

Risk Factor Analysis of Intravesical Recurrence After Laparoscopic Nephroureterectomy for Upper Tract Urothelial Carcinoma

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Abstract

Background: One of the major concerns of patients with upper tract urothelial carcinoma (UTUC) treated with nephroureterectomy is intravesical recurrence (IVR). The purpose of the present study was to investigate the predictive risk factors for IVR after laparoscopic nephroureterectomy (LNU) for UTUC.

Methods: Clinicopathological and surgical information were collected from the medical records of 73 patients treated with LNU for non-metastatic UTUC, without a history of or concomitant bladder cancer. The association between IVR after LNU and clinicopathological and surgery-related factors, including preoperative urine cytology and pneumoperitoneum time, was analyzed using Cox proportional hazards regression models and the Kaplan–Meier method with log-rank test.

Results: During the median follow-up time of 39.1 months, 18 (24.7%) patients had subsequent IVR after LNU. The 3- and 5-year IVR-free survival rates were 76.5% and 74.3%, respectively. In the multivariate Cox regression analysis, positive preoperative urine cytology (hazard ratio [HR]: 3.55; 95% confidence interval [CI]: 1.326–11.327; $p=0.011$) and prolonged pneumoperitoneum time of ≥ 210 min (HR: 3.40; 95% CI: 1.271–10.692; $p=0.014$) were independent prognostic factors for IVR-free survival. In patients with positive urine cytology, the Kaplan–Meier method with log-rank test revealed that the 3-year and 5-years IVR free survival rates were 46.3% and 39.7%, respectively, in patients with a prolonged pneumoperitoneum time of ≥ 210 min, which was significantly lower than that in their counterparts (76% and 76%, respectively, $p=0.041$).

Conclusions: In UTUC patients with positive urine cytology, the occurrence of IVR is highly probable when the pneumoperitoneum time of LNU is prolonged (≥ 210 min). Strict follow-up after LNU is highly recommended for these patients.

Background

Upper tract urothelial carcinoma (UTUC) is a relatively uncommon condition and accounts for 5–10% of all urothelial malignancies [1]. Nephroureterectomy (NU) with excision of the bladder cuff is the gold standard treatment for non-metastatic UTUC. However, intravesical recurrence (IVR) after NU for UTUC frequently occurs, with an incidence rate of approximately 22–47% [1–4]. Several studies have investigated the risk factors of IVR after NU for UTUC. Reportedly, the risk factors for IVR after NU for UTUC include positive preoperative urine cytology, preoperative diagnostic ureteroscopic biopsy for UTUC, surgery-related factors, such as laparoscopic surgery or endoscopic approach of the bladder cuff excision, lymphovascular invasion (LVI), and concomitant carcinoma in situ (CIS) [4–8].

Recently, laparoscopic NU (LNU) is being performed globally for UTUC. However, there have been discussions about whether LNU increases the risk of postoperative IVR compared to open NU, and a consensus is yet to be reached [9–13]. On the other hand, few studies have investigated the risk factors of IVR after LNU, including surgery-related factors.

The purpose of the present study was to investigate the association between IVR after LNU for UTUC and clinicopathological and surgical factors, including preoperative urine cytology, urinary bladder tumor antigen (BTA), urinary nuclear mitotic apparatus protein 22 (NMP22), and pneumoperitoneum time.

Methods

Patient selection

We retrospectively identified 102 patients treated with LNU for non-metastatic UTUC at Nippon Medical School Hospital between 2012 and 2020. UTUC was diagnosed using computed tomography (CT), magnetic resonance imaging (MRI), and urine cytology. A diagnostic ureteroscopic biopsy was performed when required. All patients underwent preoperative cystoscopy. Of the 102 patients, 29 patients with a history of bladder cancer or concomitant bladder cancer were excluded from our study. Finally, 73 patients were included in the study.

Clinicopathological data

From the medical records, we collected clinicopathological and surgical information of the patients, including age, sex, laterality and location of the main tumor, presence or absence of hydronephrosis, preoperative urine cytology, preoperative urinary BTA level, preoperative urinary NMP22 level, necessity of diagnostic ureteroscopic biopsy, pneumoperitoneum time, total operating time, multifocality of the tumor, tumor size, pathological characteristics, necessity of adjuvant systemic chemotherapy (ASC), and oncological outcomes. Tumors were staged according to the 2002 American Joint Committee of Cancer tumor-node-metastasis (TNM) classification and were graded according to the 2004 World Health Organization classification [14].

