Clinical Understaging in Patients With Prostate Adenocarcinoma Submitted to Radical Prostatectomy: Predictive Value of Serum Chromogranin A

Alessandro Sciarra,[1]* Giuseppe Voria,[1] Salvatore Monti,[2] Luigi Mazzone,[1] Gianna Mariotti,[1] Mariangela Pozza,[1] Giuseppe D'Eramo,[1] and Franco Di Silverio[1]

[1]*University La Sapienza, Department of Urology, Rome, Italy*
[2]*University La Sapienza, Endocrinology Clinic, Rome, Italy*

PURPOSE. To evaluate whether the pretreatment determination of serum chromogranin A (CgA) can provide information beyond that obtained with serum prostate specific antigen (PSA) and Gleason score at biopsy as a predictive factor of clinical understaging (T2-pT3) of prostate adenocarcinoma.

MATERIALS. In this prospective study, we analyzed 83 consecutive patients with clinical T2N0M0 prostate adenocarcinoma submitted to radical prostatectomy (RRP). On the same day of RRP, before surgery, a blood sample for the determination of serum total PSA and CgA levels (RIA) was obtained.

RESULTS. After RRP, 27 of the 83 cases (32.5%) showed extracapsular disease extension (pT3) at the final pathological examination and were considered clinically understaged. A significant association between serum CgA and pathological stage (r = 0.3830; $P = 0.0004$) was found. At the multivariate analysis, serum CgA and PSA, but not biopsy Gleason score, were found to be significant pretreatment independent predictors of pT3 at RRP ($P = 0.00004$ and $P = 0.0018$, respectively). The relative risk of clinical understaging significantly varied according to serum CgA levels. Using a CgA cut-off value of 60 ng/ml, PPV and NPV for clinical understaging were 0.5161 and 0.7885, respectively ($P = 0.0072$).

CONCLUSIONS. Serum CgA could be incorporated into risk assessment models of newly diagnosed prostate cancer. *Prostate 58: 421–428, 2004.* © 2003 Wiley-Liss, Inc.

KEY WORDS: prostate neoplasms; clinical staging; chromogranin A

INTRODUCTION

In patients newly diagnosed with prostate cancer, the better-defined pretreatment predictors of disease extent and outcome after radical prostatectomy (RRP) are staging, Gleason score, and serum prostate specific antigen (PSA) levels at diagnosis.

However, before surgery, organ-confined or locally advanced tumor growth is often difficult to assess accurately [1,2], and approximately 20–40% of cases clinically classified as T2 result understaged, showing an extracapsular disease (pT3) at RRP [1,3]. Therefore, it is still important to establish and compare new predictors of both local pathological stage and risk of extracapsular disease extension at RRP in clinically localized prostate cancer.

In recent years, increasing attention has been focused on neuroendocrine (NE) differentiation of prostate adenocarcinoma and, in particular, on its possible clinical significance. It has been hypothesized that NE

cells may have a local regulatory role in both growth and differentiation of the prostate tissue through production of many bioactive substances [4]. Some authors have stressed that prostate adenocarcinomas with NE differentiation (NED) tend to be more aggressive [5]. Serum levels of NE markers, particularly chromogranin A (CgA), could reflect the NE activity of prostate carcinoma and could be used during clinical evaluation: at present, CgA appears to be the best marker of NE activity in the prostate gland [6].

Clinical relevance of NE activity during progression of prostate carcinoma after androgen deprivation therapy is better recognized [5–7].

On the contrary, the value of NED as a prognostic factor of tumor progression after RRP is unclear: some studies have reported findings suggesting NED to be a prognostic marker in tumors with Gleason score 5–6, [8] but others have failed in this correlation [7].

If it was hypothesized that NE activity influence prostate cancer growth and progression, one might expect NE markers such as CgA to correlate with more adverse pathological features of prostate cancer and also to predict the extension of the tumor before surgery. The aim of the present study is to evaluate whether in clinically localized prostate cancer considered for surgery, the pretreatment determination of serum CgA levels can provide information beyond that obtained with serum PSA and Gleason score at biopsy, as a predictive factor of clinical understaging (T2-pT3) of tumors.

In particular, in clinically localized prostate adenocarcinomas submitted to RRP, we analyzed:

- correlation among serum preoperative CgA levels and established parameters such as Gleason score at biopsy and at RRP, pathological stage, and serum preoperative PSA;
- relative risk (RR) of an extracapsular extension of the tumor at RRP, according to serum CgA levels;
- predictive value of preoperative CgA, PSA levels, and Gleason score at biopsy for the extracapsular extension of the tumor at RRP.

