



Original Article

Prognostic factors for the recurrence, progression, and multiple recurrences of non-muscle-invasive bladder cancer in Eastern Taiwan

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ABSTRACT

Objectives: This study aimed to identify the prognostic factors that influence the recurrence, progression, and multiple recurrences of non-muscle-invasive bladder cancer (NMIBC) based on data from the Hualien Tzu Chi Hospital, Taiwan. **Materials and Methods:** A retrospective cohort study enrolled patients with NMIBC diagnosed between 2005 and 2022 who underwent transurethral resection of bladder tumor (TUR-BT). Demographic, clinical, and pathological data, along with recurrence outcomes, were collected. Cox proportional hazard regression models were used to analyze the factors associated with recurrence, progression to muscle-invasive disease, and risk for multiple recurrences. **Results:** Overall, 199 patients were included, with a mean follow-up duration of 4.6 years. Tumors recurred in 53.8% of the patients, which further progressed to muscle-invasive bladder cancer (MIBC) in 13.1%. Multivariate Cox regression analysis identified betel nut chewing, multiple tumors, high-grade tumors, and lack of bacillus Calmette-Guérin (BCG) therapy as significant predictors of recurrence. Age, high-grade tumors, and recurrence within 3 months after the initial TUR-BT were the significant predictors of progression. Multiple tumors and early recurrence occurring within 3 months after the initial TUR-BT were significantly associated with the risk of experiencing multiple recurrences. **Conclusion:** This study identified multiple tumors, high-grade tumors, and BCG therapy as the significant factors associated with NMIBC recurrence, with a potential link also observed for betel nut chewing. Age, tumor grade, and early recurrence emerged as the key predictors of progression to MIBC. In addition, multiple tumors and early recurrence were linked to an increased risk of experiencing multiple recurrences.

KEYWORDS: Bladder cancer, Nonmuscle invasive, Risk factors, Tumor recurrence

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INTRODUCTION

Bladder cancer is the 9th most commonly diagnosed cancer and the 13th leading cause of cancer deaths worldwide [1]. The age-standardized incidence rate (per 100,000 person-years) is 9.3 in men and 2.4 in women [1]. In Taiwan, bladder cancer ranks as the 12th most commonly diagnosed cancer and the 11th leading cause of cancer deaths among men [2]. Among women, it is the 16th most commonly diagnosed cancer and the 14th leading cause of cancer deaths [2]. The age-standardized incidence rate (per 100,000 person-years) is 8.03 in men and 2.82 in women [2].

Bladder cancer is typically classified into non-muscle-invasive bladder cancer (NMIBC) and muscle-invasive bladder cancer (MIBC), with NMIBC generally having a better prognosis. Globally, approximately 75% of newly

diagnosed cases are NMIBC, which includes Ta, T1, and carcinoma *in situ* (Cis) [3]. Although all are categorized as NMIBC, patients with Ta, T1, or Cis bladder cancer have different outcomes in terms of recurrence and progression. A long-term follow-up study showed a recurrence rate of 56.5% and progression rate of 9.4% in patients with Ta low-grade NMIBC [4]. In contrast, another study focusing on T1 bladder cancer found a recurrence rate of 55% and a progression rate of 22.1% [5].

The factors that influence recurrence and progression remain a key area of research. In earlier studies, age, tumor count, tumor size, prior recurrence rate, T category, concurrent

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Cis, and 1973 World Health Organization (WHO) tumor grade were identified as important prognostic factors [6-8]. In various risk stratification guidelines, patients are classified into low-, intermediate-, high-, and very-high-risk groups based on the aforementioned characteristics [3,9,10], with corresponding management strategies depending on the risk group.

Some consensus guidelines and various scoring models are available for predicting NMIBC recurrence and progression; however, no studies have focused on Eastern Taiwan. Thus, this study aimed to analyze the disease characteristics of patients with NMIBC living in Eastern Taiwan and identify the factors that could help predict tumor recurrence and progression using the long-term follow-up data.

