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Original Article

Single Early Intravesical Instillation of Epirubicin for Preventing Bladder Recurrence After Nephroureterectomy in Upper Urinary Tract Urothelial Carcinoma

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Running Title: Intravesical Epirubicin after Nephroureterectomy

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Abstract

Purpose

We aimed to assess the effectiveness of early single intravesical administration of epirubicin in preventing intravesical recurrence after radical nephroureterectomy for upper tract urothelial carcinoma.

Materials and Methods

Patients with upper tract urothelial carcinoma who underwent radical nephroureterectomy between November 2018 and May 2022 were retrospectively reviewed. Intravesical epirubicin was administered within 48 hours if no evidence of leakage was observed. Epirubicin (50 mg) in 50 mL normal saline solution was introduced into the bladder via a catheter and maintained for 60 min. The severity of adverse events was graded using the Clavien-Dindo classification. We compared intravesical recurrence rate between the two groups. Multivariate analyses were performed to identify the independent predictors of bladder recurrence following radical nephroureterectomy.

Results

Epirubicin (n=55) and control (n=116) groups were included in the analysis. No grade 1 or higher bladder symptoms have been reported. A statistically significant difference in the intravesical recurrence rate was observed between the two groups (11.8% at 1 year in the epirubicin group vs. 28.4% at 1 year in the control group; log-rank p=0.039). In multivariate analysis, epirubicin instillation (HR, 0.43; 95% CI, 0.20–0.93; p=0.033) and adjuvant chemotherapy (HR, 0.29; 95% CI, 0.13-0.65; p=0.003) were independently predictive of a reduced incidence of bladder recurrence.

Conclusion

This retrospective review revealed that a single immediate intravesical instillation of epirubicin

is safe and can reduce the incidence of intravesical recurrence after radical nephroureterectomy. However, further prospective trials are required to confirm these findings.

Keywords

Urologic neoplasms, Urothelium, Nephroureterectomy, Administration, Intravesical, Neoplasm recurrence, Local

Introduction

Urothelial carcinoma (UC) is the sixth most prevalent tumor in developed countries. Upper urinary tract urothelial carcinoma (UTUC) is rare, representing only 5–10% of UCs [1]. Radical nephroureterectomy (RNU) with bladder cuff excision is the gold standard method of treatment for high-risk upper UC at any location [2]. Intravesical recurrence (IVR) after treatment occurs in 22–47% of patients with UTUC [3].

As IVR following RNU is associated with worsening of oncological outcomes and additional medical costs, several treatments have been proposed. Two prospective randomized trials have documented that a single dose of intravesical chemotherapy (mitomycin C and pirarubicin) administered 2–10 days after RNU decreases the risk of IVR. Two studies reported a low risk of adverse events. Several guidelines also recommend intravesical chemotherapeutic agent instillation as adjuvant therapy for RNU [4-8].

However, in clinical practice, urologists rarely perform bladder instillation after RNU because of insufficient data on safety and unavailability of a clear protocol [9]. Similarly, in Korea, intravesical instillation of chemotherapeutic agents after RNU is rarely accepted.

In this study, we implemented intravesical instillation after RNU using epirubicin (EPI) after RNU, which has relatively little accumulated data. This study aimed to evaluate the oncological outcomes and safety profile of post-RNU single intravesical instillation of EPI. The factors associated with IVR after RNU have also been discussed.

Materials and Methods

1. Patients

This retrospective study included 307 patients with UTUC who underwent RNU at the Samsung Medical Center (Seoul, South Korea) between November 2018 and May 2022. Of the

total patients, 84 with a history of bladder cancer before surgery, 41 with concurrent bladder cancer, 23 with other intravesical chemotherapy instillation, 7 with previous distal ureterectomy, 6 with bilateral UTUC, 5 with no UC histology, and 4 with pathologic T4 were excluded. A total of 167 patients were recruited and were assigned to two groups, EPI (n=51) and control (n=116) (Fig. 1).

