Intravesical Gemcitabine versus Intravesical Bacillus Calmette-Guerin for the Treatment of Intermediate-Risk Non-Muscle Invasive Bladder Cancer: A Randomized Controlled Trial

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Key words: BCG , bladder cancer , gemcitabine , intravesical therapy

ABSTRACT

Purpose: The most common adjuvant therapy known for non-invasive muscle bladder cancer (NMIBC) is intravesical Bacillus Calmette-Guerin (BCG). Intravesical chemotherapy drugs like gemcitabine can also be used post-TURBT, which is considered as a good alternative for BCG, or can be used as a second-line treatment. Due to the common side effects of BCG, the use of chemotherapy drugs as intravesical treatments is currently increasing.

Materials and Methods: 117 intermediate-risk NMIBC cases were included in this study. All the patients underwent TURBT surgery and received 1 gr intravesical gemcitabine immediately after performing the surgery. The patients were then divided into two groups, either receiving intravesical gemcitabine or intravesical BCG weekly for 6 weeks. The patients were followed up with cystoscopy.

Results: Most patients were men who had smoking risk factors. The youngest patient was 36 years old and the oldest one was 88 years old. The rate of side effects in the group receiving gemcitabine (13.6%) was much lower than the group receiving BCG (44.8%). (P-value = 0.016). The recurrence rate during a one year period was lower in the group consisting of patients receiving gemcitabine compared to the group receiving BCG (19 patients vs. 23 patients) (p-value = 0.401)

Conclusion: The efficacy of intravesical gemcitabine and intravesical BCG was almost equal in the treatment of intermediate-risk NMIBCs. The adverse effects of gemcitabine were found to be significantly lower than BCG. Due to causing fewer complications, gemcitabine can be known as a good alternative, especially among elderly patients with comorbidities.

INTRODUCTION

Bladder cancer currently is the tenth most common cancer worldwide. As well, it is the sixth most common cancer among men, and the seventeenth most common cancer among women [(1)]. More than 90% of bladder

cancers are diagnosed in cases aged over 55 years old, and the prevalence is about four times higher in men than in women [2]. Correspondingly, its most common symptom is hematuria, which can be microscopic or gross. Other symptoms may include suprapubic pain, painful urination, dysuria or frequency. Of note, in some patients, it is asymptomatic [3].

The strongest risk factor of bladder cancer is tobacco smoking. Besides age and smoking, there are some other risk factors for bladder cancer such as workplace exposures, arsenic in the water, race, heredity, and lack of fluid intake [4]. Various studies have been previously performed on the roles of genetics and heredity in the development of bladder cancer, and the role of several genes, including MYC, fibroblast growth factor receptor (FGFR), tumor protein 53 (TP53), and retinoblastoma protein 1 (RB1), has been proven so far [5].

About 70% of bladder cancers are non-muscle invasive bladder cancer (NMIBC), which includes carcinoma in situ (CIS) and papillary carcinomas of stages Ta and T1 [6]. NMIBC cases can be divided into the following three categories: Low risk, Intermediate-risk, and High-risk patients. According to the American Urological Association (AUA) Guideline, Intermediate-risk patients are categorized into Low-Grade Ta (Recurrence < 1 year, Solitary > 3 cm or Multifocal), High-Grade Ta < 3 cm, and Low-Grade T1 groups [7]. (Table 1)

