Review – Urothelial Cancer

Oncological Outcomes of Laparoscopic Nephroureterectomy Versus Open Radical Nephroureterectomy for Upper Tract Urothelial Carcinoma: An European Association of Urology Guidelines Systematic Review

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Abstract

Context: Most series have suggested better perioperative outcomes of laparoscopic radical nephroureterectomy (RNU) over open RNU. However, the oncological safety of laparoscopic RNU remains controversial.

Objective: To systematically review all relevant literature comparing oncological outcomes of open versus laparoscopic RNU.

Evidence acquisition: A systematic literature search using the Medline, Embase, and Cochrane databases and clinicaltrial.gov was performed in December 2014 and updated in August 2016. Randomised controlled trials (RCTs) and prospective or retrospective non-randomised comparative studies comparing the oncological outcomes of any laparoscopic RNU with those of open RNU were included. The primary outcome was cancer-specific survival. The risk of bias (RoB) was assessed using Cochrane RoB tools. A narrative synthesis of the evidence is presented.

Evidence synthesis: Overall, 42 studies were included, which accounted for 7554 patients: 4925 in the open groups and 2629 in the laparoscopic groups. Most included studies were retrospective comparative series. Only one RCT was found. RoB and confounding were high in most studies. No study compared the oncological outcomes of robotic RNU with those of open RNU. Bladder cuff excision in laparoscopic groups was performed via an open approach in most studies, with only three studies reporting laparoscopic removal of the bladder cuff. Port-site metastasis rates ranged from 0% to 2.8%. No significant difference

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1. Introduction

Upper tract urothelial carcinomas (UTUCs) are relatively rare tumours with an incidence of 1.2 cases/100 000 inhabitants per year in Europe, which accounts for 5 – 10% of all urothelial carcinomas [1]. Radical nephroureterectomy (RNU) with bladder cuff excision is currently considered the standard of care for the curative management of high-risk UTUC [2]. First described in the early 1990s by Clayman et al [3], laparoscopic RNU has become widely popular during the past decade. Since then, various laparoscopic techniques of RNU have been described, such as the retroperitoneal route [4], hand-assisted laparoscopic RNU [5], or laparoendoscopic single-site RNU [6]. Several ways to manage the bladder cuff during laparoscopic RNU have also been proposed: through an open approach (either intravesical or extravesical excision), a laparoscopic approach (standard excision, endoGIA, Ligasure), or an endoscopic approach (transurethral resection with ureter stripping) [2]. More recently, a robot-assisted laparoscopic approach has been advocated by several authors in order to facilitate distal ureter management [7]. However, even though most series have suggested better perioperative outcomes using the laparoscopic route [8,9], its oncological safety remains controversial, as cases of port-site metastases and tumour cell implantation have been reported [10], which may be due to a higher risk of tumour dissemination and seeding when manipulating UTUC under CO₂ pneumoperitoneum [11]. Based on these considerations, there is an obvious need for evaluating the available evidence to define the optimal surgical approach for RNU. The primary objective of this systematic review (SR) was to assess the oncological outcomes of open RNU compared with those of laparoscopic RNU.

2. Evidence acquisition

2.1. Search strategy

A systematic literature search using the Medline, Embase, and Cochrane databases as well as clinicaltrial.gov was performed and updated by a research librarian in December 2014 and August 2016, respectively. The full search strategy was based on a free text protocol and is presented in the Supplementary material. Searches were limited to studies published from 1995 onwards and were conducted without language restrictions. Translation of any relevant non-English manuscripts was obtained from the European Association of Urology (EAU) Guidelines Office. Cited references from selected studies were also sought. The study protocol was registered in PROSPERO in April 2015 (CRD42015020737).

2.2. Inclusion and exclusion criteria

Studies were assessed using the PICOS approach in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guidelines [12]: patient, intervention, comparator, outcome, and study design.

2.2.1. Types of patients included

The study population consisted of adult patients (>18 yr old) diagnosed with any grade and clinical stage (Tany, Nany, M0) UTUC treated with RNU. Populations excluded from this SR were individuals diagnosed with any clinical M+, noncurative nephroureterectomy (NU), NU performed during excision of extra–upper tract tumour with local extension to the upper tract (eg, colon, duodenum, etc.), and NU with concomitant radical cystectomy.

2.2.2. Types of interventions and comparators included

Studies were considered eligible for this review if they compared the following:

1. Laparoscopic RNU (including robotic, laparoscopic, laparoscopic hand-assisted, and laparoendoscopic single-site RNU) with laparoscopic, endoscopic, or open bladder cuff excision
2. Open RNU with open or endoscopic bladder cuff excision

Laparoscopic RNU was categorised according to distal ureter management as pure laparoscopic RNU when bladder cuff was removed through laparoscopy, combined
RNU when bladder cuff was removed through an open approach, laparoscopic RNU with endoscopic bladder cuff excision when bladder cuff was excised through an endoscopic approach, and unspecified laparoscopic RNU when no details regarding the approach for distal ureter management were provided or when several different approaches were used in the cohort.

2.2.3. Types of outcome measures included
Our primary outcome to measure oncological effectiveness was cancer-specific survival (CSS) at 1, 3, 5, and 10 yr. The secondary outcomes of interest were overall survival (OS), bladder recurrence-free survival (BRFS), recurrence-free survival (RFS), and port-site metastasis occurrence.

2.2.4. Types of study designs included
Randomised controlled trials (RCTs), as well as prospective or retrospective nonrandomised comparative studies, were included in this SR. Noncomparative studies, case reports, editorials, letters, review articles, and meeting abstracts were excluded during the review process. Studies also had to comply with the following inclusion criteria: a minimum follow-up of 1 yr to assess the primary outcome, a minimum of 10 participants in each arm, and an appropriate comparison (ie, survival analysis) with at least one of the aforementioned oncological outcomes. Finally, if two or more studies reported outcomes of overlapping series (ie, by the same surgical team), the one with the largest sample size was selected.

2.3. Study selection process
After removal of duplicates, three authors (B.P., T.S., and J.L. D.E.) independently screened the titles and abstracts of 2363 records for eligibility. The full texts of 121 potentially eligible studies were retrieved and screened independently by two authors using a standardised form. Any disagreement was resolved by consulting the senior EAU Guidelines Associate (H.M.B.). According to the above-mentioned inclusion criteria, 41 studies were deemed relevant for this SR [5,9,13–51]. A PRISMA flowchart describing the study selection process is presented in Fig. 1.

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**Fig. 1 - A PRISMA flowchart describing the study selection process. PRISMA = Preferred Reporting Items for Systematic reviews and Meta-Analysis.**
2.4. Data extraction

Data from all selected studies were independently extracted by the same three authors who performed the study selection (T.S., B.P., and J.L.D.E.), and whom subsequently cross checked them to ensure accuracy. A standardised data extraction form was created and used to collect the following data: study design, number of patients, surgical approach (ie, laparoscopic, open, hand assisted, and robotic), surgical route (ie, transperitoneal or retroperitoneal), distal ureteral management (categorised as clipping, endoscopic, open extravesical, open intravesical, laparoscopic extravesical, or laparoscopic intravesical), pre- and postoperative clinicopathological characteristics, occurrence of port-site metastasis, and survival data, including estimated rates of CSS, OS, RFS, and BRFS at the time points available in the papers, as well as their corresponding unadjusted and adjusted hazard ratios (HRs) with 95% confidence intervals (CIs).

2.5. Assessment of risk of bias

The risk of bias (RoB) for each study was independently evaluated by three reviewers (B.P., T.S., and J.L.D.E.) during data collection and according to the principles outlined in the “Cochrane Handbook for Systematic Review of Interventions” [52]. The reviewers assessed the reports in terms of allocation, sequence generation and concealment, blinding of participants and personnel and outcome assessors, completeness of outcome data, selective outcome reporting, and other sources of bias. In addition, the main confounders for the primary outcome (CSS) were identified a priori by the EAU UTUC Guidelines Panel. The reviewers assessed if each prognostic confounder had been considered by the authors and whether it was balanced across the groups or controlled for in multivariate analysis. The risk of confounding bias was considered to be high if the confounder was not reported or if it was reported but unbalanced among the treatment groups. Conversely, the risk of confounding bias was considered low if the confounder was reported and balanced among the treatment groups, or if it was unbalanced but adjusted for statistically. A RoB summary (Fig. 2) was generated using Cochrane RevMan software v5.3 (Informatics and Knowledge Management Department, Cochrane, London, UK).

