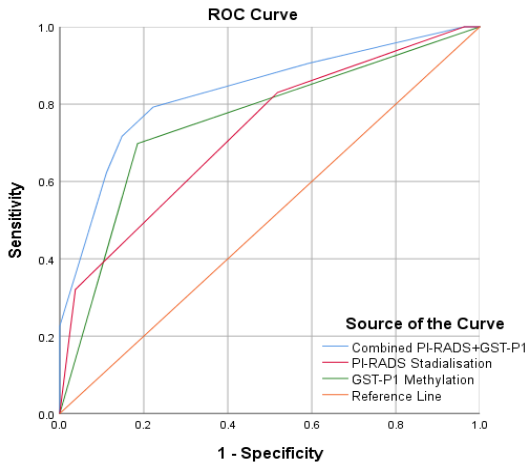

Figure 1. Comparison of ROC for Combined PI-RADS2 + GST-P1 versus alone

Discussion

A growing number of novel biomarkers are currently under investigation. Such markers include urinary biomarkers, serology-based markers or pathological tissue assessments of molecular and genetic markers [32]. Several cytokines were investigated for the possible correlation with prostate cancer, such as IL-1α, IL-1β, IL-6, and TNF-α. The incriminated mechanism is thought to be the high fat diet that simulate a pro-inflammatory state [33]. IL-6 type cytokines belong to the long-chain 4α-helix hematopoietic cytokine family, and plays multiple biological roles in inflammation, hemostasis and immune response [34]. Serum levels of IL-6 correlate with prostate tumor burden and patient morbidity. The prostate tissue itself appears to be a source of IL-6 and its receptor [35]. Other studies found that cytokines such as IL-1 and IL-3, may have a role in angiogenesis [36].

In this study, the first to assess the combined role of PI-RADS and GST-P1 in the diagnosis of prostate cancer, we observed that, for patients with borderline PSA values, both GST-P1 and PI-RADS had good diagnostic performance for detecting prostate cancer, and by using the combined results, the capacity of the test to discriminate prostate cancer patients increases.

A major role in the survival of cancer patients is the capacity of the medical system to diagnose them as early as possible. For prostate cancer, prostatic specific antigen (PSA) and digital rectal examination (DRE) are widely and well-known methods used for the diagnosis of prostate cancer [37], easy to perform and generally cheap. Using the DRE as a predictor of prostate cancer is useful, in symptomatic patients [38], and abnormal test being an indicator of cancer risk, raising the concern and determining the referral of the patients to secondary level medical care for diagnosis purposes.

At the same time, PSA can have a significant number of irrelevant results, with low sensitivity [39] when 4ng/ml limit is used, and a significant number of tests within the borderline values. These cases require further investigation for clarification of the diagnosis [40,41], thus current research suggests PSA testing should be carefully evaluated and discussed with the patients [42] in order to maximize the benefits and limit the harm this procedure can have.

In the current study, we observed that PI-RADS values of at least 4 ensured a very high specificity for prostate cancer diagnosis, of 96.3%. Such a results offers very good perspectives in using it for ruling out healthy patients with borderline PSA values. These results are similar to the ones reported in the literature when PI-RADS was used in diagnosing prostate cancer [43,44].

When combined with GST-P1 testing, the precision of the imagistic method of diagnosing prostate cancer increased in a statistically significant way (p=0,014).

The results within this study suggest that by combining different methods of evaluating the patients, the success rate of a correct and timely diagnosis improves significantly.

Conclusions

PI-RADS lesions and GST-P1 methylation testing when PSA levels are in a “grey-zone”, provide a better specificity and sensitivity by comparison to single testing. Testing patients with inconclusive PSA-levels, allows a more accurate diagnosing and less over diagnosing by non-invasive procedures, such as repeated biopsies. These results further sustain the potential of improved diagnostics by interleaved imaging studies and prostate biomarkers.

Highlights

- ✓ Early diagnosis in prostate cancer is extremely important for achieving a high 5 years survival rate.
- ✓ The use of GST-P1 and PI-RADS tests in patients with inconclusive PSA-levels, allows less over-diagnosing by non-invasive procedures, such as repeated biopsies.

Conflict of interest disclosure

There are no known conflicts of interest in the publication of this article. The manuscript was read and approved by all authors.

Compliance with ethical standards

Any aspect of the work covered in this manuscript has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

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