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Influence of lymph node dissection in patients undergoing radical nephrectomy for non-metastatic renal cell carcinoma: a systematic review and meta-analysis

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Abstract. – OBJECTIVE: Whether lymph node dissection (LND) should be performed concomitantly with radical nephrectomy (RN) for non-metastatic renal carcinoma has still been controversial recently. We conducted a meta-analysis assessing oncologic outcomes of radical nephrectomy with lymph node dissection (LND) and without lymph node dissection (non-LND) in non-metastatic renal cell carcinoma (NMRCC).

PATIENTS AND METHODS: A systematic review was performed until April 2018 using a comprehensive search in PubMed, EMBASE, and Cochrane Library databases to identify eligible comparative studies. A formal meta-analysis was performed for studies comparing radical nephrectomy with LND and radical nephrectomy with non-LND for cT_1-$T_4N_xM_0$ tumors. Furthermore, a subgroup analysis for locally advanced renal cell carcinoma (cT_3-$T_4N_xM_0$) was conducted.

RESULTS: Thirteen studies on patients with LND and non- LND were identified and included in the analysis. LND group did not have a significantly better survival than non-LND group for cT_1-$T_4N_xM_0$ tumors (HR 0.93, 95% CI 0.78-1.11, p=0.45), However, in the subgroup of locally advanced renal cell carcinoma (cT_3-$T_4N_xM_0$), it showed a significantly better OS rate in patients who had undergone LND compared to those without LND (HR 0.73, 95% CI 0.60-0.90; p=0.003).

CONCLUSIONS: LND offers better cancer control and better long-term survival in locally advanced renal cell carcinomas (cT_3-$T_4N_xM_0$). This conclusion should be confirmed by a prospective randomized clinical trial.

Key Words:
Renal cancer, Survival factors, Lymphadenectomy, Lymph node dissection, Oncologic outcomes.

Abbreviations

LND: lymph node dissection; non-LND: without lymph node dissection; RN: radical nephrectomy; NMRCC: non-metastatic renal cell carcinoma; RCC: Renal Cell Carcinoma; CT: computed tomography; MR: magnetic resonance; OS: overall survival; PFS: progression-free survival; HR: hazard ratio; RR: risk ratio; CIs: confidence intervals; RCT: randomized controlled trial.

Introduction

In several urological cancers[1,2], such as bladder cancer and prostate cancer, lymph node dissection (LND) is considered a standard of surgical management, but the role of LND in Renal Cell Carcinoma (RCC) remains controversial. The only prospective randomized trial EORTC 30881[3] demonstrated that there was no survival advantage among patients with clinical N_0M_0 RCC undergoing LND, while the latest meta-analysis by Bhindi et al[4] suggested that there was no therapeutic benefit of LND in both M_0 or M_1 RCC. Several retrospective studies[5-8] suggested that LND may be beneficial for patients with locally advanced carcinoma and unfavorable pathologic features.

On the other hand, evidence was insufficient on the effect of LND on the long-term survival of RCC. The EORTC study enrolled the clinical N_0M_0 RCC patients, most of them were low-stage (pT_1 or pT_2), which was only the subgroup of the RCC population. Therefore, the conclusion drawn from this work should be applied to low-risk cases and not be generalized for clinically locally

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advanced stage ($cT_{3-4}N_xM_0$) patients. In addition, the meta-analysis by Bhindi et al[4] just concerned the therapeutic benefit of LND in the whole patients either M_0 or M_1. Furthermore, there was no discussion on the therapeutic benefit of LND according to T stage, especially in locally advanced carcinoma.

Although a systematic review by Bekema et al[9] reported that there was insufficient evidence that LND+RN have a better survival compared to RN alone for patients of $cT_{3-4}N_0M_0$ RCC, several studies had similar research on this topic during the last 5 years. In light of controversial data, we systemically searched and analyzed the available comparative studies to assess the oncologic outcomes compared the RN with LND and without LND (non-LND) in non-metastatic RCC ($cT_{1-4}N_xM_0$) and in clinically locally advanced stage ($cT_{3-4}N_xM_0$) patients.

Patients and Methods

Search Strategy

A comprehensive literature search was performed of electronic databases including PubMed (http://www.ncbi.nlm.nih.gov/pubmed/), EMBASE (https://www.elsevier.com/solutions/embase-biomedical-research) and the Cochrane Library (http://www.cochranelibrary.com/) (last search date: 16 April 2018). There were no language restrictions. The following terms and their combinations were conducted in the [All field] while performing literature search: "kidney OR renal" AND "cancer OR carcinoma OR neoplasm OR tumor OR tumor OR mass" AND "lymphadenectomy OR lymph-node dissection OR lymph node dissection" AND "radical nephrectomy OR nephrectomy". The search was broadened by "related articles" function in electronic databases and was supplemented with manual searches for reference articles of all the included studies.

