Contemporary outcomes and disease burden of high-grade T1 bladder cancer

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ABSTRACT

Introduction: High-grade T1 (HGT1) bladder cancer is considered to have high five-year recurrence and progression rates, at 50–70% and 25–50%, respectively; however, contemporary data are lacking. We examined the contemporary outcomes of HGT1 bladder cancer to inform patient counseling, management, and clinical trial design.
Methods: We identified patients aged ≥18 years with a new diagnosis of HGT1 bladder cancer between 2010 and 2022 treated at our institution. Recurrence-free (RFS), progression-free (PFS), and cancer-specific (CSS) survival were estimated using the Kaplan-Meier method. Associations of baseline characteristics with outcomes were evaluated using Cox regression.
Results: A total of 213 patients were included, representing 332 cancer occurrences. Median age at diagnosis was 72 (interquartile range [IQR] 65–80) years. Median followup for RFS, PFS, and CSS was 13, 20, and 36 months, respectively. The one-, three-, and five-year event-free rates were 65%, 51%, and 48% for RFS; 85%, 78%, and 72% for PFS; and 99%, 95%, and 95% for CSS. There was a median of 1 (IQR 1–2) recurrence per patient, with a median time to first recurrence of seven months (IQR 4–14) and a median time between recurrences of seven months (IQR 5–18). Larger tumor size was associated with increased risks of recurrence. Receipt of adjuvant intravesical therapy was associated with reduced risks of recurrence and progression.
Conclusions: Contemporary five-year recurrence and progression rates for HGT1 bladder cancer remain high at 53% and 28%, respectively. The disease burden is substantial, with a median time between recurrences of seven months. These results can inform patient counseling, management, and clinical trial design.

INTRODUCTION

Non-muscle invasive bladder cancer (NMIBC) accounts for 75% of bladder cancer diagnoses worldwide.[1] It represents a chronic disease that carries a substantial social and economic burden, with high costs attributable to lifelong follow-up, frequent recurrences, and intensive treatments, especially for high-risk disease.[1–4] Among patients with high-risk NMIBC, high-grade T1 (HGT1) tumors represent the worst prognosis, with 5-year recurrence and progression rates traditionally considered as high as 50-70% and 25-50%, respectively.[5–7] Consequently, HGT1 bladder cancer is managed aggressively, with consideration of early radical cystectomy supported by clinical practice guidelines for patients unresponsive to BCG.[8]

The optimal, risk-adapted management of NMIBC requires an accurate understanding of its natural history, including predictors of recurrence and progression. To this end, various predictors of recurrence and progression for NMIBC in general have been identified and incorporated into several seminal risk prediction models.[7,9] However, it is unclear how temporal changes in disease biology and treatment strategies have impacted the outcomes of HGT1 bladder cancer. For example, novel technologies and treatment paradigms have emerged in the last decade, including enhanced diagnostic tools and salvage intravesical therapies for BCG unresponsive disease.[10] Moreover, it is unclear whether traditional risk prediction variables, obtained from analysis of randomized clinical trials, can be accurately applied to real-world populations.[7,9] Finally, the contemporary disease burden of HGT1 bladder cancer remains understudied, with existing evidence reflecting older study populations, before the widespread implementation of re-TURBT and BCG maintenance protocols.

We therefore examined the contemporary, real-world outcomes of HGT1 bladder cancer, characterized the attributable disease burden, and evaluated the clinicopathologic predictors of recurrence and progression to inform patient counseling, risk-adapted management, and clinical trial design.

METHODS

Study cohort

After obtaining institutional review board approval, we identified patients with a new diagnosis of high-grade T1 cN0 cM0 urothelial carcinoma of the bladder between 2010-2022 who underwent initial resection at Beth Israel Deaconess Medical Center (BIDMC) or who underwent initial resection outside of BIDMC with pathology re-reviewed at BIDMC. Patients with non-urothelial histology and those upstaged to ≥T2 at repeat endoscopic resection were excluded from analysis (Supplementary Figure 1).

Clinicopathologic features and outcomes

We abstracted the following clinicopathologic features from the electronic health record: age, gender, Charlson comorbidity score, smoking status, race, family history of bladder cancer, presence of preoperative hydronephrosis, American Society of Anesthesiologists (ASA) score, number of tumors, maximum tumor diameter, presence of tumor multifocality, depth of lamina propria invasion (focal or non-focal), lymphovascular invasion, presence of concomitant variant histology, and presence of muscularis propria in the initial TURBT specimen. In addition, we recorded use of immediate postoperative chemotherapy instillation, 90-day postoperative

complication rates, performance of repeat endoscopic resection (re-TURBT), and use and type of adjuvant intravesical therapy (including both induction and maintenance therapy).

The primary endpoints were recurrence-free (RFS), progression-free (PFS), and cancer-specific survival (CSS). Recurrence was defined as the first pathologically confirmed cancer recurrence either on TURBT or office biopsy (if no TURBT was performed), or the diagnosis of clinical nodal (N1-3) or distant (M1) metastatic disease. Progression was defined as the first pathologically confirmed cancer recurrence of stage T2-4, or the diagnosis of clinical nodal (N1-3) or distant (M1) metastatic disease N1-3.

Statistical analysis

Baseline characteristics for the overall cohort were summarized using medians and interquartile ranges (IQR) for continuous variables, and frequency counts and percentages for categorical variables. We estimated recurrence-free (RFS), progression-free (PFS), and cancer-specific (CSS) survival using the Kaplan-Meier method. Patients were followed from the date of initial pathologic diagnosis (i.e., initial TURBT or office biopsy) until occurrence of an event, loss to follow-up, performance of radical cystectomy, or death due to any cause Associations of baseline characteristics with recurrence, progression, and cancer-specific mortality were evaluated using univariable and multivariable Cox regression. Results are summarized using hazard ratios (HR) and 95% confidence intervals (CI). Clinically significant variables in the univariable regression were used as covariates in multivariable regression models (with the exception of PFS, where the five variables with the greatest magnitude of association were selected due to limited event numbers). Complete response to intravesical therapy was not included in the univariable or multivariable model as it is a "post-treatment" feature (i.e., not known or planned at the time of diagnosis). A Swimmer's plot was used to illustrate the clinical course—including recurrence, progression, no evidence of disease (NED), and death—for each individual patient who experienced at least one cancer recurrence. All patients were aligned at a common time zero. To visualize the temporal distribution of recurrence events, a kernel density plot was constructed. Each individual recurrence was treated as a separate event, and patients were included multiple times if they experienced more than one recurrence. One data point was plotted per recurrence event.

Statistical analyses were performed using R version 4.3.0 (R Foundation for Statistical Computing, Vienna, Austria). All tests were 2-sided with P values <0.05 considered statistically significant.

