World Journal of Urology (2018) 36:1621–1627
https://doi.org/10.1007/s00345-018-2299-2

ORIGINAL ARTICLE

Recurrence, progression and cancer-specific mortality according to stage at re-TUR in T1G3 bladder cancer patients treated with BCG: not as bad as previously thought

J. Palou[1] · F. Pisano[1,2] · R. Sylvester[3] · S. Joniau[4] · V. Serretta[5] · S. Larré[6] · S. Di Stasi[7] · B. van Rhijn[8] · A. J. Witjes[9] · A. Grotenhuis[9] · R. Colombo[10] · A. Briganti[10] · M. Babjuk[11] · V. Soukup[11] · P. U. Malmstrom[12] · J. Irani[13] · N. Malats[14] · J. Baniel[15] · R. Mano[15] · T. Cai[16] · E. K. Cha[17] · P. Ardelt[18] · J. Varkarakis[19] · R. Bartoletti[20] · G. Dalbagni[21] · S. F. Shariat[22] · E. Xylinas[23] · R. J. Karnes[24] · P. Gontero[2]

Received: 20 February 2018 / Accepted: 13 April 2018 / Published online: 2 May 2018

Abstract

Purpose The goals of transurethral resection of a bladder tumor (TUR) are to completely resect the lesions and to make a correct diagnosis to adequately stage and treat the patient. Persistent disease after TUR is not uncommon and is why re-TUR is recommended in T1G3 patients. When there is T1 tumor in the re-TUR specimen, very high risks of progression (82%) have been reported. We analyze the risks of recurrence, progression to muscle-invasive disease and cancer-specific mortality (CSM) according to tumor stage at re-TUR in T1G3 patients treated with BCG.

Methods In our retrospective cohort of 2451 T1G3 patients, 934 patients (38.1%) underwent re-TUR. 667 patients had residual disease (71.4%): Ta in 378 (40.5%), T1 in 289 (30.9%) patients. Times to recurrence, progression and CSM in the three groups were estimated using cumulative incidence functions and compared using the Cox regression model.

Results During a median follow-up of 5.2 years, 512 patients recurred. The recurrence rate was significantly higher in patients with a T1 at re-TUR ($P < 0.001$). Progression rates differed according to the pathology at re-TUR, 25.3% in T1, 14.6% in Ta and 14.2% in case of no residual tumor ($P < 0.001$). Similar trends were seen in both patients with and without muscle in the original TUR specimen.

Conclusions Patients with T1G3 tumors and no residual disease or Ta at re-TUR have better recurrence, progression and CSM rates than previously reported, with a CSM rate of 13.1 and a 25.3% progression rate in re-TUR T1 disease.

Keywords Non-muscle invasive bladder cancer · Re-transurethral resection of the bladder · Recurrence · Progression

Introduction

Over 120,000 new cases of bladder cancer are diagnosed each year in Europe, with a 5-year prevalence of around 410,000, consequently resulting in an important contribution to health costs [1]. About 75% of newly diagnosed bladder cancers are non-muscle-invasive (NMIBC), limited to the mucosa (Ta) or the lamina propria (T1).

Even though T1 lesions belong to the group of NMIBC, they are more likely than Ta lesions to progress to muscle-invasive tumors, with a subsequent worsening of survival. Among high-risk NMIBC, there is a sub-group of very high risk patients characterized by high recurrence and progression rates despite therapy [2, 3]. EORTC and CUETO risk tables are useful to calculate the probability of recurrence and progression [4, 5], however, they have limitations when it comes to predicting the biological behavior of the tumor to decide when radical cystectomy is mandatory [6]. Currently, treatment strategies of NMIBC are essentially based on transurethral resection (TUR) of the bladder and adjuvant intravesical instillations which take into account a patient's risk of recurrence and progression [3].

High rates of residual disease after the first TUR have been reported, ranging from 22 to 74% in Ta disease and

R. Sylvester was formerly with EORTC Headquarters, Brussels, Belgium.

✉ F. Pisano
francescapisano85@gmail.com

Extended author information available on the last page of the article

from 26.5 to 81.5% in T1 disease [7]. To minimize the risk of residual disease, European Association of Urology (EAU) Guidelines recommend repeat TUR (re-TUR) within 4–6 weeks when lamina propria involvement or high-grade disease is diagnosed at the initial TUR [3].