Surgical procedure

While performing LNU, laparoscopic procedures were performed using the retroperitoneal approach in the kidney position, with 8 mmHg CO₂ gas pressure in all cases. The CO₂ gas pressure was increased temporarily when necessary. The maximum pressure of the CO₂ gas was 12 mmHg. In the laparoscopic procedure, we clamped the ureter after ligation of the renal arteries. A small iliac incision (Gibson incision) or lower abdominal midline incision was made to retrieve the kidney and ureter and to perform resection of the bladder cuff. In our institution, we have performed LNU in patients with non-metastatic localized or locally advanced UTUC (cTa-3N0M0). Therefore, lymphadenectomy was not performed in the present study.

Adjuvant therapy and follow-up

Adjuvant intravesical therapy is not administered at our institution. Four courses of ASC, such as the gemcitabine/cisplatin regimen or gemcitabine/carboplatin regimen, were administered to select pT2–4 patients. Of these patients, those with an estimated glomerular filtration rate (eGFR) of <30

ml/min/1.73 m² received ASC with the gemcitabine/carboplatin regimen, and the other patients received ASC with the gemcitabine/cisplatin regimen. After LNU, all patients were generally followed-up using blood tests, urine analysis, urine cytology, cystoscopy, and CT scan every three months for two years, and every six months thereafter. We defined IVR as a pathologically diagnosed bladder cancer after LNU.

Endpoint of the present study

The primary endpoint of the present study was to investigate the association between IVR after LNU for UTUC and clinicopathological and surgical factors, including preoperative factors of urine cytology, urinary BTA, urinary NMP22, and pneumoperitoneum time.

Statistical analysis

Statistical analyses were performed using JMP® 13 (SAS Institute Inc., Cary, NC, USA). The value of statistical significance was set at $P < 0.05$. To determine independent factors predicting IVR after LNU, univariate and multivariate analyses were performed using the Cox proportional hazards regression model. Survival curves were constructed using the Kaplan-Meier method, and differences between the groups were evaluated using the log-rank test. The cut-off value of pneumoperitoneum time of LNU was 210 minutes, which was defined as the maximum pneumoperitoneum time in the technical certification test of laparoscopic radical nephrectomy and LNU by the Japanese Society of Endourology [15].

Results

A total of 73 patients (56 men (76.7%), 17 women (23.3%); mean age: 72.9 years; range: 49–89 years) underwent LNU for UTUC in the present study (Table 1). Among the 73 patients, 37 (50.7%) and 36 (49.3%) had UTUC on the right and left sides, respectively. The main tumors were located in the ureter of 33 (45.2%) patients and in the renal pelvis of 40 (54.8%) patients. Of the 73 patients, 24 (32.9%) had ipsilateral hydronephrosis. Preoperative urine cytology, urinary BTA, and urinary NMP22 were positive in 32 (43.8%), 29 (39.7%), and 36 (49.3%) patients, respectively. Of the 73 patients, 24 (32.9%) underwent diagnostic ureteroscopic biopsy. The mean pneumoperitoneum time was 216 min (range: 111–384 min; median: 202 min), and the mean total operating time was 357 min (range: 232–587 min; median: 352 min). Of the 73 patients, 11 (15.1%) had multiple tumors and 40 (54.8%) had tumors larger than 3 cm. Tumors were pathologically diagnosed as pTa, 1, 2, 3, and 4 in 9 (5.5%), 21 (28.8%), 18 (24.7%), 23 (31.5%), and 2 (2.7%) patients, respectively. Of the 73 patients, 36 (49.3%), 18 (24.7%), and 52 (71.2%) were grade 3, LVI positive, and had infiltrative growth (INF) \geq b, respectively. Among the 73 patients, 23 (31.5%) were treated with ASC.

Table 1
 Characteristics of patients treated with LNU for upper urinary tract carcinoma