RESULTS

A total of 213 patients with incident HGT1 urothelial carcinoma were included in the study, representing a total of 332 cancer occurrences (i.e., including subsequent recurrences). Baseline characteristics for the cohort are summarized in Table 1, and pathologic characteristics are summarized in Table 2. Median age at diagnosis was 72 years (IQR 65-80) and 171 (80%) patients were male. The majority (81%) of patients had a solitary tumor, while 34 (19%) patients had two or more tumors at diagnosis. The median maximum tumor size was 3.0 (IQR 2.0-5.0) cm. Depth of lamina propria invasion was focal in 91 (43%) patients, and muscularis propria was present in the resection specimen in 150 (70%) patients. Treatments after TURBT are summarized in Table 3. A total of 29 (14 %) patients received immediate post-operative chemotherapy instillation, and 85 (40%) patients underwent restaging TURBT at a median time

of 5.7 (IQR 4.4-8.0) weeks. Adjuvant intravesical therapy was utilized in 166 (78%) patients, most commonly with BCG (63%) or BCG-IFN (14%). Among these, complete response to initial induction intravesical therapy was achieved by 117 (71%) patients. Of those who completed an induction course of intravesical therapy, maintenance therapy was utilized in 71 (43%) patients.

Median follow-up time for RFS was 13.0 (IQR 6.0-39.0) months (27 [IQR 7-58] months among survivors), during which time 87 patients had a recurrence. The 1-, 3-, and 5-year RFS were 65% (95% CI 59-73%), 51% (95% CI 44-60%), and 48% (95% CI 40-57%), respectively (Figure 1 / Supplementary Table 1). During follow-up, there was a mean of 1.70 (SD 1.01) and a median of 1 (IQR 1-2) cancer recurrences per patient. The median (IQR) time to the first recurrence was 7 months (IQR 4-14), while the median time between all contiguous recurrences (i.e., including those after the first recurrence) was 7 months (IQR 5-18)

The distribution of cancer recurrences for each patient during follow-up is illustrated in Figure 2. Interestingly, while most recurrences begin early, there is a subset of patients who have relatively long disease-free intervals with subsequent recurrence more than 36-48 months from the last. The risk of recurrence over time for each of the first 3 recurrences is illustrated in Figure 3, and the risk of any cancer recurrence over time is illustrated in Figure 4. As can be seen in the figure, the risk of each subsequent cancer recurrence peaks early, with a gradual decrease in risk of recurrence, but with evidence of additional peaks after approximately 48 months from diagnosis, suggesting that a subset of patients experience late recurrence.

Median follow-up for PFS was 20 (IQR 7-56.0) months (26 [IQR 7 – 59] months among survivors), during which time 41 patients had a progression event. The 1-, 3-, and 5-year PFS rates were 85% (95% CI 80-91%), 78% (95% CI 72-85%), and 72% (95% CI 60-79%) (Figure 5 / Supplementary Table 2). Median follow-up for CSS was 35 (IQR 15-70.0) months (38 [IQR: 15 – 70] months among survivors), during which time 9 patients died due to bladder cancer. The 1-, 3-, and 5-year CSS were 99% (95% CI 97-100%), 95% (95% CI 92-99%), and 95% (95% CI 92-99%) (Figure 6/ Supplementary Table 3). Overall, a total of 20 (10%) patients died due to causes unrelated to bladder cancer.

The univariable and multivariable associations of baseline characteristics with recurrence, progression, and cancer-specific mortality are summarized in Tables 4 and 5. On univariable analysis, receipt of adjuvant intravesical therapy with BCG (HR 0.36, 95% CI 0.21-0.61) or another agent (HR 0.35, 95% CI 0.18-0.68) were associated with reduced risks of recurrence. Focal depth of lamina propria invasion (HR 0.85, 95% CI 0.55-1.32) and a mixed low/high tumor grade (HR 0.41, 95% CI 0.15-1.12) were associated with a reduced risk of recurrence that did not reach statistical significance. In contrast, former smoking status was associated with increased risks of recurrence (HR 1.52, 95% CI 0.97-2.40). On multivariable analysis, larger tumor size was independently associated with an increased risk of recurrence (HR 1.16, 95% CI 1.01-1.33), while receipt of intravesical BCG (HR 0.24, 95% CI 0.11-0.51) or other intravesical therapy (HR 0.15, 95% CI 0.05-0.43) remained associated with decreased risk of recurrence.

With regard to progression, on univariable analysis, a greater number of tumors (unit HR 1.58, 95% CI 1.15-2.17; HR 2.76, 95% CI 1.17-6.52 for ≥3 tumors) was associated with an increased risk of progression. In contrast, receipt of adjuvant intravesical therapy with BCG (HR 0.20, 95% CI 0.10-0.42) or another agent (HR 0.32, 95% CI 0.14-0.73), and complete response to intravesical therapy (HR 0.15, 95% CI 0.07-0.32) were associated with reduced risks of progression. On multivariable analysis, receipt of BCG (HR 0.19, 95% CI 0.06-0.63) or other

induction intravesical therapy (HR 0.19, 95% CI 0.04-0.85) were associated with decreased risks of progression.

On univariable analysis, black race was associated with an increased risk of cancer-specific mortality (HR 5.88, 95% CI 1.21-28.5). A multivariable analysis was not performed due to limited number of events.

DISCUSSION

Contemporary recurrence and progression rates for patients with HGT1 urothelial carcinoma remain high, with 53% of patients experiencing a recurrence within 5-years of initial diagnosis, and 28% of patients progressing to muscle-invasive disease within the same timeframe. It is important to emphasize that, although these estimates reflect an improvement over historical 5-year recurrence and progression rates, which have been reported to be as high as 50-70% and 25-50%, respectively, they remain high despite improvements in our understanding of NMIBC and the introduction of novel therapeutic interventions. However, CSS remains favorable, with 95% CSS at 5-years. In light of the high rates of recurrence and progression, it is critical to identify patients at the highest risk of these outcomes to allow more aggressive management. To this end, although we examined a large number of potential clinical and pathologic characteristics to predict recurrence and progression, on multivariable analysis, only two were associated with these outcomes. Larger tumor size was associated with increased risks of recurrence, while receiving any type of intravesical therapy was associated with decreased risks of recurrence and progression.