MATERIALS AND METHODS

Study population

Medical records were retrospectively screened to identify the patients with NMIBC who underwent transurethral resection of bladder tumor (TUR-BT) and were subsequently diagnosed with bladder cancer for the first time between 2005 and 2022 at Hualien Tzu Chi Hospital, Hualien, Taiwan. The study only included patients with a pathological report showing pTa, pT1, or Cis. This study was conducted in accordance with the Declaration of Helsinki and was approved by the Research Ethics Committee of Hualien Tzu Chi Hospital and the Buddhist Tzu Chi Medical Foundation (IRB code: 112-110-B, dated May 17, 2023). Informed written consent was waived by the IRB.

Data collection and definitions

Time at entry was the date of the first TUR-BT, with the pathology report confirming the diagnosis of NMIBC. The following endpoints were assessed: (1) time to first recurrence: time from the first TUR-BT to the date of the first bladder recurrence; (2) time to progression to muscle-invasive disease: time from the first TUR-BT to the date of bladder recurrence progressing to MIBC; and (3) time to second recurrence: time from the first TUR-BT to the date of the second bladder recurrence.

For each patient, 12 demographic, clinical, and pathological characteristics were reviewed, including age, sex, smoking status, alcohol consumption, betel nut chewing, history of upper tract urothelial carcinoma (UTUC), hypertension, diabetes mellitus, tumor count, T stage, tumor grade, and bacillus Calmette-Guérin (BCG) therapy [Supplementary Table 1]. Patients were divided into two groups based on their history of smoking (nonsmokers and current or former smokers), alcohol consumption (nondrinkers and current or former alcohol users), and betel nut chewing (nonbetel nut chewers and current or former betel nut chewers). Based on their history of UTUC, patients were classified into those who had UTUC before, concurrently with, or after NMIBC diagnosis, and those who never had UTUC. Regarding intravesical therapy, patients were grouped into those who received intravesical BCG therapy at least three times after the first TUR-BT and those who received other regimens or had not received intravesical BCG therapy. During the statistical analysis, two patients with grade 2 tumors

according to the 1973 WHO classification were reclassified as having high-grade tumors. Progression was defined as tumor upstaging to the MIBC. These 12 demographic, clinical, and pathological characteristics were then analyzed in relation to recurrence and progression using a Cox proportional hazard regression model.

Data from patients with at least one recurrence were further analyzed, and two additional characteristics were reviewed. The time of the first recurrence was considered, and patients were assigned to those whose first recurrence occurred within 3 months after the first TUR-BT and those whose first recurrence transpired after >3 months. The tumor location of the first recurrence was compared with the location of the first TUR-BT. The bladder was divided into the dome, posterior wall, anterior wall, lateral wall, and base (which includes the ureteral orifice, trigone, and bladder neck). Patients were further categorized into those whose first recurrence happened outside the site of the first TUR-BT and those whose first recurrence developed within the same location. Finally, whether the aforementioned demographic, clinical, and pathological characteristics influenced the number of recurrences was examined, specifically whether patients with certain characteristics were at a higher risk of experiencing two or more recurrences.

Statistical analysis

Data were analyzed using R version 4.4.1 R Core Team (2024) R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna, Austria. Differences in the demographic, clinical, and pathological characteristics between the nonrecurrence and recurrence groups were analyzed using the Chi-square test. A univariate Cox proportional hazards regression analysis was performed to evaluate the individual risk factors, and deaths before recurrence, progression, or second recurrence were treated as competing risks. Factors that were associated with the dependent variable at $P < 0.1$ were then included in the multivariate Cox regression analysis. For significant factors ($P < 0.05$) in the multivariate Cox regression model, the distributions of time to recurrence, progression, and second recurrence were estimated using the Kaplan–Meier method to visually assess and compare event-free survival probabilities across different groups. Data for three patients without grade information and two without tumor recurrence location information were imputed using the mice package in R.

RESULTS

Patient characteristics

Patients' characteristics are summarized in Supplementary Table 1. A total of 199 patients were enrolled, with follow-up times ranging from 90 days to 15.9 years and a mean follow-up duration of 4.6 years. The mean age at diagnosis was 70.8 years, with ages ranging from 25 to 94 years. The male-to-female ratio was 2.9:1, and 96 (48.2%) patients were either former or current smokers. In total, 95 (47.7%) patients were first diagnosed with a Ta tumor and 100 (50.3%) with a T1 tumor. Regarding tumor grade, pathology reports revealed low-grade tumors in 88 (44.2%) patients and high-grade ones in 106 (53.3%). Among all patients, 70 (35.2%) had received BCG therapy after the first TUR-BT.

