Technology in Cancer Research & Treatment
Volume 18: 1-9

DOI: 10.1177/1533033819844483
journals.sagepub.com/home/tct
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A Comparison of Different Prophylactic Intravesical Chemotherapy Regimens for Bladder Cancer Recurrence After Nephroureterectomy for Primary Upper Tract Urothelial Carcinomas: A Retrospective 2-center Study

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Abstract

Prophylactic intravesical chemotherapy can decrease bladder cancer recurrence rate after nephroureterectomy for upper tract urothelial carcinoma. We aimed to compare the effect of different prophylactic intravesical chemotherapy regimens in bladder recurrence-free survival. From 2000 to 2016, a total of 270 patients treated with radical nephroureterectomy at both institutions were enrolled. Patients were divided into 3 groups: multiple-instillation group, single-instillation group, and no-instillation group. Univariable and multivariable analyses with Cox regression methods were performed to calculate hazard ratios for bladder recurrence using clinicopathologic data, including our different instillation strategies. Sixty-three (23.3%) of 270 patients had subsequent intravesical recurrence. Significantly fewer patients in both the instillation groups had a recurrence compared to in the no-instillation group (13.1% vs 25.4% vs 41.5%, $P = .001$). Furthermore, there was a significant difference between both the instillation groups ($P = .016$). In different subsets of patients with upper tract urothelial carcinoma, intravesical chemotherapy, either multiple or single instillation, was a protective factor of bladder recurrence in pT2-4 ($P = .002$) and high grade ($P < .0001$). Importantly, Kaplan-Meier curves of bladder recurrence-free survival rate were increased observably in multiple-instillation group compared to that in single-instillation group ($P = .053$ in pT2-4 subgroup; $P = .048$ in high-grade subgroup, respectively). On multivariable analysis, intravesical chemotherapy ($P < .001$), especially multiple instillations (hazard ratio 0.230; 95% confidence interval 0.110-0.479), was identified an independent predictor of bladder recurrence-free survival. In conclusion, prophylactic intravesical chemotherapy effectively prevents bladder recurrence after nephroureterectomy, especially with multiple instillations, in patients with invasive upper tract urothelial carcinoma or at high-grade status.

Keywords

intravesical chemotherapy, neoplasm recurrence, nephroureterectomy, urothelium, urinary bladder

Received: November 2, 2018; Revised: January 24, 2019; Accepted: March 24, 2019.

Introduction

Urothelial carcinoma (UC) is a common malignant tumor that can involve the pelvis, ureters, and bladder. Upper tract urothelial carcinoma (UTUC) accounts for 5% to 6% of UC and 5% to 10% of renal tumors.[1] Radical nephroureterectomy (RNU) with bladder cuff excision is the standard management of UTUC,[2] but 20% to 69% of patients experience intravesical recurrence after RNU.[3-7]

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Recently, an increasing number of clinicians recognize the importance of prophylactic intravesical chemotherapy to prevent bladder recurrence of primary UTUC after RNU. Previous studies have demonstrated the efficacy of intravesical chemotherapy administered in single or multiple postoperative doses, but few studies have compared the effects of these different regimens.[8-10] Thus, the aim of this study was to identify the efficacy of single or multiple instillations of intravesical chemotherapy to prevent bladder recurrence after RNU for UTUC.

Materials and Methods

Study Design and Patients

We reviewed the records of patients with UTUC who underwent surgery at our institutions from January 2000 to December 2016. The study was approved by the institutional review board of our institutions, and the requirement for informed consent was waived owing to the retrospective nature of this study. We chose the patients based on the availability of follow-up data and excluded those who underwent neoadjuvant radiotherapy or chemotherapy, those who underwent instillation with nonchemotherapy drugs, such as Bacillus Calmette-Guerin, those with previous or concomitant bladder cancer, distant metastasis at diagnosis, or bilateral synchronous upper urinary tract tumors, and those who did not undergo RNU. The remaining 270 patients were enrolled in this study.

Treatment

The patients were divided into 3 groups: the no-instillation groups, single-instillation, and multiple-instillation. In the no-instillation group, 41 patients did not receive intravesical chemotherapy after surgery. In the single-instillation group, 130 patients received intravesical chemotherapy only once after nephroureterectomy, and in the multiple-instillation group patients received intravesical chemotherapy for more than once after nephroureterectomy, but at least 6 doses of intravesical chemotherapy weekly were recommended in our institutions. There were 99 patients in the multiple-instillation group. The intravesical agents for patients in both the instillation groups were epirubicin (30-50 mg each time, 125 cases), pirarubicin (30-50 mg each time, 89 cases), or mitomycin C (MMC; 20-40 mg each time, 15 cases), and the first instillation in both groups was initiated within 2 weeks after surgery. Patients retained the solution for at least 30 minutes. Regular follow-up examinations consisted of cystoscopy, physical examination, routine blood chemistry studies, urinalysis, urinary cytology, chest X-ray, and abdominal and pelvic computed tomography. Cystoscopy was suggested every 3 months for 2 years and every 6 months thereafter. The follow-up data of all patients were retrieved retrospectively both through hospital records and by telephone interviews. The follow-up schedule was performed at the same time at 2 institutions by 2 coauthors.