2. Radical nephroureterectomy method

Six surgeons performed RNU and each surgeon performed intravesical EPI instillation based on their preferences. Preoperative ureteroscopy with or without biopsy was performed based on the surgeon's preference and preoperative imaging readings. Patients underwent robotic, laparoscopic, or open surgery, depending on the surgeon's preference. A transperitoneal approach was employed to mobilize the kidney. Robotic surgery involved intracorporeal bladder cuff resection, and laparoscopic open surgery involved bladder cuff resection with an inguinal incision. Lymph node dissection was performed according to the surgeon's preference, or if preoperative imaging studies showed suspected lymph node metastases. Based on the results of the POUT trial, adjuvant chemotherapy was administered to patients with pathological pT3 or higher until 2021 and was administered to patients with pT2 or higher after 2022.

3. Indication of intravesical therapy

Intravesical EPI instillation after RNU was indicated if there was no history of bladder cancer, gross hematuria was absent, bladder cuffing was considered secure, and cystography showed no evidence of leakage. Intravesical EPI instillation was performed within 48 h postoperatively with cystography, which confirmed the absence of urine leakage. EPI (50 mg) in 50 mL normal saline solution was introduced into the bladder via a Foley catheter and

maintained for 60 min. After intravesical instillation, early complications were evaluated during hospitalization using the Clavien-Dindo classification. The patients were discharged after removal of the Foley catheters 5 or 6 days post operation. Patients who did not receive postoperative intravesical therapy were included as control group.

4. Follow-up protocol

Cystoscopy was routinely performed at 3 months post operation to monitor bladder recurrence. Subsequent cystoscopy was performed every 3–12 months, depending on the patient's condition. The IVR date was defined as the time when bladder recurrence was suspected on cystoscopy and confirmed via pathology with transurethral resection of the bladder tumor. Computed tomography or magnetic resonance imaging was performed to assess disease progression every 6 months for the first 2 years and annually for the next 3 years.

5. Statistical method

The primary endpoint was to compare IVR rates between the EPI and control groups in the first 12 months after RNU. The secondary endpoints were progression rate after RNU in both groups, predictive factor analysis of IVR, and safety profile after intravesical EPI instillation. Comparative examinations were carried out using Pearson's chi-square and Fisher's exact tests and focused on aspects such as sex, age, ASA classification, tumor side, tumor grade, tumor location, pathological T stage, pathological N stage, lymphovascular invasion, bladder cuffing type, preoperative ureteroscopy, and whether adjuvant chemotherapy was performed. The number of patients with concomitant carcinoma in situ were small (1 (2.0%), 4 (3.4%) in the EPI and control group, respectively), so they were not included in the analysis. The Kaplan–Meier method was used to evaluate the IVR and progression-free survival rates after RNU, and

the log–rank test was used to compare survival rates between the EPI and control groups. Univariate and multivariate analyses were performed using Cox proportional hazards models to identify the factors associated with IVR after RNU. All statistical analyses were performed using IBM SPSS for Windows (version 23.0; IBM Corp., Armonk, NY). AP-value of <0.05 was considered statistically significant.

Results

1. Baseline characteristics

The baseline characteristics of the patients are summarized in Table 1. The median follow-up period was 23.9 months. The EPI and control groups were followed up for 19.6 months (IQR 16.4–28.7 months) and 24.8 months (IQR 18.3–34.7 months). In the two groups, the variables that showed significant differences were bladder cuffing type and preoperative ureteroscopy.

2. Oncological outcomes

The 1-year IVR rate in the entire cohort was 23.4%. Comparison between the EPI and control groups revealed significantly lower recurrence rates within 1-year for the EPI group (EPI group IVR rates: 11.8%; control group IVR rates: 18.7%), which confirmed a significant difference between the two groups in the Kaplan–Meier analysis (p=0.039; Fig. 2). The mean time to recurrence was 44.1 months (95% CI 39.2–49.0) for the EPI group and 30.3 months (95% CI 27.1–33.6) for the control group.

Twenty nine patients developed cancer progression and three died. The progression rates during follow-up were 27.3% and 13.7% in the EPI group and 19.0% in the control group. There was no difference in the survival curves between the two groups (p=0.608; Fig. 3).

The predictors of post-RNU IVR, EPI instillation (HR, 0.48; 95% CI, 0.23–0.98; p=0.044) and adjuvant chemotherapy (HR, 0.46; 95% CI, 0.23–0.99; p=0.030) were related to IVR on univariate analysis (Table 2).

