BJUI
BJU International

The impact of re-transurethral resection on clinical outcomes in a large multicentre cohort of patients with T1 high-grade/Grade 3 bladder cancer treated with bacille Calmette–Guérin

Paolo Gontero[1], Richard Sylvester[2], Francesca Pisano[1], Steven Joniau[3], Marco Oderda[1], Vincenzo Serretta[4], Stéphane Larré[5], Savino Di Stasi[6], Bas Van Rhijn[7], Alfred J. Witjes[8], Anne J. Grotenhuis[8], Renzo Colombo[9], Alberto Briganti[9], Marek Babjuk[10], Viktor Soukup[10], Per-Uno Malmström[11], Jacques Irani[12], Nuria Malats[13], Jack Baniel[14], Roy Mano[14], Tommaso Cai[15], Eugene K. Cha[16], Peter Ardelt[17], John Vakarakis[18], Riccardo Bartoletti[19], Guido Dalbagni[20], Shahrokh F. Shariat[16], Evanguelos Xylinas[16], Robert J. Karnes[21] and Joan Palou[22]

[1]Urology Clinic, Città della Salute e della Scienza di Torino, University of Studies of Turin, Turin , [4]Department of Surgical, Oncological and Stomatological Sciences, University of Palermo, Palermo , [6]Policlinico Tor Vergata-University of Rome, Rome , [9]Dipartimento di Urologia, Università Vita-Salute. Ospedale S. Raffaele, Milan , [15]Department of Urology, Santa Chiara Hospital, Trento , [19]Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy, [2]Formerly Department of Biostatistics, EORTC Headquarters, Brussels , [3]Oncologic and Reconstructive Urology, Department of Urology, University Hospitals Leuven, Leuven, Belgium, [5]Department of Surgical Science, John Radcliffe Hospital, University of Oxford, Oxford, UK, [7]Department of Urology, Netherlands Cancer Institute – Antoni van Leeuwenhoek Hospital, Amsterdam , [8]Department of Urology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands, [10]Department of Urology, Motol Hospital, University of Praha, Praha, Czech Republic, [11]Department of Urology, Academic Hospital, Uppsala University, Uppsala, Sweden, [12]Department of Urology, Centre Hospitalier Universitaire La Milétrie, University of Poitiers, Poitiers, France, [13]Genetic and Molecular Epidemiology Group, Spanish National Cancer Research Centre (CNIO), Madrid , [22]Department of Urology, Fundacio Puigvert, University of Barcelona, Barcelona, Spain, [14]Department of Urology, Rabin Medical Centre, Tel Aviv, Israel, [16]Department of Urology, Weill Medical College of Cornell University in New York City , [20]Department of Urology, Memorial Sloan Kettering Cancer Center, New York, NY , [21]Department of Urology, Mayo Clinic, Rochester, MN, USA, [17]Facharzt fur Urologie, Abteilung fur Urologie. Chirurgische Universitats klinik, Freiburg, Germany, and [18]Department of Urology, Sismanoglio Hospital, University of Athens, Athens, Greece

Objectives

To determine if a re-transurethral resection (TUR), in the presence or absence of muscle at the first TUR in patients with T1-high grade (HG)/Grade 3 (G3) bladder cancer, makes a difference in recurrence, progression, cancer specific (CSS) and overall survival (OS).

Patients and methods

In a large retrospective multicentre cohort of 2451 patients with T1-HG/G3 initially treated with bacille Calmette–Guérin, 935 (38%) had a re-TUR. According to the presence or absence of muscle in the specimen of the primary TUR, patients were divided in four groups: group 1 (no muscle, no re-TUR), group 2 (no muscle, re-TUR), group 3 (muscle, no re-TUR) and group 4 (muscle, re-TUR). Clinical outcomes were compared across the four groups.

Results

Re-TUR had a positive impact on recurrence, progression, CSS and OS only if muscle was not present in the primary TUR specimen. Adjusting for the most important prognostic factors, re-TUR in the absence of muscle had a borderline significant effect on time to recurrence [hazard ratio (HR) 0.67, $P = 0.08$], progression (HR 0.46, $P = 0.06$), CSS (HR 0.31, $P = 0.07$) and OS (HR 0.48, $P = 0.05$). Re-TUR in the presence of muscle in the primary TUR specimen did not improve the outcome for any of the endpoints.

Conclusions

Our retrospective analysis suggests that re-TUR may not be necessary in patients with T1-HG/G3, if muscle is present in the specimen of the primary TUR.

 | doi:10.1111/bju.13354
Published by John Wiley & Sons Ltd. www.bjui.org

Keywords

bladder cancer, T1G3, high grade, re-TUR, recurrence, progression

Introduction

High-risk non-muscle-invasive bladder cancer (NMIBC) encompass all high-grade (HG)/Grade 3 (G3) papillary tumours, tumours with lamina propria invasion (T1), carcinoma *in situ* (CIS), as well as multiple recurrent large low-grade lesions, all tumours whose common denominator is their high risk to progress to muscle-invasive disease [1]. This especially holds true for T1G3, where long-term progression and cancer-specific death rates of up to 40% and 30%, respectively, identifies a subgroup of NMIBC of particular aggressiveness [2]. Transurethral resection (TUR), the first diagnostic and therapeutic approach for NMIBC, is currently viewed as potentially the most critical step affecting the prognosis of the disease [3]. Several quality issues, some potentially linked to the experience of the surgeon, suggest that the initial TUR may be inadequate in a high percentage of patients with high-risk NMIBC. First, dramatically higher rates of residual disease at a 'second-look' TUR, which approach 50% in Ta and 70% in T1 disease, have been reported [4]. More importantly, up to 30% of T1 disease will be upstaged to muscle-invasive disease at the re-TUR [5]. These figures have led recent guidelines to strongly recommend repeat TUR within 4–6 weeks when lamina propria involvement [1,6] or HG disease [1] is documented at the initial TUR.