Table 1. Clinical and Pathological Characteristics.

	No-Instillation Group, No. (%)	Single-Instillation Group, No. (%)	Multiple Instillation Group, No. (%)	*P*
Sex				
Male	28 (68.3)	88 (67.7)	63 (63.6)	.779
Female	13 (31.7)	42 (32.3)	36 (36.4)	
Age				
≤64	22 (53.7)	67 (51.5)	58 (58.6)	.566
>64	19 (46.3)	63 (48.5)	41 (41.4)	
Smoking				
No	24 (58.5)	81 (62.3)	72 (72.7)	.153
Yes	17 (41.5)	49 (37.7)	27 (27.3)	
Tumor side				
Right	14 (34.1)	58 (44.6)	42 (42.4)	.496
Left	27 (65.9)	72 (55.4)	57 (57.6)	
Tumor size				
≤3 cm	18 (43.9)	56 (43.1)	57 (57.6)	.076
>3 cm	23 (56.1)	74 (56.9)	42 (42.4)	
Tumor site				
Calix or pelvis	26 (63.4)	82 (63.1)	59 (59.6)	.937
Ureter	13 (31.7)	42 (32.3)	33 (33.3)	
More than 1	2 (4.9)	6 (4.6)	7 (7.1)	
Type of surgery				
Open RNU	26 (63.4)	73 (56.2)	48 (48.5)	.234
Laparoscopic RNU	15 (36.6)	57 (43.8)	51 (51.5)	
Tumor stage				
Ta-1	12 (29.3)	52 (40.0)	47 (47.5)	.129
T2-4	29 (70.7)	78 (60.0)	52 (52.5)	
Pathologic N stage				
Nx, N0	34 (82.9)	114 (87.7)	91 (91.9)	.290
N+	7 (17.1)	16 (12.3)	8 (8.1)	
Tumor grade				
Low	14 (34.1)	38 (29.2)	37 (37.4)	.424
High	27 (65.9)	92 (70.8)	62 (62.6)	
Median follow-up time, months (range)	19 (1-200)	27 (3-172)	43 (1-180)	–

Abbreviation: RNU, Radical nephroureterectomy.

We estimated the recurrence-free survival rate and time to bladder recurrence, which was defined as the time between the date of surgery and the date on which the first bladder recurrence was detected.

Statistical Analysis

All analyses were performed using SPSS version 20.0 (IBM Corp, Armonk, New York) and GraphPad Prism 5 (GraphPad Software, Inc, La Jolla, California). Information on patient demographics, histologic results, and long-term outcomes was obtained by chart review. The tumor stages and grades were confirmed according to the TNM and World Health Organization classifications, respectively. The χ^2 test was used to analyze categorical variables in the 3 groups of patients. The Kaplan-Meier method was used to calculate survival functions,