Table 1: Baseline demographics on patients with bladder tumor recurrence and non-recurrence

Clinical characteristics	Category	Non-recurrence patient (%)	Recurrence (%)	P
Total patients		92 (46.2)	107 (53.8)	
Age (years)	<65	13 (6.5)	24 (12.1)	0.134
	≥65	79 (39.7)	83 (41.7)	
Gender	Male	71 (35.7)	77 (38.7)	0.401
	Female	21 (10.6)	30 (15.1)	
Smoking	No	50 (25.1)	53 (26.6)	0.498
	Yes*	42 (21.1)	54 (27.1)	
Alcohol	No	64 (32.2)	68 (34.2)	0.371
	Yes*	28 (14.1)	39 (19.6)	
Betel nut	No	77 (38.7)	88 (44.2)	0.786
	Yes*	15 (7.5)	19 (9.5)	
UTUC combination	No	77 (38.7)	74 (37.2)	0.017
	Yes	15 (7.5)	33 (16.6)	
Hypertension	No	43 (21.6)	53 (26.6)	0.694
	Yes	49 (24.6)	54 (27.1)	
Diabetes mellitus	No	66 (33.2)	83 (41.7)	0.344
	Yes	26 (13.1)	24 (12.1)	
Number of bladder tumors	1	43 (21.6)	35 (17.6)	0.043
	>1	49 (24.6)	72 (36.2)	
T stage category	Tis	1 (0.5)	3 (1.5)	0.687
	Ta	44 (22.1)	51 (25.6)	
	T1	47 (23.6)	53 (26.6)	
	T2	43 (21.6)	63 (31.7)	
Grade of tumor	Low	48 (24.1)	40 (20.1)	0.125
	High	43 (21.6)	63 (31.7)	
	Grade 2	0	2 (1.0)	
	Unknown	1 (0.5)	2 (1.0)	
BCG therapy after 1 st TUR-BT	No	51 (25.6)	78 (39.2)	0.010
	Yes	41 (20.6)	29 (14.6)	
Recurrence ≥ 2 times	No	N/A	54 (50.5)	N/A
	Yes		53 (49.5)	
Recurrence within 3 months	No	N/A	73 (68.2)	N/A
	Yes		34 (31.8)	
Recurrence at different locations	No	N/A	46 (43.0)	N/A
	Yes		59 (55.1)	
	Unknown		2 (1.9)	
Survival	Alive	85 (42.7)	87 (43.7)	0.023
	Dead	7 (3.5)	20 (10.1)	

*Includes those who quit smoking, drinking alcohol, or chewing betel nut. UTUC: Upper tract urothelial carcinoma, BCG: *Bacillus Calmette–Guérin*, TUR-BT: Transurethral resection of the bladder tumor, N/A: Not available

Table 1 presents the characteristics of the patients based on their outcomes (nonrecurrence vs. recurrence). The proportions of patients with UTUC, multifocal tumors, and death during follow-up were significantly higher in the recurrence group, whereas the proportion of patients receiving BCG therapy after the first TUR-BT was significantly lower in the recurrence group.

Impact of clinical variables on recurrence

Tumor recurrence was noted in 107 (53.8%) patients, with a median time to the first recurrence of 7.5 months. The univariate Cox regression analysis indicated that the tumor count (solitary or multiple), tumor grade (low or high), and whether the patient received intravesical BCG therapy were associated with recurrence ($P < 0.05$), with hazard ratios (HRs) of 1.87, 1.56, and 0.38, respectively [Table 2]. Then, the history of betel nut chewing (HR = 1.60, $P = 0.079$) and the three previously mentioned factors were included

in the multivariate Cox regression analysis. All variables reached significance, with betel nut chewing (HR = 1.87, $P = 0.025$), tumor count (HR = 2.00, $P = 0.0007$), tumor grade (HR = 1.69, $P = 0.015$), and BCG therapy (HR = 0.36, $P < 0.0001$) demonstrating significant associations [Table 3]. For the significant variables in the multivariate analysis, Kaplan–Meier distributions of time to first recurrence are shown in Figure 1.

