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Radical cystectomy for pT1 urothelial carcinoma of bladder not amenable to TURBT: Long-term results

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ABSTRACT

Purpose: This study sought to identify factors associated with survival of pT1 urothelial carcinoma of bladder (UCB) after radical cystectomy (RC).
Methods: This study consists of 114 pT1 UCB [primary 83, recurrent 31, none were amenable to transurethral resection (TUR)] treated by radical cystectomy. Survival analysis using Cox regression tests were performed to identify factors associated with survival of pT1 UCB after RC.
Results: Pelvic lymph node (LN) status, age and lymphovascular invasion (LVI) are associated with survival of pT1 UCB after RC; recurrent pT1 UCB of high grade origin (HGO) tends to have poorer CSS than primary pT1 UCB or recurrent pT1 UCB of low grade origin (LGO) (5-year and 10-year CSS rates was 75% and 73% for primary cases; 77% and 77% for recurrent pT1 UCB of LGO; and 56% and 37% for recurrent pT1 UCB of HGO, $p = 0.078$).
Conclusions: LN status, age and LVI were significantly associated with survival of pT1 UCB after RC. Recurrent pT1 UCB of HGO should be managed with radical cystectomy in a timely fashion given that these cases tend to have poorer CSS than primary pT1 UCB after RC, even if they did not progress to muscle-invasive bladder cancer (MIBC).

Introduction

Urothelial carcinoma of the bladder (UCB) invading into the lamina propria (stage T1) represents a well-defined entity that differs from both muscle invasive bladder cancer (MIBC) and non-invasive tumours [Ta and carcinoma in situ (CIS)]. Among 10–20% of all new urothelial carcinoma of bladder (UCB) diagnoses, approximately 40% will recur, and approximately 20% will progress to MIBC within 5 years [1,2]. Compared with immediate radical cystectomy, delayed radical cystectomy for clinical T1HG is accompanied with a higher rate of progression and poorer survival [3]; progressive MIBC portends poorer survival than primary MIBC, as reported by some authors [4,5]. However, population-level analysis suggests that cystectomy within 1 yr of T1HG bladder carcinoma diagnosis occurs in only 4.7% of cases [6]. What if pT1 UCB does not progress and can be managed by RC in a timely manner before progression? Are there any differences between primary pT1 UCB and recurrent pT1 UCB after RC? What are the factors that affect survival of pT1 UCB not amenable to TURB after radical cystectomy? Based on the information mentioned above, we present our series of radical cystectomy for pT1 UCB (not amenable to *trans*-urethral resection of bladder tumour, TURBT, defined in the **Materials and Methods**) to identify factors associated with survival of pT1 UCB after radical cystectomy.

Materials and Methods

Patient selection

From 2000 to 2010, 530 cases of radical cystectomies with standard pelvic lymph node dissection were performed in Tianjin Medical University Second Hospital. Our rationale of radical

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cystectomy (RC) for clinical non-muscle invasive bladder cancer (NMIBC) was as follows: Taking into account the unavailability of BCG, in our daily practice, all clinically NMIBC with heavy tumour burden were potential candidates for radical cystectomy. Every patient had chest X - ray, IVU (or MRU), pelvic CT (or MRI) and cystoscopy before treatment, cold-cup biopsy or diagnostic TURBT were arranged helping to make the final decision. We define cases of T1 UCB with heavy tumour burden (multiple and/or large tumours) as "not amenable to" TURBT, on the belief that T1 NMIBC with heavy tumour burden managed by TURBT with curative intent would put the patients at high risk of hemorrhage, recurrence or progression. Under the background of tumour burden, combing with stage, grade, recurrence history (or possibility of recurrence or progression), concurrent CIS, LVI, unavailability of BCG, possibility of patients' compliance to follow-up regimen, patients' general performance status and patients' will, the decision of RC was made by the surgeon and fully-informed individual. Regarding RC specimens, cases with a pathological stage other than pT1 and histologic type other than UC were excluded. Of 135 cases with pT1 UCB, 11 were lost to follow-up, 8 patients with bladder recurrence after their initial presentation with upper urinary tract urothelial carcinoma (UTUC) and 2 patients with bladder recurrence after partial cystectomy for MIBC were excluded based on theory that UTUC vs. UCB and MIBC vs. NMIBC are different groups [7,8]. Thus, the analyses were based on 114 patients with pT1 UCB. Patients were divided into primary pT1 UCB (without prior history of UCB, $n = 83$), and recurrent pT1 UCB (with prior history of UCB, $n = 31$). Although UCB typically involves multifocal lesions and may arise synchronously or asynchronously, recurrent cases with a history of low-grade (LG, grade 1 or 2) tumours were considered of low-grade origin (LGO), recurrent cases without a history of LG tumours were considered of high-grade origin (HGO). None of the recurrent patients accepted BCG instillation (no commercially BCG available in China Mainland during that time). None of the patients in this study accepted neoadjuvant chemotherapy. Patients with pelvic lymph node (LN) metastasis were scheduled to accept adjuvant chemotherapy. The treatment protocol was approved by the ethics committee of the Second Hospital of Tianjin Medical University.

