Risk-based Management of Non-muscle Invasive Bladder Cancer: Experience from Tribhuvan University Teaching Hospital

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ABSTRACT

Background

Most of the recent evidences suggest for risk-based management of non muscle invasive bladder cancer (NMIBC) to reduce the risk of recurrence and progression.

Objective

This study was conducted to assess the recurrence and progression of non muscle invasive bladder cancer in Nepalese patients using European Organization for Research and Treatment of Cancer (EORTC) risk tables and to assess the effectiveness of intravesical therapy to reduce the risk of recurrence.

Method

A prospective observational single centre study was conducted at Tribhuvan University Teaching Hospital from January 2010- December 2012. Forty six patients with non muscle invasive bladder cancer who underwent transurethral resection of bladder tumor and completed two years follow up were included. According to the European Organization for Research and Treatment of Cancer (EORTC) risk table, the patients were divided into low, intermediate and high risk groups. The patients received postoperative adjuvant therapy and surveillance as per the European Association of Urology guidelines.

Result

Among the 46 patients, the overall two year recurrence and progression rate was 8 (17%) and 1 (2%) respectively. Out of seven patients in low risk category, none of them developed recurrence or progression of disease. Out of 15 patients in intermediate risk category the one year and two year recurrence rate was 13% and 20% respectively. Out of 24 patients in high risk category the one and two year recurrence rate was 17% and 21% respectively. The risk reduction by use of intravesical Bacillus Calmette Guerin (BCG) for recurrence in high risk category was 58% and 60% in first and second year respectively. In our study, the overall and individual risk group, the one and two year recurrence rate was lower than that predicted by European Organization for Research and Treatment of Cancer risk table.

Conclusion

Risk-based management of non muscle invasive bladder cancer by using the European Organization for Research and Treatment of Cancer risk table is a useful method of management, though its prediction rates are lower in Nepalese population.

KEY WORDS

EORTC, intravesical therapy, NMIBC, progression, recurrence, risk table

INTRODUCTION

Bladder cancer is one of the common urological malignancies with seventh and seventeenth in ranking among males and females respectively.[1,2] More than 90% of bladder cancers are urothelial carcinomas with more than 70% presenting as non-muscle invasive bladder cancer (NMIBC), in the past known as superficial bladder cancer.[3] The biological behavior of NMIBC is to recur and progress in due course of time in an unpredictable manner with five year recurrence rate of 31 to 78% and progression rate of 0.8 to 45% if treated without intravesical adjuvant therapy.[4]

Recently, prognostic models such as risk tables and nomograms have been developed to predict the recurrence and progression of NMIBC which facilitate the process of risk stratification, counseling and decision making for treatment. The European Organization for Research and Treatment of Cancer (EORTC) risk table is one of the most commonly used and validated model used for the management of NMIBC.[4] Currently, most of the evidences suggest for risk-based management of NMIBC to reduce the risk of recurrence and progression.

There is paucity of data on bladder cancer management from Nepal. This study was conducted with the aim to assess the recurrence and progression of NMIBC using EORTC risk tables and to assess the effectiveness of adjuvant intravesical therapy in Nepalese context.

METHODS

This prospective observational study was conducted at the authors institute from January 2010 to December 2012. Patients with NMIBC who underwent transurethral resection of bladder tumor (TURBT) and completed two years follow up were included. After the initial TURBT, repeat transurethral resection of bladder tumor (Re TURBT) was done in following cases: incomplete initial transurethral resection, absence of detrusor muscle in the specimen after initial resection, T1 tumors and high grade tumors. Staging of bladder cancer was done by applying the seventh edition of the American Joint Committee on cancer TNM staging system.[5] After the final histopathology report the patients were stratified into low, intermediate and high risk categories according to EORTC risk tables derived from the EORTC risk scoring system (Appendix).[4,6] EORTC calculator was used to calculate the probability of risk of recurrence and progression.[7] Data analysis was done by using Microsoft excel office 2007 version. The recurrence and progression rate was expressed as percentage.