3. Complication

In the EPI group, the intravesical EPI was maintained for at least 60 min. No adverse events related to intraperitoneal leakage of chemotherapeutic agents were reported during hospitalization. One patient complained of nonspecific abdominal pain that was not distinct from surgical site pain. Two previously reported randomized clinical trials showed a low risk of adverse events.

Discussion

The major strengths of this study are that this study reported the data on intravesical EPI instillation after RNU in patients with UTUC, which were limited. Further, this study reported data based on surgeries performed during clinical practice.

The standard treatment for UTUC is nephroureterectomy with bladder cuff removal. Even in patients undergoing standard surgery, frequent IVR remains a significant complication. Previous studies have identified patient-specific predictors (male sex, history of bladder cancer, and preoperative chronic kidney disease), tumor-specific predictors (positive preoperative urinary cytology, ureteral location, multifocality, invasive pT stage, and necrosis), and treatment-specific predictors (laparoscopic approach, extravesical bladder cuff removal, and positive surgical margins) as risk factors for IVR [10]. Risk factors for IVR have been previously reported; however, the options for delaying or preventing IVR and its progression are limited.

Intravesical chemotherapy for non-muscle-invasive bladder cancer after transurethral

or bladder tumors has been used since the 1990s. Several studies have shown that it is effective at delaying or preventing recurrence and progression [11]. However, the role of prophylactic intravesical chemotherapy in patients with primary UTUC following RNU remains unclear, with the exception of two prospective studies on mitomycin-C and pirarubicin and several small-scale studies [6,7]. Notably, except for one small study about 10 years ago, there have been no studies on intravesical EPI instillation in patients with UTUC. Our study showed that a single early intravesical instillation of EPI after RNU decreased the risk of IVR without adverse effects. This result confirms the beneficial effects of prophylactic EPI instillation after RNU, which reduced IVR in the first 2 years. These differences were statistically significant based on Kaplan–Meier recurrence-free survival curves. The EPI and control group had 1- and 2-year IVR rates of 11.8% and 28.4% vs. 18.7% and 33.5%, respectively. Using Cox regression multivariate analysis, EPI instillation (HR, 0.48; 95% CI, 0.23–0.98; p=0.044) and adjuvant chemotherapy (HR, 0.46; 95% CI, 0.23–0.99; p=0.030) were identified as risk factors associated with IVR. No significant adverse events related to EPI administration were observed.

Two previous prospective randomized clinical trials of intravesical agents after RNU for UTUC. O'Brien et al. conducted a prospective randomized unblinded clinical trial at 46 centers in the United Kingdom. This study included 284 patients with UTUC and no history of bladder cancer. Eligible patients were administered a single postoperative dose of intravesical mitomycin-C instillation (40 mg in 40 mL saline). In the mitomycin-C arm, 21 of 120 patients (17%) developed IVR in the first year compared with 32 of 119 patients (27%) in the standard treatment group. A decreasing trend for IVR was observed in the mitomycin-C group, but no significant difference in the survival curves was observed between the two groups (log-rank test, p=0.055) [8]. One limitation of this study was the lack of a standardized timing for mitomycin-C instillation. The intervention in this clinical trial was intravesical mitomycin-C

instillation at catheter removal 1 week after RNU. Intravesical mitomycin-C instillation after 7 days likely had less impact on IVR reduction because previous studies on intravesical chemotherapy instillation after transurethral bladder tumor resection in patients with non-muscle-invasive bladder cancer have reported that immediate postoperative instillation reduces IVR [11]. To complement the timing of instillation, Ito et al. conducted a phase II randomized clinical trial involving 77 patients from 11 institutions in Japan. In this study, pirarubicin (30 mg in 30 mL saline) was administered as a single intravesical instillation within 48 h of RNU in patients with UTUC. The first IVR was monitored using cystoscopy 2 years after surgery. Of the 72 patients included in the analysis, 21 experienced IVR, and IVR significantly decreased in the THP group than in the control group (16.9% at 1 year and 16.9% at 2 years in the THP arm vs. 31.8% at 1 year and 42.2% at 2 years in the control arm; (log-rank test, p=025)) [5]. Our study also conducted intravesical EPI instillation within 48 h after RNU and reported IVR rates comparable to those reported by Ito et al. (11.8% at 1 year and 18.7% at 2 years in the EPI group vs. 28.4% at 1 year and 33.5% at 2 years in the control group; log-rank p=0.039).