MATERIALS AND METHODS

This is a prospective single center study. Between June 1999 and June 2002, 102 consecutive men with clinically localized prostate cancer underwent RRP and staging lymphadenectomy at our clinic. Inclusion into this study was based on the following criteria:

- clinically localized T2N0M0 prostate adenocarcinoma;
- no previous hormonal or radiation therapy;
- no previous surgery on the prostate gland;

- histologically proven adenocarcinoma of the prostate at RRP;

All 83 patients had a biopsy proven clinically T2N0M0 prostate adenocarcinoma as determined by digital rectal examination, transrectal ultrasonography, bone scan, and computer tomography. None of these cases presented a history of other disorders or therapies or conditions known to interfere with CgA levels (NE malignancies, previous, or concomitant other neoplastic history, adrenal ''incidentalomas,'' endocrine manipulation therapies, uncontrolled hypertension). Clinical and pathological characteristics of the 83 patients are described in Table I. In all cases, a radical retropubic prostatectomy was performed by an anatomic approach, as previously described [9].

Pathological Examination

All RRP specimens were evaluated pathologically at our institution according to a routine technique. In particular, the prostate gland and seminal vesicles were whole-mounted and 3 mm step-sectioned from the apex to the base. In all 83 patients, tumor stage was assigned according to the 1997 modification of the TNM classification [10].

Tumor volume was not assessed.

Tumor grade was described according to the Gleason grading system [11]. On the basis of the histological grade, patients were then divided into two different groups: Gleason score <7 and Gleason score ≥7. On the basis of the pathological stage, patients were divided in cases who were clinically understaged (pT3) and cases who were not clinically understaged (pT2). Understaging was defined as a clinically organ-confined tumor that was at extracapsular stages (pT3 to 4) at RRP [1]. For this reason, pT3a and pT3b cases were considered together. No pT4 cases were found in this experience.

Preoperative Serum PSA and CgA Determination

On the same day of RRP, before the surgical procedure but at least 3 weeks after any prostatic manipulation, a blood sample for the determination of preoperative serum total PSA and CgA levels was obtained from all cases. Each sample was homogeneously collected in the early morning after an overnight fast. In each case, serum CgA was measured by RIA using a commercial kit (CIS bio International, Cedex, France). The detection limit of this kit was 1.5 ng/ml. The inter-assay and intra-assay coefficients of variations of CgA assay was 5.8 and 3.8%, respectively. In each case, the same serum sample was also used to determine total PSA levels (Hybritech, Inc., San

TABLE I. Clinical and Pathological Characteristics of the 83 Cases Included in the Analysis

Number of cases	83
Age (years)	64.35 ± 4.59 (65) range 50–73
Clinical stage T2N0M0	83
Pathological stage: pT2	56 (67.5%)
Pathological stage: pT3	27 (32.5%)
Lymphonode positivity pN+	0
Biopsy Gleason score <7	22 (26.5%)
Biopsy Gleason score ≥7	61 (73.5%)
RRP Gleason score <7	11 (13.2%)
RRP Gleason score ≥7	72 (86.8%)
Preoperative serum PSA (ng/ml)	13.85 ± 7.70 (11.0) range 4.70–39.60
Preoperative serum CgA (ng/ml)	61.44 ± 27.83 (56.60) range 22.80–154.83

Age and CgA values are presented as mean ± SD (median) and range. The other parameters are presented as number of cases (%).

Diego, CA). All samples were evaluated centrally in the laboratory of our University.

Tissue CgA mRNA Extraction and RT-PCR

In the first 20 consecutive prostate cancer cases included in this study, we had the opportunity to analyze CgA mRNA expression on tissue samples obtained from RRP. Prostate tissue samples were immediately frozen in liquid nitrogen and stored at −80°C until analysis. In each specimen, the diagnosis of prostate adenocarcinoma was histologically confirmed. Each sample weighted about 1 g. Gene expression of CgA was evaluated by a semiquantitative RT-PCR, using β-actin as a control. The method has been previously described [4,12,13].

Statistical Analysis

Descriptive statistics were used to characterize the age of the patients as well as PSA, CgA levels, clinical and pathological characteristics of prostate tumors. Univariate and multivariate analysis was performed to determine important predictors of understaging in our population.