Preoperative factors		n = 73 (%)
Age (years)	mean ± SD	72.9 ± 8.3
Gender	male/ female	56 (76.7)/ 17 (23.3)
Laterality	right/ left	37 (50.7)/ 36 (49.3)
Location of main tumor	ureter/ renal pelvis	33 (45.2)/ 40 (54.8)
Hydronephrosis	yes/ no	24 (32.9)/ 49 (67.1)
Urine cytology	positive/ negative	32 (43.8)/ 41 (56.2)
Urinary BTA	positive/ negative	29 (39.7)/ 44 (60.3)
Urinary NMP22	positive/ negative	36 (49.3)/ 37 (50.7)
Diagnostic ureteroscopic biopsy	yes/ no	24 (32.9)/ 49 (67.1)
Intraoperative and postoperative factors		n = 73 (%)
Pneumoperitoneum time (min)	mean ± SD	216 ± 65
	≥ 210/ <210	32 (43.8)/ 41 (56.2)
Total operating time (min)	Mean ± SD	357 ± 75
	≥ 360/ <360	32 (43.8)/ 41 (56.2)
Multifocality	multiple/ single	11 (15.1)/ 62 (84.9)
Tumor size (cm)	≥ 3/ <3	40 (54.8)/ 33 (43.8)
Pathological T stage	≤ 1/ 2/ ≥3	30 (41.1)/ 18 (24.7)/ 25 (34.2)
Grade	1, 2/ 3	37 (50.7)/ 36 (49.3)
LVI	positive/ negative	18 (24.7)/ 55 (75.3)
INF	a/ b, c	21 (28.8)/ 52 (71.2)
ASC	yes/ no	23 (31.5)/ 50 (68.5)
SD, standard deviation; BTA, bladder tumor antigen, NMP22 nuclear mitotic apparatus protein 22; LVI, lymphovascular invasion; INF, infiltrative growth; ASC, adjuvant systemic chemotherapy.		

During the median follow-up of 39.1 months after LNU, 18 (24.7%) patients had IVR. The 3-year and 5-year IVR-free survival rates were 76.5% and 74.3%, respectively (Fig. 1). The histological type of bladder cancer in 18 patients was urothelial carcinoma. In 50% of these bladder cancers, the grade was lower than that of the initial UTUC diagnosis (Fig. 2). In the other 50% of bladder cancer cases, the grade was

the same grade as the initial UTUC. None of the bladder cancers had a higher grade than the initial UTUC diagnosis.

Table 2 shows the results of univariate and multivariate Cox regression analyses to identify the risk factors for IVR. Univariate analysis revealed that positive preoperative urine cytology ($p = 0.007$) and prolonged pneumoperitoneum time of ≥ 210 min ($p = 0.009$) were significant risk factors for IVR. Multivariate analysis also revealed that positive preoperative urine cytology (hazard ratio [HR]: 3.55; 95% confidence interval [CI]: 1.326–11.327; $p = 0.011$) and prolonged pneumoperitoneum time of ≥ 210 min (HR: 3.40; 95% CI: 1.271–10.692; $p = 0.014$) were independent risk factors for IVR.

Table 2
Univariate and multivariate analysis of IVR-free survival of patients after LNU according to clinicopathological and surgery-related factors

	Univariate analysis	Multivariate analysis		
	p value	HR	95% CI	p value
Age	0.074			
Male	0.818			
Right tumor	0.583			
Ureteral tumor	0.733			
Presence of hydronephrosis	0.671			
Preoperative positive urine cytology	*0.007	3.55	1.326–11.327	0.011
Preoperative positive urinary BTA	0.058			
Preoperative positive urinary NMP22	0.470			
Diagnostic ureteroscopic biopsy	0.184			
Pneumoperitoneum time \geq 210 min	*0.009	3.40	1.271–10.692	0.014
Total operating time \geq 360 min	0.132			
Multiple	0.358			
Tumor size \geq 3cm	0.507			
Pathological T stage \geq 3	0.798			
Grade 3	0.652			
LVI	0.522			
INF b, c	0.203			
Without ASC	0.830			
HR, hazard ratio; CI, confidence interval; BTA, bladder tumor antigen, NMP22 nuclear mitotic apparatus protein 22; LVI, lymphovascular invasion; INF, infiltrative growth; ASC, adjuvant systemic chemotherapy; * p < 0.05.				

Figure 3 demonstrates the IVR-free survival of patients with negative urine cytology and positive urine cytology according to pneumoperitoneum time categorized into < 210 min and \geq 210 min. In patients with negative urine cytology, the Kaplan–Meier method with log-rank test revealed that the 3-year and 5-year IVR-free survival rates were 86.7% and 86.7%, respectively, in patients with prolonged pneumoperitoneum time of \geq 210 min, which were not significantly different from those with pneumoperitoneum time of < 210 min (91.6% and 91.6%, respectively, p = 0.579) (Fig. 3a). In patients

with positive urine cytology, the Kaplan–Meier method with log-rank test revealed that the 3-year and 5-year IVR-free survival rates were 46.3% and 39.7%, respectively, among patients with prolonged pneumoperitoneum time of ≥ 210 min, which were significantly lower than those with pneumoperitoneum time of < 210 min (76.0% and 76.0%, respectively, $p = 0.041$) (Fig. 3b). We also categorized the patients according to the duration of pneumoperitoneum and IVR rates (Fig. 4). In patients with negative urine cytology, IVR rates were 7.7% for pneumoperitoneum time of < 210 min, 25% for that of 210–270 min, and 14.3% for pneumoperitoneum time of > 270 min (Fig. 4A). In patients with positive urine cytology, IVR rates were 20% for pneumoperitoneum time of < 210 min, 55.6% for that of 210–270 min, and 62.5% for pneumoperitoneum time of > 270 min (Fig. 4B).

