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Comparing Mitomycin C and Bacillus Calmette-Guérin (BCG) for Managing Non-Muscle Invasive Bladder Cancer Patients: A Comparative Evaluation

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ABSTRACT

Background: The majority of bladder cancer cases that are initially diagnosed are non-muscle-invasive bladder cancers (NMIBCs). Recurrence and advancement are common, even though intravesical therapy and transurethral resection are common first lines of treatment. There is ongoing dispute about the best way to administer Bacillus Calmette-Guérin (BCG) and Mitomycin C (MMC), two commonly used medicines for intravesical instillation, particularly in cases involving high risk.

Objective: To compare the outcomes, recurrence risk, progression rate, and tolerability of intravesical BCG versus MMC in cases with high-risk NMIBC.

Patients and Methods: A randomized controlled trial was conducted from March 2021 to March 2023 across four Egyptian centers. A total of 90 cases with high-risk primary NMIBC were randomly assigned to either BCG or MMC treatment groups, with 45 cases in each. All participants underwent initial tumor resection followed by an immediate single dose of chemotherapy, then a six-week induction cycle with either BCG or MMC. Follow-up included routine cystoscopies, imaging, and laboratory monitoring over 24 months.

Results: Recurrence rates were lower among BCG group (around 18%) compared to MMC (approximately 29%), although not statistically significant. Time of occurring first recurrence was significantly longer among BCG arm. Progression rates were low and comparable in both groups. However, adverse effects—both local and systemic—were notably higher with BCG therapy, including cystitis, hematuria, and general symptoms like fever and fatigue.

Conclusion: The effectiveness of BCG and MMC in the management of high-risk NMIBC is comparable. It is important to carefully evaluate BCG's higher toxicity profile while choosing a treatment, even though it may more successfully delay recurrence.

Keywords: Mitomycin C, BCG, High-Risk Non-Muscle-Invasive Bladder Cancer.

INTRODUCTION

Bladder cancer stands among the most frequently encountered cancers worldwide, ranking ninth in overall incidence and contributing significantly to cancer-related deaths, positioned around the thirteenth globally[(1)]. Roughly three out of every four bladder cancer cases are initially found to be non-muscle-invasive (NMIBC), yet despite treatment, around one-fifth to a quarter of these cases eventually advance to muscle-invasive disease during a case's life[(2)].

Transitional (urothelial) carcinomas make up more than 90% of bladder tumors, with squamous cell and adenocarcinomas making up lower percentages[(3)]. The World Health Organization (WHO) and the International Society of Urological Pathology (ISUP) introduced new criteria for grading bladder tumors in 1998, expanding the previous system's categories to include papilloma, low-grade carcinoma, high-grade carcinoma, and papillary urothelial neoplasm of low malignant potential[(3)]. Tumor staging today follows the TNM system, with the "T" component assessing depth of invasion into the bladder wall[(4)].

Cases commonly present with painless visible blood in urine, and diagnosis typically follows transurethral tumor resection and pathological analysis. Management strategies for NMIBC generally involve intravesical therapy—especially for carcinoma in situ and high-grade cases. In contrast, muscle-invasive cancer often necessitates radical surgical removal of the bladder, with various types of urinary diversion considered depending on case factors[(5)]. Nonetheless, organ-sparing approaches such as transurethral resection combined with chemotherapy and radiotherapy remain valid in selected cases. Systemic chemotherapy also plays a role in advanced or metastatic settings[(5)].

Among the agents used in NMIBC, Bacillus Calmette-Guérin (BCG) and Mitomycin C (MMC) remain the most studied. Even after complete tumor resection, recurrence remains a persistent issue, potentially leading to disease progression[(6)]. BCG was first investigated for anti-cancer activity in the 1920s, with further studies expanding its application across various malignancies including lung, skin, and colon cancers[(7)]. While BCG is favored for its superior outcomes in reducing recurrence, it carries a higher risk of local and systemic side effects compared to MMC[(8)].

MMC, a cytotoxic antibiotic, continues to serve as a viable intravesical option, although recurrence rates vary widely. Its complications include chemical cystitis and skin irritation[(9)]. Given the recurrence risks and side-effect concerns associated with both agents, comparing their effectiveness and tolerability in high-risk NMIBC remains clinically relevant. Therefore, this study aims to evaluate and contrast the outcomes of

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intravesical BCG and MMC therapy in such cases, to guide more tailored and effective treatment planning.

PATIENTS AND METHODS

From March 2021 to March 2023, four medical centers—Helwan University Hospitals, Air Force Hospital, Al Maadi Military Hospital, and Kobri Al-Kobba Hospital—took part in this randomized controlled study. Patients who met the criteria were divided into two groups and given either intravenous BCG or MMC treatment in a 1:1 ratio using a sealed envelope method[10]. The recruitment process started in October 2020 and ended in mid-February 2021 with the last participant recruited.

Ethical approval:

Informed consent was collected from all cases, and the study was approved in advance by the Research Ethics Committee of the Faculty of Medicine at Helwan University (IRB: 15-2021). By utilizing coded records to anonymize identifiers, the confidentiality of case data was guaranteed. The study adhered to the Helsinki Declaration throughout its execution.

Study population:

Cases included in the study were newly diagnosed with high-risk non-muscle-invasive bladder cancer (NMIBC), as per the European Association of Urology 2020 guidelines. Eligible cases included Ta and T1 transitional cell carcinomas. Individuals with immunocompromised conditions such as HIV, organ transplantation, or cancer on immunosuppressants, also did not include females who were pregnant. Aside from high-risk and low-risk NMIBC, other exclusion criteria included recurrent bladder cancers, non-urothelial malignancies, and involvement of the upper tract[11].