2.6. Data analysis

A narrative synthesis of included studies was carried out. Descriptive statistics were used to report baseline characteristics. Continuous variables were described using mean and standard deviation, or alternatively, median and interquartile range. Proportions were used to report categorical variables. Crude rates of the above-mentioned survival outcomes were reported, as well as corresponding unadjusted and adjusted HRs. Statistical significance was defined as \( p < 0.05 \). Studies were analysed separately according to the approach used for bladder cuff excision in the laparoscopic group (pure laparoscopic RNU, combined RNU, laparoscopic RNU with endoscopic bladder cuff excision, or unspecified laparoscopic RNU).

![Fig. 2 – The RoB and confounding assessment for all included studies. CIS = carcinoma in situ; RoB = risk of bias.](image)

3. Evidence synthesis

3.1. Characteristics of included studies

Overall, the 42 included studies enrolled 7554 patients: 4925 in the open group and 2629 in the laparoscopic...
groups. The studies and patient characteristics are summarised in Table 1. The vast majority of included studies were retrospective comparative series. Only one prospective RCT was reported [9]. The retrospective series were multicentre studies [22,23,34,41,44,49] and single-centre studies [5,13–21,24–33,35–40,42,43,45–48,50,51] in six and 34 cases, respectively. Most studies had small sample sizes (only six studies included over 100 patients in each treatment arm [34,41,44,49–51]).

3.2. RoB and quality assessment of included studies

The RoB and confounding assessment for all included studies are shown in Fig. 2. Owing to their retrospective design, most included studies carried a high RoB across most fields of the Cochrane Collaboration tool. The issue of confounding was also poorly addressed by most studies as statistical adjustment was performed in only 11 out of 41 retrospective series, through multivariate analyses and match-paired comparison in nine and two cases, respectively, and all confounders were rarely taken into account. As an example, only two studies [9,44] adjusted for the use of adjuvant chemotherapy.

3.3. Results of comparisons of interventions

3.3.1. Surgical techniques

Seven studies reported the oncological outcomes of hand-assisted laparoscopic versus open RNU [5,15,16,21,22,29,35], 33 studies compared laparoscopic with open RNU [9,13,14,17–20,23–28,30–34,36–45,47–51], and one study compared both laparoscopic and hand-assisted laparoscopic RNU with open RNU [46]. No studies compared the oncological outcomes of robotic RNU with those of open RNU. Laparoscopic RNU was performed through a transperitoneal route in 14 studies [5,9,13,15,24–26,35–37,39,41,48,50], through a retroperitoneal route in 13 studies [14,16,18–20,23,26,28,29,31,32,47,51], and through either a transperitoneal or a retroperitoneal route in four studies [37,42,43,49]. The other studies did not report the route that was used (ie, transperitoneal or retroperitoneal). Lymph node dissections were rarely performed and homogeneously distributed between open and laparoscopic groups.

3.3.2. Distal ureter management

Bladder cuff excision in laparoscopic groups was performed via an open approach in most studies (16/33, combined RNU), with only three studies reporting laparoscopic extra-vesical removal of the bladder cuff in all patients [9,36,47] (pure laparoscopic RNU) and four studies reporting laparoscopic removal of the bladder cuff in a minority of patients [19,30,32,38]. The distal ureter was managed endoscopically in four studies [13–15,30] (laparoscopic RNU with endoscopic bladder cuff excision). The approach for bladder cuff removal was not specified or heterogeneous in 15 studies (unspecified laparoscopic RNU). Only two studies reported no bladder cuff excision in some patients: it accounted for over a half of either open or laparoscopic cases in Capitanio et al’s study [34], and only 1% and 3% of laparoscopic and open procedures, respectively, in the series by Kitamura et al [46].

3.3.3. Lymph node dissection

Only 22 studies reported whether a lymph node dissection was performed or not in each group, and none detailed the templates used. Of these 22 series, five reported a 100% rate of lymph node dissection in both groups [18,25,26,30,35] and three studies reported a 0% rate of lymph node dissection in each group [9,26,28]. Three of the 14 remaining studies reported significantly lower rates of lymphadenectomy in the laparoscopic group [34,41,44], while rates of lymphadenectomy were similar between the open and laparoscopic cases in the other series. Only one study reported a significant difference regarding the number of lymph nodes removed, favouring the open over the laparoscopic approach [19].

3.3.4. Pathological findings

No statistically significant differences in positive surgical margin (PSM) rates between the open and laparoscopic groups were reported in any studies. PSM rates ranged from 0% [15,24,29,32,33] to 17.4% [27] in laparoscopic cohorts and from 0% [24,29,32,33,36] to 15% [14] in open cohorts. The reported pN+ rate was below 20% in all studies and comparable in open and laparoscopic groups. Advanced disease (pT3/pT4) accounted for over half of the cases in only two studies [35,49]. It is noteworthy that the rate of renal pelvic tumour (vs ureter) was significantly higher in the laparoscopic group in three studies [21,34,39].

3.3.5. Port-site metastasis and tumour seeding

Comparisons of oncological outcomes are summarised in Table 2. Out of 18 studies that reported on port-site metastasis, four studies reported a total of six port-site metastases [9,23,41,42]. Port-site metastasis rates ranged from 0% to 2.8% [42]. No case of peritoneal or retroperitoneal carcinomatosis was reported.

