available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Urothelial Cancer

Characteristics and Outcomes of Patients with Clinical T1 Grade 3 Urothelial Carcinoma Treated with Radical Cystectomy: Results from an International Cohort

Hans-Martin Fritsche[a], *Maximilian Burger*[a], *Robert S. Svatek*[b], *Claudio Jeldres*[c], *Pierre I. Karakiewicz*[c], *Giacomo Novara*[j], *Eila Skinner*[d], *Stefan Denzinger*[a], *Yves Fradet*[e], *Hendrik Isbarn*[d], *Patrick J. Bastian*[f,k], *Bjoern G. Volkmer*[g], *Francesco Montorsi*[h], *Wassim Kassouf*[i], *Derya Tilki*[f], *Wolfgang Otto*[a], *Umberto Capitanio*[c], *Jonathan I. Izawa*[l], *Vincenzo Ficarra*[j], *Seth Lerner*[m], *Arthur I. Sagalowsky*[n], *Mark Schoenberg*[o], *Ashish Kamat*[b], *Colin P. Dinney*[b], *Yair Lotan*[n], *Shahrokh F. Shariat*[n,*]

[a] *Caritas-St. Josef Medical Centre, University of Regensburg, Regensburg, Germany*
[b] *University of Texas MD Anderson Cancer Center, Houston, Texas, USA*
[c] *University of Montréal, Montréal, Quebec, Canada*
[d] *University of Southern California, Los Angeles, California, USA*
[e] *Laval University, Québec City, Québec, Canada*
[f] *Ludwig-Maximilians-Universität München, Munich, Germany*
[g] *University of Ulm, Ulm, Germany*
[h] *Vita Salute, Milano, Italy*
[i] *McGill University Health Centre, Montréal, Quebec, Canada*
[j] *University of Padua, Padua, Italy*
[k] *University of Bonn, Bonn, Germany*
[l] *University of Western Ontario, London, Ontario, Canada*
[m] *Baylor College of Medicine, Houston, Texas, USA*
[n] *University of Texas Southwestern Medical Center, Dallas, Texas, USA*
[o] *John Hopkins University, Baltimore, Maryland, USA*

Article info

Article history:
Accepted September 3, 2009
Published online ahead of print on September 12, 2009

Keywords:
Recurrence
Survival
Bladder cancer
Radical cystectomy
T1
Urothelial carcinoma

Abstract

Background: Management of T1 grade 3 (T1G3) urothelial carcinoma of the bladder (UCB), with its variable behaviour, represents one of the most difficult challenges for urologists and patients alike.
Objective: To evaluate the characteristics and long-term outcome of patients with clinical T1G3 UCB treated with radical cystectomy (RC).
Design, setting, and participants: Data from 1136 patients treated with RC for clinical T1G3 UCB without neoadjuvant chemotherapy were collected at 12 centres located in Europe, the United States, and Canada. Median age was 67 yr (range: 29–94), with a male-to-female ratio of 4:1.
Measurements: Patients' characteristics and outcome are evaluated.

* Corresponding author. Division of Urology, Sidney Kimmel Center for Prostate and Urologic Cancer, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, Box 27, New York, NY 10065, USA.
E-mail address: sfshariat@gmail.com (S.F. Shariat).

0302-2838/$ – see back matter doi:10.1016/j.eururo.2009.09.024

Results and limitations: Of the 1136 patients, 33.4% had non–organ-confined stage at cystectomy, and 16.2% had lymph node (LN) metastasis; 49.7% were upstaged after RC to muscle-invasive disease, while 21.4% were downstaged to lower than T1G3. Within a median follow-up of 48 mo, 35.5% of patients died of metastatic UCB.

Conclusions: Approximately half of the patients treated with RC without neoadjuvant chemotherapy for clinical T1G3 UCB are upstaged to muscle-invasive UCB. These rates support the inadequacy of clinical decision making based on current treatment paradigms and staging tools. Therefore, identification of patients with clinical T1G3 disease at high risk of disease progression is of the utmost importance, as these patients are likely to benefit from early RC.

1. Introduction

Urothelial carcinoma of the bladder (UCB) is currently responsible for >200 000 new cases per year in the Western world [1,2]. Management of high-grade UCB involving the lamina propria (category T1) but not penetrating into the muscularis propria represents a challenge for both physician and patient. Although guidelines and experts agree that radical cystectomy (RC) with bilateral lymphadenectomy is indicated for patients with UCB invading into the muscularis propria [3,4], treatment of high-grade UCB confined to the lamina propria (T1 grade 3 [T1G3]) remains highly disputed. Up to 80% of patients with clinical T1G3 disease treated with transurethral resection (TUR) without intravesical therapy experience disease recurrence, and about 60% experience disease progression to muscle invasion [5,6]. Adjuvant intravesical therapy with bacillus Calmette-Guérin (BCG) decreases the overall recurrence rate by approximately 30% compared with TUR alone [7,8] and delays disease progression [8,9]. Nevertheless, up to 30% of patients with clinical T1G3 UCB eventually experience disease progression and require deferred RC [10].

Recent data support the conclusion that RC should be performed sooner rather than later for high-grade T1 cancers [11]. Schrier reported that patients who experience progression to muscle invasion have significantly worse survival rates than those who present with de novo clinical T2 disease (3-yr cancer-specific survival [CSS]: 37% vs 67%) [12]. In addition, patients with high-risk non–muscle-invasive bladder tumours (after initial treatment with TUR and BCG) who underwent earlier rather than delayed RC for tumour relapse were shown to have a better survival rate (92% for patients who underwent RC <2 yr after initial BCG therapy vs 56% for patients treated after 2 yr) [13]. Furthermore, understaging occurs in up to 50% of clinical T1G3 patients [14–16]. These data together with the limitations of current staging modalities support early RC for some patients with clinical T1G3 UCB [13,17].

The oncologic outcomes of patients treated with RC for T1G3 UCB remain, however, understudied; most studies are limited by their single-centre nature and small sample size. Therefore, we assessed the pathologic features and clinical outcomes of a large, multi-institutional cohort of patients with clinical T1G3 UCB who were treated with RC. In addition, we attempted to identify precystectomy variables that could help identify patients who are likely to be upstaged. Furthermore, we attempted to identify postcystectomy variables that could help identify patients who are likely to experience UCB recurrence/death and therefore would benefit from adjuvant chemotherapy or inclusion in clinical trials of novel therapeutics.

2. Methods

2.1. Patient selection and data collection

This is an institutional review board–approved study. All participating sites provided the necessary institutional data-sharing agreements prior to initiation of the study. Twelve centres worldwide provided data. A computerized databank was generated for data transfer. Data inconsistencies and integrity problems were corrected before final analysis.

