Laparoendoscopic single-site nephroureterectomy for upper urinary tract urothelial carcinoma: outcomes of an international multi-institutional study of 101 patients

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What's known on the subject? and What does the study add?

- LESS-NU may be an alternative minimally-invasive treatment option for patients eligible to undergo laparoscopic surgery for upper urinary tract urothelial carcinoma.
- The true benefits of LESS-NU remain to be determined and require randomized control trials in the future. Despite encouraging early findings, clinical trials still are warranted before this procedure is adopted widely, and longer follow-up is needed to determine its oncological durability.

Objective

- To report a large multi-institutional series of laparoendoscopic single-site (LESS) nephroureterectomy (NU).

Materials and Methods

- Data on all cases of LESS-NU performed between 2008 and 2012 at 15 institutions were retrospectively gathered.
- The main demographic data and perioperative outcomes were analysed.

Results

- The study included 101 patients whose mean (SD) age was 66.4 (9.9) years and mean (SD) body mass index was 24.8 (4) kg/m^2, and of whom 29.7% had undergone previous abdominal/pelvic surgery.
- The mean (SD) operating time was 221.4 (73.7) min, estimated blood loss 231.7 (348.0) mL.
- A robot-assisted LESS technique was applied in 25.7% of cases. An extra trocar was inserted in 28.7% of cases to complete the procedure. Conversion to open surgery was necessary in three cases (3.0%). There was no bladder

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cuff excision in 20.8% of cases, and excision was carried out using a variety of techniques in the remaining cases.
- Six intra-operative complications occurred (5.9%). The mean (SD) length of hospital stay was 6.3 (3.5) days. The overall postoperative complication rate was 10.0%, and most of the complications were low grade (Clavien grades 1 and 2).
- The mean tumour size was 3.1 (1.9) cm. Pathological staging was pTis in two patients, pTa in 12 patients, pT1 in 42 patients, pT2 in 20 patients, pT3 in 23 patients and pT4 in two patients. Pathological grade was high in 71 and low in 30 patients.
- At a mean follow-up of 14 months, six patients (5.9%) had died. Disease recurrence (including distant and bladder recurrence) was detected in 22.8% of patients, with a mean time to recurrence of 11.5 months.

Conclusions

- This study reports the largest multi-institutional experience of LESS-NU to date.
- Peri-operative outcomes mirror those of published standard laparoscopy series.
- Despite encouraging early findings, longer follow-up is needed to determine the oncological efficacy of the procedure.

Keywords

laparoendoscopic single-site surgery, LESS, multi-institutional, transitional cell carcinoma

Introduction

Since its first description by Clayman et al. in 1991 [1], laparoscopic nephroureterectomy (NU) for upper tract urothelial carcinoma has become an established procedure. In a recent systematic review [2], it was concluded that this procedure offers reliable peri-operative safety and comparable oncological efficacy when compared with its open counterpart, despite the lack of well-designed prospective trials.

Recently, laparoendoscopic single-site (LESS) surgery has been introduced in the field of minimally invasive urological surgery. LESS surgery is claimed to have benefits over conventional laparoscopic surgery in terms of reduced pain, shortened hospital stay and higher patient satisfaction regarding cosmetic outcome [3–7]; however, potential disadvantages include its higher technical demands, the learning curve associated with the procedure, and the higher cost of specialized instruments that are sometimes used for LESS surgery. Overall, LESS surgery can be regarded as an emerging trend in minimally invasive urological surgery that has significantly evolved, becoming a widely applicable technique in a relatively short period of time [7].

Although there have been many reports on the feasibility of radical nephrectomy by LESS surgery [8], few studies have been reported for LESS-NU, probably because of technical difficulties mostly related to bladder cuff excision and repair [9–11]. A common limitation of these early reports was the limited number of cases.

In the present study, we evaluated the surgical and early postoperative outcomes of LESS-NU for upper urinary tract urothelial carcinoma in a large multi-institutional cohort of patients.

