

Systematic Review and Individual Patient Data Meta-analysis of Randomized Trials Comparing a Single Immediate Instillation of Chemotherapy after Transurethral Resection to Transurethral Resection Alone in Patients with Stage pTa-pT1 Urothelial Carcinoma of the Bladder: Which Patients Benefit from the Instillation?

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1 **Abstract**

2 **Context**

3 EAU Non Muscle Invasive Bladder Cancer (NMIBC) Guidelines recommend all low and  
4 intermediate risk patients receive a single immediate instillation of chemotherapy after TURB,  
5 but its use remains controversial.

6 **Objective**

7 Identify which NMIBC patients benefit from a single immediate instillation.

8 **Evidence Acquisition**

9 A systematic review and individual patient data (IPD) meta-analysis of randomized trials  
10 comparing the efficacy of a single instillation after TURB to TURB alone in NMIBC patients was  
11 carried out.

12 **Evidence Synthesis**

13 13 eligible studies were identified. IPD were obtained for 11 studies randomizing 2278 eligible  
14 patients, 1161 to TURB and 1117 to a single instillation of epirubicin, mitomycin C, pirarubicin  
15 or thiotepa.

16 1128 recurrences, 108 progressions and 460 deaths, 59 due to bladder cancer, occurred. A  
17 single instillation reduced the risk of recurrence by 35%, HR = 0.65, 95% CI: 0.58-0.74,  $p < 0.001$   
18 and the 5 year recurrence rate from 58.8% to 44.8%. The instillation did not reduce recurrences  
19 in patients with a prior recurrence rate  $> 1$  recurrence/year or in patients with an EORTC  
20 recurrence score  $\geq 5$ .

21 The instillation did not prolong either the time to progression or death from bladder cancer, but  
22 resulted in an increase in the overall risk of death (HR = 1.26, 95% CI: 1.05 – 1.51, p = 0.015, 5  
23 year death rates 12.0% versus 11.2%), with the difference appearing in patients with an EORTC  
24 recurrence score  $\geq 5$ .

## 25 **Conclusions**

26 A single immediate instillation reduced the risk of recurrence, except in patients with a prior  
27 recurrence rate  $> 1$  recurrence/year or an EORTC recurrence score  $\geq 5$ . It does not prolong  
28 either time to progression or death from bladder cancer. The instillation may be associated  
29 with an increase in the risk of death in patients at high risk of recurrence in whom the  
30 instillation is not effective or recommended.

31

## 32 **Patient Summary**

33 A single instillation of chemotherapy immediately after resection reduces the risk of recurrence  
34 in non-muscle invasive bladder cancer, however it should not be given to patients at high risk of  
35 recurrence due to its lack of efficacy in this subgroup.

36

37

**38 1. Introduction**

39 In low and intermediate risk patients with non-muscle invasive bladder cancer (NMIBC), the  
40 EAU NMIBC Guidelines Panel recommends a single immediate instillation of chemotherapy  
41 after complete transurethral resection (TURB) [1]. This recommendation stems from a June  
42 2004 literature based meta-analysis of a single immediate postoperative instillation of  
43 chemotherapy. Analyzing data extracted from publications of 7 randomized controlled trials  
44 (RCTs), the meta-analysis concluded that a single instillation significantly reduced the risk of  
45 recurrence after TURB, odds ratio = 0.61, 95% CI: 0.49-0.75,  $p < 0.0001$ , number needed to treat  
46 = 8.5 [2]. The AUA also supports use of an immediate postoperative instillation in patients with  
47 small volume, low grade Ta tumors [3]. Despite these recommendations, an immediate  
48 instillation of chemotherapy is not universally used in day to day clinical practice [4-7].  
49 Several RCTs assessing the efficacy of an immediate instillation have been published since the  
50 meta-analysis, some of which questioned its efficacy, especially in intermediate risk patients  
51 [8]. One review called for it to be abandoned [9].

