Published in final edited form as:
Eur Urol. 2008 April ; 53(4): 709–719. doi:10.1016/j.eururo.2008.01.015.

The Schedule and Duration of Intravesical Chemotherapy in Patients with Non–Muscle-Invasive Bladder Cancer: A Systematic Review of the Published Results of Randomized Clinical Trials

Richard J. Sylvester[a,*], **Willem Oosterlinck**[b], and **J. Alfred Witjes**[c]

[a] *EORTC Data Center, Brussels, Belgium* [b] *Department of Urology, Ghent University Hospital, Ghent, Belgium* [c] *Department of Urology, Radboud University Medical Center, Nijmegen, The Netherlands*

Abstract

Objectives—Intravesical chemotherapy has been studied in randomized clinical trials for >30 yr; however, the optimal schedule and duration of treatment are unknown. The objective is to determine the effect of schedule and duration of intravesical chemotherapy on recurrence in patients with stage Ta T1 bladder cancer.

Methods—A systematic review was conducted of the published results of randomized clinical trials that compared intravesical instillations with respect to their number, frequency, timing, duration, dose, or dose intensity.

Results—One immediate instillation after transurethral resection (TUR) is recommended in all patients. In low-risk patients, no further treatment is recommended before recurrence. In patients with multiple tumors, one immediate instillation is insufficient treatment. Additional instillations may further reduce the recurrence rate; however, no recommendations can be made concerning their optimal duration. A short intensive schedule of instillations within the first 3–4 mo after an immediate instillation may be as effective as longer-term treatment schedules (grade C). Instillations during ≥1 yr in intermediate-risk patients seem advisable only when an immediate instillation has not been given (grade C). Higher drug concentrations and optimization of the drug's concentration in the bladder may provide better results (grade C).

Conclusions—The optimal schedule and duration of intravesical chemotherapy after an immediate instillation remain unknown. Future studies should focus on the eradication of residual disease after TUR and the prevention of late recurrences.

Keywords

Intravesical chemotherapy; Non-muscle-invasive; bladder cancer; Recurrence; Schedule; Systematic review

1. Introduction

Guidelines of the European Association of Urology for the treatment of stage Ta–T1 (non–muscle-invasive) bladder cancer recommend that all patients receive one immediate instillation

* Corresponding author. EORTC Data Center, 83 avenue E Mounier, Bte 11, 1200 Brussels, Belgium. Tel. +322 774 1613; Fax: +322 772 3545. E-mail address: richard.sylvester@eortc.be (R.J. Sylvester).

Conflicts of interest: The authors have nothing to disclose.

of chemotherapy after transurethral resection (TUR) [1]. Further treatment depends on the patient's risk of recurrence and progression to muscle-invasive disease [2]. In patients at low risk of recurrence and progression, no further treatment is recommended prior to a subsequent recurrence. In patients at high risk of progression, that is, those with high-grade tumors or carcinoma in situ (CIS), 1–3 yr of maintenance bacillus Calmette-Guérin (BCG) is recommended.

The remaining patients have an intermediate risk of progression and an intermediate to high risk of recurrence, with the risk of recurrence depending, to a large extent, on the number of tumors [2]. One immediate instillation by itself has been shown to be insufficient treatment after TUR in patients with multiple tumors [3]; however, there is no consensus whether further intravesical chemotherapy or intra-vesical BCG should be given in these patients.

Meta-analyses have shown that intravesical chemotherapy reduces the recurrence rate as compared to TUR alone [4–6], with a decrease of 8% in the percentage of patients who have recurrence [4]. However, the optimal frequency and duration of treatment remain unknown. Although one meta-analysis suggested that longer instillation schedules may be associated with greater treatment benefit [5], another meta-analysis questioned whether there was a long-term benefit beyond one immediate instillation [7].

To determine the effect of schedule and duration of intravesical chemotherapy on recurrence in patients with non–muscle-invasive bladder cancer, a systematic review of the published results of randomized clinical trials has been carried out. Because of the heterogeneity of the various treatment schedules within some of the groups being compared, it was not always justified to pool together the results from the different studies to get an overall quantitative estimate of the size of the treatment effect. Hence, meta-analyses have been carried out for only a limited number of comparisons.

2. Methods

All randomized trials in patients with stage Ta–T1 bladder cancer that compared different schedules or durations of intravesical chemotherapy after TUR were considered. Trials published or accepted for publication before May 2007 that compared intravesical instillations with respect to their number, frequency, timing, duration, dose, or dose intensity were identified by searching MEDLINE, reference lists in trial publications and review articles, and annual meeting abstracts in the Journal of Urology and European Urology. Studies assessing device-assisted chemotherapy (electromotive drug administration [EMDA] or hyperthermia) and chemotherapy relative to or in combination with BCG were not included.

Because individual patient data were not available and most publications did not provide sufficient information to compare the time to first recurrence, the primary end point was the percent of patients with recurrence. When available, for each trial the percent of patients with recurrence in each treatment group was calculated and compared using a χ^2 test unless the log-rank p value for time to first recurrence was provided.

For comparisons where a meta-analysis was done, estimates from individual studies were combined together using a fixed effects model and differences were tested for significance using the Mantel-Haenszel test stratified by study.

3. Results

Results are presented as answers to different questions about the schedule and duration of intravesical chemotherapy taking into account whether or not an immediate instillation of chemotherapy was given after TUR.

3.1. After one immediate instillation, can additional intravesical chemotherapy reduce the recurrence rate in patients with multiple tumors?

A total of 879 patients were entered in three trials comparing one immediate instillation to one immediate instillation plus additional instillations (Table 1). In two Medical Research Council (MRC) trials, which were each published twice [8–11], four additional 3 monthly instillations were given during 1 yr. In the thiotepa study [8,9], there was no reduction in the percentage of patients who had recurrence, 41.9% versus 37.5%; however, this trial has been criticized because of the low drug concentration used, 30 mg/50 ml. In the mitomycin C (MMC) trial [10,11], based on updated summary data, there was a reduction in the percentage with recurrence from 48.3% to 36.3% overall ($p = 0.04$) and from 70% to 50% in patients with multiple tumors ($p = 0.09$). However, in both of these studies, patients who recurred at 3 mo prior to starting their additional instillations were already counted as having their first recurrence, potentially diluting the size of any treatment effect. The benefit of additional instillations in patients still free of disease at 3 mo was not reported and may be underestimated by the overall results.