We examined the disease burden of HGT1 bladder cancer by presenting what is, to our knowledge, the first comprehensive analysis of the individual natural histories of HGT1 bladder cancer. Specifically, we visualize all recurrences following initial diagnosis, capturing the full burden of this disease, and examine the distributed risk over time of each individual recurrence. In this context, patients with HGT1 bladder cancer have a mean of 1.67 (SD 0.98) recurrences, with a median time of 7 (IQR 4-13.50) months to the first recurrence, and 7 (IQR 5-15) months between subsequent recurrences. Interestingly, while most recurrences do occur early – suggesting that the conditional survival improves over time – there is a subset of patients who develop later recurrences following relatively long disease-free intervals of 3-4 years. These observations emphasize the need for long-term surveillance, but perhaps more importantly, raise provocative questions regarding the heterogeneous disease biology for those with later recurrence and/or potential decrease over time of the anti-tumor immunologic response. It is important to note that the present cohort reflects contemporary technologies and treatment paradigms, including photodynamic diagnosis, immediate instillation of intravesical therapies, and salvage intravesical therapy paradigms.

It is worth noting that many features we examined were not associated with RFS or PFS. These included age, Charlson comorbidity index, and current smoking status – suggesting that host characteristics may not affect response to intravesical immunotherapy. Similarly, we did not observe associations between several potentially prognostic tumor characteristics and recurrence or progression, including lymphovascular invasion, presence of variant histology, concomitant carcinoma-in situ (CIS) or multifocality, although there appeared to be an association with depth of lamina propria invasion and high-grade proportion that did not reach statistical significance. These observations underscore the unmet need for new biomarkers to better predict the biology and outcomes of HGT1 bladder cancer. In addition, there was no association between the

presence of muscularis propria in the initial resection specimen nor utilization of immediate postoperative chemotherapy with recurrence or progression.

Planned restaging resection has been associated with improved staging and oncologic outcomes for patients with high-grade NMIBC, and is recommended by clinical practice guidelines for HG T1 bladder cancer.[8,11–13] Interestingly, we did not observe an association between re-TURBT and survival outcomes. This may be related to a high rate of muscularis propria sampling at initial TURBT in our cohort, and these findings are consistent with reports from other single institution cohorts.[14,15,16] These observations suggest that, aside from ensuring that disease is accurately staged as non-muscle invasive, the performance of a re-TURBT may not affect long-term recurrence and progression rates (i.e., by resecting residual disease). It is important to acknowledge that although the rate of restaging TURBT was low for this cohort at 39%, this is consistent with real-world reports[17] and likely represents a gap between real-world practice and guideline recommendations in the setting of a highly heterogeneous disease as NMIBC.

Early series of high-risk NMIBC reported progression rates that ranged between 25-50% and recurrence rates of 70-80%.[5,7,18] Similarly, a SEER-Medicare study reported 5-year recurrence, progression, and cancer-specific mortality rates of 72.5%, 29.5%, and 14.8% respectively for 4258 patients with HGT1 tumors[19]. A multi-center Canadian cohort of 173 patients with HGT1 NMIBC reported recurrence and upstaging rates of 57.2% and 9.2%, respectively.[20] Thomas et al evaluated oncologic outcomes in a single-center cohort of 712 high-risk patients of which 68% had T1 disease. 5-year recurrence was reported to be 56.5%, similar to the present study, but progression rates were lower, at 15.8%.[21] In a more recent study, Yong et al reported a 5-year recurrence rate of 50% with an 86% CSS in a cohort of 191 patients with HGT1 tumors treated with bladder sparring approaches – similar to the present study, although CSS was notably lower.[14] Although the present study suggests an improvement in recurrence, progression and survival rates when compared to these cohorts, our results indicate that there is still an unmet need to improve oncologic outcomes in this group of patients.

The present study is not without limitations. First and foremost, it is retrospective and subject to confounding. Furthermore, we present data from a single institution, and results may not be generalizable to other settings, such as geographic regions or practice settings. In addition, we were unable to include certain features for evaluation, such as specific imaging findings or potential biomarkers. Moreover, we only examined prognostic variables from the initial diagnosis resection, and management protocols were not uniform among providers over the study years. Additionally, only the most clinically relevant covariates were included in multivariable models, given insufficient power. Furthermore, we were unable to evaluate for the formal FDA definition of BCG unresponsive disease.[22] Additionally, statistical power was limited in multivariable analyses due to low event rates, and only the most clinically relevant covariates were included in these models. Accordingly, these results should be interpreted within this context. Nonetheless, this is, to our knowledge, the largest single-institution contemporary cohort of patients with HGT1 bladder cancer, and we examined a wide variety of clinical and pathologic characteristics as potential prognostic features. Moreover, the cohort reflects a contemporary patient population and real-world outcomes that can inform patient counseling, management, and clinical trial design.

CONCLUSIONS
The contemporary 5-year rates of recurrence and progression among patients with incident HGT1 bladder cancer remain high at 53% and 28%, respectively. Larger tumor size is associated with increased risks of recurrence, while adjuvant intravesical therapy is associated with lower risks of recurrence and progression. These results can inform patient care and clinical trial design.

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FIGURES AND TABLES

Figure 1. Recurrence-free survival (RFS).