Surgical technique

Radical cystectomies during this period were performed as open surgery with a midline lower abdominal incision made from the umbilicus to pubis. In addition, radical cystoprostatectomy with standard pelvic lymph node dissection (to the level of the bifurcation of the common iliac artery) was a routine procedure. Urinary diversion was performed based on a patient's life expectancy, general performance status and patient's will.

Histopathological evaluation

T stage was determined using the 2002 American Joint Committee on Cancer TNM staging system and histological grade was determined using the WHO grading system.

Routine lymphovascular invasion (LVI) evaluations were performed. LVI was considered present only when tumour cells were unequivocally noted within or attached to the wall of a vascular or lymphatic space in haematoxylin- and eosin-stained sections. Multiple serial sections were used in equivocal cases and in cases of aggressive tumours. Variant histology in this study was limited to urothelial carcinoma with aberrant differentiation (squamous differentiation = 26, glandular differentiation = 11), and pure non-urothelial carcinoma was not enrolled. Two independent uropathologists reviewed the haematoxylin- and eosin-stained slides.

Adjuvant therapy

For patients with pelvic lymph node metastasis, systemic chemotherapy employing methotrexate, vinblastine, doxorubicin and cisplatin (MVAC) or gemcitabine and cisplatin (GC) was initiated within 2 weeks after radical cystectomy based on published protocols [9]. Three patients received the MVAC regimen, and 6 patients received the GC regimen.

Follow-up protocol

In our hospital, for high risk non-muscle-invasive bladder cancer (NMIBC), the follow-up rules after TURBT + intravesical MMC were as follow: surveillance cystoscopy and urinary cytology were conducted at 3-month intervals within the first 2 years, 6-month intervals within the next 3 years and annually thereafter. Pelvic computed tomography and chest radiography were conducted at 6- to 12-month intervals. Intravenous urography (IVU) was performed if necessary.

The follow-up interval after radical cystectomy was 6 months within 3 years, and annually thereafter. Radiographic evaluation of the urinary diversion, upper urinary tracts (intravenous pyelography or ultrasonography), and chest radiography were performed at 6 months postoperatively and then annually thereafter unless otherwise clinically indicated. Elective bone scans and abdominal/pelvic computerized tomography scans were performed when clinically indicated.

Statistical analysis

The log-rank test was used to compare OS and CSS between groups. Kaplan-Meier analysis was performed to assess OS and CSS, which were calculated from the date of radical cystectomy to the date of death or last known follow-up. For the analysis of OS, death was counted as an event. For CSS analysis, only cancer-specific death was counted as event. Cox's proportional hazards regression model was then used to test the statistical significance of several potential prognostic factors for OS and CSS. All potential prognostic factors with $p < 0.10$ from the log-rank test were then included in a saturated model and backward elimination was used to remove factors from the model based on the likelihood ratio test in the multiple regression analysis. $P < 0.05$ was considered significant, and all p-values reported are two sided. All statistical analyses were performed using SPSS for Windows, version 17.0.

(SPSS, Inc., Chicago, IL).

Results

The study population consisted of 98 men and 16 women with a median age of 66.0 years (mean 64.8 ± 10.5, range 35–85). Table 1 lists the clinical and pathological characteristics of the patients. No positive margin was reported in the final pathologic examination. A total of 8 patients completed chemotherapy, and 1 patient withdrew due to inability to tolerate the side effects of chemotherapy.

