SCANDINAVIAN JOURNAL OF UROLOGY
2021, VOL. 55, NO. 5, 361–365
https://doi.org/10.1080/21681805.2021.1955967

ARTICLE

Cumulative incidence of ureteroenteric strictures after radical cystectomy in a population-based Swedish cohort

Jenny Magnusson[a], Oskar Hagberg[b], Firas Aljabery[c], Abolfazl Hosseini[d], Staffan Jahnson[c], Tomas Jerlström[e], Amir Sherif[f], Karin Söderkvist[g], Viveka Ströck[a,h], Anders Ullén[i], Christel Häggström[j,k], Lars Holmberg[j,l] and Henrik Kjölhede[a,h]

[a]Department of Urology, Sahlgrenska University Hospital, Gothenburg, Sweden; [b]Department of Translational Medicine, Lund University, Malmö, Sweden; [c]Division of Urology, Department of Clinical and Experimental Medicine, Linköping University, Linköping, Sweden; [d]Department of Molecular Medicine and Surgery, Karolinska Institutet and Department of Pelvic Surgery, Karolinska University Hospital, Stockholm, Sweden; [e]Department of Urology, School of Medical Sciences, Faculty of Medicine and Health, Örebro University, Örebro, Sweden; [f]Department of Surgical and Perioperative Sciences, Urology and Andrology, Umeå University, Umeå, Sweden; [g]Department of Radiation Sciences, Oncology, Umeå University, Umeå, Sweden; [h]Department of Urology, Institute of Clinical Science, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden; [i]Genitourinary Oncology and Urology Unit, Department of Oncology-Pathology, Karolinska Institutet, and Department of Pelvic Cancer, Karolinska University Hospital, Stockholm, Sweden; [j]Department of Surgical Sciences, Uppsala University, Uppsala, Sweden; [k]Northern Register Centre, Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden; [l]Translational Oncology and Urology Research (TOUR), School of Cancer and Pharmaceutical Sciences, King's College London, London, UK

ABSTRACT

Objective: The incidence of benign ureteroenteric strictures following radical cystectomy (RC) for urinary bladder cancer (UBC) is investigated mainly in single-centre studies from high-volume centres. The aim of this study was to evaluate the cumulative incidence of strictures and risk factors in a population-based cohort.

Patients and methods: Data was collected from Bladder Cancer Data Base Sweden (BladderBaSe). The primary endpoint was stricture with intervention. Secondary endpoint included hydronephrosis both with/without intervention.

Results: In total, 5,816 patients were registered as having had RC due to UBC between 1997 and 2014. After a median follow-up of 23.5 months (IQR = 9.0–63.1 months; range = 0.0–214.0 months), we found that 515 (8.9%) patients underwent intervention for stricture. Seven hundred and sixty-one (13.1%) patients were diagnosed with hydronephrosis without intervention. The cumulative incidence of strictures with intervention was 19.7% (95% CI = 16.7–23.1%) during the 17 years of follow-up. In the first year, the cumulative incidence of strictures was 5.6% (95% CI = 5.0–6.2%), and in the first 2 years 8.4% (95% CI = 7.6–9.3%). For the secondary endpoint, the cumulative incidence was 30.4% (95% CI = 26.7–33.1%) after 17 years. Only the year of RC was associated with stricture incidence in Cox regression analysis, whereas hospital cystectomy volume, patient age and patient sex were not.

Conclusion: Ureteroenteric strictures requiring intervention may be more common than previously reported, affecting nearly one fifth of patients who have undergone RC for UBC. The annual incidence was highest in the first 2 years after surgery but the cumulative incidence increased continuously during 17 years of follow-up.

ARTICLE HISTORY
Received 21 April 2021
Revised 7 June 2021
Accepted 12 July 2021

KEYWORDS
bladder cancer; ureteric stricture; population-based; radical cystectomy; complications

Introduction

Radical cystectomy performed due to urinary bladder cancer is associated with a high risk of complications. In most reports the risk of any complication is >50%, depending on the criteria and follow-up used. Most complications occur during the first 90 days after surgery, but there are late complications as well. Benign ureteroenteric stricture is a common late complication which occurs in 5–34% of patients [1–5] at a median time of 7–13 months postoperatively [6,7]. However, the true incidence of strictures may have been underestimated since previous reports mostly are single-centre studies from high-volume centres. Previous studies showed no difference or increases in the incidence of benign ureteroenteric strictures when robot-assisted radical cystectomy (RARC) with extracorporeal urinary diversion (ECUD) was compared to open radical cystectomy (ORC), but it is possible that the increasing use of RARC with intracorporeal urinary diversion (ICUD) has led to a decreased incidence of strictures [3,8]. Moreover, the reports so far are limited by a relatively short follow-up time and cannot capture a possible long-term rise in cumulative incidence.

