Long-term Efficacy of Maintenance Bacillus Calmette-Guérin versus Maintenance Mitomycin C Instillation Therapy in Frequently Recurrent TaT1 Tumours without Carcinoma In Situ: A Subgroup Analysis of the Prospective, Randomised FinnBladder I Study with a 20-Year Follow-up

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Abstract

Background: The long-term prospective data on bacillus Calmette-Guérin (BCG) and mitomycin C (MMC) instillation therapy are limited.

Objective: To compare the long-term benefit of BCG and MMC maintenance therapy in patients with recurrent bladder carcinoma.

Design, setting, and participants: Eighty-nine patients with frequently recurrent TaT1 disease without carcinoma in situ (CIS) were eligible. Originally, the patients were enrolled in the prospective FinnBladder I study between 1984 and 1987 and randomised to receive BCG or MMC. Both regimens involved five weekly instillations, followed by monthly instillations for 2 yr. Because of alkalinising the urine and adjusting the dose to bladder capacity, the average concentration of MMC was low: 30–40 mg in 150–200 ml of phosphate buffer. Overall median follow-up time was 8.5 yr, whereas the median follow-up time of the patients who were still alive was 19.4 yr.

Measurements: Primary end points were time to first recurrence and overall mortality. Secondary end points were progression and disease-specific mortality.

Results and limitations: Thirty-six of 45 patients (80.0%) in the MMC group experienced recurrence in contrast to 26 of 44 patients (59.1%) in the BCG group. This finding was reflected in significantly lower cumulative incidence estimates in the BCG group ($p = 0.005$). There was a weak trend for fewer progressions ($p = 0.1$) and cancer-specific deaths ($p = 0.2$) in the cumulative incidence analysis, as 4 patients versus 10 patients progressed and 4 patients versus 9 patients died from the disease in the BCG group versus the MMC group, respectively. No difference...
2. Materials and methods

Instillation therapy on overall mortality. The study population, however, was too small for conclusive evidence about progression or survival.

Conclusions: An intensive intravesical BCG immunotherapy results in a sustained and significant long-term reduction in recurrence in frequently recurrent bladder carcinoma. The relatively low progression rate during the long follow-up suggests that it may be difficult to show significant differences in overall mortality with a substantially larger but otherwise similar study population.

Trial registration: Registration was not considered to be necessary at this stage of the follow-up because the study was initiated as early as 1984 and the last randomisation took place in July 1987, that is, long before the current requirements concerning study registrations were implemented.

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1. Introduction

Up to 80% of urinary bladder cancer patients present with non–muscle-invasive disease, which may be treated by transurethral resection (TUR) with curative intent. The natural course of low- and intermediate-risk superficial bladder tumours is relative benign, with the risk of progression at only 0.8–6% in 5 yr [1]; however, as many as 31–62% of superficial tumours will recur after primary treatment [1]. Although the risk for progression is relatively low, even in frequently recurring tumours, every recurrence increases patient inconvenience and the costs of the health care system.

The choice between chemotherapy and immunotherapy largely depends on the main concern: recurrence or progression. According to the 2008 European Association of Urology guidelines, adjuvant chemotherapy or bacillus Calmette-Guérin (BCG) instillations are effective in preventing recurrence [2]. The efficacy of mitomycin C (MMC) instillation therapy varies significantly among the largest studies [3–5]. It seems that BCG maintenance therapy, rather than chemotherapy, reduces or at least delays progression [6–8].

Only a few studies [8–10] exist with a sufficient follow-up time to determine the long-term benefit of intravesical chemotherapy or immunotherapy instillations. In the present study, with an overall follow-up of approximately 20 yr, our principal focus was on the durability of response to instillation therapy as well as on the possible impact of instillation therapy on overall mortality.

2. Materials and methods

The study was approved by the ethical committee by the Helsinki University Hospital Department of Surgery. An oral informed consent was obtained from the patients before randomisation. The first peer-reviewed analysis of this multicentre study was published in 1991 [11]. Briefly, the material consisted of 109 eligible patients with frequently recurrent TaT1 tumours and/or carcinoma in situ (CIS) who were randomised in 1984–1987 to receive either MMC or BCG. The method of randomisation was based on date of birth. No stratification was done at randomisation between TaT1 tumours and CIS. One of the concerns at the time of the study design was that the negative purified protein derivate (PPD) test was associated with poor efficacy and serious complications in patients treated with BCG. Therefore, seven patients who were allocated to BCG therapy but tested PPD-negative were transferred, according to the protocol, to the MMC group before the start of BCG therapy. Randomisation criteria for papillary tumours were histologically confirmed cancer and at least two recurrences within 1.5 yr. Instillation treatment in both groups began 2 wk after TUR with five weekly instillations and continued with monthly instillations for up to 2 yr. The MMC dose and volume of the phosphate buffer was adjusted by the bladder capacity, with the average concentration of MMC being 30–40 mg in 150–200 ml of phosphate buffer [12,13].

