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Platinum Priority – Guidelines

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

Richard J. Sylvester[a,*], *Willem Oosterlinck*[b], *Sten Holmang*[c], *Matthew R. Sydes*[d], *Alison Birtle*[e], *Sigurdur Gudjonsson*[f], *Cosimo De Nunzio*[g], *Kikuo Okamura*[h], *Eero Kaasinen*[i], *Eduardo Solsona*[j], *Bedeir Ali-El-Dein*[k], *Can Ali Tatar*[l], *Brant A. Inman*[m], *James N'Dow*[n], *Jorg R. Oddens*[o], *Marek Babjuk*[p]

[a] *EORTC Headquarters, Department of Biostatistics, Brussels, Belgium;* [b] *Ghent University Hospital, Department of Urology, Ghent, Belgium;* [c] *University of Gothenburg, Department of Urology, Gothenburg, Sweden;* [d] *Medical Research Council Clinical Trials Unit at University College London, Department of Cancer and Other Non-Infectious Diseases, London, UK;* [e] *Royal Preston Hospital, Rosemere Cancer Centre, Preston, UK;* [f] *Skane University Hospital, Department of Urology, Malmo, Sweden;* [g] *Ospedale Sant'Andrea, University "La Sapienza," Department of Urology, Rome, Italy;* [h] *Higashi Nagoya Hospital, Department of Urology, Nagoya, Japan;* [i] *Hyvinkaa Hospital, Department of Urology, Hyvinkaa, Finland;* [j] *Valencia Oncology Institute, Department of Urology, Valencia, Spain;* [k] *Urology and Nephrology Center, Mansoura University, Department of Urology, Mansoura, Egypt;* [l] *Turkiye Yuksek Ihtisas Education and Research Hospital, Department of Urology, Ankara, Turkey;* [m] *Duke University Medical Center, Division of Urology, Durham, NC, USA;* [n] *University of Aberdeen, Academic Urology Unit, Aberdeen, UK;* [o] *Jeroen Bosch Hospital, Department of Urology, 's-Hertogenbosch, The Netherlands;* [p] *Hospital Motol and Second Faculty of Medicine, Charles University, Department of Urology, Prague, Czech Republic*

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Abstract

Context: The European Association of Urology non–muscle-invasive bladder cancer (NMIBC) guidelines recommend that all low- and intermediate-risk patients receive a single immediate instillation of chemotherapy after transurethral resection of the bladder (TURB), but its use remains controversial.
Objective: To identify which NMIBC patients benefit from a single immediate instillation.
Evidence acquisition: A systematic review and individual patient data (IPD) meta-analysis of randomized trials comparing the efficacy of a single instillation after TURB with TURB alone in NMIBC patients was carried out.
Evidence synthesis: A total of 13 eligible studies were identified. IPD were obtained for 11 studies randomizing 2278 eligible patients, 1161 to TURB and 1117 to a single instillation of epirubicin, mitomycin C, pirarubicin, or thiotepa. A total of 1128 recurrences, 108 progressions, and 460 deaths (59 due to bladder cancer [BCa]) occurred. A single instillation reduced the risk of recurrence by 35% (hazard ratio [HR]: 0.65; 95% confidence interval [CI], 0.58–0.74; $p < 0.001$) and the 5-yr recurrence rate from 58.8% to 44.8%. The instillation did not reduce recurrences in patients with a prior recurrence rate

* Corresponding author. Department of Biostatistics, EORTC Headquarters, 83 avenue E. Mounier, 1200 Brussels, Belgium. Tel. +32 2 7741613.
E-mail address: richard.sylvester@skynet.be (R.J. Sylvester).

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of more than one recurrence per year or in patients with an European Organization for Research and Treatment of Cancer (EORTC) recurrence score ≥5. The instillation did not prolong either the time to progression or death from BCa, but it resulted in an increase in the overall risk of death (HR: 1.26; 95% CI, 1.05–1.51; $p = 0.015$; 5-yr death rates 12.0% vs 11.2%), with the difference appearing in patients with an EORTC recurrence score ≥5.
Conclusions: A single immediate instillation reduced the risk of recurrence, except in patients with a prior recurrence rate of more than one recurrence per year or an EORTC recurrence score ≥5. It does not prolong either time to progression or death from BCa. The instillation may be associated with an increase in the risk of death in patients at high risk of recurrence in whom the instillation is not effective or recommended.
Patient summary: A single instillation of chemotherapy immediately after resection reduces the risk of recurrence in non–muscle-invasive bladder cancer; however, it should not be given to patients at high risk of recurrence due to its lack of efficacy in this subgroup.

1. Introduction

In low- and intermediate-risk patients with non–muscle-invasive bladder cancer (NMIBC), the European Association of Urology (EAU) NMIBC guidelines panel recommends a single immediate instillation of chemotherapy after a complete transurethral resection of the bladder (TURB) [1]. This recommendation stems from a June 2004 literature-based meta-analysis of a single immediate postoperative instillation of chemotherapy. Analyzing data extracted from publications of seven randomized controlled trials (RCTs), the meta-analysis concluded that a single instillation significantly reduced the risk of recurrence after TURB (odds ratio: 0.61; 95% confidence interval [CI], 0.49–0.75; $p < 0.0001$; number needed to treat [NNT]: 8.5) [2]. The American Urological Association (AUA) also supports the use of an immediate postoperative instillation in patients with small-volume, low-grade Ta tumors [3]. Despite these recommendations, an immediate instillation of chemotherapy is not universally used in day-to-day clinical practice [4–7].

Several RCTs assessing the efficacy of an immediate instillation have been published since the meta-analysis, some of which questioned its efficacy, especially in intermediate-risk patients [8]. One review called for it to be abandoned [9]. The meta-analysis had a limitation because it was not based on individual patient data (IPD), so time to recurrence, prognostic factor, and subgroup analyses could not be carried out to identify which patients would benefit from the instillation. Two recent literature-based meta-analyses also could not adequately answer this question [10,11].

To identify which patients benefit from an immediate instillation, a new systematic review and meta-analysis using IPD was undertaken. This project was prospectively defined in a protocol.

2. Evidence acquisition

2.1. Trial eligibility criteria

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

2.2. Literature search

Medline, Embase, and Cochrane controlled trials databases and ClinicalTrials.gov were searched for relevant studies. No time limitations were applied. The search was supplemented by hand-searching EAU and AUA meetings abstracts from 2005 to 2013, searches of reference lists, searches in Google, and discussions with clinical experts. The literature search strategy was developed beginning in July 2013 with the final search in November 2013 using the strategy outlined in Supplement 1.

