Clinical Evaluation of Patients with Mixed Low-and-High Grade Non-muscle Invasive Bladder Cancer with EORTC Risk Scores

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Abstract

Background: To evaluate the recurrence and progression rate of patients with mixed low-and-high grade (MG) non-muscle invasive bladder cancer (NMIBC), and compare these outcomes with the European Cancer Research and Treatment Organization (EORTC) prognostic risk scores.

Methods: A retrospective analysis was performed based on the data from 68 MG NMIBC patients undergoing transurethral resection of bladder treatment (TUR-BT) from October 2013 to November 2018 in our hospital. The patients received intravesical treatment, and the follow-up protocols, including cystoscopy, ultrasound and urinary cytology, for the mean follow-up period of 33 ± 10.7 months. The patients were divided into 4 groups according to the EORTC risk scores, and the recurrence rate and progression scores of tumors in each group were calculated and compared with the estimated rates based on EORTC risk scores. The log-rank test and multivariable analysis were used to analyze the possible differences between the risk groups and to identify independent prognostic factors.

Results: Among the 68 patients, averagely 67.6 years (32-86 years), 42 patients were of Stage Ta and 26 were of Stage T1; the tumor recurrence was noted in 15 patients (22.1%), 11 as LG (low grade) and 4 as HG (high grade); and tumor progression in 4 patients (5.9%), 2 stages of progression. The Kaplan-Meier curve showed a real recurrence-free survival (RFS) difference rates between Group 1-4 and Group 5-9 ($P=0.0362 < 0.05$, log-rank test); while for Group 0, Group 2-6 and Group 7-13, the real progression-free survival (PFS) was statistically different ($P=0.0077 < 0.01$, log-rank test)✕

Conclusions: The pathology and clinical behavior of MG are “benign” prior to LG even if the patients did not receive overly aggressive intravesical instillations. The EORTC risk scores can be applied to the short-term prognostic assessment of recurrence and progression risk in MG patients of the cohort. However, the value and applicability of long-term prognosis assessment are to be confirmed in further studies in the future.

Introduction

Bladder cancer (BCa) is a heterogeneous disease with high prevalence and recurrence rates(1). Notably, the stage and grade of Bca play a very important role in prognostication and risk assessment of this disease, particularly non-muscle invasive bladder cancer (NMIBC)(2). Its clinical behavior is usually related to pathological grade(3). According to the classification of World Health Organization (WHO) 1973(4) and WHO 2016(5) which are recommended by European Association of Urology (EAU)(1), the differentiation of NMIBC tumor cells is classified into three levels, i.e. G1 (well-differentiated), G2 (moderately-differentiated), G3 (poorly-differentiated); or low malignant potential (PUNLMPs), low-grade (LG) and high-grade (HG) urothelial cancer. In recent years, researchers found that there is also the condition of mixed low and high grade (MG) Bca in NMIBC patients(6–9), about 5% of NMIBC(6), representing a patient group with unique clinical features. We conducted the systematic review of the treatment and prognosis of LG and HG, and found that most of the researchers focused on the MG’s

clinical behavior. Therefore, the close monitoring is required for the prognostic tools for MG. The Genito-Urinary Cancers Group, European Organization for Research and Treatment of Cancer (EORTC) developed a scoring system and risk scores for predicting the short- and long-term probabilities of disease recurrence and progression(2). To our knowledge, no effective prognostic tools for MG have been reported. In the study, a retrospective analysis was performed based on the data from 68 patients with Ta or T1 MG NMIBC from October 2013 to November 2018, and EORTC bladder cancer prognostic risk scores were used for grouping and validation.

