RESEARCH ARTICLE

Laparoscopic Retroperitoneal Nephroureterectomy is a Safe and Adherent Modality for Obese Patients with Upper Urinary Tract Urothelial Carcinoma

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Abstract

Objective: We evaluated the association of body mass index (BMI) with perioperative outcomes in patients who underwent laparoscopic or open radical nephroureterectomy. Materials and Methods: This retrospective single-center study included 113 patients who had been diagnosed with upper urinary tract cancer from January 1998 to June 2013 and were treated with laparoscopic nephroureterectomy (Lap group, n=60) or open nephroureterectomy (Open group, n=53). Laparoscopic nephroureterectomy was performed via a retroperitoneal approach following an open partial cystectomy. The two surgical groups were stratified into a normal-BMI group (<25) and a high-BMI group (BMI≥25). The high-BMI group included 27 patients: 13 in the Lap group and 14 in the Open group. Results: Estimated blood loss (EBL) in the Lap group was much lower than that in the Open group irrespective of BMI (p<0.01). Operative time was significantly prolonged in normal-BMI patients in the Lap group compared to those in the Open group (p=0.03), but there was no difference in operative time between the Open and Lap groups among the high-BMI patients. Multivariate logistic regression analysis of the data for all the cohorts revealed that the open procedure was a significant risk factor for high EBL (p<0.0001, hazard ratio 8.02). Normal BMI was an independent predictor for low EBL (p=0.01, hazard ratio 0.25). There was no significant risk factor for operative time in multivariate analysis. There were no differences in blood transfusion rates or adverse event rates between the two surgical groups. Conclusions: Laparoscopic radical nephroureterectomy via a retroperitoneal approach can be safely performed with significantly reduced EBL even in obese patients with upper urinary tract cancer.

Keywords: Body mass index - laparoscopy - nephroureterectomy - retroperitoneum - urothelial carcinoma

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Introduction

The prevalence of obesity has been dramatically increasing worldwide for decades. Body mass index (BMI) is one of the most commonly used proxies for obesity. In Japanese aged more than 20 years, the prevalences of pre-obesity (BMI=25-29.9) and obesity (BMI>30) have been reported to be approximately 20% and 3%, respectively (Yoshiike et al., 2002). Although the proportion of obese people is lower in Japan than in Europe and the Americas, the prevalence of pre-obesity and obesity in the Japanese population has been reported to be linearly increasing in recent years.

Obesity is associated with an increased risk of postoperative complications and carcinogenesis (Mendoza et al., 1996; Rapp et al., 2005; Kruk, 2014; Oh et al., 2014; Ozbek et al., 2014). Approximately 20% of all cancers are caused by overweight (Wolin et al., 2010). Epidemiological reports have also shown that obesity results in increased incidence of and mortality from a variety of cancers (Reeves et al., 2007).

Localized upper urinary tract cancer is treated with surgical intervention, including laparoscopic and open procedures. Recently, laparoscopic radical nephroureterectomy has been used as a minimally invasive modality instead of the open procedure. Recent multi-institutional studies and a meta-analysis have shown that perioperative and oncological outcomes are comparable between open and laparoscopic surgery in patient with upper urinary tract urothelial carcinoma (Capitanio et al., 2009; Kamihira et al., 2009; Walton et al., 2011; Ni et al., 2012).

Two laparoscopic modalities are available to access the urinary tract system: the transperitoneal approach and the retroperitoneal approach. The transperitoneal approach has the benefits of a wide surgical space and easily identifiable anatomical landmarks. In contrast, the working space is narrow in the retroperitoneal approach, but it has the advantage of permitting direct, unencumbered, and rapid access to the renal hilum. Several studies have demonstrated the safety of laparoscopic radical nephrectomy in obese patients and have suggested

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that obesity need not necessarily be regarded as a contraindication for laparoscopy (Fugita et al., 2004; Feder et al., 2008). However, only two previous studies directly assessed the association between obesity and perioperative outcomes in laparoscopic surgery via the retroperitoneal approach (Inoue et al., 2006; Makiyama et al., 2008). In the present study, we compared the perioperative outcomes of laparoscopic nephroureterectomy and open nephroureterectomy among patients who had upper urinary tract cancer and were stratified on the basis of BMI status.

