

Evaluation of Prognostic Factors for Survival in Bladder Cancer

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Abstract

Carcinoma of the bladder is the second most common genitourinary malignancy and is associated with a heterogeneous clinical outcome. Prognostic assessment is essential for treatment decision-making, patient counseling, and determination of eligibility for clinical trials and could help in individualized treatment and follow up. A retrospective analysis of a single University Hospital was performed, through the electronic process of all patients undergoing radical cystectomy between January 2014 and January 2019 (5 years), to evaluate the influence of clinical and histopathological parameters on outcomes of patients with carcinoma of the bladder. Eighty-three (83) patients were analyzed. The following factors were evaluated: age, gender, smoking habits, comorbidities (Charlson Index), tumor stage, tumor differentiation, histological variant, necrosis, Lymphovascular/Perineural Invasion (LVI/PNI), concomitant Carcinoma *In Situ* (CIS), presence of lymph node metastasis, disease recurrence and performance of neoadjuvant chemotherapy. Of all the factors evaluated, a statistically significant relationship was observed between Overall Survival (OS) and tumor stage, presence of lymph node metastasis and disease recurrence. The small sample size may justify the non-association of other factors as predictive of survival. Prospective trials for better selection of patients are warranted.

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Received Date: 01 Jul 2020

Accepted Date: 24 Jul 2020

Published Date: 03 Aug 2020

Citation:

Barreira JV, Falcão G, Parmanande A, Pinheiro LC. Evaluation of Prognostic Factors for Survival in Bladder Cancer. *Clin Oncol.* 2020; 5: 1725.

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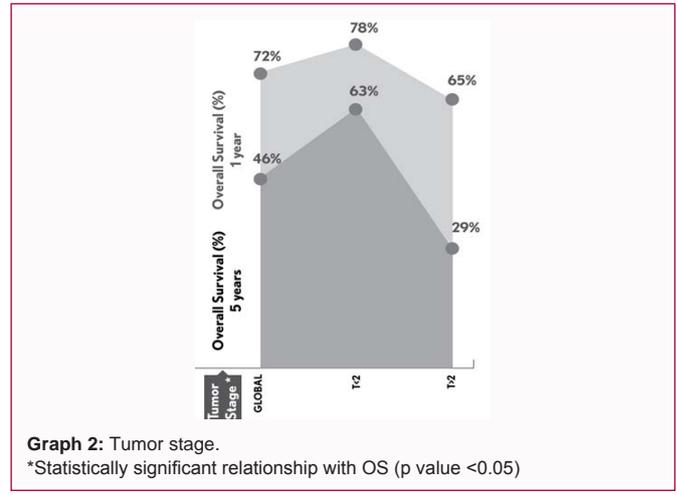
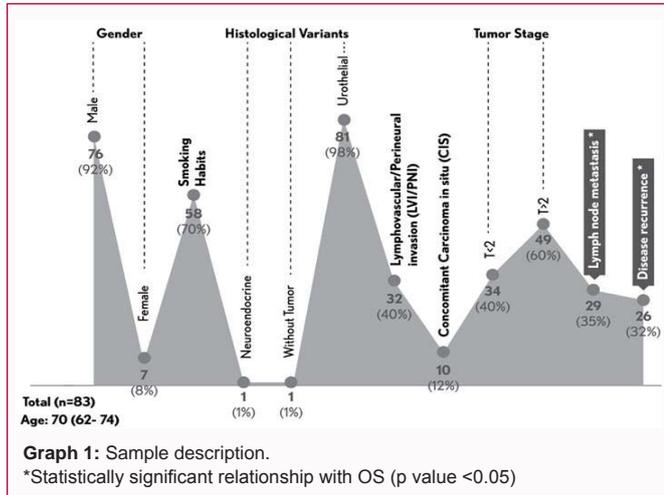
Introduction

Carcinoma of the bladder is the second most common genitourinary malignancy and is associated with a heterogeneous clinical outcome. Radical cystectomy with bilateral pelvic lymph node dissection is currently the gold standard treatment for muscle-invasive carcinoma of the bladder. Despite that, a significant proportion of patients develop disease recurrence. Several studies have evaluated the prognostic factors for survival after cystectomy.

Carcinoma of the bladder is considered to develop along two separate pathways. On the one side of the spectrum are the small solitary low-grade cancers (or LMPs) confined to the urothelium which typically do not pose a threat to patient's life, while on the other side are the high-grade muscle-invasive lesions that produce early metastases and cause death despite aggressive treatment. Several prognostic factors can be correlated to this behavior including histologic grade, the depth of penetration into the bladder wall (stage), the appearance of vascular/lymphatic invasion, and the presence of carcinoma *in situ*. Although clinically useful, histologic risk assessment is not a sufficiently sensitive discriminant in determining the specific biologic potential of a particular cancer.