2.3. Review of studies identified by the literature search

Each abstract was reviewed by at least two independent reviewers (see Acknowledgments). A study eligibility form was filled out for studies identified as potentially eligible and for studies in which eligibility was unclear. These studies were entered in an Excel database (Microsoft, Redmond, WA, USA) to keep track of their status and final disposition. Full publications were requested to allow a more detailed assessment by the reviewer. For AUA and EAU abstracts, a similar procedure was followed.

Studies proposed as eligible or in which eligibility was unclear or there was disagreement between reviewers were reviewed by at least one member of the steering committee to reach a decision.

2.4. Data collection and quality control

IPD on baseline characteristics, treatment, and outcome were requested for eligible studies using a predefined format (Supplement 2).

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

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2.5. Data synthesis and statistical evaluation

2.5.1. Outcome measures

The efficacy of a single immediate instillation of chemotherapy after TURB was compared with TURB alone with respect to primary outcome: time to first recurrence, histologically confirmed, and secondary outcomes: time to progression to muscle-invasive disease, overall duration of survival, and time to death due to bladder cancer (BCa).

2.5.2. Statistical evaluation

The primary analysis was carried out in all eligible patients with pTa or pT1 tumors. Confirmatory analyses in all randomized patients could not be done due to missing data for ineligible patients. Ignoring recurrences after the first, the NNT to prevent one recurrence within 5 yr was calculated in eligible patients and in all randomized patients assuming ineligible patients recurred within 5 yr.

For time-to-event comparisons, the starting point was date of randomization. For patients who died prior to an event of interest, death from a cause other than BCa was a competing risk, and date of death was the date of the competing risk event. Patients without an event were censored at the last date of follow-up. Times to recurrence, progression, and death due to BCa were estimated by cumulative incidence functions taking death prior to an event as competing risk. Overall duration of survival was estimated by the Kaplan-Meier technique. Median duration of follow-up was calculated in all patients based on censoring at the time of the event.

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

Fixed-effect meta-analysis forest plots were used to assess heterogeneity visually along with the Cochran Q chi-square test for heterogeneity and Higgins I^2. Heterogeneity of treatment effect was tested in a Cox proportional hazards model using treatment by covariate interactions for variables in Figure 1. This included the 2006 European Organization for Research and Treatment of Cancer (EORTC) risk scores for recurrence and progression [12] and the 2013 EAU risk group classification [1]. Subgroup analyses were carried out for factors for which the interaction was significant at 0.05.

Exploratory nonrandomized comparisons were carried out according to the chemotherapy, delay between TURB and immediate instillation, and use of postoperative irrigation. No studies or patients were excluded for quality reasons.

3. Evidence synthesis

3.1. Literature search results

Overall, 2365 abstracts were identified by the literature search (Supplement 1). After deletion of duplicates, 1559 abstracts remained and were divided among six reviewers, so each abstract was reviewed by two reviewers. They identified 171 abstracts for which the full text was reviewed. Abstracts of two potentially eligible but unpublished studies were identified [13,14]. Attempts to contact the authors of these studies were unsuccessful. One study was ineligible due to use of fulguration instead of TURB [15]. In another, a subgroup of 19 patients was potentially eligible. Because there were no recurrences in these patients, they would have not contributed to the treatment comparisons and were not included [16]. Three other potentially eligible unpublished studies without abstracts identified in ClinicalTrials.gov were reviewed: NCT01475266, NCT00003725, and NCT00445601.

After the review of 171 full texts, 13 RCTs published between 1985 and 2011 were eligible for inclusion [8,17–31]. A total of 44 studies identified from EAU and AUA meeting abstracts did not provide additional eligible studies. Further details are provided in the Preferred Reporting Items for Systematic Reviews and Meta-analysis flow diagram (Supplementary Fig. 1).

3.2. Eligible studies

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

3.3. Eligible studies with individual patient data

IPD were obtained for all 2278 eligible patients entered [8,17–29]. Four were single center [22,23,28,29] and seven were multicenter (one multinational), three with a central randomization [21,25,26] and four with envelopes or local randomization lists [8,18,20,27]. No studies were double blind.

3.3.1. Study characteristics

As found in the original publications, 2278 (84.2%) of 2705 randomized patients were eligible: 86% on control (TURB only) and 83% on a single instillation. The main reason for ineligibility was an inappropriate histology because patients were randomized and treated prior to pathologic confirmation. Overall, 1161 (51.0%) were randomized to control and 1117 (49.0%) to a single instillation. In three studies, patients in the control group received an immediate instillation of sterile water or saline after TURB [21,27,28]. Median follow-up was 6 yr for recurrence and 9 yr for survival (Table 1).

3.3.2. Baseline characteristics

Table 2 provides the distribution of baseline characteristics. Median age was 64.0 yr, 73.3% were male, and 81.4% had primary tumors and 77.3% a single tumor. The median tumor size was 2 cm, and 18.2% had a tumor $\geq$3 cm. A total of 74.3% were pTa, 52.8% G1/low grade, 6.6% G3/high grade (HG), and one patient had CIS. Among the 1620 patients for whom the EORTC recurrence score could be calculated, 609 (37.6%) had a score of 0, 789 (48.7%) a score of 1–4, and 222