52 One limitation of the meta-analysis was that it was not based on individual patient data so time  
53 to recurrence, prognostic factor and subgroup analyses could not be carried out to identify  
54 which patients benefit from the instillation. Likewise, two recent literature based meta-analyses  
55 could not adequately answer this question [10 – 11].

56 To identify which patients benefit from an immediate instillation, a new systematic review and  
57 meta-analysis using individual patient data has been undertaken.

58 This project was prospectively defined in a protocol at <https://db.tt/Q87Yvkk7>.

## 59 **2. Evidence Acquisition**

### 60 2.1 Trial Eligibility Criteria

61 All RCTs comparing a single immediate instillation of chemotherapy after TURB to TURB alone  
62 in patients with single or multiple, primary or recurrent stage pTaT1 urothelial carcinoma of the  
63 bladder were eligible. Carcinoma in situ and/or postoperative irrigation were not exclusion  
64 criteria. Trials allowing additional treatment prior to first recurrence were not eligible.

### 65 2.2 Literature Search

66 Medline, Embase, and Cochrane controlled trials databases and [clinicaltrials.gov](http://clinicaltrials.gov) were searched  
67 for relevant studies. No time limitations were applied. The search was supplemented by hand  
68 searching EAU and AUA meetings abstracts from 2005 to 2013, reference lists, searches in  
69 Google and discussions with clinical experts. The literature search strategy was developed  
70 starting in July 2013 with the final search in November 2013 using the strategy in Online  
71 Appendix 1.

### 72 2.3 Review of Studies Identified by the Literature Search

73 Each abstract was reviewed by at least 2 independent reviewers (see Acknowledgements). A  
74 Study Eligibility Form was filled out for studies identified as potentially eligible or where  
75 eligibility was unclear. These studies were entered in an Excel database to keep track of their  
76 status and final disposition. Full publications were requested to allow a more detailed  
77 assessment by the reviewer. For AUA and EAU abstracts, a similar procedure was followed.

78 Studies proposed as being eligible or where eligibility was unclear or there was disagreement  
79 between reviewers were reviewed by at least one member of the Steering Committee to reach  
80 a decision.

#### 81 2.4 Data Collection and Quality Control

82 Individual patient data on baseline characteristics, treatment, and outcome were requested for  
83 eligible studies using a pre-defined format (Online Appendix 2).

84 Data of each study were analyzed separately and compared to those in the publication. Results  
85 were sent to the principal investigator for approval along with any discrepancies noted.

#### 86 2.5 Data Synthesis and Statistical Evaluation

##### 87 2.5.1 Outcome Measures

88 The efficacy of a single immediate instillation of chemotherapy after TURB was compared to  
89 TURB alone with respect to:

90 Primary outcome: time to first recurrence, histologically confirmed.

91 Secondary outcomes: time to progression to muscle invasive disease, overall duration of  
92 survival, time to death due to bladder cancer

##### 93 2.5.2 Statistical Evaluation

94 The primary analysis was carried out in all eligible patients with pTa or pT1 tumors.

95 Confirmatory analyses in all randomized patients could not be done due to missing data for  
96 ineligible patients.

97 Ignoring recurrences after the first, the number needed to treat (NNT) to prevent one  
98 recurrence within 5 years was calculated in eligible patients and in all randomized patients  
99 assuming ineligible patients recurred within 5 years.

100 For time to event comparisons, starting point was date of randomization. For patients who died  
101 prior to an event of interest, death from a cause other than bladder cancer was a competing  
102 risk and date of death was the date of the competing risk event. Patients without an event were  
103 censored at last date of follow up.

104 Times to recurrence, progression and death due to bladder cancer were estimated by  
105 cumulative incidence functions taking death prior to an event as competing risk.

106 Overall duration of survival was estimated by the Kaplan-Meier technique. Median duration of  
107 follow up was calculated in all patients based on censoring at time of event.

108 Time to event distributions were compared using a Cox proportional hazards model stratified  
109 by study. The Fine-Gray test for competing risks was calculated as a sensitivity analysis. All tests  
110 were two sided using 0.05 significance level.