Impact of clinical variables on progression

Tumor progression to MIBC was observed in 26 (13.1%) patients. In the univariate Cox regression analysis, age and whether the first recurrence occurred within 3 months after the first TUR-BT were associated with progression ($P < 0.05$) [Table 2], with HRs of 1.05 and 4.01, respectively. The tumor grade (HR = 2.33, $P = 0.053$) and whether the patient received BCG therapy (HR = 0.45, $P = 0.063$), in addition to the two aforementioned variables, were included in the subsequent

Table 2: Univariate analysis of time to first recurrence, progression, and second recurrence

Variable	Recurrence		Progression		2 nd Recurrence	
	HR	P	HR	P	HR	P
Age	1.00	0.870	1.05	0.0056	1.01	0.240
Age: ≤65 versus >65 years	0.79	0.280	1.44	0.490	1.28	0.440
Gender: Male versus female	1.01	0.950	0.60	0.310	0.85	0.590
Smoking	1.23	0.290	1.32	0.480	1.38	0.230
Alcohol	1.39	0.100	0.89	0.770	1.05	0.860
Betel nut	1.60	0.079	0.75	0.630	1.72	0.082
Combined UTUC	1.30	0.180	0.63	0.330	1.09	0.770
Hypertension	1.00	0.990	0.64	0.270	0.82	0.450
Diabetes mellitus	0.89	0.580	0.84	0.710	1.00	0.990
Tumor count	1.87	0.0015	1.52	0.300	2.04	0.013
T stage: Tc1s, Ta, T1	0.92	0.650	0.79	0.500	0.91	0.690
Grade: Low versus high	1.56	0.026	2.33	0.053	1.76	0.056
Receiving BCG therapy	0.38	<0.0001	0.45	0.063	0.63	0.140
Recurrence within 3 months	N/A	N/A	4.01	0.001	2.48	0.0031
Recurrence at different locations	N/A	N/A	N/A	N/A	0.864	0.600

UTUC: Upper tract urothelial carcinoma, BCG: *Bacillus Calmette-Guérin*, HR: Hazard ratios, N/A: Not available

Table 3: Multivariate analysis of time to first recurrence, progression, and second recurrence

Variable	Recurrence		Progression		2 nd recurrence	
	HR	P	HR	P	HR	P
Age	N/A	N/A	1.06	0.0009	N/A	N/A
Betel nut	1.87	0.025	N/A	N/A	1.21	0.610
Tumor count	2.00	0.0007	N/A	N/A	1.95	0.023
Grade: Low versus high	1.69	0.015	2.59	0.030	1.85	0.059
Receiving BCG therapy	0.36	<0.0001	0.68	0.440	N/A	N/A
Recurrence within 3 months	N/A	N/A	4.41	0.0011	2.13	0.027

BCG: *Bacillus Calmette-Guérin*, HR: Hazard ratios, N/A: Not available

multivariate Cox regression analysis. Except for BCG therapy, all other factors demonstrated a significant association with progression, including age (HR = 1.06, $P = 0.0009$), tumor grade (HR = 2.59, $P = 0.030$), and recurrence within 3 months after TUR-BT (HR = 4.41, $P = 0.0011$) [Table 3]. For the variables that were significant in the multivariate analysis, Kaplan-Meier distributions of time to progression are shown in Figure 2.

Clinical variables and the risk of multiple recurrences

Among the 107 patients who experienced recurrence, 53 experienced at least two recurrences. The univariate Cox regression analysis showed that the tumor count and first recurrence that arose within 3 months after the first TUR-BT were associated with the risk of experiencing multiple recurrences ($P < 0.05$) [Table 2]. Besides these two factors, the history of betel nut chewing (HR = 1.72, $P = 0.082$) and tumor grade (HR = 1.76, $P = 0.056$) were included in the multivariate Cox regression analysis. The tumor count (HR = 1.95, $P = 0.023$) and recurrence that emerged within 3 months after TUR-BT (HR = 2.13, $P = 0.027$) showed a significant correlation with the risk of experiencing multiple recurrences [Table 3]. For the variables that were significant in

the multivariate analysis, Kaplan-Meier distributions of time to second recurrence are shown in Figure 2.