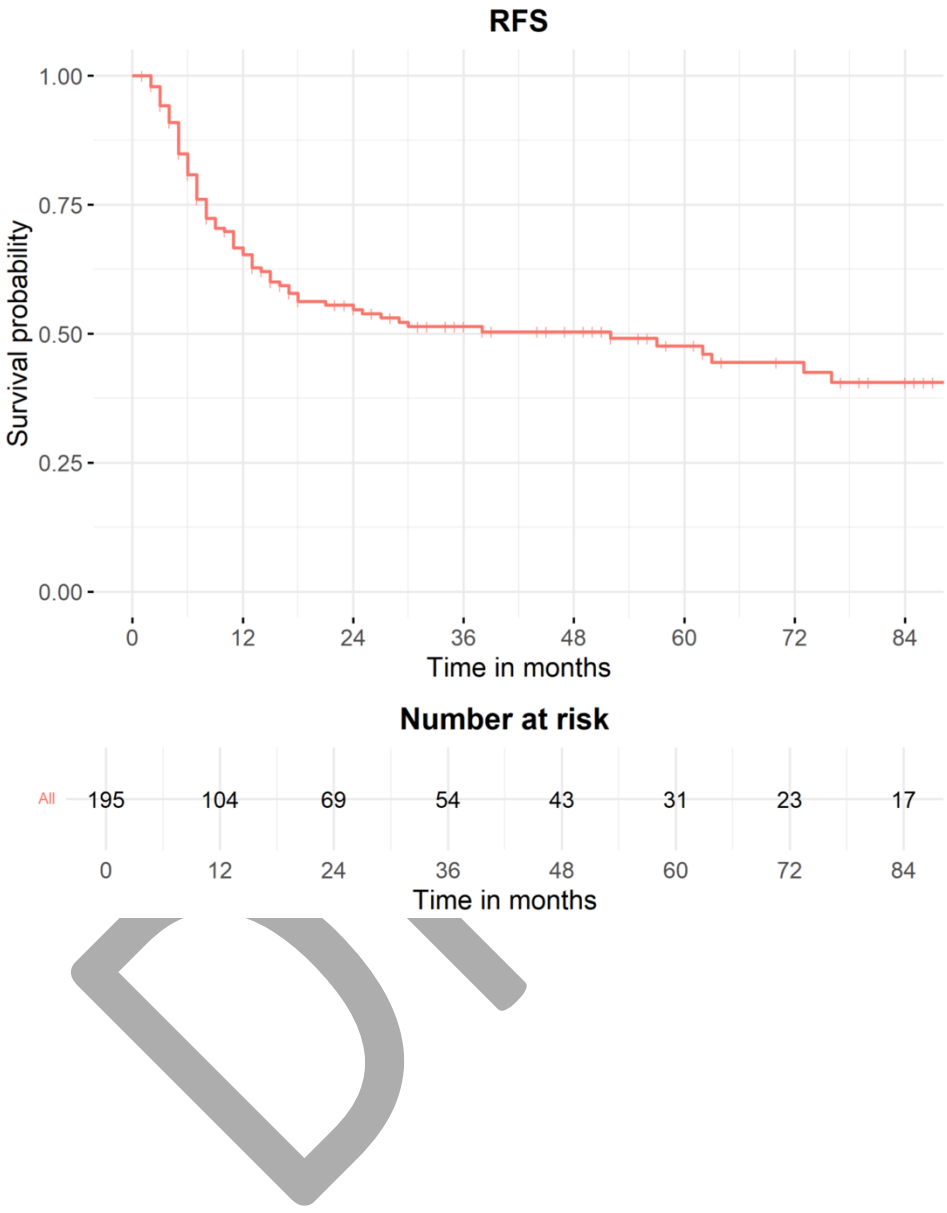

Figure 2. Swimmer's plot of cancer recurrences over time among patients with at least one recurrence (n=116).

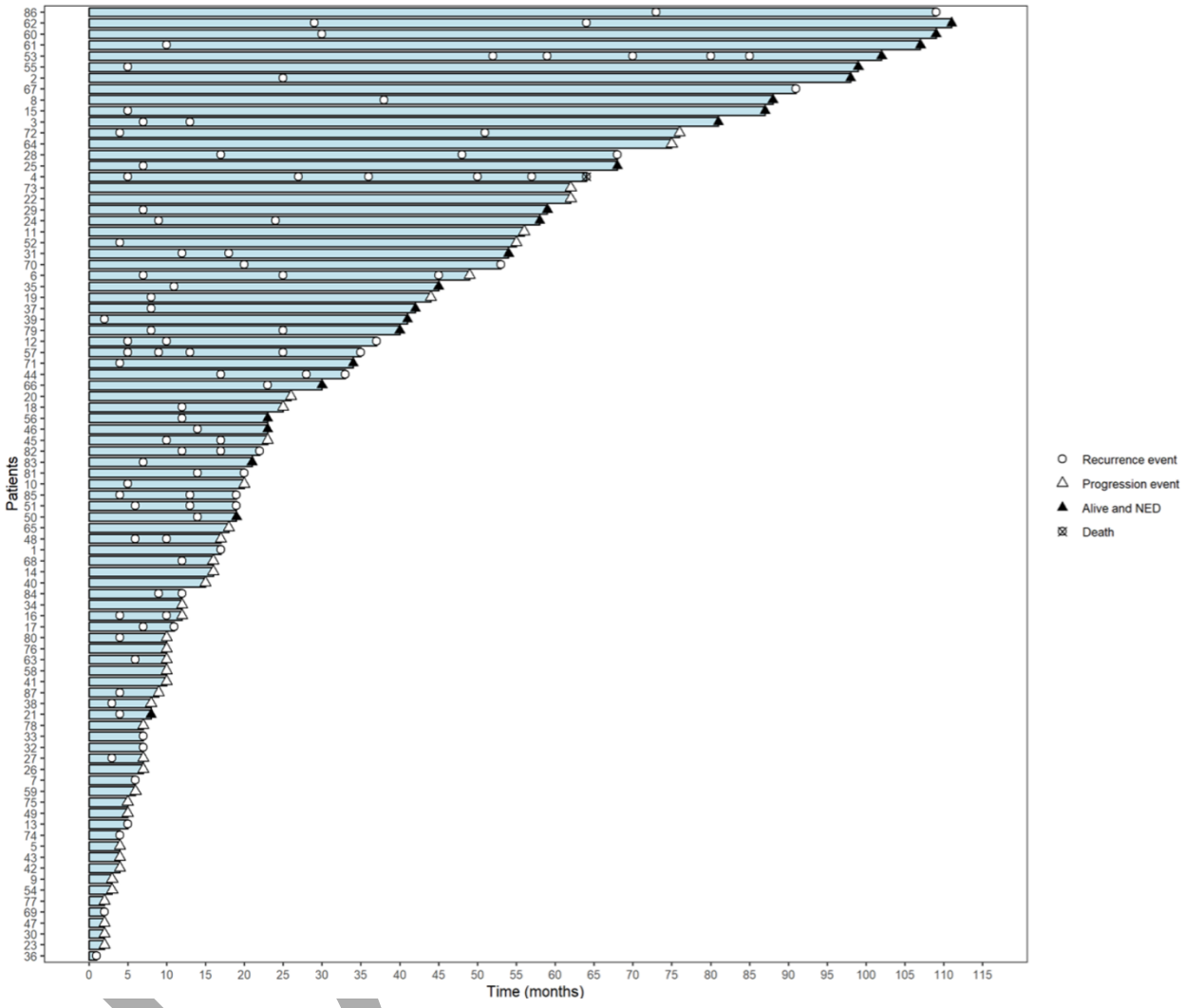

Figure 3. Kernel density plot illustrating risk of cancer recurrence over time, stratified by 1st, 2nd, or 3rd recurrence.

