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Review – Kidney Cancer

Systematic Review of Adrenalectomy and Lymph Node Dissection in Locally Advanced Renal Cell Carcinoma

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Abstract

Context: Controversy remains over whether adrenalectomy and lymph node dissection (LND) should be performed concomitantly with radical nephrectomy (RN) for locally advanced renal cell carcinoma (RCC) cT3–T4N0M0.
Objective: To systematically review all relevant literature comparing oncologic, perioperative, and quality-of-life (QoL) outcomes for locally advanced RCC managed with RN with or without concomitant adrenalectomy or LND.
Evidence acquisition: Relevant databases were searched up to August 2012. Randomised controlled trials (RCTs) and comparative studies were included. Outcome measures were overall survival, QoL, and perioperative adverse effects. Risks of bias (RoB) were assessed using Cochrane RoB tools. Quality of evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation approach.
Evidence synthesis: A total of 3658 abstracts and 252 full-text articles were screened. Eight studies met the inclusion criteria: six LNDs (one RCT and five nonrandomised studies [NRSs]) and two adrenalectomies (two NRSs). RoB was high across the evidence base, and the quality of evidence from outcomes ranged from *moderate* to *very low*. Meta-analyses were not undertaken because of diverse study designs and data heterogeneity. There was no significant difference in survival between the groups, even though 5-yr overall survival appears better for the RN plus LND group compared with the no-LND group in one randomised study. There was no evidence of a difference in adverse events between the RN plus LND and no-LND groups. No studies reported QoL outcomes. There was no evidence of an oncologic difference between the RN with adrenalectomy and RN without adrenalectomy groups. No studies reported adverse events or QoL outcomes.
Conclusions: There is insufficient evidence to draw any conclusions on oncologic outcomes for patients having concomitant LND or ipsilateral adrenalectomy compared with patients having RN alone for cT3–T4N0M0 RCC. The quality of evidence is generally low and the results potentially biased. Further research in adequately powered trials is needed to answer these questions.

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1. Introduction

Locally advanced renal cell carcinoma (RCC) accounts for approximately 25% of renal tumours [1,2]. The TNM classification defines *locally advanced RCC* as a renal tumour (1) that extends into the major veins, (2) that directly invades the adrenal gland, (3) that spreads into peripelvic and perirenal fat, or (4) that invades beyond the Gerota fascia [3]. The standard treatment is surgery; however, controversy remains as to whether concomitant adrenalectomy and/or lymphadenectomy should be performed.

The incidence of invasion into the adrenal gland varies between 2% and 10% in nonmetastatic disease and is as high as 23% in metastatic disease [4–6]. Direct adrenal gland invasion is mostly seen in upper pole tumours [4,7,8]. Adrenalectomy has been recommended when preoperative imaging suggests invasion of the adrenal gland and when the tumour is located on the upper pole and >7 cm or when there is renal vein involvement at the level of the adrenal vein [4]. However, it has also been proposed that routine ipsilateral adrenalectomy does not offer any oncologic benefit [9], but that conclusion was born of a study that was based on patients with lymph node and distant metastasis and cannot therefore be generalised to patients with clinically locally advanced RCC (ie, cT3–T4N0M0). The latest European Association of Urology (EAU) guidelines [10] do not recommend adrenalectomy for localised RCC unless preoperative imaging and preoperative findings suggest renal invasion. This recommendation is based on one prospective nonrandomised study (NRS) for patients with T1–T2 tumours, in which adrenalectomy did not improve overall survival [11]. As such, the situation regarding adrenalectomy for locally advanced RCC remains unclear.

Regarding lymph node metastases, the mean incidence in all stages of RCC is 13–21%. In localised tumours, the incidence of lymph node metastases is relatively low, at 2–9%. However, for T3a tumours, this incidence increases to 46%, and it further increases to 62–66% for advanced stages [12–17]. The EAU RCC guidelines [10] recommend using lymph node dissection (LND) only for staging purposes in the management of localised RCC; this recommendation is based on the European Organisation for Research and Treatment of Cancer (EORTC) 30881 randomised controlled trial (RCT) [12], which did not show a significant improvement in overall survival for lymphadenectomy in patients undergoing radical nephrectomy (RN). However, the EORTC trial results combined all clinical stages (ie, T1–T3N0M0); this combination may mask important prognostic differences between the localised stages (T1–T2N0M0) and locally advanced stages (≥T3N0M0) [10,12]. To add to the confusion, several narrative reviews in the literature suggested that extended lymphadenectomy may be beneficial for patients with locally advanced disease and unfavourable pathologic features [18–20]. In summary, the current literature appears to present inconsistent and apparently contradictory findings. Consequently, a rigorous systematic review incorporating methods that are robust, reliable, and transparent is needed to accurately clarify the current state of the evidence base; to provide guidance on treatment decision making, if possible; to identify knowledge gaps; and to make recommendations for further research.

This systematic review focusses on the controversial issues of adrenalectomy and lymphadenectomy and whether they should be carried out concomitantly with RN in clinically locally advanced RCC (cT3–T4N0M0). A systematic review of surgical management of localised T1–T2N0M0 RCC has addressed the LND compared with no-LND question for the localised disease patient group [21]. The primary objectives of this review are (1) to assess the oncologic and quality-of-life (QoL) outcomes of RN plus LND compared with RN alone in cT3–T4N0M0 patients and (2) to assess the oncologic and QoL outcomes of RN with concomitant ipsilateral adrenalectomy compared with RN alone in cT3–T4N0M0 patients. The secondary objectives of this review are to determine the rates of perioperative adverse effects associated with concomitant lymphadenectomy and concomitant ipsilateral adrenalectomy compared with RN alone in cT3–T4N0M0 patients.