According to the literature, patients with residual disease at re-TUR are considered to have a higher risk of progression and cancer-specific mortality (CSM) compared to those patients without residual disease [8]. In some series, the risk of progression to muscle invasive or persistent T1 at re-TUR reached 76% [9]. Since progression is associated with a poor prognosis, radical cystectomy is strongly recommended in patients with residual T1 at re-TUR [10]. Nevertheless, early cystectomy, advocated by some authors as an alternative to BCG, has shown long-term survival rates not exceeding 80% [11], meaning that it does not guarantee a cure of T1G3 tumors. Furthermore, radical cystectomy (RC) is a complex surgical procedure, affected by significant morbidity rates [12]. This aspect should be carefully considered in patients with a poor performance status, in which RC is associated with poorer outcomes and a higher incidence of complications [13]. Patient selection plays a crucial role to correctly balance tumor prognosis and surgical risks. From this perspective, oncological status at re-TUR should be carefully evaluated to predict the real risk of progression and consequently to select the best candidates for surgery.

In the current study, we retrospectively analyzed the risk of recurrence, progression and CSM according to the tumor stage at re-TUR in a large cohort of T1G3 patients treated with BCG.

Materials and methods

Design and setting

The study design and patient selection criteria have been already reported by Gontero et al. [14]. Briefly, patients with primary T1G3 (WHO 1973)/T1 high-grade (HG) (ISUP 1998/WHO 2004) tumors or secondary T1G3/HG disease in a previously BCG-naïve non-T1G3/HG NMIBC tumor formed this retrospective study cohort provided they received at least a full induction course of BCG between 1990 and 2011.

The following patient and tumor characteristics were collected: age, gender, smoking history and intensity, exposure to chemical compounds, tumor status (primary or recurrent), previous intravesical chemotherapy, tumor size (< 3 cm versus > 3 cm) tumor focality (solitary versus multiple), presence of concomitant CIS, prostatic urethra involvement with or without stromal invasion, presence of muscle in the primary tissue specimen, BCG dose and total number of instillations. Information on re-TUR (defined as a second TUR performed within 4–6 weeks after the initial TUR and before BCG administration) was also recorded. Results of pathology at re-TUR were categorized as: no evidence of disease, persistent disease with lower stage (Ta), or persistent T1 disease. Patients with muscle-invasive disease at re-TUR did not match the study inclusion criteria and were, therefore, excluded upfront.

Statistical analysis

Times to events were calculated taking the date of starting BCG as time zero. To take into account patients who died before observing the event of interest (competing risk), times to recurrence, progression and death due to bladder cancer according to residual tumor characteristics at restaging TUR were estimated using cumulative incidence functions and compared using the Cox proportional hazards regression model. Patients without an event or death prior to the event were censored at the last date of follow-up. Percentages were compared using a Chi-square test.

Results

A re-TUR was performed in 935 (41.1%) of the 2451 eligible patients. Baseline and disease characteristics of patients who underwent re-TUR are reported in Table 1. Eight hundred and forty-eight patients (90.7%) had a primary T1G3 tumor; concomitant CIS was diagnosed in 241 patients (25.8%). In 624 patients (66.8%), there was muscle in the first TUR specimen. A history of multiple and large (> 3 cm) tumors was present in 687 (73.5%) and 191 (20.4%) patients, respectively. Persistent disease at re-TUR was documented in 667 patients (71.3%), Ta in 378 (40.4%) and T1 in 289 (30.9%) of the cases (Table 2). 624 patients (66.8%) received only induction BCG. The median follow-up was 5.2 years.

Table 2 presents the pathology at re-TUR according to the presence or absence of muscle at first TUR. In the absence of muscle at first TUR, persistent disease at re-TUR was documented in 237 (85.9%) of 276 cases as compared to 406 (65.1%) of the 624 cases with muscle at the first TUR, $P < 0.001$. Likewise, 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%), $P < 0.001$.

