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ORIGINAL RESEARCH ARTICLE

RECURRENCE AND PROGRESSION OF NON-MUSCLE INVASIVE BLADDER CANCER FOLLOWING TRANS-URETHRAL RESECTION OF BLADDER TUMOUR WITH ADJUVANT INTRAVESICAL CHEMO-IMMUNOTHERAPY

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Citation

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ABSTRACT

Background: Trans-urethral resection of bladder tumor is an essential diagnostic tool as well as effective treatment modality for non-muscle invasive bladder cancer. We aimed to evaluate the recurrence and progression of the non-muscle invasive bladder cancer in Nepalese patients.

Methods: This was a retrospective study of 43 patients with non-muscle invasive bladder cancer, who underwent trans-urethral resection of bladder tumour followed by adjuvant intravesical instillation of chemo or immunotherapy between January, 2013 to December, 2018. Patients were divided into low, intermediate and high-risk groups according to the clinical and pathological factors used by the European Organization for Research and Treatment of Cancer scoring system. Outcomes were calculated in terms of recurrence and progression in each group.

Results: Out of 43 patients, 11 (25.58%) patients had low risk, 18 (41.86%) patients had intermediate risk and 14 (32.56%) patients had high risk of recurrence categories. No recurrence and progression of the disease noted in low risk group. In the intermediate risk group, out of 18 patients, 4 (22.2%) patients developed recurrence and 2 (11.1%) patients had progression of disease. In high risk group, out of 14 patients, 4 (26.8%) patients developed recurrence and 2 (14%) patients developed progression of the disease.

Conclusions: Even in a low volume centre of bladder cancer, effective treatment for non-muscle invasive bladder cancer with trans-urethral resection of bladder tumour followed by adjuvant intravesical chemo or immunotherapy can be given safely to reduce recurrence and progression of the disease.

INTRODUCTION

Bladder cancer ranks tenth most common types of cancer in the world and approximately 550,000 new cases recorded annually.[1] Bladder cancer is the second most common cancer of the genito-urinary tract after prostate cancer. It accounts for 7% of new cancer cases in men and 2% of new cancer cases in women.[2] Non-muscle invasive urothelial cancer accounts the majority of urinary bladder cancer. It is further subdivided into tumors with low, intermediate, and high risk groups which may progress into invasive or metastatic cancer. Up to 75% of patients with bladder cancer present with non-muscle invasive bladder cancer (NMIBC), and trans-urethral resection (TUR) followed by intravesical chemotherapy or immunotherapy is the treatment of choice. The recurrence and progression are the biological behavior of NMIBC during surveillance period, with five-year recurrence rate of 31 to 78% and progression rate of 0.8 to 45% if treated without intravesical adjuvant therapy. European Organization for Research and Treatment of Cancer (EORTC) developed a scoring system and risk table, which is one of the most commonly used models for the management of NMIBC to reduce the risk of recurrence and progression.[3]

This study aimed to assess recurrence and progression of the non-muscle invasive bladder cancer (NMIBC) in Nepalese patients.

METHODS

This was a single center, retrospective study, conducted at Kathmandu Model Hospital for the period of six years. Study period was from January 2013 to December 2018.After getting ethical clearance from hospital Institutional Review Committee (IRC no 016-2020), total 43 patients of NMIBC who received intravesical chemotherapy with Mitomycin C (MMC) or immunotherapy with Bacillus Calmette Guerin (BCG), after complete TURBT, were enrolled in the study. All the data were retrieved from the charts of the patients and outpatient records.

Patients with histologically confirmed NMIBC (Ta, T1, or Tis stage) and patients who were treated with intravesical Mitomycin C and BCG after trans-urethral resection of urothelial cancer were included in the study. Patients with muscle invasive bladder cancers were excluded from the study.

Staging of bladder cancer was done according to American Joint Committee on cancer TNM staging system.[4]After the initial TURBT, repeat trans-urethral resection of bladder tu-

mor (Re- TURBT) was done in incomplete initial transurethral resection, absence of detrusor muscle in the specimen after initial resection or T1 high grade tumors, as recommended by the European Association of Urology (EAU).[5]After completion of TURBT, all the patients were instilled immediate intravesical chemotherapy MMC 40 mg routinely within 6-24 hrs following the surgery, depending upon the level of hematuria requiring continuous bladder irrigation.

