Original Article

Progression and Prognostic Factors of T1 High-Grade Non-Muscle Invasive Bladder Cancer, 10-Year Follow-Up at Ramathibodi Hospital

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Background: T1 high-grade non-muscle invasive bladder cancer has a high recurrence rate and progression. The treatment options have some controversy.

Objective: To evaluate the progression of T1 high-grade non-muscle invasive bladder cancer in Ramathibodi Hospital and determine the prognostic factors that contribute to muscle invasive disease.

Materials and Methods: The authors retrospectively reviewed 70 patients diagnosed as T1 high-grade bladder cancer from 1,270 bladder cancer patients in Ramathibodi Hospital between 2007 and 2017. The primary objective was to evaluate the progression rate and related prognostic factors. The authors analyzed the risk factors contributing to the progressive muscle invasive disease. The authors also analyzed the survival rate between the progressive group and the non-progressive group. Finally, the role of early cystectomy in T1 high-grade bladder cancer was also analyzed.

Results: The mean age was 68 years old and the mean follow-up time was 40.1 months. The recurrence rate was 55.7% (39/70). The risk factors of recurrence were no muscle at the initial tumor resection and history of intravesical BCG instillation before diagnosis of T1 high-grade cancer. The progression rate was 14.3% (10/70). There was no significant risk factor contributing to progressing the disease. The median survival of non-progressive group was 45.2 months and progressive group was 18.2 months (p=0.002). The authors performed early radical cystectomy in 14 patients and there was no difference in overall survival between the non-progressive disease group and the early cystectomy group.

Conclusion: Lack of muscle at the initial resection and prior intravesical BCG instillation were the risk factors of the recurrence of T1 high-grade bladder cancer. It is obvious that progressive disease is the strongest impact on survival and early radical cystectomy does not improve survival if it was the non-progressive disease. Further studies are needed to identify the risk factors that can differentiate between non-progressive and progressive disease.

Keywords: T1 high-grade non-muscle invasive bladder cancer, Progression, Early radical cystectomy

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Bladder cancer is the ninth most common cancer in the world[1]. It can categorize into two groups, non-muscle invasive and muscle invasive. Non-muscle invasive bladder cancer includes stage Ta, T1, and carcinoma in situ (CIS), based on the 2010 American Joint Committee on Cancer staging seventh edition[2].

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Standard treatment of non-muscle invasive bladder cancer is transurethral resection of bladder tumor with or without adjunctive intra-vesical therapy such as mitomycin C or bacillus Calmette-Guérin (BCG)[3]. However, recent studies reported that T1 high-grade cancer has high recurrence and a fast progression rate. Progression rate ranges from 30% to 50%[4,5]. Therefore, Herr et al[6] proposed that early radical cystectomy would significantly improve cancer specific survival. However, this treatment option comes with high morbidity during surgery compares to standard transurethral resection of bladder tumor (TUR-BT) and probably lower quality of life[6].

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Table 1. Baseline characteristics

Variable	Total (n = 70) n (%)	Variable (continued)	Total (n = 70) n (%)
Sex		Progression	
Male	53 (75.71)	No	60 (85.71)
Female	17 (24.29)	Yes	10 (14.29)
Age (year), Mean±SD	68.0±10.4	Postoperative intravesical BCG	
Previous intravesical BCG		No	34 (48.57)
No	65 (92.86)	Yes	36 (51.43)
Yes	5 (7.14)	BCG maintenance	
Tumor multiplicity		No	33 (47.14)
Single	37 (52.86)	≤6	21 (30.00)
Multiple	33 (47.14)	>6	16 (22.86)
Tumor size (cm), Median (range)	2 (0.5 to 6)	Radical cystectomy	
Tumor size		No	48 (68.57)
<3 cm	42 (60.00)	Yes	22 (31.43)
≥3 cm	28 (40.00)	Early cystectomy	
Morphology		No	8 (36.36)
Papillary	52 (74.29)	Yes	14 (63.64)
Sessile	18 (25.71)	Dead	
Muscle layer included		No	58 (82.86)
No	25 (35.71)	Yes	12 (17.14)
Yes	45 (64.29)	Time to recurrent (month), Median (range)	12.3 (1.7 to 141.3)
Repeat TUR-BT		Time to progress (month), Median (range)	17.3 (12.8 to 47.1)
No	49 (70.00)	Time to dead (month), Median (range)	27.9 (2.0 to 62.6)
Yes	21 (30.00)	Follow-up time (month), Median (range)	40.1 (2.0 to 252.8)
Recurrence			
No	31 (44.29)		
Yes	39 (55.71)		

SD=standard deviation; BCG=bacillus Calmette-Guérin; TUR-BT=transurethral resection of bladder tumor

There is inadequate evidence of the prognosis of T1 high-grade non-muscle invasive bladder cancer in Thailand. The variability in progression rate in the literature[5,7,8] made the authors curious about the progression rate in our institution. To optimize oncological outcomes and quality of life of the patients, the authors tried to find the risk factor contributing to disease progression and time of disease progression.

