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Impact of High-risk Features and Effect of Neoadjuvant Chemotherapy in Urothelial Cancer Patients with Invasion into the Lamina Propria on Transurethral Resection in the Absence of Deep Muscle Invasion

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Abstract

Background—High-risk non–muscle-invasive bladder cancer (NMIBC) that invades into the lamina propria is frequently understaged and is associated with a risk of lymph node metastasis and death.

Objective—To identify high-risk features (HRFs) for NMIBC that may identify patients with poorer prognosis who may benefit from neoadjuvant chemotherapy (NAC) prior to radical cystectomy (RC).

Design, setting, and participants—We performed a single-center retrospective review of patients who underwent RC for NMIBC with invasion into the lamina propria between 1995 and 2013. HRFs included hydronephrosis, abnormal examination under anesthesia, lymphovascular invasion, or variant histology.

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Outcome measurements and statistical analysis—Pathology at RC, and overall (OS) and disease-specific (DSS) survival were evaluated and analyzed by Fisher's exact test, Student *t* test, Cox proportional hazards regression analysis, and the Kaplan–Meier method.

Results and limitations—We identified 336 patients with a median follow-up of 130 mo. Of these, 159 (47%) had no HRF, 140 (41.5%) had one HRF, and 37 (11%) had 2 HRFs. At RC, patients with 2 HRFs had a significantly higher rate of pathologic T stage upstaging and lymph node metastasis ($p < 0.05$). Median OS was 139 mo for those with no HRF, 127 mo for those with one HRF, and 56 mo for those with 2 HRF ($p = 0.0057$). HRFs are also associated with a decreased DSS ($p = 0.0009$). Patients with 2 HRFs (11/37) who received NAC showed improved OS (21% vs 55% 5-yr OS, $p = 0.0353$) and trended toward an improvement in DSS (25% vs 56% 5-yr OS, $p = 0.0716$) compared with RC alone.

Conclusions—The presence of 2 HRFs in NMIBC invading the lamina propria is associated with worse pathology at RC and a significant decrease in OS and DSS. NAC appears to provide benefit for these patients. Limitations include retrospective design and limited sample size.

Patient summary—The presence of high-risk features in urothelial cancer with invasion into the lamina propria has a worse prognosis that may be mitigated by neoadjuvant chemotherapy.

Keywords

T1 high-grade bladder cancer; Variant histology; Neoadjuvant chemotherapy; Cystectomy; High-risk features; Urothelial cancer; Non-muscle-invasive bladder cancer; Superficial bladder cancer

1. Introduction

Approximately 75% of patients with urothelial carcinoma of the bladder present with non-muscle-invasive bladder cancer (NMIBC), either confined to the mucosa (Ta and carcinoma in situ [CIS]) or invading the lamina propria (T1) [1]. Clinical T1 high-grade (cT1HG) NMIBC has the highest rate of local recurrence and carries a significant risk of disease progression, clinical understaging, and death from urothelial carcinoma (UC) [2,3]. The standard of care for adequately resected cT1HG NMIBC is intravesical Bacillus Calmette-Guerin (BCG) [4–6] with early radical cystectomy (RC) for recurrent or refractory cT1HG disease [6–8]. Pathological upstaging to pT2 is reported in approximately 50% when muscularis propria is absent from the original biopsy, and up to 25% will have lymph node (LN) metastases [9], which significantly increases the risk for cancer-specific death [10]. These observations imply that a subset of patients with NMIBC that invades into the lamina propria is at a higher risk for clinical understaging and death from UC and may benefit from more aggressive therapy.

Methotrexate, vinblastine, adriamycin, and cisplatin (MVAC) neoadjuvant chemotherapy (NAC) provides pathological downstaging and improved overall survival (OS) for patients with muscle-invasive bladder cancer (MIBC) undergoing RC [11,12]. However, the impact of NAC in an unselected population is modest with an approximate 6% improvement in 5-yr survival [11]. Given the potential for both acute and chronic toxicity, our approach has been to offer NAC to patients considered to be at the highest risk for developing metastatic disease, whereas those considered to be at low risk are managed with upfront RC and

adjuvant chemotherapy if clinically understaged [13]. Culp et al [13] reported that a low-risk cohort of MIBC defined by the absence of lymphovascular invasion (LVI), micropapillary or neuroendocrine differentiation, hydronephrosis, and a palpable mass on examination under anesthesia (EUA) had favorable survival following RC alone. These observations were validated in two separate cohorts [14]. We hypothesized that similar high-risk features (HRFs) might identify a high-risk subset of UC patients that could benefit from NAC in the absence of evidence for muscle invasion [2,15–20].

