



Original Article

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Laparoscopy versus Open Nephroureterectomy in Prognostic Outcome of Patients with Advanced Upper Tract Urothelial Cancer: A Retrospective, Multicenter, Propensity-Score Matching Analysis

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Purpose

The purpose of this study was to compare oncologic outcomes between open nephroureterectomy (ONU) and laparoscopic nephroureterectomy (LNU) in patients with upper tract urothelial carcinoma.

Materials and Methods

The medical records of consecutive ONU and LNU cases from five tertiary institutions were retrospectively analyzed between 2000 and 2012. The propensity-score matching methodology was used to compare the two surgical approaches in terms of age, body mass index, American Society of Anesthesiologists score, tumor location, grade, pathologic T and N categories, the presence of lymphovascular invasion, and follow-up duration. The Kaplan-Meier with log-rank tests and clustered Cox regression were used to compare the estimated rates of survival for each surgical approach and to investigate the effect of the surgical approach on each prognostic outcome.

Results

Six hundred thirty-eight propensity-score matching pairs (n=1,276) were compared; LNU was significantly better than ONU in all types of survival, including intravesical recurrence-free survival (IVRFS), disease-free survival, overall survival (OS), and cancer-specific survival (CSS) ($p < 0.05$). The 3-year OS and CSS rates were significantly higher with LNU than with ONU ($p < 0.05$). Compared with ONU, LNU had significantly better 3-year OS and CSS rates (82.9% and 86.2% vs. 78.3% and 81.8%); there were no differences at 5 years. In subgroup analysis of the early-staged group, advanced-stage group, lymph node-positive group, and lymph node-negative group, the two approaches did not significantly affect prognostic outcomes, except LNU improved the IVRFS in the lymph node-negative or no history of previous bladder cancer group.

Conclusion

LNU had a significantly better prognostic outcome than ONU after propensity-score matching.

Key words

Urothelial carcinoma, Laparoscopy, Nephroureterectomy, Prognosis, Survival

Introduction

Upper urinary tract urothelial carcinoma (UTUC) accounts for 5%-10% of all urothelial carcinomas with an estimated annual incidence of 1-2 cases per 100,000 inhabitants [1]. The gold standard curative treatment for localized UTUC is radical nephroureterectomy (RNU) with ipsilateral bladder cuff removal. The surgery provides adequate local tumor control and long-term survival, except for patients with regional nodal metastases and distant metastases with poor estimated 5-year survival rates less than 30% and 10%, respectively [2].

RNU can be performed using two different techniques: open or laparoscopically. Previous comparative series between the two techniques in UTUC showed differences in whether the perioperative outcome was better with laparoscopic RNU (LNU) and whether the oncologic outcome was better with open RNU (ONU) [3-7]. Several studies including Peyronnet et al.'s study [4] with 2,629 patients who underwent LNU and 4,925 patients who underwent ONU emphasized a poorer oncologic outcome in the LNU group than in the ONU group, especially for patients with laparoscopic bladder cuff removal and locally advanced high-risk cancer (pT3/pT4 and/or high-grade cancer) [3,7]. Another recent study by Kido et al. [8] reported an insignificant effect of the surgical technique on prognostic outcome in 229 patients (21%) with locally advanced UTUC who underwent LNU. Liu et al. [9] also reported no statistically significant differences in prognostic survival between the LNU and ONU groups among 265 patients with UTUC (stage T1-4/N0-X) who underwent RNU. However, all these conclusions came from retrospective studies and systemic reviews of patients with different baseline clinicopathological parameters and several inherent selection biases.

Therefore, the present study aimed to compare ONU and LNU in terms of multiple oncologic outcomes, including intravesical recurrence-free survival (IVRFS), disease-free survival (DFS), cancer-specific survival (CSS), and overall survival (OS), after eliminating the different baseline clinicopathological characteristics important for survival prognosis in UTUC by using the propensity-score matching methodology. Five tertiary Korean institutions collected their patients with UTUC who underwent either LNU or ONU and performed subset analyses according to the tumor stages (T1-2, T3-4, N+, and N0) to evaluate the technical differences in their prognostic outcomes.

