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Defining the optimal duration of maintenance mitomycin C in intermediate-risk Ta NMIBC: a multicenter retrospective landmark analysis

Roberto Contieri[1] · Letizia Maria Ippolita Jannello[2,3] · Mihai Dorin Vartolomei[4,5] · Beat Roth[4] · Roberto Bianchi[2,3] · Giuseppe Fallara[2,3] · Marco Tozzi[2,3] · Martina Maggi[2,3] · Francesco Chierigo[2,3] · Francesco Pellegrino[2,3] · Ludovica Cella[6] · Alessandro Uleri[6,7] · Luigi Da Pozzo[8,9] · Francesco Claps[10] · Achille Aveta[1] · Gianluca Spena[1] · Enrico Checcucci[11] · Cecilia Gatti[11] · Pierluigi Bove[12,13] · Francesca Vedovo[14] · Gian Maria Busetto[15] · Ugo Falagario[16] · Riccardo Mastroianni[17] · Alessandro Tedde[18] · Massimo Madonia[18] · Pasquale Di Tonno[19] · Giuseppe Lucarelli[19] · Saverio Forte[19] · Giorgio Ivan Russo[20] · Fabrizio Verweij[21] · Marco Racioppi[22] · Francesco Pio Bizzarri[23] · Marco Borghesi[24] · Marco Rinaldi[25] · Fabio Zattoni[26] · Luca Boeri[2,27] · Elisa De Lorenzis[2,27] · Andrea Conti[28] · Maria Angela Cerruto[29,30] · Felice Crocetto[31] · Giuseppe Simone[17] · Savino Mauro Di Stasi[12] · Cosimo De Nunzio[15] · Luca Carmignani[28] · Giovanni Liguori[14] · Angelo Porreca[32] · Biagio Barone[33] · Emanuele Montanari[27] · Albo Giancarlo[27] · Alessandro Antonelli[29,30] · Alessandro Veccia[29,30] · Fabrizio Dal Moro[26] · Giuseppe Carrieri[16] · Luigi Cormio[16] · Carlo Terrone[24] · Francesco Porpiglia[11] · Sisto Perdonà[1] · Bernardo Rocco[22] · Rodolfo Hurle[34] · Michele Catellani[8] · Matteo Ferro[2,3]

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Abstract

Purpose While mitomycin C (MMC) is widely used for intravesical therapy, the optimal maintenance regimen for non-muscle invasive bladder cancer (NMIBC) remains unclear. This study assessed the impact of MMC maintenance on recurrence-free survival (RFS) in patients with intermediate-risk Ta NMIBC and aimed to identify the optimal number of instillations for improved outcomes.

Methods We conducted a retrospective multicenter analysis of patients with Ta NMIBC treated with transurethral resection and adjuvant MMC across 13 Italian centers (2010–2023). Patients were grouped based on MMC maintenance duration: no maintenance, short-term (≤ 6 instillations), and long-term (> 6 instillations). Kaplan–Meier curves, Cox regression, and CART analysis were used to evaluate RFS and high-grade RFS (HG-RFS).

Results Among 292 patients included, maintenance therapy significantly improved 2-year and 3-year RFS compared to no maintenance (78% vs. 55% and 67% vs. 30%, respectively; $p < 0.001$). CART analysis identified > 6 instillations as the threshold for optimal benefit. Long-term maintenance was associated with a lower risk of recurrence (HR 0.23 vs. no maintenance; HR 0.39 vs. short-term; both $p < 0.001$). No significant difference in HG-RFS was observed between no maintenance, long-term, and short-term groups.

Conclusion Long-term MMC maintenance (> 6 instillations) significantly prolongs RFS in patients with Ta NMIBC. These findings suggest that extended MMC regimens may improve patients' outcomes and should be considered in clinical practice. Prospective studies are needed to confirm these results and guide evidence-based treatment strategies.

Keywords Ta NMIBC · Bladder cancer · Landmark analysis · Mitomycin C · Instillation duration

Introduction

Approximately 75% of diagnosed bladder cancers are non-muscle invasive bladder cancer (NMIBC). Tumors that do not invade the lamina propria, classified as Ta, typically exhibit a consistent risk of recurrence and a relatively low

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progression rate towards muscle-invasive disease [1]. The primary treatment for NMIBC is transurethral resection of the bladder tumor (TURBT), complemented by adjuvant intravesical instillations in selected patients [2]. These adjuvant therapies are tailored according to specific risk group classifications. Despite recent advances, Bacillus Calmette–Guerin (BCG) and mitomycin C (MMC) remain the mainstays of these treatments. Additionally, Ta tumors are variably assigned to risk groups, with a significant number falling within the intermediate risk category. It is important to note that the criteria for defining intermediate risk are not consistent across key urological associations, including the European Association of Urology (EAU), the American Urological Association (AUA), and the International Bladder Cancer Group (IBCG).