3.3.6. Combined versus open RNU

Out of 16 studies, all retrospective, assessing combined RNU versus open RNU, only one study reported significantly different oncological outcomes between the two approaches [50]. In this single-centre series, Kim et al [50] compared 271 open RNU with 100 combined RNU and found significantly poorer OS (5-yr OS: 59.1% vs 75.2%, p = 0.03) and CSS (5-yr CSS: 66.1% vs 80.2%, p = 0.01) in the laparoscopic group. On stratifying patients according to tumour stages, significant differences in OS and CSS between the two surgical approaches were observed only in patients with locally advanced disease (pT3/T4), which was confirmed in multivariate analyses (HR = 2.59, p = 0.001 and HR = 2.50, p = 0.005 for overall death and cancer-specific death, respectively). Conversely, in a large multicentre French study, Ariane et al [41] reported a trend towards better CSS in patients who underwent combined RNU in univariate (5-yr CSS: 90.7% vs 78%, p = 0.06) and multivariate analyses (HR = 0.51, 95% CI: 0.25–1.01, p = 0.06).
| Study                  | Year  | Study design            | LE | Surgical approaches | Number of patients | Surgical route | Bladder cuff excision | Median follow-up (months) | Pathological grade (%) | >pT3 stage (%) | No lymph node dissection (%) | pN + stage (%) | Positive surgical margins (%) |
|------------------------|-------|-------------------------|----|---------------------|-------------------|---------------|-----------------------|--------------------------|------------------------|----------------|-------------------------------|----------------|-----------------------------|
| **Combined laparoscopic RNU vs. open RNU** |       |                         |    |                     |                   |               |                       |                          |                        |                |                               |                |                             |
| Kawauchi et al [16]    | 2002  | Single-centre retrospective | 3  | Open                | 34                | Transperitoneal: 18% Stripping: 21% Retropertoneal: 82% NR: 79% | Mean: 48.8 | G1: 11.8% | G2: 50% | G3: 38.2% | G1: 14.7% | G2: 58.8% | G3: 26.5% | 38.2% | NR | NR | NR |
|                        |       |                         |    |                     |                   | Laparoscopic hand-assisted | 34 | Retropertoneal | Open extravesical: 92% Endoscopic: 8% | Mean: 48.8 | G1: 4.3% | G2: 65.2% | G3: 30.4% | G1: 8% | G2: 68% | G3: 24% | 35.3% | NR | NR | NR |
| Okegawa et al [20]     | 2006  | Single-centre retrospective | 3  | Open                | 24                | NR | NR | Mean: 29.2 | G1: 4.3% | G2: 65.2% | G3: 30.4% | G1: 8% | G2: 68% | G3: 24% | 35.3% | NR | NR | NR |
|                        |       |                         |    |                     |                   | Laparoscopic | 25 | Retroperitoneal | Open extravesical | Mean: 24.3 | G1: 4.3% | G2: 65.2% | G3: 30.4% | G1: 8% | G2: 68% | G3: 24% | 16% | NR | NR | NR |
| Sato et al [21]        | 2006  | Single-centre retrospective | 3  | Open                | 23                | NR | NR | Mean: 30 | G1: 34.6% | G2: 50% | G3: 15.4% | G1: 0% | G2: 54.3% | G3: 45.3% | 39.3% | 0% | 0% | NR |
|                        |       |                         |    |                     |                   | Laparoscopic hand-assisted | 36 | NR | Open extravesical | 60 | G1: 21.7% | G2: 60.9% | G3: 17.4% | G1: 16.7% | G2: 66.6% | G3: 16.7% | 30.4% | NR | 4.3% | NR |
| Roupret et al [24]    | 2007  | Single-centre retrospective | 3  | Open                | 26                | NR | NR | Mean: 78 | Low grade: 26.9% High grade: 73.1% | G1: 34.6% | G2: 50% | G3: 15.4% | G1: 0% | G2: 54.3% | G3: 45.3% | 39.3% | 0% | 0% | NR |
|                        |       |                         |    |                     |                   | Laparoscopic | 20 | Transperitoneal | Open extravesical | Mean: 69 | Low grade: 60% High grade: 40% | G1: 21.7% | G2: 60.9% | G3: 17.4% | G1: 16.7% | G2: 66.6% | G3: 16.7% | 33.4% | NR | 2.8% | NR |
| Lee et al [25]         | 2007  | Single-centre retrospective | 3  | Open                | 29                | NR | NR | Mean: 30 | G1: 34.6% | G2: 50% | G3: 15.4% | G1: 0% | G2: 54.3% | G3: 45.3% | 39.3% | 0% | 0% | NR |
|                        |       |                         |    |                     |                   | Laparoscopic | 22 | Transperitoneal | Open extravesical | Mean: 13.7 | G1: 4.3% | G2: 65.2% | G3: 30.4% | G1: 8% | G2: 68% | G3: 24% | 33.4% | NR | 2.8% | NR |
| Chung et al [26]       | 2007  | Single-centre retrospective | 3  | Open                | 41                | NR | NR | Mean: 62 | G1: 2.4% | G2: 56.1% | G3: 41.5% | G1: 4% | G2: 52% | G3: 44% | 22% | 100% | NR | NR |
|                        |       |                         |    |                     |                   | Laparoscopic | 25 | Retroperitoneal | Open extravesical | Mean: 32 | G1: 4.3% | G2: 56.1% | G3: 41.5% | G1: 4% | G2: 52% | G3: 44% | 28% | 100% | NR | NR |
| Kong et al [27]        | 2007  | Single-centre retrospective | 3  | Open                | 22                | NR | NR | Mean: 29 | NR | NR | 21.7% | NR | NR | 9% | 0% | NR | 17.4% | NR |
| Koda et al [28]        | 2007  | Single-centre retrospective | 3  | Open                | 27                | NR | NR | Mean: 46.2 | G1: 11.1% | G2: 59.3% | G3: 29.6% | G1: 12.7% | G2: 41.8% | G3: 45.6% | 25.9% | 100% | 0% | NR |
|                        |       |                         |    |                     |                   | Laparoscopic | 79 | Retroperitoneal | Open extravesical | Mean: 16.4 | NR | NR | 21.7% | NR | NR | 9% | 0% | NR | 17.4% | NR |
| Nakashima et al [29]   | 2007  | Single-centre retrospective | 3  | Open                | 37                | NR | NR | Mean: 56 | G1: 35.1% | G2: 41.5% | G3: 41.5% | G1: 35.1% | G2: 41.5% | G3: 41.5% | 29.7% | NR | NR | 0% | NR |
|                        |       |                         |    |                     |                   | Laparoscopic hand-assisted | 35 | Retroperitoneal | Open extravesical | Mean: 23 | NR | NR | 37.1% | NR | NR | 0% | NR | 0% |
| Study                  | Year | Study design                     | LE  | Surgical approaches | Number of patients | Surgical route | Bladder cuff excision | Median follow-up (months) | Pathological grade (%) | ≥pT3 stage (%) | No lymph node dissection (%) | pN + stage (%) | Positive surgical margins (%) |
|-----------------------|------|----------------------------------|-----|---------------------|-------------------|---------------|------------------------|--------------------------|------------------------|----------------|-------------------------------|----------------|-------------------------------|
| Chung et al [26]      | 2007 | Single-centre retrospective      | 3   | Open                | 36                | NR            | NR                     | 59.5                     | G1: 2.8%               | 16.7%          | 0%                            | 5.3%           | NR                            |
|                       |      |                                  |     | Laparoscopic        | 39                | Transperitoneal | Open extravesical      | 48                       | G2: 55.6%               | 30.8%          | 0%                            | 10.5%          | NR                            |
| Taweemonkongsap et al [31] | 2008 | Single-centre retrospective      | 3   | Open                | 29                | Retroperitoneal | Open extravesical      | Mean: 26.4               | Low grade: 34.5%        | 13.8%          | 70%                           | 10.3%          | NR                            |
|                       |      |                                  |     | Laparoscopic        | 31                | Retroperitoneal | Open extravesical      | Mean: 27.9               | Low grade: 58.1%        | 16.1%          | 35.5%                         | 3.2%           | NR                            |
| Waldert et al [33]    | 2008 | Single-centre retrospective      | 3   | Open                | 59                | Retroperitoneal | Open intravesical      | Mean: 41                 | Low grade: 33.9%         | 33.9%          | 20.3%                         | 10.2%          | 0%                            |
|                       |      |                                  |     | Laparoscopic        | 43                | NR              | Open intravesical      | Mean: 41                 | Low grade: 41.9%         | 41.9%          | 30.2%                         | 16.3%          | 0%                            |
| Chung et al [35]      | 2009 | Single-centre retrospective matched paired comparison | 3   | Open                | 31                | Retroperitoneal | Open extravesical      | 115                      | G1: 22.6%               | 100%           | 0%                            | 0%             | NR                            |
|                       |      |                                  |     | Laparoscopic hand-assisted | 21              | Transperitoneal | Open extravesical      | Mean: 72                 | G2: 32.2%               | 100%           | 0%                            | 0%             | NR                            |
| Ariane et al [41]     | 2011 | Multicentre retrospective        | 3   | Open                | 459               | NR             | Open extravesional: 96% Stripping: 4% | 27                      | G1: 22.6%               | 39.6%          | 52.5%                         | 10.2%          | NR                            |
|                       |      |                                  |     | Laparoscopic        | 150               | Transperitoneal | Open extravesional: 95% Stripping: 5% | NR                      | G2: 36.2%               | 36.6%          | 70%                           | 4.7%           | NR                            |
| Lotrecchiano et al [42] | 2012 | Single-centre retrospective      | 3   | Open                | 32                | NR             | NR                     | Mean: 42                 | High grade: 40.6%        | 21.9%          | 62.5%                         | 6.2%           | NR                            |
|                       |      |                                  |     | Laparoscopic        | 36                | Retroperitoneal: 69% | Open extravesional: 59% | Mean: 23                 | Low grade: 59.4%         | 8.3%           | 83.3%                         | 5.6%           | NR                            |
| Kim et al [50]        | 2016 | Single-centre retrospective      | 3   | Open                | 271               | NR             | Open extravesical      | 57.6                     | Low grade: 35.1%         | 41.3%          | 79%                           | 3.7%           | 4.1%                          |
|                       |      |                                  |     | Laparoscopic        | 100               | Transperitoneal | Open extravesical      | 38.8                     | Low grade: 64.9%         | 34%            | 87%                           | 0%             | 3%                            |
| Pure laparoscopic RNU vs. open RNU |       |                                  |     | Open                | 40                | Retroperitoneal | Open extravesical      | 44                       | Low grade: 37.5%         | 32.5%          | 100%                          | 0%             | NR                            |
| Simone et al [9]      | 2009 | Randomized controlled trial      | 1   | Open                | 40                | Open extravesal | Laparoscopic extravesical | 60                      | Low grade: 42.5%         | 30%            | 100%                          | 0%             | NR                            |