The BCG dose was 6 × 10^8 colony-forming units or 75 mg (immune BCG Pasteur strain F) in 50 ml saline. Cytology and cystoscopy were done every 3 mo for the first 2 yr. Later, the interval between controls varied between 6 and 12 mo, according to the clinician’s decision. TUR and biopsies were performed when a recurrence was suspected.

During the instillation therapy, patients were transferred to the second-line instillation in case of persistent disease over a period of 6 mo or due to severe side-effects. Of the total 109 patients, 23 were transferred, including 5 patients with CIS. In the MMC group, eight patients with TaT1 disease and without CIS were transferred to BCG therapy, all of them because of persistent disease. In the BCG group, 10 patients with TaT1 disease and without CIS were transferred to MMC therapy; 1 was transferred because of persistent disease, and the rest were transferred because of side-effects. All patients transferred to second-line therapy remained in the original treatment arm in the efficacy comparisons. Of all 109 patients, including those with the second-line treatment, 18 patients received fewer than the planned 28 instillations of the protocol.

For the present long-term subgroup analysis, we included only patients with TaT1 disease and without CIS. We identified 91 such patients from data files of the multicentre FinnBladder I trial. No distinction was made between Ta and T1 disease in the original material.

Of the original histologic slides, 51 randomisation tumour samples and 48 primary tumour samples were available for review by our pathologist. Randomisation samples of two patients presenting with CIS changes in the pathologic review were excluded. Thus, the final number of analyisable patients was 89 (Table 1).

Primary end points of the present analysis were time to first recurrence and overall mortality. Secondary end points were progression and disease-specific mortality. Recurrence was defined as biopsy-confirmed non–muscle-invasive carcinoma (TaT1) or CIS or malignant cytology. The definition of progression was T2 tumour or more advanced disease. Progression was also regarded as recurrence if it was the first event without preceding occurrence of a TaT1 tumour or CIS. We calculated the overall median follow-up time based on the longest follow-up data available for the patient, being either the time point of death or the latest entry of record of the patient who was still alive. To illustrate the follow-up duration of the present study, we...
additionally calculated the median follow-up time of those who were still alive. We used the general public license statistical software R v.2.8.1, including the `cmprsk` package. We applied the \( \chi^2 \) statistics in cross-tabulations and the unpaired \( t \) test for testing the difference of two means. Instead of the Kaplan-Meier technique, we analysed all time-related end points using the cumulative incidence functions and Gray’s test to be able to take into account the major competing risk event, death from other cause than bladder carcinoma [14]. The proportional subdistribution hazards model [15] was the method for testing the significance of possible explanatory variables such as gender, age, regimen, T category, grade, previous therapy, preceding recurrence rate, and tumour multiplicity. We considered a \( p \)-value \( \leq 0.05 \) to be statistically significant.

### 3. Results

Table 1 provides the distribution of patient characteristics by treatment group. Of the 89 eligible patients randomised in 1984–1987, 44 belonged to the BCG group and 45 belonged to the MMC group. The overall median follow-up time based on survival data was 8.5 yr (range: 1.0–22.3), whereas the median follow-up time of the 17 patients who were still alive was 19.4 yr (range: 13.0–22.3).

#### 3.1. Time to first recurrence

Thirty-six of the 45 patients in the MMC group (80.0%) experienced at least one recurrence in contrast to 26 of the 44 patients (59.1%) in the BCG group. Similarly, a significant and sustained difference in favour of the BCG therapy was evident in the cumulative incidence curves between the study groups (Fig. 1). The probability of recurrence in the BCG group versus the MMC group was 50% versus 77% at 5 yr, 57% versus 80% at 10 yr, and 59% versus 80% after 15 yr, respectively (\( p = 0.005 \)). Using the proportional subdistribution hazards model, first recurrence was the only end point generating significant covariates, with MMC therapy, tumour multiplicity, and younger age being significantly associated with increased probability of new recurrence (Table 2).