Several issues make this recommendation at least debatable. The risk of upstaging to muscle-invasive disease at re-TUR remained significant but did not exceed 7% in two recent series [7,8]. Furthermore BCG, which has proved to be effective in marker lesion studies [9], may ablate residual disease. In a small retrospective cohort of patients with T1G3 NMIBC, long-term outcomes were not improved by re-TUR [8]. The benefit of immediate re-TUR may be different according to the presence or absence of detrusor muscle in the primary TUR specimen, the former being linked to a significant reduction of the risk of up-staging and better prognosis [10]. All these figures taken together suggest that the potential benefits of re-TUR should be carefully weighed considering the healthcare burden of the procedure [11] and its side-effects [8].

In the present study, we retrospectively compared the long-term outcomes of a large series of patients with T1-HG/G3 bladder cancer treated with BCG who did not or did receive a re-TUR within 4–6 weeks of the initial TUR.

Patients and Methods

Patients with primary T1G3 (WHO 1973)/T1-HG (International Society of Urological Pathology (ISUP) 1998/WHO 2004) or secondary T1-HG/G3 disease from a previously BCG naïve non-T1-HG/G3 NMIBC tumour, formed the retrospective study cohort provided they received at least a full induction course of BCG between 1990 and 2011. Patients who previously received BCG for a tumour that was not T1-HG/G3 or did not receive BCG as the initial intravesical treatment for a T1-HG/G3 tumour were excluded. Patients with a history of muscle-invasive disease (≥T2), upper tract urothelial cancer, or a non-urothelial carcinoma were also excluded. Details are provided in a previous publication [12].

The following patient and tumour characteristics were included in the database: age, gender, smoking history and intensity, exposure to chemical compounds, tumour status (primary or recurrent), previous intravesical chemotherapy, tumour size (<3 vs ≥3 cm), tumour focality (solitary vs multiple), presence of CIS, prostatic urethra involvement with or without stromal invasion, presence of muscle in the tissue specimen, and BCG dose and total number of instillations. Any instillation beyond the six induction instillations was defined as maintenance BCG. Information on re-TUR (defined as a second TUR performed within 4–6 weeks after an initial macroscopically complete TUR and before BCG administration) was also recorded. Results of pathology at re-TUR were categorised into: no evidence of disease, persistent disease with down staging (Ta), or persistent T1 disease. Patients with muscle-invasive disease at re-TUR did not match the study inclusion criteria and were therefore excluded.

Patients were divided into four groups according to whether or not a re-TUR was done and the presence or absence of muscle in the specimen of the primary TUR: group 1 (no muscle, no re-TUR), group 2 (no muscle, re-TUR), group 3 (muscle, no re-TUR), and group 4 (muscle, re-TUR).

The presence of muscle (no/yes) and re-TUR (no/yes) according to the presence of muscle (no/yes) were compared for the following endpoints: time to first recurrence, progression to muscle-invasive disease, and the duration of cancer-specific (CSS) and overall survival (OS).

Times to events were calculated taking the date of starting BCG as time zero. OS was estimated using the Kaplan–Meier technique. To take into account patients who died before

observing the event of interest (competing risk), times to the other events were estimated using cumulative incidence functions. Patients without an event or death before the event were censored at the last date of follow-up. Times to events were compared with the Cox univariable and multivariable proportional hazards regression model using the variables previously identified [12].

Results

Information on whether or not a re-TUR had been performed was available in 2277 (92.9%) of the 2451 eligible patients. In all, 935 (41.1%) of the 2277 patients underwent re-TUR and 1342 (58.9%) did not. Baseline patient and disease characteristics according to re-TUR and no re-TUR are reported in Table 1. Patients were more likely to have undergone a re-TUR if they had tumours of ≥3 cm (34.1% vs 22.6%), multifocal tumours (50.3% vs 23.3%) or did not receive maintenance BCG (41.2% vs 33.2%).

Muscle was present in the original TUR specimen in 1768 (72.1%) of the 2451 patients, not present in 416 (17.0%), and unknown in 267 (10.9%). In all, 276 (66.4%) of 416 patients underwent a re-TUR if muscle was not present in the

Table 1 Baseline characteristics of patients according to re-TUR status.

