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Perioperative Outcomes of Laparoscopic Radical Nephroureterectomy and Regional Lymphadenectomy in Patients with Upper Urinary Tract Urothelial Carcinoma After Neoadjuvant Chemotherapy

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Abstract

Objectives—To determine the effect of neoadjuvant chemotherapy on surgical outcomes in patients undergoing laparoscopic radical nephroureterectomy (LNUX) for upper urinary tract urothelial carcinoma (UTUC).

Methods—We performed a retrospective review of all UTUC patients who underwent LNUX performed at our institution between January 2003 and June 2010. We compared differences in demographic, clinicopathological, and operative parameters, including estimated blood loss, duration of surgery, length of postoperative hospitalization, and number of complications, between patients who underwent LNUX after neoadjuvant chemotherapy and patients who underwent LNUX without neoadjuvant chemotherapy. Logistic regression analysis was performed to identify predictors of complications.

Results—We identified 82 UTUC patients who underwent LNUX; 26 received neoadjuvant chemotherapy. Patients who underwent LNUX after neoadjuvant chemotherapy had a higher body mass index, higher biopsy tumor grade, and longer operative time than patients who underwent LNUX without neoadjuvant chemotherapy. Patients who received neoadjuvant chemotherapy underwent regional lymphadenectomy more often, with more lymph nodes and lymphoadipose tissue removed, than patients who did not receive neoadjuvant chemotherapy. Neoadjuvant chemotherapy resulted in a 15% complete remission rate. No differences in median estimated blood loss, intraoperative transfusions, and length of hospitalization between the two groups were found. Perioperative complication rates were similar in both groups.

Conclusions—We found no differences in surgical outcomes between patients who underwent LNUX after neoadjuvant chemotherapy and patients who underwent LNUX without neoadjuvant chemotherapy. Our findings support the use of LNUX in selected patients undergoing neoadjuvant chemotherapy for UTUC.

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Keywords

neoadjuvant therapy; chemotherapy; transitional cell carcinoma; laparoscopic nephroureterectomy; postoperative complications; laparoscopy; surgical complications

INTRODUCTION

Upper urinary tract urothelial carcinomas (UTUCs) are especially rare,1, accounting for only 5–7% of all urinary tract tumors and < 1% of genitourinary neoplasms diagnosed each year in the United States.2,3 The imaging, staging, and treatment paradigms for UTUC are much more limited and challenging for UTUC than bladder UC, and there is evidence that survival has not improved for these patients in the contemporary era.4

Historically, the surgical treatment of choice for UTUC has been open nephroureterectomy. However, many urologists now consider laparoscopic nephroureterectomy (LNUX) to be a new standard of treatment.5 Although open nephroureterectomy and LNUX have similar oncologic outcomes, LNUX has better short-term surgical outcomes than open nephroureterectomy, including less blood loss, less postoperative pain, and shorter hospitalization times.6–9

UCs are sensitive to both neoadjuvant and adjuvant chemotherapy.10 However, given the decrease in renal function following nephroureterectomy, UTUC patients (many of whom present with underlying renal insufficiency) may not be candidates for adjuvant chemotherapy with nephrotoxic cisplatin-based regimens, which represent the most effective systemic treatments available. A recent study showed that a significant proportion of patients become ineligible to receive cisplatin based chemotherapy after nephroureterectomy. 11 Chemotherapy delivered in the neoadjuvant setting, on the other hand, capitalizes on UTUC patients' existing renal reserve, permitting the delivery of nephrotoxic therapeutic agents at higher, more effective doses.12,13 Neoadjuvant chemotherapy was recently shown to be associated with significant rates of complete response and tumor downstaging in UTUC patients.14

Although the neoadjuvant approach has been found to have efficacy in UTUC patients, its effect on surgical outcomes has not been previously reported to our knowledge. With the increasing adoption of this new paradigm, information on the relative perioperative morbidity might help with selection for the appropriate surgical approach and with patient counseling. We thus performed a retrospective study to evaluate whether neoadjuvant chemotherapy affects perioperative LNUX and regional lymphadenectomy outcomes in UTUC patients. We also investigated whether LNUX and regional lymphadenectomy is more difficult to perform in patients who have received neoadjuvant chemotherapy than in patients who have not.

