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PROGNOSTIC VALUE OF THE PERCENTAGE OF POSITIVE FRAGMENTS IN BIOPSIES FROM PATIENTS WITH LOCALIZED PROSTATE CANCER

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ABSTRACT

Objective: To assess the prognostic value of the percentage of positive fragments (PPF) in biopsies from patients with localized prostate cancer (PCa) undergoing radical prostatectomy.

Materials and Methods: During the period from March 1991 to November 2000, 440 patients were selected. Cases receiving neoadjuvant or adjuvant hormone therapy, or adjuvant radiotherapy, were excluded, as were cases presenting Gleason scores higher than 6 at biopsy. PPF was defined as the total number of fragments divided by the total number of biopsy fragments times 100. This variable was initially divided into categories from 0 to 25%, 25.1% to 50%, 50.1 to 75% and 75% to 100%. During the postoperative period, patients were assessed every 2 months for 1 year, then every 6 months for 5 years, and then yearly. Biochemical recurrence was defined as serum PSA higher than or equal to 0.4 ng/mL. Median follow-up was 60 months.

Results: One hundred and nine (24.8%) of the 440 patients under study had biochemical recurrence. In the univariate analysis, PPF significantly influenced disease-free survival (log-rank, $p < 0.001$), and patients with PPF between 75 and 100% presented a risk of a biochemical recurrence of the disease 3 times higher than patients with PPF between 0 and 25% ($p < 0.001$). After the Cox regression analysis, both serum PSA ($p = 0.001$) and PPF ($p < 0.001$) showed to be independent predictive factors for disease-free survival following surgery.

Conclusion: PPF measurement in biopsy is a simple and practical method, which should be routinely used as a predictive factor for biochemical recurrence in patients with PCa presenting Gleason scores between 2 and 6.

Key words: prostatic neoplasms; biopsy; needle; neoplasm staging
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INTRODUCTION

Currently, 50% of patients with localized prostate cancer (PCa) are treated with radical prostatectomy (1); however, the finding of organ-confined cancer in the surgical specimen does not guarantee postoperative biochemical control of the disease. Thus, approximately 30% of patients undergoing radical prostatectomy will present an increase in prostate specific antigen (PSA) on long term (2).

Currently, the biopsy's histological grade along with the PSA and clinical staging (American Joint Committee on Cancer - AJCC, 1992) are the most frequently used pre-operative prognostic variables for identifying patients with a higher risk of presenting organ-confined disease in the surgical specimen (3).

More recently, studies have demonstrated that greater detailing of pathological data obtained from prostate biopsy, in addition to merely identifying cancer and assessing its histological grade, can improve diagnostic accuracy in these patients. Thus, the percentage of fragments with cancer (PPF) has been widely used as a predictive factor for tumor volume, extracapsular extension, invasion of seminal vesicle, lymph nodal involvement and percentage of fragments with Gleason score 4 and 5 (4-8).

PPF has been used as well to predict postoperative risk of biochemical recurrence (9-14). Presti et al. (9) defined that Gleason score for biopsy and PPF are the most important predictive factors for postoperative biochemical recurrence. D'Amico et al. (10) divided patients into risk groups based on classic parameters (PSA, Gleason score and clinical staging), and during a 4-year follow-up, observed that, among patients from the low risk group, 25% and 10% had biochemical recurrence when the PPF was higher or lower than 50% respectively.

However, most studies assessing the prognostic value of PPF have limitations. All of them involve at least 2 centers and, thus, surgical procedures and pathological analyses were performed by a heterogeneous group of professionals. Moreover, they have a limited follow-up with a median of 38.5 months (maximum 46 months), and finally, they do not show an agreement concerning the ideal cut-off points that should be considered when analyzing the PPF (11-14).

The objective of this study is to assess the prognostic value of PPF for biochemical recurrence in patients with low-grade PCa undergoing radical prostatectomy.

MATERIALS AND METHODS

From March 1991 to November 2000, we selected 440 patients with localized prostate cancer undergoing radical prostatectomy at our institution. When selecting this group, those cases receiving neoadjuvant or adjuvant hormone therapy (14 patients), and adjuvant radiotherapy (1 patient) were excluded, as were cases presenting Gleason score higher than 6 at biopsy; thus, the inclusion criterion was a Gleason score $\leq$ 6 at biopsy. All surgical procedures were performed by the same surgeon and pathology analyses by the same pathologist.