Variable	No re-TUR	Re-TUR	Re-TUR unknown	All patients
N	1342	935	174	2451
Age, years				
<70, *n* (%)	726 (52.4)	549 (39.6)	110 (7.9)	1385 (56.5)
≥70, *n* (%)	616 (57.8)	386 (36.2)	64 (6.0)	1066 (43.5)
Median (interquartile range)	69 (61–75)	67 (59–74)	67 (60–72)	68 (60–74)
N (%):				
Sex				
Male	1112 (55.3)	756 (37.6)	144 (7.2)	2012 (82.1)
Female	230 (52.4)	179 (40.8)	30 (6.8)	439 (17.9)
Tumour status				
Primary T1G3	1175 (53.9)	848 (38.9)	156 (7.2)	2179 (88.9)
Recurrent after non T1G3	167 (61.4)	87 (32.0)	18 (6.6)	272 (11.1)
Previous intravesical chemotherapy				
No	1261 (54.4)	895 (38.6)	164 (7.1)	2320 (94.7)
Yes	81 (61.8)	40 (30.5)	10 (7.6)	131 (5.3)
Muscle in primary TUR specimen				
No	130 (31.3)	276 (66.4)	10 (2.4)	416 (17.0)
Yes	1092 (61.8)	624 (35.3)	52 (2.9)	1768 (72.1)
Missing/unknown	120 (72.3)	35 (21.1)	112 (6.6)	267 (10.9)
Tumour grade				
WHO 1973 G3	1090 (64.0)	442 (26.0)	171 (10.0)	1703 (69.5)
WHO 2004 HG	978 (54.9)	799 (44.9)	3 (0.2)	1780 (72.6)
G3 and/or HG	1342 (54.8)	935 (38.1)	174 (7.1)	2451 (100)
Tumour focality				
Solitary	618 (64.1)	225 (23.3)	121 (12.6)	964 (39.3)
Multiple	631 (46.2)	687 (50.3)	47 (3.4)	1365 (55.7)
Missing/unknown	93 (76.2)	23 (18.9)	6 (4.9)	122 (5.0)
Largest tumour diameter, cm				
<3	806 (70.9)	257 (22.6)	74 (6.5)	1137 (46.4)
≥3	326 (58.2)	191 (34.1)	43 (7.7)	560 (22.8)
Missing/unknown	210 (27.9)	487 (64.6)	57 (7.6)	754 (30.8)
Concomitant CIS				
No	1019 (55.0)	694 (37.5)	139 (7.5)	1852 (75.6)
Yes	323 (53.9)	241 (40.2)	35 (5.8)	599 (24.4)
Invasion of prostatic urethra				
No	936 (70.0)	401 (30.0)	0	1337 (54.6)
Yes, without stromal invasion	26 (59.1)	18 (40.9)	0	44 (1.8)
Yes, with stromal invasion	2 (40.0)	3 (60.0)	0	5 (0.2)
Missing/unknown	378 (35.5)	513 (48.2)	174 (16.3)	1065 (43.4)
Pathology at re-staging TUR*				
No residual tumour	NA	267 (28.6)	NA	267 (28.6)
Ta	NA	378 (40.4)	NA	378 (40.4)
T1	NA	289 (30.9)	NA	289 (30.9)
CIS	NA	NA**	NA	NA**
Missing/unknown	NA	1 (0.1)	NA	1 (0.1)
Maintenance BCG				
No	753 (49.7)	624 (41.2)	138 (9.1)	1515 (61.8)
Yes	589 (62.9)	311 (33.2)	36 (3.9)	936 (38.2)

**Separate information on CIS at re-TUR was not available.*

specimen as compared with 624 (35.3%) of 1768 patients when muscle was present.

Table 2 presents the patient baseline characteristics according to re-TUR status and the presence or absence of muscle in the specimen of the first TUR. Multiple tumours were more likely to undergo a re-TUR when muscle was not present in the primary TUR, 83.2% vs 44.7% when muscle was present. Patients without muscle in the primary TUR were more likely to have received maintenance BCG if no re-TUR was performed.

Persistent disease at re-TUR was documented in 85.9% of patients in the absence of muscle in the primary TUR as compared to 65.2% when muscle had been reported in the primary TUR. Similarly, the rate of persistent T1 disease was higher when no muscle was reported in the first TUR (40.2%) as compared with that of a primary TUR with muscle in the specimen (26.6%).

The median duration of follow-up was 5.2 years. Table 3 shows the distribution of clinical outcomes across the four groups according to the presence or absence of muscle in the primary TUR and whether or not a re-TUR was performed.

Table 4 reports the results of the univariable and multivariable analyses of the effect of re-TUR on recurrence, progression, CSS and OS according to whether or not muscle was present in the primary TUR. Adjusting for the most important prognostic factors including age, number of tumours, tumour size, the presence of CIS, and the use of maintenance BCG, re-TUR in the absence of muscle had a borderline significant positive impact on time to recurrence [hazard ratio (HR) 0.67, 95% CI 0.42–1.04; $P = 0.08$), time to progression (HR 0.46, 95% CI 0.20–1.03; $P = 0.06$), duration of CSS (HR 0.31, 95% CI 0.09–1.08; $P = 0.07$) and OS (HR 0.48, 95% CI 0.23–1.00; $P = 0.05$). Re-TUR in the presence of muscle in the primary TUR specimen did not improve the

Table 2 Baseline characteristics of patients according to re-TUR status and the presence or absence of muscle in the specimen of the first TUR.

