Comparison of 10-year overall survival between patients with G1 and G2 grade Ta bladder tumors

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Abstract
To compare long-term overall survival (OS) in patients with G1 and G2 grade Ta bladder cancer after transurethral resection of bladder tumors (TURBTs). Secondary aim was to investigate clinical and pathologic prognostic factors for OS of Ta patients, except G3/high grade (HG).

A total of 243 patients, retrospectively selected, with Ta nonmuscle invasive bladder cancer (NMIBC) underwent TURBT between January 2006 and December 2008 (median follow-up 109 months). Inclusion criteria were: Ta at first manifestation, G1 or G2 grade with no associated carcinoma in situ (CIS). Seventy-nine patients were excluded due to concomitant CIS (1), G3/HG tumors (47), and lost to follow-up (3). Ethical approval was obtained from the Ethical Committee of the Mures County Hospital. Statistical analysis was performed using STATA 11.0.

Following inclusion criteria, 164 patients with primary G1 or G2 Ta tumors, were enrolled. Recurrence was observed in 26 (15.8%) and progression in 5 (3%) patients. Ten-year survival in G1 patients was 67.8% (CI 54.3–78.1) and in G2 patients 59% (CI 49–67.3) (P = .31). Univariable and multivariable logistic regression analysis underlined that advanced age at diagnosis (hazard ratio [HR] 1.10) and no Bacillus Calmette–Guerin (BCG) treatment (HR 0.24 and 0.29) were independent predictors for death at 10 years after diagnosis.

Long-term analysis confirms that patients with well differentiated (G1) and moderately well differentiated (G2) Ta tumors have similar OS. A longer OS was even reported in those who underwent BCG adjuvant therapy.

Abbreviations: BC = bladder cancer, BCG = Bacillus Calmette–Guerin, CIS = carcinoma in situ, EORTC = The European Organization for Research and Treatment of Cancer, HG = high grade, HR = hazard ratio, LG = low grade, MIBC = muscle invasive bladder cancer, NMIBC = nonmuscle invasive bladder cancer, OS = overall survival, TURBT = transurethral resection of bladder tumor, WHO = World Health Organization.

Keywords: G1 and G2 grade nonmuscle invasive bladder cancer, long-term, overall survival, progression, recurrence

1. Introduction
Bladder cancer (BC) is one of the most common of the urinary tract, occupying the 2nd place after prostate cancer. Approximately half of these newly diagnosed tumors are low grade (LG) and >70% are nonmuscle invasive bladder cancer (NMIBC). The main procedure for the diagnosis and treatment of NMIBC is the transurethral resection of bladder tumor (TURBT) and according to the latest version of the European Association of Urology guidelines, “an immediate chemotherapy instillation is recommended in tumors presumed to be at low or intermediate risk.” Low-risk tumors are considered primary, solitary, TaG1 (papillary urothelial neoplasm of low malignant potential, LG), and ≪3 cm, with no carcinoma in situ (CIS). Intermediate risk tumors are those that do not fit to low category or in any of the following: T1 tumor, G3 (high grade [HG]) tumor, and CIS; or recurrent and large (>3 cm) TaG1G2/LG tumors (all features must be present).

Although NMIBC is a nonmuscle invasive tumor, it is well known for its high risk of recurrence and progression. The European Organization for Research and Treatment of Cancer (EORTC) introduced a scoring system for calculating the probability of recurrence and progression of these patients. To our knowledge, in terms of overall survival (OS), it has not been yet published any long-term comparison between well
differentiated (G1) and moderately well differentiated (G2) (according to 1973 World Health Organization [WHO] system) Ta tumors. Many large cohorts studies analyzing the long-term survival of NMIBC patients in general after TURBT and intravesical chemotherapy, survival range varies between studies but are mostly higher than in muscle-invasive bladder cancer (MIBC).

The main aim of the study was to compare the long-term OS in patients with well-differentiated (G1) and moderately well differentiated (G2) grade Ta BC after TURBT. The secondary aim was to investigate clinic and pathologic prognostic factors for OS of these patients.

2. Methods

All patients with Ta NMIBC that underwent TURBT in the urology department from Tirgu Mures – Romania, within 3 years between January 2006 and December 2008, have been enrolled. Ethical approval was obtained from the Ethical Committee of the Mures County Hospital. Inclusion criteria were: primary Ta, G1, and G2 with nonassociated in situ carcinoma are classified as low and intermediate tumors according to European Association of Urology guidelines. Exclusion criteria were: any recurrent or progressed cancer, any T1 and/or G3/HG tumor, any concomitant CIS, and all cases of lost follow-up. EORTC risk scores were calculated for each patient; EORTC risk tables allow to estimate the probability of recurrence and progression based on a number of tumors, tumor size, prior recurrence rate, T category, concomitant CIS, and grade.

