

PREDICTION OF PATHOLOGICAL STAGE IN PROSTATE CANCER THROUGH THE PERCENTAGE OF INVOLVED FRAGMENTS UPON BIOPSY

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ABSTRACT

Introduction: The need for defining the extension of disease in patients undergoing radical prostatectomy due to prostate adenocarcinoma is a relevant factor cure in such individuals. In order to identify a new independent preoperative factor for predicting the extension of prostate cancer, we assessed the role of the percentage of positive fragments upon biopsy.

Materials and Methods: A retrospective study compared the percentage of positive fragments on biopsy with the extension of disease as defined by the pathological examination of the surgical specimen from 898 patients undergoing radical prostatectomy due to clinically localized prostate cancer.

Results: On the univariate analysis, the percentage of positive fragments on biopsy showed a statistical significance for predicting confined disease ($p < 0.001$), which was found in 66.7% of the cases under study. Additionally, we observed that the total number of removed fragments exerts no influence on the extension of the disease ($p = 0.567$).

Conclusion: the percentage of positive fragments is an independent factor for predicting the pathological stage of prostate adenocarcinoma, and the number of removed fragments is not related to the extension of the disease.

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

According to data from the National Cancer Institute at the Ministry of Health, between 1979 and 2000 there was an increase of 141% in mortality due to prostate adenocarcinoma in Brazil, making this disease the second cause of death from tumors in males, second only to lung cancer. Prostate cancer also represents the second most prevalent malignant neoplasm, behind skin cancer. In 2003 in Brazil, 35,240 new cases were predicted, with 8230 deaths due to prostate adenocarcinoma (1). These figures are ap-

proximately 10 times lower than those estimated for the United States of America by the National Cancer Institute, where prostate cancer was responsible for 10% of deaths from malignant neoplasms in 2004, second only to lung cancer (2).

Among the available treatments in cases of localized prostate adenocarcinoma, the most frequently performed is radical prostatectomy, which is used in 52% of patients, followed by external radiotherapy or brachytherapy, which is used in approximately 20% of patients (3).

The great challenge in clinical practice is to perform an accurate early diagnosis of confined disease, since in more than 30% of cases judged as localized, the subsequent pathological study shows more advanced disease than was initially expected (4).

Aiming to clinically define the presence of localized disease, and thus, the feasibility for curative treatment, most experts consider especially the initial PSA levels, the tumor extension upon digital rectal examination and the degree of neoplastic differentiation as assessed by the Gleason score (5). New parameters for predicting the chances of disease recurrence and the presence of organ-confined tumors have also been studied (6,7), including the number of fragments positive to cancer on biopsy, which seems to represent an independent prognostic factor (8).

Considering that the percentage of fragments involved by tumor on biopsy represents an important prognostic factor (6,9), we devised the present study, which intends to analyze the preoperative predictive role of the percentage of positive fragments upon biopsy for predicting the extension of disease.

MATERIALS AND METHODS

We retrospectively analyzed 960 patients diagnosed with localized prostate cancer undergoing retropubic radical prostatectomy whose medical charts recorded the total number of biopsied fragments, the number of fragments with cancer, the Gleason score on biopsy, the serum PSA levels and the pathological exam of the surgical specimen. Fifty-four patients who had received neoadjuvant treatment were excluded, as were 8 patients whose diagnosis was obtained by endoscopic resection of the prostate or transvesical prostatectomy, thus totaling 62 excluded cases and 898 inclusions. Patient ages ranged from 40 to 83 years, with a mean age of 62.9 years.

The clinical staging (Table-1) used the TNM classification (10). For this purpose, auxiliary examinations were performed, including digital rectal examination, transrectal ultrasound of the prostate, abdominal and pelvic computerized tomography or magnetic resonance imaging, bone scintigraphy and thorax radiography.

Patients underwent retropubic radical prostatectomy with bilateral selective iliac lymphadenectomy. All interventions were performed by the same surgeon (MS).

All surgical specimens consisting of the prostate, seminal vesicles and obturator lymph nodes were assessed by the same pathology (KML).

The specimens were fixed in 10% formal for approximately 6 hours and underwent a routine starting with measuring and weighing the gland. Thin transversal sections were performed on the surgical margins relative to the bladder neck and the prostate apex. Using the urethra as a reference, the remaining gland was immersed in India ink stain and then sequentially sliced each 3 millimeters. 8 to 10 sections from each lobe were included for histological examination. Seminal vesicles were sectioned at the base and prepared for histological examination following longitudinal sectioning. Obturator lymph nodes were dissected and sliced in order to go through pathological examination.

