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Original article

The value of immediate postoperative intravesical epirubicin instillation as an adjunct to standard adjuvant treatment in intermediate and high-risk non–muscle-invasive bladder cancer: A preliminary results of randomized controlled trial

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Abstract

Purpose: We aimed at this study to test the value of immediate postoperative intravesical epirubicin instillation in intermediate and high-risk non–muscle-invasive bladder cancer patients.

Materials and Methods: After approval of Institutional Review Board, 260 patients were randomly allocated into 2 groups, including transurethral resection of bladder tumor (TURBT) alone in control group and TURBT plus immediate postoperative epirubicin (50 mg) in test group. Patients were monitored for postoperative complications. Adjuvant instillation therapy was administered according to risk categorization. Patients were followed every 3 months by cystourethroscopy and urine cytology. The primary end points were recurrence, progression, and/or death from cancer.

Results: Of the 260 patients, 236 were eligible and followed for a mean of 29 months. The 2 study groups were comparable regarding perioperative baseline demographic criteria. There was no statistically significant difference between the 2 groups regarding recurrence rate (27.1% vs. 26.2%), interval to first recurrence (16.3 ± 6.6 vs. 16.4 ± 6.4 months) or progression rate to muscle invasion (8.5% vs. 5.9%). Site, size, and number of recurrences were also comparable between the 2 groups. Recurrences and progression-free survival were comparable between the 2 groups (Log-rank $P = 0.88$ and 0.47, respectively). Postoperative complications were all low-grade according to modified Dindo–Clavian system, with no significant difference in their rate between the 2 groups.

Conclusions: Immediate post-TURBT epirubicin instillation is ineffective in intermediate and high-risk non–muscle-invasive bladder cancer. It neither prolongs time to recurrence and/or progression nor reduces number of recurrences. We advocate strict specification of patient and tumor criteria in which immediate instillation is indicated.

Keywords: Non–muscle-invasive bladder cancer; Chemotherapy; Single instillation; Intravesical epirubicin

1. Introduction

Immediate postoperative intravesical instillation of chemotherapy after transurethral resection of bladder tumor (TURBT) was shown by many investigators [1–3] to reduce recurrence by eradication of any floating tumor cells. According to the European Association of Urology (EAU) guidelines, 1 postoperative intravesical instillation of chemotherapy after TURBT of presumably non–muscle-invasive bladder cancer (NMIBC) is recommended [4]. Evidence supporting such practice was strengthened in

Descriptive running head: In the era of overwhelming date about the recommendation of immediate postoperative intravesical instillation of chemotherapy after transurethral resection of bladder tumor, we aimed at this study to test the value of immediate post transurethral resection of bladder tumor intravesical epirubicin in intermediate and high-risk non–muscle-invasive bladder cancer in a randomized control trial.

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2004 by European Organization of Research and Treatment of Cancer (EORTC) meta-analysis incorporating all immediate postoperative chemoprophylaxis trials published to that date. They demonstrated a significant improvement in the likelihood of recurrence for NMIBC patients who received immediate postoperative chemoprophylaxis after TURBT [5]. However, the evidence for the efficacy of this treatment originates from studies that have focused on patients with low risk for recurrence. More precisely, only 126 (16.5%) of the patients had multiple tumors, and 82 (11%) were recurrent cases. Accordingly, the evidence indicating a beneficial influence of single instillation therapy is weaker in patients with intermediate and high risk of recurrence as compared to those who are at low risk [6]. In the present study, we investigated the role of immediate post-TURBT instillation of epirubicin in intermediate and high-risk NMIBC regarding recurrence, progression, and complications.

2. Design, settings, and participants

2.1. Study population

After approval of the Institutional Review Board, patients with papillary bladder tumors seen through the outpatient clinic in the urology department (Urology and Nephrology Center, Mansoura University, Egypt) were assessed for eligibility to this randomized controlled trial. Patients who met these criteria were asked to participate in this trial and were provided with an informed consent form.

2.2. Inclusion criteria

Inclusion criteria included patients with primary or recurrent papillary bladder tumor for whom complete TURBT was done. Patients with known hypersensitivity to epirubicin, previous history of systemic chemotherapy or radiotherapy, cystoscopic finding of low volume tumor (primary, single, and/or less than 1 cm), suspicious bladder perforation during TURBT, or post-TURBT hematuria were all excluded from the study.

2.3. Randomization

Preoperatively, all patients were evaluated by medical history and physical exam including digital rectal exam, laboratory investigations, abdominal and pelvic ultrasound, and computed tomography or magnetic resonance imaging of the abdomen and pelvis if necessary. The randomization process was performed using computer-generated random tables in a 1:1 ratio. Patients were randomly assigned to the study groups on the day of surgery after TURBT.