The study focused on 1136 patients treated with RC and bilateral lymphadenectomy for clinical T1G3 UCB within a period of 30 yr (1979–2008). Re-TUR was done in nearly 70% of the patients. Those with other tumour stage than T1G3 were excluded from the study. Patients without muscle in the TUR specimens were excluded from the study. No patient received neoadjuvant chemotherapy or radiation therapy. No patient had distant metastatic disease at the time of RC.

2.2. Pathologic evaluation

All surgical specimens were processed according to standard pathologic procedures. Genitourinary pathologists assigned tumour grade according to the 1973 World Health Organization grading system. Pathologic stage was assigned according to the 2002 American Joint Committee on Cancer TNM staging system. The presence of concomitant carcinoma in situ (CIS) was defined as the presence of CIS in conjunction with another pathologic T category other than CIS alone. Pelvic lymph node dissections were examined grossly, and all lymphoid tissue was submitted for histologic examination. Positive soft tissue surgical margin (STSM) was defined as the presence of tumour at inked areas of soft tissue on the cystectomy specimen. Urethral or ureteral margin status was not considered as STSM. Lymphovascular invasion (LVI) was defined as the unequivocal presence of tumour cells within an endothelium-lined space without underlying muscular walls.

To ensure validity of the pathologic data extraction, two investigators independently reviewed pathology from 319 patients while blinded to initial data and the findings of the other reviewer. Interreader reliability measured using the intraclass correlation coefficient was >0.95 for each pathologic characteristic.

2.3. Follow-up

Follow-up was performed according to institutional protocols. Patients generally were seen postoperatively at least every 3–4 mo for the first year, semiannually for the second year, and annually thereafter. Follow-up visits consisted of a physical examination and serum chemistry evaluation, including liver function tests and alkaline phosphatase. Diagnostic imaging of the upper tracts (eg, ultrasonography, intravenous pyelography, and/or computed tomography [CT] scans of the abdomen/pelvis with intravenous contrast) and chest radiography were performed at least annually or when clinically indicated. Additional radiographic evaluations, such as bone scans and/or CT scans, were performed at the discretion of the treating physician. Detection of cancer in the ureter and/or urethra was coded as a second (metachronous) primary and not as local or distant recurrence.

When patients died, the cause of death was determined by the treating physicians by chart review corroborated by death certificates or by death certificates alone. Most patients who were identified as having died of UCB had progressive, widely disseminated, and often highly symptomatic metastases at the time of death. Perioperative mortality (ie, death within 30 d of surgery) was censored at the time of death for bladder CSS analyses.

2.4. Statistical analysis

The Fisher exact test and the χ^2 test were used to evaluate the association between categorical variables. Differences in variables with a continuous distribution across dichotomous categories were assessed using the Mann-Whitney test. Logistic regression was used for multivariate analyses of binary outcome variables. The Kaplan-Meier method was used to calculate survival functions, and differences were assessed with the log rank statistic. Univariable and multivariable Cox regression models addressed time to recurrence and cancer-specific mortality (CSM) after RC. In all models, proportional hazards assumptions were systematically verified using the Grambsch-Therneau residual-based test. All reported p values are two-sided, and statistical significance was set at $p < 0.05$. No adjustments were made for multiple statistical tests. All statistical tests were performed with SPSS v.13.0 (SPSS, Chicago, IL, USA).

3. Results

3.1. Clinical and pathologic characteristics of 1136 patients treated with radical cystectomy for clinical T1G3 urothelial carcinoma of the bladder

Descriptive clinicopathologic characteristics of the 1136 patients are shown in Table 1. Median age was 66.6 yr (range: 29.3–94.2). Of these patients, 80.4% were males, and 58.0% of the patients had had surgery between the years 2000 and 2008; 51.4% of the patients were upstaged to muscle-invasive stage (T2 or higher), and 33.4% were upstaged to non–organ-confined stage (T3 or higher with N [any] or T [any] with N+). In addition, 6.3% of the patients had a positive STSM; all patients with STSM had muscle-invasive UCB at RC. The median number of lymph nodes (LN) removed at the time of RC was 18 (interquartile range: 20); 16.2% of the patients had metastasis to LNs, and 24.3% had lymphovascular invasion (Table 1).

Table 1 – Descriptive clinicopathologic characteristics of 1136 patients treated with radical cystectomy and bilateral lymphadenectomy for clinical T1G3 urothelial carcinoma of the bladder*

Characteristic	Patients, *n* (%)
Age (yr)	1135
<50	82 (7.2)
50–59.9	208 (18.3)
60–69.9	436 (38.4)
70–79.9	349 (30.7)
>80	60 (5.3)
Gender	1121
Female	220 (19.6)
Male	901 (80.4)
Year of surgery	1134
1979–1984	47 (4.1)
1985–1989	79 (7.0)
1990–1994	94 (8.3)
1995–1999	255 (22.4)
2000–2005	477 (42.0)
2006–2008	182 (16.0)
Pathologic stage	1127
pT0 (no tumour)	68 (6.1)
pTa	42 (3.7)
pTis	132 (11.7)
pT1	325 (28.8)
pT2	239 (21.2)
pT3	219 (19.4)
pT4	102 (9.1)
>pT1	560 (49.7)
Non–organ confined (T3/4 and/or N+)	376 (33.4)
Pathologic grade	1121
0	68 (6.1)
1	24 (2.1)
2	487 (43.4)
3	542 (48.3)
Concomitant CIS	1133
Absent	532 (47.0)
Present	601 (53.0)
STSM status	1127
Absent	1056 (93.7)
Present	71 (6.3)
LVI	1094
Absent	828 (75.7)
Present	266 (24.3)
LN metastasis	1098
Absent	914 (83.2)
Present	184 (16.2)
Adjuvant chemotherapy	1128
Chemotherapy	175 (15.5)
No chemotherapy	953 (84.5)

CIS = carcinoma in situ; STSM = soft tissue surgical margin; LVI = lymphovascular invasion; LN = lymph node.
*Age was missing in one patient. Gender was missing in 15 patients. Year of surgery was missing in two patients. Postoperative pathologic stage was missing in nine patients. Grade was missing in 15 patients. Organ-confined status was not evaluable in nine patients. CIS was missing in three patients. STSM was missing in nine patients. LVI was missing in 42 patients. LN status was missing in 38 patients. Adjuvant chemotherapy status was missing in eight patients. Stage discrepancy could not be determined in nine patients.

