**ORIGINAL ARTICLE**

**Comorbidity impact on superficial urothelial carcinoma of the bladder survival**


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**KEYWORDS**
- Bladder cancer;
- Diabetes mellitus;
- High blood pressure;
- Body mass index;
- Survival; Mexico.

**Abstract**

**Aims:** To analyze the impact of comorbidities (diabetes mellitus DM, high blood pressure HBP, obesity OB, and dyslipidemia DL) on the overall survival (OS) and recurrence-free survival (RFS) rates of superficial urothelial carcinoma of the bladder (UCB).

**Methods:** A retrospective study of 152 patients diagnosed with UCB was carried out. The clinical history of the patients was registered in a database, identifying the abovementioned comorbidities, and the OS and RFS of the patients with superficial tumors (pTa) were analyzed.

**Results:** Ninety-one patients with stage Ta disease were selected; the mean OS of the patients with pTa UCB with DM was 228.2 ± 31.9 months vs. 253.6 ± 14.1 in the non-diabetic patients, resulting in statistical significance (p=0.037). The RFS in patients with stage pTa UCB with a body mass index (BMI) ≥ 30 Kg/m² was 244.3 ± 19.5 months and in patients with a BMI < 30 Kg/m², it was 269.7 ± 18.0, with a statistically significant difference of p=0.042. The survival analysis in patients with high blood pressure and dyslipidemia did not show significant impact.

**Conclusions:** DM reduced the OS in this group of patients with superficial bladder tumors, and obesity (BMI > 30 Kg/m²) reduced the RFS.
Introduction

Bladder cancer is the 4th most frequent malignant tumor in men and the 9th in women. The mean age at the time of diagnosis for both sexes is 73 years. The most important risk factor for bladder urothelial cancer (BUC) is smoking and it is implicated in 50% of the cases in men and 30% in women. There are other comorbidities such as diabetes mellitus (DM), obesity (OB), high blood pressure (HBP), and dyslipidemia (DL) that have not shown a consistent association as risk factors for BUC. However, DM has been implicated as a risk factor for certain neoplasias, including liver, colon, and pancreatic cancers.

BUC is a heterogeneous disease that represents 5% of all diagnosed cancers. Eighty-five percent of BUC is in the form of disease confined to the mucosa (stage Ta and Tis) or submucosa (stage T1). The outcome of non-muscle invading disease is excellent and the estimated survival at 5 years is reported in some case series to reach 94%.

The aim of this study was to analyze the impact of the abovementioned comorbidities on the overall survival (OS) and recurrence-free survival (RFS) of superficial BUC (pTa).

Methods

We designed a historic cohort of 152 patients diagnosed with BUC at the Department of Urology in the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán. Patient selection was based on the histopathologic diagnosis of tissue obtained through transurethral resection of bladder tumor (TURBT). Those patients diagnosed with superficial tumor (pTa) were chosen. The patients were classified by nuclear grade and pathologic stage. OS and RFS were analyzed along with the following comorbidities: smoking (SM), OB, body mass index (BMI >30 Kg/m²), DL (cholesterol above 200 mg/dL and triglycerides above 150 mg/dL), HBP, and DM, previously diagnosed. Comorbidity data were taken from the clinical records (SM, OB, HBP, and DM) and the laboratory results (total cholesterol and triglycerides) obtained immediately prior to the TURBT were used to diagnose DL.

Survival analysis was done utilizing the Kaplan-Meier survival curves with the SPSS®, version 17.0 software (SPSS Inc., Chicago IL, USA). The log rank statistical test was used to identify differences. All values were considered to have statistical significance with a \( p \leq 0.05 \).

Results

The patient base included 152 patients from which 91 were selected with stage Ta disease. The mean age was 70.59 ± 9.2 years and the range was 31 to 108 years. Sixty-four (70.3%) of those patients were men and 27 (29.7%) were women. A total of 56.7% of the patients had a history of SM, 21.7% of DM, 58% of DL, 50.6% HBP, and 27.5% OB. Thirty-nine patients were classified according to nuclear grade as pTaG1, 24 as pTaG2, and 28 as pTaG3. The OS after TURBT was 272 ± 13 months and the RFS was 73.29 ± 10.43 months. Table 1 shows the OS and RFS analysis.