2. Evidence acquisition

2.1. Search strategy

Relevant trials were identified by searching Medline (1946 to August 2012), Medline In-Process (1946 to August 2012), Web of Science (1990 to August 2012), Embase (1974 to August 2012), and the Cochrane Controlled Trials Register (Cochrane Library 7, 2012). The reference lists of relevant articles were hand searched for other possible relevant trials. There were no language restrictions.

2.2. Inclusion and exclusion criteria

There were few restrictions on study design because of the paucity of randomised evidence and prospective nonrandomised studies (NRSs). RCTs or quasi-randomised controlled trials, prospective observational studies, and retrospective comparative studies were included. Studies with no comparator group (ie, case series) were excluded. The study population was limited to patients clinically diagnosed with locally advanced T3–T4N0M0 RCC based on computed tomography scan (with and without contrast) or magnetic resonance imaging. Included interventions and comparators are outlined in Table 1.

The principal measures of effectiveness for both questions were overall and disease-specific survival at 5 and 10 yr and disease-specific QoL. Secondary measures of effectiveness included general QoL measures, perioperative outcomes, and adverse effects.

2.2.1. Primary outcomes

Primary outcomes were overall survival (5-yr overall survival rate, 10-yr overall survival rate, 5-yr disease-specific survival rate, and 10-yr disease-specific survival rate) and QoL (disease-specific measures of QoL).

2.2.2. Secondary outcomes

Secondary outcomes were cancer outcome measures (incidence of/time to local recurrence and incidence of/time

Table 1 – Interventions and comparators included

Intervention (experimental)	Comparator (control)
Radical nephrectomy with extended lymphadenectomy, which involves radical nephrectomy with removal of all lymph nodes from the crus of the diaphragm inferiorly to the bifurcation of the aorta or the vena cava	Radical nephrectomy, which encompasses the basic principles of early ligation of the renal artery, removal of the kidney outside the Gerota fascia, and excision of the ipsilateral adrenal gland
Radical nephrectomy with regional/hilar lymphadenectomy, which involves radical nephrectomy with a lymph node dissection limited to the anterior, posterior, and lateral sides of the ipsilateral great vessel (aorta or inferior vena cava) from the cephalad margin of the renal pedicle to the inferior mesenteric artery	
Radical nephrectomy with removal of the ipsilateral adrenal gland	Radical nephrectomy without adrenalectomy

to distant metastasis), immediate and early surgical outcomes (operative complications, length of operation, duration of hospital admission, need for reoperation, postoperative morbidity [30 d, 90 d], and postoperative mortality [30 d, 90 d]), and QoL (general measures of health status [eg, SF-36v2]).

2.3. Assessment of risks of bias

The Cochrane risks-of-bias (RoB) assessment tool was used to assess individual RCTs [22] (see Appendix 1). Two reviewers independently evaluated 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. Any disagreement was resolved by discussion or reference to a third reviewer.

A modified version of the Cochrane tool was used to assess NRSs, with the addition of further items to assess RoB through confounders [23].

A list of the five most important potential confounders (prognostic factors) for oncologic outcomes and the eight most important potential confounders for perioperative outcomes identified in consultation with content experts is given in Table 2. Each of the prespecified confounders in the list was assessed using a 5-point scale (explained in Table 3) on the following four criteria: whether the confounder was considered by the researchers (yes or no), the precision with which the confounder was measured, the imbalance between groups, and the care with which adjustment for confounder was carried out.

Table 2 – Important prognostic confounders considered in risk-of-bias assessment in nonrandomised studies

Oncologic confounders	Perioperative confounders
Tumour stage	Comorbidity
Tumour grade (Fuhrman)	Performance status
Tumour size	Age
Histologic cell type	Sex
Necrosis	Smoking
	Obesity
	Hypertension
	Ethnicity

The rationale behind assessing these confounders is that they are indicators of how well or poorly balanced the study groups were on important prognostic confounders. Our processes and guidance for these tools are described in depth elsewhere [21,24]. The scores for assessment of adjustment only are shown below the baseline characteristics for each NRS, because the adjustment score informs most about the RoB [23–26].

2.4. Assessment of the quality of evidence

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to score patient-important outcomes across studies [27,28]. The seven GRADE outcomes chosen in consultation with content experts were *Critical* (overall survival rate at 5 yr, cancer-specific survival at 5 yr, condition-specific QoL, incidence of local recurrence and progression, and morbidity rates) and *Important* (analgesic requirement and need for blood transfusion).

2.5. Data analysis

We wrote to the authors to obtain data from the one RCT [12]. For this RCT subgroup data, we used descriptive statistics to summarise baseline data (Table 3 and 4) and to tabulate adverse events and pathologic node status in each group. For overall survival, Kaplan-Meier survival curves were compared using the log-rank test.