2. Patients and methods

We identified all patients diagnosed with high-grade (HG) NMIBC with lamina propria invasion and no evidence of muscle invasion at the time of transurethral resection of bladder tumor (TURBT) who ultimately underwent RC between 1995 and 2013 at The University of Texas MD Anderson Cancer Center (MDACC). Patients with radiographic evidence of nodal or distant metastases, a past history of upper tract disease, neuroendocrine features, non-cisplatin-based NAC, prior radiation therapy to their pelvis, a palpable three-dimensional mass on EUA, or a history of bladder perforation were excluded. All pathological specimens, including those from other centers, were reviewed by dedicated genitourinary pathologists at MDACC.

This study was approved by the Institutional Review Board. We collected clinical, demographic, and pathological data from chart review. HRFs were defined as follows: LVI, thickening or induration on EUA, tumor-associated hydronephrosis, and variant histology. Tumors with a primary urothelial component and presence of micropapillary, squamous, sarcomatoid, nested variant, glandular, plasmacytoid, adenocarcinoma, or lymphoepithelioma components were classified as tumors of variant histology [15]. Clinical staging was defined according to the American Joint Committee on Cancer 2010 TNM Staging System [16]. Computed tomography cross-sectional imaging was used to determine the clinical nodal category and the presence of hydronephrosis.

Several intravesical regimens were delivered, but most patients (53.1%) received induction BCG with or without maintenance, while 46% received no intravesical therapy. BCG-unresponsive NMIBC was defined by current consensus statements [17].

Indication for RC included BCG-unresponsive disease, cT1HG NMIBC on repeat biopsy, or the presence of a concomitant clinical HRF at time of cT1HG diagnosis. All patients offered NAC received a platinum-based regimen. Adjuvant chemotherapy was offered to eligible patients with extravesical disease at the time of RC. Salvage chemotherapy was recommended for progressive or recurrent disease after surgery. Adjuvant and salvage chemotherapy consisted primarily of cisplatin-containing regimens. However, in patients receiving adjuvant or salvage chemotherapy who were cisplatin ineligible, noncisplatin regimens were included. The predominant reason for using a non-platinum-based regimen was poor renal function.

The primary end points of the study were OS and disease-specific survival (DSS). The cause of death was determined by reviewing patients' clinical notes and follow-up reports. In cases

in which a definitive cause of death was not evident, we determined the cause based on patients' most recent clinical status and time from the last follow-up to death. Survival was defined as the period from the date of RC to the date of death or last follow-up. Secondary end points included pathological upstaging defined as pT2 and the presence of nodal disease at the time of RC.

The log-rank test and Cox proportional hazards regression analyses were used to evaluate the association between clinicopathological factors and outcome. Fisher's exact test/chi-square test was applied to evaluate the association between categorical variables. Numbers of HRFs, NAC, and other variables with $p < 0.1$ in the univariate analyses were included in the multivariate analysis. The backward selection procedure was applied for model selection to remove one variable at a time, until all other variables in the model have $p < 0.05$. The Kaplan–Meier (KM) method was used for survival analysis of OS and DSS [18]. SAS9.4 software (SAS Institute Inc., Cary, NC, USA) and TIBCO Spotfire S+ 8.2 software (TIBCO Software Inc., Palo Alto, CA, USA) were used for statistical analysis.

3. Results

3.1. Baseline demographics

We identified 336 patients who underwent RC and who had invasion into the lamina propria without evidence of muscle invasion. Median follow-up was 130 mo (Table 1 and Supplementary Table 1). A total of 140 (42%) patients possessed one HRF and 37 (11%) had two or more HRFs. HRFs included variant histology ($n = 83$, 25%), LVI ($n = 38$, 11%), hydronephrosis ($n = 35$, 10%), and thickening or induration on EUA ($n = 29$, 8.6%; Table 2). Patients with a palpable mass were excluded. A total of 185 HRFs were identified in 177 patients. Variant histology was identified in 45% (83/185), an abnormal EUA in 16% (29/185), LVI in 21% (38/185), and hydronephrosis in 19% (35/185) of patients with at least one HRF. Among patients with ≥ 2 HRFs, 19 had LVI (51%), nine (24%) had an abnormal EUA, 15 (41%) had hydronephrosis, and 23 (62%) had a variant histology.