Table 2 – Univariate and multivariate analyses of predictors for upstaging to muscle-invasive stage or N+ at radical cystectomy

Univariate analyses	HR	95% CI	p
Female gender	1.41	1.05–1.90	0.02
Age	–	–	<0.001
Continuous	1.02	1.01–1.03	<0.001
Decades	–	–	<0.001
<60	0.45	0.27–0.76	0.03
60–69.9	0.94	0.59–1.51	0.80
70–79.9	1.04	0.64–1.68	0.89
≥80	1.38	0.70–2.74	0.35
Multivariate analysis	**HR**	**95% CI**	**p**
Female gender	1.40	1.04–1.90	0.03
Age continuous	1.02	1.01–1.03	<0.001

HR = hazard ratio; CI = confidence interval.

3.2. Predictors of upstaging in 1136 patients treated with radical cystectomy for clinical T1G3 urothelial carcinoma of the bladder

Female gender and older age were significantly associated with upstaging to muscle-invasive stage or LN metastasis at RC (Table 2). Patients <60 yr of age were significantly less likely to be upstaged.

3.3. Predictors of disease recurrence, overall survival, and disease-specific mortality in 1136 patients treated with radical cystectomy for clinical T1G3 urothelial carcinoma of the bladder

Median follow-up was 48 mo (range: 0.4–299.9). UCB recurred in 22.5% of the patients within 2 yr, and 7.3% died of metastatic disease. Cancer-specific recurrence and mortality estimation at 8 yr after RC were 34.5% and 35.5%, respectively (Table 3; Fig. 1a and b).

In univariable Cox regression analyses, older age at cystectomy, pathologic stage, stage discrepancy, tumour grade, STSM, LVI, LN status, and the number of positive LNs were associated with disease recurrence and CSM (Tables 4 and 5, respectively; Figs. 2 and 3). On multivariable analyses, LN status ($p < 0.001$), number of positive LNs ($p < 0.001$ and $p = 0.04$, respectively), LVI ($p < 0.001$), and pathologic stage ($p < 0.001$) were associated with disease recurrence and CSM (Tables 4 and 5, respectively; Figs. 2 and 3).

Table 3 – Overall recurrence and cancer-specific mortality rates

Time (yr)	2	5	8
Overall recurrence			
Percent	22.5	31.9	34.5
Overall CSM			
Percent	7.3	29.8	35.5
Overall mortality			
Percent	8.0	44.0	53.0

CSM = cancer-specific mortality.

Women showed higher recurrence and CSM rates compared to men (34.5% vs 28.7% mortality after 5 yr), but the difference was only statistically significant in univariate analysis for CSM ($p = 0.025$; Tables 4 and 5, respectively). Overall survival (OS) analysis only showed that gender lost significance compared to cancer-specific analysis (Table 6). When restricted to the years 2000–2008, no differences in the statistical significance of the results were observed.

4. Discussion

Identification of patients with clinical T1G3 disease at high risk of disease progression is of utmost importance, as these patients are likely to benefit from early RC. But which are the decisive factors regarding the suitable timing of RC and the potential candidates for RC? The present study does not answer the question of suitable timing of RC in patients with recurrent T1G3 tumours or the potential candidates for initial cystectomy, but it provides certain information about prognostic factors and their relation to survival.

Using data from a large international cohort of 1136 patients treated with RC for clinical T1G3 UCB, we found treatment outcomes for RC with bilateral lymphadenectomy for clinical T1G3 UCB to be similar to outcomes after TUR and BCG therapy, as 5-yr recurrence and CSM rates were 31.9% (95% confidence interval [CI], 28.6–35.1) and

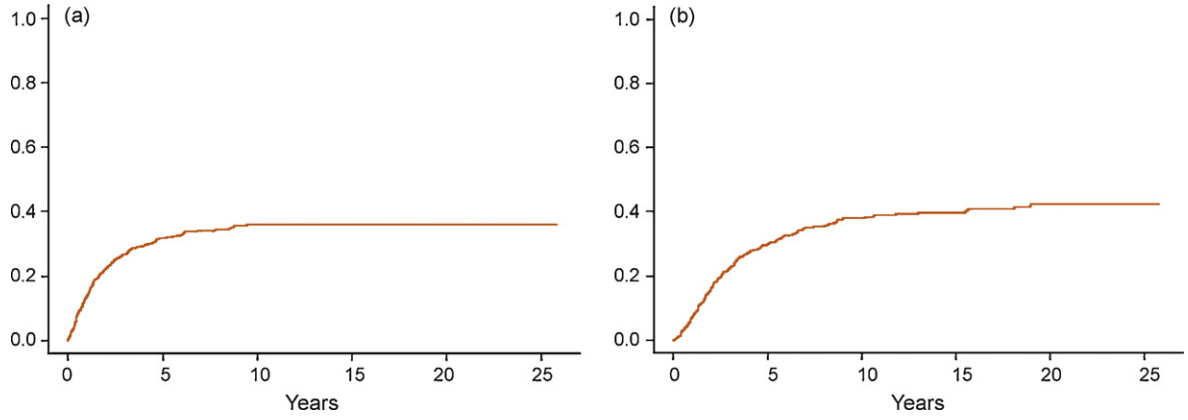

Fig. 1 – Probability estimates of (a) recurrence and (b) cancer-specific mortality in 1136 patients treated with radical cystectomy and bilateral lymphadenectomy for clinical T1G3 urothelial carcinoma of the bladder.

Table 4 – Univariate and multivariate Cox regression analyses for prediction of disease recurrence in 1136 patients treated with radical cystectomy and bilateral lymphadenectomy for clinical T1G3 urothelial carcinoma of the bladder

Univariate analyses	HR	95% CI	p
Female gender	0.79	0.61–1.04	0.09
Age continuous	1.02	1.01–1.03	0.01
Pathologic stage	–	–	<0.001
T0	1.00	Referent	–
Ta	3.19	0.74–10.29	0.13
Tis	2.04	0.67–6.20	0.21
T1	3.43	1.25–9.45	0.02
T2	6.62	2.41–18.16	<0.001
T3	14.04	5.16–38.16	<0.001
T4	18.09	6.56–49.92	<0.001
Stage discrepancy	–	–	<0.001
Downstaged	1.00	Referent	–
Same stage	1.89	1.17–3.06	0.01
Upstaged	6.01	3.91–9.24	<0.001
Grade	–	–	<0.001
No tumour	1.00	Referent	–
G1	4.03	1.08–15.00	0.04
G2	6.36	2.36–17.16	<0.001
G3	6.53	2.42–17.64	<0.001
Positive STSM status	3.61	2.56–5.08	<0.001
LVI	3.34	2.65–4.22	<0.001
Concomitant CIS	0.97	0.77–1.21	0.77
No. LN removed	1.00	0.99–1.00	0.29
No. positive LN	1.10	1.08–1.12	<0.001
LN metastasis	4.88	3.85–6.18	<0.001
Multivariate analysis	**HR**	**95% CI**	***p***
Age continuous	1.01	1.00–1.03	0.12
Pathologic stage	–	–	<0.001
T0	1.00	Referent	–
Ta	3.19	0.80–12.70	0.10
Tis	2.02	0.67–6.15	0.21
T1	3.20	1.14–8.96	0.03
T2	5.01	1.78–14.10	<0.001
T3	7.06	2.51–19.89	<0.001
T4	8.77	3.06–25.10	<0.001
Grade	–	–	0.56
No tumour	1.00	Referent	–
G2	0.85	0.29–2.54	0.78
G3	0.87	0.67–1.13	0.29
Positive STSM status	1.43	0.93–2.18	0.10
LVI	1.56	1.18–2.06	<0.001
No. positive LN	1.04	1.02–1.07	<0.001
LN metastasis	2.20	1.61–3.02	<0.001