The chemotherapeutic agents used in the two randomized clinical trials were only pirarubicin and mitomycin-C, although EPI was selected as the intravesical therapy immediately after RNU in this study. The reasons for not using mitomycin-C and pirarubicin at our institution are as follows. In Korea, intravesical chemotherapy instillation after RNU has not yet been covered by national insurance. So, we had to consider a reduction in benefits, and we excluded relatively expensive drugs such as mitomycin-C. And mitomycin-C had issues such as supply interruption and instability in the management of nonmuscle invasive bladder cancer. In addition, mitomycin-C was known to cause severe complications in the event of intraperitoneal leakage, so there were difficulties with immediate intravesical instillation with bladder cuffing after RNU [12,13]. Pirarubicin has not yet been available in Korea. Although

gemcitabine has been used as intravesical therapy in nonmuscle invasive bladder cancer [14], the insurance coverage for this treatment was only recently introduced in Korea. and a clinical study using gemcitabine is currently underway at our institution. Additionally, gemcitabine was well known to cause severe bladder irritation due to its very acidic pH of around 2 [15], and it was thought to be unsuitable for the postoperative setting such as bladder cuff excision. EPI is an analog of pirarubicin that has been widely used for intravesical therapy of nonmuscle invasive bladder cancer. It is known to be a relatively safe agent even with intraperitoneal leakage in previous studies, so we decided to administer intravesical therapy using EPI [16,17]. Informed consent for intravesical EPI instillation after RNU was obtained in all patients, and based on the current study, we plan to apply for insurance coverage for intravesical therapy after RNU.

The fixation of microscopic cancer cells in the perioperative period (seeding theory) and UC metastasis (field theory) have been reported as the causes of IVR after RNU [18-22]. Prevention of recurrence from intravesical chemotherapeutic agent instillation results from the removal of cancer cells floating in the bladder during surgery before they engraft onto the bladder mucosa. Therefore, the timing of the intravesical instillation is critical in IVR. However, according to the recent results of a European survey from a young academic urologist UC group, approximately half of the participants (47%) were regularly administered intravesical chemotherapeutic agents following RNU. Additionally, different administration protocols were adopted: ≤48 h (39%), 7–10 postoperative days (35%), >10 days (11%), and intraoperatively (10%). This evidence was supported by prospective randomized clinical trials of only 65% of responders. Among interviewees who did not receive the intervention, the most commonly reported reasons were lack of supporting data (55%), fear of potential side effects (18%), and organizational hurdles (15%) [9]. Despite the positive results and safety in two previous

randomized clinical trials, the efficacy of intravesical chemotherapeutic agent instillation after RNU bladder cuffing remains unclear. Further data on intravesical instillation after RNU are needed, and a standard protocol should be established. Further research on the efficacy and safety of the post-RNU intillation timing is essential.

Several studies have identified the risk factors for IVR after RNU [10]. In the multivariate analysis performed in our study, only EPI instillation and adjuvant chemotherapy were identified as risk factors for IVR. In contrast to data from previous studies, extravesical bladder cuffing was associated with a lower risk of IVR than was intravesical cuffing, although this finding was not significant in our study. Previously, our center reported that intravesical cuff excision reduces IVR [23], this result was not statistically significant, likely because of the small cohort size. Previous ureteroscopy is also a known risk factor for IVR [24], the surgeons in this study performed ureteroscopy before RNU based on their own preferences. In addition, whether a biopsy was conducted at the time of ureteroscopy is an important factor that has not yet been investigated separately. Therefore, in this study, a previous ureteroscopy was associated with an increased risk of IVR; however, this difference was not statistically significant.

The present study had several limitations. This study was a retrospective study. Additionally, the population was relatively small, especially in the EPI group. A large multicenter prospective study is required to validate our findings. In addition, in the treatment of RNU, intravesical EPI instillation, preoperative ureteroscopy, operation type, and method were determined according to the preferences of the six surgeons without a standardized protocol. Furthermore, this study only investigated adverse events during hospitalization; therefore, an investigation of late complications is also needed. The median follow-up period was relatively short (23.9 months, and the median time to recurrence in both groups was not

statistically significant. Finally, clear recommendations regarding the timing, dose, and duration of intravesical EPI instillation after RNU are lacking.

