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Predictors of Intravesical Recurrence After Radical Nephroureterectomy for Upper Urinary Tract Urothelial Carcinoma: An Inflammation-Based Prognostic Score

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Purpose: Systemic inflammatory responses, which are defined in terms of the Glasgow prognostic score (GPS), have been reported to be independent predictors of unfavorable outcomes in various human cancers. We assessed the utility of the GPS as a predictor of intravesical recurrence after radical nephroureterectomy (RNU) in upper urinary tract carcinoma (UTUC).

Materials and Methods: We collected data for 147 UTUC patients with no previous history of bladder cancer who underwent RNU from 2004 to 2012. Associations between perioperative clinicopathological variables and intravesical recurrence were analyzed by using univariate and multivariate Cox regression models.

Results: Overall, 71 of 147 patients (48%) developed intravesical recurrence, including 21 patients (30%) diagnosed with synchronous bladder tumor. In the univariate analysis, performance status, diabetes mellitus (DM), serum albumin, C-reactive protein, GPS, and synchronous bladder tumor were associated with intravesical recurrence. In the multivariate analysis, performance status (hazard ratio [HR], 2.33; 95% confidence interval [CI], 1.41–3.85; p=0.001), DM (HR, 2.04; 95% CI, 1.21–3.41; p=0.007), cortical thinning (HR, 2.01; 95% CI, 1.08–3.71; p=0.026), and GPS (score of 1: HR, 6.86; 95% CI, 3.69–12.7; p=0.001; score of 2: HR, 5.96; 95% CI, 3.10–11.4; p=0.001) were independent predictors of intravesical recurrence.

Conclusions: Our results suggest that the GPS as well as performance status, DM, and cortical thinning are associated with intravesical recurrence after RNU. Thus, more careful follow-up, coupled with postoperative intravesical therapy to avoid bladder recurrence, should be considered in these patients.

Keywords: *Inflammation; Recurrence; Risk factors; Transitional cell carcinoma*

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INTRODUCTION

Upper urinary tract urothelial carcinoma (UTUC) is relatively uncommon, accounting for only approximately 5% to 7% of all urothelial cancers [1-9]. The current standard treatment for UTUC remains radical nephroureterectomy (RNU) with bladder cuff excision. However, because urothelial cancer develops at multiple foci throughout the entire urinary tract, synchronously or metachronously, 15% to 50% of the patients who undergo surgical treatment for UTUC develop intravesical recurrence during the follow-up period [3-5]. Moreover, up to 80% to 90% of bladder recurrences occur within the first 2 to 3 years after RNU.

To date, several studies have identified possible risk fac-

tors for subsequent intravesical recurrence in patients treated surgically for UTUC [3-24]. Proposed risk factors include tumor configuration, tumor multifocality, tumor stage and grade, tumor location, tumor size, lymphovascular invasion (LVI), patient gender, adjuvant chemotherapy, preoperative urine cytology, synchronous bladder cancer, diagnostic ureteroscopy (DURS), hydronephrosis, and diabetes mellitus (DM). However, the results have been controversial with limited evidence to establish surveillance strategies. Thus, knowledge of potential predictive factors for bladder recurrence in UTUC would allow better prognostic evaluations and promote optimal surveillance strategies.

Systemic inflammation-based scores, including the Glasgow prognostic score (GPS), are considered to have prognostic value, independently of stage, performance status, and weight loss, in various advanced cancers and primary operable cancers [25-28]. However, no reported studies have investigated the value of the GPS to predict intravesical recurrence after RNU. Thus, in this study, we assessed the predictors of intravesical recurrence of UTUC, including previously reported risk factors and GPS. In addition, we also evaluated the predictors of overall survival of UTUC after RNU.