The main treatment for NMIBCs is transurethral resection of bladder tumor (TURBT) and then, depending on the pathology and risk classification, intravesical treatments are performed if needed [3]. In patients with muscle-invasive bladder cancer, performing more invasive treatments such as radical cystectomy or chemotherapy and radiotherapy, is suggested [8]. In an intermediate-risk patient, a clinician should consider adjuvant therapy, including the administration of a six-week course of intravesical chemotherapy or immunotherapy [4]. In this regard, the most common intravesical treatment is Bacillus Calmette-Guerin (BCG), which has been used to treat bladder cancer since the 1970s. The treatment with BCG is in the form of six induction cycles and if necessary, maintenance therapy is followed as well [9]. The recurrence rate of bladder cancer is high. In NMIBCs, the recurrence rate is between 60 and 70%. In particular, the recurrence rate in the intermediate-risk group over a one-year period is about 38%. Accordingly, this rate reaches about 62% for a 4–year period of follow-up. The Intravesical treatments could reduce the recurrence rate. BCG

injection can also reduce the recurrence rate by about 30-40%. For intravesical therapy, chemotherapy drugs such as mitomycin C, gemcitabine, and epirubicin can be used post-TURBT, which is a good alternative treatment for BCG or a second-line treatment. Gemcitabine has an anti-tumor activity and due to having proven effect on the treatment of metastatic and advanced bladder cancers, it is used in the treatment of NMIBCs [4,6,10,11]. Due to the common side effects of BCG, which can range from dysuria to sepsis, the use of chemotherapy drugs as intravesical treatments is increasing [12]. The most common side effects of intravesical gemcitabine may include cystitis, hematuria, and skin reactions [13].

Considering that few studies has been conducted on comparing BCG and gemcitabine , we designed and performed the phase III clinical trial to assess the effectiveness of intravesical gemcitabine, compared to intravesical BCG.

PATIENTS AND METHODS

Study population

The patients participating in the current study were those with Non-Muscle Invasive Urothelial Carcinoma of Bladder, the subgroup of intermediate-risk. This study was done from March 2019 to December 2021, including the newly-diagnosed patients and patients with a history of bladder cancer who met the study criteria, in Shohada-e Tajrish hospital.

The inclusion criteria were no previous history of bladder cancer or a history of PTa low-grade transitional cell carcinoma (TCC) and those who did not receive intravesical therapy. Additionally, the patients should be in the intermediate-risk group category. The exclusion criteria were immunodeficiency, pregnancy, and bladder rupture during TURBT. There was no age or sex restriction in this study. Patients who could not have regular follow-up or did not tolerate intravesical treatment were excluded from the study (22 patients). Also, 2 patients were excluded from the study due to death. Other patients had regular follow-up with cystoscopy every 3 months for at least one year.

Finally, 141 patients were enrolled in the present study, of whom 117 patients had the inclusion criteria and were divided into the two groups. Figure 1 shows the process of admitting the patients and dividing them into the case and control groups.

Study design

This study was a prospective single-center, parallel-group randomized clinical trial performed in a referral hospital in Tehran, Iran. Considering type I error of 0.05 and type II error of 0.1, 57 samples were needed in each study group. Thereafter, the patients were randomly divided into the two groups A and B using the simple randomization method. The Group A patients were treated with intravesical Gemcitabine and the Group B patients were treated with intravesical BCG. All the patients were aware of their treatment process and there was no blindness in the study.

All the patients received 1 gr vial of Gemcitabine immediately after TURBT surgery. Afterward, group A patients were followed by intravesical injection of 1 gr vial of Gemcitabine, weekly for a 6-week duration. Each vial was then dissolved in 50 ccs of normal saline and entered the bladder through nelaton catheter. The patients emptied their bladder after 2 hours.

The treatment of the group B was performed by the intravesical injection of BCG vial, weekly for a 6-week duration. Each vial was dissolved in 50 ccs of normal saline and entered the bladder through nelaton catheter. The patients emptied their bladder after 2 hours. Patients were informed of their participation in each group. Thereafter, they underwent cystoscopy every 3 months for one year. Next, according to the guideline, the follow-up was continued by cystoscopy. The patients' results and data were recorded in a pre-prepared checklist and then statistical analysis was performed.

Informed consent was obtained from each patient. This study was approved by the ethics committee of the Shahid Beheshti University of Medical Sciences (IR.SBMU.MSP.REC.1399.773). As well, it was approved by the Iranian Registry of Clinical Trials (IRCT20200402046915N1).