Inclusion Criteria, Study Eligibility, and Data Extraction

Two investigators (Xin Luo and Yuan-Ting Liu) identified the articles according to the preferred reporting items for systematic reviews and meta-analysis (PRISMA) criteria (Figure 1). Original studies comparing radical nephrectomy with LND and without LND (regardless of the technique) for non-metastatic RCC ($cT_{1-4}N_xM_0$) were included. In consideration of the paucity of randomized evidence and prospective cohort researches, there were few restrictions on work design. The study population was clinically diagnosed with non-metastatic RCC ($cT_{1-4}N_xM_0$) or locally advanced non-metastatic RCC ($cT_{3-4}N_xM_0$) based on computed tomography (CT) scan or magnetic resonance (MR) imaging. Studies without comparison were excluded. First, studies were identified through initial searches of electronic databases. The titles of the articles were screened for a primary assessment according to the inclusion criteria. The abstracts were further assessed, followed by reviewing the full text for more thorough subsequent assessment. References or related articles from the included articles were also considered if they fitted the inclusion criteria. The third reviewer (Ge Zou) resolved the discrepancies on the included article.

Our aims were to determine whether LND could improve survival among patients undergoing nephrectomy for non-metastatic RCC ($cT_{1-4}N_xM_0$) or locally advanced RCC ($cT_{3-4}N_xM_0$).

The primary outcome was total survival. Secondary outcomes were limited to overall survival (OS) and progression-free survival (PFS).

Assessment of Study Quality

The 2011 level of evidence for therapy studies (Centre for Evidence-Based Medicine, Oxford, UK) was applied to assess the quality of the included articles and it was categorized as followed: level 1 is a systematic review of randomized trials; level 2 is a randomized trial; level 3 is a non-randomized controlled cohort/follow-up study; level 4 is case-series, case-control or historically controlled studies; level 5 is mechanism-based reasoning[10].

Data Analysis

A predefined data extraction form was used for data extraction. Baseline demographics (Table I; age, tumor size) and oncologic outcome [total survival, overall survival (OS) and progression-free survival (PFS)] were extracted from the available studies.

A meta-analysis of the researches comparing RN+LND to RN for non-metastatic RCC ($cT_{1-4}N_xM_0$) was conducted. Sensitivity analysis was further performed by the subgroup of studies comparing RN+LND to RN for $cT_{3-4}N_xM_0$ RCC only.

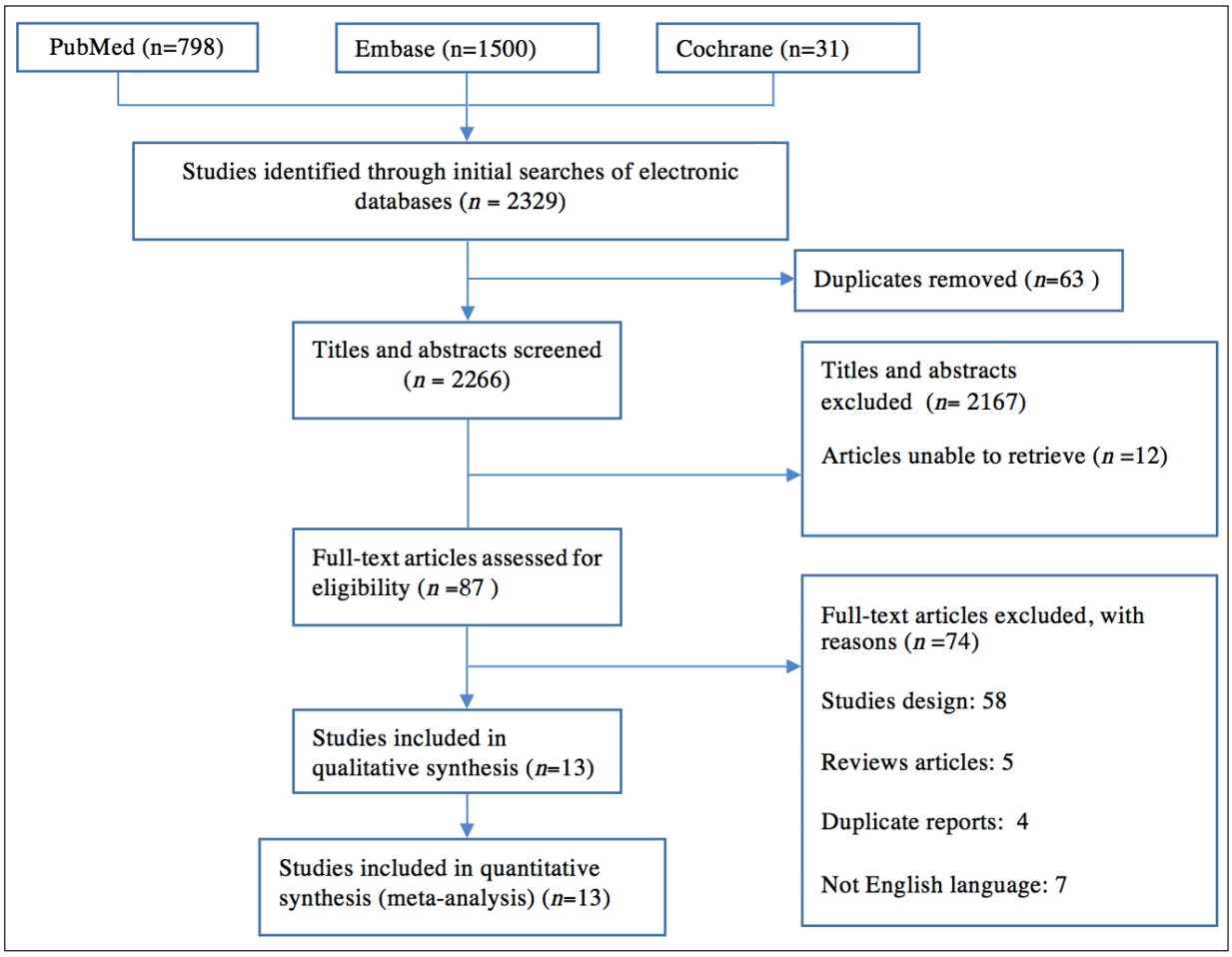

Figure 1. Flow diagram of studies identified, included, and excluded.

