Systematic Review of the Clinical Effectiveness of Surgical Management for Localised Renal Cell Carcinoma

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Mari Imamura,[1] Steven MacLennan,[1] Marie Carmela Lapitan,[2] Muhammad Imran Omar,[1] Thomas BL Lam,[1,3] Anna Melissa Hilvano-Cabungcal,[2] Pam Royle,[4] Fiona Stewart,[1,5] Graeme MacLennan,[5] Sara J MacLennan,[1] Steven J Canfield,[6] Philipp Dahm,[7] Michael Aitchison,[8] Sam McClinton,[3] T R Leyshon Griffiths,[9] Börje Ljungberg,[10] James N'Dow,[1,3] the UCAN Systematic Review Reference Group and the EAU Guideline Group for renal cell carcinoma

[1] Academic Urology Unit, University of Aberdeen, Aberdeen, UK
[2] Department of Urology, UP-PGH Medical Center, Manila, Philippines
[3] Department of Urology, Aberdeen Royal Infirmary, Aberdeen, United Kingdom
[4] Department of Population Health, University of Aberdeen, Aberdeen, UK
[5] Health Services Research Unit, University of Aberdeen, Aberdeen, UK
[6] Division of Urology, University of Texas Medical School at Houston, Houston, USA
[7] Department of Urology, University of Florida, Gainesville, Florida, USA
[8] Department of Urology, Gartnavel General Hospital, Glasgow, UK
[9] Department of Urology, University Hospitals of Leicester NHS Trust, Leicester General Hospital, Leicester, UK
[10] Department of Surgical and Perioperative Sciences, Urology and Andrology, Umeå University, Umeå, Sweden

Members of the EAU (European Association of Urology) Guideline Group for renal cell carcinoma:
Börje Ljungberg, Axel S Merseburger, Jean-Jacques Patard, Milan Hora, Markus A Kuczyk, Damian C Hanbury, Peter F A Mulders, Ioanel C Sinescu

Members of the UCAN Systematic Review Reference Group for renal cell carcinoma:
Michael Aitchison, Philipp Dahm

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Executive summary

Background: Renal cell carcinoma (RCC) accounts for approximately 2-3% of all adult malignancies. There remain uncertainties over the oncological, surgical and quality-of-life outcomes for the many different surgical approaches for managing localised RCC. Controversy also remains on the issue of whether ipsilateral adrenalectomy should be done at the time of nephrectomy, and whether lymphadenectomy (and if so, to what extent) should be done at the time of nephrectomy.

Objective: To conduct a systematic review to summarise evidence of the effectiveness and safety of established and emerging surgical treatment options in the management of localised RCC (T1-2N0M0).

Methods: An extensive electronic literature search was carried out to identify relevant studies published in any language up to October 2010. Reference lists of included studies and key conference proceedings were also screened. We included randomised or quasi-randomised (e.g. alternate allocation) controlled trials, prospective non-randomised studies with controls, retrospective matched-pair studies and studies reporting retrospective comparative analyses of data from well-defined registries or databases. Case series and single cohorts without a control group were excluded. Two reviewers independently extracted data and assessed risk of bias of all included studies using tools recommended by the Cochrane Collaboration. Quantitative data synthesis (meta-analysis) was performed with the randomised trial data. The data from the non-randomised studies were not formally combined to avoid the risk of attenuating possible systematic bias. The quality of a body of evidence was assessed using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach.

Results: A total of 4580 abstracts and 389 full-text articles were assessed independently by two reviewers. Of these, 40 studies met the inclusion criteria, including seven randomised or quasi-randomised trials (1,368 participants), and 33 non-randomised comparative studies

(22,737 participants). The included studies covered 24 treatment comparisons. The sample size varied between 24 and 4449 with the majority of studies having fewer than 200 participants. Duration of follow-up was generally short: only two randomised trials and two non-randomised comparative studies had a mean or median follow-up period of five years or longer in all study arms. The majority of studies were assessed as having a high risk of bias and the quality of evidence across outcomes was rated as either 'low' or 'very low' using GRADE.

Non-surgical management (Chapter 5). There was little evidence to show that surgery improves survival compared with non-surgical management. From a practical point of view, this is a question that could be answered through programmes of active 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.

Technique of radical nephrectomy (Chapter 6). In general, there was insufficient evidence to show any major difference between laparoscopic and open radical nephrectomy or between different laparoscopic approaches, in terms of both oncological (e.g. survival) and peri-operative outcomes. For laparoscopic radical nephrectomy, the choice of approach (retroperitoneal vs. transperitoneal) appears to have little impact on outcomes. With regard to innovations and modifications to laparoscopic radical nephrectomy, such as hand-assisted, robotic-assisted or single-port techniques, all of them appear to result in similar outcomes to standard laparoscopic radical nephrectomy, although the included studies were small and follow-up was short.

Ipsilatelal lymphadenectomy and ipsilateral adrenalectomy (Chapter 7). The included studies provided inconsistent findings regarding the performance of lymph node dissection with radical nephrectomy, such that no definitive conclutions can be drawn. No comparative data were identified from which to assess the merit of performing ipsilateral adrenalectomy with radical nephrectomy. With regard to partial nephrectomy, the available evidence from a non-randomised study does not support or refute routine removal of the ipsilateral adrenal gland to improve short- or long-term outcomes. For patients who

are selected to undergo adrenalectomy, it remains to be seen whether adrenalectomy has an impact on survival.

Partial vs. radical nephrectomy (Chapter 8, section 1). Current evidence based on randomised and non-randomised studies found no significant difference in survival between open partial and open radical nephrectomy for small tumours (≤4 cm). Non-randomised studies that combined open and laparoscopic approaches appear to show improved survival for partial nephrectomy for small tumours, although this could be due to confounding. For larger tumours (>4 cm), survival outcomes appeared similar between partial and radical nephrectomy. In all studies where renal function was reported (including one RCT), partial nephrectomy was associated with better preservation of renal function compared with radical nephrectomy.

Ablation vs. radical nephrectomy (Chapter 8, section 2). The review identified only one small non-randomised study with a short follow-up for this comparison. No conclusion can be drawn from this study.

Technique of partial nephrectomy (Chapter 8, section 3). It remains unclear if the laparoscopic approach to partial nephrectomy offers better outcomes than the traditional open route, although the laparoscopic approach was associated with a consistently longer operation time, shorter hospital stay and less blood loss. Regarding the robotic-assisted approaches to partial nephrectomy compared with standard laparoscopic partial nephrectomy, there was no strong evidence to suggest any differences in terms of peri-operative outcomes. No information was available about their long-term oncological performance, especially with regard to survival.

Ablation vs. partial nephrectomy (Chapter 8, section 4). For the comparisons of minimally invasive ablative procedures and partial nephrectomy, no definitive conclusions can be drawn because the review identified very few non-randomised studies which were uniformly small with short follow-up. The included studies provided no information about long-term survival or quality of life. Regarding peri-operative outcomes, the limited evidence that is available suggests a reduction in blood loss after ablative procedures

compared with partial nephrectomy (either open or laparoscopic), but other outcomes including renal function appear similar between the groups.

Conclusions: Current evidence suggests that localised renal cancers are best managed by nephron-sparing surgery rather than by radical nephrectomy, where technically feasible, for the perceived benefits of preservation of renal function without compromising on oncological outcomes. However, it remains unclear what the upper limit of tumour size should be beyond which partial nephrectomy loses its advantages.

The evidence around minimally invasive ablative technologies is weak due to small sample size, short follow up, high risk of bias and mixed patient populations that include benign renal lesions, rendering judgements about effectiveness unreliable.

The issues regarding the effects of adrenalectomy or lymphadenectomy remain unresolved. The available evidence does not seem to support routine ipsilateral adrenalectomy or lymphadenectomy, but these results are uncertain.

The current evidence base has significant limitations due to studies marked by high risks of bias. 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 and, ideally, standardised measures of outcomes, and have multiple centres to ensure that the studies give sufficiently precise estimates of the various outcomes. Ideally, allocation should be randomised to minimise selection bias and clinical heterogeneity. There is an urgent need for standardisation of outcome reporting in renal cancer trials, non-randomised (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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List of abbreviations

AUA = American Urological Association
ASA = American Society of Anesthesiologists
BAUS = British Association of Urological Surgeons
CI = confidence interval
CSS = Cancer-specific survival
CT = Computed Tomography
DFS = Disease-free survival
EAU = European Association of Urology
eGFR = Estimated glomerular filtration rate
EORTC = European Organisation for Research and Treatment of Cancer
FU = follow up
GFR = Glomerular filtration rate
GRADE = Grading of Recommendations Assessment, Development and Evaluation
HIFU = High intensity focused ultrasound
HR = Hazard ratio
KM = Kaplan-Meier
Lap = Laparoscopic
LND = Lymph node dissection
LPN = Laparoscopic partial nephrectomy
LRN = Laparoscopic radical nephrectomy
MD = Mean difference
MFS = Metastasis-free survival
MRI = Magnetic Resonance Imaging
NR = Not reported
NRS = Non-randomised study
NS = not statistically significant
OS = Overall survival
PN = Partial nephrectomy
PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QoL = Quality of life
Q-RCT = Quasi-Randomised Controlled Trial
RCC = renal cell carcinoma
RCT = Randomised Controlled Trial
RFS = Recurrence-free survival
RN = Radical nephrectomy
RoB = Risk of bias
RR = Relative risk
SD = Standard deviation
SEER = Surveillance Epidemiology and End Results
SF-36 = Short Form 36
TNM = Tumour Nodes Metastases
WMD = Weighted mean difference

Chapter 1 Introduction

Renal cell carcinoma accounts for approximately 2-3% of all malignancies occurring in adults. It has the highest incidence rate in the sixth to seventh decades of life, with a median age of diagnosis at 64 years and a male to female ratio of 1.5:1 to 2.5:1.[1-3] A number of risk factors for its occurrence have been proposed but evidence points only to tobacco exposure and obesity as the identifiable risk factors for the development of renal cell carcinoma.[3-6] Cigarette smoking has been shown to be a causal risk factor with a relative risk ranging from 1.4 to 2.5. It has a strong dose-response relationship and a significant decline in risk is noted following cessation of tobacco use.[3-6] The association between obesity and renal cell carcinoma has been consistent such that it is now a generally accepted risk factor for both men and women.[3-5,7]

Over the past two decades, there has been an increase in the detection of renal tumours due to the widespread use of non-invasive imaging techniques such as ultrasound and computed tomography (CT) scan in the investigation of various non-specific symptoms. Triple phase abdominal CT scan continues to be the single most important and helpful test in determining the nature of a renal mass.[8] The advances in imaging techniques have led to the earlier diagnosis of renal cell carcinoma and an increase in the number of low stage tumours detected.

Localised renal tumours, based on the 2002 TNM staging classification, are defined as tumours which are confined to the kidney (T1-T2N0M0 or stage I to stage II). More than half of all renal carcinomas detected are in the localised stage.[1] In the treatment of renal cell carcinoma, including localised disease, radical nephrectomy has been the established standard curative therapy for the past five decades.[9] However, nephron sparing surgery has been the accepted mode of treatment for localised renal cell carcinoma wherein radical nephrectomy would render the patient anephric or at high risk for subsequent renal replacement therapy.[10] 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 oncological outcomes.[11,12] The 2010 European Association of Urology guidelines recommend nephron-sparing surgery for T1 tumors whenever possible, with open partial nephrectomy advocated as the standard.[13] Currently, nephron-sparing surgery can be performed either through the open extraperitoneal or transperitoneal routes, or laparoscopically but it remains unclear if these approaches are equivalent in terms of oncological outcomes.

With the advent of minimally invasive surgery, laparoscopic nephrectomy for renal carcinoma has become an acceptable alternative to open surgery as the mode of treatment for localised tumours particularly since recent data have shown it to be oncologically equivalent to open surgery.[14] The 2010 EAU guidelines on renal cell carcinoma recommend laparoscopic radical nephrectomy for T2 renal cancer when partial nephrectomy is not suitable.[13] However, a systematic review of current evidence is needed in order to establish whether the outcomes of both of these approaches are comparable.

The presence of lymph node involvement has a significant impact on the prognosis of renal cell carcinoma. It has been argued that there is no value in performing a systematic lymph node dissection in clinically node negative patients,[15] but this finding does not discriminate between prognostically important tumour stages and therefore this finding is limited. Thus, the value of retroperitoneal lymph node dissection and the extent of dissection (extended or hilar) in localised disease is not clearly defined and continues to be debated.[14] It is necessary to establish clearly the indications for lymphadenectomy in all stages of renal carcinoma.

In the standard radical nephrectomy, ipsilateral adrenalectomy is concomitantly performed. However, it has been argued that its performance may not be necessary, particularly in localised tumours with no evidence of adrenal involvement on pre-operative imaging studies, and not involving the upper pole.[13,16-18] A systematic review of current evidence is needed to elucidate the value, if any, of adrenalectomy in the treatment of localised renal cell carcinoma.

Minimally invasive therapy for low stage, localised renal cell carcinoma, employing cryotherapy, radiofrequency ablation or high intensity focused ultrasonography (HIFU), is also considered to be an alternative to nephron-sparing procedures particularly in patients in whom surgical excision may not be suitable. However, because of the relatively recent application of these techniques, their oncologic efficacy has not been fully established, particularly in the long term, and no clear recommendations regarding these options have been presented.[12,19] These treatments also have the potential advantage of minimising adverse effects such as damage to adjacent structures, since treatment delivery can be tightly controlled and confined to within a few millimetres of accuracy. A systematic review should establish the safety and efficacy of these procedures compared with the standard surgical treatment, as well as in comparison with each other.

Although guidelines exist in relation to the various interventions for localised renal cancer,[13,20] a systematic review of current evidence is needed in order to establish whether the outcomes of all these competing interventions are comparable. This is particularly vital for new technologies, which often progress at a rapid pace such that new versions or generations of machines or equipment have emerged even before the clinical community has appropriately assessed the previous versions. The objective of this systematic review was to compare the oncological, peri-operative and quality-of-life outcomes for all interventions relevant to the management of localised RCC.

Chapter 2 Objectives

The aim of this review was to examine the clinical effectiveness of established and emerging surgical treatments for localised renal cell carcinoma. We assessed the following comparisons:

- Non-surgical treatment vs. surgical treatment
- One technique of radical nephrectomy vs. another
- Surgery for tumour with lymphadenectomy vs. surgery alone
- Surgery for tumour with adrenalectomy vs. surgery alone
- Nephron sparing surgery including:
    - Partial nephrectomy vs. radical nephrectomy
    - Ablation vs. radical nephrectomy
    - One technique of partial nephrectomy vs. another
    - Ablation vs. partial nephrectomy
    - One type of ablation vs. another

Chapter 3 Methods

A protocol for the systematic review was written *a priori*. After the review commenced, the review authors gained access to a new tool being piloted by the Cochrane Non-Randomised Study Methods Groups for assessing the risk of bias in non-randomised studies.[21] The authors also decided to incorporate the GRADE tool for assessing the quality of evidence of selected outcomes.[22] This resulted in some modification in the methods used, although the overall aim of the review remained unchanged.

In the initial stages of the systematic review, we created a care pathway with the input of a number of clinical content experts from national and professional international bodies (for instance, BAUS and EAU), to reflect all the plausible treatment options for localised renal cancer. The Care pathway is shown in Appendix 1. The treatment options shown in the care pathway were used to formulate research questions and to drive the search strategy, as they facilitate the essential interventions systematic review structure of patients, interventions, comparisons and outcomes (PICO) (see MacLennan and colleagues[23] for further detail).

3.1. Criteria for considering studies for this review

3.1.1. Types of Studies

All randomised controlled trials (RCTs) and quasi-RCTs (e.g. alternate allocation) were included. Since there were very few randomised trials in this area, the review also included prospective non-randomised comparative studies. Retrospective comparative studies were eligible only if they used a matched-pair design or if they were based on a well-defined registry or database. Studies with no control or comparator group, case series and case-note reviews were excluded.

3.1.2. Types of participants

All patients diagnosed with localised renal cell carcinoma based on CT scan or MRI, defined as clinical stage T1a-T2N0M0. Studies that reported pathological T3 cases were included so long as the clinical staging was T1-2N0M0.

3.1.3. Types of intervention

The following interventions were included:

- Radical nephrectomy: use of the basic principles of early ligation of the renal artery, removal of the kidney outside Gerota's fascia, excision of the ipsilateral adrenal gland
- Partial nephrectomy (nephron-sparing surgery): removal of the affected portion of the kidney with a margin of normal appearing parenchyma beyond the visual limits of the tumour
- Laparoscopic surgery for radical or partial nephrectomy
- Hand-assisted laparoscopic surgery for radical or partial nephrectomy
- Robot-assisted surgery for radical or partial nephrectomy
- Complete regional (extended) lymphadenectomy: lymph node dissection from the crus of the diaphragm to the aortic bifurcation
- Partial regional (limited) lymphadenectomy: lymph node dissection to an extent less than that of complete extended lymphadenectomy
- Adrenalectomy: complete removal of the ipsilateral adrenal gland
- Radiofrequency ablation: heat generated by high frequency electrical current to destroy cancer tissue
- Cryoablation: freezing of target cancer tissue to effect cancer cell death
- High intensity focused ultrasound: destruction of cancer cells using thermal energy generated using high intensity focused ultrasonic waves.

A valid comparator was no intervention or any of the specified interventions.

3.1.4. Types of outcome measures

Table 3.1 outlines the outcome measures that were sought. The primary outcome was overall survival. For long-term data such as survival, both time-to-event data and categorical data were extracted. For categorical data, we collected event rates at five and ten years, and where such data were not reported, data at last follow-up were collected.

Table 3.1. Outcome measures

Category	Outcomes
Oncological outcomes	• Overall survival • Cancer specific survival • Recurrence-free survival • Metastasis • Positive margin rate after surgery or tumour-free rates on biopsy after ablative technique

Peri-operative outcomes and adverse effects	• Blood loss
	• Need for blood transfusion
	• Operative morbidity
	  ○ Surgical site infection
	  ○ Pneumonia
	  ○ Urinary tract infection
	  ○ Deep venous thrombosis
	  ○ Haemorrhage
	• Post-operative mortality
	• Analgesic requirement
	• Time to normal activity level

Resource utilisation	• Duration of operation • Length of hospital stay
Quality of life	• Condition-specific quality of life • General health status measures, e.g. Short Form 36[24]
Health economics	• Direct costs of interventions • Resource implication of the effects of treatment • Cost effectiveness of intervention

3.2. Search methods for identification of studies

The electronic databases searched were: MEDLINE (1950-October 2010), 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. All abstracts and full-text articles were screened independently by two reviewers. Any disagreement was resolved by discussion or was referred to a third reviewer. Full details of the search strategies used are provided in Appendix 2.

3.3. Data extraction

Two reviewers independently extracted data using a standard data extraction form designed for this review (Appendix 3). The form also included a checklist developed by the Cochrane Non-Randomised Studies Methods Group (convenor: Professor Barnaby Reeves, University of Bristol, UK) to record study design features of non-randomised studies.[25] The checklist included two questions: (1) How were treatments allocated?, and (2) Which parts of the study were prospective? The intention is to highlight potential selection bias inherent in non-randomised studies. Discrepancies in data extraction were resolved by discussion, with involvement of a third reviewer where necessary.

3.4. Assessment of risk of bias

The included studies were assessed for their potential risk of bias according to Cochrane risk of bias domains (Appendix 4). Two reviewers independently undertook the assessment. Any differences of opinion were resolved by consensus or by consulting a third party.

The risk of bias in RCTs and quasi-RCTs was assessed using the standard tool recommended by the Cochrane Collaboration.[26] This included random sequence generation, allocation

concealment, blinding of participants, therapists and outcome assessors, completeness of outcome data, selective outcome reporting and other potential sources of bias.

An extended version of this Cochrane RCT risk-of-bias tool was applied to non-randomised studies (NRS).[21] This included three additional items: (a) the risk of findings being explained by confounding (selection bias); (b) whether the NRS had an *a priori* protocol; and (c) whether the NRS had an *a priori* analysis plan. Reviewers found items (b) and (c) difficult to assess because of poor quality of reporting and therefore replaced them with another item: (d) whether review board approval was specified.

For (a), a list of the most important potential confounders for oncological (e.g. survival) and peri-operative (e.g. morbidity) outcomes were identified *a priori* in consultation with clinical experts. A list of these confounders is given in Table 3.2. We had ranked the pre-specified confounding factors in order of importance so that the overall assessment could be weighted. However, this made the assessment process too complex and therefore a pragmatic decision was made not to do this.

Table 3.2. Key confounding factors identified *a priori* for the assessment of risk-of-bias in non-randomised studies

Oncological outcomes (e.g. survival) and quality of life	Peri-operative outcomes (e.g. morbidity, time to return to normal activity)
• Histological cell type • Clinical tumour size • Pathological tumour stage • Tumour grade • Necrosis	• Performance status • Age • Co-morbidity • Ethnicity

Each of the pre-specified confounding factors was then assessed on the following four criteria: (1) whether the confounder was considered by the study author, (2) precision of measurement, (3) baseline imbalance between groups, and (4) quality of case-mix adjustment. Imbalance was judged by consensus between two clinical experts, while the other criteria were assessed independently by two systematic reviewers. Because the

assessment of precision and imbalance were related to the assessment on adjustment, a pragmatic decision was made to use the adjustment score as a summary indicator of the overall risk of confounding in NRS in this review.

We had initially attempted to assess the degree of care with which adjustment was carried out (e.g. methods used for controlling for confounding, quality of matching by characteristics of subjects and whether adjustment was done at design stage or at analysis stage) on five-point scales. In practice this was difficult because of the limited information available in the published report, and also because the methodological quality of the included studies was in general very low and there did not appear to be enough variation to warrant five different categorisations. We therefore decided to use a simplified scale: a study was rated as 1 if *any* attempts were made to control for the specific confounder, or otherwise it was rated as 5, as shown in Table 3.3.

Table 3.3. Scoring guideline used for assessing risk of confounding in non-randomised studies

Case-mix adjustment score, as a summary indicator of overall risk of confounding	
1 =	The study groups were judged to be balanced at baseline, or the study used statistical methods that attempted to control for the specific confounder.
5 =	The specific confounder was either not reported, or was not balanced between the groups at baseline and not adjusted for in the analysis.

Similarly, the other criteria of the tool were piloted on a subset of the papers first (using five-point scales), after which a set of guidelines was drawn up and all the included NRS assessed (using simplified scales). Our detailed guidelines, drawn up with clinical, statistical and methodological advice from members of the Cochrane Non-Randomised Studies Methods Group and the GRADE working group, are shown in Appendix 5.

3.5. Assessment of the quality of evidence (GRADE)

To offer clarity and standardisation in making judgements about the quality of evidence, we used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.[27] The GRADE approach classifies the quality of evidence into four categories: high, moderate, low and very low (Table 3.4). Randomised studies begin as 'high' quality evidence, whereas non-randomised studies, due to their inherent bias, default to low quality evidence. Evidence quality is rated up or down according to pre-defined characteristics. Quality is lowered by limitation of study design (risk of bias), inconsistency of results (heterogeneity), indirectness of evidence, imprecision, and other sources of bias such as publication bias. Quality is raised by large magnitude of effect, dose-response gradient, or confounding which would reduce the effect or suggest a spurious effect if no effect was observed.[28,29] A summary of the GRADE approach is given in Table 3.4.

Table 3.4. A summary of GRADE approach to rating the quality of evidence in this review

Quality of evidence	• **High** (further research is very unlikely to change our confidence in the estimate of the effect) • **Moderate** (further research is likely to have an important impact on our confidence in the estimate of the effect and may change the estimate) • **Low** (further research is very likely to have an important impact on our confidence in the estimate of the effect and is likely to change the estimate) • **Very low** (Any estimate of effect is very uncertain)
Quality is lowered by	• **Risk of bias** (including confounders) o -1 in randomised trials if no allocation concealment/blinding/incomplete accounting of patients and outcome events/selective outcome reporting o -1 in non-randomised studies if two or more pre-specified confounders are not balanced at baseline and not statistically controlled for • **Inconsistency** o -1 for unexplained heterogeneity across studies • **Indirectness** o -1 if short FU <5 years (for long-term outcomes), or proxy outcome (for example, cancer-specific deaths as a proxy for

	overall survival) • **Imprecision** ○ -1 if there are small sample sizes and wide 95% confidence intervals (95% CI crosses the line of no effect and the threshold for appreciable benefit/harm) • **Publication bias** ○ -1 if there was strong suspicion that only small trials reporting positive results were published
Quality is raised by: (this may only occur if an outcome has not been downgraded on any other domains)	• Large magnitude of effect • Dose response • All plausible residual confounding which would reduce a demonstrated effect, or would suggest a spurious effect if no effect was observed

Source: Balshem, Helfanda, Schünemann et al.[30]

GRADE also designates that the quality of evidence rating is outcome-specific and asks reviewers to rank the relative importance of outcomes to patients and clinical decision makers as critical, important and not important. The quality of a body of evidence is assessed for each of the critical and most important outcomes. The seven outcomes chosen for this systematic review in consultation with clinical experts appear in Table 3.5. Of these, it was difficult to extract data for the overall morbidity rate because morbidity was reported inconsistently between studies. It was usual for some studies to report rates for a specific morbidity or a few specific morbidities (for example, surgical site infection, pneumonia, or deep vein thrombosis rates) and for other studies in the same comparison to report some of these, or other morbidity rates. It was uncommon for studies to report overall morbidity rates, and difficult to construct this measure from the extracted data because to add different rates of morbidities together and have a single summary score was meaningless. Instead, we used 'length of hospital stay' as a proxy outcome because it was commonly reported and can be used to indicate overall morbidity rates. Nonetheless, the quality of evidence was downgraded for 'indirectness' in GRADE.

Table 3.5. Patient-important outcomes chosen for the assessment of the quality of evidence according to the GRADE approach

Outcome	Relative importance to patients
Overall survival at 5 years	Critical
Condition-specific quality of life	Critical
Recurrence-free survival at 5 years	Critical
Overall morbidity rate	Critical
Time to normal activity level	Critical
Analgesic requirement	Important
Need for blood transfusion	Important

3.6. Data analysis

Quantitative data synthesis (meta-analysis) was performed with randomised trial data only. The data from non-randomised studies were not formally combined in data synthesis to avoid the risk of attenuating possible systematic bias inherent in any non-randomised studies. To calculate summary estimates with 95% confidence intervals for the trial data, fixed effects models were used to derive relative risk (RR) for dichotomous variables and weighted mean difference (WMD) for continuous variables.

When using relative risks, if 95% confidence intervals in individual studies do not cross the line of no effect (i.e. 1) then the result can be regarded as statistically significant at the 5% (p-value = 0.05) level. When using mean difference, if 95% confidence intervals in individual studies do not cross the line of no effect (i.e. 0), then the result can be regarded as statistically significant at the 5% level.

Statistical heterogeneity between studies was assessed by the χ^2 test for heterogeneity and I^2 statistics.[31] Quantitative synthesis was performed using the standard Cochrane software RevMan 5. Where a quantitative synthesis was considered to be inappropriate or not feasible, data were tabulated and summarised according to the comparison made.

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 to renal tumours
- Different ASA grades
- Different tumour stages.

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

Chapter 4 Description of included studies

4.1. Number and type of studies identified

The initial search generated 4580 reports, of which 56 reports were selected for inclusion in the review. The study selection process is outlined in Figure 4.1 (PRISMA diagram). These described 40 studies including seven randomised or quasi-randomised trials,[15,32-37] and 33 non-randomised comparative studies. Of the 33 non-randomised studies, six were prospective cohorts,[38-43] 12 were retrospective matched-pair studies,[27,44-54] and the other 15 were retrospective database reviews.[55-69]

The included studies covered 24 treatment comparisons (Table 4.1). The list of included studies and associated references appear in Appendix 6. Reasons for exclusions for a subset of the excluded papers are described in Appendix 7.

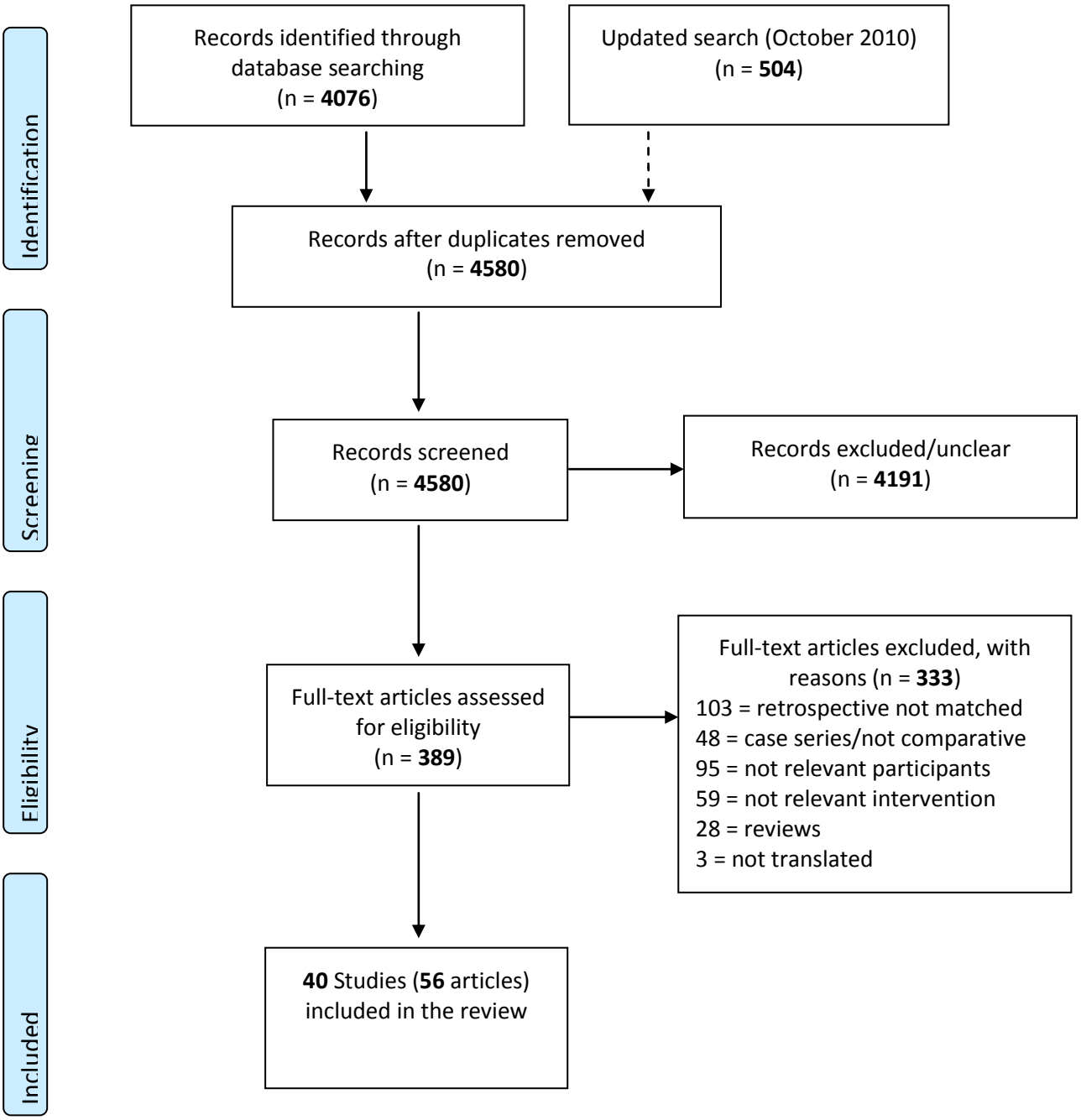
Table 4.1. Number and type of studies identified

	Type of comparisons	*Number of studies*	*Study name*	*Study design*
	A. Non-surgical vs. surgical treatment			
A1	Non-surgical vs. surgical management	1	Zini 2009a[53]	Database review
	B. Technique of radical nephrectomy			
B1	Laparoscopic RN vs. open RN	3	Gratzke 2009[60] Hemal 2007[38] Peng 2006[36]	Database review Prospective cohort RCT
B2	Retroperitoneal laparoscopic RN vs. transperitoneal laparoscopic RN	3	Dasai 2005a[33] Nadler 2006[34] Nambirajan 2004[35]	RCT Q-RCT RCT
B3	Hand-assisted laparoscopic RN vs. transperitoneal laparoscopic RN	1	Nadler 2006[34]	Q-RCT
B4	Hand-assisted laparoscopic RN vs. retroperitoneal laparoscopic RN	1	Nadler 2006[34]	Q-RCT
B5	Hand-assisted laparoscopic RN vs. standard (trans- or retro-peritoneal) laparoscopic RN	1	Gabr 2009[59]	Database review
B6	Robotic RN vs. lapaprascopic RN	1	Hemal 2009[39]	Prospective cohort
B7	Portless (i.e. single port) laparoscopic RN vs. laparoscopic (3 ports) RN	2	Park 2009[50] Soga 2008[43]	Matched-pair Prospective cohort
	C. Lymphadenectomy/adrenalectomy			
C1	RN with lymphadenectomy vs. RN alone	2	Blom 2009;[15] Herrlinger 1991[40]	RCT subgroups Prospective cohort
C2	PN with adrenalectomy vs. PN alone	1	Lane 2009[55]	Database review
	D. Nephron sparing surgery			
	Partial vs. radical nephrectomy			
D1	Open PN vs. open RN	7	Butler 1995[56] D'Armiento 1997[32] Gratzke 2009[60] Lee 2007[27] Poulakis 2003[42] Shekarriz 2002[52] Van Poppel 2007[37]	Database review RCT Database review Matched-pair Prospective cohort Matched-pair RCT
D2	Laparoscopic PN vs. laparoscopic RN	1	Simmons 2009[68]	Database review
D3	Open or laparoscopic PN vs. open or laparoscopic RN	8	Crépel 2010[45] Dash 2006[57] Huang 2009[61] Patard 2004[63] Patard 2008[51] Thompson 2008[64] Thompson 2009[69] Weight 2010[65] Zini 2009b[54]	Matched-pair Database review Database review Database review Matched-pair Database review Database review Database review Matched-pair

	Type of comparisons	*Num-ber of studies*	*Study name*	*Study design*
	Ablation vs. radical nephrectomy			
D4	Radiofrequency ablation vs. laparoscopic RN	1	Onishi 2007[41]	Prospective cohort
	Technique of partial nephrectomy			
D5	Laparoscopic PN vs. Open PN	4	Gill 2007[67] Gong 2008[46] Lane 2010[62] Marszalek 2009[48]	Database review Matched-pair Database review Matched-pair
D6	Robotic laparoscopic PN vs. laparoscopic PN	1	Aron 2008[44]	Matched-pair
D7	Radiofrequency ablation-assisted robotic clampless PN vs. laparoscopic PN	1	Wu 2010[66]	Database review
	Ablation vs. partial nephrectomy			
D8	Laparoscopic cryoablation vs. laparoscopic PN	2	Desai 2005b[58] O'Malley 2007[49]	Database review Matched-pair
D9	Laparoscopic cryoablation vs. open PN	1	Ko 2008[47]	Matched-pair
D10	HIFU vs. PN	0		
	Types of ablation			
D11	Radiofrequency ablation vs. cryoablation	0		
D12	HIFU vs. Cryoablation	0		
D13	HIFU vs. Radiofrequency ablation	0		
D14	Percutaneous cryotherapy vs. laparoscopic cryotherapy	0		
D15	One dose or treatment protocol of radiofrequency ablation vs. another	0		

HIFU = High-Intensity Focused Ultrasound; PN = partial nephrectomy; RN = radical nephrectomy; RCT = randomised controlled trial; Q-RCT = quasi-randomised controlled trial; matched-pair = retrospective matched-pair study

Figure 4.1: PRISMA Flow Diagram



4.2. Characteristics of included studies

The characteristics of the 40 randomised and non-randomised studies included in the review is summarised in Table 4.2. A more detailed description is provided in Appendix 8. Most studies were published between 2000 and 2010. More than two thirds of the studies reported single institution experience (71% of randomised trials and 67% of non-randomised studies). The sample size ranged from 24 to 4449 with the majority of studies having fewer than 200 participants. The total number of participants was 1,368 in the randomised or quasi-randomised studies and 22,737 in the non-randomised comparative studies. Duration of follow-up was generally short: only two of the seven (29%) trials[15,32] and two of the 33 (6%) non-randomised studies[55,64] had a mean or median follow-up period of five years or longer in all study arms.

The seven randomised and quasi-randomised studies were conducted in five geographical areas: two in the USA,[33,34] two in multiple European countries,[15,37] and one each in Austria,[35] China,[36] and Italy.[32] Nearly two thirds of the non-randomised studies (20 out of 33) occurred in the USA;[44-46,49,52-59,61,62,64-69] three in Korea,[27,47,50] two each in Germany,[40,42] India[38,39] and Japan,[41,43] and one in Austria;[48] and three non-randomised studies were conducted in collaboration across countries.[51,60,63]

The included studies were conducted in 24 study institutions (Table 4.3). The largest number of studies come from the Cleveland Clinic in the USA (seven studies), all of which reported retrospective analyses of the prospectively maintained institutional database. The majority of other retrospective studies similarly derived data from prospectively maintained databases or registries, e.g. the SEER (Surveillance, Epidemiology and End Results) programme, although for some databases it was not clear whether they were prospective or retrospective design.

Table 4.4 summarises the study design features of the non-randomised studies, and in particular how study groups were created, based on a checklist developed by the Cochrane Non-Randomised Studies Methods Group.[25] With regard to the question of how treatments

were allocated, five studies stated that this was done by both health care decision makers (the surgeon) and patient preference.[38,43,47,65,68] Another five studies[41,52,56-58] reported that treatments were allocated by the surgeon, while in another study[39] this was done by patient preference. Two further studies[48,60] formed treatment groups by location difference with another[66] by time difference (historical control). The remainder of the studies (19 out of 33) did not stipulate how study groups were created. Based on the available information, the majority of studies may be considered to be at high risk of selection bias.

The six prospective non-randomised studies included in the review did not provide sufficient information with regard to the second question as to which parts of the study were prospective. Nevertheless, we judged that all specified components on the checklist (identification of participants, assessment of baseline and intervention allocation, assessment of outcomes, and generation of hypothesis) were prospective in three studies; this includes two studies[41,43] that stated that patient consent was obtained, and the third[42] that stated that the last 51 consecutively treated patients as part of a larger retrospective study were prospectively followed up for up to one year after surgery. The other three studies[38-40] merely mentioned that clinical data were prospectively evaluated and it was therefore unclear which parts were prospective.

Data on the number of surgeons and surgeon experience were not reported consistently across studies. The limited information that was available is reported in Appendix 8 (Study Characteristics).

Table 4.2. Characteristics of included studies by study design

Criteria	Randomised or quasi-randomised controlled trial (7 studies)	Non-randomised comparative study (33 studies)
Study design		
Randomised controlled-trial (RCT)	6 (86%)	--
Quasi-RCT	1 (14%)	
Prospective cohort	--	6 (18%)
Retrospective matched-pair study	--	12 (36%)
Database review	--	15 (45%)
Year of publication		
<2000	1 (14%)	2 (6%)
2000-2010	6 (86%)	31 (94%)
Setting		
Single centre	5 (71%)	22 (67%)
Multi-centre	2 (29%)	11 (33%)
Overall sample size		
1 to 99	4 (57%)	10 (30%)
100 to199	1 (14%)	8 (24%)
200 to 499	0	3 (9%)
500 to 999	2 (29%)	3 (9%)
1000+	0	9 (27%)
Mean or median follow-up		
<60 months	4 (57%)	29 (88%)
60 months or longer in all groups	2 (29%)	2 (6%)
Unclear or not reported	1 (14%)	2 (6%)
Country in which the study was conducted		
Austria	1 (14%)	1 (3%)
China	1 (14%)	0
Germany	0	2 (6%)
India	0	2 (6%)
Italy	1 (14%)	0
Japan	0	2 (6%)
Korea	0	3 (3%)
USA	2 (29%)	20 (61%)
Canada, Italy, France, USA	0	1 (3%)
Europe (EORTC)	2 (29%)	0
France, Italy, The Netherland, USA	0	1 (3%)
Germany, Switzerland	0	1 (3%)

EORTC = European Organisation for Research and Treatment of Cancer

Table 4.3. Study institutions by study design

Study centre	Description	Study name	Study design*
Randomised studies			
Elizabethinen Hopsital, Linz		Nambirajan 2004[35]	RCT
European Organisation for Research and Treatment of Cancer (EORTC)		Blom 2009[15]	RCT (subgroup)
		Van Poppel 2007[37]	RCT
Glickman Urological Institute, Cleveland Clinic Foundation, USA		Desai 2005a[33]	RCT
Northwestern University Feinberg School of Medicine, Chicago, USA		Nadler 2006[34]	Q-RCT
Second Military Medical University, Shanghai		Peng 2006**[36]	RCT
Università degli Studi di Napoli 'Frederico II', Naples		D'Armiento 1997[32]	RCT
Prospective non-randomised studies			
All India Institute of Medical Sciences		Hemal 2007[38]	Prospective cohort
		Hemal 2009[39]	Prospective cohort
Mie University Graduate School of Medicine, Japan		Onishi 2007[41]	Prospective cohort
		Soga 2008[43]	Prospective cohort
North-west Academic Teaching Hospital of Johann Wolfgang Goethe University , Germany		Poulakis 2003[42]	Prospective cohort (subgroup)
University of Erlangen-Nuernberg, Germany		Herrlinger 1991[40]	Prospective cohort (subgroup)
Retrospective non-randomised studies			
Basel University Hospital, Basel, and University Hospital Grosshadern, Munich		Gratzke 2009[60]	Database review
Cleveland Clinic, USA	Prospectively maintained database	Aron 2008[44]	Matched-pair
		Butler 1995[56]	Database review
		Desai 2005b[58]	Database review
		Lane 2009[55]	Database review

Study centre	Description	Study name	Study design*
		Lane 2010[62]	Database review
		Simmons 2009[68]	Database review
		Weight 2010[65]	Database review
Cleveland Clinic, Mayo Clinic and The Johns Hopkins Hospital	Prospective and retrospective databases	Gill 2007[67]	Database review
Klagenfurt General Hospital, Carinthia, Austria, and Viennal Donauspital, Vienna		Marszalek 2009[48]	Matched-pair
Korea University School of Medicine	Prospectively maintained database	Ko 2008[47]	Matched-pair
Mayo Clinic	Prospectively maintained database. <3% lost to FU.	Thompson 2008[64]	Database review
Mayo Clinic and Memorial Sloan-Kettering Cancer Centre	Prospectively maintained databases	Thompson 2009[69]	Database review
Memorial Sloan-Kettering Cancer Centre, USA	Prospectively maintained database	Dash 2006[57]	Database review
New York University School of Medicine, USA		O'Malley 2007[49]	Matched-pair
Northwestern University Feinberg School of Medicine, Chicago, USA	Prospectively maintained database	Wu 2010[66]	Database review
Surveillance, Epidemiology and End Results (SEER) Program, USA	Prospective database representing 28% of US population	Huang 2009[61]	Database review
		Crépel 2010[45]	Matched-pair
		Zini 2009b[54]	Matched-pair
		Zini 2009a[53]	Matched-pair
University of Chicago, USA	Prospectively collected data analysed retrospectively	Gong 2008[46]	Matched-pair
University of Michigan Health System, USA	Prospectively maintained database	Gabr 2009[59]	Database review
University of Ulsan College of Medicine, Seoul, Korea		Lee 2007[27]	Matched-pair
Wayne State University and Karmanos Cancer Institute, USA		Shekarriz 2002[52]	Matched-pair

Study centre	Description	Study name	Study design*
Unclear	Korea. Abstract only.	Park 2009[50]	Matched-pair
	7 international academic centres	Patard 2004[63]	Database review
	Multi-centred. Abstract only.	Patard 2008[51]	Matched-pair

* All included matched-pair studies were retrospective design.