In a third trial, which assessed 4 weekly instillations of epirubicin starting within 24 h of TUR followed by monthly instillations to month 12 (15 instillations), there was a small nonsignificant reduction in the percent of patients with recurrence, from 31.8% to 24.0% ($p = 0.11$) [12].

There is thus a suggestion that additional instillations may reduce the recurrence rate, but no definitive conclusions can be drawn. Approximately 70% of the patients had a single tumor and only one study provided separate results for single and multiple tumors.

3.2. If further intravesical chemotherapy is given after one immediate instillation, how long should it continue?

Although there is no conclusive proof that additional chemotherapy after one immediate instillation is of benefit, three trials including a total of 598 patients compared 12 mo of treatment to either 6, 3, or 1 mo of treatment (Table 2).

Comparing nine instillations of MMC or Adria-mycin given during 6 mo to 15 instillations given during 12 mo, there was no difference in the percentage of patients with recurrence [13]; however, no results were presented taking 6 mo as time zero. In another study, no difference was found when comparing six instillations of epirubicin during 1 mo to 17 instillations in 12 mo [14]. A third study comparing nine instillations of epirubicin given during 3 mo to 19 instillations in 12 mo found that fewer patients had recurrence with 12 mo of treatment, 13% versus 31.5% ($p = 0.005$) [15].

The results are thus contradictory concerning whether 12 mo of treatment is more effective than a shorter duration of treatment after an immediate instillation.

3.3. In low-risk patients, can the same or better results be obtained with one immediate instillation as compared to multiple delayed instillations after TUR?

Three epirubicin trials including a total of 512 patients compared one immediate instillation to delayed instillations during 12 mo (Table 3).

No differences were found in trials comparing one immediate instillation to either 8 weekly instillations starting 1–2 wk after TUR followed by monthly instillations to 1 yr (18 instillations) [16] or to weekly instillations for 6–8 wk followed by monthly instillations to 1 yr (16–18 instillations) [17]. In another trial comparing one immediate instillation to 4 weekly instillations starting 2 wk after TUR followed by monthly instillations to 1 yr (15 instillations),

fewer patients had recurrences in the delayed multiple instillation group, 24.8% versus 30.2% (p = 0.05) [12].

These results suggest that one immediate instillation of epirubicin might not be less effective than a delayed course of multiple epirubicin instillations in patients at low to intermediate risk.

3.4. Is an immediate instillation still important if it is planned to give long-term chemotherapy?

3.4.1. Six months of chemotherapy—Two trials assessed the benefit of an immediate instillation when chemotherapy was given during 6 mo (Table 4). In the first trial in which patients were randomized to start immediately or start 1–2 wk after TUR (9 instillations of MMC or Adriamycin during 6 mo), fewer patients receiving immediate chemotherapy had recurrence, 43.8% versus 55.8% (p = 0.03) [13]. However, in the second trial in which patients received 4 weekly instillations of epirubicin followed by 5 monthly instillations (9 instillations in 6 mo) preceded or not by one “immediate” instillation within 48 h, no significant difference was found [18]. This last study has been criticized because the first instillation was not given on the same day as the TUR; however, there was no difference according to whether or not the immediate instillation was given within 24 h.

3.4.2. Twelve months of chemotherapy—Three trials with 784 patients compared 4 weekly instillations starting within 24 h to 4 weekly instillations starting within 1–2 wk, followed in both arms by 11 monthly instillations to month 12 (Table 5). In the first two studies, the percentage with recurrence in the two treatment groups was similar [12,13]. In the third study, more patients had recurrences on the delayed treatment (p = 0.04); however, patients on delayed treatment tended to have a worse prognosis [19]. Combining these three studies, the percentage with recurrence on the immediate and delayed arms was similar. In a fourth study, there were no significant differences in the 3-yr recurrence rates [20].

These results suggest that one immediate instillation may still be necessary if further chemotherapy is given during only 6 mo; however, it might not be necessary if chemotherapy is given during 12 mo.

3.5. If one immediate instillation is not given, how long should further chemotherapy be continued?

Table 6 summarizes nine trials comparing delayed short-term instillations to delayed long-term instillations.

3.5.1. One year of chemotherapy—Three trials using various drugs compared short-term instillations of 5–6 mo to instillations during 1 yr [13,18,21]. In one study, fewer patients had recurrence with 12 mo of MMC or Adriamycin (15 instillations) as compared to 6 mo of treatment (9 instillations), 41.2% versus 55.8% (p = 0.01) [13]. However, in another study comparing 11 instillations of epirubicin during 12 mo to 9 instillations during 6 mo, no difference was found [18]. Likewise, no difference was found in a study comparing 19 instillations of epirubicin during 12 mo to 12 instillations during 5 mo [21]. In all three of these trials there is a possible dilution of the size of the treatment effect due to recurrences in the long-term treatment arm prior to starting the long-term instillations at 5 or 6 mo.

In another study comparing 12 instillations of Adriamycin during 6 wk to an additional 15 instillations to 1 yr, no difference was found [22]. A further study comparing 4 mo (40 mg/40 ml) to 7 mo (30 mg/40 ml) to 12 mo (20 mg/40 ml) of epirubicin found a higher percentage of patients with recurrence on the 12-mo arm, but treatment duration is confounded with drug

concentration so no conclusions can be drawn from this study concerning the optimal duration of treatment [23].

Although some evidence suggests that 1 yr of chemotherapy may be better than shorter durations, the study results are inconsistent.

3.5.2. Two years of chemotherapy—Two trials compared weekly instillations of Epodyl or Adriamycin during 6 wk to 6 weekly instillations followed by monthly instillations during 2 yr (30 instillations) [24,25]. There was no difference in the percentage of patients who had recurrences in the two treatment groups in either study.

3.5.3. Three years of chemotherapy—Weekly instillations of MMC for 20 wk were compared to either weekly instillations for 8 wk followed by monthly instillations to 3 yr (42 instillations) or to instillations every 2 wk during 1 yr followed by monthly instillations during year 2 and 3 monthly instillations during year 3 (42 instillations) [26,27]. There was no difference in the percentage who had a recurrence on 20 wk or 3 yr of treatment; however, the comparisons are confounded by different treatment intensities during the initial 20 wk.