Adjuvant Intravesical Therapy

Within six hours of TURBT, immediate intravesical Mitomycin C (40 mg) was given routinely except in cases with residual tumor, bladder perforation and gross hematuria requiring continuous irrigation. A total of 32(70%) patients received immediate intravesical mitomycin C after initial TURBT. The patients in intermediate risk group received 10 doses of adjuvant intravesical Mitomycin C (40 mg per instillation reconstituted in 20 ml distilled water), comprising of 6 induction and 4 maintenance doses. Patients in high risk group received intravesical Bacillus Calmette Guerin (OncoBCG™, Serum Institute India, 80 mg each instillation, reconstituted in 50 ml of normal saline). During the induction phase of BCG therapy the patients received six instillations, weekly for six weeks. During the maintenance phase of BCG therapy the patients received one instillation every week for three consecutive weeks at 3, 6, 12,18 and 24 months.[8]

Surveillance Protocol

Follow up was done according to risk stratification. Patients in low risk category underwent active surveillance alone with check cystoscopy at 3 months, 9 months and yearly thereafter. The patients in intermediate and high risk group had undergone check cystoscopy and urine cytology every three monthly. Upper tract imaging with CT urography was done annually for high risk group of patients. End point of the study was recurrence or progression of the disease. Tumors found at first check cystoscopy and on subsequent examinations were resected and sent for histopathological examination. Recurrence was defined as tumors with same stage; while progression was defined when the tumor involved the detrusor muscle, had nodal or distant metastasis.[8]

RESULTS

Out of 75 patients with urothelial carcinoma of bladder treated during the study period, 58(77.3%) were diagnosed to have NMIBC. Out of them, 46 fulfilled the criteria for final data analysis. Patient and tumor characteristics are shown in Table 1. Majority of the patients had high grade T1 tumors with high risk of recurrence. Overall recurrence rate within the first and second year was 13% and 17% respectively. On subgroup analysis, there was no recurrence during 2 years of follow up among low risk category. Among the intermediate risk category patients, the first and second year recurrence rate was 13% and 20% respectively. Among the patient with high risk category, the first and second year recurrence rate was 17% and 21% respectively. These findings were compared with EORTC risk table for risk of recurrence as shown in Table 2.

On comparing with EORTC risk table, actual recurrence risk reduction due to use of intravesical induction and maintenance Mitomycin C in intermediate risk category was 49.6%. Intravesical Mitomycin C was well tolerated by the patients without any major side effects. Only one patient in this group refused maintenance Mitomycin C due to social reason. Likewise, actual recurrence risk reduction due to induction and maintenance BCG was 60% among the high risk category.(Table 3) In the intravesical BCG group three patients developed severe cystitis with reduced bladder

capacity, two of them were managed with hydrodistention and one had undergone radical cystectomy with ileal conduit. Three patients refused BCG maintenance schedule in high risk category and all of them had recurrence. Only one patient (2%) had progression of disease during this period which was from the high risk category.

Table 1. Patient Demographics

Patient characteristics	(n=46)
Age (years)	
Mean± SD	62±11.8
Gender	
Male	39(84.7%)
Female	7(15.3%)
Smoker	33(71.7%)
Symptoms	
Hematuria	26 (56.5%)
Storage symptoms	7 (15.2%)
Incidental diagnosis	13(28.3%)
T stage	
Ta	18 (39.1%)
Cis	4 (8.8%)
T1	24 (52.1%)
Tumor Grade	
Low	17(37%)
High	29(63.0%)
Recurrence risk Group	
Low	7(15.2%)
Intermediate	15(32.6%)
High	24(52.2%)

Table 2. Recurrence among patients with NMIBC and Comparison with Predicted Probability of Recurrence by EORTC Risk Table[4]

