

SERUM PSA AND CURE PERSPECTIVE FOR PROSTATE CANCER IN MALES WITH NONPALPABLE TUMOR

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ABSTRACT

Introduction: Many studies have shown the association between PSA levels and the subsequent detection of prostate cancer. In the present trial, we have studied the relationship between preoperative PSA levels and clinical outcome following radical prostatectomy in men with clinical stage T1c.

Materials and Methods: 257 individuals with clinical stage T1c undergoing retropubic radical prostatectomy were selected in the period from 1991 to 2000. Following surgery, biochemical recurrence-free survival curves were constructed according to PSA levels between 0-4; 4.1-10; 10.1-20 and > 20 ng/mL.

Results: Of the total of 257 selected patients, 206 (80%) had Gleason scores from 2 to 6 and 51 (20%), presented Gleason scores 7 and 8, as defined by the pathological report from prostate biopsy. There was no biochemical recurrence of disease when the PSA was lower than 4, regardless of Gleason score. Biochemical recurrence-free survival according to PSA between 0-4; 4.1-10; 10.1-20 and > 20 was 100%, 87.6%, 79% and 68.8% for Gleason scores 2-6 and 100%; 79.4%; 40% and 100% for Gleason scores 7-8 respectively. When all individuals were grouped, regardless of their Gleason scores, the probability of biochemical recurrence-free survival was 100%, 65.1%, 53.4% and 72.2% according to PSA between 0-4; 4.1-10; 10.1-20 and > 20 ng/mL respectively.

Conclusion: Non-palpable prostate cancer presents higher chances of cure when the PSA is inferior to 4 ng/mL.

Key words: prostate-specific antigen; prostatic neoplasms; prostatectomy; treatment outcome
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INTRODUCTION

Approximately 75% of men over 50 years old are screened for prostate cancer (PCa) by testing the prostate-specific antigen (PSA) (1); among those with altered PSA, two thirds will be identified as having PCa in stage T1c (2).

The indication for prostate biopsy when the PSA exceeds 4 ng/mL should be assessed on an indi-

vidual basis, especially after recent data that showed PCa in 23.9 to 26.9% of men with PSA between 2 and 4 ng/mL (3).

One concern about the indiscriminate use of PSA is the diagnosis of insignificant tumors (4) and the treatment of eventual tumors with low biological aggressiveness. However, despite the initial identification of PCa, 25 to 33% of individuals will die as a consequence of the disease, though the majority is

identified as T1c (2). The detection of early PCa increases the chances of disease confined to the prostate with lower risks of cancer recurrence following the treatment (5), while some authors already believe that the disease-related mortality is decreasing (6).

Due to the increasing debate concerning the upper normal limits for PSA (7), this study aims to assess preoperative PSA levels in individuals with PCa clinical stage T1c undergoing radical prostatectomy, as well as their postoperative outcome.

MATERIALS AND METHODS

The study assessed 257 men presenting a clinical diagnosis of PCa stage T1c, with a mean age of 63.2 ± 7.5 years (47 - 76). The mean preoperative serum PSA was 8.7 ± 5.6 ng/mL (0.3-32.0), and the mean postoperative follow-up time was 85.4 ± 6.1 months. These were retrospectively assessed.

The initial PSA was collected before prostate biopsy. During staging, all patients underwent anamnesis and physical examinations, alkaline phosphatase dosing, total and prostatic acid phosphatase, pelvic computerized tomography and bone scintigraphy in order to rule out extraprostatic disease.

All participants underwent retropubic radical prostatectomies with bilateral pelvic iliac lymphadenectomy at our institution from March 1991 to November 2000. The same surgeon (MS) performed all surgical procedures and the same pathologist (KRL) performed all pathological analyses.

Clinical staging was defined according to the American Joint Committee on Cancer classification (8), and histological grade according to Gleason score (9).

For selection of this group, cases receiving neoadjuvant or adjuvant hormone therapy (14 patients), as well as adjuvant radiotherapy (one patient), were excluded.