Methods

Study Population

This was a multi-institutional retrospective study comprising patients who underwent LESS-NU for upper urinary tract urothelial carcinoma between 2008 and 2012. Fifteen international institutions provided data including patient demographics, data related to the surgical procedure, pre- and peri-operative outcomes, and postoperative complications. Each group performed LESS-NU according to its own protocols, entry criteria and techniques. Raw data with no identifier were retrospectively collected and gathered into a standardized datasheet, which was specifically built for the purpose of the present study. Institutional review board approval or a waiver was obtained by each participating centre based on its specific regulations.

Analysis

Patient demographics including age, gender, race, body mass index (BMI), history of abdominal/pelvic surgery, American Society of Anesthesiologists score, European Cooperative Oncology Group performance status, and Charlson comorbidity index score were analysed. Operative variables including operating time, estimated blood loss, intra-operative adverse events, change in serum creatinine concentration, change in haemoglobin levels, and length of stay were analysed. Oncological outcomes including tumour size, tumour location, pathological stage, tumour grade, performance of lymphadenectomy, number of harvested lymph nodes, co-existing lymphovascular invasion and carcinoma *in situ* (CIS), and tumour recurrence were analysed. With regard to the pathological stage, the tumours were classified according to the 2002 TNM staging system, and tumour grades were classified

according to the 2004 WHO classification. Operative data related to the surgical procedure including access site (umbilical or extra-umbilical), approach (transperitoneal or retroperitoneal), use of articulating or prebent laparoscopic instruments, use of the da Vinci® robot, type of single-port device, use of an additional laparoscopic port, and conversion to conventional laparoscopic or open surgery were assessed. Skin incision length was measured at the completion of the operation. Complications were graded according to the Clavien–Dindo classification of surgical complications [12].

Continuous data were presented as mean (SD) values. Categorical variables were expressed as numbers and percentages for the group.

Results

In all, 101 patients were included in the analysis (Table 1). The mean (SD) patient age was 66.4 (9.9) years and the mean (SD) BMI was 24.8 (4) kg/m^2. In all, 30 patients (29.7%) had undergone previous abdominal/pelvic surgery. The mean (SD) Charlson comorbidity index score was 2.5 (1.9). The primary tumour location was pelvocalyceal (57.4% of cases).

The most common access site was the umbilicus (93.1% of cases) and transperitoneal access was most commonly used (99/101 patients). The da Vinci® robot was used in 26 patients (25.7%). Various LESS port devices were used for LESS-NU. In 62.4% of cases a homemade device was used and in 37.6% of cases various commercially available port devices were used. An additional port was used in 28.7% of cases to complete the procedure. In 10% of these, a 2- to 3-mm extra port was used, and in the remaining 90% an extra 5- to 12-mm additional port was used. LESS-NU was completed in 98 patients (97%), and conversion to open surgery was required in three cases owing to the difficulty of dissection (3.0%). The mean (SD) skin incision length at closure was 5.0 (1.7) cm.

Peri-operative outcomes are shown in Table 2. The mean (SD) operating time was 221.4 (73.7) min and estimated blood loss was 231.7 (348.0) mL. Six intraoperative complications (5.9%) were experienced, all of which were intraoperative bleeding managed with blood transfusion. There were no peri-operative mortalities. Postoperative complications occurred in 10 patients (9.9%). These complications included superficial wound infection ($n = 2$), intra-abdominal abscess ($n = 2$), anaemia ($n = 2$), ileus ($n = 2$), acute renal failure ($n = 1$), and fever ($n = 1$). Most postoperative complications were Clavien grade 1 (9/10 cases). The mean changes in serum creatinine and haemoglobin levels were 0.16 mg/dL and −0.92 g/dL, respectively. The mean (SD) duration of hospital stay was 6.3 (3.5) days with a mean (SD) pain visual analogue score at discharge of 1.5 (1.3) on a 10-point scale.

The main pathological findings are shown in Table 3. The mean (SD) tumour size was 3.1 (1.9) cm. Most tumours

Table 1 Patient demographics.

No. of patients	101
Mean (SD) age, years	66.4 (9.9)
Male gender, *n* (%)	67 (66.3)
Mean (SD) BMI, kg/m^2	24.8 (4.0)
Previous abdominal/pelvic surgery, *n* (%)	30 (29.7)
ASA score, *n* (%)	
1	35 (34.7)
2	45 (44.5)
3	21 (20.8)
ECOG performance status, *n* (%)	
0	67 (66.3)
1	26 (25.7)
2	8 (8.0)
Mean (SD) Charlson comorbidity index score	2.5 (1.9)
Mean (SD) tumour size, cm	3.1 (1.9)
Primary tumour location, *n* (%)	
Pelvocalyceal	58 (57.4)
Ureteric	38 (37.6)
Multifocal	5 (5.0)

ASA, American Society of Anesthesiologists; ECOG, European Cooperative Oncology Group.