Survival after radical cystectomy

For the entire cohort, with a median follow-up of 133.0 months (range 97–211), the 5-year and 10-year CSS rates were 73% and 70%, and the 5-year and 10-year OS was 60% and 49%, respectively. Recurrent pT1 UCBs of HGO tend to have poorer CSS than primary pT1 UCB or recurrent pT1 UCB of LGO (5-year and 10-year CSS were 75% and 73% for primary cases, 77% and 77% for recurrent cases of LGO, and 56% and 37% for recurrent cases of HGO, respectively, $p = 0.078$) (Fig. 1). The median interval between initial diagnosis of

Table 1
Clinical and pathologic characteristics of 114 patients with pT1 UCB after RC.

Variables	No.Pts
Gender	
male	98
Female	16
Age	
<65 y	52
≥65 y	62
Primary or recurrent	
primary	83
recurrent	31
Multicentricity	
single	24
multiple	90
Tumour size	
<3 cm	60
≥3 cm	54
Grade	
High (grade 3)	90
Low (grade 1 or 2)	24
Lymphovascular invasion (LVI)	
Yes	13
No	101
Lymph node metastasis	
Yes	9
No	105
Concominent Carcinoma in situ(CIS)	
Yes	14
No	100
Variant histology	
Yes	37
No	77
Origin of recurrent UCB	
LGO	16
HGO	15

LVI, lymphovascular invasion; CIS, carcinoma in situ; UCB, urothelial carcinoma of bladder; RC, radical cystectomy; LGO, low grade origin; HGO, high grade origin.

UCB and RC were 39.0 months (mean: 65.9 ± 70.4, range 5–240) for recurrent cases of LGO and 28.5 months (mean: 24.9 ± 13.9, range 6–44) for recurrent cases of HGO, respectively. The median TURs before RC were 2.5 (mean: 2.5 ± 1.5, range 1–5) for recurrent cases of LGO and 1.0 (mean: 1.7 ± 1.2, range 1–4) for recurrent cases of HGO, respectively. The log-rank test results of differences in 5-year survival rates between subgroups stratified by the evaluated variables are shown in Table 2. Kaplan-Meier curves for CSS and OS stratified by lymph node status (LN), age and LVI are shown in Fig. 2.

At the end of the follow-up period, 31 patients died of bladder cancer with a median survival time of 27.0 months (range 6–130), 26 patients died of other causes with a median survival time of 62.0 months (range 1–120), and 57 patients survived with a median follow-up time of 133.0 months (range 97–211).

Potential prognostic factors underlying survival

For patients younger than 65 years (n = 52), 9 patients died of bladder cancer with a median survival time of 42.0 months (range 8–130), 5 patients died of other causes with median survival time of 41.0 months (range 3–69). For patients equal or older than 65 years (n = 62), 22 patients died of bladder cancer with a median survival time of 24.0 months (range 6–72), and 21 patients died of other causes with a median survival time of 67.0 months (range 1–121). Age was associated with CSS (HR 2.699, CI 1.192–6.108, $p = 0.017$) and OS (HR 3.660, CI 1.960–6.836, $p < 0.001$).

LVI was identified in 13 cases, and seven of these patients died of bladder cancer with a median survival time of 23.0 months (range 8–53). LVI was associated with CSS (HR 3.373, CI 1.398–8.135, $p = 0.007$) and OS (HR 2.183, CI 1.041–4.578, $p = 0.039$).

LN metastasis was identified in 9 patients, and five of these patients died of bladder cancer with median survival time of 10.0 months (range 6–15). LN metastasis was associated with CSS (HR 6.416, CI 2.248–18.148, $p < 0.001$) and OS (HR 3.768, CI 1.526–9.303, $p = 0.039$).

Although LG tumours (grade 1 or 2) and tumours of LGO showed a trend towards better survival compared with HG tumours (grade 3) and tumours of HGO, respectively (Table 2), the difference was not as significant as expected. Both were not associated with survival (Table 3).

Discussion

Currently, most studies focus on clinical T1HG NMIBC, understaging (20%–50%), recurrence and progression [3,10,11]. Survival analysis of cT1HG managed by immediate radical cystectomy or delayed radical cystectomy, is actually a mixture of MIBC (understaged or progressive) and NMIBC. Risk factors for recurrence, progression and survival of cT1HG were based on a mixture of pathological NMIBC and MIBC, while data on radical cystectomy for pure pT1 UCB are lacking. In this study, cases with a pathologic stage other than pT1 were excluded, and risk factors associated with survival after radical cystectomy for pT1 UCB were analysed.

