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European Association of Urology

Platinum Priority – Review – Urothelial Cancer

Editorial by Morgan Rouprêt on pp. 1154–1155 of this issue

Laparoscopic Versus Open Nephroureterectomy for the Treatment of Upper Urinary Tract Urothelial Carcinoma: A Systematic Review and Cumulative Analysis of Comparative Studies

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Article info

Article history:
Accepted February 7, 2012
Published online ahead of print on February 14, 2012

Keywords:
Laparoscopy
Nephroureterectomy
Urothelial carcinomas
Upper urinary tract
Recurrence
Survival
Cumulative analysis

Abstract

Context: Laparoscopic nephroureterectomy (LNU) has increasingly been used as a minimally invasive alternative to open nephroureterectomy (ONU), but studies comparing the efficacy and safety of the two surgical procedures are still limited.
Objective: Evaluate the oncologic and perioperative outcomes of LNU versus ONU in the treatment of upper urinary tract urothelial carcinoma.
Evidence acquisition: A systematic review and cumulative analysis of comparative studies reporting both oncologic and perioperative outcomes of LNU and ONU was performed through a comprehensive search of the Medline, Embase, and the Cochrane Library electronic databases. All analyses were performed using the Review Manager (RevMan) v.5 (Nordic Cochrane Centre, Copenhagen, Denmark) and Meta-analysis In eXcel (MIX) 2.0 Pro (BiostatXL) software packages.
Evidence synthesis: Twenty-one eligible studies (1235 cases and 3093 controls) were identified. A significantly higher proportion of pTa/Tis was observed in LNU compared to ONU (27.52% vs 22.59%; $p = 0.047$), but there were no significant differences in other stages and pathologic grades (all $p > 0.05$). For patients who underwent LNU, the 5-yr cancer-specific survival (CSS) rate was significantly higher, at 9% ($p = 0.03$), compared to those who underwent ONU, while the overall recurrence rate and bladder recurrence rate were notably lower, at 15% ($p = 0.01$) and 17% ($p = 0.02$), respectively. However, there were no statistically significant differences in 2-yr CSS, 5-yr recurrence-free survival (RFS), 5-yr overall survival (OS), 2-yr OS, and metastasis rates between LNU and ONU (all $p > 0.05$). Moreover, there were no significant differences between LNU and ONU in terms of intraoperative complications, postoperative complications, and perioperative mortality (all $p > 0.05$). The results of our study were mainly limited by the retrospective design of most of the individual studies included as well as selection biases based on different management of regional lymph nodes and pathologic characteristics.
Conclusions: Our data suggest that LNU offers reliable perioperative safety and comparable oncologic efficacy when compared to ONU. Given that some limitations cannot be overcome, well-designed prospective trials are needed to confirm our findings.

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  doi:10.1016/j.eururo.2012.02.019

1. Introduction

The current standard of care for the treatment of localised upper urinary tract urothelial carcinomas (UUT-UC) is open radical nephroureterectomy (ONU), which includes the excision of the distal ureter, because of the high potential for recurrence, multifocality, and progression [1,2]. Laparoscopic techniques have been widely used in many malignant diseases, such as renal cell carcinoma [3] and prostate cancer [4], with less efficacy than conventional open surgical approaches. Since first being documented by Clayman et al. in 1991 [5], laparoscopic nephroureterectomy (LNU) has been increasingly used as a minimally invasive approach, with improvements in perioperative outcomes such as less blood loss, faster recovery times, and shorter hospitalisation times compared with ONU [6]. However, it is unknown whether LNU is an effective and safe substitute for ONU in the management of UUT-UCs.

In recent years, a number of studies have been published in an attempt to explore this issue; but the results are inconsistent [6–26]. For example, the 5-yr cancer-specific survival (CSS) rates ranged from 75.7% [7] to 95.2% [16] in LNU. Moreover, limitations such as small sample size and single-centre research prevent strong conclusions from being drawn. Although nonrandomised, comparative studies (NRCS) of LNU and ONU treatment modalities could either exaggerate or underestimate any actual differences in the two procedures [27], a cumulative analysis of well-designed NRCSs of surgical procedures has proven feasible [28–30], and the results were remarkably similar to those of contemporaneous randomised controlled trials (RCT) [31]. As a result, a systematic review and cumulative analysis of comparative studies was performed.

2. Evidence acquisition

The analysis of previous studies was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [32] and Meta-analysis of Observational Studies in Epidemiology (MOOSE) [33] guidelines. A comprehensive search was carried out to identify all trials that compared the safety and efficacy of LNU to ONU before July 2011 using the keywords *upper urinary tract, urothelial carcinoma, open radical nephroureterectomy, laparoscopic nephroureterectomy*, and *comparative study* in the Medline, Embase, and Cochrane Library electronic databases. Review articles and bibliographies of other relevant studies identified were personally searched to find additional studies. The search was restricted to articles in English.

To be considered eligible, the study had to meet the following selection criteria: (1) The diagnosis of UUT-UC had to be confirmed pathologically; (2) studies focusing on pure LNU were included, while those on personally assisted surgeries were excluded; (3) studies had to be direct comparative trials; (4) the baseline characteristics of patients from two arms had to be included; (5) original data for dichotomous and continuous variables had to be provided or calculable from the data source; and (6) for studies with the same or overlapping data by the same authors, the most recent study with the greatest number of subjects was chosen. Two investigators (Ni and Chen) independently extracted data, and all disagreements about eligibility were resolved by a third reviewer (Wang).

The primary and secondary outcome measures were oncologic and perioperative outcomes, respectively. Two measurements on oncologic outcomes were evaluated. First, we looked at the 5-yr recurrence-free survival (RFS) rate, 2- and 5-yr CSS rates, 2- and 5-yr overall survival (OS) rates, recurrence rate, bladder recurrence rate, and metastasis rate. *Recurrence* was defined as tumour relapse during the follow-up period; it was further categorised as *loco-regional recurrence*, including the surgical bed and regional lymph nodes, and *recurrence in the remnant urothelium*, including bladder and contralateral UUT. The data on recurrence had to be extracted according this criterion. Because some studies reported on 2-yr outcomes and others on 5-yr outcomes, data were extracted separately. Second, to evaluate the perioperative safety of LNU, continuous variables such as operation time, blood loss, and length of hospitalisation were extracted. Intraoperative complications included bleeding and accidental injuries. Postoperative complications that occurred during the 30 d after surgery were divided into minor (Clavien grades 1 and 2) and major (Clavien grades 3–5) groups according to the Clavien-Dindo classification system [34].

