When to biopsy seminal vesicles


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Abstract

Objectives: The involvement of seminal vesicles in prostate cancer can affect the prognosis and determine the treatment. The objective of this study was to determine whether we could predict its infiltration at the time of the prostate biopsy to know when to indicate the biopsy of the seminal vesicles.

Material and methods: Observational retrospective study of 466 patients who underwent seminal vesicle biopsy. The indication for this biopsy was a prostate-specific antigen (PSA) level greater than 10 ng/ml or an asymmetric or obliterated prostatovesimal angle. The following variables were included in the analysis: PSA level, PSA density, prostate volume, number of cores biopsied, suspicious rectal examination, and preservation of the prostatovesimal angle, studying its relationship with the involvement of the seminal vesicles.

Results: Forty-one patients (8.8%) had infiltrated seminal vesicles and 425 (91.2%) had no involvement. In the univariate analysis, the cases with infiltration had a higher mean PSA level (P < .01) and PSA density (P < .01), as well as a lower mean prostate volume (P < .01). A suspicious rectal examination (20.7% of the infiltrated vesicles) and the obliteration or asymmetry of the prostatovesimal angle (33.3% of the infiltrated vesicles) were significantly related to the involvement (P < .01). In the multivariate analysis, we concluded that the probability of having infiltrated seminal vesicles is 5.19 times higher if the prostatovesimal angle is not preserved (P < .01), 4.65 times higher for PSA levels > 19.60 ng/dL (P < .01) and 2.95 times higher if there is a suspicious rectal examination (P = .01). Furthermore, this probability increases by 1.04 times for each unit of prostate volume lower (P < .01). The ROC curves showed maximum sensitivity and specificity at 19.6 ng/ml for PSA and 0.39 for PSA density.

Conclusions: In this series, greater involvement of seminal vesicles was associated with a PSA level > 20 ng/ml, a suspicious rectal examination and a lack of prostatovesimal angle preservation.

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¿Cuándo biopsiar las vesículas seminales?

Resumen

Objetivos: La afectación de las vesículas seminales en el cáncer de próstata puede afectar al pronóstico y condicionar el tratamiento. El objetivo es conocer si podemos predecir su infiltración en el momento de realizar la biopsia prostática para saber cuándo hay que indicar la biopsia de las mismas.

Material y métodos: Estudio retrospectivo observacional sobre 466 pacientes a los que se les realizó biopsia de vesículas seminales. La indicación de esta biopsia fue: PSA mayor de 10 ng/ml o ángulo prostatoseminal no conservado. En el análisis se incluyeron las siguientes variables: PSA, densidad de PSA, volumen prostático, número de cilindros biopsiados, tacto rectal sospechoso y conservación del ángulo prostatoseminal, estudiándose su relación con la afectación de las vesículas seminales.

Resultados: Cuarenta y un sujetos (8,8%) con vesículas seminales infiltradas y 425 (91,2%) libres de afectación. En el análisis univariado los casos con infiltración tenían una media superior en PSA ($p < 0,01$) y densidad de PSA ($p < 0,01$), además de una media de volumen prostático menor ($p < 0,01$). El tacto rectal sospechoso (20,7% de las infiltradas) y la no conservación del ángulo prostatoseminal (33,3% de las infiltradas) se relacionaron de forma significativa con la afectación ($p < 0,01$). En el análisis multivariado se concluye que la probabilidad de tener vesículas seminales infiltradas es 5,19 veces mayor si el ángulo prostatoseminal no está conservado ($p < 0,01$), 4,65 veces mayor si el PSA > 19,60 ng/dl ($p < 0,01$) y 2,95 veces mayor si existe tacto rectal sospechoso ($p = 0,014$). Asimismo, aumenta en 1,04 veces por unidad de volumen menor ($p < 0,01$). Las curvas ROC mostraron máxima sensibilidad y especificidad en 19,6 ng/ml para PSA y 0,39 para densidad de PSA.

Conclusiones: En esta serie se asocian con mayor afectación de vesículas seminales un PSA mayor o igual a 20 ng/ml, un tacto rectal sospechoso, o la ausencia de conservación del ángulo prostatoseminal.

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Introduction

The therapeutic management of localized prostate cancer involves assessing various aspects; from PSA levels to the Gleason obtained in the prostate biopsy, going through tumor burden or patient preferences. The infiltration of the seminal vesicles may have prognostic implications and may cause the urologist to opt for one or another form of treatment.

