The impact of positive vas deferens in the biochemical relapse in patients with stage T3b prostate cancer submitted

O impacto do acometimento dos ductos deferentes na recidiva bioquímica em pacientes com neoplasia de próstata estádio T3b submetidos a prostatectomia radical

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ABSTRACT
The study aimed to evaluate the influence of invasion of the vas deferens and seminal vesicles in patients undergoing radical prostatectomy for stage T3b tumor on biochemical recurrence.

Methods: Retrospective analysis of 53 patients submitted to radical prostatectomy with anatomopathological stage T3b, at Hospital de Clínicas da Unicamp, between 1997 and 2014. After exclusion criteria were applied, statistical analysis of 32 participants separated into 2 groups, in which 20 patients (62.5%) without involvement of the vas deferens (group 1) and 12 (37.5%) with invasion of the vas deferens (group 2). Biochemical recurrence was defined as an increase in prostate specific antigen (PSA) greater than or equal to 0.2 ng/ml after surgery.

Results: Regarding the disease-free survival analysis, group 2 has a 3.05 times greater risk of having a biochemical recurrence compared to group 1 (HR 3.05, 95% CI 1.12-8.32, p=0.03), calculated by regression of Cox and Log Rank test.

Conclusion: In conclusion, this study has identified an elevated risk of biochemical recurrence in patients with both ductus deferens and seminal vesicle invasion.

Keywords: vas deferens, radical prostatectomy, biochemical relapse.

1 INTRODUCTION
Prostate cancer (CAP), has been under constant study for improvements in diagnosing and controlling the disease. Understanding the etiological and anatomopathological aspects of
the tumor, as well as prognostic factors, determines medical follow-up and can potentially alter therapeutic strategies (HSING; CHOKKALINGAM, 2006).

With the rise of early diagnosis, the frequency of seminal vesicle involvement has been observed to be no more than 10-15% in specimens from radical prostatectomy (RP), a trend noticed over the years. The involvement of seminal vesicles is linked to higher rates of biochemical recurrence, distant metastases, and cancer-specific mortality (GRÖNBERG, 2003; PARKIN; BRAY; DEVESA, 2001). On the other hand, the vas deferens is connected bilaterally to the seminal vesicles and should also be considered an independent organ apart from the prostate and seminal vesicles themselves. Moreover, this duct possesses a more substantial muscular layer compared to the seminal vesicles, rendering it more resistant to tumor invasion. When affected, it could signify a more aggressive behavior of the cancer (BRAND et al., 2006).

However, it remains unclear whether invasion of the ductus deferens is linked to a worse prognosis when associated with seminal vesicle invasion (GRÖNBERG, 2003). The primary objective of this study is to analyze the influence of vas deferens invasion in patients submitted to RP due to tumor stage T3b, in terms of biochemical recurrence, when compared to patients with invasion-free vas deferens.

2 MATERIALS AND METHODS

Inclusion criteria in the study were patients submitted to RP at Hospital de Clínicas da Unicamp diagnosed with CaP and involvement of seminal vesicles confirmed by anatomopathological examination, maintained under postoperative outpatient followup. Exclusion criteria were patients submitted to RP with a diagnosis of CaP, without involvement of the seminal vesicles confirmed by the anatomopathological, patients with no relevant information in the file of medical records, patients whose surgical anatomopathological specimens were not accessible for eventual review and patients who did not have PSA levels below 0.2 ng/ml after surgery or those with no postoperative PSA levels.

After retrospective analysis of medical records and application of inclusion criteria, participants were divided into two groups for statistical evaluation: without involvement of the vas deferens (group 1) and with involvement of the vas deferens (group 2).

A positive surgical margin was defined when neoplastic cells were in contact with Indian ink on the surface of the specimen. Extraprostatic extension was diagnosed when the carcinoma invaded the periprostatic adipose tissue. There was invasion of the seminal vesicle or vas deferens when the neoplastic tissue invaded the muscular layer. Biochemical recurrence
was defined as an increase in PSA greater or equal to 0.2 ng/ml after RP (PARKIN; BRAY; DEVESA, 2001).