HR = hazard ratio; CI = confidence interval; STSM = soft tissue surgical margin; LVI = lymphovascular invasion; CIS = carcinoma in situ; LN = lymph node.

Table 5 – Univariate and multivariate Cox regression analyses for prediction of cancer specific mortality in 1136 patients treated with radical cystectomy and bilateral lymphadenectomy for clinical T1G3 urothelial carcinoma of the bladder

Univariate analyses	HR	95% CI	p
Female gender	0.72	0.54–0.96	0.025
Age continuous	1.03	1.02–1.05	<0.001
Pathologic stage	–	–	<0.001
T0	1.00	Referent	–
Ta	2.90	0.65–12.96	0.16
Tis	2.08	0.58–7.45	0.26
T1	3.37	1.05–10.84	0.04
T2	6.37	1.99–20.46	0.02
T3	16.14	5.10–51.02	<0.001
T4	17.82	5.53–57.43	<0.001
Grade	–	–	<0.001
No tumour	1.00	Referent	–
G1	2.89	0.58–14.30	0.19
G2	6.60	2.10–20.74	<0.001
G3	6.95	2.21–21.86	<0.001
Positive STSM status	4.19	2.91–6.04	<0.001
LVI	3.722	2.87–4.82	<0.001
Concomitant CIS	0.93	0.72–1.19	0.55
No. LN removed	1.00	0.99–1.00	0.18
No. positive LN	1.08	1.06–1.09	<0.001
LN metastasis	5.33	4.10–6.92	<0.001
Multivariate analysis	**HR**	**95% CI**	***p***
Female gender	0.82	0.59–1.13	0.23
Age continuous	1.03	1.01–1.04	<0.001
Pathologic stage	–	–	<0.001
T0	1.00	Referent	–
Ta	3.99	0.83–19.09	0.83
Tis	2.00	0.56–7.19	0.29
T1	2.96	0.90–9.76	0.07
T2	4.28	1.29–14.17	0.02
T3	7.01	2.13–23.06	<0.001
T4	7.59	2.26–25.51	<0.001
Grade	–	–	0.36
No tumour	1.00	Referent	–
G2	0.46	0.10–2.11	0.32
G3	0.84	0.63–1.13	0.26
Positive STSM status	1.68	1.08–2.61	0.02
LVI	1.82	1.34–2.47	<0.001
No. positive LN	1.03	1.00–1.05	0.04
LN metastasis	2.48	1.75–3.52	<0.001

HR = hazard ratio; CI = confidence interval; STSM = soft tissue surgical margin; LVI = lymphovascular invasion; CIS = carcinoma in situ; LN = lymph node.

29.8% (95% CI, 26.5–33.1), respectively. This might be explained by a high proportion of recurrent patients, deduced from the high incidence of CIS of 53% (Table 1). One can hypothesize that RC seems to alter the natural history of UCB in patients with clinical T1G3, as only 30% of patients died of bladder cancer within 5 yr, while 50% had muscle-invasive disease and, if left untreated, would have experienced disease progression and eventual demise. Furthermore, these rates support the inadequacy of our clinical decision making based on current treatment paradigms and staging tools.

We found that 51.4% of the patients were upstaged to muscle-invasive disease, and 16.2% had LN metastases. These immense numbers approve reports of other, smaller studies with upstaging in 26–78% of patients and nodal metastasis in 6–19% [18–28]. Cheng et al reported 78% (43 of 55) of patients with clinical T1G3 disease having advanced-stage carcinoma at cystectomy [23]. An inadequate initial TUR, failure to perform a re-TUR, delay between TUR and RC, as well as error and variation in pathologic interpretation might be responsible for understaging. For example, the presence of residual T1 tumour on re-resection has been shown to be associated with an exceedingly high rate of progression to muscle invasion [29]. Another limitation is that patients were treated by