During staging, all patients underwent anamnesis and physical examination, dosing alkaline phosphatase, total and prostatic acid phosphatase, serum PSA, pelvic computerized tomography and bone scintigraphy, aiming to rule out any signs of extraprostatic disease. Diagnoses were made through transrectal biopsy of the prostate motivated by increases in serum PSA or changes in the digital rectal examination. Postoperatively, patients were assessed every 2 months for 1 year, then every 6 months for 5 years, and then yearly. During each assessment, patients underwent digital rectal examination of the prostate cavity and analysis of serum PSA. Imaging studies were repeated every year. Biochemical progression was defined as a serum PSA higher or equal to 0.4 ng/mL, a cut-off value also instituted by other authors (15). Median follow-up was 60 months (2 – 130.5 m). Only four patients (0.9%) were lost during follow-up. The patients' mean age was 62.5 ± 7.4 years, ranging from 40 to 79 years.

Clinical staging was defined according to the AJCC classification, 1992 (16), and histological grade according to the Gleason score (17). 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 PPF was defined as the total number of fragments with cancer divided by the total number of fragments in biopsy times 100. This variable was divided into categories from 0 to 25%, 25.1% to 50%, 50.1 to 75% and 75% to 100%.

The patient distribution according to clinical staging is listed on Table-1. Tables-2, 3 and 4 stratify patients according to pre-operative PSA, PPF and the pathological stage of the surgical specimen respectively.

A survival analysis approach was used for the statistical analysis considering a biochemical recurrence of the disease as the event of interest. This was defined by a PSA value higher or equal to 0.4 ng/mL. For disease-free survival curves, the Kaplan-Meier method and the log-rank test were used for comparing the curves of percentage of affected fragments. On the multivariate analysis, a Cox proportional-haz-

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

Clinical Staging	N. of Patients
T1C	206 (46.8%)
T2A	122 (27.7%)
T2B	93 (21.1%)
T2C	17 (3.9%)
T3A	2 (0.5%)
Total	440 (100%)

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

PSA Levels	N. of Patients
0 to 4	43 (10%)
4.1 to 10	234 (53%)
10.1 to 20	123 (28%)
> 20	40 (9%)

Table 3 – *Patient distribution according to the percentage of positive fragments (PPF) at pre-operative biopsy.*

PPF	N. of Patients
0 to 25%	149
25.1 to 50%	197
50.1 to 75%	53
75.1 to 100%	41

Table 4 – *Patient distribution according to pathological stage.*

Pathological Stage	N. of Patients
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%)
Total	440 (100%)

ards regression model was adjusted. The assumption of proportional risks in the adopted model was checked by construction log-minus-log graphs, which did not indicate violation of the proportional hazard assumption. P values $p < 0.05$ were considered statistically significant.

RESULTS

During a median follow-up period of 60 months (2 – 130.5 m), 109 (24.8%) of the 440 patients under study presented biochemical recurrence. Figure-1 shows the mean disease-free survival time estimated at 97 months with 95% confidence interval. We can observe that at 116 months, the likelihood of a patient being disease-free was approximately 50.7%.

The number of biopsied fragments ranged from 2 to 19, with means and medians of 7.01 and 6.0 fragments respectively, with 40.6% of fragments affected by cancer.

On the univariate analysis, Table-5 shows the patient distribution according to the cut-off points for PPF and the probability of biochemical recurrence. We can observe that more than one half of patients presenting PPF > 75% had biochemical recurrence. Figure-2 shows the disease-free survival curves in relation to PPF according to predefined cut-off points. We observe that PPF significantly influenced disease-free survival (log-rank, $p < 0.001$).

After Cox regression analysis to control for pre-operative serum PSA, we observed that both serum PSA and PPF were independent predictive fac-

Table 5 – *Relationship between the percentage of positive fragments (PPF) at pre-operative biopsy and the number of biochemical recurrences.*

PPF	N. of Biochemical Recurrences
0 to 25%	23 (15%)
25.1 to 50%	47 (24%)
50.1 to 75%	17 (32%)
75.1 to 100%	22 (54%)