Numerator and denominator information was often not reported in the included NRSs when reporting survival. Therefore, to summarise 5- and 10-yr overall and cancer-specific survival, as well as disease-free survival, we report percentages at specific time points, where available. Subgroup analyses were planned for separate T stages, histologic grade, nuclear grade, and performance status, but these analyses were not possible because of the lack of data. A quantitative synthesis (meta-analysis) was also planned, but there was only one RCT, and combining randomised and nonrandomised data was considered inappropriate in this instance. Instead, a narrative data synthesis is provided [29], whereby the findings of individual studies are tabulated to facilitate qualitative assessment of potential heterogeneity across studies.

3. Evidence synthesis

3.1. Characteristics of included studies

The study selection process is outlined in the Preferred Reporting Items for Systematic Reviews and Meta-analyses diagram in Figure 1. The search returned 3658 abstracts. A total of 252 full-text articles were screened. Eight studies met the inclusion criteria—six concerning LND (one RCT and

Table 3 – Baseline characteristics for radical nephrectomy with lymph node dissection (various extent) compared with radical nephrectomy alone with risk-of-bias assessment for adjustment in nonrandomised studies

Study	Intervention	No.	FU (overall), mo, range	Age, yr, median (range)	Male/ female, no	Tumour size, cm	Stage	Staging tool	Histologic cell type, no.	WHO performance status, no.	Tumour grade, no.	Necrosis	CT, yes/no
Blom et al. [12]; RCT subgroup (cT3) from individual patient data	RN + eLND	110	median: 151.2 (max = 206.4)	63 (27–83)	68/42	Median: 8	All T3	TNM 1978	Clear: 67 Granular: 10 Spindle: 1 Oncocytic: 2 Mixed: 23	0: 93 1: 15 2–4: 2	G0: 3 G1: 19 G2: 53 G3: 23 G4: 2 Gx: 1	NR	All cases
	RN	101		63 (27–86)	66/34	Median: 7	All T3	TNM 1978	Clear: 61 Granular: 7 Spindle: 2 Oncocytic: 5 Mixed: 13	0: 81 1: 14 2–4: 5	G0: 2 G1: 24 G2: 41 G3: 19 G4: 1 Gx: 2	NR	All cases
Yamashita et al. [30]; retrospective comparative	RN + eLND	13	12–240	57.3 (26–78)	38/17	NR	T2–T4 overall	Unclear	NR	NR	Reported overall but not by T stage	NR	NR
	RN	2				NR		Unclear	NR	NR		NR	NR
Adjustment	NA	NA	NA	5	NA	5	5	NA	5	5	5	5	NA
Herrlinger et al. [31]; prospective comparative, published subgroup	RN + eLND	155	48–252	NR	NR	NR	T3a: 65 (41.9%) T3b: 90 (58.1%) analysed separately	Robson staging; TNM unclear T3a: infiltration into perirenal fat T3b: renal vein invasion	NR	NR	NR	NR	NR
	RN	90		NR	NR	NR	T3a: 34 (37.7%) T3b: 56 (62.3%)	Robson staging; TNM unclear T3a: infiltration into perirenal fat T3b: renal vein invasion	NR	NR	NR	NR	NR
Adjustment	NA	NA	NA	5	NA	5	1	NA	5	5	5	5	NA
Sullivan et al. [32]; retrospective comparative	RN + rLND	15	24–60	Mean: 56	5/2	NR	Robson II	Robson staging	NR	NR	NR	NR	Only most recent cases
	RN	9		Mean: 62		NR	Robson II	Robson staging	NR	NR	NR	NR	
Adjustment	NA	NA	NA	1	NA	5	1	NA	5	5	5	5	NA
Siminovitch et al. [33]: retrospective comparative	RN + eLND	11	0–120	NR	NR	NR	T3a: 5 (45.5%) T3b: 6 (54.5%)	NR	NR	NR	NR	NR	Selected cases
	RN + rLND	30		NR	NR	NR	T3a: 12 (40%) T3b: 18 (60%)	NR	NR	NR	NR	NR	
	RN	5		NR	NR	NR	T3a: 2 (40%) T3b: 3 (60%)	NR	NR	NR	NR	NR	
Adjustment	NA	NA	NA	5	NA	5	1	NA	5	5	5	5	NA
Peters and Brown [34]; retrospective comparative	RN + eLND	69 overall	60–180	NR	NR	NR	All stage B	Robson staging	NR	NR	NR	NR	NR
	RN			NR	NR	NR	All stage B	Robson staging	NR	NR	NR	NR	NR
Adjustment	NA	NA	NA	5	NA	5	1	NA	5	5	5	5	NA

RN = radical nephrectomy; eLND = extended lymph node dissection; rLND = regional lymph node dissection; NR = not reported; NA = not applicable; FU = follow-up; SD = standard deviation; WHO = World Health Organisation; CT = computed tomography; RCT = randomised controlled trial; max = maximum.
For adjustment scores, 1 = adjustment done at the design stage or preplanned, or no adjustment needed because of no significant imbalance; 2 = adjustment done on the basis of data (ie, post hoc); 5 = adjustment not done when needed or unclear.