Table 4.4. Study design features of the non-randomised comparative studies

Criteria	Number of non-randomised studies
Were treatments allocated by?*	
Health care decision maker	10/33 (30%)
Participant preference	6/33 (18%)
Location difference	2/33 (6%)
Time difference	1/33 (3%)
Unclear	19/33 (58%)
For prospective studies only (N = 6), what parts of the study were prospective?*	
Identification of participants	3/33 (9%)
Assessment of baseline and intervention allocation	3/33 (9%)
Assessment of outcomes	3/33 (9%)
Generation of hypothesis	3/33 (9%)
Unclear	3/33 (9%)

* Multiple answers possible

Based on a checklist developed by the Cochrane Non-Randomised Studies Methods Group.[25]

4.3. Risk of bias in included studies

Table 4.5 presents a summary of the assessment of risk of bias in the included studies by type of study design. Details of the risk of bias assessment are shown in Appendix 9. The assessment of blinding and incomplete outcome data was made for each of the following outcomes: oncological (e.g. survival), peri-operative (e.g. blood loss) and self-reported quality of life. Quality of life was not reported by any of the included RCTs. The risk of bias in one RCT by Peng and colleagues[36] could not be assessed because the report was published in Chinese and the English translation was not available at the time of writing.

Table 4.5. Assessment of risk of bias by the standard Cochrane tool[26]

Criteria	*Yes*	*No*	*Un-clear*	*NA*
Randomised studies (N =-7)				
Was the allocation sequence adequately generated?	4 (57%)	1 (14%)	2 (29%)	0
Was allocation adequately concealed?	2 (29%)	1 (14%)	4 (57%)	0
Was the knowledge of the allocated interventions adequately prevented during the study ('blinding')? [Oncological outcomes]	0	2 (29%)	4 (57%)	1 (14%)
Was the knowledge of the allocated interventions adequately prevented during the study ('blinding')? [Peri-operative outcomes]	0	2 (29%)	4 (57%)	1 (14%)
Was the knowledge of the allocated interventions adequately prevented during the study ('blinding')? [Quality-of-life outcomes]	0	0	1 (14%)	6 (86%)
Were incomplete outcome data adequately addressed? [Oncological outcome]	4 (57%)	1 (14%)	1 (14%)	1 (14%)
Were incomplete outcome data adequately addressed? [peri-operative outcome]	4 (57%)	1 (14%)	1 (14%)	1 (14%)
Were incomplete outcome data adequately addressed? [Quality-of-life outcomes]	0	0	1 (14%)	6 (86%)
Are reports of the study free of suggestion of selective outcome reporting?	4 (57%)	0	3 (43%)	0
Was the study apparently free of other problems that could put it at a risk of bias?	0	1 (14%)	6 (86%)	0
Non-randomised comparative studies (N = 33)				
Was the (random) allocation sequence adequately generated?	0	33 (100%)	0	0
Was allocation adequately concealed?	0	33 (100%)	0	0
Was the knowledge of the allocated interventions adequately prevented during the study ('blinding')? [Oncological outcomes]	1 (3%)	14 (42%)	9 (27%)	9 (27%)
Was the knowledge of the allocated interventions adequately prevented during the study ('blinding')? [Peri-operative outcomes]	0	7 (21%)	10 (30%)	16 (48%)
Was the knowledge of the allocated interventions adequately prevented during the study ('blinding')?	0	1 (3%)	1 (3%)	31 (94%

Criteria	*Yes*	*No*	*Un-clear*	*NA*
[Quality-of-life outcomes]				)
Were incomplete outcome data adequately addressed? [Oncological outcome]	10 (30%)	2 (6%)	12 (36%)	9 (27%)
Were incomplete outcome data adequately addressed? [peri-operative outcome]	11 (33%)	2 (6%)	4 (12%)	16 (48%)
Were incomplete outcome data adequately addressed? [Quality-of-life outcomes]	1 (3%)	1 (3%)	0	31 (94%)
Are reports of the study free of suggestion of selective outcome reporting?	10 (30%)	1 (3%)	22 (67%)	0
Was the study apparently free of other problems that could put it at a risk of bias?	1 (3%)	2 (6%)	30 (91%)	0
*Was the institutional review board approval specified?	16 (48%)	17 (52%)	--	--

NA = not applicable, as relevant outcomes were not reported
* An additional item for non-randomised studies only

4.3.1. Risk of bias in randomised controlled trials (7 trials)

Of the seven randomised trials (Table 4.5), four[15,32,33,37] reported adequate random allocation sequence generation, whereas one[34] reported an inadequate, quasi-randomisation method (alternation based on dates presented for surgery). The method of allocation sequence generation was not clear in the other two.[35,36] Allocation concealment was adequate in two trials,[15,33] inadequate in one[34] and unclear in the other four.[32,35-37]

None of the trials stipulated that blinding of participants, healthcare providers or outcome assessors was ensured or attempted. Although blinding may not always be feasible for surgical interventions, blinding of outcome assessors should be possible. Lack of blinding is more likely to introduce bias in subjective outcomes (e.g. post-operative pain) and other outcomes based on surgeons' estimates (e.g. intra-operative blood loss) than in objective outcomes such as mortality.

Incomplete outcome data (e.g. attrition, exclusions) for oncological and peri-operative outcomes was addressed in four trials.[15,33-35] We considered that incomplete outcome data were not adequately addressed in one trial[32] that reported oncological outcomes based on the as-treated analysis rather than the intention-to-treat approach, and in another trial[37] that reported peri-operative outcomes which did not describe reasons for missing data in sufficient detail.

Four trials[15,32-34] were judged to be free of selective outcome reporting, whereas this was unclear in the other three. It was unclear (difficult to judge) if all the included trials were free of any other biases. In general, the quality of reporting was poor and the trial authors did not describe the methods in sufficient detail to assess susceptibility to any bias.

4.3.2. Risk of bias in non-randomised comparative studies (33 studies)

The non-randomised studies were assessed by an extended version of the Cochrane RCT risk-of-bias tool (see chapter 3, Methods). This required that all the assessment criteria applicable to RCTs should also be applied to non-randomised studies in order to provide a common standard. Two additional items included whether the institutional review board approval was specified, and the risk of findings being explained by confounding.

The assessment based on the standard Cochrane tool is given in Table 4.5. As expected, treatment allocation was not concealed in any of the non-randomised studies. Blinding was reported in only one study,[64] which stated that pathological analysis was performed by a blinded pathologist. Incomplete outcome data was addressed in ten[27,40,47,48,55-57,59,62,63] of the 24 studies that reported oncological outcomes, 11[38,39,43,44,47-50,56,60,63] of the 17 studies that reported peri-operative outcomes, and one[41] of the two studies that reported quality-of-life outcomes. One needs to be cautious especially with regard to retrospective studies and database reviews because, although outcome data may appear complete within the published study, it is often difficult to judge the extent and nature of data missing or excluded from the original sample from which the study sample was taken. Ten studies[39-41,44,48,49,52,55,60,63] were considered to be free of selective outcome reporting, although this

was difficult to assess. The assessment was done by matching the outcomes reported in the method section and the outcomes reported in the results section, but it is possible that outcomes with negative findings are omitted from the publication altogether.

The institutional review board approval was specified in just under half (16 out of 33) of the studies.[42,43,46,48,49,55,57,58,60,62,64-69]

With respect to the risk of findings being explained by confounding, the results of this assessment are reported at the beginning of the results section according to the treatment comparison made. We used an arbitrary cut-off whereby a non-randomised study was considered to have high risk of bias if two or more of the pre-specified confounders per outcome (as shown in Table 4.5 above) were not balanced at baseline and statistically controlled for.

In the following chapters, results are grouped into 4 chapters: comparison between non-surgical and surgical interventions (Chapter 5), comparison of different techniques of radical nephrecomy (Chapter 6), the effectiveness of lymphadenectomy and adrenalectomy (Chapter 7), and comparison of nephron sparing surgery (Chapter 8).

Characteristics of included studies such as inclusion and exclusion criteria and the description of interventions are provided in Appendix 8.

A summary of baseline characteristics of the study participants (e.g. age, ethnicity, tumour stage) in the included studies (both randomised and non-randomised) with the assessment of risk of confounding bias (performed for non-randomised studies only) is provided at the beginning of each chapter or section. This is detailed in Appendix 10.

The assessment of other standard risk-of-bias domains (e.g. allocation concealment, blinding) is shown in Appendix 9.

Outcomes are grouped by: oncological outcomes, peri-operative outcomes, resource utilisation, health-related quality of life and other outcomes such as post-operative renal

function. Data are presented in the forest plots where possible. These are given in Appendix 11. Other data that could not be included in the forest plots are tabulated in the main text.

The GRADE assessment of the quality of a body of evidence for key outcomes across studies is summarised at the end of each chapter or section. This is detailed in Appendix 12.

Chapter 5 Results: non-surgical treatment

5.1. Non-surgical treatment versus surgical treatment (comparison A1)

One database review[53] compared non-surgical with surgical treatment of localised renal cell cancer. The baseline characteristics and the assessment of risk of confounders are shown in Table 5.1. More details are available in Appendix 10.

The study was based on the SEER (Surveillance Epidemiology and End Results) cancer registry data from 1988 to 2004 (Table 5.1). A total of 10,291 cases with localised small renal masses (≤4 cm) were identified, including 433 (4.2%) receiving non-surgical management (surveillance or observation, non-ablative) and 9,858 (95.8%) that underwent nephrectomy [both radical (n=7650) and partial (n=2208)]. Of these, 430 non-surgical cases and 1,545 surgical cases were matched in terms of age, tumour size and year of diagnosis or of nephrectomy.

The study groups were considered to be balanced at baseline on clinical tumour size and pathological tumour stage (Table 5.1). However, information on other major confounders for oncological outcomes such as tumour grade, histological cell type and necrosis was not reported and assessed as having a high risk of bias. Peri-operative outcomes were not reported.

The study has a number of limitations. Firstly, patients who did not receive surgery were much older than those who did receive surgery (mean 73 vs. 61.4 years) and it is likely that they were generally more frail and less likely to be suitable candidates for surgery. The study is thus at risk of indication bias. Secondly, the authors also note some drawbacks of the SEER database: (1) potential misclassification of the cause of deaths, and (2) histological confirmation of malignancy was not available for the non-surgical group so that some patients might have had benign histology. In addition, whereas date of diagnosis was used

as the starting point in survival analyses for the non-surgery group, date of surgery was used in the surgical group, potentially causing lead-time bias and more favourable prognosis for the surgery group. Mean duration of follow-up was also considerably shorter for the non-surgical management group, reflecting the fact that use of observation as a treatment option is a more recent phenomenon compared with surgery.

Table 5.1. Baseline characteristics of studies comparing non-surgical management with surgical management (comparison A1)

Study ID	Study design	Comparator	Number of partici-pants	Duration (month, mean or median*)	Age (years, mean or median*)	Pre-specified confounders for oncological outcomes and quality-of-life in non-randomised studies**					Pre-specified onfounders for peri-operative outcomes in non-randomised studies**			
						Clinical tumour size	Pathological tumour stage	Tumour grade	Histological cell type	Necrosis	Age	Ethnicity	Performance status	Co-morbidity
Zini 2009a,[53] USA	Matched-pair (SEER)	Non-surgical	430	16*	73	1	1	5	5	5	-	-	-	-
		Surgical	1545	50*	61.4									

**1 = The study groups were judged to be balanced at baseline, or the study used statistical methods that attempted to control for the specific confounder; 5 = The specific confounder was either not reported or was not balanced between the groups at baseline and not adjusted for in the analysis.

Oncologic outcomes

The results, based on the matched-pair analysis, showed higher mortality rates for non-surgical management relative to surgery. Cancer-specific mortality rates for one, two and five years (after accounting for other-cause mortality) were 1.6%, 2.2% and 4.4% in the surgical group and 6.1%, 7.8% and 12.4% in the non-surgical group (Table 5.2). Other-cause mortality was also substantially higher in the non-surgical group compared with the surgical group: over a quarter (28.1%) of the patients in the non-surgical group died within a year compared with 4.2% amongst those who underwent surgery (Table 5.2). One explanation may be that a significant proportion of those who did not have surgery were affected by frailty or co-morbidity, which could have influenced treatment decisions and also could have impacted negatively on their cancer-specific survival. The study did not report other oncological and peri-operative outcomes.

Table 5.2. Survival data for non-surgical management vs. radical/partial nephrectomy (A1)

Study	Measure	Non-surgical		Surgical		Reported p-value	Notes
		N	%	N	%		
Zini 2009a[53]	CS deaths at 5 years	430	12.4%	1545	4.4%	NR	Matched for age, tumour size, and year of diagnosis. Analysis without matching also reported. Cumulative incidence after accounting for
Zini 2009a[53]	Other-cause deaths at 5 years	430	57.4%	1545	22.4%	NR	Matched for age, tumour size, and year of diagnosis. Analysis without matching also reported.

CS = cancer-specific; NR = not reported

5.2. Summary of evidence for non-surgical management (comparison A1)

A summary of the effect sizes for the seven outcomes and the assessment of the quality of evidence according to the GRADE approach are given in Table 5.3. Overall, there was little evidence to show that surgery improves survival. From a practical point of view, this is a question that could be answered through programmes of active 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.

Table 5.3. Summary of the quality of evidence assessment (GRADE) of the data for non-surgical vs. surgical treatment (comparison A1)

Outcomes and summary estimates	Number of studies with data	Number of participants		Quality of evidence (GRADE)
Overall survival at 5 years Not reported but inferred from: Cancer-specific deaths at 5 years 12.4% vs. 4.4% Other cause deaths at 5 years 57.4% vs. 22.4%	1	430	1545	Very low
Recurrence free survival at 5 years Not reported	0			
Condition-specific quality of life Not reported	0			
Overall morbidity, inferred from length of hospital stay (days) Not reported	0			
Time to normal activity Not reported	0			
Analgesic requirement (person time) Not reported	0			
Need for blood transfusion Not reported	0			

RCT = randomised or quasi-randomised controlled trial; NRS = non-randomised comparative study; CI = confidence interval

Chapter 6 Results: Technique of radical nephrectomy

Ten studies assessed various techniques of radical nephrectomy (RN), including three RCTs,[33,35,36] one quasi-RCT[34] and six non-randomised studies.[38,39,43,50,59,60] The studies were grouped into seven pair-wise comparisons:

- Laparoscopic RN vs. open RN (section 6.1, comparison B1)
- Retroperitoneal vs. transperitoneal laparoscopic RN (section 6.2, comparison B2)
- Hand-assisted laparoscopic RN vs. transperitoneal laparoscopic RN (section 6.3, comparison B3)
- Hand-assisted laparoscopic RN vs. retroperitoneal laparoscopic RN (section 6.4, comparison B4)
- Hand-assisted laparoscopic RN vs. trans- or retroperitoneal laparoscopic RN (section 6.5, comparison B5)
- Robotic RN vs. laparoscopic RN (section 6.6, comparison B6)
- Portless (single port) laparoscopic RN vs. laparoscopic (3 ports) RN (section 6.7, comparison B7)

The baseline characteristics of all studies and the assessment of risk of confounders in the non-randomised studies are shown in Table 6.1. More details are available in Appendix 10.

Table 6.1. Baseline characteristics of studies comparing different techniques of radical nephrectomy (comparisons B1-B7)

Study ID	Study design	Comparator	Number of partici-pants	Duration (month, mean or median*)	Age (years, mean or median*)	Pre-specified confounders for oncological outcomes and quality-of-life in non-randomised studies**					Pre-specified confounders for peri-operative outcomes in non-randomised studies**			
						Clinical tumour size	Pathological tumour stage	Tumour grade	Histological cell type	Necrosis	Age	Ethnicity	Performance status	Co-morbidity
Desai 2005a,[33] USA	RCT	Retroperitoneal lap RN	52	13.5	64.5	-	-	-	-	-	-	-	-	-
		Transperitoneal lap RN	50	15	62.8									
Gabr 2009,[59] USA	Database review	Hand-assisted lap RN	108	30*	61.3	1	1	1	1	5	1	5	1	5
		Lap RN	147		62.7									
Gratzke 2009,[60] Germany and Switzerland	Database review (with prospective evaluation of quality of life)	Lap RN	36	22	67.8	5	5	5	5	5	5	5	1	5
		Open RN	37		61.1									
Hemal 2007,[38] India	Prospective cohort	Lap RN	41	51.4	52.5	1	1	5	5	5	1	5	1	5
		Open RN	71	57.2	52.7									
Hemal 2009,[39] India	Prospective cohort	Robotic RN	15	8.3	50.3	1	1	1	1	5	1	5	5	5
		Lap RN	15	9.1	52.7									
Nadler 2006,[34] USA	Q-RCT	Hand-assisted lap RN	11	20*	61	-	-	-	-	-	-	-	-	-
		Retroperitoneal lap RN	11		63									
		Transperitoneal lap RN	11		57									
Nambirajan 2004,[35] Austria	RCT	Retroperitoneal lap RN	20	15	66.8	-	-	-	-	-	-	-	-	-
		Transperitoneal lap RN	20	17	62.2									
Park 2009,[50] Korea	Matched-pair	Single port lap RN	9	NR	'matched' (no data)	-	-	-	-	-	1	5	5	5
		Lap RN	18	NR	'matched'									

Study ID	Study design	Comparator	Number of partici-pants	Duration (month, mean or median*)	Age (years, mean or median*)	Pre-specified confounders for oncological outcomes and quality-of-life in non-randomised studies**					Pre-specified confounders for peri-operative outcomes in non-randomised studies**			
						Clinical tumour size	Pathological tumour stage	Tumour grade	Histological cell type	Necrosis	Age	Ethnicity	Performance status	Co-morbidity
					(no data)									
Peng 2006,[36] China	RCT	Lap RN	27	Range 6-12	50.67	-	-	-	-	-	-	-	-	-
		Open RN	26		52.53									
Soga 2008,[43] Japan	Prospective cohort	Portless (single port) RN	14	7.1*	57	1	1	5	5	5	1	5	1	5
		Lap RN	15	27.2*	53.7									

PN = partial nephrectomy; RN = radical nephrectomy; lap = laparoscopic;

**1 = The study groups were judged to be balanced at baseline, or the study used statistical methods that attempted to control for the specific confounder; 5 = The specific confounder was either not reported or was not balanced between the groups at baseline and not adjusted for in the analysis.

6.1. Laparoscopic radical nephrectomy vs. open radical nephrectomy (comparison B1)

Three studies compared laparoscopic and open radical nephrectomy, including one RCT,[36] one prospective cohort[38] and a retrospective database review[60] (Table 6.1). The prospective study by Hemal and colleagues[38] recruited patients with large renal tumours (a clinical stage T2), whereas the other studies also included smaller tumours (T1-2).

With regard to risk of confounders in the non-randomised studies (Table 6.1), the groups in the Hemal study[38] appear to be balanced at baseline in terms of tumour size and stage, age and performance status but the other major confounders were not considered by the study (high risk of bias). The other non-randomised study by Gratzke and colleagues[60] was assessed as being at high risk of bias for all confounders except performance status. In this study, peri-operative data were available for all patients, but the data from the quality of life questionnaire were available for 67% (24/36) of the patients receiving laparoscopic radical nephrectomy, and 73% (27/37) of those who received open radical nephrectomy.

Oncological outcomes

Only one non-randomised study[38] provided data on survival. This is shown in Table 6.2. The mean length of follow-up was over 50 months in both groups. The results showed that overall, cancer-specific and recurrence-free survival rates at five years were similar for both groups. In the other non-randomised study[60] there were few incidents of all-cause deaths (3/36 vs. 1/37, Plot 1.1) and cancer-specific deaths (1/36 vs. 1/37, Plot 1.2) during mean follow-up of 22 months, although these data are unadjusted results, not censored, and mean follow-up was short at only 22 months.

The included studies under this comparison reported no local recurrence (0/41 vs. 0/71, Plot 1.3) and few distant metastases (2/36 vs. 3/37 in Gratzke 2009;[60] 3/41 vs. 7/71 in Hemal;[38]

Plot 1.4) during the study period. The randomised trial by Peng and colleagues[36] did not provide any information on oncological outcomes.

Table 6.2. Survival data for laparoscopic radical nephrectomy vs. open radical nephrectomy (comparison B1)

Study	Measure	Lap RN		Open RN		Reported p- value	Notes
		N	%	N	%		
Hemal 2007[38]	OS at 5 years	41	87.8%	71	88.7%	0.87	Published KM estimate
Hemal 2007[38]	CSS at 5 years	41	95.12%	71	94.36%	0.79	Published KM estimate
Hemal 2007[38]	RFS at 5 years	41	92.6%	71	90.1%	0.91	Published KM estimate

OS = overall survival; CSS = cancer-specific survival; RFS = recurrence-free survival; KM = Kaplan-Meier

Peri-operative outcomes

All three studies reported the amount of blood loss for patients during the operation. The reported blood loss varied widely across studies. Data from non-randomised studies also showed larger differences between groups [MD -193 ml, 95% CI (-320, -67) in Gratzke 2009;[60] MD -292, 95% CI (-342, -242) in Hemal 2007;[38] Plot 1.5.2] than the trial data [MD -82, 95% CI (-93, -72) in Peng 2006;[36] Plot 1.5.1). Nevertheless, all studies favoured the laparoscopic surgery group.

Two non-randomised studies[38,60] reported the number of participants receiving blood transfusion (Plot 1.6). Compared with the open surgery group, the rate for the laparoscopic surgery group was slightly lower in one study [15% (6/41) vs. 32% (23/71) in Hemal 2007[38]] but higher in the other [6% (2/36) vs. 0% (0/37) in Gratzke 2009[60]]. However, the differences were small and not statistically significant in either study.

In all studies that reported adverse events during the post-operative period, there were slightly fewer surgical infections in the laparoscopic surgery group compared with the open surgery group (Plot 1.7) but the number of haemorrhages was similar between groups (Plot

1.10). There was one case of pneumonia (Plot 1.8) and one case of post-operative death (Plot 1.11) both in the open surgery group. No cases of deep venous thrombosis were reported.

In one non-randomised study,[38] the laparoscopic surgery group was associated with significantly lower analgesic requirement [MD -18.60 mg morphine equivalent, 95% CI (-20.73, -16.47), Plot 1.12] and significantly shorter convalescence time [MD -1.74 weeks, 95% CI (-1.96, -1.52), Plot 1.14] compared with the open surgery group. The results from the RCT[36] also showed lower analgesic requirement for the laparoscopic group (MD -18 person time), though statistical significance could not be tested because a measure of spread (e.g. standard deviation) was not reported.

Resource utilisation

The mean duration of operation was significantly longer in the laparoscopic surgery group compared with the open surgery group in two non-randomised studies by 16 minutes[38] to 33 minutes[60] (Plot 1.15.2). However, no such difference was apparent in the RCT data [MD -2.38 minutes, 95% CI (-8.20, 3.44) in Peng 2006;[36] Plot 1.15.1].

All three studies reported shorter hospital stay in the laparoscopic surgery group than in the open surgery group. The differences in all studies reached statistical significance with the RCT showing the largest difference of around five days [MD -4.50 days, 95% CI (-5.20, -3.80), Plot 1.16).

Health-related quality of Life

One non-randomised study[60] provided information on general health-related quality of life using SF-36. The study found no significant differences between the groups in the mean summary score for either the mental component (48 vs. 48.3) or the physical component (47.4 vs. 48) at a mean follow up of 22 months. The study authors noted that patients who

had post-operative complications (regardless of the type of surgery) tended to report worse quality of life compared with patients who did not have any complications.

Other outcomes – renal function

Post-operative renal function measured by level of serum creatinine in one study[60] was on average worse for laparoscopic radical nephrectomy compared with open radical nephrectomy: at six months after surgery it remained 34% and 18% above baseline, respectively. However, it is unclear if the difference is statistically significant.

6.2. Retroperitoneal laparoscopic radical nephrectomy vs. transperitoneal laparoscopic radical nephrectomy (comparison B2)

Two RCTs[33,35] and one quasi-RCT[34] compared between retroperitoneal and transperitoneal laparoscopic radical nephrectomy (Table 6.1). The RCT by Desai and colleagues[33] recruited consecutive patients with a renal tumour. This included six cases in each group with perirenal fat involvement but the study did not provide the breakdown by tumour stage. This was assumed to be clinically localised disease. The second RCT by Nambirajan and colleagues[35] included patients with stage cT1-T2 renal cancer. The quasi-RCT by Nadler and colleagues[34] was a three-arm trial (the other arm being hand-assisted laparoscopic radical nephrectomy) based on patients with stage T1 renal tumours. Since all included studies for this comparison are randomised, meta-analyses were performed where possible.

Oncological outcomes

The included studies did not provide any survival data. There were slightly more all-cause deaths (8% (4/52) vs. 4% (2/50), RR 1.92, 95% CI (0.37, 10.04), Plot 2.1] but fewer local recurrences [1% (1/80) vs. 4% (3/76), RR 0.32, 95% CI (0.03, 2.98), Plot 2.3] and metastases [2% (1/63) vs. 5% (3/61), RR 0.32, 95% CI (0.03, 2.98), Plot 2.4] for the retroperitoneal

approach compared with the transperitoneal approach. However, the differences were not statistically significant. No cancer-specific deaths (Plot 2.2) or positive surgical margins (Plot 2.5) were reported in any of the studies.

Peri-operative outcomes

Meta-analysis of data from the three trials on intra-operative blood loss found no significant difference between the two approaches [WMD 24 ml, 95% CI (-7, 55), Plot 2.6]. Other adverse events during the post-operative period appear uncommon in the included studies. There was one patient requiring blood transfusion [1/20 vs. 0/20, RR 3.00, 95% CI (0.13, 69.52), Plot 2.7] and one other patient who had deep venous thrombosis [1/52 vs. 0/50, RR 2.89, 95% CI (0.12, 69.24), Plot 2.9] after surgery with the transpritoneal approach. One patient in each group also had surgical infection [1/52 vs. 1/50, RR 0.96, 95% CI (0.06, 14.96), Plot 2.8]. In all of these peri-operative outcomes, there were no clear differences between the two laparoscopic approaches and confidence intervals were (implausibly) wide.

Analgesic requirement did not differ between the groups [WMD 0.16 mg morphine equivalent, 95% CI (-9.28, 9.61), Plot 2.10]. Time to normal activity was assessed using different measures. One RCT[33] using convalescence time reported a statistically significant difference favouring the transperitoneal approach [MD 1.70 weeks, 95% CI (0.09, 3.31), Plot 2.12]. However, one small quasi-RCT[34] examining the number of patients returning to work at 2 weeks after surgery found no significant difference between the groups [0% (0/9) vs. 55% (6/11), RR 0.09, 95% CI (0.01, 1.45), Plot 2.11).

Resource utilisation

All three trials provided information on operation time and length of hospital stay. Meta-analysis on operation time found a small difference favouring the retroperitoneal approach [WMD -20.50 minutes, 95% CI (-36.39, -4.61), Plot 2.13], although there was significant statistical heterogeneity (I^2 = 89%). The reason for heterogeneity is unclear. There was no

clear difference in length of hospital stay between the two approaches [WMD 0.30 day, 95% CI (-0.17, 0.77), Plot 2.14].

6.3. Hand-assisted laparoscopic radical nephrectomy vs. transperitoneal laparoscopic radical nephrectomy (comparison B3)

There was one quasi-RCT[34] that compared between hand-assisted and transperitoneal laparoscopic radical nephrectomy (Table 6.1).

Oncological outcomes

The study conducted no survival analysis. There were no cancer-specific deaths, recurrences, metastases or positive surgical margins at a median follow-up of 20 months (Plots 3.1 to 3.4), but it should be noted that the study sample was small with only eleven patients in each arm.

Peri-operative outcomes

No difference was discernible between the groups in terms of intra-operative blood loss [MD 6 ml, 95% CI (-62, 74), Plot 3.5], analgesic requirement [MD 6 mg morphine equivalent, 95% CI (-10.43, 22.43), Plot 3.6] and the number of patients who returned to work at two weeks after surgery [2/9 vs. 6/11, RR 0.41, 95% CI (0.11, 1.55), Plot 3.7].

Resource utilisation

Duration of operation was significantly shorter by around one hour [MD -57 minutes, 95% CI (-82.09, -31.91), Plot 3.8] but hospital stay was significantly longer by around one day [MD 1.3 day, 95% CI (0.21, 2.39), Plot 3.9] for the hand-assisted procedure compared with the transperitoneal procedure.

6.4. Hand-assisted laparoscopic radical nephrectomy vs. retroperitoneal laparoscopic radical nephrectomy (comparison B4)

One small quasi-RCT[34] compared between hand-assisted and retroperitoneal laparoscopic radical nephrectomy (Table 6.1).

Oncological outcomes

There were no reported cancer-specific deaths, recurrences, metastases or positive surgical margins during the study period (Plots 4.1 – 4.4). However, this is probably due to the short follow-up time (median 22 months).

Peri-operative outcomes

Intra-operative blood loss was equivalent between the groups [MD 26 ml, 95% CI (-49, 101), Plot 4.5]. The groups were also comparable in terms of analgesic requirement [MD -4 mg morphine equivalent, 95% CI (-34.13, 26.13), Plot 4.6] and the number of patients returning to work at two weeks after surgery [2/9 vs. 0/9, RR 5.00, 95% CI (0.27, 91.52), Plot 4.7].

Resource utilisation

Mean operative time was 139 minutes for the hand-assisted procedure, which was significantly shorter than the retroperitoneal procedure by 46 minutes [MD -46 minutes, 95% CI (-71.96, -20.04), Plot 4.8]. Length of hospital stay was similar between the two procedures [MD -0.20 day, 95% CI (-1.71, 1.31), Plot 4.9].

6.5. Hand-assisted laparoscopic radical nephrectomy vs. transperitoneal or retroperitoneal laparoscopic radical nephrectomy (comparison B5)

One non-randomised study,[59] which was a retrospective database review, compared hand-assisted laparoscopic radical nephrectomy (n = 108) with 'standard' laparoscopic radical nephrectomy (n = 147). The standard procedure was carried out with either transperitoneal (89.1%) or retroperitoneal procedures.

Risk of confounding was rated as low (score of 1) in terms of tumour size, stage and grade, histological cell type, age and performance status, but unclear or high (score of 5) on necrosis, ethnicity and co-morbidity (Table 6.1).

Oncological outcomes

Adjusted hazard ratios for overall survival, cancer-specific survival and recurrence-free survival showed that on average the hand-assisted procedure was better (point estimate <1) than the 'standard' procedure but the differences were not statistically significant (Table 6.3a). The estimated rates at 5 years for 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) were comparable between the two procedures (Table 6.3b).

Table 6.3a Survival data for hand-assisted laparoscopic radical nephrectomy (hand-assisted LRN) vs. standard (trans- or retro-peritoneal) laparoscopic radical nephrectomy (standard LRN) (comparison B5): Time-to-event data

First author	Measure	Hand-assisted LRN	Standard LRN	HR (95% CI) and reported p-value; Standard LRN = 1, referent	Notes
		N	N		
Gabr 2009[59]	Overall survival	108	147	HR 0.407 (0.150, 1.395)	Adjusted for specimen handling (intact/ morcellation), mass size, pathological risk (based in UCLA integrated staging) and histological subtype.
Gabr 2009[59]	Cancer-specific survival	108	147	HR 0.385 (0.087, 1.694)	Adjusted for specimen handling (intact or mocellation), mass size, pathological risk (based on UCLA integrated staging, inkling T-stage), and histological subtype.
Gabr 2009[59]	Recurrence -free survival	108	147	HR 0.384 (0.122, 1.209)	Adjusted for specimen handling (intact or mocellation), mass size, pathological risk (based on UCLA integrated staging, inkling T-stage), and histological subtype.

HR = hazard ratio; HR<1 denotes advantage to hand-assisted LRN and HR>1 denotes advantage to standard LRN; CI = confidence interval

Table 6.3b Survival data for hand-assisted laparoscopic radical nephrectomy (hand-assisted LRN) vs. standard (trans- or retro-peritoneal) laparoscopic radical nephrectomy (standard LRN) (comparison B5): Categorical data

Study	Measure	Hand-assisted LRN		Standard LRN		Reported p-value	Notes
		N	% (95% CI)	N	% (95% CI)		
Gabr 2009[59]	OS at 5 years	108	74% (63%, 85%)	147	79% (68%, 90%)	0.6864	Published KM estimate
Gabr 2009[59]	CS at 5 years	108	87.2 (79%, 95%)	147	88.9% (81%, 97%)	0.7589	Published KM estimate
Gabr 2009[59]	RFS at 5 years	108	81.3% (72%, 91%)	147	76.5% (64%, 89%)	0.8663	Published KM estimate

OS = overall survival; CSS = cancer-specific survival; RFS = recurrence-free survival; KM = Kaplan-Meier; CI = confidence interval

Peri-operative outcomes

Compared with the standard procedure, the hand-assisted procedure had more intra-operative blood loss [MD 123 ml, 95% CI (-0.29, 246.29), Plot 5.1] with fewer patients requiring a blood transfusion [7% (8/108) vs. 10% (15/147), RR 0.73, 95% CI (0.32, 1.65), Plot 5.2), but the differences were not statistically significant.

Pain scores at six weeks did not differ between the procedures [MD -0.4, 95% CI (-0.87, 0.07), Plot 5.3]. Time to non-strenuous activity [MD 3.10 days, 95% CI (0.83, 5.37), Plot 5.4] and time to driving [MD 1 day, 95% CI (-1.43, 3.43), Plot 5.5] were on average longer for the hand-assisted procedure but only the former found this difference to be statistically significant.

Resource utilisation

Operative times did not differ significantly between the two procedures [MD 11 minutes, 95% CI (-5.54, 27.54), Plot 5.6] and neither did length of hospital stay [MD 0.4 day, 95% CI (-0.01, 0.81), Plot 5.7].

Health-related quality of Life

General health-related quality of life based on SF-12 were similar between the groups in terms of both mental scores [MD -1.80, 95% CI (-4.52, 0.92), Plot 5.8) and physical health scores (MD -0.80, 95% CI (-3.64, 2.04), Plot 5.9) at six weeks after surgery.

6.6. Robotic radical nephrectomy vs. lapaprascopic radical nephrectomy (comparison B6)

One small non-randomised prospective cohort study[39] compared robotic with laparoscopic radical nephrectomy. The groups were similar at baseline in terms of tumour size, stage and grade, histological cell type, age, but the study provided no baseline data on necrosis, ethnicity, performance status and co-morbidity and was therefore assessed at high risk of confounding from these factors (Table 6.1). Follow-up was short at less than one year in both groups.

Oncological outcomes

Both robotic and laparoscopic radical nephrectomy cases had no recurrence or metastasis (Plot 6.1 and 6.2). No survival analysis was reported.

Peri-operative outcomes

There was no clear difference between the groups in terms of intra-operative blood loss [MD 15 ml, 95% CI (-4, 34), Plot 6.3] the need for blood transfusion [3/15 vs. 2/15, RR 1.50, 95% CI (0.29, 7.73), Plot 6.4] and the number of surgical site infections [1/15 vs. 1/15, RR 1.00, 95% CI (0.07, 14.55), Plot 6.5]. Analgesic requirements [MD -0.10 mg morphine equivalent, 95% CI (-0.21, 0.01), Plot 6.6] and convalescence time [MD 0.10 week, 95% CI (-0.22, 0.42), Plot 6.7] were also similar between the robotic and traditional laparoscopic groups.

Resource utilisation

Mean operating time was significantly longer with the use of the robot [MD 45.70 minutes, 95% CI (22.86, 68.54), Plot 6.8]. No difference was found between groups in length of hospital stay [MD 0.10 day, 95% CI (-0.01, 0.21), Plot 6.9].

6.7. Portless (single port) laparoscopic radical nephrectomy vs. laparoscopic (3 ports) radical nephrectomy (comparison B7)

Two non-randomised studies, including one prospective cohort[43] and one retrospective matched-pair study[50] compared portless (i.e. single port) with 3-port laparoscopic radical nephrectomy (Table 6.1).

In the prospective cohort study[43] involving 29 patients with T1 renal cell cancer, both groups were similar in terms of tumour size and stage, age, and performance status but no baseline comparison was possible in terms of histology or histologic grading, ethnicity or co-morbidity (Table 6.1). The group with the portless procedure had a shorter median follow up period (7.1 months, range 2.7 to 17.3) compared with the group with the conventional procedure with 3 ports (27.2 months, range 19.5 to 39.1).

The matched-pair study[50] was based on consecutive patients from a renal cancer hospital registry and involved nine cases of single-site laparoscopic radical nephrectomy and 18 cases of conventional radical nephrectomy. Matching was by age, gender, side of the operation, and mass size, though it was unclear if the groups were balanced at baseline on any other confounders (Table 6.1). Duration of follow-up was not reported.

Oncological outcome

No information was available on oncological outcomes except for one study[43] reporting that there were no cases of local recurrence among 29 patients during the relatively short study period (Plot 7.1).

Peri-operative outcomes

Both studies reported on intra-operative blood loss (Plot 7.2). Compared with the 3-port group, the amount of blood loss in the portless group was on average larger in one study[43] (MD 130 ml, 95% CI -27 to 286) but similar in the other[50] (MD 2 ml). Only one of these studies reported standard deviation[43] and the difference was not statistically significant. One study[43] (N = 29) reported that none of the patients required blood transfusion (Plot 7.3). There was also no strong evidence to suggest any significant differences between groups in analgesic requirement in terms of the number of non-steroid anti-inflammatory drug suppository [MD 1.00, 95% CI (-0.19, 2.19), Plot 7.4] and pain scores at Day 3 (MD -1.4, 95% CI not estimable, Plot 7.5).

Resource utilisation

Duration of operation (Plot 7.6) and length of hospital stay (Plot 7.7) were reported by both studies. In one study,[43] the portless laparoscopy group compared with the 3-port laparoscopy group was associated with slightly longer operation time [MD 19 minutes, 95% CI (-9.11, 47.11), Plot 7.6] and hospital stay [MD 0.2 day, 95% CI (-2.43, 2.83), Plot 7.7] but the differences were small and not statistically significant. The results from the other study[50] showed slightly longer operation time (by 46 minutes, Plot 7.6) but slightly shorter hospital stay (by 1.2 day, Plot 7.7). However, the study did not report a measure of spread (e.g. standard deviation) and so statistical significance could not be tested.

Other outcomes – Cost

One study[43] reported a higher average total cost of disposable instruments for the 3-port laparoscopic group (US$ 1398.00 versus US$282.30).

6.8. Summary of evidence for the technique of radical nephrectomy (comparisons B1-7)

A summary of effect sizes with the GRADE assessment of quality of evidence concerning the technique of radical nephrectomy is given in Tables 6.4 to 6.10.

Regarding oncological outcomes and especially survival, there was insufficient evidence to suggest any major difference between laparoscopic and open radical nephrectomy (comparison B1) or between different laparoscopic approaches (comparisons B2-7). All included studies were small and follow-up was short.

Comparison B1. In terms of peri-operative outcomes, hospital stay and convalescence time were significantly shorter, and blood loss and analgesic requirement significantly less with the laparoscopic approach compared to the open approach. Duration of operation was significantly longer with the laparoscopic approach in two non-randomised studies, but no such difference was apparent in one RCT. No evidence was found of a difference in blood transfusion rates, surgical complications, operative mortality or quality of life measures between the two approaches. Laparoscopic radical nephrectomy has become the established standard of care for ≤T2 tumours[13,70] to the extent that this comparison is unlikely to have any relevance to current practice.

Comparison B2. Concerning the choice of approach in performing laparoscopic radical nephrectomy, both retroperitoneal and transperitoneal approaches appear to have similar peri-operative outcomes, although there are some inconsistencies in the direction of effect between studies. It is likely that the choice of approach will be guided by tumour location, patient's body habitus, previous intra-abdominal surgery and surgeon preference.

Comparisons B3-5. Laparoscopic radical nephrectomy has undergone many innovations and modifications partly to circumvent the steep learning curve traditionally associated with laparoscopic radical nephrectomy. One of the modifications has been the development of the hand-assisted technique of laparoscopic nephrectomy. The limited evidence suggests

that, in general, when compared with standard laparoscopic radical nephrectomy, the hand-assisted technique of laparoscopic nephrectomy appears to have similar peri-operative outcomes. However, for different laparoscopic approaches, the hand-assisted technique may require longer recovery than transperitoneal laparoscopic and shorter recovery than retroperitoneal laparoscopic approaches.

Comparison B6. Another innovation has been the use of robotic technology to augment the laparoscopic procedure. Robot-assisted laparoscopic radical nephrectomy has equivalent peri-operative outcomes and complication rates as standard laparoscopic radical nephrectomy, but this is based on only one small prospective cohort study.

Comparison B7. Other developments were introduced to reduce patient morbidity, and this includes the single-port technique for laparoscopic surgery in urology. For laparoscopic radical nephrectomy, there is little evidence to indicate that the single-port technique is superior to the standard three-port technique in various peri-operative outcome measures such as pain intensity, analgesic requirement and speed of recovery due to inconsistent reporting and poor methodology in included studies.

