Original Article
Urinary diversion by neobladder reconstruction after radical cystectomy in the elderly: outcomes and survival

Shi-Yu Mao[1*], Da-Bo Xiong[2*], Tian-Bao Huang[3], Ke-Ke Cai[1], Liang Xu[1], Jun-Hua Zheng[1], Ding-Wei Ye[4], Xu-Dong Yao[1]

[1]Department of Urology, Shanghai Tenth People's Hospital, Tongji University, Shanghai 200072, P. R. China; [2]Anhui Medical University, Hefei 230032, P. R. China; [3]Department of Urology, Northern Jiangsu People's Hospital, Yangzhou University, Yangzhou 225001, Jiangsu, P. R. China; [4]Department of Urology, Cancer Hospital, Fudan University, Shanghai 200032, P. R. China. *Equal contributors.

Abstract: This 2-center retrospective study compared the outcomes after open radical cystectomy of older patients who underwent urinary diversion (UD) by orthotopic ileal neobladder reconstruction (Studer technique) or ileal conduit (Bricker). Between April 2005 and August 2013, 216 suitable consecutive patients aged ≥65 years underwent UD after cystectomy, either by ileal conduit using the Bricker method, or orthotopic ileal neobladder reconstruction in accordance with the Studer technique. Rates of the following were noted: transfusions; complications; 30-day mortality; urethral recurrence; overall and cancer-specific survival; and for the Studer group, continence. The mean age of the study population was 72 (range, 65-83) years. Thirty-one patients (14%) underwent the Studer procedure, 185 (86%) received the Bricker. The rates of early complications were 41.9% and 49.2% in the Studer and Bricker groups, respectively (*P*=0.454); late complications were 54.8% and 40.4% (*P*=0.135); and 30-day mortality was 0% and 3.8% (*P*=0.597). The median follow-up was 48 months. The 2-y and 5-y overall survival rates were 80.6% and 60.5% in the Studer group, and 55.1% and 31.8% in the Bricker group. The 2- and 5-y cancer-specific survivals were 89.7% and 78.6% in the Studer group; 76.3% and 61.8% in the Bricker group. After the neobladder reconstructions, the daytime continence rate was 97%, nocturnal was 67%. Therefore, the complications and oncological outcomes of older patients given UD by orthotopic ileal neobladder reconstruction in accordance with Studer are similar relative to that of patients given an ileal conduit by the Bricker method. The complete continence rates for the elders by neobladder are satisfactory. With careful patient selection, it is appropriate to perform an orthotopic neobladder for elderly patients after cystectomy.

Keywords: Cystectomy, elderly, functional outcome, orthotopic neobladder, survival

Introduction

Increasing age is an independent risk factor for many health problems, including cancer. This is especially true for bladder cancer-patients 65 years and older account for 71.4% of new bladder cancer diagnoses [1]. This is likely due to their accumulated exposure to carcinogens (especially, tobacco smoke) and cellular and genetic alterations [2].

The gold standard treatment for muscle-invasive bladder cancer is radical cystectomy (RC) with urinary diversion (UD). The Studer orthotopic neobladder form of UD was first introduced in the early 1980s, and improvements in surgical technique and perioperative management have made it often preferred by both surgeons and patients, particularly in high-volume centers [3]. However, in elderly patients UD is more commonly implemented with an ileal conduit, which is a simple and shorter procedure [4].

Age has been positively associated with both incidence of bladder cancer, and poorer cancer-specific survival after RC [5, 6]. The elderly also have more serious comorbidities such as low serum albumin concentration and anemia, which positively correlate with complications of RC. There is concern that elderly patients with a complex neobladder are subject to higher morbidity and mortality rates associated with RC.

However, there are studies indicating that RC with a neobladder is feasible in elderly patients, with acceptable morbidity and mortality [7, 8],

and neobladders account for 30% of UDs [9]. Yet, studies are scarce that have compared the outcomes and survival of elderly populations stratified by UD type, and performing an orthotopic neobladder in these patients remains controversial.

In the present retrospective study, we compared the transfusion rates, early and late complication rates, functional results, and cancer control of elderly patients who underwent UD either by ileal conduit or orthotopic ileal neobladder reconstruction.

Material and methods

Between April 2005 and August 2013, 233 consecutive patients (age ≥65 y) with primary transitional cell carcinoma of the bladder received an RC with an ileal conduit, or an orthotopic bladder substitution, at 2 medical institutions. Seventeen patients with incomplete follow-up data were excluded. The remaining 216 patients (mean age 72 y, range 65-84 y) with complete available perioperative and follow-up information were included in this study.