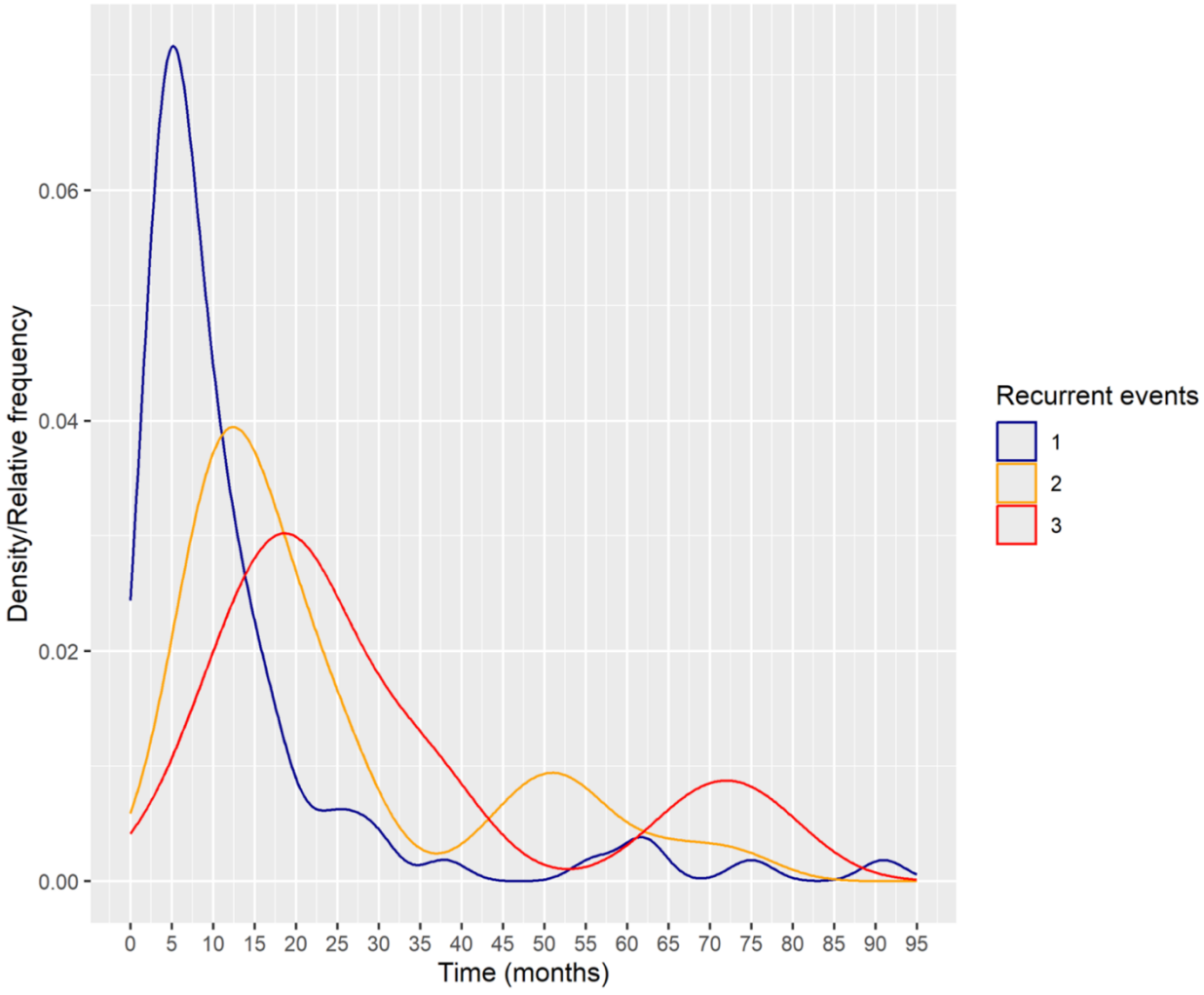

Figure 4. Kernel density plot illustrating risk of any cancer recurrence over time.

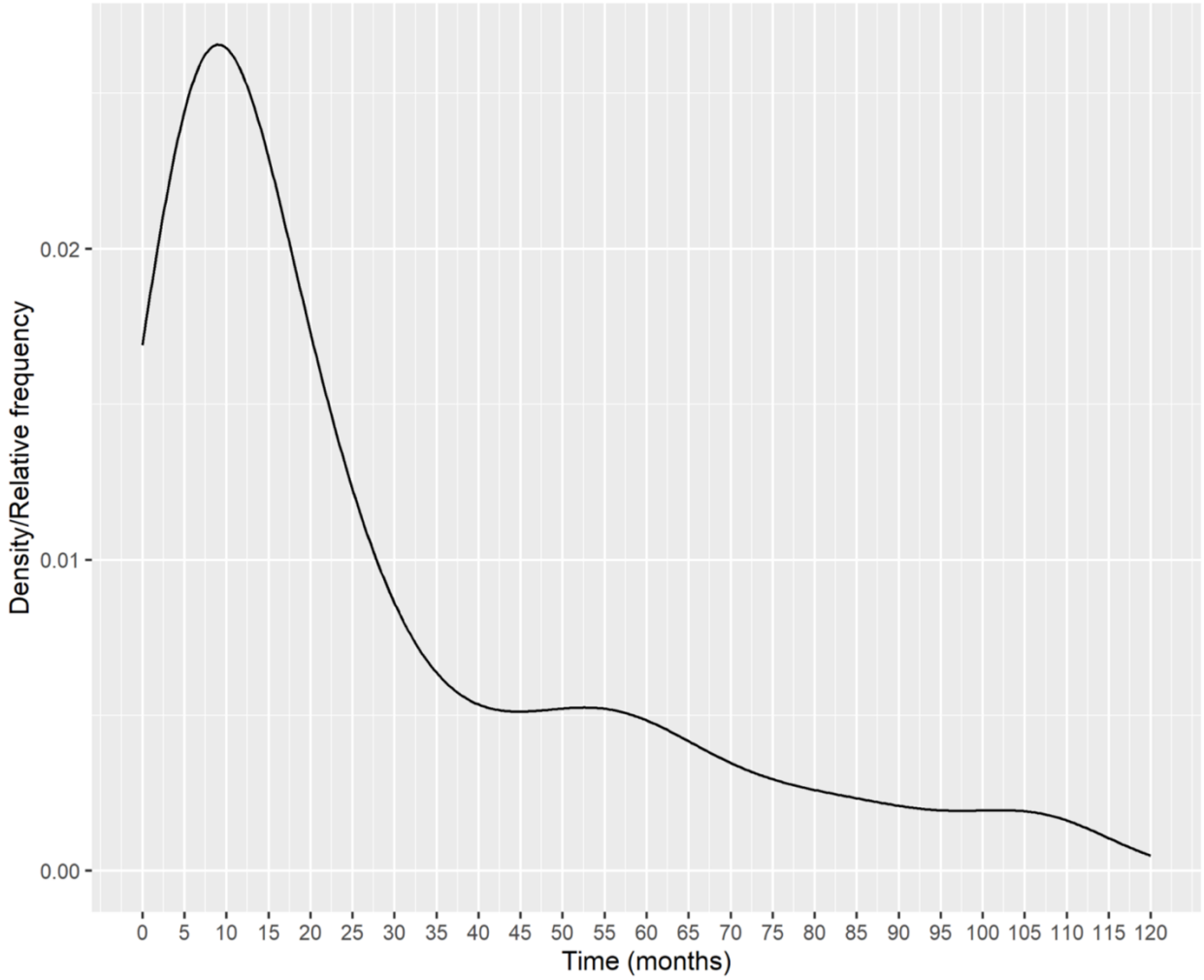

Figure 5. Progression-free survival (PFS).