Table 6.4. Summary of the quality of evidence assessment (GRADE) of the data for laparoscopic radical nephrectomy vs. open radical nephrectomy (comparison B1)

Outcomes and summary estimates	Number of studies with data	Number of participants		Quality of evidence (GRADE)
Overall survival at 5 years Published Kaplan-Meier estimates 87.8% vs. 88.7%, p = 0.87	1 NRS	41	71	Very low
Recurrence free survival at 5 years Published Kaplan-Meier estimates 92.6% vs. 90.1%, p = 0.91	1 NRS	41	71	Very low
Condition-specific quality of life Not reported	0			--
Overall morbidity, inferred from length of hospital stay (days) MD -4.5 (-5.2, -3.8)	1 RCT	27	26	Very low
Convalescence time (weeks) MD -1.74 (-1.96, -1.52)	1 NRS	41	71	Very low
Analgesic requirement (person time) MD -18 (95% CI not estimable)	1 RCT	27	28	Very low
Need for blood transfusion Data from individual studies (not pooled): RR 5.14 (0.26, 103.39) RR 0.45 (0.20, 1.02)	2 NRS	77	108	Very low

RCT = randomised or quasi-randomised controlled trial; NRS = non-randomised comparative study; MD = mean difference; CI = confidence interval

Table 6.5. Summary of the quality of evidence assessment (GRADE) of the data for retroperitoneal laparoscopic radical nephrectomy vs. transperitoneal laparoscopic radical nephrectomy (comparison B2)

Outcomes and summary estimates	Number of studies with data	Number of participants		Quality of evidence (GRADE)
Overall survival at 5 years RR 1.92 (0.37 to 10.04)	1 RCT	52	50	Very Low
Recurrence free survival at 5 years RR 0.32 (0.03 to 2.98)	3 RCTs	80	76	Very low
Condition-specific quality of life Not reported	0	--	--	--
Overall morbidity, inferred from length of hospital stay (days) MD 0.30 (-0.17 to 0.77)	3 RCTs	83	81	Very low
Convalescence time (weeks) MD 1.7 (0.09 to 3.31)	1 RCT	52	50	Low
Analgesic requirement (person time) MD 0.16 (-9.28 to 9.61)	3 RCTs	83	81	Low
Need for blood transfusion RR 3 (0.13 to 69.52)	1 RCT	20	20	Low

RCT = randomised or quasi-randomised controlled trial; NRS = non-randomised comparative study; RR = relative risk; MD = mean difference

Table 6.6. Summary of the quality of evidence assessment (GRADE) of the data for hand-assisted laparoscopic radical nephrectomy vs. transperitoneal laparoscopic radical nephrectomy (comparison B3)

Outcomes and summary estimates	Number of studies with data	Number of participants		Quality of evidence (GRADE)
Overall survival at 5 years Not reported but no cancer-specific deaths during study period (proxy)	1 RCT	11	11	Very low
Recurrence free survival at 5 years Not reported; no recurrence during study period (proxy)	1 RCT	11	11	Very low
Condition-specific quality of life Not reported	0			
Overall morbidity, inferred from length of hospital stay (days) MD 1.30 (0.21, 2.39)	1 RCT	11	11	Very low
Time to normal activity (number of patients who returned to work at 2 weeks) RR 0.41 (0.11, 1.55)	1 RCT	9	11	Very low
Analgesic requirement (mg morphine equivalent) MD 6 (-10.43, 22.43)	1 RCT	11	11	Low
Need for blood transfusion Not reported	0			

RCT = randomised or quasi-randomised controlled trial; NRS = non-randomised comparative study; RR = relative risk; MD = mean difference; CI = confidence interval

Table 6.7. Summary of the quality of evidence assessment (GRADE) of the data for hand-assisted laparoscopic radical nephrectomy vs. retroperitoneal laparoscopic radical nephrectomy (comparison B4)

Outcomes and summary estimates	Number of studies with data	Number of participants		Quality of evidence (GRADE)
Overall survival at 5 years Not reported but no cancer-specific deaths during study period (proxy)	1 RCT	11	11	Very low
Recurrence free survival at 5 years 5-year data not reported but no recurrence during study period (proxy).	1 RCT	11	11	Very low
Condition-specific quality of life Not reported	0			
Overall morbidity, inferred from length of hospital stay (days) MD -0.2 (-1.71, 1.31)	1 RCT	11	11	Very low
Time to normal activity (number of patients who returned to work at 2 weeks) RR 5 (0.27, 91.52)	1 RCT	9	9	Low
Analgesic requirement (mg morphine equivalent) MD 4.0 (-34.13, 26.13)	1 RCT	11	11	Low
Need for blood transfusion Not reported	0			

RCT = randomised or quasi-randomised controlled trial; NRS = non-randomised comparative study; RR = relative risk; MD = mean difference; CI = confidence interval

Table 6.8. Summary of the quality of evidence assessment (GRADE) of the data for hand-assisted laparoscopic radical nephrectomy vs. trans- or retro-peritonea laparoscopic radical nephrectomy (comparison B5)

Outcomes and summary estimates	Number of studies with data	Number of participants		Quality of evidence (GRADE)
Overall survival (time to event) HR 0.407 (0.15 to 1.395)	1 NRS	108	147	Very low
Overall survival at 5 years Published Kaplan-Meier estimates 74% vs. 79%, p = 0.6864	1 NRS	108	147	Low
Recurrence free survival (time to event) HR 0.384 (0.122 to 1.209)	1 NRS	108	147	Very low
Recurrence free survival at 5 years Published Kaplan-Meier estimates 81.3% vs. 76.5%	1 NRS	108	147	Low
Condition-specific quality of life Not reported	0			
Overall morbidity, inferred from length of hospital stay (days) MD 0.4 (-0.01, 0.81)	1 NRS	108	147	Very low
Time to normal activity, indicated by time to non-strenuous activity (days) MD 3.10 (0.83, 5.37)	1 NRS	108	147	Very low
Analgesic requirement, inferred from pain score at 6 weeks on 10-point VAS MD -0.40 (-0.87, 0.07)	1 NRS	108	147	Very low
Need for blood transfusion RR 0.73 (0.32, 1.65)	1 NRS	108	147	Very low

RCT = randomised or quasi-randomised controlled trial; NRS = non-randomised comparative study; RR = relative risk; MD = mean difference; CI = confidence interval

Table 6.9. Summary of the quality of evidence assessment (GRADE) of the data for robot-assisted laparoscopic radical nephrectomy vs. laparoscopic radical nephrectomy (comparison B6)

Outcomes and summary estimates	Number of studies with data	Number of participants		Quality of evidence (GRADE)
Overall survival at 5 years Not reported				
Recurrence free survival at 5 years Not reported; but no recurrence during study period (proxy)	1 NRS	15	15	Very low
Condition-specific quality of life Not reported				
Overall morbidity, inferred from length of hospital stay (days) MD 0.1 (-0.1, 0.21)	1 NRS	15	15	Very low
Convalescence time (days) MD 0.1 (-0.22, 0.42)	1 NRS	15	15	Very low
Analgesic requirement (person time) MD -0.10 (-0.21, 0.01)	1 NRS	15	15	Very low
Need for blood transfusion RR 1.5 (0.29, 7.73)	1 NRS	15	15	Very low

RCT = randomised or quasi-randomised controlled trial; NRS = non-randomised comparative study; RR = relative risk; MD = mean difference; CI = confidence interval

Table 6.10. Summary of the quality of evidence assessment (GRADE) of the data for single port laparoscopic radical nephrectomy vs. laparoscopic radical nephrectomy (comparison B7)

Outcomes and summary estimates	Number of studies with data	Number of participants		Quality of evidence (GRADE)
Overall survival at 5 years Not reported	0			
Recurrence free survival at 5 years Not reported; but no recurrence during study period (proxy)	1 NRS	14	15	Very low
Condition-specific quality of life Not reported	0			
Overall morbidity, inferred from length of hospital stay (days) Data from individual studies (not pooled): MD -1.2, 95% CI not estimable MD 0.20 (-2.43, 2.83)	2 NRS	23	33	Very low
Time to normal activity Not reported	0			
Analgesic requirement (number of NSAID suppository) MD 1.00 (-0.19, 2.19)	1 NRS	14	15	Very low
Need for blood transfusion None	1 NRS	14	15	Very low

RCT = randomised or quasi-randomised controlled trial; NRS = non-randomised comparative study; RR = relative risk; MD = mean difference; CI = confidence interval; NSAID = non-steroid anti-inflammatory drug

Chapter 7 Results: Ipsilateral lymphadenectomy and ipsilateral adrenalectomy

The baseline characteristics of three studies identified for lymphadenectomy and adrenalectomy and the assessment of risk of confounders are shown in Table 7.1. More details are available in Appendix 10.

Table 7.1. Baseline characteristics of studies for ipsilateral lymphadenectomy and adrenalectomy (comparisons C1-C2)

Study ID	Study design	Comparator	Number of partici-pants	Duration (month, mean or median*)	Age (years, mean or median*)	Pre-specified confounders for oncological outcomes and quality-of-life in non-randomised studies**					Pre-specified confounders for peri-operative outcomes in non-randomised studies**			
						Clinical tumour size	Pathological tumour stage	Tumour grade	Histological cell type	Necrosis	Age	Ethnicity	Performance status	Co-morbidity
Blom 2009,[15] Europe	RCT (subgroup)	RN with lymphadenectomy	271	151.2*	58.7	-	-	-	-	-	-	-	-	-
		RN without lymphadenectomy	288		58.6									
Herrlinger 1991,[40] Germany	Prospective cohort (subgroup)	RN + systematic LND	109	Range 48-251	<72	5	1	5	5	5	-	-	-	-
		RN + facultative LND	82											
Lane 2009,[55] USA	Database review	PN with adrenalectomy	48	74.4*	62*	1	5	5	1	5	-	-	-	-
		PN without adrenalectomy	2017	66*	61*									

PN = partial nephrectomy; RN = radical nephrectomy;

**1 = The study groups were judged to be balanced at baseline, or the study used statistical methods that attempted to control for the specific confounder; 5 = The specific confounder was either not reported or was not balanced between the groups at baseline and not adjusted for in the analysis.

7.1. Radical nephrectomy with lymphadenectomy vs. radical nephrectomy (comparison C1)

Two studies were identified (Table 7.1). The first study is a subgroup analysis of the cT1 and cT2 population from a large EORTC (European Organisation for Research and Treatment of Cancer) trial by Blom and colleagues.[15] In this trial the patients were randomly allocated to either a radical nephrectomy plus a complete lymph-node dissection or radical nephrectomy alone. It should be noted that the lymphadenectomy in this trial was not standardised and therefore may be subject to variations in technique, extent and procedural quality.

The second study is a non-randomised prospective study by Herrlinger and colleagues,[40] which compared two groups of patients who underwent transabdominal radical nephrectomy: one with 'facultative lymphadenectomy', which means that lymph-nodes had been removed only on occasions when they are macroscopically abnormal or for staging purposes, and the other group with 'systematically performed lymphadenectomy', which means that they underwent radical nephrectomy, including extended dissection of the regional retroperitoneal lymph-nodes.

For the purpose of this review, the baseline characteristics of the subgroups from the Blom trial[15] are considered randomised and the randomisation process protects against selection and indication bias present in non-randomised studies. Baseline comparability of the non-randomised study by Herrlinger and colleagues[40] is, however, questionable (Table 7.1): the study groups were balanced at baseline in terms of pathological tumour stage but no information was available on other important confounders such as clinical tumour size, tumour grade, histology and tumour necrosis (and therefore assessed as having a high risk of bias).

Oncological outcome

Regarding overall survival, time-to-event data from the trial showed no evidence of a difference between the groups [HR 1.096, 95% CI (0.81, 1.47), log rank p = 0.55, Table 7.2a]. However, the data from the non-randomised study[40] reported a significant survival benefit for patients who underwent extended (or 'systematic') lymphadenectomy compared with those who had no (or 'facultative') lymphadenectomy (p<0.01, no further data available). In the non-randomised study data,[40] survival estimates based on categorical data are consistent with the time-to-event data with the rates at five and ten years considerably better with lymphadenectomy than without lymphadenectomy (Table 7.2b).

Table 7.2a. Overall survival data for radical nephrectomy with lymphadenectomy vs. radical nephrectomy alone (comparison C1): time-to-event data

Study	Measure	With LND	Without LND	HR (95% CI) No LND = 1 referent	Notes
		N	N		
Blom 2009[15]	Overall survival	271	288	HR 1.096 (0.808, 1.486)	Unadjusted. Log rank p = 0.554.
Herrlinger 1991[40]	Overall survival	109	82	NR	'Better survival rates' for patients who underwent LND calculated with the KM method. Log rank test p <0.01

HR = hazard ratio; hazard ratio (HR) is calculated so that HR<1 denotes advantage to lymphadenecrtomy and HR>1 denotes advantage to no lymphadenectomy; KM = Kaplan-Meier; CI = confidence interval; LND = lymphadenectomy; NR = not reported

Table 7.2b. Overall survival data for radical nephrectomy with lymphadenectomy vs. radical nephrectomy alone (comparison C1): categorical data

First author	Out-come Definition	With LND		Without LND		P-value	Notes
		N	%	N	%		
Herrlinger 1991[40]	OS at 5 years	109	91.6%	82	81.3%	NR	KM estimates from graph.
Herrlinger 1991[40]	OS at 10 yeas	109	80.2% (SD 12.6)	82	54% (SD 14.1)	NR	Published KM estimates.

OS = overall survival; KM = Kaplan-Meier; CI = confidence interval; NR = not reported

Peri-operative outcomes

The trial data[15] show that groups were comparable in terms of post-operative complications, although event rates were generally low. Reported complications included bleeding over one litre [7% (17/253) vs. 5% (12/261), RR 1.46, 95% CI (0.71, 3.00), Plot 8.1], infection [5% (13/253) vs. 6% (15/259), RR 0.89, 95% CI (0.43, 1.83), Plot 8.2] and embolism [2% (5/253) vs. 0.4% (1/260), RR 5.14, 95% CI (0.60, 43.67), Plot 8.3].

7.2. Partial nephrectomy with adrenalectomy vs. partial nephrectomy (comparison C2)

We identified no comparative studies looking at radical nephrectomy with ipsilateral adrenalectomy. One database review by Lane and colleagues[55] met the inclusion criteria examining partial nephrectomy plus ipsilateral adrenalectomy compared with partial nephrectomy alone. The study used strict criteria based on radiographic and intra-operative assessment to justify adrenalectomy only in certain situations (i.e. suspicion of adrenal invasion) and out of 2,065 patients undergoing partial nephrectomy, identified 48 patients (2.3%) who underwent concurrent ipsilateral adrenalectomy. The study authors note that renal tumours in the adrenalectomy group were more commonly upper pole (65% vs. 31%), had higher stage (pT2 or greater 19% vs. 6%) and were slightly larger (median 3.6 vs. 3.0 cm) (Table 7.1). It is unclear if renal cancers of all study participants were localised, although it was assumed that the majority were.

Oncological outcomes

Hazard ratio (time-to-event data) for overall survival was not reported but the study authors reported 'no significant difference in overall survival' (log rank test p-value = 0.8, Table 7.3a). Similarly, categorical data for overall survival were similar between the groups at five years (82% vs. 85%) or ten years (68% vs. 72%) (Table 7.3b).

Of the 1501 patients with cancer (i.e. excluding benign kidney findings) who underwent partial nephrectomy without concomitant adrenalectomy, renal cell carcinoma recurred in 61 (4.0%) patients during a median follow-up of 5.5 years (Plot 9.1), of which 11 (0.74%) had adrenal involvement and subsequently underwent adrenalectomy. The equivalent figure for the patients with cancer who underwent concomitant adrenalectomy was 16% (6/38) for recurrence (Plot 9.1) and 11% (4/38) for contralateral adrenal involvement. On multivariate analysis, upper pole location was not predictive of adrenal involvement [HR 0.482, 95% CI (-0.050, 1.043), p =0.08], but tumour size was significantly associated with adrenal involvement [HR 0.262, 95% CI (0.074, 0.416), p = 0.01].

This observation should be interpreted with caution. Given that the study used strict criteria to justify ipsilateral adrenalectomy, it is possible that those who received adrenalectomy and those who did not had different disease characteristics. Indeed, patients who underwent ipsilateral adrenalectomy were more likely to have higher stage disease than those who did not. It is unknown how adrenalectomy impacted on the survival of such patients. One interpretation may be that by using strict criteria to perform adrenalectomy, it is possible to achieve reasonable survival for patients with adrenal involvement. However, there is insufficient evidence for or against routine ipsilateral adrenalectomy with partial nephrectomy.

Table 7.3a. Overall survival data for partial nephrectomy with ipsilateral adrenalectomy vs. partial nephrectomy alone (comparison C2): time-to-event data

Study	Measure	With adrenal ectomy	Without adrenal ectomy	HR (95% CI) No adrenalectomy = 1 referent	Notes
		N	N		
Lane 2009[55]	Overall survival	48	2017	NR	'No significant difference in overall survival' calculated with the MK method. Log rank test p = 0.8

HR = hazard ratio; KM = Kaplan-Meier; CI = confidence interval; NR = not reported

Table 7.3b. Overall survival data for partial nephrectomy with ipsilateral adrenalectomy vs. partial nephrectomy alone (comparison C2): categorical data

Study	Outcome Definition	With adrenalectomy		Without adrenalectomy		Reported P-value	Notes
		N	% (95% CI)	N	% (95% CI)		
Lane 2009[55]	OS at 5 years	48	82.3 (71.0, 93.5)	2017	85.3 (83.5, 87.0)	0.56	Published KM estimates
Lane 2009[55]	OS at 10 yeas	48	67.6 (49.6, 85.6)	2017	72.4 (69.7, 75.1)	NR	Published KM estimates

OS = overall survival; KM = Kaplan-Meier; CI = confidence interval; NR = not reported

7.3. Summary of evidence for ipsilateral lymphadenectomy and ipsilateral adrenalectomy (comparisons C1-2)

The performance of complete lymph node dissection with radical nephrectomy for increasing overall, recurrence-free and cancer-specific survival for localised RCC remains unanswered due to large inconsistencies across the two studies identified in this review. One should also note that the extent of lymphadenectomy in the included RCT was variable. Regarding the rate of surgical complications, the RCT data found no statistically significant differences between lymphadenectomy and no lymphadenectomy, although event rates were low. Overall, the included studies did not provide sufficient information with which to draw definitive conclusions regarding lymphadenectomy.

No studies were eligible with which to assess the merit of performing ipsilateral adrenalectomy with radical nephrectomy. With regard to partial nephrectomy, the available evidence from a non-randomised study does not strongly support or refute routine removal of the ipsilateral adrenal gland to improve short- or long-term outcomes. However, the study suggests that using an adrenal-preserving policy where adrenalectomy is only done in certain circumstances, reasonable oncological outcomes can be achieved, due to the low incidence of metastasis affecting the adrenal gland. For patients who are selected to undergo adrenaletomy, it remains to be seen whether adrenalectomy has an impact on survival.

Table 7.4. Summary of the quality of evidence assessment (GRADE) of the data for radical nephrectomy with lymphadenectomy vs. radical nephrectomy (comparison C1)

Outcomes and summary estimates	Number of studies with data	Number of participants		Quality of evidence (GRADE)
Overall survival (time to event) HR 1.096 (0.81, 1.47)	1 RCT	271	288	Moderate
Overall survival at 5 years Published Kaplan-Meier estimates 91.6% vs. 81.3%	1 NRS	109	82	Very low
Overall survival at 10 years Published Kaplan-Meier estimates 80.2% vs. 54%	1 NRS	109	82	Very low
Recurrence free survival at 5 years Not reported	0			
Condition-specific quality of life Not reported	0			
Overall morbidity, inferred from length of hospital stay (days) Not reported	0			
Time to normal activity Not reported	0			
Analgesic requirement Not reported	0			
Need for blood transfusion Not reported	0			

RCT = randomised or quasi-randomised controlled trial; NRS = non-randomised comparative study; RR = relative risk; MD = mean difference; CI = confidence interval

Table 7.5. Summary of the quality of evidence assessment (GRADE) of the data for radical nephrectomy with adrenalectomy vs. radical nephrectomy (comparison C2)

Outcomes and summary estimates	Number of studies with data	Number of participants		Quality of evidence (GRADE)
Overall survival at 5 years Published Kaplan-Meier estimates 82.3% vs. 85.3%	1 NRS	48	2017	Very low
Overall survival at 10 years Published Kaplan-Meier estimates 67.6% vs. 72.4%	1 NRS	48	2017	Very low
Recurrence free survival at 5 years Not reported	0			
Condition-specific quality of life Not reported	0			
Overall morbidity, inferred from length of hospital stay (days) Not reported	0			
Time to normal activity Not reported	0			
Analgesic requirement Not reported	0			
Need for blood transfusion Not reported	0			

RCT = randomised or quasi-randomised controlled trial; NRS = non-randomised comparative study; RR = relative risk; MD = mean difference; CI = confidence interval

Chapter 8 Results: Nephron-sparing surgery

8.1. Partial vs. radical nephrectomy

A total of 16 studies examined the effectiveness of partial nephrectomy compared with radical nephrectomy. Information about the surgical approach used (whether open or laparoscopic) was not clearly reported in some studies. The surgery was assumed to be the open approach if (1) there was no mention of 'laparoscopy' in the intervention description in the paper, (2) surgery was performed before the year 2000, or (3) the description of surgical techniques used in the paper strongly indicated the open approach. If there was not sufficient information to determine the surgical approach used, studies were classified as 'open or laparoscopic'. Consequently, the included studies were classified into three pairwise comparisons:

- Open partial nephrectomy vs. open radical nephrectomy (Section 8.1.1)
- Laparoscopic partial nephrectomy vs. laparoscopic radical nephrectomy (Section 8.1.2)
- Open or laparoscopic partial nephrectomy vs. open or laparoscopic radical nephrectomy (Section 8.1.3)

There has been controversy as to whether partial nephrectomy should be used for larger tumours and a cut-off of 4 cm has been recommended. However, some study authors have argued that partial nephrectomy is feasible for tumours up to 7 cm with no reduction in oncological control or overall survival. For this reason the data in this section are tabulated where possible according to studies reporting populations with tumour sizes ≤4 cm or >4 cm.

8.1.1. Open partial nephrectomy vs. open radical nephrectomy (comparison D1)

Seven studies compared open partial with open radical nephrectomy. Two of these were randomised controlled trials,[32,37] one was a non-randomised prospective cohort study,[42] two were matched-pair studies[27,52] and two were database reviews.[56,60] The baseline characteristics of these studies and and the assessment of risk of confounders are shown in Table 8.1. More details are available in Appendix 10.

One RCT[32] recruited 40 patients with T1-2 renal cancer (tumour <4 cm) with normal contralateral kidney. No lymph node dissection was done in either group. The participants were followed up for a mean of 70 months. Another RCT[37] was a European Organisation for Research and Treatment of Cancer (EORTC) multicentre randomised trial, among patients with localised renal cancer (tumour ≤5 cm) with a normal contralateral kidney. Nephrectomy was performed with either limited or radical lymph node dissection in both groups. Duration of follow-up was not reported. No meta-analysis was possible for the RCT data because different outcomes were reported.

The study by Poulakis and colleagues[42] featured a retrospective review of 357 patients in which a subset of 51 patients were followed up prospectively. The data extracted for this review come from the subset of 51 patients only. Baseline data were not reported separately for these prospectively followed patients, and therefore it was not possible to assess potential risk of confounders (it was assumed to be high risk).

Two studies[27,52] reported retrospective matched-pair data. In one study[27] participants (with a small mass of <4 cm) were matched for tumour size, pathological T stage, pathological grade and follow-up time. However, the study did not provide information about other pre-specified confounders such as histological cell type and necrosis and therefore risk of confounding from these factors was assessed as high. The other matched-pair study[52] matched participants (with a single renal tumour of <7 cm) for age, sex, tumour location, tumour size and pathological T stage but did not report on other confounders such as ethnicity, performance status and co-morbidity.

Two database reviews also met the inclusion criteria.[56,60] Butler and colleagues[56] reported a review of 88 cases with a single tumour of less than 4 cm. Groups were comparable in

terms of age, sex, clinical tumour size, location and stage, renal function (serum creatinine level), diabetes and hypertension. However, it should be noted that treatment allocation was based on the status of the contralateral kidney: partial nephrectomies were performed due to compromised contralateral kidney function or because of elevated risk of future disease. There were more incidental cases in the partial nephrectomy group than in the radical nephrectomy group. Furthermore, no data were available on other potential confounders such as histological tumour grade, cell type and tumour necrosis.

In the other database review study by Gratzke and colleagues,[60] health-related quality of life of the study participants (T1-2) was assessed prospectively, whereas all other oncological and peri-operative outcomes were assessed retrospectively. The data come from a three-arm study with the third arm being laparoscopic radical nephrectomy (see section 6.1, comparison B1). The study was considered to be balanced at baseline on performance status and age (mean 60.7 vs. 61.1) but not on pathological T stage (pT1a 80% vs. 24%). Other important baseline characteristics, such as co-morbidity, clinical tumour size and tumour grade, histological cell type and necrosis were not reported (high risk of bias).

Overall, tumour size inclusion criteria in the majority of studies included for this comparison can be generally classified as small renal tumours, although they were not strictly ≤4cm: in three studies[27,32,56] the tumour size was 4cm or less and in one study[37] it was ≤5cm. The other studies appear to include larger tumours. In the study by Shekarriza and colleagues,[52] which used the inclusion criteria of less than 7cm, the reported mean tumour sizes were close to 4cm and the standard deviations imply that a proportion of the participants had tumours in the 4-7cm range in both the radical and partial nephrectomy groups (4.2 (1.9) vs. 3.8 (2.46) cm). In Gratzke's study[60] the reported pathological tumour stage suggests that tumour sizes in the radical nephrectomy group were larger (pT2 or greater) than in the partial nephrectomy group. The breakdown of tumour sizes in Poulakis' study[42] was unclear.

Table 8.1. Background characteristics of studies comparing partial nephrectomy with radical nephrectomy (comparison D1)

Study ID	Study design	Comparator	Number of partici-pants	Duration (month, mean or median*)	Age (years, mean or median*)	Pre-specified confounders for oncological outcomes and quality-of-life in non-randomised studies**					Pre-specified confounders for peri-operative outcomes in non-randomised studies**			
						Clinical tumour size	Pathological tumour stage	Tumour grade	Histological cell type	Necrosis	Age	Ethnicity	Performance status	Co-morbidity
Butler 1995,[56] USA	Database review	Open PN	46	40	60	1	1	5	5	5	1	5	5	1
		Open RN	42	66	64									
D'Armiento 1997,[32] Italy	RCT	Open PN	19	70	51.4	-	-	-	-	-	-	-	-	-
		Open RN	21	70	48.7									
Gratzke 2009,[60] Germany and Switzerland	Database review†	Open PN	44	22	60.7	5	5	5	5	5	1	5	1	5
		Open RN	37		61.1									
Lee 2007,[27] Korea	Matched-pair	Open PN	56	37.1	51.8	1	1	1	5	5	-	-	-	-
		Open RN	56	39	52.5									
Poulakis 2003,[42] Germany	Prospective cohort (subgroup)	Open PN	29	20*	NR	5	5	5	5	5	-	-	-	-
		Open RN	22		NR									
Shekarriz 2002,[52] USA	Matched-pair	Open PN	60	NR	62	-	-	-	-	-	1	5	5	5
		Open RN	60	NR	65									
Van Poppel 2007,[37] EU, USA, Canada	RCT	Open PN	268	NR	≤60y 44%; 61-70y 35%; >70y 21%	-	-	-	-	-	-	-	-	-
		Open RN	273	NR	≤60y 45%; 61-70y 35%; >70y 20%									

PN = partial nephrectomy; RN = radical nephrectomy; NR = not reported. **1 = The study groups were judged to be balanced at baseline, or the study used statistical methods that attempted to control for the specific confounder; 5 = The specific confounder was either not reported or was not balanced between the groups at baseline and not adjusted for in the analysis. †With prospective evaluation of quality of life

Oncological outcomes

Only three of the seven studies included in this comparison[27,32,56] reported oncological outcomes. These three studies included only patients with tumour sizes 4cm or less. Therefore, no data were available on oncological outcomes for tumours more than 4cm in this comparison.

The RCT[32] reported the two approaches had an equal median survival time of 96 months, although hazard ratios for survival or survival rates were not available.[32]

Table 8.2 shows estimated overall, cancer-specific and disease-free survival rates at five years from the other two non-randomised studies.[27,56] Regarding overall survival, data from one study[56] favoured the radical nephrectomy group (75% vs. 80%), whereas data from the other study[27] favoured the partial nephrectomy group (98.2% vs. 88.8%), although reported p-values from neither study suggested that the differences were statistically significant. Cancer-specific survival rates were consistently higher for partial nephrectomy across studies but again the differences were not statistically significant. There was no clear difference between groups in disease-free survival at five years (92.4% vs. 95.6%, reported p-value = 0.18). These estimates should be viewed with caution, as the length of follow-up was short with the mean of 40 vs. 66 months in one study[56] and 37 vs. 39 months in the other.[27]

The number of all-cause and cancer-specific deaths and disease-free rates at last follow-up were similar between the groups (the results were unadjusted and not censored) (Plots 10.1, 10.2 and 10.5). The included studies all reported low rates of recurrence and metastases in either group (Plot 10.3 and 10.4). There were no cases of positive surgical margins (Plot 10.6).

In summary, there is no evidence of a difference in overall survival, cancer specific survival, recurrence and metastases rates and instances of positive surgical margins between open partial and open radical nephrectomy.

Table 8.2 Survival data for open partial nephrectomy (open PN) vs. open radical nephrectomy (open RN) (comparison D1)

Study	Measure	Open PN		Open RN		Reported p-value	Notes
		N	%	N	%		
Tumour ≤4 cm							
Butler 1995[56]	OS at 5 years	46	75%	42	80%	NS	Published KM estimates
Lee 2007[27]	OS at 5 years	56	98.2%	56	88.8%	0.63	Published KM estimates (matched by size of tumour, pathological T stage, tumour grade and follow-up time)
Butler 1995[56]	CSS at 5 years	46	100%	42	97%	NS	Published KM estimates
Lee 2007[27]	CSS at 5 years	56	100%	56	97.9%	0.98	Published KM estimates (matched by size of tumour, pathological T stage, tumour grade and follow-up time)
Lee 2007[27]	DFS at 5 years	56	92.4%	56	95.6%	0.18	Published KM estimates (matched by size of tumour, pathological T stage, tumour grade and follow-up time)

OS = overall survival; CSS = cancer-specific survival; RFS = recurrence-free survival; DFS = disease-free survival; KM = Kaplan-Meier; NS = not statistically significant

Peri-operative outcomes

One RCT[37] reported that the proportion of participants with intra-operative blood loss of less than 500 ml was statistically significantly lower in the partial nephrectomy group compared with the radical nephrectomy group [87% (230/265) vs. 96% (254/264), RR 0.90, 95% CI (0.86, 0.95), Plot 10.8]. Two non-randomised studies[52,60] reported the amount of blood loss during the operation (Plot 10.7). Blood loss in the open partial nephrectomy group (by 70 ml) was higher in one study[60] but lower (by 92 ml) in the other[52] compared

with the open radical nephrectomy group, although the differences were small and not statistically significant in either study.

Three non-randomised studies[52,56,60] reported on blood transfusion requirement with no discernible difference in favour of either intervention (Plot 10.9). The transfusion rates ranged from 5% to 24% in the partial nephrectomy group and 0% to 31% in the radical nephrectomy group.

Complications such as surgical site infection, pneumonia, urinary tract infection, deep venous thrombosis and pulmonary embolism were uncommon and did not favour one intervention over the other (Plots 10.10 to 10.14). Only one case of post-operative mortality was reported in each group in three non-randomised studies examining this outcome (Plot 10.17).

One RCT[37] reported that the partial nephrectomy group had a slightly higher rate of *severe* haemorrhage (defined as blood loss >1 litre) than the radical nephrectomy group [3.4% (9/265) vs. 1.1% (3/264), RR 2.99, 95% CI (0.82, 10.92), Plot 2.16]. The rate of haemorrhage in two non-randomised studies that reported this outcome tended to be lower in the partial nephrectomy group compared with the radical nephrectomy group [2.2% (1/46) vs. 4.8% (2/42) in Butler 1995;[56] 4.5% (2/44) vs. 5.4% (2/37) in Gratzke 2009;[60] Plot 10.15]. However, in none of these studies did the difference reach statistical significance.

Resource utilisation

Two non-randomised studies provided information on the duration of operation.[52,60] Both studies showed that the average duration was longer for the open partial nephrectomy group compared with the open radical nephrectomy group and in one of these studies[52] the difference was statistically significant [MD 44.10 minutes, 95% CI (24.15, 64.05), Plot 10.18].

Of the three non-randomised studies that reported on the length of hospital stay, two[56,60] reported marginally longer average hospital stay (by up to 0.7 day) for the partial

nephrectomy group and one[52] reported no difference. No statistically significant difference was detected (Plot 10.19).

Health-related quality of life

Two non-randomised studies[42,60] examined health-related quality of life post-surgery for renal cancer. In one prospective non-randomised study[42] with 51 participants, those who underwent partial nephrectomy reported better scores, improving with time, in many aspects of quality of life as measured by SF-36 and EORTC QLQ-30, whereas those who underwent radical nephrectomy reported an increased level of anxiety higher degree of fear associated with living with only one kidney, but also less fear of recurrence.

The other study[60] conducted a survey using the SF-36 questionnaire with a mean follow-up of 22 months after surgery. Response rates were 77% (34/44) for the open partial nephrectomy group and 73% (27/37) for the open radical nephrectomy group. The mean mental (44.5 vs. 48.3) and physical (47.2 vs. 48) component scores were similar between the groups. The study authors reported that the results were within one standard deviation of the age-matched norm, although, as might be expected, patients who had higher complications rates had a trend towards lower quality of life scores.

Other Outcomes -- Post-operative Renal Function

Three studies consistently reported better renal function after partial nephrectomy compared to radical nephrectomy.[27,37,56] The RCT data[37] reported a significantly lower median creatinine level at follow up in the partial nephrectomy group than in the radical nephrectomy group (1.29 mg/dL vs. 1.50 mg/dL; reported p-value <0.0001). Similarly, one non-randomised study[56] found a statistically significant increase in mean (SD) post-operative serum creatinine level from the baseline in the radical nephrectomy group (pre-op, 1.5 (0.4) mg/dL; post-op, 1.1 (0.3) mg/dL; reported p-value <0.001) but no such increase was observed over time in the partial nephrectomy group (pre-op, 1.3 (0.6) mg/dL; post-op, 1.3 (0.4) mg/dL; reported p-value not significant). However, the study authors reported that

both groups 'maintained satisfactory and stable renal function' throughout the follow-up period.[56] In another non-randomised study[27] a significantly greater proportion of patients in the radical nephrectomy group (in the non-matched sample) had impaired post-operative renal function than those in the partial nephrectomy group (defined as a serum creatinine value greater than 1.6 mg/dL) (reported p-value = 0.045)

Other outcomes – Cost

Shekarriz and colleagues[52] reported that the overall cost did not vary significantly between the two procedures (US$20,819 (6,750) for partial nephrectomy vs. US$19,759 (20,183.3) for radical nephrectomy for the years 1995-1997, reported p-value = 0.81).

8.1.2. Laparoscopic partial nephrectomy vs. laparoscopic radical nephrectomy (comparison D2)

One non-randomised study,[68] which was a single institution database review,[65] compared laparoscopic partial nephrectomy (n = 35) with laparoscopic radical nephrectomy (n = 75) over a 5-year period (2001-2005) (Table 8.3 and Appendix 10). The inclusion criteria were organ-confined pathologically confirmed renal cell cancer >4 cm in size. Median follow-up was similar between the groups (3.3 vs. 4.4 years). There were significantly smaller tumours (mean 4.6 vs. 5.3 cm, p = 0.026) and a smaller proportion with pT3 (15% vs. 40%), tumour grade III or greater (37% vs. 57%) and clear cell carcinoma (66% vs. 85%) in the partial nephrectomy group relative to the radical nephrectomy group, and analyses did not control for these potentially confounding factors (Table 8.3). Information about co-morbidity and ethnicity was not reported.

Table 8.3. Background characteristics of studies comparing laparoscopic partial nephrectomy with laparoscopic radical nephrectomy (comparison D2)

Study ID	Study design	Comparator	Number of partici-pants	Duration (month, mean or median*)	Age (years, mean or median*)	Pre-specified confounders for oncological outcomes and quality-of-life in non-randomised studies**					Pre-specified confounders for peri-operative outcomes in non-randomised studies**			
						Clinical tumour size	Pathologlgical tumour stage	Tumour grade	Histological cell type	Necrosis	Age	Ethnicity	Performance status	Co-morbidity
Simmons 2009,[68] USA	Database review	Lap PN	35	44*	63.5	5	5	5	5	5	1	5	1	5
		Lap RN	75	57*	63.4									

PN = partial nephrectomy; RN = radical nephrectomy; lap = laparoscopic;

**1 = The study groups were judged to be balanced at baseline, or the study used statistical methods that attempted to control for the specific confounder; 5 = The specific confounder was either not reported or was not balanced between the groups at baseline and not adjusted for in the analysis.

Oncological outcomes

Simmons and colleagues[68] found no statistically significant difference between the groups in overall or cancer-specific survival at 80 months, although survival estimated in the partial nephrectomy group tended to be slightly higher (Table 8.4). The results were similar for recurrence-free survival but again were not statistically significant (Table 8.4). Note, however, that these survival data include pT3 tumours [15% (5/35) in the partial nephrectomy group vs. 40% (30/75) in the radical nephrectomy group]. Plots 12.1 and 12.2 show the number of all-cause (overall) deaths and cancer-specific deaths at last follow-up.

For the pT1-2 subgroup of the study population, there was one case of local recurrence in the partial nephrectomy group and none in the radical nephrectomy group (Plot 12.3). Systemic recurrence was reported in one participant in each group (Plot 12.4). These event rates change little with the addition of the pT3 patients in the analysis. The study reported no cases of positive surgical margins (Plot 12.5).

Table 8.4. Survival and Recurrence for Laparoscopic Partial Nephrectomy (LPN) vs. Laparoscopic Radical Nephrectomy (LRN) (comparison D2)

Study	Measure	Lap PN		Lap RN		Reported p- value	Notes
		N	% (95% CI)	N	% (95% CI)		
Tumours >4 cm							
Simmons 2009[68]	OS at 80 months	35	74% (67%, 76%)	75	72% (67%, 76%)	0.660	Published KM estimates
Simmons 2009[68]	CS at 80 months	35	81% (74%, 87%)	75	77% (75%, 80%)	0.986	Published KM estimates
Simmons 2009[68]	RFS at 80 months	35	81% (74%, 87%)	75	77% (74%, 79%)	0.495	Published KM estimates

OS = overall survival; CSS = cancer-specific survival; RFS = recurrence-free survival; DFS = disease-free survival; KM = Kaplan-Meier; CI = confidence interval; NR = not reported

Other Outcomes – Post-operative GFR

Simmons and colleagues[68] reported that a decrease in the estimated GFR (glomerular filtration rate) was significantly less after laparoscopic partial nephrectomy compared with laparoscopic radical nephrectomy (decrease of 13 vs. 24 ml/min, p = 0.03). The proportion of post-operative renal dysfunction was significantly lower in the partial nephrectomy group, with a 2-stage increase in the CKD (chronic kidney disease) stage occurring in 0% in the partial nephrectomy group compared with 12% in the radical nephrectomy group (p = 0.04).

8.1.3. Open or laparoscopic partial nephrectomy vs. open or laparoscopic radical nephrectomy (comparison D3)

Nine studies compared radical and partial nephrectomy cases.[45,51,54,57,61,63-65,69] The surgical approach used (whether open or laparoscopic) in these studies was not clearly described and thus classified as 'open or laparoscopic'. The baseline characteristics of these studies and the assessment of risk of confounders are shown in Table 8.5. More details are available in Appendix 10.

All studies were retrospective analyses of data from registries or databases and three of these studies[45,51,54] used matched-pair designs. Four studies analysed data from prospectively maintained databases from a single institution such as the Cleveland Clinic,[65] Memorial Sloan-Kettering Cancer Centre,[57] Mayo Clinic,[64] or combined data from Mayo Clinic and Memorial Sloan-Kettering Cancer Centre.[69] Three studies[45,54,61] used data from the prospectively maintained SEER (Surveillance Epidemiology and End Results) cancer registry database. The other two studies[51,63] derived data from multi-institutional and multi-national databases.

There was a variation in terms of the study inclusion criteria regarding the size of renal tumours: 4 cm or less in three studies,[54,61,64] >4 to 7 cm in four studies,[45,57,65,69] anything up

to 7 cm in one study,[63] and >4 cm to >10 cm (T1b-T2) in one study.[51] In the Patard study,[63] results were divided by subgroups of ≤4cm (T1a) and >4 to 7 cm (T1b).

The mean or median length of follow-up was relatively longer in these studies compared with other studies included in the review. The mean or median length of follow-up ranged from 21 months to 112.8 months.

The included studies reported oncological outcomes only. With respect to the risk of the five pre-specified confounders (tumour size, stage and grade, histological cell type and tumour necrosis) for oncological outcomes, five studies[45,54,57,63,65] addressed all confounders except one (tumour necrosis), two studies addressed at least three confounders[51,64] and two studies addressed at least two confounders.[61,69] All studies under this comparison were considered to be balanced between groups at baseline, or study authors attempted to adjust for them in the analysis, in terms of tumour size and stage.

Table 8.5. Background characteristics of studies comparing partial nephrectomy with radical nephrectomy (open or laparoscopic unspecified) (comparison D3)

Study ID	Study design	Comparator	Number of partici-pants	Duration (month, mean or median*)	Age (years, mean or median*)	Pre-specified confounders for oncological outcomes and quality-of-life in non-randomised studies**					Pre-specified confounders for peri-operative outcomes in non-randomised studies**			
						Clinical tumour size	Pathological tumour stage	Tumour grade	Histological cell type	Necrosis	Age	Ethnicity	Performance status	Co-morbidity
Crépel 2010,[45] USA	Matched-pair	Open/Lap PN	163	34	61	1	1	1	1	5	-	-	-	-
		Open/Lap RN	636	39.4	61									
Dash 2006,[57] USA	Database review	Open/Lap PN	45	21*	56.7	1	1	1	1	5	-	-	-	-
		Open/Lap RN	151		63.1									
Huang 2009,[61] USA	Database review	Open/Lap PN	556	43 overall; 48 in those alive at end of FU	66-69y 28%; 70-79y 60%; 80y+ 12%	1	1	5	5	5	-	-	-	-
		Open/Lap RN	2435		66-69y 22%; 70-79y 59%; 80y+ 19%									
Patard 2004,[63] USA, Europe	Database review	Open/Lap PN	379	50.7	59.7	1	1	1	1	5	-	-	-	-
		Open/Lap RN	1075	66.6	60									
Patard 2008,[51] Europe	Matched-pair	Open/Lap PN	289	54	59.3	1	1	1	5	5	-	-	-	-
		Open/Lap RN	257		61									

Study ID	Study design	Comparator	Number of partici-pants	Duration (month, mean or median*)	Age (years, mean or median*)	Pre-specified confounders for oncological outcomes and quality-of-life in non-randomised studies**					Pre-specified confounders for peri-operative outcomes in non-randomised studies**			
						Clinical tumour size	Pathological tumour stage	Tumour grade	Histological cell type	Necrosis	Age	Ethnicity	Performance status	Co-morbidity
Thompson 2008,[64] USA	Database review	Open/Lap PN	358	67.2*	64*	1	1	5	1	5	-	-	-	-
		Open/Lap RN	290	112.8*	65*									
Thompson 2009,[69] USA	Database review	Open/Lap PN	286	40.8*	<65y 57%; ≥65y 43%	1	1	5	5	5	-	-	-	-
		Open/Lap RN	873	63.6*	<65y 48%; ≥65y 52%									
Weight 2010,[65] USA	Database review	Open/Lap PN	524	46*	63	1	1	1	1	5	-	-	-	-
		Open/Lap RN	480	50*	65									
Zini 2009b,[54] USA	Matched-pair	Open/Lap PN	1283	35*	59.6	1	1	1	1	5	-	-	-	-
		Open/Lap RN	3166	46*	61.3									

PN = partial nephrectomy; RN = radical nephrectomy; lap = laparoscopic;

**1 = The study groups were judged to be balanced at baseline, or the study used statistical methods that attempted to control for the specific confounder; 5 = The specific confounder was either not reported or was not balanced between the groups at baseline and not adjusted for in the analysis.

Oncological outcomes

Survival data were reported inconsistently with diverse measures, making comparison across studies difficult. Within the limited data available, five studies[54,61,64,65,69] provided information on overall survival. Of these, four studies reported time-to-event data in the form of adjusted hazard ratios (Table 8.6a).[54,61,65,69] Relative to radical nephrectomy, partial nephrectomy was associated with statistically significantly lower all-cause mortality risk (hazard ratio <1) in two of these studies based on the SEER database[54,61] that included smaller tumours (≤4 cm) but no difference was found in the other two[65,69] that included larger tumours (>4 to 7 cm).