In a recent study comparing 6 weekly instillations of MMC to 6 weekly instillations followed by monthly instillations during 3 yr (42 instillations), there was a large decrease in the percentage of patients with recurrence in the group receiving 3 yr of MMC, 25.7% versus 10.5% ($p = 0.0006$) [28].

Based on these contradictory results, no clear conclusions can be drawn concerning the optimal duration of chemotherapy when one immediate instillation is not given. One year and 2 yr of treatment do not appear to be superior to 6 wk, and 3 yr of treatment was not found to superior to 20 wk, so it was unexpected when 3 yr was recently reported to be more effective than 6 wk [28].

3.6. Does dose intensity or frequency of instillation influence the recurrence rate?

3.6.1. Total dose and dose concentration—Five trials, as summarized in Table 7, compared different total doses or drug concentrations.

Comparing 180 mg of epirubicin instilled within 6–11 wk (6 instillations) to 360 mg instilled within 10–12 wk (12 instillations), fewer patients had recurrences on the higher total dose, 31.8% versus 70.2% ($p = 0.012$) [29].

One study showed that the efficacy of MMC can be improved by increasing the drug's concentration in the bladder. A dose of 20 mg/20 ml was compared to an optimized dose with 40 mg/20 ml and pharma-cokinetic manipulations to maintain a high drug concentration in the bladder, with fasting to decrease the urine volume and urine alkalinization to stabilize the drug [30]. It is not known which, if any, of these three factors was the most important.

Other studies did not, however, find a difference in efficacy between different drug concentrations [31–34]. Two concentrations of Adriamycin, 20 mg/40 ml and 30 mg/30 ml, were compared using two different treatment schedules: 8 instillations within 4 wk (160 mg vs. 240 mg) or 21 instillations within 2 yr (420 mg vs. 630 mg) [31,32]. No difference in efficacy was found between the two doses for either 4 wk or 2 yr of treatment. When 18 instillations of epirubicin were given within 1 yr, there was no difference between 50 mg/50 ml (900 mg) and 80 mg/50 ml (1440 mg) in the percentage who had recurrence, 25.0% versus 17.6%, respectively [33]. Likewise, there was no difference in efficacy in a trial comparing 30 mg/30 ml to 60 mg/60 ml of thiotepa where instillations were given every 4 wk for a maximum

of 2 yr [34]. Once again the results of the different trials are inconsistent and no definitive conclusions can be drawn.

3.6.2. More intense or frequent short-term instillations compared to less intense long-term instillations

3.6.2.1. Frequent short-term instillations versus less frequent early instillations followed by long-term instillations (different total dose): Weekly instillations of MMC 20 mg/20 ml for 20 wk were compared to weekly instillations for 8 wk followed by monthly instillations to 3 yr (42 instillations) and to instillations every 2 wk during 1 yr followed by monthly instillations during year 2 and 3 monthly instillations during year 3 (42 instillations). There was no difference in efficacy between the frequent short-term instillations and either of the less intense long-term instillations [26,27].

3.6.2.2. Intense short-term instillations versus less intense long-term instillations (same total dose): Comparing 20 mg/40 ml of epirubicin (17 instillations in 12 mo) to 30 mg/40 ml (12 instillations in 7 mo) to 40 mg/40 ml (9 instillations in 4 mo), the percentage of patients with recurrence decreased as the drug concentration increased despite the decrease in the duration of treatment [23].

3.6.2.3. Frequent early instillations versus less frequent early instillations followed by long-term instillations in both arms (same total dose): Weekly MMC instillations for 8 wk followed by monthly instillations to 3 yr were compared to instillations every 2 wk during 1 yr followed by monthly instillations during year 2 and 3 monthly instillations during year 3 (42 instillations). There was a small nonsignificant decrease in the percentage of patients with recurrence in the group receiving 8 weekly instillations, 17.7% versus 24.4% [26,27].

Thus, evidence indicates that frequent, dose intense, short-term instillations may provide results that are at least as good as less intense instillations given over a longer period of time.

4. Discussion

Although the schedule and duration of intravesical chemotherapy have been the subjects of many studies, the optimal instillation scheme remains unknown. Controversy exists because underpowered trials have produced inconsistent results. Comparisons of different treatment durations have been diluted because patients have had recurrences and gone off the study before the time when additional long-term instillations should have started. The benefit of continuing treatment in patients who were free of disease at the end of the short-term treatment period was not assessed. In addition, trials have included varying proportions of good- and intermediate-risk patients, making it difficult to draw conclusions according to risk of recurrence. Different chemotherapeutic agents and different doses have also been used and the quality of TUR may differ among studies. Although there are no concrete data proving that one drug is more effective than another, one cannot rule out differences in efficacy according to the regimen used. For all these reasons, firm conclusions based on a high level of evidence cannot be drawn for most comparisons.

One immediate instillation reduces the recurrence rate, not only in good-risk patients with single tumors but also in patients with multiple tumors for whom one instillation is an incomplete treatment [3]. Beyond this, the results of this systematic review are disappointing and only limited conclusions can be drawn concerning the value of further treatment.

This review suggests that after one immediate instillation, additional instillations may further reduce the recurrence rate, especially in patients with multiple tumors, but no definitive

conclusions can be drawn (Table 1). Likewise, if further treatment is given, no recommendations can be given concerning its optimum duration (Table 2).

If one immediate instillation is not given, a minimum of 12 mo of treatment appears to be necessary to achieve the same prophylactic effect on recurrence as compared to one immediate instillation, either without (Table 3) or with additional instillations (Tables 4 and 5).

Although some evidence suggests that 1 yr may be better than 5–6 mo of treatment when one immediate instillation has not been given [13], results among the different studies were inconsistent (Table 6). There was no suggestion that 1 or 2 yr of treatment is more effective than 6 wk or that 3 yr is more effective than 5 mo; however, the number of patients studied is insufficient to draw definitive conclusions. On the other hand, a recent study showed a large decrease in the percent of patients recurring with 3 yr as compared to 6 wk of MMC [28]; it is unknown if this difference will lead to fewer cystectomies, progressions, and deaths due to bladder cancer. In an European Organization for Research and Treatment of Cancer (EORTC) study comparing 3 yr of epirubicin and BCG in intermediate- and high-risk patients, the results with epirubicin were disappointing despite an immediate instillation having been given [35]. Based on these contradictory results, no clear conclusions can be drawn concerning the optimal duration of chemotherapy when an immediate instillation has not been given.