Materials and Methods

1. Patient population

We retrospectively reviewed data from 1,521 patients with UTUC underwent either ONU (n=906) or LNU (n=615) with bladder cuffing from five participating tertiary Korean institutions (National Cancer Center, Asan Medical Center, Samsung Medical Center, Seoul National University Hospital, and Korea University Hospital) in the Urothelial Cancer-Advanced Research and Treatment (UCART) Study Group between January 2000 and December 2012. We excluded patients with previous or concomitant radical cystectomy, bilateral UTUC, no complete follow-up records, partial ureterectomy, and a history of neoadjuvant chemotherapy. Medical records were reviewed for age at surgery, sex, body mass index (BMI), American Society of Anesthesiologists (ASA) score, previous bladder cancer, concomitant bladder cancer, tumor location, pathological tumor stage, tumor grade, the presence of lymphovascular invasion (LVI) or concomitant carcinoma *in situ*, lymph node status, receipt of adjuvant chemotherapy, follow-up, and oncologic outcomes. The 1998 World Health Organization/International Society of Urologic Pathology consensus classification was used for tumor grading [8], and the 2010 American Joint Committee on Cancer/Union Internationale Contre le Cancer [Tumor-Node-Metastasis] classification was used for tumor staging [9].

RNU was performed using the open or laparoscopic technique according to the standard surgical methodology (intra-vesical or extra-fascial dissection of the kidney with the entire length of the ureter and with the adjacent segment of the bladder cuff). The indications for ONU or LNU and their operative techniques were mainly based on the surgeon's discretion, which have previously been described [3,10]. Dissection of the hilar and regional lymph nodes adjacent to the ipsilateral great vessel was performed according to the surgeon's discretion if the lymph node was intraoperatively palpable or enlarged on preoperative axial imaging. To eliminate the learning curve of LNU, the early cases of LNU in the first 5 years of performing LNU were excluded from the data collection. Adjuvant chemotherapy was administered according to the pathologic stage for those who generally had non-organ-confined disease (stages 3-4).

2. Follow-up schedule

Patients were generally evaluated every 3-4 months during the first year after RNU, every 6 months during years 2-5, and annually thereafter. However, not all follow-up protocols were standardized because of the retrospective, multi-center study design. Cystoscopy, blood tests, and urine tests

Table 1. Baseline characteristics before and after propensity-score matching

| Variable | Original data set | | | Matched cohort set | | | | |
|-----------------------------------|---------------------|---------------------|---------------------|--------------------|---------------------|---------------------|---------------------|---------|
| | Total (n=1,693) | ONU (n=978) | LNLU (n=715) | p-value | Total (n=1,276) | ONU (n=638) | LNLU (n=638) | p-value |
| Age (yr) | 65.00 (24.00-89.98) | 65.00 (24.00-89.98) | 65.00 (29.49-87.71) | 0.646 | 65.69 (24.00-89.98) | 66.00 (24.00-89.98) | 65.00 (29.49-86.00) | 0.842 |
| Sex | | | | | | | | |
| Male | 1,247 (73.66) | 715 (73.11) | 532 (74.41) | 0.550 | 941 (73.75) | 460 (72.10) | 481 (75.39) | 0.190 |
| Female | 446 (26.34) | 263 (26.89) | 183 (25.59) | | 335 (26.25) | 178 (27.90) | 157 (24.61) | |
| BMI (kg/m ²) | 24.21 (10.12-48.23) | 24.13 (10.12-48.23) | 24.42 (15.28-39.50) | 0.011 | 24.28 (10.12-48.23) | 24.23 (10.12-48.23) | 24.30 (15.28-37.97) | 0.899 |
| ASA score | | | | | | | | |
| 1 | 419 (24.75) | 269 (27.51) | 150 (20.98) | < 0.001 | 298 (23.35) | 154 (24.14) | 144 (22.57) | 0.750 |
| 2 | 1,137 (67.16) | 619 (63.29) | 518 (72.45) | | 890 (69.75) | 439 (68.81) | 451 (70.69) | |
| 3 | 102 (6.02) | 60 (6.13) | 42 (5.87) | | 77 (6.03) | 39 (6.11) | 38 (5.96) | |
| Unknown | 35 (2.07) | 30 (3.07) | 5 (0.70) | | 11 (0.86) | 6 (0.94) | 5 (0.78) | |
| Previous bladder cancer | | | | | | | | |
| No | 1,365 (80.63) | 776 (79.35) | 589 (82.38) | 0.163 | 1,028 (80.56) | 502 (78.68) | 526 (82.45) | 0.218 |
| Previous bladder tumor Hx. | 205 (12.11) | 135 (13.39) | 74 (10.35) | | 161 (12.62) | 92 (14.42) | 69 (10.82) | |
| Concomitant bladder tumor Hx. | 123 (7.27) | 71 (7.26) | 52 (7.27) | | 87 (6.82) | 44 (6.90) | 43 (6.74) | |
| Concomitant bladder cancer | | | | | | | | |
| No | 1,570 (92.73) | 907 (92.74) | 663 (92.73) | 0.992 | 1,189 (93.18) | 594 (93.10) | 595 (93.26) | 0.914 |
| Yes | 123 (7.27) | 71 (7.26) | 52 (7.27) | | 87 (6.82) | 44 (6.90) | 43 (6.74) | |
| Tumor location | | | | | | | | |
| Renal pelvis | 757 (44.71) | 431 (44.07) | 326 (45.59) | 0.033 | 573 (44.91) | 286 (44.83) | 287 (44.98) | 0.958 |
| Ureter | 643 (37.98) | 358 (36.61) | 285 (39.86) | | 498 (39.03) | 246 (38.56) | 252 (39.50) | |
| Both renal pelvis and ureter | 293 (17.31) | 189 (19.33) | 104 (14.55) | | 205 (16.07) | 106 (16.61) | 99 (15.52) | |
| Tumor grade | | | | | | | | |
| I | 46 (2.72) | 28 (2.86) | 18 (2.52) | < 0.001 | 33 (2.59) | 16 (2.51) | 17 (2.66) | 0.647 |
| II | 536 (31.66) | 339 (34.66) | 197 (27.55) | | 393 (30.80) | 198 (31.03) | 195 (30.56) | |
| III | 427 (25.22) | 271 (27.71) | 156 (21.82) | | 310 (24.29) | 159 (24.92) | 151 (23.67) | |
| Missing/ Unknown | 684 (40.40) | 340 (34.76) | 344 (48.11) | | 540 (42.32) | 265 (41.54) | 275 (43.10) | |
| Tumor grade II | | | | | | | | |
| Low grade | 512 (30.24) | 284 (29.40) | 228 (31.89) | 0.341 | 381 (29.86) | 178 (27.90) | 203 (31.82) | 0.367 |
| High grade | 1,136 (67.10) | 670 (68.51) | 466 (65.17) | | 863 (67.63) | 445 (69.75) | 418 (65.52) | |
| Unknown | 45 (2.66) | 24 (2.45) | 21 (2.94) | | 32 (2.51) | 15 (2.35) | 17 (2.66) | |