Postoperatively, patients were assessed every 2 months during the first year, then every 6 months for 5 years, and yearly from then on. During each assessment, patients underwent digital rectal examinations of the prostate cavity and analysis of serum PSA. Imaging exams (chest radiography, bone scintigraphy, abdominal tomography) were repeated ev-

ery year. Biochemical progression was defined as a serum PSA higher than or equal to 0.4 ng/mL, a cut-off value that was used by other authors as well (10).

The preoperative PSA was divided into categories of from 0 to 4 ng/mL, 4.1 to 10 ng/mL, 10.1 to 20 ng/mL and higher than 20 ng/mL. (The distribution of patients according to preoperative PSA is in Table-1). Initially, we divided the patients into 2 groups: low risk (Gleason scores 2-6) and high risk (Gleason scores 7-10). Subsequently, we grouped all individuals together to build the survival curve.

For the statistical analysis, we used an approach of survival analysis considering the biochemical recurrence of the disease as the event of interest, defined by a PSA value higher than or equal to 0.4 ng/mL. For the disease-free survival curves, we used the Kaplan-Meier method and the Breslow and Log-Rank tests. A Cox regression model with proportional risks was adjusted on the multivariate analysis. P values < 0.05 were considered to be statistically significant.

RESULTS

Table-1 presents the distribution of 257 patients with clinical stage T1c showing the incidence in relation to PSA values, where we can observe that 60% of them had PSA between 4.1 and 10.0.

Table-2 presents the 206 patients with clinical stage T1c and Gleason scores of 2-6 (low risk) in relation to PSA levels and events in relation to the assessed PSA categories. In Figure-1, we can see that PSA levels influenced the disease-free survival rates of patients with clinical stage T1c ($p = 0.008$). We can also observe that none of the patients with PSA

Table 1 – PSA distribution in patients with clinical stage T1c.

PSA	N (%)
0 - 4.0	17 (6.7)
4.1 - 10.0	155 (60.3)
10.1 - 20.0	67 (26)
> 20.0	18 (7)
Total	257 (100.0)

Table 2 – Distribution of patients with clinical stage T1c and Gleason scores 2-6, according to PSA levels.

PSA Levels	N Patients	N Events	% Censorships
0 - 4.0	12	-	100.0%
4.1 - 10.0	121	15	87.6%
10.1 - 20.0	57	12	79.0%
> 20.0	16	5	68.8%

between 0 and 4.0 presented a recurrence of disease during the assessment period. When PSA levels oscillated between 4.1 and 20 ng/mL, they showed the same prognosis ($p = 0.102$) in relation to the expectancy of biochemical recurrence-free survival.

Table-3 represents the distribution of 51 patients with clinical stage T1c and Gleason scores of 7 and 8 according to PSA levels. It is important to stress that there was no patient with a Gleason score of 9 or 10. The survival probability curve for bio-