Materials And Methods

Patients and study design

A retrospective analysis was performed on 68 subjects with Ta or T1 MG NMIBC from October 2013 to November 2018. One investigator was responsible for collecting data in the study and two pathologists reviewed the histological specimens. Pathologic staging was performed according to 2010 TNM system(10), and the grading was defined with 2016 WHO/ISUP grading system(5). The following data were collected: (i) Patient demographics; (ii) Tobacco use; (iii) Number of tumors, tumor size, carcinoma in situ (CIS) concomitant, tumor grade, T stage, recurrence; (iv) Intravesical therapy; (v) surgery approach; and (vi) Recurrence, progression and survival after surgery. The largest tumor dimension indicated in the pathologic gross description was adopted as the tumor size. Multifocality was assessed based on the number of specimens in the macroscopic pathology reports. According to 2016 WHO classification, only G2 grade may contain both LG and HG, so we classified the tumor grade of MG patients into G2 stage in the statistics. In our study, a tumor was designated as MG when LG and HG elements were both present in the same lesion, but less than 50% of it was HG; and the tumor was considered HG when more than 50% of the tumor was HG. The reason why the cutoff was 50% was that prior research suggested a difference in prognosis between HG-containing tumors with high “primary grade” and those with low “primary grade”(11). The inclusion criteria of eligible patients are as follows: (I) Patients received transurethral resection of bladder treatment; and (II) Patients had Ta/T1 urothelial cancer according to 2010 TNM system. The exclusion criteria are as follows: Patients had squamous or other pathological types of bladder tumors, or patients underwent radiotherapy and/or chemotherapy for non-urothelial tumor during the study period and incomplete follow-up.

The patients were verified with the intravesical treatment upon inclusion to the study and during the follow-up period, and were classified into 2 categories: patients with primary, solitary, TaG1 (PUNLMP), LG, < 3 cm and no CIS used immediately after instillation of epirubicin; and patients using epirubicin for 1 year, because patients with MG did not receive instillation treatment of BCG at that time in China.

The follow-up was conducted according to 2019 EAU guidelines and was risk adapted according to EORTC risk scores(1). Cystoscopy, ultrasound and urinary cytology were used for all patients. The recurrence was defined as reappearance of any disease, and the progression was defined as: (i) Any increase in grade to high grade (> 50% high grade), including development of CIS; (ii) Histologic

confirmation at tumor stage T2 to T4 (progression to muscle-invasive tumor stage or tumor metastasis was found). The patients were divided into 4 groups according to the EORTC recurrence and progression prediction risk scores. Six parameters were analyzed: tumor grade, size, and number, pT stage, previous recurrence rate, and carcinoma-in-situ. The time to progression, risk score, and progression probabilities were calculated and compared with the probabilities obtained from the EORTC model.

Statistical Analysis

All statistical analyses were performed using SPSS version 21.0. The multivariate analysis (Cox regression models) was built for study of the recurrence rate and progression scores of tumors in each group. Combined with the RFS and PFS data, Kaplan-Meier method was applied for univariate survival analysis (Log-rank test), and survival curves were plotted. Statistically significant difference was defined as $P < 0.05$.

Results

Patient characteristics

A total of 56 men (82.4%) and 12 women (17.6%) were included in our study, with the median age of 67 years (32–86 years). The mean follow-up duration was 33 months (12–73 months), and 2 patients (2.9%) died of tumor. The clinical data of all the patients, including sex, tobacco use, number of tumors, tumor size, prior recurrence rate, tumor T stage (Ta or T1), tumor grade, and presence of concomitant carcinoma in situ (CIS), respectively, is shown in Table 1. In addition, among 68 patients with MG, the tumor recurrence was noted in 15 patients (22.1%), 11 as LG and 4 as HG; and tumor progression noted in 4 patients (5.9%), 2 stages of progression. In this subgroup of patients, the most significant characteristics related to progression were pTa stage (61.8%), size of tumor < 3 cm (54.4%) and primary tumors (80.9%).

Applicability of the EORTC risk scores in our cohort

We compared variables in the EORTC risk scores, with the results of multivariate analysis shown in Table 2. The tumor size, number of tumors, tumor grade, T category, and prior recurrence rate were associated with a higher recurrence risk after TURBT. Meanwhile, the variables proven to be predictive to the progression risk were tumor size, prior recurrence rate, CIS, T category, and tumor grade.