2.4. Post-TURBT care

After TURBT, patients were referred to the recovery room. Careful monitoring was carried out for the first 30 minutes, and then eligible patients were randomly assigned into 2 groups. The first (control) group did not receive intravesical epirubicin, while the second (test or epirubicin) group received intravesical instillation of epirubicin 50 mg in 50 ml saline 0.9%. The solution was kept in the bladder for 1 hour. To obtain a high intravesical concentration of epirubicin, fluid restriction was advised 6 hours before instillation. Patient position was changed every 15 minutes during the instillation. During the dwell time, the patients were monitored for local and/ or systemic adverse events (acute abdomen, chills, fever, hot flushes, abdominal rigidity, and hematuria after declamping of the catheter). The process of administration of intravesical epirubicin (within 2 hours after transurethral resection [TUR]) and early monitoring (first 4 hours after TUR) was carried out in the recovery room under close observation of anesthesia nursing staff and operating urologist.

2.5. Adjuvant treatment and follow-up

Intra-operative and early postoperative parameters of interest were recorded and compared between the 2 groups including examination under anesthesia findings, tumor characteristics during cystoscopy (white light), postinstillation adverse events, cytology, and biopsy results. The stage and grade were determined according to the 1987 Tumor, Nodes and Metastasis (TNM) classification [7] and World Health Organization (WHO) grading systems (1973 and 2004) [8,9].

Second TUR was planned for patients with T1 or high grade disease, or in patients with multiple/large tumors. It is routinely done 2 to 6 weeks after the first resection. The procedure included scanning of the whole bladder for any new lesion and/or any residual tumor including resection of the primary tumor site/s.

After discharge, patients were stratified into either intermediate or high-risk histopathologically confirmed NMIBC based on EORTC risk scores [10]. They were followed-up at the outpatient clinic and received adjuvant intravesical instillation of chemotherapy or immunotherapy (Bacillus Calmette-Guérin; BCG) according to EAU-matched Mansoura protocol for adjuvant treatment of NMIBC as shown in Fig. 1.

Patients were followed-up by cystourethroscopy and urine cytology 12 weeks after discharge, and thereafter every 3 months during the first 2 years and then every 6 months until 5 years in intermediate-risk patients, while, in high-risk patients, cystoscopy was performed every 3 months during the whole follow-up period. Upper tract imaging (computed tomography or magnetic resonance imaging) was done for cystoscopic documented recurrent tumors which included the trigone or ureteral orifices. In

Induction schedule of adjuvant intravesical instillation therapy for intermediate and high-risk groups:

Induction schedule	No instillation for the first 2 weeks post TURBT	1st w	2nd w	3rd w	4th w	5th w	6th w
BCG	X	√	√	√	√	√	√

Maintenance schedule of adjuvant intravesical instillation therapy for intermediate risk group:

	1st month	2nd month	3rd month	4th month	5th month	6th month	7th month	8th month	9th month	10th month	11th month	12th month
Maintenance schedule	Epi	BCG	Epi	BCG	Epi	BCG	Epi	BCG	Epi	BCG	Epi	BCG

Maintenance schedule of adjuvant intravesical instillation therapy for high risk group:

	1st month	2nd month	3rd month	4th month	5th month	6th month	7th month	8th month	9th month	10th month	11th month	12th month
Maintenance schedule	BCG	BCG	BCG	BCG	BCG	BCG	BCG	BCG	BCG	BCG	BCG	BCG

*Epi: Epirubicin

Fig. 1. Induction and maintenance schedule for intermediate and high-risk NMIBC.

addition, staging imaging was done for cases which progressed to muscle-invasive disease.

2.6. Outcome measures

The primary outcome included recurrence, progression, and/or death from cancer. The secondary outcome included systemic and/or local complications of immediate intravesical epirubicin. Early postoperative complications were graded according to modified Dindo–Clavian system [11].

2.7. Statistical analysis and sample size

In most of the previous studies the median recurrence free time in the control treatment was 1 year, showing that the true hazard ratio (relative risk) of control subjects relative to experimental subjects was 0.62 after the 2 year follow-up, so that, we needed to study 96 experimental and 96 control subjects to be able to reject the null hypothesis that the experimental and control survival curves are equal with $P = 0.800$. Type I error probability with this test of this null hypothesis is 0.05. The number was increased by 25% (to 120 patients) to allow for losses among patients in the 2 groups.

All data were computed using a commercial program "SPSS 20" (Chicago, Illinois, USA). Intention-to-treat analysis was performed for all eligible randomized patients. Categorical variables were compared using chi-square test. Continuous variables were compared using t test. Kaplan–Meier curves and log-rank test were used to assess recurrence and progression free survival. P value < 0.05 was considered significant.

3. Results

3.1. Baseline demographics

From July 2014 to November 2015, 260 patients met the study criteria. As shown in the study flowchart Fig. 2. After excluding patients with bladder cancer other than urothelial carcinoma and muscle-invasive bladder cancer or benign disease, 236 patients were included in the final analysis.