For intermediate-risk bladder tumors, which regimen, number of instillations, and modality of administration is most appropriate is still a debatable question [2]. For instance, BCG scheme and 1 year of optimal 40 mg/40 ml MMC treatment (11 months maintenance) were shown to have similar oncological outcomes in terms of recurrence-free survival (RFS) and progression-free survival (PFS) [3]. Furthermore, a recent meta-analysis of 11 trials comparing BCG vs. MMC in a maintenance setting confirmed no difference in intermediate-risk NMIBC (2-year RFS: 78 vs. 76%, respectively) [4]. A meta-analysis that included 31 trials comparing MMC with other treatments for NMIBC recurrence reported a statistically significant risk reduction of 37% (pooled RR = 0.63; 95% CI 0.58–0.68) [5]. Despite the substantial body of literature, the EAU guidelines remain ambiguous regarding the administration regimen for MMC, stating that "the optimal schedule and duration of intravesical chemotherapy instillation has not been defined; however, it should not exceed 1 year" [2]. In this multicentre retrospective study, we assessed the impact of maintenance therapy on recurrence rates among patients with Ta NMIBC treated with various adjuvant MMC regimens.

Methods

Data source and study population

This retrospective multicenter study focused on patients with EAU 2021 intermediate-risk Ta NMIBC who underwent TURBT and adjuvant intravesical instillations with MMC across 13 Italian centers between 2010 and 2023. The primary objective of this study was to evaluate the impact of MMC maintenance therapy on RFS compared to no maintenance therapy.

The secondary objective was to identify the optimal threshold for the number of instillations associated with a reduced recurrence risk.

A tertiary objective was to investigate whether an extended maintenance regimen (exceeding the identified threshold) was associated with improved RFS and High Grade–RFS (HG–RFS) compared to short-term maintenance (below the threshold) and no maintenance.

Repeat TURBT (re-TURBT) was generally performed within 2–6 weeks, following European guidelines. A single, immediate postoperative instillation of chemotherapy was administered according to each participating center's standard practice and at the discretion of the treating clinician. Surveillance cystoscopy schedules were standardized across centers, adhering to current NMIBC guidelines. Induction therapy was defined as a weekly schedule of usually 4–6 MMC instillations, whereas maintenance therapy was defined as monthly instillations following induction, consistent with previous studies on MMC use [6]. Maintenance MMC regimens varied across centers and were determined by individual providers according to institutional protocols, patient preference, presence of risk factors, and bladder functionality. Maintenance instillations were administered monthly. Follow-up schedules were based on clinician discretion, following European guidelines.

Variables and endpoint

Covariates consisted of patient demographics, tumor stage, tumor grade (classified according to both WHO 1973 and WHO 2004/2022 systems), tumor size, multifocality, and the administration of immediate single intravesical instillations.

The primary endpoint of the study was RFS, defined as the time (months) from the date of diagnosis to the first histologically confirmed recurrence.

Secondary endpoints included HG-RFS, defined as the time (months) from diagnosis to the first histologically confirmed high-grade recurrence.

Statistical analyses

Descriptive statistics were employed to summarize the study cohort. Categorical variables were presented with frequencies and proportions, while medians and interquartile ranges (IQRs) were used for continuous variables. Categorical variables were analyzed using Pearson's chi-square test or Fisher's exact test, as appropriate. The median follow-up duration was estimated using the reverse Kaplan–Meier method. Survival estimates were calculated using the Kaplan–Meier method, and differences between groups were assessed using the log-rank test. A landmark analysis was conducted with t_0 set at 12 months to minimize lead-time bias. Cox proportional hazards regression models accounting for potential confounders such as tumor size > 3 cm, multifocality, and recurrent tumors, and stratified by institution, were employed to evaluate the association between the duration

of maintenance MMC therapy and oncological outcomes. A Classification and Regression Tree (CART) analysis was performed to identify the optimal cut-off for the number of instillations associated with a reduced recurrence risk.

Subsequently, all analyses were repeated after stratification according to the optimal cut-off for the number of instillations. To confirm the robustness of the multivariable Cox models, we performed a bootstrap validation with 1000 replications. In this analysis, stratification by center was omitted because bootstrap resampling can lead to convergence issues.

As a complementary analysis, we calculated absolute risk differences (ARD) in RFS at years by subtracting Kaplan–Meier survival estimates between groups, and derived the corresponding number needed to treat (NNT) as the inverse of the ARD. Hazard ratios (HRs) with 95% confidence intervals (CIs) were reported for Cox regression analyses.

The statistical significance threshold was set at $p < 0.05$. All statistical analyses were performed using Stata/SE version 18 (StataCorp, College Station, TX, USA).

Results

A total of 292 patients treated with adjuvant MMC instillations were included in the analysis. The demographic and pathological characteristics of the cohort are summarized in Table 1. Among the 44 patients (15%) who underwent re-TURBT, the median time to re-TURBT was 4 weeks (IQR 3–5). Only 8% received a one-shot postoperative instillation.

All patients received at least one induction cycle, with a median of 6 instillations (IQR 3–8). Additionally, 249 patients (85%) underwent maintenance therapy, with a median of 6 instillations (IQR 4–9).

The median follow-up was 33 months (IQR 6–57). Overall, 147 patients (50%) experienced disease recurrence, with 56 (19%) developing high-grade recurrence and 14 (5%) progressing to muscle-invasive disease.