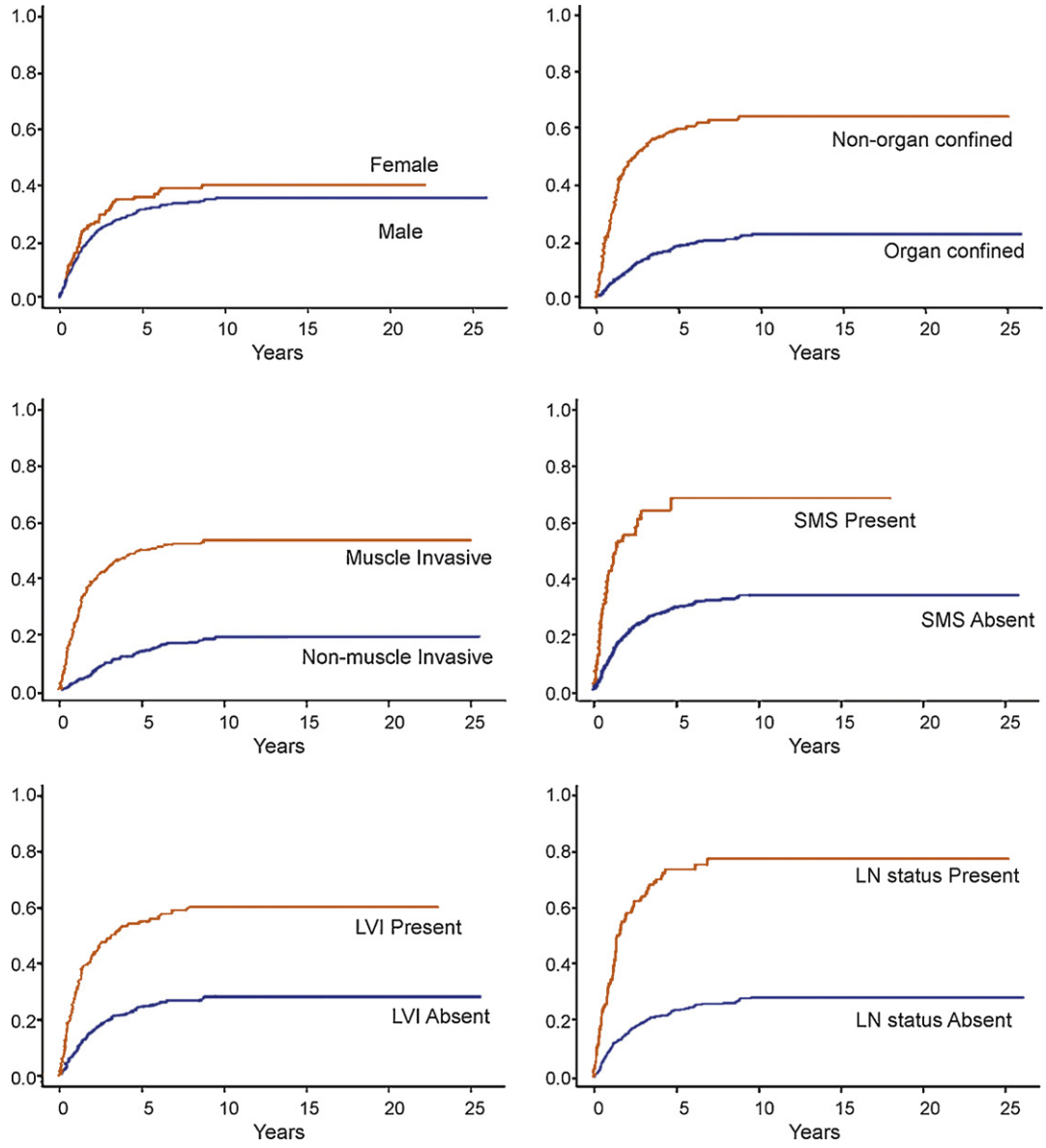

Fig. 2 – Probability estimates of recurrence stratified by select clinical and pathologic variables in 1136 patients treated with radical cystectomy and bilateral lymphadenectomy for clinical T1G3 urothelial carcinoma of the bladder.
SMS = surgical margin status; LVI = lymphovascular invasion; LN = lymph node.

various physicians, and the specimens were evaluated by various pathologists over a long time period. Besides the quality and technique of TUR [30], the issue of staging arises from errors and variation in pathologic interpretation. In a large multicentre study of 1400 patients examining interpathologic and intrapathologic variation in diagnosis of Ta/T1 UCB, an agreement between local and reviewing pathologist was seen in only 50% of the T1G3 cases: 10% of the patients had muscle-invasive T2 disease and were understaged [31]. Thus, we do not attribute this phenomenon only to insufficient resection techniques. The impossibility of ascertaining stage by TUR is possibly decisive towards a more profound understanding of T1G3. Despite the lack of muscle invasion in initial and subsequent TUR specimens obtained by larger institutions and assessed by experienced uropathologists, one is bound to find muscle invasion in the majority of cases. This uncertainty needs to be addressed during patient counselling and warrants timely consideration of cystectomy all the more.

However, despite technical advances that may minimize the impact of bladder removal on health-related quality of life, such as nerve-sparing techniques and the application of orthotopic urinary diversion to a broad array of patients in certain centres, the functionality of diversion typically falls short of that of the native bladder. Furthermore, the perioperative consequences of RC are not trivial, with morbidity and mortality rates approaching 40% and 1–2%, respectively [31]. Furthermore, understaging leads to a surprisingly high rate of positive STSM in 6.3% of patients. All of them had muscle-invasive stages. This rate might be