Table 4 – Baseline characteristics for radical nephrectomy with ipsilateral adrenalectomy compared with radical nephrectomy alone with risk-of-bias assessment in nonrandomised studies

Study	Intervention	No.	FU, mo, mean	Age, yr, mean (range)	Male/ female, no.	Tumour size, cm, mean (range)	Stage	Staging tool	Histologic cell type	Performance status	Tumour grade	Necrosis	CT, yes/no
Scattoni et al. [35]: retrospective comparative (data from T3aN0M0 subgroup)	RN + adr	15	41.2	NR	NR	NR	pT3a	NR	NR	NR	NR	NR	Yes
	RN	12	43.3	NR	NR	NR	pT3a	NR	NR	NR	NR	NR	Yes
Adjustment	NA	NA	NA	5	NA	5	1	NA	5	5	5	5	NA
Xu et al. [36]: retrospective comparative (data from T3abN0M0 subgroup)	RN + adr	17	36 minimum	55 (15–76)	59/23	7 (1.5–19) total population 7.7 (1.8–17.5) total population	T3abN0M0	TNM 4, 1987	NR	NR	NR	NR	NR
	RN	28	overall	50 (13–73)	62/34		T3abN0M0	TNM 4, 1987	NR	NR	NR	NR	NR
Adjustment	NA	NA	NA	1	NA	1	1	NA	5	5	5	5	NA

FU = follow-up; SD = standard deviation; CT = computed tomography; RN = radical nephrectomy; adr = adrenalectomy; NR = not reported; NA = not applicable.
For adjustment scores, 1 = adjustment done at the design stage or preplanned, or no adjustment needed because of no significant imbalance; 2 = adjustment done on the basis of data (ie, post hoc); 5 = adjustment not done when needed or unclear.

five NRSs) [12,30–34] and two concerning adrenalectomy—both nonrandomised [35,36]. The baseline characteristics and confounder scores can be viewed in Table 3 and 4.

3.2. Risks-of-bias assessment

Most of the included studies were assessed as having high RoB (Appendix 1). Only one of the seven studies (the RCT) had adequate sequence generation and allocation concealment. It was unclear if any of the studies used blinding for any patients or personnel, but it is unlikely, as most of the studies are retrospective. It was unclear if there was selective outcome reporting in most studies. It was unclear if any studies, other than the one RCT, had a priori protocols or analysis plans.

The included studies did not consistently report data for the known oncologic and perioperative confounders (Table 3 and 4). This situation introduces further RoB and uncertainty when interpreting results.

3.3. Results

3.3.1. *Does radical nephrectomy with extended lymph node dissection result in better oncologic outcomes compared with radical nephrectomy alone?*

One RCT [12] (once subgroup analysis had been performed on trial data), one prospective cohort study [31], and four retrospective comparative studies [30,32–34] met inclusion criteria. Figure 2 shows Kaplan-Meier survival curves (death from any cause) for RN plus LND compared with RN alone in the cT3N0M0 population from the trial of Blom et al. [12]. This was an intention-to-treat analysis.

There was no significant difference in survival between the RN with LND and RN-alone groups (hazard ratio: 0.81; 95% confidence interval, 0.54–1.20; p = 0.29) (Table 5). However, overall survival at 5 yr appears better for the RN plus LND group compared with the no-LND group by approximately 15%, although the difference is not statistically significant. In addition, the trend of the survival curves suggests better overall survival for the RN with LND group across the 15-yr time period. The curves in Figure 2 overlap at approximately 15 yr, but it is important to note that very few patients survive to this time point. This trend is potentially clinically important, as the lack of statistical significance may simply be a reflection of the trial not being powered to address this question in this subgroup of locally advanced patients. Two possible explanations for this finding are offered in the Discussion. It is interesting to note that an analysis of overall survival between RN plus LND and RN alone for T1 and T2 patients only in the same trial did not reveal any appreciable difference between the two groups [21].

The studies by Herrlinger et al. [31] and Siminovitch et al. [33] show improvement in overall survival in favour of RN plus LND compared with RN alone, and the study by Peters and Brown [34] shows no evidence of a difference; in contrast, Yamashita et al. show better 5-yr overall survival for the RN arm compared with the RN plus LND arm [30]. However, the sample sizes in all these studies were very