DISCUSSION

This study revealed that the presence of multiple tumors, high-grade tumors, betel nut chewing, and BCG therapy significantly influence recurrence in patients with NMIBC. Age, tumor grade, and early recurrence are key predictors of the progression to MIBC. In addition, multiple tumors and early recurrence were significantly associated with the risk of experiencing multiple recurrences. These findings suggest that more proactive treatment strategies should be considered for patients at higher risk of recurrence, progression, or multiple recurrences.

One of the strengths of this study is its setting in Eastern Taiwan, where the residents of this region rarely move between cities and tend to stay at the same hospital for medical care. This stability allowed for consistent long-term follow-up. Of the 199 patients included, 167 (83.9%) were followed for more than 1 year, and 132 (66.3%) for more than 2 years.

In this study, the tumor count, tumor grade, receipt of BCG therapy after the first TUR-BT, and betel nut chewing were significantly associated with recurrence. Specifically, patients with multiple tumors and high-grade tumors had a higher recurrence risk, which is consistent with the results of previous studies identifying these factors as important prognostic indicators for recurrence in patients with NMIBC [6,7]. A previous study showed that TUR-BT combined with intravesical BCG therapy reduced the recurrence risk at 12 months compared with TUR-BT alone [11]. Furthermore, when compared with intravesical chemotherapy using agents such as mitomycin, epirubicin, doxorubicin, or sequential mitomycin and doxorubicin, intravesical BCG therapy reduced short-term and long-term treatment failure [12]. These results align with the findings of the present study, where BCG therapy significantly reduced the recurrence risk compared with patients who did not receive intravesical therapy or who received intravesical chemotherapy.

Although betel nut chewing was not significant in the univariate Cox regression analysis (HR = 1.60, $P = 0.079$), it became a significant factor that influences recurrence when the tumor count, tumor grade, and receipt of BCG therapy were included in the multivariate Cox regression model (HR = 1.87, $P = 0.025$). The International Agency for Research on Cancer classified betel nuts as a group I carcinogen. Several studies have highlighted that betel nut chewing is a risk factor for oral [13] and pharyngeal [14] cancers and that it is significantly associated with an increased risk of head and neck cancer mortality [15]. However, the relationship between betel nut chewing and bladder cancer remains unclear. Wen *et al.* indicated that nonsignificant increased risks of cancer deaths associated with betel nut chewing were observed for bladder cancer [16]. In another study, Cao *et al.* identified heavy betel nut chewing as an independent factor that influences recurrence [17], which may be the only study linking betel nut chewing to NMIBC recurrence.

One possible explanation for the effect of betel nut chewing on NMIBC recurrence could be the high prevalence