#### 3.2. Progression

In three patients, no earlier time point of progression was recorded than that of death from bladder carcinoma. Only 14 of 89 patients (15.7%) experienced progression, 4 in the BCG group and 10 in the MMC group. Only a weak trend for the lower probability of progression in the BCG group was evident in the cumulative incidence estimates of progression in the presence of competing risks (\( p = 0.1 \)). A clear separation of the progression curves occurred after 5 yr, as no later progressions existed in the BCG group in contrast to six additional events in the MMC group, with the latest one occurring 17 yr after randomisation (Fig. 2).

#### 3.3. Disease-specific and overall mortality

Fig. 3 shows the cumulative incidence curves for disease-specific and competing mortality. Of the 14 patients who experienced progression, 13 died from bladder carcinoma.
Therefore, the cumulative incidence curves for disease-specific mortality and the nonsignificant $p$-value are very similar to those in connection with progression. Excluding the 3 patients in whom progression was confirmed at death, the median time from progression to bladder cancer death was 14.6 mo (range: 1.6–49) in the remaining 10 patients.

Overall, 36 patients died in each of the MMC and BCG groups (80.0% vs 81.8%) by the time of the present analysis. As only 13 of the total of 72 deaths (18%) were due to bladder carcinoma and the overall mortality rates were equal in practice, the observed weak trends in progression and disease-specific mortality were undetectable in the overlapping overall mortality curves in Fig. 4 ($p = 0.7$).

4. Discussion

Our finding of the superiority of BCG over MMC in time to recurrence is consistent with the results of two large meta-analyses with a considerably shorter median follow-up time [3,4]. In a meta-analysis of 2749 patients with intermediate- to high-risk tumours, Böhle et al [3] found a significant superiority of BCG over MMC, with 61% of the patients in the BCG group and 53% in the MMC group being recurrence free after a median follow-up time of 29 mo. In contrast, Shelley et al [4] found no significant difference in the efficacy between BCG and MMC therapy in their overall meta-analysis of 1901 patients; however, they reported a highly significant reduction in recurrence in favour of BCG in a subgroup analysis involving highly recurrent patients. Both meta-analyses included patients from our study based on the published early results with a short follow-up.

Böhle et al concluded that at least 12 BCG instillations or a 1-yr duration of therapy were needed to achieve the significant superiority of BCG over MMC. In the present study, we had an intensive instillation schedule for up to 2 yr. Malmström et al [16] used a similar intensive instillation regimen for the first year, followed by quarterly instillations during the second year. The disease-free estimates in their subgroup of patients with non–muscle-invasive tumours and without CIS were approximately 50% in the BCG group and 35% in the MMC group ($p = 0.22$) at 3 yr compared with the corresponding inverse values of cumulative incidence estimates, 61% and 31%, in the present study. Likewise, the results of the prematurely terminated trial of Lamm et al [17] are in agreement with those of Malmström et al [16] and with ours. In their study of 377 patients with non–muscle-invasive tumours and without CIS, they used an intensive 1-yr instillation schedule [17]. At 3 yr, the disease-free estimates were approximately 50% and 35% in the BCG and MMC groups, respectively ($p = 0.017$).
Friedrich et al [5] reported a disease-free estimate as high as approximately 85% at 3 yr in the intensive 3-yr MMC treatment arm, which is in striking contrast with the results of the above studies. As Kaasinen has pointed out earlier [18], the explanation for the discrepancy is more likely the great variation of patient characteristics among various studies rather than the duration of therapy. This suggestion is supported by the fact that a difference as high as 30–50% in the disease-free estimates is already evident at 1 yr between the 3-yr arm of Friedrich et al’s study [5] and the 1- and 2-yr MMC arms of Lamm et al’s [17] and Malmström et al’s [16] studies, despite the similar therapy during the first year. Additionally, approximately one-third of the patients in Friedrich et al’s study [5] had T1 tumours and underwent a second resection, which results in fewer observed recurrences during the later follow-up, regardless of the instillation therapy. As for the optimal duration of chemotherapy instillations, data are incomplete and controversial for determining the optimal schedule and duration of chemotherapy [2,19].

