Correlation between the number of positive cores and extraprostatic disease in patients that underwent radical prostatectomy

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\textbf{KEYWORDS}
Extraprostatic disease; Adenocarcinoma; Prostate; Biopsy; Mexico.

\section*{Abstract}

\textit{Background}: Adenocarcinoma of the prostate is currently recognized as one of the main medical problems confronting the male population. It is the second cause of death by cancer in men. Pretreatment clinical staging is of the utmost importance for offering improved treatments, given the increase in nonsurgical therapeutic options. Using a statistical analysis test, we detected extraprostatic disease based on the number of positive cores in prostate biopsy.

\textit{Methods}: From a total of 136 patients that underwent radical prostatectomy within the time frame of 2010 to 2012 at the Hospital Central Militar, the presence of extraprostatic disease and the number of positive cores from prior biopsy were determined.

\textit{Results}: Of the 136 patients, 58 (43\%) had organ-confined disease, 72 (53\%) had extraprostatic disease, and disease was unreported in 6 (4\%) patients. Spearman’s rank correlation coefficient was positive with a value of 0.344, (p<0.0001).

\textit{Conclusions}: There was a positive correlation of 0.344 for the presence of extraprostatic disease, taking into account the number of positive cores from prior prostate biopsy in patients that underwent radical prostatectomy at the Hospital Central Militar.

Correlación entre número de cilindros positivos y enfermedad extraprostática en pacientes operados de prostatectomía radical

\section*{Resumen}

\textit{Introducción}: El adenocarcinoma de próstata actualmente es reconocido como uno de los principales problemas médicos que enfrenta la población masculina. Es la segunda causa de muerte por cáncer en población masculina.
La estadificación clínica pretratamiento es de suma importancia para ofrecer mejores tratamientos, dado el incremento en opciones terapéuticas no quirúrgicas. Usando una prueba de análisis estadístico detectamos la correlación de la enfermedad extraprostática basada en el número de cilindros positivos en la biopsia prostática.

**Material y métodos**: Obtuvimos un total de 136 pacientes operados de prostatectomía radical entre 2010 y 2012 en el Hospital Central Militar, se determinó la presencia de enfermedad extraprostática, así como el número de cilindros positivos en la biopsia previa.

**Resultados**: De los 136 pacientes, 58 (43%) tuvieron enfermedad órgano-confinada, 72 (53%) presentaron enfermedad extraprostática y 6 (4%) no reportados, así como una correlación positiva Spearman Rho=0.344 (p<0.0001).

**Conclusiones**: En los pacientes operados de prostatectomía radical en el Hospital Central Militar, existe una correlación positiva de 0.344 para presencia de enfermedad extraprostática, tomando en cuenta el número de cilindros positivos en la biopsia prostática previa.

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### Introduction

Prostate cancer is currently recognized as one of the main medical problems confronting the male population. In Europe, prostate cancer is the most frequent solid tumor, with an incidence rate of 214 cases for every 1,000 men, surpassing lung and colorectal cancers in number. In the United States, it is the most frequent visceral neoplasia in men and currently represents one third of all those cancers and is the fourth most frequent malignant neoplasia worldwide. Opportune prostate cancer detection offers the prospect of curative treatment to those patients.¹

Given the natural prolonged progression of low-grade cancers detected in the era of prostate-specific antigen (PSA), prostate cancer treatment is not expected to have a substantial effect on mortality statistics for another 10 to 15 years.

There was a substantial change toward a more favorable stage at the time of presentation in men with recently diagnosed disease. This migration of clinical stage is largely, or perhaps exclusively, due to systematic detection through PSA and transrectal prostate biopsy, increasing the incidence of locoregional disease, while the incidence of metastatic disease was reduced.

Non-palpable cancers (T1c) now represent 75% of recently diagnosed disease. Together with these changes, the percentage of patients that underwent radical prostatectomy due to clinically localized disease increased substantially.¹²

### Adenocarcinoma

Adenocarcinoma of the prostate is multifocal in 85% of the cases and most of the tumor burden is located in the peripheral zone.

Because the prostate lacks a histologically differentiated capsule, the term "extraprostatic extension" is preferred to "capsular penetration" for referring to a tumor that has extended outside of the prostate and into the bland periprostatic tissue.