111 Fixed effect meta-analysis Forest plots were used to visually assess heterogeneity along with  
112 Cochran's Q chi-square test for heterogeneity and Higgins I<sup>2</sup>. Heterogeneity of treatment effect  
113 was tested in a Cox proportional hazards model using treatment by covariate interactions for  
114 variables in Figure 3. This included the 2006 EORTC risk scores for recurrence and progression  
115 [12] and the 2013 EAU risk group classification [1]. Subgroup analyses were carried out for  
116 factors where the interaction was significant at 0.05.



117 Exploratory non-randomized comparisons were carried out according to the chemotherapy,  
118 delay between TURB and immediate instillation, and use of post-operative irrigation.

119 No studies or patients were excluded for quality reasons.

### 120 **3. Evidence Synthesis**

#### 121 3.1 Literature Search Results

122 2365 abstracts were identified by the literature search (Online Appendix 1). After deletion of  
123 duplicates, 1559 abstracts remained and divided among 6 reviewers so that each abstract was  
124 reviewed by two reviewers. They identified 171 abstracts for which the full text was reviewed.

125 Abstracts of two potentially eligible but unpublished studies were identified [13,14]. Attempts  
126 to contact the authors of these studies were unsuccessful. One study was ineligible due to use  
127 of fulguration instead of TURBT [15]. In another, a subgroup of 19 patients was potentially  
128 eligible. Since there were no recurrences in these patients, they would have not contributed to  
129 the treatment comparisons and were not included [16]. Three other potentially eligible  
130 unpublished studies without abstracts identified in clinicaltrials.gov were reviewed:  
131 NCT01475266, NCT00003725 and NCT00445601.

132 After review of 171 full texts, 13 RCTs published between 1985 and 2011 were eligible for  
133 inclusion [8, 17–31].

134 44 studies identified from EAU and AUA meeting abstracts did not provide additional eligible  
135 studies.

136 Further details are provided in the PRISMA flow diagram (Online Figure 1).

## 137 3.2 Eligible Studies

138 Table 1 lists the 13 eligible studies. For 2 studies with 106 (4.4%) of the 2384 eligible patients, it  
139 was not possible to obtain individual patient data [30-31]. In these two studies and the two  
140 unpublished studies with abstracts [13-14], a single instillation reduced the recurrence rate as  
141 compared to TURB alone.

## 142 3.3 Eligible Studies with Individual Patient Data

143 Individual patient data were obtained for all 2278 eligible patients entered [8, 17-29].

144 Four were single center [22,23,28,29] and seven were multicenter (1 multi-national), three with  
145 a central randomization [21,25,26] and four with envelopes or local randomization lists  
146 [8,18,20,27]. No studies were double blind.

### 147 3.3.1 Study Characteristics

148 As found in the original publications, 2278 (84.2%) of 2705 randomized patients were eligible:  
149 86% on control (TURB only) and 83% on a single instillation. The main reason of ineligibility was  
150 an inappropriate histology as patients were randomized and treated prior to pathological  
151 confirmation. 1161 (51.0%) were randomized to control and 1117 (49.0%) to a single  
152 instillation. In three studies, patients in the control group received an immediate instillation of  
153 sterile water or saline after TURB [21,27,28].

154 Median follow up was 6.0 years for recurrence and 9.0 years for survival (Table 1).

### 155 3.3.2 Baseline characteristics

156 Table 2 provides the distribution of baseline characteristics. Median age was 64.0 years, 73.3%  
157 were male, 81.4% had primary tumors and 77.3% a single tumor. The median tumor size was 2  
158 cm and 18.2% had a tumor  $\geq$  3 cm. 74.3% were pTa, 52.8% G1/LG, 6.6% G3/HG and 1 patient  
159 had CIS. Among the 1620 patients for whom the EORTC recurrence score could be calculated,  
160 609 (37.6%) had a score of 0, 789 (48.7%) a score of 1-4 and 222 (13.7%) a score of 5-11. In the  
161 1865 patients for whom the EORTC progression score could be calculated, 879 (47.1%) had a  
162 score of 0, 699 (37.5%) a score of 2-6 and 287 (15.3%) a score of 7-17.

