



Single postoperative instillation for non-muscle invasive bladder cancer: are there still any indication?

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Abstract: Intravesical chemotherapeutical agents after transurethral resection have shown to be effective in reducing the risk of recurrence and progression during the follow up. Specifically, an early single chemotherapeutical instillation (SI) might play an important role but the efficacy of this treatment has been questioned. For these reasons, we sought to review and summarize the current evidence with a non-systematic Medline/PubMed literature search. Level 1a evidence strongly supports the utility of SI in reducing recurrence in low-intermediate risk non-muscle invasive bladder cancer (NMIBC) patients, with about 35% of relative reduction rates in patients with single, <3 cm and low-intermediate stage and grade tumors. The efficacy of this procedure is particularly evident when epirubicin or mitomycin C is administered. However, no randomized controlled trials compared the effect of the different types of drugs for SI. Only few trials have analyzed the effect of timing in SI, therefore, the optimal delivery timeframe is not yet completely clear with some series suggesting that a delivery within the first 2 hours after surgery might have an impact on recurrence rates and others that show no differences with those treated within 24 hours. None of the patients included in the randomized controlled trials analyzed in this review suffered from systemic toxicity. On the other hand, other side effects were recorded, including: chemical cystitis and skin reaction. Although it is a safe procedure, rare severe complications have been reported in the literature, mostly due to extravasation of drugs in patients who underwent extended resection or bladder perforation. To avoid potential deadly complications, SI should not be administered in these patients.

Keywords: Bladder cancer (BCa); epirubicin instillation; mitomycin; non-muscle invasive bladder cancer (NMIBC); single instillation

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Introduction

Urinary bladder cancer (BCa) accounts for about 7% of all new cancers in the United States with 81,190 estimated new cases and 17,240 deaths in 2018 (1). Of all patients with BCa, approximately 75% will be diagnosed with a non-muscle-invasive BCa (NMIBC) (2) affected by an average

recurrence and progression rates of 60–80% and 10–30%, respectively (3). As a direct consequence of the high recurrence and progression rates, NMIBC accounts for the highest lifetime treatment cost per patient of all cancers (4). Depending on the country, BCa costs from diagnosis-to-death between \$89,287 and \$202,203 per person and it will likely increase as survival rates increase. Costly surveillance

and treatment of BCa can lead to financial toxicity, defined as treatment-related financial distress, with an estimated rate of 24% (5).

Optimization of treatment and surveillance intervals is pivotal to reduce recurrence and progression and to optimize costs. The risk estimation of harboring recurrence or progression depends on multiple factors and several classifications have been proposed to stratify patients, such as EORTC Genito-Urinary Cancer Group scoring system (6) and CUETO risk calculators (7).

Intravesical chemotherapeutical agents after transurethral resection (TURB) have shown to be effective on reducing the risk of recurrence and progression during the follow up (8). Specifically, an early single chemotherapeutical instillation (SI) might play a role for certain patients. On the other hand, the efficacy of this treatment has been questioned and many urologist are reluctant to its use (9,10). For all these reasons, we sought to review and summarize the current evidence regarding the possible impact on recurrence and progression of SI.

Evidence acquisition

A non-systematic Medline/PubMed literature search was performed with different combination of terms as “bladder cancer”, “early instillation”, “single instillation”, “Immediate instillation”, “chemotherapy”, “TURB”, “Epirubicin”, “Mitomycin” and “non-muscle invasive bladder cancer”. Only articles in English language were retained for the review. Time period included articles between 1988 and 2018. Meta-analyses and original articles on randomized controlled trials comparing a single instillation of chemotherapy after TURB and TURB alone or TURB plus placebo or TURB with delayed instillation with endpoints recurrence and progression rate were selected and assessed from authors’ bibliographies.

Overview of the management of NMIBC and risk grouping

Most of newly diagnosed cases of BCa require a conservative management (2). The final decision on subsequent diagnostic/therapeutic process is usually based upon specimen obtained at TURB. To optimize treatment, patients could be stratified in risk classes to predict separately short- and long-term recurrence and progression risk. Patients are stratified in 3 risks group (low, intermediate and high) based on several pathological

and clinical features with some differences among available guidelines: EAU (European Association of Urology) (2), National Institute for Health and Care Excellence (NICE), Canadian Urological Association (CUA) (11) and American Association of Urology (AUA) (12) incorporate this strategy into their guidelines whereas National Comprehensive Cancer Network (NCCN) (13) does not. All guidelines recommend SI for certain categories of patients. *Figure 1* illustrates a flow chart with summary data regarding the therapeutical management of BCa after TURB.