MATERIALS AND METHODS

1. Patients

Between 2004 and 2012, 172 patients with UTUC underwent RNU at our institution. We excluded 9 patients with local recurrence and 16 with distant metastasis. In total, 147 patients were reviewed retrospectively. No patient had received preoperative chemotherapy or radiotherapy. No patient included in this study had a previous history of bladder cancer. All patients underwent RNU with excision of the bladder cuff without regional lymph node dissection. All patients were followed similarly every ~3 to 4 months the first year after RNU, every 6 months from the second through the fifth year, and annually thereafter. At each follow-up, the patient's symptoms, history, performance status, and physical examination were evaluated by physicians, and blood samples for serum chemistry and hematological testing and bladder urine washing for cytology were obtained. If a bladder tumor was suspected, transurethral resection was also performed. Intravesical recurrence and distant metastasis were investigated by cystoscopically evaluating the urinary bladder, by a chest radiograph, and by radiographic evaluation of the contralateral upper urinary tract by computed tomography annually as indicated clinically. Bladder cancer occurrences that were demonstrated histologically were defined as intravesical recurrence.

2. Pathological analysis

All surgical specimens were processed according to standard pathological procedures and were reviewed by pathologists. The histological grade was classified according to previously established criteria. Tumor staging was according to the 2002 American Joint Committee on Cancer TNM staging system. The tumor grade was assessed according to the 1998 World Health Organization/International Society of Urologic Pathology consensus classification.

3. Eastern Cooperative Oncology Group Performance Status and GPS

Eastern Cooperative Oncology Group Performance Status (ECOG-PS) was recorded at the time of diagnosis. The GPS was determined as described previously [25-27]. Patients with both elevated C-reactive protein (CRP) and hypoalbuminemia were assigned a score of 2. Patients with only one of these biochemical abnormalities were assigned a score of 1. Patients without either abnormality were assigned a score of 0. Routine laboratory testing for CRP and albumin was performed perioperatively. Serum CRP was measured by latex turbidimetric immunoassay by use of a Hitachi 7600 analyzer (Hitachi, Tokyo, Japan). The CRP limit of detection was 0.03 mg/dL, and 1.0 mg/dL was the upper limit of the normal range. Coefficients of variation over the range of measurements were 5% in routine quality control.

4. Classification of hydronephrosis

The hydronephrosis grade was assessed by preoperative imaging, CT, excretory urography, and renal ultrasonography. Cases without caliceal or pelvic dilation were classified as grade 0 hydronephrosis, cases with pelvic dilation only were classified as grade 1, and cases with accompanying mild calix dilation were classified as grade 2. Severe calix dilation was grade 3, and calix dilation accompanied by renal parenchyma atrophy was classified as grade 4. Mild, moderate, and severe hydronephrosis were defined as grade 1, grade 2, and grades 3–4, respectively.

5. Adjuvant chemotherapy

Adjuvant chemotherapy was usually given for patients above pathologic T2 stage. Patients were administered 1,000 mg/m^2 gemcitabine on days 1, 8, and 15, and 70 mg/m^2 cisplatin on day 2 for the GC regimen on 3 cycles. The dose of cisplatin was reduced from 50% to 70% of the normal dose when the estimated glomerular filtration rate was under 70 mL/min, and none of the UTUC patients received postoperative intravesical chemotherapy.

6. Statistics

Statistical analyses were performed by using SPSS ver. 17.0 (SPSS Inc., Chicago, IL, USA). Differences in clinicopathological variables according to bladder recurrence after RNU were analyzed by using the chi-square test. Univariate and multivariate analyses (stepwise forward procedure) were performed by using the Cox proportional hazard analysis to identify risk factors affecting intravesical recurrence-free survival and overall survival after RNU. The factors included in the model were age, gender, ECOG-PS, DM, preoperative hemoglobin, albumin, CRP,