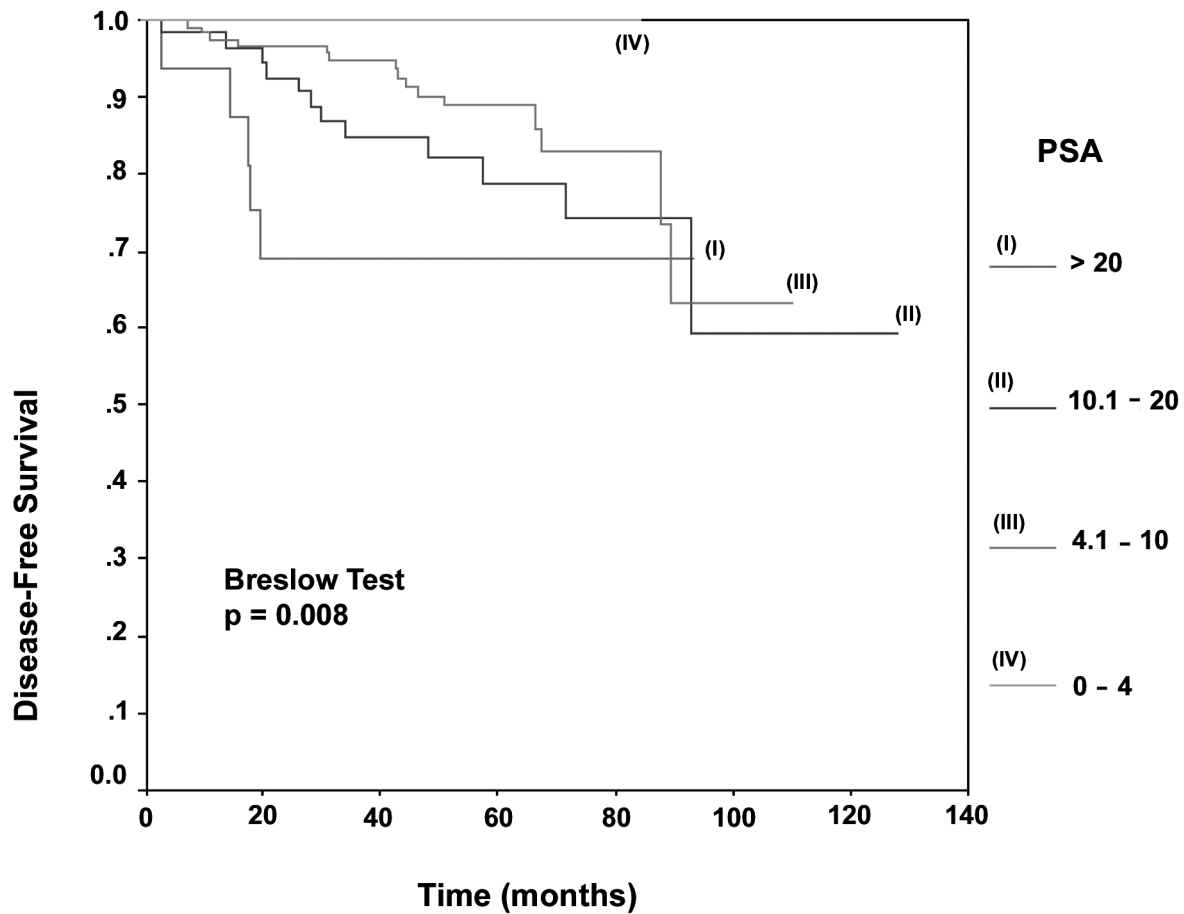


Figure 1 – Probability curve for recurrence-free survival according to PSA categories in patients with clinical stage T1c, and Gleason scores 2 - 6.

Table 3 – Distribution of patients with clinical stage T1c and Gleason scores 7 - 8, according to PSA levels.

PSA Levels	N Patients	N Events	% Censorship
0 - 4.0	5	0	100.0%
4.1 - 10.0	34	7	79.4%
10.1 - 20.0	10	6	40.0%
> 20.0	2	0	100.0%

chemical recurrence of disease according to PSA categories for patients with clinical stage T1c, Gleason scores 7 and 8 (Figure-2) show statistical significance ($p = 0.039$), when comparing PSA levels < 4 ng/mL, 4.1-10 ng/mL and 10.1-20 ng/mL. Only 2 patients had Gleason 7-8 and PSA > 20 ng/mL; however, they did not present recurrence of dis-

ease. These particular individuals had a follow-up of 19.5 months. Moreover, both specific individuals had PSA values of 21 ng/mL and 23.5 ng/mL.

Finally, we constructed a graph (Figure-3) which groups all individuals, regardless of Gleason score, which is summarized in Table-4. In addition to the absence of biochemical recurrence with PSA < 4