Spearman correlation coefficients were calculated to measure the association among parameters. Our cases were classified according to the pathological stage in organ confined (pT2) and non-organ confined (pT3) cases: variations in the parameters in each group were reported and Fisher's exact test was performed. Some factors such as Gleason score were dichotomized (<7 and ≥7) and transformed into indicator variables. PSA and CgA were used as continuous variables. In the last part of our study, we analyzed the positive and negative predictive value of two cut-offs for PSA (10 ng/ml) and CgA (60 ng/ml), respectively.

A logistic regression model was used to test the predictive value of the covariates in predicting clinical understaging.

A 5% level of significance was used for all statistical testing.

RESULTS

General Considerations

After RRP, 27 of the 83 (32.5%) cases with clinically localized prostate cancer showed extracapsular disease extension (pT3) at the final pathological examination (17 pT3a and 10 pT3b cases) (Table I) and were considered to be clinically understaged.

If we compare the postoperative Gleason score taken from the prostatectomy specimens with the Gleason score from the biopsy, in our series, undergrading between the biopsy and the final surgical specimen occurred in 9 of 22 cases (40.9%) for biopsy Gleason score <7 and in 4 of 61 cases (6.5%) for biopsy Gleason score ≥7, whereas overgrading occurred in 0 and 1 case, respectively, in the two groups. Mean ($P = 0.0004$) and median ($P = 0.0002$) preoperative serum PSA but only mean ($P = 0.0005$) and not median ($P = 0.0811$) CgA values were significantly lower in patients without extracapsular disease compared to those with extracapsular disease at RRP (Table II). A similar distribution of the biopsy Gleason score (<7 vs. ≥7) was found in pT2 and pT3 cases ($P = 0.6049$) (Table II).

Associations Among the Different Clinical and Pathological Variables

We evaluated associations among the different clinical and pathological parameters obtained from our population of 83 prostate cancer (Table III).

TABLE II. Clinical and Pathological Characteristics of our Cases Distinguished on the Basis of Clinical Understaging

	pT2	pT3	*P* value
No cases	56 (67,5%)	27 (32.5%)	
Age (years)	64.77 ± 4.28 (65) range 56–73	63.55 ± 5.09 (65) range 50–72	0.856 (*t*-Student)
Preoperative serum PSA (ng/ml)	11.80 ± 6.26 (9.65) range 4.70–35.1	18.11 ± 8.73 (16.3) range 7.8–39.6	0.0004 (*t*-Student)
Preoperative serum CgA (ng/ml)	53.97 ± 14.41 (56.0) range 22.80–85.2	76.62 ± 40.64 (65.50) range 28.6–154.83	0.0005 (*t*-Student)
Biopsy Gleason score <7	16 (28.6%)	6 (22.3%)	0.6049 (Fisher' exact test)
Biopsy Gleason score ≥7	40 (71.4%)	21 (77.7%)	
RRP Gleason score <7	7 (12.5%)	4 (14.8%)	0.7426 (Fisher' exact test)
RRP Gleason score ≥7	49 (87.5%)	23 (85.2%)	

Age, PSA, and CgA values are presented as mean ± SD (median) and range. The distribution of Gleason score is presented as number of cases (%).

Serum PSA and CgA were used as continuous variables.

In particular, in our cases, we did not find a significant correlation between serum preoperative PSA and CgA values ($P = 0.6970$). A similar and significant association between serum CgA and pathological stage (pT2 vs. pT3) ($r = 0.3830$; $P = 0.0004$) and between serum PSA and pathological stage ($r = 0.3861$; $P = 0.0003$) was found. A lower association was found between biopsy Gleason score and pathological stage ($r = 0.2922$; $P = 0.0073$).

Multivariate Analysis

We used the multivariate analysis to determine whether serum CgA added predictive information in terms of risk for clinical understaging that was independent of that obtained using serum PSA and Gleason score at biopsy. The analysis was performed with extracapsular disease extension at RRP as the dependent variable (Table IV). Serum PSA and CgA were used as continuous variables.