| Study                        | Year   | Study design      | LE            | Surgical approaches | Number of patients | Surgical route                  | Bladder cuff excision | Median follow-up (months) | Pathological grade (%) | ≥pT3 stage (%) | No lymph node dissection (%) | pN + stage (%) | Positive surgical margins (%) |
|-----------------------------|--------|-------------------|---------------|--------------------|--------------------|---------------------------------|------------------------|--------------------------|-------------------------|----------------|-------------------------------|----------------|-----------------------------|
| Greco et al [36]            | 2009   | Single-centre retrospective | 3 Open    | Retropitoneal      | 70                 | Open extravesical             | 60                     | G1: 24.3%                 | G2: 64.3%               | G3: 11.4%       | 1.4%                            | NR             | NR                           | 0%               |
|                             |        |                   |              |                    |        | Laparoscopic                    |                        | G1: 21.5%                 | G2: 67.1%               | G3: 11.4%       | 4.2%                            | NR             | NR                           | 1.4%             |
| Fang et al [47]             | 2014   | Single-centre retrospective | 3 Open    | Laparoscopic       | 36                 | NR                             | Mean: 30.8              | NR                       | NR                      | NR             | NR                            | NR             | NR                           |
|                             |        |                   |              |                    |        | Retroperitoneal                 | Mean: 22.4             | NR                       | NR                      | NR             | NR                            | NR             | NR                           |
|                             |        |                   |              |                    |        | Laparoscopic extravesical       |                        | G1: 21.5%                 | G2: 67.1%               | G3: 11.4%       | 4.2%                            | NR             | NR                           | 1.4%             |
|                             |        |                   |              |                    |        |unnamed                         |                        | G1: 24.3%                 | G2: 64.3%               | G3: 11.4%       | 1.4%                            | NR             | NR                           | 0%               |
|                             |        |                   |              |                    |        |unnamed                         |                        | G1: 21.5%                 | G2: 67.1%               | G3: 11.4%       | 4.2%                            | NR             | NR                           | 1.4%             |
| Unspecified/Heterogeneous laparoscopic vs. open RNU |        |                   |              |                    |        |unnamed                         |                        | G1: 24.3%                 | G2: 64.3%               | G3: 11.4%       | 1.4%                            | NR             | NR                           | 0%               |
| Kim et al [17]              | 2005   | Single-centre retrospective | 3 Open    | Laparoscopic       | 17                 | NR                             | Mean: 25.6              | NR                       | NR                      | NR             | 20%                            | NR             | NR                           |
|                             |        |                   |              |                    |        | NR                             | Mean: 19                | NR                       | NR                      | NR             | 10%                            | NR             | NR                           |
| Tsujihata et al [18]        | 2006   | Single-centre retrospective | 3 Open    | Laparoscopic       | 24                 | NR                             | 22.1                   | G1: 4.2%                 | G2: 45.8%               | G3: 50%         | 16.7%                           | 0%             | 0%                           | NR               |
| Hattori et al [19]          | 2006   | Single-centre retrospective | 3 Open    | Laparoscopic       | 60                 | NR                             | 35                     | G1: 10%                  | G2: 60%                 | G3: 30%         | 38.3%                           | 12%             | NR                           | 0%               |
| Raman et al [5]             | 2006   | Single-centre retrospective | 3 Open    | Laparoscopic       | 38                 | Retropitoneal                  | Mean: 51               | Low grade: 63.5%          | High grade: 36.5%     | NR             | NR                            | NR             | NR                           |
|                             |        |                   |              |                    |        | Mean: 17                      | 60%                    | Low grade: 60.5%          | High grade: 39.5%     | NR             | NR                            | NR             | NR                           |
|                             |        |                   |              |                    |        | Open extravesal: 40%            | Laparoscopic extravesal: 60% | G1: 15.7%                | G2: 53.5%               | G3: 34.8%       | 30.3%                           | 13.5%           | NR                           | 0%               |
|                             |        |                   |              |                    |        | Open extravesal: 61%            | Open intravesal: 39%    | G1: 10%                  | G2: 60%                 | G3: 30%         | 38.3%                           | 12%             | NR                           | 0%               |
|                             |        |                   |              |                    |        | Open extravesal: 58%            | Open intravesal: 53%    | G1: 15.7%                | G2: 53.5%               | G3: 34.8%       | 30.3%                           | 13.5%           | NR                           | 0%               |
|                             |        |                   |              |                    |        | Open intravesal: 21%            | Endoscopic: 21%         | G1: 15.7%                | G2: 53.5%               | G3: 34.8%       | 30.3%                           | 13.5%           | NR                           | 0%               |
| Hsueh et al [22]            | 2007   | Multicentre retrospective | 3 Open    | Laparoscopic       | 77                 | NR                             | Mean: 53.6             | G1: 3.9%                 | G2: 50.6%               | G3: 45.5%       | 22.1%                           | NR             | NR                           |
|                             |        |                   |              |                    |        | Laparoscopic hand-assisted      | Mean: 37.6             | G1: 1.5%                 | G2: 39.4%               | G3: 59.1%       | 24.2%                           | NR             | NR                           |
|                             |        |                   |              |                    |        |unnamed                         |                        | G1: 9%                   | G2: 52.4%               | G3: 38.6%       | 48.2%                           | NR             | NR                           |
|                             |        |                   |              |                    |        |unnamed                         |                        | G1: 6.9%                 | G2: 53.4%               | G3: 39.7%       | 41.4%                           | NR             | NR                           |
| Manabe et al [23]           | 2007   | Multicentre retrospective | 3 Open    | Laparoscopic       | 166                | NR                             | Mean: 28               | G1: 9%                   | G2: 52.4%               | G3: 38.6%       | 48.2%                           | NR             | NR                           |
|                             |        |                   |              |                    |        | Laparoscopic                    | Mean: 13.6             | G1: 6.9%                 | G2: 53.4%               | G3: 39.7%       | 41.4%                           | NR             | NR                           |
| Study            | Year    | Study design                  | LE     | Surgical approaches | Number of patients | Surgical route | Bladder cuff excision | Median follow-up (months) | Pathological grade (%) | ≥pT3 stage (%) | No lymph node dissection (%) | pN + stage (%) | Positive surgical margins (%) |
|------------------|---------|-------------------------------|--------|--------------------|--------------------|---------------|-----------------------|---------------------------|------------------------|----------------|--------------------------------|----------------|-------------------------------|
| Hemal et al [32] | 2008    | Single-centre retrospective   | 3      | Open               | 27                 | Retroperitoneal | Open extravesical     | 57                        | G1: 29.6%              | G2: 48.1%       | G3: 22.2%                      |                 | 11.1%                         |
|                  |         |                               |        |                    |                    |                |                       |                           |                       |                | 9.5%                          | 28.6%          | 4.8%                          |
|                  |         |                               |        |                    |                    |                |                       |                           |                       |                | 29.6%                         | 7.4%           | 0%                            |
| Capitanio et al  | 2009    | Multicentre retrospective     | 3      | Open               | 979               | NR             | Open extra or intravesical: 41% | 63                        | Low grade: 40.3% | G1: 5.7% | G2: 44.1%                      | G3: 50%         | 35.2%                         |
|                  |         |                               |        |                    |                    |                | No bladder cuff: 59% |                           |                       |                | 24.2%                         | 57%            | 9.6%                          |
|                  |         |                               |        |                    |                    |                |                       |                           |                       |                | 24.2%                         | 5.9%           | NR                            |
| Aguilera et al   | 2009    | Single-centre retrospective   | 3      | Open               | 31                | Transperitoneal: 43% | Open extravesical: 43% | 52.7                     | G1: 5.7%              | G2: 44.1%       | G3: 50%                      |                 | G1: 12%                      |
|                  |         |                               |        |                    |                    |                | Retropertioneal: 57% |                           |                       |                | 24.2%                         | 57%            | 9.6%                          |