Materials and Methods

The authors retrospectively database-reviewed 70 patients diagnosed as T1 high-grade non-muscle invasive bladder cancer from 1,270 cases of bladder cancer in Ramathibodi Hospital between April 2007 and April 2017. The exclusion criteria were the patients who had incomplete tumor resection, patients with another primary cancer, patients with concomitant upper tract urothelial cancer, patients with non-urothelial cancer, patients with kidney transplantation, and incomplete data.

The grade and T stage were determined by pathologists using the 2004 World Health Organization classification of non-invasive papillary urothelial tumors and the 2010 American Joint Committee on Cancer staging, respectively[2,9]. The progression was defined as recurrent tumor that progressed to stage II or more after complete resection or had lymph node or distant metastasis. The present study collected demographic data, overall survival, progression rate, tumor morphology, tumor number, tumor size, and post-operative adjunct intravesical therapy.

The primary objective was to evaluate the progression rate and related prognostic factors. The

Table 2. Univariate and multivariate analysis of the recurrent risk factor

Variables	Univariate		Multivariate	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Sex				
Male	1			
Female	1.074 (0.52 to 2.21)	0.846		
Age (years)				
≤65	1			
>65	0.832 (0.43 to 1.58)	0.578		
Previous intravesical BCG				
No	1		1	
Yes	3.384 (1.25 to 9.14)	0.016	3.277 (1.21 to 8.87)	0.019
Morphology				
Papillary	1			
Sessile	1.205 (0.59 to 2.43)	0.603		
Muscle layer included				
Yes	1		1	
No	1.928 (1.02 to 2.43)	0.045	1.894 (1.00 to 3.59)	0.049
Postoperative intravesical BCG				
No	1			
Yes	0.915 (0.48 to 1.74)	0.785		

HR=hazard ratio; CI=confidence interval; BCG=bacillus Calmette-Guérin

authors analyzed the risk factors of progressive disease and survival between progressive group and non-progressive group. The role of early cystectomy in T1 high-grade bladder cancer was also analyzed.

Statistical analysis

Baseline characteristics were compared using the Student's t-test for continuous variables and Chi-square or Fisher's exact tests for categorical variables. Survival curves were plotted using the Kaplan-Meier method and compared by the log-rank test. Multivariate analysis was used to identify independent prognostic variables using a stepwise Cox proportional hazards regression model. Statistics were analyzed by using Stata version 14. Statistics were significant with p-value less than 0.05 with 95% confidence intervals (CIs).

Results

The study included 70 patients diagnosed as T1 high-grade bladder cancer in Ramathibodi Hospital. The mean age was 68 years old. Patients were predominant male (75.71%). The median follow-up time was 40 months, ranging from 2 to 258 months. The present study found the recurrence rate and progression rate were 44.29% and 14.29%, respectively. Twelve patients died during the follow-up period. Fourteen cases had early radical cystectomy, of which six cases were refractory to initial intravesical therapy, three cases were high grade disease in bladder diverticulum, three cases where patients chosed early radical cystectomy after thoroughly counselling, and the last two cases were high grade disease with lymphovascular invasion. Baseline characteristics are shown in the Table 1.

There were thirty-nine recurrences. The authors analyzed the prognostic factors that contributed to recurrence using univariate and multivariate analyses. In univariate analysis, previous intravesical BCG and the absence of muscle in the first transurethral resection specimen were significantly related to the recurrence of tumor (p=0.016 and 0.045, respectively). These two factors were also significant positive in multivariate analysis (p=0.019 and 0.049, respectively). The Hazard ratio was 3.277 for previous intravesical BCG and 1.894 for no muscle in TUR-BT

Table 3. Univariate and multivariate analysis of the progression risk factor

Variables	Univariate		Multivariate	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Sex				
Male	1			
Female	0.654 (0.14 to 3.08)	0.592		
Age (year)				
≤65	1			
>65	0.997 (0.28 to 3.53)	0.996		
Previous intravesical BCG				
No	1			
Yes	1.328 (0.17 to 10.49)	0.788		
Morphology				
Papillary	1			
Sessile	0.649 (0.14 to 3.06)	0.586		
Muscle layer included				
Yes	1			
No	1.742 (0.50 to 6.02)	0.381		
Recurrence				
No	1			
Yes	1.536 (0.39 to 5.95)	0.534		
Postoperative intravesical BCG				
No	1			
Yes	0.579 (0.16 to 2.05)	0.398		
Dead				
No	1			
Yes	12.446 (3.37 to 45.93)	<0.001	9.192 (2.36 to 35.79)	0.001
Radical cystectomy				
No	1			
Yes	10.440 (2.20 to 49.44)	0.003	7.847 (1.59 to 38.49)	0.011

HR=hazard ratio; CI=confidence interval; BCG=bacillus Calmette-Guérin

specimen. The detail of other interesting factors are shown in Table 2.