(Continued to the next page)

Table 1. Continued

| Variable | Original data set | | | Matched cohort set | | | p-value |
|---------------------------------|---------------------|---------------------|---------------------|---------------------|---------------------|---------------------|---------|
| | Total (n=1,693) | ONU (n=978) | LNu (n=715) | Total (n=1,276) | ONU (n=638) | LNu (n=638) | |
| Pathological T category | | | | | | | |
| pTis/pT _a | 255 (15.06) | 150 (15.34) | 105 (14.69) | 192 (15.05) | 98 (15.36) | 94 (14.73) | 0.868 |
| pT ₁ | 443 (26.17) | 247 (25.26) | 196 (27.41) | 339 (26.57) | 162 (25.39) | 177 (27.74) | |
| pT ₂ | 290 (17.13) | 158 (16.16) | 132 (18.46) | 226 (17.71) | 112 (17.55) | 114 (17.87) | |
| pT ₃ | 666 (39.34) | 394 (40.29) | 272 (38.04) | 500 (39.18) | 256 (40.13) | 244 (38.24) | |
| pT ₄ | 35 (2.07) | 28 (2.86) | 7 (0.98) | 16 (1.25) | 9 (1.41) | 7 (1.10) | |
| Unknown | 4 (0.24) | 1 (0.10) | 3 (0.42) | 3 (0.24) | 1 (0.16) | 2 (0.31) | |
| Pathological N category | | | | | | | |
| pN _x | 910 (53.75) | 537 (54.91) | 373 (52.17) | 701 (54.94) | 354 (55.49) | 347 (54.39) | 0.606 |
| pN ₀ | 653 (38.57) | 342 (34.97) | 311 (43.50) | 515 (40.36) | 255 (39.97) | 260 (40.75) | |
| pN ₁ | 130 (7.68) | 99 (10.12) | 31 (4.34) | 60 (4.70) | 29 (4.55) | 31 (4.86) | |
| Concomitant LVI | | | | | | | |
| No | 1,325 (78.26) | 746 (76.28) | 579 (80.98) | 1,018 (79.78) | 507 (79.47) | 511 (80.09) | 0.774 |
| Yes | 368 (21.74) | 232 (23.72) | 136 (19.02) | 258 (20.22) | 131 (20.53) | 127 (19.91) | |
| Concomitant CIS | | | | | | | |
| No | 1,454 (85.88) | 845 (86.40) | 609 (85.17) | 1,086 (85.11) | 538 (84.33) | 548 (85.89) | 0.420 |
| Yes | 239 (14.12) | 133 (13.60) | 106 (14.83) | 190 (14.89) | 100 (15.67) | 90 (14.11) | |
| LN dissection | | | | | | | |
| Not performed | 910 (53.75) | 537 (54.91) | 373 (52.17) | 701 (54.94) | 354 (55.49) | 347 (54.39) | 0.697 |
| Performed | 783 (46.25) | 441 (45.09) | 342 (47.83) | 575 (45.06) | 284 (44.51) | 291 (45.61) | |
| Adjuvant chemotherapy | | | | | | | |
| No | 1,310 (77.38) | 743 (75.97) | 567 (79.30) | 1,018 (79.78) | 510 (79.94) | 508 (79.62) | 0.884 |
| Yes | 383 (22.62) | 235 (24.03) | 148 (20.70) | 258 (20.22) | 128 (20.06) | 130 (20.38) | |
| Length of follow-up (mo) | 45.27 (0.10-184.37) | 49.51 (0.10-184.37) | 41.13 (0.23-157.91) | 40.45 (0.10-184.37) | 37.79 (0.10-184.37) | 44.25 (0.23-157.91) | 0.053 |