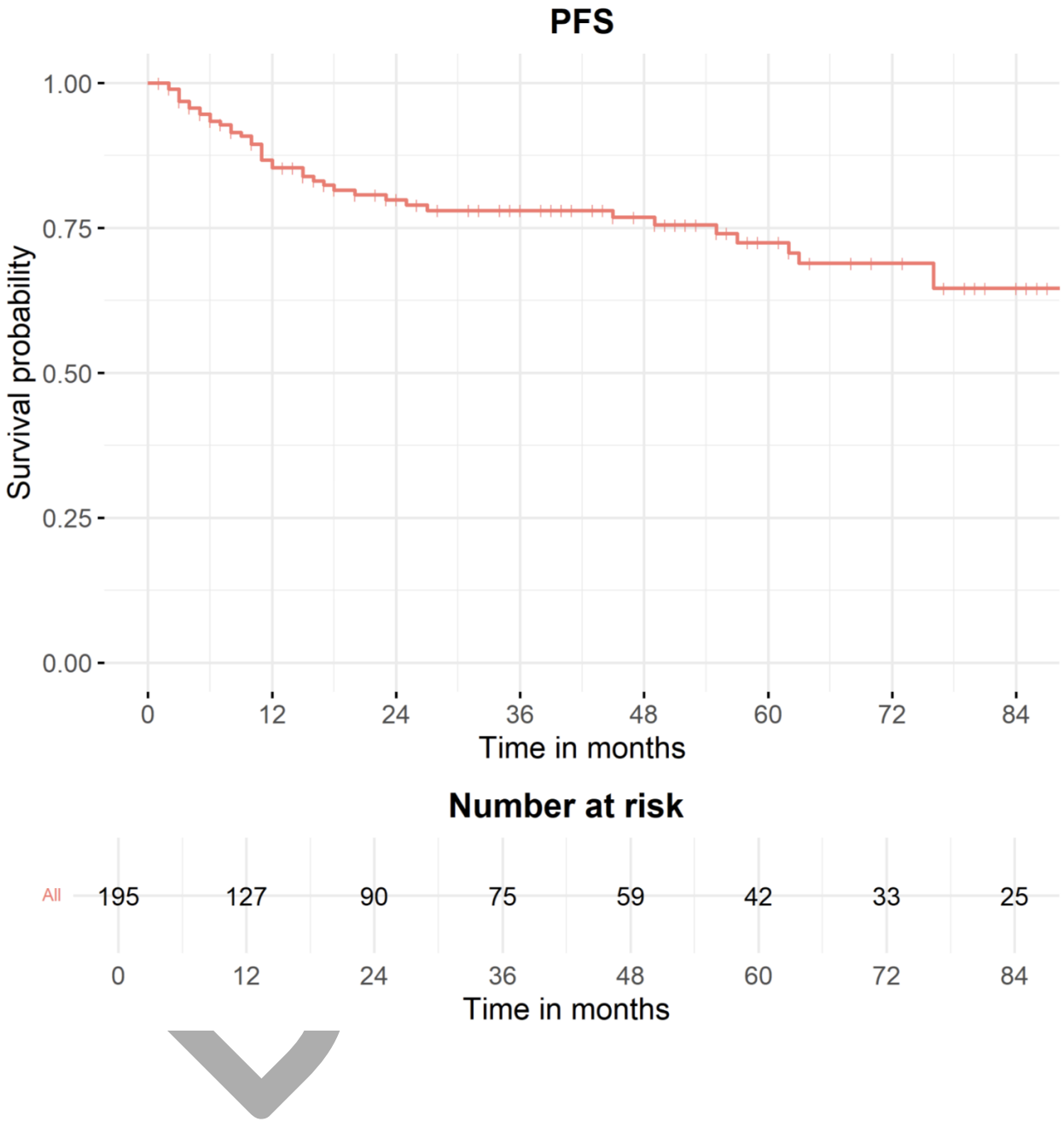

Figure 6. Cancer-specific survival (CSS).