3. Evidence synthesis

3.1. Statistical analyses

For dichotomous variables, the risk ratio (RR) was determined along with the corresponding 95% confidence interval (CI). Interstudy heterogeneity was measured using the Q-test. Heterogeneity was also quantified with the I^2 metric, which is independent of the number of studies included in the cumulative analysis. The scale of I^2 values ranges between 0% and 100%, with higher values denoting a greater degree of heterogeneity. Data were pooled using both fixed-effect and random-effect models. In the absence of interstudy heterogeneity, the fixed-effect and random-effect models provided identical results. The random-effect model incorporates an estimate of the interstudy variance and tends to provide wider CIs; it was employed when heterogeneity was present. The Begg's funnel plot and the Egger's test were conducted to identify potential publication bias. In the Begg's funnel plot, an asymmetrical plot suggests a possible publication bias. If asymmetry was detected, then funnel plot asymmetry was assessed by the Egger's linear regression test. The significance of the intercept was determined by the t test. Continuous parameters such as operation time, blood loss, and length of hospitalisation were analysed by using the estimated weighted mean differences. However, only 2 of the 21 studies included standard deviation calculations for the length of hospitalisation. In addition, only two studies provided information about postoperative pain, which made it difficult to perform subgroup analyses. Therefore,

the mean or median of the pertinent continuous parameters and the compared averages of each parameter were extracted whenever possible. Sensitivity analyses were carried out by study design, sample size, pathologic tumour stage, grade, and the type of removal of the distal ureter. At the same time, subgroup analyses were performed by locoregional recurrence, recurrence in the remnant urothelium, and the type of LNU approach (transperitoneal or retroperitoneal). All analyses were performed using the Review Manager (RevMan) v.5 (Nordic Cochrane Centre, Copenhagen, Denmark; http://www.cc-ims.net/revman/download) and Meta-analysis In eXcel (MIX) 2.0 Pro (BiostatXL; http://www.meta-analysis-made-easy.com/download/index.html) software packages. All p values were calculated using the 2-tailed Student t test, and p values were considered statistically significant when <0.05.

3.2. Quality of the comparative studies and level of evidence

One hundred fifty-three articles were found at first—97 in Medline, 56 in Embase, and none in the Cochrane Library. In addition to using the keywords to find eligible studies, six studies were identified by further identification of potentially relevant studies in Medline. In total, 21 eligible studies, including 1235 patient cases and 3093 controls, were identified according to our predefined selection criteria (Fig. 1). The Downs and Black quality assessment method [35] and the US Preventive Services Task Force grading system [36] were utilised to assess the quality of every study included in our meta-analysis. The Downs and Black scale, a list of 27 criteria against which to evaluate both randomised and nonrandomised comparative studies, assesses study reporting, external validity, and internal validity (ie, bias and confounding) and has been ranked in the top six quality assessment scales suitable for use in systematic reviews. The higher score was associated with the higher quality of study. Moreover, the score ranges were usually grouped into the following four quality levels: 26–28, 20–25, 15–19, and <14 [35]. Most of the studies included in our analysis were retrospective [6–9,11–26], and only one was an RCT [10]. The Downs and Black quality assessment score of all studies was ≥14 (mean: 15.19; standard deviation: 1.29). Also, the demographic and pathologic characteristics, surgical modality, and oncologic and perioperative outcomes were extracted individually from each study and listed Table 1.

3.3. Cumulative analyses

3.3.1. Oncologic outcomes

For oncologic outcomes, our data showed that the 5-yr CSS rate in the LNU arm was significantly higher, at 9%, than that of the ONU arm ($p = 0.03$; Fig. 2), while the overall recurrence and bladder recurrence rates during the follow-up period were remarkably lower, at 15% ($p = 0.01$; Fig. 3) and 17% ($p = 0.02$; Fig. 3), respectively. However, there were no statistically significant differences between LNU and ONU with respect to the 2-yr CSS rate ($p = 0.31$; Fig. 2), 5-yr RFS rate ($p = 0.68$; Fig. 2), 5-yr OS rate ($p = 0.56$; Fig. 2), 2-yr OS rate ($p = 0.10$; Fig. 2), and the metastasis rate ($p = 0.52$; Fig. 3).

The pathologic characteristics of patients included in this analysis are listed in Table 2 and Table 3. A significantly higher proportion of pTa/Tis was observed in patients who

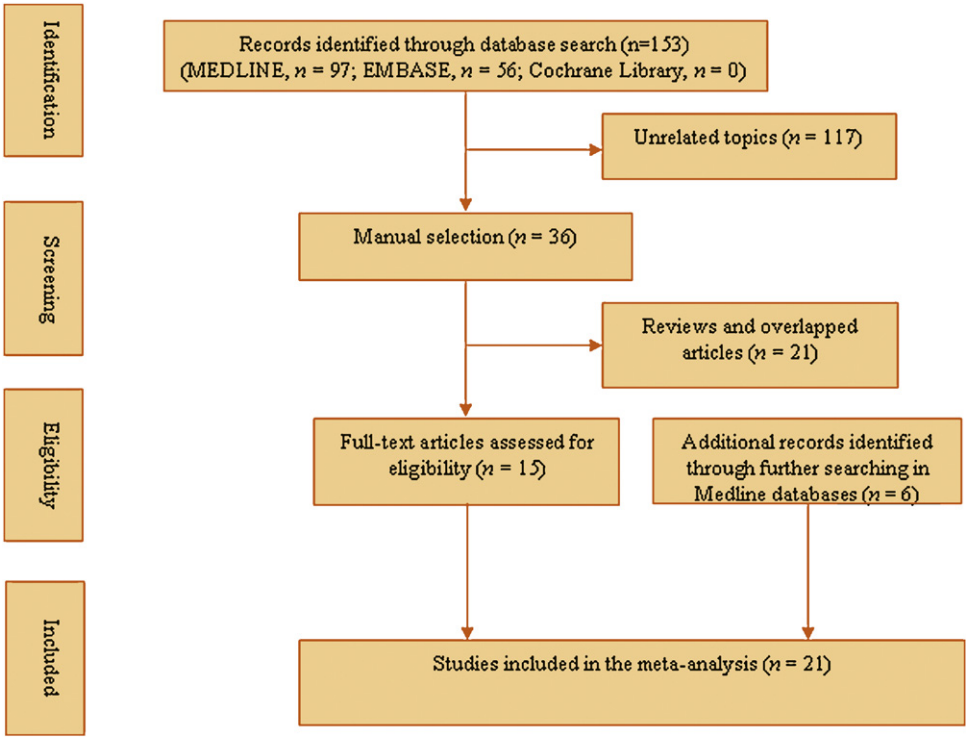

Fig. 1 – Flow diagram of our method of evidence acquisition.