Risk factors associated with survival

Age has been identified as risk factor for cancer-specific survival after RC for mainly MIBC cases in a multicentre study [12], and age correlated with pathologic grade, stage and LVI. In our study, although patients with higher age had higher rate of HG (grade 3) tumours (73.1% for younger vs 83.9%for higher age), age did not correlated with grade, LVI or LN metastasis ($p = 0.159$, 0.527 and 0.941, respectively). The fact that age itself (independent of grade, LVI and LN metastasis) was significantly associated with CSS ($p = 0.017$) and OS ($p < 0.001$) (Table 3) may be attributed to decreased immunity of the host or the inherent invasiveness of the tumour.

Lymphovascular invasion (LVI) in the context of MIBC is associated with clinical and pathologically aggressive disease [13]. Its value as a prognostic marker in cT1HG is less robust. Approximately 10–36% of patients presenting with cT1 UCB are reported to have LVI, and LVI in the TUR specimen was associated with understaging, recurrence, progression and LN metastasis of cT1HG [2,14–16]. LVI correlated with pathologic stage [17], and the prevalence of LVI among cT1 UCB does not equal its prevalence among pT1 cases as clinical T1 tumours contain a variable proportion of understaged pT2+ tumours. These facts made conclusions about LVI drawn based on cT1 population debatable. Branchereau et al. [15] found LVI was a poor prognostic factor when patients underwent delayed radical cystectomy but not when T1HG patients underwent initial radical cystectomy; therefore, the risk associated with LVI in “pT1” HG may be negated in patients by offering an early radical cystectomy. Of note, in that study, greater than 30%(6 out of 19) and greater than 50%(10 out of 19) of “pT1” UCB in early cystectomy group have LN metastasis and LVI, respectively, and the author did not mention the pathologic stage after radical cystectomy. The readers tend to believe that a considerable proportion of understaged MIBC was included in that study. It should be noted that the evaluation of LVI on TUR specimen is difficult due to specimen fragmentation, retraction artefact from cautery and disorientation of the pathologic specimen (compared with RC specimen). TUR in one piece (en bloc) by examining the vertical resection margin on the completely step-sectioned tumour specimen may help to overcome understaging; using this technique, Rinzo et al. showed