CONTACT Jenny Magnusson jenny.m.magnusson@vgregion.se Department of Urology, Sahlgrenska University Hospital, Bruna Stråket 11B, Gothenburg 413 45, Sweden

Supplemental data for this article can be accessed here.

Bladder Cancer Data Base Sweden (BladderBaSe) is a population-based nation-wide database created in 2014 which links data from the Swedish National Register of Urinary Bladder Cancer (SNRUBC), started in 1997, to several healthcare and demographic registers, amongst these the National Patient Register which holds data on all diagnoses and medical and surgical procedures performed for all patients in Sweden [9].

We investigated the long-term cumulative incidence of ureteroenteric strictures in a cohort based on data in BladderBaSe. The hypothesis was that the cumulative incidence in this large population-based cohort would be higher than reported in single-centre studies from high-volume centres.

Patients and methods

BladderBaSe

Data was collected from BladderBaSe. All new cases of bladder cancer in Sweden among patients 18 years or older are requested to be reported in SNRUBC, which was started in 1997 and has a validated national coverage of 97% for the period 1997 to 2014 [9]. It provides information on tumour location, size, TNM classification, grade, and primary treatment. Since 2011, SNRUBC also includes more detailed information about radical cystectomy [10] including mode of surgery, neoadjuvant chemotherapy and stage of the cystectomy specimen (pT). BladderBaSe link data from the SNRUBC with data from, amongst others, the Patient Register. The Patient Register includes procedure codes, coded according to the Classification of Healthcare Procedures (KVÅ), which is a national classification of procedures defined by the Swedish Board of Health and Welfare, and diagnosis codes, coded according to the International Classification of Diseases (ICD) 9th edition or ICD-10, and date of the procedure/diagnosis for all patients in Sweden.

BladderBaSe was approved by the Research Ethics Board in Uppsala (permit no. 2015/277) for studying, *inter alia,* the effects of treatment of urinary bladder cancer.

Study population and endpoints

The study population was defined as all patients with a registered procedure code for cystectomy (KCC*) or pelvic exenteration (LCE*) for urinary bladder cancer in the Patient Register between 1997 and 2014.

To evaluate the cumulative incidence of benign ureteroenteric strictures we used a composite endpoint, defined as intervention against obstruction of the upper urinary tract, excluding events with a code indicating other causes than benign ureteroenteric strictures. Specifically, events were defined as procedure codes TKA10 (placement of percutaneous nephrostomy tube), KBV02 (placement of ureteral stent), KBH40, 45, 62, 96, 97 or 98 (reconstruction or dilatation of the ureter), KAC00 (nephrectomy), KAC01 (percutaneous endoscopic nephrectomy), KAC20 (nephroureterectomy) or KAC21 (percutaneous endoscopic nephroureteretomy), but not in combination with ICD codes N20 (urolithiasis), C65 (malignant neoplasm of renal pelvis), C66 (malignant neoplasm of ureter) or C64 (malignant neoplasm of kidney, except renal pelvis). Patients with such a code indicating other causes were censored at the time of that diagnosis or procedure, thus contributing healthy non-event years up to that time to avoid overestimating the incidence of ureteroenteric strictures. An event was defined as the first time a patient fulfilled the criteria described above, which implies that each patient could only have an event once. Some patients got an intervention in the immediate post-operative period, which was likely due to other complications than ureterenteric strictures. Therefore, any intervention in the first 30 postoperative days was ignored.

To account for the possible cases of the normal radiological finding of hydronephrosis post-cystectomy and stricture that did not lead to an intervention, e.g. due to co-morbidity or age, we also created a secondary definition of the endpoint where, in addition to the above definition of hydronephrosis with intervention, we included hydronephrosis (ICD code N13) both with and without any intervention.