|                  |         |                               |        |                    |                    |                |                       |                           |                       |                | 20%                           | 88%            | 0%                            |
| Favretto et al   | 2010    | Single-centre retrospective   | 3      | Open               | 109               | Retropertioneal | Open extravesical     | 23                        | Low grade: 12% | G1: 12% | G2: 38.5%                      | G3: 30.4%       | 13%                           |
|                  |         |                               |        |                    |                    |                | Open or laparoscopex: 66% |                           |                       |                | 32%                           | 30%            | 13%                           |
|                  |         |                               |        |                    |                    |                | Retropertioneal: 75% |                           |                       |                | 17                            | 32%            | NR                            |
| Stewart et al    | 2011    | Single-centre retrospective   | 3      | Open               | 39                | Transperitoneal | NR                   | 177                       | G1: 10.2%             | G2: 51.2%       | G3: 38.5%                      |                 | G1: 2%                        |
|                  |         |                               |        |                    |                    |                |                       |                           |                       |                | 33.6%                         | 77%            | 6.8%                          |
|                  |         |                               |        |                    |                    |                |                       |                           |                       |                | 33.6%                         | 77%            | 6.8%                          |
| Walton et al     | 2011    | Multicentre retrospective     | 3      | Open               | 703               | NR             | Endoscopic: 13%       | 36                        | G1: 12.4%             | G2: 31.2%       | G3: 36.3%                      |                 | G1: 15.7%                     |
|                  |         |                               |        |                    |                    |                | NR: 87%               |                           |                       |                | 32.8%                         | 70%            | 2.9%                          |
|                  |         |                               |        |                    |                    |                |                       |                           |                       |                | 13%                           | 32.8%          | 2.9%                          |
| Hamada et al     | 2013    | Single-centre retrospective   | 3      | Open               | 50                | Transperitoneal: 32% | NR                   | 55                        | G1: 4%                | G2: 14%         | G3: 62%                      |                 | 41.2%                        |
|                  |         |                               |        |                    |                    |                | Retropertioneal: 68% |                           |                       |                | 41.2%                         | 6%             | NR                            |
|                  |         |                               |        |                    |                    |                |                       |                           |                       |                | 46%                           | 0%             | NR                            |
| Study               | Year | Study design       | LE Surgical approaches | Number of patients | Surgical route                     | Bladder cuff excision          | Median follow-up (months) | Pathological grade (%) | ≥pT3 stage (%) | No lymph node dissection (%) | pN + stage (%) | Positive surgical margins (%) |
|---------------------|------|--------------------|------------------------|--------------------|-----------------------------------|-------------------------------|---------------------------|-------------------------|----------------|-------------------------------|----------------|-------------------------------|
| Fairey et al [44]  | 2013 | Multicentre retrospective | 3 Open                | 403 NR             | Open extravesical: 42% Open intravesical: 51% Endoscopic: 4% NR: 3% | 26 Low grade: 31% High grade: 69% | NR |                        | 31%        | 68%                           | 10%           | 11%                           |
|                     |      |                    |                       |                    | Laparoscopic: 446 NR              |                               |                           |                         |                |                               |                |                               |
| Izumi et al [45]   | 2013 | Single-centre retrospective | 3 Open                | 19 NR              | No bladder cuff: 3% No bladder cuff: 1% Endoscopic: 11% NR: 8% | 60 G1: 5.3% G2: 78.9% G3: 15.8% G1: 6.5% G2: 63% G3: 30.5% | NR |                        | 36.7%      | 42.1%                         | 15.8%         | NR                            |
|                     |      |                    |                       |                    | Laparoscopic: 46 NR              |                               |                           |                         |                |                               |                |                               |
| Kitamura et al [46] | 2014 | Single-centre retrospective | 3 Open                | 34 NR              | No bladder cuff: 3% No bladder cuff: 1% Endoscopic: 11% NR: 8% | 60 G1: 3% G2: 41% G3: 56% G1: 3% G2: 50% G3: 47.3% | NR |                        | 47%        | NR                           | NR            | NR                            |
|                     |      |                    |                       |                    | Laparoscopic: 74 NR              |                               |                           |                         |                |                               |                |                               |
|                     |      |                    |                       |                    | Laparoscopic hand-assisted: 12%   |                               |                           |                         |                |                               |                |                               |
| Zou et al [48]     | 2014 | Single-centre retrospective | 3 Open                | 101 Transperitoneal | NR                               | 53 Low grade: 53.6% High grade: 46.5% Low grade: 57.1% High grade: 42.9% | NR |                        | 22.8%      | NR                           | NR            | 2%                            |
|                     |      |                    |                       |                    | Laparoscopic: 21 Transperitoneal |                               |                           |                         |                |                               |                |                               |
| Miyazaki et al [49]| 2016 | Multicentre retrospective | 3 Open                | 527 Transperitoneal: 19.8% Extraperitoneal: 80.2% Transperitoneal: 14% Extraperitoneal: 86% | NR | 39 Low grade: 53.6% High grade: 46.5% Low grade: 57.1% High grade: 42.9% | NR |                        | 70.8%      | 63.6%                         | 11.4%         | NR                            |
|                     |      |                    |                       |                    | Laparoscopic: 222 Transperitoneal |                               |                           |                         |                |                               |                |                               |
| Shan et al [51]    | 2015 | Single-centre retrospective | 3 Open                | 118 NR             | Open extravesical Open extravesical: 43.2 Open extravesical: 40.7% Open extravesical: 42.9% Open extravesical: 43.4% Open extravesical: 43.7% | NR |                        | 7.6%       | 4.2%                         | NR            | 4.2%                         |
|                     |      |                    |                       |                    | Laparoscopic: 100 Retroperitoneal |                               |                           |                         |                |                               |                |                               |
| Study                        | Year | Study design     | LE  | Surgical approaches | Number of patients | Surgical route                      | Bladder cuff excision          | Median follow-up (months) | Pathological grade (%) | ≥pT3 stage (%) | No lymph node dissection (%) | pN + stage (%) | Positive surgical margins (%) |
|-----------------------------|------|------------------|-----|---------------------|--------------------|-------------------------------------|--------------------------------|-------------------------|------------------------|----------------|-------------------------------|----------------|-----------------------------|
| Shalhav et al [13]          | 2000 | Single-centre   | 3   | Open                | 17 NR              | NR                                 | Mean: 43                       | G1: 29%                  | G2: 47%                | G3: 24%            | NR              | NR                            | NR            | NR                          | Laparoscopic 25 Transperitoneal Endoscopic: 96% stripping: 4% JR | Laparoscopic 42 Retroperitoneal Endoscopic Mean: 11.1 G1: 17% G2: 29% G3: 46% Unknown: 8% G1: 21% G2: 24% G3: 55% | 22% NR 5% 7% |
| Gill et al [14]             | 2000 | Single-centre   | 3   | Open                | 35 NR              | NR                                 | Mean: 34.4                     | G1: 17%                  | G2: 29%                | G3: 46%            | NR              | NR                            | NR            | NR                          | Laparoscopic 42 Retroperitoneal Endoscopic Mean: 11.1 G1: 17% G2: 29% G3: 46% Unknown: 8% G1: 21% G2: 24% G3: 55% | 22% NR 5% 7% |
| Stifelman et al [15]        | 2001 | Single-centre   | 3   | Open                | 17 Retroperitoneal  | NR                                 | Mean: 17                       | Low grade: 9%            | High grade: 91%        | High grade: 82%      | NR              | NR                            | NR            | NR                          | Laparoscopic 11 Transperitoneal Endoscopic Mean: 13 Low grade: 9% High grade: 91% Low grade: 18% High grade: 82% | Laparoscopic 11 Transperitoneal Endoscopic Mean: 13 Low grade: 9% High grade: 91% Low grade: 18% High grade: 82% | NR NR 9% |
| Muller et al [30]           | 2007 | Single-centre   | 3   | Open                | 19 Transperitoneal  | 16% Open extraskeletal: 74%         | Mean: 24                       | Low grade: 26.3%          | High grade: 52.6%       | Low grade: 82%        | 0%              | 0%                             | 5.3% NR       | 10.5% NR                    | Laparoscopic 19 Transperitoneal: 84% Open extraskeletal: 26% | Low grade: 26.3% High grade: 52.6% Low grade: 47.4% High grade: 42.1% | 0% 0% |