Three of these studies[54,61,65] and one other study[64] also provided categorical data for the same outcome (overall survival). The data are shown in Table 8.6b. These categorical data confirm the results of the time-to-event analysis with a reduction of mortality at five and ten years after partial nephrectomy compared with radical nephrectomy. Only one of these studies[64] reported a p-value that was statistically significant. It should be noted that this study was based on a subgroup analysis of patients younger than 65 years. In this study when all patients were included in the analysis no difference was found between radical and partial nephrectomy in terms of all-cause death [RR 1.2, 95% CI (0.80 ,1.56), p = 0.522]. However, after controlling for age, radical nephrectomy was associated with a significantly higher risk of death compared with partial nephrectomy in a subset of patients under 65 years of age [RR 2.16 95% CI (1.09, 4.23), p = 0.022].

Caution is required, as some patients in the partial nephrectomy group may have been more unfit and potentially less suitable to undergo radical nephrectomy. The raw number of patients who died during the study period (unadjusted and not censored) is shown in Plot 13.1.

Table 8.6a. Overall survival data for open or laparoscopic partial nephrectomy (PN) vs. open or laparoscopic radical nephrectomy (RN) (comparison D3): time-to-event data

Study	Mea-sure	Open/ Lap PN N	Open/ Lap RN N	HR (95% CI) and p-value RN = 1 referent	Notes
Tumour ≤4 cm					
Huang 2009[61]	OS	556	2435	HR 0.72 (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 co-morbidity. Unadjusted HR = 0.68, p<0.001.
Zini 2009b[54]	OS	1283	3166	HR 0.84, p = 0.048	Matched for age, tumour size, year of surgery and Fuhrman Grade. HR from another analysis matched for age, tumour size and year of surgery = 0.81 (p = 0.001).
Tumour >4 to 7 cm					
Thompson 2009[69]	OS	286	873	HR 1.06 (0.79, 1.45), p = 0.665	Adjusted for age, Charlson index, impaired renal function, tumour size, tumour stage, and histological subtype (benign vs.. RCC). Unadjusted HR 0.95 (0.71, 1.28), p = 0.8
Weight 2010[65]	OS	524	480	HR = 0.903 (0.56, 1.5), p = 0.68	Multivariate models stratified according to the propensity to undergo PN, and also including multiple predicting variables, namely pathological stage and post-operative eGFR. HR from univariate analysis stratified according to the propensity to undergo PN = 0.62 (0.40, 0.94), p = 0.030.

HR = hazard ratio; published hazard ratio (HR) is re-calculated so that HR<1 denotes advantage to PN and HR>1 denotes advantage to RN;
CI = confidence interval

Table 8.6b. Overall survival data for open or laparoscopic partial nephrectomy (PN) vs. open or laparoscopic radical nephrectomy (RN) (comparison D3): categorical data

First author	Mea-sure	Open/ Lap PN		Open/ Lap RN		Reported p-value	Notes
		N	% (95% CI)	N	% (95% CI)		
Tumour ≤4 cm							
Thompson 2008[64]	OS at 10 years	187	93%	140	82%	0.022	Published KM estimates. RR 2.16, 95% CI 1.12 to 4.19, p = 0.022. Subgroup: age <65 years only.
Zini 2009b[54]	OS at 10 years	1283	70.9%	3166	68.8%	NR	Published KM estimates. Matched for age, tumour size, year of surgery and Fuhrman grade.
Huang 2009[61]	OS at 5 years	556	74%	2435	68%	NR	Published KM estimates.
Zini 2009b[54]	OS at 5 years	1283	88.9%	3166	85.5%	NR	Published KM estimates. Matched for age, tumour size, year of surgery and Fuhrman grade.
Tumour >4 to 7 cm							
Weight 2010[65]	OS at 5 years	524	85% (81.4%, 88.6%)	480	78% (73.7%, 82.3%)	NR	Published KM estimates.

OS = overall survival; KM = Kaplan-Meier; CI = confidence interval; NR = not reported

With respect to cancer-specific survival, three studies[45,65,69] with larger tumours (>4 to 7 cm) reported adjusted hazard ratios (time-to-event data), with point estimates showing reduced mortality after partial nephrectomy, but the differences were not statistically significant (Table 8.7a). A fourth study[51] also including larger tumours (>4 to >10 cm) only reported a p-value (0.9) suggesting no significant difference between groups (Table 8.7a).

A categorical data analysis for the same outcome (cancer-specific survival) by Patard and colleagues[63] reported two subgroups of patients with stage T1a (tumour ≤4 cm) and T1b tumours (>4 to 7 cm) and found no statistically significant difference in either subgroup (Table 8.7b). Two other studies[45,65] including larger tumours (>4 cm) also reported

categorical data for cancer-specific survival with slightly lower estimates for five-year survival (increased mortality) for partial nephrectomy compared with radical nephrectomy, but a statistical test was not performed to provide corresponding p-values (Table 8.7b). The raw number of patients who died of any cause during the study period (unadjusted and not censored) are shown in Plots 13.2.

Table 8.7a. Cancer-specific survival data for open or laparoscopic partial nephrectomy (PN) vs. open or laparoscopic radical nephrectomy (RN) (comparison D3): time-to-event data

Study	Mea-sure	Open/ Lap PN N	Open/ Lap RN N	HR (95% CI) and reported p-value RN = 1 referent	Notes
Tumour 4-7 cm					
Crépel 2010[45]	CSS	163	636	HR 0.8; log rank, p = 0.4	Matched for age, tumour size, year of surgery and Fuhrman grade.
Thompson 2009[69]	CSS	239	704	HR 0.51 (0.24, 1.09), p = 0.079	Adjusting for age, impaired renal function, tumour stage and tumour size. Unadjusted HR 0.46 (0.22, 0.96), p = 0.039.
Weight 2010[65]	CSS	438	429	HR 0.77 (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 (1.07, 1.83), p = 0.01.
Tumour >4 to >10 cm					
Patard 2008[51]	CSS	289	257	NR	"Survival curves perfectly overlapped". Log rank test p = 0.9.

HR = hazard ratio; published hazard ratio (HR) is re-calculated so that HR<1 denotes advantage to PN and HR>1 denotes advantage to RN; CI = confidence interval; NR = not reported

Table 8.7b. Cancer-specific survival data for open or laparoscopic partial nephrectomy (PN) vs. open or laparoscopic radical nephrectomy (RN) (comparison D3): categorical data

First author	Out-come Definition	Open/ Lap PN		Open/ Lap RN		Reported p-value	Notes
		N	% (95% CI)	N	% (95% CI)		
Tumour ≤4 cm							
Patard 2004[63]	CSS at 5 years (T1a only)	314	97%	499	97%	NR	KM estimates from graph. χ^2 test p = 0.8, log rank test, p = 0.7.
Tumour >4 to 7 cm							
Crépel 2010[45]	CSS at 5 years	163	90.1%	636	93.8%	NR	Published KM estimates.
Patard 2004[63]	CSS at 5 years (T1b only)	65	96%	576	91%	NR	KM estimates from graph. χ^2 test, p = 0.6; log rank test, p = 0.8.
Weight 2010[65]	CSS at 5 years	438	87.6% (84%, 91.2%)	429	94% (91.3%, 96.7%)	NR	Published KM estimates.

CSS = cancer-specific survival; KM = Kaplan-Meier; CI = confidence interval; NR = not reported

One study[57] including larger tumours (>4 cm) reported adjusted hazard ratio for disease-free survival which shows that, on average, partial nephrectomy was better (reduced mortality) compared with radical nephrectomy but not statistically significantly so [PN vs. RN, HR 0.36, 95%CI (0.05, 2.82), Table 8.8a]. Estimates for five-year disease-free survival rates derived from the same analysis are shown in Table 8.8b and are consistent with the time-to-event data.

Table 8.8a. Disease-free survival data for open or laparoscopic partial nephrectomy (PN) vs. open or laparoscopic radical nephrectomy (RN) (comparison D3): time-to-event data

Study	Mea-sure	Open/ Lap PN N	Open/ Lap RN N	HR (95% CI) and reported p-value RN = 1 referent	Notes
Tumour >4 to 7 cm					
Dash 2006[57]	DFS	45	151	HR 0.36 (0.05, 2.82), p = 0.3	Adjusted for disease severity (confounder score approach). HR from the propensity score model = 1.75 (0.5, 6.14), p = 0.4. Unadjusted HR = 0.22 (0.03, 1.66), p = 0.14.

HR = hazard ratio; published hazard ratio (HR) is re-calculated so that HR<1 denotes advantage to PN and HR>1 denotes advantage to RN; CI = confidence interval; DFS = disease-free survival;

Table 8.8b. Disease-free survival data for open or laparoscopic partial nephrectomy (PN) vs. open or laparoscopic radical nephrectomy (RN) (comparison D3): categorical data

First author	Out-come Definition	Open/ Lap PN		Open/ Lap RN		Re-ported p-value	Notes
		N	%	N	%		
Tumour >4 to 7 cm							
Dash 2006[57]	DFS at 5 years	45	83%	151	71%	NR	KM estimates from graph.

DFS = disease-free survival; KM = Kaplan-Meier; CI = confidence interval; NR = not reported

Recurrence was reported by one non-randomised study at a mean follow-up of 62.5 months.[63] There was no clear difference between groups in terms of local recurrence [2/151 vs. 6/393, RR 0.87, 95% CI (0.18, 4.25), Plot 13.3] but the rate of distant recurrence was statistically significantly lower in the partial nephrectomy group compared with the radical nephrectomy group [5/151 vs. 42/393, RR 0.31, 95% CI (0.12, 0.77), Plot 13.4]. When the data were stratified by tumour stage, local or distant recurrence rates did not differ significantly between the type of surgery performed for T1a (p = 0.6) or T1b (p = 0.5): local recurrence rates for T1a and T1b were 0.8% (1/123) vs. 0.6% (1/175) and 3.6% (1/28) vs. 2.3% (5/218), respectively, and distant recurrence rates were 2.4% (3/123) vs. 4.6% (8/175) for T1a and 7.1% (2/28) vs. 15.6% (34/218) for T1b.

Other outcomes - Post-operative renal function

Dash and colleagues[57] reported that, in patients with tumours >4 to 7 cm, partial nephrectomy appeared to diminish the rise in serum creatinine level: compared with radical nephrectomy, the increase in mean creatinine level in the partial nephrectomy group was significantly smaller both at three months [MD 0.23 mg/dl, 95% CI (0.11, 0.34), $p < 0.001$] and at 6-12 months [MD 0.21 mg/dl, 95% CI (0.09, 0.34), $p < 0.001$] after surgery.

Other outcomes – Cardiovascular events and deaths

The study by Huang and colleagues[61] (tumours ≤ 4cm) reported more occurrence of cardiovascular events (15.1% vs. 21.6%) or deaths (4.9% vs. 6%) in radical nephrectomy patients (N = 2435) than partial nephrectomy patients (N = 556). However, the study authors note that partial nephrectomy patients tended to be younger (age 75 years or older 38% vs. 47%), male (63% vs. 56%), married (66% vs. 61%), and treated more recently (year 2000 or later 73% vs. 57%). Partial nepherctomy patients were also more likely to have pre-existing renal insufficiency (12% vs. 8%) but less likely to have cerebrovascular disease at baseline (13% vs. 17%). Survival analyses that controlled for patient characteristics found no significant association between type of surgery and time to first cardiovascular event (HR 1.21, $p = 0.10$) or death (HR 0.95, $p = 0.84$).

8.1.4. Summary of evidence for partial nephrectomy compared with radical nephrectomy (comparisons D1-3)

Current evidence based on randomised and non-randomised studies found no significant difference in survival between open partial and open radical nephrectomy (comparison D1) for small tumours (≤4 cm). However, two non-randomised studies,[54,61] both based on the SEER database, that combined open and laparoscopic approaches (comparison D3), appeared to show improved overall survival for partial nephrectomy when compared with radical nephrectomy for small tumours. For larger tumours (>4 cm), survival outcomes appeared similar between partial and radical nephrectomy, regardless of whether studies

combined both open and laparoscopic approaches (comparison D3) or a laparoscopic approach alone (comparison D2).

Recurrence and metastasis were sparsely reported. Nevertheless, one non-randomised study[63] that included 544 participants with tumours >4 cm showed a reduction in distant recurrence rates after patial nephrectomy compared with radical nephrectomy (laproscopic and open cases combined) at a mean follow-up of 62.5 months [RR 0.31, 95% CI (0.12, 0.77)], although the rate of local recurrence was similar between the groups and confidence intervals were wide [RR 0.87, 95% CI (0.18, 4.25)].

In all studies where renal function was reported (including one RCT), partial nephrectomy was associated with better preservation of renal function compared with radical nephrectomy regardless of choice of approach of nephrectomy (open or laparoscopic). Only two non-randomised studies[42,60] reported on quality of life, with inconsistent results. Other peri-operative outcomes such as blood loss, transfusion requirements, complication rates, duration of operation and duration of hospital stay did not differ between the two techniques.

For other outcomes, very few data were available. Most of such data had variable outcome measures (e.g. adjusted or unadjusted analysis) as did the type of data reported (e.g. percentages rather than hazard ratio), which makes comparison across studies difficult.

The observation that partial nephrectomy had better survival over radical nephrectomy is, at first glance, counter-intuitive. Such differences may be due to other confounding factors and may also stem from the fact that laparoscopic and open cases were combined in some studies, as there may be reasons why the patients underwent laparoscopic or open surgery. For instance, certain patients may be contra-indicated to laparoscopic or open surgery and this may have introduced indication bias. Oncologically, radical nephrectomy is considered to be the 'gold standard' and would be expected to achieve either equivalent or a greater degree of cancer clearance than partial nephrectomy. However, the possible overall survival benefit conferred by partial nephrectomy may be explained, at least in part, by its more favourable impact on renal function. The main objective of patial nephrectomy is to

preserve renal function, without compromising on oncological outcomes such as cancer-specific survival and recurrence rates. As such, it is possible that the benefits of preserving renal function from partial nephrectomy may contribute to improved overall survival.

Based on current evidence, partial nephrectomy appears comparable to radical nephrectomy in terms of cancer-specific outcomes, or at least there was no strong evidence to suggest that partial nephrectomy results in worse cancer-specific outcomes. At the same time, partial nephrectomy results in better preservation of renal function, and possibly to better overall survival, although data on overall survival was inconsistent. Taking everything into consideration, the evidence base indicates that nephron sparing surgery should be applied when technically feasible. However, it remains unclear if the potential benefits of partial nephrectomy also apply to larger tumours and what the threshold in regard to tumour size should be, beyond which partial nephrectomy should not be performed.

The interpretation of these results requires caution. Although the majority of studies included in this comparison attempted to adjust for prognostic factors such as age and tumour stage, other known and unknown confounders may not be accounted for and these unaccounted confounding variables are likely to have influenced the outcome.

Table 8.9. Summary of the quality of evidence assessment (GRADE) of the data for open partial nephrectomy vs. open radical nephrectomy (comparison D1)

Outcomes and summary estimates	Number of studies with data	Number of participants		Quality of evidence (GRADE)
Overall survival at 5 years Not pooled	2 NRS	100	93	Very low
Recurrence free survival at 5 years Not reported; but no recurrence during study period (proxy)	1 RCT	19	21	Very low
Condition-specific quality of life (EORTC QLQ-30) No summary score available	1 NRS	29	22	Very low
Overall morbidity, inferred from length of hospital stay (days) Data from individual studies (not pooled): MD 0.70 (-1.34, 2.74) MD 0.50 (-0.95, 1.95) MD 0.00 (-1.13, 1.13)	3 NRS	150	139	Very low
Time to normal activity Not reported	0			
Analgesic requirement Not reported	0			
Need for blood transfusion Data from individual studies (not pooled): RR 0.77 (0.39, 1.53) RR 4.22 (0.21, 85.27) RR 0.36 (0.12, 1.08)	3 NRS	150	139	Very low

RCT = randomised or quasi-randomised controlled trial; NRS = non-randomised comparative study; RR = relative risk; MD = mean difference; CI = confidence interval

Table 8.10. Summary of the quality of evidence assessment (GRADE) of the data for laparoscopic partial nephrectomy vs. laparoscopic radical nephrectomy (comparison D2)

Outcomes and summary estimates	Number of studies with data	Number of participants		Quality of evidence (GRADE)
Overall survival at 80 months Published Kaplan-Meier estimates 74% vs. 72%, p = 0.660	1 NRS	35	75	Very low
Recurrence free survival at 80 months Published Kaplan-Meier estimates 81% vs. 77%, p = 0.495	1 NRS	35	75	Very low
Condition-specific quality of life Not reported	0			
Overall morbidity, inferred from length of hospital stay (days) Not reported	0			
Time to normal activity Not reported	0			
Analgesic requirement Not reported	0			
Need for blood transfusion Not reported	0			

RCT = randomised or quasi-randomised controlled trial; NRS = non-randomised comparative study; RR = relative risk; MD = mean difference; CI = confidence interval

Table 8.11. Summary of the quality of evidence assessment (GRADE) of the data for partial or laparoscopic partial nephrectomy vs. partial or laparoscopic radical nephrectomy (comparison D3)

Outcomes and summary estimates	Number of studies with data	Number of participants		Quality of evidence (GRADE)
Overall survival (time to event) Data from individual studies (not pooled): HR 0.72 (0.59, 0.88), p<0.001 HR 1.06 (0.79, 1.45), p = 0.665 HR = 0.903 (0.56, 1.5), p = 0.68 HR 0.84, p = 0.048	4 NRS	2649	6954	Low
Overall survival at 5 years Data from individual studies (not pooled): Published Kaplan-Meier estimates 74% vs. 68% Published Kaplan-Meier estimates 85% vs. 78% Published KM estimates 88.9% vs. 85.5%	3 NRS	2363	6081	Low
Overall survival at 10 years Data from individual studies (not pooled): Published Kaplan-Meier estimates 93% vs. 82% Published KM estimates 70.9% vs. 68.8%	2 NRS	1470	3306	Low
Recurrence free survival at 5 years Not reported; the number of recurrence during study period (proxy) RR 0.87 (0.18, 4.25)	1 NRS	151	393	Very low
Condition-specific quality of life Not reported	0			
Overall morbidity, inferred from length of hospital stay (days) Not reported	0			
Time to normal activity Not reported	0			
Analgesic requirement Not reported	0			
Need for blood transfusion Not reported	0			

RCT = randomised or quasi-randomised controlled trial; NRS = non-randomised comparative study; RR = relative risk; MD = mean difference; CI = confidence interval

8.2. Ablation vs. radical nephrectomy

8.2.1. Radiofrequency ablation vs. laparoscopic radical nephrectomy (comparison D4)

A small prospective non-randomised study with 37 participants[41] compared the health-related quality of life after percutaneous radiofrequency ablation and laparoscopic radical nephrectomy.

As shown in Table 8.12 (more details in Appendix 10), the study was considered to be balanced between groups in terms of tumour size and stage but at high risk of confounding from other pre-specified confounders for the quality of life outcome such as tumour grade, histological cell type and tumour necrosis (no baseline data available).

Table 8.12 Baseline characteristics of studies comparing ablation with radical nephrectomy (comparison D4)

Study ID	Study design	Comparator	Number of partici-pants	Duration (month, mean or median*)	Age (years, mean or median*)	Pre-specified confounders for oncological outcomes and quality-of-life in non-randomised studies**					Pre-specified confounders for peri-operative outcomes in non-randomised studies**			
						Clinical tumour size	Pathological tumour stage	Tumour grade	Histological cell type	Necrosis	Age	Ethnicity	Performance status	Co-morbidity
Onishi 2007,[41] Japan	Prospective cohort	Radiofrequency ablation	20	24 weeks	65.9	1	1	5	5	5	-	-	-	-
		Lap RN	17		53									

PN = partial nephrectomy; RN = radical nephrectomy; lap = laparoscopic;

**1 = The study groups were judged to be balanced at baseline, or the study used statistical methods that attempted to control for the specific confounder; 5 = The specific confounder was either not reported or was not balanced between the groups at baseline and not adjusted for in the analysis.

Oncological outcomes

No data were available for oncological outcomes.

Peri-operative outcomes

No major surgical or post-operative complication was encountered by the study patients.

Health-related quality of life

The study[41] utilised SF-36 scores questionnaires at 1, 2, 12 and 24 weeks after surgery. The patients having radiofrequency ablation were reported to have a baseline (pre-operative) scores that were significantly lower than that of the laparoscopic surgery group on a number of the SF-36 components. The study authors postulate that this could be due to the fact that patients who underwent radiofrequency ablation were significantly older than the laparoscopic group (mean 65.9 vs. 53 years) and included those with single kidney, renal dysfunction, double cancer or those for whom general anaesthesia would not be appropriate.

Comparing with the baseline mean values, SF-36 scores in the laparoscopic surgery group were significantly lower one week after surgery, and recovered at 4-12 weeks post-operatively. On the other hand, the radiofrequency ablation group showed no reduction in scores at one week after surgery and the scores improved over time in the post-operative period. Nevertheless, the study found no significant difference between the groups in any of the SF-36 components during follow-up periods after surgery.

8.2.2. Summary of evidence for ablation compared with radical nephrectomy (comparison D4)

The review identified only one small non-randomised study with a short follow-up for this comparison. No conclusion can be drawn from this study. The study addressed none of the seven outcomes chosen for the GRADE assessment of the quality of evidence (Table 8.13).

Table 8.13. Summary of the quality of evidence assessment (GRADE) of the data for radiofrequency ablation vs. laparoscopic radical nephrectomy (comparison D4)

Outcomes and summary estimates	Number of studies with data	Number of participants		Quality of evidence (GRADE)
Overall survival at 5 years Not reported	0			
Recurrence free survival at 5 years Not reported	0			
Condition-specific quality of life Not reported	0			
Overall morbidity, inferred from length of hospital stay (days) Not reported	0			
Time to normal activity Not reported	0			
Analgesic requirement Not reported	0			
Need for blood transfusion Not reported	0			

RCT = randomised or quasi-randomised controlled trial; NRS = non-randomised comparative study; RR = relative risk; MD = mean difference; CI = confidence interval

8.3. Technique of partial nephrectomy

Six studies compared different techniques of partial nephrectomy.[44,46,48,62,66,67] These are grouped into three pairwise comparisons:

- Laparoscopic partial nephrectomy vs. open partial nephrectomy (section 8.3.1)
- Robotic laparoscopic partial nephrectomy vs. laparoscopic partial nephrectomy (section 8.3.2)

- Radiofrequency ablation-assisted robotic clampless partial nephrectomy vs. laparoscopic partial nephrectomy (section 8.3.3).

Baseline characteristics of these studies and the assessment of risk of confounders are shown in Tables 8.14. More details are available in Appendix 10.

Table 8.14. Baseline characteristics of studies comparing different techniques of partial nephrectomy (comparison D5-D7)

Study ID	Study design	Comparator	Number of partici-pants	Duration (month, mean or median*)	Age (years, mean or median*)	Pre-specified confounders for oncological outcomes and quality-of-life in non-randomised studies**					Pre-specified confounders for peri-operative outcomes in non-randomised studies**			
						Clinical tumour size	Pathological tumour stage	Tumour grade	Histological cell type	Necrosis	Age	Ethnicity	Performance status	Co-morbidity
Aron 2008,[44] USA	Matched-pair	Robotic lap PN	12	7.4	64	-	-	-	-	-	1	5	1	5
		Lap PN	12	8.5	61									
Gill 2007,[67] USA	Database review	Lap PN	771	14.4*	59.4	5	5	5	5	5	1	5	5	5
		Open PN	1029	33.6*	61.6									
Gong 2008,[46] USA	Matched-pair	Lap PN	76	21.7	60.1	1	1	5	5	5	1	5	5	5
		Open PN	77	20.6	57.7									
Lane 2010,[62] USA	Database review	Lap PN	672	48*	61*	1	1	1	1	5	-	-	-	-
		Open PN	944	68.4*	61*									
Marszalek 2009,[48] Austria	Matched-pair	Lap PN	100	44.4	62.3	1	1	5	1	5	1	5	5	5
		Open PN	100	42	62.5									
Wu 2010,[66] USA	Database review	Radiofrequency ablation-assisted robotic clampless PN	42	25.8	56	1	5	5	1	5	1	5	1	5
		Lap PN	36	7.8	58									

PN = partial nephrectomy; RN = radical nephrectomy; lap = laparoscopic;

**1 = The study groups were judged to be balanced at baseline, or the study used statistical methods that attempted to control for the specific confounder; 5 = The specific confounder was either not reported or was not balanced between the groups at baseline and not adjusted for in the analysis.

8.3.1. Laparoscopic partial nephrectomy vs. open partial nephrectomy (comparison D5)

Four non-randomised studies compared laparoscopic and open techniques of partial nephrectomy. Two of these were database reviews,[62,67] both involving the Cleveland Clinic kidney cancer patient registry, and two were matched-pair studies[46,48] (Tables 8.14). The study by Gong and colleagues[46] included patients with a clinical T1a tumour (≤4 cm), whereas the other three studies included tumours 7cm or less (T1).

Of the five pre-specified confounding factors for oncological outcomes (tumour size, stage, grade, histology and necrosis), the study groups were considered to be balanced at baseline or statistically adjusted for in the analysis on four factors in one study,[62] three in one study,[48] two in one study[46] and none in one study[67] (Table 8.14). All studies appear to be balanced in terms of age but did not always provide information about other confounders (ethnicity, performance status and co-morbidity) specified for peri-operative outcomes (considered to be high risk of bias).

In particular, in the study by Gill and colleagues,[67] patients who had open surgery were more likely to have a tumour >4 cm in size (cT1b 8.8% vs. 31.4%), a solitary functioning kidney (4.2% vs. 21.6%) and decreased performance status (ASA score 3 or greater 45.9% vs. 75.8%) compared with those receiving laparoscopic surgery. Tumour grade was measured but the data were not reported. Some of these factors were adjusted for in the analysis for peri-operative outcomes but not for oncological outcomes.

Oncological outcomes

Survival data were reported inconsistently across studies using diverse measures, and the interpretation of the available data is therefore extremely difficult. With respect to overall survival, time-to-event data reported by one study[62] in the form of adjusted hazard ratio (Table 8.15a) suggest reduced mortality for laparoscopic surgery compared with open surgery (HR<1), although the difference was only marginally significant (p = 0.07). Survival rates (categorical data) at seven years from the same study[62] were similar between the

groups, whereas the five-year estimates from another study[48] appear to favour the laparoscopic surgery group (Table 8.15b). The actual number of deaths from any cause in these studies is shown in Plot 14.1.

Table 8.15a. Survival data for laparoscopic partial nephrectomy (lap PN) vs. Open partial nephrectomy (open PN) (comparison D5): time-to-event data

		Lap PN	Open PN	HR (95% CI) Open PN = 1, referent	
First author	Outcome Definition	N	N		Notes
Lane 2010[62]	Overall survival (RCC with minimum FU of 1 year)	499	762	HR 0.69 (0.45-1.02), p = 0.07	Adjusted for age, gender, race, Charlson-Romano Index, tumour size, hypertension, pre-operative GFR, and oncological potential (calculated as predicted risk of recurrence estimated based on path tumour size, histological subtype, path stage, and symptoms at presentation).

HR = hazard ratio; HR<1 denotes advantage to lap PN and HR>1 denotes advantage to open PN; FU = follow-up; RCC = renal cell carcinoma

Table 8.15b. Overall survival data for laparoscopic partial nephrectomy (lap PN) vs. Open partial nephrectomy (open PN) (comparison D5): categorical data

Study	Measure	Lap PN		Open PN		Report-ed p-value	Notes
		N	% (95% CI)	N	% (95% CI)		
Marszalek 2009[48]	OS at 5 years (pT1 only)	81	96% (92%, 99%)	66	85% (79%, 92%)	0.1	Published KM estimates
Lane 2010[62]	Survival at 7 years (subset: RCC with min FU of 7ysr)	77	83.1%	310	83.5%	NR	Actual rate (not adjusted or censored)

OS = overall survival; KM = Kaplan-Meier; CI = confidence interval; FU = follow-up; NR = not reported; RCC = renal cell carcinoma

Table 8.16 shows cancer-specific survival rates (categorical data) from two studies, with one study[67] reporting estimates at three years, and the other[62] at seven years (two subgroups).

The results show no strong evidence of a difference between the open and laparoscopic surgery groups at either time point (Table 8.16). The actual number of cancer-specific deaths from one of these studies (Lane 2010) is shown in Plot 14.2.

Table 8.16. Cancer-specific survival for laparoscopic partial nephrectomy (lap PN) vs. Open partial nephrectomy (open PN) (comparison D5): categorical data

Study	Measure	Lap PN		Open PN		Report-ed p-value	Notes
		N	% (95% CI)	N	% (95% CI)		
Gill 2007[67]	CSS at 3 years (pathological RCC only)	514	99.3% (98.0%, 100%)	676	99.2% (98.4%, 100%)		Published KM estimates. Without adjusting for other factors (tumour size, stage and grade). Log rank test p>0.05.
Lane 2010[62]	CSS at 7 years (subgroup of RCC with min FU of 1 yr)	499	96.9%, (94.3%, 99.5%)	762	97.7%, (96.3%, 99.1%)	0.79	Published KM estimated
Lane 2010[62]	CSS at 7 years (subgroup of RCC with min FU of 7ysr)	55	92.7%	249	95.6%	NR	Actual rate (51/55 vs. 238/249)

CSS = cancer-specific survival; KM = Kaplan-Meier; CI = confidence interval; FU = follow-up; NR = not reported; RCC = renal cell carcinoma

Table 8.17 shows the published estimates for recurrence-free survival and metastasis-free survival (categorical data). Two studies provided information on local recurrence and found little difference between the groups (recurrence-free survival at five years 97% vs. 98% in Marszalek 2009;[48] local recurrence rates at 3 years 1.4% vs. 1.5% in Gill 2007[67]). Metastasis-free survival (or distant recurrence-free survival) was reported by three studies (including one study with two subgroups). The percentage-point difference between the groups ranges from 0.2% higher for laparoscopic surgery to 3.9% higher for open surgery. However, no trend favouring either surgical group was discernible. The reported

(unadjusted) rates of recurrence and metastasis at last follow-up appear in Plots 14.3 and 14.4.

Table 8.17. Recurrence-and metastasis-free survival for laparoscopic partial nephrectomy (lap PN) vs. Open partial nephrectomy (open PN) (comparison D5): categorical data

Study	Measure	Lap PN		Open PN		Report-ed p-value	Notes
		N	% (95% CI)	N	% (95% CI)		
Marszalek 2009[48]	RFS at 5 years (local recurrence in pT1 only)	81	97% (94%, 99%)	66	98% (95%, 100%)	NR	Published KM estimates. Log rank test, p = 0.8.
Gill 2007[67]	Local recurrence rate at 3 years (pathological RCC only)	514	1.4% (0%, 2.8%)	676	1.5% (0.4%, 2.6%)	NR	Published KM estimates. Without adjusting for other factors (tumour size, stage and grade). Log rank test p>0.05.
Lane 2010[62]	MFS at 7 years (RCC with min FU of 1 yr only)	499	97.5%, (95.9%, 99.0%)	762	97.3%, (95.9%, 98.7%)	0.47	Published KM estimated
Lane 2010[62]	MFS at 7 years (RCC with min FU of 7yrs only)	55	90.9%	249	94.8%	NR	Actual rate (50/55 vs. 234/249)
Marszalek 2009[48]	RFS at 5 years (distant recurrence in pT1 only)	81	99% (94%, 100%)	66	96% (92%, 99%)	NR	Published KM estimates. Log rank test, p = 0.2
Gill 2007[67]	Distant recurrence rate at 3 years (pathological RCC only)	514	0.9% (0%, 2.2%)	676	2.1% (0.7%, 3.4%)	NR	Published KM estimates

RFS = recurrence-free survival; DFS = disease-free survival; MFS = metastasis-free survival; KM = Kaplan-Meier; CI = confidence interval; NR = not reported; RCC = renal cell carcinoma

All four studies provided information on positive surgical margin. All studies reported higher rates for laparoscopic surgery than for open surgery, but only one study[67] found the difference to be statistically significant [22/771 vs. 13/1029, RR 2.26, 95% CI (1.15, 4.45), Plot 14.5].

Peri-operative outcomes

The four studies presented inconsistent findings with regard to the surgical parameters for laparoscopic and open partial nephrectomy.

Mean intraoperative blood loss in one study[67] was shown to be less for laparoscopic surgery compared with open surgery (MD -76 ml; Plot 14.6). After controlling for clinical tumour size, age, solitary kidney and bilateral tumours, laparoscopic surgery was associated with a significant reduction in blood loss [RR 0.80, 95% CI (0.74, 0.83)]. This was consistent with the (unadjusted) results from another study[46] [MD -174 ml, 95% CI (-256, -91), Plot 14.6].

Of the three studies that reported blood transfusion rates (Plot 14.7), one study[67] reported a significantly higher rate following laparoscopy surgery compared with open surgery [5.8% (45/771) vs. 3.4% (35/1029), RR 1.76, 95% CI (1.12, 2.77)] but two smaller studies showing slightly lower rates in the laparoscopic surgery group[46,48] found no significant difference between the groups.

Post-operative complications were classified differently across studies so that the results are not directly comparable. Gill and colleagues[67] reported more post-operative complications occurring in patients undergoing laparoscopic surgery than open surgery [24.9% (192/771) vs. 19.2% (198/1029)]. The results changed little after controlling for clinical tumour size, age, solitary kidney and bilateral tumours, with significantly higher risk of urological complications [RR 2.14, 95% CI (1.39, 3.31)], non-urological complications (RR 1.53, 95% CI 1.12 to 2.10) and haemorrhage [RR 3.52, 95% CI (1.82, 6.77)] associated with laparoscopic surgery compared with open surgery.

Gong and colleagues[46] similarly reported fewer post-operative complications after laparoscopic surgery compared with open surgery (39% vs. 22%, p = 0.026). According to the classification of complications proposed by Clavien and colleagues,[71] 'major'

complications (grades 2-4) were significantly more common in the open surgery group [9% (7/76) vs. 29% (22/77), p = 0.002], whereas the incidence of 'minor' complications (grade 1) were similar in both groups [11% (8/76) vs. 12% (9/77), p = 0.819].

In contrast, another study by Marszalek and colleagues[48] found no significant difference between groups in the number of post-operative complications graded according to the system developed by Simmonsand colleagues[68] and Gill and colleagues,[67] based on the National Cancer Institute Common Toxicity Criteria (14/100 vs. 19/100, p = 0.8).

The reported number of individual pre-specified adverse events is shown in Plots 14.8 to 14.14.

Resource utilisation

The length of operative time varied across studies and was reported using different measures. Overall, one study[46] reported a significantly longer average operative time for laparoscopic partial nephrectomy [MD 32.10 minutes, 95% CI (12.02, 52.18), Plot 14.15], while two studies reported that it is significantly shorter, with a mean difference of 55 minutes in one study[67] and a median difference of 65 minutes (p<0.001) in the other.[48] Of note, the study by Gill and colleagues[67] reported that the results changed little after controlling for other factors [RR 0.78, 95% CI (0.75, 0.81)].

Hospitalization was shorter by 2.5 days to 3 days in two studies that reported this outcome[46,67] (Plot 14.16). In the study by Gill and colleagues,[67] the difference was statistically significant on multivariate analysis [RR 0.59, 95% CI (0.56, 0.61)]. The unadjusted results by Gong and colleagues[46] also found the difference to be statistically significant [MD -3.1 days, 95% CI (-3.92, -2.28), Plot 14.16].

Other outcomes - Post-operative renal function

The three studies reported post-operative renal function at different points in time. Marzalek and colleagues[48] found the decline of GFR from pre- to post-operation (24 hours after surgery) was significantly greater after laparoscopic partial nephrectomy than after open partial nephrectomy (8.8% vs. 0.8%, $p < 0.001$). However, after a mean of 3.6 years, the decline in GFR from their pre-operative baseline was similar in both groups (10.9% vs. 10.6%, $p = 0.8$). At three months post-surgery, Gill and colleagues[67] reported that renal functional outcomes were similar for both laparoscopic and open surgery groups, with 97.9% and 99.6% of renal units retaining function, respectively. In this study, mean pre-operative and post-operative nadir serum creatinine was 1.01 and 1.18 mg/dL for the laparoscopic procedure and 1.25 and 1.42 mg/dL for the open procedure. Gong and colleagues[46] found that mean pre-operative and postopearive creatinine were similar at the last available follow-up (around 20 months) with 1.1 (0.7) and 1.3 (1.3) for the laparoscopic procedure and 1.2 (0.9) and 1.2 (0.7) for the open procedure; the differences between the groups were not statistically significant (reported p-values 0.470 pre-operation and 0.659 post-operation).

8.3.2. Robotic laparoscopic partial nephrectomy vs. laparoscopic partial nephrectomy (comparison D6)

One small non-randomised study[44] conducted a matched-pair study on the basis of age, gender, body mass index, ASA score, tumour size, location and specific technique used (early versus conventional unclamping) in 12 patients who underwent robotic and 12 who had standard laparoscopic partial nephrectomy (Table 8.14). The study was considered to be balanced in terms of age and performance status but unclear on ethnicity and co-morbidity (high risk of bias).

Oncological outcomes

No survival data were reported. One of the two conversions to standard laparoscopic nephrectomy was due to the finding of a positive margin noted on frozen section of the excised tumour (Plot 15.1).

Peri-operative outcomes

There was no strong evidence to suggest that the robotic approach was more effective than the comparator in terms of intra-operative blood loss [MD 29 ml, 95% CI (-252, 310), Plot 15.2], operative time [MD -14 minutes, 95% CI (-69.93, 41.93), Plot 15.5] and length of hospital stay [MD 0.3 day, 95% CI (-1.19, 1.79), Plot 15.6]. There was one case each of pulmonary embolism and haemorrhage (leading to blood transfusion among patients receiving robotic surgery (Plot 15.3-15.4).

Other outcomes – post-operative renal function

Renal functional outcomes were comparable between the groups both in terms of serum creatinine (mean, SD, mg/dL) [0.97 (0.2) vs. 1 (0.2), p = 0.73, before surgery; 1.12 (0.2) vs. 1.15 (0.2), p = 0.74, 3 months after] and estimated GFR (mean, SD, mL/min) [88 (22.2) vs. 85 (21.9), p = 0.77, before surgery; 75 (22.6) vs. 72 (17.0), p = 0.71, 3 months after].

8.3.3. Radiofrequency ablation-assisted robotic clampless partial nephrectomy vs. laparoscopic partial nephrectomy (comparison D7)

A database review by Wu and colleagues[66] compared peri-operative and oncologic outcomes of patients who underwent radiofrequency ablation-assisted robotic clampless partial nephrectomy (n = 42) with those who underwent standard laparoscopic partial nephrectomy (n = 36) (Table 8.14). In the robotic group, radiofrequency ablation was used as a haemostatic device and the renal hilar vessels were not clamped. The study was

considered to be balanced on histological cell type and performance status at baseline and also attempted to adjust for age and tumour size. However, information about other pre-specified confounders is not available (high risk of bias). Note that the study included a large number of benign tumours [23.8% (10/42) vs. 33.3% (12/36)].

Oncological outcomes

There was one case of local recurrence in the robotic group, and also one case of positive surgical margin in the standard laparoscopic surgery group (Plots 16.1 and 16.2). The study did not report any longer-term survival data.

Peri-operative outcomes

The study[66] found no statistically significant difference in any of the pre-specified peri-operative outcomes. In general, the robotic partial nephrectomy group was associated with increased intraoperative blood loss by around 90 ml compared with the standard laparscopic nephrectomy group [mean 337 ml (range 50-3500) vs. 250 ml (range 100-800), reported p-value = 0.36). Blood transfusion was less common after the robotic procedure than after the conventional procedure [7% (3/42) vs. 11% (4/36), RR 0.64, 95% CI (0.15, 2.68), Plot 16.4], and so was haemorrhage [5% (2/42) vs. 11% (4/36), RR 0.43, 95% CI (0.08, 2.20), Plot 16.7]. There was one case of superficial wound infection after the robotic procedure, and another case of pneumonia in the conventional procedure (plots 16.5-16.6). Note, however, that the sample size was small and may not be adequately powered to detect adverse effects.

Resource utilisation

Compared with the conventional procedure, mean operative time was reported to be significantly longer after the robotic procedure by 80 minutes (mean 373 minutes vs. 293

minutes, reported p-value <0.001) but no difference was found in the length of hospital stay [mean 4.4 (range 2-12) days vs. 3.8 days (range 1-14), reported p-value = 0.21].

Other outcomes: post-operative renal function

Post-operative renal function did not differ between the groups. Mean pre-operative and post-operative (at last follow-up) serum creatinine levels were 0.99 and 1.15 for the robotic procedure and 0.95 and 1.08 for the laparoscopic procedure, with no statistically significant differences between the groups (reported p-values 0.53 pre-operation and 0.39 post-opration). Note that mean length of follow-up was significantly longer in the laparoscopic group (7.8 vs. 25.8 months).

8.3.4. Summary of evidence for the technique of partial nephrectomy (comparisons D5-7)

A summary of effects and the quality of evidence according to the GRADE approach is given in Tables 8.18 to 8.20.

Comparison D5. It remains unclear if the laparoscopic or open approach to partial nephrectomy offers better outcomes than the traditional open route, although the laparoscopic approach was associated with a consistently longer operation time, shorter hospital stay and less blood loss. There was no evidence of a difference in all other important peri-operative outcomes and renal function outcomes.

Comparisons D6-D7. Regarding the robot-assisted approaches to partial nephrectomy compared with standard laparoscopic partial nephrectomy, there was no strong evidence to suggest any differences in terms of peri-operative outcomes. No information was available about their long-term oncological performance, especially with regard to survival.

Table 8.18. Summary of the quality of evidence assessment (GRADE) of the data for laparoscopic partial nephrectomy vs. open partial nephrectomy (comparison D5)

Outcomes and summary estimates	Number of studies with data	Number of participants		Quality of evidence (GRADE)
Overall survival (time to event) HR 0.69 (0.45, 1.02)	1 NRS	499	762	Very low
Overall survival at 5 years Published Kaplan-Meier estimates 96% vs. 85%, p = 0.1	1 NRS	81	66	Very low
Recurrence free survival at 5 years Published Kaplan-Meier estimates 97% vs. 98%	1 NRS	81	66	Very low
Condition-specific quality of life Not reported	0			
Overall morbidity, inferred from length of hospital stay (days) Data from individual studies (not pooled): MD -2.5, 95% CI not estimable MD -3.10 (-3.92, -2.28)	2 NRS	847	1106	Very low
Time to normal activity Not reported				
Analgesic requirement Not reported				
Need for blood transfusion Data from individual studies (not pooled): RR 1.76 (1.12, 2.77) RR 0.73 (0.29, 1.84) RR 0.52 (0.18, 1.46)	3 NRS	947	1206	Very low

RCT = randomised or quasi-randomised controlled trial; NRS = non-randomised comparative study; RR = relative risk; MD = mean difference; CI = confidence interval

Table 8.19. Summary of the quality of evidence assessment (GRADE) of the data for robotic partial nephrectomy vs. laparoscopic partial nephrectomy (comparison D6)

Outcomes and summary estimates	Number of studies with data	Number of participants		Quality of evidence (GRADE)
Overall survival at 5 years Not reported	0			
Recurrence free survival at 5 years Not reported	0			
Condition-specific quality of life Not reported	0			
Overall morbidity, inferred from length of hospital stay (days) MD 0.3 (-1.19, 1.79)	1 NRS	12	12	Very low
Time to normal activity Not reported	0			
Analgesic requirement Not reported	0			
Need for blood transfusion Not reported	0			

RCT = randomised or quasi-randomised controlled trial; NRS = non-randomised comparative study; RR = relative risk; MD = mean difference; CI = confidence interval

Table 8.20. Summary of the quality of evidence assessment (GRADE) of the data for radiofrequency ablation-assisted robotic clampless partial nephrectomy vs. laparoscopic partial nephrectomy (comparison D7)

Outcomes and summary estimates	Number of studies with data	Number of participants		Quality of evidence (GRADE)
Overall survival at 5 years Not reported				
Recurrence free survival at 5 years Not reported; the number of recurrence during study period (proxy) RR 3.00 (0.13, 71.15)	1 NRS	34	34	Very low
Condition-specific quality of life Not reported	0			
Overall morbidity, inferred from length of hospital stay (days) Not reported	0			
Time to normal activity Not reported	0			
Analgesic requirement Not reported	0			
Need for blood transfusion RR 0.64 (0.15, 2.68)	1 NRS	42	36	Very low

RCT = randomised or quasi-randomised controlled trial; NRS = non-randomised comparative study; RR = relative risk; MD = mean difference; CI = confidence interval

8.4. Ablation vs. partial nephrectomy

Three studies compared ablation with partial nephrectomy.[47,49,58] These studies examined two pair-wise comparisons:

- Laparoscopic cryoablation vs. laparoscopic partial nephrectomy (section 8.4.1)
- Laparoscopic cryoablation vs. open partial nephrectomy (section 8.4.2).