After receiving the final histopathology reports, patients were stratified into each risk group according to several factors, which included tumor stage (Ta versus T1/Tis), tumor grade (low versus high), tumor multiplicity (single versus multiple) and tumor size (<3 cm versus ≥3 cm).[5] Eventually, NMIBC patients were categorized into low, intermediate, and high risk groups according to EORTC risk tables derived from the EORTC risk scoring system.[6] The recurrence and progression rate were expressed in percentage. No specific analytical statistical tools were used in the study.

Patients with tumor size <1 cm were resected by en-bloc technique, in which the specimen contained the complete tumor with part of the underlying tissue. Larger tumors were resected completelyby starting from the exophytic portion to the tumor base and the edges of the resection area were fulgurated routinely. After complete resection of the tumor, we routinely resected the tumor base and sent it for histopathology examination separately.

Once the final histopathology reports were available, patients were classified in to low, intermediate and high-risk groups. Low risk group and intermediate group received MMC. The commonly used dose was 40 mg diluted in 40 mL of normal saline or sterile water, administered weekly for six weeks. Patients in high risk group received intravesical BCG (OncoBCG™, India), 80 mg diluted in 40 ml normal saline. During the induction phase of BCG therapy, the patients received six instillations, weekly for six weeks. Where as in 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.

All the patients had undergone active surveillance with urine cytology and cystoscopy every 3 monthly. If negative, subsequent cystoscopy and cytology were repeated every 3 months for a period of 2 years, and every 6 months thereafter until 5 years, and then yearly. Upper tract imaging with CT urogram (CTU)was done annually for high risk group of patients. Tumors found at first cystoscopy surveillance and on subsequent examinations, were resected and sent for histopathological examination. Recurrence was defined as a new lesion after the treatment of the primary tumor, diagnosed by cystoscopy and confirmed by histopathology reports with same T stage; while progression was defined when the tumor involved the detrusor muscle.[5]

RESULTS

Total 43 patients were enrolled in this study with a mean age of 66.2 years. The study showed a male predominance, male 28 (65.1%) and female 15 (34.9%). Majority of the patients were smoker 36 (83.70%) and the commonest presenting symptom was hematuria which was found in 33 (76.74%). About 31(72.1%) patients had NMIBC low grade (Figure 1) and 12 (27.9%) patients had NMIBC high grade (Figure 2). Demography and tumour characteristics are described in details in Table 1. The mean follow up period of our study was 36.1 months.

Table 1: Patients and tumor characteristics (n=43)

Variables	Frequency (%)
Age (Years) (Mean)	66.2
Gender	
Male	28 (65.10)
Female	15 (34.90)
Smoker	36 (83.70)
Presenting Symptoms	
Hematuria	33 (76.74)
Storage symptoms	6(14)
Incidental findings	4(9.30)
T stage	
Ta	15 (34.90)
T1	28 (65.10)
CIS	0
Tumor grade	
Low grade	31 (72.1)
High grade	12 (27.9)
Tumor risk group	
Low risk group	11 (25.58)
Intermediate risk group	18 (41.86)
High risk group	14 (32.56)

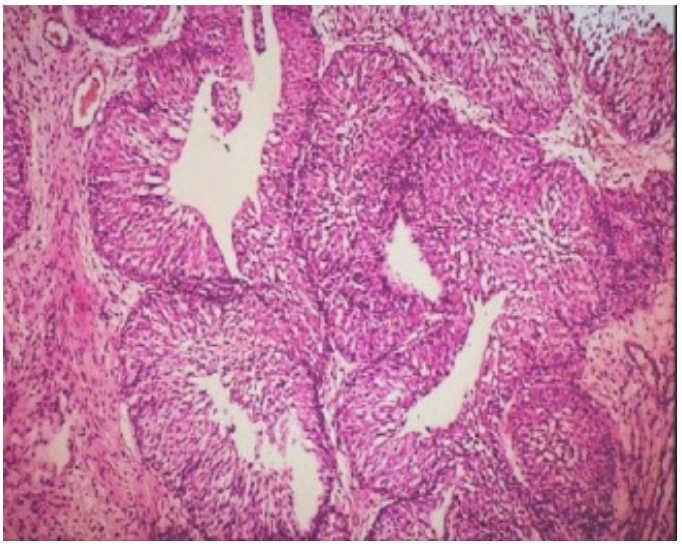

Figure 1: Non-muscle invasive urothelial carcinoma, low-grade (100x H&E stain)

All 43 patients underwent TURBT followed by intravesical instillation of MMC for low and intermediate risk groups and intravesical BCG was given to the high-risk group. Patients receiving MMC, well tolerated induction course without significant side effects. Where-

as, those receiving intravesical BCG, two patients developed severe cystitis during induction schedule.