In our cohort, 252 patients (76%) underwent a re-resection with no significant difference in the rates of re-resection between the HRF subgroups ($p > 0.05$). Of the 81 patients who went directly to RC without re-resection (24%), 51 (15%) had progressed to T1 high grade (T1HG) on BCG. Muscularis propria was present in 91% of specimens, and there was no difference in the proportion of patients with 0, 1, and ≥ 2 HRFs who had muscle in the specimen ($p > 0.05$).

Cisplatin-based NAC was administered to 7% of patients (26/336). Four percent (14/336) received MVAC, 2% (7/336) received gemcitabine and cisplatin, and 1.5% received MVAC with avastin (5/226). No patients without an HRF received NAC. Fewer patients were administered NAC if they had one HRF (15/140, 11%) compared with those with ≥ 2 HRF (11/37, 30%, $p = 0.004$; Supplementary Table 1).

Postoperative chemotherapy was administered to 13% of patients (45/336). Twenty-five patients received adjuvant and 33 received salvage chemotherapy. There was no significant difference in the proportion of patients with 0, 1, or ≥ 2 HRFs who received adjuvant therapy

($p > 0.05$). Among patients with no HRF, 8% (12/159) received salvage chemotherapy compared with 9% (12/140) with one HRF, and 24% (9/37) with two or more HRFs ($p = 0.05$; Supplementary Table 1). The most common agents administered in the adjuvant or salvage setting were MVAC (16/336, 4.8%), dose-dense MVAC (8/336, 2.4%), gemcitabine and cisplatin (8/336, 2.4%), or cisplatin, gemcitabine, and ifosfamide (6/336, 1.8%). Ifosfamide, adriamycin, gemcitabine, etoposide, and methotrexate were administered to 2% of patients (7/336) who were cisplatin ineligible.

3.2. Pathological outcome at the time of RC

Of the patients, 28% (94/336) were upstaged to pT2 disease at RC, with 14% (45/336) upstaged to pT3/T4 disease. Of patients with <1 HRF, 27% (81/299) had pT2 at RC compared with 35% (13/37) of patients with ≥ 2 HRFs ($p = 0.4484$). Among patients who did not receive NAC, 28% (79/284) with ≤ 1 HRF and 46% (12/26) with ≥ 2 HRFs were upstaged to pT2 disease at RC ($p = 0.0480$).

The median number of LNs dissected was 20 with an interquartile range (IQR) of 12–28. LN metastasis occurred in 30 patients (9%), with a median number of positive nodes of 1 (1–2 IQR). Of patients, 8% (24/299) with ≤ 1 HRF and 16% (6/37) with ≥ 2 HRFs had LN metastasis ($p = 0.1208$). In patients undergoing RC alone, 8% (23/284) with ≤ 1 HRF and 23% (6/26) with ≥ 2 HRFs had LN metastasis ($p = 0.0236$). In patients with LN metastasis, the median numbers of positive LN metastasis were 1 (1–2.5 IQR) and 1.5 (1–2 IQR) for patients with ≤ 1 HRF and ≥ 2 HRFs, respectively.

3.3. Effect of HRFs on survival

The 90-d postoperative mortality rate was 1.8% (6/337). There were 211 (63%) deaths from any cause and 72 (21%) deaths from UC. Median OS was 139 mo for those with no HRF, 127 mo for those with one HRF, and 56.3 mo for those with ≥ 2 HRFs ($p = 0.0057$). The presence of ≥ 2 HRFs was associated with a decrease in OS and DSS ($p < 0.05$; Fig. 1). On a reduced model multivariate analysis, having ≥ 2 HRFs was significant for reduced OS (hazard ratio [HR] 2.61, 95% confidence interval [CI] 1.517–4.49, $p = 0.0005$) and DSS (HR 2.87, 95% CI 1.423–5.779, $p = 0.0032$; Table 3, and univariate analysis in Supplementary Tables 2 and 3). Young age, good Eastern Cooperative Oncology Group performance status, and NAC were significant for improved OS, while the administration of NAC was also associated with improved DSS ($p < 0.05$).