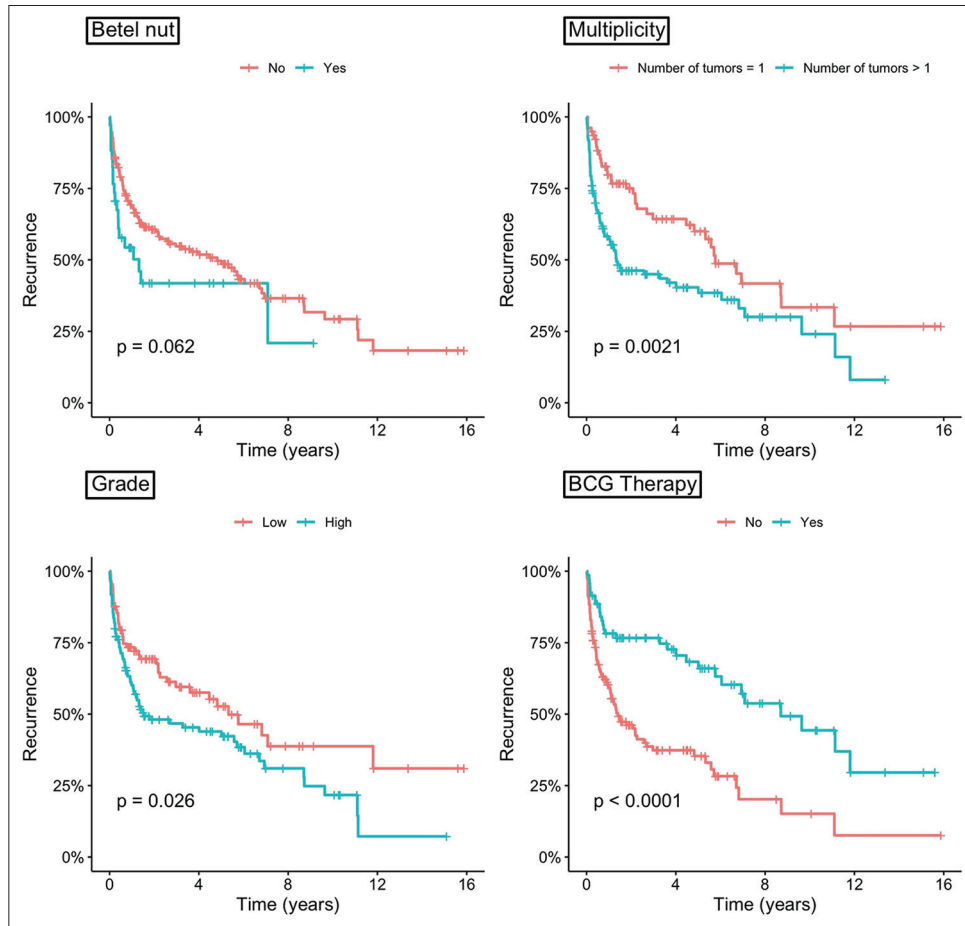


Figure 1: Kaplan–Meier distributions of the time to the first recurrence for the four variables significant in the multivariate Cox analysis: betel nut, multiplicity, tumor grade, and *Bacillus Calmette–Guérin* therapy

of smoking among betel nut chewers. In a study by Wen *et al.*, 85.2% of Taiwanese betel nut chewers were also current smokers [18]. Similarly, in the present study, 28 out of 34 betel nut chewers were current or former smokers. Although smoking was not identified as a risk factor for recurrence in this study, a systematic review by Ślusarczyk *et al.* revealed that current and former smokers were at a higher risk for recurrence than never smokers [19]. It is also possible that smokers who chew betel nuts may smoke more than smokers who do not chew betel nuts, which could contribute to the increased risk of NMIBC recurrence. However, data on smoking intensity were not available in this study, limiting a more precise evaluation of this interaction. More studies are needed to better understand the relationship among betel nut chewing, smoking behavior, and NMIBC recurrence.

Besides smoking, socioeconomic status and lifestyle patterns might be possible confounding factors with betel nut chewing. Betel nut use is more common among individuals with lower socioeconomic status, who may have less access to healthcare, lower treatment adherence, and delayed follow-up, all of which can contribute to worse oncological outcomes, including higher recurrence rates. In a study by Noel *et al.*, patients in the lowest neighborhood socioeconomic status quintile had a 45% less likelihood of receiving intravesical therapy compared to the highest neighborhood socioeconomic

status group [20]. Betel nut chewers may also share other lifestyle habits such as poor diet, alcohol consumption, or physical inactivity, which could influence cancer outcomes. These factors may partially explain the observed association.

According to data from the Ministry of Health and Welfare, the proportions of people who had chewed betel nuts in the past 6 months or had quit chewing betel nuts in Hualien in 2021 were 19%, 29%, and 9.9% in the overall, male, and female populations, respectively [21], which is notably higher than those in other cities in Taiwan. Given the high prevalence of betel nut chewing in Hualien, it may be an important factor to consider when assessing the recurrence risk of patients with NMIBC.

Tumor progression to MIBC remains one of the most feared outcomes for patients with NMIBC. In this study, age, tumor grade, and first recurrence that occurred within 3 months of the initial TUR-BT were significantly associated with progression. These findings are consistent with those of other studies in the literature. A study by the Spanish Urological Club for Oncological Treatment (Club Urológico Español de Tratamiento Oncológico, or CUETO) reported that high-grade tumors and recurrence at 3-month cystoscopy increased the progression risk [22]. Age was also identified as a potential progression indicator in their study, as the difference was nearly significant ($P = 0.052$) [22].

