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Predictive preoperatory variables of the prostate tumor volume

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Abstract

Prostate cancer (PCa) is the second most frequent malignant tumor in men worldwide and the most common form of cancer in men over 50-year-old. The adequate preoperative estimation of tumor volume in order to identify small tumors that lack a short-term aggressive behavior and do not necessitate a forthwith-radical prostatectomy (RP) is the subject of various recent studies and numerous debates. In this study, that included 128 cases, we attempted to evaluate some of the common preoperative variables (patient's age, total prostate volume determined on ultrasound examination, serum PSA, the number of positive biopsies and tumor size, the percentage of tumor length and the Gleason score) that could predict the tumor volume on the final RP. Based on these correlations, we develop a scoring system that combines only the Gleason score, the number of positive biopsies and the percentage of tumor length and that has been statistically proved to be correlated and predictive for the tumor volume. Our study brings additional and practical information about a true and effective prospective evaluation of the volume of the PCa.

***Keywords*:** prostate biopsy, radical prostatectomy, tumor volume, scoring system, Gleason score.

Introduction

After lung cancer, prostate cancer (PCa) is the second most frequent malignant tumor in men worldwide. In Europe it is the most common solid neoplasm, with an incidence rate of 370 000 per 100 000 men, outnumbering lung and colorectal cancer [1]. Furthermore, it is the most frequent form of cancer in men over 50-year-old and the second most common cause of cancer death in men [2, 3].

Due to the recent screening programmes that assess the PSA serum levels, an increase of small, localized, well-differentiated PCa have been reported. These generally small volume tumors lack clinical significance, because this type of cancer has a slow, progressive growth that can still develop aggressive potential along its evolution. The definition of an insignificant tumor comprises tumor volume (smaller than 0.5 cm^3), tumor extension (which should be confined within the limits of the prostate) and Gleason score (≤7) [4].

Thus, these tumors do not need immediate radical surgical treatment, although a preoperative assessment of the tumor volume is still important in order to choose the adequate therapy.

In the USA and Northern European countries, where the incidence of PCa is high, several attempts have been made to use biopsy data for the prediction of tumor volume and its prognostic value [5–9]. The results of these studies are not very convincing and yet there is no consensus over the possibility to preoperatively assess the volume of the tumor.

In this study, we attempted to evaluate some variables that could predict tumor volume, namely the patient's age, total prostate volume determined on ultrasound examination, serum PSA values, the number of positive biopsies, tumor size, the percentage of tumor length, and the Gleason score.

We attempted to establish a correlation between these variables determined on prostate biopsies and the tumor volume on radical prostatectomy (RP) specimens and to develop a scoring system that can help to predict it.

If this scoring system is proved to be predictive for the tumor volume, it could be useful in detecting small volume tumors and consecutively the radical surgical treatment and its accompanying complications that severely impact the quality of life can be avoided.

Materials and Methods

Type of study and the target population

In this transversal study, we included 128 consecutive cases of patients diagnosed with PCa on prostate needle biopsy (PNB) and consecutively treated by radical prostatectomy (RP) in the Pathology Department

of the Lyon Sud Hospital, France, from June 2003 until December 2005.

In order to equalize the data, the selection of the cases was done after applying the following *inclusion criteria*: patients who were diagnosed with PCa on prostate biopsies and followed by RP, complete preoperative examination consisting of digital rectal examination, prostate ultrasound examination and evaluation of the PSA serum levels.

Concomitantly, the *exclusion criteria* were: patients who underwent preoperative treatment, patients diagnosed with tumor types other than adenocarcinoma, extra-prostatic tumors, tumors with lymph node metastases, RP specimens with technical artefacts that render them unusable.

Clinical and biological data known before PNB

The patient's age, their preoperative total prostate volume measured on ultrasound examination and the PSA serum levels were recorded in a data chart build for each patient.

Prostate needle biopsy

Each patient underwent 12 ultrasound-guided PNB performed with 18 G needles mounted on an automated biopsy gun. All biopsies were processed and examined following a standard protocol (they were embedded in separate cassettes, fixed in Bouin's fluid and serially sectioned).

On the Hematoxylin–Eosin stained section we evaluated: *the number of positive biopsies* (that had tumor glands), *tumor size* (total length of tumor foci), *the percentage of tumor length* (total length of tumor foci related to total biopsy length) and *Gleason score*, recognized as the most important prognosis factors.

