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QUANTIFICATION OF TUMOR EXTENSION IN PROSTATE BIOPSIES – IMPORTANCE IN THE IDENTIFICATION OF CONFINED TUMORS

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ABSTRACT

Objective: To assess the importance of quantifying the adenocarcinoma in prostate biopsies when determining the tumor's final stage in patients who undergo radical prostatectomy. To identify the best methodology for obtaining such data.

Patients and Methods: Prostate biopsies from 132 patients were examined, with determination of Gleason histological grade and tumor volume in number of involved fragments, tumor extent of the fragment mostly affected by the tumor and the total percentage of tumor in the specimen. Theses parameters were statistically correlated with the neoplasia's final stage following the evaluation of radical prostatectomy specimens.

Results: An average of 12 and a median of 14 biopsy fragments were evaluated per patient. In the univariate analysis the Gleason histological grade, the largest tumor extent in one fragment and the total percentage of tumor in the specimen were correlated with tumor stage of the surgical specimen. In the multivariate analysis, the Gleason histological grade and the total percentage of tumor were strongly correlated with the neoplasia's final stage. The risk of the tumor not being confined was 3 for Gleason 7 tumors and 10.6 for Gleason 8 tumors or above. In cases where the tumor involved more than 60% of the specimen, the risk of non-confined disease was 4.4 times. Among 19 patients with unfavorable histological parameters, Gleason > 7 and extension greater than 60% the tumor final stage was pT3 in 95%.

Conclusion: When associated to the Gleason histological grade, tumor quantification in prostate biopsies is an important factor for determining organ-confined disease, and among the methods, total percentage of tumor is the most informative one. Such data should be included in the pathological report and must be incorporated in future nomograms.

Key words: prostate neoplasms; biopsy, needle; pathology; quantitative evaluation; neoplasms staging
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INTRODUCTION

The selection of the best treatment for the prostate cancer patient depends basically on the status of the primary tumor. Curative therapies are indicated exclusively for confined tumors, with interstitial radiotherapy being indicated for low grade, small and absolutely confined tumors. With that purpose, the pre-operative nomogram of Partin et al. (1) is frequently used by surgeons, oncologists, and radiotherapists. In the equation, one must consider the serum level of PSA, clinical staging and Gleason histologi-

cal grade. Currently the literature has discussed the importance of quantifying the tumor in the prostate biopsy (2-4). Such assessment can be made in several ways, such as the measurement of the neoplasia in millimeters, the analysis of percentage of tumor in every fragment, the percentage of the most involved fragment and the number of fragments that are infiltrated by the neoplasia.

The objective of this study is to assess the importance of quantifying the carcinoma in prostate biopsies, when determining the tumor final stage.

PATIENTS AND METHODS

The study comprises the retrospective analysis of prostate biopsies from 132 patients with mean age of 63 years, who underwent radical prostatectomy between January 1999 and March 2001. The mean number of analyzed fragments was 12, the median 14, ranging from 5 to 14. The mean and the median values for fragment length was 13 mm, ranging from 7 to 18 mm. Biopsies were fixed in formalin 10%, embedded in paraffin, stained by hematoxylin-eosin and analyzed by one only pathologist (KRML). The Gleason histological grade was used for evaluating the histological differentiation and for statistical analysis, and was divided in 3 groups, ≤ 6, 7, and > 7. For quantifying the tumor, the following were analyzed: 1) Relationship between the number of positive fragments over the total of biopsied fragments, 2) Percentage of a fragment that is more involved by the neoplasia, 3) Total percentage of tumor in the fragments, that is, the arithmetic mean between the percentages of each isolated fragment.

The specimens of radical prostatectomy were fixed in buffered formalin 10% for a period of 4 to 16 h. Each gland was submitted to histological study in accordance to the previously described recommendations (5). After weighting and measuring the gland, thin transversal sections were performed in the surgical margins related to the bladder neck and the prostate apex. The seminal vesicles were sectioned in the base and longitudinal sections were submitted to histological examination. The entire gland was included for study after having their margins painted with India ink. The right and left lobes were separated, with sequential transversal sections being performed every 3 mm, designed from the proximal region towards the distal one. Between 10 and 12 sections from each lobe were included for histological study. The lymph nodes from the fat related to the resection of the iliac chain were dissected and sections representative of each nodular structure were included for study. The specimens of radical prostatectomy underwent the usual processing with inclusion in paraffin. Sections of 4 to 6 μm were stained by hematoxylin-eosin, and analyzed by one only pathologist as well (KRML).

The Gleason histological grade was used for evaluating the histological differentiation. The assessment of tumor extent was performed with the aid of the grid card, as described by Humphrey & Vollmer (6). The invasion of adipose tissue and the periprostatic neurovascular plexus was considered as involvement of extra-prostatic tissue and, therefore, non organ-confined disease. The staging system was TNM 2002 (7).

Non-parametric analyses (Mann-Whitney) were performed for assessing the significance between the biopsy variables and the neoplasia's final stage. The qui-square test was used for evaluating the Gleason score and the status of the surgical specimen. The multivariate logistic regression determined the relative risk of non organ-confined disease for the multiple variables. The tests were performed in the software SPSS version 11 (SPSS Inc. Chicago, IL).

RESULTS

The number of biopsied fragments ranged from 5 to 14, with mean of 12 and median of 14. The number of fragments that were positive for tumor ranged from 1 to 11 with mean and median values of 3. The Gleason histological grade ranged from 5 to 9, with the mean of 6.7 and median of 6. The relation between the number of positive fragments and the total biopsied ranged from 7 to 100, with a mean of 29 and median of 25. While analyzing the extent of the fragment that was most involved by the tumor, the numbers ranged from 5% to 100%, with the mean of 57% and median of 60%. The total percentage of tumor in multiple fragments of biopsy ranged from 0.4% to 100%, with a mean of 35% and median of 25% (Table-1).