Infiltration of these organs results in extracapsular extension of the prostate carcinoma, reaching a stage T3b in the UICC TNM classification. This is important both in the prognosis and in the management that will be carried out with the patient, since this involvement is predictive of local recurrence and distant metastasis. Thus, we can understand the importance in detecting infiltration of seminal vesicles.

To find this extracapsular involvement, several methods can be used. One is the simple visualization in transrectal ultrasound, although by means of this technique, about 60% of pt3 tumors are not detected. We also studied endorectal MRI, concluding that it is a reliable method if used by expert genitourinary radiologists. The seminal vesicle biopsy is another tool that can be used to increase the accuracy of preoperative staging of the disease. It is not recommended as routine screening, but it is recommended in patients with high probabilities of extraprostatic involvement. Some authors recommend this type of biopsy in cases of PSA greater than 20 ng/ml, or when there is a Gleason of 7 or more; others defend seminal vesicle biopsy in cases of PSA greater than 10. What is certain is that individuals with a PSA between 15 and 20 ng/ml have a possibility of infiltration of vesicles of 20–25%. Other data have been linked to the positivity of involvement of the seminal vesicles, such as the percentage of tissue affected by tumor in the biopsy or a greater number of tumor biopsies.

Therefore, there are no strict indications to follow to biopsy seminal vesicles. The main objective of the study was to identify clinical factors predictive of seminal vesicle involvement in prostate biopsy.

Materials and methods

Retrospective study in which we collected in the database of prostate biopsies of our department all the seminal vesicle biopsies performed for eight years, from April 2004 to May 2012. During this period, the indication for biopsy of seminal vesicles was: PSA greater than 10 ng/ml or absence of preservation of the prostatic-seminal vesicle angle (PSVA) on transrectal ultrasound. In all patients, we performed the protocol used in our center for performing any transrectal prostate biopsy: antibiotic prophylaxis with 500 mg ciprofloxacin, one every 12 h for 5 days, starting the night before the test; administration of a cleansing enema the morning of the test, biopsy with 18-G needle and 25-cm
length; anesthesia prior to sampling with 10 ml of 2% lidocaine; interruption of antiplatelet therapy one week before the test, or substitution by low-molecular-weight heparin in case of treatment with anticoagulants.

Locating the biopsy site by means of ultrasound, a sample of each vesicle was taken by tru-cut needle. Moreover, the data of the variables previous to the biopsy with which we wanted to study the possible relation to the positivity in the infiltration were also recorded: PSA, PSA density (PSAd), prostate volume, number of biopsied cylinders, suspicious digital rectal examination, and preservation of the prostatic-seminal vesicle angle in ultrasound.

With regard to PSA and PSAd, the latest present values were taken before the prostate biopsy. Prostate volume was measured at the time of the completion of the transrectal ultrasound. As for the number of biopsied cylinders, it ranged from 8, 10 to 12, depending on the change of criterion over the 8 years that the patient record lasted. All males were performed a digital rectal examination before performing the ultrasound, considered suspicious if there was stony consistency, irregular surface, poorly-defined limits, or adherence to neighboring planes. The preservation or not of the prostatic-seminal vesicle angle was observed during the course of the transrectal ultrasound. We accept the involvement of this angle as the alteration of the fat signal intensity at this location (hypoechoic region at the prostate base adjacent to the seminal vesicle) or directly the loss of the existing natural angle between the vesicles and prostate.

Regarding the statistical analysis, parametric tests were used to analyze the association between these pre-biopsy variables and the positivity in the infiltration of the seminal ones: Student’s t and Chi-square. Furthermore, we also attempted to meet the independent predictive factors using multiple logistic regression. We used ROC curves to establish the PSA and PSAd levels with greater diagnostic yield for infiltration of seminals.

Results

A total of 466 individuals were recorded, with a mean age of 65.64 ± 6.09 years. Of these, 41 (8.8%) corresponded to patients resulting in infiltration of vesicular seminals in the pathological examination of the biopsy, and 425 (91.2%) did not show this involvement.

Table 1 shows the characteristics of the sample.

The histological study of the cores obtained directly from the prostate concluded that 41.2% of cases were compatible with prostate adenocarcinoma, 28.3% with chronic prostatitis, 27.3% with absence of disease, and 3% were different from previous results.