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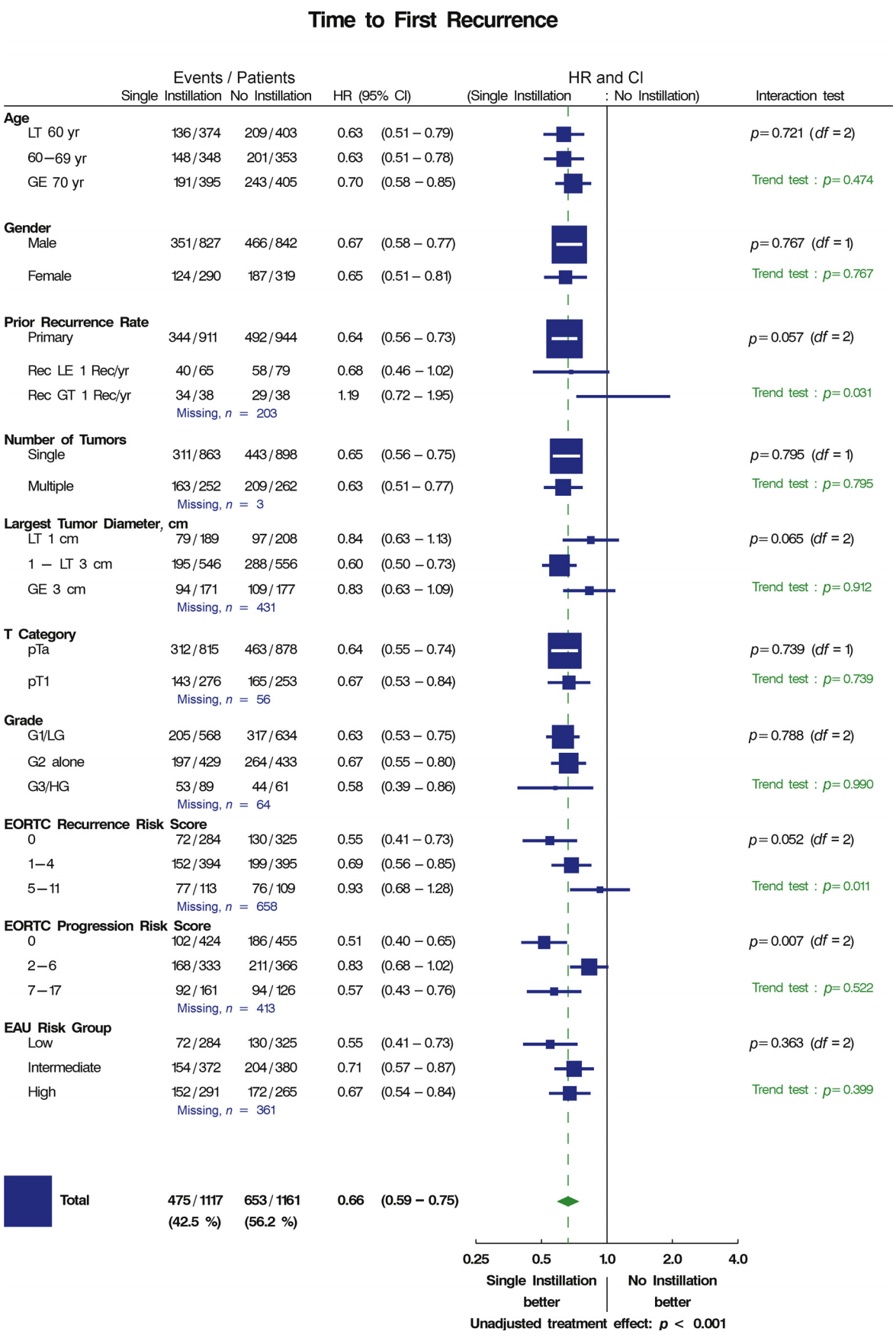

Fig. 1 – Effect of an immediate instillation on recurrence by patient characteristics.
CI = confidence interval; EAU = European Association of Urology; EORTC = European Organization for Research and Treatment of Cancer; HG = high grade; HR = hazard ratio; LG = low grade; Rec = recurrence.

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Table 1 – Eligible studies

Study	Patient entry	Year of publication	Chemotherapy after TURB	Control group	Postoperative irrigation	Randomization	Number randomized	Number eligible (%)	Median follow-up*
Medical Research Council [17,18]	1981–1984	1985 1994	Thiotepa 30 mg/50 ml	TURB alone	Some patients	Multicenter local randomization	281	256	12.2 yr 14.4 yr
Tolley et al [19,20]	1984–1986	1988 1996	Mitomycin C 40 mg/40 ml	TURB alone	Some patients	Multicenter local randomization	338	306	9.7 yr 11.8 yr
Oosterlinck et al [21]	1986–1989	1993	Epirubicin 80 mg/ 50 ml	Immediate instillation of 50 ml sterile water after TURB	Yes	Multicenter central randomization	512	421	5.3 yr 5.5 yr
Ali-El-Dein et al [22]	1992–1996	1997	Epirubicin 50 mg/ 50 ml	TURB alone	No	Single center	120	109	2.8 yr –
Solsona et al [23]	1988–1992	1999	Mitomycin C 30 mg/50 ml	TURB alone	No	Single center	131	121	11.8 yr 20.9 yr
Rajala et al [24,25]	1991–1994	1999 2002	Epirubicin 100 mg/ 100 ml	TURB alone	No	Multicenter central randomization	189 (estimated)	134	6.1 yr –
Okamura et al [26]	1994–1998	2002	Pirarubicin 30 mg/ 30 ml	TURB alone	Unknown	Multicenter central randomization	170	160	3.2 yr 3.5 yr
Berrum-Svennung et al [27]	1998–2003	2008	Epirubicin 50 mg/ 50 ml	Immediate instillation of 50 ml saline after TURB	Unknown	Multicenter local randomization	404	307	1.6 yr –
Gudjonsson et al [8]	1997–2004	2009	Epirubicin 80 mg/ 50 ml	TURB alone	Unknown	Multicenter local randomization	305	219	3.7 yr –
Tatar et al [28]	2007–2009	2011	Mitomycin C 40 mg/50 ml	Immediate instillation of distilled water or saline after TURB	Yes	Single center	45	43	1.0 yr 1.0 yr
De Nunzio et al [29]	2000–2009	2011	Mitomycin C 40 mg/50 ml	TURB alone	Yes	Single center	210	202	7.2 yr 7.0 yr
Subtotal with patient data							2705	2278 (84.2)	6.0 yr 9.0 yr
Barghi et al [30]	2003–2005	2006	Mitomycin C 30 mg/30 ml	Immediate instillation of distilled water after TURB	Yes	Single center	50	43	15.7 mo
El-Ghobashy et al [31]	2002–2005	2007	Mitomycin C 30 mg/50 ml	TURB alone	Unknown	Single center	63 (unknown)	63	Unknown
Subtotal without data							113	106 (93.8)	
Grand total							2818	2384 (84.6)	

TURB = transurethral resection of the bladder.
* Recurrence, survival.