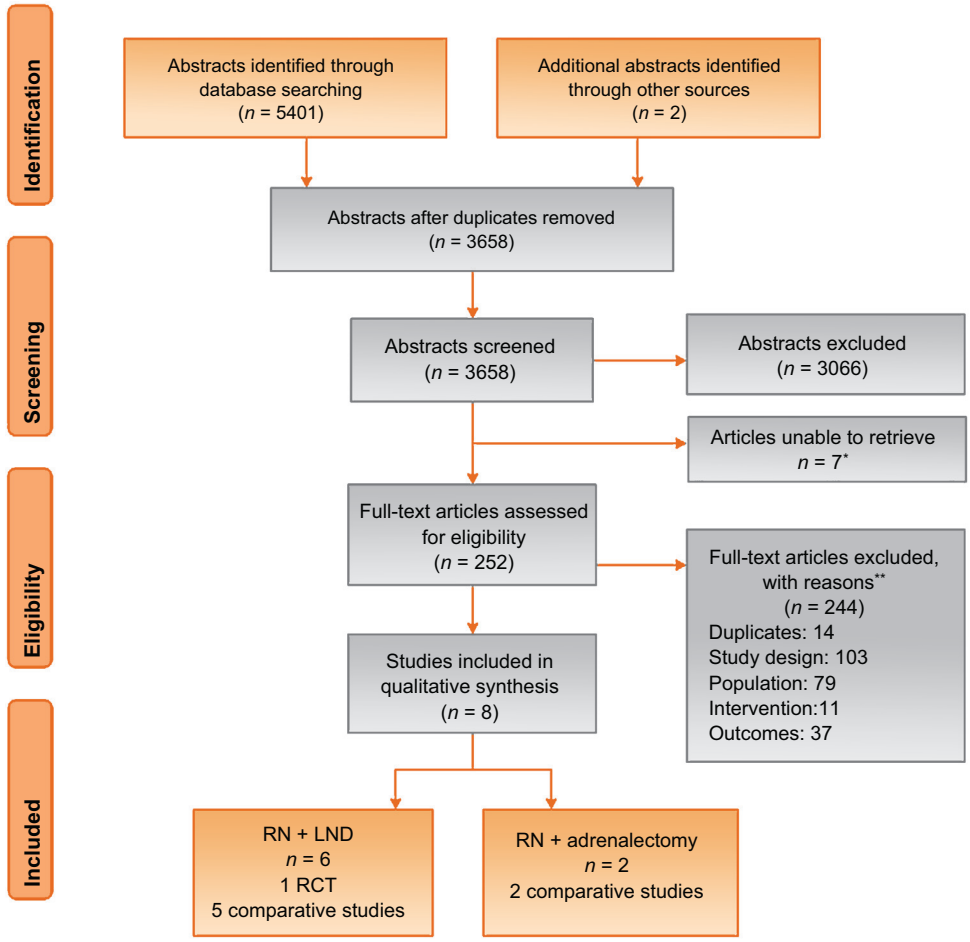

Fig. 1 – Preferred Reporting Items for Systematic Reviews and Meta-analyses flow diagram for locally advanced renal cell carcinoma [52]. *Population* includes nodal or distant metastases, genetic disorders. *Intervention* includes additional treatments such as chemotherapy, radiotherapy, or angiogenesis inhibitors. *Outcomes:* no relevant outcomes reported or not stratified by subgroup. RN = radical nephrectomy; LND = lymph node dissection; RCT = randomised controlled trial.
* Not available at British libraries.
** Study design: meeting abstracts, reviews, editorials, and commentaries.

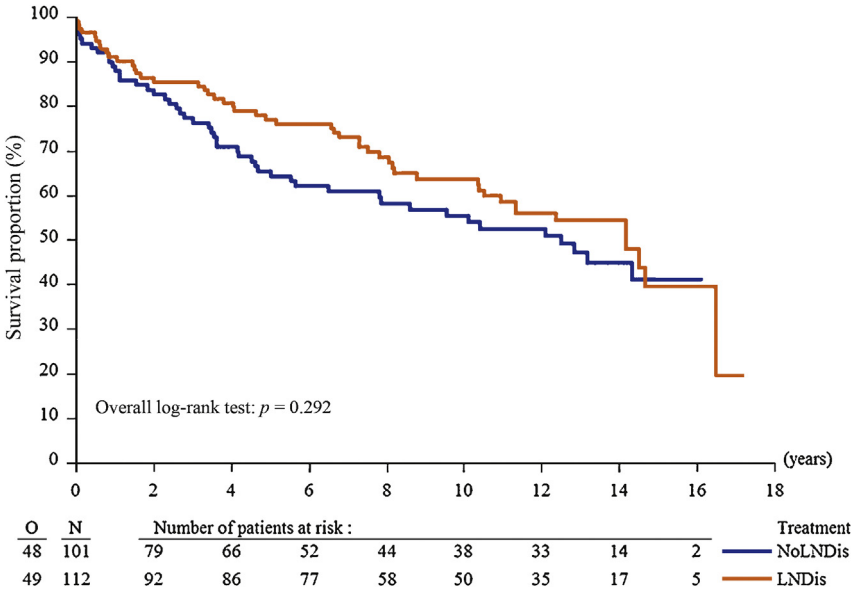

Fig. 2 – Overall survival (in years) for cT3 with and without lymph node dissection (subgroup analysis of Blom et al. [12]). NoLNDis = radical nephrectomy without lymph node dissection; LNDis = radical nephrectomy with lymph node dissection; O = observed events; N = number at baseline.

Table 5 – Perioperative complications by intervention for cT3 subgroup from EORTC trial 30881

Outcome	RN + LND, no. (%)	RN, no. (%)	Total, no. (%)
Bleeding >1 l	18 (16.1)	14 (13.9)	32 (15.1)
Pleural damage	6 (5.4)	7 (7)	13 (6.2)
Infection	8 (7.9)	6 (5.4)	14 (6.6)
Bowel damage	0	3 (3)	3 (1.4)
Embolism	3 (2.7)	3 (3)	6 (2.8)
Drainage of lymph fluid	3 (2.7)	3 (3)	6 (2.8)
Total	110	101	211

RN = radical nephrectomy; LND = lymph node dissection.

small, and none of the studies adjusted appropriately for important prognostic covariates. Any findings should be interpreted with caution (Table 6).

3.3.2. Does radical nephrectomy with extended lymph node dissection result in worse perioperative and quality-of-life outcomes than radical nephrectomy alone?

Perioperative data were generally poorly reported, with the exception of the RCT of Blom et al. [12]. None of the NRSs reported any perioperative data, and no study reported QoL data. The data from EORTC trial 30881 (reported by Blom et al. [12]) were obtained, and subgroup analyses for only the cT3 group were run. Event rates were generally low, and there were no marked differences between the groups (Table 5).

