FEBRILE URINARY TRACT INFECTION AFTER RADICAL CYSTECTOMY WITH URINARY DIVERSION: DIFFERENT CHARACTERISTICS IN PATIENTS WITH ILEAL CONDUIT AND ORTHOTOPIC NEOBLADDER

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ABSTRACT

Keywords:

INTRODUCTION

Radical cystectomy with pelvic lymph node dissection followed by the formation of urinary diversion represents a standard of care for muscle invasive bladder cancer.[1,2] The most common diversion types are orthotopic neobladder (ONB) and ileal conduit (IC).[3] However, urinary diversion is associated with many complications, including bowel obstruction, prolonged ileus, urinary tract infections (UTIs), stoma problem, ureteral stricture, metabolic acidosis, electrolyte imbalance, urolithiasis, and renal dysfunction.[4] Improvements in surgical technique and modern perioperative care have diminished perioperative complications rate substantially.

However, febrile UTI occurs frequently in patients who have undergone radical cystectomy.[5–7] In most cases, managements are complicated due to accompanying conditions, thus affecting prognosis of patients.

The objective of this study was to analyze the incidence, timing, risk factors, and microorganisms of febrile UTI in patients with bladder cancer treated by radical cystectomy according to methods of urinary diversion after radical cystectomy.

MATERIALS AND METHODS

This study was approved by the Institutional Review Board of our hospital (Approval No. 06-2014-006). Between January 2009 and January 2018, a total of 184 patients at our hospital underwent radical cystectomy with urinary diversion by a single surgeon (JKN), including 164 patients who had been observed at least 2 years postoperatively.

We excluded patients who didn't undergo a postoperative follow-up of less than 2 years (n = 10), patients who died within 2 years (n = 6), and patients who had undergone another major surgery (n = 4).

These 164 patients were used as subjects of this study. Indications for radical cystectomy included muscle invasive bladder cancer without distant metastasis, recurrent multifocal super cial tumor refractory to repeated transurethral resection, and bacillus Calmette–Guerin resistant carcinoma in situ. Radical cystectomy with urinary diversion was performed using standard technique. ONB was performed as Studer's ONB technique. Patients underwent urinary catheterization with Foley catheter and neobladder irrigation for 2 weeks in general. In the IC surgery, ureters were spatulated and anastomosed independently to the ileal segment. In both surgeries, ureteral stents were inserted for 8 weeks in general.

Preoperative urine culture was obtained from all patients, and if positive, we underwent radical cystectomy with urinary diversion after treatment. In all patients, low residual diet was performed from 2 days before surgery and bowel preparation was performed in the night before surgery. Follow-up was conducted every 3 months during the rst postoperative year and every 6 months thereafter. We performed computed tomography or magnetic resonance imaging to recurrence, laboratory study including urine culture, and a medical examination by interview. Febrile UTI was d ned as a pyuria in the presence of fever (≥38 °C), chills with or without associate ank or abdominal pain.

Febrile UTI observed was prospectively listed and subsequently compared. Baseline

clinicopathological characteristics abstracted included age, sex, weight, height, smoking status, diabetes, stage, grade, Clavien–Dindo classification of surgical complications, length of hospital stays, operative time, estimated blood loss, chemotherapy, and timing of febrile UTI.

Those who were aged ≥65 years were considered as elderly patients. Body mass index was dichotomized as obese (≥25 kg/m^2) versus non-obese (<25 kg/m^2) according to WHO proposed cut points for adult Asians.[8] Pathological stage was based on 2010 American Joint Committee on cancer TNM staging system for bladder cancer.[9] Urinary diversion was classified as two groups: ONB and IC. Incidence of febrile UTI, clinicopathological characteristics, and growth of microorganism were compared between the two diversion method groups. Mann-Whitney U test and Fisher's exact test were used to compare categorical variables.

Estimated probability of febrile UTI was calculated with Kaplan–Meier method, and predictors of febrile UTI were evaluated using univariable and multivariable Cox regression models. Any p-value of less than 0.05 was considered statistically significant. Statistical analyses were performed using SPSS software version 18.0.

RESULTS

A total of 164 patients were eligible for this comparative analysis. The mean age of the patients was 68 years (range, 40–84) with average follow-up in patients who are alive at 62.8 months (range, 24–132). Of these individuals, 52 received ONB diversion, and 112 received IC diversion. A total of 49 (29.9%) patients were diagnosed with febrile UTI. Clinicopathological characteristics of these subjects are summarized in Table 1.