Recurrence Risk Group	First Year Recurrence		Second Year Recurrence	
	Author's Series	EORTC Predicted	Author's series	EORTC Predicted
All Patients (n=46)	6(13%)	32.7%	8(17%)	43.6%
Low Risk (n=7)	0(0%)	16.3%	0(0%)	22.9%
Intermediate Risk (n=15)	2(13%)	28.7%	3(20%)	39.7%
High Risk (n=24)	4(17%)	40.1%	5(21%)	52.2%

DISCUSSION

Our study showed that NMIBC constitutes major bulk of urothelial carcinoma (77.3%). Majority of the patients had high grade tumor (63%) with high risk of recurrence (52.2%). The reason behind this might be the wide prevalence of smoking in our population and some genetic predisposition, yet to be proven by further researches. This highlights for the need of more aggressive therapy and surveillance. Our finding is similar to the finding of Seo and colleagues nine who had compared recurrence and progression rates between the EORTC risk tables and their own cohort of Korean patients. They had also found the more aggressive patient and tumor characteristics of the Korean cohort of NMIBC.

Table 3. Reduction of the Risk of Recurrence with the use of Intravesical Adjuvant Therapy[4]

Recurrence Risk Group	First Year Recurrence			Second Year Recurrence		
	Author's Series	EORTC Predicted	Risk Reduction	Author's series	EORTC Predicted	Risk Reduction
Intermediate Risk*	2(13.3%)	28.7%	53.6%	3(20%)	39.7%	49.6%
High Risk**	4(16.7%)	40.1%	58%	5(20.8%)	52.2%	60%

*Treated with Intravesical Mitomycin C, **Treated with Intravesical BCG

We are managing the patients with NMIBC as per the European Association of Urology (EAU) guideline, which is helping us to stratify the patients into different risk categories and to decide for adjuvant therapy. Our study showed that with risk-based management of NMIBC, the short term recurrence and progression is less than that predicted by EORTC. The likely reasons for this might be: routine immediate postoperative Mitomycin C instillation, strict reTURBT protocols and appropriate adjuvant therapy.

In our centre one immediate postoperative instillation of Mitomycin C is given routinely unless it is contraindicated. This practice is supported by the existing literature and available guidelines as well. Studies have shown that early single instillation has been shown to function by the destruction of circulating tumor cells resulting from TUR, and by an ablative effect on residual tumor cells at the resection site and on small overlooked tumors.[10,11] In a meta-analysis of 1476 patients, one immediate instillation of chemotherapy after TUR significantly reduced recurrence rate by 11.7% compared with TUR alone.[12]

In our centre Mitomycin C is used for intermediate risk group for the induction and maintenance intravesical chemotherapy. It was well tolerated by our patients with 53.6% and 49.6% reduction of recurrence during the first and second year respectively. Currently International bladder cancer group (IBCG) recommends this for intermediate risk NMIBC as intravesical chemotherapy though BCG is an option.[13] A meta-analysis of 3703 patients from 11 RCTs showed a highly significant 44% reduction in the odds of recurrence at one year in favor of chemotherapy instillations over TUR alone but no effect on tumor progression.[14] Mitomycin C, epirubicin, and doxorubicin have all shown a beneficial effect, with no efficacy comparisons made between the drugs.[12]

In the current study, intravesical BCG in high risk group reduced the first and second year recurrence by 58% and 60% respectively with some toxicities and intolerance.

Recurrence was observed in the patients who failed to continue maintenance therapy. This highlights the need of maintenance BCG therapy for optimal effect. Currently intravesical BCG therapy is indicated for high risk category of NMIBC (T1, cis, high grade tumor). This is a viable option for intermediate risk category as well.[15] Main drawbacks of BCG therapy are poor compliance and toxicities. Intravesical BCG was introduced as a treatment for urothelial cancer of the bladder more than 35 years ago by Morales et al.[16] Since then several studies and meta-analyses have shown that TURBT followed by intravesical BCG is superior to TURBT alone as well as to TURBT plus intravesical chemotherapy for delaying time to first recurrence. One meta-analysis 17 evaluated the individual data from 2820 patients enrolled in nine RCTs that compared Mitomycin C versus BCG. In the trials with BCG maintenance, a 32% reduction in the risk of recurrence for BCG compared with Mitomycin C was found, whereas there was a 28% increase in the risk of recurrence for patients treated with BCG in the trials without BCG maintenance. Two meta-analyses support that BCG therapy prevents, or at least delays, the risk of tumor progression.[18,19]