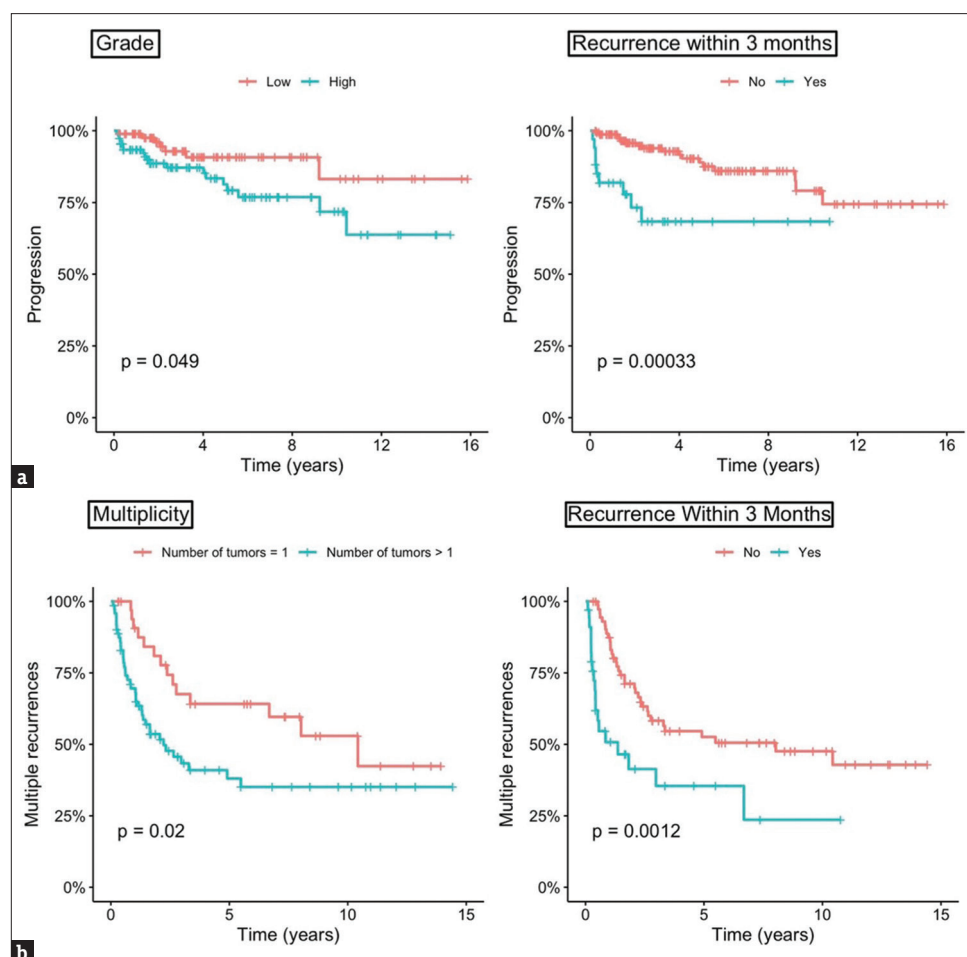


Figure 2: (a) Kaplan–Meier distributions of the time to progression for the variables significant in the multivariate Cox analysis: tumor grade and recurrence occurring within 3 months. (b) Kaplan-Meier distributions of time to second recurrence for the two variables significant in the multivariate Cox analysis: multiplicity and recurrence occurring within 3 months

Multiple recurrences were also assessed in this study. The tumor count and recurrence within 3 months of the initial TUR-BT were significantly linked to the risk of experiencing two or more recurrences. Patients with multiple tumors and those who experienced their first recurrence within 3 months are at a higher risk of experiencing multiple recurrences. Deng *et al.* focused on multiple recurrences and found that the shorter the period between resection and recurrence, the higher the risk of multiple recurrences [23], which aligns with our findings regarding the relationship between recurrence timing and the number of recurrences. In this study, the location of the first recurrence was also compared with the initial site of the first TUR-BT to determine whether patients with recurrence outside the original location have a higher risk of experiencing multiple recurrences. However, this did not reach significance, and the location of recurrence may not be a significant factor in multiple recurrences.