Surgical procedure

All the included patients underwent antibiotic therapy before surgery and underwent TURBT by a single urologist. The masses were completely resected. If bladder perforation was suspected, gemcitabine injection was not performed for the patients. Afterward, the patients underwent cystoscopy for follow-up. In case of any recurrence, the patients underwent TURBT by the same surgeon.

Outcome assessment

The main outcome of this study was the comparison of the effects of Gemcitabine and BCG on reducing recurrence of bladder cancer in the studied patients, at least one year from intravesical injection. The recurrence was evaluated and then confirmed by cystoscopy.

Secondary outcomes included the caused side effects following intravesical treatment. Possible complications have been questioned, evaluated, and finally recorded. Moreover, some variables such as the number of tumors, tumor location in the bladder, the initial pathology, and possible risk factors of the patients were examined.

Statistical methods

The obtained data were analyzed with SPSS statistical for windows version 23. Quantitative and qualitative variables were described using Mean ± sd and frequency (percent), respectively. The Chi-Square test was used for comparing data between the two groups. P-values less than 0.05 were considered as statistically significant.

RESULTS

Patients were divided into two groups receiving intravesical gemcitabine (n=59) and intravesical BCG (n=58). The maximum follow-up period of the patients was two years (6 patients). The mean duration of follow-up was 13.74 ± 3.44 months. Patient's characteristics were also similar in both groups and there was no significant difference in this respect. (Table 2)

Most of the included patients were men (78.63%) who had a risk factor of smoking (79.48%). The youngest patient was 36 years old and the oldest one was 88 years old. In terms of educational level, most of the patients in both groups were under diploma. Despite the fact that the most common reason for referring patients was gross hematuria, most of them referred to the clinic on an outpatient basis. In 17.09% of the patients, the mass was found incidentally and the patient had no symptoms.

There was no significant difference between the two study groups in terms of tumor characteristics. (Table 3) 62.39% of all the cases had a solitary tumor. 60.68% of the patients had LG Ta pathology reports, followed by HG Ta (27.35%) and the lowest rate was LG T1 (11.96%). In the group receiving gemcitabine, the most common site of the tumor was the posterior wall of the bladder (18.7%) and in the BCG group, the most common site was the left lateral wall of the bladder (21.8%). In general, the most common sites of mass in the patients' bladder were the followings: right wall, left wall, and posterior wall. The most uncommon site of the mass was the prostatic urethra (only one patient). No specific area of the bladder was statistically significant in either group.

In terms of the caused side effects, the difference between the two groups was significant. (Table 4)

The rate of side effects in the group receiving gemcitabine (13.6%) was much lower than the group receiving BCG (44.8%). (P-value = 0.016) The most common adverse effect in both groups was cystitis, including symptoms such as dysuria, frequency, and urgency. Three patients needed hospitalization due to these side effects, all of whom were in the BCG group.

Notably, the severity of the disease increased in 7 patients (5.98%) during the treatment period, of whom 3 patients were in the group receiving gemcitabine and 4 patients were in the group receiving BCG. The recurrence rate during one year period was lower in the group of the patients receiving gemcitabine compared to the group receiving BCG (19 patients vs. 23 patients), but this difference was not significant.(p-value = 0.401)

In total, in the group receiving gemcitabine, treatment was successful in 40 patients (67.79%) and no recurrence occurred, and in the BCG group, the rate was 35 patients (60.34%). The mean survival time of

recurrence in Gemcitabine group was 14.36 ± 0.73 months and in BCG group was 13.60 ± 0.77 months. (P-Value = 0.415). The recurrence rate in each group at 3-month interval is shown in Table 3 and Figure 2. BCG might prolong the peak recurrence rate than gemcitabine.