Discussion

One of the greatest concerns of UTUC patients treated with NU remains to be the occurrence of IVR. Previous studies have reported that IVR after NU occurs with an incidence of approximately 22–47% [1–4]. In the present study, the rate of IVR incidence was 24.7%, which was consistent with previous studies. In this study, we demonstrated that positive urine cytology (HR: 3.55; 95% CI: 1.326–11.327; $p = 0.011$) and a prolonged pneumoperitoneum time of ≥ 210 min (HR, 3.40; 95% CI: 1.271–10.692, $p = 0.014$) were independent risk factors for IVR occurrence (Table 2). In a previous study investigating the association between pneumoperitoneum time and IVR, Sigeta et al. revealed that the duration of pneumoperitoneum time was positively correlated with the rate of recurrence [8]. They analyzed a cohort similar to the present study that excluded patients with a history of bladder cancer or concomitant bladder cancer; the IVR rate after LNU was 47.3% during the median follow-up of 31.1 months after LNU. They performed LNU with 10 mmHg CO₂ gas pressure and the median pneumoperitoneum time was 150 min; meanwhile, the median pneumoperitoneum time of the present study was 202 min, which was significantly longer than that of the previous study. However, in the present study, the IVR rate after LNU was 24.7% during the median follow-up of 39.1 months after LNU, which was significantly lower than the IVR rate of the study by Sigeta et al. Their conclusions could not explain the low IVR rates obtained. Comparing their cohort and methods with ours, one of the differences was observed in pneumoperitoneum pressure. Laparoscopic surgery is generally performed with 5–15 mmHg CO₂ gas pressure [20]. Therefore, the CO₂ gas pressure during the laparoscopic procedure of LNU differs between institutions. In recent studies on LNU, laparoscopic procedures were performed with 10–14 mmHg CO₂ gas pressure [8, 16, 17]. It was suggested that a low CO₂ gas pressure of 8 mmHg in the present study might have influenced the low IVR rates.

In the present study, 210 min, which is close to the mean and median pneumoperitoneum time, was used as the cut-off value for pneumoperitoneum time. In patients with negative urine cytology, IVR-free survival did not differ between patients with prolonged pneumoperitoneum time (≥ 210 min) and those with pneumoperitoneum time of < 210 min (Fig. 3A) ($p = 0.579$). On the other hand, in patients with positive urine cytology, IVR-free survival was significantly lower in patients with prolonged pneumoperitoneum time (≥ 210 min) than in those with pneumoperitoneum time of < 210 min ($p = 0.041$) (Fig. 3B). In

addition, in positive urine cytology, the rate of IVR incidence tended to increase as the operation time was prolonged (Fig. 4B). The present study is the first to demonstrate that in patients with positive urine cytology, prolonged pneumoperitoneum time increases the frequency of IVR after LNU for UTUC. Further studies comparing different CO₂ gas pressures are required to investigate the impact of CO₂ gas pressure on IVR after LNU.

Recent molecular genetic studies have suggested that intraluminal seeding is one of the main mechanisms of IVR after NU [18–20]. It was also reported that continuous intravesical irrigation with distilled water or physiological saline solution during LNU decreased the rate of IVR incidence [21]. They concluded that continuous intravesical irrigation might eliminate cancer cells floating in the bladder during surgery before they become engrafted on the mucous membrane of the bladder. This result suggests that IVR after NU occurs due to intraluminal seeding. Recent studies demonstrated that prolonged pneumoperitoneum time and diagnostic ureteroscopic biopsy are independent factors of IVR after NU [5, 8]. Based on these results of past studies, long-term pneumoperitoneum pressure to the tumor and direct destruction of the tumor by diagnostic ureteroscopic biopsy might contribute to intraluminal seeding. In the present study, in patients with preoperative positive urine cytology, prolonged pneumoperitoneum time was a risk factor for IVR after LNU. UTUC with positive urine cytology is a type of cancer that releases cancer cells into the urine, and long-term pneumoperitoneum pressure during LNU might promote the release of cancer cells into the urine. In the present study, the grade of bladder cancer with IVR was not higher than that of initial UTUC (Fig. 1). It has also been suggested that IVR tumors are caused by intraluminal seeding from UTUC.

