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ANALYSIS OF RISK FACTORS OF INVOLVEMENT OF SEMINAL VESICLES IN PATIENTS WITH PROSTATE CANCER UNDERGOING RADICAL PROSTATECTOMY

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ABSTRACT

Objective: To determine through preoperative serum PSA level, Gleason score on biopsy and percentage of fragments affected by tumor on biopsy, the probability of involvement of the seminal vesicles.

Materials and Methods: During the period between March 1991 to December 2002, we selected 899 patients undergoing radical prostatectomy for treatment of localized prostate adenocarcinoma. The analyzed preoperative variables were PSA, percentage of positive fragments and Gleason score on the biopsy. Pre-operative PSA was divided in scales from 0 to 4.0 ng/mL, 4.1 to 10 ng/mL, 10.1 to 20 ng/mL and > 20 ng/mL, Gleason score was categorized in scales from 2 to 6. 7 and 8 to 10, and the percentage of affected fragments was divided in 0 to 25%, 25.1% to 50%, 50.1% to 75%, and 75.1% to 100%. All these variables were correlated with the involvement of seminal vesicles in the surgical specimen.

Results: Of the 899 patients under study, approximately 11% (95% CI, [9% - 13%]) had involvement of seminal vesicles. On the multivariate analysis, when PSA was ≤ 4, the Gleason score was 2 to 6, and less than 25% of fragments were involved on the biopsy, only 3.6%, 7.6% and 6.2% of patients respectively, had involvement of seminal vesicles. On the multivariate analysis, we observed that PSA, Gleason score and the percentage of involved fragments were independent prognostic factors for invasion of seminal vesicles.

Conclusion: The preoperative variables used in the present study allow the identification of men with minimal risk (lower than 5%) if involvement of seminal vesicles.

Key words: prostatic neoplasms; neoplasm staging; prostate-specific antigen; biopsy; seminal vesicle
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INTRODUCTION

Radical prostatectomy (RP) is the most effective approach for treating localized prostate cancer (PCa) (1). However, almost 30% of patients will present biochemical recurrence of the disease on the long term (2). The involvement of seminal vesicles constitutes one of the main prognostic factors following RP (2-4), since these patients present higher incidence of lymph nodal metastases and rates of biochemical recurrence in up to 60% of cases within 5 years (3,4). Moreover, (6 to 26%) of patients undergoing RP have involvement of the seminal vesicles (4,5), and for all these reasons, since its original de-

scription in 1905 by Young (6), the classic technique of retropubic RP involves the en-bloc removal of all prostate and seminal vesicles.

With the advent of the prostate specific antigen (PSA), the majority of patients are diagnosed in early stages of disease, and currently more than 60% are classified as T1c (7). Thus, less frequently patients undergoing RP present involvement of seminal vesicles, and their resection may be unnecessary in more than 90% of cases (5).

Since the removal of the seminal vesicles can be technically difficult in some cases, increasing the surgical time and blood loss, and their removal can exert some influence on the erectile function and recovery of urinary continence, in many patients (3,8,9), the preoperative identification of cases with low risk of involvement of seminal vesicles might select cases for surgery with preservation of seminal vesicles, improving the quality of life of these patients following the surgery.

Since digital rectal examination of the prostate, imaging studies, and biopsy of the seminal vesicles fail to detect the involvement of seminal vesicles in patients with localized PCa (3), the preoperative prognostic factors more commonly used for predicting tumor extension are PSA, Gleason score and clinical staging (7). Recently, some authors proposed that in patients with PSA lower than to 10.0 ng/mL, when the Gleason score was lower than 7 or less than 50% of fragments were involved, there would be a risk of involvement of seminal vesicles lower than 5%, and they could be preserved during RP (5).

In the present study, the objective was to assess the probability of involvement of seminal vesicles using preoperative PSA, Gleason score and the percentage of positive fragments on prostate biopsy.

MATERIALS AND METHODS

During the period from March 1991 to December 2002, we selected 960 patients undergoing RP for management of localized PCa at Syrian Lebanese Hospital, São Paulo, Brazil. The same surgeon performed all procedures and the same pathologist performed the pathologic analyses of the specimen.

Data from the 960 selected patients, as well as the number of fragments removed on biopsy, the number of fragments with cancer, Gleason score, PSA and the pathological study of the surgical specimen were retrieved from our database.

We excluded 54 patients who received neoadjuvant treatment and 7 who were diagnosed through endoscopic resection of the prostate or transvesical prostatectomy, leaving a total of 899 patients. All patients underwent clinical staging, using the TNM classification (AJCC, 1992), using diagnostic testes that included dosage of serum PSA, digital rectal examination, transrectal prostate biopsy, abdominal and pelvic computerized tomography, bone scintigraphy and chest radiography.