Materials and Methods

Patients

From January 1998 to June 2013, 125 consecutive patients were diagnosed with operable upper urinary tract cancer. Among these patients, five underwent simple nephrectomy, four underwent partial ureterectomy, and three underwent nephroureterectomy plus radical cystectomy; these patients were excluded from this study. The remaining 113 patients underwent radical nephroureterectomy with bladder cuff resection, either laparoscopic (Lap group, n=60) or open (Open group, n=53). Six surgeons conducted the laparoscopic procedures, and eight conducted the open procedures. The decision of whether to perform a laparoscopic or open procedure was left to the discretion of the attending physicians. Patients with suspected metastasis or regional lymph node enlargement, as indicated by computed tomography or magnetic resonance imaging, were excluded from surgical treatment. None of the patients were treated preoperatively with either systemic chemotherapy or radiation therapy. The mean age of all patients was 68.5 years (range 44-83).

BMI (kg/m^2, defined as patient weight divided by the square of patient height) was calculated for all patients. Patients with a BMI of ≥25.0 were classified as obese (high-BMI group), and those with a BMI of <25.0 were classified as non-obese (normal-BMI group), in accordance with the criteria of the Japan Society for the Study of Obesity. Estimated glomerular filtration rate (eGFR in ml/minute/1.73 m^2) was used as an indicator of renal function. Operative time, estimated blood loss (EBL), and pre- and postoperative eGFR were reviewed retrospectively and compared between the groups.

Surgical procedures

Open procedures were performed extraperitoneally using the lumber and midline lower or lumber and lateral lower abdominal approach. The choice of continuous or separate skin incision was made by the attending physician. All laparoscopic nephroureterectomies were performed via the retroperitoneal approach with the patient in a lateral position using four trocars to isolate the kidney and upper ureter. Lower ureter dissection, bladder management, and specimen removal were performed via a midline lower abdominal extraperitoneal approach with the patient in a supine position. Bladder management used either the extravesical or the transvesical approach. Limited lymphadenectomy was performed in the region of the tumor location. Vascular injury occurred in two cases, and these two patients were converted to the open surgery; they were included in the Lap group for further analyses.

Statistical analysis

The Fisher exact test was used to evaluate the associations between gender, age (≤65 years versus >65 years), tumor side (right versus left), main tumor location (ureter versus renal pelvis), bladder management (extravesical versus transvesical), pathological stage (T2 or less as urinary tract confined disease versus T3 or greater as non-urinary tract confined disease), lymphadenectomy status, blood transfusion, and perioperative adverse events. Adverse events were classified according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0). The differences in EBL and operative time between the two surgical procedures and the high-BMI and normal-BMI groups were evaluated by the Fisher exact test. The Mann-Whitney U test was used to evaluate associations of surgical procedures with BMI, operative time, EBL, and pre- and postoperative eGFR. The Shapiro-Wilk W test was used to determine the distribution of the variables. The correlation between continuous variables was investigated by simple regression analysis. Multivariate analyses were performed with the logistic regression model, controlling for BMI, age, gender, tumor side and location, surgical procedure, bladder management, and pathological stage.

Table 1. Patient Characteristics and Surgical Management

	Laparoscopy (%)	Open (%)	P value$^+$
No. of patients	60	53	
Gender			
Male	47 (78.3)	43 (81.1)	
Female	13 (21.7)	10 (18.9)	0.82
Age			
65 years or less	22 (36.7)	23 (43.4)	
More than 65 years	38 (63.3)	30 (56.6)	0.56
Pathological stage			
Ta, Tis, T1, T2	35 (58.3)	33 (62.3)	
T3, T4	25 (41.7)	20 (37.7)	0.7
Tumor side			
Right	30 (50.0)	24 (45.3)	
Left	30 (50.0)	29 (54.7)	0.71
Tumor location			
Pelvis	38 (63.3)	28 (52.8)	
Ureter	22 (36.7)	25 (47.2)	0.34
Lymphadenectomy			
Performed	29 (48.3)	33 (62.3)	
Not performed	31 (51.7)	20 (37.7)	0.18
Bladder management			
Extravesical	52 (86.7)	48 (90.6)	
Transvesical	8 (13.3)	5 (9.4)	0.57
BMI (kg/m^2)	22.5	22.6	0.93*
EBL (ml)	244	565	<0.0001*
Operative time (min)	326	283	0.02*
Preoperative eGFR (ml/min/1.73 m^2)	60.5	56.6	0.30*
Postoperative eGFR (ml/min/1.73 m^2)	44.0	45.1	0.37*