LE = level of evidence; NA = Not applicable; NR = not reported; RNU = radical nephroureterectomy.
| Study | Surgical approaches | Number of patients | Port-site metastasis 5-yr cancer-specific survival | p value | 5-yr overall survival | p value | 5-yr recurrence-free survival | p value | HR (LNU vs ONU) 95% CI | p value | Multivariable Cox regression analysis |
|-------|---------------------|-------------------|-----------------------------------------------|--------|----------------------|--------|-------------------------------|--------|---------------------------|--------|----------------------------------|
| **Combined laparoscopic RNU vs open RNU** |
| Kawauchi et al [16] | Open Laparoscopic hand assisted | 34 | NA | NR | NR | NR | NR | NR | NR | 49 mo: 38.2% | NR | NR | NR | NR | 49 mo: 8.8% | NR | NR | NR | NR | 29 mo: 17% | NS | NR | NR | NR | 29 mo: 20% | 0.67 | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR |NR
| Study                        | Surgical approaches | Number of patients | Port-site metastasis | 5-yr cancer-specific survival | 5-yr overall survival | 5-yr recurrence-free survival | 5-yr bladder recurrence-free survival | Multivariable Cox regression analysis |
|-----------------------------|---------------------|--------------------|----------------------|------------------------------|----------------------|------------------------------|--------------------------------------|-------------------------------------|
| Hattori et al [19]          | Open                | 60                 | NA                   | 78%                          | 0.89                 | NR                           | 71%                                  | 0.91                                | 66%                                | 0.38 | NR | NR | NR | HR (LNU vs ONU) |
|                             | Laparoscopic        | 89                 | 0                    | 81%                          | NR                   | NR                           | 71%                                  | 0.91                                | 51%                                | NR | NR | NR | NR | 95% CI |
| Raman et al [5]             | Open                | 38                 | NA                   | NR                           | NR                   | NR                           | NR                                   | 61 mo: 34.6%                       | 32 mo: 28.9%                       | NR | NR | NR | NR | 5% |
|                             | Laparoscopic hand assisted | 52 | 0 | NR | NR | NR | NR | NR | 54 mo: 24.7% | 38 mo: 20% | NR | NR | NR | NR | 5% |
| Hsueh et al [22]            | Open                | 77                 | NA                   | NR                           | 0.98                 | NR                           | 0.74                                 | 2 yr: 73%                           | 2 yr: 77%                          | 95% | 5 mo: 11.1% | NR | NR | BRFS (HALNU vs ONU): 5.52 |
|                             | Laparoscopic hand assisted | 66 | 0 | NR | NR | NR | NR | NR | 54 mo: 9.5% | NR | BRFS (LNU vs ONU): 2.05–14.6 |
| Manabe et al [23]           | Open                | 166                | NA                   | 2 yr: 87%                    | 0.89                 | 2 yr: 83.6%                  | 0.53                                 | NR                                  | NR                                  | NR | 28 mo: 38% | 14 mo: 32.8% | NR | NR | CSS: 1.54 |
|                             | Laparoscopic        | 16                | 1 (1.7%)             | NR                           | 85.2%                | NR                           | 88.8%                                | 57 mo: 111%                        | 11 mo: 4%                          | NR | NR | NR | NR | CSS: NR |
| Hemal et al [32]            | Open                | 979                | NA                   | 73.1%                        | 0.008*               | NR                           | 76.2%                                | 86.8%                               | NR                                  | NR | NR | NR | NR | CSS: 0.1 |
|                             | Laparoscopic        | 66                 | NR                   | NR                           | NR                   | NR                           | NR                                   | NR                                  | NR                                  | NR | NR | NR | NR | RFS: 0.1 |
| Capitanio et al [34]        | Open                | 31                 | NA                   | NR                           | NR                   | NR                           | NR                                   | NR                                  | NR                                  | NR | NR | NR | NR | NR |
|                             | Laparoscopic        | 21                 | 0                    | NR                           | NR                   | NR                           | NR                                   | NR                                  | NR                                  | NR | NR | NR | NR | NR |
| Fairey et al [44]           | Open                | 403                | NA                   | 71%                          | 0.32                 | 67%                          | 0.39                                 | 44%                                 | NR                                  | NR | NR | NR | NR | 64% |
|                             | Laparoscopic        | 446                | NR                   | 76%                          | 68%                  | 33%                          | 0.06                                 | NR                                  | NR                                  | NR | NR | NR | NR | 52% |
| Izumi et al [45]            | Open                | 19                 | NA                   | NR                           | NR                   | NR                           | 0.41                                 | NR                                  | 0.17                                | NR | 0.80 | NR | NR | NR |
|                             | Laparoscopic        | 46                 | NR                   | NR                           | NR                   | NR                           | NR                                   | NR                                  | NR                                  | NR | NR | NR | NR | NR |
| Kitamura et al [46]         | Open                | 34                 | NA                   | 74.2%                        | 0.56                 | NR                           | 57.2%                                | 65.8%                               | 0.04*                               | 71.1%                        | 0.002* | 0.08 | NR | NR | 95% CI |
|                             | Laparoscopic hand assisted | 74 | NR | 72.9% | 88.7% | NR | NR | NR | 107% | 98% | 62% | 11% | 0.08 | BRFS (HALNU vs ONU): 2.05–14.6 |
| Zou et al [48]              | Open                | 101                | NA                   | 79.2%                        | 0.56                 | NR                           | 57.2%                                | 65.6%                               | 0.04*                               | 71.1%                        | 0.002* | 0.08 | NR | NR | 95% CI |
|                             | Laparoscopic        | 21                 | NR                   | 85.7%                        | NR                   | NR                           | NR                                   | NR                                  | NR                                  | NR | NR | NR | NR | 95% CI |
| Miyazaki et al [49]         | Open                | 527                | NA                   | 3 yr: 73%                    | 0.09                 | 3 yr: 69.5%                  | 0.13                                 | 3 yr: 72.4%                        | NR                                  | NR | NR | NR | NR | CSS: 0.16 |
|                             | Laparoscopic        | 222                | NR                   | 3 yr: 76%                    | 66%                  | 33%                          | 0.10                                 | 77%                                 | 0.75                                | NR | NR | NR | NR | CSS: NR |
| Shan et al [51]             | Open                | 118                | NA                   | NR                           | 83.8%                | 69%                          | 66%                                  | 79%                                 | NR                                  | NR | NR | NR | NR | 5% |
|                             | Laparoscopic        | 100                | NR                   | 80.8%                        | 66%                  | 66%                          | 54%                                  | 79%                                 | 0.75                                | NR | NR | NR | NR | 5% |
| **Laparoscopic RNU with endoscopic bladder cuff excision vs open RNU** |                     |                     |                      |                     |                     |                     |                                      |                                      |                                      |                     |                     |                     |                     |                     |
| Shalhav et al [13]          | Open                | 17                 | NA                   | 42 mo: 90%                  | 0.56                 | NR                           | 40 mo: 81%                           | NR                                  | NR                                  | NR | NR | NR | NR | CSS: 0.71–2.93 |
|                             | Laparoscopic        | 25                 | 0                    | 24 mo: 90%                  | NR                   | NR                           | 24 mo: 90%                           | NR                                  | NR                                  | NR | NR | NR | NR | BRFS: 0.08–174 |
| Gill et al [14]             | Open                | 35                 | NA                   | 34 mo: 87%                  | 0.59                 | 34 mo: 94%                  | 0.59                                 | 34 mo: 77%                         | NR                                  | NR | NR | NR | NR | 0.58 |
|                             | Laparoscopic        | 42                 | NR                   | 11 mo: 97%                  | NR                   | NR                           | NR                                   | NR                                  | NR                                  | NR | NR | NR | NR | CSS: NR |
| Stifelman et al [15]        | Open                | 11                 | NA                   | NR                           | NR                   | NR                           | NR                                   | NR                                  | NR                                  | NR | NR | NR | NR | CSS: NR |
|                             | Laparoscopic hand assisted | 17 | 0 | NR | NR | NR | NR | NR | 17 mo: 36.4% | 13 mo: 27.3% | NR | NR | NR | NR | NR |
| Müller et al [30]           | Open                | 19                 | NA                   | 67%                          | 0.53                 | 67%                          | 0.53                                 | 2 yr: 49.5%                        | 2 yr: 55.1%                       | NR | NR | NR | NR | NR |