Sample size:

The calculated minimum required sample size was 82, based on previously published data comparing BCG and MMC with a 29.5% difference in progression-free survival, alpha error of 0.05, and 80% power. To account for potential dropouts, the sample was expanded by 10%, bringing the final sample size to 90—equally divided into 45 cases in each group[12].

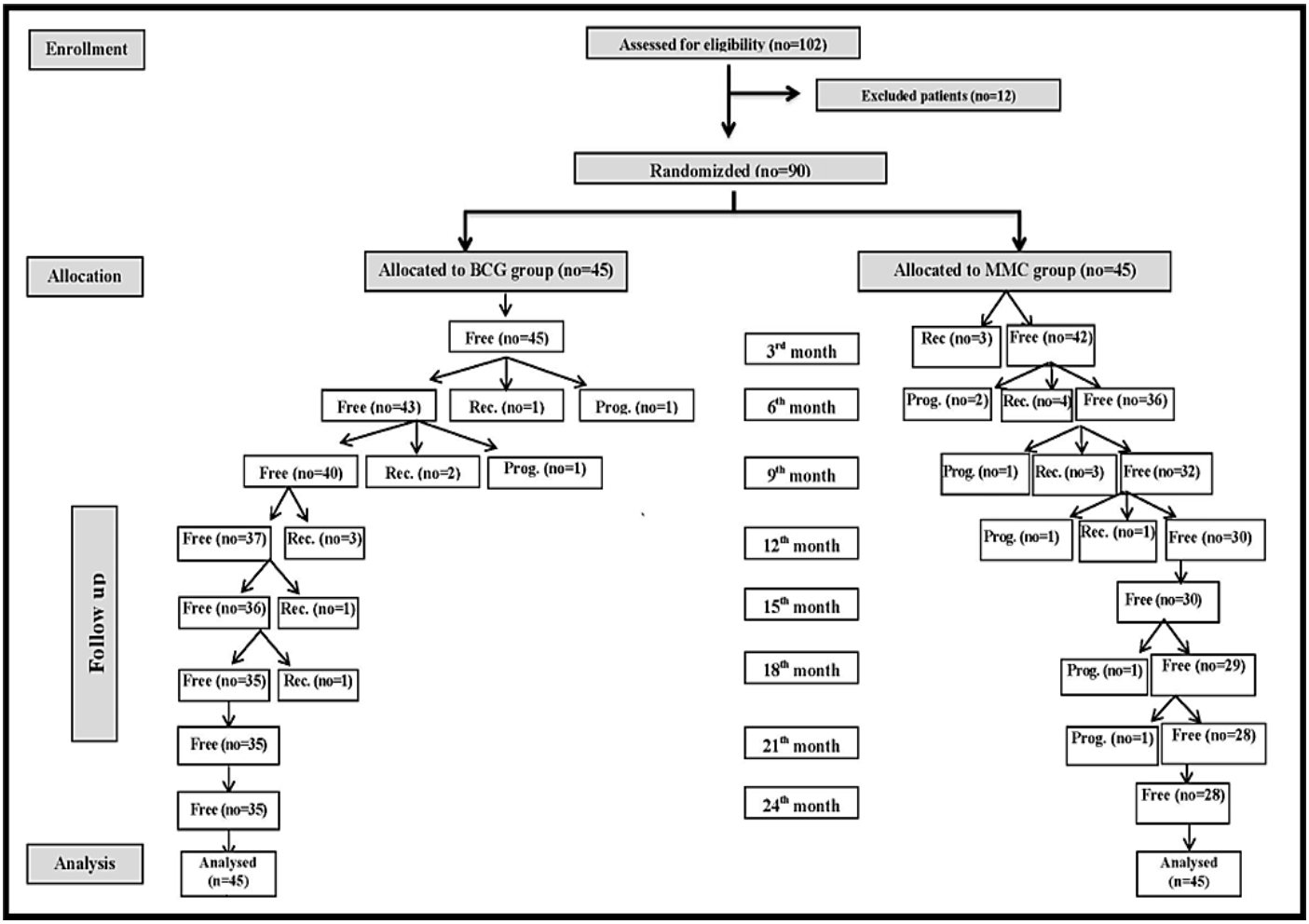

Figure (1): Consort flowchart

Sampling and randomization:
A simple random sampling approach was used. Eligible cases were randomized into two groups: Group A received intravesical BCG, and Group B received MMC. Allocation was determined using sealed, opaque envelopes to ensure allocation concealment.

Pre-treatment evaluation:
All cases underwent a complete clinical evaluation, including history-taking and physical examination. Laboratory tests included routine blood work and imaging via pelvic ultrasound and contrast-enhanced CT of the abdomen and pelvis. All cases had undergone transurethral resection of the bladder tumor (TURBT), and T1 cases or incomplete resections were followed by a second-look TURBT to ensure complete resection and muscle sampling[13].

Treatment protocol:
Post-TURBT, all cases received a single immediate instillation of MMC (40 mg in 20 ml saline) within 6 to 24 hours. After a 3–4 week healing period, cases began a six week induction course with either BCG (50 mg Tice strain in 50 ml saline) or MMC (40 mg in 20 ml saline). Maintenance differed by group: BCG cases received 3 weekly instillations at 3 and 6 months, then every 6 months for up to 2 years. MMC cases received a single monthly dose for one-year[14].

Follow-up and outcomes:
Cases were observed every three months in the first year and every six months in the second year by the use of cystoscopy and urine cytology. Imaging of the upper urinary tract was done biannually. Blood tests, including CBC, renal, and liver function, were repeated monthly. Study endpoints included tumor recurrence, progression to muscle-invasive disease, adverse effects, and time of occurring first recurrence or progression. All outcomes were recorded and analyzed[15].