3.4. Impact of NAC in patients with lamina propria invasion and absence of muscle invasion

NAC was administered to 26 patients, all with at least one HRF. Of patients with one HRF, 11% (15 of 140) and of those with ≥ 2 HRFs, 30% (11 of 37) received NAC. NAC was associated with a significant improvement in OS (HR 0.339, 95% CI 0.135–0.854, $p = 0.0217$) and DSS (HR 0.228, 95% CI 0.054–0.964, $p = 0.0445$) on multivariate analysis. Baseline demographics, and clinical and pathological variables for those who received NAC are compared with those who did not (Table 4). Among patients with ≥ 2 HRFs, 12/26 (46%) who did not receive NAC and 1/11 (9%) who received NAC were upstaged to pT2 ($p = 0.032$). Among patients with ≥ 2 HRFs, LN metastasis were more common in those who did

not receive NAC (6/26, 23%) compared with those who received NAC (0/11), although the difference was not statistically significant ($p = 0.148$). NAC was associated with a statistically significant improvement in OS (21% vs 55% 5-yr OS, $p = 0.0353$) and a trend toward an increase in DSS (25% vs 56% at 5 yr, $p = 0.0716$) on KM analysis (Fig. 2A and 2B).

4. Discussion

We evaluated the utility of a panel of clinical and pathological features (LVI, thickening or induration on EUA, hydronephrosis, or variant histology) in patients who had HG NMIBC with lamina propria invasion to support the hypothesis that, even in the absence of documented MIBC, these patients had an unfavorable prognosis and might benefit from NAC. These features are considered to represent cT3 disease in patients with biopsy-proven MIBC, but have not been formally introduced into current staging systems or guidelines [6,7,19]. For this analysis, we excluded patients with a palpable 3D mass on EUA and the presence of neuroendocrine features because it is our practice to treat these patients uniformly with NAC [20]. The remaining variants were grouped as a single risk factor due to the small sample size [15]. We found that, for UC invading into the lamina propria, the presence of 2 HRFs was associated with pathological upstaging and LN metastasis, and worse OS and DSS. In addition, we observed less pathological upstaging after NAC and significantly improved OS and DSS. The poor survival of these patients suggests that the presence of these HRFs identify clinical T1HG NMIBC with a natural history more aligned with locally advanced MIBC.

Currently, there is no established role of NAC for NMIBC [11], although it is recognized that T1HG NMIBC is an aggressive neoplasm with a propensity for progression [21]. While many patients can be successfully treated by TURBT and maintenance BCG, an unacceptable number progress or are upstaged at RC after an attempt at bladder preservation. Variant histology and LVI have been incorporated into the recent American Urological Association risk stratification as high-risk NMIBC, but our results suggest these patients have a risk that is more in line with MIBC [7]. CIS, LVI, variant histology, sessile appearance, and depth of invasion reportedly identify patients for consideration of upfront RC [2,9,17,22–24]. Expanding our high-risk definition to incorporate those additional features was noninformative. However, we cannot discount the potential of these variables given our small sample size.

There are clear limitations to our study. First, given the practice patterns for NMIBC, relatively few patients were treated with NAC that precluded validation of our observations. Furthermore, given our retrospective study design, selection bias is inherent. It is inescapable that many patients who are ineligible for NAC remain surgical candidates and that those same factors increase their risk of death from comorbidities. Patients who received NAC were younger than those managed by RC alone, and this could have a bearing on the significant improvement in OS seen in those patients. However, we did see a significant improvement in DSS and less upstaging at RC. Among those at the highest risk of death from UC with 2 HRFs, 5-yr DSS was 56% for those receiving NAC compared with 25% for those who did not, although this difference was not statistically significant. Thus, the

limited number of patients treated with NAC is a confounder that limits our ability to make solid claims as to its benefit for select patients with T1HG NMIBC. Finally, we included patients without muscle in the transurethral resection specimen and patients who did not undergo re-resection, since this is a surgical series in which, for some, the decision to proceed to RC was based on the clinical scenario. We considered both as potential HRFs, but neither achieved significance on univariate analysis and both were independent of the presence of HRFs, so the impact on outcomes may be minimal. Nonetheless, we see the need for further investigation to determine the role of multimodal therapy for high-risk NMIBC. It is also likely that ongoing efforts to deeply characterize the genomic features of NMIBC [25–28] will generate new hypotheses for therapy.