Statistical analysis

Statistical calculations were performed with IBM SPSS Statistics for Windows, Version 24.0 (IBM Corp., Armonk, NY). Kaplan-Meier analysis was used to calculate the cumulative incidence of strictures. Confidence intervals (CI) for the cumulative incidences were calculated according to Hosmer and Lemeshow [11] . Start of follow-up in these analyses was date of cystectomy, and end of follow-up was date of stricture, date of death, date of censoring as described above, or December 31, 2014, whichever occurred first. Time in months from date of cystectomy was used as time scale in the calculations. To test for possible confounders that could affect the risk of strictures and explain any differences in cumulative incidence, Cox regression and Kaplan-Meier analyses were performed. Hospital cystectomy volume, patient age, patient sex, and year of cystectomy were included in the Cox model. Descriptive statistics were used with median value, interquartile range (IQR), and range.

Results

In total, 5,816 patients in BladderBaSe were registered as having had a cystectomy or pelvic exenteration due to urinary bladder cancer. Three patients were excluded because they lacked follow-up time, leaving 5,813 for analysis. The clinical characteristics of the study cohort are detailed in Table 1.

For the entire cohort, the median follow-up time was 23.5 months (IQR = 9.0–63.1 months; range = 0–214.0 months). The median follow-up time among those without stricture was 26.1 months (IQR = 9.9–66.9 months; range = 0–214.0 months). Overall mortality during the follow-up period was 46.1%.

The number of patients with an event suggesting stricture with intervention was 515 (8.9%). For the secondary

Table 1. Descriptive statistics of the clinical characteristics of all patients who had a cystectomy done in Sweden in 1997–2014.

n	5,813
Age, years, median (IQR)	68 (62–74)
Sex, *n* (%)	
Male	4,416 (76.0)
Female	1,397 (24.0)
Stage at diagnosis, *n* (%)	
cT	
Tis	155 (2.7)
Ta	543 (9.3)
T1	1,278 (22.0)
T2	2,639 (45.4)
T3	727 (12.5)
T4	296 (5.1)
Missing	175 (3.0)
cN	
N0	2,996 (51.5)
N+	472 (8.1)
NX	2,236 (38.5)
Missing	109 (1.9)
cM	
M0	3,414 (58.7)
M1	117 (2.0)
MX	2,150 (37.0)
Missing	132 (2.3)
Type of diversion, *n* (%)	
Ileal conduit	4,322 (74.4)
Neo-bladder	868 (14.9)
Continent cutaneous reservoir	429 (7.4)
Missing	194 (3.3)
Mode of surgery,[a] *n* (%)	
Open surgery	1,162 (20.0)
Robot-assisted	290 (5.0)
Missing	4,361 (75.0)
Neo-adjuvant chemotherapy,[a] *n* (%)	
Yes	591 (10.2)
No	1,263 (21.7)
Missing	3,963 (68.2)
Stage cystectomy specimen,[a] *n* (%)	
pT0	278 (4.8)
pTis	132 (2.3)
pTa	54 (0.9)
pT1	130 (2.2)
pT2	290 (5.0)
pT3	375 (6.5)
pT4	183 (3.1)
Missing	4,371 (75.2)
Hospital cystectomy volume preceding year, *n* (%)	
<10	1,678 (28.9)
10–24	2,256 (38.8)
25–86	1,831 (31.5)
Missing	48 (0.8)
Time from diagnosis to cystectomy, *n* (%)	
0–6 months	4,304 (74.0)
6–12 months	477 (8.2)
>12 months	960 (16.5)
Missing	72 (1.2)
Year of cystectomy, *n* (%)	
1997–2002	1,228 (21.1)
2003–2008	2,040 (35.1)
2009–2014	2,548 (43.8)

[a]Data from the Cystectomy Register, only available from 2011.

definition, 761 (13.1%) patients were registered with codes suggesting stricture with or without intervention.

The most common procedure leading to an event was placement of percutaneous nephrostomy tube in 431 (83.7%) patients and placement of ureteral stent in 48 (9.3%) patients. Of the patients undergoing placement of percutaneous nephrostomy tube or ureteral stent, 34 patients later underwent nephrectomy or nephroureterectomy and 62 underwent secondary surgery of the ureter, most commonly endoluminal dilatation ($n = 46$). In the first 30 postoperative days, 76 patients received a nephrostomy tube, 47 of which later fulfilled the primary endpoint definition. The most common cause of censoring in patients with an intervention was urolithiasis in 46 patients followed by malignant neoplasm of the renal pelvis, ureter or kidney in 36 patients. The details are listed in Table 2.

Table 2. Procedures and diagnoses that caused an event or censoring during follow-up of the 5,813 patients included in the study.