A summary of baseline characteristics of these studies and the assessment of risk of confounders are shown in Table 8.21. These are described in more detail in Appendix 10.

Table 8.21. Baseline characteristics of studies comparing ablation with partial nephrectomy (comparisons D8-D9)

Study ID	Study design	Comparator	Number of partici-pants	Duration (month, mean or median*)	Age (years, mean or median*)	Pre-specified confounders for oncological outcomes and quality-of-life in non-randomised studies**					Pre-specified confounders for peri-operative outcomes in non-randomised studies**			
						Clinical tumour size	Pathological tumour stage	Tumour grade	Histological cell type	Necrosis	Age	Ethnicity	Performance status	Co-morbidity
Desai 2005b,[58] USA	Database review	Lap cryoablation	78	24.6	65.55	1	1	5	1	5	1	5	5	5
		Lap PN	153	5.8	60.59									
O'Malley 2007,[49] USA	Matched-pair	Lap cryoablation	15	11.9	76.1	1	1	5	5	5	1	5	1	1
		Lap PN	15	9.83	75.7									
Ko 2008,[47] Korea	Matched-pair	Lap cryoablation	20	27.3	56.3	1	1	1	1	5	1	5	5	5
		Open PN	20	28.7	57.6									

PN = partial nephrectomy; RN = radical nephrectomy; lap = laparoscopic;

**1 = The study groups were judged to be balanced at baseline, or the study used statistical methods that attempted to control for the specific confounder; 5 = The specific confounder was either not reported or was not balanced between the groups at baseline and not adjusted for in the analysis.

8.4.1. Laparoscopic cryoablation vs. laparoscopic partial nephrectomy (comparison D8)

Two non-randomised studies were identified that compared minimally invasive procedures with extirpative surgery, including one prospective cohort study[58] and one matched-pair study[49] (Table 8.21).

Desai and colleagues[58] included 231 patients with small renal tumours (≤3 cm). Compared with laparoscopic partial nephrectomy patients, laparoscopic cryoablation patients were less healthy (American Society of Anesthesiologists class 3 or4, 75% vs. 46%), had a lower baseline serum creatinine (mean 105.1 vs. 90.1 mg/dL), and had more cases of solitary kidneys (20% vs. 5%). According to the pre-specified confounder risk assessment, the study was considered to be balanced on tumour size and stage, histological cell type (clear cell 56% vs. 62%) and age (mean 60.6 vs. 65.6 years) but not balanced or unclear on performance status (see ASA class above), tumour grade, necrosis, ethnicity, and co-morbidity. The overall length of follow-up was short and in particular it was much shorter in the partial nephrectomy group (mean six months) compared with the cryoablation group (mean 25 months). It should also be noted that the study sample included a large number of benign tumours [38% (34/89) vs. 32% (49/153)].

The matched-pair study by O'Malley and colleagues[49] included 30 patients with small (<4cm) tumours matched by age and tumour size. The study groups were reported to be similar in age (mean 76.1 vs. 75.7 years), performance status (ASA class 3 or 4, 62% vs. 53%), the likelihood of more than one co-morbidity (47% vs. 47%) and baseline renal function (mean creatinine 1.17 vs. 1.21 mg/dL). No information was available on tumour grade, histology, necrosis and ethnicity. The overall mean length of follow-up was again short at less than one year.

Oncological outcomes

Desai and colleagues[58] reported that three patients (3/78, 4%) in the cryoablation group and none in the partial nephrectomy group (0/153) died during the study period (Plot 17.1). The

same study[58] also reported two cases of local recurrence occurring after cryoablation and one after partial nephrectomy (Plot 17.2). No mortality or recurrence was reported in the study by O'Malley and colleagues.[49] The difference in recurrence rates between the studies may be a reflection of different definitions and ways of establishing disease recurrence following cryoablation. For example, determining local recurrence on imaging alone is known to be subjective. Neither study conducted longer-term survival analysis.

Peri-operative outcomes

Compared with laparoscopic partial nephrectomy, laparoscopic cryoablation was associated with a statistically significant reduction in intra-operative blood loss by up to 160 ml and this finding was consistent across the two studies [MD -111 ml, 95% CI (-162, -59) in Desai 2005;[58] MD -163 ml, 95% CI (-256, -70) in O'Malley 2007;[49] Plot 17.3]. All instances of blood transfusion were in the laparoscopic partial nephrectomy group, although events were uncommon in both studies (Plot 17.4).

Post-operative complications were again uncommon but laparoscopic partial nephrectomy tended to have a slightly higher incidence in terms of pneumonia (two cases each in both groups), deep venous thrombosis (none for cryoablation and three for nephrectomy) and pulmonary embolism (none for cryoablation and one for nephrectomy) (Plots 17.5-17.7).

Resource utilisation

Operative time was significantly shorter for laparoscopic cryoablation compared with laparoscopic partial nephrectomy in the O'Malley study[49] [MD -96.20 minutes, 95% CI (-32.00, -60.40), Plot 17.8], but no such difference was found in the Desai study[58] [MD -2.33 minutes, 95% CI (-18.76, 14.10), Plot 17.8].

Patients in both groups were comparable in terms of the length of hospital stay (mean 2.1 vs. 2.3 days in Desai 2005;[58] mean 3.3 vs. 4.4 days in O'Malley 2007;[49] Plot 17.9) and convalescence time (mean 4.45 vs. 4.39 weeks in Desai 2005,[58] Plot 17.10).

Other outcome - post-operative serum creatinine

Serum creatinine levels were comparable for both groups in the Desai study[58] in terms of post-operative levels (mean, SD, mg/dL) [1.41 (0.65) vs. 1.27 (1.92), p = 0.31] and percent rise from baseline (mean %, SD) [13.7 (37.9) vs. 16.4 (21), p = 0.081].

Similarly, the O'Malley study[49] reported that creatinine levels (mean, SD, mg/dL) after surgery did not differ between the groups [1.19 (0.29) vs. 1.18 (0.24), p = 0.891].

8.4.2. Laparoscopic cryoablation vs. open partial nephrectomy (comparison D9)

A small matched-pair study by Ko and colleagues[47] compared laparoscopic cryoablation with open partial nephrectomy for small (<4 cm) renal tumours (Table 8.21). The study was considered to be balanced in terms of tumour grade, histology, and age but not balanced on performance status (ASA grade 3 or 4, 40% vs. 15%). No information was available on tumour necrosis, ethnicity and co-morbidity and so there is high risk of confounding from these factors.

Oncological outcomes

After a follow-up period of 27-28 months, there were no local recurrences or metastasis in either group with 20 patients each (Plot 18.1-2).

Peri-operative outcomes

Compared with the open partial nephrectomy group, the laparoscopic cryoablation group was associated with a significant reduction in intra-operative blood loss [MD -253 ml, 95% CI (-328, -178), Plot 18.3] and marginally significant reduction in blood transfusion rates [2/20 vs. 8/20, RR 0.25, 95% CI (0.06, 1.03), Plot 18.4].

Resource utilisation

The duration of operation was similar in both groups [MD -9.00 minutes, 95% CI (-27.65, 9.65), Plot 16.5]. The length of hospital stay was significantly shorter in the cryoablation group by around four days [MD -3.99 days, 95% CI (-5.23, -2.75), Plot 18.6].

8.4.3. Summary of evidence for ablation compared with partial nephrectomy

For the comparisons of minimally invasive ablative procedures and partial nephrectomy, no definitive conclusions can be drawn because the review identified only a few non-randomised studies which were uniformly small with short follow-up. The included studies provided no information about long-term survival or quality of life. Regarding peri-operative outcomes, the limited evidence that is available suggests a reduction in blood loss after ablative procedures compared with partial nephrectomy (either open or laparoscopic), but other outcomes including renal function outcome appear similar between the groups.

A summary of effects for ablation compared with partial nephrectomy is shown in Tables 8.22-8.23.

Table 8.22. Summary of the quality of evidence assessment (GRADE) of the data for laparoscopic cryoablation vs. laparoscopic partial nephrectomy (comparison D8)

Outcomes and summary estimates	Number of studies with data	Number of participants		Quality of evidence (GRADE)
Overall survival at 5 years Not reported; all cause deaths during study period (proxy) RR 13.65 (0.71, 260.91)	1 NRS	78	153	Very low
Recurrence free survival at 5 years Not reported. Data on local recurrence rate during study period (proxy, not pooled): Study 1 -- RR 3.92 (0.36, 42.60) Study 2 – No cases of recurrence during study period	2 NRS	93	168	Very low
Condition-specific quality of life Not reported	0			
Overall morbidity, inferred from length of hospital stay (days) Data from individual studies (not pooled): MD -0.20 (-0.98, 0.58) MD -1.10 (-3.69, 1.49)	2 NRS	93	168	Very low
Convalescence time (weeks) MD 0.06 (-0.89, 1.01)	1 NRS	78	153	Very low
Analgesic requirement Not reported				
Need for blood transfusion Data from individual studies (not pooled): RR 0.39 (0.02, 8.02) RR 0.33 (0.01, 7.58)	2 NRS	93	168	Very low

RCT = randomised or quasi-randomised controlled trial; NRS = non-randomised comparative study; RR = relative risk; MD = mean difference; CI = confidence interval

Table 8.23. Summary of the quality of evidence assessment (GRADE) of the data for laparoscopic cryoablation vs. open partial nephrectomy (comparison D9)

Outcomes and summary estimates	Number of studies with data	Number of participants		Quality of evidence (GRADE)
Overall survival at 5 years Not reported				
Recurrence free survival at 5 years Not reported; no recurrence during study period (proxy)	1 NRS	20	20	Very low
Condition-specific quality of life Not reported				
Overall morbidity, inferred from length of hospital stay (days) MD -3.99 (-5.23, -2.75)	1 NRS	20	20	Very low
Time to normal activity Not reported				
Analgesic requirement (person time) Not reported				
Need for blood transfusion RR 0.17 (0.03, 0.92)	1 NRS	20	20	Very low

RCT = randomised or quasi-randomised controlled trial; NRS = non-randomised comparative study; RR = relative risk; MD = mean difference; CI = confidence interval

Chapter 9 Discussion

Principal findings

Non-surgical management (Chapter 5). For the comparison of surgical management with non-surgical management of renal tumours, there was insufficient evidence to show that surgery improves survival. 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.

Technique of radical nephrectomy (Chapter 6). For the comparison of laparoscopic and open approaches in performing radical nephrectomy, there was no evidence of a difference in terms of survival. With regard to peri-operative outcomes, laparoscopic radical nephrectomy had shorter hospital stay, shorter convalescence time and requires less analgesia than the open radical nephrectomy approach. Mean duration of operation was significantly longer with the laparoscopic approach than with the open approach in two non-randomised studies, but no such difference was apparent in one RCT. There was no evidence of a difference in blood transfusion rates, surgical complications, operative mortality or quality of life measures between the two approaches.

The review found no evidence of a difference in survival between different laparoscopic approaches in performing radical nephrectomy. For the comparison of retroperitoneal and transperitoneal approaches, peri-operative outcomes also appeared to be similar between the groups, although there were some inconsistencies in the direction of effect between studies. It is likely that the choice of approach will be guided by tumour location, patient's body habitus, previous intra-abdominal surgery and surgeon preference. In terms of modifications to standard laparoscopic nephrectomy, limited comparative data were available for three approaches: hand-assisted, robot-assisted, and single-port laparoscopic radical nephrectomy. Peri-operative outcomes from both hand-assisted and robot-assisted

laparoscopic radical nephrectomy appeared similar to those from standard laparoscopic radical nephrectomy. There is little evidence to indicate that the single-port technique is superior to the standard three-port technique in various peri-operative outcome measures such as pain intensity, analgesic requirement and speed of recovery due to inconsistent reporting and poor methodology in included studies. Caution is required, as all included studies examining different techniques of radical nephrectomy were small and follow-up was short.

Ipsilateral lymphadenectomy and ipsilateral adrenalectomy (Chapter 7). The question of whether the performance of complete lymph node dissection during radical nephrectomy improves oncological outcomes remains unanswered due to large inconsistencies in the data. Regarding the rate of surgical complications, there were no statistically significant differences between lymphadenectomy and no lymphadenectomy, although event rates were low. Overall, the included studies did not provide sufficient information with which to draw definitive conclusions regarding lymphadenectomy during radical nephrectomy.

No comparative studies were identified with which to assess the merit of performing ipsilateral adrenalectomy with radical nephrectomy. With regard to partial nephrectomy, the available evidence from a non-randomised study suggests that, using a policy whereby the default position is adrenal preservation except in certain circumstances, reasonable cancer-specific outcomes can be achieved, since the risk of either synchronous or metastatic disease within the ipsilateral adrenal gland is extremely low. However, for patients who fulfil the criteria for ipsilateral adrenalectomy, it is unclear how adrenalectomy impacts on survival. There was no comparative study on which to make conclusions concerning concomitant adrenalectomy and peri-operative as well as quality of life outcomes.

Partial vs. radical nephrectomy (Chapter 8, section 1). Current evidence based on randomised and non-randomised studies found no significant difference in survival between open partial and open radical nephrectomy for small tumours (≤4 cm). However, two non-randomised studies[54,61] that combined open and laparoscopic approaches appear to show improved overall survival for partial nephrectomy when compared with radical nephrectomy for small tumours. Nevertheless, there was no evidence of a difference in

survival between the treatment groups for tumours >4cm. Recurrence rates and metastases were sparsely reported, although one non-randomised study[63] showed a reduction in distant recurrence rates after patial nephrectomy compared with radical nephrectomy (laproscopic and open cases combined) for tumours >4 cm.

Partial nephrectomy was associated with better preservation of renal function in comparison with radical nephrectomy in all studies that reported this outcome. This advantage is maintained regardless of choice of approaches (open or laparscopic) of partial nephrectomy. Only two non-randomised studies[42,60] reported on quality of life, with inconsistent results. Other peri-operative outcomes such as blood loss, transfusion requirements, complication rates, duration of operation and duration of hospital stay did not differ between partial and radical nephrectomy.

Such findings confirm data from retrospective case series that demonstrated better preservation of renal function from partial nephrectomy over radical nephrectomy for renal tumours under 4cm[72] and from retrospective comparative studies showing better renal preservation with partial nephrectomy and increased risk of chronic kidney disease with radical nephrectomy.[73] These findings are also consistent with non-randomised research on radical versus partial nephrectomy for clinical T1, but pathologically benign renal tumours, where better five-year overall survival and cardiac-specific survival have been linked to better renal function in partial nephrectomy patients.[74]

In view of the benefit of better preservation of renal function, equivalent cancer-specific outcomes, and either equivalent or better overall survival with partial nephrectomy, the evidence base indicates that nephron sparing surgery should be applied when possible. However, it remains unknown if the advantage is applicable to larger tumours.

Ablation vs. radical nephrectomy (Chapter 8, section 2). The review identified only one small non-randomised study with a short follow-up for this comparison. No conclusion can be drawn from this study.

Technique of partial nephrectomy (Chapter 8, section 3). With regard to different techniques of partial nephrectomy, oncological outcomes were reported using diverse measures, making interpretation of these data difficult. Nevertheless, for the comparison of open and laparoscopic partial nephrectomy, no trend was discernible favouring either treatment group. In terms of peri-operative outcomes, it remains unclear if the laparoscopic approach of performing partial nephrectomy is better than the traditional open route, although the laparoscopic approach was associated with a consistently longer operation time, shorter hospital stay and less blood loss. There was no evidence of a difference in all other important peri-operative outcomes and renal function outcomes. Regarding the robot-assisted approaches to partial nephrectomy compared with standard laparoscopic partial nephrectomy, there was no strong evidence to suggest any differences in terms of peri-operative outcomes. No information was available about their long-term oncological performance, especially with regard to survival.

Ablation vs. partial nephrectomy (Chapter 8, section 4). For the comparisons of minimally invasive ablative procedures and partial nephrectomy, no definitive conclusions can be drawn because the review identified only a few non-randomised studies which were uniformly small with short follow-up. The included studies provided no information about long-term survival or quality of life. Regarding peri-operative outcomes, the limited evidence that is available suggests a reduction in blood loss after ablative procedures compared with partial nephrectomy (either open or laparoscopic), but other outcomes including renal function outcome appear similar between the groups.

Strengths and limitations

The strength of this review is that it adopted the rigorous and best available systematic review methods recommended by the Cochrane Collaboration[75] and a reporting standard recommended by PRISMA.[76] The review also incorporated a novel tool to assess risk of bias in non-randomsied studies,[21] and requested peer review throughout from a reference group of international experts. An extensive literature search was undertaken by an experienced information scientist and study selection was performed by two systematic reviewers

independently. The scope of the review was also comprehensive. At the outset, a clinical care pathway was formulated in consultation with stakeholders including international experts drawn from the British Association of Urological Surgeons (BAUS) Section of Oncology, and the European Association of Urology (EAU) Renal Cancer Guideline Panel. This enabled the identification of all plausible treatment options and comparisons. An in-depth description of this consensus building process has been previously reported.[23]

The review used strict inclusion and exclusion criteria especially for the study population and excluded N+ patients. Exclusion of clinically N+ patients meant that the review did not cover studies of adjuvant treatments. However, the expert panel felt that it was important to be sure that study populations were as consistent as possible across studies to make the review findings generalisable.

The major limitation of this systematic review includes 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 widened to include study designs from further down the hierarchy of evidence than is desirable. However, given a paucity of randomised trials and high quality prospective non-randomised studies, a reliance on non-randomised studies, including retrospective studies and reviews of national and regional databases, was unavoidable. The benefit of having undertaken the review in this manner is that it allows statements to be generated based on the best available evidence (rather than resorting to expert opinion) and also demonstrates the major limitations of the evidence base, necessitating much caution when interpreting the results. In essence, by employing the most rigorous methods, this review describes the state of current evidence in the management of localised renal cell carcinoma.

The inclusion of non-randomised studies, however, meant that the findings should always be treated with some caution due to their inherent bias, most notably selection bias. In non-randomised studies treatments are commonly allocated to patients for specific prognostic reasons and consequently participants in the experiment and control groups are drawn from two different groups. Some non-randomised studies will also have recruited participants who are considered suitable for only one of the two treatments under study.

This is in sharp contrast to randomised trials where all participants must be deemed suitable for both treatments.[77] The review attempted to address this issue through employing a novel tool to assess risk of bias resulting from confounding in non-randomised studies.[21] Assigning scores which indicate how well individual studies were controlled for on a set of important confounders identified through clinical expert consensus, highlights the baseline imbalances between groups which may impact on effect estimates and therefore affect internal validity. Some of the included non-randomised studies controlled for the major confounders well, but in general, this was poorly done and resulted in uncertainties in outcome estimates. It was for this reason that we chose not to perform meta-analyses of the data from non-randomised studies.

Another persistent problem encountered in the evidence synthesis is the lack of consistency in outcomes used in primary studies. Outcome definitions and measurements not only varied considerably across studies but they were also poorly reported. Furthermore, outcomes were also reported in a variety of ways (e.g. for survival data, percentages rather than hazard ratios, and for event rates, median and range rather than means and standard deviations). This problem was encountered repeatedly for all of the outcomes of interest such that it became almost impossible to summarise the data across studies. As far as surgical complications are concerned, these should be reported by way of classification systems which have been validated, such as the Clavien grading system.[78] Outcome reporting inconsistency is increasingly being recognised as a form of bias which hinders evidence synthesis which ultimately affects the overall quality of the evidence.[79]

It should also be noted that very few studies assessed quality-of-life outcome measures. Patients with renal tumours are increasingly presenting at an earlier stage of their disease; indeed data from prospective studies show that the majority of tumours diagnosed are localised and <7cm.[1] Such small tumours are generally associated with a good prognosis, such that the focus is now shifting to procedures which are not only minimally invasive but also focal in nature in order to preserve renal function. Central to the comparative assessment of such procedures is their impact on generic and disease-specific quality-of-life measures. It is imperative that future studies of novel therapies on localised renal cancer include quality-of-life outcomes as main outcome measures.

The lack of standardisation in outcome reporting also limited the usefulness of the GRADE evidence profiles. GRADE enables the assessment of the quality of the body of the evidence across studies for each outcome identified by an expert panel as the most important for clinicians and patients. However, even where a relatively large number of studies have been identified for a particular comparison, only one or two studies report the outcomes that have been chosen for the GRADE assessment. Furthermore, the data were often from studies with small sample sizes, and had wide confidence intervals around estimates. Consequently, the GRADE quality of evidence for the majority of outcomes in this systematic review was deemed to be either 'low' or 'very low'.

A further limitation of the review was that the limited amount of data available precluded the performance of planned subgroup analyses. Many of the included studies on particular approaches and techniques have also been performed in high volume, training centres by the pioneers and experts of the procedures and this may have limited the generalisability of the findings.

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 renal cancer. The review methodology underpinning both guidelines differs from that used in this systematic review mainly on the point of strict and transparent inclusion criteria for primary studies and the assessment of the potential risk of bias in the included studies. One advantage of using the systematic review method presented in this study is that the included studies represent, methodologically, the best empirical evidence currently available. While it is true that the strict inclusion criteria resulted in the review including few or no studies with which to answer research questions addressing a clinical uncertainty, the inclusion of poorer quality studies would run the risk of relying on evidence that may be misleading. As noted above, despite the use of strict inclusion criteria, the majority of the GRADE evidence profiles for included studies indicate

'low' or 'very low' quality of evidence. This in itself, however, is an important finding: it indicates that the current evidence base is poor and future research needs to address this by using study designs that minimise risks of bias, reporting a core set of outcomes, and ensuring the measurement of those outcomes are standardised. This is an enterprise that will take considerable collaborative effort in the urological community.

There are specific methodological limitations of the research underpinning the AUA Renal Cancer Guideline, such as the conduct of meta-analyses of observational studies. The guideline itself acknowledged that it may not be methodologically appropriate to conduct such meta-analyses, and recommended that its findings must be interpreted with caution. The AUA guidelines explicitly acknowledge the inherent risks of bias in the evidence base, stating: "*The overwhelming majority of studies available to the Panel were observational, retrospective, reported findings on samples of convenience that were not randomized to treatments and involved only one treatment group. There are inherent, unknown and unquantifiable biases within each study because of the lack of randomization*"[20] (emphasis in original). The AUA guidelines also recognise the potentially misleading estimates in observational studies and made an effort to include studies which controlled for some important confounders: "*Three confounding variables that differed across interventions were focused on in detail: patient age, tumor size and follow-up duration. For most outcomes, the influence of confounding variables could not be separated from possible intervention effects, making interpretation of statistically significant differences difficult. For this reason, only comparisons for which confounding variables appear to exert minimal influence are presented*"[20] (emphasis in original).

The current internationally recognised EAU Renal Cancer Guidelines includes many case series (i.e. no comparator groups) which are susceptible to selection biases, although the authors acknowledge that in some instances where there are no comparative studies, case series from well-defined registries may provide important information on long-term outcomes. In co-authoring this systematic review with the UCAN Systematic Review Team, EAU Renal Cancer Guideline Panel members have now applied a more rigorous research method to assess all available evidence for the management of localised renal cell carcinoma.

Other published systematic reviews on this topic includes a review conducted by Hui and colleagues[80] examining percutaneous versus surgical approaches to renal tumour ablation (cryoablation and radiofrequncy ablation were considered together). The study found no comparative studies and included only case series and the authors acknowledge that this represents low quality evidence.[81] Laparoscopic and open techniques were grouped together as 'surgical' and hence this could be regarded as a confounder. Furthermore, the percentage of benign tumours in the review is unclear and therefore any conclusions about oncological outcomes may be biased. Hui and colleagues[80] also drew attention to the need to adhere to standardised reporting methods.

Another review by Nabi and colleagues[82] was a Cochrane review of randomised studies on the surgical management of localised renal cell carcinoma. The review included only three RCTs, comparing the different laparoscopic approaches to nephrectomy (i.e. transperitoneal versus extraperitoneal), and found no statistically significant differences in operative or peri-operative outcomes between the two treatment groups. The authors reached the same conclusions as we did, which is that the rationale for the current practice of laparoscopic nephrectomy for renal cancer is largely drawn from low quality evidence (i.e. case series, small retrospective studies and very few small RCTs).

Other published reviews are available, but were either not performed using systematic review methods[83] or were based on uncontrolled case series.[84,85] These will not be considered any further.

The challenges encountered in our review and other published systematic reviews illustrate the difficulty of evidence-based medicine in areas where there are no or few RCTs. If the review adopts strict inclusion criteria, we may end up with few studies addressing clinical uncertainty, but if studies from further down the hierarchy of evidence are included, then uncertainties in the estimates of effect are amplified rather than reduced. Nevertheless, systematic reviews offer arguably the most robust method for addressing clinical uncertainty, and in areas where there is a paucity of high quality randomised evidence, it enables the mapping of the best available evidence in a structured and transparent way

which aids in identifying gaps in the knowledge base and highlighting areas for future research.

Chapter 10 Authors' conclusions

Patient and tumour characteristics permitting, current evidence suggests that localised renal cancers are best managed by nephron-sparing surgery rather than by radical nephrectomy, irrespective of surgical approach (open or laparoscopic), for the perceived benefits of preservation of renal function without compromising on oncological outcomes. Where open surgery is deemed necessary, the oncological outcomes of open partial nephrectomy are at least as good as those of open radical nephrectomy and should be the preferred option when technically feasible, until further evidence indicates otherwise. However, it remains unclear what the upper limit of tumour size should be beyond which partial nephrectomy loses its advantages.

With regard to the innovations or modifications to laparoscopic nephrectomy, such as hand-assisted, robot-assisted or single-port techniques, all of them appear to have similar outcomes to standard laparoscopic radical nephrectomy, although the quality of evidence is very low.

The evidence around minimally invasive ablative technologies is weak due to small sample size, short follow up, high risk of bias and mixed patient populations that include benign renal lesions, rendering judgements about effectiveness unreliable. Minimally invasive procedures show promise in having reduced blood loss without compromising on safety and recovery. However, there is a need to assess the impact of these procedures on long-term survival and patient quality of life.

There is no evidence to either support or refute ipsilateral adrenalectomy during radical nephrectomy. For partial nephrectomy, the evidence base indicates that in the absence of obvious tumour involvement of the adrenal gland, routine adrenalectomy should not be

performed, since the risk of either synchronous or metastatic disease within the ipsilateral adrenal gland is extremely low under such circumstances. However, for patients with suspicious lesions within the ipsilateral adrenal gland with otherwise small, localised renal tumours, it is unclear if concomitant ipsilateral adrenalectomy improves survival. In addition, it remains unclear whether complete lymph node dissection has any role in the management of localised renal cancer due to large inconsistencies in limited data and it is therefore, based on currently available evidence, best not to be offered to patients with otherwise small, localised renal tumours.

The current evidence base has significant limitations due to studies marked by high risks of bias. 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 and, ideally standardised, measures of outcomes, and be multicentred to ensure that the studies give sufficiently precise estimates of the various outcomes. Ideally, allocation should be randomised to minimise selection bias and clinical heterogeneity. There is an urgent need for standardisation of outcome reporting in renal cancer 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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Members of the EAU Guideline Group for renal cell carcinoma are:

Börje Ljungberg, Axel S Merseburger, Jean-Jacques Patard, Milan Hora, Markus A Kuczyk, Damian C Hanbury, Peter F A Mulders, Ioanel C. Sinescu, Nigel C Cowan

Members of the UCAN Systematic Reivew Reference Group for renal cancer are:

Michael Aitchison, Philipp Dahm

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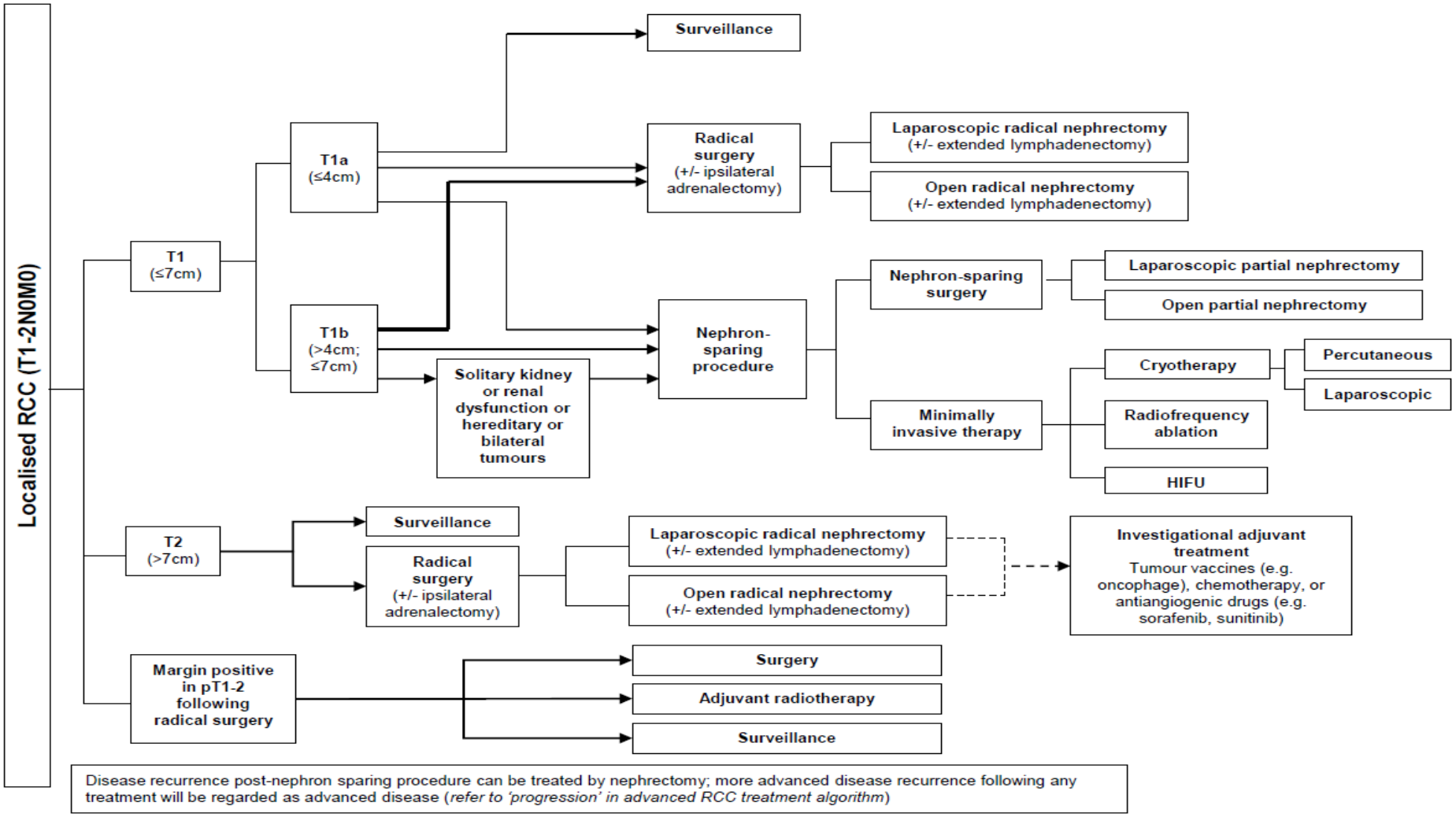
Appendix 1: Localised Renal Cell Cancer Care Pathway



Appendix 2: Search strategies

(1) Ovid MEDLINE: 1950 – 24th October 2010

1. exp Kidney Neoplasms/su [Surgery]
2. ((kidney or renal) adj2 (cancer$ or carcinoma$ or neoplasm$ or tumo?r$)).tw.
3. renal mass$.tw.
4. exp *Kidney Neoplasms/
5. 3 or 2
6. 4 and 5
7. 6 or 1
8. ((kidney or renal) adj2 (cancer$ or carcinoma$ or neoplasm$ or tumo?r$)).ti.
9. renal mass$.ti.
10. 8 or 9
11. 7 or 10
12. exp *Nephrectomy/
13. (nephrectom$ or nephron sparing surgery).ti.
14. nephroureterectom$.ti.
15. exp *Lymph Node Excision/
16. lymphadenectomy.ti.
17. exp *Adrenalectomy/
18. adrenalectomy.ti.
19. (Minimally invasive or radiofrequency or cryotherapy or cryoablat* or cryosurg$ or ablation or high intensity focused ultrasound or HIFU).ti.
20. exp *Ablation Techniques/
21. exp *Chemotherapy, Adjuvant/
22. exp *Radiotherapy, Adjuvant/
23. adjuvant.ti.
24. 21 or 17 or 12 or 20 or 15 or 14 or 22 or 18 or 23 or 13 or 16 or 19
25. 11 and 24
26. exp Carcinoma, Renal Cell/th [Therapy]
27. exp *Cancer Vaccines/
28. (tumo?r adj2 vaccine$).m_titl.
29. 27 or 28
30. 26 and 29
31. 25 or 30
32. limit 31 to humans
33. (case reports or letter or editorial or comment).pt.

34. 32 not 33

(2) Ovid EMBASE: 1980 – 24th October 2010

1. exp *Kidney Tumor/su [Surgery]
2. ((kidney or renal) adj2 (cancer$ or carcinoma$ or neoplasm$ or tumo?r$)).ti.
3. renal mass$.ti.
4. 1 or 3 or 2
5. exp *Nephrectomy/
6. (nephrectom$ or nephron sparing surgery).ti.
7. (nephroureterectom$ or lymphadenectom$ or adrenalectom$).ti.
8. (Minimally invasive or radiofrequency or cryotherapy or cryoablat* or cryosurg$ or ablation or high intensity focused ultrasound or HIFU).ti.
9. 8 or 6 or 7 or 5
10. 4 and 9
11. exp *Kidney Carcinoma/th [Therapy]
12. exp *Cancer Vaccine/
13. (tumo?r adj2 vaccine$).ti.
14. 11 and 12
15. 13 or 14
16. 4 and 15
17. 16 or 10
18. limit 17 to human
19. Editorial/
20. Letter/
21. Note/
22. "Review"/
23. 22 or 21 or 19 or 20
24. 18 not 23

(3) Web of Science® – with Conference Proceedings: 1970 – 24th October 2010

Title=((kidney or renal) and (cancer or carcinoma or neoplasm* or tumor* or tumour*)) AND Title=(nephrectom* or nephroureterectom* or nephron sparing or ablation or radiofrequency or cryotherapy or cryoablat* or cryosurgery or ultrasound or vaccine* or adjuvant) . Limited to Document type = meeting abstract.

(4) Cochrane Library – all sections. Issue 4, October 2010

(kidney or renal) and (cancer or carcinoma or neoplasm* or tumor* or tumour*) in Title, Abstract or Keywords AND (nephrectom* or nephroureterectom* or nephron sparing or ablation or radiofrequency or cryotherapy or cryoablat* or cryosurgery or ultrasound or vaccine* or adjuvant) in Title, Abstract or Keywords

(5) ASCO (American Society of Clinical Oncology) meeting abstracts

http://www.asco.org/ASCOv2/Meetings/Abstracts up to October 2010

(6) NICE (National Institute for Health and Clinical Excellence)

Guidance on Urogenital topics
http://www.nice.org.uk/guidance/index.jsp?action=byTopic&o=7317

Appendix 3: Data Extraction Form

Reviewer initial:

Comparison	
Study ID	
Citation	
Type of publication	[ ] complete article [ ] abstract only [ ] abstract of meeting [ ] proceedings [ ] Others(specify):
Country	
No. of Centres	[ ] single [ ] multi-centre : ____
Type of Centre (if single centre)	[ ] community hospital [ ] university-training hospital [ ] specialty centre
Funding	
Recruitment period	
Duration of follow-up (months)	
METHODS	
Type of study	[ ] RCT [ ] quasi RCT [ ] prospective cohort [ ] retrospective matched pair [ ] database review
Were groups formed by:	[ ] Randomisation? [ ] Quasi-randomisation? [ ] By other action of researchers? [ ] Time differences? [ ] Location differences? [ ] Health care decision makers? [ ] Participant preferences? [ ] On the basis of outcome? [ ] Some other process (specify)? [ ] Unclear
(If prospective) What parts of the study were prospective?	[ ] Identification of participants? [ ] Assessment of baseline and intervention allocation? [ ] Assessment of outcomes? [ ] Generation of hypotheses?
Notes:	

PARTICIPANTS	
Inclusion criteria	
Exclusion criteria	

PARTICIPANTS: Numbers	**Intervention 1: NAME HERE**	**Intervention 2: NAME HERE**	**Pro**
Number randomised/ allocated			
Number of dropouts			
Reasons for dropouts			
Number not analysed (other than above)			
Reason for non-analysis			

PARTICIPANTS: Characteristics	**Intervention 1:**	**Intervention 2:**	**Pro**
Age (years, mean, SD)			
Gender			
BMI			
Histologic cell type			
Tumor size/stage			
Tumor grade (Fuhrman)			
Necrosis			
Performance status			
Co-morbidity			
Ethnicity			
Side			
Comments:			

INTERVENTION	
Name of intervention	Description (e.g. surgical approach, access)
Group 1:	
Group 2:	
Group 3:	
Additional information (e.g. surgeon experience):	

RESULTS:

Surgical outcomes	Intervention 1:		Intervention 2:		Pro
	N analyzed	Value	N analyzed	Value	
Intra-operative					
Duration of operation (minutes, mean, SD)					
Blood loss (ml, mean, SD)					
Need for blood transfusion					
Opposite method initiated (pre-operative)					
Conversion (intra-operative)					
Post-operative					
Surgical site infection					
Pneumonia					
Urinary tract infection					
Deep venous thrombosis					
Hemorrhage requiring transfusion					
Positive surgical margins (after partial nephrectomy)					
30-day mortality					
90-day mortality					
Length of hospital stay					
Analgesic requirement (specify)					
Time to return to normal activities (days)					

Quality of life and adverse effects	Intervention 1:		Intervention 2:		Pro
	N analyzed	Value	N analyzed	Value	
Condition-specific quality of life scores (specify)					
General health status measure (e.g. SF36)					
Number of people with overall morbidity (specify)					
Number of people with serious adverse events (specify)					
Number of people dropping out due to adverse effects					
Please provide any available data on costs here					
Other					

Analysis	[ ] Adjusted [ ] Unadjusted	Describe confounders controlled for on page XX

Long-term outcome	**Intervention 1:**		**Intervention 2:**		**Pro**
	N analyzed	**Value**	**N analyzed**	**Value**	
Duration of follow-up					
Overall survival					
Disease free rate					
Progression free rate					
Cancer specific survival					
Local recurrence					
Time to local recurrence					
Local progression					
Incidence of metastasis					
Time to metastasis					
Tumor-free rates on biopsy (after ablative technologies)					
Other:					

Other Comments / Notes Regarding Study :
CONTACT AUTHOR

Appendix 4. Risk of Bias Assessment Form

(Source: Higgins and Altman 2008;[26] Reeves, Shea and Wells 2010[21])

Study ID: **Reviewer :** **Date:**

RISK OF BIAS	
Adequate sequence generation?	[ ] Yes [ ] No [ ] Unclear
Allocation concealment?	[ ] Yes [ ] No [ ] Unclear
Major confounders controlled for?[a] Outcome 1: [SURVIVAL]	Score 1-5
Major confounders controlled for?[a] Outcome 2: [SURGICAL OUTCOMES]	Score 1-5
Blinding? Outcome 1: [SURVIVAL]	[ ] Participant [ ] Personnel [ ] Assessor [ ] None [ ] Unclear
Blinding? Outcome 2: [SURGICAL OUTCOMES]	[ ] Participant [ ] Personnel [ ] Assessor [ ] None [ ] Unclear
Incomplete outcome data addressed? Outcome 1: [SURVIVAL]	[ ] Yes [ ] No [ ] Unclear
Incomplete outcome data addressed? Outcome 2: [SURGICAL OUTCOMES]	[ ] Yes [ ] No [ ] Unclear
Free of selective outcome reporting?	[ ] Yes [ ] No [ ] Unclear
Free of other bias?	[ ] Yes [ ] Early stopping [ ] Others [ ] Unclear
A priori protocol? [b]	[ ] Yes [ ] No [ ] Unclear
A priori analysis plan? [c]	[ ] Yes [ ] No [ ] Unclear

[a] Based on list of confounders considered important at the outset and defined in the protocol for the review (and assessment against worksheet); [b] Did the researchers write a protocol defining the study population, intervention and comparator, primary and other outcomes, data collection methods, etc. in advance of starting the study?; [c] Did the researchers have an analysis plan defining the primary and other outcomes, statistical methods, subgroup analyses, etc. in advance of starting the study?

WORKSHEET: Confounders described by researchers
Enter / preprint pre-specified list of confounders (rank order in importance? Important in bold?)
Tick (yes/no judgement) if confounder considered by the researchers [Cons'd?]
Score (1 to 5) precision with which confounder measured
Score (1 to 5) imbalance between groups
Score (1 to 5) care with which adjustment for confounder was carried out.

OUTCOME				
Confounder	Considered (yes/no)	Precision (1 to 5)	Imbalance (1 to 5)	Adjustment (1 to 5)
Histologic cell type				
Tumor size/stage				
Tumor grade (Fuhrman)				
Necrosis				
Performance status				
Age				
Co-morbidity				
Ethnicity				

Assessment of how researchers dealt with confounding	
Method for *identifying* relevant confounders described by researchers: If yes, describe the method used:	☐ ☐
Method used for controlling for confounding At design stage: matching by characteristics of subjects (see below for matching by propensity score) Variables on which subjects matched: …… …… …… …… At analysis stage: stratification multivariable regression propensity scores (matching) propensity scores (multivariable regression)	☐ ☐ ☐ ☐ ☐

Appendix 5: Guidelines for assessing risk of bias in non-randomised studies in this review

Our guidelines, drawn up with clinical, statistical and methodological advice are as follows.

