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Systematic review of oncological outcomes following surgical management of localised renal cancer

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ABSTRACT

Context: Renal cell carcinoma (RCC) accounts for 2-3% of adult malignancies. There remain uncertainties over the oncological outcomes for the surgical management of localised RCC. **Objective**: To systematically review relevant literature comparing oncological outcomes of surgical management of localised RCC (T1-2N0M0). **Evidence Acquisition**: Relevant databases including MEDLINE, Embase and the Cochrane Library were searched up to October 2010, and an updated scoping search was performed up to January 2012. Randomised or quasi-randomised controlled trials (RCTs), prospective observational studies with controls, retrospective matched-pair studies, and comparative studies from well defined registries/databases were included. The main outcomes were overall survival, cancer-specific survival, recurrence and metastases. The Cochrane risk of bias (RoB) tool was used to assess RCTs and an extended version was used to assess Non Randomised Studies (NRS). The quality of evidence was assessed using GRADE. **Evidence Synthesis**: 4580 abstracts and 389 full text articles were assessed. 34 studies met the inclusion criteria (6 RCTs and 28 NRSs). Meta-analyses were planned but were deemed inappropriate due to data heterogeneity. There were high risks of bias and low quality evidence across the evidence base. Open radical nephrectomy and open partial nephrectomy showed similar cancer-specific and overall survival, but when both open and laparoscopic approaches are considered together the evidence showed improved survival for partial nephrectomy for tumours ≤4cm. Overall, the evidence suggests either equivalent or better survival with partial nephrectomy. Laparoscopic radical nephrectomy offered equivalent survival to open radical nephrectomy, and all laparoscopic approaches achieved equivalent survival. Open and laparoscopic partial nephrectomy achieved equivalent survival. The issue of ipsilateral adrenalectomy or complete lymph node dissection with radical nephrectomy or partial nephrectomy remains unresolved. **Conclusions**: The evidence base suggests localised RCC are best managed by nephron sparing surgery where technically feasible. However, the current evidence base has significant limitations due to studies of low methodological quality marked by high risks of bias.

1. Introduction

Renal cell carcinoma (RCC) accounts for approximately 2-3% of all adult malignancies. More than 50% of all RCCs diagnosed are of a localised stage (i.e. T1-T2N0M0 or stage I-II) [1]. Open radical nephrectomy was the standard curative intervention for localised RCC for the past five decades [2]. Furthermore, there were controversies over whether radical

nephrectomy should be performed in conjunction with ipsilateral adrenalectomy as originally described by Robson, or if the adrenal should be preserved [3-6] and whether ipsilateral extended retroperitoneal lymphadenectomy or limited hilar lymphadenectomy should be performed [7,8].

With the advent of minimally invasive surgery, laparoscopic radical nephrectomy has become an acceptable alternative to open surgery for localised RCCs [6,7]. Another recent controversy is the use of nephron-sparing surgery (partial nephrectomy). Nephron-sparing surgery has been the accepted mode of treatment when radical nephrectomy would render the patient anephric or at high risk for subsequent renal replacement therapy [9]. This organ-preserving approach has recently emerged as a viable alternative for small renal tumours (< 4cm or T1a) in patients with a normal contralateral kidney, with encouraging short-term and long-term oncological outcomes [10,11]. The era of increasing use of nephron-sparing surgery has also witnessed the development of minimally invasive nephron-sparing interventions such as cryoablation, radiofrequency ablation (RFA) and high-intensity focused ultrasound (HIFU), for the treatment of localised renal cancer [10,11].

Although various guidelines exist in relation to the various interventions for localised RCC [6,12], it is important to recognise that such guidelines were based on reviews which were not systematically undertaken, and often using methodology which was not transparent, reproducible nor robust. Consequently, a systematic review of current evidence is urgently needed in order to establish whether the outcomes of competing treatment options are comparable. Furthermore, methodological rigour is needed in assessing risks of bias and quality of evidence in a standardised and transparent way to highlight weaknesses in the evidence base and to make recommendations for future research.

The objective of this systematic review was to compare the oncological outcomes for all interventions relevant to the management of localised RCC. This article reports the oncological outcomes, and a separate article reports the surgical and quality of life outcomes from this systematic review. There is also a full report published online (see full report) with extra methodological information and data for oncological and surgical outcomes [13].

2. Evidence Acquisition

2.1 Search Strategy

The databases searched were: MEDLINE (1950-October 2010) and Embase (1980–October, 2010), Cochrane Library-all sections (Issue 4, 2010), Web of Science – with Conference Proceedings (1970-October 2010), and ASCO (American Society of Clinical Oncology) meeting abstracts (up to October 2010). The searches were not limited by language. Auto-alerts in MEDLINE were also run during the course of the review. Reference lists of relevant articles were also checked (full report) [13]. All abstracts and full-text articles were screened independently by two reviewers. Disagreement was resolved by discussion, and where no agreement was reached, a third independent party acted as an arbiter. In addition, an updated scoping search was performed up to January 2012.

2.2 Types of study design included

All relevant randomised or quasi-randomised controlled trials (RCTs) were included. Due to the small number of RCTs, we also included non-randomised studies (NRS). Prospective observational studies with controls, retrospective matched-pair studies, and comparative studies from well defined registries/databases were also included. Studies with no comparator group (for example, case series); non-matched retrospective studies and chart reviews were excluded.

2.3 Types of participants included

The study population was patients diagnosed with localised RCC based on CT scan or MRI, defined as clinical stage T1a-T2, N0, M0. Studies that reported pathological T3 cases were included so long as the clinical staging was T1-2 N0 M0.

2.4 Types of interventions included

The following interventions were compared:

- Radical nephrectomy
- Partial nephrectomy (Nephron-sparing surgery)
- Laparoscopic surgery for radical or partial nephrectomy
- Hand-assisted laparoscopic surgery for radical or partial nephrectomy
- Robotic-assisted laparoscopic surgery for radical or partial nephrectomy
- Complete regional (extended) lymphadenectomy
- Partial regional (limited) lymphadenectomy
- Adrenalectomy
- Radiofrequency ablation
- Cryoablation
- High intensity focused ultrasound

A valid comparator was no intervention or any of the specified interventions (see full report for definitions of interventions) [13].

2.5 Types of outcome measures included

The principal oncological measure of effectiveness was overall survival rate at 5 and 10 years. Other oncological measures of effectiveness were considered such as cancer-specific survival, local recurrence, metastasis and positive surgical margins (or tumour-free rates on ablative technique). Other outcome measures including surgical outcomes (encompassing perioperative complications and long-term adverse effects), impact on quality of life, patient satisfaction and cost-effectiveness were considered and will be reported in a separate article. For long-term outcomes, time to event data and categorical data were extracted. For categorical data, we collected event rates at 5 and 10 years (pre-specified) or if such data were not reported, we also collected data at last follow-up.

2.6 Assessment of risks of bias

The risk of bias (RoB) in the included studies was assessed using the Cochrane Risk of Bias Assessment tool for RCTs [14]. This included sequence generation, allocation concealment, blinding of participants, therapists and outcome assessors, completeness of outcome data, selective outcome reporting and other potential sources of bias. Two reviewers independently assessed these domains. Any differences of opinion were resolved by consensus or by consulting a third party.

A modified version of the RoB assessment tool was used in assessing NRS with the addition of further items (domains) to assess risk of bias through confounders [15].

A list of the five most important potential confounders (prognostic factors) for oncological outcomes identified a priori in consultation with content experts (drawn from the British Association of Urological Surgeons Section of Oncology and European Association of Urology Renal Cell Carcinoma Guideline Panel) is given below:

- Tumour stage
- Tumour size
- Tumour grade (Fuhrman)
- Necrosis
- Histological cell type

Each of the pre-specified confounders in the above list was assessed on the following four criteria:

- Whether the confounder was considered by the researchers (yes or no)
- Precision with which confounder was measured

- Imbalance between groups
- Care with which adjustment for confounder was carried out

Our guidelines, drawn up with clinical, statistical and methodological advice from members of the Cochrane Non-randomised Studies Methods Group and GRADE Working Group can be seen in the full report (full report) [13].

2.6.1 Assessment of the quality of evidence

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) evidence quality assessment tool was used to assess patient-important outcomes across studies (full report for GRADE evidence profiles) [13]. Out of the seven outcomes chosen for GRADE quality assessment in consultation with clinical content experts, two were oncological outcomes and five were non-oncological outcomes. The two chosen oncological outcomes for GRADE quality assessment are reported in this review article:

- Overall survival
- Local recurrence or progression

2.7 Data analysis

A quantitative synthesis (meta-analysis) was performed for trial data only. Heterogeneity of data made meta-analysis inappropriate for NRS. In analysing dichotomous outcomes in the comparison of intervention effects, fixed effect models were used to derive relative risk (risk ratios) with 95% confidence intervals. In analysing continuous outcomes, means and standard deviations were used to summarise the data and compare interventions with (weighted) mean difference and 95% confidence intervals.

Heterogeneity between studies was assessed by visual inspection of plots of the data, the χ^2 test for heterogeneity and the I^2 statistic[16]. Where meta-analysis was not feasible, then a narrative synthesis is provided [17]. Analysis was performed in the Cochrane RevMan software.

Separate or subgroup analyses were planned for the following groups of patients:

- those in chronic renal failure
- elderly patients (above 65 years)
- those with a solitary kidney, or a solitary functioning kidney
- patients with disease predisposing them to renal tumours
- different ASA grades
- different tumour stages

However, the data were not sufficient to address any of these meaningfully.

3. Evidence synthesis

3.1. Risk of Bias and Quality assessment of the included studies

The study selection process is outlined in the PRISMA Diagram (Fig 1). There were 44 studies that met inclusion criteria, and 34 of them reported oncological outcomes (6 RCTs and 28 NRSs). The Cochrane risk of bias assessment can be viewed in Appendix 1. The additional NRS risk of bias assessment adjustment scores (outlined above) are displayed in Table 1 which reports baseline characteristics (all study designs) and adjustment scores (NRSs only).

3.2 Comparisons of interventions results

Principal results can be viewed in Table 2 and in the Forest plots in Figures 2 and 3. Further data can be viewed in the full report of this systematic review (full report) [13].

3.2.1 Surgical (radical or partial nephrectomy) vs Non-surgical management

One database review (Zini, 2009a) [18] assessed this comparison. Non-surgical management included pT1a patients who had either observation or active surveillance only. The analysis, which was based on a matched pair population, revealed that surgical management had a 5 year cancer-specific mortality benefit over non-surgical (4.4% vs. 12.4%) (Table 2). However, even though this study was matched, it is marked by indication bias. That is, the surveillance group were indicated to that intervention and not randomly allocated to it; surveillance patients were older (mean 73 vs. 61.4 years) (Table 1) and it is likely they were generally more frail and less likely to be suitable candidates for surgery. The study was marked by other methodological flaws such as uncertain disease status in the surveillance group (indicated by failing to measure and control for two of the main prognostic confounders i.e. Fuhrman grade and histological cell type) (Table 1).