Two studies in Table 7 suggest that more intense treatment during the initial 3–4 mo, either with respect to number of instillations [29] or drug concentration [30], reduces the recurrence rate. Other studies did not find a difference in efficacy between different drug concentrations [31–34,36]. Weekly instillations during 5 mo appear to be as effective as long-term instillations during 3 yr, which were given less frequently during the initial 5- mo period [26,27]. Thus, some evidence indicates that an initial intense schedule of instillations is of benefit and may be as effective as less intense long-term treatment.

The schedule and duration of intravesical chemotherapy should be guided by recurrence rates observed over time. Several publications have focused on the high recurrence rate at the first follow-up cystoscopy after TUR due to an incomplete resection or residual tumor [37–39]. There is thus justification for giving an early intense schedule of instillations to eradicate residual tumor after TUR.

The effect of one immediate instillation occurs early on, mainly during the first 1–2 yr, and is not effective in preventing late recurrences [40]. One study found two patterns of recurrence after TUR alone, early and late, with multiple tumors showing a peak in recurrence at 4 mo and solitary tumors showing a peak in recurrence at 1 yr. The effect of intravesical epirubicin or Adriamycin continued for a maximum of 500 d after TUR [41]. Another study with epirubicin found peaks in the recurrence rate at 18 mo and 4 yr, but with an earlier and increased risk of recurrence on short-term treatment of 3 mo as compared to 12 mo treatment [15]. These results suggest that additional therapy should be given prior to or at 1 yr in an attempt to prevent late recurrences.

Although intravesical chemotherapy reduces the recurrence rate, there is no proof that long-term chemotherapy will lead to fewer cystectomies, fewer progressions, or fewer deaths due to bladder cancer. In addition, its impact on quality of life is unknown. Long-term chemotherapy has, however, certain drawbacks including its costs, inconvenience, toxicity, and possible carcinogenicity [7]. Thus, it should not be given for a longer period of time than is necessary. Restarting instillations only after recurrence in intermediate-risk patients might in the long-term be as effective as immediate treatment, thus sparing patients from needless instillations. Hence, the cost effectiveness of long-term chemotherapy needs to be considered.

One could hypothesize that the excellent results that were recently reported with 3 yr of chemotherapy [28] might also have been obtained with an immediate instillation followed by an early short intensive course of instillations and an additional course of maintenance instillations at approximately 1 yr. However, randomized trials are required to test this strategy.

5. Conclusions

One immediate instillation after TUR reduces the recurrence rate and is recommended in all patients with papillary tumors except in the case of a perforated bladder or extended TUR (grade A). In patients at low risk of recurrence, no further treatment is recommended prior to recurrence.

In patients with multiple tumors for whom one instillation is insufficient treatment, the results of this systematic review are inconclusive and firm recommendations cannot be provided. The effect of one immediate instillation lasts for approximately 1.5 yr (level of evidence 1B). Additional instillations may be able to further reduce the recurrence rate although no recommendations can be given concerning their optimal duration. A short intensive schedule of instillations within the first 3–4 mo after an immediate instillation may be as effective as longer term treatment schedules (grade C).

Additional instillations at or after 1 yr may be useful in preventing late recurrences in intermediate-risk patients, but results of trials studying the benefit of 1, 2, and 3 yr of treatment are conflicting (grade C). Long-term instillations during ≥1 yr seem advisable only when an immediate instillation has not been given (grade C).

Higher drug concentrations and optimization of the drug's concentration in the bladder by decreasing the urine volume and controlling urine pH may provide better results (grade C).

Acknowledgements

This research project was supported by the EORTC Charitable Trust through a grant from the Fondation contre le Cancer (Belgium). This publication was supported by grant number 5U10 CA11488-37 from the National Cancer Institute (Bethesda, MD, USA). Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the National Cancer Institute.

References

1. Oosterlinck, W.; van der Meijden, A.; Sylvester, R., et al. Guidelines on TaT1 (non-muscle invasive) bladder cancer. European Association of Urology; 2006.
2. Sylvester RJ, van der Meijden AP, Oosterlinck W, et al. Predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer using EORTC risk tables: a combined analysis of 2596 patients from seven EORTC trials. Eur Urol 2006;49:466–77. [PubMed: 16442208]
3. Sylvester RJ, Oosterlinck W, van der Meijden APM. A single immediate postoperative instillation of chemotherapy decreases the risk of recurrence in patients with stage Ta T1 bladder cancer: a meta-analysis of published results of randomized clinical trials. J Urol 2004;171:2186–90. [PubMed: 15126782]
4. Pawinski, A.; Sylvester, R.; Kurth, KH., et al. J Urol. 156. 1996. A combined analysis of European Organization for Research and Treatment of Cancer and Medical Research Council randomized clinical trials for the prophylactic treatment of stage TaT1 bladder cancer; p. 1934-41.
5. Huncharek M, Geschwind JF, Witherspoon B, McGarry R, Adcock D. Intravesical chemotherapy prophylaxis in primary superficial bladder cancer: a meta-analysis of 3703 patients from 11 randomized trials. J Clin Epidemiol 2000;53:676–80. [PubMed: 10941943]
6. Huncharek M, McGarry R, Kupelnick B. Impact of intra-vesical chemotherapy on recurrence rate of recurrent superficial transitional cell carcinoma of the bladder: results of a meta-analysis. Anticancer Res 2001;21:765–70. [PubMed: 11299841]