Statistical analysis

The data was analyzed with the help of Jamovi and SPSS version 24. The Shapiro-Wilk test was used to determine if the quantitative data was normally distributed. When reporting data that did not follow a normal distribution, we utilized the median and range instead of the standard deviation and mean. For categorical variables, we used the chi-square test, and for continuous variables, we used the t-test. Use of the Kaplan-Meier curve allowed for the evaluation of the recurrence and progression rates. The results of the Cox regression analysis were presented as hazard ratios (HR) and 95% confidence intervals (CI), and they were used to discover factors that may be used to predict recurrence and progression. For statistical purposes, a p-value below 0.05 was deemed significant.

RESULTS

The two treatment groups, each with forty-five cases, showed no meaningful differences in their general characteristics at baseline. The average age was just above sixty-four among BCG group and nearly sixty-six in the MMC group. The difference between the two means wasn't statistically important. Sex-wise, men made up the vast majority in both arms—over ninety percent among BCG group and close to eighty-seven percent in the MMC arm. Smoking habits were also similar across both groups, with roughly seven out of ten among BCG group and slightly more in the MMC group reporting tobacco use (Figure **2**).

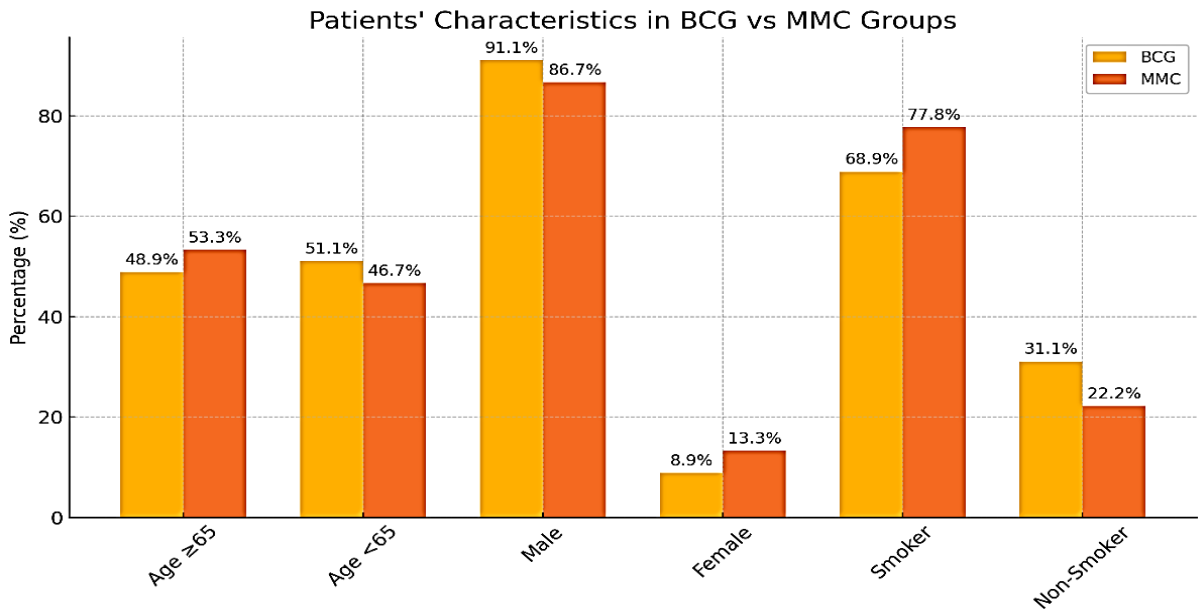

Figure (2): Demographic data of both groups.

The number, size, and other characteristics of tumors were comparable between both sets of cases. Most individuals had multiple tumors, and about four out of every five tumors were larger than three centimeters. The presence of carcinoma in situ, tumor stage (Ta or T1), and tumor grade (low or high) didn't show any significant imbalances between the two groups at the time of recruitment (Figure 3).