Table 3 and Figs. 1, 2 and 3 present the effect of the pathology at re-TUR on event rates and time to event for recurrence, progression and CSM, respectively. Overall, 512 (54.8%) of 934 patients with known pathology recurred and 166 (17.8%) progressed to muscle-invasive disease. Patients with T1 tumors were more likely to recur compared to patients with Ta tumors and patients without residual disease (71.6, 51.1 and 41.9%, respectively) and

Table 1 Baseline patient characteristics in 935 patients undergoing re-TUR

Age, years	
< 70, *n* (%)	549 (58.7)
≥ 70, *n* (%)	386 (41.3)
Median (interquartile range)	67 (59–74)
Sex	
Male	756 (80.9)
Female	179 (19.1)
Tumor status	
Primary T1G3	848 (90.7)
Recurrent after non-T1G3	87 (9.3)
Previous intravesical chemotherapy	
No	895 (95.8)
Yes	40 (4.2)
Muscle in primary TUR specimen	
No	276 (29.5)
Yes	624 (66.8)
Missing/unknown	35 (3.7)
Tumor grade	
WHO 1973 G3	442 (47.2)
WHO 2004 HG	799 (85.4)
G3 and/or HG	935 (100)
Tumor focality	
Solitary	225 (24.1)
Multiple	687 (73.5)
Missing/unknown	23 (2.4)
Largest tumor diameter (cm)	
< 3	257 (27.5)
≥ 3	191 (20.4)
Missing/unknown	487 (51.2)
Concomitant CIS	
No	694 (74.2)
Yes	241 (25.8)
Invasion of prostatic urethra	
No	401 (42.9)
Yes, without stromal invasion	18 (1.9)
Yes, with stromal invasion	3 (0.3)
Missing/unknown	513 (54.9)
Pathology at re-staging TUR[a]	
No residual tumor	267 (28.6)
Ta	378 (40.4)
T1	289 (30.9)
CIS	NA[a]
Missing/unknown	1 (0.1)
Maintenance BCG	
No	624 (66.8)
Yes	311 (33.2)

[a]Separate information on CIS at re-TUR was not available

had a shorter time to recurrence (Fig. 1, $P < 0.001$). Progression rates according to the pathology at re-TUR were higher in T1 patients (25.3% in T1 patients, 14.6% in Ta patients and 14.2% in case of no residual tumor) and the time to progression was shorter (Fig. 2, $P < 0.001$). Similar trends were seen in patients with and in patients without muscle in the original TUR specimen. Overall, 202 patients (21.6%) died, 85 (9.1%) due to bladder cancer. CSM was higher in T1 patients compared to Ta patients and patients without residual disease (13.1, 8.2 and 6.0%, respectively) and T1 patients had a shorter time to death due to bladder cancer (Fig. 3, $P = 0.001$).

For all three endpoints of time to recurrence, progression and CSM, pathology at re-TUR was the most important prognostic factor in a multivariate model, which also included tumor multiplicity, the presence or absence of concomitant CIS and whether or not the patient received maintenance BCG.

Discussion

In accordance with the available literature [9, 10, 15, 16], we found that patients with T1 residual disease at re-TUR had higher recurrence and progression rates and shorter times to recurrence and progression compared to patients with no residual disease or with Ta tumors. The presence of residual disease at re-TUR was also associated with a higher CSM and a shorter time to death due to bladder cancer, especially for patients with persistent T1 disease. Subgroup analyses revealed similar outcomes regardless of the presence or absence of muscle in the primary TUR specimen.

The role of pathology at re-TUR as a prognostic factor has been supported by accumulating evidence in high-risk NMIBC, mainly in the worst group of T1G3 lesions. The presence of a T1 residual tumor in the re-TUR specimen has especially been advocated as a strong indication for radical treatment. Herr et al. [9] evaluated clinical outcomes according to the pathology at re-TUR in 710 patients. The progression rate for patients with residual T1 disease was 76%, while in case of no residual tumor or tumor < T1, the risk of disease progression decreased to 14%. One year later, the same group reported a 82% of progression rate in patients with residual T1 disease at re-TUR, with a median survival of 15 months [10]. Due to this dramatic worsening of prognosis, the authors suggested to completely abandon conservative treatment and do an immediate cystectomy in case of T1 disease at re-TUR. More recently, Bishr et al. [8] reached similar conclusions. In their population of 94 NMIBC patients, the risk of progression was significantly higher in the presence of residual disease at re-TUR. Moreover, the pathological stage at re-TUR was an independent

Table 2 Pathology at re-TUR according to the presence or absence of muscle in the specimen of first TUR

Variable	No muscle at first TUR, *N* (%)	Muscle at first TUR, *N* (%)	Muscle at first TUR unknown, *N* (%)	All patients
Patients	276	624	35	935
Pathology at re-TUR[a]				
No residual tumor	39 (14.1)	217 (34.8)	11 (31.4)	267 (28.6)
Ta	126 (45.7)	240 (38.5)	12 (34.3)	378 (40.4)
T1	111 (40.2)	166 (26.6)	12 (34.3)	289 (30.9)
CIS	NA[a]	NA[a]	NA[a]	NA[a]
Missing/unknown	0	1 (0.02)	0	1 (0.1)

