

## นิพนธ์ต้นฉบับ

# การผ่าตัด nephroureterectomy ในผู้ป่วยมะเร็งระบบปัสสาวะส่วนบน ในโรงพยาบาลราชวิถี : ประสบการณ์ 8 ปี

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หน่วยศัลยกรรมทางเดินปัสสาวะ กลุ่มงานศัลยกรรม โรงพยาบาลราชวิถี กรุงเทพฯ

### บทคัดย่อ

**วัตถุประสงค์:** เพื่อศึกษาผลการรักษามะเร็งระบบปัสสาวะส่วนบน ชนิด transitional cell โดยการผ่าตัด radical nephroureterectomy แบบเปิด และส่องกล้อง

**ผู้ป่วยและวิธีการศึกษา:** ศึกษาแบบย้อนหลังจากเวชระเบียนผู้ป่วย ตั้งแต่ มกราคม 2551 ถึง ธันวาคม 2558 ในผู้ป่วยที่ได้รับการผ่าตัด radical nephroureterectomy ที่โรงพยาบาลราชวิถี โดยข้อมูลที่ศึกษา ได้แก่ ข้อมูลทั่วไปของผู้ป่วย ผลการรักษา และภาวะแทรกซ้อนระหว่างและหลังการผ่าตัด

**ผลการศึกษา:** ผู้ป่วยได้รับการผ่าตัด nephroureterectomy จำนวน 65 ราย จำแนกเป็น 2 กลุ่ม คือ ได้รับการผ่าตัดแบบเปิด จำนวน 28 ราย (ร้อยละ 43.1) และผ่าตัดแบบส่องกล้อง จำนวน 37 ราย (ร้อยละ 56.9) พบว่า ในกลุ่มที่ได้รับการผ่าตัดแบบส่องกล้อง มีการเสียเลือดในปริมาณน้อยกว่า และมีความต้องการในการได้รับยาแก้ปวดน้อยกว่า กลุ่มผ่าตัดแบบเปิด อย่างมีนัยสำคัญทางสถิติ สำหรับกลุ่มที่ได้รับการผ่าตัดแบบเปิด พบว่า ใช้ระยะเวลาในการผ่าตัดน้อยกว่ากลุ่มที่ผ่าตัดส่องกล้องอย่างมีนัยสำคัญทางสถิติ และจากการศึกษา ไม่พบความแตกต่างของภาวะแทรกซ้อน ระหว่างผ่าตัด และหลังผ่าตัด

**สรุป:** การผ่าตัด nephroureterectomy แบบส่องกล้องเป็นแนวทางการรักษาที่เป็นทางเลือกที่ปลอดภัย ในการรักษาผู้ป่วยมะเร็งทางเดินปัสสาวะส่วนบน โดยมีข้อดี คือ เสียเลือดปริมาณน้อย และอาการปวดหลังผ่าตัดน้อย

**คำสำคัญ:** การผ่าตัด nephroureterectomy แบบส่องกล้อง, มะเร็งระบบปัสสาวะส่วนบน

## Original article

## Nephroureterectomy for upper urinary tract transitional cell carcinoma in Rajavithi Hospital: Experience in the last 8 years

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### Abstract

**Objective:** To evaluate operative outcomes after open and laparoscopic nephroureterectomy for upper urinary tract transitional cell carcinoma.

**Material and methods:** From Jan 1998 to Dec 2015, retrospective descriptive analysis was performed in 65 patients underwent radical nephroureterectomy at Rajavithi Hospital. Demographics, tumor characteristics, intraoperative and postoperative data were collected. Statistical analysis was performed using percentage, mean, mode and standard deviation (SD) for descriptive data and the Student T-test, Mann-Whitney U test, Chi-square test and Fisher Exact test for comparisons of the data.

**Results:** Twenty-eight patients (43.1%) and 37 patients (56.9%) underwent open and laparoscopic nephroureterectomy, respectively. The analysis revealed significantly lower blood loss (395.15 ml VS 738.89 ml,  $P < 0.05$ ) and morphine administration (5.37 doses VS 11.36 doses,  $P < 0.05$ ) in the laparoscopic nephroureterectomy group, however, the operation had significantly longer operative times than the open nephroureterectomy group (329.82 min VS 430.50 min,  $P < 0.05$ ). No significant differences of time to first diet and time to removal of catheter were observed.