Interestingly, although BCG therapy was associated with a decreased risk of recurrence, it was not significantly linked to a reduced likelihood of experiencing multiple recurrences. This finding indicates that BCG therapy may not be a protective factor against multiple recurrences. In a systematic review and meta-analysis, Chen *et al.* indicated that BCG

induction followed by BCG maintenance after TUR-BT, as opposed to BCG induction alone, significantly lowers the risk of tumor recurrence and progression, with the risk ratios for recurrence and progression reduced by 21% and 19%, respectively [24]. However, as regards multiple recurrences, whether maintenance BCG therapy is more effective than induction BCG alone remains unclear; thus, further research is needed.

Several limitations of this study should be acknowledged. First, although betel nut chewing was found to be significantly associated with NMIBC recurrence in multivariate analysis, the high co-occurrence of smoking among betel nut users raises the possibility of residual confounding. Without stratified analysis or interaction modeling to account for smoking status – such as distinguishing between heavy and light smokers – a causal interpretation remains uncertain. Unfortunately, detailed information on smoking intensity was not available. Second, the study was solely based on clinicopathological parameters and did not include molecular or genomic biomarkers, which are increasingly recognized for their prognostic value in NMIBC. Including such data could improve risk assessment and understanding of tumor behavior. Third, while BCG therapy was included in the analysis, data

on whether patients received induction-only or induction-plus maintenance protocols were not collected, which may limit the clinical interpretability of these findings.

CONCLUSION

In line with previous literature, multiple tumors, high-grade tumors, and BCG therapy were significantly associated with NMIBC recurrence. A significant association between betel nut chewing and recurrence was also observed, though this finding should be interpreted cautiously and validated in future research. Age, tumor grade, and early recurrence are key predictors of progression to MIBC. Moreover, multiple tumors and early recurrence were significantly associated with the risk of experiencing multiple recurrences. In conclusion, further studies are warranted to clarify the role of betel nut chewing in recurrence and explore the effect of maintenance BCG therapy on multiple recurrences.

Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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Conflicts of interest

Dr. Hann-Chorng Kuo and Dr. Yuan-Hong Jiang, the editorial board members at *Tzu Chi Medical Journal*, had no role in the peer review process of or decision to publish this article. The other author declared no conflicts of interest in writing this paper.

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SUPPLEMENTARY MATERIAL

Supplementary Table 1: Patient demographics

Clinical characteristics	Category	Patient number (%)
Age	≤50	12 (6.0)
	51–60	29 (14.6)
	61–70	62 (31.2)
	71–80	52 (26.1)
	81–90	39 (19.6)
	>90	5 (2.5)
Gender	Male	148 (74.4)
	Female	51 (25.6)
Smoking	No	103 (51.8)
	Yes*	96 (48.2)
Alcohol	No	132 (66.3)
	Yes*	67 (33.7)
Betel nut	No	165 (83.1)
	Yes*	34 (16.9)
UTUC combination	No	151 (75.9)
	History of UTUC	21 (10.6)
	Concomitant NMIBC	10 (5.0)
	UTUC after NMIBC	17 (8.5)
Hypertension	No	96 (48.2)
	Yes	103 (51.8)
Diabetes mellitus	No	149 (75.0)
	Yes	50 (25.0)
Number of bladder tumors	1	78 (39.2)
	>1	121 (60.8)
T stage category	Tis	4 (2.0)
	Ta	95 (47.7)
	T1	100 (50.3)
Grade of tumor	Low	88 (44.2)
	High	106 (53.3)
	Grade 2	2 (1.0)
	Unknown	3 (1.5)
BCG therapy after 1 st TUR-BT	No	129 (64.8)
	Yes	70 (35.2)
Recurrence	No	92 (46.2)
	Yes	107 (53.8)
Progression	No	173 (86.9)
	Yes	26 (13.1)
Survival	Alive	172 (86.4)
	Dead	27 (13.6)

*Includes those who quit smoking, drinking alcohol, or chewing betel nut.
 UTUC: Upper tract urothelial carcinoma, BCG: *Bacillus* Calmette–Guérin,
 TUR-BT: Transurethral resection of the bladder tumor, NMIBC: Nonmuscle
 invasive bladder cancer