TABLE 1. Baseline characteristics of the enrolled patients

Characteristic	Bladder recurrence		p-value[a]
	Negative	Positive	
Age (y)			0.213
<70	41 (53.9)	31 (43.7)	
≥70	35 (46.1)	40 (56.3)	
Gender			0.077
Male	26 (34.2)	15 (21.1)	
Female	50 (65.8)	56 (78.9)	
ECOG-PS			0.130
0	53 (69.7)	41 (57.7)	
≥1	23 (30.3)	30 (42.3)	
Diabetes mellitus			0.001
Negative	63 (82.9)	35 (49.3)	
Positive	13 (17.1)	36 (50.7)	
Hemoglobin (g/dL)			0.641
>12	52 (68.4)	46 (64.8)	
≤12	24 (31.6)	25 (35.2)	
Albumin (g/dL)			0.001
≥3.5	72 (94.7)	40 (56.3)	
<3.5	4 (5.3)	31 (43.7)	
C-reactive protein (mg/dL)			0.001
≤1.0	74 (97.4)	24 (33.8)	
>1.0	2 (2.6)	47 (66.2)	
Glasgow prognostic score			0.001
0	70 (92.1)	17 (23.9)	
1	6 (7.9)	30 (42.3)	
2	0 (0)	24 (33.8)	
Diagnostic ureteroscopy			0.404
Performed	52 (68.4)	53 (74.6)	
Not performed	24 (31.6)	18 (25.4)	
Adjuvant chemotherapy			0.515
Performed	51 (67.1)	44 (62.0)	
Not performed	25 (32.9)	27 (38.0)	
Synchronous bladder tumor			0.027
Negative	65 (85.5)	50 (70.4)	
Positive	11 (14.5)	21 (29.6)	
T stage			0.914
Non–muscle-invasive	40 (52.6)	36 (50.7)	
Muscle-invasive	19 (25.0)	17 (23.9)	
Non–organ-confined	17 (22.4)	18 (25.4)	
Grade			0.916
Low	24 (31.6)	23 (32.4)	
High	52 (68.4)	48 (67.6)	
Location			0.331
Renal pelvis	37 (48.7)	37 (52.1)	
Upper ureter	13 (17.1)	10 (14.1)	
Mid ureter	14 (18.4)	7 (9.9)	
Lower ureter	12 (15.8)	17 (23.9)	
Hydronephrosis			0.700
None, mild	48 (63.2)	47 (66.2)	
Moderate, severe	28 (36.8)	24 (33.8)	
Cortical thinning			0.981
Negative	59 (77.6)	55 (77.5)	
Positive	17 (22.4)	16 (22.5)	
Operative method			0.004
Open	18 (23.7)	33 (46.5)	
Laparoscopy	58 (76.3)	38 (53.5)	
Lymphovascular invasion			0.871
Negative	69 (90.8)	65 (91.5)	
Positive	7 (9.2)	6 (8.5)	
Tumor size (cm)			0.265
<3	38 (50.0)	29 (40.8)	
≥3	38 (50.0)	42 (59.2)	

Values are presented as number (%).
ECOG-PS: Eastern Cooperative Oncology Group Performance Status.
[a]:Chi-square test.

GPS, DURS, adjuvant chemotherapy, presence of synchronous bladder tumor, stage, grade, tumor location, tumor size, LVI, hydronephrosis, cortical thinning, and operative method. Statistical significance was set at $p < 0.05$ for all analyses.

RESULTS

1. Clinicopathological characteristics

The clinicopathological characteristics of the 147 patients with UTUC are summarized in Table 1. There were 41 males and 106 females, with a median age of 70 years (range, 44–84 years). The primary tumor location was the renal pelvis in 74 patients (50%) and the ureter in 73 patients (50%). Of the patients, 42 (29%) underwent preoperative DURS, and 32 (21.7%) were diagnosed with synchronous bladder tumors. Open RNU was performed in 51 patients (34.6%) and laparoscopic RNU was performed in 96 patients (65%). The median tumor size was 3.0 cm (range, 0–14 cm). The pathological stage was divided into three groups: non–muscle-invasive (pTis/pTa/pT1), muscleinvasive (pT2), and non–organ-confined (pT3), which were identified in 76 (51.7%), 36 (24.5%), and 35 (23.8%) cases, respectively.

The median follow-up period was 33 months (range, 1–191 months). Intravesical recurrence occurred in 71 of 147 patients (48%). The median time to intravesical recurrence was 13 months (range, 0.4–91 months).

Comparing clinicopathological variables between the intravesical recurrence categories, there was no significant difference between the groups in terms of age, gender, histological grade, tumor stage, tumor size, LVI, adjuvant chemotherapy, or DURS. However, history of DM, GPS score, albumin and CRP levels, presence of synchronous bladder cancer, and operation method did show significant differences ($p < 0.05$) (Table 1).