Out of fourteen patients in high risk group, two patients developed disease progression during surveillance and maintenance schedule of BCG and managed by radical cystectomy and ileal conduit.

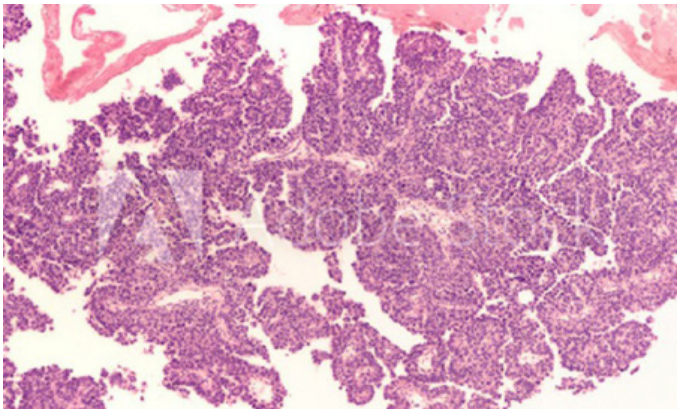

Figure 2: Non-muscle invasive urothelial carcinoma, high-grade (100x H&E stain)

According to the European Association of Urology (EAU) guideline, we stratified the patients into different risk groups for adjuvant chemo or immunotherapy.

Out of 43 patients, 11(25.58%) had low risk, 18(41.86%) had intermediate risk and 14(35.1%) had high risk of recurrence categories. Out of them, no recurrence and progression of disease noted in low risk group. In the intermediate risk group, out of 18 patients, 4(22.2%) patients developed recurrence and 2(11.1%) patients had progression of disease. Whereas in high risk group, out of 14 patients, 4(26.8%) patients developed recurrence and 2(14%) patients developed progression of the disease (Table 2).

According to EORTC risk table, the risk of recurrence and progression of the disease in 3 years were 25 % in low risk group, 40-56% in intermediate group and 76% in high risk group respectively. Whereas predicting progression of the disease in 3 years were 0.8% in low risk group, 4-11% in intermediate risk group and 30% in high risk group.

Table 2: Recurrence and progression: our study versus EORTC prediction

Tumor Risk Group	Mean Follow Up (Months)	3 Years Recurrence		3 Years Progression	
		Author's study	EORTC	Author's study	EORTC
Low	37.1	0	25%	0	0.8%
Intermediate	36	4(22.2%)	20-56%	2(11.1%)	4-11%
High	35.1	4(28.6%)	75%	2(14%)	30%

DISCUSSION

Trans-urethral resection of bladder tumor (TURBT) is an essential diagnostic tool as well as effective treatment modality for NMIBC. Post-operatively, adjuvant chemo or immunotherapy is required to achieve the good prognosis in NMIBC. High rate of recurrence (50-70%)and progression (10-20%) of the tumor can be challenging for the clinicians in the management of NMIBC after TURBT alone.[5,7]Thus, it is necessary to consider adjuvant chemo-immunotherapy in most of the patients to prevent recurrence and progression of the disease.

With the natural history of NMIBC alone is difficult to predict recurrence and progression of the disease due to the unpredictable biological behavior of the tumors. To predict the risks of recurrence and progression in individual patients of NMIBC, a scoring system and risk tables, which were based on clinical and pathological factors, including tumor multiplicity, tumor size, prior recurrence rate, T stage, presence of Carcinoma In Situ(CIS) and tumor grade, were developed by the European Organization for Research and Treatment of Cancer (EORTC) and validated by several investigators.[8-10] The Spanish Urological Club for Oncological Treatment (CUETO) scoring model was also developed to stratify the risk of recurrence and progression in NMIBC treated with BCG.[11]

In our study, the recurrence and progression rates of NMIBC were less than that predicted in EORTC risk score system in lower and high-risk groups, and similar in intermediate risk group at 3 years when compared to the EORTC table. The possible explanations for this might be the routine immediate postoperative MMC instillation,continuous bladder irrigation with normal saline after TURBT for 24 hours, strict re-TURBT protocols and appropriate adjuvant chemo or immunotherapy. Kaasinen and Colleagues[12] were the first to suggest the efficacy of immediate instillation of chemotherapy(MMC) in patients who received subsequent BCG therapy. In a meta-analysis of 1476 patients, one immediate instillation of chemotherapy after TURBT significantly reduced recurrence rate by 11.7 to 13% compared with TURBT alone.[13]

In our institute, we routinely use continuous normal saline bladder irrigation, which could be another reason of low recurrence and progression of NMIBC. Recently, Do et al.[14] reported that overnight continuous saline irrigation after TURBT was effective in preventing early recurrence of NMIBC. Sylvester et al[15] carried out a systemic review of the published results of randomized clinical trials and reported that post-operative irrigation reduced the risk of recurrence in a non-randomized comparison of 1592 NMIBC patients, and adjusting for the randomized treatment and EORTC recurrence risk score, post-operative irrigation reduced the relative risk of recurrence by 21%.

