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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 nonrandomised 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 in oncological outcomes was

reported in most series. However, three studies, including the only RCT, reported significantly poorer oncological outcomes in patients who underwent laparoscopic RNU, especially in the subgroups of patients with locally advanced (pT3/pT4) or high-grade upper tract urothelial carcinoma (UTUC), as well as in instances when the bladder cuff was excised laparoscopically.

Conclusions: The current available evidence suggests that the oncological outcomes of laparoscopic RNU may be poorer than those of open RNU when bladder cuff is excised laparoscopically and in patients with locally advanced high-risk (pT3/pT4 and/or high-grade) UTUC.

Patient summary: We reviewed the literature comparing the outcomes of two different surgical procedures for the treatment of upper tract urothelial carcinoma. Open radical nephroureterectomy is a surgical procedure in which the kidney is removed through a large incision in the abdomen, while in laparoscopic radical nephroureterectomy, the kidney is removed through a number of small incisions. Our findings suggest that the outcomes of laparoscopic radical nephroureterectomy may be poorer than those of open radical nephroureterectomy, particularly when the bladder cuff is also required to be removed. Laparoscopic radical nephroureterectomy may also be less effective in patients with locally advanced (pT3/pT4) or high-grade upper tract urothelial carcinomas.

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 Figure 1.

2.5. 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.), who subsequently cross checked 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 stripping, 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 provided by the authors, as well as their corresponding unadjusted and adjusted hazard ratios (HRs) with 95% confidence intervals (CIs).

2.6. 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, 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 v.5.3 (Informatics and Knowledge Management Department, Cochrane, London, UK).

2.7. 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).

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 Figure 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 extravesical 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 pelvis 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, $p = 0.06$).

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 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 (ie, laparoscopic nephrectomy with open excision of the bladder cuff and distal ureter). Given that one out of three studies assessing pure laparoscopic (ie, 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 RNUs 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, a description of the approach used for bladder cuff removal was 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 was 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.

Author contributions: Benoit Peyronnet had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Peyronnet, Roupret, Seisen, Bruins, Dominguez-Escrig, Babjuk.

Acquisition of data: Peyronnet, Seisen, Bruins, Dominguez-Escrig, Yuan.

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Critical revision of the manuscript for important intellectual content: Babjuk, Comperat, Zigeuner, Sylvester, Burger, Mostafid, van Rhijn, Gontero, Palou, Shariat.

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

Fig. 2 – The RoB and confounding assessment for all included studies. CIS = carcinoma in situ; RoB = risk of bias.

		Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias	confounder pathological stage	confounder pathological grade	confounder adjuvant chemotherapy	confounder tumour location	confounder lymph node status	confounder concomitant CIS	confounder lymphovascular invasion
Aguilera et al, 2009		-	-	-	-	-	-	-	-	-	-	-	-	-	-
Ariane et al, 2012		-	-	-	-	-	-	-	+	+	-	+	+	-	+
Capitanio et al, 2009		-	-	-	-	-	-	-	+	+	-	+	+	+	+
Chung et al, 2007		-	-	-	-	-	-	-	-	-	-	-	-	-	-
Chung et al, 2009		-	-	-	-	-	-	-	+	-	-	-	-	-	-
Chung et al, J endourol 2007		-	-	-	-	-	-	-	-	-	-	-	-	-	-
Fairey et al, 2013		-	-	-	-	-	-	-	+	+	+	-	+	+	-
Fang et al, 2014		-	-	-	-	-	-	-	-	-	-	-	-	-	-
Favaretto et al, Eur Urol 2010		-	-	-	-	-	-	-	-	-	-	-	-	-	-
Gill et al, 2000		-	-	-	-	-	-	-	-	-	-	-	-	-	-
Greco et al, 2009		-	-	-	-	-	-	-	-	-	-	-	-	-	-
Hamada et al, 2013		-	-	-	-	-	-	-	-	-	-	-	-	-	-
Hattori et al, 2006		-	-	-	-	-	-	-	-	-	-	-	-	-	-
Hemal et al, 2008		-	-	-	-	-	-	-	-	-	-	-	-	-	-
Hsueh et al, 2007		-	-	-	-	-	-	-	+	+	-	-	-	-	-
Izumi et al, 2013		-	-	-	-	-	-	-	-	-	-	-	-	-	-
Kawauchi et al, 2002		-	-	-	-	-	-	-	-	-	-	-	-	-	-
Kim et al, 2005		-	-	-	-	-	-	-	-	-	-	-	-	-	-
Kim et al, 2015		-	-	-	-	-	-	-	+	+	-	+	+	+	+
Kitamura et al, 2014		-	-	-	-	-	-	-	-	-	-	-	-	-	-
Koda et al, 2007		-	-	-	-	-	-	-	-	-	-	-	-	-	-
Kong et al, 2007		-	-	-	-	-	-	-	-	-	-	-	-	-	-
Lee et al, 2007		-	-	-	-	-	-	-	-	-	-	-	-	-	-
Lotrecchiano et al, 2012		-	-	-	-	-	-	-	-	-	-	-	-	-	-
Manabe et al, 2007		-	-	-	-	-	-	-	-	-	-	-	-	-	-
Miyazaki et al, 2015		-	-	-	-	-	-	-	+	-	-	-	-	-	-
Muller et al, 2007		-	-	-	-	-	-	-	-	-	-	-	-	-	-
Nakashima et al, 2007		-	-	-	-	-	-	-	-	-	-	-	-	-	-
Okegawa et al, 2006		-	-	-	-	-	-	-	-	-	-	-	-	-	-
Raman et al, 2006		-	-	-	-	-	-	-	-	-	-	-	-	-	-
Roupřet et al, 2007		-	-	-	-	-	-	-	-	-	-	-	-	-	-
Satto et al, 2006		-	-	-	-	-	-	-	-	-	-	-	-	-	-
Shalav et al, 2000		-	-	-	-	-	-	-	-	-	-	-	-	-	-
Shan et al, 2015		-	-	-	-	-	-	-	-	-	-	-	-	-	-
Simone et al, 2009		+	+	-	+	+	+	+	+	+	-	+	+	+	+
Stewart et al, 2011		-	-	-	-	-	-	-	-	-	-	-	-	-	-
Stifelman et al, 2001		-	-	-	-	-	-	-	-	-	-	-	-	-	-
Taweemonkongsap et al, 2008		-	-	-	-	-	-	-	+	+	-	-	-	-	-
Tsujiyata et al, 2006		-	-	-	-	-	-	-	-	-	-	-	-	-	-
Waldert et al, 2008		-	-	-	-	-	-	-	+	+	-	-	+	-	-
Walton et al, 2011		-	-	-	-	-	-	-	+	+	-	+	+	+	+
Zou et al, 2014		-	-	-	-	-	-	-	+	+	-	+	+	+	+