163 Baseline characteristics are well balanced in the treatment groups, except there are slightly  
164 more T1 patients, 24.7% versus 21.8%, and HG/G3 patients, 8.0% versus 5.3%, on immediate  
165 instillation. There are thus more patients at high risk of progression on a single instillation.

166 Epirubicin was used in 5 studies, mitomycin C in 4, pirarubicin in 1 and thiotepa in 1. Time of  
167 instillation was available in 837 patients: 335 (40.0%) received the instillation within 2 hours,  
168 467 (55.8%) between 3 to 12 hours and 35 (4.2%) after 12 hours (Table 3).

169 Post-operative irrigation (non-randomized) was used in 898 (56.4%) patients while 694 (43.6%)  
170 patients did not receive irrigation. (Online Table 1).

### 171 3.3.3 Time to First Recurrence

172 1128 (49.5%) of 2278 patients recurred: 475 (42.5%) allocated to a single instillation and 653  
173 (56.2%) to TURB (Table 4). Median tumor diameter at first recurrence was 3 mm in both groups  
174 (Online Table 2).

175 The difference in time to first recurrence between treatments is statistically significant in favor  
176 of immediate instillation, with a reduction of 35% in the relative risk of recurrence: HR = 0.65,  
177 95% CI: 0.58 – 0.74,  $p < 0.001$ . 5 year recurrence rates were 44.8% (95% CI: 41.6% – 48.0%) on a  
178 single instillation and 58.8% (95% CI: 55.7% – 61.9%) on TURB. Median times to first recurrence  
179 were 12 and 3 years, respectively (Figure 1).

180 The NNT to prevent 1 recurrence within 5 years is 7 eligible patients, 95% CI: 5.5 – 10, and 10  
181 randomized patients, 95% CI: 7 - 15.

182 Figure 2 shows the Forest Plot of time to first recurrence stratified by chemotherapy and study.  
183 There was significant heterogeneity between studies,  $p < 0.0001$ ,  $I^2 = 73.8$ . Immediate  
184 instillation was not effective in the thiotepa study, interaction test  $p = 0.002$ . Reductions in  
185 relative risks of recurrence were similar for the other 3 chemotherapies. Non randomized  
186 comparisons suggest better efficacy when the instillation is given within two hours after TURB.

### 187 3.3.3.1 Effect of an Immediate Instillation according to Patient Characteristics

188 In Figure 3, the test for interaction is significant only for the prior recurrence rate and EORTC  
189 Recurrence Risk Score. Recurrent patients with a prior recurrence rate  $> 1$  recurrence per year  
190 (Online Figure 2) and patients with a recurrence score  $\geq 5$  (Online Figure 3) did not benefit from  
191 the instillation.

### 192 3.3.3.2 Post-Operative Irrigation

193 In a non-randomized comparison of 1592 patients, post-operative irrigation reduced the risk of  
194 recurrence, both overall (HR = 0.69, 95% CI: 0.59, 0.88,  $p < 0.001$ ) and in the two treatment

195 groups. Adjusting for the randomized treatment and EORTC Recurrence Risk Score, post-  
196 operative irrigation reduced the relative risk of recurrence by 21%, HR = 0.79, 95% CI: 0.67 –  
197 0.93,  $p = 0.004$ . A single instillation reduced the risk of recurrence, both in patients receiving  
198 and not receiving post-operative irrigation.

### 199 3.3.4 Time to Progression

200 Time to progression data were available in 8 studies with 1765 patients. 108 patients (6.1%)  
201 progressed, 57 (6.6%) of 866 patients receiving a single instillation and 51 (5.7%) of 899 patients  
202 on TURB alone (Table 4).

203 Figure 4 presents the time to progression by treatment. The difference was not statistically  
204 significant: HR = 1.21, 95% CI: 0.83 – 1.78,  $p = 0.32$ . Five year progression rates were 5.6% (95%  
205 CI: 3.8% – 7.4%) on a single instillation and 4.8% (95% CI: 3.2% – 6.5%) on TURB alone.

