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Serum levels of chromogranin are not predictive of poorly differentiated prostate cancer: Results from a multicenter radical prostatectomy cohort

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Abstract

Background: Recently a possible link between elevated Chromogranin A (CgA) levels and poorly differentiated prostate cancer has been proposed. The aim of our study was to explore the association of CgA levels and the risk of poorly differentiated prostate cancer (PCa) in men undergoing radical retropubic prostatectomy (RRP).

Materials and Methods: From 2012 onwards, 335 consecutive men undergoing RRP for PCa at three centers in Italy were enrolled into a prospective database. Body mass index (BMI) was calculated before RRP. Blood samples were collected and tested for total prostate-specific antigen (PSA) levels and chromogranin A (CgA). We evaluated the association between serum levels of CgA and upstaging and upgrading using logistic regression analyses.

Results: Median age and preoperative PSA levels were 65 years (interquartile range [IQR]: 60–69) and 7.2 ng/ml (IQR: 5.3–10.4), respectively. Median BMI was 26.1 kg/m^2 (IQR: 24–29) with 56 (16%) obese (BMI ≥ 30 kg/m^2). Median CgA levels were 51 (39/71). Overall, 129/335 (38,5%) presented an upstaging, and 99/335 (30%) presented an upgrading. CgA was not a predictor of upstaging or upgrading on RP.

Conclusions: In our multicenter cohort of patients, CgA is not a predictor of poorly differentiated PCa on radical prostatectomy. According to our experience, CgA should not be considered a reliable marker to predict poorly differentiated or advanced prostate cancer.

KEYWORDS

chromogranin A, prostate cancer, prostate cancer markers, radical prostatectomy

1 | INTRODUCTION

Prostate cancer (PCa) is the second most common cancer in men, and it represents the seventh cause of cancer death in the entire world.[1] In patients with PCa, an accurate assessment of the tumor characteristics is crucial to deliver the best treatment. Unfortunately, current methods to clinically assess PCa grade and stage are not accurate with the 33% risk of upgrading and upstaging on pathological examination.[2]

For years prostate-specific antigen (PSA) has been considered the standard marker to identify patients at risk of upstaging and upgrading. However, because of its limitations, new markers such as PSA velocity, PSA density, and Prostate Health Index have been introduced in clinical practice to reduce unnecessary invasive procedures.[3–6]

Chromogranin A (CgA) is an acidic glycoprotein commonly expressed in all neuroendocrine cells and serum levels are increased in patients with neuroendocrine tumors.[7] Neuroendocrine activity can also be detected in prostate cancer as a marker of its neuroendocrine differentiation; more specifically, CgA levels are elevated in castration-resistant PCa patients.[8–11]

In recent years, the prognostic capacity of CgA as a biomarker for PCa has been extensively evaluated. Hong et al. in their recent meta-analysis indicated that having high CgA levels represents an independent predictor of worse overall survival (OS) and progression-free survival (PFS) in castration-resistant prostate cancer (CRPC) patients.[12] Although several studies have demonstrated that high serum CgA levels are related to high-grade, advanced-stage disease and poor prognosis; to date, the results remain widely controversial.[13,14]

With this knowledge in mind, the aim of our study was to explore the association of CgA levels and the risk of upgrading and upstaging in men undergoing radical retropubic prostatectomy (RRP).

2 | MATERIALS AND METHODS

From 2017 onwards, 335 consecutive men undergoing Radical Retropubic Prostatectomy (RRP) for PCa at three centers in Italy (Department of Urology, Sant'Andrea Hospital, "Sapienza" University, Rome, Italy; Department of Urology, "Regina Elena" National Cancer Institute, Rome, Italy; and Department of Urology, "San Giovanni Bosco" Hospital, Turin, Italy) were enrolled into a prospective database. Patients who could not interrupt drugs interfering with CgA levels were excluded from the study.

Preoperatively, age, body mass index (BMI), and prostate volume were recorded. Blood samples were collected and processed by our laboratories to evaluate PSA and CgA levels.