Table 1 – Baseline characteristics of included trials

First author, yr	Design, LOE	Downs and Black score	No. of cases/ controls	Average cases/ controls*	Follow-up, mo*, cases/ controls	LNU approach	LND	Distal ureter surgery
Ariane, 2011 [6]	Retrospective, 3	14	150/459	69.5/69.8	24.5/40.4	Transperitoneal	Selectively performed	Mixed
Walton, 2011 [7]	Retrospective, 3	14	70/703	70/68	17/36	Transperitoneal	Selectively performed	Mixed
Favaretto, 2010 [8]	Retrospective, 4	15	53/109	73/71	23/23	Mixed	Selectively performed	Mixed
Waldert, 2009 [9]	Retrospective, 4	15	43/59	65.56/68.46	41/41	Mixed	Most of the patients	Open
Simone, 2009 [10]	Prospective, randomised, 2	20†	40/40	59.6/61.3	41/41	Transperitoneal	Not performed	LigaSure
Greco, 2009 [11]	Retrospective, 4	15	70/70	66.4/67.2	60/60	Transperitoneal	NR	LigaSure
Capitanio, 2009 [12]	Retrospective, 3	14	270/979	70.2/68.3	30.6/70.7	N/A	Selectively performed	N/A
Aguilera, 2009 [13]	Retrospective, 4	14	25/70	66.7/67.5	24/52.7	Transperitoneal	Selectively performed	Mixed
Taweemonkongsap, 2008 [14]	Retrospective, 4	15	31/29	63.8/66.8	26.4/27.9	Retroperitoneal	Selectively performed	Open
Terakawa, 2008 [15]	Retrospective, 4	15	120/120	68.7/71.3	25.2/33.8	Retroperitoneal	Selectively performed	Open
Hemal, 2008 [16]	Retrospective, 4	16	21/27	54.3/57.1	53/57	Retroperitoneal	Most of the patients	Mixed
Rouprêt, 2007 [17]	Retrospective, 4	15	20/26	65.8/71.1	69/78	Transperitoneal	NR	Open
Manabe, 2007 [18]	Retrospective, 4	15	58/166	72/72	13.6/28.0	Retroperitoneal	NR	Open
Koda, 2007 [19]	Retrospective, 4	15	79/27	71.4/67.4	16.4/46.2	Retroperitoneal	Not performed	Open
Hattori, 2006 [20]	Retrospective, 4	15	53/60	67.1/65.5	17/35	Retroperitoneal	Most of the patients	Endoscopy
Tsujihata, 2006 [21]	Retrospective, 4	16	25/24	66.6/68.3	22.4/22.1	Retroperitoneal	NR	Open
Rassweiler, 2004 [22]	Retrospective, 4	14	23/21	62.2/70.5	NR	Retroperitoneal	NR	Open
Bariol, 2004 [23]	Retrospective, 4	15	25/40	69.5/69.4	101/96	Transperitoneal	NR	Open
Goel, 2002 [24]	Retrospective, 4	15	9/5	58.8/55	15.0/19.0	Retroperitoneal	NR	Open
McNeill, 2000 [25]	Retrospective, 4	16	25/42	68/69.1	32.9/42.3	Transperitoneal	NR	Open
Shalhav, 2000 [26]	Retrospective, 4	16	25/17	69.7/62	24/24	Transperitoneal	NR	Mixed

LOE = level of evidence; LND = lymphadenectomy; NR = not reported; N/A = not applicable; RCT = randomised controlled trial.
* Mean or median.
† RCT.

underwent LNU compared to patients who underwent ONU (27.52% vs 22.59%; $p = 0.047$), indicating that LNU was performed in patients with lower-grade tumours. However, there were no significant differences in other stages and pathologic grades (all $p > 0.05$).

At present, independent prognostic factors after radical nephroureterectomy (RNU) for UUT-UC include tumour stage [6,7,9,13,37], grade [9,13], and the degree of tumour necrosis [38] but do not consist of tumour location [37] or the surgical procedure employed [9,15]. In this analysis, no studies focused on the prognostic role of tumour necrosis and tumour location. Our analysis found that LNU had similar or better oncologic efficacy than ONU. The reasons for those inconsistent results could be explained as follows. We acknowledge that a small sample size probably made it difficult to detect the true relative efficacy of the two procedures by low statistical power. The number of patients included in our comparative analysis of the 2-yr CSS, 5-yr OS, and 2-yr OS rates was much less than the number of patients used for the 5-yr CSS rate analysis. More importantly, all the oncologic outcomes should have been compared by pathologic stage and grade as preplanned. Unfortunately, such analyses could not be achieved because of insufficient data. In the study by Capitanio et al. [12], LNU was associated with a statistically significantly lower rate of recurrence ($p < 0.001$) and CSS ($p < 0.001$) than ONU. However, the reported differences were not statistically significant after adjusting for the tumour stage. There were no significant differences in other stages and pathologic grades (all $p > 0.05$). Similar to other laparoscopic procedures, LNU could be selectively performed in favourable-risk patients at an earlier stage of tumour development, which could suggest that our oncologic findings favouring LNU could be attributed mainly to a bias in tumour stage.

The management of the distal ureter has been a controversial subject. Various disposal methods have been described with varying degrees of oncologic safety, including open surgery, the "pluck" technique [25], the transvesical laparoscopic detachment and ligation technique [39], laparoscopic stapling using the ENDO GIA stapler (Covidien, Dublin, Ireland) [26], intussusception [40], and the LigaSure system (Covidien) [10,11]. Li et al. [41] retrospectively evaluated 301 patients with primary UUT-UC who underwent RNU; intravesical incision, extravesical incision, and transurethral incision (TUI) were performed in 81, 129, and 91 of the patients, respectively. No significant differences were reported in any of the evaluated oncologic outcomes; therefore, these researchers validated the TUI method of distal ureter control in patients with primary UUT-UC without coexistent bladder tumours. In our meta-analysis, we also observed diversity in the selection of LNU or ONU, with the most popular technique being ONU (12 of 21, 57.1%), which is one of the most oncologically reliable and effective techniques [16]. Unfortunately, subgroup analysis could not be performed to compare the efficacy of different procedures because of insufficient data. Although increasing effort has been undertaken with respect to modifications to and innovations of minimally invasive techniques for UUT-UCs that aim to reduce morbidity, certain fundamental oncologic principles must be followed, including the removal of the entire specimen en bloc with no spillage of urine from the ipsilateral kidney and ureter. To