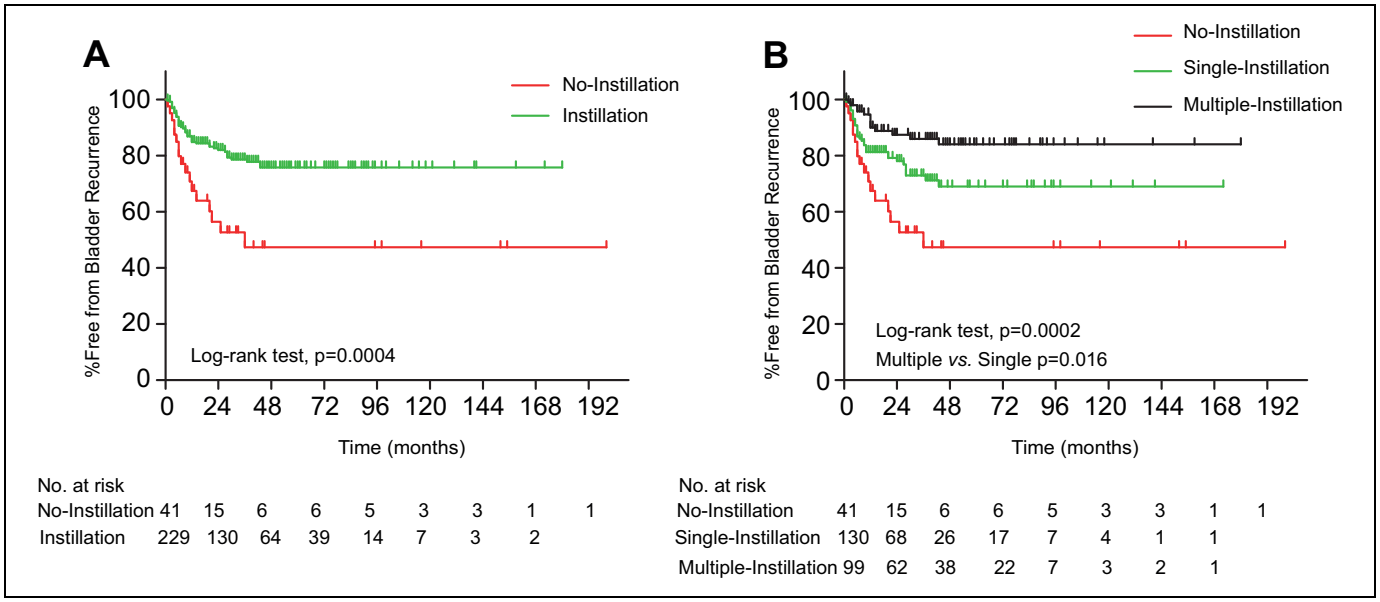

Figure 1. Bladder cancer recurrence-free survival rates between the no-instillation group and instillation groups (A) and among these 3 groups (B).

and the log-rank test was applied to assess differences. Cox regression models were used to compare bladder recurrence rates among these groups while controlling for other risk factors, including sex, tumor location, smoking, stage, grade, lymph node, and instillation agents. A backward stepdown selection process was applied to the multivariable models to eliminate the least informative variables. Statistical significance in this study was set at $P < .05$, and all reported P values were 2-sided.

Results

The descriptive variables of the 270 evaluable patients are shown in Table 1. Their median age was 64 years (interquartile range [IQR]: 56-72 years), and 66.3% of patients were male. The histopathologic T stages, N stages, and tumor grades are shown in the 3 groups. There were no significant differences in sex, age, tumor side, site, size, stage, grade, and lymph node status between the groups.

The median follow-up time is 27.5 months (IQR: 10.8-52.8 months). Of the 270 patients, 63 (23.3%) developed bladder recurrence, of these 63 patients, 53 (84%) had recurrence within 2 years after RNU. In the no-instillation group, recurrence was observed following surgery in 17 (41.5%) of 41 patients, 33 (25.4%) of 130 in the single-instillation group, and 13 (13.1%) of 99 in the multiple-instillation group. The follow-up times of the 3 groups are shown in Table 1. The recurrence rate was significantly higher in the no-instillation group than in the single-instillation and multiple-instillation groups ($P = .001$). Kaplan-Meier curves showed that the recurrence-free survival rate was significantly different between the no-instillation group and the instillation groups ($P = .0004$; Figure 1A) and between the 3 groups ($P = .0002$; Figure 1B), and a significant difference were found between the multiple-instillation and single-instillation groups ($P = .016$; Figure 1B)

In order to provide more precise estimate, survival analysis was performed with regard to intravesical chemotherapy regimens in subset of patients with different tumor histopathological grades and pT stages. The results showed that intravesical instillation was a prognostic factor in patients with UTUC having pT2-4 ($P = .002$; Figure 2C) and high-grade ($P < .0001$; Figure 3C). Furthermore, compared to single instillation, intravesical chemotherapy with multiple instillations showed a statistical significance with regard to the bladder recurrence outcome of high-grade patients ($P = .048$; Figure 3D) and a borderline statistical significance in pT2-4 ($P = .053$; Figure 2D). No significant differences were observed when comparing between the 3 groups in bladder recurrence in patients with UTUC having pTa-1 ($P = .211, .277$; Figure 2A and B) and low grade ($P = .816, .509$; Figure 3A and B)

In univariable analyses, both multiple-instillation and single-instillation groups were significantly associated with bladder recurrence after RNU. Multivariable analyses showed that the single- and multiple-instillation groups were significant factors predictive of intravesical recurrence (multiple vs no: relative risk = 0.230; 95% confidence interval [CI], 0.110-0.479; $P < .001$; single vs no: relative risk = 0.472; 95% CI, 0.262-0.853; $P = .013$). Both instillation regimens were the factors to independently predict better bladder recurrence-free survival rates. In addition, sex ($P = .011$), tumor location ($P = .040$), grade ($P = .041$), and pathologic N stage ($P = .044$) were also independent predictors of bladder recurrence-free survival (Table 2).