For the landmark analysis of RFS, patients censored or those experiencing recurrence within 12 months of diagnosis ($n = 96$) were excluded. Similarly, for HG-RFS, patients censored or those developing a high-grade recurrence within 12 months ($n = 65$) were excluded. Among patients who did not receive maintenance therapy, the 2-year and 3-year RFS rates were 55% (95% CI 32–73%) and 30% (95% CI 13–50%), respectively. In contrast, among those receiving maintenance therapy, the 2-year and 3-year RFS rates were significantly higher at 78% (95% CI 71–84%) and 67% (95% CI 59–74%), respectively. Kaplan–Meier curves for RFS stratified by maintenance therapy status are shown in Fig. 1, demonstrating a statistically significant difference ($p < 0.001$).

Table 1 Baseline demographic and tumor characteristics of the 292 patients with Ta NMIBC treated with adjuvant mitomycin C

Variables	Overall population ($N = 292$)
Age, *n* (%)	
> 70 years	169 (58%)
Recurrent tumor, *n* (%)	
Yes	210 (72%)
Multifocality, *n* (%)	
Yes	188 (64%)
Maximum diameter > 3 cm, *n* (%)	
Yes	64 (22%)
WHO grade 1973, *n* (%) ($N = 271$)	
G1	129 (48%)
G2	118 (43%)
G3	24 (9%)
WHO grade 2004/2016, *n* (%)	
Low-grade	255 (87%)
High-grade	37 (13%)
Re-TURBT, *n* (%)	
Yes	44 (15%)
Single postoperative instillation (%)	
Yes	22 (8%)

In a Cox regression analysis adjusted for tumor size > 3 cm, multifocality, and recurrent tumors stratified by institution, maintenance therapy was associated with a significantly lower risk of recurrence (HR 0.13, 95% CI 0.06–0.31, $p < 0.001$).

We employed CART analysis to identify a threshold for the minimum number of monthly instillations associated with a reduced recurrence risk beyond 12 months. The analysis determined that receiving more than 6 monthly instillations was the optimal cut-off (Relative HR 0.63).

Based on this threshold, patients who underwent maintenance therapy with MMC were stratified into two groups: short-term maintenance (≤ 6 instillations) ($n = 137$, 55%) and long-term maintenance (> 6 instillations) ($n = 112$, 45%). The demographic and pathological characteristics of the cohort, stratified according to maintenance therapy status, are summarized in Table 2. The 2-year and 3-year RFS were 67% (95% CI 33–73%) and 49% (95% CI 35–62%) in patients receiving short-term maintenance and 86% (95% CI 77–91%) and 77% (95% CI 67–84%) in patients receiving long-term maintenance. At 3 years, the absolute difference in RFS between patients receiving long-term (> 6 instillations) versus short-term maintenance was 28%, corresponding to an estimated NNT of approximately 4 to prevent one recurrence within 3 years.

Kaplan–Meier curves stratified by maintenance therapy status (long vs short vs no maintenance) are shown in