TABLE III. Associations Among the Different Parameters (r = Spearman Correlation Coefficient) Evaluated in the 83 Patients

Association	r	*P* value
PSA-CgA	0.040	0.6970
PSA-pT	0.3861	0.0003
CgA-pT	0.3830	0.0004
PSA-Gleason biopsy	0.3355	0.0019
PSA-Gleason RRP	0.4260	<0.0001
CgA-Gleason biopsy	0.1106	0.3197
CgA-Gleason RRP	0.1532	0.1668
Gleason biopsy-pT	0.2922	0.0073

TABLE IV. Multivariate Analysis for Prediction of Extracapsular Disease at RRP CI = Confidential Interval

Variable	Coefficient	95% CI	*P* value
Serum CgA	0.00595	0.0027–0.0091	0.0004
Serum PSA	0.01973	0.0075–0.0319	0.0018
Biopsy Gleason score	0.09631	−0.0372–0.2299	0.1546

Serum CgA and PSA, but not biopsy Gleason score, were found to be significant independent predictors of an extracapsular extension ($P = 0.0004$ and $P = 0.0018$, respectively).

Figure 1 shows that the RR of an extracapsular extension at RRP increases according to serum CgA levels; the highest increase in RR was found for serum CgA levels over 60 ng/ml. In fact, using 30 ng/ml (lowest CgA level in our population) as reference, for CgA values of 50 ng/ml or lower, the RR was lower than 0.90 (CgA 50 ng/ml: RR = 0.867 (lower limit = 0.463, upper limit = 1.621)), whereas it increased at 2.440 (lower limit = 1.305, upper limit = 4.562) and 3.60 (lower limit = 2.112, upper limit = 6.153) for CgA levels of 60 and 70 ng/ml, respectively. For CgA values over 70 ng/ml, RR remained high, but it did not increase over 4.0 (CgA 100 ng/ml: RR = 3.947 (lower limit = 2.676, upper limit = 5.822)).

Positive and Negative Predictive Values of Clinical Understaging

On the basis of the results of the multivariate analysis (Fig. 1), we tried to analyze a cut-off value of 60 ng/ml for serum CgA, compared to that of 10 ng/ml for PSA.
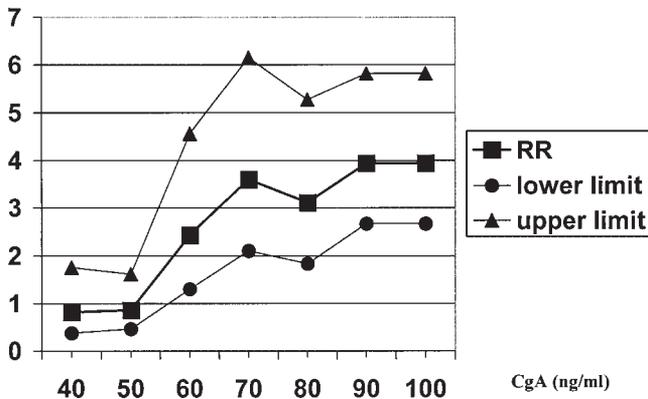
Fig. I. Modification of relative risk (RR) for clinical understaging, based on serum CgA levels. (Coefficient = 0.00595 (95% CI 0.0027–0.0091); $P = 0.0004$). Based on our population data are reported for a patient with clinical T2 prostate cancer, 65 year old.

Using these two cut-offs for PSA and CgA, we analyzed their positive and negative predictive value of clinical understaging. Significant results were found either for PSA or CgA; a higher sensitivity but a lower specificity in predicting extracapsular extension at RRP was found for serum PSA when compared to serum CgA (Table V). No significant predictive values were found using the biopsy Gleason score ($P = 0.6049$).

CgA mRNA Tissue Expression in the Subgroup of 20 Cases

In the first 20 consecutive cases included in the study, we analyzed CgA mRNA expression at tissue level.

In this subgroup, after RRP, 35% of cases (7 out of these 20 cases) showed extracapsular disease extension (pT3) at the final pathological examination.

In all samples examined, the expression of CgA mRNA has been found. No amplification was observed when cDNA was replaced with distilled water (negative control) or with total RNA.

Densitometric analysis of CgA prostate adenocarcinoma products, normalized to that of β-actin, had demonstrated that prostate adenocarcinoma samples obtained from pT3 cases presented levels of CgA

mRNA higher (about 30%) than those from pT2 cases, but the difference did not reach statistical significance ($P = 0.060$).

Moreover, in this subgroup of 20 patients, serum concentration of CgA were positively and significantly associated with mRNA levels of CgA ($r = 0.469$; $P = 0.039$).

DISCUSSION

To our knowledge, this is the first study in the literature that specifically analyzes serum CgA as a predictor of clinical understaging in prostate cancer. Other previous studies have immunohistochemically analyzed the role of NED as a prognostic factor of prostate tumor extension and progression after treatment. Studies on the prognostic value of NED in RRP specimens have revealed conflicting results [14–16].