All the patients with Clavien–Dindo classification 3 complication underwent insertion of percutaneous nephrostomy or ureteral stent for UTI. In some cases, temporary anastomosis site stricture caused UTI. In addition, the patients with Clavien–Dindo classification 4 complication underwent intensive care unit care due to severe UTI. All those cases were recovered from the complications, and there were no recurrence UTI in 3 months.

Compared to IC group, ONB group had significantly higher incidence of young age ($p < 0.001$), dominant male patients ($p = 0.019$), lower cancer stage ($p = 0.013$), longer hospital stay ($p = 0.049$), and longer operation time ($p < 0.001$). During the first 3 months after surgery, 26.9% of the patients with ONB and 8% of the patients with IC had a febrile UTI episodes ($p = 0.006$). Figure 1 compares the total percentage of infections at 3 months interval during the first 2 years after surgery for patients with ONB and IC diversion.

We investigated on the basis of first febrile UTI within 3 months. Table 2 reports univariable and multivariable analyses of the predictors of febrile UTI. On univariable analysis, factors associated with significantly increased febrile UTI risk were current smoker ($p = 0.041$), diabetes ($p < 0.001$), and ONB diversion ($p = 0.014$). On multivariable analysis, factors associated with febrile UTI risk were diabetes (odds ratio [OR]: 4.52; 95% confidence interval [CI]: 2.862–5.571; $p = 0.002$) and ONB diversion (OR: 2.563; 95% CI: 1.630–2.948; $p = 0.031$) (Table 2). Forty-four (89.8%) patients were culture positive. However, significant difference in microorganisms was not detected between patients who underwent ONB or IC diversion (Table 3). Table 3 details the common pathogens involved in febrile UTI episodes stratified by diversion type.

Escherichia coli (20%), *Enterococcus faecium* (20%), and *Pseudomonas aeruginosa* (16%) were common causative pathogens in patients with ONB; patients with IC had comparable rates of *Enterococcus faecium* (16%), *E. coli* (16%), *Klebsiella pneumoniae* (16%), *Candida albicans* (11%), and *Staphylococcus aureus* (11%). However, significant differences in microorganisms were not detected among the two groups of patients according to urinary diversion.

TABLE 1 Clinicopathological Characteristics of Patients

		Total cohort (n=164)	ONB (n=52)	IC (n = 112)	*p*-value
Mean age		68 (40, 84)	62.6 (40, 77)	70.0 (40, 84)	<0.001
Sex (Male:Female)		140: 24	50: 2	90: 22	0.019
Mean BMI		22.78	23.66	22.66	0.189
Current smoker	Yes	41	10	31	0.121
	No	123	42	81	
Diabetes	Yes	34	8	26	0.132
	No	130	44	86	
Stage	≤pT1	27	14	13	0.013
	pT2	39	10	29	
	pT3	68	24	44	
	pT4	30	4	26	
	pN+	42	11	31	0.468
Grade	1	1	0	1	0.646
	2	59	17	42	
	3	104	35	69	
≥2 Complication (within 3 months, Clavien–Dindo classi cation)		69	30	39	0.736
	2	51	23	28	
	3	14	6	8	
	4	4	1	3	
Febrile UTI (within 3 months)		24 (14.6%)	14 (26.9%)	10 (8.9%)	0.006
Mean length of admission (day)		17 (9, 55)	20.6 (10, 38)	18.4 (9, 41)	0.049
Mean operative time (hour)		4 (2, 11)	6.17 (3, 11)	4.76 (2, 10)	<0.001
Median estimated blood loss (L)		1.00 (0.1, 3.5)	1.00 (0.1, 3)	0.99 (0.1, 3.5)	0.722

ONB, orthotopic neobladder; IC, ileal conduit; BMI, body mass index; UTI, urinary tract infection.
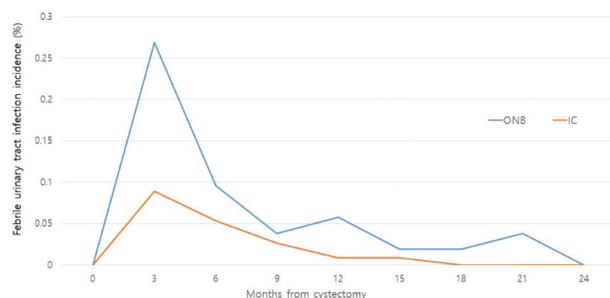

FIG. 1 Rates of febrile urinary tract infection within the rst 3 months after surgery according to diversion type.