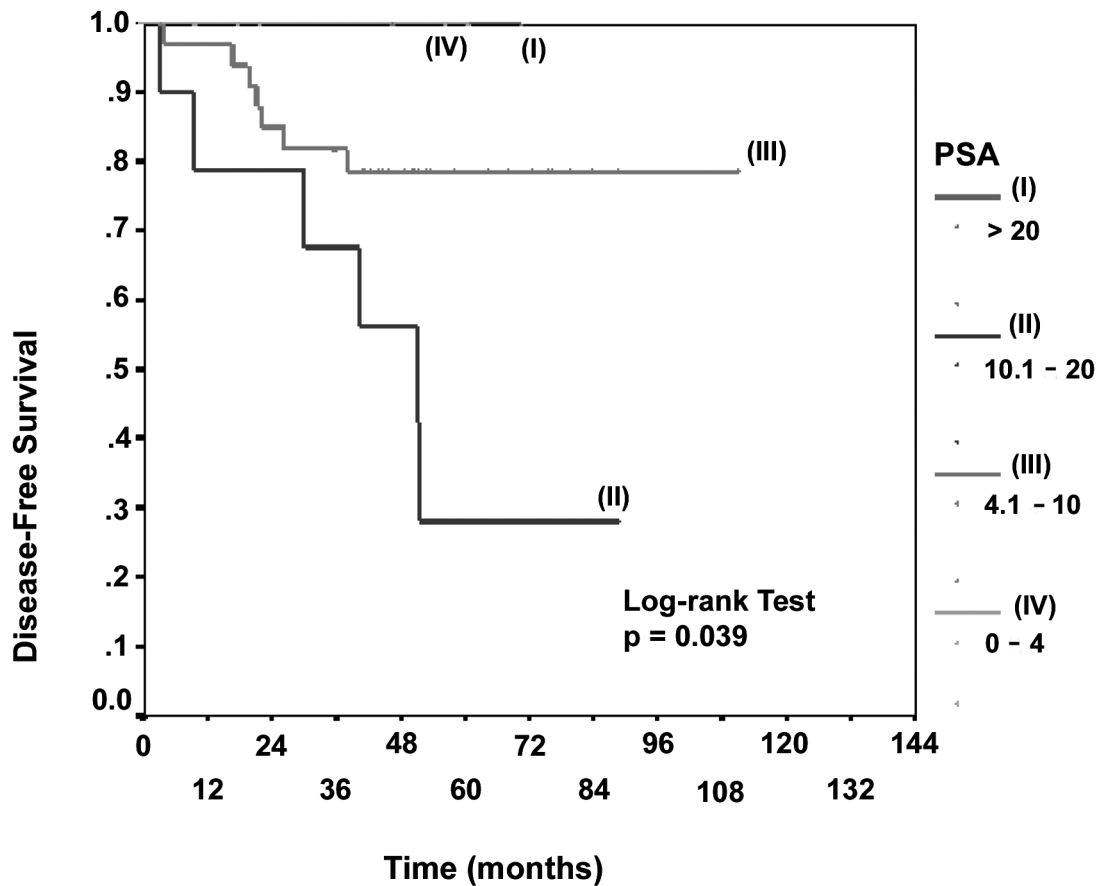


Figure 2 – Probability curve for recurrence-free survival according to PSA categories in patients with clinical stage T1c, and Gleason scores 7 - 8.