Ten patients progressed to muscle invasive bladder cancer (14.3%). The mortality rate was also significant higher in the progression group (10% versus 60%). However, the univariate and multivariate analyses showed no significant risk factor that contributed to progression. The univariate and multivariate analyses are shown in Table 3.

The authors analysed overall survival and plotted in Kaplan-Meier graph. The survival was not different when compared between the recurrent and non-recurrent patients (p=0.765) as shown in Figure 1a. However, the survival in the progression group was poorer than non-progression group (log rank test p<0.001) (Figure 1b). The 5-year survival in the progression group was 43.75% compare to 84.73% in the non-progression group. Mean time to progression was 17.3 months. The authors performed early cystectomy in 14 cases. The survival in early cystectomy group was comparable with the non-progression group and better than the progression

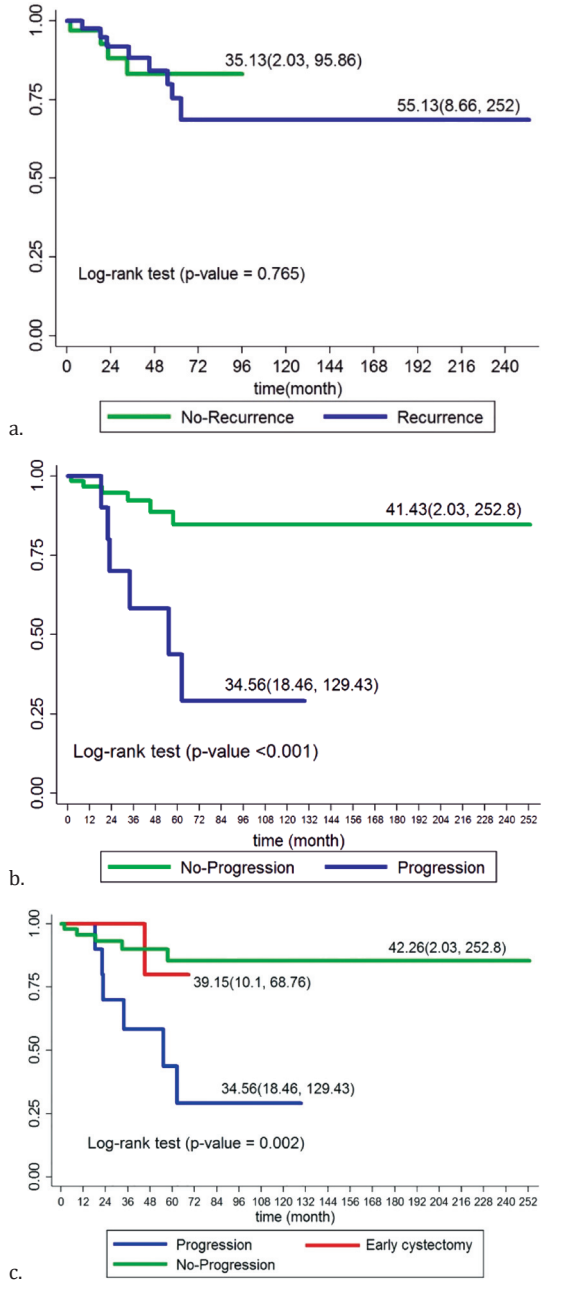

Figure 1. Overall survival: (a) recurrent versus non-recurrent group, (b) progression versus non-progression group, (c) progression versus non-progression versus early radical cystectomy.

group (Figure 1c).

Discussion

The incidence of T1 high-grade non-muscle invasive bladder cancer was 20%[10]. This tumor has a chance of aggressive behavior in some patients and the treatment is still controversial. The authors still performed the transurethral resection as the first line treatment just like the low grade disease, but it has additional risk for incomplete resection or disease progression. Early radical cystectomy is widely adopted to ensure the highest oncological outcome, but it comes with higher morbidity and lower quality of life.