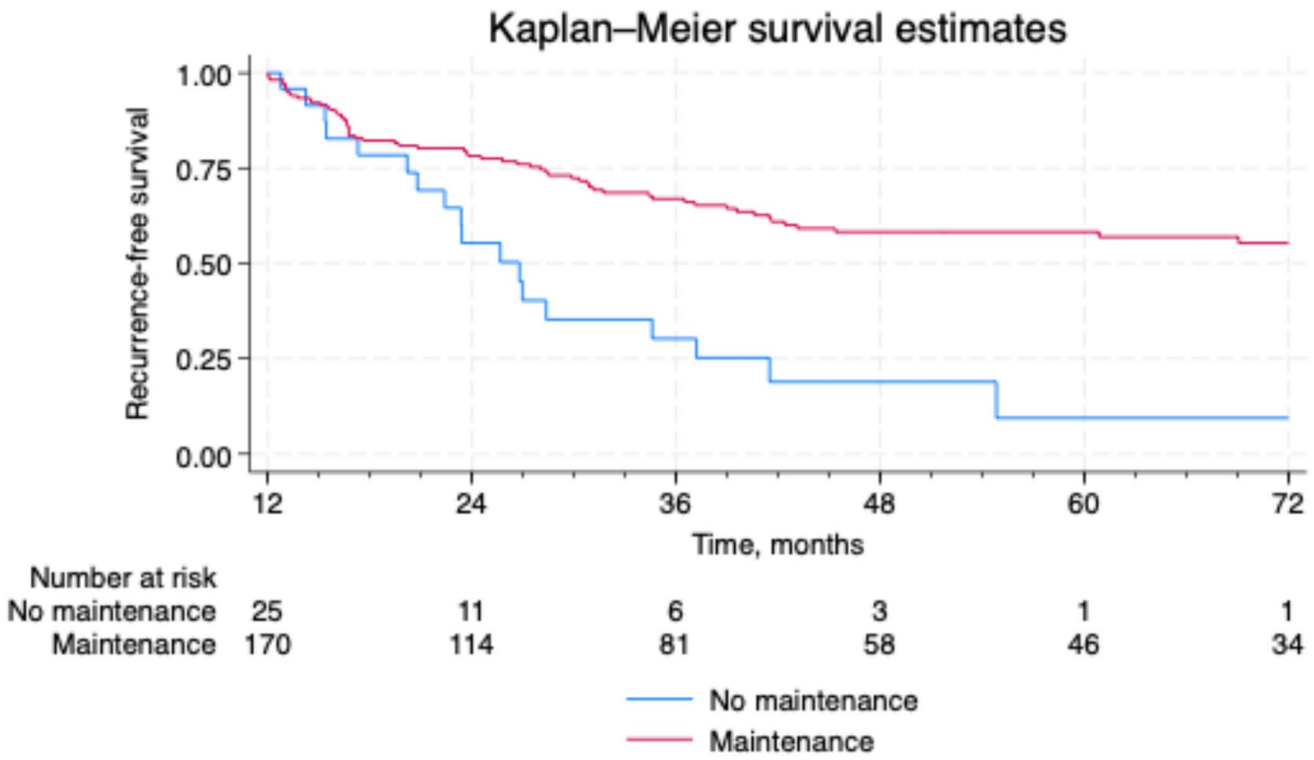

Fig. 1 12-Months landmark Kaplan–Meier estimates of RFS in 195 patients, stratified by receipt of MMC maintenance therapy (no maintenance in blue vs. maintenance in red)

Fig. 2, demonstrating a statistically significant difference ($p < 0.001$).

In a Cox regression analysis accounting for tumor size > 3 cm, multifocality, and recurrent tumors, stratified by institution, patients receiving more than 6 monthly instillations demonstrated a significantly lower risk of recurrence compared to both those who did not receive maintenance therapy (HR 0.09, 95% CI 0.03–0.22, $p < 0.001$) and those who underwent short-term maintenance (HR 0.22, 95% CI 0.09–0.57, $p = 0.002$) (Suppl. Table 1A–B).

These findings were confirmed by bootstrap validation with 1000 replications, demonstrating a consistently lower risk of recurrence both versus no maintenance (HR 0.23, 95% CI 0.12–0.43, $p = 0.001$) and versus short-term maintenance (HR 0.38, 95% CI 0.23–0.65, $p < 0.001$).

The 2-year and 3-year HG–RFS rates in patients who did not receive maintenance therapy were 92% (95% CI 72–98%) and 84% (95% CI 62–94%), respectively.

Among patients who underwent short-term maintenance, the 2-year and 3-year HG-RFS rates were both 92% (95% CI 83–96%), while patients receiving long-term maintenance exhibited HG-RFS rates of 93% (95% CI 87–97%) at 2 years and 90% (95% CI 83–95%) at 3 years.

Kaplan–Meier curves stratified by maintenance therapy status (long-term vs. short-term vs. no maintenance) are shown in Fig. 3, demonstrating no statistically significant difference ($p = 0.063$).

In a Cox regression analysis accounting for tumor size > 3 cm, multifocality, and recurrent tumors, stratified by institution, patients receiving more than 6 monthly instillations did not exhibit a significantly lower risk of HG-RFS compared to those who did not receive maintenance therapy (HR 0.52, 95% CI 0.12–2, $p = 0.34$) or underwent short-term maintenance (HR 0.67, 95% CI 0.22–2.03, $p = 0.48$) (Suppl Table 2A2–B).

Discussion

While the BCG scheme is standardized, induction plus 3-weekly instillations at 3, 6, and 12 months, the optimal schedule for chemotherapy maintenance is unknown [2, 7]. We aimed to assess the impact of MMC maintenance on RFS and identify the optimal threshold of MMC instillations that confer a protective effect against disease relapse. To address this knowledge gap, we relied on a multicenter database composed of 13 centers from 2010 to 2023 and made several noteworthy observations.

The first main outcome of our study was to assess the impact of MMC maintenance on RFS. We found that

Table 2 Baseline demographic and tumor characteristics of the 292 patients with Ta NMIBC treated with adjuvant mitomycin C, stratified by maintenance therapy status

	No maintenance	Maintenance ≤ 6 months	Maintenance > 6 months	*p*-value
	N = 43	*N* = 137	*N* = 112	
Age, *n* (%)				
> 70 years	30 (70%)	81 (59%)	58 (52%)	0.12
Recurrent tumor, *n* (%)				
Yes	41 (95%)	107 (78%)	62 (55%)	**< 0.0001**
Multifocality, *n* (%)				
Yes	24 (56%)	88 (64%)	76 (68%)	0.5
Maximum diameter > 3 cm, *n* (%)				
Yes	8 (19%)	20 (15%)	36 (32%)	**0.003**
WHO grade 1973, *n* (%) (*N* = 271)				
G1	18 (44%)	57 (48%)	54 (49%)	
G2	21 (51%)	49 (41%)	48 (44%)	0.6
G3	2 (5%)	14 (12%)	8 (7.3%)	
WHO grade 2004/2016, *n* (%)				
Low-grade	37 (86%)	114 (83%)	104 (93%)	
High-grade	6 (14%)	23 (17%)	8 (7%)	0.072
Re-TURBT, *n* (%)				
Yes	5 (12%)	22 (16%)	17 (15%)	0.8
Single postoperative instillation (%)				
Yes	3 (7%)	13 (10%)	6 (5%)	0.5
Patients at risk for RFS after 12 months				
Yes	25 (58%)	71 (52%)	99 (88%)	–