Cause	*n*	%
Event		
Percutaneous nephrostomy tube	431	7.4
Ureteral stent	48	0.8
Nephrectomy	18	0.3
Reconstruction or dilatation of the ureter	18	0.3
Censoring		
Urolithiasis	135	2.3
Malignant neoplasm of ureter/kidney	135	2.3
Death	2,679	46.1
End of study	2,349	40.4
Total	5,813	100

In the Kaplan Meier analysis, the 17 years' cumulative incidence of strictures with intervention was 19.7% (95% CI = 16.7–23.1%) (Figure 1). The median time to a stricture event was 10.7 months (IQR = 5.1–24.6 months; range = 1.0–178.1 months). During the first and second years after surgery, the cumulative incidence of strictures was 5.6% (95% CI = 5.0–6.2%) and 8.4% (95% CI = 7.6–9.3%), respectively.

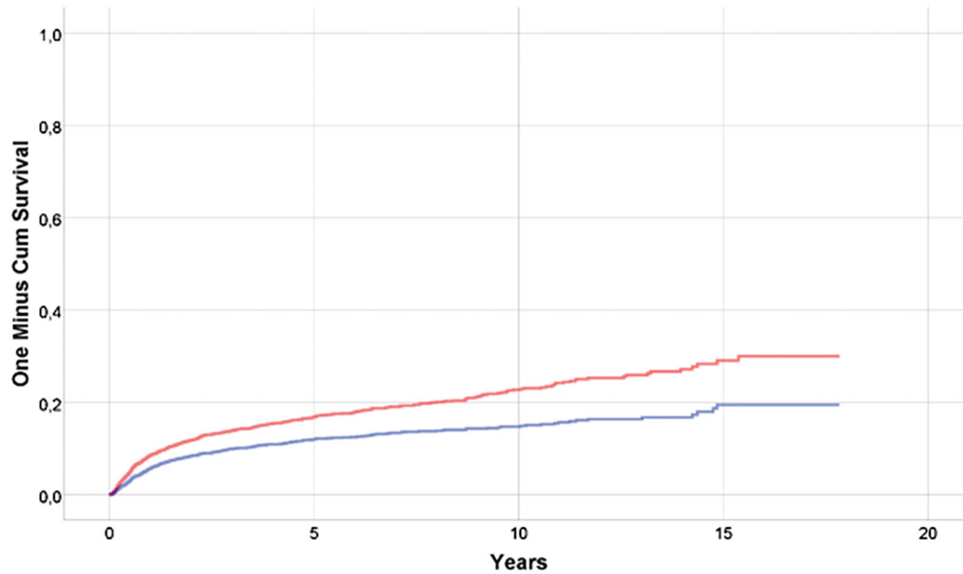
For the secondary definition, stricture with or without intervention, the 17 years' cumulative incidence was 30.4% (95% CI = 26.7–33.1%). The median time to event was 10.1 months (IQR = 4.5–26.8 months; range = 1.0–184.4 months).

Kaplan-Meier diagrams and Cox regression analysis of potential factors affecting the cumulative incidence are shown in Supplementary Tables S1 and S2 and Figure S1. Cox regression analysis on stricture with intervention did not show any differences in stricture incidence in high vs low volume centres, when adjusting for year of cystectomy, patient age and gender. Only year of cystectomy was associated with an increasing stricture incidence with a higher risk of stricture when surgery was performed late in the study period.

Discussion

In this Swedish population-based cohort of 5,813 patients treated with cystectomy for urinary bladder cancer, the 17 years' cumulative incidence of strictures with intervention was 19.7%, which is higher than previously reported in single-centre studies from high-volume centres, with shorter follow-up. Most strictures occurred during the first 2 post-operative years, but thereafter we found a continued increase in cumulative incidence during the entire follow-up period.

The results in the present study imply that the cumulative incidence is higher than what has been previously reported [1–5]. Similarly, in a multi-centre population-based study, a total incidence of ureteroenteric strictures 2 years postoperatively was found to be 14.6% vs 11.4% for RARC with ECUD vs ORC [5]. In comparison, the 2-year cumulative stricture rate in the present study was 8.4%, with the difference possibly due to different definitions of strictures. For example, in



No. at risk	0 yrs	5 yrs	10 yrs	15 yrs
Secondary	5813	1477	486	91
Primary	5813	1530	515	96

Figure 1. Cumulative incidence of strictures. Strictures requiring intervention (primary endpoint) in blue and strictures including hydronephrosis both with and without intervention (secondary endpoint) in red. The annual incidence is highest in the first 2 years, but there is a continued increasing cumulative incidence during the entire study period.

the study by Goh et al. [5], placement of nephrostomy tube without further intervention did not qualify as a stricture, whereas in our study it did. The main reason for including it in the present study was that not all cases of endoluminal dilatation are registered in the Patient Register when the procedure is performed in a Radiology department. When we, in addition to hydronephrosis with intervention, also included hydronephrosis without any further intervention, the 17 years' cumulative incidence was 30.4%. This is possibly an overestimate, but among these cases there could also be a significant number of patients with stricture formation, but for whom intervention was not done due to comorbidity or progression of disease.