Table 1 – Characteristics of included studies

Study	Year	Study design	LE	Surgical approaches	Number of patients	Surgical route	Bladder cuff excision	Median follow-up (mo)	Pathological grade	≥pT3 stage (%)	No lymph node dissection (%)	pN+ stage (%)	Positive surgical margins (%)
<i>Combined laparoscopic RNU vs open RNU</i>													
Kawauchi et al [16]	2002	Single-centre retrospective	3	Open	34	Transperitoneal: 18% Retroperitoneal: 82%	Stripping: 21% NR: 79%	Mean: 48.8	G1: 11.8% G2: 50% G3: 38.2%	38.2	NR	NR	NR
				Laparoscopic hand assisted	34	Retroperitoneal	Open extravesical: 92% Endoscopic: 8%	Mean: 48.8	G1: 14.7% G2: 58.8% G3: 26.5%	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%	21.7	NR	NR	NR
				Laparoscopic	25	Retroperitoneal	Open extravesical	Mean: 24.3	G1: 8% G2: 68% G3: 24%	16	NR	NR	NR
Sato et al [21]	2006	Single-centre retrospective	3	Open	23	NR	Open extravesical	60	G1: 21.7% G2: 60.9% G3: 17.4%	30.4	NR	4.3	NR
				Laparoscopic hand assisted	36	NR	Open extravesical	25	G1: 16.7% G2: 66.6% G3: 16.7%	33.4	NR	2.8	NR
Rouprêt et al [24]	2007	Single-centre retrospective	3	Open	26	NR	NR	Mean: 78	Low grade: 26.9% High grade:	38.4	NR	19.2	0

				Laparoscopic	20	Transperitoneal	Open extravesical	Mean: 69	73.1% Low grade: 60% High grade: 40%	35.9	NR	5	0
Lee et al [25]	2007	Single-centre retrospective	3	Open	29	NR	NR	Mean: 30	G1: 34.6% G2: 50% G3: 15.4%	39.3	0	0	NR
				Laparoscopic	22	Transperitoneal	Open extravesical	Mean: 13.7	G1: 0% G2: 54.5% G3: 45.5%	54.5	0	0	NR
Chung et al [26]	2007	Single-centre retrospective	3	Open	41	NR	Open extravesical	62	G1: 2.4% G2: 56.1% G3: 41.5%	22	100	NR	NR
				Laparoscopic	25	Retroperitoneal	Open extravesical	32	G1: 4% G2: 52% G3: 44%	28	100	NR	NR
Kong et al [27]	2007	Single-centre retrospective	3	Open	22	NR	NR	29	NR	21.7	NR	NR	9
				Laparoscopic	23	NR	Open extravesical	14	NR	0	NR	NR	17.4
Koda et al [28]	2007	Single-centre retrospective	3	Open	27	Retroperitoneal	Open extravesical	Mean: 46.2	G1: 11.1% G2: 59.3% G3: 29.6%	25.9	100	0	NR
				Laparoscopic	79	Retroperitoneal	Open extravesical	Mean: 16.4	G1: 12.7% G2: 41.8% G3: 45.6%	39.3	100	0	NR
Nakashima et al [29]	2007	Single-centre retrospective	3	Open	37	Retroperitoneal	Open extravesical	56	G3: 35.1%	29.7	NR	NR	0
				Laparoscopic hand assisted	35	Retroperitoneal	Open extravesical	23	G3: 41.5%	37.1	NR	NR	0
Chung et al. [26]	2007	Single-centre retrospective	3	Open	36	NR	NR	59.5	G1: 2.8% G2: 55.6% G3:	16.7	0	5.3	NR