Significant differences were observed in the prevalence of recurrent tumors and tumor diameter > 3 cm

p-values below the threshold of *p* 0.05 are reported in bold

patients receiving maintenance therapy exhibited significantly improved 2-year and 3-year RFS compared to those who did not receive maintenance therapy, supporting previous findings in the literature [8]. Moreover, our results align with prior meta-analyses indicating that MMC provides a recurrence risk reduction comparable to BCG in intermediate-risk NMIBC patients [4]. The adjusted Cox regression model further confirmed that maintenance therapy was associated with a markedly lower recurrence risk (HR 0.40, $p < 0.001$). These findings highlight the protective role of MMC maintenance in prolonging RFS. The second main point of our study was to determine if there was a time cut-off where maintenance had a distinct advantage. To obtain the strongest results, we relied on multiple statistical tools. First, we employed a machine-learning model (CART) to identify the threshold number of MMC instillations beyond which patients exhibit a reduced risk of recurrence.

Second, to minimize immortal time and treatment exposure bias, we performed a 12-month landmark analysis. This approach excluded patients who experienced early recurrence and therefore received fewer instillations than planned or did not receive maintenance at all, allowing a more standardized comparison of different maintenance schedules on long-term recurrence outcomes.

This analysis further validated the benefit of maintenance MMC, particularly in patients receiving more than 6 months of instillation maintenance. The 2-year and 3-year RFS rates were significantly higher in the long-term maintenance group compared to both the short-term maintenance and no-maintenance groups. Moreover, long-term MMC therapy was associated with a significantly lower risk of recurrence compared to no maintenance (HR 0.23, $p < 0.001$) and short-term maintenance (HR 0.39, $p = 0.001$). Interestingly, when considering HG-RFS, no statistically significant difference was observed, indicating that while MMC maintenance reduces overall recurrence, its impact on high-grade recurrences warrants further investigation.

Risk stratification of Ta NMIBC remains challenging [9]. HG-Ta tumors are associated with a greater risk of progression, and most clinical guidelines recommend BCG as the preferred treatment for these patients [10, 11]. However, the EAU guidelines classify some patients with HG Ta disease within the intermediate-risk group, suggesting either one year of BCG maintenance or MMC, similarly to patients with recurrent LG Ta tumors [2]. Moreover, in clinical practice, many clinicians consider MMC appropriate for HG disease only in cases where BCG is unavailable (e.g., due to BCG shortages).

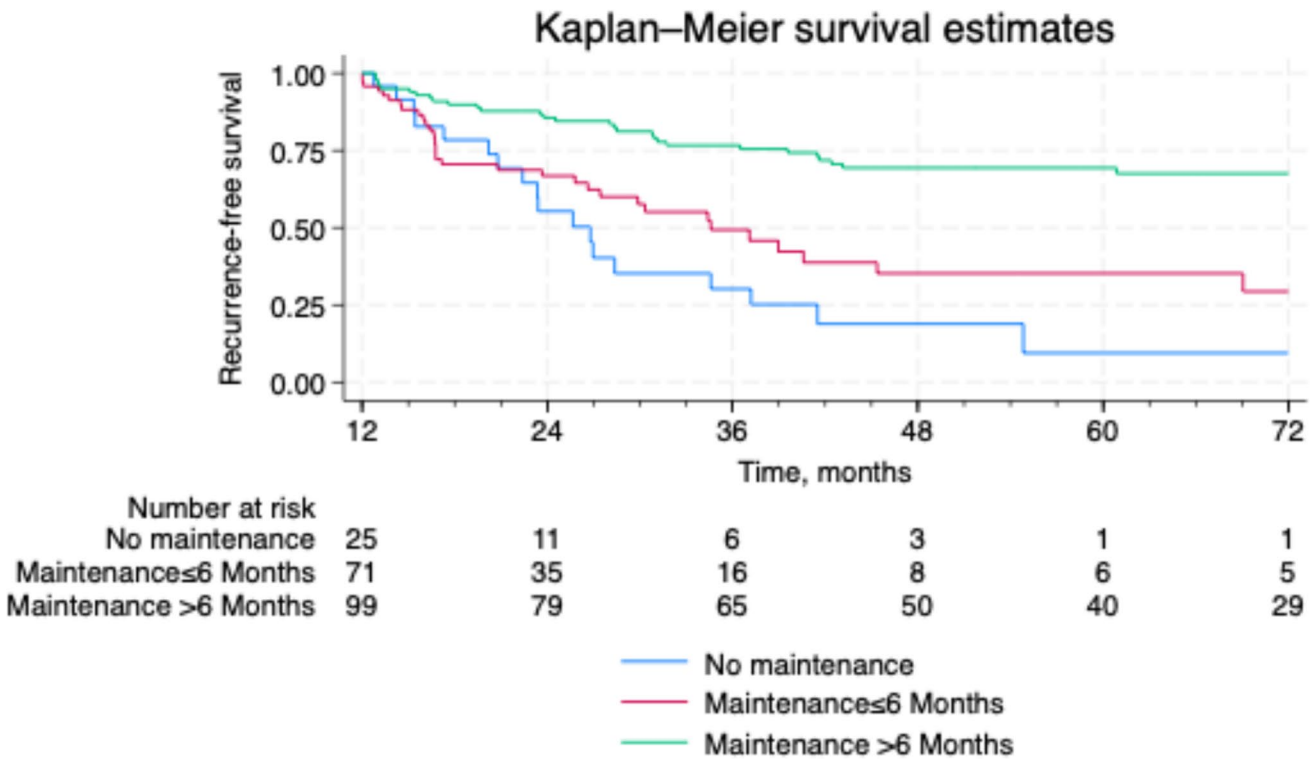

Fig. 2 12-Months landmark Kaplan–Meier estimates of RFS in 195 patients stratified by maintenance therapy status (maintenance ≤ 6 months in green vs. maintenance > 6 months in red vs. no maintenance in blue)