3.2.2 Technique of radical nephrectomy

3.2.2.a. Laparoscopic vs. Open radical nephrectomy

There were no randomised studies assessing oncological outcomes. A prospective cohort study (Hemal, 2007) [19] and a retrospective database review (Gratzke, 2007) [20], both of low methodological quality, found similar oncological outcomes with 5-year overall survival for laparoscopic versus open radical nephrectomy reported at 87.8% versus 88.7% ($p = 0.87$) respectively in Hemal's study [19] (Table 2); and all-cause deaths were 3/36 versus 1/37 respectively in Gratzke's study [20] (Fig. 2). There was no evidence of any difference in cancer-specific and recurrence-free survival at 5 years reported in Hemal's study [19] (Table 2).

3.2.2.b. Retroperitoneal vs. transperitoneal radical nephrectomy

Two randomised studies (Desai 2005a; Nambirajan 2004) [21,22] and one quasi-randomised study (Nadler 2006) [23] compared retroperitoneal and transperitoneal laparoscopic radical nephrectomy.

Both approaches were found to have similar oncological outcomes. No cancer-specific deaths were reported by Nadler [23] (Fig. 3), and while Desai [21] reported more all-cause deaths in the retroperitoneal approach (4/52 vs. 2/50) (Fig. 2), the result was not statistically significant. A very low number of metastatic events were reported across the studies: Nadler [23] and Nambirajan [22] reported none whilst Desai [21] reported 1/52 versus 3/50 for retroperitoneal versus transperitoneal radical nephrectomy respectively (plot 2.4, full report). No incidences of positive surgical margins were reported (plot 2.5, full report).

3.2.2.c. Hand-assisted laparoscopic radical nephrectomy vs. standard laparoscopic radical nephrectomy

One RCT (Nadler 2006) [23] and one database review (Gabr 2009) [24] compared hand-assisted and transperitoneal laparoscopic radical nephrectomy. There were no cancer-specific deaths (Fig. 3), positive surgical margins, or recurrences (plots 3.1-3.4, full report [13]) in Nadler's trial [23] (which used the transperitoneal approach only), but it should be noted that study numbers were very low with only 11 patients in each arm and follow-up was short (median = 20 months). Oncological outcomes were comparable in Gabr's study [24] (which used transperitoneal and retroperitoneal approaches). Estimated 5-year overall survival (74% vs 79%, p = 0.69), cancer-specific survival (87.2% vs 88.9%, p = 0.76), and recurrence free survival (81.3% vs 76.5%, p = 0.87) rates were comparable between hand-assisted and standard laparoscopic radical nephrectomy respectively (Table 2). Reported hazard ratios favoured the hand-assisted procedure, however the estimated confidence intervals were wide indicating considerable uncertainty, for example: overall survival adjusted HR 0.407 (0.150, 1.395) (Table 2).

3.2.2.d. Hand-assisted laparoscopic radical nephrectomy vs. retroperitoneal laparoscopic radical nephrectomy

Only one small RCT [23] (n = 22) compared hand-assisted and retroperitoneal laparoscopic radical nephrectomy (Nadler, 2006). There were no reported cancer deaths, positive surgical margins, or recurrences (plots 4.1-4.4, full report [13]), however, probably due to the short follow-up time, median of 20 months.

3.2.2.e. Robot-assisted laparoscopic radical nephrectomy vs. laparoscopic radical nephrectomy

Only one small prospective cohort study (n = 30) compared robotic and laparoscopic radical nephrectomy (Hemal 2009) [25]. There were no local recurrences, port-site or distant metastases (plot 6.1-6.2, full report [13]). The study groups were comparable but sample size was small and follow-up was less than 1 year.

3.2.2.f. Single port laparoscopic radical nephrectomy vs. laparoscopic radical nephrectomy

One prospective cohort study compared 'portless' (n = 14) and 3-port (n = 15) laparoscopic radical nephrectomy (Soga 2008) [26]. There were no local recurrences, but the study was small with a short follow-up (especially in the portless group: mean = 7.1 months; range 2.7-17.3) (plot 7.1, full report [13]).

3.2.3 Ipsilateral lymphadenectomy and ipsilateral adrenalectomy

3.2.3a. Radical or partial nephrectomy with limited or extended lymphadenectomy vs. radical or partial nephrectomy alone

Blom (2009) [8] was a European-wide multi-centre RCT (n=772) comparing radical nephrectomy with or without complete lymph node dissection. The subgroup analysis of the cT1 and cT2 population from this trial [8] showed no evidence of a difference between the groups (HR 1.096 (0.81, 1.47); log rank p = 0.55). However, the lymphadenectomy in this trial was not standardised.

Herrlinger (1991) [27], performed a retrospective observational study, comparing radical nephrectomy with either extended lymphadenectomy or facultative lymphadenectomy (i.e. no lymph node dissection or node sampling for staging purposes). Using the life table analysis method, the authors reported an overall survival benefit at 10 years (80.2% vs. 54% p = <0.01) with extended lymphadenectomy (n = 109) compared to a facultative lymphadenectomy (n = 82). However, the study did not report important baseline information about Fuhrman grade and cell type (Table 1) and these results should therefore be treated with caution [25].

3.2.3b. Radical or partial nephrectomy with ipsilateral adrenalectomy vs. radical or partial nephrectomy alone

One prospective NRS met inclusion criteria (Lane, 2009) [28] comparing partial nephrectomy with ipsilateral adrenalectomy versus without adrenalectomy. Using strict criteria based on radiographic (suspicious nodule) and intra-operative assessment (adrenal involvement) to justify adrenalectomy, out of 2,065 patients who underwent partial nephrectomy, only 48 patients (2.3%) underwent concurrent ipsilateral adrenalectomy of which 42 (87%) were histologically benign lesions. On multivariate analysis, upper pole location was not predictive of adrenal involvement (HR 0.482 (0.050–1.043) p =0.08), but tumour size was statistically significantly predictive of adrenal involvement (HR 0.262 (0.074–0.416) 0.01). After a follow-up of 5.5 years, only 15 patients out of 2,017 (0.74%) subsequently underwent ipsilateral adrenalectomy. There was no evidence of a difference in overall survival at 5 years (82% with adrenalectomy vs. 85% without adrenalectomy, p = 0.56) or 10 years (72.4% with adrenalectomy vs. 68% without adrenalectomy, p value not reported). However, this observation should be interpreted with caution as it remains unknown how adrenalectomy impacted on the survival of this patient population.

3.2.4 Nephron-sparing interventions

3.2.4a. Partial nephrectomy vs. radical nephrectomy

i. Open partial nephrectomy vs. open radical nephrectomy

One RCT (D'Armiento 1997) [29], a prospective cohort study (Gratzke, 2007) [20], a database review (Butler, 1995) [30] and one retrospective matched pair study (Lee, 2007) [31] were identified that compared various aspects of the oncological effectiveness of open radical nephrectomy with open partial nephrectomy. D'Armiento's [29], Bulter's [30] and Lee's [31] study populations included only patients with tumour sizes less than 4cm. Gratzke's [20] study does not give any information on tumour size but T1-T2 patients were included. However there were prognostically relevant baseline imbalances in the radical vs. partial nephrectomy tumour stages (see Table 1). It is important to describe the tumour sizes in terms of whether they are greater than or less than 4cm because historically there has been clinical uncertainty over whether partial resection is appropriate for tumours larger than 4cm.

The RCT by D'Armiento [29] reported an equal median survival time of 96 months, although hazard ratios for survival or survival rates were not available. Two NRS reported the estimated overall survival rates at 5 years. There was an inconsistency in the direction of effect: Butler [30] reported 75% vs. 80%; whilst Lee [31] reported 98.2% vs. 88.8% (p = 0.63) (Table 2) for open partial vs. open radical nephrectomy respectively. However, these estimates should be interpreted with caution as data were available for a shorter follow-up period in partial nephrectomy cases (40 ±26 months) than in radical nephrectomy cases (66±30 months) (Butler, 1995) [30]. In addition, neither study was randomised and prognostically important covariates, such as tumour grade and cell type were not reported. The estimated cancer-specific survival rates at 5 years for radical versus partial nephrectomy respectively were 97% versus 100% [30] and 97.9% versus 100% (p = 0.98) [31] (Table 2).

The numbers of all-cause deaths, cancer-specific deaths, local recurrences and metastases events for open radical versus open partial nephrectomy (plots 10.1-10.4, full report [13]) were similar but marked by low event rates and small sample sizes. Disease-free rates were similar for open versus partial nephrectomy (plot 10.5, full report [13]).

ii. Laparoscopic partial nephrectomy vs. laparoscopic radical nephrectomy

One NRS (a database review by Simmons 2009) [32] compared laparoscopic partial nephrectomy (n = 35) and laparoscopic radical nephrectomy (n = 75) in tumours larger than 4cm. There was no evidence of a difference in estimated overall survival, cancer-specific survival and recurrence-free survival rates respectively at 80 months (Table 2).

iii. Open or Laparoscopic partial nephrectomy vs. Open or Laparoscopic radical nephrectomy

There has been controversy as to whether partial nephrectomy should be used for larger tumours and a cut-off of 4cm has been recommended. However, some study authors have argued that partial nephrectomy is feasible up to 7cm with no reduction in oncological control or overall survival. For this reason this section is split into two: studies reporting populations with tumour sizes </= 4cm, and studies with populations reporting 4-7cm. The surgical approach used (whether open or laparoscopic) was not clearly reported in these

studies. Furthermore, these results should be treated with caution because there is limited high quality evidence.

iii.a. Open or Laparoscopic partial nephrectomy vs. Open or Laparoscopic radical nephrectomy ≤ 4cm

Huang (2009) [33], Zini (2009b) [34], Thompson (2008) [35] and Patard (2004) [36] studied small renal tumours. Huang (2009) [33] and Zini (2009b) [34] both report data from the SEER database. Huang limited the population to those aged over 66 years whilst Zini [34] included those aged over 18 years, and both studies adopted different analytic approaches (Huang [33] used multivariate logistic regression and Zini [34] used calliper matching).

In Huang's study [33], about 30% of the patients died during the study period, including 110 (19.8%) in the partial nephrectomy group and 782 (32.1%) in the radical nephrectomy group. The 5-year survival probability was 74% after partial nephrectomy, and 68% after radical nephrectomy. After adjusting for patient characteristics, radical nephrectomy was found to be significantly associated with death from any cause: HR 0.72, (0.59, 0.88), p < 0.001 (Table 2).