No.: number, BMI: body mass index, EBL: estimated blood loss, eGFR: estimated glomerular filtration rate. $^+$Fisher exact test. *Mann-Whitney U test

Table 2. Differences in Estimated Blood Loss and Operative Time between Surgical Management Groups According to Body Mass Index

		Laparoscopy (range)	Open (range)	P value*
Normal BMI (less than 25)	No. of patients	47	39	
	EBL (ml)	248 (10-1400)	483 (80-2430)	<0.0001
	Operative time (min)	318 (200-500)	279 (90-520)	0.03
High BMI (25 or more)	No. of patients	13	14	
	EBL (ml)	232 (20-890)	792 (290-2580)	0.0002
	Operative time (min)	355 (200-525)	296 (138-490)	0.22

BMI, body mass index; No, number; EBL, estimated blood loss;* Mann-Whitney U test

Table 3. Multivariate Analysis of Association of High Estimated Blood Loss with Clinical Factors

Group	All cohorts			Laparoscopy			Open		
	HR	95% CI	p value	HR	95% CI	p value	HR	95% CI	p value
Gender male / female	0.73	0.22-2.38	0.6	2.84	0.17-47.3	0.47	0.34	0.07-1.72	0.19
Age 65 or less / more than 65	1.13	0.43-3.02	0.8	2.96	0.56-15.7	0.2	0.53	0.13-2.21	0.38
BMI less than 25 / 25 or more	0.25	0.08-0.76	0.01	0.45	0.06-3.53	0.45	0.09	0.02-0.58	0.01
Pathological stage pT2 or less / pT3 or more	1.44	0.53-3.90	0.47	0.33	0.05-2.22	0.25	3.49	0.81-15.1	0.09
Tumor side right / left	3.61	1.32-9.86	0.01	6.01	0.86-41.8	0.07	3.11	0.68-14.2	0.14
Tumor location ureter / pelvis	1.91	0.68-5.41	0.22	7.43	1.03-53.8	0.04	1.17	0.29-4.81	0.82
Surgical procedure open / laparoscopy	8.02	2.85-22.6	<0.0001	-	-	-	-	-	-
Lymphadenectomy yes / no	1.88	0.67-5.27	0.23	4.14	0.53-32.1	0.17	0.99	0.21-4.77	0.99
Bladder management extravesical / transvesical	0.95	0.17-5.20	0.95	1.04	0.06-17.8	0.98	0.62	0.06-6.49	0.69

*HR, hazard ratio, CI: confidence interval, BMI: body mass index

In multivariate analyses, all factors were evaluated as dichotomized valuables. EBL and operative time were dichotomized at their corresponding mean values. All analyses were performed with StatView (ver. 5.0, SAS Institute, Cary, NC, USA), and $p<0.05$ was considered to indicate statistical significance.

Results

Histological findings indicated that all patients had urothelial carcinoma except for one who had squamous cell carcinoma. Patient characteristics are shown in Table 1. There were no significant differences between the two surgical groups in terms of gender, age, pathological stage, tumor side, tumor location, bladder management, or lymphadenectomy status.

The mean BMIs of the Lap and Open groups were 22.5 (range 15.2-29.4) and 22.6 (range 15.4-28.3), respectively, and there was no significant difference between the two groups. The mean EBLs in the Lap and Open groups were 244 ml (range 10-1400) and 565 ml (range 80-2580), respectively, and the mean operative times in the Lap and Open groups were 326 min (range 200-525) and 283 min (range 90-520), respectively. The Lap group showed lower EBLs and longer operative times than the Open group ($p<0.0001$ and $p=0.02$, respectively). There were no significant differences in pre- and postoperative eGFR between the two surgical groups.

Simple regression analysis showed no correlation between BMI and EBL in the Lap group ($p=0.55$, $r^2=0.006$) or in the Open group ($p=0.17$, $r^2=0.036$). There was also no correlation between BMI and operative time in either the Lap group ($p=0.08$, $r^2=0.052$) or the Open group ($p=0.65$, $r^2=0.004$).