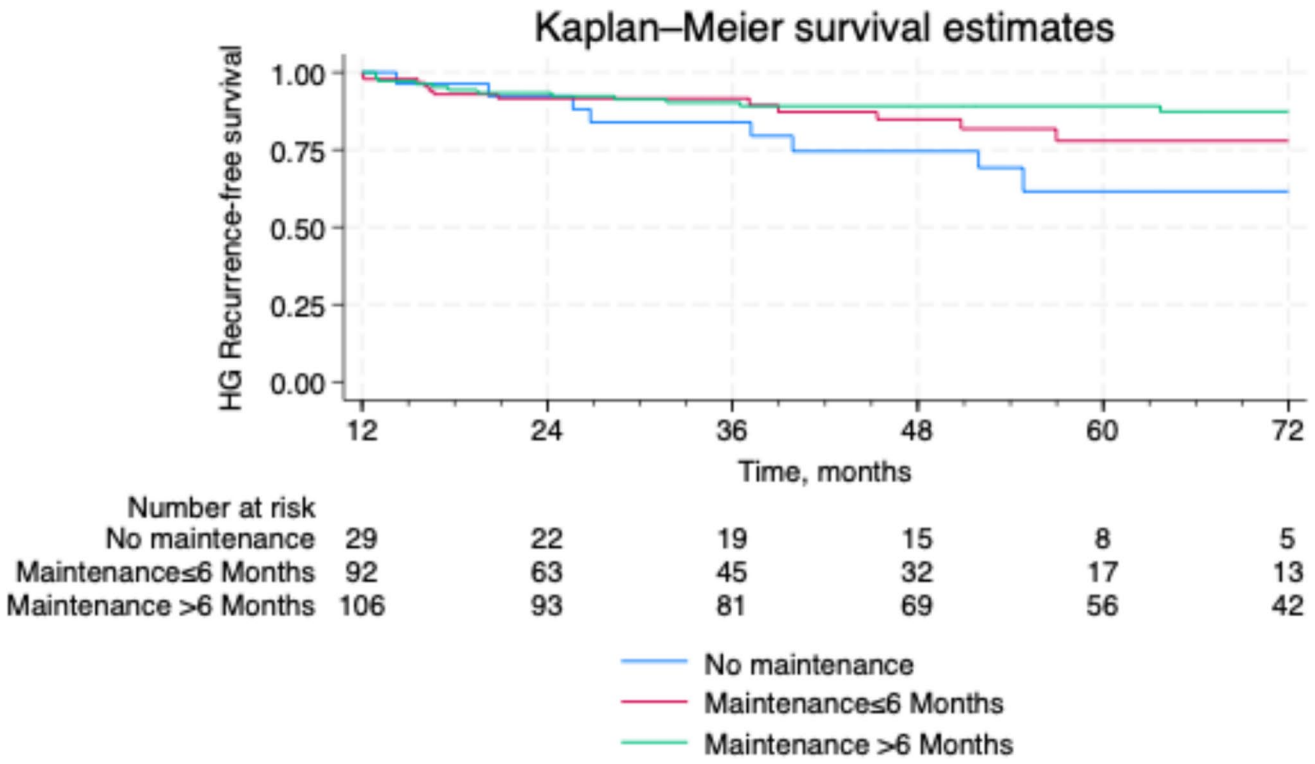

Fig. 3 12-month landmark Kaplan–Meier estimates of HG-RFS in 227 patients, stratified by maintenance therapy status (maintenance ≤ 6 months in green vs. maintenance > 6 months in red vs. no maintenance in blue)

Prior studies have shown that while some intermediate-risk patients respond well to MMC maintenance therapy, others may require more aggressive treatment strategies, including BCG or combination therapies [3]. This variability underscores the need for individualized treatment approaches, risk stratification tools, and further research to refine treatment algorithms tailored to different subsets within the intermediate-risk NMIBC population [12, 13]. In our population, the vast majority of patients harbored recurrent tumors (72%), multifocal (64%), and G1 (WHO 1973) or low-grade (WHO 2004/2016) classification. Only 8% received a one-shot postoperative instillation. These numbers are similar to those reported in other intermediate-risk NMIBC cohorts [14]. Moreover, we stratified our population according to no maintenance, short MMC maintenance ≤ 6 months, and long MMC maintenance > 6 months. Interestingly, we observed significant differences in the prevalence of recurrent tumors and tumor size (diameter > 3 cm). For instance, patients with larger tumors were more likely to receive a prolonged MMC maintenance regimen—32% in the long maintenance group compared to 15% and 19% in the short and no maintenance groups, respectively. This likely reflects a clinician-driven decision to extend therapy in patients perceived as being at higher risk.