The analysis results of Student’s t for independent groups are shown in Table 2. Significant differences were found with p < 0.01 between infiltration of seminals and PSA, PSAd, and volume. The cases with infiltrated seminal vesicles had a mean significantly higher in the PSA (mean difference 23.39, 95% CI: 11.01–35.97, p < 0.01) and PSAd (mean difference 0.85, 95% CI: 0.47–0.22, p < 0.01). In the case of volume, infiltrated seminal subjects had a significantly lower mean (mean difference −28.3, 95% CI: −34.22 to −22.38, p < 0.01). Furthermore, no relationship with the number of cylinders (p = 0.601) was observed.

<table>
<thead>
<tr>
<th>Quantitative variables</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>65.64</td>
<td>6.09</td>
</tr>
<tr>
<td>No. of cylinders</td>
<td>10.82</td>
<td>1.75</td>
</tr>
<tr>
<td>PSA</td>
<td>21.61</td>
<td>23.92</td>
</tr>
<tr>
<td>PSAd</td>
<td>0.50</td>
<td>0.68</td>
</tr>
<tr>
<td>Prostate volume</td>
<td>63.78</td>
<td>38.33</td>
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Categorical variables

<table>
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<tr>
<th>DRE</th>
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<th></th>
</tr>
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<tbody>
<tr>
<td>Suspicious</td>
<td>150</td>
<td>32.19</td>
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<tr>
<td>Non-suspicious</td>
<td>316</td>
<td>67.81</td>
</tr>
<tr>
<td>PSVA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preserved</td>
<td>400</td>
<td>85.84</td>
</tr>
<tr>
<td>Non-preserved</td>
<td>66</td>
<td>14.16</td>
</tr>
</tbody>
</table>

Table 1 Description of the sample (n = 466).

Age is measured in years, the PSA in ng/dl, and prostate volume in cm³. SD: Standard deviation; PSAd: PSA density; PSVA: prostatic-seminal vesicle angle.

The result of the analysis of categorical variables with the Chi-square test is also shown in Table 2. The cases with infiltration of seminal vesicles are present more often in patients with suspicious digital rectal examination, or with non-preserved prostatic-seminal vesicle angle.

The study also aimed to find the PSA and PSAd cut-off points from which there was correlation with the positive diagnosis of seminal vesicle involvement. To do so, ROC curves were used. In the case of the PSA, the area under the curve was 0.777 (95% CI: 0.695–0.859), statistically significant with p < 0.01. The point of maximum sensitivity and specificity was found in PSA = 19.6 ng/ml. The results of sensitivity, specificity, and predictive values setting this PSA value are shown in Fig. 1. The correlation between PSA with this cut-off point and the positive diagnosis of infiltrated seminals was statistically significant with p < 0.01 (Chi-square = 40.41; 1 gl; p < 0.01).

In the case of PSAd, the area under the curve was 0.833 (95% CI: 0.778–0.889) achieving statistical significance with p < 0.01. The point of greatest sensitivity and specificity was set at PSAd = 0.39. Taking this cut-off point, the results shown in Fig. 1 are obtained. The correlation between PSAd with this cut-off point and the positive diagnosis of infiltrated seminals was also statistically significant with p < 0.001 (Chi-square = 40.11; 1 gl; p < 0.01).

Finally, based on the results above, we proceeded to perform a multivariate prediction by means of binary logistic regression of the infiltration of the seminal vesicles. For this, we took as predictive factors the pre-biopsy variables that had proven significant (shown in Table 2), and they were all except for the number of cylinders. The PSA and PSAd variables were entered into the model already dichotomized from the cut-off points proposed in the immediately preceding ROC analyses. Likewise, we considered the possible inclusion of age in the model.

In the end, the adjusted model confirms as significant (p < 0.05) the factors: non-preserved prostatic-seminal vesicle angle, PSA > 19.60, suspicious DRE, and volume.
Table 2  Univariate analysis. Relationship between pre-biopsy quantitative variables and infiltration of seminal vesicles.