Baseline patients and tumor characteristics were comparable between the 2 groups (Table 1). Regarding patients with recurrent NMIBC, both groups were comparable regarding number of recurrences, interval from the last recurrence to the new event, last tumor stage and grade (Table 1). Out of the 236 patients who were included in the final analysis, 183 patients (93 patients in the control and 90 patients in epirubicin group) were subjected to second look resection. No significant differences were observed between the 2 groups as regard to timing of re-TURBT, cystoscopic findings, biopsy technique, and/ or pathology results (Table 1).

Patients in the intermediate-risk group were 24 and 28 in the control and epirubicin group, respectively ($P = 0.64$) and in the high-risk group 94 and 90 patients,

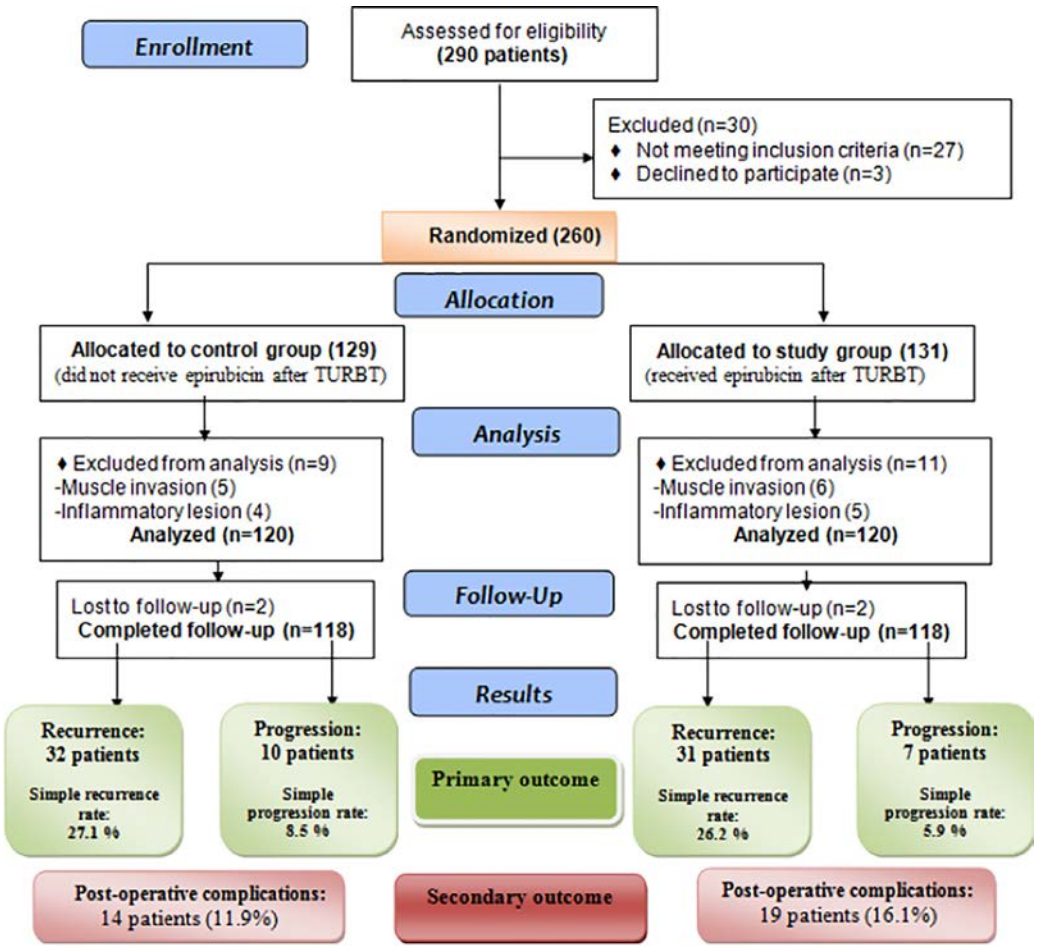

Fig. 2. Consort flowchart for study participation.

respectively ($P = 0.64$). As shown in Table 1, the mean EORTC recurrence score ± SD was 6.4 ± 2.2 versus 6.5 ± 2.3 in the 2 groups, respectively (P = 0.89).

The mean follow-up period ± SD was 29.6 ± 4 versus 29.2 ± 4.2 months in the 2 groups, respectively ($P = 0.5$; Table 1). During the follow-up period, maintenance adjuvant intravesical treatment was administered in all patients in the form of sequential monthly BCG and epirubicin or monthly BCG only in 24 and 94 patients in the control group, respectively, versus 28 and 90 patients in the epirubicin group, respectively ($P = 0.33$).

For the planned adjuvant treatment, 94 (79.6%) versus 97 patients (82.2%) completed the treatment protocol in the control and study group, respectively ($P = 0.74$), while the remaining patients did not due to recurrence/progression during follow-up. For those patients, 86 versus 87 patients were shown to be tumor free during period of follow-up, respectively.

3.2. Outcome measures

Check cystoscopy at 3 months: Ten patients (8.5%) in the control versus seven (5.9%) in epirubicin group showed recurrence at the 3-month check cystoscopy ($P = 0.62$). Those patients were admitted and managed by TURBT of the pathologically proven true NMIBC recurrence.