On the other hand, the majority of patients who did not receive MMC maintenance had recurrent tumors (95%), while the percentage decreased in the short-term MMC maintenance group (78%) and the long-term group (55%). This may be influenced by selection bias. Specifically, the older age distribution in the no maintenance group (> 70 years; 70%) might have led to less intense treatment approaches due to concerns over tolerability and comorbidities. Previous studies have indicated that elderly patients are less likely to receive maintenance therapy despite potential oncological benefits [12, 15, 16]. Hence, the oncological outcomes and the clinical decision may also be driven by a perceived higher risk of adverse oncological outcomes. However, no direct comparisons could be made as prior studies have not specifically investigated the optimal timing of MMC maintenance.

Taken together, our findings provide strong evidence supporting the role of maintenance MMC therapy in intermediate-risk NMIBC patients. Specifically, receiving more than 6 months of instillation maintenance therapy significantly improves RFS compared to both short-term maintenance and no maintenance therapy. These results contribute to the growing body of literature emphasizing the importance of maintenance intravesical therapy in reducing recurrence risk. However, the lack of significant differences in HG-RFS raises questions regarding the efficacy of MMC in preventing high-grade recurrences, suggesting the need for additional studies focusing on alternative agents or combination therapies.

Despite the strengths of this multicenter study, certain limitations must be acknowledged. First, the retrospective nature of the study introduces potential selection biases and unmeasured confounders. The relatively low inclusion rate across centers may reflect patient loss to follow-up (e.g., treatment performed outside the reporting institution) and heterogeneous inclusion periods, potentially introducing selection bias. Additionally, given the long inclusion period and multicenter design, internal protocols for re-TURBT indications, follow-up intensity, and early instillation use may have changed over time, introducing some variability in patient management. Second, maintenance MMC regimens were determined by individual providers, introducing heterogeneity in treatment protocols. However, this variability allowed for the comparison of different maintenance schemes. Third, while our study establishes an optimal threshold of 6 months' instillation maintenance, further prospective trials are needed to confirm this cut-off and assess the long-term impact of different MMC maintenance durations. Fourth, results must be interpreted in the context of the landmark population, as patients experiencing early recurrence or censoring before the landmark were excluded. This approach may reduce generalizability but was chosen to minimize immortal time bias and allow a standardized comparison of maintenance regimens. In addition, the definitions of short- and long-term maintenance were operationalized for the exploratory landmark analysis, and the resulting cut-off inevitably simplifies treatment exposure; thus, these findings should be interpreted as hypothesis-generating. Lastly, the follow-up duration, while reasonable, may not fully capture late recurrences or long-term progression risks, necessitating extended observational studies.

Conclusion

In patients with Ta NMIBC, administration of MMC maintenance was associated with improved RFS in this multicenter retrospective cohort. Our observations warrant cautious interpretation and should be validated through prospective research. Nevertheless, these findings may offer useful real-world evidence to support shared decision-making regarding maintenance therapy in this patient population.

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Author contributions R.C. (Roberto Contieri) conceived the study idea, conducted the literature review, and wrote the initial manuscript draft. L.M.I.J., G.F., M.T., M.M., F.C., F.P., L.C., A.U., and F.C. (Francesco Claps) contributed to data collection, statistical analysis, and methodological refinement. M.D.V., B.R., R.B., L.D.P., A.A., G.S., E.C., C.G., P.B., F.V., G.M.B., U.F., R.M., A.T., M.M., P.D.T., G.L., S.F., G.I.R., F.V., M.R., F.P.B., M.B., M.R., F.Z., L.B., E.D.L., A.C., M.A.C., F.C., G.S., S.M.D.S., C.D.N., L.C., G.L., A.P., B.B., E.M., A.G., A.A., A.V., F.D.M., G.C., L.C., C.T., F.P., S.P., B.R., R.H., M.C., and M.F. contributed to supervision, critical manuscript review, and final approval of the version to be published. M.F. (Matteo Ferro) and S.P. (Sisto Perdonà) provided senior oversight, coordinated the multicenter collaboration, and critically revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

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Data availability Roberto Contieri and Matteo Ferro have full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Declarations

Conflict of interest The authors declare that there are no competing interests.