The adjusted hazard ratio (HR)/risk ratio (RR) and 95% CIs were extracted from the included articles. Adopting a hierarchical series of steps described by Tierney et al[11], HR and 95% CIs were calculated from those works which only performed survival curves.

Data analyses were performed by Review Manager 5.3 (Cochrane Collaboration, Oxford, UK) and Stata/SE, ver10.0 (StataCorp LLC, College Station, TX, USA). Meta-analysis was conducted for the association between retroperitoneal lymph node dissection and oncologic outcome. To incorporate within-study and between-study variations, the Der Simonian random-effects model was used to pool the estimates (HR or RR) and 95%CIs. We assessed heterogeneity between studies using the Q test (heterogeneity was defined for $p < 0.10$) and the I^2 statistic (proportion of total variation in study estimates due to inconsistency between studies). A funnel plot and Egger's test[12] was used to screen for potential publication bias. Subgroup analysis was performed to analyze the association between retroperitoneal lymph node dissection and different oncologic outcomes. The sensitivity analysis was conducted to verify the main effect excluding each individual included study. To avoid the risk of bias from different cancer stage, a further analysis was to assess OS in clinically locally advanced stage ($cT_{3\text{-}4}N_xM_0$) patients. A two-sided p-value of <0.05 was considered to indicate statistical significance.

When two publications were duplicated in the same study population, the most recent and informative data were included. This was the case for the series reported by Alekseev et al[13].

Heterogeneity across studies was evaluated by the Chi-squared test. Random-effects models were applied in case of inconsistency between studies[14-16].

Results

A total of 2329 studies were identified according to the search strategy. 63 studies were excluded due to duplication and 2167 studies were excluded after the screening of the titles and abstracts. The remaining 87 studies were evaluated in the full text, after which 74 studies were excluded due to study design, narrative reviews, duplicate reports or non-English language. Figure 1 shows the flow diagram of the identified studies, included and excluded. Thirteen studies[3,13,17-27] with a total of 31,644 patients were included in our study. There was a 94% agreement between the two reviewers for the study selection and 93% for the quality assessment of trials.

The clinical and pathological characteristics of the included studies[3,13,17-27] are shown in Table I. The follow-up varied from 8 to 180 months. Thirteen studies[3,13,17-27] examined the overall survival outcomes in non-metastatic RCC ($cT_{1-4}N_xM_0$), with or without LND (Table I). The only RCT to examine this topic (EORTC 30881) reported no difference in oncologic outcomes with LND[3], the majority of included patients were pT1-T2 stage disease. One prospective cohort research[21] concluded that the systematic and extended lymphadenectomy improves the survival rates of patients with RCC. Eleven retrospective studies[13,17-20,22-27] compared RN+LND with RN, four of them reported a survival benefit in patients undergoing nephrectomy+LND for RCC, while no significant association was indicated in other studies.

Figure 2 summarizes no significant association between oncologic outcomes and LND (HR 0.93, 95% CI 0.78-1.11, $p = 0.43$). Due to the heterogeneity indicated between studies with the Q test ($p < 0.001$), we excluded any included article to verify the main effect. It also showed no significant association between oncologic outcomes and LND (HR 0.89, 95% CI 0.79-1.01, $p = 0.07$, heterogeneity test $p = 0.12$, Figure 3) excluding the study of Marchioni et al[20]. No publication bias was observed in our study, regardless of whether the study of Marchioni et al[20] was excluded or not (Begg's test: $p = 0.807$ in total and 0.891 when excluded, Figures 4 and 5).

We further analyzed the OS and PFS according to lymph node dissection for patients of non-metastatic RCC ($cT_{1-4}N_xM_0$). It suggested that LND was not associated with any benefit either on the OS or PFS of non-metastatic RCC ($cT_{1-4}N_xM_0$) (OS HR: 0.93, 95% CI 0.83-1.04, $p = 0.19$, Figure 6; PFS HR: 0.93, 95% CI 0.83-1.04, $p = 0.19$, Figure 7).

Subgroup analysis suggested a significant survival benefit to LND in patients undergoing nephrectomy for locally advanced RCC ($cT_{3-4}N_xM_0$). The pooled HR was 0.73 (95%CI 0.60-0.90, $p = 0.003$, Figure 8). Seven studies compared RN+LND (n = 492) to RN (n = 313) were included in this specific subgroup of $cT_{3-4}N_xM_0$ tumors (Table I)[3,21-27].

Discussion

We conducted the meta-analysis of 13 studies comparing RN+LND with RN for non-metastatic RCC ($cT_{1-4}N_xM_0$) and locally advanced stage RCC ($cT_{3-4}N_xM_0$). The overall analysis results suggested that there was no significantly better OS and PFS rate between patients undergoing RN+LND and RN alone. However, subgroup analysis showed that RN+LND added OS benefits compared to RN specific for patients with RCC with locally advanced stage ($cT_{3-4}N_xM_0$). The heterogeneous was small according to Figure 4.