Preoperative variables analyzed were PSA, the percentage of positive fragments and Gleason score on biopsy. Preoperative PSA was categorized in scales from 0 to 4.0 ng/mL, 4.1 to 10 ng/mL, 10.1 to 20 ng/mL and > 20 ng/mL, and the Gleason score was divided in scales from 2 to 6. 7 and 8 to 10. The percentage of positive fragments was defined as the number of fragments with cancer divided by the total number of fragments on biopsy, divided in ranges from 0 to 25%, 25.1% to 50%, 50.1% to 75%, 75.1% to 100%. All these variables were related to the involvement of the seminal vesicles in the surgical specimen.

Mean age was 62.8 ± 7.4 years (ranging from 40 to 83 years). Mean PSA was 10.1 ± 7.7 ng/mL (ranging from 0.3 to 72 ng/mL). In relation to the clinical stage, 432 (48%) patients were classified as T1c, 219 (24%) as T2a, 173 (19.3%) as T2b, 68 (7.6%) as T2c and 7 (0.8%) as T3a. The mean percentage of affected fragments was 41% ± 24% (ranging from 5% to 100%). Mean Gleason score on biopsy was 5.8 ± 1.3, ranging from 2 to 9.

RP specimens (prostate, seminal vesicles and obturator lymph nodes) were fixed, in average during 6 hours, in 10% formalin and underwent a routine consisting of measurement and weighting of the gland in a digital balance sensitive to 2 decimal places. Thin transversal sections were made on the surgical margins relative to the bladder neck and prostate apex. Considering the urethra for reference, the remaining gland, after its margins had been stained with India

ink, were sequentially sliced at each 3 millimeters. Eight to 10 sections from each lobe were included for the histological study. The seminal vesicles were sectioned at the base, and were prepared for histological examination after longitudinal sectioning. The involvement of seminal vesicles was considered only when there was parenchymal invasion, without considering adventitial invasion.

Statistical assessment was performed through Pearson qui-square test and trend test for univariate analysis. For multivariate analysis, an approach of logistic regression was used. A significance level of 5% was adopted, thus, p values < 0.05 were considered statistically significant.

RESULTS

Of the 899 patients under study, approximately 11% (95% CI, 9% - 13%) had involvement of seminal vesicles. In relation to preoperative PSA, we observed that 9.3% (84) of the total of assessed patients presented levels lower or equal to 4.0 ng/mL. Table-1 shows the distribution of patients according to the involvement of seminal vesicles and preoperative PSA levels. The likelihood of presenting involvement of seminal vesicles increases according to the increase in preoperative serum PSA levels ($p < 0.001$).

Gleason score on biopsy showed association with the involvement of seminal vesicles as well ($p < 0.001$). Observing the Table-2 we verified that there is no statistically significant difference between the distribution of Gleason score 7 and 8 to 10 ($p = 0.994$), therefore we constructed a new category for scores between 7 to 10. According to the Table-3, approximately 8% of patients with Gleason score between 2 and 6 had involvement of seminal vesicles. On the other hand, among men with Gleason score between 7 and 10, 46 (19%) out of 245 had involvement of seminal vesicles.

The qui-square test showed a significant association between the percentage of affected fragments and involvement of seminal vesicles ($p < 0.001$). The Table-4 shows that as the percentage of affected fragments increase there is an increase in the

Table 1 – *Distribution of PSA levels according to the involvement of seminal vesicles (ISV).*

PSA (ng/mL)	Patients N (%)	With ISV N (%)	Without ISV N (%)
0 – 4.0	84 (9.3)	3 (3.6)	81 (96.4)
4.1 – 10.0	512 (57.0)	43 (8.4)	469 (91.6)
10.1 – 20.0	236 (26.3)	36 (15.2)	200 (84.8)
> 20.0	67 (7.4)	14 (20.9)	53 (79.1)
Total	899 (100.0)	96 (10.7)	803 (89.3)

Table 2 – *Distribution of Gleason score according to the involvement of seminal vesicles (ISV).*

Gleason Score	Patients N (%)	With ISV N (%)	Without ISV N (%)
2 to 6	654 (72.8)	50 (7.6)	604 (92.4)
7	165 (18.3)	31 (18.8)	134 (81.2)
8 to 10	80 (8.9)	15 (18.7)	65 (81.3)
Total	899 (100.0)	96 (10.7)	803 (89.3)

Table 3 – *Distribution of grade according to the involvement of seminal vesicles (ISV).*