2. Predictors of intravesical recurrence-free survival

In the univariate analysis, performance status (hazard ratio [HR], 1.88; 95% confidence interval [CI], 1.16–3.03; p=0.009), DM (HR, 2.52; 95% CI, 1.58–4.03; p=0.001), se-

TABLE 2. Results of univariate and multivariate analysis of variables affecting intravesical recurrence-free survival after radical nephroureterectomy

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age, ≥70 y	1.59 (0.99–2.55)	0.051		
Male gender	1.38 (0.77–2.45)	0.268		
ECOG-PS, ≥1	1.88 (1.16–3.03)	0.009	2.33 (1.41–3.85)	0.001
Diabetes mellitus	2.52 (1.58–4.03)	0.001	2.04 (1.21–3.41)	0.007
Hemoglobin, ≤12 g/dL	1.38 (0.85–2.26)	0.189		
Albumin, <3.5 g/dL	2.88 (1.80–4.62)	0.001		
C-reactive protein, >1.0 mg/dL	5.73 (3.47–9.45)	0.001		
Glasgow prognostic score				
1	7.73 (4.22–14.1)	0.001	6.86 (3.69–12.7)	0.001
2	6.36 (3.40–11.9)	0.001	5.96 (3.10–11.4)	0.001
Diagnostic ureteroscopy	0.87 (0.51–1.49)	0.615		
Adjuvant chemotherapy	0.85 (0.52–1.38)	0.507		
Synchronous bladder tumor	1.69 (1.01–2.82)	0.045		
T stage				
Muscle-invasive	1.17 (0.66–2.10)	0.576		
Non-organ-confined	0.86 (0.48–1.54)	0.632		
Grade, high	0.93 (0.56–1.53)	0.776		
Location				
Upper ureter	1.05 (0.52–2.13)	0.872		
Mid ureter	0.62 (0.27–1.39)	0.247		
Lower ureter	1.22 (0.69–2.18)	0.485		
Hydronephrosis, moderate, severe	1.44 (0.87–2.37)	0.149		
Cortical thinning	1.56 (0.89–2.73)	0.120	2.01 (1.08–3.71)	0.026
Operative method, laparoscopy	0.72 (0.45–1.16)	0.181		
Lymphovascular invasion	1.57 (0.66–3.72)	0.301		
Tumor size, ≥3 cm	1.43 (0.88–2.30)	0.140		

HR, hazard ratio; CI, confidence interval; ECOG-PS, Eastern Cooperative Oncology Group Performance Status.

rum albumin (HR, 2.88; 95% CI, 1.80–4.62; p=0.001), CRP (HR, 5.73; 95% CI, 3.47–9.45; p=0.001), GPS (score of 1: HR, 7.73; 95% CI, 4.22–14.1; p=0.001; score of 2: HR, 6.36; 95% CI, 3.40–11.9; p=0.001), and synchronous bladder tumor (HR, 1.69; 95% CI, 1.01–2.82; p=0.045) were associated with intravesical recurrence-free survival. In the multivariate analysis, performance status (HR, 2.33; 95% CI, 1.41–3.85; p=0.001), DM (HR, 2.04; 95% CI, 1.21–3.41; p=0.007), cortical thinning (HR, 2.01; 95% CI, 1.08–3.71; p=0.026), and GPS (score of 1: HR, 6.86; 95% CI, 3.69–12.7; p=0.001; score of 2: HR, 5.96; 95% CI, 3.10–11.4; p=0.001) remained significant predictors of bladder recurrence-free survival after RNU (Table 2).

3. Predictors of overall survival

Univariate and multivariate analysis of the clinicopathologic data influencing overall survival are shown in Table 3. In the univariate analysis, ECOG-PS (HR, 3.99; 95% CI, 1.86–8.57; p=0.001), high-grade tumor (HR, 2.77; 95% CI, 1.09–7.03; p=0.031), and tumor size≥3 cm (HR, 2.69; 95% CI, 1.14–6.37; p=0.024) were significantly associated with a poor outcome. The independent prognostic factors for overall survival were ECOG-PS (HR, 3.81; 95% CI, 1.76–8.26; p=0.001) and high-grade tumor (HR, 2.58; 95% CI, 1.02–6.67; p=0.040).

DISCUSSION

Despite definitive surgery such as RNU with bladder cuff excision, a high potential for local and distant recurrence of UTUC has been reported. Previous studies have estimated the intravesical recurrence rate after RNU to range from 13% to 49% [3-5]. Similar to other reports, we found that 48% of UTUC patients who underwent RNU experienced bladder recurrence. Although numerous studies have attempted to delineate clinicopathological criteria for predicting such recurrences, none of the reported studies involved more than 300 cases, and the results were inconsistent.