7. Lamm DL, Riggs DR, Traynelis CL, Nseyo UO. Apparent failure of current intravesical chemotherapy prophylaxis to influence the long-term course of superficial transitional cell carcinoma of the bladder. J Urol 1995;153:1444–50. [PubMed: 7714962]
8. Medical Research Council Working Party on Urological Cancer. Br J Urol. 57. 1985. An MRC study. The effect of intravesical thiotepa on the recurrence rate of newly diagnosed superficial bladder cancer; p. 680-5.
9. Medical Research Council Working Party on Urological Cancer, Subgroup on Superficial Bladder Cancer. Br J Urol. 73. 1994. The effect of intravesical thiotepa on tumor recurrence after endoscopic treatment of newly diagnosed superficial bladder cancer. A further report with long-term follow-up of a Medical Research Council randomized trial; p. 632-8.
10. Tolley, DA.; Hargreave, TB.; Smith, PH., et al. Br Med J. 296. 1988. Effect of intra-vesical mitomycin C on recurrence of newly diagnosed superficial bladder cancer: interim report from the Medical Research Council Subgroup on Superficial Bladder Cancer (Urological Cancer Working Party); p. 1759-61.
11. Tolley DA, Parmar MKB, Grigor KM, Lallemand G. the Medical Research Council Superficial Bladder Cancer Working Party. The effect of intravesical mitomycin C on recurrence of newly diagnosed superficial bladder cancer: a further report with 7 years of followup. J Urol 1996;155:1233–8. [PubMed: 8632538]
12. Selvaggi FP, de Micheli P, Pamparana F, Sacchetti G. Epirubicina endovesicicale nella profilassi delle recidive dei tumori superficiali della vesica. Studio multicentrico, randomizzato. Acta Urol Ital 1990;1:331–3.
13. Bouffioux C, Kurth KH, Bono A, et al. Intravesical adjuvant chemotherapy for superficial transitional cell bladder carcinoma: results of 2 European Organization for Research and Treatment of Cancer randomized trials with mitomycin C and doxorubicin comparing early versus delayed instillations and short-term versus long-term treatment. J Urol 1995;153:934–41. [PubMed: 7853578]
14. Okamura K, Kinukawa T, Tsumura Y, et al. A randomized study of short- versus long-term intravesical epirubicin instillation for superficial bladder cancer. Eur Urol 1998;33:285–9. [PubMed: 9555553]
15. Koga K, Kuroiwa K, Yamaguchi A, Osada Y, Tsuneyoshi M, Naito S. A randomized controlled trial of short-term versus long-term prophylactic intravesical instillation chemotherapy for recurrence after transurethral resection of Ta/T1 transitional cell carcinoma of the bladder. J Urol 2004;171:153–7. [PubMed: 14665865]
16. Ali-el-Dein B, Nabeeh A, El-Baz M, Shamaa S, Ashamallah A. Single-dose versus multiple instillations of epirubicin as prophylaxis for recurrence after transur-ethral resection of pTa and pT1 transitional-cell bladder tumors: a prospective, randomized controlled study. Br J Urol 1997;79:731–5. [PubMed: 9158511]
17. Liu B, Wang Z, Chen B, et al. Randomized study of single instillation of epirubicin for superficial bladder carcinoma: long-term clinical outcomes. Cancer Invest 2006;24:160–3. [PubMed: 16537185]
18. Hendricksen K, Kiemeney LA, Caris C, Janzing R, Witjes W, Witjes JA. Three schedules of adjuvant intravesical epirubicin in patients with non-muscle invasive bladder cancer: a comparative study. Eur Urol Suppl 2007;6:60.abstract no. 149
19. Juan, I Iborra; Torrent, JV Ricos; Lliso, JL Monros; Martinez, R Dumont; Ramon-Borja, JC.; Narbon, E Solsona. Resultados de un studio de quimioprofilaxis intravesical, prospectivo, doble aleatorio, entre dos drogas: la adriamicina y el mitomycin; y dos modos de iniciar las instilaciones: precoz y tardio. Efecto sobre la recidiva y la progresion. Arch Esp de Urol 1992;45:1001–7.
20. Ueda T, Naito S, Iguchi A, et al. Adjuvant chemotherapy with early intravesical instillation of adriamycin and long-term oral administration of 5-fluorouracil in superficial bladder cancer. Cancer Chemother Pharmacol 1992;30(suppl):S31–6. [PubMed: 1394813]
21. Nomata K, Noguchi M, Kanetake H, et al. Intravesical adjuvant chemotherapy for superficial transitional cell bladder carcinoma: results of a randomized trial with epirubicin comparing short-term versus long-term maintenance treatment. Cancer Chemother Pharmacol 2002;50:266–70. [PubMed: 12357299]
22. Rubben H, Lutzeyer W, Fischer N, et al. Natural history and treatment of low and high risk superficial bladder tumors. J Urol 1988;139:283–5. [PubMed: 3339726]