Our study showed that with risk-based management of NMIBC, the short term risk of recurrence and progression is less than that predicted by EORTC. On literature review, there are variable results on recurrence and progression of the disease using risk based management of NMIBC based on EORTC risk tables. Our findings are similar to that of the study done by Fernandez-Gomez et al.[20] According to their study the one year probability of recurrence was 0%, 8% and 30.2% for low, intermediate and high risk group respectively which was lower than that predicted by EORTC risk table. In their series all the patients received intravesical BCG irrespective of risk category.

Van Rhijn et al. have validated the EORTC risk scores for primary NMIBC in a clinical and biomarker setting.[21] In their study besides, EORTC risk score, molecular grade (mG) based on fibroblast growth factor receptor 3 (FGFR3) gene mutation status proved highly reproducible and predictive. They have concluded that long-term results justify an independent prospective analysis of mG and EORTC risk scores. Seo et al. compared recurrence and progression rates between the EORTC risk tables and their own cohort of 251 Korean patients.[9] All recurrence rates of the Korean patients were lower than in the EORTC cohort, except for the one year recurrence rate in the intermediate-risk group, which was comparable with that of the EORTC cohort. Likewise, Sakano et al. have validated the European Association of Urology (EAU) guidelines on risk group stratification to predict recurrence in Japanese patients with stage Ta and T1 bladder tumors.[22] They have concluded that the risk group stratification of the EAU guidelines for recurrence might not be applicable to Japanese patients with Ta and T1 bladder tumors, but the subgroup classification of intermediate risk could be appropriate.

Hernandez et al. performed an external validation of EORTC risk table in 417 patients with primary NMIBC.[23] In general, probabilities for both recurrence and progression in their cohort were higher than in the EORTC cohort. Their results validated the EORTC risk tables in terms of recurrence but not in terms of progression because of the low number of patients that progressed. Pillai et al. validated the EORTC risk model in 109 patients with primary and recurrent NMIBC.[24] They found significantly higher 1 and 5 year probabilities of recurrence for all groups compared with the EORTC model.

Our study corroborates with findings of many of the above mentioned studies which confirm the higher recurrence and progression rates in original EORTC risk tables than those found in contemporary practice. Currently the standard of management of NMIBC has changed with integration of immediate intravesical chemotherapy, reTURBT protocols, adjuvant chemotherapy and BCG therapy. These practices helped to reduce the recurrence rate of NMIBC.

Current study was done in a single centre, thus incorporates small sample size. The power and validity must have been increased by making it multicentric study with larger sample size. In fact this is our interim result of only two years follow up and we are continuing this study to complete five years of follow up. The diagnostic modality utilized by us are visual confirmation of tumor with white light cystoscopy which definitely has low yield as compared to ultramodern endoscopic imaging such as photodynamic diagnosis (PDD) and narrow band imaging (NBI) to diagnose the recurrence.[25,26] Recent advances in molecular diagnostic modalities like molecular grade has not been incorporated in this study.

CONCLUSION

The European Organization for Research and Treatment of Cancer risk table is a useful tool to predict the recurrence and progression in non muscle invasive bladder cancer and to stratify them into risk categories, though its prediction rates are higher than most of the contemporary series. Mitomycin C is well tolerated by patients in intermediate risk group but weak in preventing recurrence. Intravesical Bacillus Calmette Guerin is quite effective in preventing recurrence in high risk category by adherence to maintenance schedule. However, it is associated with reduced compliance and higher toxicity.

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