

EORTC risk tables are more suitable for Chinese patients with nonmuscle-invasive bladder cancer than AUA risk stratification

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Abstract

Background: Patients with non-muscle-invasive bladder cancer (NMIBC) need accurate estimations of the risk of recurrence and progression. Physicians can offer individualized therapy after identifying high-risk tumors. In our study, we compared the applicability of European Organization for Research and Treatment of Cancer (EORTC) risk tables and American Urological Association (AUA) risk stratification in Chinese patients with NMIBC.

Methods: We retrospectively studied 301 patients with NMIBC who underwent transurethral resection of bladder tumor (TURBT) between October 2000 and July 2009 at Huashan Hospital of Fudan University and analyzed their parameters. The recurrence and progression rates at 1 and 5 years postoperatively were calculated along with 95% confidence intervals. We compared them with results obtained from the EORTC risk tables and AUA risk stratification. *P* values <.05 were considered statistically significant.

Results: The median patient age was 67 years (21–92 years) and the median follow-up duration was 46 months (2–151 months). We used EORTC risk tables to classify patients into 3 groups, depending on whether they suffered recurrence or progression after TURBT. Kaplan–Meier curves showed significant differences among the 3 recurrence-free survival (RFS) levels (*P* < .0001, log-rank test) and among the 3 progression-free survival (PFS) levels (*P* < .0001, log-rank test). AUA risk stratification showed the same results. Both classifications were suitable to predict recurrence and progression in Chinese patients. However, for high-risk patients in both series, Kaplan–Meier curves showed significant differences between RFS levels (*P* < .0001, log-rank test) and between PFS levels (*P* < .0001, log-rank test). EORTC risk tables were stricter and AUA was more sensitive in assigning patients to a high-risk group.

Conclusion: EORTC risk tables are better than AUA risk stratification for predicting recurrence and progression in Chinese patients with NMIBC, especially among high-risk patients.

Abbreviations: AUA = American Urological Association, BCa = bladder cancer, BCG = Bacillus Calmette–Guerin, CIS = carcinoma in situ, EORTC = European Organization for Research and Treatment of Cancer, NMIBC = nonmuscle-invasive bladder cancer, PFS = progression-free survival, RFS = recurrence-free survival, TURBT = transurethral resection of the bladder tumor.

Keywords: non-muscle-invasive bladder cancer, prognostic factors, progression, recurrence

1. Introduction

Bladder cancer (BCa) is one of the most common urinary tumors with an estimated 330,400 new cases diagnosed and 123,100

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attributable deaths worldwide in 2012.^[1] The morbidity of BCa patients is highest in Europe, followed by the United States and Asia.^[2] Up to 85% of BCa patients who present with tumors confined to the mucosa (stage Ta and Tis) or submucosa (stage T1) are diagnosed with non-muscle-invasive bladder cancer (NMIBC).^[3] Notably, NMIBC patients suffer frequent recurrence and progression from muscle-invasive diseases, necessitating close follow-up postoperatively, including cystoscopy. When tumor recurrence or progression are diagnosed, aggressive management should be considered.^[4] Tumor stage and grade are well-established prognostic factors for BCa.^[5] In recent years, transurethral resection of bladder tumor (TURBT) and postoperative intravesical instillation chemotherapy have been recommended by major guidelines; hence, TURBT and cystectomy will remain the main treatments for the foreseeable future.^[6] Nevertheless, only 20% to 30% patients have a relatively benign type of urothelial carcinoma with a low recurrence rate and do not show progression during their life-long surveillance.^[7] Therefore, close monitoring is required for patients with the high-risk tumor type.^[8]

The management of NMIBC is controversial. Accurate estimations of the risk of recurrence and progression are needed to recommend individualized therapy, especially to identify high-risk tumors. According to our previous study, 301 patients in our institution who underwent TURBT were followed up and we concluded that, although the immediate instillation of

intravesical chemotherapy may reduce recurrence risk, European Organization for Research and Treatment of Cancer (EORTC) risk tables could predict recurrence and progression in Chinese patients with NMIBC.^[9] However, the American Urological Association (AUA) risk stratification is also a widely used guideline. This guideline attempts to improve a clinician's ability to evaluate and treat each patient.^[10] EORTC risk tables^[11] evaluate the risk of recurrence and progression for patients who undergo TURBT, and AUA risk stratification^[10] classifies the patients into 3 groups with different risks of recurrence and progression. This raises the question of whether EORTC risk tables are more suitable for Chinese patients with NMIBC than AUA risk stratification. The purpose of this study is to compare the effectiveness between EORTC risk tables and AUA risk stratification and to determine which is more suitable for Chinese patients with NMIBC.