Table 2 shows tumor recurrence, number of recurrences, mean interval to first recurrence, site, size, and grade of recurrence in the 2 groups. Thirty-two patients (27.1%) and 31 patients (26.2%) developed recurrence during follow-up, in the 2 groups, respectively ($P = 0.95$). The mean interval to the first recurrence ± SD was 16.3 ± 6.6 and 16.4 ± 6.4 months in the 2 groups, respectively ($P = 0.39$). Using the 1973 WHO grading system, the number of patients with grade 3 recurrence was higher in the control than the epirubicin group. On the other hand, using the 2004 WHO/ISUP system, there was no significant difference in the grade of recurrence between the 2 study groups.

Progression rate, interval to progression, and the active treatment given for these patients after progression were comparable between the 2 groups (Table 2).

There was no significant difference between the 2 groups on sub-grouping analysis (intermediate vs. high-risk) as regard to tumor recurrence or progression (Table 2).

Table 1
Patients and tumor baseline criteria in the control and study (epirubicin) groups

	Control group "118 patients"		Epirubicin group "118 patients"		*P* value
	Mean ± SD	Median (range)	Mean ± SD	Median (range)	
Age (y)	61.2 ± 1.1	62 (30−81)	60.8 ± 1.1	61 (24−83)	0.72
Gender; no. (%)					0.84
• Male		104 (88.1)		106 (9.8)	
• Female		14 (11.9)		12 (10.2)	
Presentation; no. (%)					0.27
• Hematuria		75 (63.6)		67 (56.8)	
• Dysuria-suprapubic pain		4 (3.4)		4 (3.4)	
• Follow-up post-TURBT		37 (31.4)		41 (34.7)	
• Follow-up post-Upper Tract Urothelial Carcinoma (UTUC)		2 (1.6)		6 (5.1)	
Primary/recurrent; no. (%)					0.27
• Primary		83 (70.3)		74 (62.7)	
• Recurrent		35 (29.7)		44 (37.3)	
Duration from last recurrence (mo)	26 ± 15	17 (3:44)	14 ± 6	16 (4:21)	0.31
Last recurrence T-stage; no. (%)					0.4
• Ta		4 (11.4)		3 (7)	
• T1		31 (88.6)		41 (93)	
Last recurrence grade (1973 system); no. (%)					0.49
• G1		4 (11.4)		4 (9.1)	
• G2		29 (82.9)		34 (77.3)	
• G3		2 (5.7)		6 (13.6)	
Last recurrence grade (2004 system); no. (%)					0.56
• Low-grade		30 (85.7)		35 (79.5)	
• High-grade		5 (14.3)		9 (20.5)	
Number; no. (%)					0.35
• Single		63 (53.4)		52 (44.1)	
• 2−7		52 (44.1)		63 (53.4)	
• ≥8		3 (2.5)		3 (2.5)	
Tumor macroscopic appearance; no. (%)					0.08
• Papillary		111 (94.4)		117 (99.2)	
• Solid		4 (3.4)		1 (0.8)	
• Others		3 (2.5)		−	
Size; no. (%)					0.32
• <3 cm		47 (39.8)		55 (46.6)	
• ≥3 cm		71 (60.2)		63 (53.4)	
Size in mm	27.8 ± 8	30 (10−50)	27.1 ± 8	30 (10−40)	0.49
Cytology results; no. (%)					0.18
• Hyperplasic		4 (3.4)		5 (4.2)	
• Low-grade malignant		72 (61)		84 (71.2)	
• High-grade malignant		42 (35.6)		29 (24.6)	
T stage					0.51
• Ta		25 (21.1)		28 (23.7)	
• T1		93 (79.9)		90 (76.3)	
Associated Carcinoma in situ (CIS)					1
• No		115 (97.5)		115 (97.5)	
• Yes		3 (2.5)		3 (2.5)	
Grade (1973 system)					0.63
• G1		13 (11)		11 (9.3)	
• G2		64 (54.2)		70 (59.4)	
• G3		41 (34.7)		37 (31.3)	
Grade (2004 system)					0.9
• Low-grade		62 (52.5)		76 (64.4)	
• High-grade		56 (47.5)		42 (35.6)	
Second TUR					
-no (%)		93 (78.8)		90 (76.2)	0.9
-Interval between first resection and second resection (wk)	4 ± 1.2	4 (3:6)	4 ± 1.3	4 (3:6)	0.92
-Pathology of second look biopsy; no. (%)					0.78
No residual malignancy		69 (74.4)		69 (77.5)	
Residual NMIBC		24 (25.6)		21 (22.5)	
MIBC		None		None	

(*continued*)

Table 1 (***Continued***)

	Control group "118 patients"		Epirubicin group "118 patients"		*P* value
	Mean ± SD	Median (range)	Mean ± SD	Median (range)	
Risk category group; no. (%)					0.64
• Intermediate risk	24 (20.3)		28 (23.7)		
• High-risk	94 (79.7)		90 (76.3)		
EORTC recurrence score	6.4 ± 2.2	6 (2:11)	6.5 ± 2.3	6 (2:13)	0.89
EORTC progression score	6.4 ± 2.2	6 (2:11)	8 ± 3.1	9 (4:15)	0.08

EORTC = European Organization of Research and Treatment of Cancer; NMIBC = non−muscle-invasive bladder cancer; MIBC = muscle invasive bladder cancer; TUR = transurethral resection; TURBT = transurethral resection of bladder tumor.