Variable	No muscle, no re-TUR	No muscle, re-TUR	Muscle, o re-TUR	Muscle, re-TUR	Unknown	All patients
N	130	276	1092	624	329	2451
Age, years						
<70, *n* (%)	74 (5.3)	173 (12.5)	582 (42.0)	361 (26.1)	195 (14.1)	1385 (56.5)
≥70, *n* (%)	56 (5.3)	103 (9.7)	510 (47.8)	263 (24.7)	134 (12.6)	1066 (43.5)
Median (interquartile range)	68 (61–75)	65 (57–73)	69 (61–75)	68 (60–74)	67 (61–74)	68 (60–74)
N (%)						
Sex						
Male	101 (5.0)	217 (10.8)	907 (45.1)	512 (25.5)	275 (13.7)	2012 (82.1)
Female	29 (6.6)	59 (13.4)	185 (42.1)	112 (25.5)	54 (12.3)	439 (17.9)
Tumour status						
Primary T1G3	110 (5.1)	244 (11.2)	967 (44.4)	575 (26.4)	283 (13.0)	2179 (88.9)
Recurrent after non T1G3	20 (7.4)	32 (11.8)	125 (46.0)	49 (18.0)	46 (16.9)	272 (11.1)
Previous intravesical chemotherapy						
No	118 (5.1)	263 (11.3)	1031 (44.4)	598 (25.8)	310 (13.4)	2320 (94.7)
Yes	12 (9.2)	13 (9.9)	61 (46.6)	26 (19.9)	19 (14.5)	131 (5.3)
Tumour focality						
Solitary	47 (4.9)	35 (3.6)	539 (55.9)	178 (18.5)	165 (17.1)	964 (39.3)
Multiple	48 (3.5)	238 (17.4)	541 (39.6)	438 (32.1)	100 (7.3)	1365 (55.7)
Missing/unknown	35 (28.7)	3 (2.5)	12 (9.8)	8 (6.6)	64 (52.5)	122 (5.0)
Largest tumour diameter, cm						
<3	65 (5.7)	35 (3.1)	684 (60.2)	210 (18.5)	143 (12.6)	1137 (46.4)
≥3	24 (4.3)	29 (5.2)	291 (52.0)	152 (27.1)	64 (11.4)	560 (22.8)
Missing/unknown	41 (5.4)	212 (28.1)	117 (15.5)	262 (34.8)	122 (16.2)	754 (30.8)
Concomitant CIS						
No	103 (5.6)	215 (11.6)	814 (44.0)	454 (24.5)	266 (14.4)	1852 (75.6)
Yes	27 (4.5)	61 (10.2)	278 (46.4)	170 (28.4)	63 (10.5)	599 (24.4)
Invasion of prostatic urethra						
No	82 (6.1)	53 (4.0)	812 (60.7)	342 (25.6)	48 (3.6)	1337 (54.6)
Yes, without stromal invasion	0	2 (4.6)	25 (56.8)	16 (36.4)	1 (2.3)	44 (1.8)
Yes, with stromal invasion	0	1 (20.0)	2 (40.0)	2 (40.0)	0	5 (0.2)
Missing/unknown	48 (4.5)	220 (20.7)	253 (23.8)	264 (24.8)	280 (26.3)	1065 (43.4)
Pathology at re-staging TUR*						
No residual tumour	NA	39 (14.1)	NA	217 (34.8)	11 (3.3)	267 (28.6)
Ta	NA	126 (45.7)	NA	240 (38.5)	12 (3.6)	378 (40.4)
T1	NA	111 (40.2)	NA	166 (26.6)	12 (3.6)	289 (30.9)
CIS	NA	NA**	NA	NA**	NA**	NA**
Missing/unknown	NA	0	NA	1 (.02)	NA	1 (0.1)
Maintenance BCG						
No	89 (5.9)	245 (16.2)	627 (41.4)	373 (24.6)	181 (12.0)	1515 (61.8)
Yes	41 (4.4)	31 (3.3)	465 (49.7)	251 (26.8)	148 (15.8)	936 (38.2)

**Separate information on CIS at re-TUR was not available.*

Table 3 Clinical outcome according to re-TUR status and the presence or absence of muscle in the specimen of the first TUR.

Variable	No muscle, no re-TUR, *n* (%)	No muscle, re-TUR, *n* (%)	Muscle, no re-TUR, *n* (%)	Muscle, re-TUR, *n* (%)	Unknown, *n* (%)	All patients, *n* (%)
N	130	276	1092	624	329	2451
Recurrence						
No	52 (40.0)	115 (41.7)	561 (51.4)	281 (45.0)	198 (60.2)	1207 (49.3)
Yes	60 (60.0)	161 (58.3)	531 (48.6)	343 (55.0)	131 (39.8)	1244 (50.7)
Progression						
No	102 (78.5)	238 (86.2)	871 (79.8)	504 (80.8)	271 (82.4)	1986 (81.0)
Yes	28 (21.5)	38 (13.8)	221 (20.2)	120 (19.2)	58 (17.6)	465 (19.0)
Cancer specific mortality						
No	115 (88.5)	257 (93.1)	998 (91.4)	563 (90.2)	297 (90.3)	2230 (91.0)
Yes	15 (11.5)	19 (6.9)	94 (8.6)	61 (9.8)	32 (9.7)	221 (9.0)
OS						
Alive	89 (68.5)	219 (79.4)	812 (74.4)	485 (77.7)	250 (76.0)	1855 (75.7)
Dead	41 (31.5)	57 (20.6)	280 (25.6)	139 (22.3)	79 (24.0)	596 (24.3)

Table 4 Univariable and multivariable analyses of time to recurrence, time to progression, duration of bladder CSS and OS.