This retrospective cohort study revealed that a single immediate intravesical instillation of EPI is safe and reduces the IVR rate after RNU. These results will contribute to the accumulation of more data for urologists concerned about intravesical chemotherapeutic agent instillation after RNU. However, further prospective trials are required to confirm these findings.

Ethical Statements

This study was performed in accordance with the applicable laws and regulations, good clinical practice, and ethical principles described in the Declaration of Helsinki. The Institutional Review Board of the Samsung Medical Center approved this study (IRB No. 2023-10-016). The board waived the requirement for informed consent.

Author Contributions

Conceived and designed the analysis: Lee JH, Sung HH.

Collected the data: Lee JH, Lee CU, Chung JH, Song W, Kang M, Jeon HG, Jeong BC, Seo SI, Jeon SS, Sung HH.

Contributed data or analysis tools: Lee JH, Sung HH.

Performed the analysis: Lee JH, Sung HH.

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Conflicts of Interest

Conflict of interest relevant to this article was not reported.

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Table 1. Baseline characteristics

	EPI Group (n=51)		Control Group (n=116)		
Characteristic	**No.**	**%**	**No.**	**%**	**p value**
Sex					0.296
Male	38	74.5	77	66.4	
Female	13	25.5	39	33.6	
Age, years					0.921
< 70	29	56.9	65	56.0	
≥ 70	22	43.1	51	44.0	
ASA classification					0.940
I	3	5.9	6	5.2	
II	38	74.5	88	75.9	
III	9	17.6	21	18.1	
IV	1	2.0	1	0.9	
Tumor side					0.058
Right	17	33.3	57	49.1	
Left	34	66.7	59	50.9	
Tumor grade					0.968
I	1	2.0	3	2.6	
II	26	51.0	58	50.0	
III	24	47.1	55	47.4	
Tumor location					0.869
Ureter only	25	49.0	49	42.2	
Ureter multiple	1	2.0	3	2.6	
Pelvis only	23	45.1	58	50.0	
Ureter and pelvis	2	3.9	6	5.2	
pT stage					0.554
pTa or pTis	7	13.7	9	7.8	
pT1	15	29.4	44	37.9	
pT2	10	19.6	22	19.0	
pT3	19	37.3	41	35.3	
pN stage					0.661
Nx, N0	48	94.1	111	95.6	
N1, N2	3	5.9	5	4.3	
LVI					0.889
No	44	86.3	101	87.1	
Yes	7	13.7	15	12.9	
Concomitant CIS					
No	50	98.0	112	96.6	1.000
Yes	1	2.0	4	3.4	
Bladder cuffing					0.014
Intravesical	44	86.3	79	68.1	
Extravesical	7	13.7	37	31.9	
Preoperative URS					<0.001
No	40	78.4	55	47.4	

Yes	11	21.6	61	52.6	
Adjuvant Chemotherapy					0.310
No	32	62.7	82	70.7	
Yes	19	37.3	34	29.3	

EPI, epirubicin; ASA, American Society of Anesthesiologists; LVI, lymphovascular invasion; URS, ureteroscopy.

Table 2. Univariate and Multivariate Analysis of Factors Associated with Intravesical Recurrence

	Univariate			Multivariate		
Variable	**HR**	**95%CI**	**p**	**HR**	**95%CI**	**p**
EPI instillation	0.48	0.23 to 0.98	0.044	0.43	0.20 to 0.93	0.033
Sex						
male vs. female	0.90	0.49 to 1.68	0.749	0.70	0.35 to 1.40	0.311
Age						
<70 vs. ≥ 70	1.23	0.70 to 2.15	0.479	1.30	0.70 to 2.43	0.407
ASA classification						
III vs. IIIIV	1.16	0.58 to 2.33	0.677	0.83	0.37 to 1.84	0.643
Tumor side						
Right vs. Left	1.13	0.94 to 2.00	0.679	1.31	0.69 to 2.49	0.404
Tumor grade						
III vs. III	0.93	0.53 to 1.63	0.794	1.11	0.56 to 2.19	0.767
Presence of ureter tumor	1.06	0.61 to 1.86	0.839	0.99	0.53 to 1.86	0.985
pT stage						
Ta T1 vs. T2 T3	1.08	0.62 to 1.91	0.783	2.05	0.89 to 4.74	0.092
Pn stage						
Nx N0 vs. N1-2	0.88	0.22 to 3.64	0.865	0.81	0.18 to 3.58	0.782
Lymphovascular invasion	1.70	0.82 to 3.51	0.152	2.01	0.87 to 4.66	0.104
Bladder cuffing						
Intravesical vs. Extravesical	0.64	0.32 to 1.29	0.210	0.53	0.25 to 1.12	0.098
Preoperative ureteroscopy	1.67	0.95 to 2.93	0.075	1.42	0.79 to 2.58	0.245
Adjuvant chemotherapy	0.46	0.23 to 0.93	0.030	0.29	0.13 to 0.65	0.003