To identify the potential confounding effect of different intravesical instillation agents on bladder recurrence, the comparisons of bladder recurrence-free survival were performed according to this factor. Although 3 different agents (epirubicin,

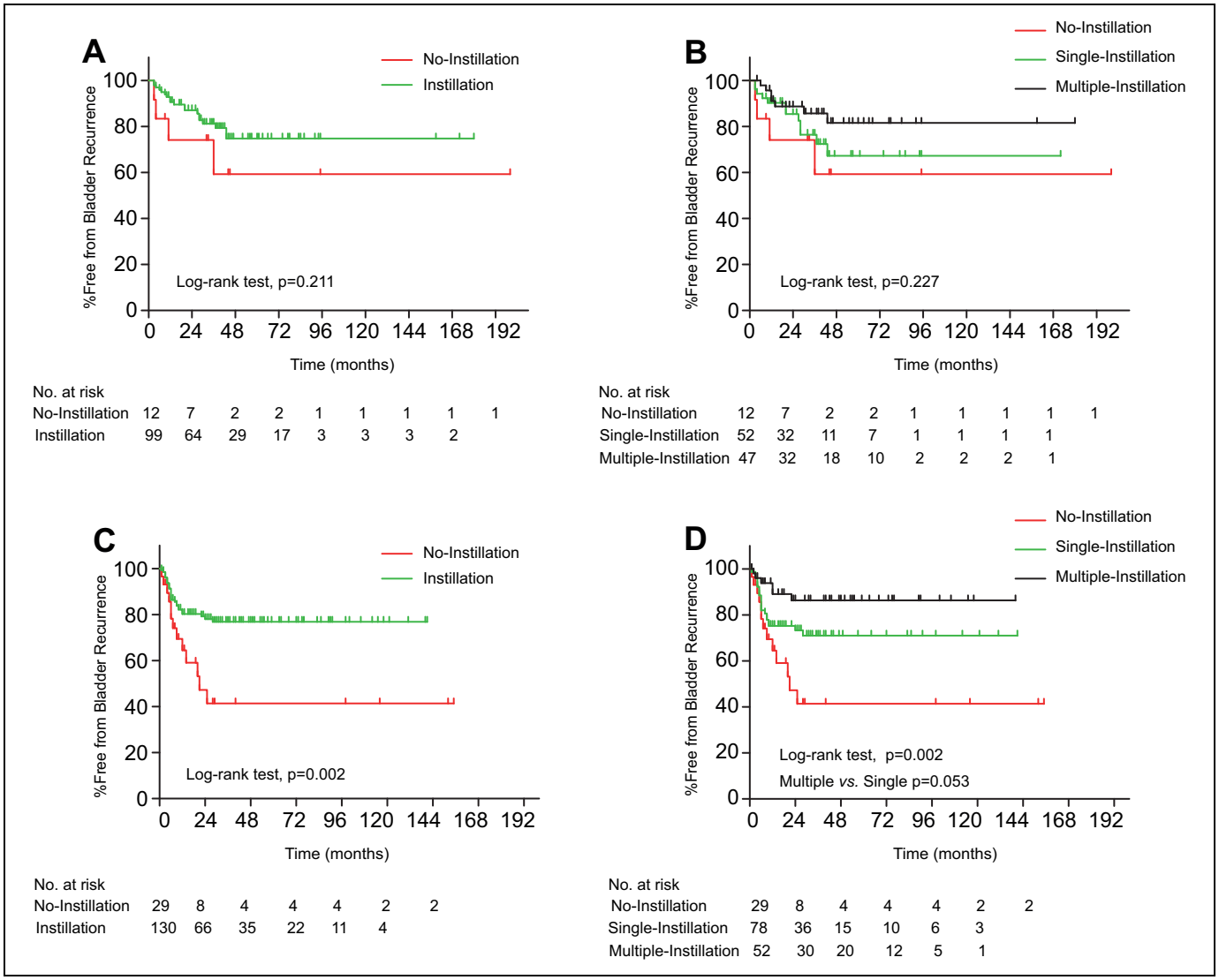

Figure 2. Bladder cancer recurrence-free survival rates between the no-instillation group and instillation groups and among these 3 groups. Superficial upper tract urothelial carcinomas (Ta-1; A, B) and invasive upper tract urothelial carcinomas (T2-4; C, D).

pirarubicin, and MMC) were administered for intravesical instillation, the significant differences were only found between the instillation groups and no-instillation group (epirubicin, pirarubicin, or MMC vs No, $P = .002$, .004, or .012, respectively; Figure 4A), and it was not shown a significant difference among these different agents ($P = .591$; Figure 4A). Subgroup analyses in patients with different instillation regimen also showed no significant difference in bladder recurrence-free survival among these different agents ($P > .05$; Figure 4B and C).