The BTA test detects the human complement factor H-related protein secreted in the urine. While the NMP22 test detects the protein level of the nuclear mitotic apparatus. Positive urinary BTA and NMP22 have been reported as predictors of the presence of bladder cancer and UTUC, along with positive urine cytology [22–25]. In the present study, the risk factor for IVR was not positive urinary BTA or urinary NMP22, but positive urine cytology. Urinary BTA and NMP22 are considered unsuitable for predicting IVR after LNU because the values of urinary BTA and NMP22 generally have a positive correlation with tumor volume; however, urinary BTA and NMP22 do not directly detect cancer cells.

Recently, two prospective randomized trials have demonstrated that a single early intravesical chemotherapy cycle using mitomycin C or pirarubicin after NU decreased the risk of IVR [26, 27]. However, the type of patients that will benefit from this treatment remains unclear. From our results, we strongly recommend that patients with positive urine cytology with pneumoperitoneum time of ≥ 210 min should receive a single early intravesical chemotherapy after LNU with 8 mmHg CO₂ gas pressure.

The present study has several limitations. UTUC is a relatively uncommon condition. We excluded patients with a history of bladder cancer or concomitant bladder cancer, because the purpose of the present study was to investigate the risk factors for IVR after LNU for UTUC. In addition, this study was conducted in a single institution; therefore, the cohort in this study was small. Since the study was a retrospective analysis, there might be a selection bias for the surgeons. In this study, 13 surgeons

performed the LNU procedure. However, three experienced surgeons who had performed more than 100 laparoscopic surgeries performed or supervised all of the LNU procedures. In addition, the rate of IVR incidence in our study was lower than that reported in previous studies. Based on these facts, we believe that the participation of inexperienced surgeons in LNU had little impact on the IVR rate in the present study. To reduce these limitations, prospective studies with larger cohorts from several institutions are required.

Conclusions

Positive urine cytology was the strongest factor for IVR after LNU with 8 mmHg CO₂ gas pressure. In patients with positive urine cytology, a prolonged pneumoperitoneum time of ≥ 210 min was a significant factor for IVR after LNU with 8 mmHg CO₂ gas pressure. For patients with positive urine cytology, it is necessary to devise a strategy to shorten the pneumoperitoneum time. In addition, when the pneumoperitoneum time is prolonged (≥ 210 min) in LNU with 8 mmHg CO₂ gas pressure for patients with positive urine cytology, strict follow-up after LNU is highly recommended.

Abbreviations

ASC: adjuvant systemic chemotherapy, **BTA:** bladder tumor antigen, **CI:** confidence interval, **CIS:** carcinoma in situ, **CT:** computed tomography, **eGFR:** estimated glomerular filtration rate, **HR:** hazard ratio, **INF:** infiltrative growth, **IVR:** intravesical recurrence, **JSE:** Japanese Society of Endourology

LNU, laparoscopic nephroureterectomy; **LVI,** lymphovascular invasion; **NMP22,** nuclear mitotic apparatus protein 22; **NU,** nephroureterectomy; **UTUC,** upper tract urothelial carcinoma

Declarations

Ethics approval and consent to participate

This study was performed in line with the principles of the Declaration of Helsinki. The Ethics Committee at Nippon Medical School Hospital approved this study (approval number: 30-03-1100). All study participants provided informed consent.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Competing interests

The authors declare that they have no competing interests.

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No funding was received for this study.

Authors' contributions

Conception and Design: MY Collection of data: MY and YE Data analysis: MY. Manuscript writing: All authors. Final approval of the manuscript: All authors.