For those matched by age, tumour size and year of surgery, Zini (2009b) [34] reported an overall mortality hazard ratio of 0.84 (p 0.048) in favour of patients who underwent partial nephrectomy based on Cox regression modelling (Table 2). The 5-year overall survival rates of the partial nephrectomy and radical nephrectomy groups were 89.3% and 84.4%, respectively and the 10-year overall survival rates were 71.3% and 68.2% in favour of partial nephrectomy [34] (Zini 2009b) (Table 2).

Thompson (2008) [35] reported data from the Mayo clinic institutional databases and found no evidence that radical and partial nephrectomy were different in terms of all cause death: RR 1.2 (0.80,1.56) p = 0.52. However, when age was controlled for in the analysis, in a subset of patients under 65, radical nephrectomy was significantly associated with death from any cause compared with partial nephrectomy: RR 2.16 (1.09,4.23), p = 0.02. Furthermore, the increased risk of death from any cause persisted after adjusting for year of surgery (RR 2.34 (1.17,4.69), p = 0.016), preoperative creatinine (RR 2.15 (1.12,4.19), p = 0.027), Charlson-Romano index (RR 2.14 (1.05,4.35), p = 0.037), symptoms at presentation (RR 2.17 (1.11,4.24), p = 0.023), diabetes at presentation (RR 2.23 (1.09,4.56), p = 0.028) and histology (RR 2.32 (1.18,4.55), p = 0.015).

In a subset of T1a patients (i.e. </= 4cm), Patard (2004) [37] noted no difference in cancer specific survival at 5 years (log rank test p = 0.7) in a multi-institutional study. There was no evidence of differences in partial vs. radical nephrectomy respectively in local (1/123 vs. 1/175) or distant (3/123 vs. 8/175) recurrence at a mean follow-up of 62.5 months (plots 13.1-13.4, full report [13])

iii.a. Open or Laparoscopic partial nephrectomy vs. Open or Laparoscopic radical nephrectomy >4cm

Thompson (2009) [38], Dash (2006) [39], Weight (2010) [40], Crepel (2010) [41], Patard (2008) [36] and Patard (2004) [37] report on tumours 4-7cm. Thompson (2009) [38], combining Mayo clinic and Sloan-Kettering memorial institutional databases, and Weight (2010) [40] reporting SEER database data, failed to show evidence of differences between partial nephrectomy and radical nephrectomy: HR 1.06 (0.79, 1.45) and HR 0.903 (0.56, 1.5), p = 0.68 respectively.

Four studies reported adjusted hazard ratios for cancer-specific survival again showing no evidence of differences between partial nephrectomy and radical nephrectomy, (Crépel (2010) (HR 0.8; p = 0.4) [41], Patard (2008), (p = 0.9) [36], Thompson (2009) (HR 0.51 (0.24,1.09), p = 0.079) [38], Weight (2010) (HR 0.77 (0.41, 1.42), p = 0.4) [40] (Table 2).

One database review (Dash 2006) [39], using Memorial Sloan-Kettering data, reported adjusted hazard ratio for disease-free survival and failed to show evidence of a difference between partial nephrectomy and radical nephrectomy: HR 0.36, (0.05,2.82), p = 0.3 (Table 2).

In Weight's SEER database study (Table 2), at a median follow-up of 48 months, controlling for the propensity to undergo a partial nephrectomy (age, tumour size, presence of contralateral disease, solitary kidney, surgery type (laparoscopic versus open) and Charleson co-morbidity index), partial nephrectomy was associated with better overall survival (HR 0.62 (0.4,0.94), p = 0.03). However, when pathological stage and reduction in eGFR were included in the model, partial nephrectomy was no longer a significant predictor of survival (HR 0.903 (0.56,1.5), p = 0.68). The Kaplan Meier estimates of overall survival at 5 years were 85% and 78.8% in the partial and radical nephrectomy groups respectively.

In a subset of T1b patients (i.e.4-7cm), Patard (2004) [37] noted no difference in cancer specific survival at 5 years (log rank test p = 0.8) in a multi-institutional study. There were no statistically significant differences in partial vs. radical nephrectomy respectively in local (1/28 vs. 5/218) or distant (8/28 vs. 34/218) recurrence at a mean follow-up of 62.5 months.

3.2.4b. Minimally invasive ablative procedure vs. laparoscopic radical nephrectomy

There were no comparative studies that reported on oncological outcomes.

3.2.4c. Technique of partial nephrectomy

i. Laparoscopic partial nephrectomy vs. open partial nephrectomy

Two database reviews (Gill 2007, Lane 2010) [42,43] and two matched-pair analyses (Marzalek 2009, Gong 2008) [44,45] compared laparoscopic and open techniques of partial nephrectomy.

Lane (2010) [43] noted an overall survival benefit estimate in laparoscopic versus open partial nephrectomy patients when adjusting for age, gender, race, Charleson-Romano Index, tumour size, hypertension, pre-operative eGFR, and oncological potential (defined as predicted risk of recurrence at 5 years) in those patients with a minimum of 1 year follow-

up: HR 0.69 (0.45,1.02), p = 0.07). At 7 years follow-up, there was no evidence of a difference between the two groups. There were no differences in 3-year cancer-specific survival [42] (Gill 2007) and 5 year overall survival (Marszalek 2009) [45] (Table 2).

Regarding the number of deaths during the study period, a lower risk of all cause death was shown in the laparoscopic group (RR 0.4 [0.28,0.59], p = ,0.0001) (Lane 2010) [43] (Fig 2).

The Gill [42] and Marszalek [45] studies reported no statistically significant difference in the recurrence patterns between laparoscopic and open partial nephrectomy (Table 2).

It is important to note that the evidence base for this comparison remains poor, with all studies suffering from methodological flaws inherent in most NRS.

ii. Robotic partial nephrectomy vs. laparoscopic partial nephrectomy

There were no comparative studies that reported on oncological outcomes.

iii. Radiofrequency-assisted robotic clampless partial nephrectomy vs. laparoscopic partial nephrectomy

A database review by Wu (2010) [46] compared patients who underwent standard laparoscopic partial nephrectomy (n = 36, but only 24 were RCCs) and radiofrequency-assisted robotic laparoscopic partial nephrectomy (RFRCPN) (n = 42, but only 32). The groups were comparable for positive surgical margins (0/42 versus 1/36) and recurrence rates (1/34 versus 0/34) (plots 16.1-16.2 full report [13]) for the RFRCPN and RFA assisted robotic laparoscopic nephrectomy, but the study was marked by very low event rates, a high number of benign tumours, and lacked longer term survival data.

3.2.4d. Partial nephrectomy vs. minimally invasive ablative procedures

i. Laparoscopic cryoablation vs. laparoscopic partial nephrectomy

Data was obtained from one database review (Desai 2005b) [47] and one matched pair study (O'Malley 2006) [48]. For the cryoablation and partial nephrectomy arms respectively 3/78 and 0/153 deaths were reported by Desai [47] at last follow-up (Fig. 3). Time to detection of local recurrence was noted at a mean follow-up time of 5.8 months among those who underwent partial nephrectomy (1/153), and 24.6 months after cryoablation (2/78) (Desai 2005b) [47] (plot 17.1, full report [13]). No recurrences were reported in either treatment group after a mean follow-up of 9.8 and 11.9 months in O'Malley's report [48] (plot 17.2, full report [13]). Oncological outcomes in terms of development of recurrence therefore differed between the two studies. This may be a reflection of different definitions and ways of establishing disease recurrence following cryoablation. The study also includes data on benign tumours and therefore should be treated with caution. Determining local recurrence on imaging alone is known to be subjective.

ii. Laparoscopic cryoablation vs. open partial nephrectomy

Data were obtained from one matched comparison (Ko, 2008) [49]. There were no local recurrences or metastasis in either group (plots 18.1-18.2, full report [13]). However, there were only 20 patients in each arm and follow-up was short at 27-28 months.

4. Discussion

Principal Findings:

Open radical nephrectomy and open partial nephrectomy show no difference in either overall or cancer-specific survival. However, if data from studies comparing open or laparoscopic radical nephrectomy versus open or laparoscopic partial nephrectomy is considered, the evidence base indicates improved survival for partial nephrectomy in tumours ≤4cm. However, there is no evidence of a difference in tumours >4cm. Recurrence rates and metastases appear similar for all approaches. Although the included studies differed in quality and outcomes reported, overall the evidence suggests either equivalent or better survival with partial nephrectomy, suggesting that nephron sparing surgery should be applied when possible.

Laparoscopic radical nephrectomy appears to offer equivalent survival to open radical nephrectomy and all laparoscopic approaches achieve equivalent survival. Open and laparoscopic partial nephrectomy achieves equivalent survival. Different laparoscopic and ablative techniques also achieve similar survival but studies are of low methodological quality.

There is no evidence to support removal of the ipsilateral adrenal gland with radical nephrectomy. The performance of complete lymph node dissection with radical nephrectomy for localised RCC remains unanswered due to large inconsistencies in the data.

Although this systematic review compared surgical management with non-surgical management for renal tumours, the evidence available falls short of proving that surgery improves survival, due to the absence of high quality studies. However, from a practical point of view, this is a question that could be answered for surveillance of small renal masses but it is unlikely to be answered for larger or more advanced tumours due to the ethical implications of withholding treatment.

Since the last search update for this review (October 2010), several potentially relevant studies have been published. An updated scoping exercise performed in January 2012 returned 240 abstracts, from which 4 relevant studies were identified; 2 of which are RCTs (van Poppel 2011 [50]; and Yu 2010 [51]), and 2 are non-randomised retrospective matched-pair analysis (Klatte 2011 [52]; and Antonelli 2011 [53]). van Poppel's study was a multi-centre RCT of nephron-sparing surgery (NSS) versus radical nephrectomy for T1-T2 renal cancers. Despite being an RCT, the study had significant limitations (including premature closing of the study due to poor accrual, a change in protocol and being significantly underpowered), a fact acknowledged by the authors. The results from the intention-to-treat analysis showed a lower overall survival for NSS compared with radical nephrectomy, although this difference becomes not significant if the analysis is restricted to the targeted population of RCC patients and those who are clinically and pathologically eligible. Given such methodological flaws and uncertainty, the results from this study should be interpreted cautiously. Yu 2010 [51] was a RCT comparing open partial nephrectomy versus open radical nephrectomy, and similar oncological outcomes were reported at a minimum of 5 years. Klatte 2011 [52] was a retrospective matched-pair study comparing laparoscopic

cryoablation with open partial nephrectomy for T1a renal tumours only. The results showed substantially higher local recurrence rate at 3 years for laparoscopic cryoablation. Antonelli 2011 [53] was a retrospective analysis comparing elective open partial nephrectomy with open radical nephrectomy for clinical T1 tumours only. However, patients with pathological T2 and T3 tumours in the open radical nephrectomy group were excluded from the analysis. The results showed similar recurrence rate and cancer-specific mortality for both procedures.