<table>
<thead>
<tr>
<th>Quantitative variables</th>
<th>Seminals</th>
<th>Mean</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA</td>
<td>Infiltrated s.</td>
<td>42.94 ± 38.74</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>Non-infiltrated s.</td>
<td>19.55 ± 20.92</td>
<td></td>
</tr>
<tr>
<td>PSAd</td>
<td>Infiltrated s.</td>
<td>1.27 ± 1.17</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>Non-infiltrated s.</td>
<td>0.42 ± 0.56</td>
<td></td>
</tr>
<tr>
<td>Volume</td>
<td>Infiltrated s.</td>
<td>37.96 ± 14.81</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>Non-infiltrated s.</td>
<td>66.26 ± 38.98</td>
<td></td>
</tr>
<tr>
<td>No. cylinders</td>
<td>Infiltrated s.</td>
<td>10.93 ± 1.35</td>
<td>0.601</td>
</tr>
<tr>
<td></td>
<td>Non-infiltrated s.</td>
<td>10.81 ± 1.78</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Categorical variables</th>
<th>N</th>
<th>Infiltrated sem. (%)</th>
<th>Non-infiltrated sem. (%)</th>
<th>Chi-square value</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>DRE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Sospicious</td>
<td>150</td>
<td>20.7</td>
<td>79.3</td>
<td>38.671</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Non-sospicious</td>
<td>315</td>
<td>3.2</td>
<td>96.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSVA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-preserved</td>
<td>66</td>
<td>33.3</td>
<td>66.7</td>
<td>57.68</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Preserved</td>
<td>400</td>
<td>4.8</td>
<td>95.3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


PSVA: prostatic-seminal vesicle angle; PSA: prostate specific antigen; PSAd: PSA density.

Figure 1  ROC curves of PSA and PSAD for infiltrated seminal vesicles. Sp: specificity; S: sensitivity; NPV: negative predictive value; PPV: positive predictive value.

dismissed as not significant (p > 0.05) PSAd > 0.39 and age. The summary of results can be seen in Table 3.

The complete model reaches statistical significance with p < 0.001, getting a good degree of adjustment \( R^2 = 0.409 \), and correctly classifying 92.3% of cases. The likelihood of having infiltrated seminals is: 5.19 times higher in cases with non-preserved prostatic-seminal vesicle angle, 4.65 times higher in cases with PSA > 19.60, and 2.95 times higher in

Table 3  Multiple logistic regression model for infiltrated seminals.

<table>
<thead>
<tr>
<th>Variables introduced</th>
<th>OR</th>
<th>95% CI of OR</th>
<th>Wald</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-preserved PSVA</td>
<td>5.195</td>
<td>2.337–11.550</td>
<td>16.342</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>PSA &gt; 19.60</td>
<td>4.648</td>
<td>2.065–10.463</td>
<td>13.772</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Suspicious DRE</td>
<td>2.949</td>
<td>1.249–6.963</td>
<td>6.086</td>
<td>0.014</td>
</tr>
<tr>
<td>Volume</td>
<td>1.036</td>
<td>1.015–1.057</td>
<td>11.750</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

PSVA: prostatic-seminal vesicle angle; SD: standard deviation; PSA: prostate specific antigen.
patients with suspicious vesicles. Likewise, it increases 1.04 times per lower volume unit. The confidence intervals of ORs can be seen in Table 3.

Discussion

At present, there is no consensus in the literature or in the clinical guidelines of which should be the absolute criteria for seminal vesicle biopsy. The fact of knowing whether or not there is involvement of this organ, prior to the decision of patient management in prostate cancer, provides the urologist with information that is valuable, because it will have both prognostic considerations and an influence on the final treatment decision.

With this work we wanted to collect a large sample of patients with seminal vesicle biopsy, so studying the relationship of different pre-biopsy variables with the involvement of seminal vesicles, we could shed some light on the matter. They are easy-to-record measures in all patients (PSA, prostate volume, DRE, etc.), so they are useful in daily practice.

With regard to the PSA, due to the production of this protein serine by the benign and malignant prostatic tissue, there is no direct relationship between serum concentration of PSA and clinical and anatomopathological stage of the tumor. However, it was found that men with PSA between 15 and 20 ng/ml have a possibility of infiltration of seminal vesicles of 20–25%. Therefore, we think that it is a parameter to consider when making the decision to biopsy the seminal vesicles. The data obtained in our study conclude that the PSA value with greater sensitivity and specificity to obtain an involvement of seminal vesicles stands at 19.6 ng/ml. This PSA value around 20 ng/ml is consistent with what published in the literature, although some authors set the PSA value from which the biopsy of seminal vesicles is valuable at 10 ng/ml.