2. Methods

2.1. Patients and follow-up

The 301 patients who underwent TURBT in Huashan Hospital of Fudan University, Shanghai, China between October 2000 and July 2009 were included. All of them were histologically diagnosed with NMIBC. Data on age, sex, number of tumors, tumor size, and prior recurrence rate were collected. Paraffin sections of tumors in 301 cases were restaged and regraded in accordance with the 2002 TNM^[12] classification and the 1973 World Health Organization (WHO)^[13] classification by 2 pathologists with 10 years of experience in the pathology department. The pathologists were blind to the patients' clinical data. In our study, the initial event was defined as the time after complete TURBT. During our research, informed consent for each patient was obtained as patient privacy rights and they were always observed. Our research was approved by the institutional review board in our hospital.

For all patients, the follow-up strategies were standardized as below: quarterly cystoscopy during the first 2 years, then every 6 months until 5 years, and annually thereafter. We defined tumor recurrence as urothelial cancer that was discovered/histologically diagnosed during follow-up after complete resection of NMIBC, and progression was defined as development of muscle-invasive BCa (pT2 or higher) and/or metastasis. The endpoint for patients without recurrence/progression was the date of the last available follow-up cystoscopy; for patients with recurrence or progression, the endpoint was the time of tumor recurrence or progression confirmed using histopathology, as we described in our study in 2014.^[9]

According to EORTC risk tables (www.uroweb.org/guidelines), we evaluated the risk of recurrence and progression for patients who underwent TURBT. According to AUA risk stratification,^[10] we classified the patients into 3 groups with different risks of both recurrence and progression.

2.2. Statistical analysis

All statistical analyses were performed using SPSS version 22.0 (New York). The chi-square test was used to assess the association between clinical variables. Univariate analysis and multivariate analysis (Cox regression models) were used to identify independent predictive parameters of recurrence and progression. The Kaplan–Meier method was applied to estimate time to progression with differences assessed using log rank

Table 1

Patient characteristics.

Characteristics	Present series, numbers, %
Age, y	
≤60	107 (35.6)
61–70	85 (28.2)
71–80	82 (27.2)
>80	27 (9.0)
Sex	
Male	244 (81.1)
Female	57 (18.9)
Tumor size, cm	
<3 cm	202 (67.1)
≥3 cm	99 (32.9)
Number of tumors	
1	188 (62.5)
2–7	99 (32.8)
≥8	14 (4.7)
Prior recurrence rate	
Primary	249 (82.7)
Recurrent, <1 rec/y	31 (10.3)
Recurrent, >1 rec/y	21 (7.0)
Carcinoma in situ	
No	285 (94.7)
Yes	16 (5.3)
Tumor stage	
Ta	179 (59.5)
T1	122 (40.5)
Tumor grade	
1	103 (34.2)
2	161 (53.5)
3	37 (12.3)
Immediate intravesical treatment	
Yes	184 (61.1)
No	117 (38.9)
Recurrence	
No	191 (63.5)
Yes	110 (36.5)
Progression	
No	269 (89.4)
Yes	32 (10.6)

statistics. These hazards were estimated with their 95% confidence interval. A *P* value of <.05 was considered statistically significant.

3. Results

3.1. Patient characteristics

A total of 244 men (81.1%) and 57 women (18.9%) were enrolled in our series. The median age of patients was 67 years (21–92 years). The median follow-up duration was 46 months (2–151 months). The clinical data of all the patients, including age, sex, number of tumors, tumor size, prior recurrence rate, tumor T stage (Ta or T1), tumor grade, presence of concomitant carcinoma in situ (CIS), and intravesical treatment are summarized in Table 1.

According to EORTC risk tables, patients were evaluated for the risk of recurrence and progression separately. The numbers of patients with a low risk of recurrence and progression were 50 and 84, the numbers with an intermediate risk were 232 and 192, and the numbers with a high risk were 19 and 25, respectively. Patients were also classified into 3 risk levels for both recurrence

Table 2**The numbers of patients in different risk levels of both series.**

	AUA numbers, %	EORTC numbers, %	
		Recurrence	Progression
Low risk	50 (16.61)	50 (16.61)	84 (27.91)
Intermediate risk	119 (39.53)	232 (77.08)	192 (63.79)
High risk	132 (43.85)	19 (6.31)	25 (8.31)
Total	301	301	301

AUA = American Urological Association, EORTC = European Organization for Research and Treatment of Cancer.

and progression using AUA risk stratification. The number of patients in the low-risk group was 50, while in the intermediate risk group it was 119, and in the high-risk group it was 132. The numbers of patients in the different groups are summarized in Table 2.

3.1. Applicability of the EORTC risk tables and the AUA risk stratification in our cohort

We compared variables in the EORTC and AUA series, the results of univariate analysis of both risk tables are shown in Table 3 and those of multivariate analysis are shown in Table 4.

The number of tumors, tumor size, prior recurrence rate, CIS, T category, and grade were associated with a higher recurrence risk after TURBT. Similarly, tumor size, tumor status, CIS, T category, and tumor grade were variables associated with a higher progression risk. Multivariate analysis indicated that the number of tumors, tumor size, tumor stage, tumor grade, and

recurrence rate were associated with recurrence risk. The variables that were proven to predict progression risk were tumor size, tumor stage, tumor grade, tumor status, and concomitant CIS.