Strengths and limitations:

The strength of this review is the systematic approach taken to review the evidence base using a methodologically rigorous review process including Cochrane methodology throughout, reporting standards such as PRISMA, using novel tools to assess risks of bias in NRS and requesting peer review throughout from a reference group of international experts. A clinical care pathway identifying the major comparisons of interest was formulated in consultation with international experts. An in-depth description of this consensus building process has been previously reported [54].

The major limitation of this systematic review results from the methodological concessions that needed to be made to ensure the review reflects the current state of the available evidence base. In particular, the inclusion criteria had to be more inclusive of study designs from further down the hierarchy of evidence than is desirable (full report [13]). Another limitation is that NRS have inherent biases, meaning that they should always be treated with caution. The review has addressed this through employing a methodologically rigorous system of assessing risks of bias in NRS (see full report [13]). In addition, it was not possible to perform meta-analyses for all outcomes of interest, due to statistical and trial design limitations. However, in order to derive the highest possible level of evidence for the review, uncontrolled case series (i.e. non-randomised studies without a control arm) were excluded, since such studies can provide Level 4 evidence only at best [55] for comparative assessments of interventions.

How this systematic review compares with other recent systematic reviews and technology assessments by guideline panels

The current EAU and AUA Renal Cancer Guidelines provide primary reference points for the management of localised RCC. The review methodology underpinning both guidelines differ from that offered in this systematic review mainly on the point of strict inclusion criteria for primary reports and the assessment of the methodological quality of those included reports (full report [13]).

There are specific methodological limitations of the research underpinning the AUA Renal Cancer Guideline, such as conduct of meta-analyses of observational studies. The guideline itself acknowledged that it may not be methodologically appropriate to do so [56,57]. The current internationally recognised EAU Renal Cancer Guidelines include many case series (i.e. no comparator groups) which are susceptible to selection biases. In co-authoring this systematic review, EAU Renal Cancer Guideline Panel members and the UCAN Systematic Review Team have used the most rigorous research methods to assess the best evidence

available for the management of localised renal cell carcinoma. A comparison between this systematic review with two other reviews [58,59] can be accessed in the full report [13]. Other reviews were either not systematically performed [60] or were based on non-comparative case series [61,62]; these will not be considered any further.

5. Conclusions:

Patient and tumour characteristics permitting, current oncological outcomes evidence base suggests that localised RCC are best managed by nephron-sparing surgery rather than by radical nephrectomy irrespective of surgical approach. Where open surgery is deemed necessary, open nephron sparing surgery oncological outcomes are at least as good as open radical nephrectomy and should be the preferred option when technically feasible. The evidence around minimally invasive ablative technologies is weak due to low methodological quality studies and mixed patient populations that include benign renal lesions making judgements about effectiveness unsafe. In the absence of obvious tumour involvement of the ipsilateral adrenal gland, the evidence available does not support routine removal of the adrenal and it remains unclear whether complete lymph node dissection has any role in the management of localised RCC due to large inconsistencies in limited data and therefore on currently available evidence it is best not to offer it to patients. Future research efforts must aim to rectify this paucity of evidence with well-designed and well-reported prospective studies especially for newer interventions. Studies should use pre-defined, ideally standardised, measures of outcome, and be multicentre to ensure that the studies give sufficiently precise estimate of the various outcomes. Ideally, allocation should be randomised. There is an urgent need for standardisation of outcome reporting in RCC trials, observational studies and registry databases. Such standardisation will make it easier to compare, contrast and synthesise the results of such studies, reduce the risk of inappropriate outcomes being measured and reduce outcome reporting bias.

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Table 1: Baseline characteristics and oncological confounder adjustment scores

Study, design and adjustment	Interventions	N	FU (months) mean (SD), *median [range]	Age: Mean (SD), *median [range]	Tsize (cm) Mean (SD) [range], *median	path Tstage	T grade N (Fuhrman unless stated)	Histological cell type	Necrosis
Zini 2009a [18]; matched pair	SM	430	*16 [0.1, 146]	73 [Unmatched, N = 433]	2.8 [Unmatched, N = 433]	All pT1a	NR	NR	NR
	NSM	1545	*50 [0.1,203]	61.4 [Unmatched, N = 433]	2.8 [Unmatched, N = 433] (p = 0.5)	All pT1a	NR	NR	NR
Adjustment	NA	NA	NA	NA	1	1	5	5	5
Gratzke 2009 [20]; database review Ludwig-Maximillian and Basel University)	LRN	36	22, [11-71]	67.8 (12.8)	NR	pT1a: 12 (33.3%) pT1b: 17 (47.2%) pT2: 0 pT3: 4 (11.1%)	NR	NR	NR
	ORN	37	22, 11-71]	61.1 (12.7)	NR	pT1a: 9 (24%) pT1b: 20 (54%) pT2: 8 (22%) pT3: 0	NR	NR	NR
Adjustment	NA	NA	NA	NA	5	5	5	5	5
Hemal 2007 [19]; prospective cohort	HALRN	41	51.4 [3, 78]	52.5 (11.3)	9.9 (2.2)	All T2	NR	NR	NR
	SLRN	71	57.2 [4, 80]	52.7 (11.8)	10.1 (3.2)	All T2	NR	NR	NR
Adjustment		NA	NA	NA	1	1	5	5	5
Nambirajan 2004 [22]; QRCT	RLRN	20	15 [6-26]	66.8 [43-82]	4.29 (1.83)	pT1 = 17, pT2 = 0, pT3a = 2, pT3b = 0, benign =1	NR	NR	NR
	TRLN	20	17 [6-16]	62.2 [41-80]	4.58 (1.56)	pT1 = 12, pT2 = 2, pT3a = 2, pT3b = 3, benign =1	NR	NR	NR
Nadler 2006 [23]; QRCT	RLRN	11	Overall *20 [0-51]	61 [42-85]	NR	All cT1	NR	NR	NR
	TRLN	11		63 [50-86]	NR	AllTc1	NR	NR	NR
Desai 2005a [21]; RCT	RLRN	52	13.5 (11.9) [0.5 – 40]	64.5 (12.3) [29-89]	5 (2) [2-10.2	All cT1	G 1: 5 (10%) G 2: 17 (34%) G 3: 12 (24%) G 4: 5 (10%)	RCC: 39 (75%); TCC 0; Angiomylipoma: 7 (11%) Oncocytoma: 1 (2%); Other: 5 (10%) Clear cell: 25 (50%); Granular: 2 (4%); Sarcomatoid: 2 (4%); Papillary: 5 (10%); Mixed: 5 (10%);	NR

Study, design and adjustment	Interventions	N	FU (months) mean (SD), *median [range]	Age: Mean (SD), *median [range]	Tsize (cm) Mean (SD) [range], *median	path Tstage	T grade N (Fuhrman unless stated)	Histological cell type	Necrosis
								Other 0	
	TRLN	50	15 (6.2) [3-24]	62.8 (13.3)[30-38]	5.3 (2.8) [1.7-15]	All cT1	G 1: 7 (14%) G 2: 16 (32%) G 3: 13 (26%) G 4: 6 (12%)	RCC: 42 (84%) TCC: 0 Angiomylipoma: 1 (2%) Oncocytoma: 4 (8%) Other: 2 (4%) Clear cell: 27 (54%); Granular: 1 (2%); Sarcomatoid: 0; Papillary 8: (16%); Mixed 2: (4%); Other 4: (8%)	NR
Nadler 2006 [23]; QRCT	HALRN	11	Overall *20 [0-51]	61 [42-85]	NR	All cT1	NR	NR	NR
	TLRN	11		57 [42-58]	NR	All cT1	NR	NR	NR
Gabr 2009b [24]; database review (University of Michigan Health System)	HALRN	108	Overall mean of 35.2 (25) [0.3-114]; median 30 mos	61.3 (12.7	6.9 (2.8)	T1a 23 (21.3%); T1b 31 (28.7%); T2 25 (23.1%); T3 29 (26.9%)	G 1-2: 49 (50%); G 3: 37 (37.8%); G 4: 12 (12.2%)	Low risk (papillary and chromophobe): 22 (20.4%); Clear cell: 85 (78.7%); High risk (collecting duct, Spindle cell and Unclassified tumours): 1 (0.8%)	NR
	TLRN	147		62.7 (12.9)	4.9 (21.9) p = <0.0001	T1a 54 (36.7%); T1b 67 (45.6%); T2 11 (7.5%); T3 15 (10.2%) P = <0.0001	G 1-2: 77 57.9(%); G 3: 45 (33.8%); G 4: 11 (8.3%) P <0.0001	Low risk: 38 (25.9%); Clear cell: 103 (70.1%); High risk 6 (4.1%) P = 0.1568	NR
Adjustment	NA	NA	NA	NA	1	1	1	1	5
Nadler 2006 [23] QRCT	HALRN	11	Overall *20 [0-51]	61 [42-85]	NR	All cT1	NR	NR	NR
	RLRN	11		63 [50-86]	NR	All cT1	NR	NR	NR
Hemal 2009 [25]; prospective cohort	Robotic-RN	15	8.3 [1-12]	50.3 (10.2)	6.7 (2.3)	pT1a = 5, pT1b = 6, pT2 = 4, pN0 = 14, pN1 = 1	G1: 3 G2: 8 G3: 4 G4: 0	Clear cell: 12, Papillary: 2, Chromophobe: 1	NR