Tumors were staged according to the 2002 tumor-node-metastasis classification of the International Union Against Cancer. RC was performed conventionally. After the RC, either of 2 types of UDs were constructed in the standard fashion: The ileal conduit was installed in accordance with the method of Bricker (Bricker group), and the orthotopic neobladder as in Studer et al [10] (Studer group).

The orthotopic neobladder was primarily offered to patients with no tumor in the prostatic urethra. Patients who were not able to understand the selection or were without motivation were advised to select the ileal conduit. The final decision regarding the type of diversion was the patient's, after consultation with the urologist and gastroenterologists.

Follow-up data were collected until death of the patient or July 2015. Patients were scheduled for follow-up at 3-month intervals for the first year, semiannually the next 2 years, and thereafter annually, or more frequently when indicated. The follow-up consisted of physical examination, blood tests, urine culture, cytological examination of urine, radiographic evaluation by pelvic-abdominal CT scan, bone scans if indicated clinically, ultrasound and chest X-ray, and cystoscopy in patients with an orthotopic neobladder. All the patients had ≥2 years of follow-up.

Morbidity and 30-day mortality rates were determined with detailed in-hospital and outpatient clinical records. Complications were defined as early, if they occurred in-hospital or within 30 days after RC, and late thereafter. The oncological outcomes evaluated were: urethral recurrence, overall survival (OS), and cancer-specific survival (CSS). All patients with urethral recurrence were assessed with cystoscopy and cytological examination of urine, and ultimately with a pathologic biopsy-confirmed tissue diagnosis. OS was estimated as the time from RC to date of death from any cause. CSS was estimated as time from RC to date of death from progressive bladder cancer; patients dying without recurrence were classified as censored observations at the time of death for CSS. Patients who were alive at the time of the last follow-up for OS and CSS were censored.

For the functional results of continent diversions, daytime and nighttime continence were compared. Complete continence was defined as no involuntarily leakage of urine and no pad use, satisfactory continence as rare leakage with one pad or less per day/night, and poor continence as leakage requiring multiple pads per day/night.

Survival probabilities were calculated using the Kaplan-Meier method, with the log-rank test evaluating significance. Fisher's exact test, the *t*-test, or Pearson's chi-squared test were applied to assess differences between groups. Multivariate logistic regression analyses were performed to assess the association between clinical and pathologic variables and the risks for OS, and CSS. *P*-values lower than 0.05 were considered statistically significant. All *P*-values were two-sided. All analyses were performed using SPSS software version 19 (SPSS, Chicago IL).

Results

Patient characteristics

Analyzed in this study were 163 men and 53 women patients who underwent RC (**Table 1**). Of these patients, 185 received an ileal conduit (Bricker group), and 31 received a neobladder (Studer group). The women patients were less likely to undergo an orthotopic neobladder UD than the men (*P*=0.006). Patients in the Studer

Table 1. Patient characteristics according to type of UD

Variable	Total	Bricker		Studer		x^2	P
		n	(%)	n	(%)		
Gender							
Male	163	133	72	30	97	7.585	0.006[a]
Female	53	52	28	1	3		
Age, yr							
Median (range)		73	(65-83)	68	(65-74)	9.177	0.000[b]
Tumor stage							
<T1	35	33	18	2	6	3.650	0.161[a]
T1-2	88	72	39	16	52		
T3-4	93	80	43	13	42		
Nodal status							
Positive	62	54	29	8	26	0.148	0.700[a]
Negative	154	131	71	23	74		
Neoadjuvant chemotherapy							
No	204	174	94	30	97	0.035	0.851[a]
Yes	12	11	6	1	3		
Previous radiotherapy							
No	202	172	93	30	97	0.161	0.688[a]
Yes	14	13	7	1	3		
Intraoperative blood transfusion							
No	119	98	53	21	68	2.341	0.126[a]
Yes	97	87	47	10	32		
Total	216	185	86	31	14		

UD: urinary diversion; [a]Person's chi-squared test; [b]t-test.

Table 2. Early complications according to type of UD

Complication	Bricker		Studer		x^2	P
	n	(%)	n	(%)		
Pneumonia	24	13.0	2	6.5	0.539	0.463
Wound dehiscence	9	4.9	1	3.2	0.000	1.000
Sepsis	20	10.8	3	9.7	0.000	1.000
Pulmonary embolus	6	3.2	1	3.2	0.000	1.000
Bleeding	5	2.7	–		–	1.000
Small bowel obstruction	13	7.0	–		–	0.223
Ureteroileal leakage	2	1.1	–		–	1.000
Intestinal suture leakage	1	0.5	–		–	1.000
Death	7	3.8	–		–	0.597
Others	39	21.1	9	29.0	0.971	0.324
Total	91	49.2	13	41.9	0.560	0.454

UD: urinary diversion.

