Univariate and Multivariate Analysis of Pathological Prognostic Factors of Urothelial Bladder Cancer in Patients Undergoing Radical Cystectomy and Lymphadenectomy

Endric Hasegawa, Marcos Francisco Dall’Oglio*, Daniel Kanda Abe, Emanoela Batista Feitosa, Alexandre Crippa, José Pontes Junior and Miguel Srougi

Abstract

Objective: To identify the most important pathologic prognostic factors for urothelial bladder cancer treated by radical cystectomy and pelvic lymphadenectomy in our institution. To analyze the impact of these factors on recurrence and mortality and suggest a group of factors that can predict the evolution after radical surgery.

Patients and methods: We review all cases of radical cystectomy and lymphadenectomy at the Clinical Hospital Medical School from 2006 to 2009. We study pathologic prognostic factors like tumor stage (pT), lympho-nodal metastasis (N+), lymphovascular invasion (LVI), perineural invasion (PNI) and presence of in situ carcinoma (CIS) and correlates with recurrence and mortality. The chi square, Fisher, log rank and cox regression models were used to determine the significance. We considered a significant association when p<0.05.

Results: From 166 cystectomies performed to treat urothelial bladder cancer, we selected 128 cases. There were 20 (15.6%) females and 108 (84.4%) males with ages ranging from 41 years to 84 years with an average 67 years old. Through univariate analyses, the recurrence was associated with tumor stage (pT) and lympho-nodal metastasis (N+) (p=0.032, p=0.003), but only the latter showed independence in multivariate analysis. (OR 3.2, p=0.003). The pT, N+, lymphovascular invasion (LVI) and perineural invasion (PNI) correlate with early general mortality. The univariate analysis presents the worst overall survival when PNI (p=0.01), pT > pT2 (p=0.001) and N+ (p=0.036). The Kaplan Meier curve found that pT>pT2, N+, LVI and PNI associated with reduced overall survival time. Specific survival time was influenced by pT>pT2 (p=0.001), LVI (p=0.038), N+ (p=0.034), and PNI (p=0.024). The multivariate analysis found that pT>pT2 is the most important prognostic factor associated with specific and overall survival (OR 4.44, p=0.002 and OR 4.28, p=0.001). The grouping of pT, N, LVI and PNI can easily and correct predict recurrence and mortality when compared with current nomograms.

Conclusion: The pathologic prognostic factors after radical cystectomy show that lymphatic metastasis (N+) has a strong association with recurrence and the tumor stage (pT) is a predictor for overall and specific survival. The combination of the factors pT, N, LVI and PNI can be compared to actual nomograms on evolution prediction.

Keywords: Cystectomy; Lymph node excision; Bladder cancer; Prognosis

Introduction

Bladder cancer is the seventh mostly common diagnosed tumor in men worldwide and 297,300 new cases predicted to this year [1]. According to the National Cancer Institute, 74,000 new cases are estimated for 2012 in the United States, in addition to 15,000 deaths ascribed to the disease within the same period [2]. In Brazil, bladder cancer is the tenth most frequent neoplasia in men with 6,210 predicted new cases for 2012 [3]. The most frequent histological type is urothelial carcinoma, found in 90% of the cases. Among these, 20-25% is found in its muscle-invasive form. These cases require radical cystectomy, regardless of improved knowledge about anatomy, surgical techniques, and mainly about post-operative care, the specific survival period remains on a 50-60% basis in years [4].

Estimating treatment efficacy is fundamental to advise patients of prognoses and indicate adjuvant therapies. Therefore, several prognosis-predictive factors have been recently investigated, they can be grouped into the following: clinical, molecular, and pathological this one is considered to be the most important [5]. The insufficiency of each pathological factor to be used isolatedly in prognosis prediction played an important role to stimulate the grouping, which gave origin to the nomograms [5-9]. The difficulty to obtain data standardization from diverse institutions and the regional differences found in neoplasia are reflected in many nomograms as well as the subsequent questioning over its actual usefulness [10,11]. Not many studies are available on urothelial cancer after radical cystectomy, so we noticed the urge to evaluate them and, afterwards, elaborate reliable methods to stratify recurrence as well as death risks.