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Figures

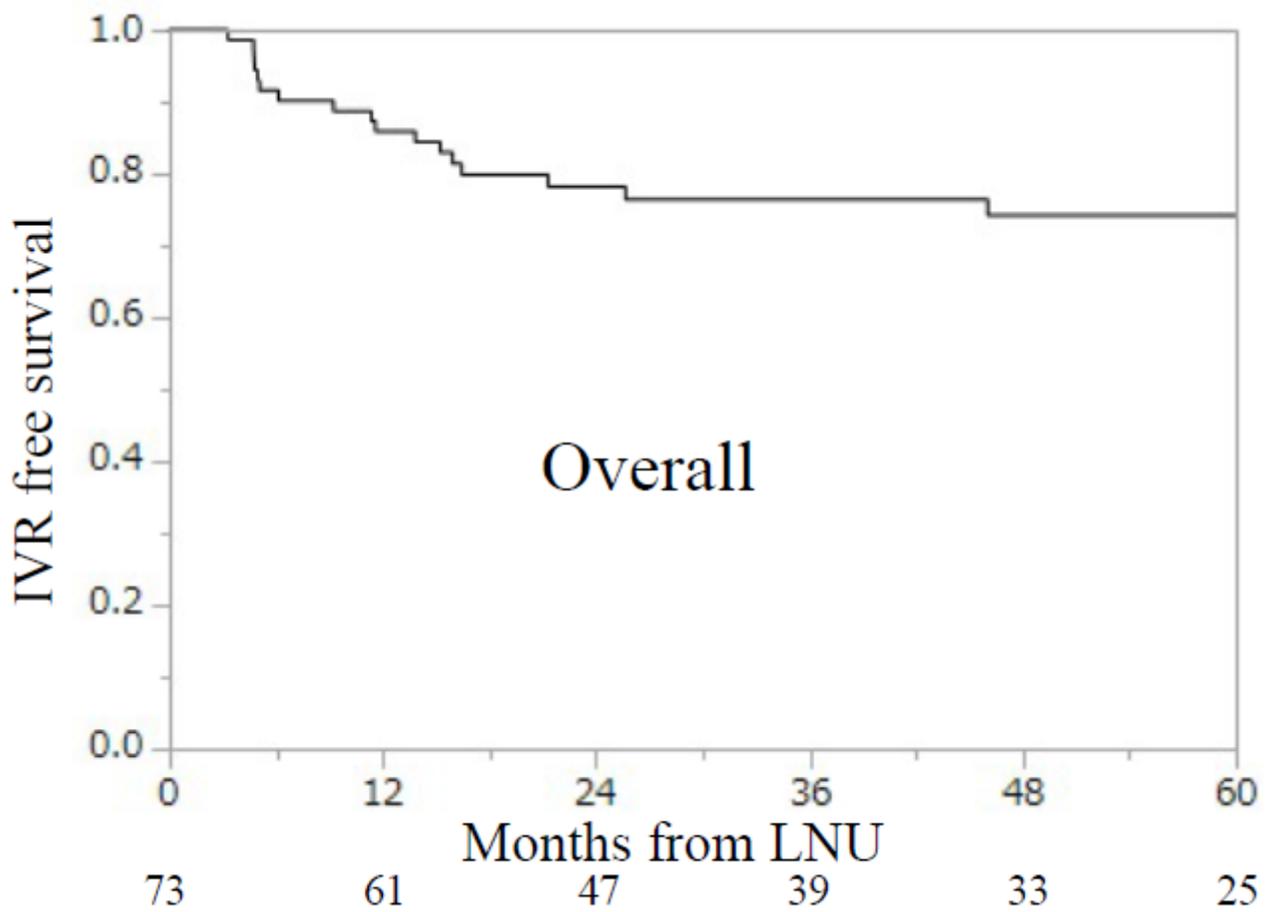


Figure 1

IVR-free survival in 73 patients Kaplan-Meier curves of IVR-free survival in 73 patients The 3-and 5-year IVR-free survival rates were 76.5% and 74.3%, respectively.