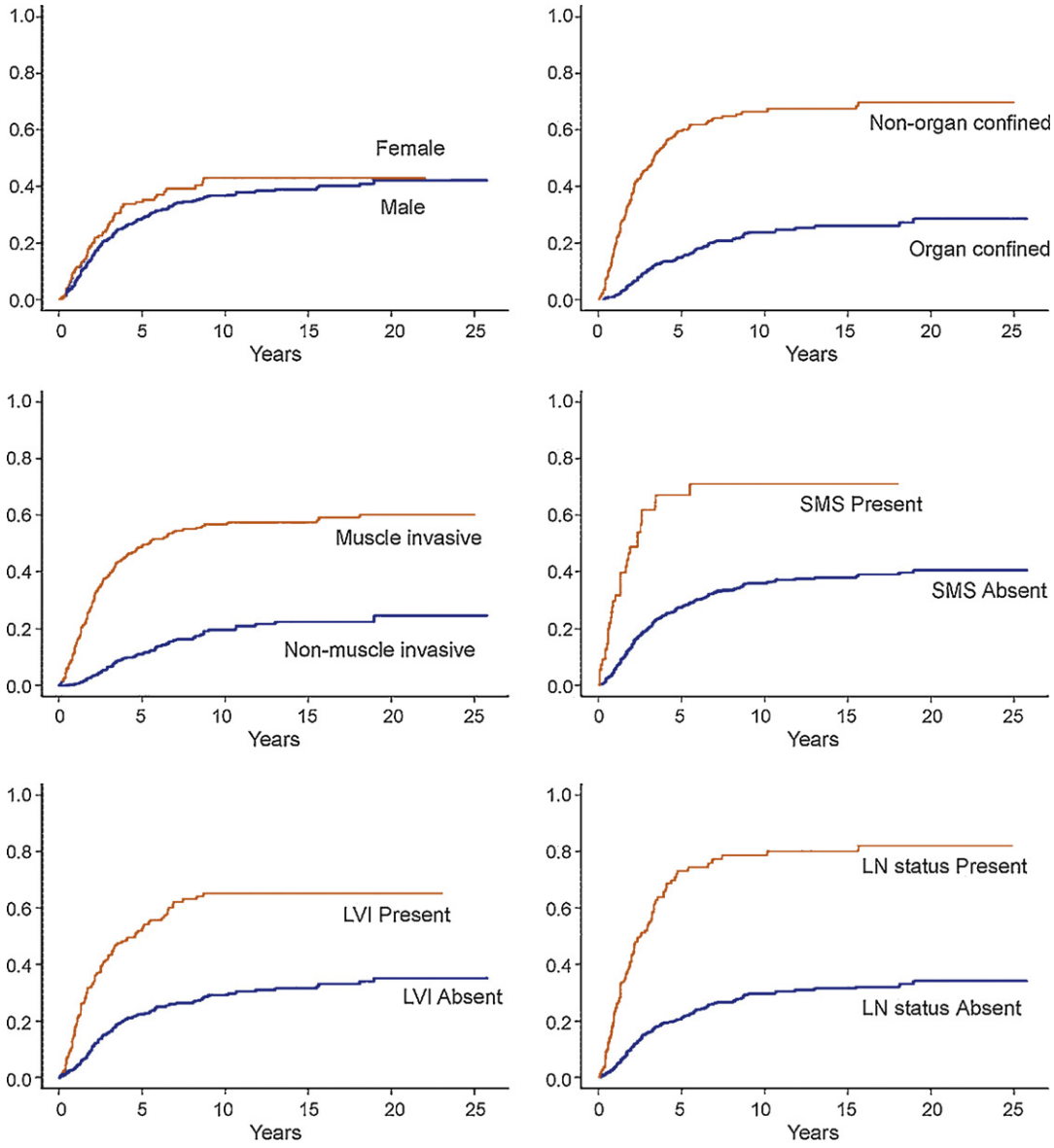

Fig. 3 – Probability estimates of cancer-specific mortality stratified by select clinical and pathologic variables in 1136 patients treated with radical cystectomy and bilateral lymphadenectomy for clinical T1G3 urothelial carcinoma of the bladder.
SMS = surgical margin status; LVI = lymphovascular invasion; LN = lymph node.

attributed to poor surgical technique, but our positive surgical margin rate is only slightly higher than reported in previous series of muscle-invasive stages (eg, with Dotan et al [32]).

Although understaging as a prognostic factor did not reach statistical significance related to cancer-specific recurrence and mortality in multivariate analysis, we found that advanced age was associated with an increased risk of upstaging and LN metastasis. Several investigators have demonstrated a direct correlation between patient age and poor oncologic outcomes after RC [33–37]. For example, Clark et al found that higher age was associated with a higher rate of early complications, disease recurrence, and overall mortality in 1054 cystectomy patients [34]. Reasons for this could be a change in the biologic potential of the tumour cell, a decrease in the host's defence mechanisms with advancing age, or even a detrimental effect of differences in care patterns in elderly compared to younger patients (ie, selection for RC, delay in RC, decreased administration of adjuvant chemotherapy, and/or decreased performance of extended lymphadenectomy). It may also be the result of a less robust immune response with BCG in older patients, resulting in progression [38], or there may be a reluctance to perform radical surgery in older patients with comorbidities, resulting in cystectomy delay, which may be responsible for upstaging [34,39]. But taking into account current literature, there is still great disagreement about the role of RC delay [40,41].

We found that female gender was associated with an increased risk of upstaging and LN metastasis in

Table 6 – Univariate and multivariate Cox regression analyses for prediction of overall mortality death in 1136 patients treated with radical cystectomy and bilateral lymphadenectomy for clinical T1G3 urothelial carcinoma of the bladder

Univariate analyses	HR	95% CI	*p*
Female gender	0.796	0.67–0.99	0.045
Age continuous	1.039	1.028–1.050	<0.001
Pathologic stage	1.463	1.365–1.569	<0.001
Stage discrepancy	1.883	1.643–2.160	<0.001
Positive STSM status	3.028	2.204–4.159	<0.001
LVI	2.569	2.102–3.141	<0.001
Concomitant CIS	1.018	0.844–1.228	0.852
No. LN removed	0.993	0.987–0.999	0.022
No. positive LN	1.066	1.051–1.080	<0.001
LN metastasis	3.001	2.413–3.732	<0.001
Multivariate analysis	**HR**	**95% CI**	***p***
Female gender	0.883	0.694–1.123	0.310
Age continuous	1.038	1.026–1.051	<0.001
Pathologic stage	1.258	1.154–1.371	<0.001
Positive STSM status	1.266	0.859–1.866	0.234
LVI	1.516	1.191–1.930	0.001
No. positive LN	1.037	1.014–1.061	0.001
LN metastasis	1.749	1.314–2.328	<0.001

HR = hazard ratio; CI = confidence interval; STSM = soft tissue surgical margin; LVI = lymphovascular invasion; CIS = carcinoma in situ; LN = lymph node.

cancer-specific analysis, while when analyzing OS, it lost its significance. The explanation might be that men die younger of other causes, abrogating the worse cancer-specific outcome of females.

Previous series have provided substantial insight into the treatment of T1G3 disease by cystectomy. But the present series is not only larger: It is derived from the highest number of international institutions reported to date and overlooks the longest span of time we are aware of. All these factors improve the generalizability of findings. Thus, the present series reflects the true nature of the broad application of cystectomy in T1G3 UCB more correctly than any previous publication. Although most centres contributing to the present series are referral centres and the surgical quality may be comparable in between certain centres, the end point of the present analysis was survival in relation to patient characteristics, which is much better reflected in larger series, providing advantageous statistical evaluation regardless of the centres contributing.

But the referral centre character of most of the contributing centres in the present series may also hold some bias because of a negative selection of patients: Many patients with solitary and small tumours might never have been seen at these centres, and referral centres get patients with a delay after treatment by the referring urologist. More limitations to our study have to be mentioned: Our study did not evaluate other promising precystectomy features that have been associated with upstaging and poor outcomes, such as tumour multifocality, larger tumour size (>3 cm), CIS, tumour at first follow-up cystoscopy after treatment, LVI, depth of lamina propria invasion, tumour marker expression, and delay between TUR and RC [18,27,42].

Moreover, the retrospective nature and the failure to adjust for the individual indications for RC limit conclusions from our study. In addition, we did not adjust for the performance of repeat TUR [43], prostatic involvement, multifocal tumours, invasion into the muscularis mucosa or depth of invasion into the lamina propria, quality of TUR, and pathologic interpretation [44–46]. Similarly, the long span of the study period suggests that practice patterns may have changed when compared to those used when some of the patients were treated. For example, indication for early cystectomy, CT staging, percent performance of re-TUR, number of LN removed, and follow-up protocols have changed over time. In contrast, the differences in practice patterns across the institutions in our study are reflective of the real world, making the conclusions of our study more generalizable.

5. Conclusions

Pathologic upstaging to muscle-invasive disease was present in approximately half of the patients treated with RC for clinical T1G3 UCB. Despite preoperative assumption of "non–muscle-invasive" UCB, 35.5% of patients with clinical T1G3 disease die of metastatic disease within 8 yr after RC. This study does not address the impact of early cystectomy, but it reveals the inadequacy of clinical decision making based on current treatment paradigms and staging tools.