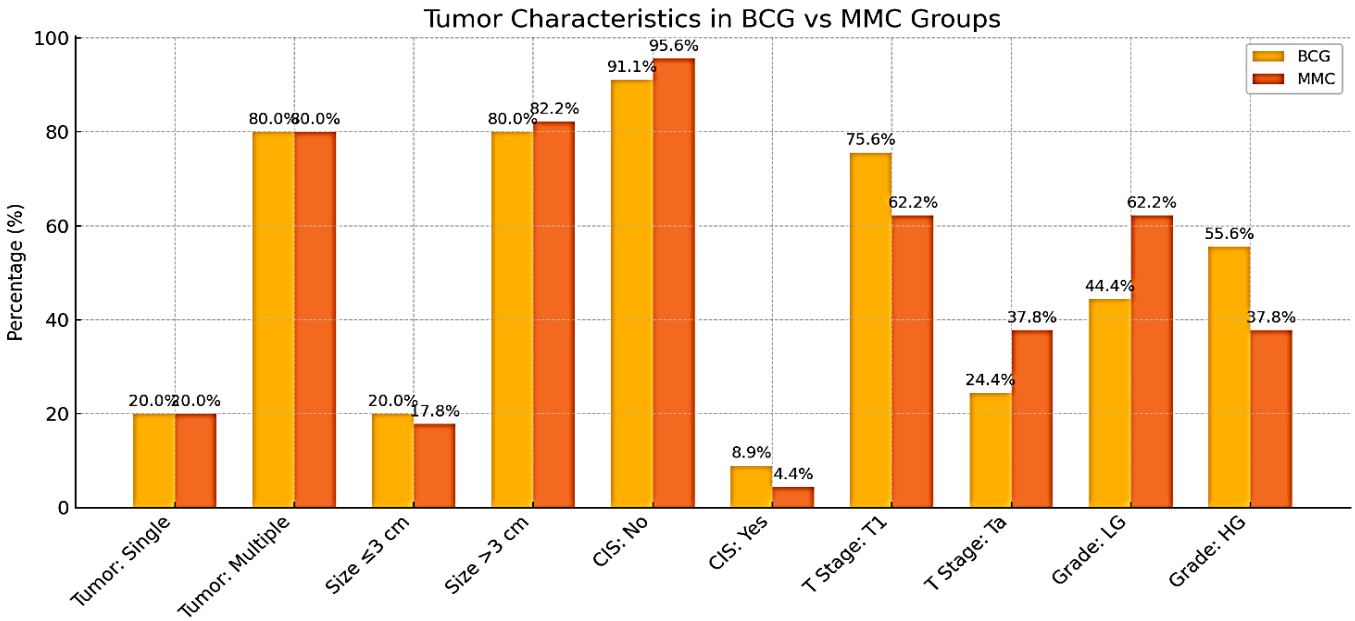

Figure (3): Tumor features among the both studied groups

Cases who received BCG had a noticeably higher occurrence of local side effects. For instance, four in ten reported bladder irritation or cystitis, compared to less than two in ten among MMC recipients. Visible bleeding was also more common with BCG—around one in four versus just a small number in the MMC group. Overall, three-quarters of BCG cases had some kind of local issue, whereas this happened in only about one in four in the MMC group (Figure **4**).

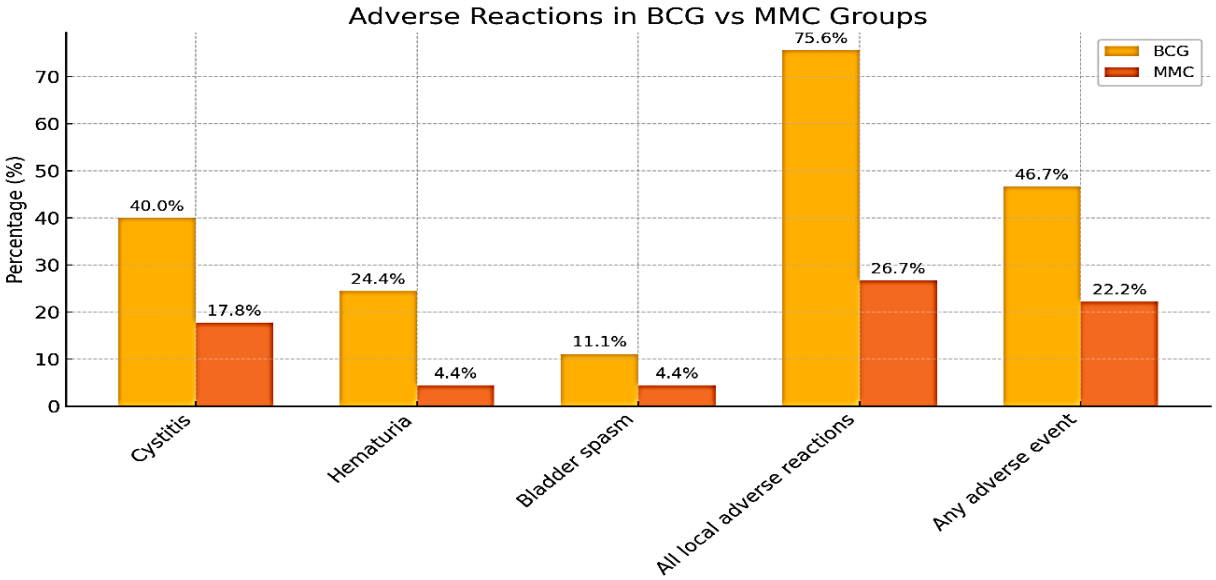

Figure (4): Adverse reactions in BCG Vs MMC groups

Systemic symptoms followed a similar pattern, with more cases among BCG group experiencing problems such as fever, fatigue, and joint pain. Fever occurred in 13.3% of BCG cases but was almost absent (2.2%) in those who received MMC. Complaints of general fatigue were also higher among BCG group. Altogether, more than 60% of BCG-treated cases reported systemic side effects, compared to less than 10% in the MMC arm (Figure **5**).