DISCUSSION

The BCG vaccine was firstly developed by Albert Calmette over a hundred years ago. Its effect on bladder cancer was proposed by Dr. Alvaro Morales about forty years ago. In 1990, BCG was approved by the Food and Drug Administration (FDA) for the treatment of NMIBC and then became the first-line drug in NMIBC up to now [14]. Intravesical BCG is associated with developing some complications that sometimes lead patient to discontinue the treatment. About 19% of the patients are forced to discontinue their treatment during the maintenance therapy with BCG. Accordingly, these complications include hematuria, urinary tract infection, epididimo-orchitis, bladder contracture, systemic BCG infection, and urosepsis [15,16].

Ryan L.Steinberg et al. in their study have discussed the use of intravesical chemotherapy drugs, including mitomycin C, gemcitabine, and epirubicin for NMIBC cases. These drugs have fewer side effects and in some cases have equal or even better efficacy compared to BCG [17]. AK DAS et al. in their research have shown that intravesical chemotherapy in NMIBC is associated with the reduced cancer-specific mortality, but it has no effect on overall mortality rate [18]. Intravesical chemotherapy drugs cause very few side effects, most of which was dysuria [18,19].

In our study, 19 patients in the gemcitabine group had a recurrence during one-year follow-up, which was 32.2%. In the BCG group, 23 patients had a recurrence, the rate which was equal to 39.7%. Despite lower recurrence rate in the group receiving gemcitabine, this difference was not significant (P-Value = 0.401). MA Han et al. have reviewed 7 studies with a total of 1222 patients, which showed that gemcitabine reduced recurrence and progression of bladder cancer among high-risk NMIBCs compared to BCG [20]. Similar

studies have also shown the superiority of gemcitabine over BCG and mitomycin in reducing recurrence and disease's progression in NMIBCs [10].

In addition, 8 patients receiving gemcitabine (13.6%) developed some adverse effects, most of which were cystitis and none of them required hospitalization. In the BCG group, 26 patients developed adverse effects (44.8%), of whom 3 patients required hospitalization. Accordingly, the most common complications in this group included cystitis and suprapubic discomfort. It is noteworthy that the complications in gemcitabine were significantly less than BCG (P-Value = 0.016). Fewer side effects can lead to better patient reception and the continuation of the full treatment process. This is especially important among the elderly with comorbidities. In similar studies, the side effects caused by gemcitabine were significantly lower than those of BCG [17,21]. In a study by Prasanna T et al., the rate of the BCG complications was about 44%, while gemcitabine caused side effects in only 7% of patients [10]. In a study that compared the side effects of intravesical gemcitabine and BCG in 592 patients with NMIBC, Cooper et al. have found that the amount of physical pain in the gemcitabine group was higher than that of BCG, while the rate of hematuria in the BCG group was much higher compared to the other group [22].

Despite all the benefits of using gemcitabine, BCG is still used as the first line of treatment in NMIBC. This may possibly be due to the extensive studies on BCG and its proven role in this field [21]. Due to its efficacy and fewer side effects, gemcitabine may be known as a viable alternative to BCG.

In the current study, there were some potential limitations, including the limited sample size, duration of the patients' follow-up, and the Covid-19 pandemic, which affected the patients' follow-up. A study on the comparison of the High-Risk group with the Intermediate-Risk group is also needed.

CONCLUSION

This study results indicate that gemcitabine has a lower recurrence rate compared to BCG, but this difference was not significant. Therefore, the efficacy of both drugs is almost equal in the treatment of intermediate-risk patients. However, the side effects of gemcitabine are significantly lower than those of BCG. Due to causing

fewer complications, it can be a good alternative, especially among elderly patients with comorbidities. Certainly, further studies with greater statistical population and more follow-up time duration are needed to determine if gemcitabine can be known as the first-line treatment in NMIBC.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Figure legends