				Laparoscopic	39	Transperitoneal	Open extravesical	48	41.7% G1: 2.6% G2: 56.4% G3: 41%	30.8	0	10.5	NR
Taweemon kongsap et al [31]	2008	Single-centre retrospective	3	Open	29	Retroperitoneal	Open extravesical	Mean: 26.4	Low grade: 34.5% High grade: 65.5%	13.8	70	10.3	NR
				Laparoscopic	31	Retroperitoneal	Open extravesical	Mean: 27.9	Low grade: 58.1% High grade: 41.9%	16.1	35.5	3.2	NR
Waldert et al [33]	2008	Single-centre retrospective	3	Open	59	Retroperitoneal	Open intravesical	Mean: 41	G1: 6.8% G2: 52.5% G3: 40.7%	33.9	20.3	10.2	0
				Laparoscopic	43	NR	Open intravesical	Mean: 41	G1: 13.9% G2: 44.2% G3: 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% G2: 32.2% G3 : 45.2%	100	0	0	NR
				Laparoscopic hand assisted	21	Transperitoneal	Open extravesical	72	G1: 0% G2: 42.9% G3: 57.1%	100	0	0	NR
Ariane et al [41]	2011	Multicentre retrospective	3	Open	459	NR	Open extravesical: 96% Stripping: 4%	27	G1: 8.5% G2: 36.2% G3: 55.3%	39.6	52.5	10.2	NR
				Laparoscopic	150	Transperitoneal	Open extravesical: 95% Stripping: 5%	NR	G1: 7.3% G2: 27.3% G3: 65.3%	36.6	70	4.7	NR

Lotrecchiano et al [42]	2012	Single-centre retrospective	3	Open	32	NR	NR	Mean: 42	Low grade: 40.6% High grade: 59.4%	21.9	62.5	6.2	NR
				Laparoscopic	36	Transperitoneal: 69% Retroperitoneal: 31%	Open extravesical	Mean: 23	Low grade: 69.4% High grade: 30.6%	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% High grade: 64.9%	41.3	79	3.7	4.1
				Laparoscopic	100	Transperitoneal	Open extravesical	38.8	Low grade: 30% High grade: 70%	34	87	0	3
Pure laparoscopic RNU vs open RNU													
Simone et al [9]	2009	Randomised controlled trial	1	Open	40	Retroperitoneal	Open extravesical	44	Low grade: 37.5% High grade: 62.5%	32.5	100	0	NR
				Laparoscopic	40	Transperitoneal	Laparoscopic extravesical	60	Low grade: 42.5% High grade: 57.5%	30	100	0	NR
Greco et al [36]	2009	Single-centre retrospective	3	Open	70	Retroperitoneal	Open extravesical	60	G1: 24.3% G2: 64.3% G3: 11.4%	1.4	NR	NR	0
				Laparoscopic	70	Transperitoneal	Laparoscopic extravesical	60	G1: 21.5% G2:	4.2	NR	NR	1.4

Fang et al [47]	2014	Single-centre retrospective	3	Open	36	NR	NR	Mean: 30.8	67.1% G3: 11.4%	NR	NR	NR	NR
				Laparoscopic	29	Retroperitoneal	Laparoscopic extravesical	Mean: 22.4	NR				
Unspecified/heterogeneous laparoscopic vs open RNU													
Kim et al [17]	2005	Single-centre retrospective	3	Open	17	NR	NR	Mean: 25.6	NR	NR	NR	NR	NR
				Laparoscopic	10	NR	NR	Mean: 19	G1: 10% G2: 60% G3: 30%				
Tsujiyata et al [18]	2006	Single-centre retrospective	3	Open	24	NR	NR	22.1	G1: 4.2% G2: 45.8% G3: 50%	16.7	0	0	NR
				Laparoscopic	25	Retroperitoneal	NR	22.4	G1: 20% G2: 60% G3: 20%				
Hattori et al [19]	2006	Single-centre retrospective	3	Open	60	NR	NR	35	G1: 10% G2: 51.7% G3: 38.3%	38.3	NR	12	NR
				Laparoscopic	89	Retroperitoneal	Open extravesical: 40% Laparoscopic extravesical: 60%	31	G1: 15.7% G2: 53.5% G3: 34.8%				
Raman et al [5]	2006	Single-centre retrospective	3	Open	38	Retroperitoneal	Open extravesical: 61% Open intravesical: 39%	17 Mean: 51	Low grade: 63.5% High grade: 36.5%	NR	NR	NR	NR
				Laparoscopic hand assisted	52	Transperitoneal	Open extravesical: 58% Open intravesical: 21% Endoscopic: 21%	Mean : 31.7	Low grade: 60.5% High grade: 39.5%				
Hsueh et al [22]	2007	Multicentre retrospective	3	Open	77	NR	NR	Mean: 53.6	G1: 3.9% G2: 50.6%	22.1	NR	NR	NR