Comparison of the use of EORTC risk scores in MG patients with NMIBC

We used EORTC risk scores to classify 68 patients into different risk groups and compared them with their actual prognosis. Among the 68 patients in the study, the probabilities of recurrence and progression rates stratified by risk group obtained in our series at Year 1 were compared with those reported by Sylvester et al (Table 3). Based on EORTC risk scores, we divided the patients into 4 groups for predicting the possibility of recurrence and progression: Group 0, Group 1–4, Group 5–9, and Group 10–17; and

Group 0, Group 2–6, Group 7–13, and Group 14–23. The data were different from the predicted scores with EORTC risk scores, and were evaluated retrospectively. The 1-year recurrence rates of the patients were lower than the values presented in EORTC risk scores, mainly in Group 1–4 (11.5% vs 24.0%), and Group 5–9 (31.3% vs 38.0%), except for the 1-year recurrence rate of the group with scores of 0 and 10–17, with no case of recurrence. However, the 1-year progression rates of the patients were higher than the values presented in EORTC risk scores, mainly in Group 0 (5.0% vs 0.2%), Group 2–6 (6.3% vs 1.0%), and Group 7–13 (6.3% vs 5.0%), except for the 1-year progression rate of the group with scores of 14–23, with no case of progression. Then we further compared MG patients in both series. Kaplan–Meier curves in Fig. 1 show the significant differences among the 2 recurrence-free survival (RFS) levels ($P = 0.0362 < 0.05$, log-rank test). For progression after TURBT, we used a similar statistical method. Kaplan–Meier curves in Fig. 2 also showed significant differences among the 3 progression-free survival (PFS) levels ($P = 0.0077 < 0.01$, log-rank test).

Table 1
Patient characteristics and outcomes for MG urothelial carcinoma cohort

Variables	Present series, numbers, %
Sex	56 (82.4)
Male	12 (17.6)
Female	
Tobacco use	
Yes	38 (55.9)
No	30 (44.1)
Tumor size(cm)	
<3	37 (54.4)
≥3 cm	31 (45.6)
Number of tumors	
1	64 (94.1)
2–7	4 (5.9)
≥8	0
Prior recurrence rate	
Primary	55 (80.9)
Recurrent, < 1 rec/y	13 (19.1)
Recurrent, > 1 rec/y	0
Carcinoma in situ	
No	67 (98.5)
Yes	1 (1.5)
Tumor stage	
Ta	42 (61.8)
T1	26 (38.2)
Tumor grade	
G1	0
G2	68 (100)

Variables	Present series, numbers, %
G3	0
Recurrence	
Yes	15 (22.1)
No	53 (77.9)
Progression	
Yes	5 (7.4)
No	63 (92.6)
Grade progression	2(3.0)
Stage progression	2(3.0)
Survival	2 (2.9)
Died	66 (97.1)
Alive	
Death by malignance	2 (2.9)

Table 2
Multivariate analysis of both risk scores.

Variable	Recurrence		Progression	
	HR	P Value	HR	P Value
Number of tumors: single, multiple	1.678 (1.264,2.536)	0.004	1.039 (0.721, 1.699)	0.362
Tumor size: <3 cm, ≥ 3 cm	1.954 (1.531,2.425)	0.005	1.955 (1.287,2.464)	0.002
Tumor status: primary, recurrent	-	-	2.508 (1.548,3.397)	0.013
Primary, 1 rec/y, > 1 rec/y	1.769 (1.264, 2.244)	< 0.001	-	-
T category: Ta, T1	1.597 (1.124, 2.067)	0.002	2.878 (1.957, 4.035)	0.032
Grade 2: no, yes	-	-	2.532 (2.047, 3.146)	0.012
Carcinoma in situ: no, yes	1.426 (0.933, 2.758)	0.238	2.134 (1.596, 2.890)	< 0.001
HR = hazard ratio.				

Table 3
Probability of recurrence according to total score in EORTC and study Groups of Year
1

Recurrence score	No. of patients	Study Group	EORTC
0	0	0	15.0(10.0–19.0)
1–4	52	11.5(2.6–20.5)	24.0(21.0–26.0)
5–9	16	31.3 (5.7–56.8)	38.0(35.0–41.0)
10–17	0	0	61.0(55.0–67.0)
	68	16.2 (7.2–25.2)	

Discussion

For recurrence and progression, their most important prognostic factors are the number, size, the prior recurrence rate, T category, grade, and CIS' presence of tumors, these factors represent the biological aggressiveness of Bca (2). Furthermore, NMIBC shows quite diverse natural histories and prognoses(12). Previous studies have identified tumor grade to be one of the most important prognostic factors for recurrence or progression of NMIBC(3).