Radical prostatectomy specimens

The radical prostatectomy specimens were weighed, measured, fixed and inked. Following fixation, the apex, base and seminal vesicles were entirely submitted for examination. The remaining prostate was serially sectioned from the apex to the base and whole mount sections were taken for microscopic examination.

All RP specimens were reviewed by two pathologists. In order to calculate the tumor volume the pathologists used the method described by Chen ME *et al.* [10] as a simple, easy to use in everyday practice. In order to apply it, for each prostatectomy a chart was assigned in which all-prostate sections and surgical limits (prostate apex, base and seminal vesicles) were represented. Tumor foci present on each section were marked on the charts, thus facilitating the recognition of the largest focus, which was subsequently used in calculating the tumor volume.

The width (W) and length (L) of the largest focus were inscribed into an ellipsoidal shape (Figure 1), while the height (H) was acquired by multiplying the number of positive sections with their thickness.

The formula used is $L \times W \times H \times 0.4$, 0.4 being represented by a coefficient arising from the geometric inscription of an irregular shape into an ellipsoid. A retraction coefficient, variable in each laboratory with values between 1 (no retraction) and 1.5, should be applied. We used a coefficient of 1.5 in our calculations.

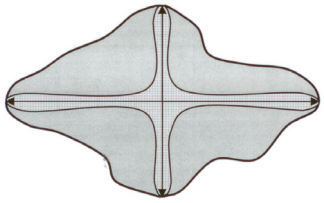

Figure 1 – ***Irregularly shaped tumor inscribed into an ellipsoid.***

Statistical analysis

Age, PSA serum value, preoperative total prostate volume measured on ultrasound examination, tumor size, percentage of cancer length on biopsy and Gleason score were compared to the tumor volume in RP specimens by using univariate and multivariate analysis. A p-value of under 0.05 was considered to be statistically significant. There we used logistic regression (β, p-value) and correlation (r, p-value).

Results

Clinical and biological data

Age: most of the patients with the diagnosis of PCa (59.2%) were in the 7th decade of life followed by those of the 50–59 year-old group (22.4%). In our study, there were very few cases of patients under 50-year-old (1.6%).

The preoperative total prostate volume measured on ultrasound examination had a mean value of 37.5 cm^3, ranging from 13–144. It is worth mentioning here that, in most of the cases (111) the volume was lower than 50 cm^3 and in only 17 of them was the prostate total volume over 50 cm^3. In a single case, an extreme value of 144 cm^3 was recorded.

Serum PSA levels had a mean value of 10.2 ng/mL, ranging from 1.16 to 44 ng/mL.

Preoperative variables in PNB (histo-prognostic factors on PNB)

Number of positive biopsies

In most of the cases included in this study 12 biopsies were performed. The number of biopsies showing tumor infiltration ranged from 1 to 6 in most of the cases (110) and only in one case were all the biopsy cores positive (Figure 2).

Gleason score on PNB

Most of the tumors were well-differentiated carcinomas having a combined Gleason score of 6 or 7. In detail, the Gleason score on PNB was 6 in 50 cases (39.1%), 7 in 62 cases (48.5%) and ≥8 in other 16 of them (12.5%).

Tumor size

The mean value of tumor total length was 22.2 mm (ranging from 0.5 to 133) (Figure 3) as compared to the mean value of 154.2 mm (ranging from 73 to 214) representing the biopsy total length (Figure 4).