3.1. Comparison of the use of EORTC risk tables and AUA risk stratification in Chinese patients with NMIBC

We used EORTC risk tables and AUA risk stratification to classify 301 patients into different risk groups and compared them with their actual prognosis. Among the 301 patients in the present study, the recurrence rate was 16.3% at 1 year and 37.7% at 5 years. The tumor progression rate was 2.3% at 1 year and 14.3% at 5 years.

According to the EORTC risk tables, we divided the patients into 3 groups to predict the possibility of recurrence; these were the low-risk, intermediate-risk, and high-risk groups. The Kaplan–Meier curves in Fig. 1 show significant differences among the 3 recurrence-free survival (RFS) levels ($P < .001$, log-rank test). For progression after TURBT, we also divided patients into 3 groups using the same risk tables (Fig. 2). The Kaplan–Meier curves also showed significant differences ($P < .001$, log-rank test).

The AUA risk stratification classified patients into 3 different risk levels, which were low-, intermediate-, and high-risk groups, irrespective of recurrence or progression. We evaluated them retrospectively. Patients were divided into 3 groups and the data were analyzed using Kaplan–Meier curves (Fig. 3), which showed significant differences among the 3 RFS levels ($P < .001$, log-rank test). We used a similar statistical method for progression

Table 3**Univariate analysis of both risk tables.**

Variable	Recurrence		Progression	
	HR	P value	HR	P value
Sex: male, female	0.917	.724	1.317	.469
Age: ≤ 65 y, > 65 y	1.339	.135	1.015	.962
Number of tumors: single, multiple	2.693	$< .001$	1.768	.077
Tumor size: < 3 cm, ≥ 3 cm	2.770	$< .001$	3.196	$< .001$
Tumor status: primary, recurrent	–	–	4.333	$< .001$
Primary, ≤ 1 rec/y, > 1 rec/y	3.139	$< .001$	–	–
T category: Ta, T1	2.984	$< .001$	5.570	$< .001$
Grade: G1, G2, G3	2.948	$< .001$	–	–
Grade 3: no, yes	–	–	4.725	$< .001$
Carcinoma in situ: no, yes	2.548	.003	7.341	$< .001$

HR = hazard ratio.

Table 4**Multivariate analysis of both risk tables.**

Variable	Recurrence		Progression	
	HR	P value	HR	P value
Number of tumors: single, multiple	1.770 (1.192, 2.629)	.005	1.142 (0.552, 2.361)	.720
Tumor size: < 3 cm, ≥ 3 cm	2.183 (1.480, 3.219)	$< .001$	2.725 (1.303, 5.696)	.008
Tumor status: primary, recurrent	–	–	2.720 (1.284, 5.760)	.009
Primary, ≤ 1 rec/y, > 1 rec/y	1.770 (1.340, 2.338)	$< .001$	–	–
T category: Ta, T1	1.685 (1.070, 2.654)	.024	3.112 (1.167, 8.300)	.023
Grade: G1, G2, G3	1.671 (1.168, 2.390)	.005	–	–
Grade 3: no, yes	–	–	2.709 (1.164, 6.302)	.021
Carcinoma in situ: no, yes	1.610 (0.846, 3.064)	.147	3.935 (1.678, 90229)	.002

HR = hazard ratio.