				Laparoscopic hand assisted	66	NR	NR	Mean: 37.6	G3: 45.5% G1: 1.5% G2: 39.4%	24.2	NR	NR	NR
Manabe et al [23]	2007	Multicentre retrospective	3	Open	166	NR	NR	Mean: 28	G3: 59.1% G1: 9% G2: 52.4%	48.2	NR	NR	NR
				Laparoscopic	58	Retroperitoneal	NR	Mean: 13.6	G3: 38.6% G1: 6.9% G2: 53.4%	41.4	NR	NR	NR
Hemal et al [32]	2008	Single-centre retrospective	3	Open	27	Retroperitoneal	Open extravesical	57	G3: 39.7% G1: 29.6% G2: 48.1%	11.1	29.6	7.4	0
				Laparoscopic	21	Retroperitoneal	Open extravesical: 57% Laparoscopic extravesical: 33% Endoscopic: 10%	53	G3: 22.2% G1: 28.6% G2: 52.4%	9.5	28.6	4.8	0
Capitanio et al [34]	2009	Multicentre retrospective	3	Open	979	NR	Open extra- or intravesical: 41% No bladder cuff: 59%	63	G3: 19% Low grade: 40.3% High grade: 59.7%	35.2	57.6	7.2	NR
				Laparoscopic	270	NR	Open or laparoscopic extravesical: 29% Endoscopic: 21% No bladder cuff: 50%	25.9	Low grade: 38.1% High grade: 61.9%	23.4	75.6	2.2	NR
Aguilera et al [37]	2009	Single-centre retrospective	3	Open	31	Transperitoneal: 43% Retroperitoneal: 57%	Open extravesical: 43% Retroperitoneal: 57%	52.7	G1: 5.7% G2: 44.3% G3: 50%	24.2	57	5.9	NR
				Laparoscopic	21	Transperitoneal	Open extravesical: 56% Endoscopic: 44%	24	G1: 12% G2: 56% G3: 32%	20	88	0	NR
Favaretto et al [38]	2010	Single-centre retrospective	3	Open	109	Retroperitoneal	Open extravesical	23	Low grade:	32	19	16	NR

				Laparoscopic	53	Transperitoneal: 66% Retroperitoneal: 34%	Open extravesical: 75% Laparoscopic extravesical: 21% Endoscopic: 4%	17	12% High grade: 86% Low grade: 9% High grade: 87%	32	30	13	NR
Stewart et al [39]	2011	Single-centre retrospective	3	Open	39	Transperitoneal	NR	177	G1: 10.2% G2: 51.2% G3: 38.5%	23.1	NR	NR	NR
				Laparoscopic	23	Transperitoneal	NR	146	G1: 13% G2: 30.4% G3: 56.5%	13	NR	NR	NR
Walton et al [40]	2011	Multicentre retrospective	3	Open	703	NR	Endoscopic: 13% NR: 87%	36	G1: 12.4% G2: 31.2% G3: 56.3%	33.6	77	6.8	NR
				Laparoscopic	70	NR	NR	17	G1: 15.7% G2: 7.1% G3: 77.1%	32.8	70%	2.9%	NR
Hamada et al [43]	2013	Single-centre retrospective	3	Open	50	Transperitoneal: 32% Retroperitoneal: 68%	NR	NR	G1: 4% G2: 34% G3: 62%	41.2	NR	6	NR
				Laparoscopic	55	NR	NR	NR	G1: 2% G2: 32% G3: 66%	46	NR	0	NR
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%	31	68	10	11