Early complications

Within the first 30 days, 104 patients experienced one or more complications, resulting in an early complication rate of 48% (**Table 2**). There were no significant differences in early complication rates between the Bricker (49.2%) and Studer (41.9%) groups (P=0.454). None of the patients in the Studer group died within the first 30 days (0/31 patients), but 4% (7/185) in the Bricker group died. This was not a significant difference in 30-day mortality (P=0.597, relative risk 1.174, 95% CI: 1.110-1.243).

Late complications

Late complications occurred in 89 patients (42.6%; **Table 3**). Patients in the Bricker group had a lower risk of developing late complications compared with those in the Studer group, but the difference was not significant (40.4% and 54.8%, respectively; P=0.135). The most

group were significantly younger (mean, 68 y) than those in the Bricker group (mean 73 y; t-test: P<0.001). The 2 groups were statistically similar with regard to receiving an intraoperative blood transfusion (Bricker, 32%; Studer, 47%; P=0.126).

Table 3. Later complications according to type of UD

Complication	Bricker		Studer		x^2	P
	n	(%)	n	(%)		
Hydronephrosis	—		1	3.2	—	0.148
Fistula	6	3.4	1	3.2	0.000	1.000
Ureteroileal stenosis	19	10.7	2	6.4	0.113	0.736
Urethral stricture	—		2	6.4	—	0.021
Urolithiasis	—		2	6.4	—	0.021
Herniation	7	3.9	4	12.9	2.877	0.090
Stoma stenosis	5	2.8	—		—	1.000
Urinary tract infection	39	21.9	12	38.7	4.575	0.032
Others	7	3.9	2	6.5	0.041	0.840
Total	72	40.4	17	54.8	2.778	0.096

UD: urinary diversion.

common complication in both groups was urinary tract infection.

Functional results

Continence was investigated in 30 patients in the Studer group at 6 months (there was one death at 5 months). Daytime continence was complete in 28 of the 30 (93%) patients (dry); satisfactory (<1 pad/day) in 1 of the 30 patients (3%); and unsatisfactory (≥1 pad/day) in 1 of the 30 patients (3%). Nighttime continence was complete in 16 of the 30 patients (53%); satisfactory in 4 of the 30 patients (13%); and unsatisfactory in 10 of the 30 patients (33%). One woman experienced day and night incontinence. The daytime continence rate was 97% (30 patients) and the nocturnal continence rate was 67%. Of the 30 patients, only one woman used intermittent self-catheterization.

Urethral recurrence, OS and CSS

The mean follow-up was 48 months (range, 1-118 months) (original data in Supplementary Table). Urethral recurrence occurred in none of the patients in the Studer group, but did occur in 12 (6.7%) of the patients in the Bricker group (*P*=0.221). In multivariate models adjusted for the effects of clinical grade and stage, urethral recurrence was not associated with OS or CSS (test for trend: P=0.674 and 0.654, respectively) (**Table 4**).

Patients had a mean estimated OS of 84 months (95% CI: 67-101) in the Studer group, and 43 months (95% CI: 38-49) in the Bricker group (*P*<0.001; **Figure 1A**). The actuarial OS at 2 and 5 years after RC in the Studer group

(80.6% and 60.5%, respectively) was significantly higher than that of the Bricker group (55.1% and 31.8%). Through the multivariate Cox regression analyses, we found that age, which was analyzed as a continuous variable, was associated with 5-yall-cause death (hazard ratio: 1.289, 95% CI: 1.210-1.373; *P*<0.001). In addition, pathologic nodal involvement (pN+; HR, 1.873; 95% CI, 1.239-2.832; *P*=0.003), pathologic tumor (pT) stage ≥2 (HR, 1.758; 95% CI, 1.506-2.053; *P*<0.001), and intraoperative blood transfusion (HR: 1.762; 95% CI, 1.157-2.684; *P*=0.008) were significantly associated with the risk of 5-yall-cause mortality, but we found no relationship between UD with all-cause mortality (*P*=0.727). None of the other factors was associated with OS.