23. Kuroda M, Niijima T, Kotake T, Akaza H, Hinotsu S. Effect of prophylactic treatment with intravesical epirubicin on recurrence of superficial bladder cancer—the 6th trial of the Japanese Urological Cancer Research Group (JUCRG): a randomized trial of intravesical epirubicin at dose of 20 mg/40 ml, 30 mg/40 ml, 40 mg/40 ml. Eur Urol 2004;45:600–5. [PubMed: 15082202]
24. Flamm, J.; Kuhnel, W.; Dona, S. Urologe A. 28. 1989. Kurzzeit-versus langzeitch-emorezidiv-prophymitlaxe epodyl nach TUR beim oberflachlichen harnblasenkarzinom; p. 99-102.
25. Flamm J. Long-term versus short-term doxorubicin hydrochloride instillation after transurethral resection of superficial bladder cancer. Eur Urol 1990;17:119–24. [PubMed: 2178939]
26. Huland H, Kloppel G, Feddersen I, et al. Comparison of different schedules of cytostatic intravesical instillations in patients with superficial bladder carcinoma: final evaluation of a prospective multicenter study with 419 patients. J Urol 1990;144:68–72. [PubMed: 2113590]
27. Schwaibold H, Pichlmeier U, Klingenberger HJ, Huland H. Long-term follow-up of cytostatic intravesical instillation in patients with superficial bladder carcinoma. Is short-term, intensive instillation better than maintenance therapy? Eur Urol 1997;31:153–9. [PubMed: 9076457]
28. Friedrich MG, Pichlmeier U, Scwaibold H, Conrad S, Huland H. Long-term intravesical adjuvant chemotherapy further reduces recurrence rate compared with short-term intravesical chemotherapy and short-term therapy with bacillus Calmette-Guerin (BCG) in patients with non–muscle-invasive bladder carcinoma. Eur Urol 2007;52:1123–30. [PubMed: 17383080]
29. Mitsumori K, Tsuchiya N, Habuchi T, et al. Early and large-dose intravesical instillation of eoirubicin to prevent superficial bladder carcinoma recurrence after transurethral resection. BJU Int 2004;94:317–21. [PubMed: 15291859]
30. Au JLS, Badalament RA, Wientjes MG, et al. Methods to improve efficacy of intravesical mitomycin C: results of a randomized phase III trial. J Natl Cancer Inst 2001;93:597–604. [PubMed: 11309436]
31. Akaza H, Isaka S, Koiso K, et al. Comparative analysis of short-term and long-term prophylactic intravesical chemotherapy of superficial bladder cancer. Cancer Chemother Pharmacol 1987;20 (Suppl):91–6.
32. Niijima T, Koiso K, Akaza H. Randomized clinical trial on chemoprophylaxis of recurrence in cases of superficial bladder cancer. Cancer Chemother Pharmacol 1983;11(Suppl):79–82.
33. Ali-el-Dein B, El-Baz M, Aly ANM, Shamaa S, Ashamallah A. Intravesical epirubicin versus doxorubicin for superficial bladder tumors (stages pTa and pT1): a randomized prospective study. J Urol 1997;158:68–74. [PubMed: 9186325]
34. Koontz WW, Prout GR, Smith W, Frable WJ, Minnis JE. The use of intravesical thio-tepa in the management of non-invasive carcinoma of the bladder. J Urol 1981;125:307–12. [PubMed: 6782251]
35. van der Meijden APM, Brausi M, Zambon V, Kirkels W, de Balincourt C, Sylvester R. Intravesical instillation of epirubicin, bacillus Calmette-Guérin and bacillus Calmette-Guérin plus isoniazid for intermediate and high risk Ta, T1 papillary carcinoma of the bladder: a European Organization for Research and Treatment of Cancer Genito-Urinary Group randomized phase III trial. J Urol 2001;166:476–81. [PubMed: 11458050]
36. Masters JRW, Popert RJM, Thompson PM, Gibson D, Coptcoat MJ, Parmar MKB. Intravesical chemotherapy with epirubicin: a dose response study. J Urol 1999;161:1490–3. [PubMed: 10210379]
37. Brausi M, Collette L, Kurth K, et al. Variability in the recurrence rate at first follow-up cystoscopy after TUR in stage Ta T1 transitional cell carcinoma of the bladder: a combined analysis of seven EORTC studies. Eur Urol 2002;41:523–31. [PubMed: 12074794]
38. Jakse G, Algaba F, Malmström PU, Oosterlinck W. A second-look TUR in T1 transitional cell carcinoma: why? Eur Urol 2004;45:539–46. [PubMed: 15082193]
39. Divrik T, Yildirim U, Eroglu A, Zorlu F, Ozen H. Is a second transurethral resection necessary for newly diagnosed pT1 bladder cancer. J Urol 2006;175:1258–61. [PubMed: 16515974]
40. Solsona E, Iborra I, Ricos JV, Monros JL, Casanova J, Dumont R. Effectiveness of a single immediate mitomycin C instillation in patients with low risk superficial bladder cancer: short and long-term followup. J Urol 1999;161:1120–3. [PubMed: 10081851]
41. Hinotsu S, Akaza H, Ohashi Y, Kotake T. Intravesical chemotherapy for maximum prophylaxis of new early phase superficial bladder carcinoma treated by transurethral resection. Cancer 1999;86:1818–26. [PubMed: 10547556]

Table 1

TUR plus one immediate instillation versus TUR plus one immediate instillation plus maintenance

Study	Year	Drug	% single tumors	Recurrence/total no. of patients		*p*
				TUR + 1 instillation	TUR + 1 instillation + maintenance	
MRC [8,9]	1985 1994	Thiotepa 30 mg/50 ml	69%	52/124 (41.9%)	45/120 (37.5%)	0.92*
Tolley [10,11]	1988 1996	MMC 40 mg/40 ml	Single Multiple 75%	51/119 (42.9%) 21/30 (70.0%) 72/149 (48.3%)	32/104 (30.8%) 21/42 (50.0%) 53/146 (36.3%)	0.06 0.09 0.04
Selvaggi [12]	1990	Epirubicin 50 mg/50 ml	69%	55/173 (31.8%)	40/167 (24.0%)	0.11

Maintenance treatment: References 8–11: 4 additional 3 monthly instillations during 12 mo starting at month 3 (total 5 instillations); for reference 12: 3 additional instillations during the first 4 wk followed by 11 monthly instillations to month 12 (total 15 instillations).

TUR = transurethral resection; MRC = Medical Research Council; MMC = mitomycin C.

*Log-rank test.

Eur Urol. Author manuscript; available in PMC 2009 April 1.

Table 2

TUR plus one immediate instillation followed by short-term versus long-term instillations during 12 mo

Study	Year	Drug	% single tumors	Recurrence/total no. of patients		*p*
				Short-term instillations	Long-term instillations (12 mo)	
Bouffioux [13]	1995	MMC 30 mg/50 ml ADM 50 mg/50 ml	62%	70/160 (43.8%)	67/150 (44.7%)	0.87
Okamura [14]	1998	Epirubicin 40 mg/40 ml	67%	NA/69 (22.8%) 2 yr	NA/69 (24.9%) 2 yr	0.62*
Koga [15]	2004	Epirubicin 30 mg/30 ml	61%	23/73 (31.5%)	10/77 (13.0%)	0.005* 0.006

Treatment schedules: reference 13: 9 instillations during 6 mo vs. 15 instillations during 12 mo; reference 14: 6 instillations during 1 mo vs. 17 instillations during 12 mo; reference 15: 9 instillations during 3 mo vs. 19 instillations during 12 mo. TUR = transurethral resection; MMC = mitomycin C; ADM = Adriamycin; NA = not available.

* Log-rank test.