Precision

Precision for categorical data

- 1 = n/N
- 2 = % only
- 3 = either:
    - categories are merged and cannot be unpicked (for example, T1 and T2 reported together as T2 or<), or
    - confounders are presented as a total across the whole study and not separable (i.e. sum of intervention and control group characteristics)
- 5 = not reported/no data/unclear

Precision for continuous data

- 1 = Mean and measure of spread:
    - SD
    - or SE
    - or p-value
    - or CI
    - or some other way of calculating SD
    - graphs that make measure of central tendency and spread of data interpretable
    - Mean/Median and IQR
        - Range is not acceptable because of susceptibility to outliers
- 2 = Mean and p <0.05. This would enable a statistician to input a measure of spread by assuming a worst case scenario that p = 0.049.
- 3 = Measure of location only and no measure/way of estimating spread.
- 5 = not reported/no data/unclear

Imbalance

We drafted guidelines with statistical and clinical advice to assist two clinical experts, with advice from the review team, to score imbalance:

- 1 = no significant imbalance (i.e. unlikely to have a large effect on the outcome estimate)
- 2 = significant imbalance (i.e. likely to have a large effect on the outcome estimate)
- 5 = unclear

Adjustment

Imbalance and adjustment scores are interlinked because it is difficult to score one without consideration of the other. For instance if there is no imbalance then there is no need to adjust, but this is not the same as not adjusting for a confounder that is identified and in need of adjustment. With statistical advice we used the *a priori* identification and adjustment for confounders at the design stage as the most appropriate way to control for confounders. It was noted, with statistical advice, that although some adjustment methods may be used inappropriately, no method for adjusting should be ranked higher than another. Here we also did not consider the precision of adjustment, e.g. whether age was adjusted for using a continuous or categorical variable, or by 1 year or 10 years.

- 1 = Adjustment done at the design stage or pre-planned, or no adjustment needed because of no significant imbalance
- 2 = Adjustment done on the basis of data (i.e. post hoc)
- 3 = adjustment done, but not with appropriate methods
- 5 = adjustment not done when needed/unclear.

We acknowledge that, compared with the original draft tool,[21] our modified scoring guidelines may be criticised for focusing too much on the quality of reporting but it improved the degree of agreement among reviewers. This highlights the need for more concrete guidance for reviewers using this tool. Criteria for assessing confounder specified in the original draft tool[21] are shown below.

Table. Criteria for assessing confounder specified in the draft extended Cochrane RoB tool for NRS[21]

Criteria	Assess-ment	Description/Rationale
Whether most important confounders were (from pre-specified list) were **considered**	Yes/no	
Precision or resolution with which confounders were measured	1 to 5	The better that a confounder is measured (e.g. dichotomous vs. continuous variable), the better able one is to adjust.
Extent of **imbalance** between groups at baseline	1 to 5	This is not merely a statistical judgement, e.g. imbalance if p>0.05.
Care with which **adjustment** was done	1 to 5	A judgement about the statistical modelling carried out by authors, including: • Importance as well as number of confounders adjusted for • Method of adjustment (e.g. matching, modelling +/- propensity scores) • Variables included in the model or dropped from analysis

Appendix 6: References of studies included in the review

* denotes the primary reference

Aron 2008

Aron M, Koenig P, Kaouk JH, Nguyen MM, Desai MM, Gill IS. Robotic and laparoscopic partial nephrectomy: a matched-pair comparison from a high-volume centre. *BJU Int* 2008;**102** :86-92.

Blom 2009

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Dash A, Vickers AJ, Schachter LR, Bach AM, Snyder ME, Russo P. Comparison of outcomes in elective partial vs radical nephrectomy for clear cell renal cell carcinoma of 4-7 cm. *BJU Int* 2006;**97**:939-45.

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Gratzke C, Seitz M, Bayrle F, Schlenker B, Bastian PJ, Haseke N et al. Quality of life and peri-operative outcomes after retroperitoneoscopic radical nephrectomy (RN), open RN and nephron-sparing surgery in patients with renal cell carcinoma. *BJU Int* 2009;**104**:470-5.

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Lane BR, Tiong HY, Campbell SC, Fergany AF, Weight CJ, Larson BT et al. Management of the adrenal gland during partial nephrectomy. *J Urol* 2009;**181**:2430-6.

Lane 2010

Lane BR, Gill IS. 7-year oncological outcomes after laparoscopic and open partial nephrectomy. *J Urol* 2010;**183**:473-9.

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Lee JH, You CH, Min GE, Park JS, Lee SB, Ahn H et al. Comparison of the surgical outcome and renal function between radical and nephron-sparing surgery for renal cell carcinomas. *Korean J Urol* 2007;**48**:671-6.

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Patard JJ, Bensalah KC, Pantuck AJ, Klatte T, Crepel M, Verhoest G et al. Radical nephrectomy is not superior to nephron sparing surgery in PT1B-PT2N0M0 renal tumours: A matched comparison analysis in 546 cases. *Eur Urol Suppl* 2008;**7**:194.

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Peng B, Zheng J-H, Xu D-F, Ren J-Z. Retroperitoneal laparoscopic nephrectomy and open nephrectomy for radical treatment of renal cell carcinoma: A comparison of clinical outcomes. *Academic Journal of Second Military Medical University* 2006;**27**:1167-9.

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Shekarriz B, Upadhyay J, Shekarriz H, de Assis Mendes GF, Jr., Bianco FJ, Tiguert R et al. Comparison of costs and complications of radical and partial nephrectomy for treatment of localized renal cell carcinoma. *Urology* 2002;**59**:211-5.

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*Simmons MN, Weight CJ, Gill IS. Laparoscopic Radical Versus Partial Nephrectomy for Tumors >4 cm: Intermediate-term Oncologic and Functional Outcomes. *Urology* 2009;**73**:1077-82.

Simmons MN, Weight CJ, Larson BT, Gill IS. Long term oncologic and renal functional outcomes for laparoscopic partial versus laparoscopic radical nephrectomy for renal cell carcinoma > 4cm. *J Urol* 2008;**179(Suppl)**:439-40.

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Soga N, Kato M, Masui S, Nishikawa K, Hasegawa Y, Yamada Y et al. Comparison of radical nephrectomy techniques in one center: Minimal incision portless endoscopic surgery versus laparoscopic surgery. *Int J Urol* 2008;**15**:1018-21.

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Thompson RH, Boorjian SA, Lohse CM, Leibovich BC, Kwon ED, Cheville JC et al. Radical nephrectomy for pT1a renal masses may be associated with decreased overall survival compared with partial nephrectomy. *J Urol* 2008;**179**:468-71.

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*Thompson RH, Siddiqui S, Lohse CM, Leibovich BC, Russo P, Blute ML. Partial Versus Radical Nephrectomy for 4 to 7 cm Renal Cortical Tumors. *J Urol* 2009;**182**:2601-6.

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Van Poppel H, Da Pozzo L, Albrecht W, Matveev V, Bono A, Borkowski A et al. A prospective randomized EORTC intergroup phase 3 study comparing the complications of elective nephron-sparing surgery and radical nephrectomy for low-stage renal cell carcinoma. *Eur Urol* 2007;**51**:1606-15.

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*Weight CJ, Larson BT, Fergany AF, Gao T, Lane BR, Campbell SC et al. Nephrectomy induced chronic renal insufficiency is associated with increased risk of cardiovascular death and death from any cause in patients with localized cT1b renal masses. *J Urol* 2010;**183**:1317-23.

Weight C, Larson,B, Lane,B, Fergany,A, Campbell,S, Kaouk,J et al. *A nonrandomized comparison of overall survival in patients with clinical t1b renal tumors treated with radical nephrectomy (RN) or partial nephrectomy (PN).* Genitourinary Cancers Symposium; 2009 [accessed September 2011]. Available from: http://www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=64&abstractID=20241

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Wu SD, Viprakasit DP, Cashy J, Smith ND, Perry KT, Nadler RB. Radiofrequency ablation-assisted robotic laparoscopic partial nephrectomy without renal hilar vessel clamping versus laparoscopic partial nephrectomy: a comparison of peri-operative outcomes. *J Endourol* 2010;**24**:385-91.

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Zini L, Perrotte P, Jeldres C, Capitanio U, Duclos A, Jolivet-Tremblay M et al. A population-based comparison of survival after nephrectomy vs nonsurgical management for small renal masses. *BJU Int* 2009;**103**:899-904.

Zini 2009b

Zini L, Perrotte P, Capitanio U, Jeldres C, Shariat SF, Antebi E et al. Radical versus partial nephrectomy: effect on overall and noncancer mortality. *Cancer* 2009;**115**:1465-71.

Appendix 7: Examples of excluded studies with reasons for exclusion

Study ID	*Reference*	*Reason for exclusion*
Antonelli 2008	Antonelli A, Cozzoli A, Nicolai M, Zani D, Zanotelli T, Perucchini L et al. Nephron-sparing surgery versus radical nephrectomy in the treatment of intracapsular renal cell carcinoma up to 7cm.[see comment]. *Eur Urol* 2008;**53**:803-9.	This study is a retrospective analysis of a prospectively maintained database. Inclusion criteria are pT1/pT2 and some patients have cT3a.
Battaglia 2004	Battaglia M, Ditonno P, Martino P, Palazzo S, Annunziata G, Selvaggi FP. Prospective randomized trial comparing high lumbotomic with laparotomic access in renal cell carcinoma surgery. *Scand J Urol Nephrol* 2004;**38**:306-14.	It includes pT3a patients and there are no separate results for the localize and the locally-advanced tumors.
Clark 2001	Clark PE, Schover LR, Uzzo RG, Hafez KS, Rybicki LA, Novick AC. Quality of life and psychological adaptation after surgical treatment for localized renal cell carcinoma: impact of the amount of remaining renal tissue. *Urology* 2001;**57**:252-6.	Quality of life questionnaire after surgery. No baseline data so judged to be cross-sectional rather than cohort.
Clark 2008	Clark AT, Breau RH, Morash C, Fergusson D, Doucette S, Cagiannos I. Preservation of renal function following partial or radical nephrectomy using 24-hour creatinine clearance.[see comment]. *Eur Urol* 2008;**54**:143-9.	There is no explicit declaration of the stage of the included patients. Unclear if all patients were clinically T1-2N0M0 or 'localised' RCC.
Finney 1973	Finney.R. An evaluation of post-operative radiotherapy in hypernephroma treatment--a clinical trial. *Cancer* 1973;**32**:1332-40.	Adjuvant therapy
Galligioni 1993	Galligioni E, Francini M, Quaia M, Carbone A, Spada A, Sacco C et al. Randomized study of adjuvant immunotherapy with autologous tumor cells and BCG in renal cancer. *Ann N Y Acad Sci* 1993;**690**:367-9.	Adjuvant therapy

Study ID	*Reference*	*Reason for exclusion*
Galligioni 1996	Galligioni E, Quaia M, Merlo A, Carbone A, Spada A, Favaro D et al. Adjuvant immunotherapy treatment of renal carcinoma patients with autologous tumor cells and bacillus Calmette-Guerin: five-year results of a prospective randomized study. *Cancer* 1996;**77**:2560-6.	Related to Galligioni 1993.
Guazonni 2006	Guazzoni G, Cestari A, Naspro R, Riva M, Rigatti P. Cost containment in laparoscopic radical nephrectomy: feasibility and advantages over open radical nephrectomy. *J Endourol* 2006;**20**:509-13.	Unclear whether participants had localized RCC. The paper reports the tumour diameter but no specific mention of the stage of the cancer. (Keep for discussion, re: learning curve).
Hayata 1994	Hayata S. Adjuvant therapy with HLBI and UFT for renal cell carcinoma. *Nishi Nihon Hinyokika* 1994;**56**:15-20.	Adjuvant therapy
Hinshaw 2008	Hinshaw JL, Shadid AM, Nakada SY, Hedican SP, Winter TC, III, Lee FT, Jr. Comparison of percutaneous and laparoscopic cryoablation for the treatment of solid renal masses. *AJR Am J Roentgenol* 2008;**191**:1159-68.	Retrospective study using an 'ongoing' ablation database. Percutaneous (N = 30) vs. laparoscopic (N = 60) cryotherapy. Not one of pre-specified comparisons for this review.
Jeldres 2008	Jeldres C, Suardi N, Patard JJ, Bensalah K, Avakian R, Crepel M et al. Nephron-sparing surgery vs. radical nephrectomy in patients with renal cell carcinoma > 7 cm. with no evidence of nodal or distant metastatsis. *J Urol* 2008;**179**:417-8.	It is possible that some locally-advanced cases (i.e. T3) were included because the population includes >7cm; no distant or nodal mets but could still include T3 and we suspect they did because they matched for T-stage. If only localized cases were included, then no need for matching because one is just left with T2 (since <7cm have been excluded).

Study ID	*Reference*	*Reason for exclusion*
Kozak 1996	Kozak W, Holtl W, Pummer K, Maier U, Jeschke K, Bucher A. Adrenalectomy--still a must in radical renal surgery? *British Journal of Urology* 1996;**77**:27-31.	Retrospective study using data from 6 centres but no explicit mention of 'database' or 'registry'. Radical nephrectomy with (N = 109) and without (N = 116) adrenalectomy. Survival data for pT1/2 and pT3 reported separately. (Keep for discussion – this is the only we study we have for adrenalectomy, apart from the Blom trial).
Landman 2004	Landman J, Olweny E, Sundaram CP, Chen C, Rehman J, Lee DI et al. Prospective comparison of the immunological and stress response following laparoscopic and open surgery for localized renal cell carcinoma. *J Urol* 2004;**171**:1456-60.	Results are combined for both open radical and open partial in one arm. Study is about stress response
Lane 2008	Lane BR, Novick AC, Babineau D, Fergany AF, Kaouk JH, Gill IS. Comparison of laparoscopic and open partial nephrectomy for tumor in a solitary kidney.[see comment]. *J Urol* 2008;**179**:847-51.	The study sample only includes patients with a solitary functioning kidney. Open vs. partial nephrectomy for 7 cm or smaller tumours. Retrospective comparison based on cancer registry.
Lopéz Cubillana 2004	Lopez Cubillana P, Prieto GA, Gomez GG, Cao AE, Lopez Lopez AI, Maluff TA et al. Hand-assisted laparoscopic radical nephrectomy vs. open nephrectomy in the treatment of clinically localized renal cell carcinoma. Comparative study].[see comment. *Arch Esp Urol* 2004;**57**:833-7.	Spanish. Reads as a retrospective study. There is nothing in the text that reads as "prospective.
Makhoul 2004	Makhoul B, de La TA, Vordos D, Salomon L, Sebe P, Audet JF et al. Laparoscopic radical nephrectomy for T1 renal cancer: the gold standard? A comparison of laparoscopic vs open nephrectomy. *BJU Int* 2004;**93**:67-70.	Retrospective review of data

Study ID	*Reference*	*Reason for exclusion*
Matin 2002	Matin SF, Gill IS, Worley S, Novick AC. Outcome of laparoscopic radical and open partial nephrectomy for the sporadic 4 cm. or less renal tumor with a normal contralateral kidney. *J Urol* 2002;**168**:1356-9.	Retrospective comparison from a single clinic using a prospectively designed database. Laparoscopic radical (N = 35)vs. open partial (N = 82) nephrectomy for the sporadic 4cm or less renal tumour with a normal contralateral kidney. Not one of pre-specified comparisons for this review.
May 2009	May M, Kendel F, Hoschke B, Gilfrich C, Kiessig S, Pflanz S et al. Adjuvant autologous tumour cell vaccination in patients with renal cell carcinoma: Overall survival analysis with a follow-up period in excess of more than 10 years. *Urologe - Ausgabe A* 2009;**48**:1075-83.	Matched-pair study comparing surgery with and without adjuvant vaccine. The sample Includes pT2, N1 and data for pT2, N0 only are not available. German publication.
Miller 2008	Miller DC, Schonlau M, Litwin MS, Lai J, Saigal CS, Urologic Diseases in America Project. Renal and cardiovascular morbidity after partial or radical nephrectomy. *Cancer* 2008;**112**:511-20.	This SEER-based study includes 'regional' as well as localised RCC. According to SEER, 'regional' include node-positive (http://www.cancer.gov/cancertopics/factsheet/Detection/staging).
Mitchell 2006	Mitchell RE, Gilbert SM, Murphy AM, Olsson CA, Benson MC, McKiernan JM. Partial nephrectomy and radical nephrectomy offer similar cancer outcomes in renal cortical tumors 4 cm or larger. *Urology* 2006;**67**:260-4.	Include T3 (N0M0) or greater: nearly 50%.
Nakada 2001	Nakada SY, Fadden P, Jarrard DF, Moon TD. Hand-assisted laparoscopic radical nephrectomy: comparison to open radical nephrectomy.[see comment]. *Urology* 2001;**58**:517-20.	A retrospective study with no explicit matching performed by the researchers (no evidence in the method section. The abstract does say that patients were 'matched' for age, etc. but we think this simply means there is no statistical difference between groups, rather than matched-pair design.

Study ID	*Reference*	*Reason for exclusion*
Nelson 2002	Nelson CP, Wolf JS, Jr. Comparison of hand assisted versus standard laparoscopic radical nephrectomy for suspected renal cell carcinoma. *J Urol* 2002;**167**:1989-94.	Included 2 patients with metastasis. The paper also indicated that "except for 3 patients, all were localized". There is no separate analysis for these non-localized cases.
Ogan 2005	Ogan K. Laparoscopic and percutaneous radiofrequency ablation of small renal tumors atone institution. *J Endourol* 2005;**19**:A208.	No comparisons made
Onishi 1985	Onishi T, Masuda F, Nakada J. Effect of radiotherapy on renal cell carcinoma. *Japanese Journal of Urology* 1985;**76**:1154-60.	Retrospective review of data.
Pace 2003	Pace KT, Dyer SJ, Stewart RJ, Honey RJ, Poulin EC, Schlachta CM et al. Health-related quality of life after laparoscopic and open nephrectomy. *Surg Endosc* 2003;**17**:143-52.	Includes non-cancer patients, no subgroup analysis
Patard 2009	Patard JJ, Thuret R, Bigot P, Bensalah K, Crepel M, de la Taille A et al. Nephron Sparing Surgery (Nss) Is Superior to Radical Nephrectomy in Preserving Renal Function Outcome in Tumors Larger Than 4 Cm. *J Urol* 2009;**181**:321.	Retrospective study.
Pizzocaro 1983	Pizzocaro G, Di FG, Piva L, Salvioni R, Ronchi E, Cappelletti V et al. Adjunctive medroxyprogesterone acetate to radical nephrectomy in category M0 renal cell carcinoma. Preliminary report of a prospective randomized trial. *Eur Urol* 1983;**9**:202-6.	Related to Pizzocaro 1986
Pizzocaro 1986	Pizzocaro G, Piva L, Salvioni R, Di FG, Ronchi E, Miodini P. Adjuvant medroxyprogesterone acetate and steroid hormone receptors in category M0 renal cell carcinoma. An interim report of a prospective randomized study. *J Urol* 1986;**135**:18-21.	Adjuvant therapy

Study ID	*Reference*	*Reason for exclusion*
Pizzocaro 1987	Pizzocaro G, Piva L, Di FG, Giongo A, Cozzoli A, Dormia E et al. Adjuvant medroxyprogesterone acetate to radical nephrectomy in renal cancer: 5-year results of a prospective randomized study. *J Urol* 1987;**138**:1379-81.	Related to Pizzocaro 1986
Satake 1989	Satake I, Tari K, Ohwada F, Saitoh T, Negishi T. Prophylactic effects of peri-operatively administered neocarzinostatin in renal cell carcinoma. *Journal of Japan Society for Cancer Therapy* 1989;**24**:809-16.	Included stage II (those lymph node involvement and with venous thrombus) with no separate analysis of these cases. Individual data reported but no clear evidence that the study is prospective or matched-pair design.
Seregin 2002	Seregin AV. Comparative evaluation of the quality of life in patients with kidney cancer after organ-preserving operations and radical nephrectomy. *Urologiia* 2002;**3**:6-8.	Russian – by looking at table layout, though, it does not appear to be eligible.
Thuret 2009	Thuret R, Bigot P, Bensalah K, de la Taille A, Salomon L, Abbou CC et al. Nephron sparing surgery (NSS) is superior to radical nephrectomy in preserving renal function outcome: is it true even when expanding NSS tumour size indications? *Eur Urol Suppl* 2009;**8**:200.	Data from 11 academic institutions. No mention of 'database' or 'registry'. Partial (N = 690) vs. radical (N = 649) nephrectomy. Abstract only which reports on GFR.
van der Werf-Messing 1973	van der Werf-Messing B. Proceedings: Carcinoma of the kidney. *Cancer* 1973;**32**:1056-61.	Adjuvant therapy
van der Werf-Messing 1981	van der Werf-Messing B, van der Heul RO, Ledeboer RC. Renal cell carcinoma trial. *Strahlentherapie - Sonderbande* 1981;**76**:169-75.	Related to van der Werf-Messing 1973.

Study ID	*Reference*	*Reason for exclusion*
Wood 2004	Wood CG, Escudier B, Gorelov S, Krajka K, Lacombe L, Fossa S et al. A multicenter randomized study of adjuvant heat-shock protein peptide-complex 96 (HSPPC-96) vaccine in patients with high-risk of recurrence after nephrectomy for renal cell carcinoma (RCC) - a preliminary report. *Journal of Clinical Oncology* 2004;**22(Suppl)**:192.	Related to Wood
Wood 2008	Wood C, Srivastava P, Bukowski R, Lacombe L, Gorelov AI, Gorelov S et al. An adjuvant autologous therapeutic vaccine (HSPPC-96; vitespen) versus observation alone for patients at high risk of recurrence after nephrectomy for renal cell carcinoma: a multicentre, open-label, randomised phase III trial. *Lancet* 2008;**372**:145-54.	2004The paper is about accrual of subjects and the vaccine production. Include cT1b-T4, N0M0, or cTany N1-2M0. Survival presented separately for T1-2 but may still include node positive. Vaccine after resection of locally advanced cancer.

Appendix 8: Study characteristics

Study ID	Aron 2008[44]
Setting	USA, single centre (Cleveland Clinic)
Funding	Not mentioned
Recruitment period	July 2006 – Aug 2007
METHODS	
Type of study	Retrospective matched pair. Matched for age (within 10 years), gender, BMI (within 5 points), American Society of Anesthesiologists (ASA) score, tumour side, size (within 10 mm), and location (upper, middle or lower pole) and the specific technique used (early hilar unclamping vs. conventiona unclamping).
Analysis	Survival: not reported Surgical outcomes: Univariate
Was treatment allocated by:	[ ] Randomisation? [ ] Quasi-randomisation? [ ] Health care decision makers? [ ] Participant preferences? [X] Unclear
(If prospective) What parts of the study were prospective?	[ ] Identification of participants? [ ] Assessment of baseline and intervention allocation? [ ] Assessment of outcomes? [ ] Generation of hypotheses? [ ] Unclear
PARTICIPANTS	
Inclusion criteria	"Single small unilateral mass" (p.86). Note that not all pts were pathologically RCC, see table 2, p. 90, but most were.
Exclusion criteria	Hilar tumours and completely intraparenchymal tumour (because this study was initial experience of robotic lap partial nephrectomy)

INTERVENTION	
Group 1: Robotic lap partial	The robot is docked after the hilum has been prepared for clamping, and the kidney surface has been laparoscopically scored. After docking the robot, the table-side assistant clamps the hilum and the console surgeon excises the tumour robotically. Reconstruction of the kidney is completed robotically (similar to LPN technique) and the hilum is unclamped. Additional sutures are placed as needed to ensure haemostasis. The robot is undocked and laparoscopic exit completed.
Group 2: Lap partial	Done by experts in laparoscopy; strategic renal de-fatting, maintaining fat over the tumour, lap ultrasonography to score the line of resection, en bloc hilar clamping, tumor excision with cold scissors, suture-repair of the collecting system and transected vessels and sutured renorrhaphy using hemostatic agent and a surgicel bolster

PARTICIPANTS: Numbers	**Group 1**	**Group 2**	**Group 3**
Number allocated	12	12	
Number analysed	12	12	

Additional information (e.g. surgeon experience):

- Conversion: 2 participants in the robotic lap partial nephrectomy group received lap partial.
- Surgeon experience: The study institution had experience with laparoscopic partial nephrectomy with >800 contemporary cases, whereas robotically-assisted partial nephrectomy was their 'initial experience' (p. 87). The authors note that their team was more experienced with lap partial nephrectomy than robotically-assisted partial nephrectomy and found the latter 'more difficult' (p.89).

Study ID	Blom 2009[15]
Setting	Europe, multi-centred (EORTC)
Funding	
Recruitment period	May 1988 to September 1991
METHODS	
Type of study	RCT (subgroup)
Analysis	Survival: Kaplan-Meier analysis and a log-rank test Surgical outcomes: univariate
Was treatment allocated by:	[X] Randomisation? [ ] Quasi-randomisation? [ ] Health care decision makers? [ ] Participant preferences? [ ] Unclear
(If prospective) What parts of the study were prospective?	[X] Identification of participants? [X] Assessment of baseline and intervention allocation? [X] Assessment of outcomes? [X] Generation of hypotheses? [ ] Unclear
PARTICIPANTS	
Inclusion criteria	Resectable, clinically staged N0 M0 adenocarcinoma of the kidney. Tumour categories 1-3 were allowed, provided that a radical nephrectomy with curative intent was feasible. Note: Data used in this review are from a subgroup of cT1 and cT2 patients only.
Exclusion criteria	Patients who had clinically detectable lymph-node metastases or distant metastases before surgery
INTERVENTION	
Group 1:	Radical nephrectomy with a complete lymph-node dissection
Group 2:	Radical nephrectomy alone

PARTICIPANTS: Numbers	**Group 1**	**Group 2**	**Group 3**
Number allocated	271	288	
Number analysed	271	288	
Additional information (e.g. surgeon experience):			

Study ID	Butler 1995[56]
Country	USA, single centre (Cleveland Clinic)
Funding	
Recruitment period	Jan 1st 1975 Dec 31st 1992
METHODS	
Type of study	Database review. Database contains info on all patients with RCC treated at the Cleveland Clinic.
Analysis	Survival: Kaplan-Meier estimates with log rank tests Surgical outcomes: univariate
Was treatment allocated by:	[ ] Randomisation? [ ] Quasi-randomisation? [X] Health care decision makers? [ ] Participant preferences? [ ] Unclear **Treatment allocation was based on the status of the contralateral kidney. Partial nephrectomy if contralateral kidney absent, non- or poorly functioning or at risk for future impairment (e.g. diabetes. In patients with radical nephrectomy, all but one case had a well-functioning contralateral kidney.**
(If prospective) What parts of the study were prospective?	[ ] Identification of participants? [ ] Assessment of baseline and intervention allocation? [ ] Assessment of outcomes? [ ] Generation of hypotheses?
PARTICIPANTS	
Inclusion criteria	All patients with RCC treated at the Cleveland Clinic. Single, small (less than 4cm), localized, unilateral RCC, sporadic RCC.
Exclusion criteria	Bilateral RCC, documented metastatic disease, von Hippel-Lindau disease, multiple RCCs, or a tumor 4 cm or larger.

INTERVENTION	
Group 1: Radical nephrectomy	Reviewer note: Based on the publication date, the interventions are assumed to be open surgery.
Group 2: Partial nephrectomy	Reviewer note: Based on the publication date, the interventions are assumed to be open surgery.

PARTICIPANTS: Numbers	**Intervention 1: RN**	**Intervention 2: NSS**	**Group 3**
Number allocated	45	46	
Number analysed	42	46	

Additional information (e.g. surgeon experience):

- Treatment allocation: Primary selection criteria for treatment with radical or partial nephrectomy was the status of the contralateral kidney (i.e. partial nephrectomy performed when contraleteral kidney absent or not fully functioning. Partial nephrectomy performed when the contralateral kidney was absent, non functioning, poorly functioning, or functioning adequately but at risk for future impairment due to an intercurrent benign disorder; but there were some cases done even with a completely normal contralateral kidney.

Study ID	Crépel 2010[45]
Country	USA, multi-centred (9 SEER cancer registries)
Funding	
Recruitment period	1984-2004 (year of diagnosis)
METHODS	
Type of study	Retrospective matched-pair. Matched for age (by decade), tumour size (within 1 cm), year of surgery (by decade) and Fuhrman grade.
Analysis	Survival: Kaplan-Meier and Cox regression models. Competing-risks regression models for cancer-specific survival after adjusting for non-cancer-related mortality. Surgical outcomes: not reported.
Were groups formed by:	[ ] Randomisation? [ ] Quasi-randomisation? [ ] Health care decision makers? [ ] Participant preferences? [X] Unclear
(If prospective) What parts of the study were prospective?	[ ] Identification of participants? [ ] Assessment of baseline and intervention allocation? [ ] Assessment of outcomes? [ ] Generation of hypotheses?
PARTICIPANTS	
Inclusion criteria	Patients diagnosed with primary invasive kidney cancer between 1988 and 2004 identified within 9 SEER cancer registries. Patients Withiout nodal or mets disease, 18 or older, treated for tumours 4-7cm.
Exclusion criteria	
INTERVENTION	
Group 1:	Partial nephrectomy. No further details.
Group 2:	Radical nephrectomy. No further details.

PARTICIPANTS: Numbers	Intervention 1: NSS	Intervention 2: RN	Pro
Number allocated	**275** **163**	**1100** **636**	Matching done on age, T size, and year of surgery (1) When Fuhrman grade added to the matching variables (2)
Number of dropouts			
Additional information (e.g. surgeon experience): • The cause of death was defined according to SEER specific cause of death (code 29020). Patients who did not die of RCC were considered to have died of other causes.			

Study ID	D'Armiento 1997[32]
Country	Italy, single centre (Università degli Studi di Napoli 'Frederico II', Naples)
Funding	
Recruitment period	1988 - 1993
METHODS	
Type of study	RCT
Analysis	Survival: Kaplan-Meier estimates Surgical outcomes: not reported
Was treatment allocated by:	[X] Randomisation? [ ] Quasi-randomisation? [ ] Health care decision makers? [ ] Participant preferences? [ ] Unclear
(If prospective) What parts of the study were prospective?	[X] Identification of participants? [X] Assessment of baseline and intervention allocation? [X] Assessment of outcomes? [X] Generation of hypotheses?
PARTICIPANTS	
Inclusion criteria	T1-2N0M0, < 4cm
Exclusion criteria	
INTERVENTION	
Group 1: Partial nephrectomy	No lymphadenectomy. Reviewer note: Participants from 1988 to 1993 but patients had surgery between 1978 and 1987 and therefore assumed to be open surgery.
Group 2: Radical nephrectomy	No lymphadenectomy Reviewer note: Assumed to be open surgery as above.

PARTICIPANTS: Numbers	**Group 1**	**Group 2**	**Group 3**
Number allocated	19	21	
Number analysed	19	21	
Additional information (e.g. surgeon experience):			

Study ID	Dash 2006[57]
Setting	USA, single centre (Memorial Sloan-Kettering Cancer Centre)
Funding	
Recruitment period	March 1998 – July 2004
METHODS	
Type of study	Database review. Authors note that the database is maintained prospectively but some data were collected retrospectively
Analysis	Survival: Kaplan-Meier estimates. Multivariate Cox proportional hazards models using the confounder score (disease severity) approach; predictors include age, stage, grade, size, date of surgery, vascular invasion, whether the patient was symptomatic at presentation, Fuhrman grade (1 and 2 = low; 3 and 4 = high), and pathologic stage (T1 or T3). Further multivariate models using a propensity score approach using 'planned operation (planned partial nephrectomy)' also reported. Surgical outcomes: not reported
Was treatment allocated by:	[ ] Randomisation? [ ] Quasi-randomisation? [ ] By other action of researchers? [X] Health care decision makers? – **by surgeons** [ ] Participant preferences? [ ] Unclear **Protocol was to offer partial nephrectomy (PN) first. Radical nephrectomy was done if multifocal, invasion into segmental or main vessels, minimal parenchyma after PN; treatment rendered was at the surgeon's discretion.**
(If prospective) What parts of the study were prospective?	[ ] Identification of participants? [ ] Assessment of baseline and intervention allocation? [ ] Assessment of outcomes? [ ] Generation of hypotheses?
PARTICIPANTS	
Inclusion criteria	Clear cell RCC 4-7cm
Exclusion criteria	

INTERVENTION	
Group 1 : Partial nephrectomy (PN)	With itntra-operative ultrasound
Group 2 : Radical nephrectomy (RN)	Includes both open and laparoscopic: 'Fourteen patients had a laparoscopic RN'.

PARTICIPANTS: Numbers	**Group 1 PN**	**Group 2 RN**	**Group 3**
Number allocated	45 (4 = pT3)	151 (27 = pT3)	
Number analysed			
Comments (e.g. surgeon experience):			

Study ID	Desai 2005a[33]
Country	USA, single centre (Glickman Urological Institute, Cleveland Clinic Foundation)
Funding	
Recruitment period	June 1999 – June 2001
METHODS	
Type of study	RCT
Analysis	Mortality/metastasis: unadjusted Surgical outcomes: unadjusted
Was treatment allocated by:	[X] Randomisation? [ ] Quasi-randomisation? [ ] Health care decision makers? [ ] Participant preferences? [ ] Unclear
(If prospective) What parts of the study were prospective?	[X] Identification of participants? [X] Assessment of baseline and intervention allocation? [X] Assessment of outcomes? [X] Generation of hypotheses?
PARTICIPANTS	
Inclusion criteria	Consecutive patients with a renal tumour. Reviewer note: The study includes some T3 cases (e.g. 6 cases in each group with perirenal fat involvement), although the study does not give us the breakdown by stage. However, it is assumed that it is still 'clinically localized disease'.
Exclusion criteria	BMI greater than 35 Prior abdominal surgery in quadrant of interest
INTERVENTION	
Group 1:	Laparoscopic radical nephrectomy with transperitoneal approach
Group 2:	Laparoscopic radical nephrectomy with retroperitoneal approach

PARTICIPANTS: Numbers	**Intervention 1: Trans LRN**	**Intervention 2: Retro LRN**	**Pro**
Number randomised/ allocated	50	52	
Number of dropouts	No missing data for surgical outcomes; Unclear for long-term outcomes.	No missing data for surgical outcomes; Unclear for long-term outcomes.	
Additional information (e.g. surgeon experience): • Surgeon experience not mentioned			

Study ID	Desai 2005b[58]
Setting	USA, single centre (Cleveland Clinic)
Funding	
Recruitment period	Lap partial nephrectomy: Aug 1999 – June 2003 Lap cryoabluation: Sept 1997 – June 2003
METHODS	
Type of study	Database review. Authors note: '… baseline, peri-operative, and follow-up data were prospectively collected …. From this ongoing database (N = 318) we retrospectively identified 231 consecutive patients (73%)' (p. 23).
Analysis	Survival: not reported Surgical outcomes: univariate
Was treatment allocated by:	[ ] Randomisation? [ ] Quasi-randomisation? [ ] By other action of researchers? [X] Health care decision makers? – **by staff surgeon** [ ] Participant preferences? [ ] Unclear
(If prospective) What parts of the study were prospective?	[ ] Identification of participants? [ ] Assessment of baseline and intervention allocation? [ ] Assessment of outcomes? [ ] Generation of hypotheses?
PARTICIPANTS	
Inclusion criteria	Consecutive patients with suspicious peripheral nonhilar mass </= 3 cm. Reviewer note: We assume all patients being considered as a case of renal malignancy pre-operatively. Note that 2 patients died of pre-existing metastatic disease.
Exclusion criteria	

INTERVENTION	
Group 1: Lap partial nephrectomy (LPN)	Renal hilar clamping, sharp excision of tumor with cold endoshears surtured hemotstatic renorrhaphy, sutured repair of collecting system as necessary Retroperitoneal (n = 64 tumours) Transperitoneal (n = 89 tumours) Combined (n = 0)
Group 2: lap cryoablation (LCA)	Double freeze thaw cycle with liquid nitrogen or argon based cryoablation, 4.8 mm cryoprobe, under realtime, lap-guidance. Retroperitoneal (n = 61 tumours) Transperitoneal (n = 27 tumours) Combined (n = 1 tumour)

PARTICIPANTS: Numbers	**Group 1: LPN**	**Group 2: LCA**	**Group 3**
Number randomised/ allocated	153 (153 tumours)	78 (89 tumours)	
Number analysed	Not reported	Not reported	
Comments (e.g. surgeon experience): • '… baseline, peri-operative, and follow-up data were prospectively collected … From this ongoing database (N = 318), we retrospectively identified 231 consecutive patients (73%) …'			

Study ID	Gabr 2009[59]
Country	USA, single centre (Univ of Michigan Health System)
Funding	
Recruitment period	Aug 1996 – Feb 2007
METHODS	
Type of study	Database review. '… an institutional review board approved, prospectively derived database'
Analysis	Survival: Kaplan-Meier method and log rank tests. Multivariate proportional hazards model was used including specimen handling (intact or morcellation), mass size, pathological risk (low, intermediate or high), and histological subtype ('low risk' = papillary and chromophobe tumours; 'clear cell'; or 'high risk' = collecting duct, spindle cell and unclassified tumours). Pathological risk group was assigned based on a modification of the UCLA Integrated Staging System, incorporating staging, grade and N+ status. Surgical outcomes: unadjusted
Was treatment allocated by:	[ ] Randomisation? [ ] Quasi-randomisation? [ ] Health care decision makers? [ ] Participant preferences? [X] Unclear
(If prospective) What parts of the study were prospective?	[ ] Identification of participants? [ ] Assessment of baseline and intervention allocation? [ ] Assessment of outcomes? [ ] Generation of hypotheses?
PARTICIPANTS	
Inclusion criteria	Patients who underwent unilateral laparoscopic radical nephrectomy for pathologically confirmed and presumed localized RCC – note there are some pT3 in the results
Exclusion criteria	

INTERVENTION	
Group 1:	Hand-assisted laparoscopic radical nephrectomy (HALRN) with transperitoneal approach.
Group 2:	Standard laparoscopic radical nephrectomy (SLRN) with with either transperitoneal (89.1%) or retroperitoneal approach

PARTICIPANTS: Numbers	**Intervention 1: HALRN**	**Intervention 2: SLRN**	**Pro**
Number randomised/ allocated	108	147	
Number of dropouts	NR	NR	'Of 255 patients 244 had adequate radiographic follow-up' (p. 875)
Additional information (e.g. surgeon experience): • Number of trainee as primary surgeon (Table 1): 57/108 (54.2%) in hand-assisted LRN vs. 109/147 (75.2%) in standard LRN.			

Study ID	Gill 2007[67]
Setting	USA, multi-centred (Cleveland Clinic, Johns Hopkins, Mayo)
Funding	
Recruitment period	Jan 1998 – Aug 2005
METHODS	
Type of study	Database review. Based on 3 prospective and retrospective registries (Laparoscopic PN at Cleveland Clinic and The Johns Hopkins Hospital and Open PN at Cleveland Clinic and Mayo Clinic).
Analysis	Survival: Kaplan-Meier estimates with a log rank statistics Surgical outcomes: unadjusted and adjusted. Multivariable logistic regression of surgical outcomes include clinical size, age, solitary kidney and bilateral tumours.
Was treatment allocated by:	[ ] Randomisation? [ ] Quasi-randomisation? [ ] Health care decision makers? [ ] Participant preferences? [X] Unclear
(If prospective) What parts of the study were prospective?	[ ] Identification of participants? [ ] Assessment of baseline and intervention allocation? [ ] Assessment of outcomes? [ ] Generation of hypotheses?
PARTICIPANTS	
Inclusion criteria	Single tumor, T <7cm, localized, suspected sporadic RCC. Consecutive patients with cT1.
Exclusion criteria	Familial syndromes, multifocal tumors, locally advanced, metastatic. Conversions from lap partial to open radical (N = 28).

INTERVENTION	
Group 1 : Laparoscopic partial nephrectomy (LPN)	They procedures have been described elsewhere – the authors gives references. Elective (48%), imperative (36.2%), absolute (15.8%). Transperitoneal approach in 78.5% of cases.
Group 2 : Open partial nephrectomy (OPN	Elective (35%), imperative (29%), absolute (36%).

PARTICIPANTS: Numbers	**Intervention 1: LPN**	**Group 2: OPN**	**Group 3**
Number allocated	?	?	
Number analysed	771	1029	
Additional information (e.g. surgeon experience): •			

Study ID	Gong 2008[46]
Country	USA, single centre (University of Chicago)
Funding	
Recruitment period	Oct 2002 – Jan 2006 (Lap partial) 1995 – 2003 (Open partial)
METHODS	
Type of study	Retrospective matched pair. Authors note: "Despite matched for tumours of 4 cm or smaller, a significant mean difference as found between the open and laparoscopic cohorts' (p. 954); '… although data collection was prospective, analysis was performed in a retrospective manner' (p. 959).
Analysis	Mortality/surgical outcomes: univariate
Was treatment allocated by:	[ ] Randomisation? [ ] Quasi-randomisation? [ ] Health care decision makers? [ ] Participant preferences? [X] Unclear
(If prospective) What parts of the study were prospective?	[ ] Identification of participants? [ ] Assessment of baseline and intervention allocation? [ ] Assessment of outcomes? [ ] Generation of hypotheses?
PARTICIPANTS	
Inclusion criteria	Solitary clinical T1a tumor (<=4cm), without a history of ipsilateral renal surgery. Consecutive patients for the laparoscopic partial nephrectomy group.
Exclusion criteria	

INTERVENTION	
Group 1:	Open partial nephrectomy (OPN). Had cold ischemia (all but one case).
Group 2:	Laparoscopic partial nephrectomy (LPN). Used warm ischemia (all cases)

PARTICIPANTS: Numbers	**Group 1: OPN**	**Group 2: LPN**	**Group 3**
Number allocated	77	76	
Number lost to follow-up	9	4	
Additional information (e.g. surgeon experience): • Conversion to open surgery: 6/76 cases in the laparoscopy group			

Study ID	Gratzke 2009[60]
Country	Germany and Switzerland, multi-centred (2)
Funding	
Recruitment period	Open radical and open partial nephrectomy = Jan – Dec 2005; retroperineoscopic (i.e. laparoscopic) radical nephrectomy = 2001-2005
METHODS	
Type of study	Database review of surgical outcomes with the prospective evaluation of health-related quality of life at mean 22 months after surgery.
Analysis	Survival: not reported QoL: unadjusted Surgical outcomes: unadjusted
Were groups formed by:	[ ] Randomisation? [ ] Quasi-randomisation? [X] Location differences? [ ] Health care decision makers? [ ] Participant preferences? [ ] Unclear **Patients undergone retroperineoscopic radical nephrectomy at Basel University Hospital, and open radical and open partial nephrectomy at University Hospital Grosshadern, Munich.**
(If prospective) What parts of the study were prospective?	[ ] Identification of participants? [ ] Assessment of baseline and intervention allocation? [ ] Assessment of outcomes? [ ] Generation of hypotheses?
PARTICIPANTS	
Inclusion criteria	Patients who had undergone RRN (retroperineoscopic radical nephrectomy) at Basel University Hospital (2001-2005), and those who had undergone open radical and open partial nephrectomy at University Hospital Grosshadern, Munich (Jan-Dec 2005.
Exclusion criteria	

INTERVENTION	
Group 1:	RRN = retroperineoscopic radical nephrectomy. Laparoscopic procedure.
Group 2:	ORN = open radical nephrectomy
Group 3:	PN = partial nephrectomy with a retroperitoneal approach. 3/44 mandatory, 41/44 elective. Open procedure.

