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Original article

# Conditional analyses of recurrence and progression in patients with TaG1 non–muscle-invasive bladder cancer

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**Abstract**

**Objective:** To determine conditional recurrence-free survival (RFS) and progression-free survival (PFS) and improve decision-making toward surveillance protocols and scheduling. Furthermore, evaluating the evolution of predictors for disease recurrence over time, because TaG1 non–muscle-invasive bladder cancer harbors a risk of disease recurrence and progression.

**Material and methods:** The retrospective multicenter design study includes 1,245 TaG1 bladder cancer patients with median follow-up of 62.7 (interquartile range: 34.3–91.1) months. Conditional RFS and PFS estimates were calculated using the Kaplan-Meier method. Multivariable Cox regression model was calculated proportional for the prediction of recurrence and progression (covariables: age, tumor size, multiple tumors, prior recurrence, and immediate postoperative instillation of chemotherapy).

**Results:** After 3 months without event, the conditional RFS and PFS (to ≥pT2) rates for 5 additional years without event were 57.5% and 93.4%, respectively. Given a 1-, 2-, 3-, and 5-year survival, the conditional RFS rates for 5 additional years without event improved by +9.8 (67.3%), +5.2 (72.5%), +6.5 (79.0%), +2.0 (81.0%), and +1.0% (82.0%), respectively. In contrast, the 5-year conditional PFS rates were more or less stable with 94.3% after 1 year to 94.1% after 5 years. Multivariable analyses showed decreasing impact of risk parameters on RFS estimates over time. Based on these findings, we suggest a risk stratification to individualize follow-up for intermediate risk TaG1. Main limitation was the retrospective design.

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**Conclusions:** Conditional-survival analyses demonstrates that the patient risk profile changes over time. RFS rates rise with increasing survival whereas PFS rates were stable. The impact of prognostic features decreases over time. Our findings can be used for patient counseling and planning of personalized follow-up. 

*Keywords:* Non–muscle invasive; Bladder cancer; Recurrence and progression; Conditional analysis; Urothelial carcinoma

## 1. Introduction

Depending on invasion pattern, bladder cancer (BC) can be distinguished in non–muscle-invasive (NMIBC) which represents the majority of primary BC with approximately 85% and muscle invasive BC [1,2]. TaG1 presents in approximately 40% of primary NMIBC and has a substantial recurrence rate (30%–60%) with a small risk of progression to higher stages (1%–6%) over the first 5 years [3–8].

According to international guideline recommendations, complete transurethral resection (TURB), and immediate postoperative instillation of chemotherapy (IPIC) represent the treatment of choice for NMIBC [1,2]. Follow-up routine depends on endoscopic work-up alongside with sonography of the urinary tract, cytology, and urine sediment [5–8].

Even though mostly relying on retrospective studies in patient populations with heterogeneous tumor characteristics, the European Organization for Research and Treatment of Cancer (EORTC) established a score to assess the individual risk of recurrence and progression in patients with NMIBC after TURB [3]. This score includes information on tumor size and number of tumors, recurrence status, carcinoma in situ (CIS), clinical T-stage, and grade [3].

Moreover, physicians regularly use published recurrence-free survival (RFS) and progression-free survival (PFS) rates to assess cancer control and to individualize patients' prognosis and treatment [9]. The EAU guidelines panel introduced a simplified risk stratification into 3 groups for NMIBC which is based on the EORTC risk tables but more easily applicable in daily practice [1]. After a first follow-up at 3 months after TURB in every patient, EAU guidelines recommend yearly follow-up via cystoscopy in low-risk disease and every 3 months via cystoscopy and cytology in high-risk BC whereas a risk adapted regimen including cystoscopy and cytology is suggested in intermediate-risk disease [1]. However, guideline recommendations do not comprise precise instruction on the follow-up schedule of intermediate-risk patients and leave it to the discretion of the treating urologist. BC risk for recurrence or progression changes over time and is higher during the first years of follow-up [10]. Hence, conditional survival (CS) analysis would be useful for individual patient counseling and planning of follow-up [11].

Unfortunately, stage specific conditional RFS or PFS are not readily available for NMIBC. The only existing study on conditional RFS and PFS in patients with NMIBC was performed in a heterogeneous study population including Ta and T1 tumors with all adherent limitations [12]. There is no study that has focused exclusively on individuals diagnosed with TaG1 BC using conditional analysis to examine recurrence and progression to any higher stage (PAHS) as well as progression to ≥pT2 (PT2). Therefore, the aim of the present study was to assess conditional RFS and PFS rates in a large multicenter cohort of patients with TaG1, to examine predictors of recurrence at different time points during follow-up and of progression.

## 2. Material and methods

This was an institutional review board approved study. The study cohort consisted of 1,542 patients who underwent TURB at 8 institutions for TaG1 BC (1996–2007). Patients who received adjuvant intravesical chemotherapy with bacillus Calmette-Guérin ($n = 82$), who harbored concomitant CIS ($n = 23$), or who had incomplete follow-up data ($n = 191$) were excluded. The final study population consisted of 1,245 patients. A repeated TURB was not regularly performed. IPIC (40 mg mitomycin, 80 mg epirubicin, or 50 mg doxorubicin) was administered at the surgeons' discretion. This cohort was subdivided into low-risk and intermediate-risk patients according to EAU risk categories [1,13]:

- *Low risk*: primary, solitary, size <3 cm
- *Intermediate risk*: all tumors that are not low nor high risk
- *High risk*: recurrent and multiple tumors with a size ≥3 cm

### 2.1. Pathologic evaluation

Genitourinary pathologists processed all surgical specimens according to standard pathologic procedures using the 1973 World Health Organization (WHO) grading system and the 2009 American Joint Committee on Cancer TNM staging system [14].

### 2.2. Follow up

Follow-up was performed according to the standard of each participating institution in coherence with international guidelines. Patients were followed every 3 to 6 months during the first 2 years after TURB, biannually up to 5 years, and annually thereafter [1]. Follow-up consisted of a