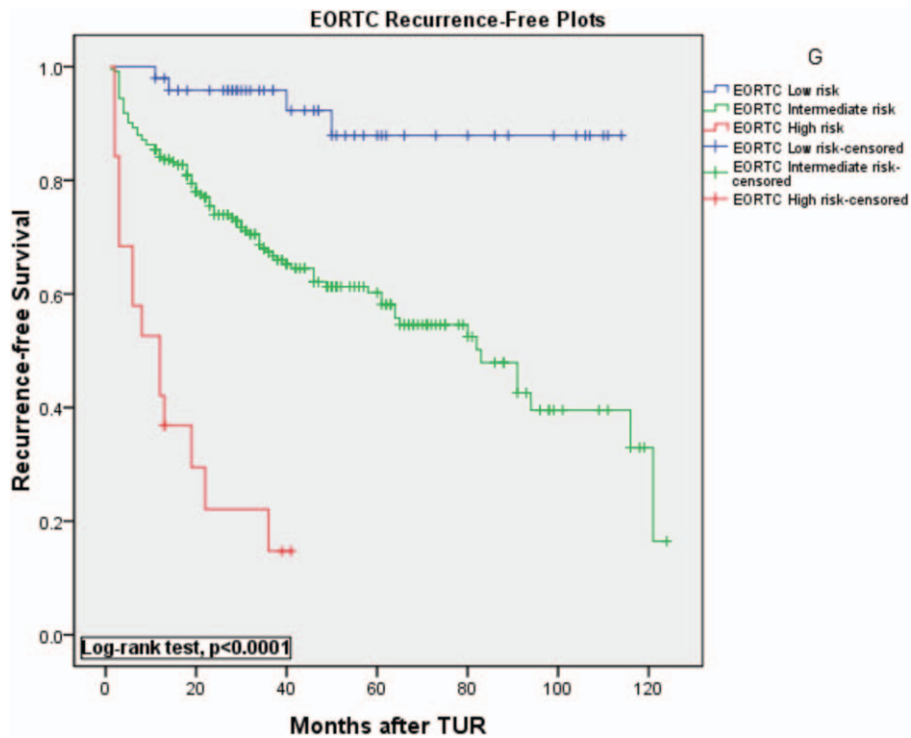


Figure 1. Recurrence-free plots of 3 different risks according to European Organization for Research and Treatment of Cancer (EORTC) risk tables.

evaluation and the Kaplan–Meier curves are shown in Fig. 4 ($P < .001$, log-rank test).

We compared the numbers of patients with the risk of recurrence in each group (Fig. 5). The numbers of patients in the

low-risk groups in both series were the same. However, the high-risk group was the largest group in the AUA series, while the EORTCs low-risk group was much smaller, which was all comprised in the AUAs high-risk group. For progression risk

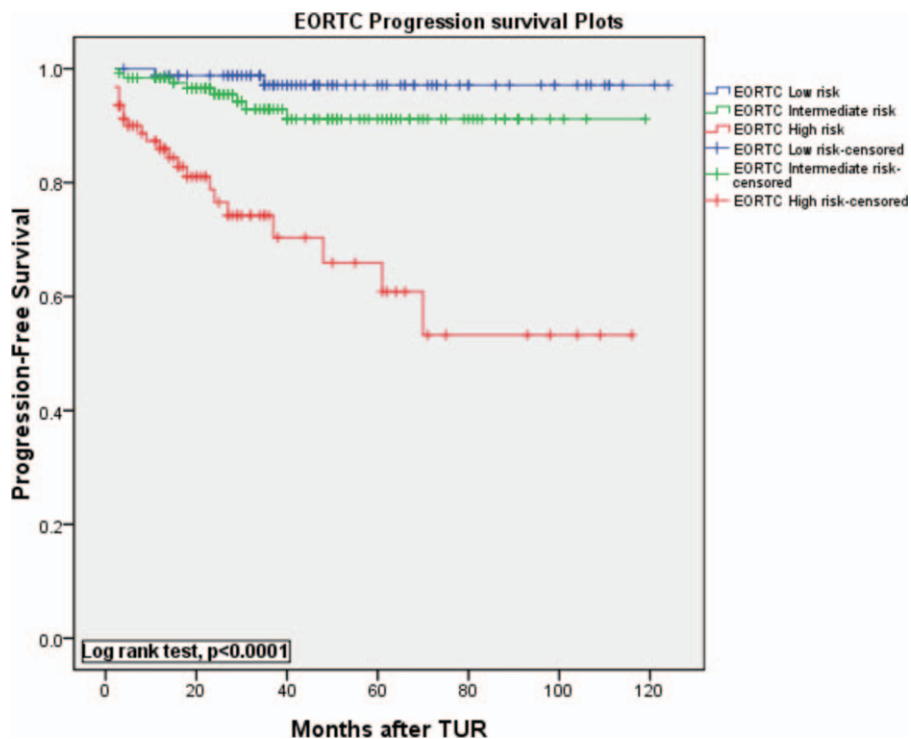


Figure 2. Progression-free plots of 3 different risks according to European Organization for Research and Treatment of Cancer (EORTC) risk tables.