Propensity-score matching variables: age, BMI, ASA score, tumor location, tumor grade, pathological T category, pathological N category. ONU, open nephroureterectomy; LN_U, open nephroureterectomy; LVI, lymphovascular invasion; CIS, carcinoma *in situ*; LN, lymph node; BMI, body mass index; ASA, American Society of Anesthesiologists.

were included in the routine surveillance protocol. Abdominal and chest computed tomography or magnetic resonance imaging was suggested annually or more often, depending on the patient's clinical stage. Other protocols, including urine cytology, ultrasonography, and elective bone scans, were performed when clinically indicated. Cases of death were determined by reviewing records from the National Cancer Registry.

3. Statistical analysis

To compensate for the multicenter heterogeneity of baseline characteristics between eligible participants who underwent RNU, propensity-score matching was used to evaluate the prognostic effect of the two surgical approaches. The propensity score was estimated by a logistic regression model of nine factors with significantly different baseline characteristics, including age, BMI, ASA score, tumor location, grade, pathologic T and N categories, the presence of lymphovascular invasion, and follow-up duration.

Demographic data are presented as a median with minimum and maximum for continuous variables or a frequency with percentage for categorical variables. To identify the difference between the two approaches, the chi-square test and Mann-Whitney U test were used to analyze the original data set. In the matched cohort set, the McNemar or Bowker test and Wilcoxon signed-rank test were used in consideration of the dependency arising from the propensity-score matching. The Kaplan-Meier estimator was used to estimate the rates of prognostic outcomes, and the survival curves were compared using the stratified log-rank test. Clustered Cox regression was used to investigate the effect of the surgical approach for each prognostic outcome. In addition to controlling for confounding factors, the 3-year and 5-year survival rates were estimated by the Kaplan-Meier estimator and compared by the z-test. In pre-specified subgroup analyses, which were constructed based on factors known to significantly affect the prognosis in the original data set, the Cox proportional hazard model was selected to assess the effect of the surgical approaches on the prognostic outcomes, alone and after adjusting for potential confounders.

4. Ethical statement

This retrospective multicenter study's protocol was approved by the institutional review board of the National Cancer Center (approval no. NCC-2016-0040) and complied with the principles of the Declaration of Helsinki. The requirement for written informed consent was waived because of the retrospective design. All patient data and records were anonymized before the analysis.

Results

Among all the 1,693 patients who underwent RNU for UTUC, the baseline clinicopathological demographic characteristics were compared between the 978 patients (57.8%) who underwent ONU and the 715 patients (42.2%) who underwent LNU. This comparison resulted in significant baseline differences of BMI, the ASA score, tumor location, tumor grade, pathological T and N categories, concomitant presence of LVI, and duration of follow-up ($p < 0.05$) (Table 1). To equilibrate those significantly different baseline characteristics, 638 propensity-score matching pairs were obtained among 1,276 patients.