Adenocarcinomas that are situated in the peripheral zone of the prostate tend to extend beyond the gland by invading the perineural space. Perineural invasion, itself, in prostatectomy samples does not worsen outcome because it only represents tumor extension along a less resistant plane, and not lymphatic vessel invasion. In contrast, vascular invasion increases the risk for recurrence after radical prostatectomy. Extraprostatic extension is preferentially produced toward the posterior and posteroexternal surface, similar to the location of the majority of adenocarcinomas.

Ulterior local tumor dissemination can trigger seminal vesicle invasion that is diagnosed when the tumor extends to their muscle walls. The most frequent pathway of seminal vesicle invasion is through tumor penetration into the prostatic capsule at the base of the gland, with growth and invasion into the soft tissue surrounding the vesicles and ultimately into the seminal vesicles.

Direct invasion through the ejaculatory ducts into the seminal vesicles or from the base of the prostate and inside the seminal vesicle wall is less frequent and isolated metastases in the seminal vesicle are even less common. Local prostate cancer spread can compromise the rectum, where it is sometimes difficult to distinguish from primary rectal cancer.

The lymph nodes and bone are the most frequent sites of prostate cancer metastases. Pulmonary metastases from prostate cancer are frequently found at autopsy and there is almost always bone involvement. The metastatic lesions tend to take the form of numerous small nodules or diffuse lymphatic spread.

### Grade

The histologic grading system proposed by Gleason is the most widely used and is based on the glandular pattern of the tumor identified at a relatively low magnification. Cytologic characteristics do not have an influence on tumor staging. Primary (predominant) and secondary (second most prevalent) structural patterns are identified and assigned a grade of 1 to 5, 1 being the most differentiated and 5 the least differentiated. Gleason scores vary from 2 (1+1=2), which represents tumors composed of a uniform Gleason 1 pattern, up to 10 (5+5=10), which represents totally undifferentiated tumors. In radical prostatectomy samples,
high-grade tertiary components (third most frequent pattern) have been seen to adversely affect biologic behavior and are not always equivalent to the sum of the primary pattern and the pattern of the highest grade. In radical prostatectomy samples, it is recommended to register the Gleason score, obtained from the 2 most prevalent patterns in relation to cell architecture, with a note mentioning the existence of a high-grade tertiary pattern.

Tumors with Gleason 1 and 2 patterns are made up of relatively circumscribed nodules of single glands that are medium-sized, uniform, separate, but closely packed. Tumors with Gleason 3 pattern infiltrate the non-neoplastic prostate and the glands present with a marked variation in size and shape, with smaller glands than those observed in Gleason 1 or 2 patterns. The glands with Gleason 4 pattern are no longer single and isolated, as those seen in patterns 1 to 3. In Gleason 4 pattern, large irregular cribriform glands can be distinguished compared with the usually smaller and more circumscribed nodules of the cribriform Gleason 3 pattern. It is important to recognize Gleason 4 pattern tumors because they have a much worse outcome than those with pure Gleason 3 pattern. It has also been demonstrated that in radical prostatectomy surgical specimens, tumors with a Gleason score of 4+3=7 have a poorer prognosis than those with a score of 3+4=7.

The tumor with a Gleason 5 pattern does not show glandular differentiation and is composed of solid sheets, cords, isolated cells, or solid tumor nests with central comedonecrosis (fig. 1).

Some patients with low-grade tumors develop high-grade tumors after several years. It is not clear whether the low-grade residual cancer progressed or if a later development of a more aggressive multifocal tumor was produced. Even though larger tumors are generally high-grade and smaller tumors are low grade, there are exceptions. There is a tendency to believe that tumors begin with a low grade and when they reach a certain size they dedifferentiate into higher grade lesions, which explains the relation between size and grade. On the other hand, tumors can be high grade from the start, but are detected with a more advanced size due to rapid growth. Likewise, low-grade tumors can progress so slowly that they tend to be detected with lower volumes. There is no evidence indicating that prostate cancer worsens during a period of 1.5 to 2 years after biopsy.