The mean OS of the patients presenting with stage Ta BUC and DM was 228.2 ± 31.9 months vs. 253.6 ± 14.1 in non-diabetics, being statistically significant (\( p=0.037 \)).

The RFS in the patients with stage pTa BUC that had a BMI ≥ 30 was 244.3 ± 19.5 months vs. 269.7 ± 18.0 in the patients with BMI < 30, with a statistically significant difference of \( p=0.042 \). The analysis of survival with hypertension arterial and dyslipidemia did not show significant impact.

Conclusión: La DM disminuye la SG en este grupo de pacientes con tumores vesicales superficiales, y la obesidad (IMC > 30 Kg/m²) disminuye la SLR.

Impacto de comorbididades en la supervivencia del cáncer urotelial vesical superficial

Resumen

Objetivo: Analizar el impacto de las comorbilidades (diabetes mellitus DM, hipertensión arterial HAS, obesity OB y dislipidemia DL) en la supervivencia global (SG) y libre de recurrencia (SLR) del cáncer urotelial vesical (CUC) superficial.

Material y métodos: Estudio retrospectivo de 152 pacientes con diagnóstico de CUC pTa, se registró el historial clínico en una base de datos, identificando a las comorbilidades antes mencionadas, y se analizó la SG y SLR de pacientes con tumores superficiales (pTa).

Resultados: Se seleccionaron 91 pacientes en estadío Ta. La SG media de los pacientes con CUC pTa con DM fue de 228.2 ± 31.9 meses vs. 253.6 ± 14.1 en no diabéticos, siendo estadísticamente significativo (\( p=0.037 \)).

La SLR en los pacientes con CUC pTa con índice de masa corporal (IMC) ≥ 30 Kg/m² fue de 244.3 ± 19.5 meses, y la de los pacientes con IMC < 30 Kg/m² fue de 269.7 ± 18.0, con diferencia estadísticamente significativa (\( p=0.042 \)). El análisis de supervivencia con hipertensión arterial y dislipidemia no mostró impacto significativo.

Conclusión: La DM disminuye la SG en este grupo de pacientes con tumores vesicales superficiales, y la obesidad (IMC > 30 Kg/m²) disminuye la SLR.
Discussion

The direct impact that age and certain comorbidities such as OB, DM, HBP, and DL have on OS and RFS in patients presenting with BUC has been described in numerous studies.

Different studies have reported that the high mortality from BUC in patients over 60 years of age is due to the abovementioned comorbidities, and DM stands out as the greater predictor for overall mortality.

Some studies, including a meta-analysis, have investigated the association between DM and the increase in mortality from BUC.

The use of insulin in patients with type 2 DM has been proposed as a malignant tumor growth promoter, thus explaining the increased risk for cancer in adults with DM. DM is characterized by a long subclinical period of hyperinsulinemia, in response to insulin resistance, which explains the increased risk for presenting with malignant tumors.

In our survival analysis, we found that DM was the comorbidity that had the greatest significant impact on OS ($p = 0.037$), coinciding with that described above.

![Survival curve](image)