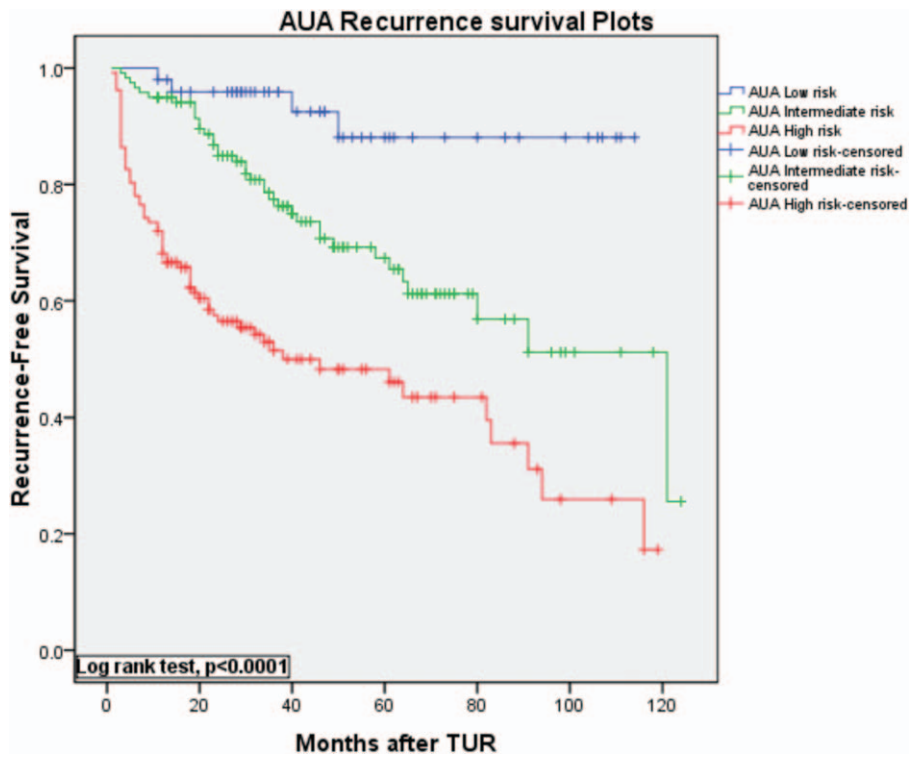


Figure 3. Recurrence-free plots of 3 different risks according to American Urological Association (AUA) risk stratification.

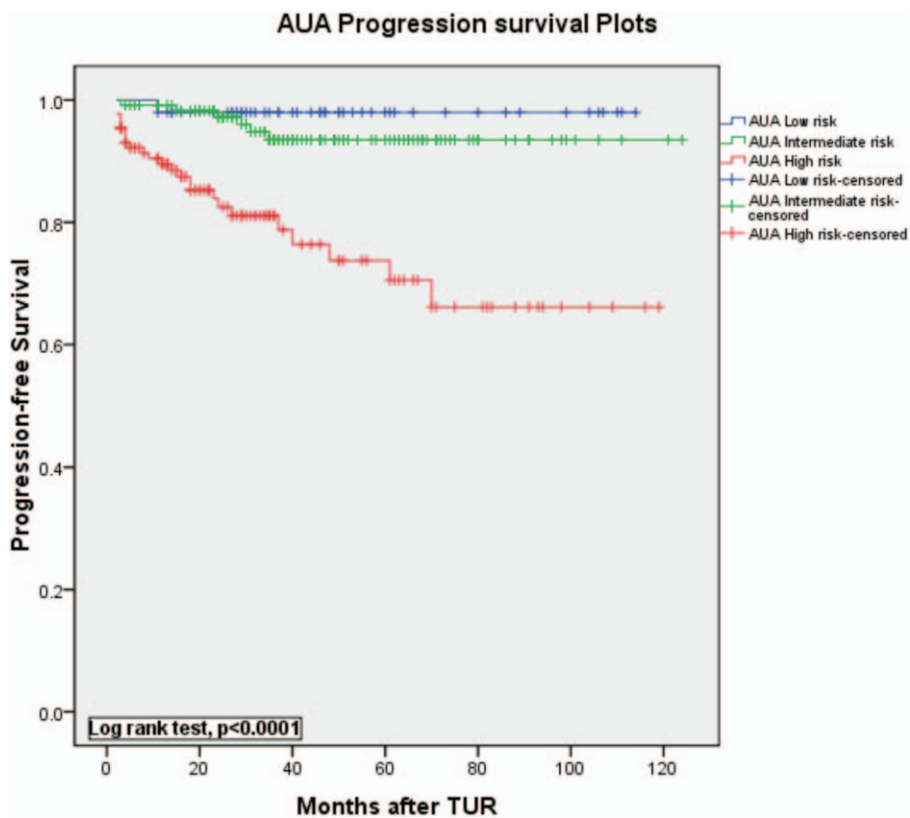


Figure 4. Progression-free plots of 3 different risks according to American Urological Association (AUA) risk stratification.