***Table 1** – Pre-operative clinical and pathological characteristics of the 132 patients under study.*

Patients (N)	132
Mean Age ± SD	63 + 8.4
Gleason Score (%)	
5 –6	67 (50.8)
7	26 (19.7)
8 – 9	39 (29.5)
Mean ± SD	6.7 + 1.2
Median	6
% Positive Fragments	
Mean ± SD	29 + 19.4
Median	25
Total % of Tumor	
Mean ± SD	35 + 29.2
Median	25
% of Tumor in 1 Fragment	
Mean ± SD	57 + 28.8
Median	60

The univariate analysis demonstrated a statistically significant difference for confined and non-confined tumors concerning larger tumor extension in one single biopsy fragment, total percentage of tumor and Gleason histological grade. Results are shown in Table-2.

Results from the multivariate analysis showed that there was statistical significance only for total percentage of tumor and Gleason histological grade concerning the tumor's final stage. The risk of non-confined disease was 3 times higher for Gleason 7 tumors and 10.6 times for adenocarcinomas with Gleason > 7 ($p < 0.0001$). The risk of involvement of extra-prostatic tissue was 4.4 times higher for those tumors that occupied more than 60% of the specimen ($p = 0.002$).

Nineteen cases were considered unfavorable, since they presented Gleason > 7 and total percentage above 60%. Ninety five percent of these tumors were classified as pT3.

DISCUSSION

Our results show the power of tumor quantification for determining the final stage of prostate adenocarcinomas. The current nomograms of Partin et al. (1) and the recently validated nomogram of Graefen et al. (8) include in the equation one single biopsy information (Gleason histological grade), without considering the tumor volume.

The first studies concerning the quantification of prostate adenocarcinoma demonstrated the value of the number of fragments that were involved by tumor for identifying non-confined tumors. According to those, the probability of extra-prostatic tumor extension varies from 7 to 38% when a single biopsy fragment is involved by tumor, and if this num-

***Table 2 –** Univariate relation between pre-operative factors and final pathological stage *. Median and range.*

	pT2	**pT3**	**p Value**
Gleason Score	6 (5 - 9)	8 (5 - 9)	< 0.0001
% Positive Fragments	21 (7 - 75)	29 (7 - 100)	0.058
Total % of Tumor	20 (0.4 - 90)	40 (1.1 - 100)	< 0.0001
% of Tumor in 1 Fragment	40 (5 - 100)	80 (10 - 100)	0.001

** The qui-square test was used to calculate the significance of the Gleason score. For the other variables, the Mann-Whitney non-parametric test was used.*

ber is 4 or above the percentage of non-confined tumor ranges from 47 to 100% (9-11).

Rubin et al. had already demonstrated the relation between different methods for quantifying the prostate carcinoma in biopsies and adverse pathological aspects of the surgical specimen (12). In univariate analysis, they showed that the probability of a tumor being no longer confined was 77% for tumors that involve more than 80% of a single biopsy fragment. Subsequently, Gao et al. confirmed the importance of such determination for low risk patients. While studying 62 patients, they showed that 38% of the tumors were no longer confined when there was an involvement of 25% or more in the extent of a single biopsy fragment (13). In our casuistry, the higher percentage of tumor in one single biopsy fragment was significant for determining the final stage only in univariate analysis. The median of the percentage of tumor in one fragment was 40% in confined tumors and 80% in non-confined tumors ($p = 0.001$).

In multivariate analysis, we demonstrated the value of total percentage of tumor in biopsies, together with Gleason histological grade for predicting of the tumor's final status. The median of the total percentage of tumor in biopsies was 20% for confined tumors and 40% for non-confined tumors ($p < 0.0001$). More interestingly, the logistic regression analysis demonstrated a risk 4.4 times higher of non organ-confined disease for tumors involving 60% of biopsies or more. Freedland et al. (14,15), were able to stratify patients with intermediate risk (Gleason 7 and/or PSA of 10 to 20 ng/ml) and high risk (Gleason higher than 7 and/or PSA above 20 ng/ml) in subgroups when they considered tumor extent in the biopsies. For patients with intermediate risk, the indexes of biochemical recurrence following radical prostatectomy were significantly higher in patients with involvement of more than 20% of the biopsy specimen. For high-risk patients, those with involvement of more than 55% of the specimen had higher indexes of biochemical recurrence following surgery.

Our data confirm those from the literature with an important differential that is the number of analyzed fragments. The mean and median of biopsies analyzed per patient were respectively 12 and 14, twice as those analyzed by Freeland et al. (14). Currently, the sextant biopsies with representation of only 6 fragments is considered insufficient for diagnosing prostate tumors (16), and are being replaced by wider representations of the gland, thus our data are important for directing new analyses.

In addition to tumor quantification, we confirmed the importance of the Gleason histological grade for identifying the final status of the tumor. We demonstrated a risk of non-confined disease that is 3 times higher for Gleason 7 tumors and 10.6 times for tumors with Gleason grade equal or higher than 8.

An interesting event was the identification of a group that we called unfavorable, whose histological grade was higher than 7 and total percentage of tumor was higher than 60%. Nineteen patients had tumors with such characteristics, and 95% of them were classified as pT3 after radical prostatectomy.

We concluded that tumor quantification in prostate biopsy is important for identifying non-confined tumors, and among the studied parameters, the total percentage of tumor was the most informative one, along with the Gleason histological grade. We suggest that this data is incorporated to the pathological report and that it is considered in the design of new nomograms.

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