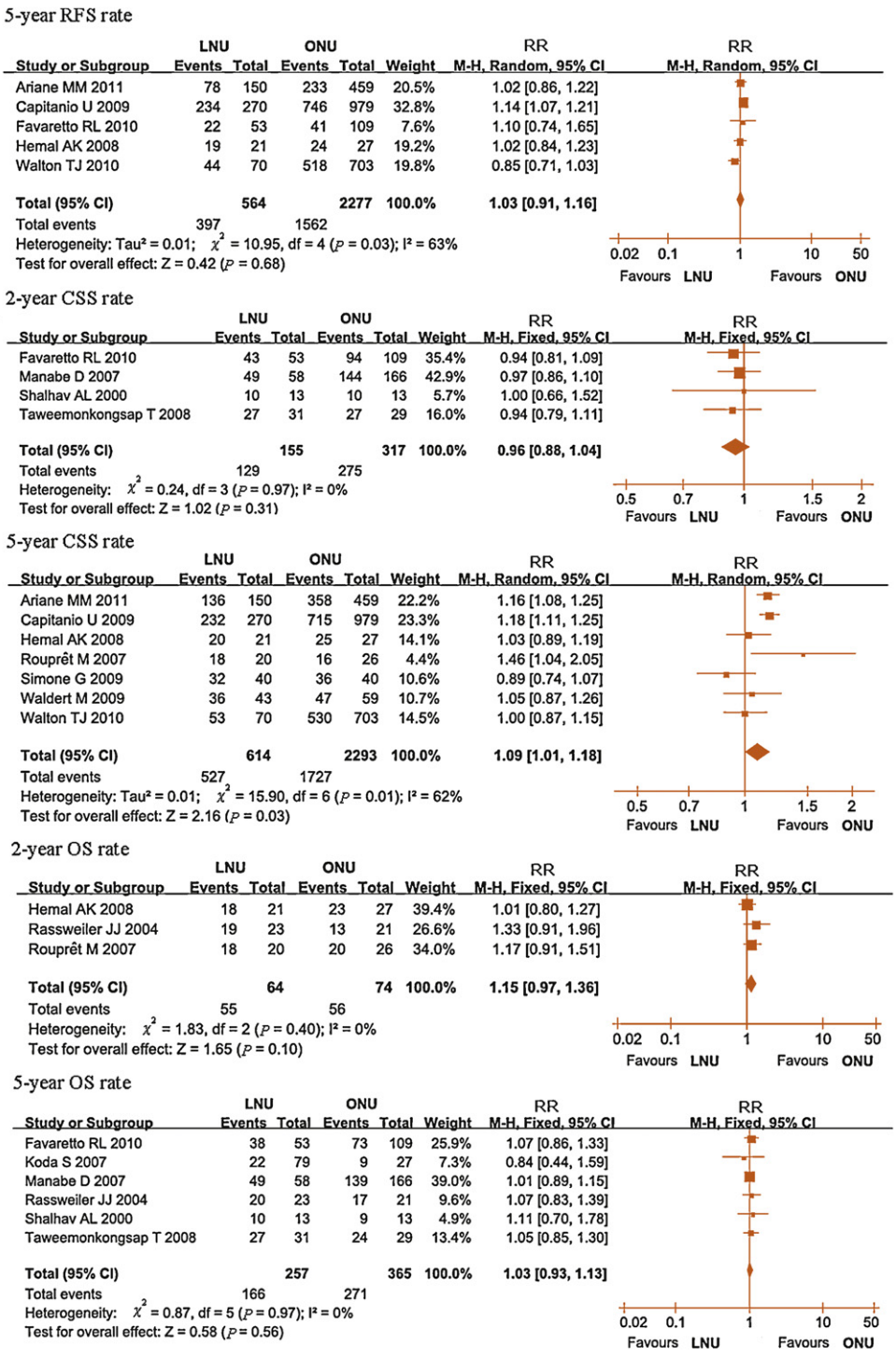

Fig. 2 – Cumulative analysis of studies comparing laparoscopic nephroureterectomy to open radical nephroureterectomy in upper urinary tract urothelial carcinoma with respect to survival rates.
RFS = recurrence free survival; LNU = laparoscopic nephroureterectomy; ONU = open nephroureterectomy; RR = risk ratio; CI confidence interval; CSS = cancer-specific survival; OS = overall survival.

date, no standard LNU procedure with reliable oncologic efficacy and minimal morbidities has been well established or merits further investigation.

The difference in the management of lymph nodes was a confounding factor. Emerging evidence has demonstrated that regional lymph nodes are the most common metastatic site in UUT-UC, and lymph node status is considered a significant predictor of patient outcomes. Although the role, indication, or extent of lymphadenectomy (LND) is still controversial, several retrospective studies have reported that an extended LND can improve disease staging and may be a curative treatment modality for patients with limited