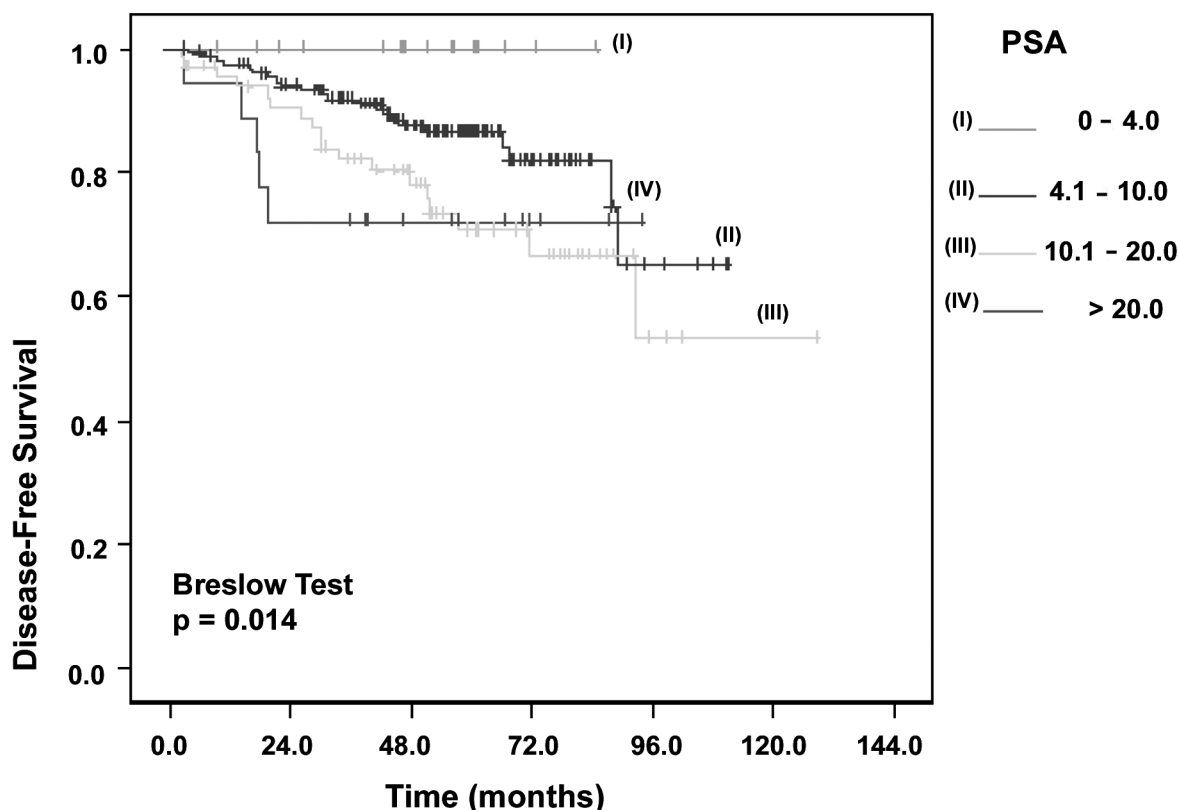


Figure 3 – Probability curve for recurrence-free survival according to PSA categories in patients with clinical stage T1c, and Gleason scores 2 - 8.

ng/mL, even after a median follow-up of 85.4 months, it is important to stress that, for individuals with PSA 4.1 to 10.0 ng/mL after 89.1 months, the probability of remaining free of biochemical recurrence is 65.1%. For patients with PSA of 10.1 to 20.0 ng/mL, after 92.6 months the probability of being free of biochemical recurrence is 53.4%. Finally, in men with PSA > 20.0 ng/mL, the probability of being free of biochemical recurrence is 72.2%; however, in this particular group, we stress that the

median follow-up was substantially shorter – only 19.5 months.

COMMENTS

The study demonstrated that the life expectancy free of biochemical recurrence in individuals with PCa clinical stage T1c and undergoing radical prostatectomy is higher in those with PSA inferior to 4.

Table 4 – Distribution of patients with clinical stage T1c and Gleason scores 2 - 8, according to PSA levels.

PSA Levels	N Patients	N Events	% Censorship
0 - 4.0	17	-	100.0%
4.1 - 10.0	155	22	85.8%
10.1 - 20.0	67	18	73.1%
> 20.0	18	5	72.2%

From 1986 and 1999, the use of PSA for screening has reduced the incidence of metastatic PCa from 50 to 70% (11). Considered more lethal than cardiac disease for between 60 and 80 year olds, the PCa is currently diagnosed in its localized form in 86% of men (12). Additionally, pathological changes of the prostate are identified during autopsies in 64% of men aged between 60 and 70 years of age (13).

The assessment of PSA for screening PCa has enabled an early diagnosis and treatment of the disease. This statement can be corroborated by one study, which compared men with PCa clinical stage T1c and PSA between 2.6 and 4 ng/mL, and individuals with PSA between 4.1-10 ng/mL (5). The study demonstrated that in the first group there are higher chances of organ-confined disease and lower tumor volume.

Johansson et al. (14) showed that observation could be dangerous to men with a life expectancy of over 10 years, demonstrating that after 15 years under a surveillance regimen the cancer-specific mortality increased from 15 to 44/1000, progression-free survival dropped from 45% to 36%, metastasis-free survival decreased from 76.9% to 51.2% and cancer-specific survival dropped from 78.7% to 54.4%. These figures confirm that a long follow-up is required in PCa so that the benefits of early diagnosis and treatment can be observed. Additionally, the probability of death due to disease progression after 15-year surveillance increases from 4 to 30% with Gleason scores of 2-6 and 42 to 87% for Gleason scores of 7-10 (15).

In individuals under a surveillance regimen, the need for treatment was confirmed in 57% and 73.2% after 2 and 4 years respectively, with an increase in Gleason score in 24% of men after 3.8 years (16).