EAU guidelines (2) recommend intravesical single instillation for all patients with low risk tumors [according to EORTC score (6)] after a complete TURB. Instead, for patients with intermediate risk, one-year full dose BCG treatment or instillations of chemotherapy should be provided with the addition of one SI in patients with previous recurrence rate ≤ 1 per year and expected EORTC recurrence score < 5 . In the AUA guidelines (12) SI is suggested for patients with suspected or known low- or intermediate-risk BCa whereas CUA (11) and NICE guidelines recommends SI in all patients with a suspected NMIBC. In all guidelines except for NICE it is underlined that SI should not be administered in extended resections or in suspicion of bladder perforation.

The effect of single postoperative instillation after TUR

Table 1 illustrates a selection of randomized control trials testing the impact of SI on recurrence and progression rates. In the last 15 years, several meta-analyses were published testing the effect of SI in BCa patients treated with TURB. Sylvester *et al.* (30) analyzed in 2004, 1,476 patients affected by TaT1 single and multiple BCa with a median follow up of 3.4 years. Patients treated with SI recorded a decrease of 39% recurrence risk [odds ratio (OR) 0.61, confidence interval (CI): 0.49–0.75, $P < 0.0001$]. The effect was similar between trials using epirubicin, mitomycin C and pirarubicin whereas no benefit was observed using thiotepa. Abern *et al.* (31) analyzed data from 18 randomized trials with a total of 3,103 patients reporting an absolute reduction of 13% in recurrence for patients who received immediate SI. Perlis *et al.* (32) in a meta-analysis published in 2013 found a prolonged recurrence free interval for patients treated with SI by 38% (HR: 0.62, 95% CI: 0.50–0.77; $P < 0.001$) (32). The most recent meta-analysis was performed on individual patients’ data (n=2,278) obtained from 11 randomized studies

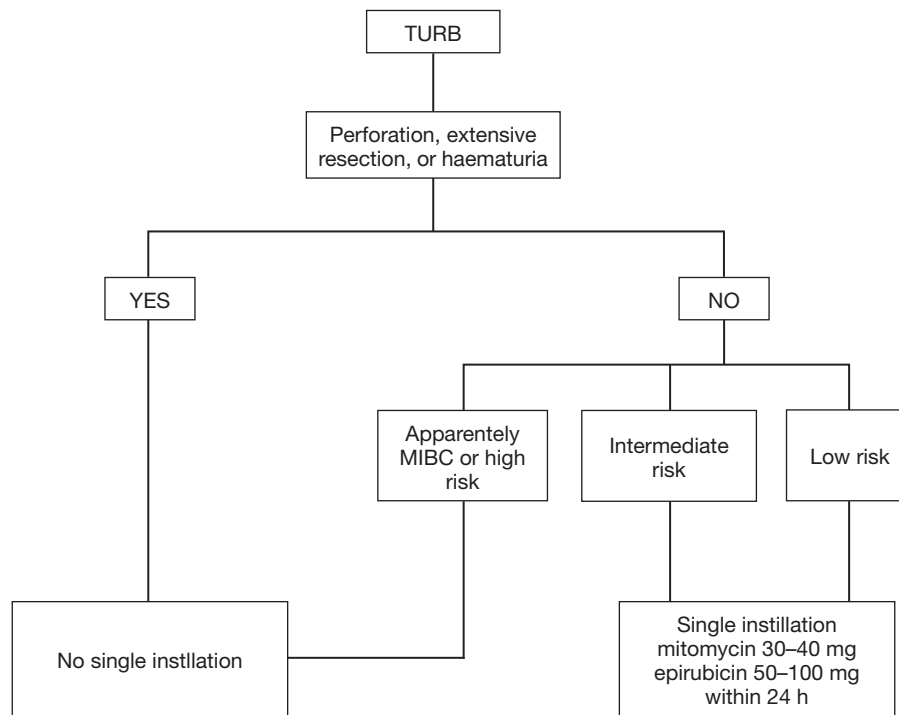


Figure 1 Flow chart of usage of SI in primary/recurrent BCG-naïve tumors and recurrent tumor after BCG. TURB, transurethral resection of bladder; MIBC, muscle invasive bladder cancer; BCG, bacille calmette guerin.