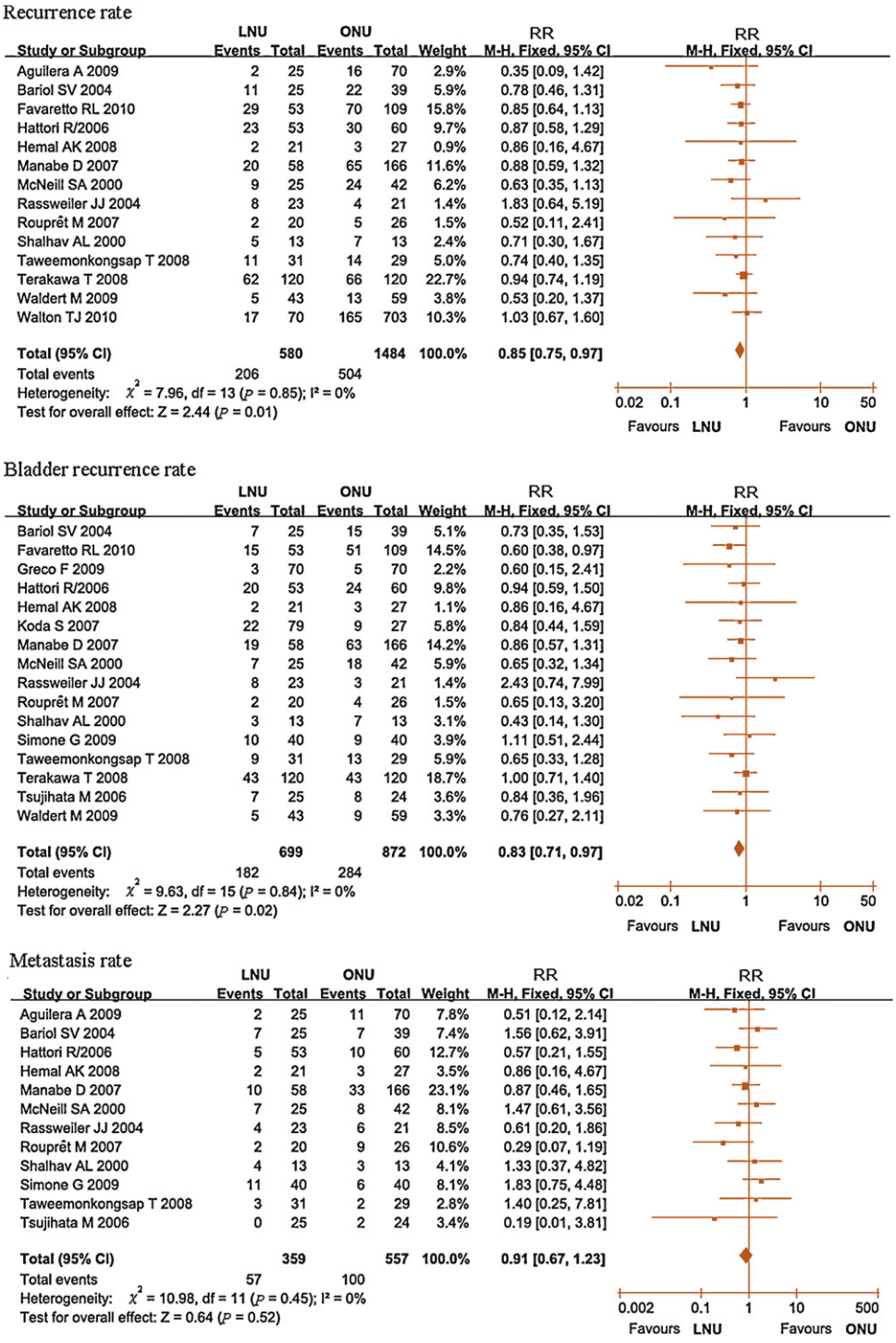

Fig. 3 – Cumulative analysis of studies comparing laparoscopic nephroureterectomy to open radical nephroureterectomy in upper urinary tract urothelial carcinoma with respect to recurrence and metastasis rates.
LNU = laparoscopic nephroureterectomy; ONU = open nephroureterectomy; RR = risk ratio; CI = confidence interval.

nodal disease [42]. In the present analysis, regional LND was performed in 10 studies (47.6%), which may have affected our conclusions to some extent. Subgroup analysis on this issue cannot be conducted because of a lack of accurate data in the included studies. The role of LND in LNU remains unclear and merits further investigation.

The port-site metastasis rate of patients who have undergone LNU has been debated since the 1990s, and the rate of port-site metastasis has been estimated at approximately 1–2% [10]. To date, only 12 port-site metastases have been reported [43,44], and 5 patients (5 of 1235, 0.4%) who displayed port-site metastasis were

Table 2 – Pathologic stage of included trials

First author, yr	T_a/T_{is} (%)		T_1 (%)		T_2 (%)		T_3 (%)		T_4 (%)	
	LNU	ONU	LNU	ONU	LNU	ONU	LNU	ONU	LNU	ONU
Ariane, 2011 [6]	44 (29.33)	119 (25.93)	31 (20.67)	113 (24.62)	20 (13.33)	45 (9.80)	53 (35.33)	153 (33.33)	2 (1.33)	29 (6.32)
Walton, 2011 [7]	19 (27.14)	153 (21.76)	20 (28.57)	175 (24.89)	8 (11.43)	139 (19.77)	19 (27.14)	196 (27.88)	4 (5.71)	40 (5.69)
Favaretto, 2010 [8]	26 (49.06)	56 (51.38)	NR	NR	10 (18.87)	18 (16.51)	17 (32.08)	35 (32.11)	NR	NR
Waldert, 2009 [9]	11 (25.58)	13 (22.03)	9 (20.93)	16 (27.12)	5 (11.63)	10 (16.95)	18 (41.86)	20 (33.90)	NR	NR
Simone, 2009 [10]	NR	NR	20 (50.00)	12 (30.00)	8 (20.00)	15 (37.50)	12 (30.00)	13 (32.50)	NR	NR
Greco, 2009 [11]	13 (18.57)	14 (20.00)	17 (24.29)	16 (22.86)	39 (55.71)	37 (52.86)	1 (1.43)	3 (4.29)	NR	NR
Capitanio, 2009 [12]	103 (38.15)	204 (20.84)	69 (25.56)	229 (23.39)	35 (12.96)	202 (20.63)	59 (21.85)	306 (31.26)	4 (1.48)	38 (3.88)
Aguilera, 2009 [13]	2 (8.00)	10 (14.29)	17 (68.00)	36 (51.43)	1 (4.00)	7 (10.00)	5 (20.00)	12 (17.14)	NR	5 (7.14)
Taweemonkongsap, 2008 [14]	NR	NR	16 (51.61)	13 (44.83)	10 (32.26)	12 (41.38)	4 (12.92)	4 (13.79)	1 (3.23)	NR
Terakawa, 2008 [15]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Hemal, 2008 [16]	3 (14.29)	4 (14.81)	8 (38.10)	9 (33.33)	8 (38.10)	11 (40.74)	2 (9.52)	3 (11.11)	NR	NR
Rouprêt, 2007 [17]	6 (30.00)	6 (23.08)	9 (45.00)	5 (19.23)	2 (10.00)	5 (19.23)	2 (10.00)	7 (26.92)	1 (5.00)	3 (11.54)
Manabe, 2007 [18]	12 (20.69)	29 (17.47)	16 (27.59)	41 (24.70)	6 (10.34)	16 (9.64)	24 (41.38)	73 (43.98)	NR	7 (4.22)
Koda, 2007 [19]	17 (21.52)	8 (29.63)	20 (25.32)	6 (22.22)	11 (13.92)	6 (22.22)	28 (35.44)	7 (25.93)	3 (3.80)	NR
Hattori, 2006 [20]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Tsujihata, 2006 [21]	3 (12.00)	6 (28.57)	9 (36.00)	9 (42.86)	11 (44.00)	2 (9.52)	2 (8.00)	4 (19.05)	NR	NR
Rassweiler, 2004 [22]	12 (52.17)	3 (14.29)	4 (17.39)	5 (23.81)	3 (13.04)	3 (14.29)	4 (17.39)	8 (38.10)	NR	2 (9.52)
Bariol, 2004 [23]	10 (41.67)	21 (53.85)	7 (29.17)	7 (17.95)	4 (16.67)	2 (5.13)	3 (12.50)	9 (23.08)	NR	NR
Goel, 2002 [24]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
McNeill, 2000 [25]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Shalhav, 2000 [26]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Total	281 (27.52)	646 (22.59)	272 (27.15)	692 (24.32)	181 (18.06)	530 (18.63)	253 (25.25)	853 (29.98)	15 (1.50)	124 (4.36)
	$p = 0.047$		$p = 0.079$		$p = 0.105$		$p = 0.062$		$p = 0.051$	

LNU = laparoscopic nephroureterectomy; ONU = open nephroureterectomy; NR = not reported.

reported from 3 studies that were included in our analysis [6,10,18]. One theory entertains the possibility that LNU may accelerate the gravitational migration of tumour cells by the procedure-required elevated-pressure pneumoperitoneum and eventually facilitate local recurrence and port-site metastasis [45]. However, with the improvement in surgical techniques, especially the use of a secured Endobag for extracting the specimen, the incidence rate of port-site metastasis has been declining in recent years [11].