**Figure 1**  Gleason grade illustration.

**Needle biopsy evaluation**

When biopsies are taken from different sectors of the prostate, they should be sent to the anatomopathologist in separate containers. Underdiagnosis of prostate-limited adenocarcinomas in puncture biopsy is one of the most common problems in prostate pathology. Many benign lesions are also very similar to prostate adenocarcinoma. In some cases, the use of antibodies against high molecular weight cytokeratin and p63 can resolve the diagnosis. The benign glands contain basal cells and are marked by these antibodies, whereas prostate cancer does not stain. Immunohistochemistry techniques with anti-a-methylacyl-CoA racemase antibodies can also be used; they preferentially mark in prostate cancer and high-grade intraepithelial neoplasia. These techniques are adjuvants in the diagnosis of circumscrip tumors and even so, pathologists should be careful, because cases of false negative and false positive stains with a-methylacyl-CoA racemase have been reported. In some cases there are findings that are suggestive, but not diagnostic, of carcinoma.

In the literature, there is a mean incidence of atypical cases in the samples obtained from prostate biopsy of 7.6% with a median of 5.2%. Anatomopathologists should report the atypical cases with a complete description, such as a “focus of atypical glands” and adding a commentary describing why the focus is suspected to be cancerous. The probability of the definitive diagnosis being cancer after the diagnosis of atypia is 42% to 49%. Whatever the serum level of PSA, all the patients with an initial diagnosis of atypia in the prostate biopsy sample require a second biopsy. In general, adverse findings in the prostate biopsy precisely predict adverse findings in the radical prostatectomy surgical specimen. However, favorable findings in the prostate biopsy do not necessarily anticipate favorable findings in the radical prostatectomy specimen, as a result of error in obtaining the samples. In the prostate biopsy, cancer can be measured in terms of the number of positive samples, the total millimeters of cancer in all the samples, the percentage of cancer in each sample, and the total percentage of cancer in the total sample. No single technique has been uniformly adopted, because an equal number of studies postulate that each technique is superior to the others. One proposal is that the anatomopathologists communicate the number of positive samples together with another measure of tumor extension. Cancer extension can be quite precisely predicted by combining the grade obtained from the puncture biopsy with the clinical stage and serum PSA values.

When perineural invasion is observed in the prostate biopsy, it is associated with increased risk for extraprostatic extension in the prostatectomy specimen. There are contradictory studies as to whether perineural invasion in the prostate biopsy enables an independent prediction of extraprostatic extension beyond that foreseen by Gleason grade in the biopsy and preoperative serum PSA levels. Perineural invasion in the prostate biopsy has also shown that it independently predicts lymph node metastases and postoperative progression. The confirmation obtained from
the prostate biopsy reports for deciding whether to sacrifice the neurovascular bundles on one side in the cases with greater probability of extension beyond the prostate can also be predicted.

Extraprostatic extension (outcome)

Only 25% of the patients with seminal vesicle invasion and none of those with lymph node metastasis are progression-free, from the biochemical perspective, at 10 years after radical prostatectomy. The presence of extraprostatic dissemination and its extension also influences progression. Pathologists frequently underdiagnose extraprostatic progression. When the tumor extends beyond the prostate gland it induces a dense desmoplastic response in the periprostatic adipose tissue, where it can be difficult to judge whether the tumor has extended beyond the gland or into the fibrous tissue of the prostate. The posterior, posterolateral, and lateral regions are responsible for 18%, 17%, and 4% of positive margins, respectively. An important source of discrepancy is that, even in cases in which margins appear positive in the histology, the additional tissue resected from the site does not always show tumor. It has also been demonstrated that the tumor near the margins does not produce greater risk for recurrence. Artificially positive margins are related to the scarcity of tissue surrounding the prostate that can easily suffer effraction during surgery or the anatomopathologic evaluation of the gland.

Gleason grade, extraprostatic extension, and resection margins are independent predictive factors of progression (elevated serum PSA level after surgery). Patients with Gleason scores between 8 and 10 have poor outcome after prostatectomy and lymph node metastases are a primary determinant of poor prognosis.2,3

Prostate echography

Transrectal ultrasound has become the cornerstone of many interventions, including prostate biopsy, brachytherapy, and cryotherapy and it has also been used in the evaluation of benign prostatic hyperplasia.4

Figure 2 Anatomic prostate zones.