When considering the level of evidence for RN with extended LND compared with RN alone, only two of the prespecified critically important outcomes were addressed (both in one RCT). This situation offers a moderate quality of evidence for the reported outcomes (Table 7).

3.3.3. Does radical nephrectomy with regional lymph node dissection result in better oncologic outcomes than radical nephrectomy alone?

Siminovitch et al. [33] and Sullivan et al. [32] showed 5-yr overall survival results that favour RN and regional LND compared with RN alone (Table 6). However, these studies were inadequately powered to detect clinically meaningful differences and did not control for known prognostic confounders (Table 3), so the results should be interpreted with caution. No perioperative or QoL outcomes were reported for this comparison. The assessment of the quality of evidence (Table 7) shows that only two of the prespecified critical outcomes were reported, by two studies for overall survival at 5 yr and one study for cancer-specific survival at 5 yr, and the quality of evidence is very low.

3.3.4. Does radical nephrectomy with ipsilateral adrenalectomy result in better oncologic outcomes than radical nephrectomy alone?

Two retrospective studies compared patients who had RN with patients who had RN with ipsilateral adrenalectomy [35,36] (see Table 4 for baseline characteristics and adjustment scores). The studies by Scattoni et al. [35] and Xu et al. [36] are hampered by small sample sizes, wide confidence intervals, and short follow-up (Table 8), and therefore no conclusions can be drawn.

There were no perioperative or QoL outcomes reported in these studies. The assessment of the quality of evidence

Table 6 – Oncologic outcomes for radical nephrectomy with extended lymph node dissection compared with radical nephrectomy alone and radical nephrectomy with regional lymph node dissection compared with radical nephrectomy alone

Study	Outcome	No. at baseline		Value		Reported *p* value	Note
		RN + eLND	RN	RN + eLND	RN		
Blom et al. [12]	Overall survival	110	101	HR: 0.81 (95% CI, 0.54–1.20)		0.29	Subgroup analysis of RCT data
Herrlinger et al. [31] T3aN0M0	5-yr overall survival	65	34	76%	54.5%	NR	Proportions from published KM curve
Herrlinger et al. [31] T3bN0M0	5-yr overall survival	90	56	60%	50%	NR	Proportions from published KM curve, numerator not reported
Peters and Brown [34]	5-yr overall survival	69		42.3%	40.4%	NR	Baseline number not reported separately
Yamashita et al. [30]	5-yr overall survival	13	2	46%	50%	NR	Proportions from published KM curve, numerator not reported
Siminovitch et al. [33]	5-yr overall survival	11	5	4/8 (50%)	1/4 (25%)	NR	Denominator derived from number at risk at 5 yr
Herrlinger et al. [31] T3aN0M0	10-yr overall survival	65	34	58.2%	41.2%	$p<0.01$	Proportions from published KM curve
Herrlinger et al. [31] T3bN0M0	10-yr overall survival	90	56	48.4%	34.4%	NS	Proportions from published KM curve
		RN + rLND	RN	RN + rLND	RN		
Siminovitch et al. [33]	5-yr overall survival	30	5	7/17 (41.2%)	1/4 (25%)	NR	Denominator derived from number at risk at 5 yr
Sullivan et al. [32]	5-yr overall survival	15	9	6/7 (85.7%)	6/9 (66.7%)	NR	Denominator derived from number at risk at 5 yr
Sullivan et al. [32]	10-yr overall survival	15	9	2/6 (33.3%)	3/8 (37.5%)	NR	Denominator derived from number at risk at 10 yr

NR = not reported; RN = radical nephrectomy; eLND = extended lymph node dissection; rLND = regional lymph node dissection; HR = hazard ratio; CI = confidence interval; NS = not significant; RCT = randomised controlled trial; KM = Kaplan-Meier.

Table 7 – Summary of the quality-of-evidence assessment

GRADE outcomes	RN + eLND vs RN		RN + rLND vs RN		RN + adr vs RN	
	Studies reporting outcome, no.	Quality of evidence (GRADE)	Studies reporting outcome, no.	Quality of evidence (GRADE)	Studies reporting outcome, no.	Quality of evidence (GRADE)
Overall survival at 5 yr	1 RCT	Moderate	2 NRSs	Very low	0	NA
Cancer-specific survival at 5 yr	0	NA	1 NRS	Very low	1 NRS	Very low
Condition-specific quality of life	0	NA	0	NA	0	NA
Incidence of local recurrence	0	NA	0	NA	0	NA
Overall morbidity rates	1 RCT	Moderate	0	NA	0	NA
Analgesic requirement	0	NA	0	NA	0	NA
Need for blood transfusion	0	NA	0	NA	0	NA

RCT = randomised controlled trial; NRS = nonrandomised study; RN = radical nephrectomy; eLND = extended lymph node dissection; rLND = regional lymph node dissection; adr = adrenalectomy; NA = not applicable; GRADE = Grading of Recommendations Assessment, Development and Evaluation.