EPI, epirubicin; ASA; American Society of Anesthesiologists; HR, harzard ratio.

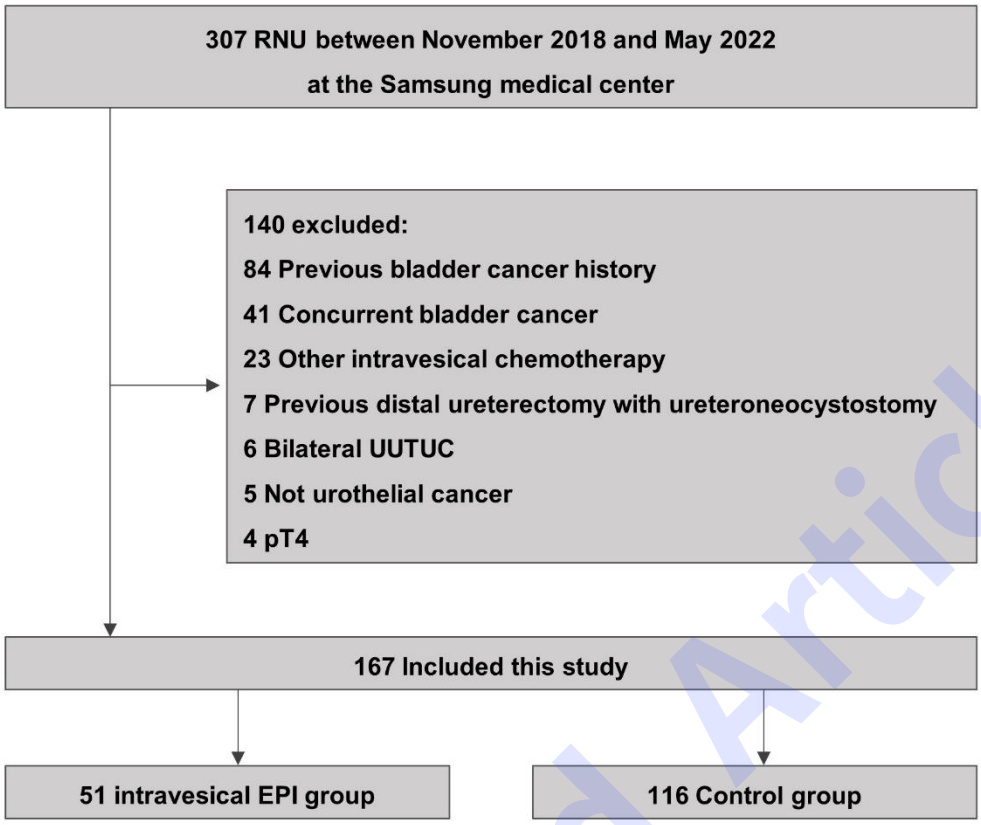

Fig. 1. Participants flow diagram.