**Conclusion:** Laparoscopic nephroureterectomy seems to be a safe alternative treatment for upper urinary tract TCC and offers the advantages of the laparoscopic procedure, i.e., less intraoperative blood loss and postoperative pain. Thus, the results of our study support the continued development of the laparoscopic technique in the management of upper urinary tract urothelial carcinoma.

**Keywords:** laparoscopic nephroureterectomy, upper urinary tract, transitional cell carcinoma

## Introduction

Urothelial carcinoma, or transitional cell carcinoma (TCC), is the fourth most common tumor in the general population. The tumor can be located in the lower urinary tract (bladder and urethra) or the upper urinary tract (pyelocaliceal cavities and ureter). Upper urinary tract transitional cell carcinoma is uncommon and found in only about 5-10% of urothelial carcinomas<sup>1</sup>.

Radical nephroureterectomy with bladder cuff excision is the gold-standard therapy for upper-tract cancer<sup>1</sup>. The operation afforded 5-year recurrence-free survival in 69% of patients and 5-year cancer-specific survival in 73% of patients<sup>2</sup>.

In 1991, Clayman et al<sup>3</sup>, first described the technique of laparoscopic nephroureterectomy, since then, it has been accepted as an alternative treatment option for upper tract TCC<sup>4</sup>.

In this study, we analyzed the data of patients in Rajavithi Hospital who were diagnosed with upper tract TCC and treated with radical nephroureterectomy. The aims of this study were to compare the intraoperative and post-operative outcomes between the open nephroureterectomy group and laparoscopic nephroureterectomy group.

## Material and methods

### 1. Study design

From January 2008 to December 2015, 65 patients underwent radical nephroureterectomy with bladder cuff excision for upper tract TCC at Rajavithi Hospital.

All data were collected and analyzed, including patient demographics, operation type, type of bladder cuff excision, hospital stay, morphine usage, operative time, time to first diet, mean blood loss, PRC requirement, mean time to removal of urethral catheter and pathologic stage.

### 2. Surgical technique

Standard open nephroureterectomy (ONU) was performed via a flank or subcostal incision. The distal ureterectomy and bladder cuff excision were performed using the standard technique with Gibson incision.

Patients with concomitant bladder tumor underwent transurethral resection before nephroureterectomy.

Laparoscopic nephroureterectomy (LNU) was performed using the intraperitoneal approach. Patients were placed in a lateral position. The camera port was inserted by open technique at the umbilicus. After inserting the camera port, the pneumoperitoneum was maintained with carbon dioxide at 15 mmHg. Two or 3 working ports were inserted in the usual manner. After port placement, the colon was mobilized medially. Dissection of Gerota's fascia and the renal pedicle were performed. Renal vessels were dissected and cleaned. Renal artery and vein were isolated, clipped and divided, respectively. The ureter was divided at the level of common iliac vessels. Finally the kidney was completely mobilized. Lymphadenectomy was performed at the surgeon's discretion. Distal ureterectomy and bladder cuff excision were performed using 2 techniques. One was the open technique, like in the ONU group. The other was the total laparoscopic approach. Specimen was removed en bloc via camera port.

### 3. Statistical analysis

Statistical analysis was performed with the Statistical Package for the Social Sciences v.17.0 (SPSS Inc, Chicago, IL, USA). The percentage, mean, mode and standard deviation (SD) were used for descriptive data. Comparisons between the 2 groups were carried out using the Student T-test, Mann-Whitney U test, Chi-square test and Fisher Exact test. For all statistical tests,  $p < 0.05$  was considered to indicate a statistic significant.

## Result

Sixty-five patients underwent radical nephroureterectomy. Mean age was 64.74 years (SD=13.065). The demographic data are described in Table 1.

Renal pelvis was the most common location of cancer (53.8%), followed by distal ureter (23.1%), proximal ureter (13.8%) and multiple locations (9.2%), respectively. Tumor characteristics are described in Table 2.