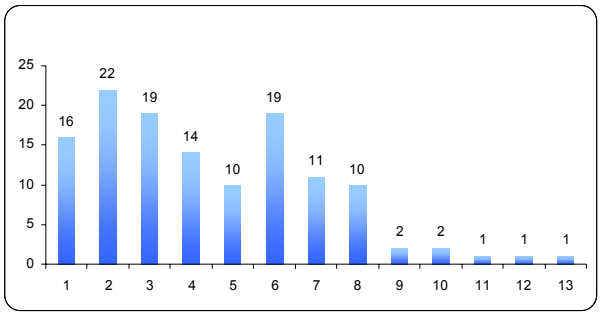

Figure 2 – ***Case distribution according to the number of positive biopsies.***

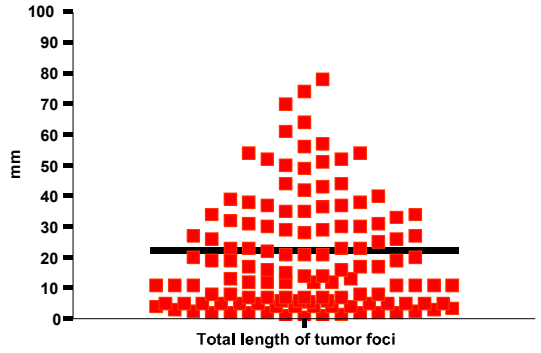

Figure 3 – ***Case distribution according to total length of tumor foci.***

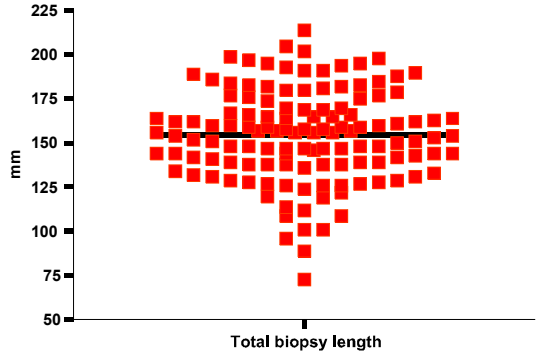

Figure 4 – ***Case distribution according to total biopsy length.***

In order to estimate the tumor size, we took into account the total length of all tumor foci identified on biopsy cores belonging to every single patient (Figure 3) but also the percentage of tumor length. More than half of the cases (51.37%) were characterized by a percentage of tumor length higher than 20% of the biopsy length as it is detailed in Figure 5.

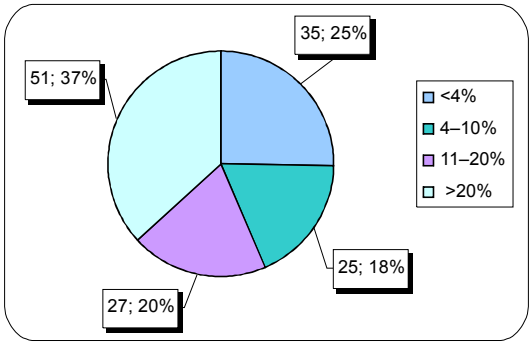

Figure 5 – ***Case distribution according to percentage cancer length on biopsies.***

Postoperative variables on RP specimen

Tumor volume

According to the literature [4, 6] we divided the cases into three categories of small, moderate and high tumor volume as follows as shown in Table 1.

Table 1 – ***Three-category tumor volume scheme***

Small	Moderate	High
<0.5 cm^3	0.5–4 cm^3	>4 cm^3

Seventy-two cases were of medium volume (56.3%) followed by 51 with high tumor volumes (39.8%). In only five cases, a small tumor volume (3.9%) was measured. The average of postoperatively measured tumor volume was 4.2 cm^3 (ranging from 0.1 to 25) (Figure 6).

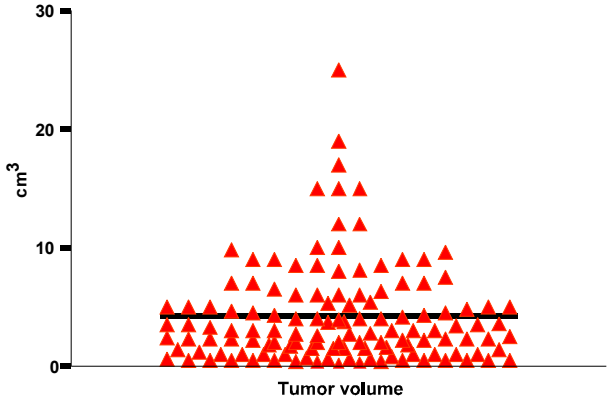

Figure 6 – ***Case distribution according to the three categories of tumor volume.***

We studied the relationship between pre-biopsy variables, PNB variables and tumor volume in RP specimens by using logistic regression.

Following statistical analysis, we concluded that serum PSA levels (Pearson's coefficient r=0.146, p=0.102) and the preoperative total prostate volume (r=0.238, p=0.07) measured on ultrasound are not predictive for total tumor volume as compared with the volume on RP specimens.

We also demonstrated that the *Gleason score* (β-coefficient =0.426, p<0.001), the *number of positive biopsies* (β-coefficient =0.447, p<0.001), *tumor size* (correlation coefficient =0.708, p<0.001) and the *percentage of tumor length* (correlation coefficient =0.712, p<0.001) are independently predictive factors for tumor volume.

To predict the tumor volume on RP specimens based on the variables with a proven independently predictive value on PNB, we designed a **scoring system** taking into account the *Gleason score, the number of positive biopsies* and *the percentage of tumor length*. We attributed points for all these variables determined on PNB (Table 2).