				Laparoscopic	446	NR	Open extravesical: 34% Open intravesical: 46% Endoscopic: 19% NR: 1%		Low grade: 36% High grade: 64%	31	77	4	10
Izumi et al [45]	2013	Single-centre retrospective	3	Open	19	NR	NR	NR	G1: 5.3% G2: 78.9% G3: 15.8%	36.7	42.1	15.8	NR
				Laparoscopic	46	NR	NR	NR	G1: 6.5% G2: 63% G3: 30.5%	40	82.6	4.4	NR
Kitamura et al [46]	2014	Single-centre retrospective	3	Open	34	NR	No bladder cuff: 3% NR: 97%	60	G1: 3% G2: 41% G3: 56%	47	NR	NR	NR
				Laparoscopic: 88% Laparoscopic hand assisted: 12%	74	NR	No bladder cuff: 1% Endoscopic: 11% NR: 88%		G1: 3% G2: 50% G3: 47.3%	43.2	NR	NR	NR
Zou et al [48]	2014	Single-centre retrospective	3	Open	101	Transperitoneal	NR	53	Low grade: 53.6% High grade: 46.5%	22.8	NR	NR	2
				Laparoscopic	21	Transperitoneal	NR		Low grade: 57.1% High grade: 42.9%	14.3	NR	NR	4.8
Miyazaki et al [49]	2016	Multicentre retrospective	3	Open	527	Transperitoneal: 19.8% Extraperitoneal: 80.2%	NR	39	NR	70.8	63.6	11.4	NR
				Laparoscopic	222	Transperitoneal: 14% Extraperitoneal: 86%	NR		NR	73.9	67.3	6.8	NR
Shan et al [51]	2015	Single-centre retrospective	3	Open	118	NR	Open extravesical	43.2	G1: 40.7% G2: 49.2% G3:	NR	7.6	4.2	NR

			Laparoscopic	100	Retroperitoneal	Open extravesical: 67.3% Endoscopic: 32.7%			10.1% G1: 36.4% G2: 50.9% G3: 12.7%	NR	10.9	2.7	NR
<i>Laparoscopic RNU with endoscopic bladder cuff excision vs open RNU</i>													
Shalhav et al [13]	2000	Single-centre retrospective	3	Open	17	NR	NR	Mean: 43	G1: 29% G2: 47% G3: 24%	NR	NR	NR	NR
				Laparoscopic	25	Transperitoneal	Endoscopic: 96% Stripping: 4%	Mean: 24	G1: 48% G2: 24% G3: 28%	NR	NR	NR	NR
Gill et al [14]	2000	Single-centre retrospective	3	Open	35	NR	NR	Mean: 34.4	G1: 17% G2: 29% G3: 46% Unknown : 8%	23	NR	3	15
				Laparoscopic	42	Retroperitoneal	Endoscopic	Mean: 11.1	G1: 21% G2: 24% G3: 55%	22	NR	5	7
Stifelman et al [15]	2001	Single-centre retrospective	3	Open	11	Retroperitoneal	NR	Mean: 17	Low grade: 9% High grade: 91%	NR	NR	NR	9
				Laparoscopic hand assisted	11	Transperitoneal	Endoscopic	Mean: 13	Low grade: 18% High grade: 82%	NR	NR	NR	0
Müller et al [30]	2007	Single-centre retrospective	3	Open	19	Transperitoneal: 16% Retroperitoneal: 84%	Open extravesical: 74% Endoscopic: 26%	Mean: 24	Low grade: 26.3% High grade: 52.6%	0	0	5.3	NR
				Laparoscopic	19	Transperitoneal: 10% Retroperitoneal: 90%	Open extravesical: 37% Endoscopic: 53% Laparoscopic extravesical: 10%	Mean: 17	Low grade: 47.4% High grade: 42.1%	0	0	10.5	NR

LE = level of evidence; NA = Not applicable; NR = not reported; RNU = radical nephroureterectomy.

