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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 (31). 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.[1] Approximately half of these newly diagnosed tumors are low grade (LG)[2] and >70% are nonmuscle invasive bladder cancer (NMIBC).[3] 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."[2] 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).[3]

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.[4] To our knowledge, in terms of overall survival (OS), it has not been yet published any long-term comparison between well

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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,[5,6] survival range varies between studies but are mostly higher than in muscle-invasive bladder cancer (MIBC).[7]

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.[8]

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.[9–11] 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–Meyer 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).

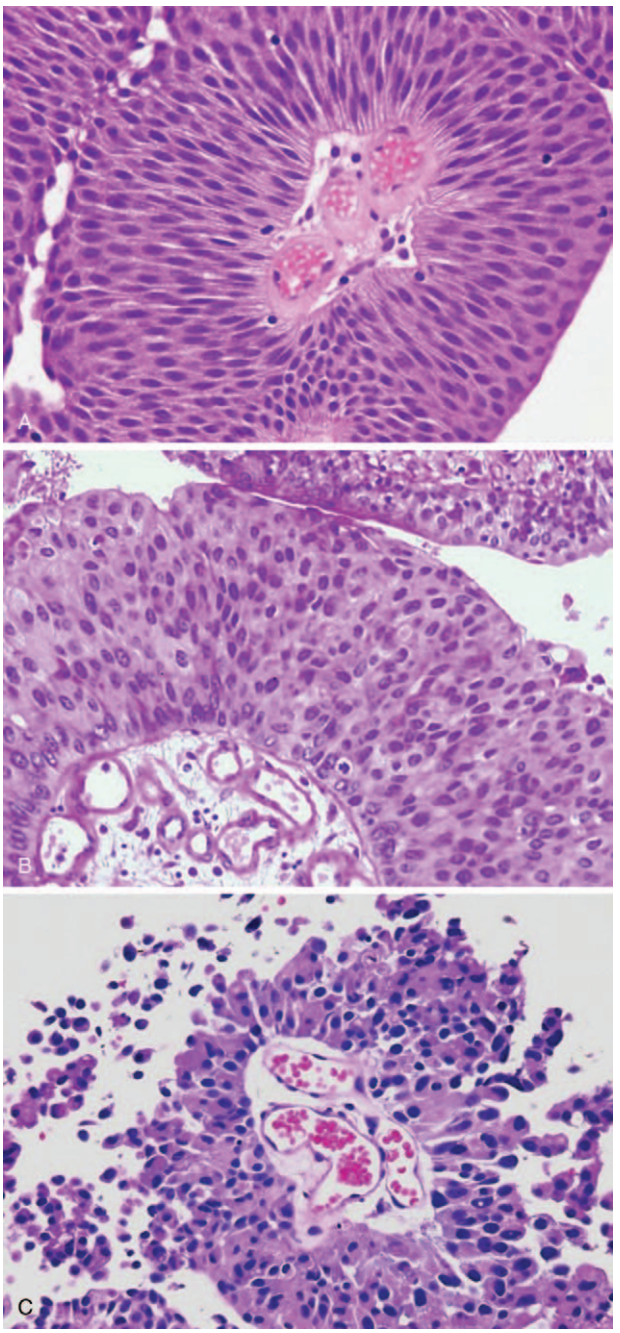

Figure 1. Histological grading according to World Health Organization (WHO) 1973 grading system: (A) G1: transverse section of a papilla; thickened urothelium with slender fibrovascular core; uniform elongated nuclei with preserved nuclear polarity and differentiation to the surface, no mitosis; (B) G2: moderately altered polarity, larger nuclei, variable in size, dense or irregular nuclear chromatin; visible nucleoli; some mitosis can be identified; (C) G3: deep architectural disorganization and severe nuclear atypia; coarse chromatin; massive cellular desquamation.

3. Results

A total of 243 patients, with G1 and G2 Ta tumors, have been included and 164 met inclusion criteria. Seventy-nine patients

Table 1

Characteristics of 164 patients with low and intermediate grade Ta bladder tumors at diagnosis.