Following the usual preparation in paraffin, the sections were stained by HE and analyzed under binocular light microscope. Parameters assessed were:

Infiltration of periprostatic tissue – Periprostatic involvement was defined as the neoplastic invasion of fat tissue and periprostatic neurovascular plexus. In such cases, the disease was classified as non-confined.

Infiltration of seminal vesicles – The involvement of seminal vesicles was considered only when their parenchyma – and not the adventitial region – was involved in the tumor.

Metastases to lymph nodes – Obturator lymph nodes that were involved by tumor were classified as having metastases.

Table 1 – Patient distribution according to clinical stage.

Clinical Stage	N (%)
T1c	432 (48)
T2a	218 (24.3)
T2b	173 (19.3)
T2c	68 (7.6)
T3a	7 (0.8)
Total	898 (100.0)

Postoperative pathological staging – the TNM staging system was used for the final analysis (10). The distribution of patients under study is reported in Table-2.

The frequency of organ-confined disease, periprostatic extension and invasion of seminal vesicles was compared with the percentage of positive fragments. For this purpose, the percentage of positive fragments was divided into four categories: 0 - 25%; 25.1 - 50%; 50.1 - 75% and 75.1 - 100%. We also divided the number of fragments collected on biopsy into 3 categories: less than 6; 6; and more than 6, and compared them with the extension of disease.

Statistical Analysis

In order to compare the percentages of positive fragments on biopsy with confined or non-confined disease, we used the Pearson’s Qui-Square test (univariate analysis). For comparing the mean percentage of positive fragments on biopsy with confined or non-confined disease, we used the student’s t test following the analysis of distribution normality for percentages of positive fragments. A significance level of 5% was adopted, with results being consid-

Table 2 – Patient distribution according to postoperative pathological stage.

Pathological Stage	N (%)
T2a	194 (21.6)
T2b	168 (18.7)
T2c	237 (26.4)
T3a	182 (20.3)
T3a/N+	1 (0.1)
T3b	11 (1.2)
T3c	95 (10.6)
T3c/N+	7 (0.8)
T4a	1 (0.1)
T4a/N+	2 (0.2)
Total	898 (100.0)

ered as statistically significant when they showed $p < 0.05$.

RESULTS

Figure-1 shows that the number of fragments removed on biopsy did not interfere with the patho-

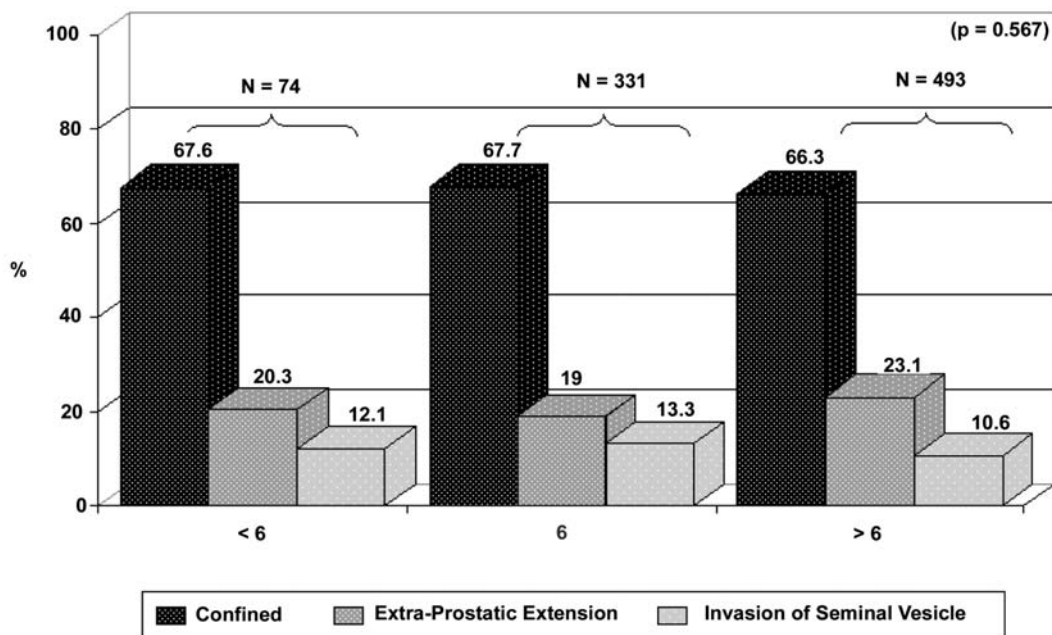


Figure 1 – Distribution of total number of collected fragments and distribution of lesions identified on biopsy.

logical results of surgical specimens ($p = 0.567$), thus evidencing the uniformity of cases under study.