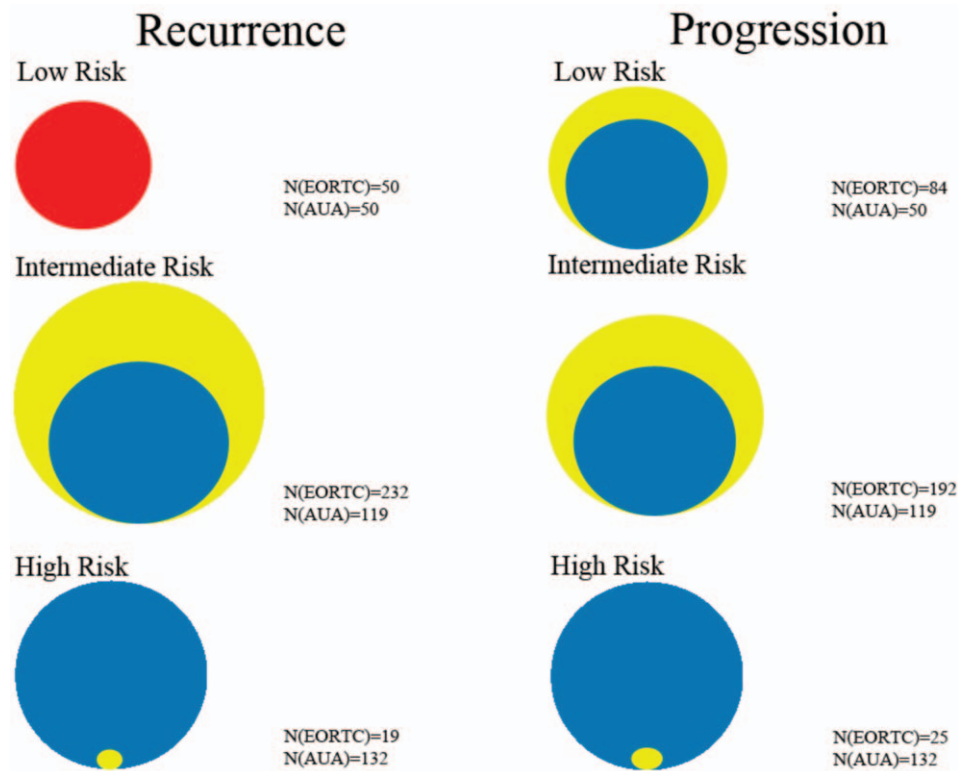


Figure 5. The numbers of patients in 3 risk groups according to both series for recurrence and progression.

(Fig. 5), the number of patients in the low-risk group of AUA risk stratification was less than that using the EORTC risk tables. The patients in the high-risk group of EORTC risk tables were included in the AUAs high-risk group. After that, we compared both series' high-risk patients further. The Kaplan–Meier curves in Figs. 6 and 7 showed significant differences between the 2 RFS levels ($P < .001$, log-rank test) and between the 2 progression-free survival (PFS) levels ($P < .001$, log-rank test).

4. Discussion

NMIBC shows diverse natural histories and prognoses.^[14] High recurrence and progression rates after surgery make BCa a serious public health problem.^[15] For NMIBC patients who have undergone their first TURBT, urologists require tools to accurately estimate the risk of recurrence and progression to recommend an individualized therapy. In our study, multivariate analysis indicated that the number of tumors, tumor size, tumor stage, tumor grade, and tumor status (primary vs recurrence) showed independent significance for predicting tumor recurrence, while tumor size, tumor stage, tumor grade, tumor status (primary vs recurrence), and concomitant CIS were associated with the risk of tumor progression. Some studies have reported a worse prognosis in patients with CIS and without any treatment; approximately 54% of patients with CIS progress to muscle-invasive disease.^[16,17] In our study, CIS was not an independent factor for predicting tumor recurrence, which may be because of the relatively small sample size in our cohort. Therefore, further study is required.

The EORTC risk tables and AUA risk stratification were made to guide future treatments by using factors that can easily be

applied clinically and provide several methods to predict the probability of NMIBC recurrence and progression. Some scholars report that EORTC risk tables are useful for predicting progression of NMIBC and it is essential to update new risk markers to improve risk classification and prediction of progression.^[18] Nevertheless, the Chinese Urological Association guidelines choose AUA risk stratification to manage NMIBC patients. Hence, our study aimed to determine which of these methods is better for Chinese patients with NMIBC. Neither of these models are perfect; however, to judge their applicability and performance in patients currently undergoing treatment, validation using external and contemporary datasets is important.^[19] The EORTC risk tables were based on the individual data of 2596 patients; intravesical therapy was performed for nearly 80% of them, which does not represent the real rate in clinical practice.^[20] Besides, the main limitations of the EORTC risk tables are that the majority of the patients were treated with older intravesical chemotherapy regimens and some other factors, such as immediate chemotherapy instillation and second TUR, were not considered.^[7,20,21] The predictive values of the EORTC risk tables are influenced by the factors mentioned above. Nonetheless, an EORTC model successfully stratified progression risks in a Brazilian cohort and was useful in predicting the progression of NMIBC.^[22] In addition, our previous study showed that EORTC risk tables could predict recurrence and progression in Chinese patients with NMIBC.^[9]

AUA risk stratification is a rather simple tool. While there are similarities between AUA and EORTC risk tables, it should be noted that they are not based on a meta-analysis or original studies, and instead represent the panel's consensus regarding the likelihood of recurrence and progression.^[10,11] Prior Bacillus Calmette–Guerin (BCG) intravesical therapy was under