Anatomic echography of the prostate

The prostate is situated between the bladder neck and the urogenital diaphragm, immediately in front of the rectum; it is an ideal position for taking images through transrectal ultrasound. The prostate gland is traditionally described based on the architecture of the pathologic region. These divisions consist of the anterior fibromuscular stroma that is deprived of glandular tissue, the transitional zone, the central zone, the periurethral zone, and the peripheral zone. Unfortunately these regions are not visible in echography as separate entities5 (fig. 2).

Nevertheless, the transitional zone can often be discerned from the peripheral zone and central zone, especially in glands with significant benign prostatic hyperplasia.5

Before the advances in transrectal ultrasound and the diffusion of serum PSA tests, physicians relied mainly on rectal examination as the prostate cancer detection method and performed biopsies of the lesion directed by digital rectal examination (DRE). Today, as a consequence of PSA screening tests in asymptomatic men, transrectal ultrasound-guided biopsy has become the standard procedure for the histopathologic study of the prostate.7,8

The advent of transrectal ultrasound (TRUS)-guided prostate biopsy revolutionized the techniques of prostate biopsy and has increased its diagnostic precision.

Prostate biopsy indications

Transrectal ultrasound-guided prostate needle biopsy continues to be the standard procedure for diagnosing prostate cancer.

Biopsy is recommended once serum PSA levels are above 4.0 ng/mL. However, much research is being done to identify the optimum PSA threshold for recommending prostate biopsy in the asymptomatic patient.

The presence of focal nodules in the rectal examination is an absolute indication for prostate biopsy; it should be taken with the transrectal ultrasound technique no matter what the PSA levels are. The presence of high-grade prostatic intraepithelial neoplasia has an elevated predictive value for prostate adenocarcinoma in subsequent biopsies (27% to 79%); there is also a high risk for cancer in
subsequent biopsies when atypia is found (45%-49%). Therefore, whatever the follow-up PSA values, current recommendations are to take a repeat sample within 3 to 6 months in all patients with high-grade prostatic intraepithelial neoplasia or small atypical acinar proliferation in the initial biopsy specimen.

Regardless of the initial PSA value, an ascending PSA velocity greater than 0.75 to 1 ng/mL per year is associated with prostate cancer and justifies biopsy.

Currently, there are different management options for organ-confined prostate cancer that produce good results, ranging from radical surgery to radio or brachytherapy. In relation to potentially curative results, radical prostatectomy is more efficacious when the disease is organ-confined. The precise preoperative prediction of the final pathologic stage is important for adequate patient selection in order to determine who will obtain the maximum benefit from radical prostate surgery. Numerous researchers have combined preoperative characteristics such as PSA, Gleason score, and clinical stage in order to determine the predictive factors.9-16

Methods

A descriptive study was conducted, with a data search and collection from April to October 2013. The pathology reports of the patients that underwent retropubic or laparoscopic radical prostatectomy within the time frame of January 2010 to December 2012 were reviewed. The name, registration number, age, and histopathologic report with Gleason annotations (primary and secondary patterns), presence of extraprostatic disease, seminal vesicle invasion, lymphovascular invasion, and perineural invasion were collected.

For these same patients, the database of the Pathologic Anatomy Electronic Archive was searched for the previous transrectal prostate biopsy reports; data in relation to the Gleason score (primary and secondary patterns) and number of positive cores were obtained. Clinical case records and electronic clinical records of selected patients were reviewed in order to obtain complementary information such as initial PSA, date of transrectal prostate biopsy, and date of radical prostate surgery. All the patients were listed on an electronic calculation sheet and the data of the abovementioned variables were captured. In accordance with the TNM of the 2013 AJCC, extraprostatic disease was regarded as those tumors found in stage: T3a, unilateral or bilateral extracapsular extension; T3b, tumor invasion of the seminal vesicles; and T4, tumor invasion of adjacent structures different from the seminal vesicles such as the bladder, the levator ani muscle, or the pelvic wall. The presence of extraprostatic disease (seminal vesicle, lymphovascular, and perineural invasion) was coded as follows: 0 = absent, 1 = present, and 2 = not reported.

The rest of the variables were coded with numerical values (quantitative).