Figure-2 compares the percentage of positive fragments and the presence of organ-confined disease. According to the data obtained in the study, there is a positive association between the percentage of positive fragments on biopsy and the stage of disease ($p < 0.001$).

Table-3 compares the mean percentage of positive fragments between confined and non-confined disease. The percentage of positive fragments on average is $9.72\% (\pm 1.68)$ higher in patients with non-confined disease ($p < 0.001$).

Table-4 shows that regardless of results from the surgical specimen, approximately 55% of patients had more than six fragments removed.

In Table-5 we can see that regardless of results from the surgical specimen, the average of collected fragments was 8 ± 3 , with a minimum of 2 and a maximum of 22 fragments removed on biopsy.

We can see in Table-6 that regardless of results from the surgical specimens, the average of positive frag-

Table 3 – Descriptive measures for the percentage of affected fragments on biopsy according to the presence of confined or non-confined cancer.

	Confined	Non Confined
Mean	38%	47.7%
Standard deviation	22.7%	25.4%
Median	33.3%	50%
Minimum	5.3%	5%
Maximum	100.0%	100.0%
Total	601	297

ments was 3.2 ± 2.1 , with the minimal number of positive fragments being one and the maximal 20.

COMMENTS

In our study, 66.7% of patients had neoplasm confined to the gland following radical prostatectomy, with this figure ranging from 13 to 82% (11,12). This variation depends mainly on Gleason score, PSA,

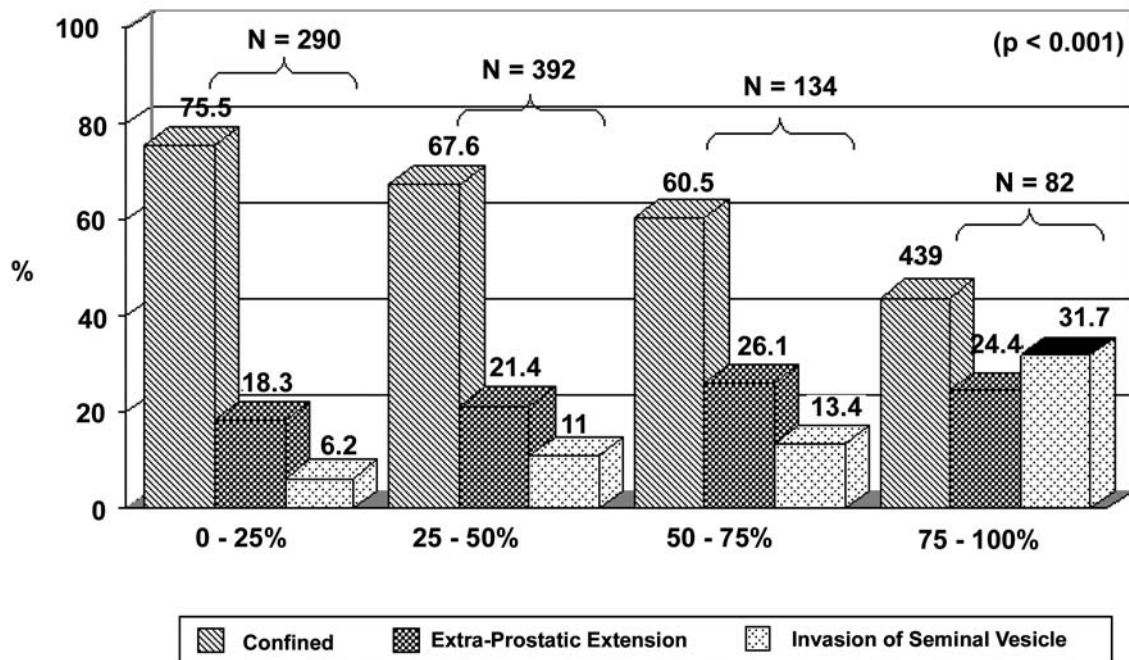


Figure 2 – Distribution of percentage of positive fragments according to the extension of prostate cancer.

PCa AND INVOLVED FRAGMENTS ON BIOPSY

Table 4 – Patient distribution according to the number of collected fragments and pathological result.

N Fragments	Confined	Extra-prostatic Extension	Invasion of Seminal Vesicle	Total Number of Fragments
< 6	50 (67.6%)	15 (20.3%)	9 (12.1%)	74 (8.2%)
6	224 (67.7%)	63 (19%)	44 (13.3%)	331 (36.9%)
> 6	327 (66.3%)	114 (23.1%)	52 (10.6%)	493 (54.9%)
Total	601 (66.9%)	192 (21.4%)	105 (11.7%)	898 (100.0%)

clinical stage and, currently, the percentage of positive fragments on biopsy.