Table 1 Patient demographic data.

|                            | RNU            | ONU            | LNU             | P-value |
|----------------------------|----------------|----------------|-----------------|---------|
| No of patients (N (%))     | 65 (100)       | 28 (43.1)      | 37 (56.96)      | 0.264   |
| Age (yrs (SD))             | 64.74 (13.07)  | 63.18 (12.61)  | 59.59 (14.27)   | 0.407   |
| Sex (N (%))                |                |                |                 | 0.692   |
| Male                       | 40 (61.5)      | 18 (45)        | 22 (55)         |         |
| Female                     | 25 (38.5)      | 10 (40)        | 15 (60)         |         |
| Weight (Kgs (SD))          | 60.34 (13.76)  | 61.32 (13.26)  | 59.59 (14.28)   | 0.62    |
| Height (cms (SD))          | 160.62 (9.725) | 161.75 (8.855) | 159.76 (10.372) | 0.511   |
| Underlying disease (N (%)) |                |                |                 |         |
| DM                         | 11 (16.9)      | 5 (45.5)       | 6 (54.5)        | 0.861   |
| HT                         | 29 (44.6)      | 10 (34.5)      | 19 (65.5)       | 0.209   |
| CAD                        | 2 (3.1)        | 1 (50)         | 1 (50)          | 1       |
| CKD                        | 5 (7.7)        | 2 (40)         | 3 (60)          | 1       |
| Other                      | 14 (21.5)      | 5 (35.7)       | 9 (64.3)        | 0.53    |
| Operative side (N (%))     |                |                |                 | 0.643   |
| Right                      | 35 (53.8)      | 16 (45.7)      | 19 (54.3)       |         |
| left                       | 30 (46.2)      | 12 (40)        | 18 (60)         |         |

#### Intraoperative outcome

Mean operative time of the LNU group was longer than the ONU group (329.82 min vs 430.50 min  $p < 0.05$ ). On other hand, intraoperative blood loss of the LNU group was lower than the RNU group (395.15 ml vs 738.89 ml  $p < 0.05$ ) (Table 3).

The open conversion rate was 18.91%(7 patients). Causes of open conversion were vascular injury and failure of progression as shown in Table 4. In the LNU group, there were 2 types of bladder cuff excision; 83.11% of patients underwent open bladder cuff excision; 16.9% of patients underwent pure laparoscopic nephroureterectomy. No differences in complications were found in either type of bladder cuff excision.

#### Post-operative outcome

Mean doses of morphine usage for RNU were 8.26 doses. The LNU group used fewer doses of morphine than the ONU group (5.37 vs 11.36  $p < 0.05$ ). Mean hospital stay, time to first diet, time to remove catheter of RNU was 19.02 days, 2.78 days, 11.02 days, respectively. There were no differences in the LNU group and ONU group (Table 3).

Sixteen post-operative complications were found. Using the Clavien-Dindo grading system for the classification of surgical complications<sup>5</sup>, there were 5 in Grade I, 2 in Grade II, 3 in Grade III and 6 in Grade IV. There were no significant differences in the LNU group and ONU group (Table 5).

**Table 2** Tumor characteristics.

|                               | RNU       | ONU       | LNU       | P-value      |
|-------------------------------|-----------|-----------|-----------|--------------|
| <b>Tumor location (N (%))</b> |           |           |           | <b>0.909</b> |
| Renal pelvis                  | 35 (53.8) | 15 (42.9) | 20 (57.1) |              |
| Proximal ureter               | 9 (13.8)  | 3 (33.3)  | 6 (66.7)  |              |
| Distal ureter                 | 15 (23.1) | 7 (46.7)  | 8 (53.3)  |              |
| Multiple location             | 5 (9.2)   | 3 (50)    | 3 (50)    |              |
| <b>TNM staging (N (%))</b>    |           |           |           |              |
| <b>T stage</b>                |           |           |           | <b>0.930</b> |
| TIs                           | 3 (4.6)   | 1 (33.3)  | 2 (66.7)  |              |
| T1                            | 30 (46.2) | 12 (40)   | 18 (60)   |              |
| T2                            | 23 (35.4) | 11 (47.8) | 12 (52.2) |              |
| T3                            | 9 (13.8)  | 4 (44.4)  | 5 (55.6)  |              |
| T4                            | 0 (0)     | 0 (0)     | 0 (0)     |              |
| <b>N stage</b>                |           |           |           | <b>0.381</b> |
| N0                            | 64 (98.5) | 28 (43.8) | 36 (56.3) |              |
| N1                            | 1 (1.5)   | 0 (0)     | 1 (100)   |              |
| N2                            | 0 (0)     | 0 (0)     | 0 (0)     |              |
| N3                            | 0 (0)     | 0 (0)     | 0 (0)     |              |
| <b>M stage</b>                |           |           |           | <b>0.569</b> |
| M0                            | 64 (98.5) | 28 (43.8) | 36 (56.3) |              |
| M1                            | 1 (1.5)   | 0 (0)     | 1 (100)   |              |
| <b>Tumor grading (N (%))</b>  |           |           |           | <b>0.793</b> |
| Grade 1                       | 16 (24.6) | 8 (50)    | 8 (50)    |              |
| Grade 2                       | 23 (35.4) | 9 (39.1)  | 14 (60.9) |              |
| Grade 3                       | 26 (40)   | 11 (42.3) | 15 (57.7) |              |