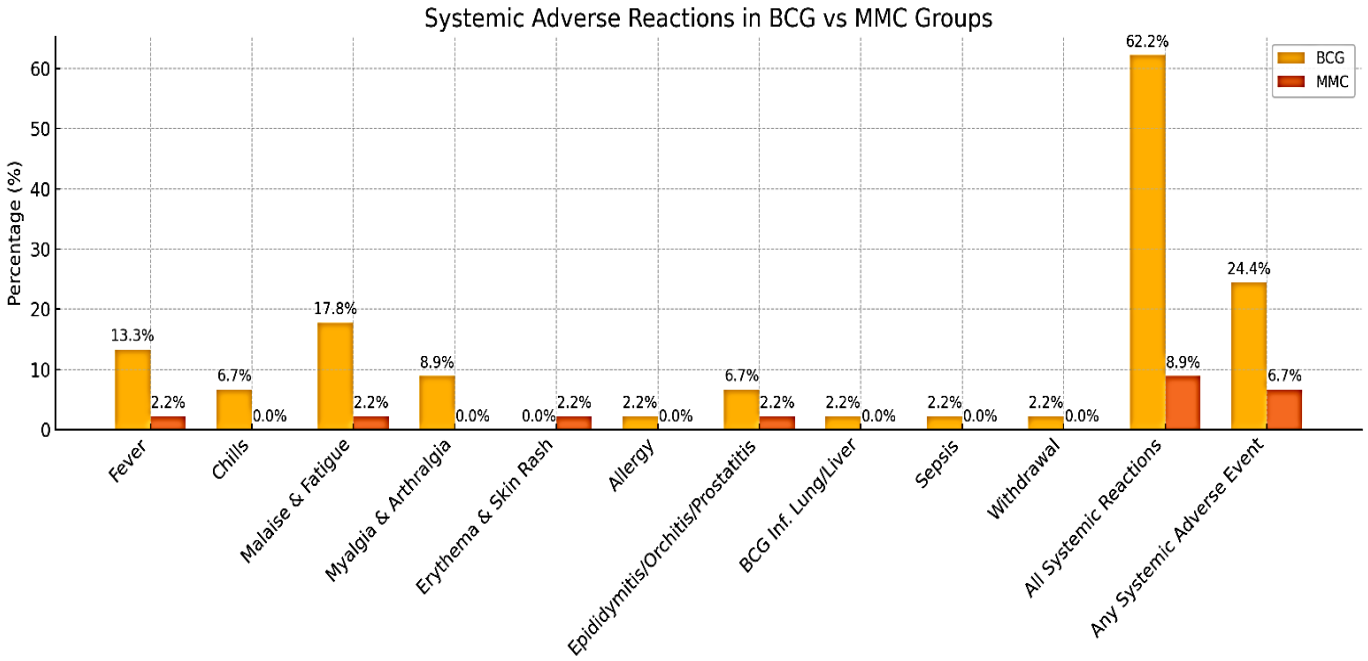

Figure (5): Systemic adverse reactions in BCG Vs MMC groups

Although the overall recurrence rate was lower among BCG group—under 18%—compared to about 29% in the MMC group, this difference was not statistically significant. However, the time before the first recurrence happened was longer for those who received BCG (over eleven months on average), compared to just over eight months in the MMC group. One-year recurrence-free survival was higher among BCG group, at about 86%, compared to 75% for MMC. At two years, the same pattern held: roughly 82% for BCG versus 70% for MMC. Progression to more invasive disease occurred in a small number of cases across both groups—two among BCG arm and four in the MMC arm. This difference wasn't statistically meaningful. The average time before progression was similar between the two treatments (Figures **6**,**7**).