Table 3 – Pathologic grade of included trials

First author, yr	G_1 (%)		G_2 (%)		G_3 (%)	
	LNU	ONU	LNU	ONU	LNU	ONU
Ariane, 2011 [6]	11 (7.33)	39 (8.50)	41 (27.33)	166 (36.17)	98 (65.33)	254 (55.34)
Walton, 2011 [7]	11 (15.71)	88 (12.52)	5 (7.14)	219 (31.15)	54 (77.14)	396 (56.33)
Favaretto, 2010 [8]	NR	NR	NR	NR	NR	NR
Waldert, 2009 [9]	6 (13.95)	4 (6.78)	19 (44.19)	31 (52.54)	18 (41.86)	24 (40.68)
Simone, 2009 [10]	6 (15.00)	5 (12.50)	22 (55.00)	22 (55.00)	12 (30.00)	13 (32.50)
Greco, 2009 [11]	15 (21.43)	17 (24.29)	47 (67.14)	45 (64.92)	8 (11.43)	8 (11.43)
Capitanio, 2009 [12]	NR	NR	NR	NR	NR	NR
Aguilera, 2009 [13]	3 (12.00)	4 (5.71)	14 (56.00)	31 (44.29)	8 (32.00)	35 (50.00)
Taweemonkongsap, 2008 [14]	NR	NR	NR	NR	NR	NR
Terakawa, 2008 [15]	NR	NR	NR	NR	NR	NR
Hemal, 2008 [16]	6 (28.57)	8 (29.63)	11 (52.38)	13 (48.15)	4 (19.05)	6 (22.22)
Rouprêt, 2007 [17]	NR	NR	NR	NR	NR	NR
Manabe, 2007 [18]	4 (6.90)	15 (9.04)	31 (53.45)	87 (52.41)	23 (39.66)	64 (38.55)
Koda, 2007 [19]	10 (12.66)	3 (11.11)	33 (41.77)	16 (59.26)	36 (45.57)	8 (29.63)
Hattori, 2006 [20]	NR	NR	NR	NR	NR	NR
Tsujihata, 2006 [21]	5 (20.00)	NR	15 (60.00)	11 (47.83)	5 (20.00)	12 (52.17)
Rassweiler, 2004 [22]	1 (4.35)	NR	12 (52.17)	8 (38.10)	10 (43.48)	13 (61.90)
Bariol, 2004 [23]	5 (20.83)	4 (10.26)	6 (25.00)	20 (51.28)	13 (54.17)	15 (38.46)
Goel, 2002 [24]	NR	NR	NR	NR	NR	NR
McNeill, 2000 [25]	NR	NR	NR	NR	NR	NR
Shalhav, 2000 [26]	NR	NR	NR	NR	NR	NR
Total	83 (13.22)	187 (10.97)	256 (40.76)	669 (39.26)	289 (46.02)	848 (49.77)
	$p = 0.226$		$p = 0.109$		$p = 0.148$	

LNU = laparoscopic nephroureterectomy; ONU = open nephroureterectomy; NR = not reported.

Table 4 – Perioperative outcomes of included trials

First author, yr	Operative time, min*, cases/controls	Blood loss, ml, cases/controls	Hospital stay, d*, cases/controls
Ariane, 2011 [6]	240/180	NR	8.0/9.0
Walton, 2011 [7]	NR	NR	NR
Favaretto, 2010 [8]	265/164	200/250	3.0/5.0
Waldert, 2009 [9]	220/212	300/542	8.1/13.8
Simone, 2009 [10]	82/78	104/430	2.3/3.7
Greco, 2009 [11]	240/190	NR	NR
Capitanio, 2009 [12]	NR	NR	NR
Aguilera, 2009 [13]	189/205	130/525	N/A
Taweemonkongsap, 2008 [14]	259/191	289/314	9.3/8.7
Terakawa, 2008 [15]	346.3/209.2	358.8/434.3	N/A
Hemal, 2008 [16]	219/156	299/526	N/A
Rouprêt, 2007 [17]	165/155	275/328	3.7/9.2
Manabe, 2007 [18]	NR	NR	NR
Koda, 2007 [19]	299/350	NR	NR
Hattori, 2006 [20]	258/324	354/665	NR
Tsujihata, 2006 [21]	306/271	322/558	2.2/4.0
Rassweiler, 2004 [22]	200/188	450/600	10.0/13.0
Bariol, 2004 [23]	NR	NR	NR
Goel, 2002 [24]	189/184	275/570	5.1/9.2
McNeill, 2000 [25]	165/165	NR	9.1/10.7
Shalhav, 2000 [26]	462/234	199/441	3.6/9.6
Mean	241.4/203.3	273.5/476.3	5.9/8.7

NR = not reported; N/A = not applicable.
* Mean or median.

3.3.2. *Perioperative outcomes*

As shown in Table 4, most studies demonstrated that patients who underwent LNU had a longer operation time compared to ONU (mean: 241.4 vs 203.3 min); however, the average hospital stay was shorter for patients who underwent LNU than for patients who underwent ONU (mean: 5.9 vs 8.7 d). Blood loss for patients who underwent LNU was much less than that of those who underwent ONU (mean: 273.5 vs 476.3 ml).

Of all the included studies, only one [6] adopted the Clavien classification for surgical morbidity. Minor events included wound infections and delayed postoperative bleeding, while major postsurgical complications included ileus, incisional hernia, and pneumothorax. The intraoperative complication rate in patients who underwent LNU was less than that in those who underwent ONU (4.4% vs 5.1%), but the difference was not statistically significant ($p = 0.94$; Fig. 4). Furthermore, no significant differences were detected between the LNU and ONU arms in terms of postoperative complication rates (minor: 5.7% vs 7.8%; $p = 0.40$; Fig. 4; major: 4.6% vs 3.8%; $p = 0.61$; Fig. 4). Differences between the two surgical techniques were also not significant with respect to perioperative mortality (1.6% vs 0.7%; $p = 0.27$; Fig. 4). All of the results of our meta-analysis are summarised in Table 5.