In the descriptive analysis, continuous variables were expressed in terms of summary measures: mean, median, standard deviation and quartiles. Categorical variables were expressed in terms of percentages. For the comparison of two groups in the continuous variables, the t test was used in those in which the assumption of normality was previously met by the Anderson-Darling test. In the variables where this assumption was not met, Bartlett's test was used for the homogeneity of variances. Then, the nonparametric tests of Mann-Whitney and Brunner-Munzel were used, respectively, for the variables of homogeneous variances and heterogeneous variances. For comparison of categorical variables, Fisher's exact test or chi-square test was used. Survival analysis for recurrence was performed using Cox regression and it was possible to calculate the Relative Risk (RR) between groups and using the Kaplan-Meier curve in conjunction with the LogRank test. The significance level adopted was 5%.

3 RESULTS

Fifty-three medical records of patients who underwent RP with anatomopathological stage T3b at the Unicamp Hospital de Clínicas between 1997 and 2014 were reviewed. Of the total, 8 were excluded due to lack of information about the anatomopathological analysis of the surgical specimen. Another 13 patients were excluded because they did not reach a postoperative PSA dosage lower than 0.2 ng/ml, making it impossible to assess biochemical recurrence, totaling 32 participating patients. Of these, 20 (62.5%) had no involvement of the vas deferens (group 1), while 12 (37.5%) had invasion of the vas deferens (group 2). Epidemiological differences were evaluated in groups 1 and 2 and are demonstrated in Table 1.
Table 1: Epidemiological differences of the groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group</th>
<th>Average</th>
<th>Standard Deviation</th>
<th>Median</th>
<th>Number</th>
<th>P Value</th>
<th>Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1</td>
<td>64.85</td>
<td>5.69649</td>
<td>64</td>
<td>20</td>
<td>0.339</td>
<td>Mann-Whitney Test</td>
</tr>
<tr>
<td>Age</td>
<td>2</td>
<td>62.3833</td>
<td>7.35414</td>
<td>62</td>
<td>12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Max PSA</td>
<td>1</td>
<td>0.2359</td>
<td>0.52523</td>
<td>0.07</td>
<td>20</td>
<td>0.143</td>
<td>Mann-Whitney Test</td>
</tr>
<tr>
<td>Max PSA</td>
<td>2</td>
<td>0.41833</td>
<td>0.56048</td>
<td>0.24</td>
<td>12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSA nadir</td>
<td>1</td>
<td>0.03025</td>
<td>0.03563</td>
<td>0.01</td>
<td>20</td>
<td>0.375</td>
<td>Mann-Whitney Test</td>
</tr>
<tr>
<td>PSA nadir</td>
<td>2</td>
<td>0.13842</td>
<td>0.33781</td>
<td>0.035</td>
<td>12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre operative PSA</td>
<td>1</td>
<td>14.5075</td>
<td>10.33339</td>
<td>12.06</td>
<td>20</td>
<td>0.627</td>
<td>Mann-Whitney Test</td>
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<tr>
<td>Pre operative PSA</td>
<td>2</td>
<td>14.47833</td>
<td>7.59088</td>
<td>12.35</td>
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<td></td>
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<tr>
<td>Time of Follow up</td>
<td>1</td>
<td>50.9</td>
<td>41.10052</td>
<td>44</td>
<td>20</td>
<td>0.119</td>
<td>Mann-Whitney Test</td>
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<tr>
<td>Time of Follow up</td>
<td>2</td>
<td>28.25</td>
<td>29.40972</td>
<td>17.5</td>
<td>12</td>
<td></td>
<td></td>
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<td>Time until Recurrence</td>
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<td>50.4</td>
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<td>46.5</td>
<td>20</td>
<td>0.243</td>
<td>Mann-Whitney Test</td>
</tr>
<tr>
<td>Time until Recurrence</td>
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<td>27.5833</td>
<td>27.86154</td>
<td>15.5</td>
<td>12</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Source: Author

Regarding the disease-free survival analysis, group 2 has a 3.05 times greater risk of having a biochemical recurrence compared to group 1 (HR 3.05, 95% CI 1.12-8.32, p=0.03), calculated by regression of Cox and Log Rank test.

In relation to the positive margins, 11 patients (55%) in group 1 and 9 patients (75%) in group 2 were compromised. In comparison to free margins, group 1 presented 9 patients (45%) while group 2 presented 3 patients (25%). The statistical analysis in both groups showed p value equal to 0.452 by Fisher's Exact Test.