comparing TURB with TURB plus SI. The difference in time of first recurrence between treatments was statistically significant in favor of single instillation, with a reduction of 35% in relative risk of recurrence [hazard ratio (HR): 0.65, 95% CI: 0.58–0.74, $P < 0.001$]. The 5-years 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 (33). The last randomized trial (29) published in the literature compared patients who underwent immediate single instillation (given within < 24 h) with Mitomycin C versus delayed instillation (2 weeks after TURB). At 3 years of follow up, there was a recurrence risk of 27% (95% CI: 24–30%) in the immediate group versus 35% (95% CI: 33–39%) for the delayed group with a 34% of relative risk reduction on recurrence (HR: 0.66, 95% CI: 0.56–0.79, $P < 0.001$) (29). To summarize, results of randomized controlled trials and meta-analysis strongly support that SI of chemotherapeutical agent reduces recurrence in NMIBC, with about 35% of relative reduction rates. Theories explaining this effect include the prevention of implantation of floating cells into the bladder urothelium following resection (34–36), and the ablative effect on residual tumor cells at the tumor site and on small unnoticed tumors left

behind TURB. It should be emphasized that in the majority of the studies included in this review, patients were strictly selected including only low grade and stage tumors. Few data exist regarding high-risk BCa patients. Bosschietter *et al.* (29) in a sub-analysis, considered patients based upon their risk group and report a benefit of SI even in the high-risk subgroup (at 3 years of follow up recurrence rates were for SI *vs.* delayed instillation, 28% *vs.* 35%, $P = 0.007$).

Some authors analyzed the impact of SI on the bases of tumor characteristics, such as size and numbers of tumors. Berrum-Svennung *et al.* (25) reported that only patients with tumors < 5 mm might benefit from SI in reducing recurrence whereas no differences were found in tumors > 5 mm. Gudjónsson *et al.* (26) reported no recurrence rates benefit for SI in patients with multiple and recurrent tumors; these results were corroborated by a meta-analysis published in 2004 (30). In the last meta-analysis published by Sylvester *et al.* (33) a subgroup of patients (those with multiple tumors, tumors ≥ 3 cm, T1 or high recurrent tumors) did not benefit from SI and this indication was included in the EAU and AUA guidelines (2,12,33). Considering these results, patients with single, < 3 cm and low-intermediate stage and grade seem most suitable to

Table 1 A summary of phase III- randomized controlled trials testing the effect of single postoperative instillation on recurrence and progression rate after transurethral resection due to bladder cancer

Study	Patient entry	Year of publication	Study design	Number of eligible patients	Chemotherapy drug group (number of patients)	Control group (number of patients)	Timing (TURB to SI)	Median follow-up (years)	Recurrence rates	Significance	Progression	Significance
Tolley <i>et al.</i> (14)	1984-1986	1988	Multicenter RCT, phase III, not-blinded	397	MMC 40 mg/40 mL SI [129]	TURB alone [130]	<24 h	1	24 months: 35% vs. 39%,	Not significant difference	-	-
Oosterlinck <i>et al.</i> (15)	1986-1989	1993	Multicenter RCT, phase III, not-blinded	420	EPI 80 mg/50 mL SI [205]	TURB + PBO [215]	<6 h	2 (mean)	Overall: 29.0% vs. 41%	<0.0001 significant for EPI 80 mg/50 mL SI group	-	-
Fujita <i>et al.</i> (16)	1983-1993	1994	Single center RCT, phase III, not-blinded	90	Peplomycin 30 mg/40 mL SI [46]	TURB alone [44]	Immediately after TURB	2.25 (mean)	Not significant difference	Not significant difference	-	-
Medical Research Council (17)	1981-1984	1994	Multicenter RCT, phase III, not-blinded	379	Thiotepa 30 mg/50 mL SI [126]	TURB alone [131]	Immediately after TURB	8,75	24 months: 65% vs. 62%	Not significant difference	-	-
Tolley <i>et al.</i> (18)	1984-1986	1996	Multicenter RCT, phase III, not-blinded	452	MMC 40 mg/40 mL SI [149]	TURB alone [157]	<24 h	7	HR 0.66, 95% CI: 0.48-0.91, P=0.01; overall: MMC 40 mg/40 mL SI group	P=0.01 significant for MMC 40 mg/40 mL SI group	-	-
Ali-el-Dein <i>et al.</i> (19)	1992-1996	1997	Single center RCT, phase III, not-blinded	168	EPI 50 mg/50 mL SI [55]	TURB alone [54]	Immediately after TURB	2.8	Overall: 24.0% vs. 51.8%	P=0.001 significant for EPI 50 mg/50 mL SI group	9.3% vs. 3.4%	Not significant difference
Solsona <i>et al.</i> (20)	1988-1992	1999	Single center RCT, phase III, not-blinded	121	MMC 30 mg/50 mL SI [57]	TURB alone [64]	<6 h	11.8	Overall: 40.3% vs. 54.1%, P=0.115	Not significant difference	Overall: 1.7% vs. 1.7%	Not significant difference
Rajala <i>et al.</i> (21)	1991-1994	1999-2002	Multicenter RCT, phase III, not-blinded	134	EPI 100 mg/100 mL SI [68]; INF SI [66]	TURB alone [66]	Immediately after TURB	6.1	Overall: 72.7% vs. 68.2% vs. 45.6%	P=0.002 significant for EPI 100 mg/100 mL group	-	-