It is possible that non-palpable prostate tumors evidence significant disease, since this study has revealed a 12.4% chance of biochemical recurrence in individuals with PSA from 4.1 to 10 ng/mL and 21% when PSA are between 10.1 and 20 ng/mL, in spite of stage T1c even in low risk tumors, with Gleason scores of 2-6. On the other hand, when we group all individuals regardless of Gleason score, the expectancy of biochemical recurrence-free survival remains at 100% when PSA < 4 ng/mL and decreases

drastically to 65.1 % and 53.4 % when the PSA is 4.1 - 10 and 10.1 - 20 ng/mL respectively.

When analyzing Figure-2, for PSA levels of 4.1-10 ng/mL and 10.1-20 ng/mL, it is important to stress that the biochemical recurrence-free survival drops from 79.4% to 40% when only the Gleason score 7-8 is assessed, however it is 100% both in individuals with PSA lower than four and in the two patients with PSA higher than 20 ng/mL. However, when all individuals are grouped (both low and high risk tumors as represented in Figure-3), the apparently contradictory probability of biochemical recurrence occurring in 72.2% of men with PSA > 20 ng/mL is broken down – especially if we observe that in those particular cases the follow-up lasted only 19.5 months. Probably this percentage will decrease with evolving follow-up.

The need for surveillance in men between the fifth and the sixth decades of life should be considered. Some authors, by the way, advocate the performance of prostate biopsy establishing a PSA value up to 2.6 ng/mL as the upper normal limit (8) for men aged less than 60 years of age (11).

Since the classical concept by Whitmore (17) about the paradox existing in the treatment of PCa (is cure required when it is possible, or is it possible when it is required?), with the wide use of PSA in screening and the dramatic increase in the detection of organ-confined disease, the concept of clinically significant disease has become very important due to the risk of over treating the PCa. The main studies comparing radical prostatectomy with a surveillance regimen have been initiated in order to answer these questions. The Scandinavian prospective randomized study (6) assessing the development of metastasis in localized PCa has shown that metastases occurred in 13.4% and 27.3% for the surgery and the surveillance regimen groups respectively; in the untreated group the risk of metastases was 37% higher than in the group undergoing surgery with a median follow-up of 6 years. The risk of death after 8 years was 7.1% and 13.6% for the surgery and the surveillance regimen groups respectively; after a 10-year follow-up the risk of death increases to 16.8% in untreated men.

The concern to avoid over treatment in men with PCa should be carefully considered, however,

the majority of T1c tumors are already significant tumors; that is, they present one of the following features on biopsy: Gleason pattern 4, = 3 positive fragments on biopsy and a fragment more than 50% affected by tumor (18). Carter et al. (19) obtained 31% of progression of disease during the first year of surveillance regimen in low risk tumors on the initial biopsy; that is, absence of primary Gleason pattern 4/5, < 3 positive fragments /12, no fragment more than 50% affected and PSA density of < 0.15).

With the possibility of over treating the PCa, currently 25% of men undergoing radical prostatectomy require a second therapy during the first 5 years following surgery (20). This figure begs the question of the correct PSA value that should be considered normal for each individual.

In order to illustrate the great dilemma concerning PCa screening, we need to evaluate the following situation: in Brazil, according to data from the Ministry of Health in 2005, there are approximately 23 million men between 40 and 79 years old. Among these men, and if we apply the worldwide statistics to our country, approximately 92% of men have PSA < 4 ng/mL. Of those 8% of individuals with PSA > 4, we will find 25% or 500,000 men with PCa. These figures are, to say the least, disturbing.

This study has some limitations, since it is retrospective and the digital rectal examination can be subjective. On the other hand, we considered as a positive factor the fact that it as a homogeneous group with follow-up longer than 7 years, which was assessed and operated on by the same surgeon.

We must make every effort to understand the natural history of prostate cancer, which is often unpredictable, and try to find the best moment for indicating prostate biopsy based on PSA.

CONCLUSION

With the acknowledgement of limitations in accuracy for identifying men with small volume cancer prostate, the attitude of avoiding biopsy can delay the diagnosis and result in losing the opportunity to cure.

Adriana Sañudo performed the statistical analysis

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