CgA assays were performed in the morning of the day of prostate biopsy using a competitive chemiluminescent enzyme immunoassay and measured in ng/ml. Patients had been asked to interrupt any treatment with proton pump inhibitors or H-2 antagonists, if present, 3 weeks before the prostate biopsy, as these drugs may determine a significant modification of CgA serum concentrations. For diagnosis, 12 core transrectal ultrasound prostate biopsy samples were obtained and processed by a dedicated uropathologist in each center to perform histological examinations. All patients were staged preoperatively with a digital rectal examination (DRE), transrectal ultrasound, contrast-enhanced computed tomography (CT), and bone scan.

All patients underwent robotic radical prostatectomy and European Association of Urology (EAU) guidelines were used both for Staging and for Extended lymph-node dissection (eLND) indications. After surgery RP specimens were examined by the same dedicated uropathologist. The American Joint Committee on Cancer TNM 6th edition (2002) has been used for pathologic staging; tumor grade has been assigned according to the recommendations of International Society of Urological Pathology (ISUP).[15–17] All the biopsy and pathological specimens were evaluated for the presence of CgA by immunohistochemistry as suggested the manufacturer (Agilent, Dako Omnis). Upgrading was defined as any Epstein grade upgrading and upstaging as any cT≤2 → pT≥ 3 (Table 4).

2.1 | Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS v.24, IBM Corp.). Evaluation of data distribution using the Kolmogorov–Smirnov test showed a non-normal distribution of the study data set. The risk of high-grade disease and advanced disease was evaluated with univariate and multivariate binary logistic regression analysis.

3 | RESULTS

Data from 335 patients overall were considered for the analysis. On pathological immunochemistry analysis, none of the patients presented CgA on pathological specimens.

The characteristics of the study population are described in Table 1. The median age was 66 (interquartile range [IQR]: 60–69) and BMI was 26 (IQR: 24–29).

TABLE 1 Patients' characteristics

	Overall
No of patients	335
Age (years)	66 (60–69)
PSA (ng/ml)	7 (5–11)
BMI (kg/m^2)	26 (24–29)
TRUS volume (ml)	48 (23–68)
Chomogranine ng/ml	53 (40–73)

Abbreviations: BMI, body mass index; PSA, prostate-specific antigen.

On RP 129/335 (38.51%) patients presented upstaging. Upstaging patients were younger (64 vs. 66 years; $p < 0.05$), with smaller prostates (PV: 42.5 vs. 49cc; $p < 0.05$) and higher preoperative PSA levels (9 vs. 6 ng/ml; $p < 0.05$) (Table 2). CgA levels were not significantly different between two groups ($p > 0.05$).

On the other hand, 99/335 (30.37%) patients presented an upgrading. Upgrading patients presented higher BMI and higher CgA levels (56 vs. 49.5; $p < 0.05$). On binary logistic regression analysis, none of the variables were predictors of upgrading. On univariate binary logistic regression analysis, age (odds ratio [OR] 1.06; $p = 0.008$), BMI (OR 1.08; $p = 0.035$), prostate volume (OR: 0.99; $p = 0.046$), and PSA (OR: 1.06; $p = 0.01$) values were predictors of upstaging.

On multivariate binary logistic regression analysis, age (OR:1.07; $p = 0.004$), PSA (OR:1.12; $p = 0.001$), and BMI (OR: 1.12 $p = 0.015$) were independent predictors of upstaging (Table 3).

4 | DISCUSSION

An accurate preoperative assessment of tumor grade and stage is essential for the treatment of patients with PCa. The available methods of staging and grading are still suboptimal and several patients present upgrading and upstaging after RP. In the present study, we evaluated the possible role of CgA levels in the prediction of adverse pathological outcomes after radical prostatectomy. On univariate analysis CgA levels were higher in patients with upgrading (56 vs. 49, $p = 0.047$). However, data were tested in multivariate analysis where it was not statistically significant nor clinically relevant. To corroborate this data, we have also performed a correlation analysis that shows no significant Pearson correlation between upgrading and CgA ($r = -0.098$; $p = 0.077$; data not shown). As expected, age, PSA, and BMI are predictors of high-grade and advanced disease on RP specimens. These results are in line with the peer-reviewed literature and confirm the internal validity of our results.