[a]Separate information on CIS at re-TUR was not available

Table 3 Clinical outcomes according to pathology at re-TUR in 934 patients

Residual tumor at re-TUR	Recurrence *N* (%)	Progression *N* (%)	CSM *N* (%)
No residual tumor (267 patients)	112 (41.9)	38 (14.2)	16 (6.0)
Ta tumor (378 patients)	193 (51.1)	55 (14.6)	31 (8.2)
T1 tumor (289 patients)	207 (71.6)	73 (25.3)	38 (13.1)
Total (934 patients)	512 (54.8)	166 (17.8)	85 (9.1)
P value	$P<0.001$	$P<0.001$	$P=0.01$

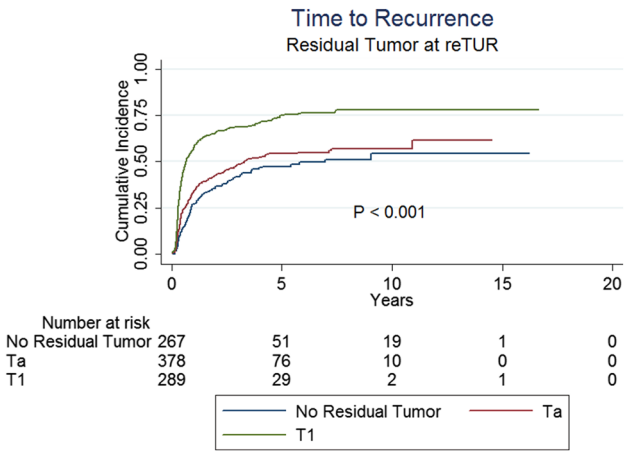

Fig. 1 Time to recurrence according to the presence or absence of residual disease at re-TUR and the pathology at re-TUR

predictor of recurrence-free- and progression-free survival in multivariate analysis.

Even if our results have confirmed the increased risk of progression to muscle-invasive disease in patients with residual T1 disease, we could not confirm an increased risk of progression in patients with residual Ta disease. Moreover, in patients who were T1 at re-TUR, we found a progression rate of 25.3% as compared to 14% in both patients with no residual tumor and in patients with residual Ta tumors.

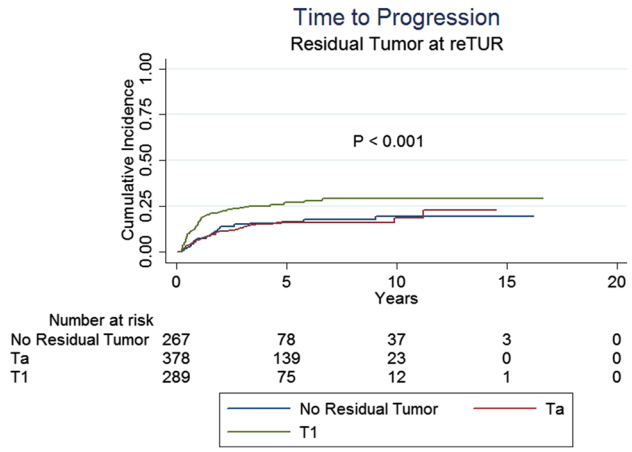

Fig. 2 Time to progression according to the presence or absence of residual disease at re-TUR and the pathology at re-TUR

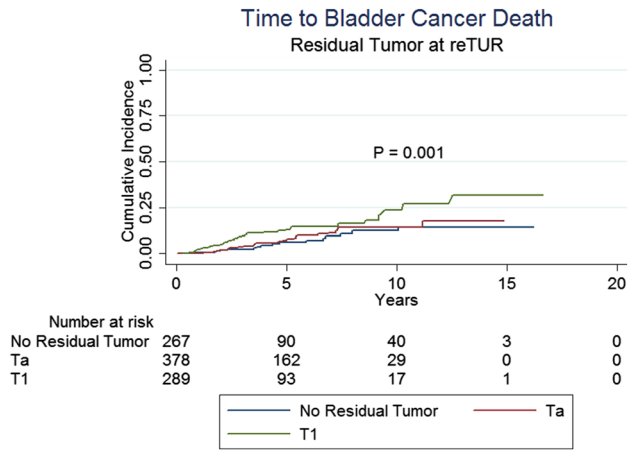

Fig. 3 Time to bladder cancer death according to the presence or absence of residual disease at re-TUR and the pathology at re-TUR

Similar progression rates were recently obtained by Gordon et al. In their retrospective cohort of 932 patients with high-risk NMIBC, those with T1 disease at re-resection had a risk

of progression of 22% [17]. Since these progression rates are not as high as previously reported in the other series, conservative management may still be considered with a very close follow-up in these high-risk patients, deferring radical cystectomy except in case of a high recurrence rate or progression to muscle-invasive disease.