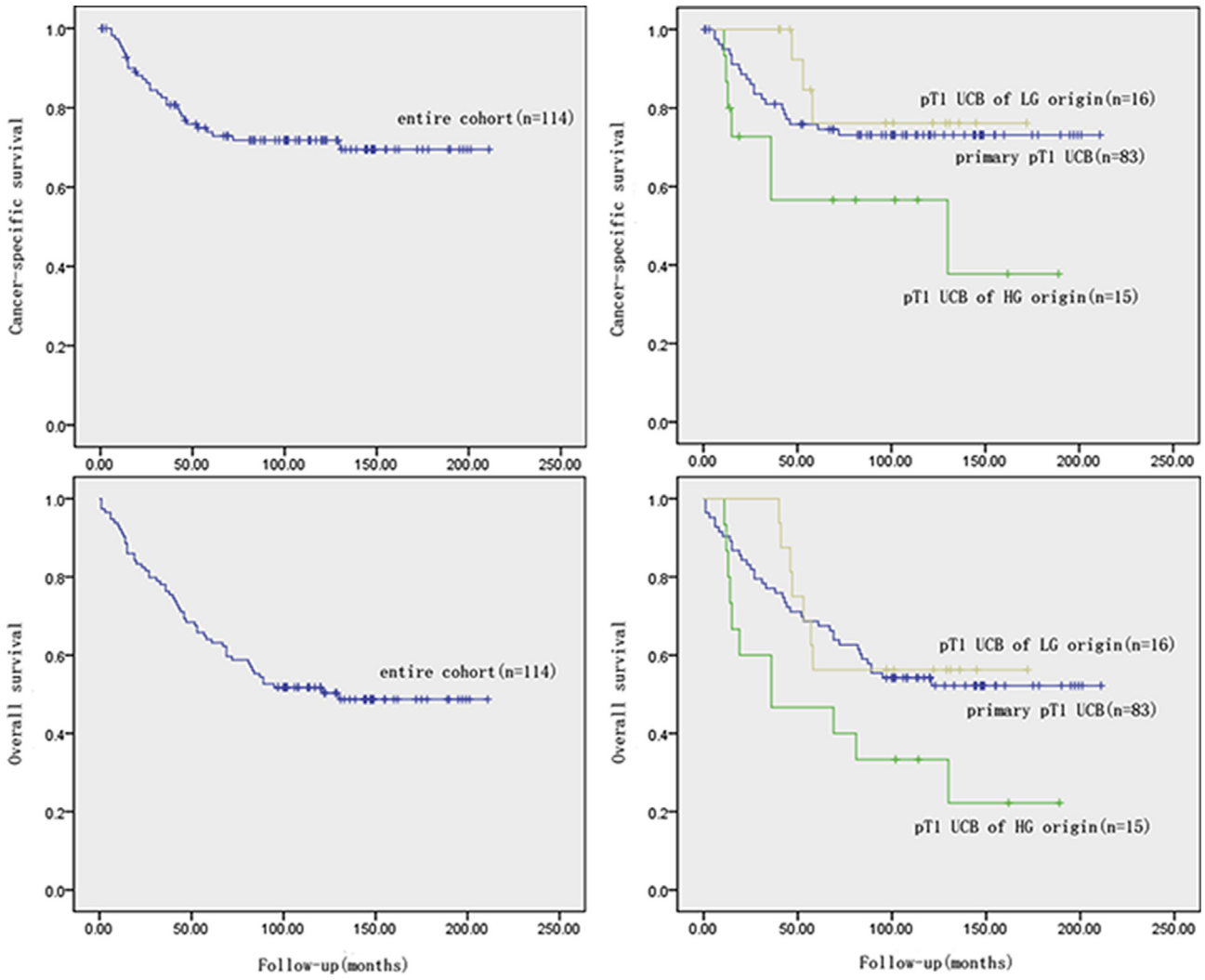

Fig. 1. Kaplan-Meier curves of CSS and OS in 114 patients with pT1 UCB (left column) after radical cystectomy, and Kaplan-Meier curves of CSS and OS stratified by the categorical variable: origin of pT1 UCB (right column). OS, overall survival; CSS, cancer-specific survival; UCB, urothelial carcinoma of bladder.

Table 2
Log-rank test of variables affecting CSS and OS.

	CSS		OS	
	5-year CSS(%)	p Value	5-year CSS(%)	p Value
Gender (male vs female)	73 vs 75	0.706	58 vs 69	0.687
Age (<65 vs ≥ 65)	84 vs 63	0.012	75 vs 47	0.000
Origin of UCB(LGO vs HGO)	77 vs 56	0.059	56 vs 40	0.057
Multicentricity (Single vs multiple)	67 vs 75	0.515	58 vs 60	0.509
Tumour size: (<3 cm vs ≥ 3 cm)	75 vs 71	0.978	67 vs 67	0.660
Tumour grade (Grade 3 vs 1or 2)	82 vs 70	0.174	71 vs 57	0.040
Variant histology(yes vs no)	70 vs 74	0.857	57 vs 61	0.907
Concominent CIS(yes vs no)	70 vs 73	0.552	57 vs 60	0.425
LVI(yes vs no)	40 vs 77	0.002	31 vs 63	0.017
LN metastasis(yes vs no)	39 vs 76	0.001	33 vs 62	0.026

LGO, low grade origin; HGO, high grade origin; LVI, lymphovascular invasion; CSS, cancer-specific survival; OS, overall survival; CIS, carcinoma in situ; UCB, urothelial carcinoma of bladder.

that the presence of LVI was an independent prognostic factor associated with PFS and CSS in patients with HG pT1 UCB [16].

