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Original article

Long-term follow-up of TaG1 non–muscle-invasive bladder cancer

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Abstract

Objectives: To retrospectively assess the long-term outcome of patients initially diagnosed with TaG1 non–muscle-invasive bladder cancer (NMIBC) with no immediate postoperative instillation of intravesical chemotherapy and evaluate the reproducibility of the European Organization for Research and Treatment of Cancer (EORTC) scoring system for predicting bladder cancer outcome.

Methods and materials: A retrospective analysis of 481 consecutive cases of initially diagnosed TaG1 NMIBC according to the 1973 World Health Organization classification between 1995 and 2008 in a single institution was performed. Time to first recurrence, time to progression to T1 or G3 bladder cancer, and time to progression to muscle-invasive bladder cancer were studied. Time to event distributions was estimated by means of cumulative incidence functions to accurately take into account the patients who died (competing risk) before recurrence or progression. The Harrell *c* statistic calculation was used for our study's data results as well the original data from EORTC to compare the predictive power of a survival model.

Results: The median follow-up was 88 months (interquartile range: 51–135 mo). The 10-year recurrence-free, T1 or G3 NMIBC progression-free, and muscle-invasive bladder cancer progression-free survival rates were 64.2%, 96.6%, and 97%, respectively. In multivariate analysis, tumor size and number of lesions were prognostic variables of the risk of recurrence. In our study and EORTC data sets, the Harrell *c* values obtained were $c = 0.85$ (95% CI: [0.75, 0.93]) and $c = 0.85$ (95% CI: [0.75, 0.93]), respectively.

Conclusion: Our study reports a detailed and extensive outcome of TaG1 NMIBC treated by TURB with no immediate postoperative intravesical instillation of chemotherapy. Our results suggest that the EORTC is a useful external validation scoring system for predicting bladder cancer outcome. © 2014 Elsevier Inc. All rights reserved.

Keywords: Immediate postoperative intravesical chemotherapy; Outcome assessment; TaG1 urothelial carcinoma of the bladder; Transurethral resection

1. Introduction

In Western countries, bladder cancer (BC) is the fourth and ninth most common cancer in men and women, respectively [1]. Approximately 75% of BCs are non–muscle invasive at initial diagnosis [2,3]. TaG1 urothelial carcinoma represents a large subgroup of non–muscle invasive BCs (NMIBCs). In fact, TaG1 accounts for 40% of all new BCs.

Transurethral resection of a bladder tumor (TURB) is the mainstay for histopathological diagnosis and treatment [3]. In the context of TaG1 BC, TURB may be sufficient to obtain a complete remission. With its reported more favorable oncological outcome [4], follow-up of patients treated for TaG1 BC is subject to risks of recurrence and progression after TURB [3,5–7]. Risks of recurrence and progression after TURB are calculated for each patient based on the score introduced by the European Organisation for Research and Treatment of Cancer (EORTC) [5]. Therefore, the main problem in the clinical management of TaG1 BC is frequent recurrence, especially in multifocal disease.

These risks have justified performing immediate post-operative intravesical instillation of chemotherapy (IPOIC), especially in the early postoperative setting, as well as an

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invasive and costly monitoring via cystoscopy. However, despite evidence regarding prevention of recurrence, the use of IPOIC still remains under debate [8]. A huge disparity in its use has been reported in both European and North American patient populations [6,8]. The main reasons that have been provided are organizational and primarily security issues. IPOIC is not used in our department.

Among the trials that were included in the EORTC prognosis factor analysis, i.e., EORTC 30831 and 30863 studies, including 1,029 patients, each had an experimental arm that evaluated IPOIC. The EORTC scoring system can easily be used to calculate the probabilities of recurrence and progression in a patient with superficial BC based on 6 clinical and pathological factors (number of tumors, tumor size, prior recurrence rate, T category, carcinoma in situ [CIS], and grade). Consequently, an issue remains regarding the validation of a prognostic model in the setting of TaG1 tumors treated with TURB and no further IPOIC.

The aim of our study was to assess the very long-term outcome of initially diagnosed TaG1 NMIBC after TURB without further IPOIC at a single institution (with a strict follow-up based on programed fibroscopy) and to determine risk factors for recurrence and progression to a high-grade or muscle-invasive tumor. Based on these data, reproducibility of the EORTC scoring system for predicting BC outcomes was assessed in our retrospective patient population.

2. Materials and methods

2.1. Patient database

Between 1995 and 2008, 1,276 patients underwent a first TURB without further IPOIC at a single institution. Individual patient data were collected at inclusion. Tumor category and grade were determined by 2 uropathologists with a central review according to the TNM classification and the grade according to the 1973 World Health Organization classification. The inclusion criteria were initially diagnosed TaG1 NMIBC. Patients with an upper urinary tract tumor or primary concomitant CIS were excluded. Thus, only 481 patients were included in our study based on the aforementioned criteria.

Patient follow-up included repeated cytology and flexible cystoscopy (the first cystoscopy after TURB at 3 mo, then every 3 mo for a period of 2 y, and every 6 mo thereafter until 5 y, and then yearly) and computed tomographic scan examination every 2 years to investigate the upper urinary tract. If patients decided to discontinue follow-up participation, they were contacted by phone to maintain a strict follow-up. Coagulation was not used, and if a new small tumor appeared, patients underwent a new TURB.

The following were the 3 end points of this study:

Time to first recurrence was defined as the time from cancer diagnosis to the date of the first BC recurrence. Patients who were still alive and without recurrence were censored at the date of the last available follow-up cystoscopy. Recurrence was defined as a new TaG1 or TaG2 tumor.

Time to progression to T1 or G3 BC or CIS was defined as time from diagnosis to the date of progression to higher NMIBC in T1 category or grade G3 or CIS emergence. Patients who were still alive and without the progression defined earlier were censored at the date of the last available follow-up cystoscopy.

Time to progression to muscle-invasive BC (MIBC) was defined as time from diagnosis to the date of first increase to T2 category or higher. Patients who were still alive and without muscle invasion were censored at the date of the last available follow-up cystoscopy.

For all 3 end points, deaths before progression were analyzed as a competing risk.

To define low-, intermediate-, and high-risk groups of our patients, the EORTC risk tables were used to stratify the score of recurrence and progression [5].

- Low risk was defined as a score $= 0$ in the recurrence score and the progression score.
- Intermediate risk was defined as a score between 1 and 9 in the recurrence score and 2 and 13 in the progression score.
- High risk was defined as a score >9 in the recurrence score and >13 in the progression score.

2.2. Statistical analysis

Statistical analyses were primarily based methods according to Sylvester et al. [5] and Tournoux-Facon et al. [9]. Population characteristics are described using standard statistical methods. The description of the 3 end points was reported.

2.3. Assessment of end points

The assessment of end points was based on the European Association of Urology guidelines [3]. Moreover, because of possible variations in the maximum follow-up for long-term survivors, we used a cutoff value at 10 years after initial diagnosis. Median follow-up was then estimated using the reverse Kaplan-Meier test. Time to event distributions was estimated by means of cumulative incidence functions to properly take into account the patients who had died (competing risk) before recurrence or progression. They were compared using the Gray univariate test and the multivariate Cox proportional hazards regression model. When investigating the risk of recurrence, we did not include progression before recurrence, as it rarely occurred.

The prognostic importance of recurrence as well as progression to T1 or G3 BC or MIBC was also evaluated using time-dependent variables.

Because of the anticipated number of progression events of each type, a backward variable selection was also used.

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