Given the potential benefits and trade-offs associated with RC for clinical T1 UCB, the ideal candidate for conservative treatment of T1 bladder cancer needs to be defined. Better markers of progression and outcomes are needed to predict which patients will progress faster and thus will benefit from an earlier RC [47]. Until then, urologist and patient need to rely on large and representative retrospective data. However, physicians and patients alike should be aware that clinical T1G3 tumours are not "superficial" entities and that serious risks are associated with indiscriminate bladder-sparing approaches.

Author contributions: Shahrokh F. Shariat had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Shariat, Fritsche.
Acquisition of data: Fritsche, Shariat, Svatek, Jeldres, Skinner, Denzinger, Isbarn, Fradet, Bastian, Volkmer, Kassouf, Tilki, Capitanio, Izawa, Ficarra, Schoenberg, Novara, Burger, Kamat, Dinney, Sagalowsky, Lotan.
Analysis and interpretation of data: Shariat, Karakiewicz, Fritsche.
Drafting of the manuscript: Fritsche, Shariat.
Critical revision of the manuscript for important intellectual content: Novara, Denzinger, Kamat, Dinney, Sagalowsky, Lotan, Montorsi, Lerner, Otto.
Statistical analysis: Shariat, Karakiewicz.
Obtaining funding: None.
Administrative, technical, or material support: None.
Supervision: Novara, Burger, Kamat, Dinney, Sagalowsky, Lotan, Montorsi, Lerner.
Other (specify): None.

Financial disclosures: I certify that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

Funding/Support and role of the sponsor: National Institutes of Health T32 training grant (SFS; T32CA082088).

References

[1] Ferlay J, Autier P, Boniol M, Heanue M, Colombet M, Boyle P. Estimates of the cancer incidence and mortality in Europe in 2006. Ann Oncol 2007;18:581–92.
[2] Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2008. CA Cancer J Clin 2008;58:71–96.
[3] Babjuk M, Oosterlinck W, Sylvester R, Kaasinen E, Böhle A, Palou-Redorta J. EAU guidelines on non-muscle-invasive urothelial carcinoma of the bladder. Eur Urol 2008;54:303–14.
[4] 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.
[5] Heney NM. Natural history of superficial bladder cancer. Prognostic features and long-term disease course. Urol Clin North Am 1992;19:429–33.
[6] Heney NM, Ahmed S, Flanagan MJ, et al. Superficial bladder cancer: progression and recurrence. J Urol 1983;130:1083–6.
[7] Shelley MD, Court JB, Kynaston H, Wilt TJ, Coles B, Mason M. Intravesical bacillus Calmette-Guerin versus mitomycin C for Ta and T1 bladder cancer. Cochrane Database Syst Rev 2003:CD003231.
[8] Huncharek M, Kupelnick B. The influence of intravesical therapy on progression of superficial transitional cell carcinoma of the bladder: a metaanalytic comparison of chemotherapy versus bacilli Calmette-Guerin immunotherapy. Am J Clin Oncol 2004;27:522–8.
[9] 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.
[10] Shahin O, Thalmann GN, Rentsch C, Mazzucchelli L, Studer UE. A retrospective analysis of 153 patients treated with or without intravesical bacillus Calmette-Guerin for primary stage T1 grade 3 bladder cancer: recurrence, progression and survival. J Urol 2003;169:96–100.
[11] Studer UE. Radical cystectomy—often too late? Yes, but . . . Eur Urol 2006;50:1129–38.
[12] Schrier BP, Hollander MP, van Rhijn BW, Kiemeney LA, Witjes JA. Prognosis of muscle-invasive bladder cancer: difference between primary and progressive tumours and implications for therapy. Eur Urol 2004;45:292–6.
[13] Herr HW, Sogani PC. Does early cystectomy improve the survival of patients with high risk superficial bladder tumors? J Urol 2001;166:1296–9.
[14] Chang BS, Kim HL, Yang XJ, Steinberg GD. Correlation between biopsy and radical cystectomy in assessing grade and depth of invasion in bladder urothelial carcinoma. Urology 2001;57:1063–7.
[15] Van Der Meijden A, Sylvester R, Collette L, Bono A, Ten Kate F. The role and impact of pathology review on stage and grade assessment of stages Ta and T1 bladder tumors: a combined analysis of 5 European Organization for Research and Treatment of Cancer Trials. J Urol 2000;164:1533–7.
[16] Shariat SF, Palapattu GS, Karakiewicz PI, et al. Discrepancy between clinical and pathologic stage: impact on prognosis after radical cystectomy. Eur Urol 2007;51:137–51.
[17] Stein JP. Indications for early cystectomy. Urology 2000;18:289–95.
[18] Huguet J, Crego M, Sabaté S, Salvador J, Palou J, Villavicencio H. Cystectomy in patients with high risk superficial bladder tumors who fail intravesical BCG therapy: pre-cystectomy prostate involvement as a prognostic factor. Eur Urol 2005;48:53–9.
[19] Denzinger S, Fritsche H-M, Otto W, Blana A, Wieland W-F, Burger M. 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 2008;53:146–52.
[20] Cheng L, Neumann RM, Weaver AL, et al. Grading and staging of bladder carcinoma in transurethral resection specimens: correlation with 105 matched cystectomy specimens. Am J Clin Pathol 2000;113:275–9.
[21] Ficarra V, Dalpiaz O, Alrabi N, Novara G, Galfano A, Artibani W. Correlation between clinical and pathological staging in a series of radical cystectomies for bladder carcinoma. BJU Int 2005;95:786–90.
[22] Amling CL, Thrasher JB, Frazier HA, Dodge RK, Robertson JE, Paulson DF. Radical cystectomy for stages Ta, Tis and T1 transitional cell carcinoma of the bladder. J Urol 1994;151:31–6.
[23] Cheng L, Neumann RM, Weaver AL, et al. Grading and staging of bladder carcinoma in transurethral resection specimens. Correlation with 105 matched cystectomy specimens. Am J Clin Pathol 2000;113:275–9.
[24] Freeman JA, Esrig D, Stein JP, et al. Radical cystectomy for high risk patients with superficial bladder cancer in the era of orthotopic urinary reconstruction. Cancer 1995;76:833–9.
[25] Masood S, Sriprasad S, Palmer JH, Mufti GR. T1G3 bladder cancer—indications for early cystectomy. Int Urol Nephrol 2004;36:41–4.
[26] Wiesner C, Pfitzenmaier J, Faldum A, Gillitzer R, Melchior SW, Thuroff JW. Lymph node metastases in non-muscle invasive bladder cancer are correlated with the number of transurethral resections and tumour upstaging at radical cystectomy. BJU Int 2005;95:301–5.
[27] Dutta SC, Smith JA, 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.
[28] Thalmann GN, Markwalder R, Shahin O, Burkhard FC, Hochreiter WW, Studer UE. Primary T1G3 bladder cancer: organ preserving approach or immediate cystectomy? J Urol 2004;172:70–5.
[29] Herr HW. The value of a second transurethral resection in evaluating patients with bladder tumors. J Urol 1999;162:74–6.
[30] Herr HW, Donat SM. Quality control in transurethral resection of bladder tumours. BJU Int 2008;102:1242–6.
[31] Donat SM, Shabsigh A, Savage C, et al. Potential impact of postoperative early complications on the timing of adjuvant chemotherapy in patients undergoing radical cystectomy: a high-volume tertiary cancer center experience. Eur Urol 2009;55:177–86.
[32] Dotan ZA, Kavanagh K, Yossepowitch O, et al. Positive surgical margins in soft tissue following radical cystectomy for bladder cancer and cancer specific survival. J Urol 2007;178:2308–12.
[33] Nielsen ME, Shariat SF, Karakiewicz PI, et al., For the Bladder Cancer Research Consortium (BCRC). Advanced age is associated with poorer bladder cancer-specific survival in patients treated with radical cystectomy. Eur Urol 2007;51:699–708.
[34] Clark PE, Stein JP, Groshen SG, et al. Radical cystectomy in the elderly: comparison of clinical outcomes between younger and older patients. Cancer 2005;104:36–43.
[35] Resorlu B, Beduk Y, Baltaci S, Ergun G, Talas H. The prognostic significance of advanced age in patients with bladder cancer treated with radical cystectomy. BJU Int 2009;103:480–3.
[36] Cai T, Bartoletti R. Re: Matthew E. Nielsen, Shahrokh F. Shariat, Pierre I. Karakiewicz, et al. Advanced age is associated with poorer