CI = confidence interval; HR = hazard ratio; LNU = laparoscopic nephroureterectomy; HALNU = hand-assisted laparoscopic nephroureterectomy; ONU = open nephroureterectomy; BRFS = bladder recurrence-free survival; RFS = recurrence-free survival; OS = overall survival; CSS = cancer-specific survival; NR = not reported; NA = not applicable; NS = not statistically significant; RNU = radical nephroureterectomy.
3.3.7. Pure laparoscopic versus open RNU

The only RCT included in this SR was also one of the three studies comparing pure laparoscopic RNU with open RNU [9]. In this RCT, 80 patients were randomly assigned to laparoscopic RNU (n = 40) or open RNU (n = 40). CSS, BRFS, and metastasis-free survival (MFS) were found to be similar between the two groups when the entire cohort was considered (p = 0.2, p = 0.86, and p = 0.12, respectively). However, in the subgroups of pT3 UTUC and high-grade tumours, the authors reported better CSS and MFS in open, compared with laparoscopic, RNU (p = 0.04 and p = 0.004, respectively, for pT3; p = 0.01 and p = 0.01, respectively, for high-grade disease) [9]. Greco et al [36] retrospectively compared 70 laparoscopic RNU with 70 open RNU, and found similar CSS but poorer RFS in the open group (5-yr RFS: 73% vs 75%, p = 0.04). Finally, in a small retrospective series without statistical adjustment, Fang et al [47] reported no significant differences between laparoscopic and open RNU regarding oncological outcomes.

3.3.8. Unspecified/heterogeneous laparoscopic versus open RNU

Most of the 19 studies comparing unspecified/heterogeneous laparoscopic RNU with open RNU reported comparable oncological outcomes between both groups, notably two series with a relatively large sample size and statistical adjustment through multivariate analysis (HR = 0.88, p = 0.6 and HR = 1.48, p = 0.13 for RFS, respectively, in the studies of Favaretto et al [38] and Walton et al [40]). However, in a multicentre series, Fairey et al [44] found a trend towards an independent association between laparoscopic RNU and poorer RFS in univariate and multivariate analysis (HR = 1.24, p = 0.08). In the largest series published to date, Capitanio et al [34] reported better CSS and RFS in laparoscopic RNU in univariate analysis (p = 0.008 and p < 0.001, respectively), but this difference was attributed to a selection bias favouring the laparoscopic group (ie, lower tumour grades and stages in the laparoscopic group). On multivariate analysis, a tendency towards an adverse impact of laparoscopy on survival was observed (HR = 1.54 for CSS, HR = 1.44 for RFS, p = 0.10 in both cases). Finally, in a single-centre study including 108 patients in total, Kitamura et al [46] reported similar oncological outcomes between laparoscopic and open RNU, but significantly poorer BRFS in laparoscopic hand-assisted RNU than in open RNU (5-yr BRFS: 12.5% vs 71.1%, p = 0.002), which was confirmed in multivariate analysis (HR = 5.52, p = 0.001). Interestingly, endoscopic ureteral management was performed in most laparoscopic hand-assisted RNU (66.7%), while bladder cuff and distal ureter were removed through an open approach in laparoscopic RNU [46].

3.3.9. Laparoscopic RNU with endoscopic bladder cuff excision versus open RNU

None of the four studies comparing laparoscopic RNU with endoscopic bladder cuff excision to open RNU reported statistically significant differences between the two approaches in terms of CSS, OS, RFS, or BRFS [13–15,30]. However, it should be noted that all were small-sample, retrospective, single-centre series.

3.3.10. Subgroups of locally “advanced diseases”

Ten studies assessed the oncological efficacy of laparoscopic versus open NU in the subgroup of advanced diseases defined as pT3/pT4 and/or pN+ and/or high-grade tumours [9,22,34,35,38,40,41,44,49,50]. The results of these subgroup analyses are summarised in Table 3. Four studies reported significantly poorer oncological outcomes with laparoscopic RNU compared with open RNU in advanced diseases [9,41,44,50]. As mentioned above, in a prospective RCT including 80 patients, Simone et al [9] reported better OS and RFS in pT3 (p = 0.04 and p = 0.004, respectively) and high-grade tumours (p = 0.01 and p = 0.01, respectively) for open compared with laparoscopic RNU. In a single-centre retrospective series, Kim et al [50] observed poorer CSS and OS using the laparoscopic approach in pT3/pT4 UTUC in univariate (p = 0.007 and p = 0.005, respectively) and multivariate analyses (p = 0.005 and p = 0.001, respectively). Similarly, Ariane et al [41] reported significantly better CSS with the open approach for pT3/pT4 tumours (p = 0.05) and Fairey et al [44] reported better RFS for open RNU in pN+ tumours (HR = 1.3, p = 0.03). None of the 10 studies compared the local recurrence rates of open versus laparoscopic RNU in the subgroup of “high-risk” patients.

3.4. Discussion

Oncological efficacy of laparoscopy for the surgical management of urothelial carcinomas has raised concerns throughout the urological community for many years because of the expected higher risk of urine spillage [11]. While the perioperative benefits of laparoscopic RNU are supported by a large body of evidence [53], there is still controversy regarding its oncological safety. In a recent meta-analysis that assessed oncological outcomes of open versus laparoscopic RNU, published in 2012, Ni et al [10] included 21 studies and performed cumulative analyses. They found no significant differences between the two approaches in terms of OS, CSS, and RFS and concluded that laparoscopic RNU could offer comparable oncological efficacy to open RNU [10]. In the most recent meta-analysis, Zhang et al [54] found that laparoscopic NU could provide equivalent prognostic effects for UTUC, and could be associated with better extravesical RFS and CSS compared with open RNU. However, it should be emphasised that such a meta-analysis of retrospective data has inherent methodological flaws. Firstly, the authors pooled results from very heterogeneous series, analysing multiple surgical techniques (notably regarding distal ureter management) with different study designs (RCT or retrospective reports). Secondly, the selection bias favouring the laparoscopic group observed in most of the included studies [5,9,13–51] could not be statistically overcome by the meta-analytic approach. Conversely, in the present SR, given the low quality of available data in general, only a narrative analysis of included studies was performed. As opposed to the studies by Ni et al [10] and Zhang et al [54], in our SR some evidence emerged suggesting that laparoscopic RNU may not be as safe as open RNU, notably when the bladder cuff is
Table 3 - Subgroup analysis in “advanced diseases” (pT3/pT4 and/or high-grade and/or pN+).