LNU continues to be accepted worldwide as a promising minimally invasive surgical option by many urologic communities because of certain advantages over open access surgery, including decreased postoperative pain, a lower analgesic requirement, less blood loss, quicker recovery times, shorter hospital stays, and lower cost [46]. The data from our analysis corroborated some of these advantages by showing that LNU was associated with less blood loss and shorter hospitalisation times compared to ONU. Nevertheless, our analysis demonstrated that there were no significant differences between LNU and ONU in terms of intraoperative complications, postoperative complications, and perioperative mortality. Considering that minor complications (Clavien 1 or 2) are notably common and are probably underestimated in open surgery in most retrospective studies, our results may support the perioperative safety of LNU compared to ONU.

LNU can be divided into two steps: nephrectomy and distal ureterectomy. LNU is conducted via transperitoneal or retroperitoneal access in a pure laparoscopic or hand-assisted technique. Our data focused solely on pure LNU by transperitoneal (nine studies), retroperitoneal (nine studies), or mixed (two studies) access. The present review did not address this issue because of insufficient data for subgroup analysis; therefore, the optimal peritoneal approach is mainly determined by the surgeons' preference and laparoscopic expertise [47]. Advocates of transperitoneal access emphasised more working space and easier manipulation [23], while supporters of the retroperitoneal approach argue that rapid access to renal hilar vessels with less disruption of the intraperitoneal organs could reduce the operating time and the chance of intraperitoneal contamination by malignant cells [16].

3.4. *Publication bias and sensitivity analysis*

The funnel plots and Egger's tests (Table 5) revealed that significant publication bias existed in only 1 (intraoperative complications) of the 12 comparisons performed in the present analysis. For the sensitivity analyses, we excluded the RCT [10] as well as studies with small sample sizes (<20) [24]. Our subgroup analyses revealed that the 5-yr CSS rate (RR: 1.12; 95%

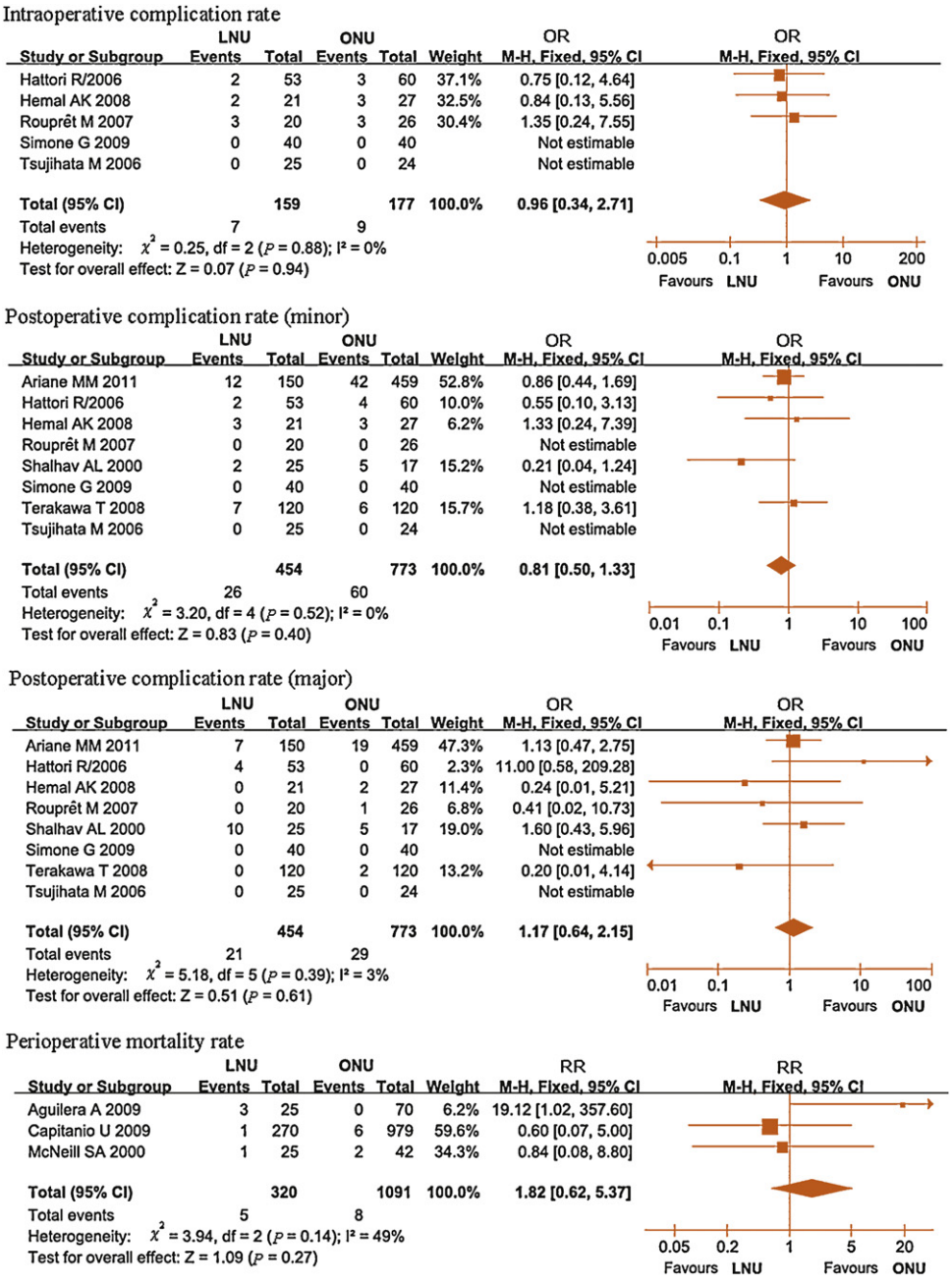

Fig. 4 – Cumulative analysis of studies comparing laparoscopic nephroureterectomy to open radical nephroureterectomy in upper urinary tract urothelial carcinoma with respect to complication and perioperative mortality rates.
LNU = laparoscopic nephroureterectomy; ONU = open nephroureterectomy; OR = odds ratio; CI = confidence interval; RR = risk ratio.

CI, 1.05–1.20; $p = 0.0007$), bladder recurrence rate (RR: 0.82; 95% CI, 0.70–0.96; $p = 0.02$), metastasis rate (RR: 0.82; 95% CI, 0.60–1.14; $p = 0.24$), intraoperative complication rate (RR: 0.96; 95% CI, 0.34–2.71; $p = 0.94$), and minor postoperative complication rate (RR: 0.81; 95% CI, 0.50–1.33; $p = 0.40$) did not change significantly after excluding the RCT and studies with small sample sizes. Because the necessary data were not available, neither the sensitivity analyses by pathologic tumour stage, grade, and type of removal of the distal ureter nor the subgroup analyses by locoregional recurrence, recurrence in the remnant urothelium, and type of different LNU approach could not be performed as preplanned.

