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SURVIVAL OF PATIENTS WITH PROSTATE CANCER AND NORMAL PSA LEVELS TREATED BY RADICAL PROSTATECTOMY

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ABSTRACT

Introduction: The unpredictability of prostate cancer has become a daily challenge for the urologist, with different strategies being required to manage these cases. In this study, we report on the perspectives for curing prostate cancer in males undergoing radical prostatectomy with Gleason score of 2-6 on prostate biopsy in relation to pre-operative PSA levels.

Materials and Methods: From 1991 – 2000, we selected 440 individuals whose pathological diagnosis revealed a Gleason score of 2-6 upon prostate biopsy and who subsequently underwent retro-pubic radical prostatectomy due to localized prostate cancer. The clinical stage identified in the group under study was T1c: 206 (46.8%); T2a: 122 (27.7%); T2b: 93 (21.1%); T2c: 17 (3.9%); T3a: 2 (0.5%). Following surgery, we constructed a biochemical recurrence-free survival curve according to pre-operative PSA levels between 0-4; 4.1-10; 10.1-20 and > 20 ng/mL, with a median follow-up of 5 years.

Results: Following radical prostatectomy, the pathological stage was confirmed as pT2a: 137 (31.1%); T2b: 118 (26.8%); T2c: 85 (19.3%); T3a: 67 (15.2%); T3b: 6 (1.4%); T3c: 22 (5%). The biochemical recurrence-free survival, according to PSA values between 0-4; 4.1-10; 10.1-20 and > 20 ng/mL, was 86.6%, 62.7%, 39.8% and 24.8% respectively.

Conclusion: Better chances for curing low-grade prostate cancer occur in individuals with normal PSA for whom a biopsy is not usually recommended.

Key words: prostatic neoplasms; prostate-specific antigen; diagnosis; biopsy; prostatectomy
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INTRODUCTION

Approximately 75% of men over 50 years old are screened for prostate cancer (PCA) through assessment of the prostate specific antigen (PSA) and digital rectal examination of the prostate (1). This means there has been an increase in early detection of PCA with higher likelihood of prostate-confined disease (2), and lower chances of disease recurrence following treatment, thus reducing mortality (3). However, there are controversies about the cost-benefit relationship in PSA screening as well as on the best time for indicating prostate biopsies in suspected cases. This becomes even more relevant at a PSA range of from 2.5 to 4 ng/mL. While this is usually considered normal, it can nevertheless predict detectable cancer. In order to stimulate this debate, recently Thompson et al. (4) identified PCA in 23.9 % of males with PSA between 2 and 3 ng/mL and 26.9% of males with PSA between 3 and 4 ng/mL.

Due to the heterogeneous features of PCA and the difficulties for predicting its evolution, this study

is intended to assess individuals with low-risk PCA (defined as Gleason score 2-6 upon biopsy) who underwent radical prostatectomy, and their post-operative clinical outcomes in relation to the initial PSA levels that led to the diagnosis.

MATERIALS AND METHODS

This retrospective study consisted of 440 men clinically diagnosed with PCA, presenting a Gleason score of 2-6 on prostate biopsy, with a mean age of 62.5 ± 7.4 years of age (40-79), a mean pre-operative PSA of 8.7 ± 5.6 ng/mL (0.3-32.0), and median follow-up of 60 months (2-130). Only 4 patients (0.9%) were lost during the follow-up period.

Initial PSA was collected before the prostate biopsy. During staging, all patients underwent anamnesis and physical examinations, a dosing of alkaline phosphatase, total and prostatic acid phosphatase, pelvic computerized tomography and bone scintigraphy in order to rule out extra-prostatic disease.

All participants underwent radical retro-pubic prostatectomies with bilateral pelvic iliac lymphadenectomies at our institution over the period of March 1991 to November 2000. The same surgeon performed all surgical procedures and pathological analyses were conducted by the same pathologist.

Clinical staging was defined based on the American Joint Committee on Cancer classification (5), and histological grades according to Gleason scores (6).

In selecting the group, we excluded cases that had received neoadjuvant or adjuvant hormone therapy (14 patients), and adjuvant radiotherapy (one patient), as well as cases presenting Gleason scores higher than 6 on biopsy.