In our study, LVI was associated with survival even for pT1 UCB after timely radical cystectomy. The 5-year CSS of pT1 UCB with LVI was similar to those with LN metastasis (40% vs 39%), and the major difference between LVI and LN metastasis was that the latter had a steeper survival cure (indicative of shorter survival time after RC) (Fig. 2). Our results were consistent with results from another study which showed that among patients undergoing radical cystectomy, the clinical results predicted by LVI were similar to those predicted by lymph node involvement; additionally, patients with LVI even had poorer survival than those with LN metastasis [18]. The poor

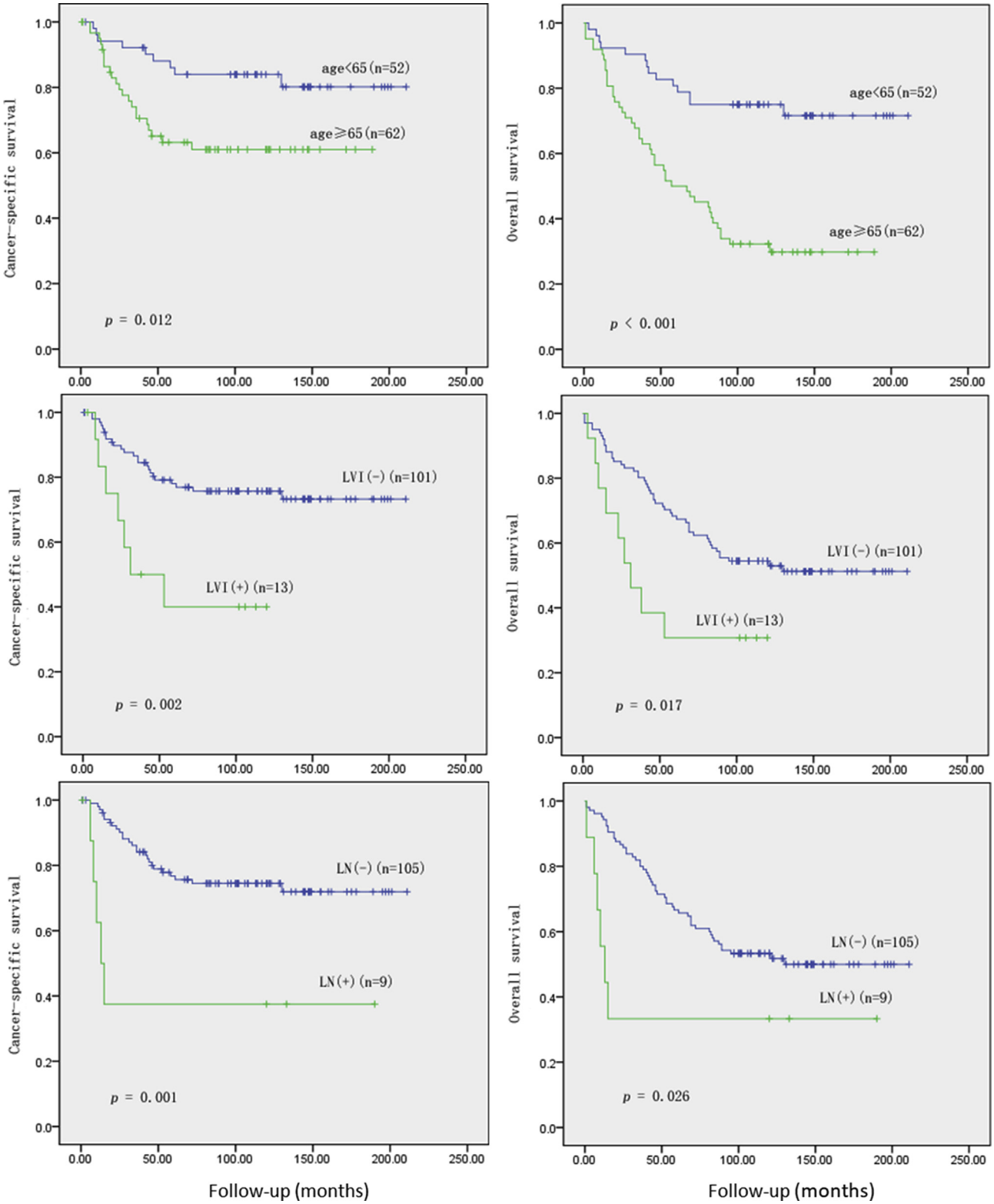

Fig. 2. Kaplan-Meier curves of CSS and OS in 114 patients with pT1 UCB after radical cystectomy, stratified by age, LVI and LN status. LVI, lymphovascular invasion; LN, lymph node; CSS, cancer-specific survival; OS, overall survival; UCB, urothelial carcinoma of bladder.

survival of LVI may indicate that LVI is an indicator of micro-metastasis given that most of the cases with LVI (11 out of 13) in this study had a negative pelvic LN. It is uncertain whether adjuvant or neoadjuvant chemotherapy would have improved survival of patients with pT1 UCB with LVI and negative LN. A prospective RCT of adjuvant chemotherapy for pT1N0 with LVI is needed. The author tends to believe that LVI on TUR specimen before planned radical cystectomy would justify neoadjuvant chemotherapy as pT1 UCB

Table 3
Cox regression analysis of variables that predict CSS and OS.