The absence of preservation of the prostatic-vesicle angle was the variable studied with the greatest OR (5.19). This datum was recorded during the performance of transrectal ultrasound. It is known that this examination has a limited value in some respects, such as the fact of performing biopsies targeted to suspicious prostatic areas rather than systematic biopsies. In addition, it is estimated that about 60% of prostatic tumors with extracapsular involvement cannot be detected preoperatively only with transrectal ultrasound. However, it has been demonstrated as a useful tool in detecting pT3 cancers if combined with other scans, such as digital rectal examination. Despite all this, the preservation of the prostatic-vesicle angle is an easy parameter to objectify while performing transrectal ultrasound. Currently, there is no defined criterion on what the ultrasound signs of suspected invasion of the seminal vesicles are. However, in our work we decided to accept as suspicious images both the presence of a hypoechogenic area at the base of the prostate adjacent to the seminal vesicle, such as the loss of the existing natural angle between the prostate and the vesicles, as we consider that they were signs easy to objectify during the scanning. Although the combination of both ultrasound images has not been considered in our study, the elevated OR presented by this variable of prostatic-vesicle angle alteration in the presence of any of the 2 signs separately, makes it an aspect to consider in daily clinical practice, regardless in addition of the DRE or the PSA level according to the results of our multivariate analysis.

In our study up to one in 3 patients with absence of preservation of the angle turned out to have infiltration of seminal vesicles in the anatomopathological biopsy result. These results regarding ultrasound allow us to reflect on the importance of imaging techniques in preoperative staging of the disease. In our study, 33.3% of patients with non-preserved prostatic-vesicle angle had a pathology consistent with the suspicion. There are other techniques that show promising results in terms of preoperative staging, as in the case of multiparameter magnetic resonante imaging, which shows detection of 65% of cases of infiltration of seminal vesicles when combined with guided biopsy in suspected cases with resonance images.

With regard to the DRE, the significance it has on the diagnosis in the case of prostate cancer has been studied, a suspicious DRE being absolute indication for prostate biopsy regardless of the PSA value. A suspicious DRE in patients with a PSA of up to 2 ng/ml has a positive predictive value of 5–30%. In addition, there are studies that defend the usefulness of the DRE, even for detecting extracapsular involvement in prostate cancer. In our study, we classified as suspicious digital rectal examination not only the one with fixation to adjacent tissues, but anyone who showed some abnormality (nodule, roughness, change of consistency) although this was limited to the prostatic surface. Even though at first it might seem that this issue is not related to the involvement of seminal vesicles, about one in 5 patients included in the study with suspicious DRE and PSA greater than 10 presented involvement of this organ, there being a meaningful relationship.

Another finding in our study was that, for every lower unit of prostate volume, the risk of seminal vesicle involvement increases by 1.04. That is to say, the smaller a prostate with cancer, the greater the probability of seminal vesicle involvement, this finding being significant in the multivariate analysis. However, the risk, although significantly, increases very little per lower volume unit, so very little volumes would be necessary for this aspect to have clinical relevance.

Other variables studied prior to the biopsy, as the number of cylinders, were unrelated to the involvement of seminal vesicles. The patients in the study ranged from 8, 10 to 12 cylinders biopsied depending on the periods, following the guidelines described in the clinical guidelines and in various publications. With a mean of 10.82 ± 1.75 cylinders obtained in the biopsy, no statistical significance was found.

The PSAd density is defined as the ratio between the PSA and the prostate volume. It has long been accepted that PSAd values greater than 0.15 are suggestive of prostate cancer. Recent studies provide new conclusions about the PSAd, such as its usefulness in predicting disease progression in cases of active surveillance for prostate cancer.
Moreover, today it is still used in Epstein criteria for predicting insignificant prostate cancers. Although its usefulness has been demonstrated by some authors to predict the infiltration of the seminals, in our multivariable analysis the PSAd was outside the predictor model, probably due to the influence of the level of PSA and prostate volume. The point with greater sensitivity and specificity in ROC curves was 0.39.

We consider that all the variables studied are easy to register and access for all patients who will undergo a prostate biopsy, so that the findings of this study may have relevance in clinical practice.

However, we believe that the work has some limitations. Although the seminal vesicle biopsy has proven to be a reliable test to study the actual infiltration of this organ, maybe the data of positivity or negativity in the infiltration of seminal vesicles obtained by biopsy should be compared with the positivity or negativity in the infiltration of seminals in the surgical specimen. Another limitation may be the number of individuals within the group of infiltrators seminals, only with 41 subjects. In terms of the work design, it presents the limitations of any retrospective study, being more subject to bias than prospective ones. For example, it might be that some patient with criteria of seminal vesicle biopsy was not performed the biopsy for a certain reason, unnoticed in the data record.

Conclusion

In this series, a PSA greater than or equal to 20 ng/ml, a suspicious DRE, or the absence of preservation of the prostatic-vesical angle are associated with increased seminal vesicle involvement.

Conflict of interest

The authors declare that they have no conflict of interest.

References