Table 2 – Oncological outcomes

Study	Surgical approaches	Number of patients	Port-site metastasis	5-yr cancer-specific survival	<i>p</i> value	5-yr overall survival	<i>p</i> value	5-yr recurrence-free survival	<i>p</i> value	5-yr bladder recurrence-free survival	<i>p</i> value	Multivariable Cox regression analysis		
												HR (LNU vs ONU)	95% CI	<i>p</i> value
<i>Combined laparoscopic RNU vs open RNU</i>														
Kawauchi et al [16]	Open	34	NA	NR		NR		NR		49 mo: 38.2%				
	Laparoscopic hand assisted	34	0	NR	NR	NR	NR	NR	NR	49 mo: 8.8%	NR	NR	NR	NR
Okegawa et al [20]	Open	24	NA	NR	0.86	NR	NR	NR	0.76	29 mo: 17%	NS	NR	NR	NR
	Laparoscopic	25	0	NR		NR		NR		24 mo: 20%				
Sato et al [21]	Open	23	NA	2 yr: 91%	0.83		NR	NR	NR	NR	0.67	NR	NR	NR
	Laparoscopic hand assisted	36	0	2 yr: 94%		NR		NR		NR				
Rouprêt et al [24]	Open	26	NA	61.5%	0.31	19.2%	1	51.2%	0.59	78 mo: 15.4%	NS	NR	NR	NR
	Laparoscopic	20	NR	90%		5%		71.6%		69 mo: 10%				
Lee et al [25]	Open	29	NA	NR	NR	30 mo: 82.7%	NR	NR	NR	30 mo: 17.2%	NR	NR	NR	NR
	Laparoscopic	22	NR	NR		14 mo: 90.9%		NR		14 mo: 4.5%				
Chung et al [26]	Open	41	NA	86.1%	0.71	72.2%	0.51	NR	0.57	NR	0.33	NR	NR	NR
	Laparoscopic hand assisted	25	NR	89.7%		82.1%		NR		NR				
Kong et al [27]	Open	22	NA	1 yr: 100%	NR	1 yr: 100%	NR	NR	NR	31 mo: 13.6%	NR	NR	NR	NR
	Laparoscopic	23	NR	1 yr: 100%		1 yr: 100%		NR		17 mo: 13%				
Koda et al [28]	Open	27	NA	NR	NR	NR	NR	NR	NR	2 yr: 60%	0.51	NR	NR	NR
	Laparoscopic	79	NR	NR		NR		NR		2 yr: 55%				
Nakashima et al [29]	Open	37	NA	2 yr: 91.4%	NS		NR	NR	NR	2 yr: 51.3%	NS	NR	NR	NR
	Laparoscopic hand assisted	35	NR	2 yr: 89.3%		NR		NR		2 yr: 51.8%				
Chung et al. [26]	Open	36	NA	86.1%	0.71	72.2%	0.51	NR	0.57	NR	0.33	NR	NR	NR
	Laparoscopic hand assisted	39	NR	89.7%		82.1%		NR		NR				
Taweemonkongsap et al [31]	Open	29	NA	2 yr: 92.5%	0.82	83.3%	0.86	NR	0.27	26 mo: 45%	0.28	RFS: 1.5	RFS: 0.67–3.35	RFS: 0.32
	Laparoscopic	31	0	2 yr: 86.3%		86.3%		NR		28 mo: 29%				
Waldert et al [33]	Open	59	NA	80%	0.62	NR	NR	76%	0.82	41 mo:	NR	NR	NR	NR

Chung et al [35]	Laparoscopic	43	0	85%		NR		79%		27.1% 41 mo: 25.6% 115 mo: 32.3% 72 mo: 19%				
	Open	31	NA	82.6%		67.7%		NR						
Ariane et al [41]	Laparoscopic	21	0	94.7%	0.17	79.6%	0.57	NR	0.19					
	hand assisted Open	459	NA	78%		NR		50.7%		NR				
	Laparoscopic	150	3 (2%)	90.7%	0.06 (for pT3/pT4: 0.05)	NR	NR	52.2%	0.7 (for pT3/4: 0.9)	NR	NR	CSS: 0.51 RFS: 1.27	CSS: 0.25– 1.01 RFS: 0.88– 1.83	CSS: 0.06 RFS: 0.18
	Open	32	NA	NR	NR	NR	NR	NR	NR	NR	NR		NR	NR
Lotrecchiano et al [42]	Laparoscopic	36	1 (2.8%)	NR		NR		NR		NR	NR		NR	NR
Kim et al [50]	Open	271	NA	80.2%		75.2%		NR		3 yr: 59.9%				
	Laparoscopic	100	NR	66.1%	0.03*	59.1%	0.01*	NR	NR	3 yr: 61.7%	0.27	CSS: 2.08 OS: 2.21	CSS: 1.23– 3.52 OS: 1.38– 3.53	CSS: 0.006* OS: 0.001*
<i>Pure laparoscopic RNU vs open RNU</i>														
Simone et al [9]	Open	40	NA	89.9%		NR		77.4%	0.12 (for pT3: 0.004*; for HG: 0.01*)	NR				
	Laparoscopic	40	1 (2.5%)	79.8%	0.2 (for pT3: 0.04*; for HG: 0.01*)	NR	NR	72.5%		NR	0.86	NR	NR	NR
Greco et al [36]	Open	70	NA	NR	NR	NR	NR	73%	0.04*	NR	NR	NR	NR	NR
Fang et al [47]	Laparoscopic	70	0	NR		NR		75%		NR				
	Open	36	NA	NR		NR		31 mo: 58.3% 22 mo: 62.1%		NR	NR	NR	NR	NR
	Laparoscopic	29	NR	NR	NR	NR	NR			NR	NR	NR	NR	NR
<i>Unspecified/heterogeneous laparoscopic vs open RNU</i>														
Kim et al [17]	Open	17	NA	NR	NR	NR	NR	NR	NR	26 mo: 11.8% 19 mo: 20% 22 mo: 33.3% 22 mo: 28%	NR	NR	NR	NR
Tsujihata et al [18]	Laparoscopic	10	NR	NR		NR		NR						
	Open	24	NA	NR	NR	NR	NR	NR	0.82		NR	NR	NR	NR
Hattori et al [19]	Laparoscopic	25	NR	NR		NR		NR						
	Open	60	NA	78%	0.89	NR	NR	71%	0.91	56%	0.38	NR	NR	NR
Raman et al [5]	Laparoscopic	89	0	81%		NR		71%		51%				
	Open	38	NA	NR	NR	NR	NR	NR	NR	51 mo:	NR	NR	NR	NR