Table 8 – Oncologic outcomes for radical nephrectomy with adrenalectomy compared with radical nephrectomy alone

Study	Outcome	Baseline no.		Number (%)		Reported *p* value	Note
		RN + adr	RN	RN + adr	RN		
Scattoni et al. [35] T3aN0M0	Disease-free survival	15	12	14 (93%)	9 (78%)	NR	At a mean follow-up of 41.2 mo (range: 3–74) in the RN + adr arm and 43.3 mo (range: 2–90) in the RN arm
Xu et al. [36]	5-yr cancer-specific survival	17	28	52.9%	56.4%	≥0.9	Proportions from published life-tables, numerator not reported, *p* from log-rank test
Xu et al. [36]	10-yr cancer-specific survival	17	28	52.9%	25%	≥0.9	Proportions from published life-tables, numerator not reported, *p* from log-rank test

RN = radical nephrectomy; adr = adrenalectomy; NR = not reported.

(Table 7) shows that only one of the prespecified critical outcomes was reported: cancer-specific survival at 5 yr, with only one NRS reporting this outcome. The quality of evidence is very low.

3.4. Discussion

3.4.1. Principal findings

The data regarding whether ipsilateral adrenalectomy at the time of RN improves oncologic outcomes or worsens perioperative outcomes are inconclusive. The included studies all have high RoB, particularly selection bias, and small sample sizes and short follow-up. More high-quality evidence is needed to state a recommendation about the place of adrenalectomy in addition to RN in the treatment of cT3–T4N0M0 RCC.

Outside clinical trials, there is no adjuvant treatment at present for locally advanced RCC. There is uncertainty over whether extended or regional LND at the time of RN improves oncologic outcomes. There was only one randomised trial [12], and it was not powered to detect a difference in the locally advanced (cT3N0M0) subgroup.

A possible difference in survival with LND at the time of RN was noted based on visual inspection of the survival curves of Blom et al. [12]. This observed difference in overall survival is not simply because of chance; the difference may have two possible explanations.

First, the apparent advantage of performing LND may be because of the therapeutic benefit of removing cancerous lymph nodes. A recent single-centre institutional database study noted therapeutic effects in removing pathologically positive nodes [37]. However, the data from the trial by Blom et al. [12] showed that of all the patients with cT3 disease who were randomised to RN plus LND, only 6.3% had pathologically confirmed nodal disease (Table 9) [12]. This finding indicates a relatively low prevalence of lymph node involvement in patients with T3 disease, which may suggest that the survival benefit is unlikely to be because of the therapeutic effect of removing cancerous lymph nodes in these clinically node-negative patients.

An alternative explanation for the possible survival benefit is the prophylactic effect of LND, whereby the removal of disease-free lymph nodes may prevent the

Table 9 – Pathologic node status by intervention in cT3 subgroup from EORTC trial 30881

	RN, no. (%)	RN + LND, no. (%)	Total, no. (%)
pN0	74 (73.2)	99 (88.3)	173 (81.2)
pN+	3 (2.9)	7 (6.3)	10 (4.7)
Unknown	24 (23.8)	6 (5.4)	30 (14.1)
Total	101 (100)	112 (100)	213 (100)

RN = radical nephrectomy; LND = lymph node dissection.

subsequent spread of the disease by removing the means of cancer spread through the lymphatic channels. A recent single-institution database study found that on multivariate analysis controlling for lymph node status, Fuhrman grade, age, symptoms at presentation, metastases at diagnosis, Eastern Cooperative Oncology Group performance status, tumour size, and presence of necrosis or sarcomatiod features, an extended LND significantly decreased cancer-specific mortality in pT4 cases [38]. Other nonsystematic review findings also suggest that despite the present lack of imaging techniques to detect micrometastases in clinically normal nodes, LND may have a protective effect in clinically node-negative patients with locally advanced tumours [18]. There is precedence for this phenomenon in other urologic cancer operations, such as extended lymphadenectomy during radical cystectomy for bladder cancer [39]. If this were the case, we would expect a high proportion of deaths in the RN-alone group to have been attributable to lymph node disease. However, a determination of death attributable to nodal disease is not available in the trial of Blom et al. [12], nor is the trial adequately powered to address this question.

The available evidence does not suggest that LND has a higher complication rate than no LND, so the issue of complication should not be used as a contraindication for performing LND. However, these findings need to be interpreted with caution, because the extent of LND was heterogeneous in the study by Blom et al. [12] because of the lack of standardisation of technique. It is possible that those patients who received the most extensive LND had greater morbidity, but this effect would be less marked when averaged estimates are provided for the entire cohort. There were no data on long-term sequelae and no studies reporting QoL data, which are important for patient decision making.

The five nonrandomised studies included did not reduce uncertainty because by design, they suffer from selection bias. Important prognostic covariates were not reported, and the studies had small sample sizes and short follow-up. There was also insufficient evidence to draw any conclusion on whether the extent of LND (extended compared with regional) worsens or improves oncologic outcomes or worsens perioperative outcomes.

3.4.2. How do these findings compare with other systematic reviews?

The current American Urological Association (AUA) [40] and EAU [10] RCC guidelines provide reference points for the management of RCC. The EAU guidelines recommend LND for staging purposes only for localised RCC but do not make any reference to LND or adrenalectomy for locally advanced disease. The AUA RCC guidelines do not mention LND or adrenalectomy procedures in the context of the locally advanced population.