The mean estimated CSS of patients in the Studer group (99 mo, 95% CI: 85-114 mo) was significantly longer than that of the Bricker group (77 mo, 95% CI: 69-85 mo, *P*=0.033; **Figure 1B**). The 2- and 5-y CSS in patients in the Studer group was 89.7% and 78.6%, respectively, and 76.3% and 61.8% in the Bricker group. Using multivariate Cox regression analyses for 5-y CSS, we found that age, when analyzed as a continuous variable, was associated with 5-y CSS (hazard ratio: 1.356, 95% CI: 1.224-1.502; *P*<0.001). In addition, pN+ (HR, 3.635; 95% CI, 1.999-6.613; *P*<0.001), pT stage ≥2 (HR, 1.686; 95% CI, 1.331-2.136; *P*<0.001), and intraoperative blood transfusion (HR: 1.996; 95% CI, 1.023-3.894; *P*=0.043) were significantly associated with the risk of cancer-specific mortality, but we found no relationship between UD with cancer-specific mortality (*P*=0.146). None of the other factors was associated with 5-yCSS.

Discussion

In this study we retrospectively evaluated the outcomes of 216 patients aged ≥65 years who underwent UD after open RC. The UD procedures involved either orthotopic ileal neobladder reconstruction (Studer group) or ileal conduit (Bricker group). The 2 groups were comparable with regard to rates of early complications, late complications, and operative mortality. The results support that RC and orthotopic neobladder reconstruction is a viable alternative for appropriately selected elderly patients.

Table 4. Multivariate analysis of clinicopathological factors associated with OS and CSS

Variable	OS		CSS	
	HR (95% CI)	P	HR (95% CI)	P
Grade				
Female	Reference	0.000	Reference	0.013
Male	0.363 (0.237-0.556)		0.406 (0.199-0.830)	
Age (years)	1.289 (1.210-1.373)	0.000	1.356 (1.224-1.502)	0.000
Tumor stage	1.758 (1.506-2.053)	0.000	1.686 (1.331-2.136)	0.000
Nodal status				
Negative	Reference	0.003	Reference	0.000
Positive	1.873 (1.239-2.832)		3.635 (1.999-6.613)	
Neoadjuvant chemotherapy				
No	Reference	0.233	Reference	0.415
Yes	1.536 (0.759-3.108)		1.505 (0.563-4.022)	
Previous radiotherapy				
No	Reference	0.603	Reference	0.889
Yes	1.210 (0.589-2.485)		1.078 (0.379-3.063)	
Intraoperative blood transfusion				
No	Reference	0.008	Reference	0.043
Yes	1.762 (1.157-2.684)		1.996 (1.023-3.894)	
Urethral recurrence				
No	Reference	0.674	Reference	0.654
Yes	0.863 (0.434-1.714)		1.221 (0.509-2.930)	
Type of diversion				
Bricker	Reference	0.727	Reference	0.146
Studer	1.134 (0.559-2.303)		2.198 (0.761-6.347)	

OS: overall survival; CSS: cancer-specific survival. Abbreviations: RC: radical cystectomy; OS: overall survival; CSS: cancer-specific survival; UD: urinary diversion.
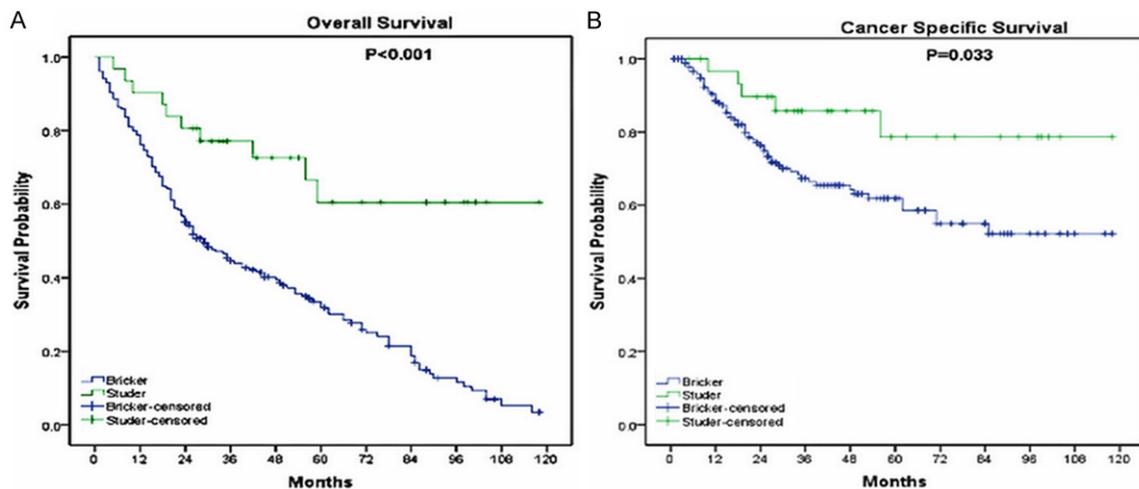

Figure 1. Kaplan-Meier calculations of (A) OS and (B) CSS probabilities in patients of the Bricker (ileal conduit) and Studer (orthotopic neobladder) groups after cystectomy for bladder transitional cell carcinoma.