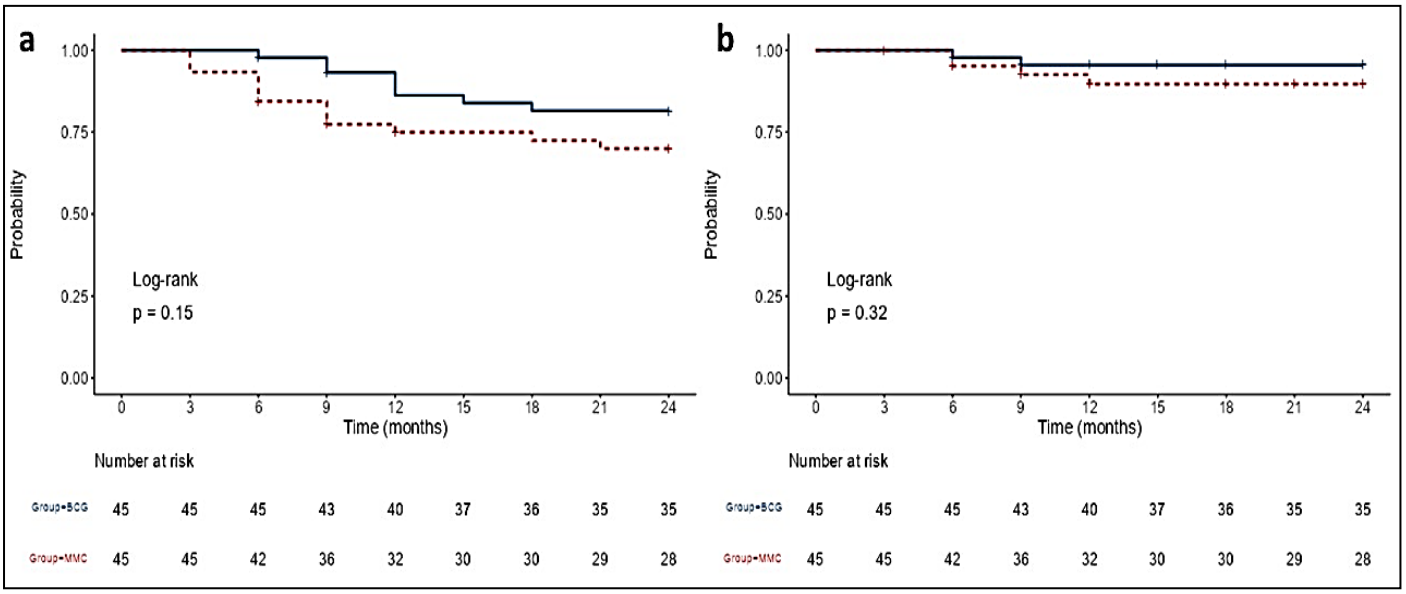

Figure (6): Kaplan-Meier curve of a) Recurrence and b) Progression

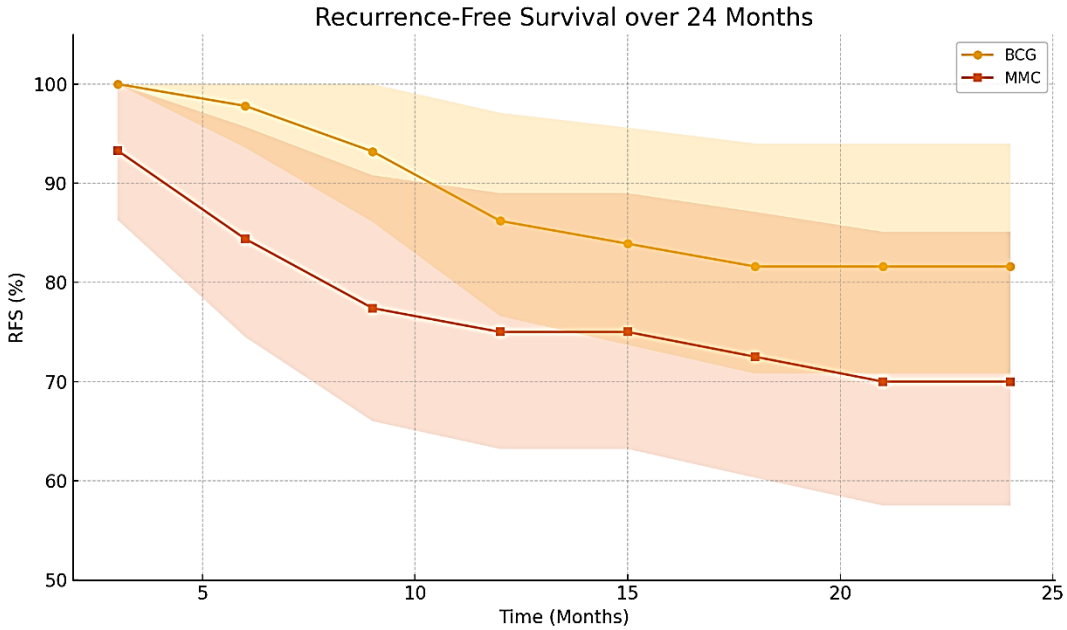

Figure (7): Recurrence-free survival over 24 months

Looking at recurrence over time, no events were reported in either group during the final six months of the two-year follow-up. The highest rates of recurrence were seen within the first year, particularly at six and nine months. By the 12-month mark, the recurrence rate remained lower among BCG group. Progression events were few, and all occurred within the first year. None were seen during the second year (Figure **8**).

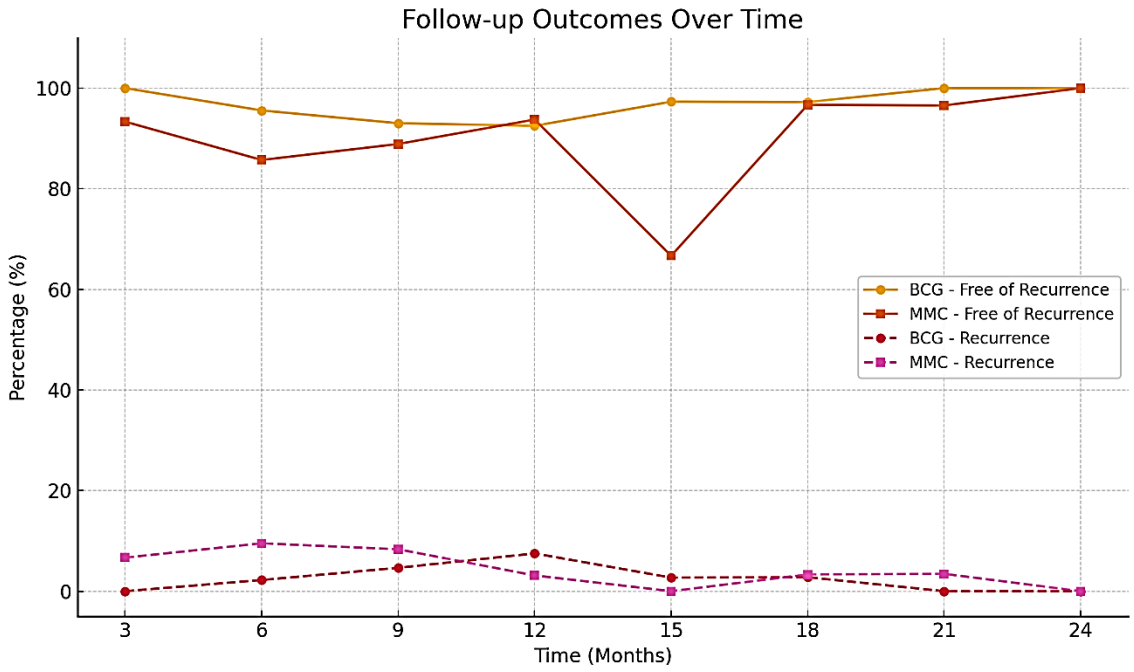

Figure (8): Follow-up outcomes over time

Predictors of Recurrence

On regression analysis, one group of cases showed a significantly higher risk for tumor recurrence: those with Ta tumors who also had large tumors (over 3 cm), more than one tumor, and were older than seventy. This group was more than twice as likely to experience recurrence compared to cases with T1 tumors. Other factors, like sex or smoking, didn't show any clear link with recurrence or progression (Figures **9**,**10**).