Using the 638 matching pair data set with a median follow-up duration of 40.5 (1.0-184.4) months, the prognostic outcomes, including IVRFS, DFS, OS, and CSS, were compared between the ONU group with a median follow-up of 37.8 months (range, 1.0 to 184.4 months) and LNU group with a median follow-up of 44.3 months (range, 1.0 to 157.9 months) ($p > 0.05$ for the follow-up duration between the ONU and LNU groups). The Cox regression analysis of the predictive risk factors in the matching data set showed that LNU was significantly better than ONU in IVRFS (hazard ratio [HR], 0.832), DFS (HR, 0.688), OS (HR, 0.524), and CSS (HR, 0.545) ($p < 0.05$) (Table 2). In the original data set, other significant clinicopathological parameters were female sex, previous and concomitant bladder tumor history, pT2 and pN1 categories, and adjuvant chemotherapy for IVRFS; previous and concomitant bladder tumor history, tumor location, pT2-4 and pN1 categories, and presence of concomitant LVI for DFS; BMI, ASA score, previous and concomitant bladder tumor history, tumor grade, pT2-4 and pN1 categories, and presence of concomitant LVI for OS; and previous and concomitant bladder tumor history, tumor grade, pT2-4 and pN1 categories, and presence of concomitant LVI for CSS ($p < 0.05$) (S1 and S2 Tables).

The comparison estimated 3-year and 5-year survival rates showed LNU had significantly better 3-year OS rate (82.9%) and CSS rate (86.2%) survival rates (ONU, 78.3% and 81.8%); however, there were no differences in 5-year OS and CSS ($p=0.104$ and $p=0.105$, respectively) (Table 3).

For further comparison analyses of the prognostic outcome between ONU and LNU in the subset of patients, subgroups were divided into the no previous bladder tumor history group, early-staged group (pT1-2), advanced-stage group (pT3-4), lymph node-positive group (pN1), and lymph node-negative group (pN0). In the subset of no previous bladder cancer history, and negative lymph-node group, LNU had significantly better IVRFS than ONU (HR, 0.782; 95% confidence interval [CI], 0.651 to 0.937; $p=0.008$; and HR, 0.730; 95% CI, 0.573 to 0.931; $p=0.011$). In the early-staged, advan-

Table 2. Comparison of ONU and LNU in bladder recurrence, PFS, OS, and CSS in the matched cohort set

| Model | HR (95% CI) | p-value |
|------------------------------------|---------------------|---------|
| IVRFS | | |
| Unadjusted LNU vs. ONU | 0.839 (0.706-0.997) | 0.047 |
| Adjusted LNU vs. ONU ^{a)} | 0.832 (0.699-0.991) | 0.039 |
| PFS | | |
| Unadjusted LNU vs. ONU | 0.690 (0.561-0.849) | < 0.001 |
| Adjusted LNU vs. ONU ^{a)} | 0.688 (0.558-0.847) | < 0.001 |
| OS | | |
| Unadjusted LNU vs. ONU | 0.544 (0.441-0.672) | < 0.001 |
| Adjusted LNU vs. ONU ^{a)} | 0.524 (0.423-0.650) | < 0.001 |
| CSS | | |
| Unadjusted LNU vs. ONU | 0.560 (0.441-0.712) | < 0.001 |
| Adjusted LNU vs. ONU ^{a)} | 0.545 (0.428-0.694) | < 0.001 |

ONU, open nephroureterectomy; LNU, open nephroureterectomy; PFS, progression-free survival; OS, overall survival; CSS, cancer-specific survival; HR, hazard ratio; CI, confidence interval; IVRFS, intravesical recurrence-free survival. ^{a)}Adjusted for the propensity score, which was estimated by the logistic regression model with 9 factors.

Table 3. Estimated 3-year and 5-year survival rates of prognostic outcomes

| Outcome | No. of events (%) | 3-Year | | 5-Year | |
|--------------|-------------------|--------------------|---------|--------------------|---------|
| | | Estimated rate (%) | p-value | Estimated rate (%) | p-value |
| IVRFS | | | | | |
| ONU | 410 (41.92) | 56.52±1.72 | 0.157 | 52.24±1.81 | 0.087 |
| LNU | 268 (37.48) | 60.22±1.97 | | 57.01±2.12 | |
| PFS | | | | | |
| ONU | 287 (29.35) | 73.09±1.49 | 0.198 | 68.81±1.60 | 0.070 |
| LNU | 174 (24.34) | 75.98±1.68 | | 73.20±1.82 | |
| OS | | | | | |
| ONU | 307 (31.39) | 78.27±1.38 | 0.024 | 71.51±1.58 | 0.104 |
| LNU | 150 (20.98) | 82.92±1.53 | | 75.50±1.88 | |
| CSS | | | | | |
| ONU | 229 (23.42) | 81.81±1.31 | 0.023 | 76.49±1.50 | 0.105 |
| LNU | 116 (16.23) | 86.17±1.41 | | 80.25±1.77 | |