The present study has been performed in a selected cohort of patients with localized/locally advanced disease with negative IHC and therefore the results apply to the enrolled population. In a recent systematic review, Kannan et al. have evaluated the role of CgA IHC in patients with PCa.[18] According to their results CgA IHC may vary between 4% and 100% underlying the high variability of CgA expression. Moreover, the authors underline that when neuroendocrine cell staining is assessed with objective criteria it identifies patients with poor clinical outcomes. Our study adds further evidence on the lack of role of serum CgA levels in patients with negative CgA IHC.

CgA is a secretory acid protein produced by neuroendocrine cells. Overall, it is associated with several different cancers derived from the neural crest such as pheochromocytoma and medullary cancer of the thyroid, or from other tissues, such as colon, gastric, and prostate cancer. Some studies suggest that patients with advanced and metastatic PCa have higher levels of CgA. Moreover, high levels of CgA in metastatic PCa have been related to a poor

TABLE 2 Patients' characteristics according to the presence/absence of upgrading and upstaging

	No upstaging	Upstaging	*p*	No upgrading	Upgrading	*p*
No of patients	206 (61.49%)	129 (38.51%)		227 (69.63%)	99 (30.37%)	
Age (years)	66 (61–69)	64 (59–70)	0.020	65 (59–68)	67 (61–70)	0.487
PSA (ng/ml)	6 (5–9)	9 (6–14)	0.001	6 (5–9)	8.5 (6–14)	0.433
BMI (kg/m^2)	26 (24–28)	27 (25–29)	0.082	26 (24–28)	27 (25–29)	0.012
TRUS volume (ml)	49 (35–63)	42.5 (31.5–75)	0.029	50 (35–70)	46 (32–58)	0.618
Chomogranine ng/ml	55 (41–75)	48 (37–67)	0.137	49.5 (39–73)	56 (41–78)	0.047

Abbreviations: BMI, body mass index; PSA, prostate-specific antigen.

TABLE 3 Variables tested for upgrading/upstaging

	Risk of upgrading		Risk of upstaging			
	Univariate		Univariate		Multivariate	
	OR; 95% CI	*p*	OR; 95% CI	*p*	OR; 95% CI	*p*
Age (years)	0.98; 0.94–1.03	0.608	1.06; 1.01–1.09	0.008	1.07; 1.02–1.12	0.004
PSA (ng/ml)	1.00; 0.98–1.02	0.585	1.06; 1.03–1.10	0.001	1.12; 1.07–1.19	0.001
BMI (kg/m^2)	0.99; 0.98–1.02	0.968	1.08; 1.01–1.16	0.035	1.12; 1.02–1.22	0.015
TRUS volume (ml)	1.00; 0.99–1.01	0.219	0.99; 0.98–0.99	0.046	0.99; 0.98–1.00	0.073
Chomogranine ng/ml	0.99; 0.99–1.00	0.103	1.00; 0.99–1.00	0.273		

Abbreviations: BMI, body mass index; CI, confidence interval; OR, odds ratio; PSA, prostate-specific antigen.

TABLE 4 (A) Biopsy and pathological grades: Dark gray cases are upgrading and light gray cases are downgrading. (B) Clinical (cT) and pathological (pT) staging: Dark gray cases are upstaging cases

A	Pathological Grade					
Biopsy Grade	1	2	3	4	5	Total
1	81/143 (57%)	49/143 (34%)	5/143(3%)	4/143 (3%)	4/143(3%)	143/335 (43%)
2	10/93 (11%)	55/93 (57%)	20/93 (24%)	5/93 (5%)	3/93 (3%)	93/335 (28%)
3	1/43 (2%)	7/43 (16%)	27/43 (63%)	6/43 (14%)	2/43 (5%)	43/335 (13%)
4	0/19	6/19 (32%)	3/19 (16%)	9/19 (47%)	1/19 (5%)	19/335 (6%)
5	0/37	3/37 (8%)	3/37 (8%)	3/37 (8%)	29/37 (79%)	37/335 (11%)
Total	92/335 (27%)	118/335 (35%)	60/335(18%)	27/335 (8%)	38/335 (11%)	335

B	Pathological Stage				
Clinical Stage	pT2	pT3a	pT3b	pT4	
cT1	155/250 (62%)	55/250 (22%)	36/250 (14%)	4/250(2%)	250
cT2	51/85 (60%)	24/85 (28%)	7/85 (8%)	3/85 (4%)	85
Total	206	79	43	7	335

response to androgen deprivation therapy due to the absence of the androgen receptor in neuroendocrine cells resulting in a poor prognosis for these patients. Moreover, it has been suggested that neuroendocrine differentiation may be one of the many mechanisms behind castration-resistant development.[12] Although CgA may have a role in PCa as a biomarker, at the moment the guidelines do not recommend its routine use.