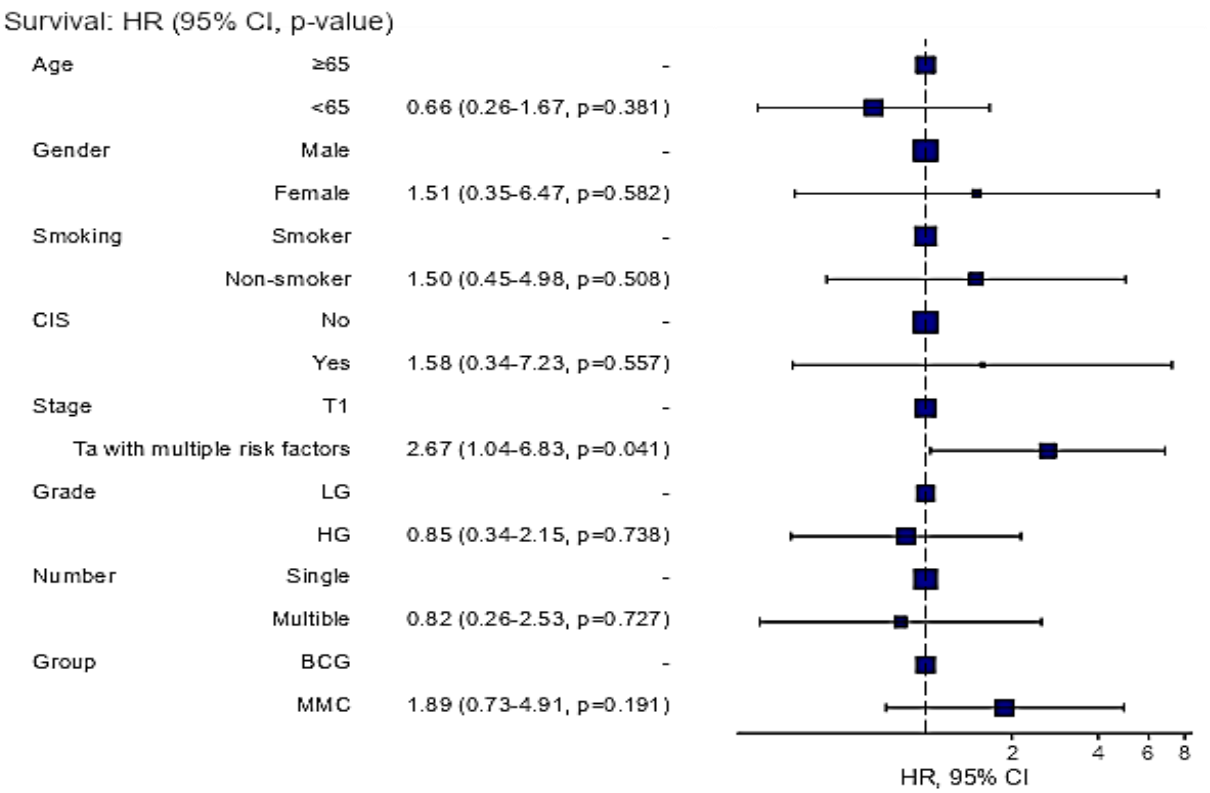

Figure (9): The Cox regression analysis of the predictors of recurrence

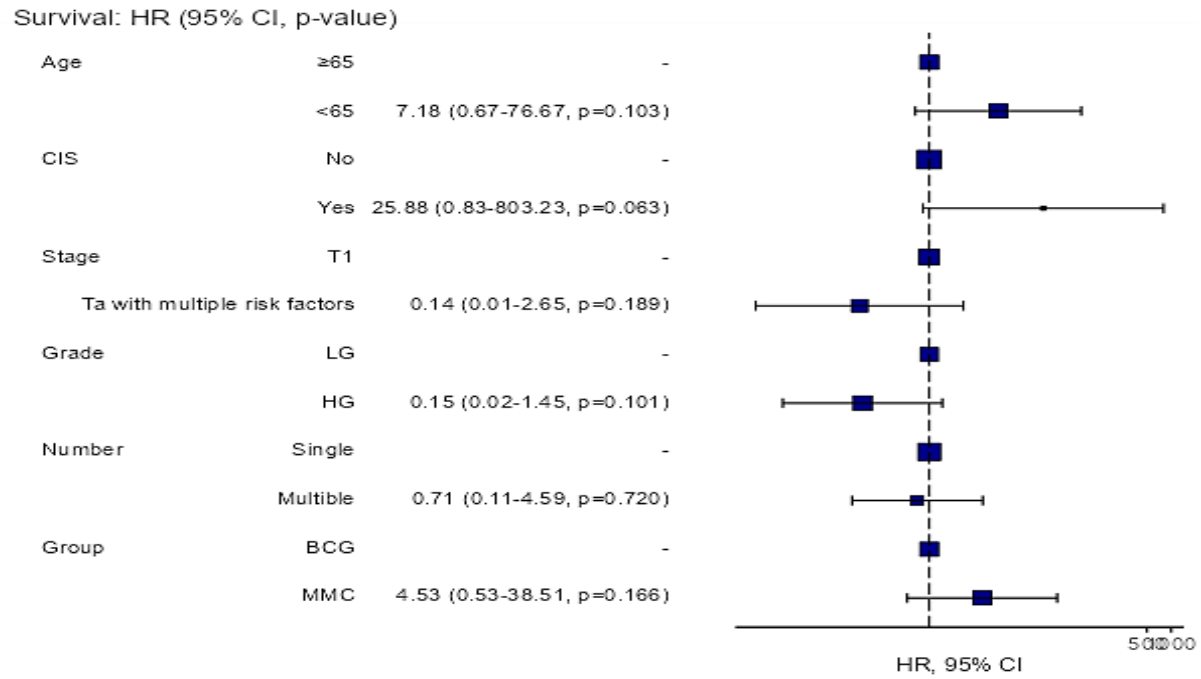

Figure (10): The Cox regression analysis of the predictors of progression

While the total number of cases who remained recurrence- and progression-free was higher among BCG group (77.8% versus 62.2% in MMC), the difference didn't reach statistical significance. What did stand out clearly was the time to first recurrence, which was significantly delayed in cases treated with BCG. All other measured outcomes—such as time to progression or overall recurrence rates—showed no major difference between the two regimens (Figure **11**).