Table 1 (continued)

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Study	Patient entry	Year of publication	Study design	Number of eligible patients	Chemotherapy drug group (number of patients)	Control group (number of patients)	Timing (TURB to SI)	Median follow-up (years)	Recurrence rates	Significance	Progression	Significance
Okamura et al. (22)	1994–1998	2002	Single center RCT, phase III, not-blinded	160	THP 30 mg/30 mL SI [81]	TURB alone [79]	<6 h	3.4	HR: 0.31, 95% CI: 0.17–0.56, P=0.0001	P=0.001 significant THP 30 mg/30 mL SI group	–	–
Barghi et al. (23)	2003–2005	2006	Single center RCT, phase III, not-blinded	43	MMC 30 mg/30 mL SI [21]	TURB + BPO [22]	6–24 h	1.3	12 months: 4.5% vs. 38.1%, P=0.007	Overall: significant for MMC 30 mg/30 mL SI group	Overall: 0.0% vs. 14.3%	Not significant difference
Ei-Ghobashy et al. (24)	2002–2005	2007	Single center RCT, phase III, not-blinded	63	MMC 30 mg/50 mL SI [31]	TURB alone [32]	<6 h	3.6 (mean)	Overall 26.9% vs. 28.6%	Not significant difference	Overall: 3.2% vs. 3.1%	Not significant difference
Berrum-Svennung et al. (25)	1998–2003	2008	Multicenter RCT, phase III, single-blinded	307	EPI 50 mg/50 mL SI [155]	TURB+PBO [152]	<6 h	7.5	24 months 51.0% vs. 62.5%	P=0.04 significant for EPI 50 mg/50 mL SI group	–	–
Gudjónsson et al. (26)	1997–2004	2009	Single center RCT, phase III, not-blinded	219	EPI 80 mg/50 mL SI [102]	TURB alone [117]	<24 h	3.6	Overall: 62.0% vs. 77.0%	P=0.016 significant for EPI 80 mg/50 mL SI	–	–
Böhle et al. (27)	2004–2005	2009	Multicenter RCT, phase III, double-blinded	328	Gem 2,000 mg/100 mL SI [166]	TURB+PBO [162]	Immediately after TURB	1.6	12 months: 77.7% vs. 75.3%; 24 months: 64.0% vs. 60.7%	Not significant difference	–	–
De Nunzio et al. (28)	2000–2009	2011	Single center RCT, phase III, single-blinded	202	C [97]	TURB alone [105]	<24 h	7.5	Overall: 10.0% vs. 43.0%	P=0.001 significant for EPI 80 mg/50 mL SI group	Overall 0.0% vs. 0.9%	Not significant difference
Boschieter et al. (29)	1988–2003	2018	Multicenter RCT, phase III, double-blinded	2,243	MMC 40 mg/50 mL SI [1,048]	MMC 40 mg/50 mL delayed 2 weeks after TURB [1,195]	<24 h	–	HR: 0.73, 95% CI: 0.63–0.85	P<0.001 significant for MMC 40 mg/50 mL SI group	Overall: 2.2% vs. 4.2%	P=0.005

TURB, transurethral resection of bladder; RCT, randomized controlled trial; MMC, mitomycin C; SI, single instillation; HR, hazard ratio; CI, confidence interval; EPI, epirubicin; PBO, placebo; INF, interferon; THP, (2'-'R)-4'-O-Tetrahydropyran-2-yl-doxorubicin; Gem, gemcitabine.

benefit from SI after TURB with about 35% of relative reduction rates.

Timing of postoperative instillation

The EAU guidelines state that the preferred time window for an immediate instillation is within 2 hour after TURB.