Histological classification was done according to 1973 WHO classification (Fig. 1). Recurrence was defined as disease recurrence at more than 3 months postoperatively, and progression was considered the evolution of HG T1 tumors or MIBC. According to European Association of Urology guidelines, intravesical immunotherapy with Bacillus Calmette–Guerin (BCG) was administrated for intermediate risk Ta tumors, following the Lamm scheme: 1 weekly instillation for 6 weeks, followed by 3 years of maintenance instillation with 3 weekly instillation every 3 or 6 months.

Follow-up was made by clinical examination and cystoscopy at 3 months in the first 2 years and another cystoscopy at 6 months in the next 3 years and then annually after that. Firstly, end-point was set at the time until the first recurrence; secondly, end-point was timed until progression, and thirdly end-point was the death of any cause (from National Health Insurance Registry).

2.1. Statistical analysis

Data were labeled as nominal or quantitative variables. Nominal variables were characterized using frequencies. Quantitative variables were tested for normality of distribution by applying the Kolmogorov–Smirnov test and were described by mean ± standard deviation or median and quartiles. The frequencies of nominal variables were compared with the chi-square test and Student t test was used to assess the differences between means of continuous variables (expressed as mean ± SD), while differences between nonparametric variables (expressed as median, range) were compared using the Mann–Whitney U test. Survival analysis was performed using the Kaplan–Meier method, and the log-rank test was used for univariate comparisons. Univariable and multivariable Cox regression models addressed the association of prognostic factors with OS after TURBT. Logistic regression analyses were performed to identify predictors for 10-year OS. All P values were 2-sided, and statistical significance was defined as a P < .05. Statistical analyses were performed using Stata 11.0 statistical software (Stata Corp., College Station, TX).

3. Results

A total of 243 patients, with G1 and G2 Ta tumors, have been included and 164 met inclusion criteria. Seventy-nine patients
were excluded due to concomitant CIS, G3/HG tumors (47), lost of follow-up, and no data about 10-year survival. Patients were followed in average 109 months (IQR 70–121 months). The mean age at diagnosis was 63.3 years (range 21–89) and 135 (82.3%) patients were males. Multiple tumors were observed in 78 (47.6%) cases, in 86 (52.4%) cases the diameter of tumor was >3 cm, G2 tumors were observed in 105 (64%) patients. Intravesical immunotherapy with BCG was administered in 32 (19.5%) patients according to guidelines recommendations at that time (intermediate risk Ta tumors) as was the only available adjuvant therapy following TURBT. Most patients had EORTC recurrence score of 1 to 4 (34.8%) and progression in 5 (3%) patients. At 10 years after diagnosis, a total of 102 patients (62.2%) were survivors (Table 1).

Table 1 presents the association between clinico-pathological features and OS in the studied cohort. Looking at deaths, advanced age at diagnosis was associated with lower OS: 69 years versus 59.8 years mean age, respectively, in survivors (P < 0.001). Mortality was higher in males (38.5%) than in females (34.3%) but not statistically significant (P = 0.68). Even if not significant, the survival rate was higher in G1 (67.8%) compared to G2 (59%) patients (P = 0.26). BCG treatment was associated with higher survival 84.4% versus 56.8%, P = 0.004.

Univariable Cox analysis showed that predicting factors for OS were the advanced age at diagnosis with a hazard ratio (HR) of 1.07; no BCG treatment HR 0.30 and progression during follow-up HR 5.25. Multivariable Cox analysis showed that independent predictors for OS were: age (HR 1.07); EORTC recurrence scores 1 to 4 (HR 0.23); EORTC recurrence scores 5 to 9 (HR 0.17); and progression (HR 5.18) (Table 3).

Univariable and multivariable logistic regression analysis underlined that the advanced age at diagnosis (HR 1.10) and no BCG treatments (HR 0.24 and 0.29) were independent predictors for death at 10 years after diagnosis (Table 4).

Kaplan–Meier survival analysis showed that there is 8% difference in the survival between G1 and G2 grade, but with no statistical significance. Five years survival was 86.4% (CI 74.7–93) in G1 patients and 84.7% (CI 76.3–90.3) in G2 patients; 10 years survival was 67.8% (CI 54.3–78.1) in G1 patients and 59% (CI 49–67.3) in G2 patients (Fig. 2A, P = .31). BCG treatment had a benefit on the OS; 5 years OS was 82.6% (CI 74.9–88) in non-BCG treated patients, and 96.8% (CI 79.8–99) in BCG treated patients, respectively. Ten years OS was 56.8% (CI 47.9–64.7) in non-BCG treated patients, and 84.4% (CI 66.4–93.1) in BCG treated patients, P = .006 (Fig. 2B).