Some of the retrospective analyses and one randomized study 3 have suggested that complete LND at radical nephrectomy did not affect the survival of patients with clinical N_0M_0 RCC, and accordingly, most patients didn't receive the LND procedure recently in RN. However, the evaluations of LND compared with non-LND in retrospective studies are subject to several biases; LND is a procedure with a considerable choice, it may depend not only on disease characteristics, such as stage or histology but also on the patient's age, coexisting conditions, or performance status. The EORTC trial[3] of lymphadenectomy also did not show a significant effect on overall survival among patients with renal cancer; however, approximately 70% of the patients enrolled in this trial were pT_1 or pT_2 and advanced renal cancer (pT_3 or pT_4) only 30%. Therefore, the conclusion was hardly applicable to clinically (cT_3-$pT_4N_xM_0$) patients. Some retrospective analyses[8] have suggested a potential survival benefit from LND+RN in patients with macroscopically completely resected advanced renal cancer. Capitanio et al[8] suggested that LND+RN affects cancer-specific survival and metastatic progression in specific sub-categories of patients with pT_{3c}-pT_4 RCC (HR 0.89, $p < 0.001$). Excision of each additional lymph node is associated with an approximately 10% reduction in progression-free survival and CSM. Likewise, the EORTC trial[3] subgroup analysis demonstrated that the overall survival rate of cT_3 tumors in patients treated with RN + LND increased by 15% at 5 years compared to those in RN group. In addition, the survival curves[9] showed that RN + LND group had a better survival rate in 15 years.

Table I. Clinical and pathological characteristics of the included studies.

Authors, year	Study design, level of evidence	Interven-tion	Cases, No.	Follow-up, months	Age, year, median (range)	Male/ female	Tumor size, cm	Staging tool	Pathological stage, n (%)	Tumor grade No.
Gershman et al, 2018	Retrospective comparative study, level 3	RN+RPLND	1039	240	NR	690/ 349	6.5 (4.5-9.0)	2010AJCC	pT1a: 195; pT1b: 301; pT2a: 136; pT2b: 71; pT3a: 253; pT3b: 54; pT3c: 18; pT4: 11	G1: 70; G2: 471; G3: 413; G4: 85
		RN	1398	240	NR	938/ 460	6.3 (4.3-9.0)		pT1a: 299; pT1b:401; pT2a:182; pT2b:96; pT3a: 321; pT3b: 64; pT3c: 23; pT4: 12	G1: 104; G2: 668; G3: 531; G4: 95
Blom et al, 2009	Prospective nonrando-mized study, level 3	RN+RPLND	383	216	61	208/ 159	5.5	TNM 1978	T1: 34; T2: 221; T3: 112	G0: 11; G1: 78; G2: 156; G3: 67; G4: 2; GX: 34
		RN	389	216	61	240/ 127	6		T1: 23; T2: 242; 1 T3: 10	G0: 11; G1: 98; G2: 152; G3: 49; G4: 2; GX: 37
Michael et al, 2014	Retrospective comparative study, level 3	RN+RPLND	334	60-66	59.2 (51.3, 67.4)	232/ 102	10.1 (8.5, 12.2)	2010AJCC	T2: 95; T3: 227;	NR
		RN	190	60-66	62.9 (53.7, 70.4)	127/ 63	9.2 (8.0, 10.9)		T2: 84; T3: 101; T4: 5	NR
Minervini et al, 2001	Retrospective comparative study, level 3	RN+RPLND	49	51 (45.19-112)	61.5 (28-85)	NR	NR	UICC and AJCC 1997	T1: 31; T2: 11; T3: 5; T4: 2	G1: 13; G2: 34; G3: 4
		RN	108	51 (45.19-112)	61.5 (28-85)	NR	NR		T1: 75; T2: 20l T3: 8l T4: 5	G1: 36; G2: 62; G3: 10
Alekseev et al, 2011	Retrospective comparative study, level 3	RN+RPLND	369	NR	NR	NR	6.5	NR	cT1: 41.8%; cT2: 24.4%; cT3: 33.3%; cT4: 0.5%	NR
		RN					5	NR	cT1: 64.9%; cT2: 19.5%; cT3: 15.6%; cT4: 0%	NR

Continued

Table I (Continued). Clinical and pathological characteristics of the included studies.