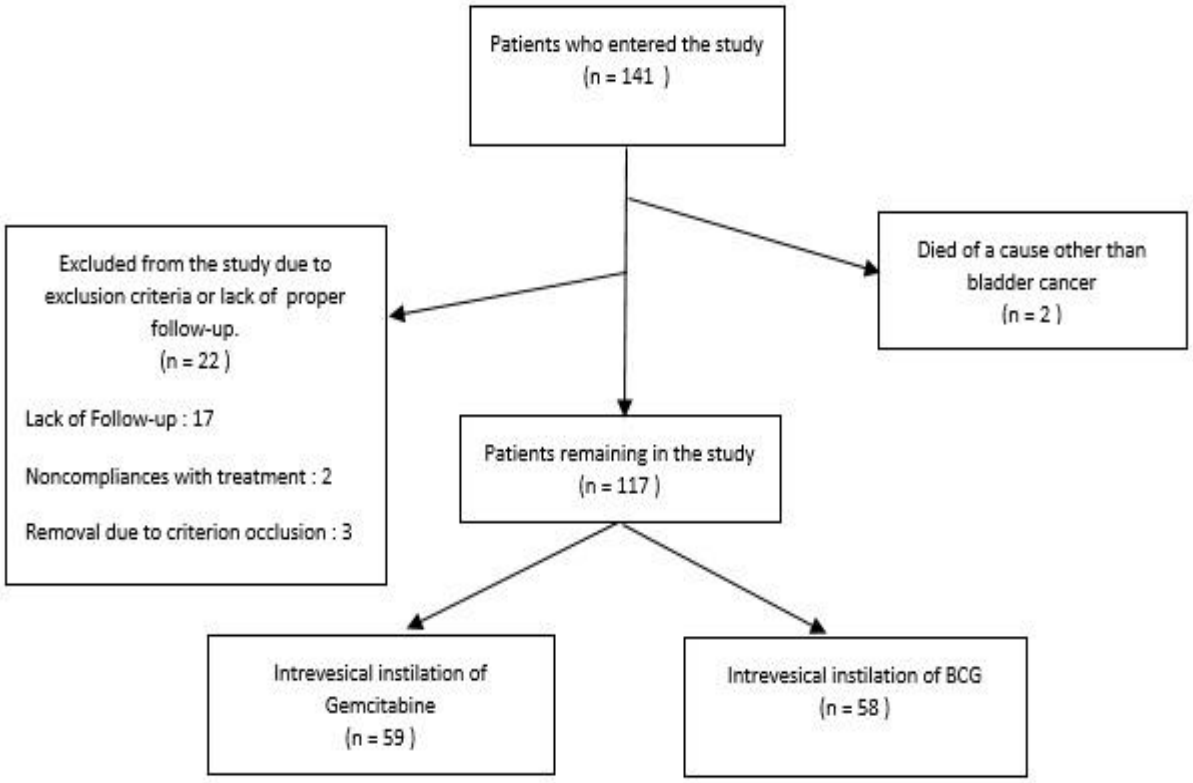

Figure 1. Patients' enrollment algorithm

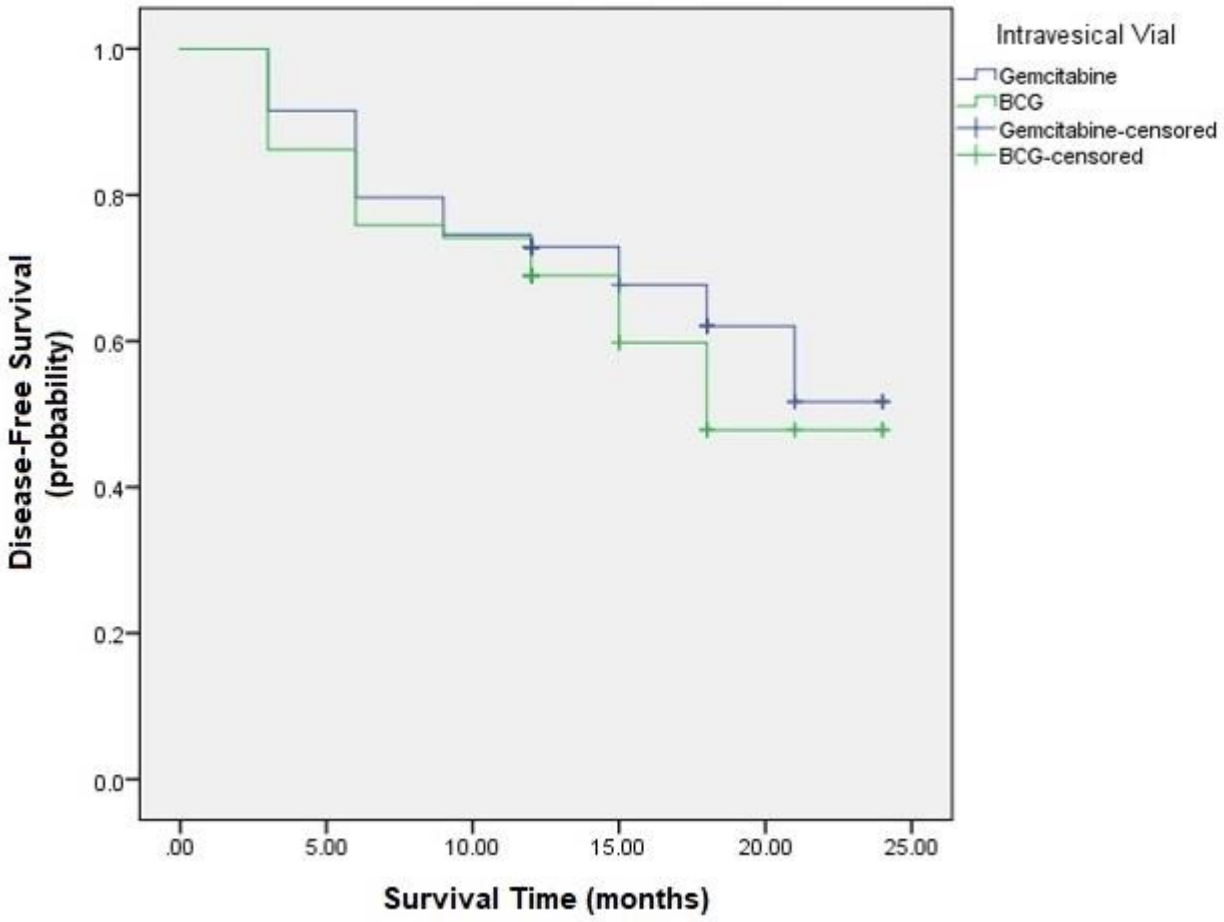

Figure 2. Kaplan-Meier estimates of disease-free survival time with gemcitabine versus BCG. BCG, Bacillus Calmette-Guerin

Table 1. Non-Muscle Invasive Bladder Cancer Risk Stratification by American Urological Association (AUA) guideline . LG : Low Grade , PUNLMP : Papillary Urothelial Neoplasm of Low Malignant Potential , HG : High Grade , CIS : Carcinoma in situ , LVI : Lymphovascular Invasion , BCG : Bacillus Calmette-Guerin

Low Risk	**LG Solitary tumor Ta <3cm , PUNLMP**
Intermediate Risk	Recurrence within 1 year LG Ta , LG Ta solitary tumor > 3 cm , LG Ta multifocal , LG T1 , HG Ta <3 cm
High Risk	HG Ta >3 cm , HG T1 , CIS , Any recurrence HG Ta , Variant histology , LVI , HG prostatic urethral involvement , BCG failure in HG patients

Table 2. Patients characteristics . GEM : Gemcitabine , BCG : Bacillus Calmette-Guerin