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Authors and Affiliations

Roberto Contieri[1] · Letizia Maria Ippolita Jannello[2,3] · Mihai Dorin Vartolomei[4,5] · Beat Roth[4] · Roberto Bianchi[2,3] · Giuseppe Fallara[2,3] · Marco Tozzi[2,3] · Martina Maggi[2,3] · Francesco Chierigo[2,3] · Francesco Pellegrino[2,3] · Ludovica Cella[6] · Alessandro Uleri[6,7] · Luigi Da Pozzo[8,9] · Francesco Claps[10] · Achille Aveta[1] · Gianluca Spena[1] · Enrico Checcucci[11] · Cecilia Gatti[11] · Pierluigi Bove[12,13] · Francesca Vedovo[14] · Gian Maria Busetto[15] · Ugo Falagario[16] · Riccardo Mastroianni[17] · Alessandro Tedde[18] · Massimo Madonia[18] · Pasquale Di Tonno[19] · Giuseppe Lucarelli[19] · Saverio Forte[19] · Giorgio Ivan Russo[20] · Fabrizio Verweij[21] · Marco Racioppi[22] · Francesco Pio Bizzarri[23] · Marco Borghesi[24] · Marco Rinaldi[25] · Fabio Zattoni[26] · Luca Boeri[2,27] · Elisa De Lorenzis[2,27] · Andrea Conti[28] · Maria Angela Cerruto[29,30] · Felice Crocetto[31] · Giuseppe Simone[17] · Savino Mauro Di Stasi[12] · Cosimo De Nunzio[15] · Luca Carmignani[28] · Giovanni Liguori[14] · Angelo Porreca[32] · Biagio Barone[33] · Emanuele Montanari[27] · Albo Giancarlo[27] · Alessandro Antonelli[29,30] · Alessandro Veccia[29,30] · Fabrizio Dal Moro[26] · Giuseppe Carrieri[16] · Luigi Cormio[16] · Carlo Terrone[24] · Francesco Porpiglia[11] · Sisto Perdonà[1] · Bernardo Rocco[22] · Rodolfo Hurle[34] · Michele Catellani[8] · Matteo Ferro[2,3]

✉ Roberto Contieri
Roberto.contieri@istitutotumori.na.it

✉ Matteo Ferro
matteo.ferro@unimi.it

[1] Department of Urology, Istituto Nazionale Tumori di Napoli IRCCS Fondazione "G. Pascale", Via Mariano Semmola, 52, 80131 Naples, NA, Italy

[2] Università degli Studi di Milano, Milan, Italy

[3] Unity of Urology, Department of Health Science, University of Milan, ASST Santi Paolo and Carlo, Via A. Di Rudinì 8, 20142 Milan, Italy

[4] Department of Urology, University of Bern, Bern, Switzerland

[5] Doctoral School, "Iuliu Haţieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania

[6] Department of Biomedical Sciences, Humanitas University, Milan, Italy

[7] Department of Urology, La Croix du Sud Hospital, Quint Fonsegrives, France

[8] Department of Urology, ASST Papa Giovanni XXIII, Piazza OMS, 1, 24127 Bergamo, BG, Italy

[9] School of Medicine, University of Milano-Bicocca, Piazza dell'Ateneo Nuovo, 1, 20126 Milan, MI, Italy

[10] Department of Oncological Urology, Veneto Institute of Oncology (IOV) IRCCS, Padua, Italy

[11] Division of Urology, Department of Oncology, School of Medicine, San Luigi Hospital, University of Turin, Turin, Italy

[12] Department of Experimental Medicine, Torvergata Oncoscience Research Centre of Excellence, TOR, University of Rome Tor Vergata, via Montpellier 1, 00133 Rome, Italy

[13] Urology Unit, San Carlo di Nancy Hospital, GVM Care and Research, Rome, Italy

[14] Urology Clinic, Department of Medical, Surgical and Health Science, University of Trieste, Trieste, Italy

[15] Department of Urology, Sapienza Rome University, Rome, Italy

[16] Department of Urology and Kidney Transplantation, University of Foggia, Foggia, Italy

[17] Department of Urology, IRCCS "Regina Elena" National Cancer Institute, Via Elio Chianesi 43, 00143 Rome, Italy

[18] Dipartimento di Medicina, Chirurgia e Farmacia, Università degli Studi di Sassari, Sassari, Italy

[19] Unit of Urology, Andrology and Kidney Transplantation, Department of Emergency and Organ Transplantation, University of Bari, Bari, Italy

[20] Department of Urology, University of Catania, Catania, Italy

[21] U.O.C. Urologia, ASST Cremona, Cremona, Italy

[22] U.O.C. Clinica Urologica, Dipartimento Universitario di Medicina e Chirurgia Traslazionale, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy

[23] Department of Urology, Ospedale Isola Tiberina - Gemelli Isola, Università Cattolica del Sacro Cuore, Rome, Italy

[24] Department of Surgical and Integrated Diagnostic Sciences, University of Genoa, 16126 Genoa, Italy

[25] Department of Urology, Santa Maria Della Misericordia Hospital, Udine, Italy

[26] Urology Unit, Department of Surgical, Oncological and Gastroenterological Sciences, University of Padua, Padua, Italy

[27] Department of Urology, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy

[28] Department of Urology, IRCCS Ospedale Galeazzi – Sant'Ambrogio, Milan, Italy

[29] University of Verona, Verona, Italy

[30] Department of Urology, Azienda Ospedaliera Universitaria Integrata Verona, Verona, Italy

[31] Department of Neurosciences, Reproductive Sciences and Odontostomatology, University of Naples Federico II, 80131 Naples, Italy

[32] Department of Urology, Humanitas Gavazzeni, Humanitas University, Bergamo, Italy

[33] Division of Urology, Department of Surgical Sciences, AORN Sant'Anna e San Sebastiano, 81100 Caserta, Italy

[34] Department of Urology, IRCCS Humanitas Research Hospital, 20089 Rozzano, Milan, Italy