The biochemical recurrence estimated by the Kaplan-Meier method (Figure 1) and Cox (Figure 2) regression showed that the group with involvement of the vas deferens presented a recurrence of 50% around 25 months of postoperative follow-up, reaching practically 100% of recurrence after 110 months. Meanwhile, the unaffected group had the same percentage of 50%.
relapse in the study patients only after 60 months, without disease progression until the end of the follow-up at 150 months.

Figure 1. Kaplan-Meier curve (axis x= time in months, axis y= biochemical recurrence)

Figure 2. Cox survival curve (axis x= time in months, axis y= biochemical recurrence)
In figure 2, similarly to the previous curve, shows that biochemical recurrence in group 1 affects 50% of patients around 25 months of postoperative follow-up, progressing to 90% of the group in the 100-month analysis. Group 2, on the other hand, achieves disease-free survival in 50% of patients after 60 months, without biochemical recurrence until the end of the analysis at 150 months, under p value 0.03.

4 DISCUSSION

It is a consensus that the involvement of the seminal vesicle by CaP is associated with a worse prognosis, higher risk of recurrence, and is used in the staging of the tumor (BORRE et al., 2011). The vas deferens, despite its proximity to the prostate and seminal vesicle, has been neglected in many anatomopathological analyses and staging, and its evaluation by the pathologist is not mandatory, according to the consensus of the International Society of Urological Pathology (KOTB; ELABBADY, 2011). Consequently, few studies have analyzed the influence of invasion of the vas deferens on the prognosis of CaP (ISHIZAKI et al., 2012).

The mechanism of seminal vesicle invasion can be classified into 3 different routes: direct invasion by extracapsular extension of the tumor by extraprostatic tissue; invasion following the ejaculatory duct; distant metastasis. The most important and most common route of invasion is by extraprostatic extension of the tumor, with invasion of the seminal vesicle wall (KWAST et al., 2011).

We can infer that the most likely route of invasion of the vas deferens is also by the same mechanism. The finding of invasion of the vas deferens and concomitant ipsilateral seminal vesicle and the absence of cases of contralateral seminal vesicle and vas deferens strengthens this theory. Furthermore, the fact that the vas deferens has a more exuberant external covering, when compared to the seminal vesicle, makes it necessary to have a tumor with more aggressive characteristics to be able to invade it, explaining the worse prognosis and earlier biochemical recurrence in these cases (ISHIZAKI et al., 2012).

Although few studies have evaluated the impact of vas deferens involvement on the prognosis and aggressiveness of CaP, Jang et al. (2017) shows a higher frequency of biochemical recurrence in patients with involvement of the vas deferens (25.1 vs 17.1%) in a study of considerable impact due to the number of patients involved and few epidemiological differences between the groups with and without involvement of the vas deferens, in addition to post-treatment follow-up more extensive and homogeneous (ISHIZAKI et al., 2012).

In the present study, it was possible to show by the methods of Cox and Log Rank that the group with involvement of the ductus deferens has a statistically significant relative risk of
major biochemical recurrence when compared to the group with free vas deferens (HR 3.05, 95% CI 1.12-8.32, p=0.03). This finding may be biased by the fact that group 2 has a higher percentage of patients with compromised margins when compared to group 1, although the difference is not significant (p 0.452).

By analyzing the biochemical recurrence graphs obtained using the Kaplan-Meier and Cox methods, we can see a clear difference between the two curves, reinforcing the study's hypothesis that impairment of the vas deferens reflects a worse survival and prognosis for cancer patients. (FREEDLAND et al., 2004).

Findings show the clinical significance of vas deferens invasion as a complementary diagnostic marker to seminal vesicle invasion. When present, it may show a more aggressive tumor phenotype. Recognizing this association has the potential to inform more tailored approaches to assessment and treatment for prostate cancer patients, with the aim of enhancing clinical outcomes and individualized therapeutic strategies.

In addition, the sample of participants limits the research, mainly due to the difficulty in analyzing the involvement of the vas deferens, since its verification by the pathologist is not mandatory and due to the patients who did not reach a PSA value below 0.2 ng/ml to enable assessment of biochemical recurrence (KOTB; ELABBADY, 2011; BERNEY et al., 2011). Therefore, more prospective studies are necessary in the future to confirm the relevance of deferens invasion.

5 CONCLUSION

In conclusion, this study has identified an elevated risk of biochemical recurrence in patients with both ductus deferens and seminal vesicle invasion.
REFERENCES