Gleason Score	Patients N (%)	With ISV N (%)	Without ISV N (%)
2 to 6	654 (72.8)	50 (7.6)	604 (92.4)
7 to 10	245 (27.2)	46 (18.8)	199 (81.2)
Total	899 (100.0)	96 (10.7)	803 (89.3)

Table 4 – *Distribution of percentage of positive fragments according to the involvement of seminal vesicles (ISV).*

Percentage	Patients N (%)	With ISV N (%)	Without ISV N (%)
0 to 25%	290 (32.3)	18 (6.2)	272 (93.8)
25.1 to 50%	393 (43.7)	37 (9.4)	356 (90.6)
50.1 to 75%	134 (14.9)	18 (13.4)	116 (86.6)
75.1 to 100%	82 (9.1)	23 (28.1)	59 (71.9)
Total	899 (100.0)	96 (10.7)	803 (89.3)

proportion of patients with involvement of seminal vesicles ($p < 0.001$).

PSA levels, Gleason score and the percentage of positive fragments contributed significantly for predicting the involvement of seminal vesicles in logistic regression ($p < 0.001$). All second- and third-order interactions were tested and shown to be non significant ($p > 0.05$). Thus, the final model included only the main effects, which were shown to be independent prognostic factors for involvement of seminal vesicles.

The figures presented in each cell of Table-5 represent the probability of involvement of seminal vesicles based on logistic regression with PSA, Gleason score and percentage of affected fragments. For example, a man with PSA lower than or equal to 4.0 ng/mL, percentage of affected fragments up to 75% and Gleason score between 2 and 6 has a chance of less than 5% of presenting involvement of seminal vesicles. The same risk is observed for men with PSA lower than or equal to 10 ng/mL, percentage of affected fragments up to 25% and Gleason score of 6. On the other hand, men with PSA higher than 10 ng/mL, more than 75% of affected fragments and Gleason score above 6 have a risk higher than 40% of presenting involvement of seminal vesicles.

COMMENTS

In the present study, the authors demonstrated that in earlier cases, the involvement of seminal vesicles is uncommon, and this probability can be determined through the studied variables. Thus, in univariate analysis, when PSA is ≤ 4, Gleason score is between 2 to 6 and less than 25% of biopsy fragments are involved, only 3.6%, 7.6% and 6.2% of patients respectively, will have involvement of seminal vesicles.

Among advantages reported in the literature concerning the preservation of seminal vesicles is the improvement in urinary continence and postoperative sexual potency (8,9). Additionally, some cases present technical difficulties during the resection, increasing surgical time and blood loss (3).

Rates of post-RP urinary continence decreased with the increasing anatomic knowledge on

Table 5 *– Prediction of involvement of seminal vesicles according to PSA, grade and percentage of fragments involved by the tumor.*

	Grade 2 to 6				Grade 7				Grade 8 to 10			
	PSA	**PSA**	**PSA**	**PSA**	**PSA**	**PSA**	**PSA**	**PSA**	**PSA**	**PSA**	**PSA**	**PSA**
Percentage	0 to 4	4.1 to 10	10.1 to 20	≥ 20	0 to 4	4.1 to 10	10.1 to 20	≥ 20	0 to 4	4.1 to 10	10.1 to 20	≥ 20
0 to 25%	2	4	7	10	5	10	17	22	5	10	17	...
25.1 to 50.0%	3	6	10	13	7	14	23	28	6	13	22	27
50.1 to 75%	3	7	12	16	8	16	26	32	x	16	25	31
75.1 to 100%	7	15	24	30	17	31	45	53	x	30	44	51

Note: The figures represent the predicted probability as a percentage. x = insufficient data for estimating probability.

neurovascular bundles. Moreover, better technical improvement, especially during dissection of the prostate apex, has enabled better preservation of the extrinsic sphincteric muscles (10). Despite these advances, urinary incontinence continues to impair the quality of life of some patients, and can reach 60% during the first 6 months after surgery (10).

Accurate surgical measures that influence post-RP urinary continence are not fully understood, and recent studies suggest that trigone innervation and posterior urethral sensitivity play an important role in continence during the immediate postoperative period (8). These nerve branches can be damaged during dissection of the prostate, posterior aspect of bladder and seminal vesicles, contributing for sphincteric incompetence (8). Thus, the preservation of seminal vesicles would prevent traction and damage to such structures, improving immediate postoperative continence.

Jonh et al. (8) studied the urinary continence in 20 patients undergoing RP with preservation of seminal vesicles and compared their results to other 34 patients undergoing classic RP. They observed that in the group with preservation of seminal vesicles, the continence rates at 6 weeks and 6 months following surgery were 60% and 95% respectively, versus 18% and 82% during the same periods for the group undergoing classic surgery.