	Univariable		Multivariable	
	HR (95% CI)	P	HR (95% CI)	P
Recurrence*				
Muscle (no/yes)	0.95 (0.92–0.98)	0.001	0.95 (0.91–0.99)	0.04
Re-TUR (no/yes), no muscle	0.97 (0.74–1.27)	0.80	0.67 (0.42–1.04)	0.08
Re-TUR (no/yes), muscle	1.30 (1.14–1.49)	<0.001	1.38 (1.17–1.64)	<0.001
Re-TUR (no/yes), all patients	1.28 (1.14–1.43)	<0.001	1.27 (1.09–1.49)	0.002
Progression**				
Muscle (no/yes)	0.99 (0.94–1.03)	0.56	1.00 (0.94–1.06)	0.97
Re-TUR (no/yes), no muscle	0.59 (0.36–0.96)	0.03	0.46 (0.20–1.03)	0.06
Re-TUR (no/yes), muscle	1.01 (0.81–1.26)	0.95	1.20 (0.93–1.55)	0.17
Re-TUR (no/yes), all patients	0.92 (0.76–1.11)	0.39	1.10 (0.86–1.39)	0.45
CSS***				
Muscle (no/yes)	1.03 (.97–1.09)	0.28	1.08 (1.01–1.15)	0.03
Re-TUR (no/yes), no muscle	0.56 (0.29–1.11)	0.10	0.31 (0.09–1.08)	0.07
Re-TUR (no/yes), muscle	1.29 (0.93–1.78)	0.13	1.60 (1.11–2.31)	0.01
Re-TUR (no/yes), all patients	1.09 (0.82–1.43)	0.56	1.32 (0.95–1.84)	0.10
OS***				
Muscle (no/yes)	0.99 (0.95–1.03)	0.62	1.02 (0.98–1.07)	0.98
Re-TUR (no/yes), no muscle	0.66 (0.44–0.99)	0.05	0.48 (0.23–1.00)	0.05
Re-TUR (no/yes), muscle	0.99 (0.81–1.22)	0.95	1.23 (0.97–1.56)	0.09
Re-TUR (no/yes), all patients	0.92 (0.78–1.10)	0.37	1.09 (0.88–1.35)	0.45

*HR <1: better outcome when muscle is present, better outcome when a re-TUR is done. HR >1: worse outcome when muscle is present, worse outcome when a re-TUR is done. *Recurrence adjusted for number of tumours, tumour size and maintenance BCG; **Progression adjusted for age, tumour size, CIS and maintenance BCG; ***Survival adjusted for age, tumour size and maintenance BCG.*

outcome for any of the endpoints after adjusting for prognostic factors. Time-to-event curves of the four groups for the time to recurrence, progression, and the duration of CSS and OS are given in Figs 1–4.

Discussion

The importance of a re-staging TUR has been supported by accumulating evidence in high-risk NMIBC, mainly in the worst subgroup of T1G3 tumours [4,13]. The finding of muscle-invasive disease in up to 50% of patients with clinical T1G3 tumours undergoing cystectomy suggests that this disease category is often under staged [14]. Even more strikingly, up to 80% of patients with T1 NMIBCs have persistent disease at re-TUR and 30% are muscle invasive [4]. Our present results, generated from a large multicentre series of patients with primary T1-HG/G3 bladder cancer receiving BCG, are consistent with these figures: of a total of 935 (38.1%) patients undergoing re-TUR, 71.3% had residual disease, with 30.9% stage T1 and 40.4% stage Ta.

In this context, re-TUR has been strongly advocated in an attempt to overcome quality issues of the initial TUR, some of them occurring even in expert hands [4,15], and to improve disease outcome [4,7]. In a randomised study, patients with T1 disease at first TUR had a two-fold increased

Fig. 1 Time to recurrence according to the presence (M+) or absence (M–) of muscle in the primary TUR specimen and whether or not a re-TUR was carried out.

