



Prolonged pneumoperitoneum time is an independent risk factor for intravesical recurrence after laparoscopic radical nephroureterectomy in upper tract urothelial carcinoma



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ABSTRACT

Objective: To evaluate the impact of pneumoperitoneum time on intravesical recurrence (IVR) in upper tract urothelial carcinoma (UTUC) patients who underwent laparoscopic radical nephroureterectomy (LRNU).

Patients and methods: We identified 129 UTUC patients who underwent LRNU at our three institutions from 2004 to 2014. We evaluated the association of IVR rate and patient clinico-pathological characteristics including operation time. By retrospectively reviewing all videotapes, we defined pneumoperitoneum time as being from the infusion of pressurized CO₂ gas with a pressure of 10–12 mmHg to extirpation of the kidney.

Results: During the median follow-up of 31.1 months, 61 (47.3%) had subsequent IVR after LRNU. Multivariate analysis revealed that prolonged pneumoperitoneum time (HR = 1.81, $p = 0.025$) and presence of lymphovascular invasion (LVI) (HR = 1.53, $p = 0.006$) were independent risk factors for subsequent IVR. The 3-year and 5-year IVR free survival rates were 43.7% and 21.8% in patients with a prolonged pneumoperitoneum time of ≥ 150 min, which were significantly lower than those in their counterparts (59.0% and 48.3%, respectively, $p = 0.024$). The subsequent IVR rates were 27.3% for a pneumoperitoneum time of < 90 min, 35.8% for that of 90–150 min, 55.0% for that of 150–210 min, 61.1% for that of 210–270 min, and 85.7% for that of > 270 min.

Conclusions: Prolongation of pneumoperitoneum time and presence of LVI might be associated with higher risk of subsequent IVR in UTUC patients who underwent LRNU.

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1. Introduction

Upper tract urothelial carcinoma (UTUC), which comprises cancer of the ureter and renal pelvis, is relatively uncommon and accounts for only approximately 5% of urothelial malignancies [1]. Open radical nephroureterectomy (ORNU) with excision of a bladder cuff has been the gold standard of treatment for localized or locally advanced UTUC. The major concern of UTUC patients is that intravesical recurrence (IVR) after surgical management often

occurs with an approximately 15%–50% incidence [2]. Therefore, various studies have attempted to verify the specific risk factors for accurate prediction of IVR [3,4]. So far, patient specific factors such as male gender and previous history of bladder cancer, tumor specific factors such as positive preoperative urinary cytology, ureteral location, tumor multifocality, pathological T (pT) stage, and lymphovascular invasion (LVI), and surgical related factors such as laparoscopic procedure, extra-vesical bladder cuff removal, and positive surgical margins have been discussed as risk factors for IVR [5,6].

There is an ongoing debate as to whether laparoscopic radical nephroureterectomy (LRNU) increases the subsequent IVR or not. Since LRNU was introduced for new surgical treatment in UTUC, it has emerged as an accepted minimally invasive treatment

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alternative to ORNU in terms of reliable perioperative safety and oncologic efficacy [7–9]. As LRNU with bladder cuff removal becomes popular as a surgical option in UTUC patients, several studies have pointed out the potential risk of a higher IVR rate in laparoscopic procedures [3,10,11]. It was initially postulated that procedure-related elevated-pressure pneumoperitoneum may accelerate the gravitational migration of tumor cells, which leads to tumor cell seeding to the bladder. However, because UTUCs are well known as rare tumors and therefore studies were conducted with a small sample size of patients with heterogeneous backgrounds, the mechanism of IVR with LRNU has not been well characterized.

Therefore, we hypothesized that the continuous pressure of CO₂ gas in a pneumoperitoneum during a laparoscopic procedure may promote the spread and dispersal of cancer cells into the lower urinary tract and result in a higher incidence of subsequent IVR. Our aim was to evaluate the association of pneumoperitoneum time on IVR in patients who underwent LRNU.

2. Patients and methods

This was an Institutional Review Board-Approved study obtained from three institutions, consisting of Keio University Hospital and 2 affiliated facilities. We retrospectively identified a total of 360 UTUC patients who underwent either ORNU or LRNU from January 2004 to March 2014. After excluding 209 patients who underwent ORNU and 22 patients who had concomitant or previous history of bladder cancer, a total of 129 patients treated with LRNU were included in the study population.

LRNU was performed according to the standard procedure, ie, extrafascial dissection of the kidney with 2/3 of the length of the ureter resected together under laparoscopic procedure. LRNU was performed using either a transperitoneal approach or retroperitoneal approach for extirpation of the kidney, and a small iliac incision (Gibson incision) was made to retrieve the kidney and ureter en bloc and to perform resection of the bladder cuff. We performed LRNU for clinical T3 or less UTUCs without positive lymph node or distant metastasis (cT_a-3N0M0). Therefore, dissection of regional lymph nodes was performed only in patients who were suspected of having enlarged nodes at intraoperative inspection.