Study, design and adjustment	Interventions	N	FU (months) mean (SD), *median [range]	Age: Mean (SD), *median [range]	Tsize (cm) Mean (SD) [range], *median	path Tstage	T grade N (Fuhrman unless stated)	Histological cell type	Necrosis
	LRN	15	9.1 [2-12]	52.7 (11.8)	6.9 (2.1)	pT1a = 4, pT1b = 8, pT2 = 3 pN0 = 15, pN1 = 0	G1: 4 G2: 9 G3: 2 G4: 0	Clear cell: 13, Papillary: 1, Chromophobe: 1	NR
Adjustment	NA	NA	NA	NA	1	1	1	1	5
Soga 2008 [26]; prospective cohort	PLRN	14	*7.1 [2.7-17.3]	57 (13.5)	3.72 (1.39) [1.6-6.9]	All cT1	NR	Clear cell: 12, Microtubular spindle: 1, Oncocytoma: 1	NR
	LRN	15	*27.2 [19.5;39.1]	53.7 (15)	3.13 (0.77) [2.4-4.4]	All cT1	NR	no data	NR
Adjustment		NA	NA	NA	1	1	5	5	5
Herrlinger 1991 [27]; prospective cohort	RN+LND	109 (sub-group)	48-251 overall	<72 overall	NR	T1-2N0M0	NR	NR	NR
	RN	82 (sub-group)			NR	T1-2N0M0	NR	NR	NR
Adjustment	NA	NA	NA	NA	5	1	5	5	5
Blom 2009 [8]; RCT , subgroup analysis (note that baseline characteristics are considered randomised as the randomisation process protects against indication biases present in observational studies)	RN+LND	271 (sub-group)	*151 (max 264) overall	58.7 (10.8) [28-84]	5.4 (2.5)[0.4-17]	T0 = 3 (1.3%) T1 = 21 (8.8%) T2 = 176 (73.3%) T3 = 40 (16.7%)	G0: 8 (3.7%) G1: 59 (27.2%) G2: 104 (47.9%) G3: 42 (19.4%) G4: 0 Missing: 4 (1.8%)	Clear cell: 40 (45.5%) Spindle cell: 0 (0%) Oncocytic: 23 (26.1%) Mixed: 2 (2.3%) Other: 13 (14.8%) Unknown: 10 (11.4%)	NR
	RN	288 (sub-group)		58.6 (11.6)[24-81]	5.9 (2.7)[0.7-17]	T0 = 4 (1.6%) T1 = 19 (7.4%) T2 = 197 (76.7%) T3 = 37 (14.4%)	G0: 9 (4%) G1: 74 (32.7%) G2: 109 (48.2%) G3: 30 (13.3%) G4: 1 (0.4%) Missing: 3 (1.3%)	Clear cell: 40 (46%) Spindle cell: 3 (3.4%) Oncocytic: 20 (23%) Mixed: 2 (2.3%) Other: 19 (21.8%) Unknown: 3 (3.4%)	NR
Lane 2009 [28]; prospective cohort	PN+Adrenalectomy	48	*6.2 [IQR 2.2-8.8]	*62 [IQR 56-69]	*3.6 [IQR2.2-6]	T0 = 10 (21%) T1a = 21 (44%) T1b = 8 (17%) T2or > = 9 (19%)	NR	Conventional RC: 30 (63%) Other Cancer (papillary, chromophobe etc): 8 (17%) Benign: 10 (21%)	NR
	PN	2017	*5.5 years [IQR2.9-9]	*61 [IQR 51-70]	*3.0 [IQR2.1-4.3]	T0 = 314 (19%) T1a = 940 (56%)	NR	Conventional RCC = 1150 (63%)	NR

Study, design and adjustment	Interventions	N	FU (months) mean (SD), *median [range]	Age: Mean (SD), *median [range]	Tsize (cm) Mean (SD) [range], *median	path Tstage	T grade N (Fuhrman unless stated)	Histological cell type	Necrosis
						T1b = 310 (19%) T2or > = 100 (6%)		Other Cancer (papillary, chromophobe etc): 351 (19%) Benign: 314 (17%)	
Adjustment	NA	NA	NA	NA	1	5	5	1	5
D'Armiento 1997 [29]; RCT	OPN	19	70 (max 98)	51.4 (13.7) [23-74]	3.34 (0.64)	NR	G1 :11, G2: 7, G3:1	NR	NR
	ORN	21	70 (max 97)	48.7 (14.7) [27-76]	3.21 (0.56)	NR	G1: 10, G2: 8, G3: 3	NR	NR
Butler 1995 [30]; database review (Cleveland Clinic)	OPN	46	40 (26)	60 (14)	2.5 (0.8)	pT1; 13 (28%), pT2: 28 (61%), pT3a: 5 (11%)	NR	NR	NR
	ORN	42	66 (30)	64 (13)	2.7 (0.8)	pT1: 9 (21%), pT2:28 (67%) pT3a: 5 (12%)	NR	NR	NR
Adjustment	NA	NA	NA	NA	1	1	5	5	5
Gratzke 2009 [20]; database review (Ludwig-Maximillian and Basel University)	OPN	44	Mean 22 months, range 11-71	60.7 (12.4)	NR	pT1a: 35 (80%) pT1b: 6 (14%) pT2: 1 (2%) pT3: 0 missing 2	NR	NR	NR
	ORN	37	Mean 22 months, range 11-71	61.1 (12.7)	NR	pT1a : 9 (24%) pT1b: 20 (54%) pT2: 8 (22%) pT3: 0	NR	NR	NR
Adjustment	NA	NA	NA	NA	5	5	5	5	5
Lee 2007 [31]; matched pair	OPN	56	37.1 (26.1)	51.8 (11.7)	2.5 (0.8)	Al pT1a	G1: 3 G2: 34 G3: 19	NR	NR
	ORN	56	39 (20.37)	52.5 (11.0)	2.5 (0.8)	Al pT1a	G1: 2 G2: 37 G3: 17	NR	NR
Adjustment	NA	NA	NA	NA	1	1	1	5	5
Simmons 2009 [32]; database review	LPN	35	* 44 (27-85)	63.5 (12)	4.6 (4.1-7.5)	pT1b: 29 (83%) pT2: 1 (3%) pT3a: 3 (9%)	Mean (SD): 2.3 (0.6); G 1: 2 (6%); G 2:	Clear cell: 23 (66%); Papillary: 12 (33%); Chromophobe: 0;	NR

Study, design and adjustment	Interventions	N	FU (months) mean (SD), *median [range]	Age: Mean (SD), *median [range]	Tsize (cm) Mean (SD) [range], *median	path Tstage	T grade N (Fuhrman unless stated)	Histological cell type	Necrosis
						pT3b: 2 (6%)	20 (57%); G 3: 12 (34%); G 4: 1 (3%)	Unspecified: 0	
	LRN	75	*57 (27-79)	63.4 (12)	5.3 (4-7.3) P = 0.026	pT1b: 43 (57%) p T2: 2 (3%) pT3a: 25 (33%) pT3b: 5 (7%)	Mean (SD): 2.6 (0.6) G 1: 2 (3%); G 2: 30 (40%); G 3: 38 (51%); G 4: 5 (6%)	Clear cell: 63 (85%); Papillary: 7 (9%); Chromophobe: 4 (5%); Unspecified: 1 (1%)	NR
Adjustment	NA	NA	NA	NA	5	5	5	5	5
Dash 2006 [39]; database review (Sloan-Kettering)	O/LPN	45	*21	56.7 (13)	4.85 (0.94)	pT1: 41 (91%), pT3: 4 (9%)	G1-2: 35 (78%), G3-4: 9 (20%), Unknown: 1 (2%)	All clear cell	NR
	ORN	151	*21	63.1 (11.5)	5.42 (0.89)	pT1: 124 (82%), pT3: 27 (18%)	G1-2: 107 (71%), G3+4: 43 (28%), Unknown: 1 (1%)	All clear cell	NR
Adjustment	NA	NA	NA	NA	1	1	1	1	5
Huang 2009 [33]; SEER database review	O/LPN	556	43 overall; 48 in pts who were alive at end of FU.	66-69: 155 (28%) 70-74: 189 (34%) 75-79: 144 (26%) 80-84: 59 (11%) 85+: 9 (1%)	<4cm	All T1a	NR	NR	NR
	O/LRN	2435	*21	66-69: 536 (22%) 70-74: 747 (31%) 75-79: 671 (28%) 80-84: 364 (15%) 85+: 117 (4%)	<4cm	All T1a	NR	NR	NR
Adjustment	NA	NA	NA	NA	1	1	5	5	5
Patard 2008 [36]; matched pair (multi institutional)	O/LPN	289	Mean 54 overall	59.3	5.47	pT1a: 273 (94.5%), pT2: 16	G1-2: 234 (81%)	NR	NR
	O/LRN	257		61	5.5	pT1a: 241 (93.8%) pT2: 16	G1-2: 204 (79.4%)	NR	NR
Adjustment	NA	NA	NA	NA	1	1	1	5	5
Patard 2004 [37]; database review (7 international centres)	O/LPN	379: pT1a 314; pT1b 65	50.7 (40.3);	59.7 (12.3)	T1a: 2.5 (0.8); T1b: 5.3 (0.8)	pT1a 314 (82.8%); pT1b 65 (17.2%)	G 1-2: T1a: 287 (91.7%); T1b: 57 (89.1%); Missing 2/579	Clear cell: 310 (82.7%); Papillary: 46 (12.3%); Chromophobe: 19 (5%)	NR

Study, design and adjustment	Interventions	N	FU (months) mean (SD), *median [range]	Age: Mean (SD), *median [range]	Tsize (cm) Mean (SD) [range], *median	path Tstage	T grade N (Fuhrman unless stated)	Histological cell type	Necrosis
	O/LRN	1075: pT1a 499; pT1b 576	66.6 (54.2)	60 (12.4)	T1a: 3.2 (0.8); T1b: 5.6 (0.8)	pT1a 499 (46.4%); pT1b 576 (53.6%)	G 1-2: T1a: 439 (88%); T1b: 470 (89.1%); Missing 2/1075	Clear cell: 909 (85.5%); Papillary: 123 (11.6%); Chromophobe: 27 (2.6%)	NR
Adjustment	NA	NA	NA	NA	1	1	1	1	5
Weight 2010 [40] USA **Matched pair (SEER database)**	O/LPN	524	* 46 [IQR 25, 75]	63 [IQR 53, 71]	5.0 [IQR 4.5, 5.6] (Pre-op) 4.3 [IQR 3.5, 5] (pathological)	pT1:394/447 (88.1%), pT2 or greater = 53/447 (11.9%);	G 3-4: 170/423 (40.2%)	Of the malignant tumours (n = 438): Clear cell: 327 (74.5%), Papillary: 77 (17.6%), Chromophobe or Oncocytic neoplasm: 24 (5.4%), Other: 10 (3.1%). Number benign 86/524 (16.4%)	NR
	O/LRN	480	* 50 [IQR 28, 73]	65 [IQR 56, 73]	5.6 [IQR 5, 6.4] (Pre-op) 5.0 [IQR4.3, 6.0] (pathological)	pT1 = 324/452 (71.7%), pT2 or greater = 128/452 (28.3%);	G 3-4: 213/406 (52.5%)	Of the malignant tumours (n = 429): Clear cell: 340 (79.2%), Papillary: 53 (12.4%), Chromophobe or Oncocytic neoplasm: 17 (4%), Other: 19 (4.4%) Number benign 51/480 (10.6%)	NR
Adjustment	NA	NA	NA	NA	1	1	1	1	5
Zini 2009b [34]; matched pair (SEER database)	O/LPN	1283	*35	59.6	2.5	All pT1a	G1:352 (27.4%), G2:735 (57.3%), G3: 180 (14%), G4: 16 (1.2%)	Clear cell: 1047 (81.6%), Papillary: 104 (8.1%), Other: 132 (10.3%)	NR
	O/LRN	3166	*46	61.3	2.8	All pT1a	G1: 917 (29%), G2: 1805 (57%), G3: 412 (13%), G4: 32 (1%)	Clear cell: 2699 (85.2%), Papillary: 152 (4.8%), Other: 315 (9.9%)	NR