In current study, we used MMC for low and intermediate risk group for 6 weeks after TURBT, and all the patients in this two

groups completed adjuvant intravesical chemotherapy without any side effects. When compared with 3 years recurrence and progression in low risk group, we found 25% and 0.8% respectively. In intermediate risk group the risk of recurrence and progression were comparable. A meta-analysis of 3703 patients from 11 RCTs showed a 44% reduction in recurrence at one year in favor of chemotherapy instillations over TUR alone but no effect on tumor progression.[16]However, another meta-analysis of 9 trials that included 2820 NMIBC patients (74% of which had intermediate risk group) found a 32% reduction in the risk of recurrence with BCG maintenance vs. maintenance MMC ($p<0.0001$).[17] So in case of intermediate risk group, we should individualize the patients risk level and administration of BCG would be more wiser decision to reduce the recurrence and progression of the disease.

In our study, we found that those patients who received intravesical BCG in high risk group, the third year recurrence was very less than in EORTC risk table (28.6% vs 76%). Recurrence was observed in the patients who failed to continue maintenance therapy. This emphasize the requirements of maintenance BCG therapy has optimal effect. Currently, intravesical BCG therapy is indicated for high risk group of NMIBC (T1, cis, high grade tumor). This is a viable option for intermediate risk category as well.[5]The high risk groups are in a higher chance of disease recurrence and progression than other NMIBC.

Therefore, adjuvant intravesical BCG immunotherapy after TURBT is currently mandatory in the management of high-grade tumors for better prognosis.[5,7] In our study, approximately 85% of patients in high risk group received BCG therapy and showed decreased recurrence and progression of the disease. The results of multivariable analysis in high grade patients showed that improved recurrence free survival (RFS) and progression free survival (PFS) was observed only in association with induction BCG therapy. These findings are parallel to the previous study.[18]

A meta-analysis compared Mitomycin C versus BCG. In the trials with BCG maintenance, they found 32% reduction in the risk of recurrence for BCG compared with MMC, whereas there was a 28% increase in the risk of recurrence for patients treated with BCG in the trials without BCG maintenance.[19]Another meta-analysis supports that BCG therapy prevents, or at least delays, the risk of tumor progression.[20]

The result of our study is comparable with the study conducted by Seo and Colleague.[8] They compared recurrence and progression rates between the EORTC risk tables and their own cohort of 251 Korean patients.Recurrence rates in all risk groups of the Korean patients were lower than in the EORTC cohort, except in the intermediate-risk group. Most of these previous studies, as well as our single centre study, indicated favorable tendencies of adjuvant therapy in all group but intermediate risk group showed comparable recurrence and progression of the diseases in EORTC risk table, whereas lower in low risk and high risk groups. So, we presume BCG would be the better option for intermediate group to reduce the recurrence and progression of NMIBC.

Most studies focus on molecular tissue markers to predict the clinical course in terms of recurrence and progression of the NMIBC. Currently, Rhijn et al[21] have validated the EORTC risk scores for primary NMIBC in a clinical and biomarker molecular grade based on fibroblast growth factor receptor 3(FGFR3) gene mutation status. They concluded that with use of molecular grading, the EORTC risk score has improved the prediction of recurrence and progression.

The major limitations of our study were the retrospective nature and the lack of randomization. We provided only a single-centre experience with a shorter follow up, and small sample size. It is suggested that prospective, multicenter, long-term follow-up studies with large sample size and including recent advances in molecular diagnostic modalities like molecular grade are needed for the additional value in the future.

CONCLUSION

Even in a low volume center of bladder cancer, effective treatment for non-muscle invasive bladder cancer (NMIBC) with trans-urethral resection of bladder tumour (TURBT) followed by adjuvant intravesical chemo or immunotherapy can be given safely to reduce recurrence and progression of the disease. The consideration of intravesical chemo or immunotherapy has important role to improve cancer specific survival rate in our patients. EORTC risk table was considered to be an essential tool into our clinical practice to determine the recurrence and progression of NMIBC.

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