4. Discussion

We evaluated the long-term survival of 164 Ta G1-G2 NMIBC patients in a single center with a median follow-up of 109 months. At 10 years after diagnosis, 62% of patients were survivors. To make it easy to understand, we demonstrated that advanced age at diagnosis was associated with worse OS and that there is no statistical significance regarding 10-year OS between patients with TaG1 compared with TaG2 patients. More interestingly was the statistically significant relationship that we found between BCG treatment and longer OS.

In 2009 Truls Gårdmark et al.[12] published the Sweden data regarding NMIBC. Several similarities could be observed in our study. They showed that Ta cancer is more common in men, but suggesting that this data may change because, in Sweden, cigarette smoking is decreasing among men and is now equally prevalent among women. They analyzed the data from 6 health...
Table 3

Univariable and multivariable Cox regression analyses predicting overall survival of 164 patients with low and intermediate Ta bladder cancer.

| Prognostic factor | Univariable | Multivariable |
|-------------------|-------------|--------------|
|                   | HR 95% CI    | P            | HR 95% CI    | P            |
| Age cont          | 1.07 1.04-1.10 | <.001* | 1.07 1.03-1.10 | <.001* |
| Gender            | 0.93 0.47-1.83 | .84  | 0.82 0.40-1.68 | .60 |
| Multifocality     | 1.29 0.78-2.13 | 0.31 | 1.90 0.81-4.43 | 0.13 |
| Diameter          | 1.26 0.76-2.08 | 0.36 | 1.18 0.49-2.81 | .70 |
| Grade             | 1.31 0.76-2.25 | 0.32 | 1.75 0.79-3.83 | .16 |
| EORTC rec         | 1-4 score 1.08 0.52-2.24 | .82 | 0.23 0.06-0.91 | .036* |
| 4-9 score         | 1.06 0.46-2.42 | .89 | 0.17 0.03-0.76 | .02* |
| EORTC prog 1–6 score | 1.52 0.87-2.67 | .13 | 1.85 0.52-6.56 | .33 |
| BCG treatment (no treat) | 0.3 0.12- 0.79 | .01* | 0.40 0.15-1.05 | .063 |
| Recurrence        | 1.28 0.67-2.46 | .44 | 1.16 0.48-2.77 | .72 |
| Progression       | 5.25 1.89-14.57 | <.001* | 5.18 1.33-20.18 | .018* |

Table 4

Univariable and multivariable logistic regression predicting overall survival of 164 patients with low and intermediate Ta bladder cancer.

| Prognostic factor | Univariable | Multivariable |
|-------------------|-------------|--------------|
|                   | HR 95% CI    | P            | HR 95% CI    | P            |
| Age cont          | 1.10 1.05-1.14 | <.001* | 1.10 1.05-1.15 | <.001* |
| Gender            | 0.84 0.36-1.94 | .68 | 0.73 0.27-1.98 | .54 |
| Multifocality     | 1.44 0.76-2.71 | 0.25 | 2.46 0.66-9.16 | .17 |
| Diameter          | 1.29 0.68-2.44 | 0.42 | 0.94 0.23-3.77 | .94 |
| Grade             | 1.46 0.74-2.85 | 0.26 | 1.84 0.67-5.00 | .23 |
| EORTC rec         | 1 1.17 0.47-2.90 | .72 | 0.30 0.05-1.56 | .15 |
|                   | 2 1.18 0.41-3.31 | .75 | 0.21 0.02-1.53 | .12 |
| EORTC prog        | 1.70 0.86-3.38 | 0.12 | 2.04 0.32-12.79 | .44 |
| BCG treatment     | 0.24 0.08-0.67 | .006* | 0.29 0.09-0.90 | .03* |

BCG=Bacillus Calmette–Guerin, CI=confidence interval, EORTC=The European Organization for Research and Treatment of Cancer, HR=hazard ratio.
Our study has several limitations. First, the retrospective design requires further confirmation in prospective cohorts. Second, patients did not receive immediate postoperative instillation of chemotherapy, although those at intermediate risk received adjuvant treatment. Third, we did not perform a central pathology review on the specimens and did not reassign the specimens to the latest WHO grading. Also, we did not have any information on the smoking status of patients, which is a well-known prognostic factor associated with outcomes in urothelial carcinomas. Furthermore cancer-specific survival should have been a primary endpoint, but unfortunately, we did not have access to death certificates of the patients. Despite these limitations, this study fulfilled its aim to compare the OS of patients with newly diagnosed G1 and G2 Ta BC at 10 years after diagnosis.

5. Conclusion

Patients with well differentiated (G1) and moderately well differentiated (G2) Ta tumors have similar long-term OS after diagnosis. BCG treatment, even if administered to intermediate risk cancers, is related to a longer OS.

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Figure 2. Kaplan–Meier survival estimates: (A) according to grade; (B) according to intravesical treatment.
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