Values are presented as number (%) or mean±standard error. The z-test was based on Klein and Moeschberger (2005) Section 7.8 [11]. IVRFS, intravesical recurrence-free survival; ONU, open nephroureterectomy; LNU, open nephroureterectomy; PFS, progression-free survival; OS, overall survival; CSS, cancer-specific survival.

ced-staged, and lymph node-positive groups, prognostic outcomes were not significantly different according to the surgical approach ($p > 0.05$) (Table 4).

Discussion

A recent systemic review of 42 studies about comparative oncological outcomes between LNU and RNU was published by Peyronnet et al. [4] who reported that LNU might have significantly poorer oncological outcomes and be a less effective procedure compared with ONU, especially in locally advanced UTUC, whereas the perioperative out-

Table 4. Comparative survival analysis between LNU and ONU according to each subgroup

| Subgroup | No. of events (%) | Univariate | | Multivariable | |
|----------------------------------|-------------------|---------------------|---------|---------------------|---------|
| | | HR (95% CI) | p-value | HR (95% CI) | p-value |
| No previous bladder | | | | | |
| IVRFS | | | | | |
| ONU | 304 (39.18) | 1 (reference) | | 1 (reference) | |
| LNU | 195 (33.11) | 0.816 (0.681-0.977) | 0.027 | 0.782 (0.651-0.937) | 0.008 |
| PFS | | | | | |
| ONU | 216 (27.84) | 1 (reference) | | 1 (reference) | |
| LNU | 137 (23.26) | 0.882 (0.712-1.094) | 0.255 | 1.027 (0.822-1.284) | 0.812 |
| OS | | | | | |
| ONU | 240 (30.93) | 1 (reference) | | 1 (reference) | |
| LNU | 115 (19.52) | 0.778 (0.621-0.975) | 0.029 | 0.856 (0.678-1.081) | 0.191 |
| CSS | | | | | |
| ONU | 171 (22.04) | 1 (reference) | | 1 (reference) | |
| LNU | 91 (15.45) | 0.809 (0.626-1.045) | 0.105 | 0.917 (0.703-1.196) | 0.522 |
| Early stage (T1, T2) | | | | | |
| IVRFS | | | | | |
| ONU | 196 (48.40) | 1 (reference) | | 1 (reference) | |
| LNU | 138 (42.07) | 0.858 (0.690-1.068) | 0.169 | 0.871 (0.699-1.087) | 0.222 |
| PFS | | | | | |
| ONU | 76 (18.77) | 1 (reference) | | 1 (reference) | |
| LNU | 50 (15.24) | 0.907 (0.634-1.298) | 0.594 | 1.229 (0.846-1.785) | 0.280 |
| OS | | | | | |
| ONU | 82 (20.25) | 1 (reference) | | 1 (reference) | |
| LNU | 49 (14.94) | 1.038 (0.723-1.491) | 0.839 | 1.102 (0.758-1.603) | 0.611 |
| CSS | | | | | |
| ONU | 48 (11.85) | 1 (reference) | | 1 (reference) | |
| LNU | 31 (9.45) | 1.042 (0.66-1.645) | 0.859 | 1.282 (0.804-2.045) | 0.297 |
| Severe stage (T3, T4) | | | | | |
| IVRFS | | | | | |
| ONU | 146 (34.60) | 1 (reference) | | 1 (reference) | |
| LNU | 84 (30.11) | 0.776 (0.592-1.015) | 0.064 | 0.793 (0.602-1.045) | 0.100 |
| PFS | | | | | |
| ONU | 201 (47.63) | 1 (reference) | | 1 (reference) | |
| LNU | 116 (41.58) | 0.825 (0.656-1.038) | 0.101 | 1.003 (0.791-1.272) | 0.979 |
| OS | | | | | |
| ONU | 204 (48.34) | 1 (reference) | | 1 (reference) | |
| LNU | 92 (32.97) | 0.749 (0.584-0.962) | 0.023 | 0.866 (0.670-1.120) | 0.273 |
| CSS | | | | | |
| ONU | 170 (40.28) | 1 (reference) | | 1 (reference) | |
| LNU | 80 (28.67) | 0.744 (0.569-0.972) | 0.030 | 0.861 (0.654-1.133) | 0.284 |
| Lymph node positive (pN1) | | | | | |
| IVRFS | | | | | |
| ONU | 19 (19.19) | 1 (reference) | | 1 (reference) | |
| LNU | 10 (32.26) | 1.481 (0.683-3.211) | 0.320 | 1.483 (0.683-3.219) | 0.319 |
| PFS | | | | | |
| ONU | 65 (65.66) | 1 (reference) | | 1 (reference) | |
| LNU | 22 (70.97) | 1.023 (0.630-1.662) | 0.927 | | |
| OS | | | | | |
| ONU | 58 (58.59) | 1 (reference) | | 1 (reference) | |
| LNU | 13 (41.94) | 0.620 (0.339-1.134) | 0.120 | 0.658 (0.359-1.207) | 0.177 |