Applying this scoring system to our cases, the score ranged between 3 and 12 and was significantly correlated with the tumor volume on RP specimens (Pearson's coefficient 5.5956 (0.4707–0.6971), p<0.001) (Figure 7).

Table 2 – ***Scoring system based on Gleason score, number of positive biopsies, and the percentage of cancer length***

	Gleason score	The number of positive biopsies	The percentage of cancer length
One point	6	one positive biopsy	<4%
Two points	7 (3+4)	2–5 positive biopsies	4–10%
Three points	7 (4+3)	six positive biopsies	10–20%:
Four points	≥8 (8, 9 or 10)	7–12 positive biopsies	>20%

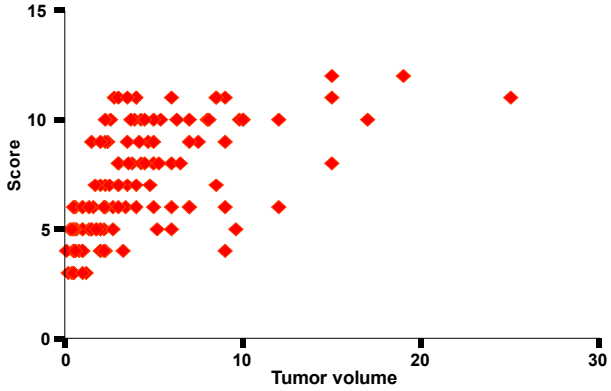

Figure 7 – ***Correlation between the score based upon PNB variables and tumor volume on RP specimens.***

Discussion

Prostate cancer is currently a real public health problem, since it is the most frequent form of cancer in men in Europe and the second cause of death after lung cancer [3]. Due to the screening strategies, a relatively high number of tumors are discovered in their early stages, when tumor volume is small and the patient may be conservatively treated.

Several predictive factors that should offer information about the tumor volume as early as the preoperative stage have recently been analyzed. Since no consensus has been reached yet and the results of other previous studies are contradictory [5–9], we attempted to identify on PNB some of the predictive variables and build a scoring system that should provide enough data in order to estimate the tumor total volume in RP specimens.

Tumor volume is an important prognostic feature in PCa, even though when assessed as an independent factor its value is controversial. This is why it was included in the second group of prognostic factors by the College of American Pathologists in 1999 [11]. The first group includes factors with proven prognostic value and clinical utility in patient management like preoperative serum PSA levels, Gleason score, pathologic stage assessed on RP specimens and the status of surgical resection margins. The second group comprises the tumor volume and histological type of the tumor, factors that were extensively evaluated on clinical and biological studies, but whose validity requires further research. Finally, the third group consists of insufficiently studied factors with uncertain prognosis value as genetic, neuroendocrine, markers of proliferation and apoptosis, perineural and lymphatic invasion, microvascular density and androgenic receptors.

Depending on tumor stage, various treatment options like radiotherapy, surgery with or without the preservation of neuromuscular bundles, and hormone therapy are now available. Consecutively, a preoperative estimation of tumor volume has a capital importance in selecting the best therapy for each patient. In this respect, we reviewed and tabulated all the preoperatively available variables (clinical, biological and imagistic data) and assessed all the diagnostic and prognosis data provided by the PNB.

The first evaluated parameter was the ***age*** of the patient now of diagnosis. In our study, most of the tumors were diagnosed in patients over 60-year-old (76%), of whom 59.2% belonged to the 60–69-year-old group. 16.8% of the tumors appeared in patients in the 50–59-year-old group, and only 1.6% of the cases involved patients under 50-year-old. These results confirm the literature data concerning PCa incidence that appears in elderly patients, mainly those over 65-year-old and that is rarely encountered before 50-year-old. Although the statistical analysis did not prove any significant relationship between the age and total tumor volume in RP specimens, still it is very important to evaluate it, since a small volume tumor in a 50-year-old patient may grow and may become clinically manifest as opposed to a similar tumor diagnosed in an 80-year-old patient.

Our study did not reveal any statistically significant correlation between ***preoperative ultrasound measured prostate volume*** and tumor volume in RP specimens (Pearson's coefficient r=0.146, p=0.102) a result that is also similar to Anast JW *et al.* study [6]. On the other hand, different studies have reported divergent results. Chen ME *et al.* [12] and Augustin H *et al.* [13] showed that small volume tumors (≤ 0.5 cm^3) appear in the same proportion as cases with a prostate volume of over but also lower than 50 cm^3. In contrast, Ochiai A *et al.* reported that small volume tumors appear more frequently in patients with a total prostate volume of over 50 cm^3 [9].