Koda et al. [18] showed that intravesical recurrence was not associated with the mode of operation; in that study, a previous history of bladder cancer was the only independent prognostic factor for intravesical recurrence. Additionally, several clinicopathological parameters were considered as prognostic factors, including patient age, tumor size, tumor stage, LVI, histological grade, and synchronous bladder cancer. In a series of 196 patients, bladder recurrence was lower in those who received mitomycin

TABLE 3. Results of univariate and multivariate analysis of variables affecting overall survival after radical nephroureterectomy

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age, ≥70 y	1.95 (0.89–4.07)	0.097		
Male gender	1.04 (0.36–2.76)	0.933		
ECOG-PS, ≥1	3.99 (1.86–8.57)	0.001	3.81 (1.76–8.26)	0.001
Diabetes mellitus	0.54 (0.24–1.21)	0.134		
Hemoglobin, ≤12 g/dL	1.38 (0.64–2.96)	0.401		
Albumin, <3.5 g/dL	0.60 (0.26–1.39)	0.239		
C-reactive protein, >1.0 mg/dL	0.97 (0.43–2.16)	0.944		
Glasgow prognostic score				
1	1.51 (0.63–3.61)	0.346		
2	0.64 (0.22–1.80)	0.399		
Diagnostic ureteroscopy	1.69 (0.74–3.90)	0.211		
Adjuvant chemotherapy	1.88 (0.87–4.04)	0.105		
Synchronous bladder tumor	1.22 (0.53–2.78)	0.637		
T stage				
Muscle-invasive	0.64 (0.20–2.04)	0.458		
Non-organ-confined	2.22 (0.99–4.98)	0.051		
Grade, high	2.77 (1.09–7.03)	0.031	2.58 (1.02–6.67)	0.040
Location				
Upper ureter	2.12 (0.87–5.17)	0.096		
Mid ureter	1.01 (0.28–3.55)	0.990		
Lower ureter	0.79 (0.25–2.43)	0.683		
Hydronephrosis, moderate, severe	1.01 (0.44–2.30)	0.978		
Cortical thinning	1.67 (0.73–3.83)	0.223		
Operative method, laparoscopy	1.09 (0.50–2.35)	0.825		
Lymphovascular invasion	1.54 (0.46–5.13)	0.476		
Tumor size, ≥3 cm	2.69 (1.14–6.37)	0.024		
Intravesical recurrence	1.01 (0.42–2.36)	0.990		

HR, hazard ratio; CI, confidence interval; ECOG-PS, Eastern Cooperative Oncology Group Performance Status.

C or epirubicin compared with those who received neither [22]. Likewise, several retrospective studies have identified prognostic parameters for predicting outcomes after RNU, including intravesical recurrence and cancer-specific survival. However, this remains a matter of debate. In our results, the previously considered prognostic factors of DURS [17], tumor stage, grade, size [23], LVI [24], location [4,5,13], adjuvant chemotherapy [14], and synchronous bladder cancer [16] were not associated significantly with bladder recurrence. However, the presence of DM, cortical thinning, GPS, and performance status were suggested to be independent prognostic parameters for bladder recurrence.

Regarding preoperative DURS, ureteroscopy may increase tumor shedding with subsequent intraluminal seeding during irrigation or manipulation. Several studies have found that DURS was associated with intravesical recurrence. However, our results did not show this. The difference may be due to the small numbers of DURS patients.

Several previous studies reported that tumor extent and pathological stage were significant, independent factors for intravesical recurrence. Hisataki et al. [11] suggested that pathological stage influenced bladder recurrence significantly and that the bladder recurrence-free rate of lower-stage disease tended to be higher than that of higher-stage disease. Terakawa et al. [12] suggested that lower pathological stage was a significant and independent risk factor for subsequent bladder cancer formation. In the present study, however, we did not see any such association. The clinical characteristics of the patients in our study may have been somewhat different from those in previous studies. Low-grade tumors made up a relatively larger proportion of our UTUC cases (32%) than seen in previous studies (7%–10%), and pathologically T2/T3 high-stage patients tended to receive adjuvant systemic chemotherapy, which might have contributed to a decrease in intravesical recurrence. Additionally, those with high-stage tumors considered to have aggressive malignant potential may die from UTUC before developing intravesical recurrence. This may also have influenced bladder recurrence [11].