Authors, year	Study design, level of evidence	Interven-tion	Cases, No.	Follow-up, months	Age, year, median (range)	Male/ female	Tumor size, cm	Staging tool	Pathological stage, n (%)	Tumor grade No.
Pantuck et al, 2003	Retrospective comparative study, level 3	RN+RPLND	238	NR	NR	NR	NR	NR	T1-T4N0M0: 238	NR
		RN	257	NR	NR	NR	NR	NR	T1-T4N0M0: 257	NR
Schafhauser et al, 1999	Retrospective comparative study, level 3	RN+RPLND	531	139±63	55.5 ±10.1	NR	8.1±3.8	NR	PT1-2: 223; PT3: 297; PT4: 11	G1-2: 69%; G3: 30%
		RN	305	139±60	66.5 ±11.3	NR	7.7 ±3.6	NR	PT1-2: 156; PT3: 149; PT4: 0	G1-2: 78%; G3: 21%
Herrlinger et al, 1991	Retrospective comparative study, level 3	RN+RPLND	155	48-252	NR	NR	NR	Robson staging	T3a: 65; T3b: 90	NR
		RN	90	48-252	NR	NR	NR		T3a: 34; T3b: 56	NR
Sullivan et al, 1979	Retrospective comparative study, level 3	RN+RPLND	15	24-60	56	NR	5	Robson staging	Robson II: 15	NR
		RN	9	24-60	62		5		Robson II: 9	NR
Siminovitch et al, 1982	Retrospective comparative study, level 3	RN+RPLND	41	0-120	NR	NR	5	NR	T3a: 17; T3b: 24	NR
		RN	7						T3a: 2; T3b: 5	NR
Yamashita et al, 1989	Retrospective comparative study, level 3	RN+RPLND	13	12-240	57.3 (26-78)	NR	NR	NR	T2-T4: 13	NR
		RN	2	12-240	NR	NR	NR	NR	T2-T4: 2	NR
Golimbu et al, 1986	Retrospective comparative study, level 3	RN+RPLND	52	60-120	NR	NR	NR	Robson staging	Robson I: 21; Robson II: 6; Robson III: 25	NR
		RN	141	60-120	NR	NR	NR		Robson I: 62; Robson II: 42; Robson III: 31	NR
Marchioni et al, 2017	Retrospective comparative study, level 3	RN+RPLND	6300	39 (16-97)	60 (52-69)	NR	9.2 (7.5-11.7)	NR	PT2: 2275; PT3: 4025	G1/G2: 2046; G3/G4: 3269; GX: 985
		RN	19057	48 (20-85)	63 (54-72)	NR	8.0 (6.4-10.0)	NR	PT2: 8268; PT3: 10789	G1/G2: 8851; G3/G4: 7204; GX: 3002

RN = radical nephrectomy; LND = lymph node dissection; NR = not reported; NA = not applicable; FU = follow-up; SD = standard deviation

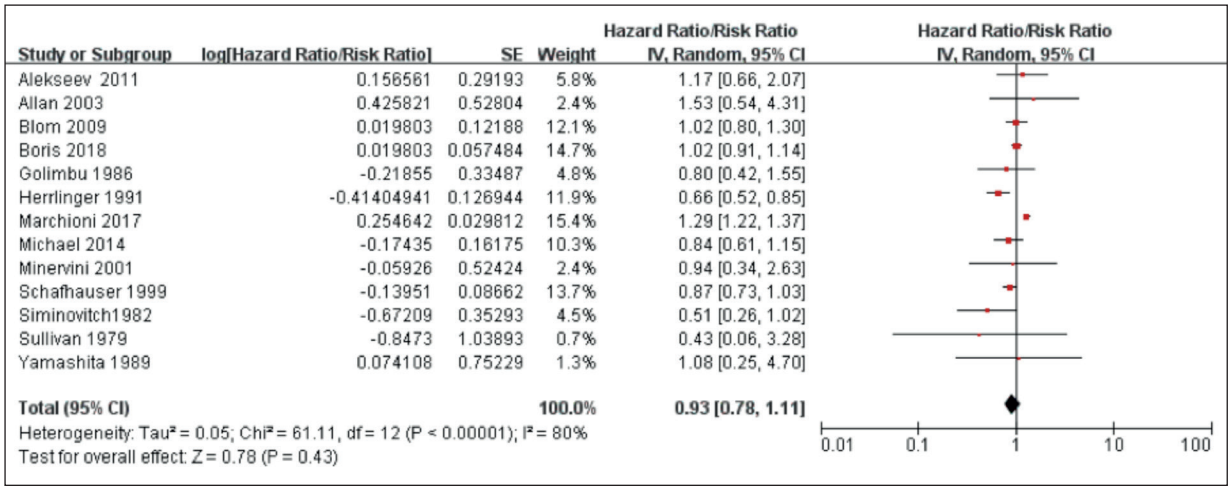

Figure 2. Forest plots of the association between the survival of non-metastatic renal cell carcinoma (cT_1-$T_4N_xM_0$) and lymph node dissection.

As we know, the advanced renal cancer patients (pT_3 or pT_4) with clinically negative nodes may have histologically diagnosed lymph node invasion (LNI). LNI was associated with ECOG PS 1 or greater cN_1 stage, increased lactate dehydrogenase, symptomatic presentation, and greater tumor size. The outcome of RCC patients with LNI is worse compared to patients without LNI. Patients with LNI shows a 7.8-fold higher risk than those without LNI[28]. Specifically, cancer-specific survival rates in patients with pN_1 RCC treated with RN+LND are 52-72%, 21-38%, and 11-29% at 1, 5, and 10 years, respectively[28,29]. Gershman et al[30] reported that the total number and density of positive lymph nodes correlated with a survival benefit. In a recent sub-analysis of patients with a low stage RCC ($cT_{1-2}N_0M_0$), LNI and/or LN progression after surgery was found in 0.6% *vs.* 1.9% *vs.* 3.9% *vs.* 9.9% cases of cT_{1a} *vs.* cT_{1b} *vs.* cT_{2a} *vs.* cT_{2b}, respectively ($p < 0.001$), suggesting that even in the low stage RCC, larger tumors are associated with increased LNI risk. Indeed, the clinical tumor size was linearly correlated with the risk of LNI and/or LN progression (odds ratio (OR): 1.27, 95%CI 1.16-1.38, $p < 0.001$). Patients with low stage (pT_{1-2}) are known to have a low incidence of positive nodes (about 4%)[3], but patients with a high stage (pT_{3-4}) RCC were twice as likely to have LNI compared to those with a low stage (pT_{1-2}) RCC ($p = 0.017$)[9]. Therefore, the risk of LNI in the locally advanced stage RCC (T_{3-4}) is higher than that at the low stage RCC (cT_{1-2}), and