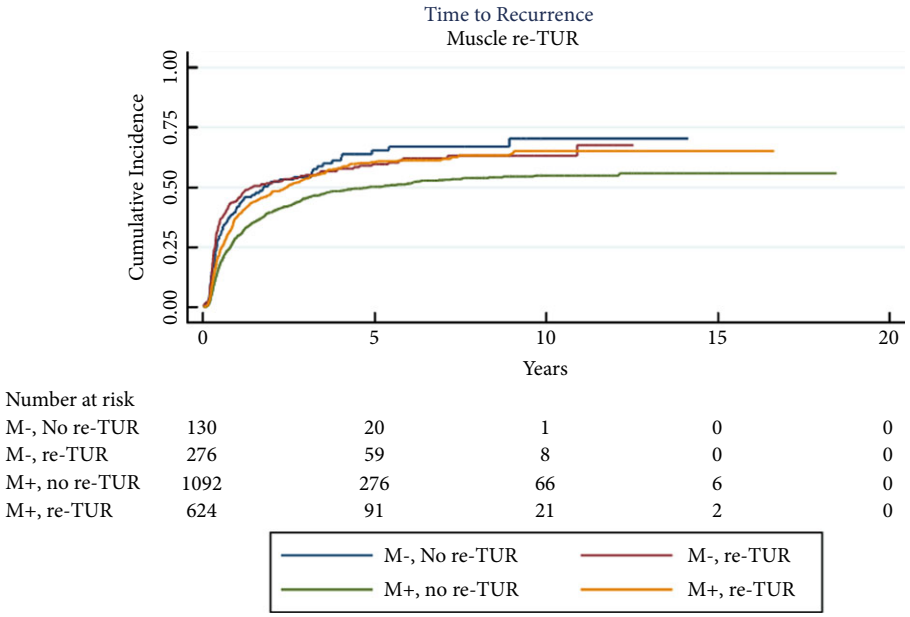
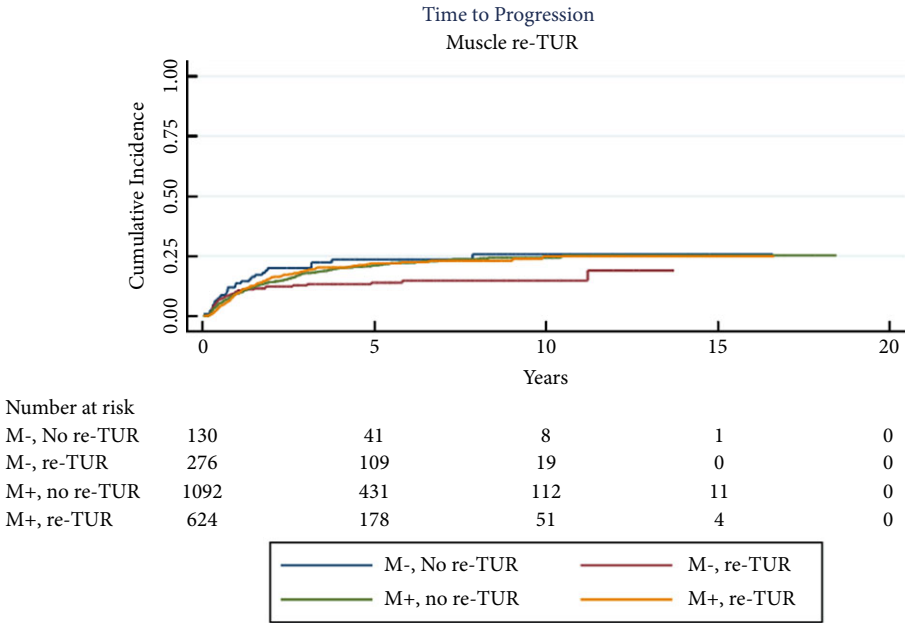


Fig. 2 Time to progression according to the presence (M+) or absence (M–) of muscle in the primary TUR specimen and whether or not a re-TUR was carried out.



risk of recurrence and a four-fold increased risk of progression when re-TUR was not done [7]. In a large retrospective series of patients with Ta and T1 high-risk NMIBC treated with BCG, the 3-month recurrence rate was as low as 9% for those with a re-TUR (87% of 1021 patients) as compared with 55% for the group treated with a single TUR [13].

Others have recently questioned the necessity for all patients with high-risk NMIBC to undergo a repeat TUR within 4–6 weeks of the initial TUR. In a retrospective series of 200 patients with T1G3 NMIBC, re-TUR impacted positively on short-term outcomes but did not play a role on the long-term risk of recurrence, progression and CSS [8]. Another study pointed out that staging inaccuracies of the primary TUR

Fig. 3 Time to death due to bladder cancer according to the presence (M+) or absence (M–) of muscle in the primary TUR specimen and whether or not a re-TUR was carried out.

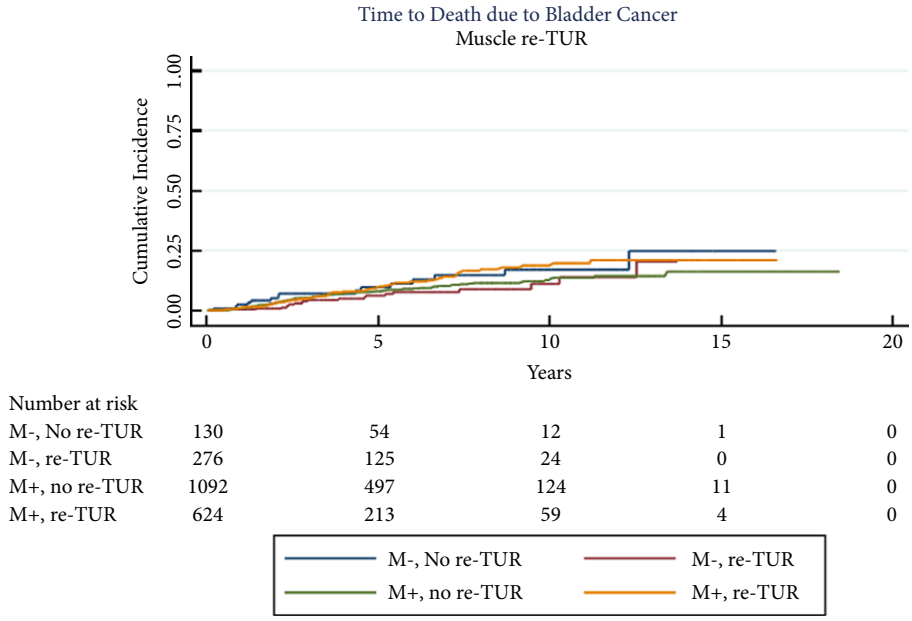
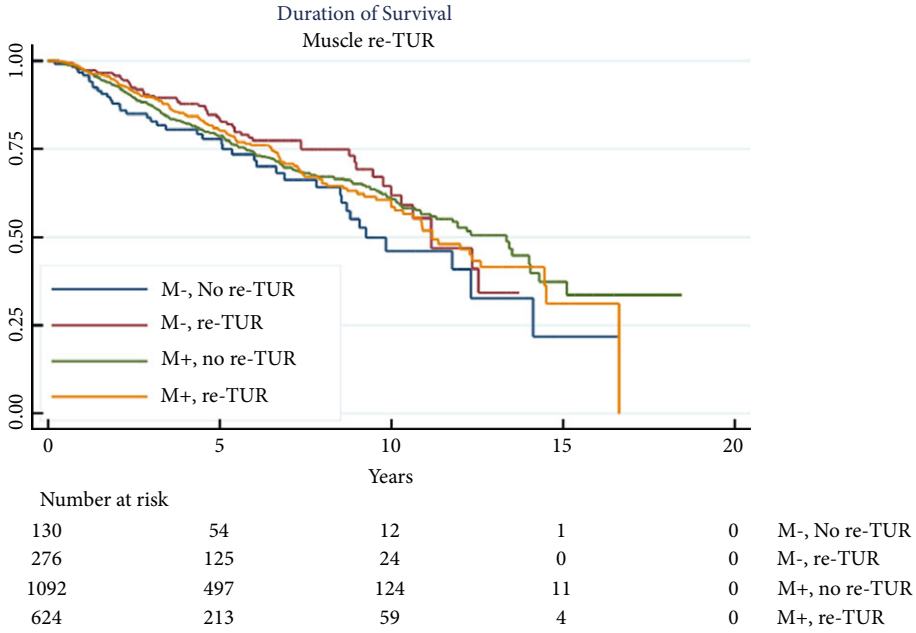