## Discussion

This descriptive retrospective study showed the mean operative time of ONU group was 325.23 min. In the LNU group, the mean operative time was 430.5 min. Jarrett and Osamu reported mean operative times were 329 and 320 min<sup>6,7</sup>, respectively, and operative time decreased with surgeon experience<sup>6</sup>.

The mean operative time of the LNU group was longer than the ONU group. This result is different from previous studies. Rassewiler and Masao reported no statistical significance in mean operative time<sup>4,8</sup>. In this study, the longer mean operative time in the LNU group might be due to surgeon experience in laparoscopy.

**Table 3** Intra- operative and post-operative results.

|  | RNU               | ONU               | LNU              | P-value |
|--|-------------------|-------------------|------------------|---------|
| <b>Intra-operative</b>                           |                   |                   |                  |         |
| Operative time (min(SD))                         | 325.23 (102.45)   | 329.82 (78.085)   | 430.50 (89.243)  | <0.05   |
| EBL (ml (Min,Max))                               | 595.16 (100,2700) | 738.89 (100,2700) | 395.15 (150,600) | <0.05   |
| PRC (ml (Min,Max))<br>requirement                | 197.42 (0,2300)   | 244.72 (0,2300)   | 131.92 (0,600)   | 0.49    |
| <b>Post-operative</b>                            |                   |                   |                  |         |
| Time to first diet<br>(days (Min,Max))           | 2.78 (1,7)        | 2.79 (1,5)        | 2.77 (2,7)       | 0.748   |
| Hospital stay<br>(days (Min,Max))                | 19.02 (10,77)     | 19.29 (10,77)     | 18.77 (11,51)    | 0.743   |
| Mophine requiment<br>(doses (Min,Max))           | 8.26 (2,18)       | 11.36 (8,18)      | 5.37 (2,18)      | <0.05   |
| Time to remove urethral<br>cath (days (Min,Max)) | 11.02 (3,20)      | 11.07 (3,20)      | 10.97 (5,15)     | 0.893   |

**Table 4** Causes of open conversion.

| <b>Causes</b>              |          |
|----------------------------|----------|
| <b>Vascular injury</b>     | <b>3</b> |
| - IVC injury               | 1        |
| - Renal vein injury        | 1        |
| - Renal artery injury      | 1        |
| <b>Failure to progress</b> | <b>4</b> |

This study shows the advantages of minimally invasive surgery, for example, that mean intraoperative blood loss was significantly lower in the LNU group. Giuseppe et al, reported less intraoperative blood loss in laparoscopic nephroureterectomy<sup>9</sup>, which is similar to the findings in this study. The pack red cell requirement was not different in either group, and

might be from pre-operative hemoglobin status.

Rate of open conversion from LNU was 18.91%. Hazem et al, had a rate of open conversion of 4%<sup>10</sup>. The higher rate of open conversion in our study might be from the surgeon's initial experience in laparoscopy. The common cause of open conversion was vascular injury, similar to Osamu's study<sup>7</sup>.

**Table 5** Post-operative complications.

| Clavien-Dindo grading      | ONU      | LNU      |
|----------------------------|----------|----------|
| <b>Grade I</b>             | <b>2</b> | <b>3</b> |
| - Wound infection          | 2        | -        |
| - Urinary tract infection  | -        | 3        |
| <b>Grade II</b>            | <b>2</b> | <b>0</b> |
| - Bowel ileus              | 2        | -        |
| <b>Grade III</b>           | <b>2</b> | <b>1</b> |
| - Wound dehiscence         | 1        | -        |
| - Bladder incision leakage | 1        | 1        |
| <b>Grade IV</b>            | <b>2</b> | <b>4</b> |
| - Sepsis                   | 1        | 2        |
| - Coagulopathy             | 1        | -        |
| - Ischemic stroke          | -        | 1        |
| - Congestive heart failure | -        | 1        |

Post-operative outcomes revealed mean hospital stay was 19.02 days, with no significant difference in the 2 groups. This result differs from previous studies. Hanna and Masao reported shorter hospital stays in the laparoscopic group<sup>11,4</sup>. Hospital stay was longer in the open bladder cuff excision group because the catheters were retained longer (mean 11 days) and removed before the patients were discharged. Time to first diet was 2.78 days; there was no significant difference in either group because LNU was performed with the intraperitoneal approach that interferes with the bowel. This study used doses of morphine required to indicate post-operative pain. Mean dosage was 8.26 doses and fewer doses were required in the LNU group. Fewer doses of morphine means patients had less post-operative pain, which is an advantage of the minimally invasive approach. Masao's study had similar results, showing that there is a lower analgesic requirement in the laparoscopic group<sup>4</sup>.