In pathology, the grade of the tumor is determined by the highest pattern even it is a small focus(13). Even though the 1973/2016 version of the WHO and ISUP system classification provide the clear histological diagnostic criteria for each diagnostic classification, Knowles et al(14)found that the condition of MG also existing in patients with urothelial carcinoma. Cheng et al(11)also found that about one-third of the 164 patients with Ta urothelial carcinoma had more than one histological grade. The reason for this phenomenon may be related to the activation of the two pathways in the same bladder, generating a mixed tumor or tumors with LG plus HG histology, including FGFR3 mutation in Ta tumors and p53 and Rb pathway alterations in muscle-invasive tumors(14). Therefore, it is difficult for pathologists to determine MG heterogeneity(14). However, the heterogeneity in the pathology and clinical behavior of bladder tumors presents significant problems in evaluation at diagnosis and in longer term clinical management.

To date, researchers have reported several studies on systematic evaluation of the incidence and clinical significance of MG tumors., and they had different opinions on this issue(6–9). They defined the biological aggressiveness of MG by comparing the recurrence and progression rates with LG and HG in NMIBC. Gofrit et al(6)first reported that the clinical course of patients with MG tumors parallels to that of patients with LG tumors (about 5% of patients with non-muscle invasive tumors). They explained that the major LG component dictated the postoperative clinical course and not the minor early HG component, but these patients all received the aggressive treatment of induction and maintenance instillations of BCG. Therefore, such results are controversial. Schubert et al(9)reported that MG exhibits a significantly better response profile to intravesical BCG therapy compared to HG. Such researchers thought that it may

be better to allow for a safe reduction in the use of toxic BCG regimens for MG patients, and it may be useful to consider grade heterogeneity in the development of new risk stratification systems for NMIBC. However, in the above studies of MG, a tumor was designated as MG when LG as well as HG elements were present in the same lesion but less than 10% or 50% of it was HG. Mai et al(7) thought that these sections diagnostically challenging and are wrongly assigned a high grade since this determines prognosis. As a result, the clinician's judgment on the prognosis and the subsequent treatment may be improper.

At the molecular level, while several molecular markers for the development, recurrence and progression of bladder cancer, such as p53 and Rb, have been studied(15–17), the limited value of these established prognostic markers called for prediction tools of Bca outcomes. In order to test the molecular markers, it is a expensive and complicated process and takes a long time; and the accuracy and reliability are to be confirmed in clinical research.

The American Joint Committee on Cancer (AJCC) TNM staging system(10) has been used widely to predict the risk of disease recurrence in patients treated with radical cystectomy (RC). However, this system has been shown to be less accurate at prediction when incorporating several clinical variables. Apart from standard oncologic features, BCa patients are generally elderly and have significant comorbidities, so it's needed to do competing-risk analyses to choose individualized therapies (18). EORTC scoring system was based on the follow six most relevant clinical and pathologic predictors of outcomes: tumor stage and grade, number of tumors, tumor size, concomitant CIS, and history of prior disease recurrence (2). EORTC risk scores were used to externally evaluate the risk of recurrence and progression for patients who undergo TURB and recommended by international guidelines(1). However, external validation of this risk score in MG patients is still required. The purpose of the present study was to evaluate the prognosis of patients with MG NMIBC and to validate the feasibility of EORTC risk scores.

In our study, the mean follow-up period was slightly shorter than the original data of Reis et al (33 vs. 39.7 months). Reis et al(8) also estimated the risk of recurrence-free survival and progression-free survival on the basis of a single institution of 31 patients with a history of LG, MG, HG NMIBC. The recurrence-free survival was (22.1 vs 45.2%) and progression-free survival was (5.9% vs 0). However, the rates of grade progression of our cohort were (3.0% vs 12.9%) and stage progression (3.0% vs 0). Our study revealed that MG patients had lower rate of recurrence and grade progression while the rate of stage progression was higher as compared with the previous studies. The main reason for the slightly higher stage progression rate might be the intravesical treatment consisting of bacillus Calmette-Guérin (BCG) in their study. However, as seen from the data, MG patients had a better prognosis even if they did not receive overly aggressive treatment. Reis et al also found that the recurrence rate and progression rate of LG and HG were 53.8%, 6.7% and 36.1%, 36.1%, respectively. Compared with LG and HG, the recurrence and progression rates of MG in our cohort were lower. The reason might be that the main component of the tumor was LG and the invasive part of the tumor was HG. The results further illustrated that the pathology and clinical behavior of MG is benign.