Table 3

TUR plus one immediate instillation versus TUR plus delayed instillations to month 12

Study	Year	Drug	% single tumors	Recurrence/total no. of patients		*p*
				TUR + 1 instillation	TUR + delayed instillations (12 mo)	
Ali-el-Dein [16]	1997	Epirubicin 50 mg/50 ml	Single	8/34 (23.5%)	5/33 (15.2%)	0.39
			Multiple	5/21 (23.8%)	10/26 (38.5%)	0.28
			59%	13/55 (23.6%)	15/59 (25.4%)	0.83
Liu [17]	2006	Epirubicin 80 mg/40 ml 40 mg/40 ml	68%	5/14 (35.7%)	11/30 (36.7%)	0.95
Selvaggi [12]	1990	Epirubicin 50 mg/50 ml	69%	55/173 (31.8%)	41/181 (22.7%)	0.05
Total				73/242 (30.2%)	67/270 (24.8%)	0.13

Delayed instillations: reference 16: 8 weekly instillations starting 1–2 wk after TUR followed by monthly instillations to month 12 (18 instillations); reference 17: 6–8 weekly instillations followed by monthly instillations to month 12 (16–18 instillations); reference 12: 4 weekly instillations starting 2 wk after TUR followed by monthly instillations to month 12 (15 instillations).

TUR = transurethral resection.

Table 4

TUR plus one immediate instillation plus additional instillations during 6 mo versus TUR plus delayed instillations during 6 mo

Study	Year	Drug	% single tumors	Recurrence/total no. of patients		*p*
				TUR + immediate instillation	TUR + delayed instillation	
Bouffioux [13]	1995	MMC 30 mg/50 ml ADM 50 mg/50 ml	62%	70/160 (43.8%)	86/154 (55.8%)	0.03
Hendricksen [18]	2007	Epirubicin 50 mg/50 ml	20%	109/238 (45.8%)	117/239 (49.0%)	0.49

Treatment schedule: reference 13: 4 weekly instillations starting immediately or 1–2 wk after TUR followed by 5 monthly instillations to month 6 (9 instillations); reference 18: 4 weekly instillations followed by 5 monthly instillations to month 6 (9 instillations) preceded or not by an “immediate” instillation within 48 h.

TUR = transurethral resection; MMC = mitomycin C; ADM = Adriamycin.

Table 5

TUR plus one immediate instillation plus additional instillations during 12 mo versus TUR plus delayed instillations during 12 mo

Study	Year	Drug	% single tumors	Recurrence/total no. of patients		*p*
				TUR + immediate instillation	TUR + delayed instillation	
Selvaggi [12]	1990	Epirubicin 50 mg/50 ml	69%	40/167 (24.0%)	41/181 (22.7%)	0.77
Bouffioux [13]	1995	MMC 30 mg/50 ml ADM 50 mg/50 ml	62%	67/150 (44.7%)	63/153 (41.2%)	0.54
Iborra [19]	1992	ADM 30 mg/50 ml	40%	15/32 (46.9%)	17/32 (53.1%)	0.62
		MMC 30 mg/50 ml		6/33 (18.2%)	17/36 (47.2%)	0.01
		Total		21/65 (32.3%)	34/68 (50.0%)	0.04
Ueda [20]	1992	ADM 30 mg/30 ml	55%	NA/40 (20.6%) 3 yr	NA/53 (32.4%) 3 yr	NS
Total [12,13,19]				128/382 (35.4%)	138/402 (34.3%)	0.75

Treatment schedule: reference 12: 4 weekly instillations starting within 24 h or 2 wk after TUR followed by 11 monthly instillations to month 12 (15 instillations); reference 13: 4 weekly instillations starting immediately or 1–2 wk after TUR followed by 11 monthly instillations to month 12 (15 instillations); reference 19: 4 weekly instillations starting within 6 h or 1–2 wk after TUR followed by 11 monthly instillations to month 12 (15 instillations); reference 20: 17 instillations over 1 yr starting at 1 wk preceded or not by additional instillations immediately after TUR and at day 2.

TUR = transurethral resection; MMC = mitomycin C; ADM = Adriamycin; NA = not available; NS = not significant.

Table 6

TUR plus delayed short-term instillations versus TUR plus delayed long-term instillations

Study	Year	Drug	% single tumors	Recurrence/total no. of patients		*p*
				TUR + delayed short-term instillations	TUR + delayed long- term instillations	
Long-term instillations: 1 yr						
Bouffioux [13]	1995	MMC 30 mg/50 ml ADM 50 mg/50 ml	62%	86/154 (55.8%)	63/153 (41.2%)	0.01
Hendricksen [18]	2007	Epirubicin 50 mg/50 ml	20%	117/239 (49.0%)	118/254 (46.5%)	0.58
Nomata [21]	2002	Epirubicin 30 mg/30 ml	56%	NA/70 (44.9%) 3 yr	NA/55 (51.5%) 3 yr	NS
Rubben [22]	1988	ADM 50 mg/50 ml	68%	NA/91 (55%) 5 yr	NA/88 (57%) 5 yr	NS
Kuroda [23]	2004	Epirubicin 40 mg/40 ml (4mo) 30 mg/40 ml (7mo) vs. 20 mg/40 ml (12 mo)	18%	NA/205 (39.9%) NA/204 (44.9%) 2 yr	NA/205 (51.3%) NA/205 (51.3%) 2 yr	0.04†
Long-term instillations: 2 yr						
Flamm [24]	1989	Epodyl 50 cc	Single Multiple 79%	15/44 (34.1%) 7/12 (58.3%) 22/56 (39.3%)	17/46 (37.0%) 6/12 (50.0%) 23/58 (39.7%)	0.78 0.68 0.97
Flamm [25]	1990	ADM 50 mg/50 ml	48%	32/76 (42.1%)	33/70 (47.1%)	0.78*
Total 2 yr				54/132 (40.9%)	56/128 (43.8%)	0.63
Long-term instillations: 3 yr						
Huland [26a]	1990	MMC	NA	15/75 (20.0%)	17/96 (17.7%)	0.70
Schwaibold [27a]	1997	20 mg/20 ml				
Huland [26b]	1990	MMC	NA	15/75 (20.0%)	51/209 (24.4%)	0.44
Schwaibold [27b]	1997	20 mg/20 ml				
Friedrich [28]	2007	MMC 20 mg/20 ml	64%	46/179 (25.7%)	16/153 (10.5%)	0.0006*