5. Conclusions

The presence of 2 HRFs from a panel including LVI, variant histology, hydronephrosis, and the presence of thickening/induration on EUA identified patients with UC invading into the lamina propria having a significantly worse pathological outcome and decreased OS and DSS following RC. NAC appears to impart a survival advantage for these patients. Our findings are hypothesis generating and support further investigation into the role of systemic therapy for the treatment of high-risk NMIBC.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1.

(A) Overall survival ($p = 0.0057$) and (B) disease-specific survival ($p = 0.0009$) after cystectomy for T1HG patients with 0, 1, or 2 high-risk features (HRFs) at the time of TURBT. HRFs are defined as the presence of lymphovascular invasion, variant histology (excluding neuroendocrine), and presence of tumor-associated hydronephrosis and thickening or induration felt on examination under anesthesia. T1HG = T1 high grade; TURBT = transurethral resection of bladder tumor.

Fig. 2.

(A) Overall survival ($p = 0.0353$) and (B) disease-specific survival ($p = 0.0716$) for patients with two or more high-risk features stratified by administration of neoadjuvant chemotherapy (NAC). High risk features are defined as the presence of lymphovascular invasion, variant histology (excluding neuroendocrine), and presence of tumor-associated hydronephrosis and thickening or induration felt on examination under anesthesia.

Table 1

Baseline characteristics		All patients	
		<i>n</i> = 336	%
Age	Median (IQR)	67 (61–73)	
Gender	Male	284	84.5
	Female	52	15.5
Smoker	Never	109	32.8
	Active	61	18.4
	Former	161	48.5
ASA	1–2	43	1.3
	3–4	255	77.5
BMI	Median (IQR)	28.3 (25.4–31.9)	
Tumor at dome		45	14.0
Tumor at trigone		119	36.0
Multifocal tumor		219	65.0
Architecture	Papillary	272	81.2
	Sessile	63	18.8
Size on endoscopy (cm)	<1	99	29.4
	1–4	136	40.4
	>4	56	16.6
Muscularis mucosa involvement		64	19.0
Complete resection		287	85.2
Muscle in specimen		304	90.2
Tumor in diverticulum		25	7.4
Intravesical therapy	None	157	46.6
	BCG	179	53.1
	Other	39	11.6
Progressed to T1HG on BCG		51	15.0
Initial management	Primary BCG with delayed RC	131	38.9
	Upfront cystectomy	205	60.8
BCG for T1HG	1 induction course	138	41.0
	2 induction courses	35	10.0
Response of T1HG to BCG	Unresponsive	151	44.8
	Refractory	99	29.4
	Early relapse	52	15.4
	Late relapse	12	3.6
	Intolerant	11	3.3
Re resection of T1HG	Performed	252	75.0
	Disease at re-resection	205	81.3

Baseline characteristics		All patients	
		<i>n</i> = 336	%
	T1HG at re-resection	156	61.9

ASA = American Society of Anesthesiology classification; BMI = body mass index; BCG = Bacillus Calmette-Guerin; IQR = interquartile range; RC = radical cystectomy; T1HG = T1 high grade. Full comparative values and statistical comparisons for patients with 0, 1, and 2 high-risk features are available in Supplementary Table 1.

Table 2

Baseline characteristics	All patients	
	<i>n</i> = 336	%
Lymphovascular invasion	38	11.30
Prostatic duct involvement	29	8.60
Abnormal EUA	29	8.60
Preop hydronephrosis	35	10.40
Variant at TURBT	83	25.00
Adenocarcinoma	2	0.60
Clear cell	0	0.00
Glandular	23	6.80
Micropapillary	32	9.50
Nested variant	1	0.30
Neuroendocrine	0	0.00
Sarcomatoid	9	2.70
Signet ring	2	0.60
Lymphoepithelioma	2	0.60
Squamous	25	7.40
Plasmacytoid	2	0.60
High-risk feature		
None	159	47.20
1	140	41.50
2	37	11.00

EUA = examination under anesthesia; TURBT = transurethral resection of bladder tumor.

High-risk features are defined as the presence of lymphovascular invasion, variant histology (excluding neuroendocrine), and presence of tumor-associated hydronephrosis and thickening or induration felt on exam under anesthesia. Full comparative values and statistical comparisons for patients with 0, 1, and 2 high-risk features are available in Supplementary Table 1.