The patients in the two surgical groups were stratified into normal- and high-BMI groups (Table 2). EBL in the Lap group was much lower than that in the Open group, irrespective of BMI ($p<0.01$). Among patients with normal BMI, operative time was significantly longer in the Lap group than in the Open group ($p=0.03$), but there was no difference between the two surgical groups among patients with high BMI. In the Open group, but not in the Lap group, EBL was higher in the high-BMI group than in the normal-BMI group ($p=0.008$). Operative time did not differ between the normal- and high-BMI groups, irrespective of surgical group.

Multivariate logistic regression analysis of the data for all cohorts (Table 3) indicated that the open procedure and having a right-side tumor were significant risk factors for high EBL ($p<0.0001$, hazard ratio 8.02; $p=0.01$, hazard ratio 3.61, respectively). Normal BMI was an independent predictor of low EBL ($p=0.01$, hazard ratio 0.25). In the Lap group, having a ureteral tumor was a significant risk factor for high EBL ($p=0.04$, hazard ratio 7.43). In the Open group, normal-BMI was the sole independent predictor for low EBL ($p=0.01$, hazard ratio 0.09). None

Table 4. Perioperative Adverse Events in Laparoscopic and Open Procedures

	Laparoscopy		Open	
	All grades	Grade 3	All grades	Grade 3
No. of patients	5	2	3	0
Cardiac chest pain	1	1	0	0
Paralytic ileus	1	1	0	0
Wound infection	2	0	1	0
Hematoma	0	0	1	0
Urinary fistula	0	0	1	0
Urinary retention	1	0	0	0

*No: number

of the clinical factors was a significant risk factor for operative time in any of the categorical groups.

In the Open group, five patients required a blood transfusion, and in the Lap group, five patients (including two patients who were converted to the open procedure) required transfusion. In the Open group, three patients had large non-urinary-tract-confined disease with prolonged operative time with bleeding; two patients had bleeding in the lumbar vein. In the Lap group, two patients had bleeding from the inferior vena cava or the renal vein; three patients were anemic owing to gross hematuria preoperatively and required blood transfusion intraoperatively. There was no difference in transfusion rate between the two surgical groups or between the two BMI status groups.

Grade 3 adverse events were observed in only two patients, both of whom were in the Lap group (Table 4). One patient experienced paralytic ileus, and the other had cardiac chest pain; however, both patients recovered with conservative treatments. There was no difference in adverse event rates between the two surgical groups.

Discussion

Obesity, a potentially life-threatening condition that has been linked to various diseases, has reached epidemic status. Elevated BMI is associated with an increased risk of various cancers (Rapp et al., 2005). Given that the prevalence of obesity is increasing around the world, an understanding of the mechanisms linking obesity and cancer is imperative for maintaining health and reducing medical costs. In addition, obesity is associated with a high incidence of perioperative complications. Because the incidence of obesity is increasing in Japan, obese patients will comprise a much greater percentage of the total number of patients requiring surgical intervention.

Previous studies exploring the association between obesity and nephroureterectomy outcomes have been reported. For example, Fazeli-Matin et al. (Fazeli-Matin et al., 1999) compared 11 obese patients (BMI>30) who underwent laparoscopic radical nephrectomy or nephroureterectomy with 17 obese patients who underwent open radical nephrectomy or nephroureterectomy. These investigators showed that patients in the laparoscopic group had longer operative times (210 versus 185 min) and lower EBL (100 versus 375 ml), but there were no differences in complication rates or blood transfusion rates. Inoue et al. (Inoue et al., 2006) reported that among patients who underwent retroperitoneal radical nephrectomy for treatment of renal cell carcinoma, operative time was longer (172 versus 137 min) and EBL was higher (195 versus 48 ml) in obese patients (BMI>25) than in non-obese patients. Makiyama et al. (Makiyama et al., 2008) reported that among patients who underwent retroperitoneal nephrectomy (including radical or simple nephrectomy) and nephroureterectomy, operative time was longer (203 versus 184 min) in the obese group (BMI>25) than in the normal-BMI group, but there were no differences in EBL, complication rates, or open conversion rates between the two groups.