DISCUSSION

Febrile UTIs after radical cystectomy include ank pain, nausea, vomiting, high fever, with or without costovertebral angle tenderness.[10] It is a common infectious complication following urinary diversion. In large series of patients undergoing radical cystectomy with urinary diversion, the rate of UTI after radical cystectomy ranges from 8.5 to 39%.[5–7,11–14] Its cumulative incidence during the rst 3 months after surgery is about 10%.[15] However, diagnostic criteria for UTI utilized in these series

TABLE 2 Univariate and Multivariate Analysis of Factors Associated with Febrile Urinary Tract Infection (within 3 Months)

	Univariate analysis			Multivariate analysis		
	Odds ratio	95% CI	*p*-value	Odds ratio	95% CI	*p*-value
Age (<65 years)	0.758	0.382–1.504	0.267	—	—	—
Sex (male)	0.383	0.124–1.185	0.066	—	—	—
Current smoker (yes)	1.892	0.922–3.883	0.041	—	—	—
Diabetes (yes)	5.000	3.584–6.944	<0.001	4.521	2.862–5.571	0.002
Obesity (BMI ≥25)	0.887	0.400–1.969	0.468	—	—	—
pT stage (3/4)	1.256	0.638–2.474	0.314	—	—	—
ONB	2.563	1.781–3.125	0.014	2.273	1.630–2.948	0.031

CI, confidence interval; BMI, body mass index; ONB, orthotopic neobladder.

TABLE 3 Cultured Microorganisms according to Urinary Diversion

		Total (n)	ONB (n)	IC (n)
Culture-documented acute pyelonephritis		44	25	19
Number of microorganisms				
1		33	18	15
≥2		11	7	4
Bacteria (Gram positive)				
	Enterococcus faecium	8	5	3
	Enterococcus faecalis	3	2	1
	Staphylococcus aureus	4	2	2
	Staphylococcus hemolyticus	1	1	
Bacteria (Gram negative)				
	Acinetobacter species	2	1	1
	Klebsiella pneumoniae	3		3
	Enterobacter cloacae	3	2	1
	Escherichia coli	8	5	3
	Pseudomonas aeruginosa	5	4	1
Fungus				
	Candida albicans	4	2	2
	Candida glabrata	1	0	1
	Yeast species	2	1	1

ONB, orthotopic neobladder; IC, ileal conduit.

are different. In fact, several studies have included patients with asymptomatic bacteriuria. Therefore, only febrile UTI was analyzed in this study to reduce selection bias. In our study, 49 (29.9%) patients had febrile UTI, including 24 (14.6%) patients who had it within 3 months after the surgery.

In a nationwide population study on complications following radical cystectomy in Sweden, patients with ONB have higher risk of UTI (OR: 1.21) than those with IC.[16] A single center series of 209 patients following robotic radical cystectomy with urinary diversion has also reported an increased complication risk of UTI among patients undergoing ONB.[6] In this study, risk factors of symptomatic UTI included the receiving of continent urinary diversion (OR: 2.563; 95% CI: 1.630–2.948; *p* = 0.031) and the presence of diabetes (OR: 4.52; 95% CI: 2.862–5.571; *p* = 0.002).

Mechanisms underlying these results are multifactorial. Some studies have examined infections after ONB diversion and suggested the following possible mechanisms.[15,17,18] First, bacteria can colonize the bowel epithelium more easily than the urothelium and then use intestine for urinary diversion, thus increasing UTI. Second, incomplete emptying of the bladder might promote infection. Some studies have shown signi cant correlation

between post-void residual urine volume and UTI. In addition, serial urodynamic examinations in patients with neobladders presented that a significant increase in maximal flow rate and bladder capacity concomitant to a decrease in residual urine volume were documented over a 6-month interval from surgery, possibly contributing to the decrease in UTI events.[19] Third, excessive mucus production by the bowel epithelium accompanied by an established infection can prevent effective clearance of microorganisms. However, after 3–6 months after surgery, atrophic changes in the intestinal mucosa lining the neobladder occur, and consequently, the neobladder is less susceptible to bacterial colonization and infection.[20,21] Finally, prolonged urinary catheterization is related to UTI. For these mechanisms, it can be suggested that UTI rate in patients with ONB decreases overtime especially after 3 months postoperatively.