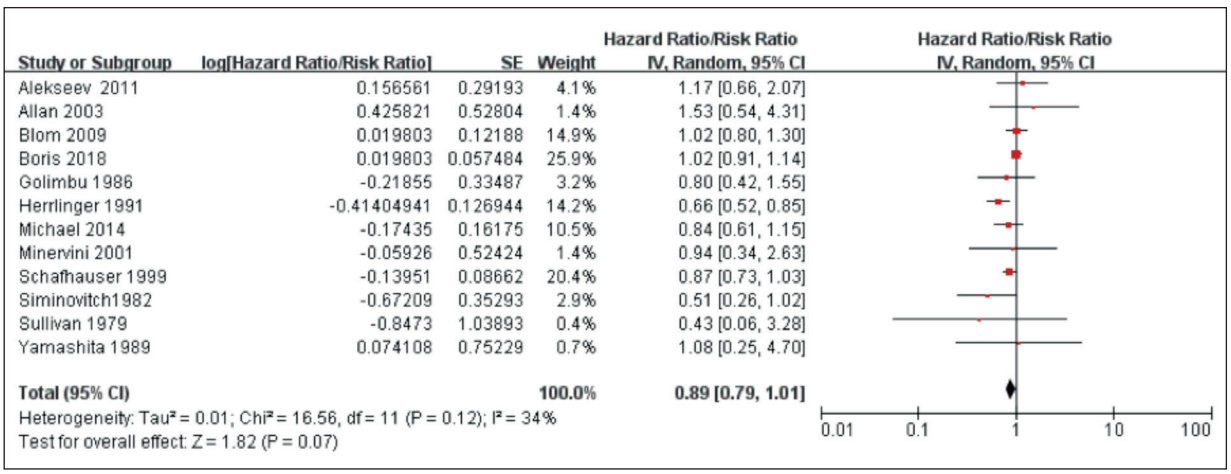

Figure 3. Forest plots of the association between the survival of non-metastatic renal cell carcinoma (cT_1-$T_4N_xM_0$) and lymph node dissection [Marchioni et al (2017) excluded].

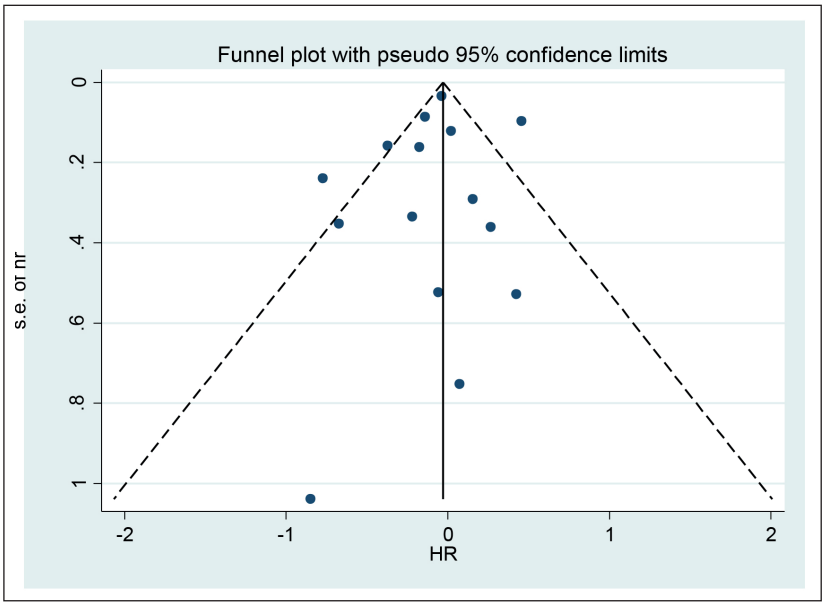

Figure 4. Funnel plots estimating publication bias from included studies (Begg's test: p=0.807).

this subgroup of patients (T_{3-4}) may benefit from LND at the time of RN. Our assumption confirmed that the removal of these LNI could reduce the residual tumor burden to such an extent that it would affect prognosis.