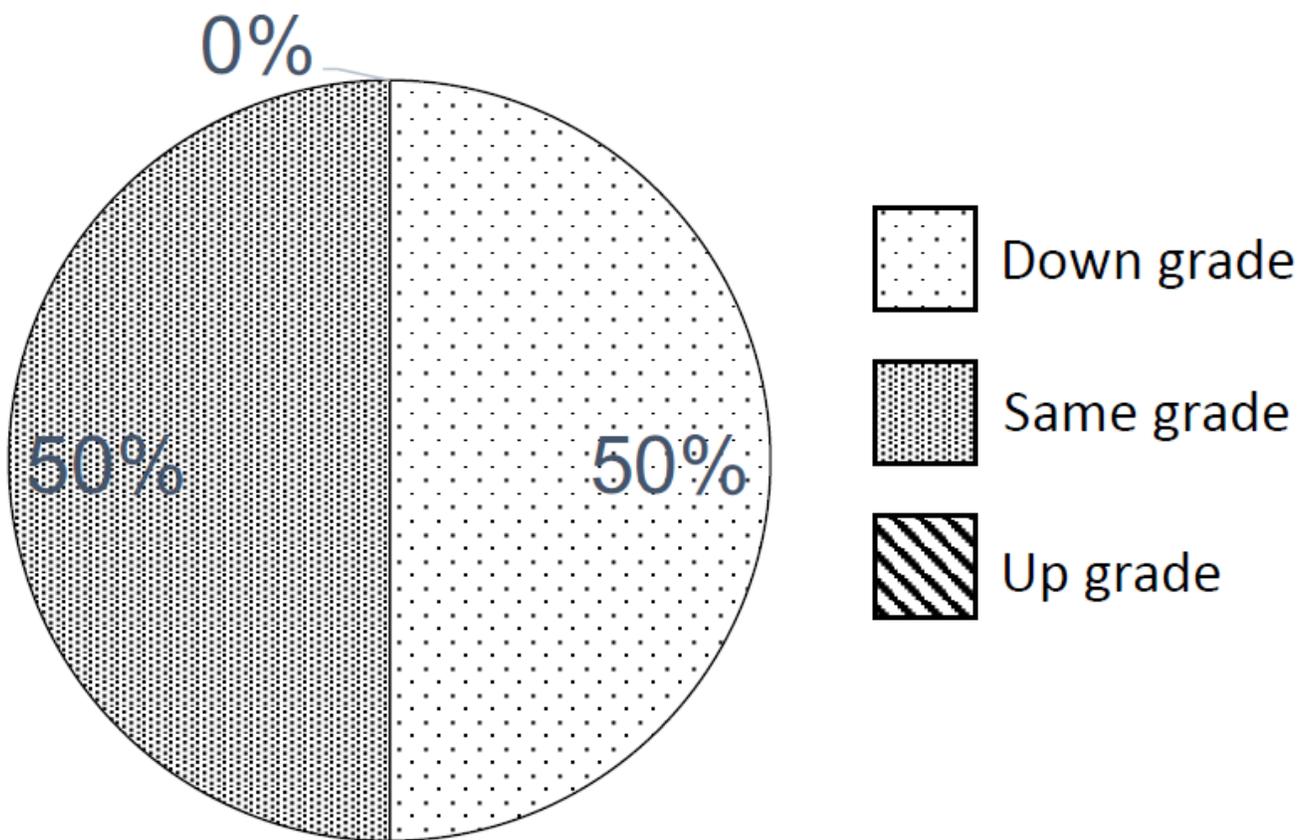


Figure 2

The percentage of change in grade of tumor of IVR compared to grade of initial UTUC. In 50% of IVR tumors, the grade was lower than that of the initial UTUC, and in the other 50% of IVR tumors, the grade was the same as the initial UTUC. None of the IVR tumors had a higher grade than the UTCU.