In some reports, tumor location was considered a prognostic factor for intravesical recurrence of UTUC, whereas it was not in other studies [4,13]. Our results suggest that tumor location was not a significant risk factor for bladder recurrence. This may have been influenced by the relatively larger proportion of our UTUC cases in the renal pelvis and upper ureter (66%) than seen in previous studies

(7%–22%).

Espiritu et al. [23] suggested that tumor size ≥ 3.0 cm was considered a significant risk factor for poor recurrence-free survival outcomes after RNU. In the current study, tumor size was only associated with shorter overall survival in the univariate analysis. In a previous study, LVI was the significant predictor for intravesical recurrence [24]. However, our results were not in accord with previous reports. This may have been influenced by the relatively smaller portion of our UTUC cases with LVI (9%) than seen in previous studies (21%). Hwang et al. [29] suggested that DM was an independent prognostic factor for bladder recurrence and prognosis in patients with non–muscle-invasive bladder cancer. Another study, performed in the same center, evaluated the association between DM and UTUC; those authors suggested that DM was a poor predictor of prognosis in UTUC. In this regard, DM may influence bladder recurrence or prognosis in non–muscle-invasive bladder cancer and UTUC [30]. Our results are consistent with those previous reports. In UTUC patients with RNU, underlying DM was suggested to be an independent prognostic parameter for bladder recurrence-free survival but to not be associated with overall survival. Also, a previous report suggested that hydronephrosis was a poor prognosis-predicting factor in UTUC [30]. However, we did not find any relationship between hydronephrosis and intravesical recurrence-free survival or overall survival. Cortical thinning was another independent prognostic factor for intravesical recurrence-free survival of UTUC in our study. It may be associated with long-term exposure of urothelial cells to nephrotoxicity and carcinogens, leading to bladder recurrence. However, no other reported study has considered cortical thinning as a risk factor. Thus, further studies are needed.

Recently, systemic inflammation-based scores have been suggested to be of prognostic value, independent of stage, performance status, and weight loss, in advanced cancers [25]. Among such scores, the GPS (including albumin and CRP values) is superior to leukocyte or lymphocyte counts and the Eastern Cooperative Oncology Group score [27,28]. Furthermore, there has also been some work in primary operable cancers showing that systemic inflammatory responses have prognostic value in GI cancer, lung cancer, RCC, and bladder cancer and were independently associated with survival in patients with primary operable cancer [25]. In the present study, we evaluated the GPS as a prognostic factor for postoperative intravesical recurrence-free survival of UTUC. We found that the GPS was strongly associated with bladder recurrence and was more useful for predicting intravesical recurrence than were other prognostic parameters, including DM, cortical thinning, and ECOG score (GPS 1: HR, 6.86; 95% CI, 3.69–12.7; p=0.001; GPS 2: HR, 5.96; 95% CI, 3.10–11.4; p=0.001).

In the prediction of overall survival, ECOG-PS and high-grade tumor showed a significant association with overall survival, but the GPS was not correlated with survival. Therefore, more research is necessary to establish the association between the GPS and overall survival in UTUC patients. To our knowledge, this has not been reported previously.

Our study had several limitations. First, it was a retrospective study of a single center's experience with a relatively uncommon disease. Thus, the size of the study was quite small versus previously reported multicenter studies. Second, the follow-up period might not have been long enough. Finally, we did not evaluate the duration of DM, which may have affected our results; there may also have been selection bias due to the probability of undiagnosed DM. Thus, further randomized clinical studies are needed to identify possible risk factors for subsequent intravesical recurrence after RNU.

CONCLUSIONS

Our results suggest that the GPS and performance status, DM, and cortical thinning are associated with intravesical recurrence after RNU. For overall survival, ECOG-PS and high grade are independently associated with poor outcome. Thus, in such patients, more careful follow-up coupled with postoperative intravesical therapy should be considered to avoid bladder recurrence.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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