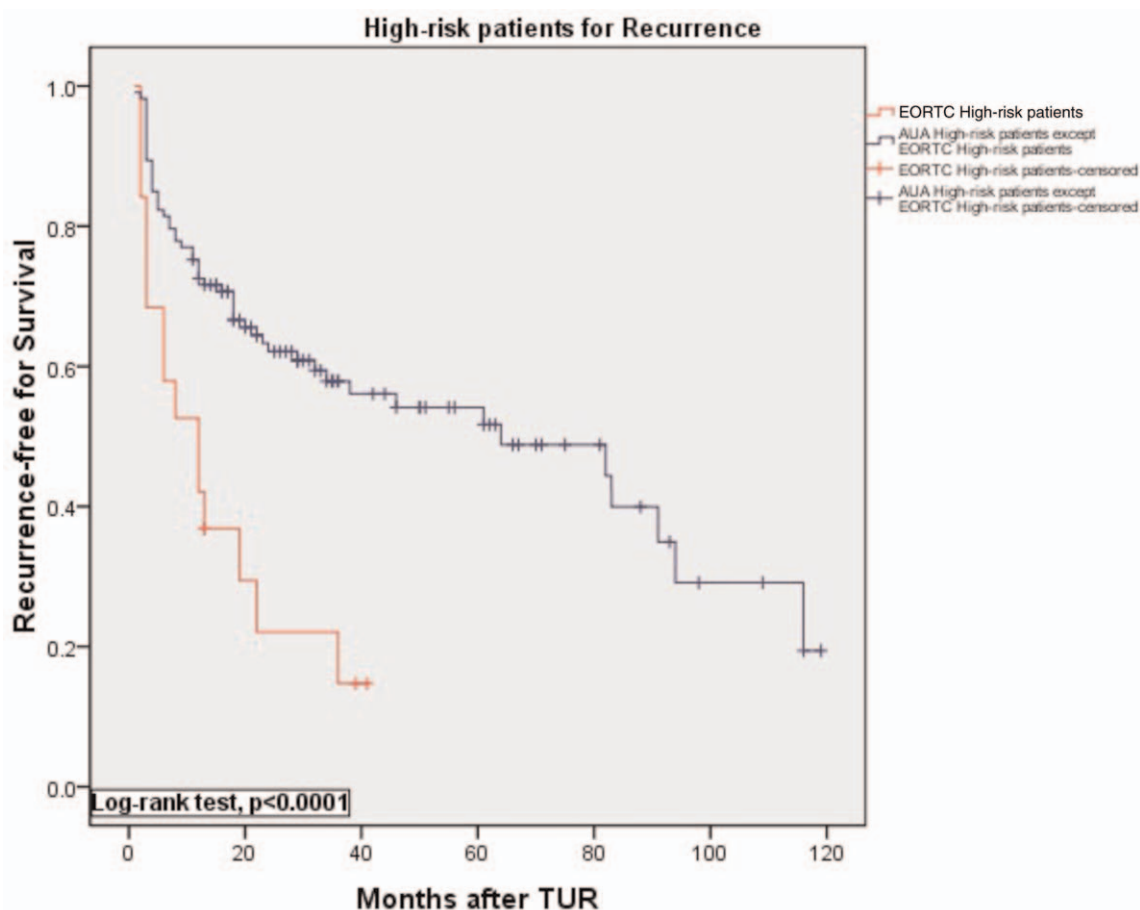


Figure 6. Recurrence-free plots of both 2 series in high risk group patients.

consideration in the AUA risk stratification because patients who have persistent or recurrent disease at 6 months following BCG therapy are at increased risk of disease progression.^[23] Similarly, patients who have an intermediate risk of progression and demonstrate BCG failure should be re-stratified into the high-risk group.^[10] AUA risk stratification seems more comprehensive than EORTC risk tables. However, it is necessary to determine which is more suitable for Chinese patients with NMIBC.

In this study, we found that EORTC risk tables and AUA risk stratification were both suitable for Chinese patients for recurrence and progression prediction. Kaplan–Meier curves showed significant differences among the 3 RFS and 3 PFS levels separately, showing that EORTC risk tables can predict tumor recurrence and prognosis of NMIBC patients. Similarly, AUA risk stratification can forecast tumor recurrence and prognosis of NMIBC patients. In both risk series, “high-risk” means that these patients are very likely to experience disease recurrence or progression.^[10,22] NMIBC is mainly treated with TUR and for patients with NMIBC, open radical cystectomy with urinary diversion or orthotopic neobladder formation has been considered.^[24] However, urinary tract reconstruction is a complex process that attempts to maximize health-related quality of life for patients after surgery.^[25] Whether NMIBC patients will develop muscle-invasive disease or not is hard to predict, so the identification of risk factors that will help to determine at an early stage should be a top research priority.^[20] High-risk patients should be classified as a priority, and

undergo more aggressive surgery, which may bring the patient maximum benefits.