Some discordance exists in the current guidelines regarding the best timing for postoperative instillations. EAU Guidelines state that the preferred time-window for an immediate instillation is within 2 hour after TURB (2). This recommendation is based on the last meta-analysis published where a non-randomized comparison suggests that the instillation should be more effective when given within 2 hours after surgery (33). CUA panel (11) suggest that the optimal timeframe is within 6 and 24 h whereas AUA guidelines proposes to administer the drug within 24 hours after TURB (12). Despite many randomized controlled trials have adopted the policy of giving early instillations immediately or within 6–24 h after TURB, there are only a few randomized studies that have analyzed the impact of timing of SI on BCa recurrence. In addition to Sylvester *et al.* (33), Hendricksen *et al.* (37) did not find benefit in recurrence rates when SI was given the day after TURB whereas SI was effective when SI was given on the same day as TURB. On the contrary Gudjónsson *et al.* (26) found a benefit in recurrence free-survival both in patients in which SI was administered the same day of TURB and in patients in which SI was given the day after TURB (within 24 hours). The same results were observed in a recent sub-analyses obtained from a prospective multicenter randomized trial published in 2018 which evaluated differences between early instillation of mitomycin C administrated within 24 h after TURB on the day of TURB (very early instillation) and administration within 24 h 1 day after TURB (early instillation) (29). More studies required to elucidate the real optimal timing of early instillation.

Drugs in postoperative instillation

Several drugs have been administered in randomized controlled trials testing the effect of SI on recurrence and progression after TURB. Gemcitabine was tested by Böhle *et al.* (27) without finding any difference in recurrence rates between treatment group and placebo. These results were confirmed in Abern *et al.* (31) meta-analysis. Studies analyzing thiotepa and peplomycin did not reveal beneficial effects regarding recurrence, in contrast to pirarubicin

that was tested by Okamura *et al.* (22) observing significant improvement of recurrence rates when compared to TURB alone. Mitomycin and epirubicin remain at the moment the mostly widely tested drugs for SI with significant advantages on recurrence rates (14,15,18-21,23-26,28,29). Their efficacy was also confirmed by Perlis *et al.* (32) and Sylvester *et al.* (33) meta-analysis. For these reasons, the majority of guidelines suggest the use of one of these two drugs for SI. However, at the time, there is no randomized controlled trial comparing the type of drug on the efficacy of SI in preventing recurrence or progression.

Adverse events after single instillation

None of the analyzed randomized trial showed (*Table 1*) severe adverse events. The most common side effects included chemical cystitis and skin irritation. For both these adverse event incidences were generally low, but rates also depend on the type of drug used and its dosage. Chemical cystitis occurred with a very low incidence (0.7%) in patients treated with mitomycin by Tolley *et al.* (14) whereas rates were higher in a publication of De Nunzio *et al.* (28) (about 9%) and Bosschieter *et al.* (29) (about 5%). About 11.7% of patients treated with epirubicin 80 mg by Oosterlinck *et al.* (15) developed chemical cystitis. Despite the relatively high dose of epirubicin (100 mg) administrated by Rajala *et al.* (21) no considerable side effects were found. Solsona *et al.* (20) reported that 3.5% of patients treated with mitomycin developed chemical cystitis and allergic skin reaction. In Bosschieter *et al.* (29) analysis, the most reported adverse event in SI with mitomycin was exanthema (5.4%)

No patient treated with SI of Peplomycin 80 mg developed side effect (16) whereas about 2.5% of patients treated with SI of Thiotepa 30 mg developed chemical cystitis (17). Böhle *et al.* (27) found that adverse events possibly related to instillation with gemcitabine treatment were rare (6.6% of patients treated with gemcitabine, all non-serious).

Although all of these trials showed a beneficial safety profile of intravesical SI a few case reports of severe complication are reported in literature. Nieuwenhuijzen *et al.* (38) reported a case of extravasation of mitomycin after instillation, resulting in severe continuous pelvic pain that required surgical debridement. Oddens *et al.* (39) reported three cases of severe complications: extravasation (which has been treated with prolonged catheterization, antibiotics and analgesics), abdominal pain (associated with a CT scan positive for an infiltrate mass between abdomen

and abdominal wall without sign of collection treated conservatively) and a paralytic ileus. For all these reasons, it is strongly recommended to omit SI in any case of overt or suspected bladder perforation or bleeding requiring bladder irrigation.

Conclusions

Randomized controlled trials and meta-analyses strongly support the use of SI after TURB in preventing recurrence in low and intermediate risk patients. This effect is mainly evident in small (<3 cm) and solitary tumors with a recurrence reduction of 35%. No randomized trials compared the effect of different type of drugs on recurrence, although epirubicin or mitomycin C seems associated with an improved recurrence effect. It is advisable to administer SI within 24 h from TURB, even if the optimal timeframe has not yet been established. Although is a safe procedure, SI should not be administered in patients who underwent extended resections or if bladder perforation is suspected since extravasation could cause potential deadly complications.

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Footnote

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