MATERIAL AND METHODS

We identified all UTUC patients who underwent LNUX with or without regional lymphadenectomy performed by a single urologist (SFM) between January 1, 2003, and June 30, 2010, at our institution. Institutional review board approval was obtained for this study. Data was obtained from the medical chart, operative notes, pathology reports, and radiographic imaging.

The UTUC diagnosis and evaluation was performed with abdominal computed tomography (CT) or magnetic resonance imaging; chest CT or radiography; hematology and blood

chemistry; cystoscopy; and cytology with or without fluorescence in situ hybridization (FISH) assay. Ureteroscopy with tumor biopsy was routinely performed whenever possible for tissue diagnosis. Additional studies such as bone scans or brain imaging were performed as clinically indicated at the discretion of the treating team.

Patients determined to have high-risk disease (defined as either high-grade on biopsy, a large-volume tumor, or sessile architecture)14 were referred to a genitourinary medical oncologist for consideration of neoadjuvant chemotherapy. Surgery was scheduled 4–6 weeks after the last course of neoadjuvant chemotherapy.

LNUX was performed as previously described,15 primarily using a conventional transperitoneal laparoscopic approach. Bladder cuff and distal ureteral dissection was performed through a 6–7cm lateral Gibson incision, which was used for extraction of the entrapped, intact specimen. In patients with high-risk disease, laparoscopic retroperitoneal lymphadenectomy was performed for renal pelvic and proximal ureteral tumors, while ipsilateral pelvic lymphadenectomy through the Gibson specimen extraction site was performed for mid- and distal ureteral tumors as previously described.15 For those with multifocal high-risk tumors, both retroperitoneal and ipsilateral pelvic lymphadenectomy was performed.

Each patient's sex, age, body mass index (BMI), ethnicity, prior history of bladder UC, tumor laterality, site of primary disease, tumor grade, highest pathologic tumor (pT) stage, and type and number of cycles of neoadjuvant chemotherapy received were recorded. Tumor grade was assigned using World Health Organization criteria, 16 and the highest pT stage was assigned using American Joint Committee on Cancer (6th edition) criteria.17 We also obtained perioperative data including surgical margin status, final pathologic analysis of lymphadenectomy specimens (the number of lymph nodes removed, the number of disease-positive lymph nodes, and the volume of resected lymphoadipose tissue as recorded in the pathology report), estimated blood loss, packed red blood cells transfused, operative time, and length of postoperative hospital stay. Complications (up to 90 days after surgery) were classified by organ system and graded using the modified Clavien system.18

We compared differences between patients who received neoadjuvant chemotherapy and underwent LNUX and patients who underwent LNUX without neoadjuvant chemotherapy. The two-tailed Mann-Whitney *U* test was used to compare differences in continuous variables, and Fisher's exact test was used to compare differences in categorical variables. Univariate and multivariate logistic regression analyses were conducted to identify predictors of postoperative complications. P values < 0.05 were considered statistically significant. All statistical analyses were performed using Vassar STATS (available online at http://faculty.vassar.edu/lowry/VassarStats.html) and StatCrunch (Integrated Analytics, College Station, TX).

RESULTS

82 UTUC patients underwent LNUX; of these, 26 received neoadjuvant chemotherapy followed by LNUX, and 56 underwent initial LNUX. Table 1 summarizes data on the neoadjuvant therapies used. The most frequently administered regimen was methotrexate, vinblastine, doxorubicin, and cisplatin. The median number of chemotherapy cycles each patient received was four. Four patients received secondary regimens after completing their primary neoadjuvant chemotherapy. Four other patients, owing to declining performance status, underwent LNUX without completing their primary regimens of neoadjuvant chemotherapy.

Patient and disease characteristics are summarized in Table 2. There were no significant differences between the two groups in sex, age, ethnicity, history of bladder UC, disease location, highest pT stage, or surgical margin status. Patients who received neoadjuvant chemotherapy had a higher median BMI than patients who did not receive neoadjuvant chemotherapy ($P = 0.012$).