Several investigators did not find a correlation between the number of NE cells and tumor stage [14].

On the other hand, Ahlegren [7] and Kruspky et al. [15] showed that in prostate cancer submitted to RRP, the extension of NED and CgA tissue expression are significant prognostic indicators of failure after surgery.

Many factors may be proposed to explain why the same prognostic significance of NED in prostate carcinoma could not be demonstrated in all studies. Some factors include methodological differences in determining the presence of malignant NE cells [16]: the rather unequal distribution of NE cells in most tumors may cause serious sampling errors if biopsy specimens or limited tissue samples have to be studied [14].

Serum levels of NE markers, particularly CgA, could reflect the NE activity of prostate adenocarcinoma and could be used during clinical evaluation. Angelsen et al. [6] demonstrated a correlation between the number of CgA positive NE cells and serum CgA levels in patients with prostate adenocarcinoma. Increased serum levels of CgA were more consistently found in patients with metastatic and androgen-insensitive prostate tumors [17,18].

Berruti et al. [19] however, showed a progressive increase in the median levels of serum PSA and serum

TABLE V. Predictive Value of a Serum Preoperative PSA > I0 ng/ml, CgA > 60 ng/ml and Biopsy Gleason Score ≥7, for Extracapsular Disease Extension at RRP (95% Confidential Interval)

	Sensitivity	Specificity	PPV	NPV	Fisher's exact test
PSA>10 ng/ml	0.8148 (0.6193–0.9369)	0.5714 (0.4319–0.7031)	0.4783 (0.3292–0.6301)	0.8649 (0.7125–0.9547)	0.0010
CgA >60 ng/ml	0.5926 (0.3877–0.7763)	0.7321 (0.5969–0.4966)	0.5161 (0.3303–0.6984)	0.7885 (0.6529–0.8894)	0.0072
Biopsy Gleason score ≥7	0.2222 (0.0863–0.4230)	0.7143 (0.5784–0.8268)	0.2727 (0.1074–0.5025)	0.6557 (0.5227–0.7724)	0.6049

CgA from patients with BPH through those with PIN, non metastatic, and metastatic prostate cancer.

In previous experiences [4,13], we found a significant correlation between serum CgA levels and CgA mRNA expression in prostate adenocarcinoma tissue, also in locally advanced non-metastatic disease. Moreover, in a recent study [20], we showed that androgen-deprivation therapy is able to significantly influence serum CgA levels not only in metastatic but also in locally advanced prostate cancers.

In the present study, we specifically analyze the role of serum CgA as a predictor of clinical understaging in prostate adenocarcinoma cases submitted to RRP, whereas we did not evaluate its potential role as prognostic factor of progression after surgery. The rationale for this kind of analysis is based on the fact that if it is hypothesized that NE activity influences prostate cancer growth, one might expect NE markers, such as CgA, to correlate with more adverse pathological features of prostate cancer and to help in predicting also the extension of the tumor before surgery.

The ability to determine the prostate cancer stage accurately before the delivery of therapy, obviously has important implications for all patients newly diagnosed with prostate cancer: it may influence the choice of the primary therapy or the decision for adjuvant therapy.

In clinically localized prostate cancer submitted to RRP, the incidence of understaging varied. Recently, Grossfield et al. [1] reported a 24% rate of understaging which was less than the 36–60% incidence previously reported in large single institute studies [21]. In our population of clinically localized prostate adenocarcinomas evaluated and submitted to RRP in a single institute, the rate of understaging was 32%.

Several authors showed that in newly diagnosed prostate cancer patients, the three well-defined pretreatment predictors of disease extent are clinical tumor stage, Gleason score at biopsy, and serum PSA [22]. Grossfield et al. [1] showed that serum PSA at diagnosis, biopsy Gleason score, and the percent of positive biopsies were significant independent predictors of understaging in a community-based population undergoing RRP. On the basis of these results, we compared preoperative serum CgA levels with previously established predictors of clinical understaging such as preoperative serum PSA and Gleason score at biopsy. We had no opportunity to systematically analyze the percent of positive biopsies as a predictor.