Table 2 – Baseline patient and tumor characteristics

	Randomized treatment		
	No instillation (n = 1161)	Single instillation (n = 1117)	Total (n = 2278)
	n (%)	n (%)	n (%)
Study			
Medical Research Council [17,18]	130 (11.2)	126 (11.3)	256 (11.2)
Tolley et al [19,20]	157 (13.5)	149 (13.3)	306 (13.4)
Oosterlinck et al [21]	215 (18.5)	206 (18.4)	421 (18.5)
Ali-El-Dein et al [22]	54 (4.7)	55 (4.9)	109 (4.8)
Solsona et al [23]	64 (5.5)	57 (5.1)	121 (5.3)
Rajala et al [24,25]	66 (5.7)	68 (6.1)	134 (5.9)
Okamura et al [26]	79 (6.8)	81 (7.3)	160 (7.0)
Berrum-Svennung et al [27]	152 (13.1)	155 (13.9)	307 (13.5)
Gudjonsson et al [8]	117 (10.1)	102 (9.1)	219 (9.6)
Tatar et al [28]	22 (1.9)	21 (1.9)	43 (1.9)
De Nunzio et al [29]	105 (9.0)	97 (8.7)	202 (8.9)
Age, yr			
<60	403 (34.7)	374 (33.5)	777 (34.1)
60–69	353 (30.4)	348 (31.2)	701 (30.8)
≥70	405 (34.9)	395 (35.4)	800 (35.1)
Age, yr			
Median	64.0	64.0	64.0
Range	17.0–97.0	19.0–94.0	17.0–97.0
Gender			
Male	842 (72.5)	827 (74.0)	1669 (73.3)
Female	319 (27.5)	290 (26.0)	609 (26.7)
Prior recurrence rate			
Primary	944 (81.3)	911 (81.6)	1855 (81.4)
Recurrent, ≤1 recurrence/yr	79 (6.8)	65 (5.8)	144 (6.3)
Recurrent, >1 recurrence/yr	38 (3.3)	38 (3.4)	76 (3.3)
Recurrent, rate unknown	100 (8.6)	103 (9.2)	203 (8.9)
No. of tumors			
1	898 (77.3)	863 (77.3)	1761 (77.3)
2–7	102 (8.8)	91 (8.1)	193 (8.5)
≥8	8 (0.7)	3 (0.3)	11 (0.5)
Missing	153 (13.2)	160 (14.3)	313 (13.7)
No. of tumors			
Single	898 (77.3)	863 (77.3)	1761 (77.3)
Multiple	262 (22.6)	252 (22.6)	514 (22.6)
Missing	1 (0.1)	2 (0.2)	3 (0.1)
Largest tumor diameter, cm			
<1	208 (17.9)	189 (16.9)	397 (17.4)
1 to <3	556 (47.9)	546 (48.9)	1102 (48.4)
≥3	177 (15.2)	171 (15.3)	348 (15.3)
Missing	220 (18.9)	211 (18.9)	431 (18.9)
Largest tumor diameter, cm			
<3	798 (68.7)	771 (69.0)	1569 (68.9)
≥3	177 (15.2)	171 (15.3)	348 (15.3)
Missing	186 (16.0)	175 (15.7)	361 (15.8)
Largest tumor diameter, cm			
Median	2.0	2.0	2.0
Range	0.1–20.0	0.1–15.0	0.1–20.0
N observed	497	473	970
T category			
pTa	878 (75.6)	815 (73.0)	1693 (74.3)
pT1	253 (21.8)	276 (24.7)	529 (23.2)
Missing	30 (2.6)	26 (2.3)	56 (2.5)
Tumor grade 1973			
G1	587 (50.6)	527 (47.2)	1114 (48.9)
G2	464 (40.0)	456 (40.8)	920 (40.4)
G3	58 (5.0)	83 (7.4)	141 (6.2)
Missing	52 (4.5)	51 (4.6)	103 (4.5)
Tumor grade 2004			
PUNLMP	1 (0.1)	1 (0.1)	2 (0.1)
LG	80 (6.9)	71 (6.4)	151 (6.6)
HG	3 (0.3)	6 (0.5)	9 (0.4)
Missing	1077 (92.8)	1039 (93.0)	2116 (92.9)
Grade			
G1/LG	634 (54.6)	568 (50.9)	1202 (52.8)
G2 alone	433 (37.3)	429 (38.4)	862 (37.8)
G3/HG	61 (5.3)	89 (8.0)	150 (6.6)
Missing	33 (2.8)	31 (2.8)	64 (2.8)
Carcinoma in situ			
No	1139 (98.1)	1096 (98.1)	2235 (98.1)
Yes	1 (0.1)	0 (0.0)	1 (0.0)
Missing	21 (1.8)	21 (1.9)	42 (1.8)
Re-TUR			
No	678 (58.4)	658 (58.9)	1336 (58.6)
Yes	0 (0.0)	1 (0.1)	1 (0.0)
Missing	483 (41.6)	458 (41.0)	941 (41.3)
EORTC recurrence risk score			
0	325 (28.0)	284 (25.4)	609 (26.7)
1–4	395 (34.0)	394 (35.3)	789 (34.6)
5–11	109 (9.4)	113 (10.1)	222 (9.7)
Missing	332 (28.6)	326 (29.2)	658 (28.9)
EORTC progression risk score			
0	455 (39.2)	424 (38.0)	879 (38.6)
2–6	366 (31.5)	333 (29.8)	699 (30.7)
7–17	126 (10.9)	161 (14.4)	287 (12.6)
Missing	214 (18.4)	199 (17.8)	413 (18.1)
Simplified risk group			
Ta–G1G2LG	861 (74.2)	793 (71.0)	1654 (72.6)
T1 or G3	265 (22.8)	290 (26.0)	555 (24.4)
Missing	35 (3.0)	34 (3.0)	69 (3.0)
EAU risk group			
Low	325 (28.0)	284 (25.4)	609 (26.7)
Intermediate	380 (32.7)	372 (33.3)	752 (33.0)
High	265 (22.8)	291 (26.1)	556 (24.4)
Missing	191 (16.5)	170 (15.2)	361 (15.8)

EAU = European Association of Urology; EORTC = European Organization for Research and Treatment of Cancer; HG = high grade; LG = low grade; PUNLMP = papillary urothelial neoplasm of low malignant potential; TUR = transurethral resection.

(13.7%) a score of 5–11. In the 1865 patients for whom the EORTC progression score could be calculated, 879 (47.1%) had a score of 0, 699 (37.5%) a score of 2–6, and 287 (15.3%) a score of 7–17.

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

Epirubicin was used in five studies, mitomycin C in four, pirarubicin in one, and thiotepa in one. Time of instillation was available in 837 patients: 335 (40.0%) received the instillation within 2 h, 467 (55.8%) between 3 and 12 h, and 35 (4.2%) after 12 h (Table 3).

Postoperative irrigation (nonrandomized) was used in 898 patients (56.4%); 694 (43.6%) did not receive irrigation (Supplementary Table 1).

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Table 3 – Intravesical chemotherapy

	Randomized treatment		
	No instillation (n = 1161)	Single instillation (n = 1117)	Total (n = 2278)
	n (%)	n (%)	n (%)
Chemotherapy			
Epirubicin	604 (52.0)	586 (52.5)	1190 (52.2)
Mitomycin C	348 (30.0)	324 (29.0)	672 (29.5)
Pirarubicin	79 (6.8)	81 (7.3)	160 (7.0)
Thiotepa	130 (11.2)	126 (11.3)	256 (11.2)
Instillation received			
Yes		894 (80.0)	
Missing		223 (20.0)	
Timing of Instillation after TURB, h			
≤2		335 (30.0)	
3–12		467 (41.8)	
13–24		30 (2.7)	
>24		5 (0.4)	
Missing		280 (25.1)	

TURB = transurethral resection of the bladder.