Variables	CSS		OS	
	HR(95% CI)	*p* Value	HR(95% CI)	*p* Value
Age	2.699(1.192–6.108)	0.017	3.660(1.960–6.836)	0.000
Grade	Not significant		Not significant	
LVI	3.373(1.398–8.135)	0.007	2.183(1.041–4.578)	0.039
LN metastasis	6.416(2.248–18.148)	0.000	3.768(1.526–9.303)	0.004
Origin of UCB	Not significant		Not significant	

CSS, cancer-specific survival; OS, overall survival; LVI, lymphovascular invasion; LN, lymph node; UCB, urothelial carcinoma of bladder.

with LVI portends poorer survival after RC even the lesion does not progress or metastasize.

For NMIBC, grade is the criterion that stratifies risk of recurrence and progression [19,20], but it is based on the observation of conservative management of NMIBC (IVT, intravesical treatment). For cT1HG UCB managed by RC, grade is associated with RFS and CSS on univariate analysis, but the significance is lost when analysed in a multivariate Cox regression model [10]. In the present study, on univariate analysis, LG (grade 1 and 2) UCBs on RC specimens tend to have better survival (82% vs. 70% for 5-year CSS, $p = 0.174$), especially OS (71% vs. 57% for 5-year OS, $p = 0.04$). However, grade was not a factor associated with CSS or OS on Cox regression models. In addition, we found that pT1 UCB of LGO seemed to have better survival than those of HGO ($p = 0.059$, Fig. 1) after radical cystectomy. This result may be partly attributed to the theories that LG and HG UCB were of different origins [21,22]. It is interesting to notice that patients with pT1 UCB of LGO who experienced multiple recurrences untill radical cystectomy have similar long-term survival (10-year CSS) compared with those with primary pT1 UCB after radical cystectomy, indicating that patients with refractory recurrent pT1 UCB of LGO may not necessarily be saved by radical cystectomy. Patients with pT1 UCB of HGO had the most pessimistic prognosis. It is reasonable to stop conservative management and perform upfront radical cystectomy for recurrent T1HG UCB before these lesions recur as tumours not amenable to TUR and accept radical cystectomy passively.

Female gender, tumour size $\geq$3 cm, and concomitant CIS are associated with progression and survival after BCG for cT1HG UCB [11,23], but gender was not associated with survival after RC for cT1HG [10]. Controversies regarding the clinical significance of variant histology among NMIBC managed by conservative methods exist, and some VH (e.g., MPBC) are associated with upstaging and LN metastasis [24]. Multicentricity of UCB has been associated with decreased time to recurrence of NMIBC treated by BCG. However, many studies have assessed progression and CSS associated with multicentricity, and any statistical significance was lost on multivariate analysis [11,20]. In our study, gender, tumour size, multicentricity, variant histology, and concomitant carcinoma in situ did not exhibit a significant influence on survival under the context of pT1 stage after RC.

Limitations of this study

This study was retrospective, and radical cystectomy surgeries were performed by different surgeons. Among recurrent pT1 UCB cases, some TURs were not performed in our hospital. In addition, and the follow-up protocols varied, and several patients did not obey our follow-up protocols strictly, which potentially cause delayed recurrence detection. All recurrent pT1 UCB did not received BCG treatment before RC because BCG was not available during time of study.

Conclusions

LN status, age and LVI were significantly associated with survival of pT1 UCB after radical cystectomy. Recurrent pT1 UCBs of high-grade origin(HGO)should be managed with radical cystectomy in a timely fashion, because these cases tend to have poorer CSS than primary pT1 UCBs after RC, even if they did not progress to MIBC.

Role of the funding source

The funding sources had no further involvement in the study other than financial.

Conflict of interest

The authors declare that they have no conflict of interest.

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