



Redefining the role of immediate intravesical instillation of mitomycin C in non-muscle invasive bladder cancer

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A little over three decades ago, early trials with intravesical instillations of chemotherapeutic agents were found disappointing (1). Later, putting forward the hypothesis that the mechanism of recurrence was the implantation of cancer cells after tumour resection, research demonstrated the role of intravesical mitomycin C (MMC) in decreasing the risks of recurrence (2). Indeed, subsequent trials helped establish the role of intracavitary MMC in the treatment of superficial non-muscle invasive bladder cancer (3). The controversy continued, however, and as late as 2009, researchers asked for the practice of postoperative chemotherapy instillation to be abandoned (4). Today, the controversy has been laid to rest, and immediate postoperative intravesical instillation of chemotherapeutic agents is accepted as best practice in the management of superficial bladder cancer by most guideline panels. Despite the evidence, there is considerable variation in the use of intravesical instillation of chemotherapy immediately after resection amongst urologists (5), leading to innovative attempts to increase compliance (6).

Seeking to define the precise indications for the use of intravesical mitomycin, Sylvester *et al.* established the type of patients that were likely to benefit from intravesical mitomycin through a meta-analysis of clinical trials. They provided evidence to suggest that patients with a historical recurrence rate higher than one year and patients with a European Organisation for Research and Treatment of Cancer (EORTC) score of greater than five were unlikely to benefit from an immediate mitomycin instillation (7).

These recommendations are now included in the European Association of Urology (EAU) guidelines (8).

The current study (9) builds upon the earlier meta-analysis by Sylvester *et al.* The authors have drawn upon their previous large randomised trial (10) and have reanalysed the data from this study. As their earlier study had not used EORTC criteria especially regarding tumour sizes, the authors have developed a modified EORTC score for the purpose of the current analysis and reclassified the patients from their earlier study on the basis of EAU risk groups and the modified EORTC score to make allowances for non-conformity to the original EORTC scoring system. Based on these new criteria, the authors provide evidence that a single instillation of mitomycin benefits all patients with non-muscle invasive bladder cancer, irrespective of the EAU risk group or the EORTC score. They have also compared outcomes in patients that had an immediate instillation of MMC versus those that had delayed instillations. In their study, time to recurrence was statistically significant in favour of those who had immediate postoperative MMC instillation.

When comparing with the earlier meta-analysis, it must be noted that the EAU risk categories and EORTC scores could only be applied to 83% and 48% of patients from the authors' clinical trial respectively. For EORTC scores, the missing numbers across all groups were quite high. For this reason, they eliminated tumour size to derive their modified score and then recalculated risk categories

based on this modified score. Furthermore, they tested for differences in treatment effect for several covariates. These tests demonstrated that the effects of treatment were similar within the subgroups for each covariate. In effect, interaction tests between treatment and age, gender, number of tumours, prior recurrence rates, T-categories, CIS, tumour size, tumour grade, EAU risk group and EORTC scores were not statistically significant. In other words, the authors demonstrate that an immediate instillation with MMC reduces the risk of recurrence in NMIBC patients irrespective of EORTC recurrence score or prior recurrence rates, though the authors admit that Sylvester's study probably had patients with a higher risk of recurrence than patients in their study.

Similarly, it is possible that the authors' modified EORTC recurrence scores may have underestimated many patients that had a large tumour size. The study has also had a considerable number of patients that had varying adjuvant instillations of MMC depending on their EAU risk categories. This factor may undoubtedly have played a part in their outcomes over a follow-up period of seven years, even though the authors state that after adjusting the data for adjuvant MMC instillations, an immediate instillation was found beneficial.

In their study, the authors have not specified their definition of immediate instillation and thus do not provide further evidence on the role of the timing of the instillation on outcomes (11).

Furthermore, earlier studies have estimated the numbers needed to treat at 8.5 or 9 (12,13). It would have been interesting if the authors could have shed any further light on this useful takeaway yardstick.

To conclude, the present study validates existing guidelines and provides additional evidence that immediate postoperative MMC instillations in non-muscle invasive bladder cancer confers benefit and should not be withheld from patients that guideline panels currently considered as unsuitable for immediate instillation of MMC.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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