Hsueh et al [22]	Laparoscopic hand assisted	52	0	NR		NR		NR		34.6%				
	Open	77	NA	NR		NR		2 yr: 73%		32 mo: 28.9%				
Manabe et al [23]	Laparoscopic hand assisted	66	NR	NR	0.98	NR	0.74	2 yr: 77%	0.95	54 mo: 24.7%	NR	NR	NR	NR
	Open	166	NA	2 yr: 87%		2 yr: 83.6%		NR		38 mo: 20%				
Hemal et al [32]	Laparoscopic	58	1 (1.7%)	2 yr: 85.2%	0.89	2 yr: 83.7%	0.53	NR	NR	14 mo: 32.8%	0.48	NR	NR	NR
	Open	27	NA	92.6%		85.2%		88.8%		57 mo: 11.1%				
Capitanio et al [34]	Laparoscopic	21	0	95.2%	1	85.7%	1	90.5%	1	54 mo: 9.5%	1	NR	NR	NR
	Open	979	NA	73.1%		NR		76.2%		NR				
	Laparoscopic	270	NR	85.8%	0.008*	NR	NR	86.8%	<0.001*	NR	NR	CSS: 1.54 RFS: 1.44	CSS: NR RFS: NR	CSS: 0.1 RFS: 0.1
Aguilera et al [37]	Open	31	NA	NR	NR	NR	NS	NR	NR	NR	NR	NR	NR	NR
Favaretto et al [38]	Laparoscopic	21	0	NR		NR		NR		NR				
	Open	109	NA	2 yr: 86%		NR		2 yr: 38%		23 mo: 46.8%			RFS: 0.57–1.38	RFS: 0.6
	Laparoscopic	53	NR	2 yr: 82%	0.9	NR	NR	2 yr: 42%	0.9	23 mo: 28.3%	NR	RFS: 0.88 BRFS: 0.78	BRFS: 0.46–1.34	BRFS: 0.4
Stewart et al [39]	Open	39	NA	80%	0.43	64%	0.51	NR	NR	58%	0.9	NR	NR	NR
Walton et al [40]	Laparoscopic	23	NR	71%		61%		NR		55%				
	Open	703	NA	75.4%		NR		73.7%		NR			CSS: 0.4–2.06	CSS: 0.91
	Laparoscopic	70	NR	75.2%	0.9	NR	NR	63.4%	0.12	NR	NR	CSS: 0.96 RFS: 1.48	RFS: 0.89–2.44	RFS: 0.13
Hamada et al [43]	Open	50	NA	80%	0.93	NR	NR	68.5%	0.97	56.7%	0.58	NR	NR	NR
Fairey et al [44]	Laparoscopic	55	NR	77.9%		NR		71.4%		57.5%				
	Open	403	NA	73%		67%		44%		NR			CSS: 0.6–1.37	CSS: 0.64
	Laparoscopic	446	NR	76 %	0.32	68%	0.19	33%	0.06	NR	NR	CSS: 0.9 OS: 0.89 RFS: 1.24	OS: 0.6–1.27 RFS: 0.98–1.57	OS: 0.52 RFS: 0.08
Izumi et al [45]	Open	19	NA	NR	NR	NR	0.41	NR	0.17	NR	0.80	NR	NR	NR

Kitamura et al [46]	Laparoscopic	46	NR	NR		NR		NR		NR				
	Open	34	NA	74.2%		NR		57.2%		71.1%				
	Laparoscopic:	74	NR	HALNU:		NR		HALNU:		HALNU:				
	88%			72.9%				12.5%		12.5%				
	Laparoscopic			LNU:				LNU:		LNU:				
	hand			87.4%				69.2%		69.2%				
	assisted: 12%				0.56		NR		0.04*		0.002*			
												BRFS (HALNU vs ONU): 2.05–14.6	BRFS (HALNU vs ONU): 0.001*	
												BRFS (LNU vs ONU): 1.1	BRFS (LNU vs ONU): 0.82	
Zou et al [48]	Open	101	NA	79.2%		NR		NR		NR				
	Laparoscopic	21	NR	85.7%		NR		NR		NR				
					0.56		NR		NR		NR			
												CSS: 2.38	CSS: 0.16	
												BRFS: 0.38	BRFS: 0.21	
Miyazaki et al [49]	Open	527	NA	3 yr:		3 yr:		NR		NR				
				73%		69.5%								
	Laparoscopic	222	NR	3 yr:	0.09	3 yr:	0.13	NR		NR		NR	NR	NR
				76%		72.4%								
Shan et al [51]	Open	118	NA	83.8%		67.1%		65.6%		77.9%		NR	NR	NR
	Laparoscopic	100	NR	80.8%	0.69	66%	0.54	68.3%	0.88	79.5%	0.75			