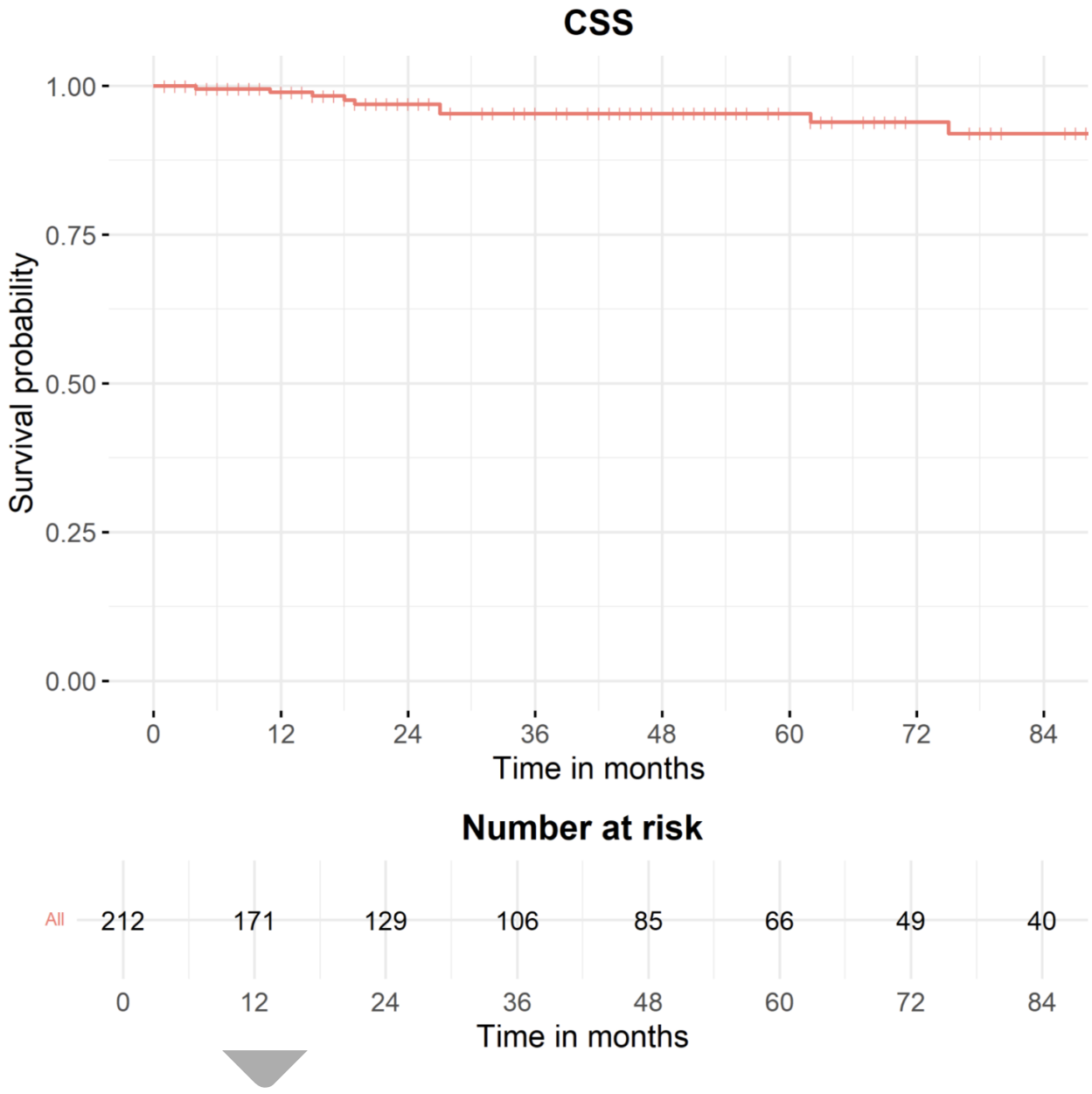

Table 1. Baseline characteristics	
Characteristic	**Overall (n=213)**
Age, years, median (q1–q3)	72 (65–80)
Gender, n (%)	
Male	169 (80)
Female	42 (20)
Charlson comorbidity index, n (%)	
0	95 (45)
1	39 (18)
2	36 (17)
3+	42 (20)
Smoking status, n (%)	
Never	88 (41)
Former	100 (47)
Current	25 (12)
Race, n (%)	
White	175 (82)
Black	13 (6)
Asian	14 (7)
Other	3 (1)
Unknown/not reported	8 (3)
Hispanic, n (%)	
Yes	8 (4)
No	199 (93)
Unknown/not reported	6 (3)
Family history of bladder cancer, n (%)	
No	206 (97)
Yes	7 (3)
Year of diagnosis, n (%)	
2010	4 (1)
2011	14 (7)
2012	20 (9)
2013	13 (6)
2014	24 (11)
2015	19 (9)
2016	23 (11)
2017	24 (12)
2018	18 (9)
2019	16 (8)
2020	16 (8)
2021	13 (6)
2022	9 (4)

Number of tumors (continuous), median (q1–q3)	1 (1, 1)
Missing	35
Number of tumors (categorical), n (%)	
1	144 (81)
2	16 (9)
3	13 (7)
4	3 (2)
5	2 (1)
Missing	35
Number of tumors, n (%)	
1	144 (81)
2-7	34 (19)
Missing	35
Maximum tumor size (continuous) (in cm), median (q1-q3)	3.0 (2.0, 5.0)
Missing	66
Maximum tumor size (in cm), n (%)	
< 3	60 (41)
>= 3	87 (59)
Missing	66
Preoperative hydronephrosis, n (%)	
No hydronephrosis	155 (91)
Left hydronephrosis	4 (2)
Right hydronephrosis	9 (5)
Bilateral hydronephrosis	2 (1)
Missing/no perioperative imaging available	43
ASA, n (%)	
I	2 (1)
II	83 (43)
III	103 (53)
IV	7 (4)
V	1 (1)
Missing	17
Intraoperative blue light cystoscopy, n (%)	
No	199 (97)
Yes	7 (3)
Missing	7

ASA: American Society of Anesthesiologists; CIS: carcinoma in situ; q: quartile.

Table 2. Pathology at initial diagnosis	
Characteristic	**Overall (n=213)**
Lamina propria invasion, n (%)	
Focal T1	91 (43)
Non-focal T1/unknown	120 (57)
High grade proportion, n (%)	
All high-grade	188 (88)
Mix of low-grade and high-grade	25 (12)
Lymphovascular invasion, n (%)	
No	203 (95)
Yes	10 (5)
Variant histology present, n (%)	
No	174 (82)
Yes	39 (18)
Concomitant CIS, n (%)	
No	165 (77)
Yes	48 (23)
Variant histology type, n (%)	
Micropapillary	13 (37)
Squamous	7 (20)
Adenocarcinoma	4 (11)
Sarcomatoid	3 (9)
Plasmacytoid	3 (9)
Rhabdoid	2 (6)
Squamous & sarcomatoid	1 (3)
Micropapillary & adenocarcinoma	2 (6)
Missing/no variant histology	178
Multifocal disease, n (%)	
No	180 (87)
Yes	28 (13)
Missing	5
Muscularis propia in specimen, n (%)	
No	63 (30)
Yes	150 (70)
Re-TURBT performed	
No	128 (60)
Yes	85 (40)

CIS: carcinoma in situ; TURBT: transurethral resection of bladder tumor.

Table 3. Treatments after TURBT	
Characteristic	**Overall (n=213)**
Immediate postoperative chemotherapy, n (%)	
No	182 (86)
Yes	29 (14)
Missing	2
Postoperative complications, n (%)	
No	192 (90)
Yes	21 (10)
Clavien Dindo, n (%)	
1	14 (62)
2	4 (24)
3a	1 (5)
3b	2 (10)
Missing/ no complications	192
Missing/ no complications	192
Re-TURBT performed, n (%)	
No	129 (61)
Yes	83 (39)
Time to Re-TURBT- in weeks, median (q1–q3)	5.7 (4.4, 8.0)
Not applicable (no Re-TURBT performed)	128
Time to re-TURBT, n (%)	
<6 weeks	44 (52)
≥6 weeks	41 (48)
Pathology at re-TURBT	
Benign	40 (48)
Ta	16 (19)
Tis	9 (11)
T1	18 (22)
Type of adjuvant intravesical therapy	
BCG	134 (63)
BCG-IFN	30 (14)
Gemcitabine-docetaxel	1 (<0.1)
Gemcitabine alone	1 (<0.1)
None	47 (22)
Cycles of induction intravesical therapy completed, n (%)	
Yes	117 (71)
No	43 (26)
Not assessed	5 (3)
Missing/unknown	1

Not applicable (No intravesical therapy administered)	47
Maintenance intravesical therapy, n (%)	
No	142 (66)
Yes	71 (34)

BCG: bacillus Calmette-Guérin; BCG-IFN: bacillus Calmette-Guérin with interferon-alpha; TURBT: transurethral resection of bladder tumor.