All our cases were prospectively and consecutively evaluated in our clinic. The clinical and pathological characteristics of our population are comparable to those of series reported in previous trials [1]. However, only clinical T2 cases were considered: in fact, from our analysis, we excluded cases previously submitted to surgical procedures on the prostate gland. As in previous reports [1], we distinguished pathological stages in pT2 and pT3 cases, and we did not separately consider patients with and without seminal vesicle invasion (pT3a and pT3b). Understaging is defined as a clinically organ-confined tumor that is at extraprostatic stages at RRP.

In this study, we confirmed that CgA is a marker independent of the role of PSA, that may produce information complementary to that obtained with serum PSA; in fact, a not significant association was found between serum PSA and CgA levels.

It is interesting to underline that, in our population, a strong correlation with Gleason score at biopsy and at RRP was found for serum PSA but not for serum CgA levels; on the contrary, either PSA or CgA showed a similar significant correlation with pathological stage (pT2 vs. pT3).

Our results consistently confirm that pretreatment serum PSA is an independent significant predictor of extracapsular disease extension at RRP. Unlike previous reports [1], Gleason score at biopsy did not reach the same level of significance. At the multivariate analysis, we showed for the first time, that pretreatment serum CgA is also a significant and independent predictor of clinical understaging in T2 prostate adenocarcinomas submitted to RRP. Figure 1 shows that a sustained increase in the RR of clinical understaging is related to serum CgA levels and in particular to values over 60 ng/ml. In fact, when compared to the lowest CgA levels in our population (30 ng/ml), the RR increases to 2.5–3.5 times for CgA levels at 60 and 70 ng/ml, respectively. We used the multivariate analysis to confirm the independent predictive value of CgA levels (when compared to PSA and biopsy Gleason score) for understaging. In cases submitted to RRP, other parameters such as creatinine serum levels [23] or insulin-like growth factor (IGF)-1 plasma levels [24] showed a significant association with pathological stage upon univariate analysis, but this significance was not confirmed at the multivariate analysis.

The elevations in CgA levels reported in our study are modest if compared with those observed in pure pathologically confirmed NE tumors. However, we must remember that NED of prostate adenocarcinoma consists of the presence of NE cells with a focal distribution in the common prostatic adenocarcinoma. Therefore, in prostate adenocarcinoma cases, it is not possible to expect the same levels and variations in CgA as those found in pure NE tumors. Moreover, at present, there are not enough data to define a normal range for CgA related to the presence of a prostate adenocarcinoma; all existing ranges refer to the presence of pure NE malignancies or diseases. In prostate adenocarcinoma populations, authors [8] arbitrarily

selected a cut-off value of serum CgA on the basis of the results of their personal experience. Based on the results of our multivariate curve, we analyzed a cut-off value of 60 ng/ml for serum CgA. Using this cut-off, the PPV and NPV of CgA for extracapsular disease extension at RRP were significant: a higher specificity but a lower sensitivity was found when compared to a PSA cut-off of 10 ng/ml. These data may support the hypothesis for a complementary role between pre-operative PSA and CgA determination. The limited number of cases included in our analysis emphasizes the need to verify all these data in a larger population, and it does not allow the multivariate analysis to be used to determine the predictive value of CgA in clinically relevant patient subgroups according to other variables (Gleason score, serum PSA).

An other possible limitation of our study must be acknowledged. As previously published [4,6], serum levels of CgA may be influenced by factors other than prostate adenocarcinoma.

For this reason, in the last part of the study, we included results on the tissue determination of CgA.

None of our cases presented a history of NE malignancies or other diseases known to interfere with CgA levels.

Only in a subgroup of 20 clinically localized prostate cancers, we had the opportunity to analyze by RT-PCR, CgA mRNA expression on tissue samples obtained from RRP: this analysis is a more specific method than immunohistochemistry to detect and quantify NE activity in prostate tissue [4,13]. The higher expression of CgA mRNA reported in pT3 as compared to pT2 cases and the significant correlation between serum and tissue expression of CgA ($r = 0.469$, $P = 0.039$) may suggest that, in our population, serum CgA levels were significantly influenced by the NE activity in prostate adenocarcinoma.

CONCLUSIONS

The multivariate analysis revealed that pretreatment serum CgA together with serum PSA are independent predictors of understaging in our population of clinical T2 prostate adenocarcinomas submitted to RRP. A combined analysis of serum PSA and CgA may better predict the risk of an extracapsular extension at surgery.

These data may support the inclusion of serum CgA in risk assessment models of newly diagnosed prostate cancers. However, no conclusions can be drawn at present. We suggest that this hypothesis be verified specifically in larger multivariate experiences.

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