Table 4 – Patient outcome

	Randomized treatment		
	No instillation (n = 1161)	Single instillation (n = 1117)	Total (n = 2278)
	n (%)	n (%)	n (%)
Recurrence			
No	508 (43.8)	642 (57.5)	1150 (50.5)
Yes	653 (56.2)	475 (42.5)	1128 (49.5)
Recurrence/competing risk			
No	414 (35.7)	530 (47.4)	944 (41.4)
Yes	653 (56.2)	475 (42.5)	1128 (49.5)
Competing risk	94 (8.1)	112 (10.0)	206 (9.0)
Progression			
No	848 (94.3)	809 (93.4)	1657 (93.9)
Yes	51 (5.7)	57 (6.6)	108 (6.1)
Missing	262	251	513
Progression/competing risk			
No	671 (74.6)	612 (70.7)	1283 (72.7)
Yes	51 (5.7)	57 (6.6)	108 (6.1)
Competing risk	177 (19.7)	197 (22.7)	374 (21.2)
Missing	262	251	513
Survival status			
Alive	554 (71.8)	495 (67.2)	1049 (69.5)
Dead	218 (28.2)	242 (32.8)	460 (30.5)
Missing	389	380	769
Cause of death			
Alive	554 (71.8)	495 (67.2)	1049 (69.5)
Bladder cancer	27 (3.5)	32 (4.3)	59 (3.9)
Other malignant disease	33 (4.3)	42 (5.7)	75 (5.0)
Associated chronic disease	136 (17.6)	146 (19.8)	282 (18.7)
Other	10 (1.3)	15 (2.0)	25 (1.7)
Unknown	12 (1.6)	7 (0.9)	19 (1.3)
Missing	389	380	769
Death bladder cancer/competing risk			
No	554 (71.8)	495 (67.2)	1049 (69.5)
Yes	27 (3.5)	32 (4.3)	59 (3.9)
Competing risk	191 (24.7)	210 (28.5)	401 (26.6)
Missing	389	380	769
Death not bladder cancer/competing risk			
No	554 (71.8)	495 (67.2)	1049 (69.5)
Yes	191 (24.7)	210 (28.5)	401 (26.6)
Competing risk	27 (3.5)	32 (4.3)	59 (3.9)
Missing	389	380	769

3.3.3. *Time to first recurrence*

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

The difference in time to first recurrence between treatments is statistically significant in favor of immediate instillation, with a reduction of 35% in the relative risk of recurrence: hazard ratio [HR]: 0.65; 95% CI, 0.58–0.74; $p < 0.001$. The 5-yr recurrence rates were 44.8% (95% CI, 41.6–48.0) on a single instillation and 58.8% (95% CI, 55.7–61.9) on TURB. Median times to first recurrence were 12 and 3 yr, respectively (Fig. 2).

The NNT to prevent one recurrence within 5 yr was 7 eligible patients (95% CI, 5.5–10) and 10 randomized patients (95% CI, 7–15).

Figure 3 shows the forest plot of time to first recurrence stratified by chemotherapy and study. There was significant heterogeneity between studies ($p < 0.0001$; $I^2 = 73.8$). Immediate instillation was not effective in the thiotepa study (interaction test $p = 0.002$). Reductions in relative risks of recurrence were similar for the other three chemotherapies. Nonrandomized comparisons suggest better efficacy when the instillation is given within 2 h after TURB.

3.3.3.1. Effect of an immediate instillation according to patient characteristics. In Figure 1, the test for interaction is significant only for the prior recurrence rate and EORTC recurrence risk score. Recurrent patients with a prior recurrence rate of more than one recurrence per year (Supplementary Fig. 2), and patients with a recurrence score ≥5 (Supplementary Fig. 3) did not benefit from the instillation.

3.3.3.2. Postoperative irrigation. In a nonrandomized comparison of 1592 patients, postoperative irrigation reduced the risk of recurrence, both overall (HR: 0.69; 95% CI, 0.59–0.88; $p < 0.001$) and in the two treatment groups. Adjusting for the randomized treatment and EORTC recurrence risk score, postoperative irrigation reduced the relative risk of recurrence by 21% (HR: 0.79; 95% CI, 0.67–0.93; $p = 0.004$). A single instillation reduced the risk of recurrence, both in patients receiving and not receiving postoperative irrigation.

3.3.4. *Time to progression*

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

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

Time to progression stratified by chemotherapy and study is provided in Supplementary Figure 4, with no significant

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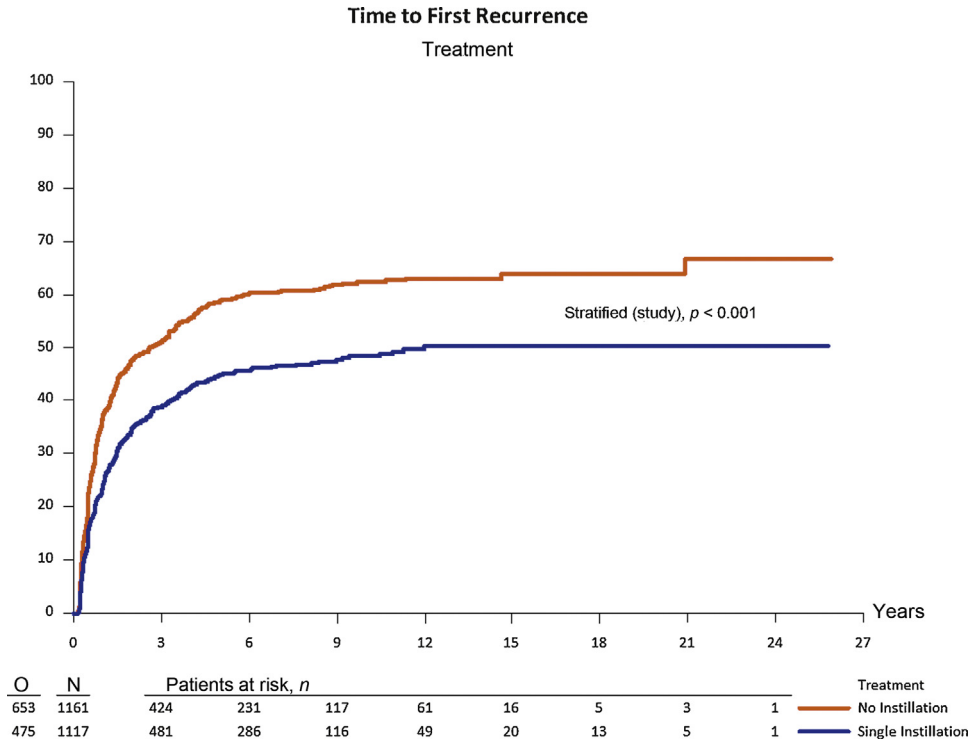

Fig. 2 – Time to first recurrence.

heterogeneity between studies ($I^2 = 13.7$). Stratification by the EORTC progression risk score yielded similar results: HR: 1.09; 95% CI, 0.74–1.60; $p = 0.68$, as did stratification by stage and grade.