Presurgical biopsies were not performed in 11 patients (20%) who did not receive neoadjuvant chemotherapy and two patients (8%) who received neoadjuvant chemotherapy. In these 13 patients, high-grade UTUC was confirmed using a combination of upper urinary tract washings and/or urine cytology and FISH assay with radiographic imaging or ureteroscopic visualization. In the patients who did undergo biopsy before LNUX, tumor grade was significantly higher in patients who received neoadjuvant chemotherapy than in patients who did not ($P = 0.001$), as expected. Of the 26 patients who received neoadjuvant chemotherapy, four patients (15%) were found to have a complete response (pT0 N0), one of whom proceeded to surgery before completing all courses. Of the 56 patients treated with initial LNUX only 1 (1.7%) was classified as pT0 as a result of ureteroscopic treatment. The median interval between the last dose of neoadjuvant chemotherapy and the day of surgery was 46 days, which allowed patients to recover from the side effects of chemotherapy, including improving hematologic parameters and performance status. This parallels the bladder cancer paradigm, in which a similar timeline is relevant.

Operative data are summarized in Table 2. Regional lymphadenectomy was performed more frequently in patients who received neoadjuvant chemotherapy than in patients who did not receive neoadjuvant chemotherapy ($P = 0.017$). A greater number of lymph nodes ($P = 0.009$) and amount of lymphoadipose tissue ($P = 0.002$) were removed from patients who received neoadjuvant chemotherapy than from patients who did not receive neoadjuvant chemotherapy. Likely owing to the higher frequency of regional lymphadenectomy, the patients who received neoadjuvant chemotherapy had longer operative times than the patients who underwent initial LNUX ($P = 0.028$). No significant differences in median estimated blood loss, packed red blood cells transfused, or length of hospital stay were observed between the two groups.

No significant differences in overall intraoperative and postoperative complication rates between patients who did and did not receive neoadjuvant chemotherapy were identified. All of the complications, no matter how low in grade, are presented in Table 3. During the first 90 days after LNUX, no patients in either group died; however, four patients (5%) had at least one major (grade 3 or higher) complication. There was no significant difference in the types of complications recorded for each group. Univariate and multivariate analyses including age, BMI, neoadjuvant chemotherapy, pT stage ≥ 3, number of lymph nodes removed, estimated blood loss, operative time, and packed red blood cells transfused identified no predictors of postoperative complications (Table 4).

COMMENT

Neoadjuvant chemotherapy did not have a negative effect on outcomes of LNUX for UTUC. We found no significant differences in estimated blood loss, number of intraoperative blood transfusions, length of inpatient hospital stay, and intraoperative and postoperative complication rates between patients who underwent LNUX after neoadjuvant chemotherapy and patients who underwent LNUX without neoadjuvant chemotherapy.

Many researchers have investigated the efficacy of chemotherapy in UC patients, and the findings of randomized controlled trials support the use of neoadjuvant in patients with bladder UC, although it remains underutilized.[19–21] At our institution, neoadjuvant

chemotherapy has been routinely offered to patients with high-risk UTUC since 2004. A recent study suggests that neoadjuvant chemotherapy in high-risk UTUC patients is associated with significant tumor downstaging and a complete response rate of 14%,14 similar to that in the current study. Survival data is still maturing, but a recent presentation showed a 94% 3-year disease specific survival in those receiving neoadjuvant chemotherapy versus 64% in those undergoing surgery 22. The impact of neoadjuvant chemotherapy on surgical outcomes following LNUX and regional lymphadenectomy, which to the best of our knowledge has not been previously evaluated, will become increasingly relevant as multidisciplinary neoadjuvant approaches to UTUC gain greater acceptance. In this series, the rate of pathologic CR was more than 7 times greater in patients receiving neoadjuvant chemotherapy.

We found no significant demographic differences between patients who did and patients who did not receive neoadjuvant chemotherapy before LNUX. Patients who received neoadjuvant chemotherapy had a significantly higher median BMI than patients who underwent LNUX alone, suggesting that these patients may have been prone to a higher rate of adverse events; however, previous studies have shown that LNUX can be performed without significant differences in operative time, estimated blood loss, or complication rates among groups of patients with BMIs as high as 45.23

The patients in the current study had estimated blood loss values, operative times, and lengths of hospital stays that were well within the ranges reported in various previous studies .7،9،13،24،25 Although the overall complication rates in the current study were higher than those previously reported, previous studies did not use the Clavien system or a similar systematic scale to grade complications; thus, some complications—predominantly those considered to be lower grade—may not have been included in the previous studies' measured rates.