Patients and Methods

We surveyed the retrospective analysis of medical files of all patients who underwent radical cystectomy and pelvic lymphadenectomy in the 2006-2009 period at the Clinical Hospital Medical School. We include all bladder urothelial carcinoma cases. The following exclusion factors were considered for this study: metastatic disease, palliative surgeries, non-urothelial carcinoma, patients under neoadjuvant therapy, and patients with insufficient medical records. Patients were evaluated during the postoperative period within 3-month intervals through laboratory and image tests. The upcoming of secondary lesions over

*Corresponding author: Marcos F Dall’Oglio, Rua Barata Ribeiro, 398-5 andar , CEP 01308-000 São Paulo, SP, Brazil, E-mail: marcosdallogliouro@terra.com.br

Received October 11, 2012; Accepted October 26, 2012; Published October 28, 2012


Copyright: © 2012 Hasegawa E, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.
survival improvement of 30 months for the organ-confined disease (p=0.002) (Table 2). The Kaplan-Meier analysis shows a significant enhancement of the disease, death derived from cancer, and 39 orthotopic neobladder (31%) cases, and four cases involving other reconstruction types, such as ureterosigmoidostomy (3%). Pelvic lymphadenectomy was noticed at an average removal rate of 15.14 (±10.4) nodes.

The bladder urothelial cancer is an extremely prevalent disease, the incidence of which can appear in two ways: muscle-invasive and non-invasive. Local invasion, lymphatic involvement, and distant metastases are typical of muscle-invasive tumors for which the radical cystectomy with pelvic lymphadenectomy is considered to be the most effective treatment (respectively p=0.003; 2.4X, p=0.037) and 2.3X, p=0.038). The lympho-nodal metastasis determines worsened survival for 50%, 60% and 55%, respectively for RFS, CSS and OS within 30 months (Figure 2).

The LVI diagnosis found in 46% of the surgical pieces under analysis showed a significant association with cancer-related death (p=0.041). It was found not relevant in our study in terms of disease recurrence (p=0.08). The Kaplan-Meier analysis showed that the presence of lymphovascular invasion determines a significant reduction in RFS, CSS, and OS (respectively 50%, 60% and 60%) (Figure 3).

The overall analysis concerning the most significant factors for the recurrence-free survival showed 70% of survival in the absence of >pT2 and pN+ stages, 55% in the presence of only one factor, and 40% in the presence of both factors (p=0.005) (Figure 5).

Together, the >pT2, pN+, LVI+ and PNI+ factors allowed the stratification of 3 risk groups regarding death caused by cancer. A 90% CSS level was observed in the absence of factors; 65% in the presence of only one factor, and 40% in the presence of 3 or more factors (p<0.05) (Figure 4).

The OS analysis presented an 85% survival rate in the absence of >pT2 and pN+ stages, 55% in the presence of only one factor, and 40% in the presence of both factors (p=0.005) (Figure 5).

The OS analysis presented an 85% survival rate in the absence of >pT2 and pN+ stages, 55% in the presence of only one factor, and 40% in the presence of both factors (p=0.005) (Figure 5).

The overall analysis concerning the most significant factors for the recurrence-free survival showed 70% of survival in the absence of >pT2 and pN+ stages, 55% in the presence of only one factor, and 40% in the presence of both factors (p=0.005) (Figure 5).

The OS analysis presented an 85% survival rate in the absence of >pT2 and pN+ stages, 55% in the presence of only one factor, and 40% in the presence of both factors (p=0.005) (Figure 5).

The overall analysis concerning the most significant factors for the recurrence-free survival showed 70% of survival in the absence of >pT2 and pN+ stages, 55% in the presence of only one factor, and 40% in the presence of both factors (p=0.005) (Figure 5).

The OS analysis presented an 85% survival rate in the absence of >pT2 and pN+ stages, 55% in the presence of only one factor, and 40% in the presence of both factors (p=0.005) (Figure 5).

The overall analysis concerning the most significant factors for the recurrence-free survival showed 70% of survival in the absence of >pT2 and pN+ stages, 55% in the presence of only one factor, and 40% in the presence of both factors (p=0.005) (Figure 5).
effective treatment. It is known that the characteristics derived from the radical cystectomy are fundamental for prognosis determination. CIS prevalence was observed in the surgical piece in 28.1%. In the literature, it was found in 25 to 53.6% [6,12]. A study by Nuhn et al. analyzed 3,973 patients who underwent radical cystectomy. The study was not able to demonstrate any association of the CIS diagnosis (43.8%) with recurrence or death due to cancer [13]. In our study, we observed CIS in 28.1% of the surgical pieces. The RFS, CSS and OS were not changed due to its presence. Despite its relevance for urothelial cancer prognosis without muscle invasion, the histological grade is still controversial in the prognosis of tumors with invasion. In the literature, it is possible to find publishing material defending a high histological grade (84.6% of cystectomies) as a prognostic factor, although most authors have not confirmed it [5-7,14]. In our case study, we identified a high grade association with recurrence, although it was not relevant for the other analyses.