Table 2 Perioperative outcomes.

Mean (SD) operating time, min	221.4 (73.7)
Mean (SD) estimated blood loss, mL	231.7 (348.0)
Intraoperative complications, *n* (%)	6 (5.9)
Mean (SD) change in serum creatinine concentration, mg/dL	0.16 (0.33)
Mean (SD) change in serum haemoglobin level, g/dL	0.92 (3.92)
Mean (SD) duration of hospital stay, days	6.3 (3.5)
Mean (SD) pain visual analogue score at discharge	1.5 (1.3)

Table 3 Histopathological outcomes.

Pathological stage, *n* (%)	
Ta	12 (11.9)
Tis	2 (2.0)
T1	42 (41.5)
T2	20 (19.8)
T3	23 (22.8)
T4	2 (2.0)
Tumour grade, *n* (%)	
Low	30 (29.7)
High	71 (70.3)
Nodal status, *n* (%)	
pNx	73 (72.3)
pN0	26 (25.7)
pN1–3	2 (2.0)
Mean (SD) no. of harvested nodes	4.9 (3.8)
Lymphovascular invasion, *n* (%)	
Absent	78 (77.2)
Present	23 (22.8)
Concomitant CIS, *n* (%)	
Absent	84 (83.2)
Present	17 (16.8)
Bladder cuff, *n* (%)	
Excised	80 (79.2)
Not excised	21 (20.8)

were low (Ta-T1) pathological stage and high grade (70.3% of cases). Lymphadenectomy was performed in 28 patients (27.7%) and the mean (SD) number of harvested lymph nodes was 4.9 (3.8). Coexisting lymphovascular invasion and CIS were reported in 23 (22.8%) and 17 (16.8%) cases, respectively. There was no bladder cuff excision in 20.8% of cases, but excision was performed using a variety of techniques in the remaining majority of cases.

At a mean follow-up of 14 months, six patients (5.9%) had died. Disease recurrence (including distant metastases and bladder recurrence) was detected in 23 patients (22.8%), with a mean time to recurrence of 11.5 months.

Discussion

Since the early description of the first nephrectomy cases [13], urological LESS surgery has been a field of intensive clinical investigation over the last 5 years, as demonstrated by the increasing number of publications of the technique for various indications [3–7]. As a general principle, all patients eligible for laparoscopic surgery may be considered for LESS surgery. Extirpative LESS procedures are more commonly performed than reconstructive ones [7], and this can be related to the recognized unfavourable ergonomics associated with LESS surgery.

Although potential advantages of LESS surgery over conventional laparoscopy include less postoperative pain, faster recovery, and shorter length of hospital stay, one of its recognized drawbacks is its unfavourable ergonomics, especially in more challenging surgical cases. Dissection and suturing are more difficult to perform owing to loss of triangulation and a decreased range of motion to manoeuvre instruments. Some of these challenges have been overcome by using articulating or prebent instruments. Another effective strategy can be the use of needlescopic or mini-laparoscopic instruments to aid in triangulation. The application of the da Vinci® robotic platform seems to help with overcoming some of the current limitations [14]. Recently, specifically designed robotic instrumentation for LESS surgery has been developed [15]. The improved ergonomics and intracorporeal suturing provided by new robotic platforms mean that robotics will play a major role in the development of LESS surgery [16]. In the present study, the da Vinci® robot was used in a quarter of the procedures.

The technical feasibility of LESS surgery might also be related to the access platform used. Interestingly, in 62% of the cases represented in the present series, homemade single-port devices were used. Several port designs have been described, but to date, there have been no studies comparing these different ports and this was also outside the scope of the present study. Another technique that can be used is the one described by Nagele et al. [17], defined as single-incision triangulated umbilical surgery, with the use of three individual trocars inserted directly through the umbilical incision.