To accurately determine the surgical outcomes associated with LRNU, we divided the total procedure into two categories; extirpation of the kidney and bladder cuff excision. We then measured the operation time in each group and defined total surgical operative time as the sum of the pneumoperitoneum time and bladder cuff excision time. We retrospectively reviewed all recorded videotapes and defined pneumoperitoneum time as that from infusing pressurized CO₂ gas with a standard pressure of 10 mmHg to maximum pressure of 12 mmHg during extirpation of the kidney. The time needed for repositioning the patient from a lateral to supine position and re-draping with sterile cloth are included in the bladder cuff excision time.

Perioperative clinico-pathological data were obtained. Tumor stage was assessed according to the 2002 American Joint Committee of Cancer tumor-node-metastasis (TNM) classification. LVI was defined as the presence of tumor cells within endothelium-lined space without underlying muscular walls [12]. Tumor location was defined into 2 areas; ureter and/or renal pelvis. Tumor multifocality was defined as pathologically confirmed tumors with 2 distinct locations within the upper urinary tract involving both the renal pelvis and ureter [13]. Urine cytology was evaluated preoperatively using voided samples before any of the manipulations such as retrograde pyelography or ureteroscopic evaluation [14,15].

Patients were generally followed up every 3 months for 2 years, every 6 months until the third year, and annually thereafter after

LRNU. Follow-up examinations after surgery consisted of medical history, urine analysis, physical examination, routine blood test, urinary cytology, and cystoscopic evaluation of the urinary bladder. Any positive examination results suggesting IVR were pathologically proven through biopsy, and/or transurethral resection. Non-bladder recurrence, contralateral upper urinary tract recurrence, and distant metastasis were also evaluated by computed tomography scan during the follow-up period.

3. Statistical analysis

The continuous variables and categorical variables of different groups were compared using the Mann-Whitney *U* test and Chi-square test, respectively. Continuous variables were dichotomized, in principle, according to their medians. The median of each operating time (pneumoperitoneum, bladder cuff excision, and total operative time) was used as a threshold value in order to discriminate between short and long operative times. Univariate Cox regression models were used to adjust for potential confounders in predicting IVR. Covariates with significant *p* values (<0.05) in univariate analysis were included in the multivariable analysis. The impact of surgical outcomes and other clinico-pathological parameters were assessed in multivariate models using Cox proportional hazard regression models with a stepwise forward selection method. Kaplan-Meier analysis was conducted for the evaluation of operation time and IVR free rate after LRNU. For all statistical analyses, tests were two-sided and *p* < 0.05 was considered to indicate statistical significance. All statistical analyses were performed using Statistical Package of the Social Sciences software, version 22.0 (SPSS, Chicago, Illinois, USA).

4. Results

4.1. Patients' background

The median age of our cohort was 71 years (range, 40–88). Males accounted for 103 (79.8%) and females 26 (20.2%) of the patients. The median follow-up time was 31.1 months (range, 11.7–128). Table 1 presents the baseline characteristics of the clinico-pathological features of the 129 patients. Overall, UTUC was located in the pelvis in 63 (48.8%) patients and in a ureter in 66 (51.2%) patients. The distribution of pT stage was 49 (38.0%) for equal or lower than pT1, 23 (17.8%) for pT2, and 57 (44.2%) for pT3. No lymph node metastasis was identified in our cohort. A transperitoneal approach was used for LRNU in 81 (62.8%) patients, while the remaining 48 (37.2%) patients underwent LRNU by a retroperitoneal procedure.

4.2. The association between related operative time and IVR rate

A total of 61 (47.3%) patients experienced IVR thereafter, and the median duration of the IVR free term was 19.4 months (range, 1.7–102.9). Referring to the surgical outcomes, the median pneumoperitoneum time was 150 min (range, 38–387), median bladder cuff time was 135 min (range, 109–678), and median total operation time was 297 min (range, 147–906). No significant association was observed between the pneumoperitoneum time (<150 vs. ≥150) and the clinico-pathological parameters tested in the study cohort (Table 1).

Table 2 indicates the result of univariate and multivariate analyses which were performed to identify the risk factors for IVR. Univariate analysis revealed that pT stage of <T3 (*p* = 0.010), the presence of LVI (*p* = 0.006), prolonged pneumoperitoneum time (*p* = 0.027), prolonged total operation time (*p* = 0.027), and adjuvant chemotherapy not performed (*p* = 0.044) were significantly

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