Post-operatively, patients were assessed every 2 months during the first year, then every 6 months for 5 years, and from then on, yearly. During each assessment, the patient underwent a digital rectal examination of the prostate cavity and analysis of the serum PSA. Imaging tests (chest radiography, bone scintigraphy, abdominal tomography) were repeated every year. Biochemical progression was defined as a serum PSA equal to or higher than 0.4 ng/mL, a cut-off level that has been used by other research authors as well (7).

Pre-operative serum PSA was divided into categories 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 patient distribution according to clinical stages is listed in Table-1, and patients according to pre-operative PSA are listed in Table-2.

For statistical analysis, we used a survival analysis approach and considered the biochemical recurrence of disease an event of interest. This was defined by PSA values equal to or higher than 0.4 ng/mL. The Kaplan-Meier method and Log-Rank test were used for the disease-free survival curves. On multivariate analyses, we adjusted a Cox regression model with proportional risks. A significance level of 5% ($p < 0.05$) was adopted.

RESULTS

During a median follow-up of 60 months (2-130.5), 109 (24.8%) of the 440 patients under study presented biochemical recurrence.

Table 1 – *Patient distribution according to clinical staging (AJCC, 1992).*

Clinical Stage	N (%)
T1c	206 (46.8)
T2a	122 (27.7)
T2b	93 (21.1)
T2c	17 (3.9)
T3a	2 (0.5)
Total	440 (100.0)

Table 2 – *Patient distribution according to pre-operative PSA levels.*

PSA Levels	N (%)
0 to 4.0	43 (10)
4.1 to 10.0	234 (53)
10.1 to 20.0	123 (28)
> 20.0	40 (9)

Figure-1 represents a graphic display of the 440 men under study on different PSA scales, and considering a biochemical recurrence of the disease as an event of interest. Biochemical recurrence-free survival rates were 86.6% for PSA values of between 0-4, 62.7% for values of between 4.1-10, 39.8% for values of between 10.1-20 and 24.8% for values > 20 ng/mL. We observed that PSA significantly influenced disease-free survival ($p < 0.001$). Among the four patients with PSA between 0 and 4.0 who presented recurrence of the disease, two of them had clinical stage T2a and another 2 had clinical stage T2b. Patient distribution according to pathological stage is represented in Table-3.

Figure-2 represents the overall biochemical recurrence-free survival in the group under study.

The analysis of relative risk for PSA in the Cox regression model reveals that there is no statistical difference when PSA levels lower than 4.0 ng/mL are compared to PSA levels between 4-10 ng/mL, despite a percentage difference of 23.9%, with serum PSA being an independent prognostic factor for disease free survival in the post-operative period (Table-4).

Table 3 – *Patient distribution according to pathological stages.*

Pathological Stage	N (%)
T2a	137 (31.1)
T2a, NX	2 (0.5)
T2b	118 (26.8)
T2b, NX	3 (0.7)
T2c	85 (19.3)
T3a	67 (15.2)
T3b	6 (1.4)
T3c	22 (5.0)
Total	440 (100.0)

COMMENTS

Our study showed that the likelihood of biochemical recurrence-free survival in PCA patients with low Gleason scores, which are usually considered favorable when these patients undergo radical prostatectomy, should be looked at more carefully even when the PSA level is lower than 4.

Increasing the dosing of PSA for screening PCA has enabled early diagnosis and management of this disease, so that significant changes have occurred in the field over the past 2 decades. Coincidently with these advancements, technical modifications in radical prostatectomy techniques have provided lower morbidity, thus reaching progression-free and cancer-specific survival rates of 68% and 97% respectively in 10 years (8).

Men with non-palpable PCA detected with PSA between 2.6 and 4 ng/mL have lower tumoral volume and organ-confined disease more frequently than those with PSA between 4.1-10 ng/mL (2). A positive predictive value for PCA between 6.6 and 26.9% was associated with PSA values between 4-10 ng/mL. Moreover, men diagnosed with localized PCA with PSA values between 3.1 and 4 ng/mL already present a high-grade tumor in 25% of cases (9).