Table 4. Univariable associations of baseline characteristics with recurrence, progression, and cancer-specific mortality

	RFS	**PFS**	**CSS**
Characteristic	Unadjusted HR (95% CI)	Unadjusted HR (95% CI)	Unadjusted HR (95% CI)
Age, years	1.00 (0.98, 1.02)	1.02 (0.99, 1.05)	1.01 (0.94, 1.08)
Gender			
Male	–	–	–
Female	0.72 (0.40, 1.30)	1.18 (0.56, 2.47)	1.24 (0.26, 5.97)
Charlson Index			
0	–	–	–
1	1.13 (0.64, 1.99)	1.08 (0.48, 2.43)	2.23 (0.50, 10.0)
2	0.77 (0.40, 1.49)	0.41 (0.12, 1.37)	–
3+	1.08 (0.61, 1.93)	0.88 (0.38, 2.06)	1.34 (0.24, 7.34)
Smoking status			
Never	–	–	–
Former	1.52 (0.97, 2.40)	0.93 (0.47, 1.83)	0.68 (0.15, 3.04)
Current	1.25 (0.61, 2.54)	1.72 (0.72, 4.14)	1.85 (0.34, 10.1)
Race			
White	–	–	–
Black	1.98 (0.86, 4.60)	2.54 (0.90, 7.21)	5.88 (1.21, 28.5)*
Others	0.99 (0.48, 2.06)	0.47 (0.11, 1.95)	–
Hispanic			
No/Unknown	–	–	–
Family history of bladder cancer			
No	–	–	–
Yes	1.08 (0.39, 2.94)	1.78 (0.55, 5.76)	–
Year of diagnosis			–
2010–2012	–	–	–
2013–2015	0.75 (0.41, 1.37)	0.51 (0.22, 1.18)	0.73 (0.10, 5.16)
2016–2018	0.80 (0.42, 1.50)	0.60 (0.25, 1.45)	1.55 (0.25, 9.61)
2019–2021	1.09 (0.57, 2.07)	1.08 (0.45, 2.59)	1.64 (0.21, 12.8)

Number of tumors (continuous)	1.16 (0.89, 1.51)	1.58 (1.15, 2.17)*	1.60 (0.84, 3.05)
Number of tumors (categorical)			
1	–	–	–
2	0.80 (0.34, 1.85)	0.76 (0.18, 3.24)	5.74 (0.96, 34.4)
≥3	1.33 (0.66, 2.69)	2.76 (1.17, 6.52)*	2.52 (0.26, 24.3)
Maximum tumor size (in cm) (continuous)	1.12 (0.98, 1.28)	1.06 (0.85, 1.32)	0.67 (0.35, 1.28)
Maximum tumor size (in cm)			
< 3	–	–	–
≥ 3	1.34 (0.79, 2.27)	1.50 (0.63, 3.60)	0.19 (0.02, 1.67)
Hydronephrosis			
No hydronephrosis	—	—	—
Left/right/bilateral	1.79 (0.89, 3.60)	2.34 (0.90, 6.07)	1.51 (0.19, 12.1)
ASA			
I/II	—	—	—
III/IV/V	1.38 (0.88, 2.17)	1.46 (0.73, 2.90)	0.81 (0.20, 3.25)
Intraoperative blue light cystoscopy			
No	–	–	–
Yes	0.85 (0.27, 2.70)	–	–
Postoperative complications			
No	–	–	–
Yes	1.11 (0.55, 2.21)	1.53 (0.64, 3.63)	2.85 (0.59, 13.7)
Lamina propria invasion			
Non-focal T1/unknown	–	–	–
Focal T1	0.85 (0.55, 1.32)	0.95 (0.50, 1.79)	1.15 (0.31, 4.30)
High-grade proportion			
All high-grade	–	–	–
Low-grade with focal high-grade/mix of low-grade and high-grade	0.41 (0.15, 1.12)	–	–
Lymphovascular invasion			
No	—	–	–
Yes	0.84 (0.27, 2.67)	1.47 (0.35, 6.12)	4.05 (0.48, 34.0)
Variant histology present			
No	–	–	–
Yes	1.30 (0.76, 2.21)	1.97 (0.99, 3.94)	0.60 (0.08, 4.82)
Concomitant CIS			
No	–	–	–
Yes	0.97 (0.60, 1.57)	0.80 (0.38, 1.68)	1.52 (0.38, 6.10)
Multifocal disease			
No	–	–	–
Yes	1.32 (0.74, 2.35)	1.43 (0.63, 3.25)	2.10 (0.42, 10.4)
Muscularis propia in specimen			
No	–	=	–

Yes	0.98 (0.62, 1.55)	0.95 (0.49, 1.84)	0.53 (0.14, 1.97)
Re-TURBT performed			
No	–	–	–
Yes	0.84 (0.55, 1.29)	0.73 (0.39, 1.38)	0.69 (0.17, 2.75)
Immediate postoperative chemotherapy			
No	–	–	–
Yes	1.07 (0.59, 1.93)	0.33 (0.08, 1.37)	—
Type of adjuvant intravesical therapy			
None	–	–	–
BCG	0.36 (0.21, 0.61)*	0.20 (0.10, 0.42)*	0.37 (0.08, 1.65)
Other	0.35 (0.18, 0.68)*	0.32 (0.14, 0.73)*	0.51 (0.08, 3.09)
Complete response to intravesical therapy			
No	–	–	–
Yes	0.05 (0.03, 0.09)*	0.15 (0.07, 0.32)*	0.62 (0.11, 3.41)
Not assessed	–	–	–

*p<0.05. CI: confidence interval; HR: hazard ratio.

Table 5. Multivariable associations of baseline characteristics with recurrence, progression, and cancer-specific mortality[a]

	RFS	**PFS**
Characteristic	**Adjusted HR (95% CI)**	**Adjusted HR (95% CI)**
Type of adjuvant intravesical therapy		
None	–	–
BCG	0.24 (0.11, 0.51)*	0.19 (0.06, 0.63)*
Other	0.15 (0.05, 0.43)*	0.19 (0.04, 0.85)*
Number of tumors (continuous)	1.18 (0.81, 1.72)	1.69 (0.99, 2.88)
Maximum tumor size (continuous)	1.16 (1.01, 1.33)*	1.18 (0.93, 1.50)
Concomitant CIS		
No	–	–
Yes	1.61 (0.88, 2.97)	1.35 (0.49, 3.75)
Lymphovascular invasion		
No	–	–
Yes	0.39 (0.05, 2.89)	–
Lamina propria invasion		
Non-focal T1/unknown	–	–
Focal T1	1.27 (0.71, 2.26)	1.48 (0.58, 3.78)
High-grade proportion		
All high-grade	–	–

Low-grade with focal high-grade/mix of low-grade and high-grade	0.33 (0.08, 1.44)	–

[a]Complete response to intravesical therapy was not included in the multivariable model as it is a "post-treatment" feature (i.e., not known or planned at the time of diagnosis). *p<0.05
BCG: bacillus Calmette-Guérin; CI: confidence interval; CIS: carcinoma-in-situ; HR: hazard ratio; TURBT: transurethral resection of bladder tumor.