The number of patients in both series with recurrence was assessed. For AUA, the high-risk group contains the largest number of patients; however, it was the smallest group in EORTC, and all patients were included in the AUAs high-risk group, meaning that EORTC risk tables are much stricter than AUA risk stratification in the selection of patients with a high risk of recurrence. Based on the patient numbers for progression, we can conclude that the number of patients in the low-risk group of AUA is smaller than that for EORTC. The high-risk group contained the smallest number of patients among the EORTC groups. However, for AUA, the high-risk group was the largest, and included all high-risk patients in EORTC risk tables, and the conclusion is similar: EORTC risk tables are much stricter than AUA risk stratification in terms of the selection of patients at a high risk of progression. There were significant differences in the RFS and PFS levels. We can conclude that the high-risk patients in EORTC risk tables have a worse prognosis than those in the AUA risk stratification; hence, EORTC is more efficient in the selection of high-risk patients. Therefore, high-risk patients in EORTC risk tables may need more aggressive treatment with regard to the second TUR, frequency of cystoscopic follow-up, adjuvant intravesical instillations, and even determining radical treatment in a timely manner to maximize the chances of bladder preservation and cancer control, while minimizing the risks of overtreatment with radical therapy.

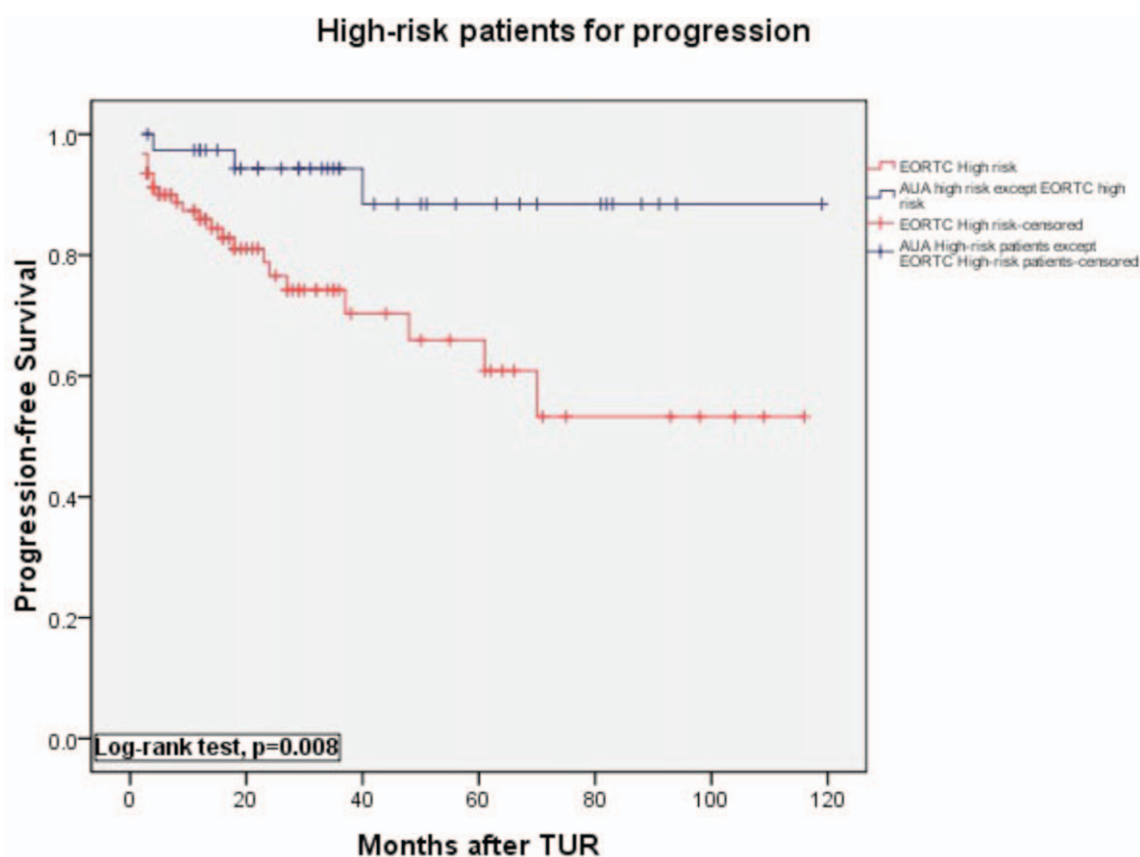


Figure 7. Progression-free plots of both 2 series in high risk group patients.

There are several limitations of our present study. Firstly, this is a retrospective study, and prospective data are required to verify our conclusion. Secondly, only 301 patients from a single institution were included in this study, which may not be completely representative of the characteristics of the Chinese population. Finally, we did not address any other potential sources of bias.

In conclusion, both EORTC risk tables and AUA risk stratification were able to predict recurrence and progression in NMIBC patients in our institution. However, EORTC risk tables are stricter, and AUA risk stratification is more sensitive in assigning patients into a high-risk group. In future studies, we plan to assess patients from several other institutions in China in order to represent characteristics of the Chinese patients. At the same time, we need to control bias.

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