Previous single-centre experiences with LESS-NU have been reported. In reporting their initial 100 LESS cases, White et al. [5] included seven cases of LESS-NU for upper urinary tract urothelial carcinoma, six of which were performed using a conventional LESS technique and one was robot-assisted LESS surgery. More recently, Seo et al. [10] reported four cases of LESS-NU with an additional lower abdominal midline incision and a bladder cuff procedure via an extravesical open technique. Jeon et al. [18] reported 50 LESS surgery cases using home-made single port devices, of which one was conventional LESS-NU and three were robot-assisted LESS-NU. Lee et al. [11] reported their initial 10 cases of LESS-NU. There were two conversions to open surgery for advanced disease, and the eight successful cases of LESS-NU had a mean operating time of 226 min with similar operative outcomes. These reports all represent single-centre, initial experiences of LESS-NU.

In the present study, the mean operating time was 221 min and estimated blood loss was 232 mL. The mean length of hospital stay for our cases was 6.3 days. The present results demonstrate equivalent operating outcomes compared with large series of standard laparoscopic NU (Table 4 [2,19,20]).

Overall, the intra-operative complication rate in our series was 5.9%, and all intra-operative bleeding was managed conservatively with blood transfusions. LESS-NU was

Table 4 Laparoscopic vs LESS nephroureterectomy: a comparative overview.

Reference	No. of patients	Operating time, min	Estimated blood loss, mL	Hospital stay, days	Intraoperative complications, *n* (%)	Conversion, *n* (%)
Schatteman et al. [19]	100	192	234	10.0	4 (4)	7 (7)
Kamihira et al. [20]	1003	320	232	Not reported	93 (9.3)	44 (4.4)
Ni et al. [2]	1235	241	273	5.9	159 (12.9)	Not reported
Present study	101	221	231	6.3	6 (5.9)	3 (3)*

**Open conversion.*

completed in 97% of cases, with the need for conversion to open surgery in three cases owing to difficulty with dissection (3.0%). Our postoperative complication rate of 10% comprised mostly low grade complications, and included any deviation from the normal postoperative course, even when requiring no additional intervention. Our complication rate of LESS-NU was similar to that reported in standard laparoscopic NU series [2,19,20], despite the challenges of the novel LESS approach.

Laparoendoscopic single-site surgery is feasible for more complex procedures such as NU. Most importantly, the oncological principles must be considered in LESS-NU for the treatment of cancer, unlike in LESS surgery for benign diseases. The 'gold-standard' surgical treatment for upper urinary tract urothelial carcinoma is NU with *en bloc* bladder cuff excision without tumour spillage. Bladder cuff excision is a much debated aspect of NU with regard to oncological outcomes, but in the present study there was no bladder cuff excision in 20% of cases. There are no data on the long-term outcomes, particularly disease-free and disease-specific survival for LESS-NU, stratified by method of bladder cuff management.

Further limitations of this study should be noted. First, it represents a retrospective analysis, although most of the centres collected data in prospectively maintained institutional databases. All data are based on different surgeons' experiences and this could represent a bias. The analysis was limited to variables that were available and of sufficient quality to allow reliable assessment across different institutions. In the present study, The da Vinci® robot was used in 26 patients (25.7%). This could represent another bias. Second, almost all invited centres had previously reported some of these data in recent years. Third, no data on a contemporary control group has been collected and considered in the present analysis.

Any new surgical technique must be enforced safely and without increasing risk to patients before becoming widely adopted. The true benefits of LESS-NU remain to be determined and require randomized control trials in the future.

The present study reports the largest multi-institutional experience with LESS-NU to date. Peri-operative outcomes of LESS-NU seem to mirror those reported for standard laparoscopy. LESS-NU is safe, feasible and reproducible in experienced hands. LESS-NU may be an alternative minimally invasive treatment option for patients eligible to undergo laparoscopic surgery for upper urinary tract urothelial carcinoma, but it remains challenging for more advanced cases. Despite encouraging early findings, clinical trials are still warranted before this procedure is adopted widely, and longer follow-up is needed to determine its oncological durability.

Conflict of Interest

None declared.

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Abbreviations: LESS, laparoendoscopic single-site; NU, nephroureterectomy; BMI, body mass index; CIS, carcinoma *in situ*.