There were no serious adverse events reported as a result of single or multiple instillations. Neither systemic side effects nor abnormal laboratory data were observed in any patients.

Discussion

Radical nephroureterectomy with bladder cuff removal is the standard procedure for UTUC. However, almost half of patients had bladder recurrence after surgery.[10,11] Several studies have demonstrated the efficacy of intravesical chemotherapy to prevent bladder recurrence. Ito *et al*[12] enrolled 72 patients clinically diagnosed with UTUC and showed that a single instillation of pirarubicin reduces the rate of bladder recurrence after RNU in patients with UTUC. O'Brien *et al*[9] found that a single postoperative dose of intravesical MMC decreased the risk of bladder recurrence within the first year following RNU in a prospective, randomized, nonblinded trial with 284 patients. Sakamoto *et al*[8] performed a comparison of 25 patients who underwent multiple instillations of cytosine arabinoside and MMC (13 patients) or no instillation (12 patients). They suggested that intravesical instillation chemotherapy might be a useful approach for reducing the risk of bladder recurrence, but their results only demonstrated a strong trend ($P = .079$) rather than a significant difference. And Wu *et al*[10] demonstrated that, in a series of 196 patients,

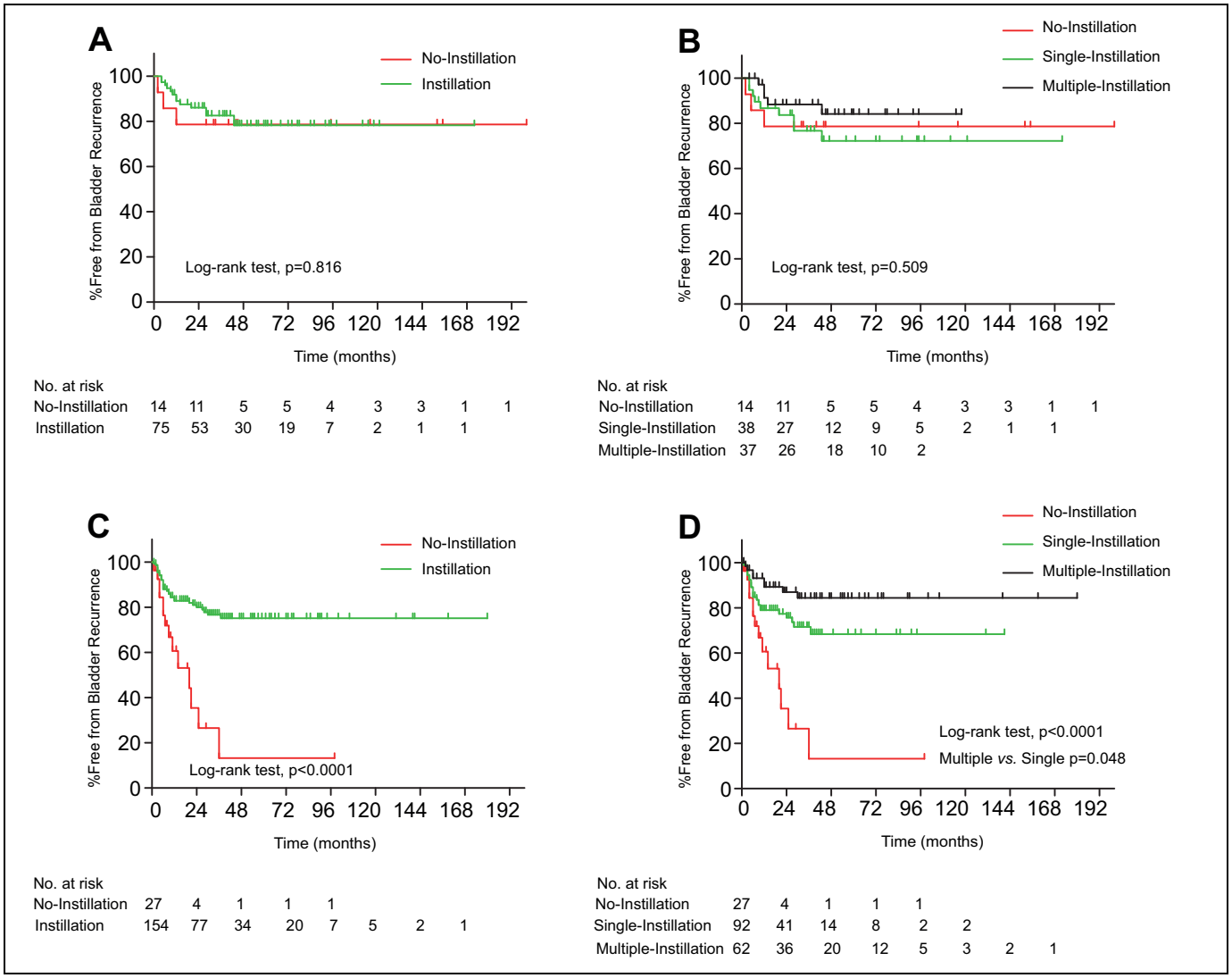

Figure 3. Bladder cancer recurrence-free survival rates between the no-instillation group and instillation groups and among these 3 groups. Low-grade upper tract urothelial carcinomas (A and B) and high-grade upper tract urothelial carcinomas (C and D).

intravesical recurrence was lower in those who received MMC or epirubicin for 6 to 8 times after RNU compared to those who received neither. However, to the best of our knowledge, only a retrospective study has compared the efficacy of single and multiple instillations, but the comparison between multiple instillations and single instillation remains undefined[13]. Although previous studies have shown that maintenance chemotherapy has benefits in terms of the prevention of recurrence in the postoperative regimen of bladder cancer,[14,15] it is unclear whether these benefits extend to UTUC because of the differences between these malignancies.[16] Therefore, the effects of these different intravesical chemotherapy regimens warrant investigation. This study compared the no-instillation group (41 patients), the single-instillation group (130 patients), and the multiple-instillation group (99 patients), the patient sample size was relatively larger than previous retrospective studies, and demonstrated that the incidence of bladder cancer in the instillation groups was significantly lower than that of the no-instillation group. The result is similar to those of previous studies.