bladder cancer-specific survival in patients treated with radical cystectomy. Eur Urol 2007;52:611–2.
[37] Thrasher JB, Frazier HA, Robertson JE, et al. Clinical variables which serve as predictors of cancer-specific survival among patients treated with radical cystectomy for transitional cell carcinoma of the bladder and prostate. Cancer 1994;73:1708–15.
[38] Joudi FN, Smith BJ, O'Donnell MA, Konety BR. The impact of age on the response of patients with superficial bladder cancer to intravesical immunotherapy. J Urol 2006;175:1634–9.
[39] Prout Jr GR, Wesley MN, Yancik R, et al. Age and comorbidity impact surgical therapy in older bladder carcinoma patients: a population-based study. Cancer 2005;104:1638–47.
[40] Gore JL, Lai J, Setodji CM, et al. Urologic Diseases in America Project. Mortality increases when radical cystectomy is delayed more than 12 weeks: results from a surveillance, epidemiology, and end results—Medicare analysis. Cancer 2009;115:988–96.
[41] Hautmann RE. Delay of cystectomy: for whom does it really matter? Curr Urol Rep 2007;8:425–6.
[42] Shariat SF. Selecting patients for immediate cystectomy. Rev Urol 2007;9:239–41.
[43] Orsola A, Cecchini L, Morote J, Re: Marko Babjuk, Willem Oosterlinck, Richard Sylvester, et al. EAU guidelines on non-muscle-invasive urothelial carcinoma of the bladder. Eur Urol 2009;55:e15–6.
[44] Fritsche HM, Burger M. Management of early-invasive high-grade transitional cell carcinoma of the bladder. Minerva Urol Nefrol 2008;60:265–71.
[45] Cheng L, Neumann RM, Weaver AL, Spotts BE, Bostwick DG. Predicting cancer progression in patients with stage T1 bladder carcinoma. J Clin Oncol 1999;17:3182–7.
[46] Gattegno B. T1G3 bladder cancer: conservative management or cystectomy? Eur Urol 2004;45:399–400.
[47] Shariat SF, Bolenz C, Godoy G, et al. Predictive value of combined immunohistochemical markers in patients with pT1 urothelial carcinoma at radical cystectomy. J Urol 2009;182:78–84.

Editorial Comment on: Characteristics and Outcomes of Patients with Clinical T1 Grade 3 Urothelial Carcinoma Treated with Radical Cystectomy: Results from an International Cohort

George Thalmann
Department of Urology, University of Bern, Bern, Switzerland
George.Thalmann@insel.ch

Fritsche et al [1] have taken it upon themselves to aggregate the data of patients with T1 grade 3 (T1G3) disease from 12 prestigious international centres, resulting in the largest series of T1G3 bladder tumours. The authors are to be complimented on this effort. In their retrospective series, they find that every second patient with T1G3 is upstaged to muscle-invasive disease at cystectomy. They conclude that patients at high risk of progression should be identified and that current evaluation methods are often inefficient.

In this context, pooling of data and evaluation of large, multicenter series have their limitations, as this publication demonstrates and as the authors acknowledge. Many of the answers to these relevant questions can hardly be extracted from such databases: no central pathologic evaluation was done; assessment algorithms change over time; resection techniques vary, especially so in centres with residency programs; referral centres often receive preselected patients, sometimes with a delay; and so forth. The high rate of upgrading of 50%, despite a second resection in 70%, is worrisome and raises the question of risk factors, both clinical and biological. The authors have identified older age and female gender as predictive factors for upgrading, supporting the reports of others.

The authors further conclude that radical cystectomy and thorough pelvic lymphadenectomy provide excellent survival for T1 tumours. Nevertheless, >30% died of metastatic disease with a median follow-up of 48 mo, which is hardly any better than after transurethral resection and bacillus Calmette-Guérin therapy [2,3]. This report in a large cohort demonstrates once again that there is a subpopulation of patients with T1G3 bladder tumours that have aggressive and rapidly progressive disease, leading almost invariably to death of the patient independent of the mode of treatment. These are the patients we need to identify, so that we can improve their management. We can only hope that the authors will be able to further elucidate the T1G3 conundrum by scrutinizing their database case by case.

References

[1] Fritsche H-M, 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.
[2] Herr HW. Tumour progression and survival in patients with T1G3 bladder tumours: 15-year outcome. Br J Urol 1997;80:762–5.
[3] Shahin O, Thalmann GN, Rentsch C, Mazzucchelli L, Studer UE. A retrospective analysis of 153 patients treated with or without intravesical bacillus Calmette-Guerin for primary stage T1 grade 3 bladder cancer: recurrence, progression and survival. J Urol 2003;169:96–100.

DOI: 10.1016/j.eururo.2009.09.027

DOI of original article: 10.1016/j.eururo.2009.09.024