Results

The database was converted for the SPSS® version 20.0 statistical program, in which each variable was assigned a label. First, descriptive statistics were used to calculate the mean and standard deviation (SD), and the minimum and maximum values for the demographic variables of age, serum PSA concentration, waiting time for surgery, and preoperative and postoperative Gleason evaluation. Also included were the histopathologic characteristics of the prostate, such as the number of positive cores, extraprostatic extension, vascular or perineural extraprostatic invasion, and seminal vesicle invasion. Inferential statistics were carried out to confirm the correlation hypothesis between the number of positive cores and the result of the different histopathologic variants, using the two-tailed Spearman rho statistical test; statistical significance was set at a p<0.05. Responder operator curves (ROC) were constructed for this statistical hypothesis to find the cut-off point of the number of cores related to greater sensitivity and specificity for finding a Gleason score of 6 in the postoperative evaluation.

A total of 177 radical prostate surgeries were performed within the 2010 to 2012 time frame. Seventeen patients diagnosed with prostate cancer through transurethral resection of the prostate, 8 whose histopathologic report did not include the number of positive cylinders, 5 patients that did not have a prostate biopsy report, 5 that were diagnosed with prostate cancer through retropubic adenectomy, 2 patients diagnosed with prostate adenocarcinoma through prostate biopsy but whose radical prostatectomy report was negative for malignancy, and 4 patients with incomplete case records, were all excluded from the present study.

A total of 136 patients were included in this study with the following demographic data:

- The mean age of the patients that underwent radical prostatectomy was 65.8 (n=136 with a SD of 6.8), with a minimum of 44 years and a maximum of 80.
- The most frequently reported age (mode) was 71 years (9.6% of the patient total). Age distribution was normal and skewed to the right (bias of -0.476 and standard error of 0.185) (fig. 3).
- The PSA value of patients that underwent radical prostatectomy was obtained for 134 patients, and of those, the mean concentration reported was 9.51 ng/dL (SD=5.3), the maximum value was 31.3 ng/dL, and the minimum value was 1.53 ng/dL.
- The waiting time for surgery (the time between the date of biopsy and prostatectomy) was a mean 96 days, with a minimum value of 15 days and a maximum of 511 days.
- The Gleason values of the total of 136 cases were reported. The mean and mode were the same, with a value of 6 points (range of 6 to 9), signifying that 68.4% of the patients reported a Gleason score of 6 points followed by 25.7% of the patients with a Gleason value of 7 points.

In the Gleason score evaluation after prostatectomy, the mean and mode values moved toward a score of 7. The minimum and maximum scores were 6 and 9, respectively. In other words, 45.6% of the cases were reported with a value of 7 and 44.1% with a value of 6.

The evaluation of the different histopathologic characteristics are shown in the following tables and figures. In regard to the number of biopsies with extraprostatic extension, more than half of the cases already presented with extraprostatic invasion (71 cases, 53.4%).
Correlation between the number of positive cores and extraprostatic disease in patients that underwent radical prostatectomy

The presence of invasion and extension was not specified in 3 cases (fig. 4) (table 1); there were also such cases when the current definition of extraprostatic disease that encompasses invasion into the seminal vesicles was considered (fig. 5) (table 2).

There was no vascular invasion in 70.6% of the biopsies, but the presence or absence of this histologic characteristic was not reported in 18.4% of the cases (table 3).

Perineural invasion was found in 72.8% of the biopsies and the presence or absence of this characteristic was not mentioned in 2 cases (table 4).

The seminal vesicles were free from invasion in 83% of the biopsy reports and this characteristic was not described in 3 of the reports (table 5).

The number of positive cores varied from 1 to 12, with a median of 2 positive cores. The most frequent finding was that of at least one positive core (36.8% of the cases) (fig. 6) (table 6).

The correlation between the different characteristics is shown, using the Spearman rho test as a contrast test.