Time to diagnosis of stricture is depending on follow-up routines, and in this cohort the routines likely varied over time and between centres. Most of the strictures were diagnosed within the first 2 years postoperatively, just as in previous reports [6–7]. Interestingly, the present results indicate that the formation of strictures continues even after 10 years postoperatively. This may reflect late diagnosis and indicates the possible need for long and individualised follow-up but it could also be explained by causes unrelated of the cystectomy. Similarly, Yang et al. [12] found 8% strictures with a median postoperative follow-up of 10.7 years, in a large single-centre study from a high-volume centre. In that study, 75% were diagnosed within 2 years postoperatively but, even after 2 years, there remained a 0.4% per year incidence of strictures with 5% of all the strictures developing beyond 10 years. In a single-centre study with 12.4 years median follow-up the incidence of strictures was only 2.6%, with a median time to diagnosis of a stricture of 10 months [13]. The radical cystectomy in that study was performed between 1971 and 2008 with a rigorous follow-up protocol including imaging studies with either computed tomography or intravenous urography, implying that lack of radiographic imaging was not the reason for the low rate of strictures, although there may be false negative cases because of follow-up being done at local hospitals instead of the tertiary centre.

The crude incidence of strictures has been reported in several single-centre studies. Hosseini et al. [3] reported a rate of 6.5% in patients who underwent RARC with ICUD. In a further high-volume single-centre study, the risk of strictures after open radical cystectomy was 4.3% [4]. In comparison, the crude stricture incidence was higher at 8.9% in the present population-based study.

In our study, patients with a code indicating stricture within the first 30 days postoperatively were not excluded (but their events not counted) since this group may include placement of a nephrostomy tube due to postoperative urine leakage which is a known risk factor for later developing a stricture [4,14]. The true incidence of post-operative urinary leakage is not known, since, e.g. drains have not been registered, but among the 1.3% of patients who received a nephrostomy tube in the early post-operative period, 62% later developed a stricture which is consistent with earlier results [4]. Other known risk factors for stricture formation are high BMI, ASA score >2, lymph node positive disease, 30-day post-operative Clavien-Dindo complications grade 3+, male sex [4], preoperative hydronephrosis, RARC with ECUD [5], postoperative urinary tract infection and running suture technique on the anastomosis [15].

In this study, there was no association between the hospital cystectomy volume and risk of strictures, after adjusting for year of cystectomy. Neither patient sex nor age were associated with strictures. Changing follow-up routines is one likely explanation for the increasing incidence during the study period, with a HR of 2.07 for the last period compared to the first. It is also possible that improved registration of procedure codes has influenced the results. Another contributing cause to the increase could be cystectomies performed on older and more comorbid patients late in the study period. However, the high number of cystectomies performed in low-volume centres does not seem to explain the higher cumulative incidence of strictures in this study.

Data regarding mode of surgery, neoadjuvant chemotherapy and stage of the cystectomy specimen (pT) was collected from the Cystectomy Register which started in 2011. This results in missing data regarding these potential risk factors for stricture formation when the cystectomy was performed before 2011. For this reason, we did not include these potential risk factors in the Cox regression analysis. However, this does not affect the conclusion of this study.

The main strengths of this study are the multi-centre design and the large nation-based study-population. To our knowledge, there are no previously published studies which have evaluated the incidence of ureteroenteric strictures in a similarly large study-population and long follow-up period.

A weakness is the composite endpoint which may lead to both false positive events, e.g. in the case of placing a nephrostomy tube due to normal post-cystectomy CT-findings with hydronephrosis, and false negative results, e.g. if a patient was censored due to urolithiasis before a stricture occurred. Furthermore, there is no procedure code for removal of a nephrostomy tube, so whether this was a permanent or temporary procedure could not be determined. To adjust for the risk of overestimating or underestimating the incidence of strictures we separately analysed the subgroup with codes indicating stricture and intervention and the subgroup diagnosed with hydronephrosis but not followed by an intervention. In most other series the endpoint is intervention for stricture but this might lead to underestimating the incidence of strictures since some patients do not undergo intervention due to co-morbidity or high age.