In our study, ***serum PSA values*** did not correlate with the tumor volume on RP (Pearson's coefficient r=0.238, p=0.07). Anast JW *et al.* reported similar results and concluded that a raised serum PSA level correlates with an increased total prostate volume [6], which is more likely to be caused by a benign prostate hyperplasia than by cancer. However, some authors showed that serum PSA value is an important predictive factor for PCa [14, 15] while others contested its value [16]. However, Furuya Y *et al.* highlighted in opposition with Cheng's results, that preoperative PSA serum levels have a significant predictive value, but only in conjunction with the Gleason score on PNB and the number of positive biopsies [5, 17].

As the PNB is the only preoperative examination that can confirm a clinical suspicion of PCa, it is consecutively indispensable to the diagnosis but also can yield information about tumor extension and aggressiveness.

Similarly to other previous studies [6–9] we also conclude, based on the statistical analysis of our present study's data, that *Gleason score* (β-coefficient =0.426, p<0.001), the *number of positive biopsies* (β-coefficient

=0.447, $p<0.001$), *tumor size* (correlation coefficient =0.708, $p<0.001$) and *the percentage of tumor length* (correlation coefficient =0.712, $p<0.001$) are ***independent predictive variables for determining tumor volume in RP specimens***.

Taking into account all these variables, we established a scoring system with values ranging between 3 and 12, as previously mentioned. Following statistical analysis, we noticed that our scoring system significantly correlates with tumor volume in RP specimens, i.e. a high score calculated on PNB correlates with a high tumor volume in RP specimens (Pearson's coefficient 5.5956 (0.4707–0.6971), $p<0.001$) (Figure 7).

The variables included in the score must be explicitly detailed in the pathology report, because they provide valuable information about the real tumor volume as early as the biopsy is performed.

Other authors have also attempted to set up various models that would yield information about tumor volume, by using several clinical, biological and histopathological variables.

Since preoperative assessment of tumor volume by a single parameter is extremely difficult and certain preoperative parameters have a significant value when studied as a group, but lose their importance if assessed individually [8], it is better to do this assessment by using multiple parameters that can be grouped in more or less elaborated models [18]. Many authors have used the amount of cancer present on biopsy cores, expressed either in millimeters (total length of tumor foci) or as a percentage (percentage cancer length = total length of tumor foci relative to total biopsy length) for this assessment. This parameter was usually associated with the Gleason score on PNB and serum PSA levels or one of its derived values.

Allan RW *et al.* showed that 80% of the patients with a tumor focus smaller than 0.5 mm, present on at most two biopsies, a PSA doubling time <0.15 and a Gleason score <7, have an "insignificant" (small) tumor [19]. Hoedemaeker RF *et al.* found that 92% of patients with insignificant tumors have a single positive biopsy, a Gleason score <7 and a serum PSA level <4 ng/mL [20]. In 2005, Ochiai A *et al.* proposed a predictive model in which he stated that a tumor of less than 2 mm on a biopsy, a Gleason score ≤3–4 and a total prostate volume >50 cm^3 are independent predictive factors for an insignificant tumor [9].

As previously shown, the results of the studies carried out so far are discordant, some authors underlining the importance of measuring PSA levels and the free PSA/total PSA ratio [13–15, 18, 19], while others considering this irrelevant [16].

The same statement is valid for the Gleason score: although some studies proved that it is an important predictive factor [16, 18, 21, 22], in others its prognostic value was found uncertain [13, 14].

Current divergent data regarding variables with the most predictive value for tumor volume assessment concern the fact that different carried out studies had different targeted populations and inclusion criteria. Additionally, RP specimens were not processed following the same protocol and the tumor volume was calculated using various methods. Other methods were proposed for calculating tumor volume, some of which are rather complicated and use computer assisted reconstruction and complex formulae [18] but we found them to be too unfeasible for current use.

Conclusions

Our results suggests that the use of the new scoring system, composed of the Gleason score on PNB, the number of positive biopsies and the percentage of tumor length, is a very useful method for preoperatively prediction of the prostate tumor volume. Thus, in cases in which a small volume tumor is suspected, a simple surveillance of the patient coupled with repeated biopsies instead of an aggressive surgical approach, could be recommended.

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