The number of positive cores had a statistically significant positive correlation with extraprostatic extension (Spearman rho=0.344, \( p<0.0001 \)), as well as with the preoperative and postoperative prostatectomy values of the Gleason report (\( r=0.316 \) and \( r=0.249 \), with values of \( p=0.0001 \) and \( p=0.004 \), respectively). Likewise, the perineural invasion was statistically significant (Spearman rho=0.336, \( p<0.001 \)). There was no significant correlation with the seminal vesicles (rho=0.044, \( p=0.61 \)). Approximately 34% and 33% of the variability in the number of positive cores had a positive correlation with the number of positive cores and the presence of extraprostatic and perineural invasion, respectively. However no correlation was found between the number of positive cores and seminal vesicle invasion.

Discussion

In order to make prostate cancer diagnosis, cancerous tissue from the prostate must be obtained during biopsy or some other procedure, such as transurethral resection of the prostate or retropubic adenomectomy.

It is reported in the international medical literature that prostate cancer is not often diagnosed in men under 50 years of age, representing less than 0.1% of all patients. A patient in our service was diagnosed at the age of 44 years. The literature also mentions an incidence peak at 70 and 74 years of age and that 85% of the patients are diagnosed after 65 years of age; the mean age of our patients at the Hospital Central Militar was 65 years.

Transrectal ultrasound of the prostate was first described in 1968 and now is used systematically in clinical practice, with the advances in ultrasound technology and its introduction into the protocols of systemic ultrasound-guided sextant biopsy. The simultaneous improvement in biopsy techniques and systemic PSA detection has resulted in an increased number of men undergoing early prostate cancer detection and prostate biopsy. Given the prevalence of prostate cancer and the frequency with which transrectal ultrasound-guided prostate biopsy is performed, much effort has been put into determining the appropriate indications for biopsy and the ideal imaging and biopsy technique. The advent of TRUS-guided prostate biopsy revolutionized the techniques involved in prostate cancer detection and has tremendously increased the diagnostic accuracy of prostate biopsy.

The use of PSA added to TRUS-guided prostate biopsy has led to a descending anatomopathologic stage migration as
demonstrated by the increased incidence of organ-confined disease in radical prostatectomy.

In the developed countries like the United States, overall 5-year survival is above 80% due to early disease detection that enables potentially curative treatments like radical prostatectomy to be offered. Nevertheless, the mid and long-term outcome of patients that undergo surgical treatment is definitely dependent on adequate patient selection in relation to pathologic stage and grade prior to surgery. The curative potential of surgical treatment is greater when the tumor is organ-confined. Clinical stage prior to prostate adenocarcinoma treatment is important because of the increase in the use of nonsurgical treatment options offered to cancer patients. Therefore, our study focused on determining the correlation between the pretreatment variable that was the number of positive cores in prostate biopsy and the presence of extraprostatic disease.

The results of numerous publications describing the presence of extraprostatic disease in patients that underwent radical prostatectomy (47%) are similar to those of our institution (53%). It should be mentioned that the mean PSA of the patients was 9.5 ng/mL, corresponding to a low-risk study (only taking the PSA value into account), which could equate our study results with those of published studies. Our results showed a positive correlation for the number of positive cores in prostate biopsy and the presence of extraprostatic disease.

<table>
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<tr>
<th>Table 1</th>
<th>The presence of extraprostatic disease in the total population</th>
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<th>The presence of extraprostatic disease in the total population (including seminal vesicles)</th>
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<tbody>
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<td>Extraprostatic extension</td>
<td>Quantity</td>
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<tr>
<td>Absent</td>
<td>58</td>
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<tr>
<td>Present</td>
<td>72</td>
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<tr>
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<th>Table 3</th>
<th>Presence of vascular invasion in the total population</th>
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<td>Seminal vesicle invasion</td>
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Conclusions

At the end of the present study, there was a correlation between the number of positive prostate adenocarcinoma cores and the presence of extraprostatic disease; a higher number of positive cores resulted in a greater probability of extraprostatic disease. Data were also obtained in relation to the number of patients that underwent radical prostatectomy at our service and that presented with extraprostatic disease, making them candidates for receiving adjuvant radiotherapy. These results are the same as those that have been established internationally.

The above can serve as a basis for further prevalence studies from which nomograms adapted to the Mexican population can be elaborated so that a higher rate of “curative” radical prostatectomy as definitive treatment can be achieved and the surgical morbidity of those patients with extraprostatic extension can be eliminated.

Conflict of interest

The authors declare that there is no conflict of interest.

Financial disclosure

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References