D’Amico et al. (9) observed that the percentage of positive fragments on biopsy is an important parameter for predicting confined disease, demonstrating that when less than 34% of the fragments are affected, 79% of the patients have gland-confined disease, and when the number of affected fragments is greater than 50%, only 43% have confined disease. In our work, we observed that when there are less than 25% of fragments affected by tumor, the chance of confined disease is 75.5%, and only 43.9% of individuals with more than 75% of positive fragments on biopsy have confined disease.

When comparing the percentage of fragments involved in cancer with the possibility of involvement of the seminal vesicles by the neoplasm, we verified that when only one fragment has neoplasm, the risk of seminal vesicles being positive to cancer is 6%; however, when there are six fragments involved, this risk raises to 83% (4). Our study revealed that involvement of the seminal vesicles in 6.2% of patients when less than 25% of fragments had cancer, versus 31.7% when more than 75% were affected.

The importance of the number of positive fragments on biopsy for predicting confined disease is related to the number of positive fragments and the results obtained with radical prostatectomy. When the disease is confined, the average of positive fragments is 35%, while in individuals with non-confined disease this average rises to 55% (7). In our work, we found similar figures, with an average of 38% for confined disease versus 47.7% for non-confined disease.

The percentage of positive fragments has a linear relationship with tumor volume in the surgical specimen (13). Additionally, for each 1% increase in the affected fragments, the risk of non-confined disease increases by 2% (14).

In cases followed over 5 years, Epstein et al. (15) observed that approximately 26% of patients with less than 4 cc of tumor in the surgical specimen evidenced a recurrence of the disease and almost 50% of patients with more than 4 cc had a progression in the disease, thus demonstrating the importance of tumor volume for the outcome of disease. Similarly, Stamey et al. (16) confirmed the prognostic importance of tumor volume and reported that 86% of patients with volume between 0.5 and 2.0 cc did not experience a

Table 5 – Descriptive measures for total number of collected fragments according to tumor location.

	Confined	Extra-prostatic Extension	Invasion of Seminal Vesicle	Total Number of Fragments
Mean	8.17	8.13	7.97	8.14
Standard deviation	3.4	2.99	3.49	3.33
Median	7	6	6	7
Minimum	2	2	2	2
Maximum	22	19	22	22
Total	601	192	105	898

Table 6 – Descriptive measures for total number of fragments with cancer according to tumor location.

	Confined	Extra-prostatic Extension	Invasion of Seminal Vesicle	Total Number of Fragments
Mean	2.9	3.4	4.1	3.2
Standard deviation	2	2	2.5	2.1
Median	2	4	4	3
Minimum	1	1	1	1
Maximum	20	12	13	20
Total	601	192	105	898

progression of the disease, in opposition to patients with more than 12 cc of tumor volume, of which 96% evidenced a biochemical recurrence of the disease. Upon understanding the importance of tumor volume in relation to the risks of recurrence of disease, the number of positive fragments on biopsy has been used to predict the occurrence of non-confined disease and recurrence following radical prostatectomy (9,17). Nevertheless, some polemics involve the subject, since some studies suggest that we should not consider the percentage of positive fragments but the percentage of cancer found in each fragment, which would be a more accurate predictive factor (18). However, studies comparing the percentage of positive fragments on biopsy with the percentage of tissue affected by cancer (14,19) have demonstrated that both methods are strongly associated with the definition of non-confined disease (20). Since the final result appears to be equal, and the calculation of the area with cancer in the fragments is more time-consuming and complex, it is advantageous to use the percentage of positive fragments on biopsy in the clinical practice.

Prostate adenocarcinoma is the third cause of death from cancer in males in the world, and its incidence and mortality are increasing in our country, due to the increase in life expectancy, improvement and dissemination of diagnostics methods, and unknown etiopathogenic factors. In order to improve the accurate preoperative diagnosis of confined disease, we should intensify the studies on the parameters that should be used, thus allowing more effective interventions and, consequently, increasing the chances of cure for patients with this disease. In this context, the present study aimed to define and con-

solidate a new parameter that should be considered for assessing the extension of disease preoperatively.

CONCLUSION

The percentage of positive fragments on biopsy is an independent preoperative factor (univariate analysis) for predicting the pathological stage of prostate cancer in the surgical specimen, and the number of fragments removed on biopsy has no influence on the extension of disease.

Adriana Sanudo performed the statistical analysis.

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