206 Time to progression stratified by chemotherapy and study is provided in Online Figure 4, with  
207 no significant heterogeneity between studies,  $I^2 = 13.7$ . Stratification by the EORTC Progression  
208 Risk Score yielded similar results: HR = 1.09, 95% CI: 0.74 – 1.60,  $p = 0.68$ , as did stratification by  
209 stage and grade.

#### 210 3.3.4.1 Effect of an Immediate Instillation according to Patient Characteristics

211 No interactions were statistically significant for progression, although the same trends as for  
212 recurrence were seen. There was a suggestion of a higher risk of progression (HR = 1.60) on an  
213 immediate instillation in the 220 patients with an EORTC Recurrence Risk Score  $\geq 5$  (Online

214 Figure 5), however instillation patients in this subgroup had a higher baseline EORTC  
215 Progression Score, 8.2 versus 7.8.

### 216 3.3.5 Overall Duration of Survival

217 Survival data were available in 7 studies with 1509 patients. The duration of follow up was  
218 similar in the two treatment groups with median of 9.0 years on a single instillation and 8.9  
219 years on TURB. 460 (30.5%) deaths were reported, in 242 (32.8%) of 737 patients receiving a  
220 single instillation and 218 (28.2%) of 772 patients with TURB alone. 59 (3.9%) died due to  
221 bladder cancer, 75 (5.0%) due to another malignant disease, and 282 (18.7%) due to associated  
222 chronic disease (Table 4).

223 The difference in survival is statistically significant in favor of no instillation with a relative  
224 increase of 26% in the risk of death on an immediate instillation: HR = 1.26, 95% CI: 1.05 – 1.51,  
225 p = 0.015 (Figure 5). 5 year survival rates were 88.0% (95% CI: 85.3% – 90.3%) with a single  
226 instillation and 88.8% (95% CI: 86.1% – 91.0%) on TURB, with the curves separating after 6  
227 years. Median survivals were 13.1 years and 14.9 years, respectively.

228 Online Figure 6 shows the duration of survival stratified by study and chemotherapy, with no  
229 evidence of heterogeneity between studies,  $I^2 = 0$ . Stratification by the EORTC Progression Risk  
230 Score yielded similar results: HR = 1.24, 95% CI: 1.02 – 1.50, p = 0.03, as did stratification by  
231 stage and grade.

#### 232 3.3.5.1 Effect of an Immediate Instillation according to Patient Characteristics

233 There was a suggestion of a shorter survival on an immediate instillation in recurrent patients,  
234 patients with an EORTC Recurrence Risk Score  $\geq 5$  and EAU high risk patients. (Online Figure 7)

### 235 3.3.6 Time to Death Due to Bladder Cancer

236 59 (3.9%) patients died due to bladder cancer, 32 (4.3%) of 737 patients receiving a single  
237 instillation and 27 (3.5%) of 772 patients on TURB (Table 4).

238 Figure 6 presents the time to death due to bladder cancer by treatment group. The difference  
239 was not statistically significant: HR = 1.31, 95% CI: 0.78 – 2.19,  $p = 0.31$ . 5 year bladder cancer  
240 death rates were 2.1% (95% CI: 1.0% – 3.3%) in patients receiving a single instillation and 2.0%  
241 (95% CI: 0.9% – 3.1%) on TURB. Online Figure 8 presents time to death due to bladder cancer  
242 stratified by chemotherapy and study, with medium heterogeneity between studies,  $I^2 = 47.3$ .  
243 Stratification by EORTC Progression Risk Score yielded a slightly reduced hazard ratio: HR =  
244 1.13, 95% CI: 0.67 – 1.91,  $p = 0.65$ , as did stratification by stage and grade.

#### 245 3.3.6.1 Effect of an Immediate Instillation according to Patient Characteristics

246 The number of deaths due to bladder cancer is small and no interactions in Online Figure 9  
247 were statistically significant, but similar trends were seen as for overall survival, with a  
248 suggestion of a shorter disease specific survival on a single instillation in patients with  
249 recurrence risk score  $\geq 5$ .