Laparoscopic RNU with endoscopic bladder cuff excision vs open RNU

Shalhav et al [13]	Open	17	NA	43 mo:		43 mo:		NR		NR				
				90%		91%								
	Laparoscopic	25	0	24 mo:	NR	24 mo:	NR	NR	NR	NR	NR	NR	NR	NR
				90%		90%								
Gill et al [14]	Open	35	NA	34 mo:		34 mo:		NR		34 mo: 37%				
				87%		94%								
	Laparoscopic	42	NR	11 mo:	0.59	11 mo:	0.59	NR	NR	11 mo: 23%	0.42	NR	NR	NR
				97%		97%								
Stifelman et al [15]	Open	11	NA	NR		NR		NR		17 mo:				
										36.4%				
	Laparoscopic	11	0	NR	NR	NR	NR	NR	NR	13 mo:	NR	NR	NR	NR
										27.3%				
Müller et al [30]	Open	19	NA	67%		67%		NR		2 yr: 49.5%		NR	NR	NR
	Laparoscopic	19	0	56.7%	0.53	56.7%	0.53	NR	NR	2 yr: 55.1%	0.82			

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.

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	<i>p</i> value	5-yr overall survival	<i>p</i> value	5-yr recurrence-free survival	<i>p</i> value	5-yr bladder recurrence-free survival	<i>p</i> value	Multivariable Cox regression analysis		
												HR (LNU vs ONU)	95% CI	<i>p</i> value
Hsueh et al [22]	Open	11		NR		NR		NR		NR				
	Laparoscopic hand assisted	13	pT3	NR	0.48	NR	0.12	NR	NR	NR	NR	NR	NR	NR
Hsueh et al [22]	Open	34		NR		NR		NR		NR				
	Laparoscopic hand assisted	38	G3	NR	0.88	NR	0.88	NR	NR	NR	NR	NR	NR	NR
Capitanio et al [34]	Open	344	NA	NR		NR		NR		NR				
	Laparoscopic	63	NR	NR	NR	NR	NR	NR	0.1	NR	NR	NR	NR	NR
Simone et al [9]	Open	40		NR		NR		NR		NR				
	Laparoscopic	40	High grade	NR	0.01*	NR	NR	NR	0.01*	NR	NR	NR	NR	NR
Simone et al [9]	Open	40		NR		NR		NR		NR				
	Laparoscopic	40	pT3	NR	0.04*	NR	NR	NR	0.004*	NR	NR	NR	NR	NR
Chung et al [35]	Open	31		82.6%		67.7%		NR		115 mo: 32.3%				
	Laparoscopic hand assisted	21	pT3N0	94.7%	0.17	79.6%	0.57	NR	0.19	72 mo: 19%	NR	NR	NR	NR
Favaretto et al [38]	Open	35	pT3/pT4	NR	NR	NR	NR	NR	>0.05	NR	NR	NR	NR	NR
Walton et al [40]	Laparoscopic	17		NR		NR		NR		NR				
	Open	48		HR: 0.36		NR		HR: 0.21		NR				
	Laparoscopic	2	pN+	95% CI: 0.04–3.00	0.35	NR	NR	95% CI: 0.03–1.81	0.16	NR	NR	NR	NR	NR
Walton et al [40]	Open	236		HR: 0.77		NR		HR: 0.91		NR				
	Laparoscopic	23	pT3/pT4	95% CI: 0.32–1.83	0.55	NR	NR	95% CI: 0.44–1.88	0.80	NR	NR	NR	NR	NR
Ariane et al [41]	Open	237	pT3/pT4	NR	0.05	NR	NR	NR	0.9	NR	NR	NR	NR	NR

Faurey et al [44]	Laparoscopic	55	pT and pN+	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Open	42		NR										
	Laparoscopic	18		NR										
Faurey et al. [44]	Open	111	PT3/pT4 pN0	NR	NR	NR	NR	HR: 1.30 95% CI: 1.03–1.65	0.03*	NR	NR	NR	NR	NR
	Laparoscopic	120		NR										
Miyazaki et al [49]	Open	379	pT3/pT4 and/or pN+	NR	NR	NR	0.29	NR	NR	NR	NR	NR	NR	NR
	Laparoscopic	167		NR										
Kim et al [50]	Open	112	pT3/pT4	62.7%	0.007*	68.4%	0.005*	NR	>0.05	NR	>0.05	CSS: 2.50 OS: 2.59	CSS: 1.32– 4.71 OS: 1.44– 4.65	CSS: 0.005* OS: 0.001*
	Laparoscopic	34		26%										

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.