| Study          | Surgical approaches | Number of patients | Subgroup | 5-yr cancer-specific survival | p value | 5-yr overall survival | p value | 5-yr recurrence-free survival | p value | 5-yr bladder recurrence-free survival | p value | Multivariable Cox regression analysis |
|----------------|---------------------|--------------------|----------|-------------------------------|---------|-----------------------|---------|-------------------------------|---------|-------------------------------|---------|-------------------------------------|
|                |                     |                    |          |                               |         |                       |         |                               |         |                               |         | HR (LNU vs ONU) 95% CI p value |
| Hsueh et al [22] | Open Laparoscopic hand assisted | 11 13              | pT3     | NR                            | 0.48    | NR                    | 0.12    | NR                            | NR      | NR                            | NR      | NR                                |
|                |                     |                    | G3       | NR                            | 0.88    | NR                    | 0.88    | NR                            | NR      | NR                            | NR      | NR                                |
| Capitanio et al [34] | Open Laparoscopic | 34 38              | NA       | NR                            | 0.88    | NR                    | 0.88    | NR                            | NR      | NR                            | NR      | NR                                |
| Simone et al [9] | Open Laparoscopic | 40 40              | High grade | NR                            | 0.88    | NR                    | 0.88    | NR                            | NR      | NR                            | NR      | NR                                |
| Simone et al [9] | Open Laparoscopic | 40 40              | pT3     | NR                            | 0.88    | NR                    | 0.88    | NR                            | NR      | NR                            | NR      | NR                                |
| Chung et al [35] | Open Laparoscopic hand assisted | 31 21              | pT3N0   | 82.6% 94.7%                   | 0.17    | 67.7% 79.6%           | 0.57    | NR                            | 0.19    | 115 mo: 32.3% 72 mo: 19%         | NR      | NR                                |
| Favaretto et al [38] | Open Laparoscopic | 35 17              | pT3/pT4 | NR                            | 0.88    | NR                    | 0.88    | NR                            | NR      | NR                            | NR      | NR                                |
| Walton et al [40] | Open Laparoscopic | 48 2               | pN+     | NR                            | 0.88    | NR                    | 0.88    | NR                            | NR      | NR                            | NR      | NR                                |
| Walton et al [40] | Open Laparoscopic | 236 23             | pT3/pT4 | HR: 0.77 95% CI: 0.32–1.83    | 0.88    | HR: 0.91 95% CI: 0.32–1.83 | 0.88    | HR: 0.91 95% CI: 0.32–1.83 | 0.88    | HR: 0.91 95% CI: 0.32–1.83 | 0.88    | HR: 0.91 95% CI: 0.32–1.83 | 0.88    | HR: 0.91 95% CI: 0.32–1.83 |
| Ariane et al [41] | Open Laparoscopic | 237 55             | pT3/pT4 | NR                            | 0.88    | NR                    | 0.88    | NR                            | NR      | NR                            | NR      | NR                                |
| Fairey et al [44] | Open Laparoscopic | 42 18              | pT and pN+ | NR                            | 0.88    | NR                    | 0.88    | NR                            | NR      | NR                            | NR      | NR                                |
| Fairey et al [44] | Open Laparoscopic | 111 120            | PT3/pT4 pN0 | NR            | 0.88    | NR                    | 0.88    | NR                            | NR      | NR                            | NR      | NR                                |
| Miyazaki et al [49] | Open Laparoscopic | 379 167           | pT3/pT4 and/or pN+ | NR            | 0.88    | NR                    | 0.88    | NR                            | NR      | NR                            | NR      | NR                                |
| Kim et al [50] | Open Laparoscopic | 112 34             | pT3/pT4 | NR                            | 0.88    | NR                    | 0.88    | NR                            | NR      | NR                            | NR      | NR                                |

BRFS = bladder recurrence-free survival; CI = confidence interval; HR = hazard ratio; RFS = recurrence-free survival; OS = overall survival; CSS = cancer-specific survival; LNU = laparoscopic nephroureterectomy; NR = not reported; NA = not applicable; ONU = open nephroureterectomy.
excised laparoscopically [9,46] and in patients with advanced (pT3/pT4) or high-grade disease [9,50].

In recent years, several studies have suggested a critical role for distal ureter management during RNU from an oncological standpoint [55,56]. Most studies included in the present SR reported a combined technique of laparoscopic RNU (i.e., laparoscopic nephrectomy with open excision of the bladder cuff and distal ureter). Given that one out of three studies assessing pure laparoscopic (i.e., with laparoscopic excision of the bladder cuff and distal ureter) versus open RNU—which was also the only randomised trial included in this review—reported poorer oncological outcomes in subgroups of patients treated with laparoscopic RNU [9], one could assume that laparoscopic bladder cuff removal may negatively impact the oncological outcomes of laparoscopic RNU. Two suppositions could be made to explain this finding. Firstly, as the laparoscopic dissection of the lower ureter may be technically challenging, the distal ureter could be incompletely excised with part of the intramural ureter and the ureteral orifice left behind, thus increasing the risk of local recurrence [57]. Although several studies have suggested the opposite [57], this risk of incomplete resection mainly concerns the laparoscopic extravesical technique [57], which was the technique used in the three series included in this review [9,36,47]. Another explanation for the presumed adverse impact of laparoscopic bladder cuff removal could be the increased risk of entering the collecting system due to the technical difficulty of such dissection, or to an opening in the bladder because of inadequate closure. As a result, laparoscopic bladder cuff removal could favour tumour spillage and tumour cell implantation [57].

Robotic RNU has spread significantly over the past few years and accounts for about a third of all RNU performed in the USA, according to recent data [58]. Given the ease of accessing the retrotrigonal region and the additional degrees of articulation afforded by EndoWrist instruments for closing the cystotomy [7], the potential benefit of the robotic approach over the laparoscopic approach for RNU would be to facilitate the laparoscopic excision of the distal ureter and bladder cuff. A key finding of the present SR is that, despite the recent surge in robotic RNU, no data were identified comparing the oncological outcomes of robotic RNU with those of open or laparoscopic RNU. Data comparing the oncological efficacy of robotic and open RNU are, therefore, urgently needed in order to address the concerns raised by the present report regarding the oncological safety of laparoscopic bladder cuff removal.

An important finding of the present SR is that in locally advanced high-risk UTUC (pT3/pT4 and/or high grade), laparoscopic RNU may result in inferior oncological outcomes compared with open RNU. Tumour biology and immunosuppression status have been shown to be the main risk factors of local recurrence [59]. Our results suggest that the potential for seeding may also be directly related to tumour aggressiveness. Another possible assumption to explain this finding is that quality of lymph node dissection may be better when performing open versus laparoscopic RNU and that this difference might, at least partly, explain the poorer oncological outcomes with laparoscopic RNU in locally advanced disease [60]. Consequently, careful patient selection based on tumour stage and grade might be paramount to ensure satisfactory oncological outcomes of laparoscopic RNU. Nonetheless, such selection could be challenging, as most of the subgroup analyses performed in the included studies were based on tumour grade and stage from the definitive pathological specimen [9,50], and it is well established that there is a poor correlation between clinical and pathological stage [61,62] even though the correlation might be better for tumour grade [63]. Another issue related to this finding is that the above-mentioned criteria that were used to define subgroups do not use the definition of risk groups according to current EAU guidelines [2], which makes it difficult to transpose these results to daily practice.

Several shortcomings of the present work should be emphasised. Firstly, very few retrospective series (nine out of 41) performed statistical adjustment for confounders, which made their findings difficult to interpret given the selection bias favouring the laparoscopic group in most of these series. Moreover, as highlighted by their large CIs and small sample size, most studies were underpowered to detect a difference in oncological efficacy between the two approaches. Another important shortcoming of this SR is that no series comparing oncological outcomes of open and robotic RNU were found, even though the latter approach, whose main theoretical advantage is the laparoscopic removal of the bladder cuff, has become increasingly popular during the past few years [58]. Furthermore, in none of the large multicentre studies, was a description of the approach used for bladder cuff removal provided. This negatively impacted our analysis as distal ureter management appeared to be a key factor of laparoscopic RNU oncological outcomes. This also prevented an assessment of the impact of bladder cuff management on oncological outcomes in each subgroup. None of the included series accounted for surgeon and hospital volume, which may be regarded as a shortcoming, as these two parameters have been shown to impact oncological outcomes of numerous surgical procedures [64]. Finally, the planned meta-analysis was not possible because of the heterogeneity of available data.

4. Conclusions

All but one of the included studies were retrospective series, and most reported similar oncological outcomes between laparoscopic and open RNU. In view of the current evidence base, and notably the only randomised trial available, the oncological equivalence of laparoscopic and open RNU is likely in most cases, but cannot be established when the bladder cuff is excised laparoscopically as well as in patients with locally advanced high-risk UTUC (pT3/pT4 and/or high grade). Distal ureter management (open vs laparoscopic) and patient selection based on tumour stage and grade could be the key points to ensure oncological efficacy of laparoscopic RNU, but these assumptions rely mostly on poor-quality data. Data comparing the oncological efficacy
of robotic and open RNU are urgently needed, as there is a recent surge in robotic RNU, the main advantage in which lies in facilitating the laparoscopic excision of the distal ureter and bladder cuff.

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Appendix A. Supplementary data

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