### 250 3.3.7 Relationship between Cause of Death and EORTC Recurrence Risk Score

251 Table 5 lists the cause of death by treatment group according to EORTC Recurrence Risk Score.  
252 In patients with Scores 0 and 1 – 4, the duration of survival and the distribution of the causes of

253 death were similar in the two treatment groups. Despite adjustment for an imbalance in tumor  
254 stage and grade, this exploratory analysis suggests that in patients with Recurrence Risk Score  $\geq$   
255 5, more patients may have died on a single instillation, 65/106 (61.3%), than on TURB alone,  
256 44/102 (43.1%), with a higher percent of patients dying from malignant disease (bladder cancer  
257 or other) compared to patients not receiving an instillation, 35 (33.0%) versus 20 (19.6%). This  
258 was not a planned subgroup analysis and these differences could have occurred by chance.

#### 259 **4. Conclusions**

260 The results of our IPD meta-analysis have clearly confirmed the efficacy of a single immediate  
261 instillation of chemotherapy. The scientific rationale and explanation for its efficacy is based on  
262 its anti-tumor effect in destroying tumors cells floating in the irrigation fluid and urine after  
263 TURB and on its ablative effect on residual tumor cells at the site of the resection and on small  
264 overlooked tumors [32,33].

265 A single immediate instillation was not effective in patients with a prior recurrence rate  $> 1$   
266 recurrence per year and in patients with EORTC recurrence score  $\geq 5$ . This last subgroup was  
267 mainly composed of patients with multiple tumors (50.9%), tumors  $\geq 3$  cm (69.8%) and T1  
268 tumors (75.7%).

269 These results can help us make more precise recommendations for clinical practice. The  
270 decision to give an early instillation should be based on information available at time of TURB:  
271 the previous recurrence rate and the size and number of tumors. The definitive stage and grade  
272 is unknown at this time. From the weight of these parameters in the EORTC Recurrence Score  
273 [12], an early instillation is recommended in patients with:



274 1) single or multiple (up to 7 lesions) primary papillary tumor(s) smaller than 3 cm

275 2) single primary papillary tumors larger than 3 cm

276 3) single small recurrent papillary tumor with an interval of more than 1 year since the previous  
277 recurrence

278 Patients with multiple tumors, at least one of which is  $\geq 3$  cm, will have an EORTC Recurrence  
279 Score  $\geq 6$ . An immediate instillation is not recommended in these patients.

280 Non-randomized comparisons suggest the instillation is more effective when given within two  
281 hours after TURB. Indirect comparisons could not detect any differences in efficacy between  
282 mitomycin C and epirubicin.

283 Once the stage and grade are available, further treatment can be planned according to the risk  
284 stratification [1].

285 The benefit of an early instillation was most pronounced in low risk patients in whom no further  
286 treatment before recurrence is recommended.

287 In intermediate risk patients, where the 5 year recurrence rate after a single instillation is nearly  
288 40%, the results support EAU guideline recommendations that a single instillation alone is  
289 insufficient and should be followed by further instillations [1]. A systematic review  
290 demonstrated the best results for schedules where an early instillation preceded further  
291 instillations of chemotherapy [34]. In high risk patients receiving BCG, the only study assessing a  
292 single instillation was inconclusive [35].

293 Recurrences in low risk patients are usually low stage, low grade [36,37]. In this meta-analysis,  
294 recurrences were mostly small, median size 3 mm. Theoretically, small recurrences can be  
295 managed by office fulguration under local anesthesia without a significant burden to the  
296 patient [9,38,39]. There are, however, no prospective randomized comparisons of this  
297 procedure.

298 This meta-analysis provides non-randomized evidence that use of post-operative irrigation also  
299 reduces recurrences. It may act by helping prevent implantation of circulating tumor cells at the  
300 site of resection. This confirms the results of a previously published abstract [40], but should be  
301 considered with caution as details about duration of irrigation are lacking and the type of fluid  
302 was not available in all patients.