(Continued to the next page)

Table 4. Continued

| Subgroup | No. of events (%) | Univariate | | Multivariable | |
|----------------------------------|-------------------|---------------------|---------|---------------------|---------|
| | | HR (95% CI) | p-value | HR (95% CI) | p-value |
| CSS | | | | | |
| ONU | 49 (49.49) | 1 (reference) | | 1 (reference) | |
| LNU | 12 (38.71) | 0.663 (0.352-1.249) | 0.203 | 0.704 (0.372-1.330) | 0.279 |
| Lymph node negative (pN0) | | | | | |
| IVRFS | | | | | |
| ONU | 167 (48.55) | 1 (reference) | | 1 (reference) | |
| LNU | 115 (36.51) | 0.707 (0.556-0.897) | 0.004 | 0.730 (0.573-0.931) | 0.011 |
| PFS | | | | | |
| ONU | 84 (24.56) | 1 (reference) | | 1 (reference) | |
| LNU | 69 (22.19) | 0.955 (0.692-1.316) | 0.777 | 0.973 (0.698-1.356) | 0.874 |
| OS | | | | | |
| ONU | 112 (32.75) | 1 (reference) | | 1 (reference) | |
| LNU | 76 (24.44) | 0.919 (0.682-1.238) | 0.578 | 0.889 (0.655-1.203) | 0.451 |
| CSS | | | | | |
| ONU | 70 (20.47) | 1 (reference) | | 1 (reference) | |
| LNU | 54 (17.36) | 0.939 (0.657-1.342) | 0.729 | 0.941 (0.651-1.354) | 0.747 |

ONU, open nephroureterectomy; LNU, laparoscopic nephroureterectomy; CI, confidence interval; HR, hazard ratio; IVRFS, intravesical recurrence-free survival; PFS, progression-free survival; OS, overall survival; CSS, cancer-specific survival.

comes of LNU were significantly better than those of ONU [6,12]. However, a recent meta-analysis of 21 studies from Ni et al. [13] showed no significant differences between the two approaches in IVBFS, OS, and CSS. They stated that LNU could offer comparable oncological efficacy to ONU. The interpretation of these data is limited since patients managed with a laparoscopic approach were more likely to have Ta/Tis or T1 disease and less likely to have T3 or T4 lesions. To overcome this baseline selection bias, adjustment of the different baseline parameters, including the stages of cancer, should be considered first, and propensity-score matching is one of the methods that can be used to adjust the baseline differences and minimize the selection bias in retrospective studies.

Another meta-analysis from Zhang et al. [14] also reported a comparable efficacy between LNU and ONU. These different oncological outcomes between ONU and LNU have been influenced by the inherent flaws of the meta-analytic methodology that differ in design, diverse surgical methodologies, and heterogeneous cohorts enrolled with different baseline clinicopathological parameters and tumor burdens, which affected interpretation of the statistical outcome. A better designed study that excludes the inherent heterogeneity of baseline differences of tumor burden is needed to determine the oncologic efficacy of LNU compared with ONU.