The role of lymphadenectomy in UTUC patients remains controversial; however, recent studies have suggested that lymphadenectomy has therapeutic value in addition to its utility in assessing metastatic disease in patients with high-grade or high-stage disease.26،27 Given the similar biology to bladder cancer, it is reasonable to assume that lymphadenectomy may provide a benefit for high-risk patients until further data is available. The extent of regional lymphadenectomy is often difficult to ascertain on the basis of the number of lymph nodes dissected, because of inter- and intraobserver variations in lymph node counting owing to a lack of standardized pathologic criteria, 28 in addition to anatomic variability. The current study took this potential for variation into account; we considered not only the number of lymph nodes removed but also the amount of lymphoadipose tissue volume removed (as indicated by dimensional measurements in the pathology report). To the best of our knowledge, this is a novel method of assessing lymph node dissection and may serve to at least partially normalize the bias inherent in the pathologic assessment of nodal specimens. 27

The current study was not without potential limitations. The data were collected retrospectively and were thus prone to the biases of any retrospective report, particularly selection bias. In addition, the classification of postoperative events as complications (specifically low grade complications) is subjective when determining if a patient's symptoms extended beyond the threshold of a normal postoperative recovery. We attempted to minimize this bias by recording the method and type of therapy delivered to each patient for his or her postoperative complication to distinguish between Clavien grades 0, 1, and 2. Also, the current study's sample size was small, as would be expected from a single-center, single-urologist study of a rare disease. Nevertheless, the current study comprises, to the

best of our best knowledge, the largest reported group of patients undergoing neoadjuvant chemotherapy and LNUX as well as LNUX with regional lymphadenectomy for UTUC.

Some of the patients described in the current study could present a surgical challenge for surgeons who perform few laparoscopic renal surgeries; thus, caution is warranted in translating our experience into a low-volume or non-oncologic setting. Patient selection is complex, but we strongly recommend a review of the pre-chemotherapy imaging, as patients with significant initial locoregional or extraluminal disease that regresses with chemotherapy are probably not ideal for a laparoscopic approach because of the potential for residual significant desmoplasia.

CONCLUSIONS

The surgical outcomes in patients who undergo LNUX and regional lymphadenectomy after neoadjuvant chemotherapy are not significantly different from those of patients who do not undergo neoadjuvant chemotherapy. Although our findings require external validation with a larger cohort of UTUC patients, they support the laparoscopic approach for high-risk UTUC patients who receive neoadjuvant chemotherapy. This data may aid in counseling UTUC patients about the relative perioperative risks and in the design of future studies.

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Table 1

Neoadjuvant chemotherapy regimens in 26 patients who underwent laparoscopic radical nephroureterectomy for high-risk urothelial carcinoma of the upper urinary tract

Variable	No. of patients (%)
Primary neoadjuvant chemotherapy regimen	
MVAC	6 (23)
CGI	5 (19)
MVAC + bevacizumab (Avastin)	4 (15)
GTA	4 (15)
IAG	2 (8)
CG	2 (8)
GT	1 (4)
Other	2 (8)
Secondary neoadjuvant chemotherapy regimen[a]	
MVAC	2 (8)
CGI	1 (4)
GTA	1 (4)
Median no. of chemotherapy cycles (range)	4 (1–7)
Premature discontinuation of primary regimen	4 (15)

Note: All data are presented as no. of patients (%) unless otherwise indicated.

Abbreviations: MVAC, methotrexate, vinblastine, doxorubicin (Adriamycin) and cisplatin; CGI, cisplatin, gemcitabine, and ifosfamide; GTA, gemcitabine, paclitaxel, and doxorubicin; IAG, ifosfamide, doxorubicin, and gemcitabine; CG, cisplatin and gemcitabine; GT, gemcitabine and paclitaxel.

[a]Given following primary regimen.