Study, design and adjustment	Interventions	N	FU (months) mean (SD), *median [range]	Age: Mean (SD), *median [range]	Tsize (cm) Mean (SD) [range], *median	path Tstage	T grade N (Fuhrman unless stated)	Histological cell type	Necrosis
Adjustment	NA	NA	NA	NA	1	1	1	1	5
Thompson 2008 [35]; database review (Mayo clinic)	O/LPN	358 (including 187 who were younger than age 65)	* 67.2 [range 8.4-211.2]	*64 [26-94	*2.5 [range 0.2-4]	All pT1a	NR	Clear cell RCC: 186 (52%); Papillary RCC: 75 (21%); Chromophobe RCC: 16 (4.5%); Collecting duct RCC: 1 (0.3%); RCC not otherwise specified: 1 (0.3%); Benign: 79 (22.1%)	NR
	O/LRN	290 (including 140 who were younger than age 65)	*112.8 [range 1.2-207.6]	*65 [24-85]	*3 [range 0.2-4] P<0.001	All pT1a	NR	Clear cell RCC: 191 (65.9%); Papillary RCC: 41 (14.1%); Chromophobe RCC 10 (3.5%); Collecting duct RCC: 0; RCC not otherwise specified: 5 (1.7%); Benign tumour: 43 (14.8%)	NR
Adjustment	NA	NA	NA	NA	1	1	5	1	5
Crepel 2010 [41]; matched pair (SEER database)	O/LPN	163	34 (23)	61 [25-84]	5.2 (5)	T1bN0M0	G1: 41 (25.2%) G2: 83 (50.9%) G3: 37 (22.7%) G4: 2 (1.2%) Unknown: 0	Clear cell: 131 (80.4%) Papillary: 23 (14.1%) Chromophobe: 7 (4.3%) Unclassified: 2 (1.2%)	NR
	O/LRN	636	39.4 (26.5)	61 [30-92]	5.2 (5)	T1bN0M0	G1: 155 (24.4%) G2: 332 (52.2%) G3: 145 (22.8%) G4: 4 (0.6%) Unknown: 0	Clear cell :592 (93%) Papillary: 29 (4.6%) Chromophobe: 10 (1.6%) Unclassified: 5 (0.8%)	NR
Adjustment	NA	NA	NA	NA	1	1	1	1	5
Thompson 2009 [38]; database review (Mayo clinic and Sloan-Kettering)	O/LPN	286	*40.8[0-204]	<65y 164 (57%) ≥65y 122 (43%)	4.1-5: 155 (61%) 5.1-6: 66 (23%) 6.1-7: 45 (16%)	pT1b: 277 (97%) pT3a: 11(4%)	NR	Clear cell: 155 (54%) Papillary: 60 (21%) Chromophobe: 32 (11%) Collecting duct :0 Other RCC: 1 (0.4%)	NR

Study, design and adjustment	Interventions	N	FU (months) mean (SD), *median [range]	Age: Mean (SD), *median [range]	Tsize (cm) Mean (SD) [range], *median	path Tstage	T grade N (Fuhrman unless stated)	Histological cell type	Necrosis
								Benign: 38 (13%)	
	O/LRN	873	63.6 [0-228]	<65 422 (48%) 65/> 451 (52%)	4.1-5: 330 (38%) 5.1-6: 289 (33%) 6.1-7: 254 (29%)	pT1b: 815 (93%) pT3a: 9 (3%)	NR	Clear cell : 629 (72%) Papillary: 100 (12%) Chromophobe: 50 (6%) Collecting duct: 2 (0.2%) Other RCC 7 (0.8%) Benign 85 (10%)	NR
Adjustment	NA	NA	NA	NA	1	1	5	5	5
Gill 2007 [42]; database review (Cleveland Clinic, Mayo Clinic and John Hopkins university)	LPN	771	*14.4 [0, 84]	59.4 [range 19-87]	2.6 [0.4-8] (pathological)	68/771 (8.8%) cT1b Otherwise cT1a	NR	NR	NR
	OPN	1029	*33.6 [0, 91.2]	61.6 [range 25.7-94.0]	3.3 [0.13-9.0] (pathological)	323/1029 (31.4%) cT1b Otherwise cT1a	NR	NR	NR
Adjustment	NA	NA	NA	NA	5	5	5	5	5
Gong 2008 [44]; matched pair	LPN	76	21.7 (25.6)	60.1 (12.5)	2.87 (0.81)	Benign: 21 (27.6%), pT1a: 53 (69.7%), pT1b: 2 (2.6%), pT2: 0	NR	NR	NR
	OPN	77	20.6 (23.1)	57.7 (13.6)	2.45 (0.87)	Benign: 17 (22.1%), pT1a: 50 (64.9%), pT1b: 9 (11.7%), pT2:1 (1.3%)	NR	NR	NR
Adjustment	NA	NA	NA	NA	1	1	5	5	5
Lane 2010 [43]; database review (Cleveland clinic)	LPN	672	*4 yrs [IQR 3.3-6.8]	*61 [IQR 51-69]	*2.6 [IQR 2.0-3.4]	pT1a 425 (85%) pT1b 42 (8.4%) pT2+ 32 (6.4%)	G1-2: 332 (70%) G3-4: 148 (30%)	Clear cell: 324 (48%) Papillary: (17%) Chromophobe: (8%) Other: (1.2%) Benign: 173 (26%)	NR
	OPN	944	*5.7 [IQR3.9-7.3]	* 61 [IQR 52-70]	*3.5 [IQR 2.5-4.5]	pT1a 510 (67%) pT1b 193 (25%) pT2+ 58 (7.6%)	G1-2: 481 (64%) G3-4: 286 (36%)	Clear cell: 554 (59%) Papillary: (14%) Chromophobe: (6%) Other: (1.8%) Benign: 182 (19%)	NR

Study, design and adjustment	Interventions	N	FU (months) mean (SD), *median [range]	Age: Mean (SD), *median [range]	Tsize (cm) Mean (SD) [range], *median	path Tstage	T grade N (Fuhrman unless stated)	Histological cell type	Necrosis
Adjustment	NA	NA	NA	NA	1	1	1	1	5
Marszalek 2009 [45]; matched pair	LPN	100	44.4 (2.4) [19.2, 110.4] (mean, SE, range)	62.3 [range 22.9-83.4]	*2.8, IQR [2.0;3.2]	All pT1a	NR	Of the malignant tumours (n = 81): Clear cell: 52 (64.2%), Papillary: 15 (18.5%), Other: 14 (17.3%). Benign = 19/100	NR
	OPN	100	42 (2.4) [12, 117.6] (mean, SE, range).	62.5 [range 21.9-84.6]	*2.9, IQR [2.3;3.5]	All pT1a	NR	Of the malignant tumours (n = 66) Clear cell : 49 (74.2%), Papillary: 10 (15.2%), Other: 7 (10.6%). Benign: 34/100	NR
Adjustment	NA	NA	NA	NA	1	1	5	1	5
Wu 2010 [46]; database review (Northwestern University of Feinberg medical School)	RF-RCPN	42	25.8 [R 0.5, 71.5]	56 [27-77]	2.8 [0.9-12]	NR	NR	RCC: 32 (76.2%) Benign: 10 (23.8%) Other malignancy 0	NR
	LPN	36	7.8 [R 1.0, 18.9]	58 [36-79]	2 [0.5-3.5]	NR	NR	RCC: 24 (66.7%) Benign: 12 (33.3%) Other malignancy: 0	NR
Adjustment	NA	NA	NA	NA	2	5	5	1	5
Desai 2005b [47]; database review	Lap-Cryo	78 (89 tumours)	24.6 [1-60]	65.55 (12.69) [28-88]	2.05 (0.56) [0.6-3]	All cT1	NR	RCC: 56% Benign: 38% Inconclusive: 6% Of the RCC (n = 50): Clear cell: 28 Papillary: 19 Other:3	NR
	LPN	153 (153 tumours)	5.8 [1-36]	60.59 (13.19) [17-87]	2.25 (0.67) [0.9-3]	All cT1	NR	RCC: 68% Benign: 32% Inconclusive: 0 Of the RCC (n = 104): Clear cell: 64	NR

Study, design and adjustment	Interventions	N	FU (months) mean (SD), *median [range]	Age: Mean (SD), *median [range]	Tsize (cm) Mean (SD) [range], *median	path Tstage	T grade N (Fuhrman unless stated)	Histological cell type	Necrosis
								Papillary: 32 Other: 8	
Adjustment	NA	NA	NA	NA	1	1	5	1	5
O'Malley 2007 [48]; matched pair	Lap-Cryo	15	11.9 (7.2)	76.1 (4.5)	2.7 (1.3)	All cT1	NR	NR	NR
	LPN	15	9.83 (8.8)	75.7 (4.6)	2.5 (1)	All cT1	NR	NR	NR
Adjustment	NA	NA	NA	NA	1	1	5	5	5
Ko 2008 [49]; matched pair	Lap-Cryo	20	27.3 (10.8)	56.3 (11.5) [24-76]	2.38 (1.67) [1.0, 4.0],	pT1	G1: 3, G2: 12, G3: 6, G4: 0	Non-clear type = 2 (of these, 1 is papillary type 1, the other is papillary type 2)	NR
	OPN	20	28.7 (14.9)	57.6 (10.9) [44-77]	2.16 (1.08) [1.3, 3.9]	pT1	G1: 4, G2: 15, G3: 0, G4: 1	Non-clear type = 1 (papillary type 2)	NR
Adjustment	NA	NA	NA	NA	1	1	1	1	5

NA = not applicable; NR = not reported; SM = surgical management; NSM = non-surgical management; HALRN – hand-assisted laparoscopic radical nephrectomy; SLRN = standard laparoscopic radical nephrectomy; RLRN = retroperitoneal laparoscopic radical nephrectomy; TLRN = transperitoneal laparoscopic radical nephrectomy; Robotic RN = robotic radical nephrectomy; LRN = laparoscopic radical nephrectomy; PLRN = portless laparoscopic radical nephrectomy; RN = radical nephrectomy; RN+LND = radical nephrectomy + lymph node dissection; OPN = open partial nephrectomy; ORN = Open radical nephrectomy; LPN = laparoscopic partial nephrectomy; O/LPN = open or laparoscopic partial nephrectomy; O/LRN = open or partial laparoscopic radical nephrectomy; RF-RCPN = radiofrequency assisted robotic clampless partial nephrectomy; Lap-cryo = laparoscopic cryoablation; RCC = renal cell carcinoma