3.3.4.1. Effect of an immediate instillation according to patient characteristics. No interactions were statistically significant for progression, although the same trends as for recurrence were seen. There was a suggestion of a higher risk of progression (HR: 1.60) on an immediate instillation in the 220 patients with an EORTC recurrence risk score $\geq$5 (Supplementary Fig. 5); however, instillation patients in this subgroup had a higher baseline EORTC progression score, 8.2 versus 7.8.

3.3.5. Overall duration of survival

Survival data were available in seven studies with 1509 patients. The duration of follow-up was similar in the two treatment groups with a median of 9.0 yr on a single instillation and 8.9 yr on TURB. Overall, 460 deaths (30.5%) were reported, in 242 (32.8%) of 737 patients receiving a single instillation and 218 (28.2%) of 772 patients with TURB alone. A total of 59 (3.9%) died due to BCa, 75 (5.0%) due to another malignant disease, and 282 (18.7%) due to associated chronic disease (Table 4).

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

Supplementary Figure 6 shows the duration of survival stratified by study and chemotherapy, with no evidence of heterogeneity between studies ($I^2 = 0$). Stratification by the EORTC progression risk score yielded similar results (HR: 1.24; 95% CI, 1.02–1.50; $p = 0.03$), as did stratification by stage and grade.

3.3.5.1. Effect of an immediate instillation according to patient characteristics. There was a suggestion of a shorter survival on an immediate instillation in recurrent patients, patients with an EORTC recurrence risk score $\geq$5, and EAU high-risk patients (Supplementary Fig. 7).

3.3.6. Time to death due to bladder cancer

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

Figure 6 presents the time to death due to BCa by treatment group. The difference was not statistically significant (HR: 1.31; 95% CI, 0.78–2.19; $p = 0.31$). The 5-yr BCa death rates were 2.1% (95% CI, 1.0–3.3) in patients receiving a single instillation and 2.0% (95% CI, 0.9–3.1) on TURB. Supplementary Figure 8 presents time to death due to BCa stratified by chemotherapy and study, with medium heterogeneity between studies ($I^2 = 47.3$). Stratification by EORTC progression risk score yielded a slightly reduced HR of 1.13 (95% CI, 0.67–1.91; $p = 0.65$), as did stratification by stage and grade.

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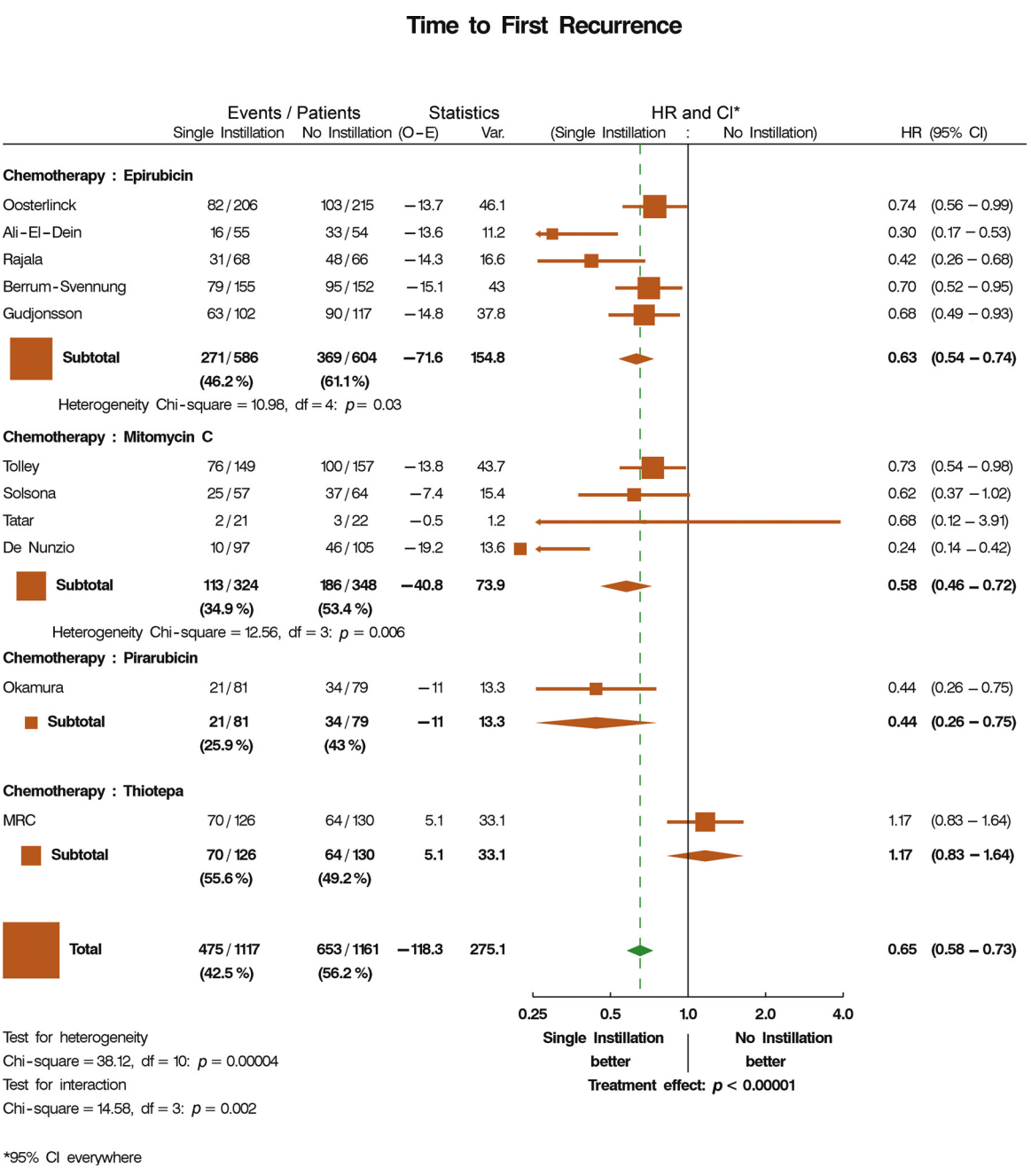

Fig. 3 – Time to first recurrence stratified by chemotherapy and study.
CI = confidence interval; HR = hazard ratio; MRC = Medical Research Council.

3.3.6.1. Effect of an immediate instillation according to patient characteristics. The number of deaths due to BCa is small, and no interactions in Supplementary Figure 9 were statistically significant, but similar trends were seen as for overall survival, with a suggestion of a shorter disease-specific survival on a single instillation in patients with a recurrence risk score ≥5.