Table 2

Demographic, pathological, and perioperative characteristics of 82 patients who underwent laparoscopic radical nephroureterectomy with or without neoadjuvant chemotherapy for upper urinary tract urothelial carcinoma

Characteristic	No. of patients (%)			*P* value
	All patients n = 82	LNUX with neoadjuvant chemotherapy n = 26	LNUX without neoadjuvant chemotherapy n = 56	
Sex				0.808
Male	51 (62)	17 (65)	34 (61)	
Female	31 (38)	9 (35)	22 (39)	
Median age, y (range)	73 (49–91)	72 (52–84)	75 (49–91)	0.087
Median BMI, kg/m^2 (range)	27.06 (20.40–46.52)	28.90 (23.05–40.65)	26.10 (20.40–46.52)	**0.012**
Ethnicity				0.455
White	73 (89)	22 (85)	51 (91)	
Other	9 (11)	4 (15)	5 (9)	
Previous bladder UC				0.473
Yes	34 (42)	9 (35)	25 (45)	
No	48 (59)	17 (65)	31 (55)	
Laterality				1
Right	49 (60)	16 (62)	33 (59)	
Left	33 (40)	10 (39)	23 (41)	
Site of primary disease				0.549
Renal pelvis	38 (46)	14 (54)	24 (43)	
Ureter	33 (40)	10 (39)	23 (41)	
Multifocal[a]	11 (13)	2 (8)	9 (16)	
Biopsy grade				**0.001**[c]
Low	24 (29)	2 (8)	22 (39)	
High	43 (52)	22 (85)	21 (38)	
Other[b]	2 (2)	0 (0)	2 (4)	
No biopsy	13 (16)	2 (8)	11 (20)	
High-grade determination by cytology and/or FISH	4	2	2	
pT stage[d]				0.156
T0	5 (6)	4 (15)	1 (2)	
Ta/Tis	30 (37)	9 (35)	21 (38)	
T1	16 (20)	6 (23)	10 (18)	
T2	12 (15)	4 (15)	8 (14)	
T3	15 (18)	2 (8)	13 (23)	
T4	4 (5)	1 (4)	3 (5)	
Surgical margins				0.588
Positive	4 (5)	2 (8)	2 (4)	
Negative	78 (95)	24 (92)	54 (96)	

Characteristic	No. of patients (%)			*P* value
	All patients n = 82	**LNUX with neoadjuvant chemotherapy n = 26**	**LNUX without neoadjuvant chemotherapy n = 56**	
Lymphadenectomy				**0.017**
Yes	65 (79)	25 (96)	40 (71)	
No	17 (21)	1 (4)	16 (29)	
Median no. of lymph nodes removed (range)	5 (0–39)	7.5 (0–33)	4 (0–39)	**0.009**
Median no. of positive lymph nodes (range)	0 (0–9)	0 (0–3)	0 (0–9)	0.500
Median volume of lymphoadipose tissue removed, cm^3 (range)[e]	24.5 (0–309.4)	34.1 (0–210)	7.7 (0–309.4)	**0.002**
Median EBL, ml (range)	200 (20–4400)	275 (60–3500)	150 (20–4400)	0.085
Median PRBC transfused, units (range)	0 (0–11)	0 (0–5)	0 (0–11)	0.576
Median operative Time, h (range)	3.7 (2.5–6.9)	4.2 (3.0–6.4)	3.5 (2.5–6.9)	**0.028**
Median LOS, d	3 (2–14)	3 (2–7)	3 (2–14)	0.535

Note: All data are presented as no. of patients (%) unless otherwise indicated.

Abbreviations: BMI, body mass index; FISH, fluorescent in situ hybridization; pT, pathologic tumor; EBL, estimated blood loss; PRBC, packed red blood cells; LOS, length of stay.

[a] Involving both the renal pelvis and ureter, or diffuse carcinoma in situ throughout the upper tract.

[b] Biopsy revealed squamous cell carcinoma in 2 patients, with final pathology confirming urothelial carcinoma.

[c] Of those patients who had a biopsy.

[d] pT0 disease in those receiving neoadjuvant chemotherapy represents complete remission of disease as all had residual viable cancer after ureteroscopy. In the one patient undergoing initial surgery with pT0 classification, complete ureteroscopic resection was performed for a T1 tumor but concern remained about residual invasive disease.