Table 3

Final multivariate analysis model for overall and disease-specific survival

Parameter		Hazard ratio	95% CI	p value
Overall survival				
NAC		0.339	0.135 0.854	0.0217
Number of high-risk features	1 vs 0	1.127	0.761 1.668	0.5512
	2 vs 0	2.61	1.517 4.49	0.0005
ECOG performance	1 vs 0	2.66	1.058 6.688	0.0375
	2 vs 0	6.911	0.939 50.841	0.0576
Age at T1HG diagnosis		1.044	1.024 1.065	<0.0001
Disease-specific survival				
NAC		0.228	0.054 0.964	0.0445
Number of high-risk features	1 vs 0	0.993	0.586 1.681	0.9777
	2 vs 0	2.87	1.425 5.779	0.0032

NAC = neoadjuvant chemotherapy; ECOG = Eastern Cooperative Oncology Group; CI = confidence interval.

All variables significant to $p < 0.1$ were kept in the model. High-risk features are defined as the presence of lymphovascular invasion, variant histology (excluding neuroendocrine), and presence of tumor-associated hydronephrosis and thickening or induration felt on examination under anesthesia.

Table 4

		2 HRFs <i>n</i> = 37	No NAC <i>n</i> = 26	NAC <i>n</i> = 11	<i>p</i> value
Variables					
Age	Median (IQR)	66 (61.5–74.5)	69.5 (63.75–77.25)	62 (59–66)	0.0447
Gender	Male	34	25	9	75.00%
	Female	3	1	2	16.70%
Smoker	Never	10	7	3	25.00%
	Active	6	4	2	16.70%
	Former	20	15	5	41.70%
ASA	1–2	5	3	1	8.30%
	3–4	29	20	8	66.70%
BMI	Median (IQR)	28.65 (26–30.75)	28.84 (26.2–31.9)	27.9 (25.4–29.6)	0.3483
Intravesical therapy	None	22	15	7	58.30%
	BCG	15	11	4	33.30%
Re-resection of T1HG	Performed	23	14	9	75.00%
	Disease at re-resection	14	9	4	33.30%
	T1HG at re-resection	14	9	5	41.70%
Tumor at dome		7	6	1	8.30%
Tumor at trigone		15	9	6	50.00%
Multifocal tumor		19	10	9	75.00%
Architecture	Papillary	28	21	7	58.30%
	Sessile	9	5	4	33.30%
Size on endoscopy (cm)	<1	1	0	1	8.30%
	1–4	7	5	2	16.70%
	>4	16	10	6	50.00%
Muscularis mucosa involvement		6	4	2	16.70%
Complete resection		29	19	10	83.30%
Muscle in specimen		34	23	11	91.70%
Tumor in diverticulum		3	25	2	16.70%

Variables		2 HRFs <i>n</i> = 37		No NAC <i>n</i> = 26		NAC <i>n</i> = 11		<i>p</i> value
		19	19	8	18	11	11	
Lymphovascular invasion		8	51.40%	8	30.80%	0	91.70%	<0.0001
Prostatic duct involvement		9	21.60%	8	30.80%	1	0.00%	0.0377
Abnormal EUA		15	24.30%	10	38.50%	5	41.70%	0.1601
Preop hydronephrosis		23	40.50%	16	61.50%	7	58.30%	0.6921
Variant at TURBT		1	62.20%	0	0.00%	1	8.30%	0.9042
	Adenocarcinoma	6	2.70%	5	0.00%	1	8.30%	0.5096
	Glandular	9	16.20%	7	19.20%	2	16.70%	0.7921
	Micropapillary	3	24.30%	3	26.90%	0	0.00%	0.5711
	Sarcomatoid	1	8.10%	1	11.50%	0	0.00%	<0.0001
	Signet ring	8	2.70%	5	3.80%	3	25.00%	0.5096
	Squamous	1	21.60%	1	19.20%	0	0.00%	0.2669
	Plasmacytoid	1	2.70%	1	3.80%	0	0.00%	0.5096

ASA = American Society of Anesthesiology Classification; BMI = body mass index; EUA = examination under anesthesia; TURBT = transurethral resection of bladder tumor; BCG = Bacillus Calmette-Guerin; HRF = high-risk feature; NAC = neoadjuvant chemotherapy; IQR = interquartile range T1HG = T1 high grade.

High-risk features are defined as the presence of lymphovascular invasion, variant histology (excluding neuroendocrine), and presence of tumor-associated hydronephrosis and thickening or induration felt on examination under anesthesia.