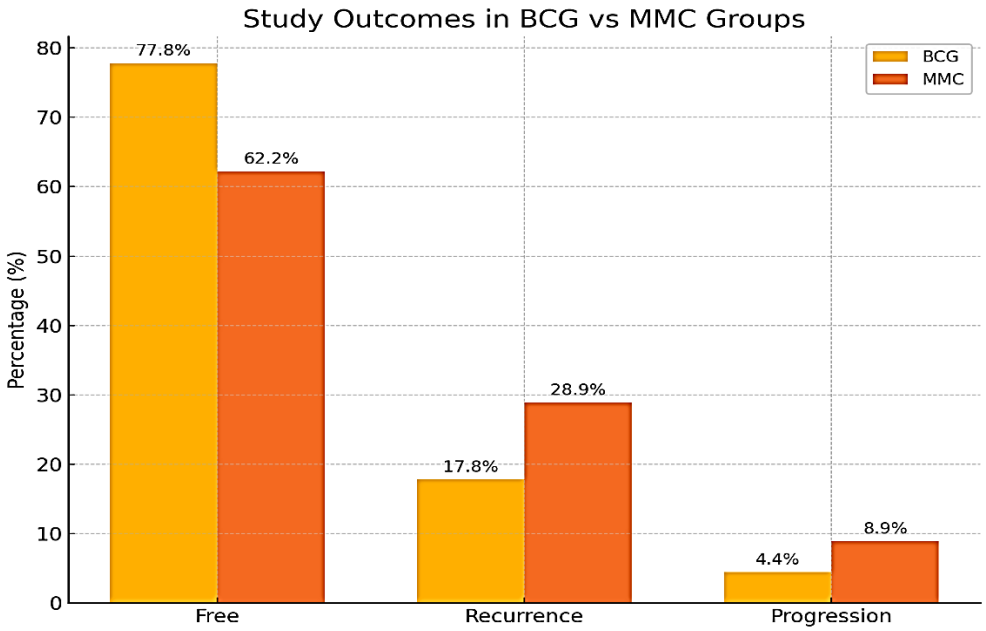

Figure (11): Study outcomes in BCG Vs MMC groups.

DISCUSSION

This randomized study explored and compared the effectiveness and safety profiles of intravesical BCG and MMC in cases with high-risk NMIBC. The main finding was that although recurrence and progression rates did not differ significantly between both groups, the BCG-treated cases had a longer interval before recurrence, but they also experienced considerably more adverse effects, both local and systemic.

The similarity in recurrence and progression percentages aligns with prior studies that showed both MMC and BCG were beneficial in managing NMIBC, particularly in high-risk cases where the likelihood of tumor regrowth is substantial. However, what stood out in our study was the delay in time of occurring first recurrence observed among BCG group, which implies a stronger early protective effect of BCG compared to MMC, even if the long-term recurrence rates were not statistically different. This may suggest that BCG, through its immune-stimulatory mechanism, could offer a temporary window of stronger disease control[16].

Yet, this advantage came at a cost. The frequency of bladder irritation, hematuria, and systemic symptoms like fever and fatigue were notably higher in those who received BCG. These side effects, while manageable, might significantly affect quality of life and case compliance with treatment, especially in older adults or those with comorbid conditions[17]. In contrast, MMC appeared to be better tolerated, with a much lower incidence of both local and systemic toxicity. This supports its continued use, particularly in cases where side effect profile plays a critical role in determining the most suitable therapy[18].

Interestingly, although recurrence-free survival at one and two years was numerically better among BCG group, the lack of a statistically significant difference underscores the need to individualize therapy rather than rely solely on broad guideline recommendations. In resource-limited settings, or when case tolerance is a major concern, MMC may still be a valid and practical alternative[19].

Regression analysis in our study also indicated that certain tumor-related factors—particularly multiple tumors, size greater than three centimeters, and case age over seventy—might independently increase the likelihood of recurrence. These findings reflect what previous literature has shown regarding tumor burden and host-related factors as important predictors of recurrence in NMIBC[20].

Overall, our findings highlight a clinical trade-off: while BCG might offer longer disease control upfront, it is accompanied by a heavier side-effect burden. Therefore, when deciding between these two agents, clinicians must balance disease characteristics, case tolerance, comorbidities, and personal preferences. In select cases, MMC may offer a safer, well-tolerated option without a major compromise in long-term outcome.

Study strengths and limitations

Despite the value of the findings, this study comes with a few points that should be kept in mind when interpreting the results. First, although randomization was applied, the relatively small sample size may have limited the strength of statistical comparisons, especially for less frequent outcomes like progression. Also, the study was carried out in only four centers, which may reduce the generalizability of the results to different clinical settings or populations. Another challenge is that case adherence to follow-up schedules and intravesical instillation protocols may vary in real-world practice, possibly affecting treatment outcomes outside the study setting. Lastly, while adverse effects were reported in detail, quality-of-life measures were

not formally assessed, which could have provided a deeper understanding of case experience with either treatment. Including such metrics in future work may help clarify the broader impact of each approach beyond just clinical endpoints.

CONCLUSION

This study compared the therapeutic outcomes and safety of BCG and MMC in patients with high-risk non-muscle-invasive bladder cancer. Both agents showed similar overall performance in reducing recurrence and halting disease progression over a two-year period. However, BCG was associated with a longer time to first recurrence, which may suggest a more durable early response. On the other hand, MMC had a noticeably better tolerability profile, with fewer patients experiencing bothersome local or systemic reactions.

These findings suggest that both treatment options remain valuable, but their use should be tailored based on individual patient characteristics, tolerance, and treatment goals. In patients who can handle the side effects, BCG may offer stronger short-term control. Meanwhile, MMC may be preferred in those who prioritize fewer complications or have conditions that make them less suitable for immunotherapy. Personalized treatment planning is essential to strike the right balance between efficacy and safety in managing high-risk NMIBC.

So, the effectiveness of BCG and MMC in the management of high-risk NMIBC is comparable. It is important to carefully evaluate BCG's higher toxicity profile while choosing a treatment, even though it may more successfully delay recurrence.

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