Therefore, there was an impending need to identify patients if they had preoperative nodal metastases for decision-making. CT or MRI were used to accurately diagnose and stage RCC preoperatively, but none of these could show good accuracy in detecting lymph node metastases[31,32], due to the presence of a non-negligible rate of false-negative cases (micrometastasis)[31]. Furthermore, the value of CT scan in determining nodal status was deemed with sensitivity and specificity values of 82% and 71%, respectively[32]. In a recent work, preoperative axial CT scans revealed at least one lymph node enlargement in 424 patients who suspected to be LNI (CN1), all lymphadenopathies were resected during the operation and only 122 patients (28.8%) were pathologically confirmed as LNI (PN1)[33]. LNI in RCC carried a poor prognosis. Therefore, several preoperative nomograms were developed to predict its occurrence and

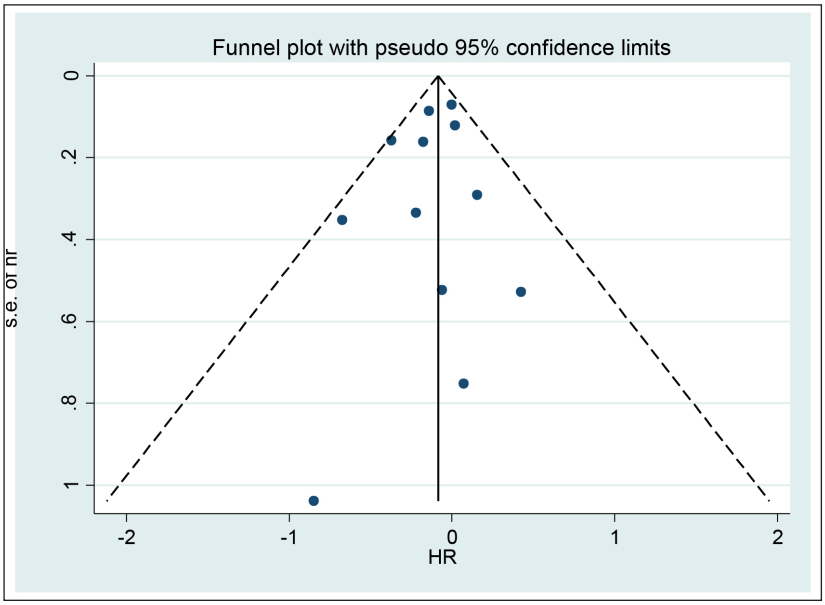

Figure 5. Funnel plots estimating publication bias from included studies [Marchioni et al (2017) excluded] (Begg's test: p=0.891).

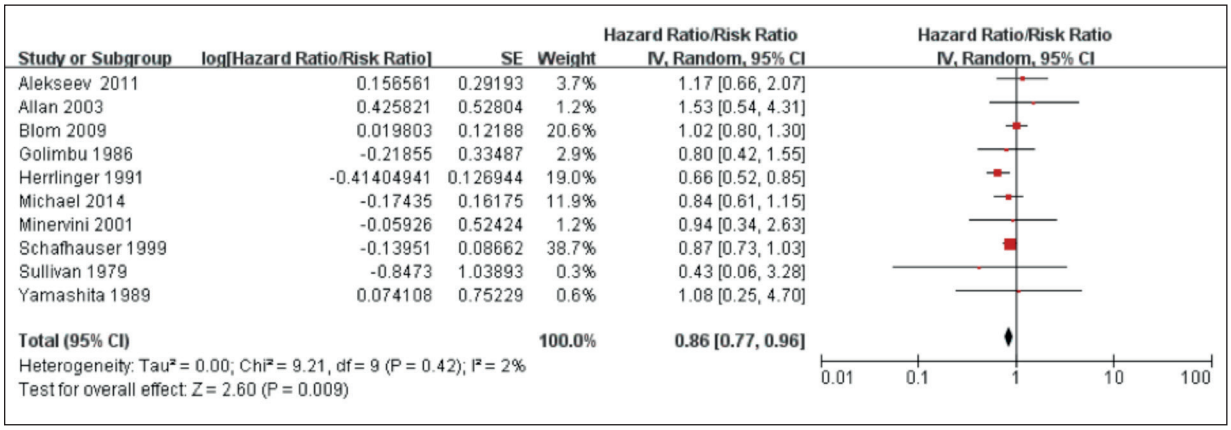

Figure 6. Forest plots of the association between the overall survival (OS) of non-metastatic renal cell carcinoma (cT1-T4NxM0) and lymph node dissection.

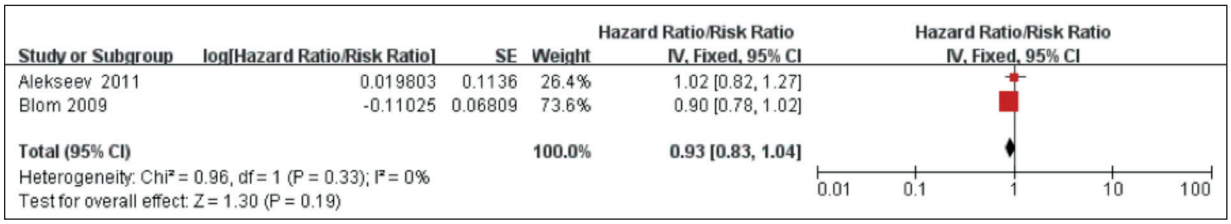

Figure 7. Forest plots of the association between the progression-free survival (PFS) of non-metastatic renal cell carcinoma (cT_1-$T_4N_xM_0$)and lymph node dissection.