Recurrence and progression-free survival using Kaplan −Meier curves were comparable between the 2 groups (log-rank test; $P = 0.88$ and 0.47, respectively, Fig. 3).

According to modified Dindo−Clavian system, postoperative complications were all low-grade and comparable between the 2 groups (Table 3).

4. Discussion

The impact of single instillation of chemotherapy on behavior of NMIBC after TURBT have been studied in many previous trials with confirmed efficacy on reduction of recurrence [11]. This is based on its antitumor effect in destroying tumors cells floating in the irrigation fluid and urine after TURBT and on its ablative effect on residual tumor cells at the site of the resection and on small overlooked tumors [12].

The EAU guidelines for NMIBC recommended 1 postoperative intravesical instillation of chemotherapy after TURBT of presumably NMIBC [4]. This evidence was strengthened by 3 large meta-analyses comprising 1,476 to 3,103 patients that have consistently shown that 1 immediate instillation of chemotherapy after TURBT significantly reduced the recurrence rate by 11.7% to 13.0% compared to TURBT alone [5,12−14]. However, the evidence for the efficacy of this treatment originates from studies that have focused on patients with low risk for recurrence.

In the current study, the recurrence rate in the group receiving immediate postoperative epirubicin was comparable to the control group. Similarly, interval to first recurrence was comparable between the 2 groups, this finding copes with the result of meta-analysis conducted by Sylvester et al. which demonstrated that patients with EORTC recurrence score more than 5 did not get benefit from immediate instillation as regard to interval to first recurrence [15].

The Gothenburg group stated that ''a single instillation of epirubicin after TUR prevents only small recurrences with a diameter less than 5 mm'' [3]. In our study, size of recurrence was comparable between the 2 groups. This conflict could be justified as the majority of cases evaluated by the Gothenburg group were low risk patients unlike our study, which focused only on intermediate and high-risk patients.

The recurrences in our study, using 1973 WHO grading system, were of lower grade in the epirubicin compared to the control group; however, this effect was not maintained when we applied the 2004 WHO/ISUP system. This disparity could be attributed to the overlap of G2 tumor in the 1973 system on low-grade and high-grade tumors in the 2004 system.

In our study, there was no statistically significant reduction in the simple progression rate in the epirubicin compared to the control group. This finding agrees with the results of meta-analysis done by Sylvester et al., which showed that immediate instillation resulted in lower progression rate (6.6% in the control group vs. 5.6% in instillation group), with no statistically significant difference [15]. The differences in the progression rates between our study and that meta-analysis can be explained by heterogeneity of the studies populations in this meta-analysis as regard to the agent used, risk category, adjuvant instillation protocols, and length of follow-up.

Immediate postoperative instillation of epirubicin was not associated with improvement in disease (recurrence and/or progression) free survival; a finding that goes hand-in-hand with the results of meta-analysis conducted by Sylvester et al. [15]. Surprisingly, this meta-analysis demonstrated a significant increase of 26% in the overall risk of death in patients with the instillation. They correlated this higher overall risk of death to the high-risk group of patients in subgroup analysis, and, theoretically, they explained this higher risk of death by higher risk of "unrecognized" perforation especially in those patients with higher prior recurrence rate [16]. In our study, no death was reported in any patient in the study groups. This could be explained by good performance status of patients included in the study with normal cardiac and hematological functions, with no other malignancy, and also to the shorter duration of follow-up in our study (mean 29 ± 4 months) as compared with the longer period of follow-up in Sylvester's meta-analysis (median 9 years).

On the other hand, we got different results from that obtained by Bosschieter et al., who found a valuable role of

Table 2
Characteristics of tumor recurrence and progression in the control and study groups