The limitations of PSA use and, more specifically, false positives and false negatives, are well known. Several investigators have tried to improve the method's sensitivity and specificity, including using PSA adjusted by age, as well as PSA density, velocity and fractions.

Table 4 – *Analysis of relative risk for PSA in Cox Regression Model.*

Variable	Relative Risk	95% CI	p Value
PSA			
(4.1 a 10 / 0 a 4.0)	2.22	[0.79 - 6.22]	0.128
(10.1 a 20 / 0 a 4.0)	3.83	[1.36 - 10.74]	0.011
(> 20 / 0 a 4.0)	6.17	[2.09 - 18.21]	0.001

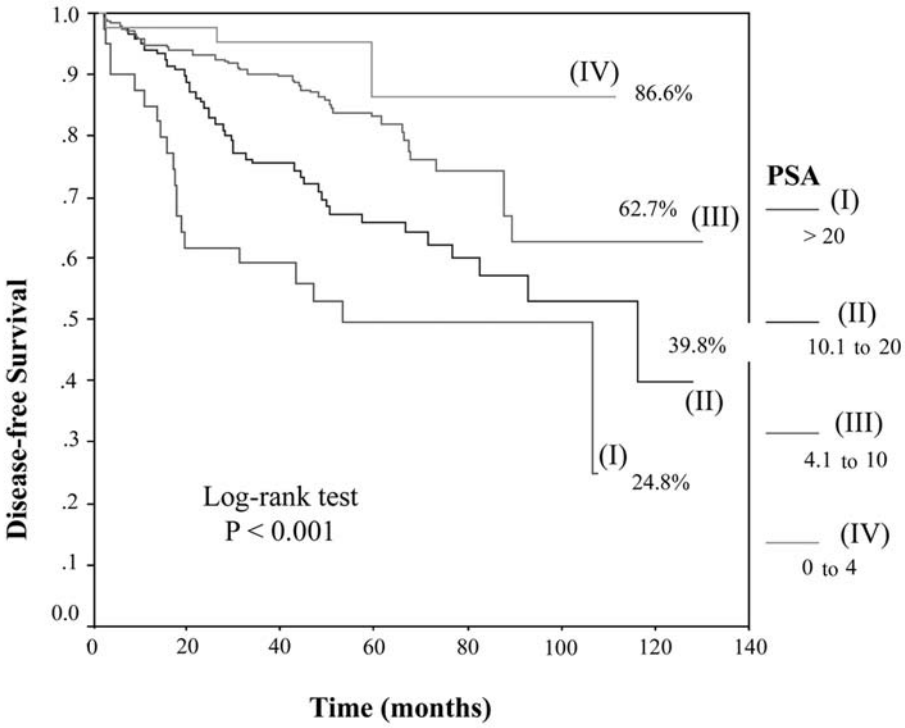

Figure 1 *– Survival probability curve for biochemical recurrence of disease according to PSA categories.*

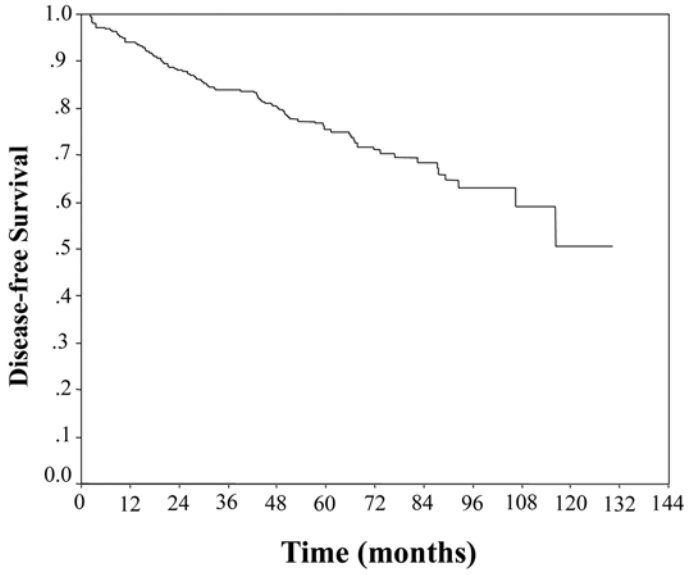

Figure 2 *– Probability curve of overall biochemical recurrence-free survival.*

The incidence of PCA in individuals with PSA between 2 and 3 ng/mL is 23.9%, and rises to 26.9% when PSA oscillates between 3 and 4 ng/mL (4). Such data are in opposition with the findings of other studies that have identified PCA in men with PSA lower than 4 ng/mL, thus advocating early prostate biopsy.