**Figure 1 Diabetes Mellitus.**

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>Overall survival Mean (months)</th>
<th>CI</th>
<th>Recurrence-free survival Mean (months)</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BMI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 30</td>
<td>244.3±19.5</td>
<td>205.9-282.7</td>
<td>108.6±20.9</td>
<td>67.6-149.6</td>
</tr>
<tr>
<td>&lt; 30</td>
<td>269.7±18.0</td>
<td>234.4-305.0</td>
<td>58.4±10.90</td>
<td>37.0-79.9</td>
</tr>
<tr>
<td>Global</td>
<td>272.1±13.3</td>
<td>245.9-298.2</td>
<td>73.2±10.40</td>
<td>52.9-93.6</td>
</tr>
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<td><strong>Diabetes M.</strong></td>
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</tr>
<tr>
<td>(+)</td>
<td>228.2±31.9</td>
<td>165.5-290.8</td>
<td>87.3±21.7</td>
<td>44.6-129.9</td>
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<tr>
<td>(-)</td>
<td>253.6±14.1</td>
<td>225.9-281.2</td>
<td>73.3±12.8</td>
<td>48.1-98.5</td>
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<tr>
<td>Global</td>
<td>268.3±14.7</td>
<td>239.3-297.2</td>
<td>76.6±11.0</td>
<td>54.8-98.3</td>
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<tr>
<td><strong>Dyslipidemia</strong></td>
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<tr>
<td>(+)</td>
<td>256.6±20.1</td>
<td>217.1-296.1</td>
<td>83.4±14.8</td>
<td>54.2-112.50</td>
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<td>(-)</td>
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<td>194.0-207.9</td>
<td>72.1±16.7</td>
<td>39.9-105.00</td>
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<tr>
<td>Global</td>
<td>267.0±15.1</td>
<td>237.3-296.6</td>
<td>78.6±11.3</td>
<td>100.8-100.8</td>
</tr>
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<td><strong>Smoking</strong></td>
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<tr>
<td>(+)</td>
<td>273.6±18.1</td>
<td>238.1-309.1</td>
<td>72.7±13.0</td>
<td>47.1-98.2</td>
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<tr>
<td>(-)</td>
<td>190.8±12.0</td>
<td>167.2-214.3</td>
<td>50.2±7.90</td>
<td>34.6-65.8</td>
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<tr>
<td>Global</td>
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<td>245.1-298.0</td>
<td>74.1±10.5</td>
<td>53.4-94.9</td>
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<td><strong>High blood pressure</strong></td>
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<td>(+)</td>
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<td>50.3-116.8</td>
<td>83.6±16.9</td>
<td>50.3-116.8</td>
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<tr>
<td>Global</td>
<td>78.6±11.3</td>
<td>56.4-100.8</td>
<td>78.6±11.3</td>
<td>56.4-100.8</td>
</tr>
</tbody>
</table>

CI: Confidence interval; BMI: Body mass index.
HPB is another comorbidity that has been thought of as a predictor of risk for BUC and also mortality from the disease. Some studies have postulated HBP as a strong mortality predictor. Nevertheless, a recent prospective study did not find an association between HBP and cancer-specific mortality. There is still very limited scientific evidence sustaining the possible related effects of HBP and cancer. Different authors have proposed that HBP conditions an inflammatory state in the vascular endothelium with vascular smooth muscle proliferation. This could contribute to tumor development. In the present study, we found no significant impact of HBP on the OS and RFS of BUC.

Metabolic syndrome (MS) is one of the comorbidities that has a greater impact on the quality of life and mortality in patients with cancer. MS is an important public health problem that has been the subject of numerous studies, and its impact on BUC mortality is striking. A prospective study and smaller cohorts analyzed MS and its components separately and did not find an increase in BUC mortality. One of the components of MS is obesity, and one of its most important reference parameters is the BMI. In analyzing the effect of BMI on survival in our group of patients, we found that those with a BMI < 30 mg/Kg had greater RFS and thus we inferred that the difference in RFS in patients with a BMI ≥ 30 Kg/m² could be related to the influence of inflammatory factors on the nuclear differentiation of the tumor or could reflect a better general nutritional and functional status, especially in this age group. The role of obesity in carcinogenesis has been studied, confirming a proinflammatory state with cellular proliferation and alterations in cellular DNA. Some studies have reported finding no significant association between BMI and BUC, and one study reported a reduced risk. However, a recent cohort of 20,000 BUC cases reported a modestly increased risk in obese whites, but not in obese blacks. The role of BMI as a factor of impact on the development of cancer and survival has currently been investigated. A prospective study showed that adult patients above the age of 60 years with a BMI > 25 mg/kg², but < 30 mg/kg² had an increase in OS. It has been suggested that this benefit is a reflection of a good nutritional status. However, this association should be evaluated in other prospective studies. In addition, it has been proved that the BMI in adults over the age of 65 years cannot be regarded as a diagnostic parameter of nutritional status, due to the age-related morphologic changes in height that result in an over-evaluation of the BMI.

The high incidence of BUC recurrence and progression has an important impact on quality of life and survival. The present study is a preliminary analysis for future studies; its main limitation was its retrospective design and the small sample size that did not allow for conclusive results in the analysis of all the variables.

Conclusions

DM reduced the OS in patients with superficial BUC and obesity (BMI > 30mg/kg) reduced the RFS.

Conflict of interest

The authors declare that there is no conflict of interest.

Financial disclosure

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References