PARTICIPANTS: Numbers	**Intervention 1: RRN**	**Intervention 2: OPN**	**Intervention 3: ORN**	**Pro**
Number allocated	36	44	37	
Number of dropouts	NR	NR	NR	Appears to be no dropout for surgical outcomes.
Number responded to the SF-36 questionnaire	24 (67%)	34 (77%)	27 (73%)	Overall 72%

Additional information (e.g. surgeon experience):

- N of surgeons: RRN 6 vs. ORN 12 vs. OPN 15
- Cases performed by Attending/Head of Department Residents: RRN 36 (100%) vs. ORN 31/37 (84%) vs. OPN 32/44 (73%)
- 'Patients who had post-operative complications (regardless of the type of surgery) had an obvious trend towards worse QoL scores compared with patients who did not have any complications. The trend reached statistical significance in the general health domain ($p<0.05$)' (p. 473).

Study ID	Hemal 2007[38]
Setting	India , single centre (All India Institute of Medical Science)
Funding	
Period covered	1998-2006
METHODS	
Type of study	Prospective cohort
Analysis	Survival: Kaplan-Meier estimates with log rank comparison Surgical outcomes: univariate
Was treatment allocated by:	[ ] Randomisation? [ ] Quasi-randomisation? [X] Health care decision makers? – **Procedure type based on patient and surgeon preference** [X] Participant preferences? [ ] Unclear
(If prospective) What parts of the study were prospective?	[ ] Identification of participants? [ ] Assessment of baseline and intervention allocation? [ ] Assessment of outcomes? [ ] Generation of hypotheses? [X] Unclear **Quote: 'Clinical data were prospectively evaluated'**
PARTICIPANTS	
Inclusion criteria	All patients undergoing radical nephrectomy for a clinical stage T2N0M0 renal tumour; tumour staging based on standard imaging criteria
Exclusion criteria	Not mentioned.
INTERVENTION	
Group 1:	Laparsoscopic radical nephrectomy (LRN). Retroperitoneal approach (N = 15) Transperitoneal approach (N = 26)

Group 2:	Open radical nephrectoy (ORN). No further details given.
Both groups	Limited hilar lymph node dissection (LND) was performed in most patients. Extended retroperitoneal LND was not routinely performed. En bloc adrenalectomy was performed in patients with superior pole or large tumours.

PARTICIPANTS numbers	**Group 1: LRN**	**Group 2: ORN**	**Pro**
Number randomised	41	71	
Number of dropouts	None missing for post-operative outcomes; Not mentioned for longer follow-up		

Comments (e.g. surgeon experience):

- 'Only surgeons with significant laparoscopic experience performed laparoscopy, while all surgeons performed open surgery' (p. 862).
- '… significant experience with retroperitoneoscopic nephrectomy' (p. 864).
- Authors note that they did not account for the learning curve and initial cases were included as well.
- Authors note that an increase in operative time in the laparoscopic surgery group may have been due to their learning curve, since this series includes all of their cases, including the intial ones (pp. 864-5).

Study ID	Hemal 2009[39]
Setting	India, single centre (All India Institute of Medical Sciences)
Funding	
Recruitment period	Oct 2006 – Aug 2007
METHODS	
Type of study	Prospective cohort
Analysis	Survival: not reported Surgical outcomes: univariate
Was treatment allocated by:	[ ] Randomisation? [ ] Quasi-randomisation? [ ] Health care decision makers? [X] Participant preferences? [ ] Unclear
(If prospective) What parts of the study were prospective?	[ ] Identification of participants? [ ] Assessment of baseline and intervention allocation? [ ] Assessment of outcomes? [ ] Generation of hypotheses? [X] Unclear **Quote: 'Our department acquired robotic system in July 2006 and this prompted us to prospectively evaluate the feasibility and safety of robotic radical nephrectomy … and to compare this with LRN'.**
PARTICIPANTS	
Inclusion criteria	T1-2N0M0 – patient choice decided intervention group.
Exclusion criteria	None given

INTERVENTION	
Group 1: Laparoscopic radical nephrectomy (LRN)	A LRN was performed using a standard transperitoneal route in all the cases. The en-bloc adrenalectomy was done, wherever indicated, and limited hilar lymph node dissection was performed in all the cases. Adrenalectomy performed in 6 cases.
Group 2 : Robotic radical nephrectomy (RRN)	A RRN using transperitoneal approach was performed in all cases. En-bloc adrenalectomy was performed in patients with superior pole or very large tumors. A limited hilar lymph node dissection was performed in all the patients. Da Vinci S surgical robot was used. Adrenalectomy performed in 5 cases.

PARTICIPANTS: Numbers	**Group 1: RRN**	**Group 2: LRN**	**Group 3**
Number randomised/ allocated	15	15	
Number of dropouts	0	0	

Comments (e.g. surgeon experience):

- All cases operated by single experience surgeon. The surgeon had been performing laparoscopy since 1992 and Robotics from 2001.
- Study institution acquired robotic system in July 2006.

Study ID	Herrlinger 1991[40]
Setting	Germany, single centre (University of Erlangen-Nuernberg)
Funding	
Period covered	Jan 1970 – Dec 1986
METHODS	
Type of study	Prospective cohort
Analysis	Survival: Kaplan-Meier estimates with log rank tests Surgical outcomes: no usable data (not reported separately for pT1-2)
Was treatment allocated by:	[ ] Randomisation? [ ] Quasi-randomisation? [ ] Health care decision makers? [ ] Participant preferences? [X] Unclear
(If prospective) What parts of the study were prospective?	[ ] Identification of participants? [ ] Assessment of baseline and intervention allocation? [ ] Assessment of outcomes? [ ] Generation of hypotheses? [X] Unclear **Quote: '… based on a prospective study of more than 500 consecutive patients'**
PARTICIPANTS	
Inclusion criteria	511 consecutive patients who underwent an operation for renal cell carcinoma between Jan 1st 1970 and Dec 31st, 1986. The study compared 2 groups of patients who underwent transabdominal radical nephrectomy with absolutely identical macroscopic and microscopic findings of the removed kidney and en bloc adherent lymph nodes. The sample includes pT3 or N+. Data for this review are extracted for Robson I, pT1-2, N0, M0, R0 only.
Exclusion criteria	

INTERVENTION	
Group 1:	Facultative lymphadenectomy, which means that lymph nodes had been removed only on occasions when they were macroscopically altered or for staging purposes. Partial lymph node dissection. Tumour positive lymph nodes were found in 10% of the patients (in the sample that includes pT3).
Group 2:	Systematically planned lymphadenectomy, that is patients underwent radical transabdominal nephrectomy, including extended dissection of the regional retroperitoneal lymph nodes. Complete lymph node dissection. Tumour positive lymph nodes were found in 17.5% of the patients (in the sample that includes pT3).
Reviewer notes	(1) unclear if CT scan was performed at baseline; (2) unclear whether all patients had impalpable nodes at surgery (equivalent to N0 on CT scan).

PARTICIPANTS: Numbers	**Group 1: Facultative**	**Group 2: Systematic**	**Notes**
Number allocated	191	320	
Number analysed	191 (Robson I 82)	320 (Robson I 82)	'The data for all patients were available for follow-up until death of any cause or until December 31, 1990.
Additional information (e.g. surgeon experience):			

Study ID	Huang 2009[61]
Setting	USA, multi-centred (SEER database)
Funding	
Period covered	1995-2002
METHODS	
Type of study	Database review
Analysis	Survival: Kaplan-Meier estimation, Cox proportional hazards regression controlling for demographic characteristics (age at diagnosis, race, marital status, urban-rural location and area level socioeconomic status) and co-morbidity. Surgical outcomes: not reported
Was treatment allocated by:	[ ] Randomisation? [ ] Quasi-randomisation? [ ] Health care decision makers? [ ] Participant preferences? [X] Unclear
(If prospective) What parts of the study were prospective?	[ ] Identification of participants? [ ] Assessment of baseline and intervention allocation? [ ] Assessment of outcomes? [ ] Generation of hypotheses?
PARTICIPANTS	
Inclusion criteria	In the linked SEER-Medicare database the study identified all first primary renal-cortical tumors (ICD-O-2 topography codes C64 and C64.9) diagnosed between 1995 and 2002. The cohort was restricted to patients 66 years old or older in whom the primary tumor was 4 cm or less.
Exclusion criteria	The study excluded patients in whom the diagnosis was made only at the time of death, those in a managed care plan during the treatment course and those who lacked part A or B Medicare coverage.

INTERVENTION	
Group 1:	Partial nephrectomy (PN). CPT code and ICD code on p. 56. Probably include laparoscopic procedures.
Group 2:	Radical nephrectomy (RN)

PARTICIPANTS: Numbers	**Group 1: PN**	**Group 2: RN**	**Group 3**
Number allocated	?	?	
Number analysed (retrospective)	556	2435	

Additional information (e.g. surgeon experience):

- The focus of the study is CV events in nephrectomy interventions – but the authors also report all cause mortality
- Regarding treatment allocation – Factors predictive of radical nephrectomy = age at surgery, female gender, and celebrovascular disease; Factors predictive of partial nephrectomy = a more recent year of surgery and pre-existing renal disease (OR 0.66).

Study ID	Ko 2008[47]
Setting	Korea, single centre (Korea University School of Medicine.)
Funding	
Recruitment period	April 2004 - June 2007
METHODS	
Type of study	Retrospective matched pair. Matched for age, gender, BMI, ASA, tumor characteristics and the indications for operation.
Analysis	Recurrence/metastasis/surgical outcomes: univariate
Was treatment allocated by:	[ ] Randomisation? [ ] Quasi-randomisation? [X] Health care decision makers? [X] Participant preferences? [ ] Unclear **Final treatment decision was made based mainly on the surgeon's and patient's preference after discussing the risks for each procedure.**
(If prospective) What parts of the study were prospective?	[ ] Identification of participants? [X] Assessment of baseline and intervention allocation? [X] Assessment of outcomes? [ ] Generation of hypotheses? **The cryoablation group was prospectively enrolled in the study, whereas the open surgery group was retrospectively selected (and matched) from a prospectively maintained database.**
PARTICIPANTS	
Inclusion criteria	20 patients who had pathologically confirmed RCC with a tumor size <4cm
Exclusion criteria	

INTERVENTION	
Group 1: LCA	Laparoscopic renal cryoablation. 12/20 patients elective.
Group 2: OPN	Open partial nephrectomy. 15/20 patients elective.

PARTICIPANTS: Numbers	**Intervention 1: LRC**	**Intervention 2: OPN**	**Note**
Number randomised/ allocated	20 (21 tumours)	20	
Number of dropouts	0	0	'all of the patients were followed for more than 12 months'

Additional information (e.g. surgeon experience):

- Intervention group was prospectively identified; data for control group was retrospectively accessed which was maintained prospectively.
- Matched with a group of 20 patients who were selected based on the pre-operative characteristics of the tumor and those of the patients from a pre-existing database of the patients who underwent OPN during the same period. Matched for age, gender, BMI, ASA, tumor characteristics and the indications for operation.

Study ID	Lane 2009[55]
Setting	USA, single centre (Cleveland Clinic)
Funding	
Recruitment period	1991-2008
METHODS	
Type of study	Database review
Analysis	Survival: Kaplan-Meier analysis and the log rank test. Surgical outcomes: not reported
Was treatment allocated by:	[ ] Randomisation? [ ] Quasi-randomisation? [ ] Health care decision makers? [ ] Participant preferences? [X] Unclear
(If prospective) What parts of the study were prospective?	[ ] Identification of participants? [ ] Assessment of baseline and intervention allocation? [ ] Assessment of outcomes? [ ] Generation of hypotheses? [ ] Unclear
PARTICIPANTS	
Inclusion criteria	Patients undergoing partial nephrectomy for suspected renal cancer
Exclusion criteria	
INTERVENTION	
Group 1:	Partial nephrectomy with adrenalectomy
Group 2:	Partial nephrectomy without adrenalectomy

PARTICIPANTS: Numbers	**Group 1**	**Group 2**	**Group 3**
Number allocated	48	2017	
Number analysed	48	2017	
Additional information (e.g. surgeon experience): •			

Study ID	Lane 2010[62]
Country	USA, single centre (Cleveland Clinic)
Funding	
Recruitment period	Sept 1999 – Dec 2008
METHODS	
Type of study	Database review. Cleveland Clinic - 'Clinical, operative and followup information … was collected prospectively, and maintained in an institutional review board approved computerized database'.
Analysis	Survival: Kaplan-Meier analysis and the log rank test. Multivariate analysis age, gender, race, Charlson-Romano Index, tumour size, hypertension, pre-operative GFR, and oncological potential (predicted risk of recurrence estimated based on path tumour size, histological subtype, path stage, and symptoms at presentation). Surgical outcomes: not reported.
Were groups formed by:	[ ] Randomisation? [ ] Quasi-randomisation? [ ] Health care decision makers? [ ] Participant preferences? [X] Unclear
D (If prospective) What parts of the study were prospective?	[ ] Identification of participants? [ ] Assessment of baseline and intervention allocation? [ ] Assessment of outcomes? [ ] Generation of hypotheses?
PARTICIPANTS	
Inclusion criteria	A single localized cT1 renal mass 7 cm or less, with at least 1 year of follow-up after surgery.
Exclusion criteria	Patients with prior or synchronous bilateral localized renal cancer (380), multiple ipsilateral tumors (53), tumor greater than 7 cm(101), or pre-operative radiographic evidence suspicious forlymph node or distant metastases (15) were excluded from study. In addition, patients younger than 18 years (33), those with a known familial RCC syndrome such as von Hippel-Lindau disease (6) or those undergoing PN for an indication other than suspected renal cancer (42) were excluded from study.

INTERVENTION	
Group 1:	LPN – laparoscopic partial nephrectomy Indication: LPN - elective 45%, imperative 50%, absolute 5.4%.
Group 2:	OPN – open partial nephrectomy Indication: OPN - elective 29%, imperative 41%, absolute 30%

PARTICIPANTS: Numbers	**Intervention 1: LPN**	**Intervention 2: OPN**	**Pro**
Number allocated	672	944	
Number of dropouts	NR	NR	Database review

Additional information (e.g. surgeon experience):

- Patients undergoing LPN less frequently had symptomatic presentation, a clinical T1b tumour and/or an absolute indication for partial nephrectomy. In addition to direct comparisons of the 2 cohorts patients in each cohort were also matched according to the propensity to undergo LPN due to these differences in pretreatment characteristics.
- Because of the increasing trend in LPN during the study period, the length of follow-up differed in the 2 cohorts, although all were operated on between 1999 and 2008. To account for this difference actual survival data are presented for those patients with a minimum of 7 years of follow-up and Kaplan-Meier estimates are presented for the entire cohort.

Study ID	Lee 2007[27] [in Korean]
Country	Korea, single centre (University of Ulsan College of Medicine, Seoul)
Funding	
Recruitment period	Jan 1995 – Feb 2004
METHODS	
Type of study	Retrospective matched pair. Matched by the size of tumour, the pathological T stage, the pathological grade and the follow-up time
Analysis	Survival: Kaplan-Meier estimates Surgical outcomes: unvariate
Was treatment allocated by:	[ ] Randomisation? [ ] Quasi-randomisation? [ ] Health care decision makers? [ ] Participant preferences? [X] Unclear
(If prospective) What parts of the study were prospective?	[ ] Identification of participants? [ ] Assessment of baseline and intervention allocation? [ ] Assessment of outcomes? [ ] Generation of hypotheses?
PARTICIPANTS	
Inclusion criteria	Patients with unilateral RCC and normal contra-lateral kidney. Tumour <4 cm, matched by the size of tumour, the pathological T stage, the pathological grade and the follow-up time
Exclusion criteria	Metastasis, diagnosis of von Hippel Lindau disease, renal failure before surgery, end stage renal failure, polucystic kidney disease, patients not recorded for creatine level more than 1 year after surgery.
INTERVENTION	
Group 1:	Partial nephrectomy (PN)
Group 2:	Radical nephrectomy (RN)

PARTICIPANTS: Numbers	**Intervention 1: PN**	**Intervention 2: RN**	**Pro**
Number allocated	56 matched (out of 92 who underwent NSS)	56 matched (out of 200 who underwent RN)	
Number of dropouts	0	0	

Additional information (e.g. surgeon experience):

- The tables with creatinine results (table 4) mentions results of unmatched patients.
- Impaired renal function is defined as a serum creatinine value greater than 1.6 mg/dl.

Study ID	Marszalek 2009[48]
Setting	Austria, multi-centred (laparoscopic surgery in Klagenfurt General Hospital; open surgery in Vienna Donauspital)
Funding	
Recruitment period	Not mentioned
METHODS	
Type of study	Retrospective matched pair. Matched by age, sex and tumour size.
Analysis	Survival: Kaplan-Meier estimates with log rank tests; a multivariate Cox proportional hazards model performed for disease recurrence (covariates include age, sex, tumour size, margin status and surgical approach). Surgical outcomes: univariate
Was treatment allocated by:	[ ] Randomisation? [ ] Quasi-randomisation? [X] Location differences? [ ] Health care decision makers? [ ] Participant preferences? [ ] Unclear
(If prospective) What parts of the study were prospective?	[ ] Identification of participants? [ ] Assessment of baseline and intervention allocation? [ ] Assessment of outcomes? [ ] Generation of hypotheses?
PARTICIPANTS	
Inclusion criteria	Laparoscopic partial : tumour size (<7cm), localization and accessibility of tumour, general health status of patient ; all done in Klagenfurt General Hospital Open partial: all done in Vienna Donauspital
Exclusion criteria	

INTERVENTION	
Group 1: Laparoscopic partial nephrectomy (LPN)	Flank, blunt dissection of retroperitoneal cavity, circumcision of tumour by choledochotom, warm ischemia, haemostasis by central suturing and fibrin glue, intact specimen retrieval using endobag. All elective surgery.
Group 2: Open partial nephrectomy (OPN)	Retroperitoneal, cold ischemia, flank position, intravenous mannitol for renal protection, sharp incision of the renal capsule, blunt separation of the lesion from parenchyma using neurosurgical brain elevator, collagen hemostat on cut surface. All elective surgery.

PARTICIPANTS: Numbers	**Intervention 1: LPN**	**Intervention 2: OPN**	**Pro**
Number randomised/ allocated	100	100	
Number not analysed	19 (pathologically benign)	34 (pathologically benign)	
Number analysed for survival outcome	81	66	

Additional information (e.g. surgeon experience):

- LPN performed by 2 ‘experienced surgeons’
- OPN performed by 5 ‘experienced surgeons’
- In the LPN group, conversub rate to open surgery was 2%.

Study ID	Nadler 2006[34]
Setting	USA, single centre (Northwestern University Feinberg School of Medicine, Chicago)
Funding	
Recruitment period	Feb 2001 – Feb 2005
METHODS	
Type of study	Quasi RCT
Analysis	Mortality/surgical outcomes: univariate
Was treatment allocated by:	[ ] Randomisation? [X] Quasi-randomisation? – **By alternation based on the date that patients presented for surgery without respect to any individual patient characterisctics.** [ ] Health care decision makers? [ ] Participant preferences? [ ] Unclear
(If prospective) What parts of the study were prospective?	[X] Identification of participants? [X] Assessment of baseline and intervention allocation? [X] Assessment of outcomes? [X] Generation of hypotheses?
PARTICIPANTS	
Inclusion criteria	Clinical stage T1 solid renal masses
Exclusion criteria	
INTERVENTION	
Group 1	Hand-assisted (HA) laparoscopic radical nephrectomy. Used GelPort
Group 2	Transperitoneal (TP) laparoscopic radical nephrectomy. Morcellation employed.
Group 3	Retroperitoneal (RP) laparoscopic radical nephrectomy. Intact specimen

PARTICIPANTS: Numbers	**Group 1: Hand assisted**	**Group 2: Transperitoneal**	**Group 3: Retroperitoneal**
Number randomised/ allocated	11	11	11
Number of dropouts	Not reported	Not reported	Not reported

Additional information (e.g. surgeon experience):

- 3 patients were excluded due to refusal to randomisation
- Surgery by one surgeon who '… had performed at least 50 radical nephrectomy using each method [HA, TP and RP]'.
- The adrenal was spared in all except 2 TP and 2 RP cases.
- Conversion from TP to HA in 1 case.

Study ID	Nambirajan 2004[35]
Country	Austria, single centre (Elisabethinen Hospital, Linz)
Funding	
Recruitment period	Dec 2001 – July 2003
METHODS	
Type of study	RCT
Analysis	Recurrence/metastasis/surgical outcomes: univariate
Was treatment allocated by:	[X] Randomisation? [ ] Quasi-randomisation? [ ] Health care decision makers? [ ] Participant preferences? [ ] Unclear
(If prospective) What parts of the study were prospective?	[X] Identification of participants? [X] Assessment of baseline and intervention allocation? [X] Assessment of outcomes? [X] Generation of hypotheses?
PARTICIPANTS	
Inclusion criteria	40 consecutive patients with clinical stage T1/2 RCC suitable for endoscopic radical nephrectomy. Tumour size up to 8 cm.
Exclusion criteria	Unsuitable for retroperitoneal approach – large tumour (>9cm) (n = 3)
INTERVENTION	
Group 1	Laparoscopic radical nephrectomy (LRN). Adrenalectomy in 13 cases. Lymphadenectomy in 5 cases.
Group 2	Retro-peritoneoscopic radical nephrectomy (RRN). Adrenalectomy in 15 cases. Lymphadenectomy in 4 cases.

Both groups	With robotic assistance (AESOP 3000, Computer Motion, Calif) to hold the camera. Adrenalectomy was deferred for tumours confied to the lower pole of the kidney. Additional lymph node sampling was performed if either pre-operative imaging or peri-operative inspection of the hilum showed suspicious nodal enlargement.

PARTICIPANTS: Numbers	**Group 1: LRN**	**Group 2: RRN**	**Group 3**
Number randomised	20	20	
Number analysed for peri-operative outcome	20	20	
Number analysed for oncological outcome (longer FU)	15	17	
Reason for non-analysis	Patients from abroad or with benign pathology	Patients from abroad or with benign pathology	

Comments (e.g. surgeon experience):

- 2 surgeons (KL, GI) with differing experience performed an equal number of procedures in both groups.
- 'One of whom had overcome the learning curve for both approaches, and one who was still learning but who had similar experience with both approaches' (p. 923).
- Assessment of the difficulty of the procedures (LRN vs. RRN) reported.

Study ID	O'Malley 2007[49]
Country	USA, single centre (New York University School of Medicine)
Funding	
Recruitment period	May 2003 – Jul 2005 (cryoablation); Jul 2002 – Jul 2005 (nephrectomy)
METHODS	
Type of study	Retrospective matched pair. Matched by age and tumour size.
Analysis	Recurrence/surgical outcomes: univariate
Was treatment allocated by:	[ ] Randomisation? [ ] Quasi-randomisation? [ ] Health care decision makers? [ ] Participant preferences? [X] Unclear
(If prospective) What parts of the study were prospective?	[ ] Identification of participants? [ ] Assessment of baseline and intervention allocation? [ ] Assessment of outcomes? [ ] Generation of hypotheses?
PARTICIPANTS	
Inclusion criteria	15 patients who had cryoablation at the authors' institution between May 2003 and July 2005. A matched group of 15 patients were selected based on age and tumour size from a pre-existing database of 104 patients, who had laparoscopic partial nephrectomy from July 2002 to July 2005.
Exclusion criteria	Not described

INTERVENTION	
Group 1 : Laparoscopic cryoablation (LCA); N = 15	Performed by one surgeon; used laparosxopic renal exposure, tumour location using ultrasound, tumour exposure through mobilizing fat, double freeze-thaw cycle used with cryoablative needle probes under lap ultrasound guidance with ice ball 1 cm beyond margins of the mass
Group 2 : Laparoscopic partial nephrectomy (LPN); N = 15	Performed by 2 surgeons; lap exposure followed by intraop ultrasound guided tumour excision; used temporary renal vascular occlusion with mannitol administration before and after renal ischemia

PARTICIPANTS: Numbers	**Group 1: LCA**	**Group 2: LPN**	**Pro**
Number allocated	15	15	
Number of dropouts	Not reported	Not reported	
Additional information (e.g. surgeon experience):			

Study ID	Onishi 2007[41]
Country	Japan, single centre (Mie University Graduate School of Medicine)
Funding	
Period covered	Dec 2004 – Sept 2006
METHODS	
Type of study	Prospective cohort
Analysis	Quality of life: univariate
Wes treatment allocated by:	[ ] Randomisation? [ ] Quasi-randomisation? [X] Health care decision makers? – **Radiofrequency ablation given on basis of contraindication for surgery** [ ] Participant preferences? [ ] Unclear
(If prospective) What parts of the study were prospective?	[X] Identification of participants? [X] Assessment of baseline and intervention allocation? [X] Assessment of outcomes? [X] Generation of hypotheses? **Quote: 'All patients who agreed to participate in this study received a questionnaire for self-administration from the author with an informed consent'.**
PARTICIPANTS	
Inclusion criteria	Consecutive patients diagnosed with cT1a RCC. Eligibility criteria for radiofrequency ablation were single kidney (7 cases), renal dysfunction (3), risk of general anaesthesia (cardiac and/or respiratory disfuction, high age; 5 cases), double cancer (2) and refusal of open or laparoscopic surgery (3).
Exclusion criteria	

INTERVENTION	
Group 1:	Radiofrequency ablation (RFA). Percutaneous RFA
Group 2:	Laparoscopic radical nephrectony (LRN)

PARTICIPANTS: Numbers	**Intervention 1: RFA**	**Intervention 2: LRN**	**Pro**
Number randomised/ allocated	20	17	
Number of dropouts	0	0	
Additional information (e.g. surgeon experience):			

Study ID	Park 2009[50] (abstract only)
Country	Korea
Funding	
Recruitment period	
METHODS	
Type of study	Retrospective matched pair. Matched for age, gender, side of operation, and mass size
Analysis	Survival: Not reported Surgical outcomes: Unadjusted
Was treatment allocated by:	[ ] Randomisation? [ ] Quasi-randomisation? [ ] Health care decision makers? [ ] Participant preferences? [X] Unclear
(If prospective) What parts of the study were prospective?	[ ] Identification of participants? [ ] Assessment of baseline and intervention allocation? [ ] Assessment of outcomes? [ ] Generation of hypotheses?
PARTICIPANTS	
Inclusion criteria	Consecutive patients with localised RCC.
Exclusion criteria	

INTERVENTION	
Group 1:	Laparoendoscopic single-site (LESS) radical nephrectomy
Group 2:	Conventional laparoscopic radical nephrectomy (LRN)

PARTICIPANTS: Numbers	**Intervention 1: LESS**	**Intervention 2: LRN**	**Pro**
Number randomised/ allocated	9	18	
Number of dropouts	NR	NR	
Additional information (e.g. surgeon experience):			

Study ID	Patard 2004[63]
Country	USA, France, The Netherland, Italy; multi-centred. 7 international academic centres including Renne (France), Saint Etienne (France), Creteil (France), Naples (Italy), Verona (Italy), Nijmegen (The Netherlands) and Los Angeles, California.
Funding	
Recruitment period	1984-2001 (years of treatment)
METHODS	
Type of study	Database review. Patients records extracted from each institutional database.
Analysis	Survival: Kaplan Meier method and log rank tests Surgical outcomes: Not reported
Was treatment allocated by:	[ ] Randomisation? [ ] Quasi-randomisation? [ ] Health care decision makers? [ ] Participant preferences? [X] Unclear
(If prospective) What parts of the study were prospective?	[ ] Identification of participants? [ ] Assessment of baseline and intervention allocation? [ ] Assessment of outcomes? [ ] Generation of hypotheses?
PARTICIPANTS	
Inclusion criteria	Partial or radical nephrectomy for pT1N0M0 renal tumors
Exclusion criteria	

INTERVENTION	
Group 1:	Partial nephrectomy. No further details
Group 2:	Radical nephrectomy. No further details

PARTICIPANTS: Numbers	**Intervention 1: PN**	**Intervention 2: RN**	**Pro**
Number allocated	379: pT1a 314 pT1b 65	1075: pT1a 499 pT1b 576	
Number of dropouts			
Additional information (e.g. surgeon experience): • Focus of the study is the cut-off size of 4cm for partial nephrectomy			

Study ID	Patard 2008[51] (abstract only)
Setting	France, US, Italy, Canada, multi-centred. Author affiliations include 12 institutions.
Funding	
Recruitment period	Not mentioned
METHODS	
Type of study	Retrospective matched pair. Matched for tumour size and Fuhrman grade.
Analysis	Survival: 'Survival curves' (assumed to be Kaplan-Meier estimates) with log rank test Surgical outcomes: not reported
Was treatment allocated by:	[ ] Randomisation? [ ] Quasi-randomisation? [ ] Health care decision makers? [ ] Participant preferences? [X] Unclear
(If prospective) What parts of the study were prospective?	[ ] Identification of participants? [ ] Assessment of baseline and intervention allocation? [ ] Assessment of outcomes? [ ] Generation of hypotheses?
PARTICIPANTS	
Inclusion criteria	pT1b-pT2N0M0.
Exclusion criteria	
INTERVENTION	
Group 1: Partial nephrectomy (PN)	No details given
Group 2: Radical nephrectomy (RN)	No details given

Both groups:	Unclear if it is open or laparoscopic. Emailed author – reply: 'There were both lap and open nephrectomies in the 2 groups. … The vast majority (>90%) was open'.

PARTICIPANTS: Numbers	**Group 1: PN**	**Group 2: RN**	**Group 3**
Number allocated	289	257	
Number of dropouts	NA (retrospective)	NA (retrospective)	

Additional information (e.g. surgeon experience):

- Predictive parameters for survival = T stage, Furhman grade and age (univariate analysis); T stage and age (multivariate analysis); surgical approach had no impact on survival.

Study ID	Peng 2006[36] [Chinese text with English abstract]
Setting	China, single centre (Second Military Medical University, Shanghai)
Funding	
Recruitment period	Jan 2005 – Jun 2005
METHODS	
Type of study	RCT
Analysis	Survival: not reported Surgical outcomes: univariate (appears to be)
Was treatment allocated by:	[X] Randomisation? [ ] Quasi-randomisation? [ ] Health care decision makers? [ ] Participant preferences? [ ] Unclear
(If prospective) What parts of the study were prospective?	[X] Identification of participants? [X] Assessment of baseline and intervention allocation? [X] Assessment of outcomes? [X] Generation of hypotheses?
PARTICIPANTS	
Inclusion criteria	With renal cell carcinoma due to receive radical renal tumor resection
Exclusion criteria	
INTERVENTION	
Group 1:	Retroperitoneal laparoscopic nephrectomy
Group 2:	Open radical nephrectomy

PARTICIPANTS: Numbers	**Group 1: Retro LRN**	**Group 2: ORN**	**Group 3**
Number randomised	27	26	
Number of dropouts	Not mentioned	Not mentioned	
Additional information (e.g. surgeon experience): • Data were extracted from the English abstract only. The English translation of the Chinese main text was not available at the time of writing.			

Study ID	Poulakis 2003[42]
Country	Germany, single centre (North-west Academic Teaching Hospital of Johann Wolfgang Goethe University)
Funding	
Recruitment period	1991 - 2001
METHODS	
Type of study	Prospective cohort (the subset of 51 patients only)
Analysis0.	Quality of life: univariate
Was treatment allocated by:	[ ] Randomisation? [ ] Quasi-randomisation? [ ] Health care decision makers? [ ] Participant preferences? [X] Unclear
(If prospective) What parts of the study were prospective?	[X] Identification of participants? [X] Assessment of baseline and intervention allocation? [X] Assessment of outcomes? [X] Generation of hypotheses? **Of the 416 patients eligible for a larger (retrospective) study, the 'last 51 consecutively treated patients were assessed before and after surgery at 3-month intervals for 1 year'.**
PARTICIPANTS	
Inclusion criteria	Patients who had undergone radical or partial nephrectomy for localized RCC from 1991-2001 (retrospective analysis). The last 51 consecutively treated patients were assessed prospectively as a subgroup.
Exclusion criteria	Those who died, those who developed metastasis and/or local recurrence, unreachable, did not read or write (criteria applied to both retrospective and prospective groups)

INTERVENTION	
Group 1:	Nephron-sparing surgery (NSS). Reviewer note: No further description given but the participants were from 1991 to 2001 so likely to be open surgery.
Group 2:	Radical nephrectomy. Reviewer note: No further description given but assumed to be open surgery for the reason above.
Both groups	The article does not provide surgical details but the participants were from 1991 to 2001 so more likely to be open surgery.

PARTICIPANTS: Numbers	**Intervention 1: NSS**	**Intervention 2: RN**	**Group 3**
Number allocated	129 (retrospective) 29 (prospective)	177 (retrospective) 22 (prospective)	
Number of dropouts			
Participation rates	Participation rates for men: 269 eligible, 231 operated (85.9%) Participation rates for women: 147 eligible, 126 operated (85.7%)		
Additional information (e.g. surgeon experience): • The data are extracted for the 51 prospectively assessed participants only. • This is a postal questionnaire of QOL patients postop, using general HRQOL using the RAND Health Survey (SF 36; Ware 2000), EORTC QLQ-C30 (Fayers 1998; European Organisation for Research and Treatment of Cancer; score range 0-100), Impact of Events Scales-Revised (Weiss 1996; Horowitz 1979)			

Study ID	Shekarriz 2002[52]
Setting	USA, multi-centred (Wayne State University and Karmanos Cancer Institute)
Funding	
Recruitment period	Jan 1991 – Dec 1997
METHODS	
Type of study	Retrospective matched pair. Matched for age, sex, location and size of tumour, and pathologic stage.
Analyisis	Survival: not reported Surgical outcomes: univariate; results stratified by time of surgery (1991-92, 1993-94, 1995-97) also reported
Was treatment allocated by:	[ ] Randomisation? [ ] Quasi-randomisation? [X] Health care decision makers? – **Based on the status of the contralateral kidney and surgeon preference.** [ ] Participant preferences? [ ] Unclear
(If prospective) What parts of the study were prospective?	[ ] Identification of participants? [ ] Assessment of baseline and intervention allocation? [ ] Assessment of outcomes? [ ] Generation of hypotheses?
PARTICIPANTS	
Inclusion criteria	All patients who underwent partial or radical nephrectomy between 1991 and 1997. Single renal tumor <7 cm, pathologic stage T3a or less, no concomitant abdominal procedure.
Exclusion criteria	History of abdominal surgery or radiotherapy, multifocal or bilateral, hereditary, metastatic disease

INTERVENTION	
1 : Radical nephrectomy (RN)	Routine lymphadenectomy not done unless enlarged nodes were found. Reviewer note: Authors note that RN was performed 'in the conventional manner'. Assumed to be open surgery.
2 : Partial nephrectomy (PN)	Selection to PN based on status of the contralateral kidney and surgeon preference; frozen section of margins done Reviewer note: Authors note that in the PN group, surgery was done according to the principles described in 1993. Assumed to be open surgery.

PARTICIPANTS: Numbers	**Group 1: RN**	**Group 2: PN**	**Group 3**
Number randomised/ allocated	60	60	
Number of dropouts	NA (retrospective)	NA (retrospective)	
Additional information (e.g. surgeon experience): • Authors report a decrease in operating time in the RN group. Difference in operating time between the groups for1991-92 (p = 0.58), 1993-94 (p = 0.037), 1995-96 (p = 0.004).			

Study ID	Simmons 2009[68]
Setting	USA, single centre (Cleveland Clinic)
Funding	
Recruitment period	2001-2005
METHODS	
Type of study	Database review. Data analysed from a prospectively-maintained database at Cleveland Clinic.
Analysis	Survival: Kaplan-Meier estimates and log rank statistics. Surgical outcomes: not reported (T1-2 not reported separately)
Was treatment allocated by:	[ ] Randomisation? [ ] Quasi-randomisation? [X] Health care decision makers? [X] Participant preferences? [ ] Unclear **The selection of LPN vs. LRN was multifactorial, according to the patient factors (e.g. age, comorbidities, performance status, baseline renal function, status of contralateral kidney), tumour factors (e.g. proximity to the rela hilar vessels and central sinus fat), and surgeon factors (e.g. judgment, experience). The selection of a transperitoneal vs. retroperitoneal approach was determined by the tumour location.**
(If prospective) What parts of the study were prospective?	[ ] Identification of participants? [X] Assessment of baseline and intervention allocation? [X] Assessment of outcomes? [ ] Generation of hypotheses?
PARTICIPANTS	
Inclusion criteria	Patients with organ-confined pathologically confirmed RCC >4 cm in size who underwent elective surgery during the specified period by the senior author (I.S.G.). 110 consecutive patients, T1b-T3N0M0.
Exclusion criteria	CT evidence of venous thrombus, lymphadenopathy, or metastatic disease; and the presence of Stage V chronic kidney disease at surgery.

INTERVENTION	
Group 1:	Laparoscopic partial nephrectomy. 17/35 (49%) by Transperitoneal approach; the remainder by retroperitoneal approach.
Group 2:	Laparoscopic radical nephrectomy. 23/75 (31%) by transperitoneal approach; the remainder by retroperitoneal approach.

PARTICIPANTS: Numbers	**Group 1: LAP PARTIAL**	**Group 2: LAP RADICAL**	**Group 3**
Number randomised/ allocated	35	75	
Number of dropouts	NA (database review)	NA (database review)	

Additional information (e.g. surgeon experience):

- Authors note that laparoscopic radical nephrectomy were more common in the first 3 years (2001-3), while laparascopic partial nephrectomy were more common in the latter 2 years.
- 'An annual trend was seen in the decreased use of LRN and increased use of LPN throughout the study period' (p. 1078; also Table 1).

Study ID	Soga 2008[43]
Country	Japan, single centre (Mie University Graduate School of Medicine)
Funding	
Recruitment period	July 2005 – December 2007
METHODS	
Type of study	Prospective cohort
Analysis	Mortality/recurrence/surgical outcomes: univariate
Was treatment allocated by:	[ ] Randomisation? [ ] Quasi-randomisation? [X] Health care decision makers? – **'The first option was PLES-RN [portless endoscopic surgery] …. The choice was made after discussing the therapy with patients ….'** [X] Participant preferences? [ ] Unclear
(If prospective) What parts of the study were prospective?	[X] Identification of participants? [X] Assessment of baseline and intervention allocation? [X] Assessment of outcomes? [X] Generation of hypotheses? [ ] Unclear **Informed consent was obtained at treatment allocation.**
PARTICIPANTS	
Inclusion criteria	Radiology diagnosis suggested RCC. Clinical diagnosis of RCC T1. No metastasis. WHO performance status < Grade 2.
Exclusion criteria	Not mentioned

INTERVENTION	
1: PLES-RN	Portless endoscopic surgery (PLES), i.e. single-port laparoscopic radical nephrectomy (PLES-RN). The procedure has been described in a previous paper (reference number 4). The renal artery and then the renal vein were clamped under endoscopic guidance.
2 : LRN	Laparoscopic radical nephrectomy (3 ports). The technique is described in previous papers (reference numbers 1 and 2). In their original operative setting, an initial 6–7 cm sub-umbilical incision was introduced under direct vision, a Lap Disc (Hakko-Medical, Tokyo, Japan) was placed for establishing an endoscopic port. The transperitoneal approach was taken using the pure laparoscopic technique.

PARTICIPANTS: Numbers	**Group 1: PLES-RN**	**Group 2: LRN**	**Group 3**
Number allocated	14	15	
Number of dropouts	Not reported	Not reported	

Comments (e.g. surgeon experience):

- In PLES-RN, seven unfixed main operators with one fixed instructive surgeon were accomplished , while only two surgeons were required in LRN.

Study ID	Thompson 2008[64]
Country	USA, single centre (Mayo Clinic)
Funding	
Recruitment period	1989-2003 (years of surgery)
METHODS	
Type of study	Dtabase review. Data from the Mayo Clinic nephrectomy registry. 'Through an ongoing collaboration with our institutional tumour registry the rephrectomy registry maintains a high degree of patient followup. … Currently fewer than 3% of the patients in the registry have been lost to followup' (p. 469).
Analysis	Survival: Kaplan-Meier method. For the subset of patients younger than 65 years, all cause mortality was evaluated using Cox proportional hazards regression models, adjusting for one variable at a time (year of surgery, pre-operative creatinine, Charlson-Romano index, sex, symptoms at presentation, constitutional symptoms at presentation, diabetes at presentation, and malignant histology). Since only 43 events were observed in this subset, multivariate analysis involving all of the clinical and pathological features studied was not performed. Surgical outcomes: Not reported
Was treatment allocated by:	[ ] Randomisation? [ ] Quasi-randomisation? [ ] Health care decision makers? [ ] Participant preferences? [X] Unclear
(If prospective) What parts of the study were prospective?	[ ] Identification of participants? [ ] Assessment of baseline and intervention allocation? [ ] Assessment of outcomes? [ ] Generation of hypotheses?
PARTICIPANTS	
Inclusion criteria	Patients treated with partial or radical nephrectomy between 1989 and 2003, with a sporadic, unilateral, solitary, enhancing renal cortical tumour of any histological subtype, and pathological size 4 cm or less.
Exclusion criteria	Patients with perinephric fat invasion, nodal or distant metastasis at surgery or imperative indications for surgery. Imperative indications included a solitary kidney or an atrophic contralateral kidney, creatinine at diagnosis greater than 1.4 mg/dl in females or greater than 1.6 mg/dl in males, or impaired renal function.

INTERVENTION	
Group 1:	Partial nephrectomy. No further details.
Group 2:	Radical nephrectomy. No further details.

PARTICIPANTS: Numbers	**Intervention 1: PN**	**Intervention 2: RN**	**Pro**
Number allocated	358 (including 187 who were younger than age 65)	290 (including 140 who were younger than age 65)	
Number of dropouts	NR	NR	
Additional information (e.g. surgeon experience): • '… RN was more commonly performed earlier in the study time frame and the observed difference in time to death likely to reflects this opportunity for longer follow-up' (p. 469).			

Study ID	Thompson 2009[69]
Country	USA, multi-centred (Mayo Clinic and Memorial Sloan-Kettering Cancer Centre)
Funding	
Recruitment period	1989-2006 (years of treatment)
METHODS	
Type of study	Database review. Combined institutional databases from Mayo clinic and Memorial Sloan-Kettering Cancer Centre.
Analysis	Survival: Kaplan-Meier method and Cox proportional hazards regression models. Overall survival adjusting for age, Charlson index, impaired renal function, tumor size, tumour stage, histological subtype (benign vs. RCC). Cancer-specific survival adjusting for age, impaired renal function, tumour stage, and tumor size. Surgical outcomes: Not reported
Were groups formed by:	[ ] Randomisation? [ ] Quasi-randomisation? [ ] Health care decision makers? [ ] Participant preferences? [X] Unclear
(If prospective) What parts of the study were prospective?	[ ] Identification of participants? [ ] Assessment of baseline and intervention allocation? [ ] Assessment of outcomes? [ ] Generation of hypotheses?
PARTICIPANTS	
Inclusion criteria	Sporadic, unilateral, solitary and localized renal masses 4.1-7 cm who underwent radical or partial nephrectomy between 1989 and 2006.
Exclusion criteria	

INTERVENTION	
Group 1:	Partial nephrectomy. 96% (n = 275) treated with open surgery and 4% (n = 11) were treated laparoscopically.
Group 2:	Radical nephrectomy. 90% (n = 785) open surgery, 10% (n = 88) lapacroscopic surgery.

PARTICIPANTS: Numbers	**Intervention 1: PN**	**Intervention 2: RN**	**Pro**
Number allocated	286	873	
Number of dropouts			

Additional information (e.g. surgeon experience):

- 'Patients treated with PN were significantly more likely to have a solitary kidney (10% vs. 0.2%, p<0.001)'.
- 'Patients treated with RN tended to be older and female, and were more likely to have larger tumours with perinephric or renal sinus fat invasion than patients treated with PN'.