When stratifying patients that had undergone radical prostatectomies into PSA categories over 10 years, Roehl et al. (8) identified biochemical recurrence-free survival rates of 78% – 91% for PSA < 4 ng/mL and 74% for PSA of 4.1-10 ng/mL, while our study reveals biochemical recurrence-free survival rates over 5 years of 86.6% and 62.7% for PSA < 4 and 4.1-10 ng/mL respectively.

The probability of identifying PCA when PSA is between 2.5-4.0 ng/mL in different studies ranges from 20 to 26% (10,11), and from 24 to 26.5% with PSA between 2-4 ng/mL (12,13) on the first biopsy and 13% on the second biopsy (13). In the individuals whose PSA levels oscillate between 2.0-4.0ng/mL, the use of complexed PSA can improve the specificity and diagnostic sensitivity over the total PSA total (14), as well as reduce the number of unnecessary biopsies (12). When performing a study similar to ours, Bhatta-Dhar et al. (15) selected 336 patients with low-risk tumors (PSA < 10 ng/mL, Gleason score = 6, clinical stage T1-2), and after a 6-year follow-up, identified 86% to 88% biochemical recurrence-free survival.

The probability of the PCA being organ-confined in individuals with PSA between 2.6-4.0ng/mL is 77%, and 67% with a PSA between 4.1-10 ng/mL (10). Another study identified 92% of confined PCA when the PSA was between 2-4 ng/mL (12). These data speak for themselves, and even with PSA lower than 4.0 ng/mL, extra-prostatic disease is identified in 23% of cases undergoing curative management. Additionally, with PSA < 4.0 ng/mL, significant PCA is identified on the biopsy in 67.6% of cases (12).

We disagree with Bastian et al. (16), who consider that the majority of non-palpable tumors are insignificant. Our opinion is that non-palpable tumors can develop aggressive behavior; our sample reveals biochemical recurrence following treatment in 13.4% of individuals with PSA lower than 4.0 ng/mL and 27.3% when PSA ranges from 4.1-10 ng/mL.

A possible limitation of our study, we believe, is that perhaps these data cannot be applied to a non-Caucasian population. Additionally, since it is a retrospective analysis, sub-staging of Gleason scores on biopsy could eventually have occurred. However, the fact that is a homogeneous group with mean follow-up of 5 years and minimal losses during follow-up can be highlighted as positive factors.

Though the indiscriminate use of PSA can diagnose insignificant tumors with low biological aggressiveness (17), it can be a transitory reality. As an example, we point out the study of PCA patients under careful investigation who, after 3.8 years of follow-up, showed an elevation in Gleason score in 24% of cases (18). Another study, conducted by Albertsen et al. (19), which assessed 767 men between 55 and 74 years of age under careful investigation showed that the risk of death due to progressive disease after 15 years increases according to the Gleason score in the following proportions: 2-4 (4-7%), 5 (6-11%), 6 (18-30%), 7 (42-70%) and 8-10 (60-87%).

This situation is more dramatic since, despite the risk of over treating PCA, currently 25% of men undergoing radical prostatectomy will require a second treatment in the first 5 years following surgery (20). Based on these data, we wonder if waiting for the PSA to exceed 4 ng/mL is a correct approach for these men. This could be the reason many authors discuss the indication of prostate biopsy, assuming PSA values of 2.6 ng/mL as upper normal level (2.10-13).

CONCLUSIONS

When considering the variability in the natural course of PCA and the apprehensiveness of the best moment for indicating prostate biopsy based on PSA, we propose a change in the paradigm if we wish to increase the real chances of cure, by indicating prostate biopsy in men with PSA between 2.5-4.0 ng/mL.

Adriana Sanudo performed the statistical analysis

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