The recurrence of T1 high-grade in Ramathobodi Hospital was 55.71%. This number was consistent with Montironi et al[4] that the recurrent rate ranges between 55% to 58%. The progression rate of T1 high-grade ranges from 27% to 61%[4,5]. The variance in the percentages of recurrence and progression in each study indicates that the research of T1 high-grade disease needs to be refined in the future, but most of the updated data shows that the incidence of progression is 15%[8]. In the present study, the progression was 14.3%, consistent with the other recent study. If the progression rate was not that high as in the old literature, non-invasive treatment of T1 high-grade tumor is probably more suitable than radical surgery in terms of oncological outcomes and quality of life of the patients.

In the present study, the recurrence rate was higher in the patients history of intravesical BCG instillation. However, this does not imply that intravesical BCG is a risk factor of tumor recurrence or intravesical BCG fails to prevent tumor recurrence. Only 51.43% of the patients in study received BCG instillation. The number of patients were quite low because BCG was out of stock due to manufacturing process many times in the past 10 years. Furthermore, some patients had intravesical BCG due to other indications such as recurrent low grade or multiple lesions before clinical progression to T1 high-grade disease. Some patients had disease recurrence before full course of intravesical BCG instillaton. Therefore, the authors believe that the patients who received intravesical BCG had high chance of disease recurence because of the aggressive nature of their tumor, whereas the patients who did not receive intravesical BCG may have a tumor that is less aggressive. This is the possible explanation for high recurrence rate after intravesical BCG instillation in the present study.

The survival is much poorer in the progression group, which is the same as reported in other clinical studies[5,7,8]. If the authors could find the patients that will progress to muscle invasive bladder cancer, the number of unneccessary radical cystectomy could be decreased. Unfortunately, the authors could not elucidate prognostic factor in the present study.

This is because of low number of the patients in the progression group (10 patients). The large meta analysis showed that deeply invasion into lamina propria was the highest risk factor. Tumors larger than three centimeters and associated with CIS are also the other significant risk factors[7]. In other trial, Orsola et al[11], showed a three-fold increase in progression rate in T1b (invade deep through muscularis mucosae) substage. In the future, the T1b substaging has to improve accuracy in pathologic interpretation to become the standard staging.

Repeat TUR-BT provides accurate staging because the chance of understaging after first TUR-BT in T1 high-grade tumor ranges from 27% to 50%[12,13]. Although Schwaibold et al[14] demonstrates worse prognostic findings in up to 25% of specimens of T1 high-grade patients, it is still uncommun in Thailand clinical practice to repeat TUR-BT. In the present study, only 30% of T1 high-grade patients received repeat TUR-BT. The rate of repeat TUR-BT in the present study was low because the guideline just changed and the large amount of operative cases in the authors' institute hampered the schedule of repeat TUR-BT. Furthermore, many Thai patients refused to repeat the operation if they did not have a recurring disease. From the present study, lack of muscle at the initial resection and prior intravesical BCG instillation therapy were the risk factors of disease recurrence. The authors encourage to repeat TUR-BT in all T1 patients to improve the staging accuracy and possibly prevent disease recurrence and progression.

Mean time to disease progression was 17.3 months. Therefore, the authors have 17.3 months to add some interventions (intravesical BCG, early radical cystectomy, etc.) before disease progression occurred. Early radical cystectomy in all T1 high-grade patients had no significant difference in survival compared to non-progressive disease patients who received TUR-BT alone. If a physician could find the risk factor for disease progression, then patients would be better selected for early radical cystectomy before progressing to muscle invasive disease and the number of unnecessary radical cystectomy would be decreased.

Limitation

There were several limitations in the present study. The number of patients was not very high due to missing or incomplete data. In addition, the study place is a tertiary referral hospital where most patients were incomplete TUR-BT and understaging because of large tumor from their prior hospital. Therefore, the data may not represent bladder cancer patients in other general hospitals.

Conclusion

Lack of muscle at the initial resection and prior intravesical BCG instillation therapy were the risk factors of recurrence of T1 high-grade bladder cancer. It is obvious that progressive disease is the strongest impact on patient survival and early radical cystectomy does not improve survival of the non-progressive disease patients. Further studies are needed to identify the risk factors that can differentiate between non-progressive and progressive disease.

What is already known about this topic?

T1 high-grade non-muscle invasive bladder cancer has high recurrence and progression. Early radical cystectomy is an alternative treatment of this spectrum of disease and has good oncologic outcome but comes with substantial morbidity.

What this study adds?

This study demonstrated recurrence and progression rate of T1 high-grade non-muscle invasive bladder cancer in Thai population. The prognostic factors of the recurrence of T1 high-grade bladder cancer were lack of muscle at the initial resection and prior received intravesical BCG instillation. Progressive disease had poor survival rate, and early radical cystectomy did not improve survival if it was the non-progressive disease. Further studies are needed to identify the risk factors that can differentiate between non-progressive and progressive disease.

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Conflicts of interest

The authors declare no conflict of interest.

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