Fig. 4 Duration of survival according to the presence (M+) or absence (M–) of muscle in the primary TUR specimen and whether or not a re-TUR was carried out.



may depend upon the presence or absence of detrusor muscle in the specimen, the latter indicating that the TUR was not deep enough to exclude involvement of the muscularis propria [15]. The risk of downstaging at second TUR was dramatically decreased when muscle was present in the primary TUR [5,16]. Absence of muscle in the primary TUR specimen was also acknowledged as an independent predictor of progression to muscle-invasive disease in a small retrospective series in patients with T1G3 bladder cancer [10]. Tumour status at second TUR was found to be significantly associated with risk of recurrence, treatment failure and borderline significant for cancer-specific death in a

prospective, randomised study conducted by the Nordic Association of Urology of 250 patients with T1 bladder cancer randomised to BCG or epirubicin plus interferon-α2b [17].

In our present series, 1768 of the 2184 (81.0%) patients for whom the information was available had detrusor muscle in the primary TUR specimen. This proportion varied between 89.4% for those who did not have a second TUR and 69.3% for those with a re-TUR, suggesting that absence of muscle in the primary TUR may have played a role in the decision for re-TUR. Detrusor muscle documented in the primary TUR specimen was associated with a lower, yet still consistent, rate of any residual disease (65.1% vs 85.9%) and chiefly of T1 NMIBC (26.6% vs 40.2%) at re-TUR as compared with absence of muscle.

Re-TUR impacted favourably on the endpoints of recurrence, progression, CSS and OS only in the absence of muscle at first TUR. We failed to show an advantage of a re-TUR after a first TUR that included detrusor muscle in the pathological specimen. Even more strikingly, such patients showed a higher risk of recurrence even after adjusting for prognostic factors such as tumour multiplicity, tumour size, and the use of maintenance BCG. We cannot provide a rational explanation for this paradoxical finding.

We can speculate that the effect of BCG, which has been shown to ablate residual disease in a marker lesion study [9] and to reduce the progression rate [18], could account for the lack of improvement in outcome with re-TUR as compared with no re-TUR when muscle was included in the first TUR. Notably, in the only study [7] reporting a significantly higher risk of disease progression in T1 NMIBC not receiving immediate re-TUR, patients were treated with intravesical chemotherapy, a treatment which has never been confirmed to prevent disease progression [1]. Nonetheless, BCG may not be effective enough to replace the need for a second TUR when muscle has not been included in the first TUR, potentially because of the significant amount of residual disease.

Our present results better refine those of a recent retrospective series of 210 untreated patients with T1G3 NMIBC, where an early re-TUR did not appear to change the long-term prognosis [8]. In the latter study, muscle in the specimen was not considered. The main clinical implication of our present findings is that re-TUR may be avoided in patients with T1-HG/G3 bladder cancer where the first TUR was deep enough to include muscle in the TUR specimen. This is likely to translate into a positive impact on the burden of healthcare costs of bladder cancer [11], while avoiding exposure of the patient to the risks of additional surgery [8].

Some limitations of our present study are to be acknowledged. The first is the lack of knowledge about the proportion of patients diagnosed with muscle-invasive disease at re-TUR that were excluded by our study design. The rate of T2 disease at re-TUR, which has been reported to be between 7% and 30% [4,7], represents the main strength in support of a re-TUR [1]. The risk of downstaging is significantly reduced but not eliminated by inclusion of muscle in the specimen of the first TUR [16]. Similarly, the patients in our present study that did not have a re-TUR, almost certainly included a higher proportion of 'downstaged' T1G3 disease as compared with the re-TUR patients. However, the finding that re-TUR improved prognosis only when muscle was not present in primary TUR suggests that the risk of downstaging at primary TUR is probably minimal when muscle is included, making re-TUR unnecessary in this latter instance. Secondly, as re-TUR was not determined by randomisation, a number of selection biases that the retrospective design of the present study cannot address may have accounted for the decision to do a re-TUR. In addition, an incomplete TUR at first TUR may also have influenced the urologists to schedule a patient for a re-TUR.