$p < 0.001$

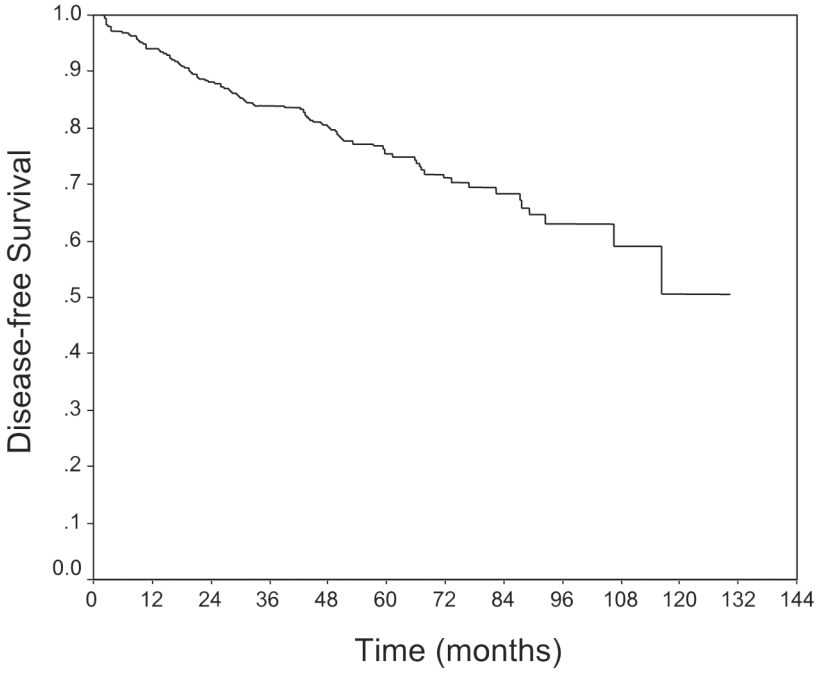

Figure 1 – *Probability curve of disease-free survival.*

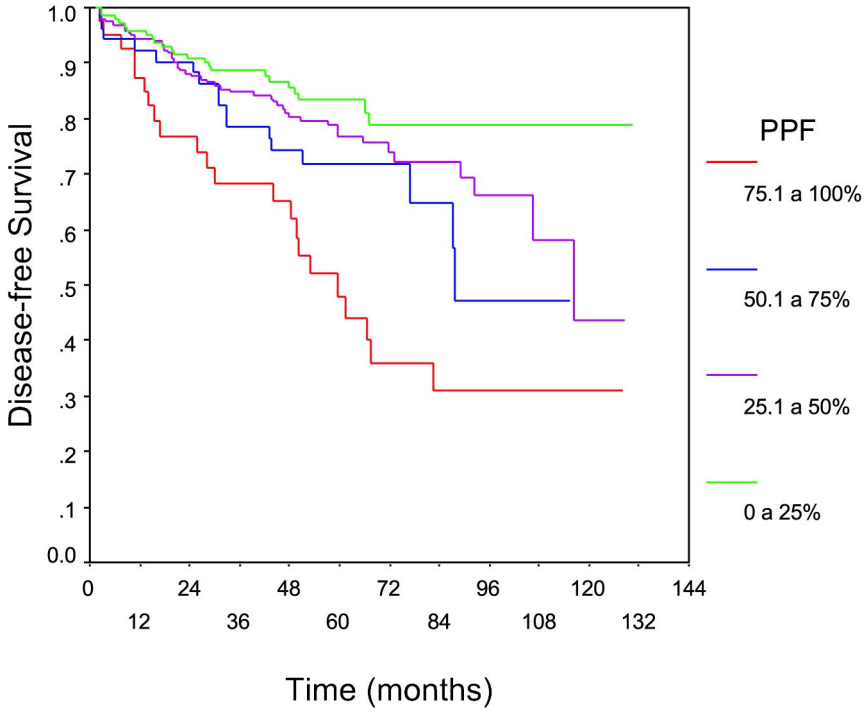

Figure 2 – *Probability curve of disease-free survival according to the percentage of positive fragments (PPF) at pre-operative biopsy.*

Table 6 *– Analysis of relative risk for PSA and percentage of positive fragments (PPF) in the Cox regression model.*

Variable	Relative Risk	95% C.I.	p-value
PSA			
(4.1 to 10 / 0 to 4)	2.22	[0.79 ; 6.22]	0.128
(10.1 to 20 / 0 to 4)	3.83	[1.36 ; 10.74]	0.011
(> 20 / 0 to 4)	6.17	[2.09 ; 18.21]	0.001
PPF			
(25.1 to 50% / 0 to 25%)	1.35	[0.82 ; 2.23]	0.234
(50.1 to 75% / 0 to 25%)	1.65	[0.88 ; 3.10]	0.122
(75.1 to 100% / 0 to 25%)	3	[1.65 ; 5.45]	< 0.001

tors for disease-free survival in the post-operative period (Table-6).

COMMENTS

This study demonstrated that the PPF at biopsy could influence postoperative biochemical recurrence in patients with Gleason scores between 2 and 6 undergoing definitive treatment by radical prostatectomy. Thus, patients who have 0 to 25% and more than 75% of fragments affected present 15% and 54% of biochemical recurrences respectively. Additionally, in the multivariate analysis controlling for pre-operative serum PSA, the PPF at biopsy was the strongest predictive factor for determining biochemical recurrence, adding prognostic information in the group of patients under study.

Pathological data obtained from prostate biopsies have been poorly explored. In clinical practice, we can observe that information obtained only through pre-operative analysis of serum PSA, the biopsy's Gleason scores and clinical staging are often insufficient to predict the pathological staging of the surgical specimen and the disease-free survival in patients undergoing definitive treatment by radical prostatectomy (3).