Treatment schedules: reference 13: 4 weekly instillations starting 1–2 wk after TUR followed by 5 or 11 monthly instillations to month 6 or 12 (9 or 15 instillations); reference 18: 4 weekly and then 5 monthly instillations to month 6 followed or not by two 3 monthly instillations to month 12 (9 or 11 instillations); reference 21: 4 weekly and then 8 twice monthly instillations to month 5 followed or not by 7 monthly instillations to month 12 (12 or 19 instillations); reference 22: twice weekly for 6 wk followed or not by twice monthly for 4.5 mo and then monthly instillations to month 12 (12 or 27 instillations); reference 23: weekly for 2 wk and every 2 wk to month 4 followed or not by monthly instillations for 3 mo followed or not by monthly instillations to month 12 (9 [40 mg/40 ml], 12 [30 mg/40 ml], or 17 [20 mg/40 ml] instillations); reference 24: weekly instillations for 6 wk followed or not by monthly instillations during 2 yr (6 or 30 instillations); reference 25: weekly instillations for 6 wk followed or not by monthly instillations during 2 yr (6 or 30 instillations); references 26a, 27a: weekly instillations for 20 wk versus weekly instillations for 8 wk followed by monthly instillations to 3 yr (20 or 42 instillations); references 26b, 27b: weekly instillations for 20 wk versus instillations every 2 wk during 1 yr, then every 4 wk during year 2, then every 3 mo during year 3 (20 or 42 instillations); reference 28: 6 weekly instillations followed or not by monthly instillations during 3 yr (6 or 42 instillations).

TUR = transurethral resection; MMC = mitomycin C; ADM = Adriamycin; NA = not available; NS = not significant.

* Log-rank test.

† Log-rank test for trend.

Table 7

Dose intensity and frequency of instillation

Study	Year	Drug	% single tumors	Recurrence/total no. of patients		*p*
				TUR + less intense or frequent schedule	TUR + more intense or frequent schedule	
Total dose and dose concentration						
Mitsumori [29]	2004	Epirubicin 30 mg/40 ml 180 mg vs. 360 mg (6–12 wk)	43%	33/47 (70.2%)	7/22 (31.8%)	0.012*
Au [30]	2001	MMC 20 mg/20 ml vs. 40 mg/20 ml with dose optimization (6 wk)	43%	73/111 (65.8%)	61/119 (51.3%)	0.005*
Akaza [31a] Niijima [32]	1987	ADM 20 mg/40 ml (160 mg) vs. 30 mg/30 ml (240 mg) (4 wk)	64%	NA/148 (48.0%) 1.5 yr	NA/149 (43.4%) 1.5 yr	NS
Akaza [31b]	1987	ADM 20 mg/40 ml (420 mg) vs. 30 mg/30 ml (630 mg) (2 yr)	60%	NA/158 (40.9%) 2 yr	NA/151 (37.7%) 2 yr	NS
Ali-el-Dein [33]	1997	Epirubicin 50 mg/50 ml (900 mg) vs. 80 mg/50 ml (1440 mg) (1 yr)	38%	16/64 (25.0%)	12/68 (17.6%)	0.30
Koontz [34]	1981	Thiotepa 30 mg/30 ml vs. 60 mg/60 ml every 4 wk (2 yr)	71%	NA/23 (37%) 1 yr	NA/23 (31%) 1 yr	NS
Frequent short-term instillations vs. less frequent early instillations followed by long-term instillations (different total dose)						
Huland [26a] Schwaibold [27a]	1990 1997	MMC 20 mg/20 ml	NA	17/96 (17.7%)	15/75 (20.0%)	0.70
Huland [26b] Schwaibold [27b]	1990 1997	MMC 20 mg/20 ml	NA	51/209 (24.4%)	15/75 (20.0%)	0.44
Frequent early instillations vs. less frequent early instillations followed by long-term instillations in both arms (same total dose)						
Huland [26c] Schwaibold [27c]	1990 1997	MMC 20 mg/20 ml	NA	51/209 (24.4%)	17/96 (17.7%)	0.19
Intense short-term instillations vs. less intense long-term instillations (same total dose)						
Kuroda [23]	2004	Epirubicin 20 mg/40 ml (12 mo) 30 mg/40 ml (7 mo) vs. 40 mg/40 ml (4 mo)	18%	NA/205 (51.3%) NA/204 (44.9%)	NA/205 (39.9%) NA/205 (39.9%)	0.04†

Treatment schedules: reference 29: 180 mg within 6–11 wk (6 instillations) vs. 360 mg within 10–12 wk (12 instillations); reference 30: MMC 20 mg/20 ml vs. 40 mg/20 ml with dose optimization (6 instillations); references 31a, 32: 8 instillations within 4 wk: 20 mg/40 ml vs. 30 mg/30 ml (160 mg vs. 240 mg); reference 31b: 21 instillations within 2 yr: 20 mg/40 ml vs. 30 mg/30 ml (420 mg vs. 630 mg); reference 33: 18 instillations within 1 yr: 50 mg/50 ml vs. 80 mg/50 ml (900 mg vs. 1440 mg); reference 34: instillations every 4 wk for a maximum of 2 yr: 30 mg/30 ml vs. 60 mg/60 ml; references 26a, 27a: weekly instillations for 20 wk vs. weekly instillations for 8 wk followed by monthly instillations to 3 yr (20 or 42 instillations); references 26b, 27b: weekly instillations for 20 wk vs. instillations every 2 wk during 1 yr, then every 4 wk during year 2, then every 3 mo during year 3 (20 or 42 instillations); references 26c, 27c: weekly instillations for 8 wk followed by monthly instillations to 3 yr vs. instillations every 2 wk during 1 yr, then every 4 wk during year 2, then every 3 mo during year 3 (42 instillations); reference 23: weekly for 2 wk and every 2 wk to month 4 followed or not by monthly instillations for 3 mo followed or not by monthly instillations to month 12 (9 [40 mg/40 ml], 12 [30 mg/40 ml], or 17 [20 mg/40 ml] instillations).

TUR = transurethral resection; MMC = mitomycin C; ADM = Adriamycin; NA = not available; NS = not significant.

* Log-rank test.

† Log-rank test for trend.