The early and late complication rates of patients in the current study were in the upper range of those that have been previously reported; early complication rates have ranged

widely from 16% to 61% and late complication rates from 24% to 66% [11]. Several studies with large populations found an association between age and perioperative complications after RC [4]. However, in our study there was no difference in complication rates between the 2 groups, although the patients in the Studer group had a slightly higher perioperative complication rate compared with that of the Bricker group. This is consistent with the observations of Sogni et al [8], in which there was a non-significant trend towards higher perioperative complications in elderly patients who received the orthotopic neobladder compared with those given the ileal conduit, after radical cystectomy for invasive bladder cancer.

Three studies have suggested an association between age at RC and transfusion rates [12, 13]. Compared with younger and healthier patients, elderly patients with concomitant cardiovascular morbidity were more likely to require transfusion during surgery. The more frequent use of anticoagulants in the elderly may be another explanation. In the present study, we found no significant differences between the Bricker and Studer groups in rates of intraoperative blood transfusion during RC. Recent studies have suggested that intraoperative blood transfusion during RC is significantly associated with an increased risk in complications, disease recurrence, overall mortality, and cancer-specific mortality [14]. Blood transfusion is known to have negative effects on the immune system, most likely by increasing the probability of entry of tumor cells into the circulatory system during surgery.

The 30-day mortality of the Studer group was lower than that of the Bricker group, although the difference was not significant. This is probably because the patients were appropriately selected for the procedure, and the imbalance in population size of the 2 groups. This is in accord with a study by Clark et al [7] of 364 patients (≥70 y), in which there was no difference in operative mortality within 30 days of surgery between groups given either ileal neobladder or ileal conduit.

In the present study, the frequency of urethral recurrence was higher in the Bricker group than the Studer, although this did not reach a level of statistical significance. Urethral recurrence has often been associated with higher-stage dis-

ease and worse prognosis [15]. In a recent series of 85 patients with urethral recurrence, Stephen et al [16] suggested that the risk of urethral recurrence was significantly influenced by UD type. Other than careful patient selection, it may be that patients given a neobladder experience a lower urethral recurrence rate because of a urine anticarcinogenic effect on the urothelium [17].

There is some controversy concerning the benefit of RC for elderly patients. Multiple studies have indicated that RC has survival benefits for elderly patients [18-20], but according to others elderly patients have worse outcomes compared with younger patients [5, 21-23]. In the present study, our data showed that the type of UD significantly influenced the risk of OS and CSS, most likely because of our careful patient selection. This conclusion was supported by a lack of association found in the multivariable analysis, after adjusting for clinical and pathological variables. This is consistent with the report of Sogni et al [8] for a study population of 85 patients (≥75 y), in which no difference in OS was determined between those given either an orthotopic neobladder or an ileal conduit after RC.

Reports are scarce regarding functional results after orthotopic neobladder substitution in elderly patients [9]. However, a study by Kessler et al [24] found that age was inversely associated with continence recovery after orthotopic neobladder substitution. In the present series, it was mainly women who experienced incontinence; day continence and night continence in men was 97% and 66%, respectively. We found that satisfactory continence rates can be reached in elderly patients undergoing RC and neobladder, and similar to the rates achieved with younger patients [25]. Again, appropriate patient selection in the elderly is responsible for good functional results, as reflected in our present study. However, we have to interpret these results with caution owing to the low number of patients and only one woman patient in Studer group. Women were gradually considered for an orthotopic neobladder after Stein reported safe and favorable outcome in the 1990s, as reported by Hugen and Daneshmand [3]. Unfortunately, there is little information concerning the continence of elderly women patients after orthotopic neobladder.

Our analysis indicates that UD by neobladder after RC may be safe in the elderly. However, these conclusions have to be interpreted with caution because of the methodological limitations inherent in retrospective studies.

In conclusion, in carefully selected patients, the complications and oncological outcomes of patients given UD by orthotopic neobladder can be similar compared with patients who receive ileal conduit after RC. The orthotopic diversion for elderly patients not only provides satisfactory continence results, but also greater preservation of the patient's body image. Therefore, elderly patients should be considered for neobladder, when appropriate.

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Disclosure of conflict of interest

None.

Address correspondence to: Xu-Dong Yao, Department of Urology, Shanghai Tenth People's Hospital, Tongji University, Shanghai 200072, P. R. China. Tel: +8613817811836; Fax: +86-21-66305158; E-mail: yaoxudong078@sina.com

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