Overall opinions from published studies and experts about the insignificant oncological outcomes according to surgical

approaches for localized UTUC have been consistently in agreement [4,7,15]. In addition, LNU has been identified significantly as having a better perioperative outcome than ONU [13]. However, in prognostic view of locally advanced UTUC, conflicting findings from different LNU and ONU groups have been in debate about whether ONU has significantly better oncological outcomes than LNU [5,7,14]. Two retrospective, multicenter studies of 265 patients from Chinese institutions and 609 patients from French multicenter institutions showed no significant differences in IVBFR, OS, and CSS between the two approaches in locally advanced stages of UTUC, suggesting LNU as an alternative procedure to ONU [5,14].

All the aforementioned retrospective and meta-analytic studies have implicated potential risk factors such as surgical experiences and the heterogeneity of the patient cohorts. The current study was designed to appropriately compare two surgical approaches and to compensate for the potential inborn bias of baseline differences of known prognostic clinicopathological parameters by adjusting and balancing the baseline characteristics and disease states using propensity-score matching of 1,276 patients (638 matched-paired cohorts), which resulted in significant non-inferior oncological outcomes of LNU compared to ONU similar to previous studies [4,14,15]. By balancing the intrinsic bias of the different characteristics of the present study's cohort population, it would be much clearer to analyze the oncological outcomes and to

better demonstrate the true oncological efficacy of LNU.

The present study was based on our previous retrospective study by the multicenter UCART research team that used this original data set; it was found that compared with ONU, LNU had a significantly non-inferior oncological outcome (the results of that study were accepted for publication by *Cancer Research and Treatment Journal* in January 2018). However, the previous study also had an inherent limitation in its retrospective design with 1,560 uncontrolled, heterogeneous cohorts from different institutions, which were important factors that affected the prognostic outcomes [16-18]. Thereby, the present study recruited patients since 2000 after considering that surgeons had overcome the learning curve of LNU, and focused on the results after adjusting for the baseline differences between the two cohorts and on the IVBFS, DFS, OS, and CSS according to different pathologic stages at specific follow-up points to better clarify the oncologic benefits of LNU compared with ONU.

To compensate for the potential inborn bias of baseline differences of known prognostic clinicopathological covariates, propensity-score matching analysis was used to form a matched cohort in consideration of various variables. Eight significant parameters were selected among the baseline characteristics, including age, to make the patients more homogeneous [19,20]. By excluding the heterogeneity of patient cohorts by propensity-score matching analysis and controlling for the potential power of the surgical period, 3-year and 5-year survival rates were analyzed to evaluate the validity of the results from 1,276 patients selected from 1,693 patients. Additionally, a comparative subgroup analysis of IVRBS, DFS, OS, and CSS between LNU and ONU was performed. As a result, the current study design showed the significantly potential efficacy of different prognoses of survival with LNU even in locally advanced UTUC, and LNU had a significantly better efficacious oncological outcome than ONU. With the previously established significant benefits of perioperative morbidity [12], LNU was one of the alternatively considered surgical managements for UTUC [5], including locally advanced stages; LNU should be further analyzed in the future in terms of specific subgroups such as operative bladder cuffing techniques.

The present study has several limitations such as selection bias because of the retrospective, nonrandomized, multicenter study design; lack of strictly standardized protocols for patient selection, the operative procedure, perioperative parameters, and postoperative follow-up; and interpersonal and interinstitutional variations of skills in bladder cuffing methods. Several prognostic factors were unidentified, which might affect the prognostic outcomes as confounding factors, and different interpersonal surgical techniques and experiences were not considered despite overcoming the learning curve of RNU by excluding all the early laparoscopic cases

before 2000s since the introduction of LNU in the 1990s. After considering the recovery of surgeons' learning curve in LNU, the oncological outcome was not significantly different between LNU and ONU considering the pathological stage [20-22]. The differing inclusion and exclusion criteria from various surgeons' experiences according to the different institutions and the 400 excluded patients from this analysis were other considerable factors that affected the prognostic outcomes. However, this is the first large-sized study of data adjusted by different baseline characteristics that compared the prognostic survival rates between ONU and LNU using propensity-score matching analysis to minimize the selection bias inherent to a retrospective study design and to adjust for the different follow-up durations.

This study showed that LNU had a significantly better prognostic outcome than ONU after propensity-score matching of baseline clinicopathological differences in terms of IVRFS, DFS, OS, and CSS. The subset analyses according to the matching pair data set also showed that LNU was not inferior to ONU in the locally advanced UTUC.

Electronic Supplementary Material

Supplementary materials are available at Cancer Research and Treatment website (<https://www.e-crt.org>).

Conflicts of Interest

Conflict of interest relevant to this article was not reported.

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