identify those who benefited from LND. A preoperative nomogram developed by Capitanio et al[34] used the clinical stage and tumor size to predict lymph node involvement and claimed an accuracy of 87%, but lacked an external validation. Meanwhile, the staging role of LND might be critical for the management of RCC patients who could choose more intensive monitoring regimens and they might be the best candidates for post-operative adaptive system therapy. Capogrosso et al[35] considered that performing LND concomitantly with radical nephrectomy improved risk stratification, resulting in a small but non-negligible clinical advantage to select high-risk patients for further treatments after surgery. Indeed, clinical metastases have developed in most patients with clinically isolated pN1 disease within 12 months of surgery[30]. Marchioni et al[20] reported that the number of positive lymph nodes increased the rate of CSM in pT_3 patients. Therefore, the LND

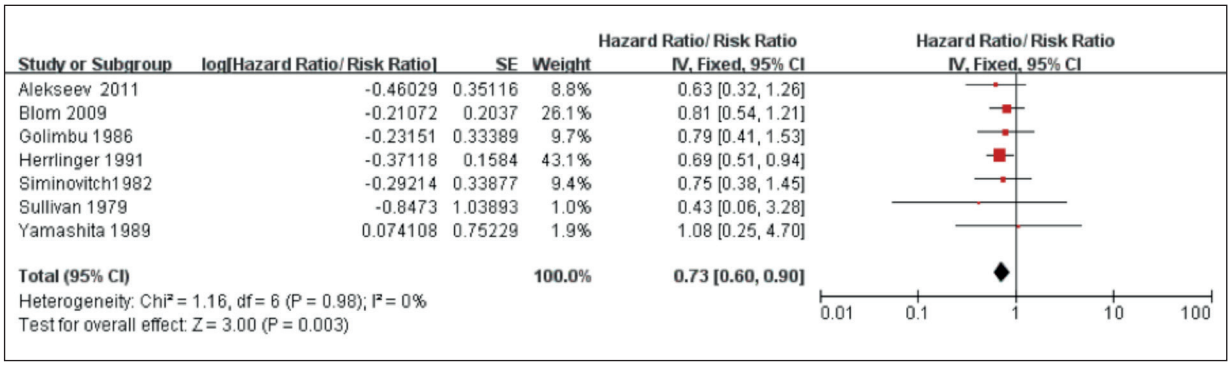

Figure 8. Forest plots of the association between the survival of locally advanced non-metastatic renal cell and lymph node dissection.

and its range could provide a prognostic impact in patients with $pT_{2-3}N_{any}M_0$. If patients had LNI status, it was easy to progress to metastatic renal cell carcinoma (MRCC), treatments were complicated, and targeted therapies such as sunitinib, everolimus could be the choice[36], but the prognosis was poor. So, the radical surgery procedure was the best way to avoid RCC progress in MRCC. John et al[37] also supported that LND concomitantly with radical nephrectomy was necessary for the high-risk cases ($\geq T_3$, size >10 cm, sarcomatoid features, etc.). Despite the lack of imaging techniques for detecting micrometastasis in clinically normal nodes, there was no doubt that lymphadenectomy could not only provide a more accurate pathological staging, but might also play a therapeutic role by removing undetectable micrometastasis.

Over the past 20 years, the importance of nephron-sparing surgery has apparently increased. Therefore, most patients included in this EORTC trial (approximately 70% were pT_1 or pT_2) may undergo partial nephrectomy today. Radical nephrectomy for patients invading the perirenal fat is still mandatory and these patients are likely to have regional lymph node metastasis. As we know, chemotherapy and radiation therapy haven't proved to be effective for locally advanced stage ($cT_{3-4}N_xM_0$) RCC. Therefore, the full pursuit of surgical therapy is recommended. Moreover, it is clear that a regional lymph node dissection for RCC is easy, doesn't prolong the operation time too much, and adds practically no morbidity, indicating that the procedure of LND is unlikely to increase the risk for the patient. Therefore, we support that LND should be performed for locally advanced patients (cT_{3-4}). This opinion is consistent with Crispen et al[38], who insisted that patients should receive LND when two or more risk factors were identified during the intraoperative pathologic assessment of the primary tumor. These factors included tumor size >10 cm, nuclear grade 3 or 4, tumor stage pT_3 or pT_4, coagulative tumor necrosis or sarcomatoid component.

Our study has some limitations. First, although meta-analysis is a powerful statistical tool, the controversy over its inherent nature has been widely recognized[39]. However, it was argued that meta-analyses should be carried out within the frame of systematic reviews to minimize biases[40], as in the case for our study. Second, we did not consider the "surgical technique" factor, such as surgical technique (open or laparoscopic), the range of LND (regional or extended). Most of the comparative studies available in our analysis have not been clearly described in the range of LND. Third, the included study came from a different region, and the time span of the study is long, the extent and degree of lymph node dissection are varying, which may impact on survival outcomes.

Conclusions

Our meta-analysis suggests that, although there was no significantly better survival rate among patients who underwent RN+LND and RN alone in patients with non-metastatic RCC ($cT_{1-4}N_xM_0$). However, in our subgroup analysis, our results showed that RN+LND added survival benefits compared to RN alone for patients with $cT_{3-4}N_xM_0$ RCC. LND should be performed in patients with $cT_{3-4}N_xM_0$ RCC at the time of radical nephrectomy. Nevertheless, our findings will be confirmed by further investigation, ideally in a prospective randomized trial.

Approval

This investigation was approved by the Ethics Committees of Panyu Central Hospital, Guangzhou, China (No.: 2018-83).

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Conflict of Interests

The Authors declared that they have no conflict of interests.

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