There were 16 post-operative complications. No significant difference in LNU and ONU group, like in Hanna's study<sup>11</sup>. The common complications were wound infection and urinary tract infection. The complications were similar to previous reports.

Osamu et al reported a 10.7% complication rate in laparoscopic nephroureterectomy, which included wound infection and wound hernia<sup>7</sup>.

In previous studies, Portis et al reported a 5-year recurrence-free survival of about 92% and a 5-year cancer specific survival of about 98% in laparoscopic nephroureterectomy<sup>12</sup>. Ricardo reported no significant difference in 2-year recurrence-free probabilities in laparoscopic and open nephroureterectomy<sup>13</sup>. However, in this study we did not report oncologic outcomes due to a limited follow-up period. The limitations of this study are its retrospective design and the limited number of subjects.

### Conclusion

Laparoscopic nephroureterectomy seems to be a safe alternative treatment for upper urinary tract TCC and offers the advantages of laparoscopic procedures, for example, less intraoperative blood loss and post-operative pain. Because of the limitations of the retrospective study, a true prospective and continued evaluation with longer follow-up data is needed before LNU should become the new standard of care for upper tract TCC.

## References

1. Rouprêt M, Babjuk M, Böhle A, et al. European Association of Urology guidelines on upper urinary tract urothelial cell carcinoma: 2015. Update European Urology 2015;68:868-79.
2. Margulis V, Shariat SF, Matin SF, et al. Outcomes of radical nephroureterectomy: A series from the upper tract urothelial carcinoma collaboration. American Cancer Society 2009.
3. Clayman RV, Kavoussi LR, Figenschau RS, et al. Laparoscopic nephroureterectomy: Initial clinical case report. J Laparoendoscopic Surg 1991;1:343-9.
4. Tsujihata M, Nonomura N, Tsujimura A, et al. Laparoscopic nephroureterectomy for upper tract transitional cell carcinoma: Comparison of laparoscopic and open Surgery. European Urology 2002;49:332-6.
5. Mitropoulos D, Artibani W, Graefen M, et al. European Association of Urology guidelines on reporting and grading of complications after urologic surgical procedures: 2015. Update European Urology Guideline 2015.
6. Jarrett TW, Chan DY, Cadeddu JA, et al. Laparoscopic nephroureterectomy for the treatment of transitional cell carcinoma of the upper urinary tract. Urology 2001;57:448-53.
7. Kamihira O, Hattori R, Yamaguchi A, et al. Laparoscopic radical nephroureterectomy: A multicenter analysis in Japan. European Urology 2009;55:1397-409.
8. Rassweiler JJ, Schulze M, Marrero R, et al. Laparoscopic nephroureterectomy for upper urinary tract transitional cell carcinoma: Is it better than open surgery?. European Urology 2004;46:690-7.
9. Simone G, Papalia R, Guaglianone S, et al. Laparoscopic versus open nephroureterectomy: Perioperative and oncologic outcomes from a randomised prospective study. European Urology 2009;56:520-6.
10. Fettouh HA, Rasseiler JJ, Schulze M, et al. Laparoscopic radical nephroureterectomy: Results of an international multicenter study. European Urology 2002;42(5):447-52.
11. Hanna N, Sun M, Trinh Q, et al. Propensity-score-matched comparison of perioperative outcomes between open and laparoscopic nephroureterectomy: A national series. European Urology 2012;61:715-21.
12. Portis A J, Landman YY, Chen J, et al. Long-term follow-up after laparoscopic radical nephrectomy. J Urol 2002;167:1257-62.
13. Favaretto RL, Shariat SF, Chade DC, et al. Comparison between laparoscopic and open radical nephroureterectomy in a contemporary group of patients: Are recurrence and disease-specific survival associated with surgical technique? Eur Urol 2010;58:645-51.