Patients characteristics	No patients, %	G1	G2	P
Age				
Mean	63.3 y	62.9 y	63.6 y	.71
Gender				
Male	135 (82.3%)	45 (76.3%)	90 (85.7%)	.12
Female	29 (17.7%)	14 (23.7%)	15 (14.3%)	
Tu diameter				
<3 cm	78 (47.6%)	34 (57.6%)	44 (41.9%)	.053
>3 cm	86 (52.4%)	25 (42.4%)	61 (58.1%)	
No tumors				
Single	86 (52.4%)	32 (54.2%)	54 (51.4%)	.73
Multiple (2–7)	78 (47.6%)	27 (45.8%)	51 (48.6%)	
Grade				
G1	59 (36%)	–	–	–
G2	105 (64%)	–	–	–
BCG treatment				
No	132 (80.5%)	45 (76.3%)	87 (82.8%)	.30
Yes	32 (19.5%)	14 (23.7%)	18 (17.2%)	
Rec EORTC score				
0	26 (15.8%)	26 (44.1%)	0	<.001*
1–4	99 (60.4%)	17 (28.8%)	82 (78.1%)	
5–9	39 (23.8%)	16 (27.1%)	23 (21.9%)	
Prog EORTC score				
0	57 (34.8%)	26 (44%)	31 (29.5%)	.06
1–6	107 (65.2%)	33 (56%)	74 (70.5%)	
Recurrence	26 (15.8%)	13 (22%)	13 (12.4%)	.10
Progression	5 (3%)	3 (5%)	2 (1.9%)	.25
Deaths	62 (37.8%)	19 (32.2%)	43 (41%)	.26

BCG = Bacillus Calmette–Guerin, CI = confidence interval, EORTC = The European Organization for Research and Treatment of Cancer, HR = hazard ratio.

Table 2

Association of clinico-pathologic factors with overall survival.

Patients characteristics	Death		P
	No (102 patients)	Yes (62 patients)	
Age mean	59.8 y	69 y	**<.001***
Gender male (no/%)	83 (61.5)	52 (38.5)	.68
Female	19 (65.5)	10 (34.5)	
Tu diameter <3 cm (no/%)	51 (65.4)	27 (34.6)	.42
>3 cm	51 (59.3)	35 (40.3)	
No tumors single (no/%)	57 (66.3)	29 (33.7)	.25
2–7 (no/%)	45 (57.7)	33 (42.3)	
Grade G1 (no/%)	40 (67.8)	19 (32.2)	.26
G2 (no/%)	62 (59)	43 (41)	
BCG treatment no (no/%)	75 (56.8)	57 (43.2)	**.004***
Yes (no/%)	27 (84.4)	5 (15.6)	
Recurrence EORTC score 0 (no/%)	17 (65.4)	9 (34.6)	.93
1–4 (no/%)	61 (61.6)	38 (38.4)	
5–9 (no/%)	24 (61.5)	15 (38.5)	
Progression EORTC score 0 (no/%)	40 (70.3)	17 (29.8)	.12
1–6 (no/%)	62 (57.9)	45 (42.1)	
Recurrence no (no/%)	87 (63)	51 (37)	.6
Yes (no/%)	15 (57.7)	11 (42.3)	
Progression no (no/%)	101 (63.5)	58 (36.5)	**.04***
Yes (no/%)	1 (20)	4 (80)	

BCG = Bacillus Calmette–Guerin, EORTC = The European Organization for Research and Treatment of Cancer.

were excluded due to concomitant CIS,[1] G3/HG tumors (47), lost of follow-up, and no data about 10-year survival.[31] 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 administrated 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: 99 (60.4%). Progression EORTC score of 1 to 6 was observed in 107 (65.2%) patients. Recurrence was observed in 26 (15.8%) and progression in 5 (3%) patients. At 10 years after diagnosis, a total of 102 patients (62.2%) were survivors (Table 1).

Table 2 presents the association between clinicopathological features and OS in the studied cohort. Looking at deaths, advanced age at diagnosis was associated with lower OS: 69 versus 59.8 years mean age, respectively, in survivals ($P < .001$). Mortality was higher in males (38.5%) than in females (34.3%) but not statistically significant ($P = .68$). Even if not significant, the survival rate was higher in G1 (67.8%) compared to G2 (59%) patients ($P = .26$). BCG treatment was associated with higher survival 84.4% versus 56.8%, $P = .004$.

Univariable Cox analysis showed that predicting factors for OS were the advanced age 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.

	Univariable			Multivariable		
Prognostic factor	**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	.31	1.90	0.81–4.43	.13
Diameter	1.26	0.76–2.08	.36	1.18	0.49–2.81	.70
Grade	1.31	0.76–2.25	.32	1.75	0.79–3.83	.16
EORTC rec			Ref.			
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***

BCG = Bacillus Calmette–Guerin, CI = confidence interval, EORTC = The European Organization for Research and Treatment of Cancer, HR = hazard ratio.

care institutions, stating that tumor grading significantly differed between institutions. This information suggests that tumor grading highly depends on the local histopathologist.