3.3.7. Relationship between cause of death and European Organization for Research and Treatment of Cancer recurrence risk score

Table 5 lists the cause of death by treatment group according to the EORTC recurrence risk score. In patients with scores of 0 and 1–4, the duration of survival and the distribution of the causes of death were similar in the two treatment groups. Despite adjustment for an imbalance in tumor stage and grade, this exploratory analysis suggests that in patients with a recurrence risk score ≥5, more patients may have died on a single instillation (65 of 106 [61.3%]) than on TURB alone (44 of 102 [43.1%]), with a higher percentage of patients dying from malignant disease (BCa or other) compared with patients not receiving an instillation, 35 (33.0%) versus 20 (19.6%). This was not a planned subgroup analysis, and these differences could have occurred by chance.

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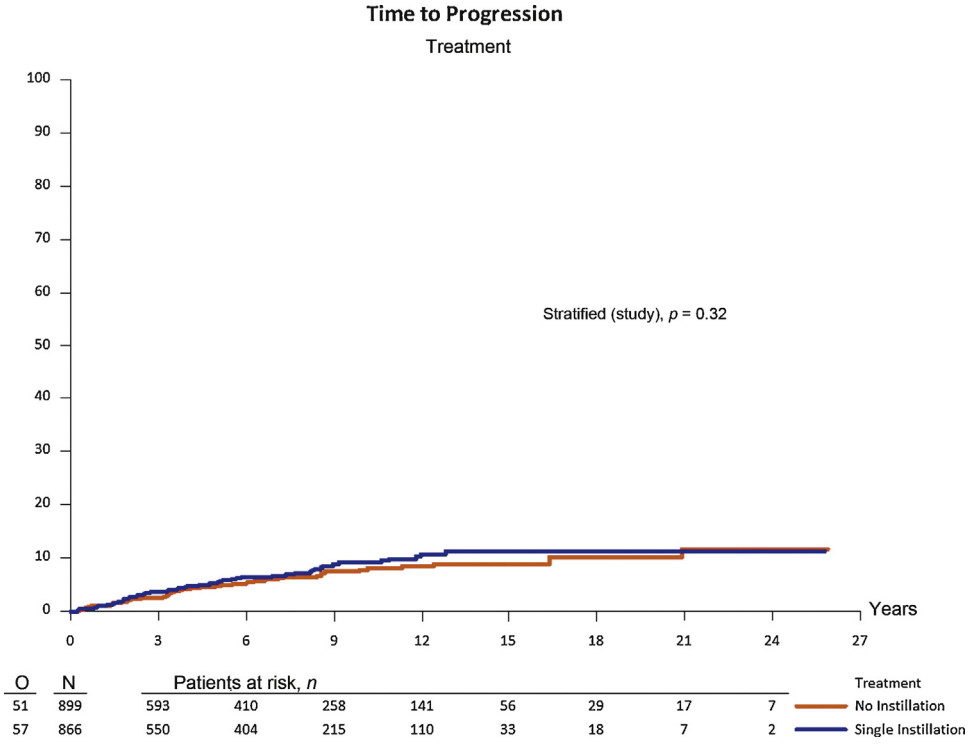

Fig. 4 – Time to progression.

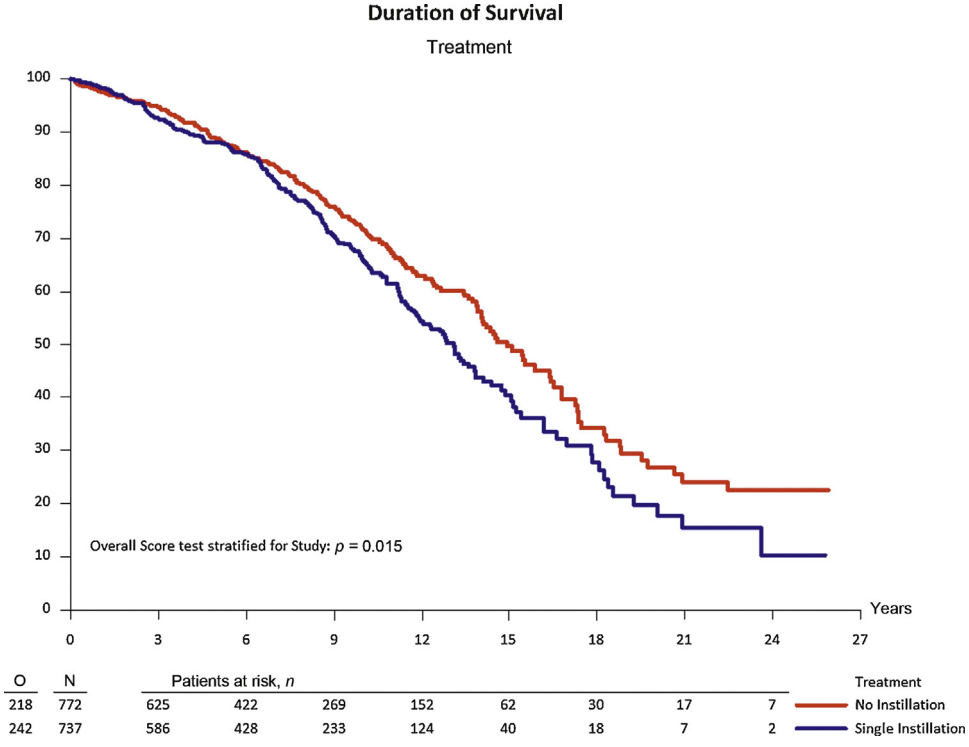

Fig. 5 – Duration of survival.

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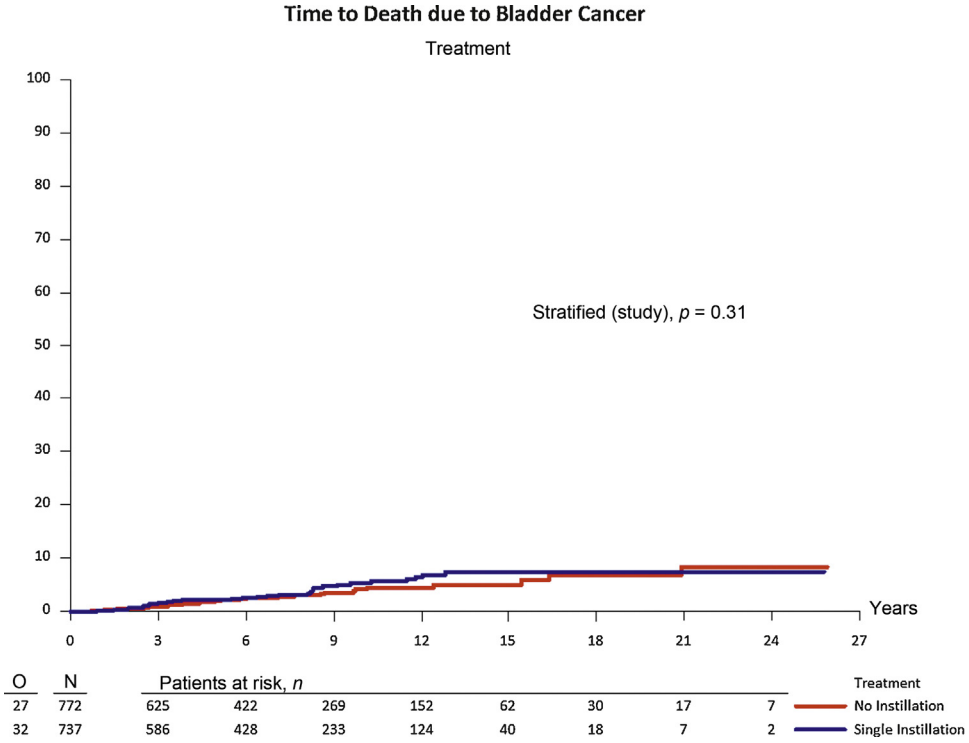