Table 2: Results

Experimental (Exp)	Control (Ctr)	Author	Outcome	N at baseline		Value		Reported P values	Note
				Exp	Ctr	Exp	Ctr		
Non surgical management	Surgery	Zini 2009a [18]	Cancer Specific Death at 5 yr	430	1545	12.4%	4.40%	NR	Matched for age, tumour size, and year of diagnosis.
		Zini 2009a [18]	Other cause death 5 yr	430	1545	57.4%	22.40%	NR	Matched for age, tumour size, and year of diagnosis.
Laparoscopic radical nephrectomy	Open radical nephrectomy	Hemal 2007 [19]	Overall Survival at 5 yrs	41	71	87.8%	88.7%	0.87	Published KM estimate
		Hemal 2007 [19]	Cancer Specific Survival at 5 yrs	41	71	95.12%	94.36%	0.79	Published KM estimate
		Hemal 2007 [19]	Recurrence Free Survival at 5 yrs	41	71	92.6%	90.1%	0.91	Published KM estimate
Hand-assisted laparoscopic radical nephrectomy	Standard laparoscopic radical nephrectomy	Gabr 2009 [24]	Overall Survival	108	147				HR 0.407 (95% CI 0.150, 1.395). Adjusted for specimen handling (intact/morcellation), mass size, pathological risk (based in UCLA integrated staging) and histological subtype.
		Gabr 2009 [24]	Cancer Specific Survival	108	147				HR 0.385 (95% CI 0.087, 1.694). Adjusted for specimen handling (intact or morcellation), mass size, pathological risk (based on UCLA integrated staging, including T-stage), and histological subtype.
		Gabr 2009 [24]	Recurrence free survival	108	147				HR 0.384 (95% CI 0.122, 1.209) Adjusted for specimen handling (intact or morcellation), mass size, pathological risk (based on UCLA integrated staging, including T-stage), and histological subtype.
		Gabr 2009 [24]	Overall Survival at 5 years	108	147	74% (95% CI 63-85)	79% (95% CI 68-90)	0.6864	Published KM estimate
		Gabr 2009 [24]	Cancer Specific Survival at 5 years	108	147	87.2 (95% CI 79-95)	88.9% (95% CI 81-97)	0.7589	Published KM estimate
		Gabr 2009 [24]	Recurrence Free Survival at 5 years	108	147	81.3% (95% CI 72-91)	76.5% (95% CI 64-89)	0.8663	Published KM estimate
Radical nephrectomy with lymph node dissection	Radical nephrectomy	Blom 2009 [8]	Overall Survival	271	288				HR = 1.096 (95%CI 0.81,1.47); log rank p = 0.55
Radical nephrectomy with extended lymph node dissection	Radical nephrectomy with facultative lymph node dissection	Herrlinger 1991 [27]	Survival rates	109	82	80.2% (SD 12.5)	54% (SD 14.1)	<0.01	Life table method
Partial nephrectomy	Partial nephrectomy	Lane 2009 [28]	Overall Survival at 5 years	48	2017	82%	85%	0.56	Published KM estimate

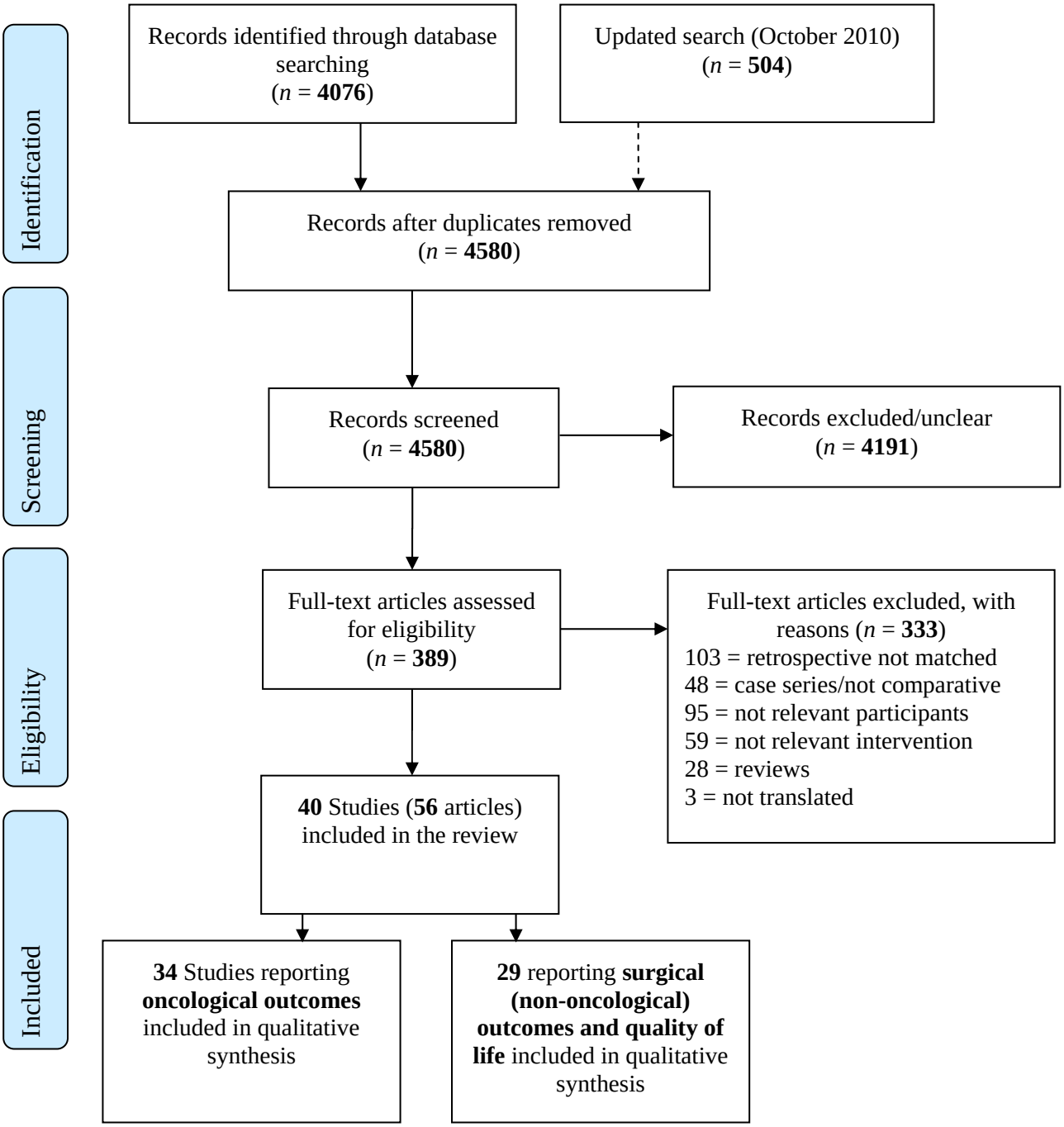
with ipsilateral adrenalectomy		Lane 2009 [28]	Overall Survival at 10 years	48	2017	72.4%	68%	NR	Published KM estimate
Open partial nephrectomy (<4cm)	Open radical nephrectomy (<4cm)	Butler 1995 [30]	Overall Survival at 5 yrs	46	42	75%	80%	NR	Published KM estimate
		Lee 2007 [31]	Overall Survival at 5 yrs	56	56	98.2%	88.8%	0.63	Published KM estimate
		Butler 1995 [30]	Cancer Specific Survival at 5 yrs	46	42	100%	97%	NR	Published KM estimate
		Lee 2007 [31]	Cancer Specific Survival at 5 yrs	56	56	100%	97.9%	0.98	Published KM estimate (matched)
		Lee 2007 [31]	Disease Free Survival at 5 yrs	56	56	92.4%	95.6%	0.18	Published KM estimate (matched)
Laparoscopic partial nephrectomy (>4cm)	Laparoscopic radical nephrectomy (>4cm)	Simmons 2009 [32]	Overall Survival rate at 80 mos, including pT3.	35	75	74% (67%-76%).	72% (67%-76%)	0.660	Published KM estimate
		Simmons 2009 [32]	Cancer Specific Survival rate at 80 mos, including pT3.	35	75	81% (74%-87%).	77% (75%-80%);	0.986	Published KM estimate
		Simmons 2009 [32]	Recurrence free survival at 80 months, including pT3.	35	75	81% (74%-87%)	77% (74%-79%)	0.495	Published KM estimate
Open or laparoscopic partial nephrectomy (<4cm)	Open or laparoscopic radical nephrectomy (<4cm)	Huang 2009 [33]	Overall Survival	556	2435				HR 0.72 (95% CI 0.59, 0.88), p<0.001. Adjusted for demographic characteristics (age at diagnosis, race, marital status, urban-rural location, area level socioeconomic status) and comorbidity. Unadjusted HR = 0.686, p<0.001.
		Zini 2009b [34]	Overall Survival	1283	3166				HR 0.84, p = 0.048. Matched for age, tumour size, year of surgery and Fuhrman Grade.
		Thompson 2008 [35]	All Cause Death (total population)	358	290				RR 1.2 (95% CI 0.80,1.56) p = 0.52
		Thompson 2008 [35]	All Cause Death (subgroup: age <65 years only)	187	140				RR 2.16 (95% CI 1.12,4.19), p = 0.02 Adjusted for: year of surgery (RR 2.34 (95% CI 1.17,4.69), p = 0.016), preoperative creatinine (RR 2.15 (95% CI 1.12,4.19), p = 0.027), Charlson-Romano index (RR 2.14 (95% CI 1.05,4.35), p = 0.037), symptoms at presentation (RR 2.17 (95% CI 1.11,4.24), p = 0.023), diabetes at presentation (RR 2.23 (95% CI 1.09,4.56), p = 0.028), histology (RR 2.32 (95% CI 1.18,4.55), p = 0.015).
		Thompson 2008 [35]	Overall Survival at 10 yrs (subgroup: age <65 years only)	187	140	93%	82%	NR	Published KM estimate
		Zini 2009b [18]	Overall Survival at 10 yrs	1283	3166	70.9%	68.8%	NR	Matched for age, tumour size, year of surgery and Fuhrman grade.