It is essential to identify the tumor characteristics that allow an initial therapeutic decision and a follow-up plan, adjusting it to the risk of tumor progression and recurrence. The definition of prognostic factors is essential to define and stratify a therapeutic strategy. Prognostic factors are, then, any characteristic of the patient or tumor that can be used to predict the natural history of the tumor, in that patient, in terms of any previously chosen outcome, such as response to treatment, survival time. The most used factors are based on clinical and histological characteristics such as tumor size, histological grade, the presence of CIS, the previous existence of recurrences, tumor invasion and lymphovascular invasion.

Prognostic factors predict the natural course of an individual cancer, distinguishing good outcome tumors from poor outcome tumors. Prognostic factors are therefore particularly important at the time of initial diagnosis of malignancy and in cancers that vary widely in patients' outcome. Bladder cancer is a potentially curable malignancy; however, in regard to the state of current therapy regimens, a plateau has been reached in both the non-muscle and muscle invasive



types. To obtain effective treatment, and consequently a decreased mortality, it has become imperative to test and understand aspects affecting prognosis. Prognostic assessment is essential for treatment decision-making, patient counseling, and determination of eligibility for clinical trials and could help in individualized treatment and follow up [1-4].

Methods

With this study, we evaluated the influence of clinical and histopathological parameters on outcomes of patients with carcinoma of the bladder. A retrospective analysis was performed through the electronic process of all patients undergoing radical cystectomy between January 2014 and January 2019 (5 years). Demographic and clinical data was collected and the information cross-checked with that of the anatomic pathological and pharmaceutical services. The study was conducted at Centro Hospitalar Universitário de Lisboa Central (CHULC). The protocol was approved by the research ethics committee of CHULC.

Informed Consent was asked to patients that fulfill the inclusion criteria. All data was collected by the Principal Investigators (PIs) by accessing to the clinical registry, after the Informed consent being signed by the participant, and all ethical and legal warranties have been assured, in particular the approval by the Hospital Commission of Ethics for Health and compliance with the GDPR (General Data Protection Regulation), according with the European regulation 2016/679, from April 27th 2016, and Portuguese laws (Law 58/2019, from August 8th and Law 59/2019, from August 8th). Each participant data was, in first, codified by the PIs, who kept and guarded the file with the codes, in a safe place, with restriction on access. Data was recorded onto a database file prepared for this study, in a secure server, with restricted access by password. No identifying data was analyzed or published.

Inclusion criteria

Adult patients (18 years old or older), with histological diagnosis of carcinoma of the bladder, undergoing radical cystectomy between January 2014 and January 2019.

The data recorded with interest to this study was: Age, gender, smoking habits, comorbidities, tumor stage, tumor differentiation, histological variant, necrosis, Lymphovascular/Perineural Invasion (LVI/PNI), concomitant Carcinoma *in Situ* (CIS), presence of lymph node metastasis, disease recurrence and performance of neoadjuvant

chemotherapy.

Our specific aim was addressed via a combination of descriptive and analytic methods. Significance (p) of less than 0.05 was considered statistically significant. Univariate analysis with the Chi-Square test was performed, and statically significant parameters were then analyzed in a multivariate regression. Statistical analysis was performed in Stata.

Results and Conclusion

Eighty-three (83) patients with a mean age of 70 years were analyzed. About 90% of the patients were male. One year survival was 72% and five year survival was 46%. 52 patients were submitted to neoadjuvant treatment.

The following factors were evaluated: Age, gender, smoking habits, comorbidities (Charlson Index), tumor stage, tumor differentiation, histological variant, necrosis, Lymphovascular/Perineural Invasion (LVI/PNI), concomitant Carcinoma *in Situ* (CIS), presence of lymph node metastasis, disease recurrence and performance of neoadjuvant chemotherapy (Graph 1).

Of all the factors evaluated, tumor stage, presence of lymph node metastasis and disease recurrence were related to a poorer OS (p = 0.03 statistically significant relationship was observed between OS and tumor stage, presence of lymph node metastasis and disease recurrence) (Graph 1 and 2).

Invasive muscle tumors of the bladder and cystectomy are associated with high morbidity and mortality, and it is important to identify prognostic factors for a better treatment of this population. In this series of patients only presence of lymph node metastasis, disease recurrence and tumor stage were associated with higher mortality.

The prognostic factors used at present are insufficient to correctly characterize the evolution of bladder tumors. The implication of such factors will help in modification of treatment strategies to improve the prognosis of bladder cancer patients. The small sample size may justify the non-association of other factors as predictive of survival.

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