In our study, the tumor size, number of tumors, tumor grade, T category, and prior recurrence rate were associated with a higher recurrence risk after TURBT. Meanwhile, the variables proven to be predictive to progression risk were tumor size, prior recurrence rate, CIS, T category, and tumor grade. It has been reported that 54% patients with CIS and without any treatment would progress to muscle-invasive disease(19). According to our study, CIS was not an independent factor for predicting tumor recurrence, possibly due to the relatively small sample size in our cohort. Therefore, further study is required in the future.

In this study, we found that EORTC risk scores are suitable for MG patients for recurrence and progression prediction. Kaplan–Meier curves showed significant differences among the 2 RFS ($P = 0.0362 < 0.05$, log-rank test) and 3 PFS ($P = 0.0077 < 0.01$, log-rank test) levels separately, demonstrating that EORTC risk scores is predictive to tumor recurrence and prognosis of MG patients. These results are consistent with previous research by Wang et al(20), who reported that EORTC risk scores were better for predicting recurrence and progression in Chinese patients with NMIBC. The results of our study showed that the short-term recurrence rate of bladder cancer is basically consistent with the EORTC system. However, the recurrence rate in each group of short-term recurrence is lower than the average value of the expected recurrence rate, because the effect of intravesical treatment in preventing tumor recurrence is fully reflected, which further reduces the recurrence rate. We can conclude that EORTC risk scores are predictive to the short-term prognosis of MG is of significance to some extent. As for the patient number with progression, the number of patients in the MG group is higher than that for EORTC risk scores. Therefore, high-risk patients in EORTC risk scores may need more aggressive treatment with regard to the adjuvant intravesical instillations of bacillus Calmette-Guérin, and even determining RC in a timely manner to maximize the chances of bladder preservation and cancer control. EORTC risk scores have some limitations in predicting the prognosis of MG, because postoperative intravesical instillations is difficult to be uniform, thus affecting the accuracy of the prognostic judgment of the system.

There were several limitations in our study:(i) This study is a retrospective study with a single center and limited sample size, so further prospective studies are needed to validate the reliability of the predictions; (ii) We classified the tumor grade of MG patients into G2 stage in the statistics. As a result, there were no patients in Group 0 and Group 10–17 in the recurrence cohort and Group 14–23 in the progression cohort, affecting the accuracy of the risk scores for the prediction to some certain extent, and causing certain bias; (iii) Due to the shorter follow-up period, only one-year recurrence rate and progression rate were compared; (iv) Study cases were limited in a subgroup of MG with no cases of LG and HG, lacking of single-center LG and (or) HG cases for the controlled study.

Conclusion

The EORTC model was successfully used for stratifying recurrence and progression risks in our MG cohort, with certain significance for guiding clinicians to choose a treatment plan. The clinical course of MG is “benign” than that of patients with LG tumors, which suggests a mild intravesical instillations

available for MG patients. However, the long-term value and feasibility are to be confirmed in further studies in the future.

Abbreviations

MG: mixed low and high grade, NMIBC: non-muscle invasive bladder cancer, WHO: World Health Organization, EORTC: European Cancer Research and Treatment Organization, TUR-BT: transurethral resection of the bladder treatment, RFS: recurrence-free survival, PFS: progression-free survival, BCa: bladder cancer, LG: low grade, HG: high grade, CIS: carcinoma in situ

Declarations

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Not applicable.

Authors' contributions

JTL, HYL and YL designed the conception, collected data, carried out statistical analysis, and drafted the manuscript. GL, MXW and YJN contributed to the conception, acquisition of data, drafted the manuscript, and provided critical revision of the manuscript. JTL and YL made substantial contributions to analysis and interpretation of data; GL and YJN contributed to the conception, design, acquisition of data, data analysis, and drafted the manuscript, and provided critical revision of the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets are available from the corresponding authors on reasonable request.

Ethics approval and consent to participate

This study was approved by an independent ethical committee/institutional review board of the Second Hospital of Tianjin Medical University, Tianjin, China. Written informed consent was obtained from all participants.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

Figure 1

Plot of recurrence-free survival of 2 different risks according to EORTC risk scores

Figure 2

Plot of progression-free survival of three different risks according to EORTC risk scores.