		Huang 2009 [33]	Overall Survival at 5 yrs	556	2435	74%	68%	NR	Published KM estimate
		Zini 2009b [18]	Overall Survival at 5 yrs	1283	3166	88.9%	85.5%	NR	Matched for age, tumour size, year of surgery and Fuhrman grade.
		Patard 2004 [37]	Cancer Specific Survival at 5 years (T1a only)	314	499	97%	97%	NR	KM estimate from graph. Chi-square test p = 0.8, log rank test, p = 0.7.
Open or laparoscopic partial nephrectomy (>4cm)	Open or laparoscopic radical nephrectomy (>4cm)	Thompson 2009 [38]	Overall Survival	286	873				HR 1.06 (95% CI 0.79,1.45), p = 0.665. . Adjusted for age, Charleson index, impaired renal function, tumour size, tumour stage, and histological subtype (benign vs. RCC). Unadjusted HR 0.95 (95% CI 0.71,1.28), p = 0.8.
		Weight 2010 [40]	Overall Survival	524	480				HR = 0.903 (95% CI 0.56, 1.5), p = 0.68. PN vs. RN. Multivariate models stratified according to the propensity to undergo PN, and also including multiple predicting variables, namely pathological stage and postoperative eGFR. HR from univariate analysis stratified according to the propensity to undergo PN = 0.62 (95% CI 0.40, 0.94), p = 0.030.
		Crépel 2010 [41]	Cancer Specific Survival	163	636				HR 0.8; log rank, p = 0.4. Matched for age, tumour size, year of surgery and Fuhrman grade
		Patard 2008 [36]	Cancer Specific Survival	289	257				"Survival curves perfectly overlapped". Log rank test p = 0.9.
		Thompson 2009 [38]	Cancer Specific Deaths	239	704				HR 0.51 (95% CI 0.24,1.09), p = 0.079. Adjusting for age, impaired renal function, tumour stage and tumour size. Unadjusted HR 0.46 (95% CI 1.0.22,0.96) p = 0.039.
		Weight 2010 [40]	Cancer Specific Survival (Pathologically malignant tumours only)	438	429				HR 0.77 (95% CI 0.41, 1.42), p = 0.4. Multivariate regression analysis including pathological size, nuclear grade, pathological T-stage, and final eGFR. HR from univariate analysis = 1.39 (95% CI 1.07, 1.83), p = 0.01.
		Dash 2006 [39]	Disease Free Survival	45	151				HR 0.36 (95% CI 0.05, 2.82), p = 0.3. Adjusted for disease severity (confounder score approach).

									HR from the propensity score model = 1.75 (95% CI 0.5, 6.14), p = 0.4. Unadjusted HR = 0.22 (95% CI 0.03, 1.66), p = 0.14.
		Weight 2010 [40]	Overall Survival at 5 yrs	524	480	85% (95% CI 81.4, 88.6)	78% (95% CI 73.7, 82.3)	NR	Published KM estimate
		Crépel 2010 [41]	Cancer Specific Survival at 5 yrs	163	636	90.1%	93.8%	NR	Published KM estimate
		Patard 2004 [37]	Cancer Specific Survival at 5 years (T1b only)	65	576	96%	91%		KM estimate from graph. Chi-square test, p = 0.6; log rank test, p = 0.8
		Weight 2010 [40]	Cancer Specific Survival at 5 yrs	438	429	87.6% (95% CI 84, 91.2)	94% (95% CI 91.3, 96.7)	NR	KM estimates
		Dash 2006* [39](open/lap vs. open)	Disease Free Survival at 5 years	45	151	83%	71%	NR	Published KM estimate
Laparoscopic radical nephrectomy	Open radical nephrectomy	Hemal 2007 [19]	Overall Survival at 5 yrs	41	71	87.8%	88.7%	0.87	
		Hemal 2007 [19]	Cancer Specific Survival at 5 yrs	41	71	95.12%	94.36%	0.79	
		Hemal 2007 [19]	Recurrence Free Survival at 5 yrs	41	71	92.6%	90.1%	0.91	
Laparoscopic partial nephrectomy	Open partial nephrectomy	Lane 2010 [43]	Overall Survival (RCC with min FU of 1 yr)	499	762				HR 0.69 (95% CI 0.45,1.02), p = 0.07. Adjusted for age, gender, race, Charleson-Romano Index, tumour size, hypertension, preoperative GFR, and oncological potential (calculated as predicted risk of recurrence estimated based on path tumour size, histological subtype, path stage, and symptoms at presentation).
		Marszalek 2009 [45]	Overall Survival at 5 years (pT1 only)	81	66	96% (95% CI 92, 99)	85% (95% CI 79, 92)	0.1	Published KM estimate
		Lane 2010 [43]	Survival at 7 years (subset: RCC with min FU of 7ysr)	77	310	83.1%	83.5%	NR	Actual rate.
		Gill 2007 [42]	Cancer Specific Survival at 3 years (pathological RCC only)	514	676	99.3% (95% CI 98.0, 100.0)	99.2% (95% CI 98.4, 100.0)	NR	Published KM estimate
		Lane 2010 [43]	Cancer Specific Survival at 7 years (RCC with min FU of 1 yr)	499	762	96.9%, (95% CI 94.3-99.5)	97.7%, (95% CI 96.3-99.1)	0.79	KM estimated
		Lane 2010 [43]	Cancer Specific Survival at 7 years (subset: RCC with min FU of 7yrs)	55	249	92.7% (51/55)	95.6% (238/249)		Actual rate
		Marszalek 2009 [45]	Recurrence Free Survival at 5 years (local recurrence in pT1 only)	81	66	97% (95% CI 94, 99)	98% (95% CI 95, 100)		KM estimates. Log rank test, p = 0.8.

		Marszalek 2009 [45]	Recurrence Free Survival at 5 years (distant recurrence in pT1 only)	81	66	99% (95% CI 94, 100)	96% (95% CI 92, 99)		KM estimates. Log rank test, p = 0.2
		Lane 2010 [43]	Metastases Free Survival at 7 years (RCC with min FU of 1 yr)	499	762	97.5%, (95% CI 95.9-99.0)	97.3%, (95% CI 95.9-98.7)	0.47	KM estimated
		Lane 2010 [43]	Metastases Free Survival at 7 years (RCC with min FU of 7yrs only)	55	249	90.9% (50/55)	94.8% (234/249)		Actual rate.
		Gill 2007 [42]	Local recurrence rate at 3 years (pathological RCC only)	514	676	1.4% (95% CI 0, 2.8)	1.5% (95% CI 0.4, 2.6)		KM estimates
		Gill 2007 [42]	Distant recurrence rate at 3 years (pathologial RCC only)	514	676	0.9% (95% CI 0, 2.2)	2.1% (95% CI 0.7, 3.4)		KM estimates
NR = Not Reported; HR = Hazard Ratio; KM = Kaplan Meier; RR									

Figure 1: PRISMA Flow Diagram



Appendix 1. Assessment of risk of bias (part I) – **According to a recommended tool for RCT by the Cochrane Handbook[14]**

Study ID	Rando-mised?	Adequate sequence generation?	Allocation conceal-ment?	Blinding: Survival	Blinding: Surgical	Bliniding: QoL	Incomplete outcome addressed? Survival	Incomplete outcome addressed? Surgical	Incomplete outcome addressed? QoL	Free of selective outcome reporting?	Free of other bias?
Blom 2009 [8]	Yes	Yes	Yes	Unclear	Unclear	NA	Yes	Yes	NA	Yes	No
Butler 1995 [30]	No	No	No	Unclear	Unclear	NA	Yes	Yes	NA	Unclear	Unclear
Crepel 2010 [41]	No	No	No	Unclear	NA	NA	Unclear	NA	NA	Unclear	Unclear
D'Armiento 1997 [29]	Yes	Yes	Unclear	Unclear	NA	NA	No	NA	NA	Yes	Unclear
Dash 2006 [39]	No	No	No	No	NA	NA	Yes	NA	NA	Unclear	Unclear
Desai 2005a [21]	Yes	Yes	Yes	No	No	NA	Yes	Yes	NA	Yes	Unclear
Desai 2005b [47]	No	No	No	No	none	NA	Unclear	Unclear	NA	Unclear	No
Gabr 2009 [24]	No	No	No	Unclear	Unclear	NA	Yes	Unclear	NA	Unclear	Unclear
Gill 2007 [42]	No	No	No	No	No	NA	No	No	NA	Unclear	Unclear
Gong 2008 [44]	No	No	No	No	No	NA	No	No	NA	Unclear	Unclear
Gratzke 2009 [20]	No	No	No	NA	No	No	NA	Yes	No	Yes	Unclear
Hemal 2007 [19]	No	No	No	Unclear	Unclear	NA	Unclear	Yes	NA	Unclear	Unclear
Hemal 2009 [25]	No	No	No	NA	Unclear	NA	NA	Yes	NA	Yes	Unclear

Study ID	Rando-mised?	Adequate sequence generation?	Allocation conceal-ment?	Blinding: Survival	Blinding: Surgical	Bliniding: QoL	Incomplete outcome addressed? Survival	Incomplete outcome addressed? Surgical	Incomplete outcome addressed? QoL	Free of selective outcome reporting?	Free of other bias?
Herrlinger 1991 [27]	No	No	No	No	NA	NA	Yes	NA	NA	Yes	Unclear
Huang 2009 [33]	No	No	No	No	NA	NA	Unclear	NA	NA	Unclear	Unclear
Ko 2008 [49]	No	No	No	No	No	NA	Yes	Yes	NA	Unclear	Unclear
Lane 2009 [28]	No	No	No	No	NA	NA	Yes	NA	NA	Yes	Unclear
Lane 2010 [43]	No	No	No	No	NA	NA	Yes	NA	NA	No	Unclear
Lee 2007 [31]	No	No	No	No	NA	NA	Yes	NA	NA	Unclear	Unclear
Marszalek 2009 [45]	No	No	No	No	No	NA	Yes	Yes	NA	Yes	Yes
Nadler (3 arm) 2006 [23]	Yes	No (quasi-RCT)	No	No	No	NA	Yes	Yes	NA	Yes	Unclear
Nambirajan 2004 [22]	Yes	Unclear	Unclear	Unclear	Unclear	NA	Yes	Yes	NA	Unclear	Unclear
O'Malley 2007 [48]	No	No	No	NA	Unclear	NA	NA	Yes	NA	Yes	Unclear
Patard 2004 [37]	No	No	No	No	No	NA	Yes	Yes	NA	Yes	Unclear
Patard 2008 [36]	No	No	No	Unclear	NR	NA	Unclear	NA	NA	Unclear	Unclear
Simmons 2009 [32]	No	No	No	Unclear	NR	NA	Unclear	NA	NA	Unclear	Unclear

Study ID	Rando-mised?	Adequate sequence generation?	Allocation conceal-ment?	Blinding: Survival	Blinding: Surgical	Bliniding: QoL	Incomplete outcome addressed? Survival	Incomplete outcome addressed? Surgical	Incomplete outcome addressed? QoL	Free of selective outcome reporting?	Free of other bias?
Soga 2008 [26]	No	No	No	NA	Unclear	NA	NA	Yes	NA	Unclear	Unclear
Thompson 2008 [35]	No	No	No	Assessor	NA	NA	Unclear	NA	NA	Unclear	Unclear
Thompson 2009 [38]	No	No	No	Unclear	NA	NA	Unclear	NA	NA	Unclear	Unclear
Weight 2010 [40]	No	No	No	Unclear	NA	NA	Unclear	NA	NA	Unclear	Unclear
Wu 2010 [46]	No	No	No	Unclear	Unclear	NA	Unclear	Unclear	NA	Unclear	Unclear
Zini 2009a [18]	No	No	No	No	NA	NA	Unclear	NA	NA	Unclear	Unclear
Zini 2009b [34]	No	No	No	No	NA	NA	Unclear	NA	NA	Unclear	Unclear

NA = not applicable (relevant outcome not reported);

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