In the urological community, the timing and patient selection for radical cystectomy in high-risk NMIBC remains an open debate. Dalbagni et al. [15] failed to find a significant difference in survival between patients who underwent immediate radical cystectomy and patients treated with delayed surgery, although the stage on restaging TUR was significantly associated with the decision to perform a deferred cystectomy. These findings suggest that the pathology at re-TUR alone is probably not enough to select the group of patients who could really benefit from an early radical treatment. According to Gontero et al. [18], 79% of T1G3 patients did not progress with up to 10 years of follow-up and cystectomy appeared to be an overtreatment in at least 70% of these high-risk patients. Regardless of the selection criteria, even if cystectomy is given to all high-risk NMIBC, the chances of cure are not 100% [19, 20]. The goal of delaying cystectomy is to better balance the risk of dying of disease and the risk of overtreatment with subsequent morbidity. Radical cystectomy still represents an invasive treatment with quite high complication rates, especially in elderly patients since age and pre-operative comorbidities are traditionally considered to be determinant factors for surgical outcome [21].

The main clinical implication of our findings is that a T1 tumor at re-TUR should not be considered alone as an absolute contraindication to a bladder-sparing approach, as indicated by Herr et al., who has suggested to completely abandon conservative treatment and to do an immediate cystectomy in case of T1 disease at re-TUR.

Some limitations of this study are to be acknowledged. First and foremost, this is a retrospective analysis. Consequently, the accuracy in reporting prognostic factors and tumor characteristics suffered from missing data for some variables, for example tumor size, and a lack of standardized assessment. Moreover, there was no central pathology review. Secondly, our series has been derived from a large retrospective T1G3 population [14] in which re-TUR was not determined by randomisation. Our re-TUR population mainly presented multiple and large tumors at first resection; moreover, an incomplete first TUR may have affected the decision to perform a re-TUR. All these aspects make the re-TUR population a selected one [17] and could explain the high rate of residual disease we found in our patients. By the way, rates of residual disease up to 60% were recently showed in a retrospective series of high-risk NMIBC [17]. Moreover, a recent review on re-TUR confirmed rates of residual disease ranging from 20 to 71% for T1 tumors [22]. Lastly, patients diagnosed with muscle-invasive disease at re-TUR were excluded by our study design and consequently no data about their prognosis are available.

Further studies are needed to individualize the clinical, pathological and molecular markers that are able to accurately select the best candidates for an immediate radical cystectomy.

Conclusions

In patients with T1G3 tumors who are treated with BCG, those with no residual disease or Ta tumor at re-TUR have better recurrence, progression and CSM rates than those with T1 tumor. Furthermore, a progression rate of 25.3% in case of T1 tumor at re-TUR is far lower than previously reported and does not a priori exclude the conservative management of these patients.

Acknowledgements The authors declare that the development of the manuscript was not supported by an honorarium, a grant, or any other sources of support, including sponsorship or any material sources of support.

Authors' contributions Study concept and design: JP, FP, PG. Acquisition of data: FP, SJ, VS, SL, SS, BR, AW, AG, RC, AB, MB, VS, PUM, JI, NM, JB, RM, TC, EC, PA, JV, RB, GD, SFS, EX, RJK. Analysis and interpretation of data: RS, PJ, FP. Drafting of the manuscript: FP. Critical revision of the manuscript for important intellectual content: RS, SJ, VS, SL, SS, BR, AW, AG, RC, AB, MB, VS, PUM, JI, NM, JB, RM, TC, EC, PA, JV, RB, GD, SFS, EX, RJK, JP. Statistical analysis: RS. Administrative, technical, or material support: FP. Supervision: JP.

Compliance with ethical standards

Informed consent For this type of study, informed consent is not required.

Conflict of interest The authors declare that they have no conflict of interest.