In the past few years, some authors have evaluated the role of CgA in localized diseases with controversial results. In 2004 an Italian group found higher levels of CgA in patients extracapsular tumor growth in 83 patients undergoing radical prostatectomy. Moreover, using a CgA cut-off value of 60 ng/ml, PPV and NPV for clinical understaging were 0.5161 and 0.7885, respectively ($p = 0.0072$).[19] However, the authors observed no correlation between high-grade disease and CgA levels. In a subsequent study, high CgA levels (>60 ng/ml) were associated with postoperative PSA recurrence.[20] As well, a study performed by our group found no association between CgA and high-grade disease in a cohort of patients undergoing prostate biopsies.[21] Finally, in a recent analysis of the correlation between preoperative CgA levels with long-term disease-specific survival, no prognostic value was found for CgA.[22] CgA levels were not associated with PFS; however, long-term disease-specific survival could not be analyzed in this study. As well, some studies have evaluated the role of CgA in the latter stages of the disease. Some studies suggest that in patients undergoing ADT, neuroendocrine differentiation represents a possible escape mechanism leading to metastatic disease. More specifically these studies have demonstrated that preoperative CgA levels are associated with the response to docetaxel, enzalutamide, and abiraterone treatment.[23–26]

In patients with CRPC some authors have evaluated genetic alterations, particularly in RB1, PTEN, and p53.[27,28] Kaur et al. have recently explored this issue in patients with NE differentiation, with high-risk PCa, and in patients with mCRPC treated with ABI ore ENZA. According to their results despite evidence of lower AR signaling, adenocarcinomas with NE differentiation did not differ by the prevalence of TP53 missense mutations, or PTEN or RB1 loss, compared with those without NE differentiation.[29] Moreover, the authors highlight the role of AR-low CGA-expressing cells that could predict resistance to neoadjuvant hormonal therapies. The present study opens some important insights into the management of these patients.

In the latest years, MRI has been implemented before prostate biopsies. Although MRI has improved the detection of clinically significant cancer its role is still controversial in terms of staging. According to the available literature, the NPV and the PPV for EPE lies in the range between 70% and 90%.[30] However, 46.5% of the patients still present upstaging on final pathology and MRI is limited in predicting upgrading events.[31] We believe that the lack of MRI in our study should be considered a limitation of our study however the lack of it does not influence the study results on the poor role of CgA as a marker for upstaging and upgrading.

The role of CgA has been widely explored in gastrointestinal neuroendocrine tumors showing that CgA levels may be normal in the absence of metastatic disease. In PCa data is heterogeneous, however,

some authors have demonstrated how CgA levels may be elevated even in the absence of metastatic disease. Sciarra et al demonstrated how 6% of patients with nonmetastatic disease and 69.7% of patients with metastatic PCa may have CgA>90ng/ml (the normal range of the kit 0–90 ng/ml).[32] Although these studies suggest a possible role for CgA as a marker of aggressive disease, our study shows no role for CgA as a marker of upgrading and upstaging.

We have to acknowledge some other limitations to the present study. First, although the database was prospectively maintained, it was analyzed retrospectively. Moreover, follow-up data was not available therefore the role of CgA as a prognostic factor could not be evaluated, however, a study is ongoing and results will be soon available. The lack of a mpMRI preoperatively may be considered a limitation of our study however nowadays mpMRI is still optional in the staging of PCa. Lastly, CgA levels were dosed a single time therefore we could not assess CgA variations in time. Notwithstanding all these limitations our multicenter study adds further evidence on the role of CgA in prostate cancer.

5 | CONCLUSIONS

CgA levels are not associated with upgrading and upstaging radical prostatectomy. Standing to the available evidence CgA should not be evaluated before radical prostatectomy.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data are available upon request.

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