The removal of seminal vesicles during RP is also partially implied as a cause of erectile dysfunction in many patients (3,8). Sexual function can be affected after RP despite the use of techniques that preserve the neurovascular bundles, showing that other mechanisms are involved in this process. The close relationship between the seminal vesicles and the lateral prostate pedicles, with penile blood supply and their own neurovascular bundles, suggest that the resection of the seminal vesicles can actually contribute for postoperative erectile dysfunction (5). Studies on sexual function with patients undergoing RP techniques with preservation of the seminal vesicles show a clear advantage when compared with patients undergoing classic RP. In a series of 191 patients that were prospectively assessed, the authors observed that sexual health in relation to the quality of life was significantly better in patients with preservation of seminal vesicles when compared with patients undergoing classic surgery (9).

In addition to these factors, the low frequency of PCa invasion to the seminal vesicles often makes their removal unnecessary. One study assessing the surgical specimens from 71 consecutive patients undergoing RP, found 12 cases (17%) of involvement of seminal vesicles, with 5 bilateral cases, but in none of theses cases the tumor had spread to the distal 1 cm of seminal vesicles. The authors comment that in cases of technical difficulty, even if a small fragment of seminal vesicles is not removed, the patient's prognosis probably will not change (11).

Thus, it is clear that preoperative identification of patients with involvement of seminal vesicles, in addition to being an important factor for staging and prognosis, can help to select cases for preservation of the seminal vesicles. In patients with localized PCa, imaging studies have limited accuracy and the biopsies of seminal vesicles have negative, posi-

tive predictive value and sensitivity of only 84 to 97%, 80% and 67% respectively (3). Thus it is necessary to identify risk factors for involvement of seminal vesicles, with main preoperative prognostic factors and serum PSA levels, Gleason score on biopsy and clinical staging (7).

The percentage of positive fragments on biopsy is associated with pathological characteristics, biochemical progression, distant metastases and overall survival in patients undergoing RP. Recent works show that this parameter must be used in preoperative models for predicting the prognosis (12). Peller et al. (13), while studying the usefulness of transrectal prostate biopsy for determining tumor extension of PCa in 102 patients undergoing RP, observed that the number of positive fragments was correlated with the involvement of seminal vesicles. Thus, when up to 50% or fragments were affected, only 10% presented involvement, versus 57% when more than 50% of fragments were affected (13). The present study demonstrated that similarly, when no more than 50% of fragments are affected, the risk of involvement of seminal vesicles is 10%, however when more than 50% of fragments are affected, such risk is superior to 28%.

The presence of positive fragments removed from the prostate base is also correlated with involvement of seminal vesicles. In a study with 763 patients with clinical stage T1c to T3 undergoing RP, 437 patients presented positive fragments at the base and 12.8% of those had involvement of seminal vesicles, versus only 1.2% of 326 patients without PCa at the base. On the multivariate analysis, serum PSA, primary Gleason grade, and the percentage of PCa at the base were the only prognostic factors implied in the involvement of seminal vesicles (3).

Zlotta et al. (5), in a retrospective study with 1238 patients, observed that when PSA was < 10.0 ng/mL, only 5.2% had involvement of seminal vesicles. On the multivariate analysis, the percentage of affected fragments on biopsy and Gleason score were predictive factors for involvement of seminal vesicles in this group of patients. Thus, in patients with PSA < 10.0 ng/mL, when the Gleason score was < 7 or less than 50% of the fragments were involved, there was a risk lower than 5% of involvement of seminal vesicles. In the present series, when the PSA was ≤ 10 ng/mL, we observed an 8.4% risk of involvement of seminal vesicles on univariate analysis. On the multivariate analysis we observed only 2 situations where the risk of involvement of seminal vesicles was lower than 5%, that is, PSA up to 4 ng/mL with a maximum of 75% of fragments affected by tumor and Gleason score lower than or equal to 6, and PSA under 10 ng/mL with up to 25% of fragments affected and Gleason score of 6 at a maximum. In no case with more than 75% of affected fragments or Gleason score higher than 6, there was a risk lower than 5% for involvement of seminal vesicles.

Since we still do not know the long-term effects of preserving the seminal vesicles, in the future this study could help to create study protocols that enable their preservation. The authors still recommend en-bloc removal of the seminal vesicles during RP however, in selected cases presenting the parameters mentioned above, non-removal of the entire seminal vesicles probably will not impair patients' prognosis due to the low risk for their involvement.

Adriana Sañudo performed the statistical analysis

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