[6,8,10] Furthermore, we demonstrated that bladder recurrence rate of the multiple-instillation group was lower than that of the single-instillation group. To our knowledge, this finding has not been described previously.

To date, intraluminal seeding[17,18] and field cancerization[19,20] have been considered 2 main hypotheses for bladder recurrence after nephroureterectomy. Previous investigators have focused on risk factors for the development of bladder recurrence after surgery and have shown that intraluminal seeding should be an important factor leading to implantation metastases,[8,9,21] and it is also the basis for the administration of a single dose of intravesical chemotherapy. However, data from present study suggest that several doses of intravesical chemotherapy following RNU can reduce the incidence of bladder recurrence more effectively (multiple vs single, 13.1% vs 25.4%). Therefore, we surmise that dispersed viable intraluminal cancer cells are not completely mopped up by a

Table 2. Univariable and Multivariable Cox Regression Models Predicting Intravesical Recurrence.

	Univariable			Multivariable		
Variable	HR	95% CI	*P*	HR	95% CI	*P*
Sex (male/female)	0.436	0.232-0.817	.010[a]	0.434	0.228-0.824	.011[a]
Age (≤64/>64)	1.361	0.829-2.234	.223			
Smoking (No/Yes)	1.750	1.067-2.869	.027[a]			
Tumor location			.067			.040[a]
Pelvis	1		–	1		–
Ureter	1.382	0.812-2.355	.234	1.539	0.895-2.644	.119
More than 1	2.543	1.124-5.753	.025[a]	2.912	1.277-6.641	.011[a]
Tumor side (left/right)	0.853	0.515-1.413	.537			
Tumor size (<3 / ≥3 cm)	1.694	1.018-2.818	.042[a]			
Type of surgery (open/laparoscopy)	1.075	0.650-1.778	.777			
pT stage (pTa-1/pT2-4)	1.522	0.906-2.557	.112			
Tumor grade (low/high)	1.674	0.958-2.928	.071	1.848	1.025-3.334	.041[a]
Pathologic N stage (Nx, N0/N+)	2.679	1.452-4.944	.002[a]	1.944	1.017-3.714	.044[a]
Instillation agents			.006[a]			
No agent	1		–			
Epirubicin	0.396	0.215-0.732	.003[a]			
Pirarubicin	0.395	0.203-0.766	.006[a]			
MMC	0.191	0.044-0.832	.027[a]			
Intravesical instillation			<.001[a]			<.001[a]
No	1		–	1		–
Single	0.501	0.279-0.899	.021[a]	0.472	0.262-0.853	.013[a]
Multiple	0.232	0.113-0.480	<.001[a]	0.230	0.110-0.479	<.001[a]

Abbreviations: CI, confidence interval; HR, hazard ratio; MMC, mitomycin C.
[a]Statistically significant.

single instillation, suggesting why maintenance chemotherapy achieves more apparent benefits in terms of recurrence.