In conclusion, our present analysis of a large retrospective series of patients with T1-HG/G3 bladder cancer treated with BCG suggests that immediate re-TUR does not improve the long-term disease outcomes of patients with detrusor muscle included in the specimen of the primary TUR. A prospective study would allow confirmation of as to whether immediate re-TUR may be spared in such cases.

Conflicts of Interest

None disclosed.

References

1 **Babjuk M, Burger M, Zigeuner R et al**. EAU guidelines on non-muscle-invasive urothelial carcinoma of the bladder: update 2013. *Eur Urol* 2013; 64: 639–53

2 **Cookson MS, Herr HW, Zhang ZF, Soloway S, Sogani PC, Fair WR**. The treated natural history of high risk superficial bladder cancer: 15-year outcome. *J Urol* 1997; 158: 62–7

3 **Herr HW, Donat SM**. A re-staging transurethral resection predicts early progression of superficial bladder cancer. *BJU Int* 2006; 97: 1194–8

4 **Herr HW**. Role of re-resection in non-muscle-invasive bladder cancer. *ScientificWorldJournal* 2011; 11: 283–8

5 **Herr HW**. The value of a second transurethral resection in evaluating patients with bladder tumors. *J Urol* 1999; 162: 74–6

6 **Hall MC, Chang SS, Dalbagni G et al**. Guideline for the management of nonmuscle invasive bladder cancer (stages Ta, T1, and Tis): 2007 update. *J Urol* 2007; 178: 2314–30

7 **Divrik RT, Sahin AF, Yildirim U, Altok M, Zorlu F**. Impact of routine second transurethral resection on the long-term outcome of patients with newly diagnosed pT1 urothelial carcinoma with respect to recurrence, progression rate, and disease-specific survival: a prospective randomised clinical trial. *Eur Urol* 2010; 58: 185–90

8 **Angulo JC, Palou J, García-Tello A, de Fata FR, Rodríguez O, Villavicencio H**. Second transurethral resection and prognosis of high-grade non-muscle invasive bladder cancer in patients not receiving bacillus Calmette-Guérin. *Actas Urol Esp* 2014; 38: 164–71

9 **Mack D**, **Höltl W**, **Bassi P et al**. The ablative effect of quarter dose bacillus Calmette-Guerin on a papillary marker lesion of the bladder. *J Urol* 2001; 165: 401–3

10 **Shindo T**, **Masumori N**, **Kitamura H et al**. Clinical significance of definite muscle layer in TUR specimen for evaluating progression rate in T1G3 bladder cancer: multicenter retrospective study by the Sapporo Medical University Urologic Oncology Consortium (SUOC). *World J Urol* 2014;32:1281–5.

11 **Svatek RS**, **Hollenbeck BK**, **Holmäng S et al**. The economics of bladder cancer: costs and considerations of caring for this disease. *Eur Urol* 2014;66:253–62.

12 **Gontero P**, **Sylvester R**, **Pisano F et al**. Prognostic factors and risk groups in T1G3 non-muscle-invasive bladder cancer patients initially treated with bacillus Calmette-Guérin: results of a retrospective multicenter study of 2451 patients. *Eur Urol* 2015; 67: 74–82

13 **Sfakianos JP**, **Shariat SF**, **Favaretto RL**, **Rioja J**, **Herr HW**. Impact of smoking on outcomes after intravesical bacillus Calmette-Guérin therapy for urothelial carcinoma not invading muscle of the bladder. *BJU Int* 2011; 108: 526–30

14 **Fritsche HM**, **Burger M**, **Svatek RS et al**. Characteristics and outcomes of patients with clinical T1 grade 3 urothelial carcinoma treated with radical cystectomy: results from an international cohort. *Eur Urol* 2010; 57: 300–9

15 **Ritch CR**, **Clark PE**, **Morgan TM**. Restaging transurethral resection for non-muscle invasive bladder cancer: who, why, when, and how? *Urol Clin North Am* 2013; 40: 295–304

16 **Dutta SC**, **Smith JA Jr**, **Shappell SB**, **Coffey CS**, **Chang SS**, **Cookson MS**. Clinical under staging of high risk nonmuscle invasive urothelial carcinoma treated with radical cystectomy. *J Urol* 2001; 166: 490–3

17 **Hemdan T**, **Johansson R**, **Jahnson S**, **Hellström P**, **Tasdemir I**, **Malmström PU**; Members of the Urothelial Cancer Group of the Nordic Association of Urology. 5-Year outcome of a randomized prospective study comparing bacillus Calmette-Guérin with epirubicin and interferon-α2b in patients with T1 bladder cancer. *J Urol* 2014; 191: 1244–9

18 **Sylvester RJ**, **van der Meijden AP**, **Lamm DL**. Intravesical bacillus Calmette-Guerin reduces the risk of progression in patients with superficial bladder cancer: a meta-analysis of the published results of randomized clinical trials. *J Urol* 2002; 168: 1964–70

Correspondence: Paolo Gontero, Division of Urology, Department of Surgical Sciences, Città della Salute e della Scienza di Torino, C.so Bramante 88/90, 10126 Turin, Italy.

e-mail: paolo.gontero@unito.it

Abbreviations: CIS, carcinoma *in situ*; CSS, cancer-specific survival; G3, Grade 3; HG, high grade; HR, hazard ratio; NMIBC, non-muscle-invasive bladder cancer; OS, overall survival; TUR, transurethral resection.