The cancer-specific survival rate varies greatly among stages, with a cancer-specific survival of 66–96% for T1–T2 RCC and 12–36% for T3–T4 RCC [41]. These proportions suggest that a different approach to treatment could benefit patients with clinically locally advanced tumours, which is a position supported by findings from the narrative review by Capitanio et al. [18]. These authors note that patients with locally advanced RCC and/or unfavourable clinical and pathologic characteristics (high Fuhrman grade, large tumour, presence of sarcomatoid features, and/or coagulative tumour necrosis) could benefit from extended LND.

This review focussed on locally advanced RCC, in which there is a clinical uncertainty about whether concomitant ipsilateral adrenalectomy at the time of RN improves survival in patients without clinical suspicion or radiologic evidence of adrenal invasion. There is insufficient evidence to draw any conclusions about routine adrenalectomy for cT3–T4N0M0 RCC without direct invasion of the adrenal gland. Radical nephrectomy with adrenalectomy may also be performed in large upper pole T2 tumours >7 cm [42–45]; however, the prognostic differences between cT1–T2N0M0 and cT3–T4N0M0 would have increased uncertainty through confounding bias, and therefore this patient population was excluded from this systematic review. The meta-analysis of O'Malley et al. [4] found that advanced tumour stage increases the risk of ipsilateral adrenal involvement. However, performing RN with concomitant adrenalectomy did not improve cancer-specific survival. Likewise, the meta-analysis of Su et al. [46] found no significant difference in overall survival for RN with concomitant adrenalectomy compared with RN alone. These numbers, however, are not stratified for tumour stage. They suggest that RN with adrenalectomy should be performed only when preoperative imaging suggests adrenal invasion.

3.4.3. Strengths and limitations

Very little high-quality evidence is available to address the questions of whether ipsilateral adrenalectomy and extended or regional LND should be performed at the time of RN. The state of the evidence is reflected in the *moderate* (for the RCT data only) and *very low* quality of evidence in the GRADE profiles. A reliance on NRSs was undesirable, yet unavoidable. This review used a methodologically rigorous system of assessing RoB in NRSs [23]. An important finding was that the prognostically important covariates that were prespecified as confounders (for this systematic review), and that are likely to introduce bias in estimates, were generally not controlled for in analyses. The benefit of having undertaken the review in this manner is that it is transparent and emphasises caution in interpreting the evidence.

This review highlights the lack of QoL outcomes in the evidence base, and these outcomes are important for patient decision making in locally advanced disease. In addition, it was not possible to perform meta-analyses for any outcomes of interest because of insufficient data and inconsistencies in outcome definition, measurement, and reporting. Initiatives that should guide research in LND and adrenalectomy for locally advanced renal cancer include using systematic approaches to assessing complex surgical procedures, such as the IDEAL model (Idea, Development, Exploration, Assessment and Long-Term Follow-up) [23,47], and addressing which outcomes are the most important for all stakeholders and should be reported in effectiveness trials, such as the Core Outcome Measures in Effectiveness Trials (COMET) initiative [23,47–50].

4. Conclusions

Despite the argument for a possible prophylactic effect in performing LND in locally advanced RCC, there is no robust evidence to suggest superior oncologic outcomes or worse perioperative outcomes for patients who had LND at the time of nephrectomy compared with patients who had nephrectomy alone for cT3–T4N0M0 RCC. Similarly, there are insufficient data to draw any conclusions about superior oncologic outcomes or worse perioperative outcomes for patients who had ipsilateral adrenalectomy at the time of nephrectomy compared with patients who had nephrectomy alone. The quality of evidence is generally low and the results biased and uncertain. Important prognostic variables are rarely reported, and outcomes are reported and measured in heterogeneous ways; these characteristics limit interpretation and applicability. Further research, preferably in the form of randomised and adequately powered trials, must be undertaken to address the issues of whether LND or adrenalectomy should be performed concurrently with RN in locally advanced RCC patients.

High-quality randomised and adequately powered research is needed to answer the research questions posed in this systematic review. Particular attention is needed regarding standardising outcomes and measurements. IDEAL and COMET are examples of initiatives that can help raise the quality of evidence and decrease uncertainty, and the principles they outline should be borne in mind for the future study of the research questions that could not be satisfactorily answered in this systematic review. If the opportunities to share information such as resource-intensive systematic reviews are capitalised on, there is a distinct advantage for international and national guideline–making bodies to use these robust reviews and tailor the findings to their specific health care environments [51].

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Appendix 1. – Assessment of risk of bias (part I) according to a recommended tool for randomized controlled trials by the *Cochrane Handbook for Systematic Reviews of Interventions* [22]

Study	Randomised?	Adequate sequence generation?	Allocation concealment?	Blinding?	Incomplete outcome data addressed ?	Free of selective outcome reporting?	Free of other bias?
Blom et al. [12]	Yes	Yes	Yes	No	Yes	Yes	No (nonstandardised surgical procedure)
Herrlinger et al. [31]	No	No	No	No	No	Unclear	Unclear
Peters and Brown [34]	No	No	No	No	No	Unclear	Unclear
Scattoni et al. [35]	No	No	No	No	Unclear	No	No (early stopping)
Siminovitch et al. [33]	No	No	No	No	Unclear	Unclear	Unclear
Sullivan et al. [32]	No	No	No	No	No	Unclear	Unclear
Xu et al. [36]	No	No	No	No	No	Unclear	Unclear
Yamashita et al. [30]	No	No	No	No	Unclear	Unclear	Unclear

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