In this context, several studies have demonstrated that PPF provides additional information for the post-operative pathological findings and clinical features of patients undergoing radical prostatectomy. One analysis of 104 patients with a mean age of 61 found a significant association between the number of affected fragments by prostate lob on the sextant biopsy and an extracapsular extension of PCa. Thus, extracapsular extension occurred in 9%, 12%, 32% and 40% of the sides presenting zero, 1, 2 and 3 of 3 fragments affected respectively (5). Other authors observed that the probability of metastases in pelvic lymph nodes was 5% and 30% when 3 and 6 fragments were affected respectively. They also observed a higher incidence of Gleason scores 4 and 5 with the increased number of affected fragments. As for logistic regression analysis, this was the best predictive factor for lymph nodal status (6). Finally, Gancarczyk et al. (8), in studies about the prognostic value of PPF at biopsy for determining the post-operative pathological staging in 1510 patients from the Center for Prostate Disease Research through uni- and multivariate analysis, divided the PPF into 3 categories: less than 30%, from 30 to 59% and equal to or higher than 60%. The authors observed that the PPF combined with the pre-operative serum PSA and Gleason scores at biopsy were the most important predictive factors for the pathological staging of the surgical specimen. Based on these findings, they included the PPF in a probability nomogram for predicting post-operative pathological findings in such patients.

PPF has also been used for predicting the post-operative biochemical progression in patients

undergoing radical prostatectomy. A retrospective study of 1094 patients from 4 institutions in the SEARCH database who were treated by radical prostatectomy defined that the PPF was an independent prognostic variable for determining post-operative pathological findings and biochemical recurrences. The study used 3 cut-off points for PPF – less than 34%, 34 to 50% and more than 50% – and when the study population was divided into risk groups based on the classic parameters (serum PSA, Gleason scores at biopsy and clinical staging), PPF provided additional prognostic information for patients with low and moderate risk, but did not add any information for the high-risk group (12).

Subsequently, this same group compared the ability of predicting biochemical recurrence in the PPF of the entire gland with the PPF of the lobe that was most affected by PCa (13). With a mean follow-up of 27 months, this multivariate analysis showed that the PPF of the dominant side was the strongest predictive factor for post-operative biochemical recurrence. Thus, it would be worse for a patient to have 80% positive fragments in one lobe and 0% in the other, than to have 40% positive fragments in each lobe.

More recently, Lotan et al. (14), found a strong association between PPF and the tumor stage, histological differentiation, biochemical progression, distant metastases and overall survival. After assessing 630 patients with mean age of 60.4 years and mean pre-operative PSA of 8.1 ng/mL who were followed for 21.2 months after radical prostatectomy, 13% of the patients presented disease progression. Patients with a PPF higher than 25% had their disease-free survival estimated at 70% versus 90% when the PPF was lower or equal to 25%. PPF was associated with biochemical recurrence on the pre- and post-operative multivariate analysis.

However, despite all these results, the most accurate method for quantifying tumor volume in the prostate biopsy is still grounds for debate. Some studies have shown that more detailed analyses of prostate biopsies, such as the total percentage of cancerous tissue or a higher percentage of cancer in one affected fragment, are the most adequate methods for measuring tumor volume in prostate biopsies (18,19). In the series from Freedland et al. (18), the percentage of cancerous tissue at biopsy was a stronger predictive factor for post-operative biochemical recurrence than PSA and Gleason scores at biopsy. It was also predictive of the involvement of seminal vesicle and extraprostatic disease. On the other hand, the measurement of tumor volume through these methods is more laborious and not all pathologists provide this information. The PPF measurement as performed in this study seems to be easier and more practical. Additionally, there is research showing that PPF was a stronger predictive factor for biochemical recurrence than the total percentage of tissue affected by carcinoma at biopsy, and the latter did not add any prognostic information to the former in patients from the intermediary-risk group (20,21). In fact, the best method for estimating tumor volume through biopsy still has to be established by controlled studies comparing these methods.

A limiting factor in series presented so far is the short follow-up period. With the present study, prognostic data highlighted in the worldwide literature were ratified, with a median follow-up of 5 years, adding at least 14 months to the follow-up period in the longer series. Additionally, new cut-off points were defined for PPF that were shown to present statistical significance, which, therefore, can be employed in clinical practice. Since the categories of 25.1% to 50%, and 50.1% to 75% had similar disease-free survival curves (Figure-2) and did not present statistical difference when compared to the category from 0 to 25% (Table-5, $p > 0.122$), in practical terms the cut-off points could be divided into lower than 25%, 25.1% to 75% and higher than 75%. Finally, the authors emphasize that the PPF measurement at biopsy is a simple and practical method that should be routinely used as a predictive factor for biochemical recurrence in patients with PCa who have Gleason scores from 2 to 6.

Adriana Sanudo performed the statistical analysis

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