Research involving human participants and/or animals The study has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

References

1. Svatek RS, Hollenbeck BK, Holmäng S et al (2014) The economics of bladder cancer: costs and considerations of caring for this disease. Eur Urol 66(2):253–262. https://doi.org/10.1016/j.eururo.2014.01.006
2. Burger M, Catto JWF, Dalbagni G et al (2013) Epidemiology and risk factors of urothelial bladder cancer. Eur Urol 63(2):234–241. https://doi.org/10.1016/j.eururo.2012.07.033
3. Babjuk M, Böhle A, Burger M et al (2017) EAU guidelines on non-muscle-invasive urothelial carcinoma of the bladder: update

2016. Eur Urol 71(3):447–461. https://doi.org/10.1016/j.eururo.2016.05.041
4. Sylvester RJ, Van Der Meijden APM, Oosterlinck W et al (2006) Predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer using EORTC risk tables: a combined analysis of 2596 patients from seven EORTC trials. Eur Urol 49(3):466–475. https://doi.org/10.1016/j.eururo.2005.12.031
5. Fernandez-Gomez J, Madero R, Solsona E et al (2009) Predicting nonmuscle invasive bladder cancer recurrence and progression in patients treated with bacillus Calmette–Guerin: the CUETO scoring model. J Urol 182(5):2195–2203. https://doi.org/10.1016/j.juro.2009.07.016
6. Xylinas E, Kent M, Kluth L et al (2013) Accuracy of the EORTC risk tables and of the CUETO scoring model to predict outcomes in non-muscle-invasive urothelial carcinoma of the bladder. Br J Cancer 109(6):1460–1466. https://doi.org/10.1038/bjc.2013.372
7. Ramirez-Backhaus M, Dominguez-Escrig J, Collado A, Rubio-Briones J, Solsona E (2012) Restaging transurethral resection of bladder tumour for high-risk stage Ta and T1 bladder cancer. Curr Urol Rep 13(2):109–114. https://doi.org/10.1007/s11934-012-0234-4
8. Bishr M, Lattouf JB, Latour M, Saad F (2014) Tumor stage on re-staging transurethral resection predicts recurrence and progression-free survival of patients with high-risk non-muscle invasive bladder cancer. J Can Urol Assoc 8(5–6):6–10. https://doi.org/10.5489/cuaj.1514
9. Herr HW, Donat SM (2006) A re-staging transurethral resection predicts early progression of superficial bladder cancer. BJU Int 97(6):1194–1198. https://doi.org/10.1111/j.1464-410X.2006.06145.x
10. Herr HW, Donat SM, Dalbagni G (2007) Can restaging transurethral resection of T1 bladder cancer select patients for immediate cystectomy? J Urol 177(1):75–79. https://doi.org/10.1016/j.juro.2007.08.070
11. Hautmann RE, Volkmer BG, Gust K (2009) Quantification of the survival benefit of early versus deferred cystectomy in high-risk non-muscle invasive bladder cancer (T1G3). World J Urol 27:347–351. https://doi.org/10.1007/s00345-009-0402-4
12. Roghmann F, Trinh Q-D, Braun K et al (2014) Standardized assessment of complications in a contemporary series of European patients undergoing radical cystectomy. Int J Urol 21(2):143–149. https://doi.org/10.1111/iju.12232
13. Nayak JG, Gore JL, Holt SK, Wright JL, Mossanen M, Dash A (2016) Patient-centered risk stratification of disposition outcomes following radical cystectomy. Urol Oncol Semin Orig Invest 34(5):235.e17–235.e23. https://doi.org/10.1016/j.urolonc.2015.11.012
14. Gontero P, Sylvester R, Pisano F et al (2016) 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. BJU Int 118(1):44–52
15. Dalbagni G, Vora K, Kaag M et al (2009) Platinum priority—bladder cancer clinical outcome in a contemporary series of restaged patients with clinical T1 bladder cancer. Eur Urol 56(6):903–910. https://doi.org/10.1016/j.eururo.2009.07.005
16. Herr HW (2011) Role of re-resection in non-muscle-invasive bladder cancer. Sci World J 11:283–288. https://doi.org/10.1100/tsw.2011.29
17. Gordon P, Thomas PC, Noon AP et al (2017) Long-term outcomes from re-resection for high risk non muscle invasive bladder cancer: a potential to rationalize use. Eur Urol Focus. https://doi.org/10.1016/j.euf.2017.10.004
18. Gontero P, Sylvester R, Pisano F et al (2015) Platinum—urothelial cancer prognostic factors and risk groups in T1G3 non-muscle-invasive bladder cancer patients initially treated with Bacillus Calmette–Gué rin: results of a retrospective multicenter study of 2451 patients. Eur Urol 7(7):4–8. https://doi.org/10.1016/j.eururo.2014.06.040
19. Denzinger S, Fritsche H-M, Otto W, Blana A, Wieland W-F, Burger M (2008) Early versus deferred cystectomy for initial high-risk pT1G3 urothelial carcinoma of the bladder: do risk factors define feasibility of bladder-sparing approach? Eur Urol 53(1):146–152. https://doi.org/10.1016/j.eururo.2007.06.030
20. Hautmann RE, Volkmer BG, Gust K (2009) Quantification of the survival benefit of early versus deferred cystectomy in high-risk non-muscle invasive bladder cancer (T1G3). World J Urol 27(3):347–351. https://doi.org/10.1007/s00345-009-0402-4
21. Novotny V, Zastrow S, Koch R, Wirth MP (2012) Radical cystectomy in patients over 70 years of age: impact of comorbidity on perioperative morbidity and mortality. World J Urol 30(6):769–776. https://doi.org/10.1007/s00345-011-0782-0
22. Cumberbatch MGK, Foerster B, Catto JWF (2018) Repeat transurethral resection in non-muscle-invasive bladder cancer: a systematic review. Eur Urol **(in press)**