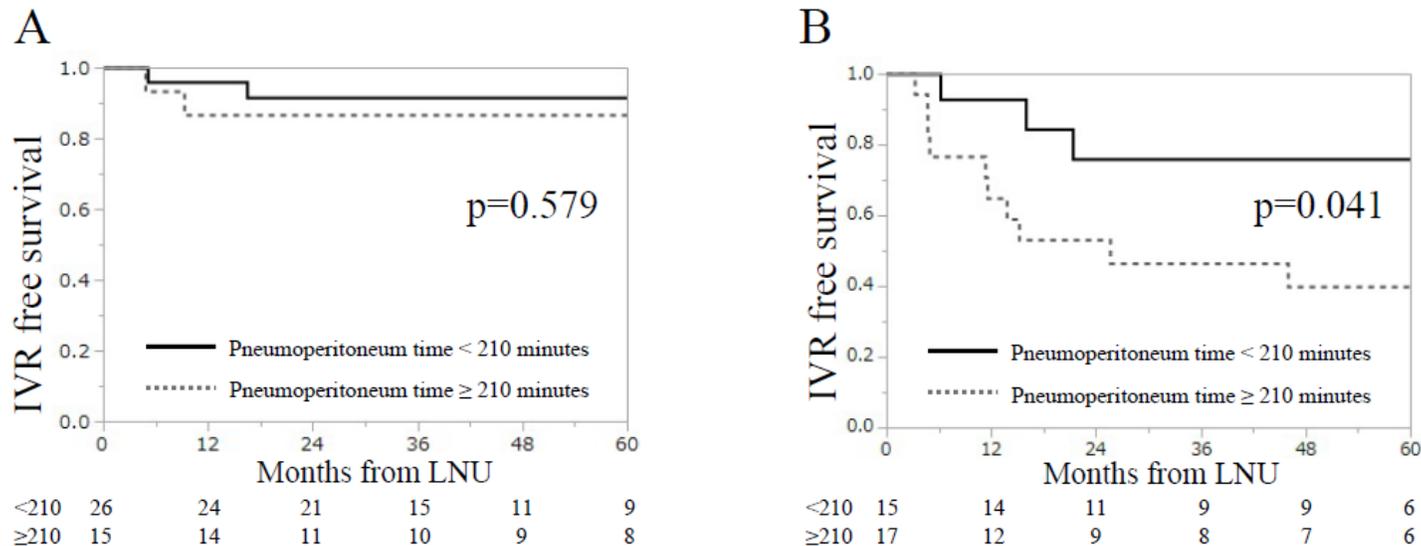


Figure 3

IVR free survival in patients with negative and positive urine cytology. Kaplan-Meier curves of IVR-free survival in (A) 41 patients with negative urine cytology and (B) 32 patients with positive urine cytology results. Comparison between patients with pneumoperitoneum time of <210 min and ≥ 210 min (A) The 3-year and 5-year IVR-free survival rates of patients with negative urine cytology with pneumoperitoneum time of <210 min were 91.6% and 91.6%, respectively, and that of patients with pneumoperitoneum time of ≥ 210 min were 86.7 and 86.7%, respectively. (B) The 3-year and 5-year IVR-free survival rates of patients with positive urine cytology with pneumoperitoneum time of <210 min were 76% and 76%, respectively, and that of patients with pneumoperitoneum time of ≥ 210 min were 46.3% and 39.7%, respectively.

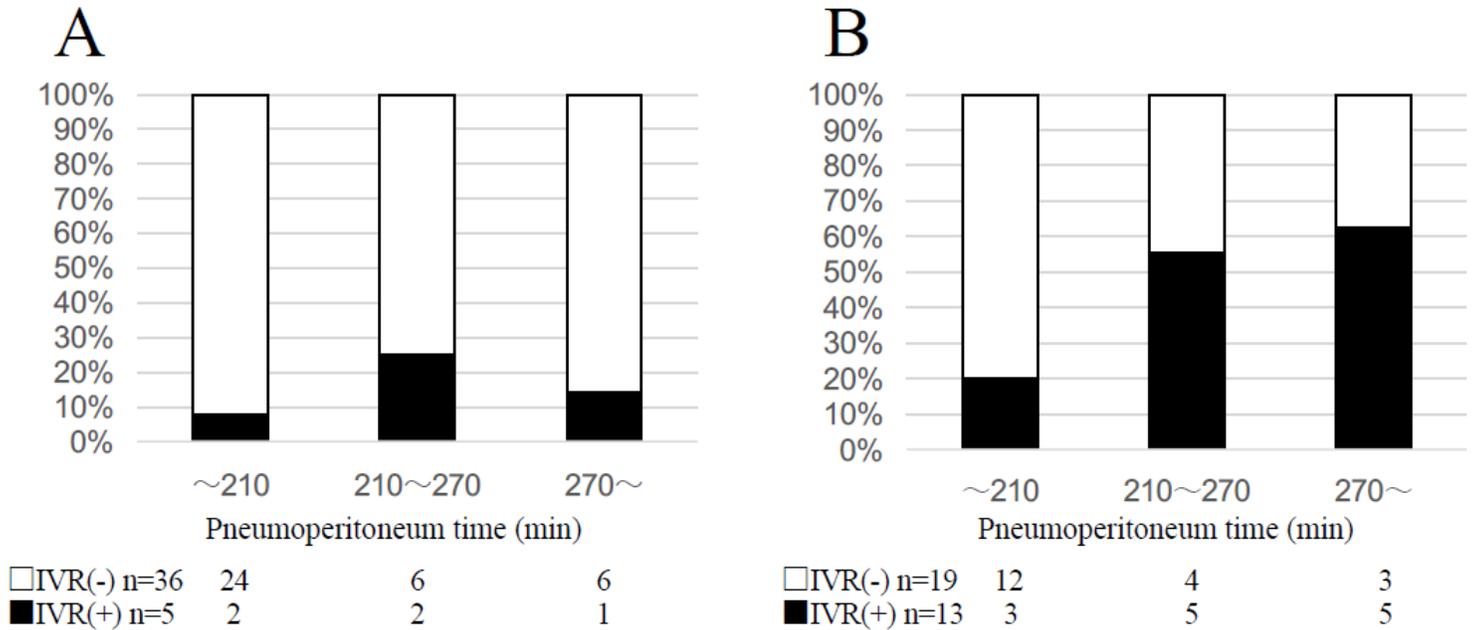


Figure 4

Recurrence rate by pneumoperitoneum time (A) IVR rate of patients with preoperative negative urine cytology (B) IVR rate of patients with preoperative positive urine cytology