A study by Bassi et al. point to the pT and OS association, but Canter et al., in their research involving 356 patients, documented deterioration in RFS, CSS and OS in >pT2 stage [14,15]. In the literature, we found prevalence of the >pT2 stage in 41.3% to 56.2% of the cases, and 53.1% in our case study [6,16]. In 2009, Manoharan et al. demonstrated that
the confined disease presented an enhanced survival with OS and RFS, respectively at 74% vs 52% and 91% vs 56% [17]. In our study, we found that the ≤ pT2 stages presented better evolution than the >pT2 stages (70%/50%, 85%/55% and 80%/50%, respectively for RFS, CSS and OS). Both univariate and multivariate analyses revealed the association of >pT2 stage with survival.

In the previous studies, the presence of lympho-nodal metastasis is associated with 56.7% and 49.5% of RFS and OS within five years [6,16]. In our study, we found 50%, 60% and 55% of RFS, CSS and OS, respectively. The univariate and multivariate analysis revealed that pathological lymph nodes make up an independent factor for cancer prognosis either in recurrence or death.

The lymphovascular invasion is found in the literature in 30 to 50% out of the radical cystectomy specimens [15,18,19]. In 2006, a
review made by Algaba suggested the association of LVI with disease recurrence [20]. In our case study, the presence of LVI determined a significant reduction in RFS from 60% to 50% within 30 months. The worst prognosis in the evaluation of its effect regarding CSS and OS was found when LVI was detected (75% to 60% and 70% to 60%, respectively). The univariate analysis demonstrated its association with cancer-specific mortality. We did not succeed in confirming its independence either in recurrence or death. However, Canter et al. found a significant reduction in RFS, CSS and OS [15]. In their multicenter study, Bolenz et al. concluded that LVI determined a greater number of recurrence and death [21].

Up to the present moment few publications are focused on PNI, which is found in 5.9% to 47.7% of the specimens [14,22]. Its real role in the prognosis is still controversial. While evaluating prognostic factors in post-radical cystectomy, Bassi et al. found that the presence of PNI determined a worse OS. However, such findings did not resist the multivariate analysis [14]. Leissner et al. demonstrated a greater recurrence in the group with PNI presenting 30% of disease-free survival when compared to 55% of the group without PNI [22]. In our case study, we found 28.9% of prevalence in surgical pieces, with a relation to both specific and general mortality. The evaluation through Kaplan-Meier showed a significant reduction in RFS, CSS and OS. Meanwhile, such findings did not confirm the independence analysis.

The evaluation of the isolate prognostic factors has been abandoned due to the nomograms, since the association of factors has proven to be more accurate [6]. The use of still unacclaimed parameters as prognostic factors leads to the questioning on the actual nomogram reliability and applicability [10,11]. Manoharan et al. [17] demonstrated the importance of the pT and pN stages. They have been gathered in three groups: Organ-confined disease, extravesical disease, and lympho-nodal disease. Such stratification showed to be practical, but it does not take LVI into account for cancer prognosis, something that has also been found in their research [17]. While evaluating recurrence in the presence of the >pT2 and pN+ stages, we observed disease-free survival at the rates of 70%, 55% and 40%, respectively in the absence of factors, presence of one factor, and presence of both factors. The inclusion of LVI+ and PNI+ to the >pT2 and pN+ stages allowed us to categorize three different groups regarding CSS. Survival rates of 90%, 65% and 50% within 30 months were found in the absence of factors, presence of one or two factors, and presence of three or more factors, respectively. Regarding OS, three risk groups were obtained through 85%, 65% and 45% of general survival within 30 months, respectively in the absence of factors, presence of one factor, and presence of two or more factors out of: >pT2, pN+ and PNI+.

Although LVI and PNI did not appear to be an independent factor in our study, they were revealed as important prognostic factors as far as the survival time is concerned. We are aware of the shortcomings presented by a retrospective study so a prospective study involving a larger case study might attest to this supposition.

Conclusion

Our study confirmed the importance of the pT and pN stages as a prognostic factor. We agree with recent publications that include LVI as a prognostic factor, and we suggest that further PNI studies are carried out, as this subject has not been fully developed so far.

References