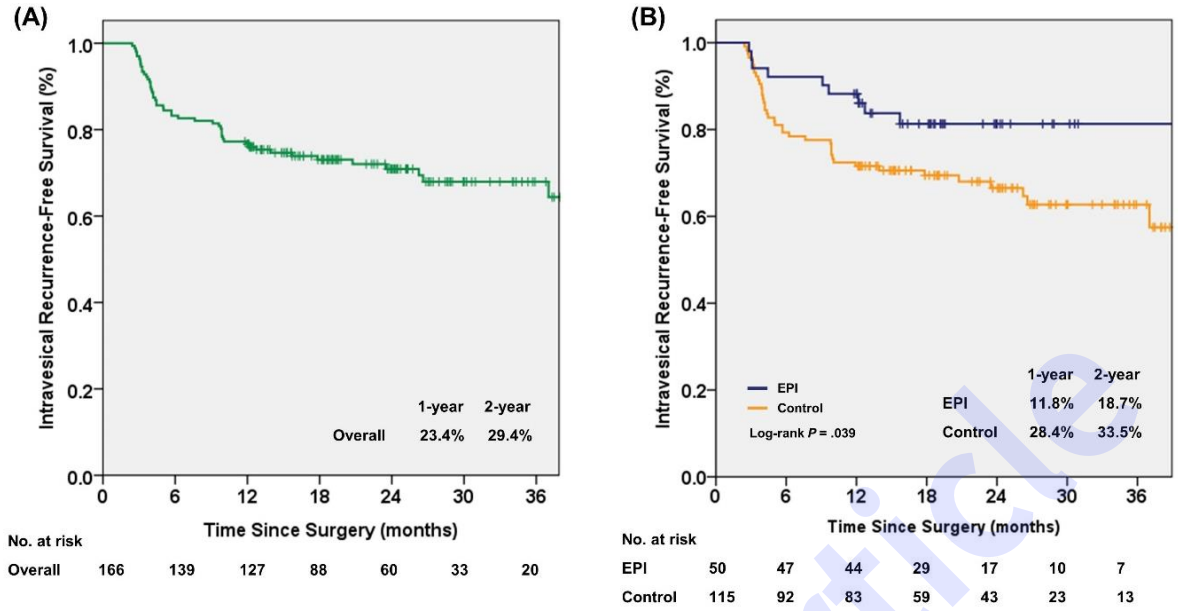

Fig. 2. Intravesical recurrence-free survival rates after nephroureterectomy. (A) Overall cohorts, (B) Epirubicin group vs. Control group.

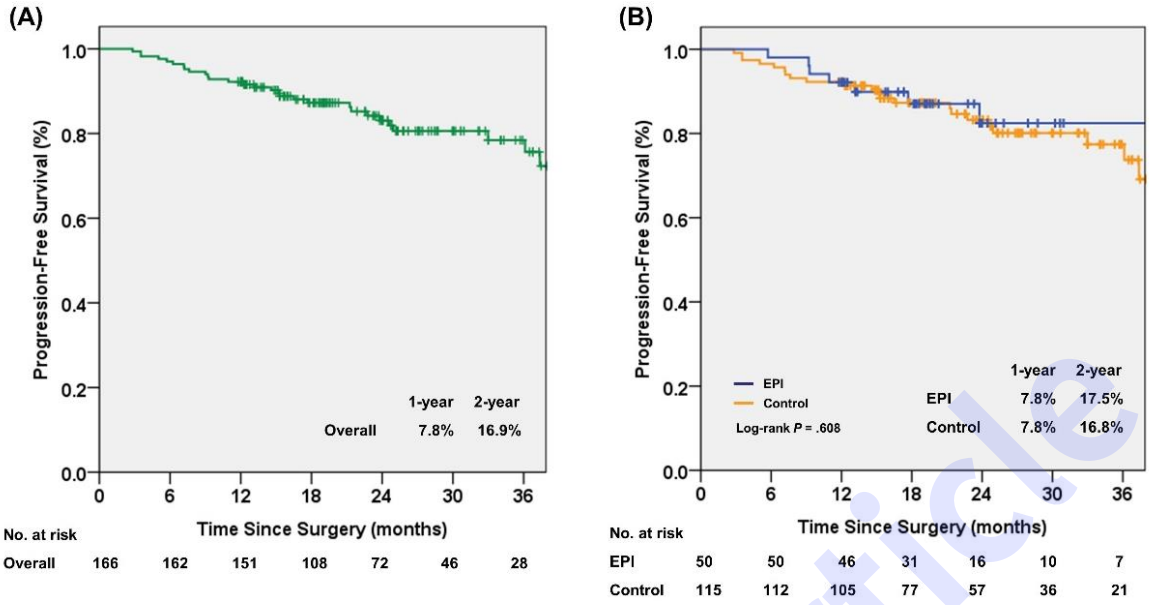

Fig. 3. Progression-free survival rates after nephroureterectomy. (A) Overall cohorts, (B) Epirubicin group vs. Control group.