One explanation for the observed poor outcome of the MMC group in the present study, albeit only marginally inferior to that in Malmström et al’s [16] or Lamm et al’s [17] studies, may be a suboptimal concentration of MMC. Based on some data at the time of our study design, an increase in the bladder surface area exposed to MMC and the alkalinity of urine were considered more important factors than the drug concentration [12,13]. As most patients of the present study had a normal bladder volume (>275 ml), the MMC was diluted to a predefined, relatively large volume of buffer. That resulted in concentrations as low as 0.2 mg/ml, being one-fifth to one-fourth of the concentration (0.8–1.0 mg/ml) used in most of the studies. In retrospect, based on more recent data, a significantly better outcome may have resulted from giving all patients 40 mg of MMC in only 20 ml and alkalinising the urine with oral sodium bicarbonate [20].

Compared with other similar prospective studies, the 20-yr overall follow-up time of the present study is exceptionally long. Although the difference in the cumulative incidence estimates appears to sustain during the whole study period, it is noteworthy that the probability of recurrence increased, even in the better treatment group, to the relatively high and sustained level of approximately 60% already before 10 yr. Moreover, only a relatively small proportion of the original patient population remained at risk for recurrence after 10 yr, due to earlier recurrences and competing causes of death. This finding emphasises the other end points, progression and mortality. Keeping the small sample size in mind, we observed a weak trend for fewer progressions in the BCG group. Our findings are consistent with the results of a meta-analysis of Böhle and Bock [7], who reported a significant benefit of BCG over MMC in a subgroup of studies applying maintenance therapy to patients with TaT1 tumours. In their study, the risk of progression related to BCG therapy was 70% of the risk related to the MMC therapy after a median follow-up of 26 mo, whereas in the present study, the difference in the estimates of progression appeared no earlier than after 5 yr. In contrast, the Swedish-Norwegian study group failed to find any difference in the progression-free or survival estimates between the BCG and MMC treatment groups after a median follow-up of 10 yr [9]. As the MMC concentration possibly was suboptimal in the present study, the results of the present study indirectly support the finding of another large meta-analysis [6] showing that BCG reduces progression in non-muscle-invasive disease.

We observed similar weak trends in progression and cancer-specific mortality resulting from the very poor outcome of the progressed patients, as all but one of these mainly elderly patients died from bladder carcinoma. Still, the finding is in agreement with those of the other studies reporting that as many as 65–80% of the patients who progressed after BCG therapy eventually died from the disease [6,9,21]. To improve these figures, recurrent T1 disease during or following BCG therapy should be considered as an indication for radical cystectomy [21].

We found no difference in the overall mortality between the treatment groups. The trial of Lamm et al [8] comparing BCG maintenance therapy with no maintenance appears to be the only study showing some weak evidence that longer term BCG therapy may improve overall survival. In Lamm et al’s study and in the Swedish-Norwegian study, despite the fact that one-third of the patient population presented with CIS, either no difference was evident in the overall survival or the small difference was lacking statistical confirmation. Additionally, less than half of the potential progressions may be prevented with BCG instillation therapy [6]. Thus, with overall survival or mortality as the main end point, it seems very difficult to design a large enough comparative study of a patient population similar to that of the present study, as the expected difference using the best available treatment options is minimal. There still remains a need to develop more effective and economical treatment modalities for this disease entity, in which reducing recurrence and morbidity rather than mortality seems to be a more realistic goal for future comparative studies.

5. Conclusions

An intensive intravesical BCG immunotherapy results in a sustained and significant long-term reduction in recurrence in frequently recurrent bladder carcinoma. The small overall number of patients allows no definitive conclusions to be drawn from the present study about progression and cancer-specific or overall mortality. The relatively low percentage of patients with progression observed during the long follow-up justifies the conclusion that even with a substantially larger but otherwise similar study population, it may be difficult to show significant differences in overall survival because of the low natural progression rate, limited effect of instillation therapy on progression, and a high percentage of deaths due to competing disease.

Author contributions: Riikka Järvinen had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Critical revision of the manuscript for important intellectual content: Järvinen, Kaasinen, Rintala.
Drafting of the manuscript: Järvinen, Kaasinen.
Analysis and interpretation of data: Järvinen, Kaasinen, Rintala.
Acquisition of data: None.

Study concept and design: Järvinen, Kaasinen, Rintala.
Acquisition of data: Järvinen, Kaasinen, Rintala, Sankila.
Analysis and interpretation of data: Järvinen, Kaasinen.

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