It is also a weakness that there is no common code in the Swedish Classification of Healthcare Procedures for re-implantation of the ureters to a urinary diversion, leading to possible missing data when this procedure has occurred. Also, because dilatation of strictures is sometimes performed by a radiology department as an out-patient procedure in Sweden, there is a possibility that the code is not registered in the Patient Register and therefore does not lead to an event. However, this should lead to underestimation of the true incidence of strictures and would therefore not affect the conclusion of this study.

Conclusions

The present study indicates that ureteroenteric strictures requiring intervention are more common than previously reported, affecting nearly one fifth of patients who have undergone radical cystectomy for urinary bladder cancer. The incidence is highest in the first 2 years after surgery but continues during the whole 17 years of follow-up. This finding indicates the need for long follow-up routines.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

The study was financed by grants from the Swedish Government under the agreement between the Swedish government and the county councils, the ALF-agreement [ALFGBG-873181].

ORCID

Henrik Kjölhede http://orcid.org/0000-0001-6441-4729

References

[1] Nassar OAH, Alsafa MES. Experience with ureteroenteric strictures after radical cystectomy and diversion: open surgical revision. Urology. 2011;78(2):459–465.
[2] Hussein AA, Hashmi Z, Dibaj S, et al. Reoperations following Robot-Assisted Radical Cystectomy: A Decade of Experience. J Urol. 2016;195(5):1368–1376.
[3] Hosseini A, Dey L, Laurin O, et al. Ureteric stricture rates and management after robot-assisted radical cystectomy: a single-centre observational study. Scand J Urol. 2018;52(4):244–248.
[4] Amin KA, Vertosick EA, Stearns G, et al. Predictors of Benign Ureteroenteric Anastomotic Strictures After Radical Cystectomy and Urinary Diversion. Urology. 2020;144:225–229.
[5] Goh AC, Belarmino A, Patel NA, et al. A Population-based Study of Ureteroenteric Strictures After Open and Robot-assisted Radical Cystectomy. Urology. 2020;135:57–65.
[6] Tal R, Sivan B, Kedar D, et al. Management of benign ureteral strictures following radical cystectomy and urinary diversion for bladder cancer. J Urol. 2007;178(2):538–542.
[7] Shimko MS, Tollefson MK, Umbreit EC, et al. Long-term complications of conduit urinary diversion. J Urol. 2011;185(2):562–567.
[8] Desai MM, Gill IS, de Castro Abreu AL, et al. Robotic intracorporeal orthotopic neobladder during radical cystectomy in 132 patients. J Urol. 2014;192(6):1734–1740.
[9] Häggström C, Liedberg F, Hagberg O, et al. Cohort profile: The Swedish National Register of Urinary Bladder Cancer (SNRUBC) and the Bladder Cancer Data Base Sweden (BladderBaSe). BMJ Open. 2017;7(9):e016606.
[10] Jerlström T, Gårdmark T, Carringer M, et al. Urinary bladder cancer treated with radical cystectomy: perioperative parameters and early complications prospectively registered in a national population-based database. Scand J Urol. 2014;48(4):334–340.
[11] Hosmer DW, Lemeshow S, May S. Applied Survival Analysis. Hoboken, NJ, USA: John Wiley & Sons, Inc.; 2008. (Wiley Series in Probability and Statistics).
[12] Yang DY, Boorjian SA, Westerman MB, et al. Persistent, long-term risk for ureteroenteric anastomotic stricture formation: the case for long term follow-up. Transl Androl Urol. 2020;9(1):142–150.
[13] Shah SH, Movassaghi K, Skinner D, et al. Ureteroenteric Strictures After Open Radical Cystectomy and Urinary Diversion: The University of Southern California Experience. Urology. 2015;86(1):87–91.
[14] Richards KA, Cohn JA, Large MC, et al. The effect of length of ureteral resection on benign ureterointestinal stricture rate in ileal conduit or ileal neobladder urinary diversion following radical cystectomy. Urol Oncol. 2015;33(2):65.e1–65.e8.
[15] Large MC, Cohn JA, Kiriluk KJ, et al. The impact of running versus interrupted anastomosis on ureterointestinal stricture rate after radical cystectomy. J Urol. 2013;190(3):923–927.