	Control group		Epirubicin group		P
	Mean ± SD	Median (range)	Mean ± SD	Median (range)	
Tumor recurrence					
Patients experienced recurrence of NMIBC during follow-up; no. (%)					0.95
• No	86 (72.9)		87 (73.8)		
• Yes (simple recurrence rate)	32 (27.1)		31 (26.2)		
Intermediate risk	20		24		0.57
-No					
- Yes	4		4		
High risk	66		63		0.9
-No					
- Yes	28		27		
Interval to first recurrence (months)	16.3±6.6	17.5 (3:28)	16.4±6.4	17 (3:28)	0.93
Number of recurrences; no. (%)					0.35
• One recurrence	23 (72)		28 (90)		
• Two recurrences	7 (22)		3 (10)		
• Three recurrences	2 (6)		None		
Site of first recurrence; no. (%)					0.88
• At the same site of initial lesions	16 (50)		14 (45)		
• At different site/es	8 (25)		9 (29)		
• Multifocal including the initial site	8 (25)		8 (26)		
Size of first recurrence; no. (%)					0.99
• Small recurrence (< 5mm)	3 (9)		3 (10)		
• Large recurrence (5mm)	29 (91)		28 (90)		
Grade of first recurrence (1973 system); no. (%)					0.02
• G1	None		5 (16)		
• G2	14 (44)		19 (61)		
• G3	18 (56)		7 (23)		
Grade of first recurrence (2004 system); no. (%)					0.12
• Low grade	14(44)		21 (68)		
• High grade	18 (56)		10 (32)		
Associated CIS; no. (%)					0.92
• No	29 (91)		29 (94)		
• Yes	3 (9)		2 (6)		
Tumor progression					
Patients experienced progression during follow-up; no. (%)					0.62
• No	108 (91.5)		111 (4.1)		
• Yes (Simple progression rate)	10 (8.5)		7 (5.9)		
Intermediate risk	23		28		0.46
-No					
- Yes	1		0		
High risk	85		83		0.8
-No					
- Yes	9		7		
Interval to progression (months)	18.7±5.1	20 (3:28)	18.5±5	19 (3:28)	0.8
Active treatment after progression of NMIBC; no. (%)					0.35
• Radical cystectomy	(80)		7 (100)		
• Systemic chemotherapy and radiotherapy	2(20)		None		

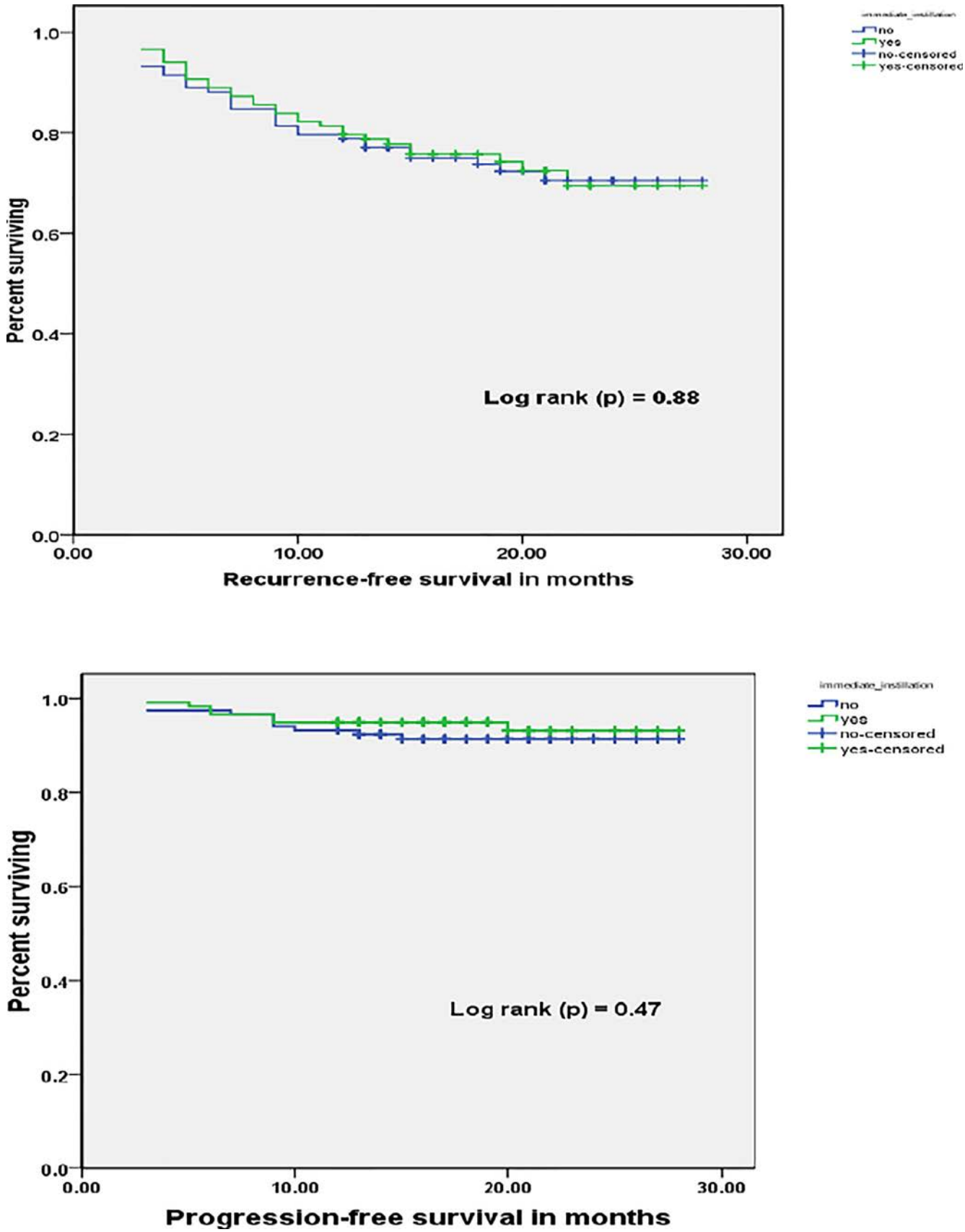

Fig. 3. Kaplan−Meier curves showing recurrence and progression free survivals in the control and study groups.