Patient Characteristics	GEM (n=59)	BCG (n=58)
Mean age, years	63.95 ± 10.5	62.36 ± 10.9
Sex		
Male	47 (79.7%)	45 (77.6%)
Education Level		
Les than high school diploma	32 (54.2%)	29 (50%)
High school diploma	16 (27.1%)	21 (36.2%)
Bachelor's degree or higher	11 (18.6%)	8 (13.8%)
Referral Situation		
Clinic	45 (76.3%)	47 (81%)
Emergency	14 (23.7%)	11 (19%)
Reason for referral		
Gross hematuria	41 (69.5%)	35 (60.3%)
Microscopic hematuria	5 (8.5%)	12 (20.7%)
Suprapubic pain	3 (5.1%)	1 (1.7%)
Incidental finding	10 (16.9%)	10 (17.2%)
Smoking	48 (81.4%)	45 (77.6%)
Opium	24 (40.7%)	24 (41.1%)
High risk job	6 (10.2%)	4 (6.9%)

Table 3. Tumor characteristics . GEM : Gemcitabine , BCG : Bacillus Calmette-Guerin , LG : Low Grade , HG : High Grade

Tumor charectristics	GEM (n=59)	BCG (n=58)	P-Value
Number of tumor foci			0.489
Single	35 (59.3%)	38 (65.5%)	
Multiple	24 (40.7%)	20 (34.5%)	
First pathology stage			0.885
LG Ta	37 (62.7%)	34 (58.6%)	
HG Ta	15 (25.4%)	17 (29.3%)	
LG T1	7 (11.9%)	7 (12.1%)	
Place of tumor involvement			
Posterior urethra	0 (0%)	1 (1%)	0.302
Trigone	9 (8.4%)	14 (13.8%)	0.210
Right ureteral orrifice	8 (7.5%)	4 (3.9%)	0.227
Left ureteral orrifice	6 (5.6%)	7 (6.9%)	0.694
Right wall	18 (16.8%)	19 (18.8%)	0.708
Left wall	16 (14.9%)	22 (21.8%)	0.203
Anterior wall	8 (7.4%)	5 (4.9%)	0.452
Posterior wall	20 (18.7%)	19 (18.8%)	0.982
Dome	10 (9.3%)	5 (4.9%)	0.221
Neck	12 (11.2%)	5 (4.9%)	0.099

Table 4. Response to therapy . GEM : Gemcitabine , BCG : Bacillus Calmette-Guerin , CI : Confidence Interval , LFT : Liver Function Test

Parameter	GEM (n=59)	BCG (n=58)	Risk Ratio (CI)	P-Value
Recurrence within One year			0.81 (0.49-1.32)	0.401
Yes	19 (32.2%)	23 (39.7%)		
No	40 (67.8%)	35 (60.3%)		
Tumor progression by stage	3 (5.1%)	4 (6.9%)	0.73 (0.17-3.15)	0.680
Recurrence in 1st follow-up	5 (8.5%)	8 (13.8%)	0.62 (0.22-1.79)	0.360
Recurrence in 2nd follow-up	10 (16.9%)	8 (13.8%)	1.25 (2.53-2.94)	0.636
Recurrence in 3rd follow-up	8 (13.6%)	3 (5.2%)	2.62 (0.73-9.39)	0.120
Recurrence in 4th follow-up	6 (10.2%)	10 (17.2%)	0.58 (0.22-1.52)	0.266
Adverse Events				0.016
Allergic Reaction	0 (0%)	2 (3.4%)	0.19 (0.01-4.01)	0.150
Rise in LFT	0 (0%)	0 (0%)	-	0.999
Urosepsis	0 (0%)	2 (3.4%)	0.19 (0.01-4.01)	0.150
Cystitis	4 (6.8%)	11 (19%)	0.36 (0.12-1.05)	0.049
Gross Hematuria	1 (1.7%)	1 (1.7%)	0.98 (0.06-15.35)	0.990
Suprapubic Discomfort	3 (5.1%)	9 (15.5%)	0.33 (0.09-1.15)	0.063
Systemic BCG Infection	0 (0%)	1 (1.7%)	0.33 (0.01-7.88)	0.311
No Adverse Event	51 (86.4%)	32 (55.2%)		0.0001