Fig. 6 – Time to death due to bladder cancer.

Table 5 – Cause of death by European Organization for Research and Treatment of Cancer recurrence risk score

EORTC recurrence risk	Randomized treatment		Total
	No instillation *n* (%)	Single instillation *n* (%)	*n* (%)
Score 0			
Patients, *n*	295	253	548
Cause of death			
Alive	243 (82.4)	197 (77.9)	440 (80.3)
Bladder cancer	3 (1.0)	3 (1.2)	6 (1.1)
Other malignant disease	6 (2.0)	7 (2.8)	13 (2.4)
Associated chronic disease	39 (13.2)	45 (17.8)	84 (15.3)
Other	1 (0.3)	0 (0.0)	1 (0.2)
Unknown	3 (1.0)	1 (0.4)	4 (0.7)
Score 1–4			
Patients, *n*	354	355	709
Cause of death			
Alive	238 (67.2)	236 (66.5)	474 (66.9)
Bladder cancer	11 (3.1)	11 (3.1)	22 (3.1)
Other malignant disease	17 (4.8)	17 (4.8)	34 (4.8)
Associated chronic disease	71 (20.1)	74 (20.8)	145 (20.5)
Other	9 (2.5)	14 (3.9)	23 (3.2)
Unknown	8 (2.3)	3 (0.8)	11 (1.6)
Score 5–11			
Patients, *n*	102	106	208
Cause of death			
Alive	58 (56.9)	41 (38.7)	99 (47.6)
Bladder cancer	12 (11.8)	18 (17.0)	30 (14.4)
Other malignant disease	8 (7.8)	17 (16.0)	25 (12.0)
Associated chronic disease	23 (22.5)	26 (24.5)	49 (23.6)
Other	0 (0.0)	1 (0.9)	1 (0.5)
Unknown	1 (1.0)	3 (2.8)	4 (1.9)

EORTC = European Organization for Research and Treatment of Cancer.

3.4. *Discussion*

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

A single immediate instillation was not effective in patients with a prior recurrence rate of more than one recurrence per year and in patients with an EORTC recurrence score ≥5. This last subgroup was mainly composed of patients with multiple tumors (50.9%), tumors ≥3 cm (69.8%), and T1 tumors (75.7%).

These results can help us make more precise recommendations for clinical practice. The decision to give an early instillation should be based on information available at the time of TURB: the previous recurrence rate and the size and number of tumors. The definitive stage and grade is unknown at this time. From the weight of these parameters in the EORTC recurrence score [12], an early instillation is recommended in patients with these characteristics: (1) single or multiple (up to seven lesions) primary papillary tumor(s) <3 cm; (2) single primary papillary tumors >3 cm; (3) single small recurrent papillary tumors with an interval >1 yr since the previous recurrence. Patients with multiple tumors, at least one of which is ≥3 cm, will have an EORTC recurrence score ≥6. An immediate instillation is not recommended in these patients.

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Nonrandomized comparisons suggest the instillation is more effective when given within 2 h after TURB. Indirect comparisons could not detect any differences in efficacy between mitomycin C and epirubicin.

Once the stage and grade are available, further treatment can be planned according to the risk stratification [1]. The benefit of an early instillation was most pronounced in low-risk patients in whom no further treatment before recurrence is recommended.

In intermediate-risk patients, for whom the 5-yr recurrence rate after a single instillation is nearly 40%, the results support EAU guideline recommendations that a single instillation alone is insufficient and should be followed by further instillations [1]. A systematic review demonstrated the best results for schedules in which an early instillation preceded further instillations of chemotherapy [34]. In high-risk patients receiving bacillus Calmette-Guérin, the only study assessing a single instillation was inconclusive [35].

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

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

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

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

This is the first meta-analysis to study this question that is based on IPD with a relatively long follow-up and identifying patients who benefit or not from an immediate instillation. Nevertheless, there are a number of limitations in the interpretation of the data, especially the long-term results. No information was collected on further treatment after recurrence or progression or on the occurrence of distant metastases. Only seven studies contributed to progression comparisons and five studies to survival comparisons, three with a median follow-up >10 yr. Survival was not a formal end point in these studies, and it is unknown to what extent the cause of death was based on autopsy evidence.

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

4. Conclusions

In summary, although a single immediate instillation of chemotherapy reduced the relative risk of recurrence by 35% and the 5-yr recurrence rate by 14%, it is not effective in patients with a prior recurrence rate of more than one recurrence per year or in patients with EORTC recurrence risk score $\geq$5. It does not prolong either the time to progression or the time to death due to BCa. Exploratory analyses suggest that the instillation may be associated with an increase in the risk of death in patients at high risk of recurrence in whom the instillation is not effective and thus not recommended. The long-term survival differences may be biased by the treatment received after recurrence and thus may be chance findings. Nonrandomized evidence indicates the use of postoperative irrigation may also reduce recurrences.

Author contributions: Richard J. Sylvester 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.

Study concept and design: Sylvester, Babjuk, Inman.
Acquisition of data: Oosterlinck, Holmang, Sydes, Gudjonsson, De Nunzio, Okamura, Kaasinen, Solsona, Ali-El-Dein, Tatar.
Analysis and interpretation of data: Sylvester.
Drafting of the manuscript: Sylvester, Babjuk.
Critical revision of the manuscript for important intellectual content: Sylvester, Oosterlinck, Holmang, Sydes, Birtle, Gudjonsson, De Nunzio, Okamura, Kaasinen, Solsona, Ali-El-Dein, Tatar, Inman, N'Dow, Oddens, Babjuk.
Statistical analysis: Sylvester.
Obtaining funding: None.
Administrative, technical, or material support: Sylvester.
Supervision: Sylvester, Inman, Kaasinen, N'Dow, Oddens, Babjuk.
Other (specify): None.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.eururo.2015.05.050.

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