3.5. *Strengths and limitations*

To the best of our knowledge, this research represents the first systematic review and cumulative analysis comparing LNU to ONU in the treatment of UUT-UC, encompassing 21 studies and 4328 patients. Publication bias was detected in

Table 5 – Cumulative analysis of laparoscopic nephroureterectomy versus open radical nephroureterectomy for upper urinary tract urothelial carcinoma

Measurements	No.*	Sample size Case/control	Heterogeneity	Pooled RR (95% CI)	Z test	Egger's test
Oncologic outcomes						
5-yr RFS rate	5	564/2277	$\chi^2 = 10.95$, $p = 0.03$, $I^2 = 63\%$	1.03 (0.91–1.16)†	$Z = 0.42$, $p = 0.68$	$p = 0.20$
2-yr CSS rate	4	155/317	$\chi^2 = 0.24$, $p = 0.97$, $I^2 = 0\%$	0.96 (0.88–1.04)	$Z = 1.02$, $p = 0.31$	$p = 0.85$
5-yr CSS rate	7	614/2293	$\chi^2 = 15.90$, $p = 0.01$, $I^2 = 62\%$	1.09 (1.01–1.18)†	$Z = 2.16$, $p = 0.03$	$p = 0.27$
2-yr OS rate	3	64/74	$\chi^2 = 0.83$, $p = 0.40$, $I^2 = 0\%$	1.15 (0.97–1.36)	$Z = 1.65$, $p = 0.10$	$p = 0.33$
5-yr OS rate	6	257/365	$\chi^2 = 0.87$, $p = 0.97$, $I^2 = 0\%$	1.03 (0.93–1.13)	$Z = 0.58$, $p = 0.56$	$p = 0.96$
Recurrence rate	14	580/1484	$\chi^2 = 7.96$, $p = 0.85$, $I^2 = 0\%$	0.85 (0.75–0.97)	$Z = 2.44$, $p = 0.01$	$p = 0.12$
Bladder recurrence rate	16	699/872	$\chi^2 = 9.63$, $p = 0.84$, $I^2 = 0\%$	0.83 (0.71–0.97)	$Z = 2.27$, $p = 0.02$	$p = 0.51$
Metastasis rate	12	359/557	$\chi^2 = 10.98$, $p = 0.45$, $I^2 = 0\%$	0.91 (0.67–1.23)	$Z = 0.64$, $p = 0.52$	$p = 0.21$
Perioperative outcomes						
Intraoperative complication rate	5	159/177	$\chi^2 = 0.25$, $p = 0.88$, $I^2 = 0\%$	0.96 (0.34–2.71)	$Z = 0.07$, $p = 0.94$	$p = 0.01$
Postoperative complication rate						
Minor	8	454/773	$\chi^2 = 3.20$, $p = 0.52$, $I^2 = 0\%$	0.81 (0.50–1.33)	$Z = 0.83$, $p = 0.40$	$p = 0.55$
Major	8	454/773	$\chi^2 = 5.18$, $p = 0.39$, $I^2 = 3\%$	1.17 (0.64–2.15)	$Z = 0.51$, $p = 0.61$	$p = 0.55$
Perioperative mortality rate	3	320/1091	$\chi^2 = 3.94$, $p = 0.14$, $I^2 = 49\%$	1.82 (0.62–5.37)	$Z = 1.09$, $p = 0.27$	$p = 0.15$

RR = risk ratio; CI = confidence interval; RFS = recurrence-free survival; CSS = cancer-specific survival; OS = overall survival.
* Number of included studies.
† Random-effects model.

only one of the comparisons, as identified by the Begg's funnel plot and Egger's tests. The overall results did not change remarkably after subgroup and sensitivity analyses were performed. Our analysis combined the data from all studies that passed our predefined criteria; therefore, we are confident of the validity of our findings.

However, we also acknowledge certain inherent limitations in the studies included in our meta-analysis that cannot be ignored when interpreting our data. First, most studies included in our analysis were retrospective, which is a reflection of the rarity of the disease. Second, the clinical and pathologic characteristics of patients, which were of great importance to the oncologic outcomes, were different in the included trials. Similar to other laparoscopic procedures, LNU might be selectively performed in favourable-risk patients at an earlier tumour stage; therefore, the results of our analysis favouring LNU could be attributed mainly to a bias in the data from the LNU study arms. More studies are needed to evaluate the role of LNU in advanced UUT-UC. Third, there were differences in the length of the follow-up period for patients, ranging from 15 to 101 mo (mean or median). Furthermore, different follow-up schemes were detected among the included studies, so that the standard scheme and results from long-term follow-up studies are expected. Fourth, urologists widely accept that distinguished differences exist in biological behaviour and patients' prognosis between locoregional recurrence and recurrence in the remnant urothelium. As with LND, subgroup analyses by different recurrence locations could not be achieved because of insufficient data; thus, the findings on overall recurrence in this study should be interpreted with caution. Finally, it is well known that the indications for LNU were much stricter than those for ONU because of more stringent requirements for comorbidities such as body mass index, cardiopulmonary disease, and previous abdominal surgery. Despite no data on the comorbidity status being reported in this analysis, it could be regarded as a confounder in patient selection.

4. Conclusions

Based on the data included in our meta-analysis, LNU was associated with a 9% higher 5-yr CCS rate, a 15% lower rate of recurrence, and a 17% lower rate of bladder recurrence than ONU. No significant differences were detected in terms of the 2-yr CSS rate, 5-yr RFS rate, 5-yr OS rate, 2-yr OS rate, metastasis rate, intraoperative complication rate, postoperative complication rate, and perioperative mortality rate for patients treated with LNU in comparison with ONU. Consequently, our data suggest that LNU offers comparable oncologic efficacy and reliable perioperative safety to ONU. Given that the limitations inherent in the retrospective design of the overwhelming majority of the included studies and the influence of patient selection bias cannot be overcome, large, multicentre, well-designed RCTs with extensive follow-up are needed to confirm our findings.

Authors' contributions: Chunyang Wang 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: Ni, Wang.
Acquisition of data: Ni, Chen.
Analysis and interpretation of data: Tao, Hu.
Drafting of the manuscript: Wang, Ni.
Critical revision of the manuscript for important intellectual content: Liu, Jiang.
Statistical analysis: Wang, Tao.
Obtaining funding: Wang.
Administrative, technical, or material support: Ni, Han.
Supervision: Han, Jiang.
Other (specify): None.

Financial disclosures: I certify that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

Funding/Support and role of the sponsor: This project was supported in part by the Research Foundation of The First Hospital of Harbin Medical University (Grant No. 2011LX001).

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