In the present study, we observed no significant difference in operative time between the two surgical procedures in the high-BMI group, whereas in the normal-BMI group, the laparoscopic surgery required a longer operative time than the open surgery. In addition, in the high-BMI group, EBL was much higher in patients who underwent open surgery than in those who underwent laparoscopic surgery. Although the our data seemed to be worse than previously reported data, nephroureterectomy in our method required an open procedure for harvesting the kidney and ureter with a low abdominal incision. However, in the Lap group, EBL, operative time, and complication rate were comparable to those of previous large studies (Kamihira et al., 2009; Ni et al., 2012). Our results demonstrate the clinical usefulness of laparoscopic surgery for upper urinary tract cancers among patients with high BMI.

Although there was no difference in complication rate between the two surgical groups, postoperative mobilization of patients with high BMI is less hampered by laparoscopy than by open, owing to the minimal trauma inflicted by the former. The decrease in postoperative pain in patients with a high BMI may be influenced by their weight and heavy abdominal tissue, which would result in higher tension on the surgical incision during postoperative mobilization than that experienced by patients with normal BMI. In addition, early postoperative mobilization may reduce the risk of postoperative thromboembolism in patients with high BMI, which can be a life-threatening problem in this group.

Obese patients can be affected by comorbidities, such as diabetes mellitus, hypercholesterolemia, and high blood pressure (Mokdad et al., 2003). Obesity and these comorbidities seem to be important factors affecting surgical outcomes (Jiganti et al., 1993; Mendoza et al., 1996; Hagiwara et al., 2011). Although obesity was formerly believed to be a contraindication for laparoscopy because of the high incidence of perioperative morbidity, the safety of laparoscopic radical nephrectomy for obese patients was demonstrated in several studies, and as a result, obesity is not considered as a contraindication for laparoscopic surgery (Fugita et al., 2004; Feder et al., 2008).

In the present study, linear regression analysis revealed that BMI was not correlated with EBL or operative time in either of the two procedures. In addition, postoperative renal function was comparable in both groups. Taken together, these results indicate that laparoscopic radical nephroureterectomy is comparable to the open procedure

for treatment of upper urinary tract cancer in regard to perioperative surgical outcomes in patients with high BMI.

Multivariate logistic regression analysis indicated that normal BMI was an independent predictor of low EBL in all cohorts and in the Open group, but not in the Lap group. Open surgery and a right-side tumor were significant risk factors for high EBL in all cohorts. These results suggest that physicians should pay attention to blood loss when performing an open procedure, particularly in patients with high BMI and that, on the contrary, BMI status does not affect EBL in patients who undergo the laparoscopic procedure. We speculate that anatomical asymmetries-the right renal vein is short, the gonadal vein is directly connected to the vena cava, and the right kidney overlays the liver-might lead to high EBL. However, we have no specific evidence for this, and the reason for the high EBL remains unknown. In the Lap group, having a ureteral tumor was a significant risk factor for high EBL, and one possible reason is that patients with ureteral tumors occasionally show hydronephrosis and hydroureter, which can directly and indirectly cause severe adhesions in the retroperitoneal spaces, leading to high EBL.

This study has several limitations. First, it was not randomized; the criteria for indication of laparoscopic versus open nephroureterectomy were not elucidated, and the choice depended exclusively on the preference of the attending physicians. Therefore, selection bias is a possibility. In addition, observational studies have been criticized owing to the possibility of negative selection bias in the open surgical group; that is, laparoscopic procedures tend to be chosen for patients with more-favorable pathological staging (Capitanio et al., 2009; Ni et al., 2012). However, in this study, there was no difference between the backgrounds of the patients in the two groups. Second, oncological studies are usually divided into two groups on the basis of whether the cancer is non-muscle invasive or muscle invasive (Matsumoto et al., 2014). However, in this study aimed at determining the perioperative parameters affecting EBL and operative time, we classified the disease as urinary tract confined (pT2 or less) and non-urinary tract confined (pT3 or more). Confined status had no effect on perioperative outcomes in the two surgical groups. In addition, there was no difference in perioperative outcome associated with muscle invasive status in either surgical group (data not shown). Third, none of the patients in this study were classified as obese according to the WHO criterion (BMI>30.0). Despite these limitations, the results of the present study suggest that laparoscopic nephroureterectomy carried out by the retroperitoneal approach can be safely performed with significantly reduced EBL in high-BMI patients with upper urinary tract cancer.

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