Affiliations

J. Palou[1] · F. Pisano[1,2] · R. Sylvester[3] · S. Joniau[4] · V. Serretta[5] · S. Larré[6] · S. Di Stasi[7] · B. van Rhijn[8] · A. J. Witjes[9] · A. Grotenhuis[9] · R. Colombo[10] · A. Briganti[10] · M. Babjuk[11] · V. Soukup[11] · P. U. Malmstrom[12] · J. Irani[13] · N. Malats[14] · J. Baniel[15] · R. Mano[15] · T. Cai[16] · E. K. Cha[17] · P. Ardelt[18] · J. Varkarakis[19] · R. Bartoletti[20] · G. Dalbagni[21] · S. F. Shariat[22] · E. Xylinas[23] · R. J. Karnes[24] · P. Gontero[2]

1 Department of Urology, Fundacio Puigvert, University of Barcelona, Barcelona, Spain

2 Dept of Urology, Ospedale "Città della Salute e della Scienza-Molinette", Corso Bramante 88, 10126 Turin, Italy

3 Department of Biostatistics, EORTC Headquarters, Brussels, Belgium

4 Oncologic and Reconstructive Urology, Department of Urology, University Hospitals Leuven, Louvain, Belgium

5 Department of Surgical, Oncological and Stomatological Sciences, University of Palermo, Palermo, Italy

6 Department of Surgical Science, John Radcliffe Hospital, University of Oxford, Oxford, UK

7 Policlinico Tor Vergata-University of Rome, Rome, Italy

8 Department of Urology, Netherlands Cancer Institute-Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands

9 Department of Urology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands

10 Dipartimento di Urologia, Università Vita-Salute. Ospedale S. Raffaele, Milan, Italy

[11] Department of Urology, Motol Hospital, University of Praha, Prague, Czech Republic

[12] Department of Urology, Academic Hospital, Uppsala University, Uppsala, Sweden

[13] Department of Urology, Centre Hospitalier Universitaire La Milétrie, University of Poitiers, Poitiers, France

[14] Genetic and Molecular Epidemiology Group, Spanish National Cancer Research Centre (CNIO), Madrid, Spain

[15] Department of Urology, Rabin Medical Centre, Tel Aviv, Israel

[16] Department of Urology, Santa Chiara Hospital, Trento, Italy

[17] Department of Urology, Weill Medical College of Cornell University, New York, NY, USA

[18] Facharzt fur Urologie, Abteilung fur Urologie, Chirurgische Universitats klinik, Freiburg, Germany

[19] Department of Urology, Sismanoglio Hospital, University of Athens, Athens, Greece

[20] Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy

[21] Department of Urology, Memorial Sloan Kettering Cancer Center, New York, NY, USA

[22] Medical University of Vienna, Vienna, Austria

[23] Department of Urology, Cochin Hospital, Paris, France

[24] Department of Urology, Mayo Clinic, Rochester, MN, USA