On the other hand, some factors, such as growth of coexisting microscopic bladder cancer and the continuous exposure of bladder epithelium to carcinogens, may also result in intravesical recurrence after RNU.[8] Some carcinogens are considered to precipitate a field cancerization effect by causing independent genetic alterations, which lead to the development of multifocal tumors in a metachronous manner.[22] Although this mechanism should perhaps be defined as representing the development of subsequent primary cancer, emerging bladder cancer following nephroureterectomy is usually grouped together and labeled as "recurrence." The biological properties of the bladder cancer in the mechanism are likely to be more similar to normal epithelial cells and will not respond to administered anticancer agents,[23] so it could be a contributing factor for "bladder recurrence" in both instillation groups.

Accurate prediction of bladder recurrence for each patient may screen the best candidates for such an adjuvant local treatment. An increasing number of studies have demonstrated some risk factors for bladder recurrence following surgery, which makes risk stratification possible.[24,25] Tumor stage and grade were recommended as the primary prognostic ones in postoperative factors of UTUC.[26] Some studies have demonstrated that higher tumor stage was significantly associated with bladder recurrence.[27,28] The invasive UTUC (pT ≥ 2) might increase potential of locally aggressive budding tumors to release cancer cells into the urinary tract. Ishioka *et al* also demonstrated that a tumor with higher pT stage might have greater risk of tumor spread.[29] According to the hypothesis of intraluminal seeding, the fragility of intercellular adhesions of invasive tumors may be an initiating factor for bladder recurrence, and it is similar to the speculation of some studies,[29,30] which can explain the remarkable effect of intravesical chemotherapy in the subgroup of patients with pT2-4 UTUC. A 22-year retrospective study of 374 patients with UTUC was reported by Huang *et al*,[7] high grade ($P < .0001$, relative risk = 3.776), independently predicted bladder recurrence based on the World Health Organization/International Society of Urological Pathology (WHO/ISUP) consensus classification. Tumor grade should be strictly related to cancer aggressiveness and be a well-established predictor of cancer-related survival, so we speculated that UTUC with high grade might represent strong tumor invasiveness and disseminate cancer cells along the urinary tract. Therefore, our study confirmed that intravesical chemotherapy, especially with multiple instillations, should be administered to the patients with invasive (pT2-4) or high-grade UTUC, but for the patients with superficial (pTa-1) or low-grade UTUC, it might be an excessive treatment, and a waiting and monitoring strategy could be more fitting to the low-risk patient population. This finding may guide administration of intravesical chemotherapy to those who are likely to benefit from it.

How many courses of intravesical chemotherapy should be administrated after RNU is still controversial. Although the European Association of Urology Guidelines have shown the