In 2016 Hernández et al[13] published an interesting paper on active surveillance in case of well selected NMIBC patients (especially TaG1), but still, experts and guidelines consider that active surveillance should be definitively abandoned for BC and banished from daily practice without further investigation.[14]

Several studies have highlighted the importance of adjuvant therapy in improving long-term oncologic outcomes of NMIBC,[15–20] resulting in higher recurrence-free survival (RFS) with the usage of BCG compared to Epirubicin[16] but no statistical difference between BCG and Mitomycin-C was reported.[21]

Gupta and Parr examined a large cohort of NMIBC and concluded that large size of tumors is not a negative prognostic factor for patients with NMIBC and that pT1G2 should be considered high-risk tumors,[22] with a median follow-up of 60 months, however, the study lacks data regarding OS.

Multiple tumors are considered as a risk factor for tumor recurrence and worsening progression according to Kobayashi et al[23]; lung cancer, hematuria, and >60 pack-years smoking history according to Starke et al.[24] In line with Herr et al[24] in our study, advanced age, lack of adjuvant therapy, and progression proved to be statistically independent prognostic factors. We also proved that advanced age is an independent prognostic factor. At 5 years, 27% of patients older than 70 years were cancer-free compared to 37% who were younger than 70 years, including high-risk NMIBC patients.[25]

Thinking about the future predictive models, to better understand urothelial neoplasm behavior and to better understand recurrence and progression multiple biomarkers have been studied as predictors for NMIBC patients outcomes,[26] the closest to be embraced in clinical practice is neutrophil-to-lymphocyte ratio, which is accessible and a less costly biomarker.[27] Elevated neutrophil-to-lymphocyte ratio was demonstrated to be an independent predictor for poor OS, cancer-specific survival, recurrence, and progression in BC patients.[28]

Data regarding long-term (at least 10 years) OS after initial diagnosis of Ta BCa lack in the literature. In a UK study, OS for Ta patients was 54% at 10 years,[29] on the other hand, OS in high-risk NMIBC patients that received BCG or Mytomicin C was 44% at 10 years.[21] Librenjak et al[18] showed, in a cohort of NMIBC, that there is no significant difference in OS between patients with BCG treatment (56% 10 years OS) and patients without BCG treatment (44% OS at 10 years). In a large multicenter cohort of TaG1 patients, the estimated OS at 5 years was 86%,[30] (similar to our study, where OS of TaG1 at 5 years was 86.4%) but more than half of the patients received immediate postoperative instillation of chemotherapy.

Table 4

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

	Univariable			Multivariable		
Prognostic factor	**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	.25	2.46	0.66–9.16	.17
Diameter	1.29	0.68–2.44	.42	0.94	0.23–3.77	.94
Grade	1.46	0.74–2.85	.26	1.84	0.67–5.00	.23
EORTC rec			Ref			
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	.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.

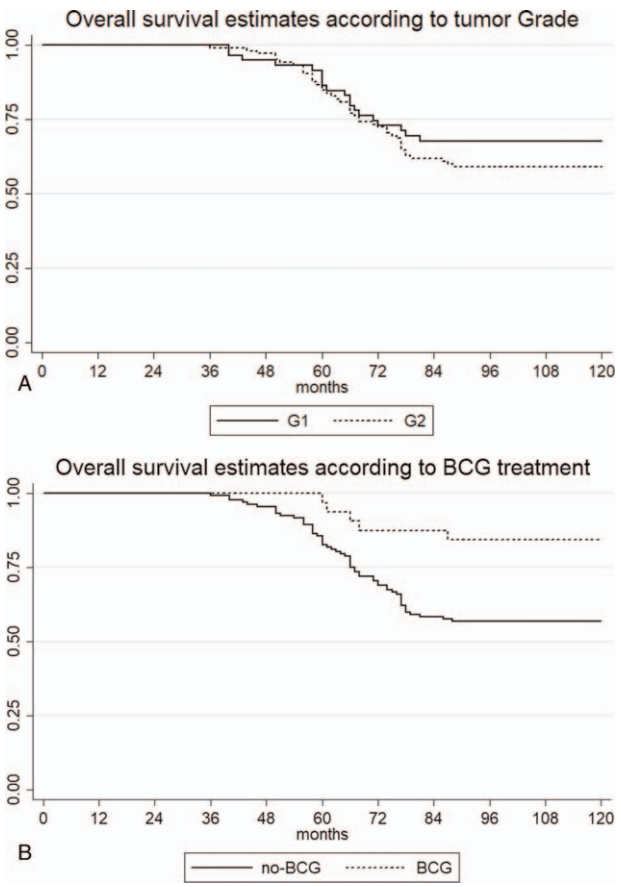

Figure 2. Kaplan–Meier survival estimates: (A) according to grade; (B) according to intravesical treatment.

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.[31] 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.[32] 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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