Table 3
Early postoperative complications in the control and study groups

	Control group no. (%)	Epirubicin group no. (%)	*P* value
Patients developed postoperative complications; no. (%)			0.45
• No	104 (88.1)	99 (83.9)	
• Yes	14 (11.9)	19 (16.1)	
Modified Dindo–Clavian grading of postoperative complications; no. (%)			0.49
• Low grade (I, II, IIIa)			
I	10 (8.5)	12 (10.1)	
II	4 (3.4)	5 (4)	
IIIa	–	2 (2)	
• High grade (IIIb, IV, V)	–	–	
Postoperative complications and its management; no. (%)			0.7
• Postoperative fever (managed by antipyretics, foments and fluids)	10 (8.5)	12 (10.1)	
• Hematuria (managed by bladder irrigation and hemostatics)	2 (1.7)	3 (2.5)	
• Febrile bacteriuria (managed by culture-based antibiotics and fluids)	2 (1.7)	2 (2)	
• Hematuria (managed by recystoscopy and hemostasis)	–	1 (0.75)	
• Obstructed kidney following resection due to involvement of the ureteric orifice (managed by antegrade JJ stent fixation	–	1 (0.75)	

early (within 24 hours) instillation of Mitomycin C (MMC) in patients with intermediate (recurrence reduction by 12%, $P = 0.037$) and high-risk (recurrence reduction by 8%, $P = 0.007$) [17]. However, this study has a major limitation that the risk categories defined in their protocol do not correspond with actual EORTC risk tables or EAU risk groups, as the study protocol was written in 1998.

In our study, there was no difference in early postoperative complications between the study groups. No high-grade complications (Clavien $\geq$ 3b) were reported in any of the study subjects. The most commonly reported complication was postoperative fever. Extravasation of the instilled epirubicin was not encountered in any patient of the instillation group. Two studies had reported serious complications associated with immediate instillation of chemotherapy post-TURBT [18,19]. The used agent in those studies was mitomycin C, and the complications were attributed primarily to extravasation of the agent and systemic absorption. Attribution of immediate instillation of epirubicin to possible adverse events as bladder scarring, ureteral orifice scarring after resection over it, or future bladder scarring is not investigated before.

Despite the reported high safety profile of immediate post-TURBT instillation of epirubicin, the obtained results of the ineffective role of immediate post-TURBT instillation of chemotherapy in intermediate and high-risk patients should be translated into the clinical practice. The challenging issue is that, the precise risk group could not be determined except after the histopathology results (T stage, grade, and associated CIS), and, the decision of immediate instillation is essentially built on the preoperative criteria (tumor recurrence) and intra-operative findings during cystoscopy (tumor size and multiplicity). Criteria of intermediate and high-risk patients as regard to the preoperative and intra-operative findings included any of the followings; prior recurrence rate (more than 1 recurrence per year), multiple papillary tumor, or single papillary tumor more than 3 cm. Any of these findings is associated with at least 3 points in the EORTC recurrence score, and this raises the probability of being at least intermediate-risk patient to 100%.

Notably in our study, second resection TURBT was shown to be valuable in detection of residual malignancy (22% and 25% in the study and control groups, respectively). These results raise the significance of second resection in those particular groups of patients (intermediate and high-risk) and its impact on risk category upgrading and suitable subsequent adjuvant treatment strategy.

To our knowledge, our study is the first randomized controlled trial, which investigated the value of immediate post-TURBT instillation of epirubicin exclusively in intermediate and high-risk patients with NMIBC. The unified protocols of adjuvant induction and maintenance instillation therapy provide another advantage to our study. Careful monitoring and documentation of early postinstillation adverse events and even postadjuvant instillation therapy adequately support the safety aspect of our study.

The main limitation of our study is the short duration of follow-up (mean 29 months). However, the long term data of this trial is still awaited. Another limitation of our study is the possible interobserver variability in histopathological evaluation of the grade of the recurrence due to inclusion of more than 1 pathologist in our study. Furthermore, the study was not repowered to detect the possible role of immediate post-TURBT instillation of chemotherapy in patients with intermediate-risk only in subgroup analysis.

5. Conclusions

Unlike the evidence-based value of single immediate post-TURBT instillation of epirubicin on reduction of recurrence rate in low risk NMIBC, it is ineffective in intermediate and high-risk patients. It neither prolongs time to recurrence, time to progression nor reduces the number of recurrences. Patients with recurrence rate more than 1 per year, single papillary tumor more than

3 cm, or multiple papillary tumors are most likely to be intermediate or high-risk patients. So, they should be abandoned from immediate post-TURBT instillation of epirubicin.