303 As can be expected from its mode of action, a single instillation did not have a positive effect on  
304 either the long-term progression or survival rates. It was surprising that a significant increase of  
305 26% in the overall risk of death was found in patients with the instillation. Despite adjustment  
306 for imbalances in tumor stage and grade, exploratory analyses suggest a single instillation may  
307 be associated with a shorter survival in patients at high risk of recurrence, i.e. with an EORTC  
308 recurrence risk score  $\geq 5$ . This subgroup, with only 222 (13.7%) of the 1620 patients for whom  
309 the score could be calculated, is precisely the subgroup of patients in which an immediate  
310 instillation is not effective or recommended. Patients with a high prior recurrence rate and risk  
311 of recurrence may be at higher risk of (unrecognized) perforation, which could contribute to  
312 their poor prognosis [41].

313 Lamm et al [42] found that intravesical chemotherapy did not influence the long-term course of  
314 the disease and raised concerns that repeated intravesical chemotherapy might be  
315 carcinogenic, however the EORTC found no evidence of carcinogenicity in 3 studies with more  
316 than 1200 patients [43,44].

317 This is the first meta-analysis to study this question which is based on individual patient data  
318 with a relatively long follow up and identify patients who benefit or not from an immediate  
319 instillation. Nevertheless, there are a number of limitations in the interpretation of the data,  
320 especially the long-term results. No information was collected on further treatment after  
321 recurrence or progression or on the occurrence of distant metastases. Only 7 studies  
322 contributed to progression comparisons and 5 studies to survival comparisons, 3 with a median  
323 follow up of more than 10 years. Survival was not a formal endpoint in these studies and it is  
324 unknown to what extent the cause of death was based on autopsy evidence.

325 Finally, no information on adverse events was collected. Although some severe complications  
326 after early instillation have been reported [45,46], their frequency is low if indications for their  
327 use are respected and proper safeguards followed.

328 In summary, although a single immediate instillation of chemotherapy reduced the relative risk  
329 of recurrence by 35% and 5 year recurrence rate by 14%, it is not effective in patients with a  
330 prior recurrence rate > 1 recurrence per year or in patients with EORTC Recurrence Risk Score  $\geq$   
331 5. It does not prolong either the time to progression or the time to death due to bladder  
332 cancer. Exploratory analyses suggest that the instillation may be associated with an increase in  
333 the risk of death in patients at high risk of recurrence in whom the instillation is not effective

334 and thus not recommended. The long-term survival differences may be biased by the treatment  
335 received after recurrence and thus may be chance findings. Non-randomized evidence indicates  
336 the use of post-operative irrigation may also reduce recurrences.

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## 6.0 References

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Table 1: Eligible Studies

Table 2: Baseline Patient and Tumor Characteristics

Table 3: Intravesical Chemotherapy

Table 4: Patient Outcome

Table 5: Cause of Death by EORTC Recurrence Risk Score

Figure 1: Time to First Recurrence

Figure 2: Time to First Recurrence Stratified by Chemotherapy and Study

Figure 3: Effect of an immediate instillation on recurrence by patient characteristics

Figure 4: Time to progression

Figure 5: Duration of survival

Figure 6: Time to Death due to Bladder Cancer

Online Table 1: Post-operative Irrigation

Online Table 2: Tumor diameter at first recurrence

Online Figure 1: PRISMA Flow Diagram

Online Figure 2: Time to First Recurrence according to Prior Recurrence Rate

Online Figure 3: Time to First Recurrence according to EORTC Recurrence Risk Score

Online Figure 4: Time to progression Stratified by Chemotherapy and Study

Online Figure 5: Effect of an immediate instillation on progression by patient characteristics

Online Figure 6: Duration of survival stratified by chemotherapy and study

Online Figure 7: Effect of an immediate instillation on survival by patient characteristics

Online Figure 8: Time to Death due to Bladder Cancer stratified by chemotherapy and study

Online Figure 9: Effect of an immediate instillation on death due to bladder cancer by patient characteristics

Online Appendix 1: Literature Search Strategy

Online Appendix 2: Individual Patient Data Requested