[e] In 10 patients, dimensions were either unavailable or too few to calculate tissue volume

Table 3

Complications in patients who underwent laparoscopic radical nephroureterectomy with or without neoadjuvant chemotherapy for upper urinary tract urothelial carcinoma

Characteristic	No. of patients (%)		*P* value
	LNUX with neoadjuvant chemotherapy n = 26	**LNUX without neoadjuvant chemotherapy n = 56**	
Complications			
Overall	15 (58)	25 (45)	0.344
Intraoperative	2 (8)	2 (4)	0.588
Postoperative	14 (54)	24 (43)	0.476
Major postoperative complication[a]	1 (4)	3 (5)	1
Highest complication grade[b]			
Grade 0	12 (46)	32 (57)	
Grade 1	7 (30)	11 (20)	
Grade 2	6 (23)	10 (18)	
Grade 3	0 (0)	2 (4)	
Grade 4	1 (4)	1 (2)	
Grade 5	0 (0)	0 (0)	
	No. of complications (%)		
	LNUX with neoadjuvant chemotherapy n = 20	LNUX without neoadjuvant chemotherapy n = 32	
Complication			
Intraoperative	2 (10)	2 (6)	1
Vascular injury	2	0	
Pleural injury	0	1	
Pancreatic injury	0	1	
Wound dehiscence	1 (5)	1 (3)	1
Bleeding	5 (25)	5 (16)	0.480
Transfusion(s)	4	5	
Hematoma	1	0	
Genitourinary	5 (25)	5 (16)	0.480
UTI	1	3	
Testicular hydrocele	2	0	
Testicular pain	1	0	
Hematuria	1	0	
Urine retention	0	1	
Acute renal failure	0	1	
GI	2 (10)	4 (13)	1
Ileus[c]	1	1	
Post-discharge vomiting	1	2	

Characteristic	No. of patients (%)		*P* value
	LNUX with neoadjuvant chemotherapy n = 26	LNUX without neoadjuvant chemotherapy n = 56	
Pancreatitis	0	1	
Cardiovascular	1 (5)	3 (9)	0.652
Atrial fibrillation	0	1	
Ventricular tachycardia	1	0	
MI	0	1	
Lymphatic leak	0	1	
Respiratory	0 (0)	3 (9)	0.276
Pneumonia	0	1	
Pulmonary edema	0	1	
Respiratory failure	0	1	
Miscellaneous	4 (20)	9 (28)	0.743
Rash	0	2	
Mental status changes	0	2	
Other	4	5	
Complication grade[b]			
1	9 (45)	14 (44)	
2	8 (40)	12 (38)	
3	0 (0)	2 (6)	
4	1 (5)	2 (6)	
5	0 (0)	0 (0)	

Note: All data are presented as no. of patients (%) unless otherwise indicated.

Abbreviations: UTI, urinary tract infection; GI, gastrointestinal; MI, myocardial infarction.

[a] Clavien grade 3–5.

[b] Not including intraoperative complications.

[c] Pronounced postoperative nausea or vomiting requiring the withholding of oral food and fluid and/or the insertion of a nasogastric tube.

Table 4

Univariate and multivariate analyses of potential predictors of postoperative complications in patients who underwent laparoscopic radical nephroureterectomy with or without neoadjuvent chemotherapy for upper urinary tract urothelial carcinoma

	Univariate		Multivariate	
Variable	**OR (95% CI)**	***P* value**	**OR (95% CI)**	***P* value**
Age	1.0338 (0.9887–1.0808)	0.144	1.0385 (0.9879–1.0917)	0.138
BMI	0.9621 (0.8832–1.0481)	0.377	0.9521 (0.8654–1.0475)	0.313
Neoadjuvant chemotherapy (vs primary surgery)	1.5556 (0.6106–3.9632)	0.355	1.9906 (0.6754–5.8670)	0.212
pT ≥ 3	1.0552 (0.3775–2.9492)	0.918	0.7056 (0.2057–2.0421)	0.579
No. of lymph nodes removed	1.0043 (0.9570–1.0538)	0.863	0.9935 (0.9404–1.0496)	0.817
EBL	1.0004 (0.9996–1.0013)	0.302	0.9996 (0.9981–1.0010)	0.567
Operative time	1.2753 (0.8475–1.9191)	0.243	1.2661 (0.7883–2.0336)	0.329
PRBC transfused	1.2863 (0.9016–1.8351)	0.165	1.3479 (0.7625–2.3828)	0.304

Abbreviations: OR, odds ratio; CI, confidence interval; BMI, body mass index; pT, pathologic tumor stage; EBL, estimated blood loss; PRBC, packed red blood cells.