Conflict of interest

The authors declare that there is no conflict of interest.

Informed consent

An informed consent was obtained from the patient(s) for their information to be published in this article.

References

[1] Ali-el-Dein B, el-Baz M, Aly AN, Shamaa S, Ashamallah A. Intravesical epirubicin versus doxorubicin for superficial bladder tumors (stages pTa and pT1): a randomized prospective study. J Urol 1997;158:68–73.

[2] Okamura K, Ono Y, Kinukawa T, Matsuura O, Yamada S, Ando T, et al. Randomized study of single early instillation of (2"R)-4′-O-tetrahydropyranyl-doxorubicin for a single superficial bladder carcinoma. Cancer 2002;94:2363–8.

[3] Rajala P, Kaasinen E, Raitanen M, Liukkonen T, Rintala E. Perioperative single dose instillation of epirubicin or interferon-alpha after transurethral resection for the prophylaxis of primary superficial bladder cancer recurrence: a prospective randomized multicenter study −FinnBladder III long-term results. J Urol 2002;168:981–5.

[4] Babjuk M, Oosterlinck W, Sylvester R, Kaasinen E, Bohle A, Palou-Redorta J. EAU guidelines on non-muscle-invasive urothelial carcinoma of the bladder. Eur Urol 2008;54:303–14.

[5] Sylvester RJ, Oosterlinck W, van der Meijden AP. A single immediate postoperative instillation of chemotherapy decreases the risk of recurrence in patients with stage Ta T1 bladder cancer: a meta-analysis of published results of randomized clinical trials. J Urol 2004;171:2186–90.

[6] Gudjonsson S, Adell L, Merdasa F, Olsson R, Larsson B, Davidsson T, et al. Should all patients with non-muscle-invasive bladder cancer receive early intravesical chemotherapy after transurethral resection? The results of a prospective randomised multicentre study. Eur Urol 2009;55:773–80.

[7] Sobin LH, Hermanek P, Hutter RV. TNM classification of malignant tumors. A comparison between the new (1987) and the old editions. Cancer 1988;61:2310–4.

[8] Epstein JI, Amin MB, Reuter VR, Mostofi FK. The World Health Organization/International Society of Urological Pathology consensus classification of urothelial (transitional cell) neoplasms of the urinary bladder. Bladder Consensus Conference Committee. Am J Surg Pathol 1998;22:1435–48.

[9] Pellucchi F, Freschi M, Moschini M, Rocchini L, Maccagnano C, Nazareno S, et al. Oncological predictive value of the 2004 World Health Organisation grading classification in primary T1 non-muscle-invasive bladder cancer. A step forward or back? BJU Int 2015;115:267–73.

[10] Sylvester RJ, van der Meijden AP, Oosterlinck W, Witjes JA, Bouffioux C, Denis L, et al. Predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer using EORTC risk tables: a combined analysis of 2596 patients from seven EORTC trials. Eur Urol 2006;49:466–75.

[11] Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004;240:205–13.

[12] Brocks CP, Buttner H, Bohle A. Inhibition of tumor implantation by intravesical gemcitabine in a murine model of superficial bladder cancer. J Urol 2005;174:1115–8.

[13] Perlis N, Zlotta AR, Beyene J, Finelli A, Fleshner NE, Kulkarni GS. Immediate post-transurethral resection of bladder tumor intravesical chemotherapy prevents non-muscle-invasive bladder cancer recurrences: an updated meta-analysis on 2548 patients and quality-of-evidence review. Eur Urol 2013;64:421–30.

[14] Abern MR, Owusu RA, Anderson MR, Rampersaud EN, Inman BA. Perioperative intravesical chemotherapy in non-muscle-invasive bladder cancer: a systematic review and meta-analysis. J Natl Compr Canc Netw 2013;11:477–84.

[15] Sylvester RJ, Oosterlinck W, Holmang S, Sydes MR, Birtle A, Gudjonsson S, et al. 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? Eur Urol 2016;69:231–44.

[16] Comploj E, Dechet CB, Mian M, Trenti E, Palermo S, Lodde M, et al. Perforation during TUR of bladder tumours influences the natural history of superficial bladder cancer. World J Urol 2014;32:1219–23.

[17] Bosschieter J, Nieuwenhuijzen JA, van Ginkel T, Vis AN, Witte B, Newling D, et al. Value of an immediate intravesical instillation of Mitomycin C in patients with non-muscle-invasive bladder cancer: a prospective multicentre randomised study in 2243 patients. Eur Urol 2018;73:226–32.

[18] Oddens JR, van der Meijden AP, Sylvester R. One immediate postoperative instillation of chemotherapy in low risk Ta, T1 bladder cancer patients. Is it always safe? Eur Urol 2004;46:336–8.

[19] Elmamoun MH, Christmas TJ, Woodhouse CR. Destruction of the bladder by single dose Mitomycin C for low-stage transitional cell carcinoma (TCC)−avoidance, recognition, management and consent. BJU Int 2014;113:31.