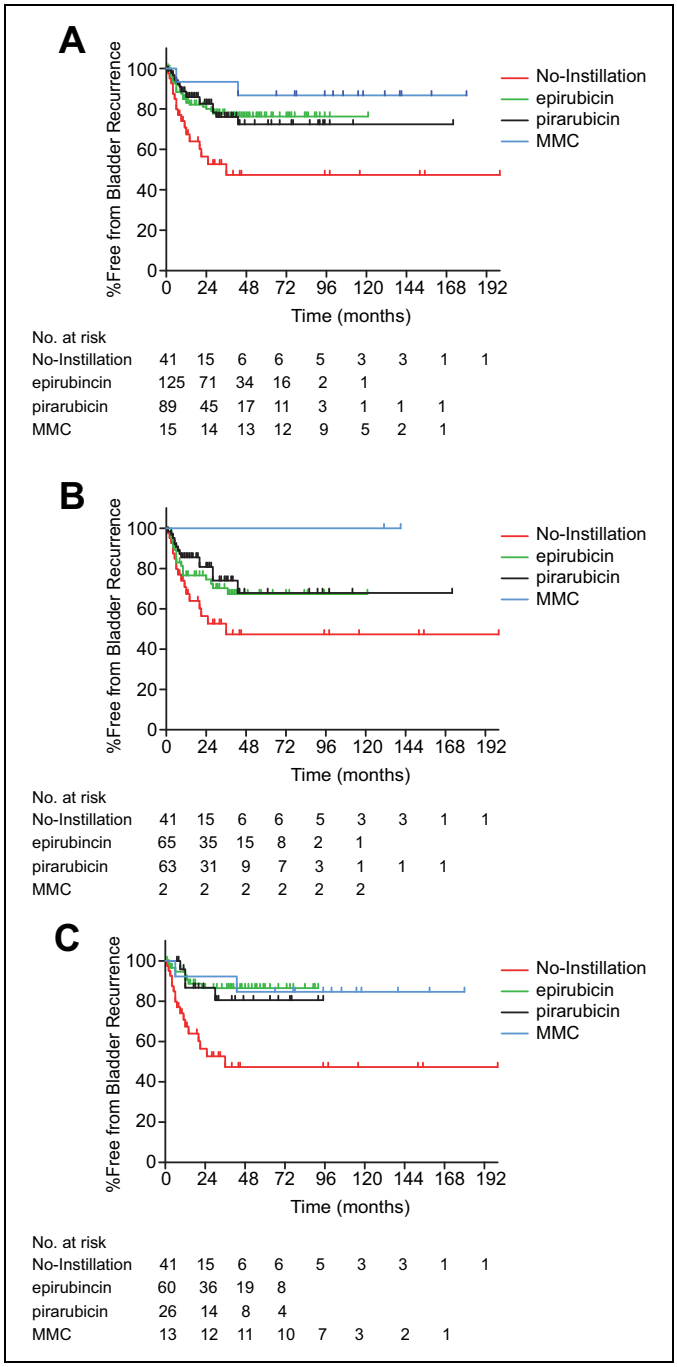

Figure 4. Bladder cancer recurrence-free survival rates of different instillation agents (A), epirubicin versus No $P = .002$, pirarubicin versus No $P = .004$, MMC versus No $P = .012$, epirubicin versus pirarubicin versus MMC $P = .591$, log-rank test; the comparison of bladder cancer recurrence-free survival rates in single-instillation subgroup (B), epirubicin versus pirarubicin $P = .515$, epirubicin versus MMC $P = .374$, pirarubicin versus MMC $P = .382$, log-rank test; the comparison of bladder cancer recurrence-free survival rates in Multiple-Instillation subgroup (C), epirubicin versus pirarubicin $P = .676$, epirubicin versus MMC $P = .966$, pirarubicin versus MMC $P = .717$, log-rank test. MMC indicates mitomycin C.

results of 2 prospective randomized trails based on a single postoperative dose of intravesical chemotherapy,[26] the effect of repeated doses of intravesical chemotherapy is not mentioned. At present, most urological physicians inclined to perform 5 to 8 times of instillation in Asian regions,[10,31] while a single instillation is popular in European countries,[9] and even 1 study has reported to perform instillation for 28 times.[8] In this study, some urologists in our institutions administrated at least 6 instillations based on the common strategy. Tumors with high T stage and/or high grade were usually considered more likely to recur, so the urologists inclined to perform intravesical chemotherapy to these postoperative patients, especially with multiple instillations. Although there was no consensus on instillation agents in the instillation groups, no significant difference in bladder recurrence-free survival was found in subgroup analyses, so our results can confirm the efficacy of intravesical chemotherapy convincingly.

Some limitation of this study should be considered. First, the main limitation of the study is that our experience does not represent a randomized study on multiple- versus single- versus no-instillation. It should be noted that different series are less comparable because of differences in patient composition. Although in this study 3 different agents were administered for intravesical instillation after RNU, there were no significant difference when comparing different agents, so negligible heterogeneity had been introduced into the treatment approach, and the comparison between both the instillation groups and no-instillation group became reasonable and meaningful. For further confirmation of the therapeutic efficacy of prophylactic intravesical chemotherapy with multiple instillations, a prospective, randomized controlled trial of intravesical chemotherapy regimens has been ongoing in 5 medical centers since August 2017. Second, although the enrollment period of the retrospective study is 16 years, more than 80% of the patients were treated in the year 2010 and thereafter. It is the reason for the relatively short median follow-up time (27.5 months). However, some studies reported that about 50% to 60% patients experienced intravesical recurrence within 2 or 3 years after RNU,[32,33] so the length of follow-up is sufficient to observe the intravesical recurrence of patients with UTUC.

Conclusions

Intravesical chemotherapy after surgery significantly reduced bladder recurrence rate of patients with UTUC, especially invasive or high-grade UTUC. Furthermore, we suggest that the effect of multiple intravesical instillations may be superior to that of a single instillation.

Authors' Note

YH, ZWL, JHL, CQM, and WC designed the study. YH, JHW, ZHC, ZHF, and YF performed the statistical analyses and interpreted the data. YH, JJC, ZWL, FJZ, and JL are involved in patient recruitment. YH, JHW, and ZHC wrote the manuscript. YH, JJC, ZWL, JHW, and

ZHC contributed equally to this work. All authors agreed with the results and conclusions.

Full name of the Ethics Board: The institutional review board of the First Affiliated Hospital, Sun Yat-sen University (Approval Number: 2019065)

Yong Huang, Junjie Cen, Zhuowei Liu, Jinhuan Wei, and Zhenhua Chen contributed equally.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work has been supported by National Key R&D Program of China (2016YFC0902602) and Guangdong Medical Science and Technology Research Foundation (A2018040).

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