UTIs in diabetic patients are common. These infections have more complex clinical course.[22,23] Increased prevalence of bacteriuria in diabetic patients might be due to differences in host responses between diabetic and nondiabetic patients or difference in the infectious bacterium itself.[22,23] Host-related mechanisms include the presence of urine glucose, functional change of leukocyte, and increased adhesion to urinary tract epithelium.[22,23] Some studies have reported increase of *Klebsiella* but decrease of *E. coli* in patients with diabetes.[14,24,25] However, recent studies have found no significant difference of bacterial species in diabetic patients,[26,27] while results of other studies are different.[28] Our results showed that the prevalence of symptomatic UTI was increased in diabetic patients. However, such increase was not due to difference in bacterial species.

Regarding identities of microorganisms following radical cystectomy, some studies have demonstrated a predominance of Gram-negative bacteria (65–91%).[23,29–31] In patients with neobladder-related UTIs, the most common implicated microorganism is *E. coli* which is responsible for 59% of monobacterial infections.[23] However, percentages of various bacteria were not the same in our study. Our results showed that Gram-negative bacteria were present in 47.7% of cultures. *Enterococcus* species, *E. coli, Pseudomonas aeruginosa, Candida species, and Enterobacter* species were common pathogens in this study. This could be due to different perioperative antibiotic uses, epidemiologic reasons, and different clinical characteristics of patients who previously received multiple course of antibiotic therapy and surgical procedures such as cystoscopic biopsy and transurethral resection of bladder tumor.

A positive urine culture is a common finding in patients with urinary diversion. However, this does not mean symptomatic infection.[32] In general, treating an asymptomatic bacteriuria is not advocated for these patients. However, controversy exists regarding appropriate treatment of asymptomatic bacteriuria in urinary diversion patients. In a recent study, 78% of patients with ONB have pyuria and nitrates based on urinalysis.[33] In the subset of patients with ONB who had evidence of UTI on urinalysis, 50% of them developed symptomatic infection.[33] Studer et al.[34] have recommended antibiotics for patients with ONB and positive urine culture result. Clearly, UTI with symptoms such as high fever, chilling, nausea, vomiting, and flank pain must be treated quickly with appropriate antibiotics. Moreover, if recurrent symptomatic UTI occurs, evaluation of ureteral obstruction or reflux is necessary using fluoroscopy of the reservoir or conduit to determine whether there is poor emptying of the ONB and identify stricture or obstructed areas.[35] Early diagnosis and prompt drainage are required to prevent consequent renal functional loss with aggravated infectious complications.

This study has some limitations. First, it was an uncontrolled and retrospective study. Among the groups of patients, there were differences in baseline characteristics such as age, sex, and pathologic stage. This might have affected our results. However, in the selection of surgical method, there are several considerations including age, renal function, cancer stage, patient's socioeconomic status, comorbidities, and

preference. In general, younger and healthy patients underwent ONB rather than IC; therefore, there were differences in characteristics between ONB and IC patients. Second, the number of patients in this study was relatively small. However, there were no signi cant differences in culture results among the groups. Therefore, comparative analysis of subgroup and culture proven microorganism is limited. Our results were different from the results of some previous studies.[23,29–31] Finally, we did not analyze preoperative and postoperative changes in voiding and renal function. Ureteral stricture, obstruction, estimated glomerular ltration rate (eGFR), and voiding function are known to be associated with acute pyelonephritis. It was very hard to evaluate eGFR of the total cohort within the follow-up periods, because each patient had different health condition. Therefore, it is needed to determine long-term changes of the parameters in the future.

CONCLUSION

The results of this study revealed that at 3 months after radical cystectomy for bladder cancer, diabetes and ONB diversion signi cantly increased the risk of febrile UTI. However, our study has many limitations, including its retrospective nature, few patients with positive cultures, and different baseline characteristics among groups. Therefore, further research is needed.

CONFLICTS OF INTEREST

The authors declare no con icts of interest.

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