Study ID	Van Poppel 2007[37]
Country	EU, USA, Canada, multi-centred (EORTC)
Funding	National Cancer Institute, Vlaamse Liga Tegen Kanker, Federation Belge contr le Cancer
Recruitment period	Apr 1992- Jan 2003
METHODS	
Type of study	RCT
Analysis	Survival: not reported Surgical outcomes: univariate
Were treatment allocated by:	[X] Randomisation? [ ] Quasi-randomisation? [ ] Health care decision makers? [ ] Participant preferences? [ ] Unclear
(If prospective) What parts of the study were prospective?	[X] Identification of participants? [X] Assessment of baseline and intervention allocation? [X] Assessment of outcomes? [X] Generation of hypotheses?

PARTICIPANTS	
Inclusion criteria	T1-2, N0, M0, normal contralateral kidney
Exclusion criteria	Tumour size >5 cm. WHO performance status >2, other cancer, solitary kidney, with VHL, with distant mets.

INTERVENTION	
Group 1: Radical nephrectomy (RN)	Removal of the entire kidney with the adrenal gland and perinephric fat within the intact Gerota's fascia. Limited lynphadenectomy done separately or enbloc. Approaches included lumbotomy, laparotomy and thoracolaparotomy and "others". Some patients had radical lymphadenectomy.

Group 2: Nephron sparing surgery (NSS)	Tumour removal was done by excavation (no enucleation), wedge resection, or partial nephrectomy after reigorous inspection of the entire renal capsula together with limited lymphadenectomy. Hilar clamping was not routine. When there is doubt of the margin status, frozen section of the resection margins was done
Both groups	Reviewer note: The description of surgical techniques used suggests that both groups had open surgery.

PARTICIPANTS: Numbers	**Group 1: RN**	**Group 2: NSS**	**Notes**
Number randomised	273 (of these 16 underwent NSS)	268 (of these 39 underwent RN)	
Number not analysed for adverse effects outcomes	9	3	These patients were not operated on and had no surgical information.

Additional information (e.g. surgeon experience):

- Authors note:'Only morbidity is reported because the data are not yet sufficiently mature to report efficacy results' (p. 1608).
- In case of positive lymphadenectomy, further treatment was left to the surgeon's discretion. Followup remained according to protocol.

Study ID	Weight 2010[65]
Country	USA, single centre (Cleveland Clinic)
Funding	
Recruitment period	1999-2006
METHODS	
Type of study	Database review. Data were obtained from an institutional review board approved, institutional kidney cancer patient registry.
Analysis	Survival: Kaplan-Meier estimates with log rank tests. • A propensity score model was used to control for selection bias. The propensity to undergo partial nephrectomy (outcome variable) was calculated using a multivariable logistic regression model and the pre-operative patient characteristics deemed likely to influence selection to radical or partial nephrectomy, including age,tumour size, presence of contraleateral disease, solitary kidney status, surgery type (laparoscopic or open) and Charlson co-morbidity index. All of these significantly predicted the choice to perform partial (rather than radical) nephrectomy. The peopensity quintile or class was then used to perform Cox multivariate proportional hazard analyses. • For overall survival: Cox proportional hazard models stratified according to propensity score class (single predicting variable, i.e. PN vs. RN); also including postop eGFR and pathological T-stage (multiple predicting variables). • For cancer specific survival: Cox multivariate regression analysis, including pathological size, nuclear grade 4 vs. other, pathological T-stage, and final eGFR. Surgical outcomes: not reported
Was treatment allocated by:	[ ] Randomisation? [ ] Quasi-randomisation? [X] Health care decision makers? – **'surgeon and patient preference'** [X] Participant preferences? [ ] Unclear
(If prospective) What parts of the study were prospective?	[ ] Identification of participants? [ ] Assessment of baseline and intervention allocation? [ ] Assessment of outcomes? [ ] Generation of hypotheses?

PARTICIPANTS	
Inclusion criteria	All patients with cT1b if they were treated by partial or radical nephrectomy.
Exclusion criteria	Metastasis, radiographic evidence of lymphadenopathy or local invasion, patients without a social security number.
INTERVENTION	
Group 1:	Radical nephrectomy (RN). Both open and laparoscopic. Number with laparoscopic technique = 354/480 (73.8%). Number elective = 298/480 (62.1%)
Group 2:	Partial nephrectomy (PN). Both open and laparoscopic. Number with laparoscopic technique = 376/524 (14.5%). Number elective = 212/524 (40.5%)

PARTICIPANTS: Numbers	**Group 1: RN**	**Group 2: PN**	**Notes**
Number allocated	480	524	
Number not analysed for adverse effects outcomes	NA (database review)	NA (database review)	
Additional information (e.g. surgeon experience):			

Study ID	Wu 2010[66]
Country	USA, single centre (Northwestern University Feinberg School of Medicine, Chicago)
Funding	
Recruitment period	Oct 2002 – May 2007 LPN June 2007-Feb 2009 RF-RCPN
METHODS	
Type of study	Database review. Prospectively collected in a centralized database.
Analysis	Recurrence: unadjusted Surgical outcomes: unadjusted; also multivariate analysis also conducted for blood loss, operative duration and length of hospital stay (adjusted for age, BMI and tumour size), as well as haemorrhage and complications (adjusted for reconstruction also).
Were groups formed by:	[ ] Randomisation? [ ] Quasi-randomisation? [X] Time differences? [ ] Health care decision makers? [ ] Participant preferences? [ ] Unclear
(If prospective) What parts of the study were prospective?	[ ] Identification of participants? [ ] Assessment of baseline and intervention allocation? [X] Assessment of outcomes? [ ] Generation of hypotheses?
PARTICIPANTS	
Inclusion criteria	Consecutive patients.
Exclusion criteria	
INTERVENTION	
Group 1:	Radiofrequency-assisted robotic clampless partial nephrectomy (RF-RCPN). Renal hilar vessels are not clamped after exposure with a transperitoneal approach. No warm ischemia to the kidney.
Group 2:	Laparoscopic partial nephrectomy

PARTICIPANTS: Numbers	Intervention 1: RF-RCPN	Intervention 2: LPN	Pro
Number allocated	42	36	
Number of dropouts	Some missing data depending on outcome	Some missing data depending on outcome	

Additional information (e.g. surgeon experience):

- Historical control – 'Starting from June 2007, only the RF-RCPN technique was utilized for partial nephrectomy in this study'.
- Surgery performed by one of 3 surgeons.
- Authors note that 'We did not discriminate based on tumour size or location to which patients we offered RF-RCPN'.
- Tumours in the RF-RCPN group were larger and more often endophytic than those in the LPN group.
- Authors also note that: 'We may have been more selective, thus introducing bias, when treating patients with LPN because of concerns over warm ischemia time and difficulty of intracorporeal suturing. Further, we began utilizing RF-RCPN later in our collective experience at which point we may have been more comfortable in attempting resection of larger and more complex tumors' (p. 389).

Study ID	Zini 2009a[53]
Country	USA, multi-centred (9 SEER cancer registries, representing 10% sample of USA population)
Funding	
Recruitment period	1988-2004
METHODS	
Type of study	Retrospective matched-pairs. For cancer-specific mortality, data for this review was taken from univariate matched competing-risks regression models after accounting for other-cause mortality. Matching was done for age, tumour size and year of either diagnosis or nephrectomy, as these variables represent independent predictors of cancer-specific mortality in multivariate competing-risk regression analyses.
Analysis	Survival: As above. Cumulative incidence plots for cancer-specific and other-cause mortality presented (probably Kaplan-Meier estimates) Surgical outcomes: not reported
Was treatment allocated by:	[ ] Randomisation? [ ] Quasi-randomisation? [ ] Health care decision makers? [ ] Participant preferences? [X] Unclear
(If prospective) What parts of the study were prospective?	[ ] Identification of participants? [ ] Assessment of baseline and intervention allocation? [ ] Assessment of outcomes? [ ] Generation of hypotheses?
PARTICIPANTS	
Inclusion criteria	2 kidney cancer diagnostic codes (international classification of Disease for Oncology 2nd ed) ICD-0-2,C64.9 and the 9th revision ICD-0-9,189, were used as inclusion criteria. pT1aN0M0; treated with partial or radical nephrectomy, tumour =/<4cm from 9 SEER registries.
Exclusion criteria	Upper tract transitional cell carcinoma; uteretic, non-cortical renal tumours (melanomas, sarcomas and lymphomas); patients before 1988 (i.e. tumour size unavailable); T3/4; any N; any M; unknown stage, tumour size >4cm, autopsy cases, pts who die before surgery, pts treated with thermal ablation or cryosurgery, patients who refused surgery.

INTERVENTION	
Group 1:	Non-surgical management. Surveillance or observation (non-ablative)
Group 2:	Surgery. Radical (N = 7650, 74.3%) or partial nephrectomy (2208, 21.4%); N and % reflect the original (unmatched) sample.

PARTICIPANTS: Numbers	**Group 1: Non surgical management**	**Group 2: Surgery**	**Group 3**
Number allocated (matched)	430	1545	
Number of dropouts	NA (database review)	NA (database review)	

Comments (e.g. surgeon experience):

- The effect of treatment type (NSM vs. nephrectomy) on RCC-specific and other cause mortality was assessed in two ways.
- First, they used univariable and multivariable competing-risks regression analyses to test the effect of treatment type on RCC-specific mortality after accounting for other-cause mortality. The covariates consisted of age, gender, tumour size and year of diagnosis or of nephrectomy.
- In 2nd part of analysis, they repeated univariate competing-risks regression analyses after matching for variables that were independent predictors for RCC specific mortality

Study ID	Zini 2009b[54]
Country	USA, multi-centred (9 SEER cancer registries)
Funding	
Recruitment period	1988 to 2004
METHODS	
Type of study	Retrospective matched pair. Matched for age (by decade), tumour size (within 1 cm), year of surgery (by decade) and Fuhrman grade.
Analysis	Survival: Kaplan-Meier estimates with log rank tests. Surgical outcomes: not reported
Was treatment allocated by:	[ ] Randomisation? [ ] Quasi-randomisation? [ ] Health care decision makers? [ ] Participant preferences? [X] Unclear
(If prospective) What parts of the study were prospective?	[ ] Identification of participants? [ ] Assessment of baseline and intervention allocation? [ ] Assessment of outcomes? [ ] Generation of hypotheses?
PARTICIPANTS	
Inclusion criteria	Patients with localized RCC (T1a, N0, M0)
Exclusion criteria	Patients with either locally advanced, metastatic or unknown stage
INTERVENTION	
Group 1:	Partial nephrectomy (PN); Unclear if it is open or laparoscopic.
Group 2:	Radical nephrectomy (RN); Unclear if it is open or laparoscopic.

PARTICIPANTS: Numbers	**Group 1: PN**	**Group 2: RN**	**Notes**
Number matched for age, tumour size, and year of surgery	2153	5616	
Number matched for all of the above and Fuhrman grade.	1283	3166	Data for this review were extracted from this population.
Number of dropouts	NA (database review)	NA (database review)	
Additional information (e.g. surgeon experience):			

Appendix 9: Assessment of risk of bias using a recommended tool by the Cochrane Collaboration (Higgins and Altman 2008, Cochrane Handbook Chapter 8)[26]

Study ID	Rando-mised?	Adequate sequence generation	Allocation conceal-ment	Blinding			Incomplete outcome data addressed			Free of selective outcome reporting	Free of other bias	Review board approval specified†
				Survival outcome	Surgical outcome	QoL outcome	Survival outcome	Surgical outcome	QoL outcome			
Blom 2009[15]	Yes	Yes	Yes	Unclear	Unclear	NA	Yes	Yes	NA	Yes	No	--
D'Armiento 1997[32]	Yes	Yes	Unclear	Unclear	NA	NA	No	NA	NA	Yes	Unclear	--
Desai 2005a[33]	Yes	Yes	Yes	No	No	NA	Yes	Yes	NA	Yes	Unclear	--
Nadler 2006[34]	Yes	No	No	No	No	NA	Yes	Yes	NA	Yes	Unclear	--
Nambirajan 2004[35]	Yes	Unclear	Unclear	Unclear	Unclear	NA	Yes	Yes	NA	Unclear	Unclear	--
Peng 2006[36]**	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	--
Van Poppel 2007[37]	Yes	Yes	Unclear	NA	Unclear	NA	NA	No	NA	Unclear	Unclear	--
Aron 2008[44]	No	No	No	NA	Unclear	NA	NA	Yes	NA	Yes	Unclear	No
Butler 1995[56]	No	No	No	Unclear	Unclear	NA	Yes	Yes	NA	Unclear	Unclear	No
Crepel 2010[45]	No	No	No	Unclear	NA	NA	Unclear	NA	NA	Unclear	Unclear	No
Dash 2006[57]	No	No	No	No	NA	NA	Yes	NA	NA	Unclear	Unclear	Yes
Desai 2005b[58]	No	No	No	No	No	NA	Unclear	Unclear	NA	Unclear	No	Yes
Gabr 2009[59]	No	No	No	Unclear	Unclear	NA	Yes	Unclear	NA	Unclear	Unclear	No
Gill 2007[67]	No	No	No	No	No	NA	No	No	NA	Unclear	Unclear	Yes

Study ID	Rando-mised?	Adequate sequence generation	Allocation conceal-ment	Blinding			Incomplete outcome data addressed			Free of selective outcome reporting	Free of other bias	Review board approval specified†
				Survival outcome	Surgical outcome	QoL outcome	Survival outcome	Surgical outcome	QoL outcome			
Gong 2008[46]	No	No	No	No	No	NA	No	No	NA	Unclear	Unclear	Yes
Gratzke 2009[60]	No	No	No	NA	No	No	NA	Yes	No	Yes	Unclear	Yes
Hemal 2007[38]	No	No	No	Unclear	Unclear	NA	Unclear	Yes	NA	Unclear	Unclear	No
Hemal 2009[39]	No	No	No	NA	Unclear	NA	NA	Yes	NA	Yes	Unclear	No
Herrlinger 1991[40]	No	No	No	No	NA	NA	Yes	NA	NA	Yes	Unclear	No
Huang 2009[61]	No	No	No	No	NA	NA	Unclear	NA	NA	Unclear	Unclear	No
Ko 2008[47]	No	No	No	No	No	NA	Yes	Yes	NA	Unclear	Unclear	No
Lane 2009[55]	No	No	No	No	NA	NA	Yes	NA	NA	Yes	Unclear	Yes
Lane 2010[62]	No	No	No	No	NA	NA	Yes	NA	NA	No	Unclear	Yes
Lee 2007[27]	No	No	No	No	NA	NA	Yes	NA	NA	Unclear	Unclear	No
Marszalek 2009[48]	No	No	No	No	No	NA	Yes	Yes	NA	Yes	Yes	Yes
O'Malley 2007[49]	No	No	No	NA	Unclear	NA	NA	Yes	NA	Yes	Unclear	Yes
Onishi 2007[41]	No	No	No	NA	NA	Unclear	NA	NA	Yes	Yes	No	No
Park 2009[50]*	No	No	No	NA	Unclear	NA	NA	Yes	NA	Unclear	Unclear	No
Patard 2004[63]	No	No	No	No	No	NA	Yes	Yes	NA	Yes	Unclear	No
Patard 2008[51]*	No	No	No	Unclear	NA	NA	Unclear	NA	NA	Unclear	Unclear	No

Study ID	Rando-mised?	Adequate sequence generation	Allocation conceal-ment	Blinding			Incomplete outcome data addressed			Free of selective outcome reporting	Free of other bias	Review board approval specified†
				Survival outcome	Surgical outcome	QoL outcome	Survival outcome	Surgical outcome	QoL outcome			
Poulakis 2003[42]	No	No	No	NA	NA	NA	NA	NA	NA	Unclear	Unclear	Yes
Shekarriz 2002[52]	No	No	No	NA	Unclear	NA	NA	Unclear	NA	Yes	Unclear	No
Simmons 2009[68]	No	No	No	Unclear	NA	NA	Unclear	NA	NA	Unclear	Unclear	Yes
Soga 2008[43]	No	No	No	NA	Unclear	NA	NA	Yes	NA	Unclear	Unclear	Yes
Thompson 2008[64]	No	No	No	Yes – Assessor	NA	NA	Unclear	NA	NA	Unclear	Unclear	Yes
Thompson 2009[69]	No	No	No	Unclear	NA	NA	Unclear	NA	NA	Unclear	Unclear	Yes
Weight 2010[65]	No	No	No	Unclear	NA	NA	Unclear	NA	NA	Unclear	Unclear	Yes
Wu 2010[66]	No	No	No	Unclear	Unclear	NA	Unclear	Unclear	NA	Unclear	Unclear	Yes
Zini 2009a[53]	No	No	No	No	NA	NA	Unclear	NA	NA	Unclear	Unclear	No
Zini 2009b[54]	No	No	No	No	NA	NA	Unclear	NA	NA	Unclear	Unclear	No

NA = not applicable (relevant outcome not reported); QoL = quality of life (self-reported)

* Abstract only;

** Full-text report in Chinese with abstract in English; The English translation of the main text was not available at the time of writing;

† Additional item for non-randomised studies only

Appendix 10: Baseline characteristics of included studies with the assessment of risk of bias (confounders)

Note: For the scoring guidelines used for assessing risk of bias (confounders) in non-randomised studies, see Appendix 5.

					*Pre-specified confounders for peri-operative outcomes in non-randomised studies**				*Pre-specified confounders for oncological outcomes and quality of life in non-randomised studies**			
Study, Year, Design, Confounder assessment	**Compa-rison**	**N**	**FU (months) mean (SD), *median [range]**	**Sex Male/ Female**	**Age: Mean (SD), *median [range]**	**Ethnicity**	**Performance status (ASA unless otherwise stated) N or Mean (SD) *median [range]**	**Co-morbidity**	**Clinical Tumour size (cm) Mean (SD), *median [range]**	**Pathological tumour stage**	**Tumour grade (Fuhrman unless stated)**	**Histological cell type**
Aron 2008,[44] USA	Robot Lap PN	12	7.4	M 8 F 4	64 (13.8)	NR	Mean 2 [1-3]	NR	2.4 (0.69)	NR	NR	NR
matched-pair	Lap PN	12	8.5	M 8 F 4	61 (13.8)	NR	Mean 2 [1-3]	NR	2.9 (0.77)	NR	NR	NR
Precision	NA	NA	NA	NA	1	5	3	5	NA	NA	NA	NA
Imbalance	NA	NA	NA	NA	1	5	1	5	NA	NA	NA	NA
Adjustment	NA	NA	NA	NA	1	5	1	5	NA	NA	NA	NA
Blom 2009,[15] Europe RCT subgroup analysis (note that baseline characteristics are considered randomised, as the randomisation process protects	RN + Lymph node dissection	271 (sub-group)	*151.2 (max 206.4) overall	M 140 (54.9%	58.7 (10.8) [28-84]	NR	WHO 0: 216 (84.7%) WHO 1: 31 (12.2%) WHO 2: 7 (2.7%) WHO 3: 1 (0.4%)	NR	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%)

					*Pre-specified confounders for peri-operative outcomes in non-randomised studies**				*Pre-specified confounders for oncological outcomes and quality of life in non-randomised studies**			
Study, Year, Design, Confounder assessment	**Compa-rison**	**N**	**FU (months) mean (SD), *median [range]**	**Sex Male/ Female**	**Age: Mean (SD), *median [range]**	**Ethnicity**	**Performance status (ASA unless otherwise stated) N or Mean (SD) *median [range]**	**Co-morbidity**	**Clinical Tumour size (cm) Mean (SD), *median [range]**	**Pathological tumour stage**	**Tumour grade (Fuhrman unless stated)**	**Histological cell type**
against indication biases present in observational studies)	RN	288 (sub-group)		M 172 (64.7%)	58.6 (11.6) [24-81]	NR	WHO 0: 232 (87.2%) WHO 1: 31 (11.7%) WHO 2: 3 (1.1%) WHO 3: 0	NR	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%)
Butler 1995,[56] USA (Cleveland clnic) Database review	Open PN	46	40 (26)	M 32 (70%), F 14 (30%)	60 (14)	NR	NR	Diabetes: 8 (17%), Hypertension: 29 (63%), Smoke: 24 (52%), Other: 8 (17%)	2.5 (0.8)	pT1 13 (28%), pT2 28 (61%), pT3a 5 (11%)	NR	NR
	Open RN	42	66 (30)	M 22 (52%), F 20 (48%)	64 (13)	NR	NR	Diabetes: 6 (14%), Hypertension: 20 (48%), Smoke: 13 (31%), Other: 6 (14%)	2.7 (0.8)	pT1 9 (21%), pT2 28 (67%), pT3a 5 (12%)	NR	NR
Precision	NA	NA	NA	NA	1	5	5	1	1	1	5	5
Imbalance	NA	NA	NA	NA	1	5	5	1	1	1	5	5
Adjustment	NA	NA	NA	NA	1	5	5	1	1	1	5	5

					*Pre-specified confounders for peri-operative outcomes in non-randomised studies**				*Pre-specified confounders for oncological outcomes and quality of life in non-randomised studies**			
Study, Year, Design, Confounder assessment	**Compa-rison**	**N**	**FU (months) mean (SD), *median [range]**	**Sex Male/ Female**	**Age: Mean (SD), *median [range]**	**Ethnicity**	**Performance status (ASA unless otherwise stated) N or Mean (SD) *median [range]**	**Co-morbidity**	**Clinical Tumour size (cm) Mean (SD), *median [range]**	**Pathological tumour stage**	**Tumour grade (Fuhrman unless stated)**	**Histological cell type**
Crépel 2010,[45] USA (SEER database) Matched-pair	Open or lap PN	163	34 (23)	M 99 (60.7%)	61 [25-84]	NR	NR	NR	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%)
	Open or lap RN	636	39.4 (26.5)	M 383 (60.2%)	61 [30-92]	NR	NR	NR	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%)
Precision	NA	NA	NA	NA	NA	NA	NA	NA	1	1	1	1
Imbalance	NA	NA	NA	NA	NA	NA	NA	NA	1	1	1	1
Adjustment	NA	NA	NA	NA	NA	NA	NA	NA	1	1	1	1
D'Armiento 1997,[32] Italy RCT	Open PN	19	70 (max 98)	M 14 F 5	51.4 (13.7) [23-74]	NR	NR	NR	3.34 (0.64)		G1 :11 G2: 7 G3:1	NR
	Open RN	21	70 (max 97)	M 13 F 8	48.7 (14.7) [27-76]	NR	NR	NR	3.21 (0.56)		G1: 10 G2: 8 G3: 3	NR

					*Pre-specified confounders for peri-operative outcomes in non-randomised studies**				*Pre-specified confounders for oncological outcomes and quality of life in non-randomised studies**			
Study, Year, Design, Confounder assessment	**Compa-rison**	**N**	**FU (months) mean (SD), *median [range]**	**Sex Male/ Female**	**Age: Mean (SD), *median [range]**	**Ethnicity**	**Performance status (ASA unless otherwise stated) N or Mean (SD) *median [range]**	**Co-morbidity**	**Clinical Tumour size (cm) Mean (SD), *median [range]**	**Pathological tumour stage**	**Tumour grade (Fuhrman unless stated)**	**Histological cell type**
Dash 2006,[57] USA (Sloan-Kettering) **Database review**	Open or lap PN	45	*21	M 32 (71%), F 13	56.7 (13)	NR	NR	Vascular invasion absent: 19 (42%), present: 1 (2%), unknown: 25 (56%)	4.85 (0.94)	pT1: 41 (91%) pT3: 4 (9%)	G1-2: 35 (78%), G3-4: 9 (20%), Unknown: 1 (2%)	All clear cell
	Open or lap RN	151	*21	M 99 (66%), F 52	63.1 (11.5)	NR	NR	Vascular invasion absent: 97 (64%), present: 6 (4%), unknown: 48 (32%)	5.42 (0.89)	pT1: 124 (82%) pT3: 27 (18%)	G1-2: 107 (71%), G3+4: 43 (28%), Unknown: 1 (1%)	All clear cell
Precision	NA	NA	NA	NA	NA	NA	NA	NA	1	1	1	1
Imbalance	NA	NA	NA	NA	NA	NA	NA	NA	2	2	1	1
Adjustment	NA	NA	NA	NA	NA	NA	NA	NA	1	1	1	1

					*Pre-specified confounders for peri-operative outcomes in non-randomised studies**				*Pre-specified confounders for oncological outcomes and quality of life in non-randomised studies**			
Study, Year, Design, Confounder assessment	**Compa-rison**	**N**	**FU (months) mean (SD), *median [range]**	**Sex Male/ Female**	**Age: Mean (SD), *median [range]**	**Ethnicity**	**Performance status (ASA unless otherwise stated) N or Mean (SD) *median [range]**	**Co-morbidity**	**Clinical Tumour size (cm) Mean (SD), *median [range]**	**Pathological tumour stage**	**Tumour grade (Fuhrman unless stated)**	**Histological cell type**
Desai 2005[a],[33] USA **RCT**	Rretro lap RN	52	13.5 (11.9) [0.5 – 40]	M 33 (64%)	64.5 (12.3) [29-89]	NR	2.8 (0.6) [1-4]	NR	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%); Other 0
	Trans lap RN	50	15 (6.2) [3-24]	M 26 (52%)	62.8 (13.3)[30-38]	NR	2.7 (0.6) [2-4]	NR	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%)

Desai 2005b,[58] USA **Data base review**	Lap cryo	78 (89 tumours)	24.6 [1-60]	M54 (69%), F24	65.55 (12.69) [28-88]	NR	≥3: 55	NR	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
	Lap PN	153 (153 tumours)	5.8 [1-36]	M89 (58%), F64	60.59 (13.19) [17-87]	NR	≥3: 71	NR	2.25 (0.67) [0.9-3]	All cT1	NR	RCC: 68% Benign: 32% Inconclusive: 0 Of the RCC (n = 104): Clear cell: 64 Papillary: 32 Other: 8
Precision	NA	NA	NA	NA	1	5	1	5	1	1	5	1
Imbalance	NA	NA	NA	NA	1	5	2	5	1	1	5	1
Adjustment	NA	NA	NA	NA	1	5	5	5	1	1	5	1
Gabr 2009b,[59] USA (University of Michigan Health **(System) database review**	Hand-assisted lap RN	108	Overall 35.2 (25) [0.3-114]; *30 mos	M 73 F 35	61.3 (12.7)	NR	≥3: 49	NR	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%)

					*Pre-specified confounders for peri-operative outcomes in non-randomised studies**				*Pre-specified confounders for oncological outcomes and quality of life in non-randomised studies**			
Study, Year, Design, Confounder assessment	**Compa-rison**	**N**	**FU (months) mean (SD), *median [range]**	**Sex Male/ Female**	**Age: Mean (SD), *median [range]**	**Ethnicity**	**Performance status (ASA unless otherwise stated) N or Mean (SD) *median [range]**	**Co-morbidity**	**Clinical Tumour size (cm) Mean (SD), *median [range]**	**Pathological tumour stage**	**Tumour grade (Fuhrman unless stated)**	**Histological cell type**
	Lap RN (trans- or retro-perito-neal)	147		M 81 F 56	62.7 (12.9)	NR	≥3: 52 P = 0.12	NR	4.9 (21.9) p = <0.001	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
Precision	NA	NA	NA	NA	1	5	1	5	1	1	1	1
Imbalance	NA	NA	NA	NA	1	5	1	5	2	2	1	1
Adjustment	NA	NA	NA	NA	1	5	1	5	1	1	1	1
Gill 2007,[67] USA (Cleveland Clinic, Mayo Clinic and John Hopkins university)	Lap PN	771	*14.4 [0, 84]	M 442 F 329	59.4 [19-87]	NR	≥3: 336/732 (45.9%) ECOG ≥1: 11/771 (1.4%)	Smoking history: 127 N of solitary kidney: 32	2.6 [0.4-8] (pathological)	68/771 (8.8%) cT1b Otherwise cT1a	NR	NR
database review	Open PN	1029	*33.6 [0, 91.2]	M 724 F 305	61.6 [25.7-94.0]	NR	≥3: 398/525 (75.8%) ECOG ≥1:133/903 (14.7%)	Smoking history: 417 N of solitary kidney: 222	3.3 [0.13-9.0] (pathological)	323/1029 (31.4%) cT1b Otherwise cT1a	NR	NR
Precision1	NA	NA	NA	NA	3	5	1	5	3	1	5	5
Imbalance	NA	NA	NA	NA	1	5	5	5	2	2	5	5
Adjustment	NA	NA	NA	NA	1	5	5	5	5	5	5	5

					*Pre-specified confounders for peri-operative outcomes in non-randomised studies**				*Pre-specified confounders for oncological outcomes and quality of life in non-randomised studies**			
Study, Year, Design, Confounder assessment	**Compa-rison**	**N**	**FU (months) mean (SD), *median [range]**	**Sex Male/ Female**	**Age: Mean (SD), *median [range]**	**Ethnicity**	**Performance status (ASA unless otherwise stated) N or Mean (SD) *median [range]**	**Co-morbidity**	**Clinical Tumour size (cm) Mean (SD), *median [range]**	**Pathological tumour stage**	**Tumour grade (Fuhrman unless stated)**	**Histological cell type**
Gong 2008,[46] USA **Design: matched-pair**	Lap PN	76	21.7 (25.6)	M 35 (46.1%) F 41 (53.9%)	60.1 (12.5)	NR	NR	NR	2.87 (0.81)	Benign: 21 (27.6%), pT1a: 53 (69.7%) pT1b: 2 (2.6%) pT2: 0	NR	NR
	Open PN	77	20.6 (23.1)	M 42 (54.5%) F 35 (45.5%)	57.7 (13.6)	NR	NR	NR	2.45 (0.87)	Benign: 17 (22.1%) pT1a: 50 (64.9%) pT1b: 9 (11.7%) pT2:1 (1.3%)	NR	NR
Precision	NA	NA	NA	NA	1	5	5	5	1	1	5	5
Imbalance	NA	NA	NA	NA	1	5	5	5	1	1	5	5
Adjustment	NA	NA	NA	NA	1	5	5	5	1	1	5	5
Gratzke 2009,[60] Germany and Switzerland **Design: Database review (QoL evaluated prospectively)**	Lap RN	36	Mean 22 months, range 11-71	M 23 (64%)	67.8 (12.8)	NR	1: 0 2: 20 (56%) 3: 16 (44%) 4: 0	NR	NR	pT1a 12 (42%) pT1b 17 (38%) pT2 0 pT3 4 (10%)	NR	NR
	Open PN	44		M 29 (66%)	60.7 (12.4)	NR	1: 2 (4%) 2: 30 (67%) 3: 12 (26%) 4: 1 (2%)	NR	NR	pT1a :35 (80%) pT1b: 6 (14%) pT2: 1 (2%) pT3: 0 missing: 2	NR	NR
	Open RN	37		M 23 (62%)	61.1 (12.7)	NR	1: 3 (8%) 2: 21 (57%) 3: 13 (35%) 4: 0	NR	NR	pT1a: 9 (24%); pT1b: 20 (54%) pT2: 8 (22%) pT3: 0	NR	NR
Precision	NA	NA	NA	NA	1	5	1	5	5	1	5	5
Imbalance	NA	NA	NA	NA	2	5	1	5	5	2	5	5

					*Pre-specified confounders for peri-operative outcomes in non-randomised studies**				*Pre-specified confounders for oncological outcomes and quality of life in non-randomised studies**			
Study, Year, Design, Confounder assessment	**Compa-rison**	**N**	**FU (months) mean (SD), *median [range]**	**Sex Male/ Female**	**Age: Mean (SD), *median [range]**	**Ethnicity**	**Performance status (ASA unless otherwise stated) N or Mean (SD) *median [range]**	**Co-morbidity**	**Clinical Tumour size (cm) Mean (SD), *median [range]**	**Pathological tumour stage**	**Tumour grade (Fuhrman unless stated)**	**Histological cell type**
Adjustment	NA	NA	NA	NA	5	5	1	5	5	5	5	5
Hemal 2007,[38] India	Lap RN	41	51.4 [3, 78]	24/17	52.5 (11.3)	NR	ASA 1.95 (0.95)	NR	9.9 (2.2)	All T2	NR	NR
prospective cohort	Open RN	71	57.2 [4, 80]	47/24	52.7 (11.8)	NR	ASA 1.75 (0.745)	NR	10.1 (3.2)	All T2	NR	NR
Precision	NA	NA	NA	NA	1	5	1	5	1	1	5	5
Imbalance	NA	NA	NA	NA	1	5	1	5	1	1	5	5
Adjustment	NA	NA	NA	NA	1	5	1	5	1	1	5	5
Hemal 2009,[39] India	Robot RN	15	8.3 [1-12]	M8, F7	50.3 (10.2)	NR	NR	NR	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
prospective cohort	Lap RN	15	9.1 [2-12]	M6, F9	52.7 (11.8)	NR	NR	NR	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
Precision	NA	NA	NA	NA	1	5	5	5	1	1	1	1
Imbalance	NA	NA	NA	NA	1	5	5	5	1	1	1	1
Adjustment	NA	NA	NA	NA	1	5	5	5	1	1	1	1

					*Pre-specified confounders for peri-operative outcomes in non-randomised studies**				*Pre-specified confounders for oncological outcomes and quality of life in non-randomised studies**			
Study, Year, Design, Confounder assessment	**Compa-rison**	**N**	**FU (months) mean (SD), *median [range]**	**Sex Male/ Female**	**Age: Mean (SD), *median [range]**	**Ethnicity**	**Performance status (ASA unless otherwise stated) N or Mean (SD) *median [range]**	**Co-morbidity**	**Clinical Tumour size (cm) Mean (SD), *median [range]**	**Pathological tumour stage**	**Tumour grade (Fuhrman unless stated)**	**Histological cell type**
Herrlinger 1991,[40] Germany	RN + syste-matic lymph node dissection	109 (sub-group)	48-251 overall	NR	<72 (overall)	NR	NR	NR	NR	T1-2N0M0	NR	NR
prospective cohort	RN + facul-tative lymph node dissection	82 (sub-group)		NR		NR	NR	NR	NR	T1-2N0M0	NR	NR
Precision	NA	NA	NA	NA	NA	NA	NA	NA	5	1	5	5
Imbalance	NA	NA	NA	NA	NA	NA	NA	NA	5	1	5	5
Adjustment	NA	NA	NA	NA	NA	NA	NA	NA				
Huang 2009,[61] USA (SEER database) **Database review**	Open or lap PN	556	43 overall; 48 in pts who were alive at end of FU.	M351 (63%), F204	66-69: 155 (28%) 70-74: 189 (34%) 75-79: 144 (26%) 80-84: 59 (11%) 85+: 9 (1%)	NR	NR	Diabetes: 163/556, Acute myocardinal infarction (MI): 50/556, Congestive heart failure (CHF): 123/556 Cardiovascular disease: 70/556, Vascular disease: 117/556, Renal insufficiency: 69/556 Hypertension: 135/556	<4cm	All T1a	NR	NR

					*Pre-specified confounders for peri-operative outcomes in non-randomised studies**				*Pre-specified confounders for oncological outcomes and quality of life in non-randomised studies**			
Study, Year, Design, Confounder assessment	**Compa-rison**	**N**	**FU (months) mean (SD), *median [range]**	**Sex Male/ Female**	**Age: Mean (SD), *median [range]**	**Ethnicity**	**Performance status (ASA unless otherwise stated) N or Mean (SD) *median [range]**	**Co-morbidity**	**Clinical Tumour size (cm) Mean (SD), *median [range]**	**Pathological tumour stage**	**Tumour grade (Fuhrman unless stated)**	**Histological cell type**
	Open or lap RN	2435	21*	M1363 (56%), F1074	66-69: 536 (22%) 70-74: 747 (31%) 75-79: 671 (28%) 80-84: 364 (15%) 85+: 117 (4%)	NR	NR	Diabetes: 647/2435, Acute MI: 200/2435, CHF: 581/2435, Cardiovascular disease: 404/2435, Vascular disease: 516/2435, Renal insufficiency: 205/2435, Hypertension: 546/2435	<4cm	All T1a	NR	NR
Precision	NA	NA	NA	NA	NA	NA	NA	NA	3	5	5	5
Imbalance	NA	NA	NA	NA	NA	NA	NA	NA	1	5	5	5
Adjustment	NA	NA	NA	NA	NA	NA	NA	NA	1	5	5	5
Ko 2008,[47] Korea **Matched-pair**	Lap cryo-ablation	20 (21 tumours)	27.3 (10.8)	M 14 F6	56.3 (11.5) [24-76]	NR	1: 5 2: 7 3: 7 4: 1	NR	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)
	Open PN	20 (20 tumours)	28.7 (14.9)	M 15 F 5	57.6 (10.9) [44-77]	NR	1: 8, 2: 9 3: 3 4: 0	NR	2.16 (1.08) [1.3, 3.9]	pT1	G1: 4, G2: 15, G3: 0, G4: 1	Non-clear type = 1 (papillary type 2)

					*Pre-specified confounders for peri-operative outcomes in non-randomised studies**				*Pre-specified confounders for oncological outcomes and quality of life in non-randomised studies**			
Study, Year, Design, Confounder assessment	**Compa-rison**	**N**	**FU (months) mean (SD), *median [range]**	**Sex Male/ Female**	**Age: Mean (SD), *median [range]**	**Ethnicity**	**Performance status (ASA unless otherwise stated) N or Mean (SD) *median [range]**	**Co-morbidity**	**Clinical Tumour size (cm) Mean (SD), *median [range]**	**Pathological tumour stage**	**Tumour grade (Fuhrman unless stated)**	**Histological cell type**
Precision	NA	NA	NA	NA	1	5	1	5	1	1	1	1
Imbalance	NA	NA	NA	NA	1	5	2	5	1	1	1	1
Adjustment	NA	NA	NA	NA	1	5	5	5	1	1	1	1
Lane 2009[55] **Database review**	PN + adrena-lectomy	48	*74.4 [IQR 26.4, 105.6]	M: 27 (56%)	*62 [IQR 56-69]	NR	NR	NR	*3.8 [IQR 2.5-5.5]	T0 = 10 (21%) T1a = 21 (44%) T1b = 8 (17%) T2or > = 9 (19%)	NR	Conventional RCC: 30 (63%) Other Cancer (papillary, chromophobe etc): 8 (17%) Benign: 10 (21%)
	PN	2017	*66 [IQR 34.8, 108]	M: 1324 (66%)	*61 [IQR 51-70]	NR	NR	NR	*3.6 [IQR 2.6-5.0]	T0 = 314 (19%) T1a = 940 (56%) T1b = 310 (19%) T2or > = 100 (6%)	NR	Conventional RCC: 1150 (63%) Other Cancer (papillary, chromophobe etc): 351 (19%) Benign: 314 (17%)
Precision	NA	NA	NA	NA	NA	NA	NA	NA	1	1	5	1
Imbalance	NA	NA	NA	NA	NA	NA	NA	NA	1	2	5	1
Adjustment	NA	NA	NA	NA	NA	NA	NA	NA	1	5	5	1

					*Pre-specified confounders for peri-operative outcomes in non-randomised studies**				*Pre-specified confounders for oncological outcomes and quality of life in non-randomised studies**			
Study, Year, Design, Confounder assessment	**Compa-rison**	**N**	**FU (months) mean (SD), *median [range]**	**Sex Male/ Female**	**Age: Mean (SD), *median [range]**	**Ethnicity**	**Performance status (ASA unless otherwise stated) N or Mean (SD) *median [range]**	**Co-morbidity**	**Clinical Tumour size (cm) Mean (SD), *median [range]**	**Pathological tumour stage**	**Tumour grade (Fuhrman unless stated)**	**Histological cell type**
Lane 2010,[62] USA (Cleveland Clinic) **Database review**	Lap PN	672	* 48 [IQR 39.6, 81.6]	M 395 F 277	* 61 [IQR 51-69]	Caucasian 613 (92%) African-American 33 (4.9%) Other 26 (3.9)	*2 [IQR 2-3]	NR	Median 2.6 [IQR 2.0-3.4]	pT1a 425 (85%) pT1b 42 (8.4%) pT2+ 32 (6.4%)	I/II: 332 (70%) III/IV: 148 (30%)	Clear cell 324 (48%) Papillary (17%) Chromophobe (8%) Other (1.2%) Benign 173 (26%)
	Open PN	944	*68.4 [IQR 46.8, 87.6]	M 626 F 318	* 61 [IQR 52-70]	Caucasian 825 (87%) African-American 65 (6.8%) Other 54 (5.7%)	*2 [IQR 2-3]	NR	Median 3.5 [IQR 2.5-4.5]	pT1a 510 (67%) pT1b 193 (25%) pT2+ 58 (7.6%)	I/II: 481 (64%) III/IV: 286 (36%)	Clear cell 554 (59%) Papillary (14%) Chromophobe (6%) Other (1.8%) Benign 182 (19%)
Precision	NA	NA	NA	NA	1	1	1	5	1	1	1	1
Imbalance	NA	NA	NA	NA	1	1	1	5	1	1	1	1
Adjustment	NA	NA	NA	NA	1	1	1	5	1	1	1	1
Lee 2007,[27] Korea	Open PN	56	37.1 (26.1)	M 48 F8 (14%)	51.8 (11.7)	NR	NR	HT: 14 DM: 13	2.5 (0.8)	Al pT1a	G1: 3 G2: 34 G3: 19	NR
Matched-pair	Open RN	56	39 (20.37)	M 42 F 14 (25%)	52.5 (11.0)	NR	NR	HT: 21 DM: 11	2.5 (0.8)	Al pT1a	G1: 2 G2: 37 G3: 17	NR
Precision	NA	NA	NA	NA	1	5	5	1	1	1	1	5
Imbalance	NA	NA	NA	NA	1	5	5	1	1	1	1	5
Adjustment	NA	NA	NA	NA	1	5	5	1	1	1	1	5

					*Pre-specified confounders for peri-operative outcomes in non-randomised studies**				*Pre-specified confounders for oncological outcomes and quality of life in non-randomised studies**			
Study, Year, Design, Confounder assessment	**Compa-rison**	**N**	**FU (months) mean (SD), *median [range]**	**Sex Male/ Female**	**Age: Mean (SD), *median [range]**	**Ethnicity**	**Performance status (ASA unless otherwise stated) N or Mean (SD) *median [range]**	**Co-morbidity**	**Clinical Tumour size (cm) Mean (SD), *median [range]**	**Pathological tumour stage**	**Tumour grade (Fuhrman unless stated)**	**Histological cell type**
Marszalek 2009,[48] Austria **Matched-pair**	Lap PN	100	44.4 (SE 2.4) [19.2, 110.4]	M 60 F 40	62.3 [22.9-83.4]	NR	NR	NR	* 2.8, IQR [2.0;3.2]	pT1	NR	Of the malignant tumours (n = 81): Clear cell: 52 (64.2%), Papillary: 15 (18.5%), Other: 14 (17.3%). Benign = 19/100
	Open PN	100	42 (SE 2.4) [12, 117.6]	M 60 F 40	62.5 [21.9-84.6]	NR	NR	NR	* 2.9, IQR [2.3;3.5]	pT1	NR	Of the malignant tumours (n = 66) Clear cell : 49 (74.2%), Papillary: 10 (15.2%), Other: 7 (10.6%). Benign: 34/100
Precision	NA	NA	NA	NA	3	5	5	5	1	1	5	1
Imbalance	NA	NA	NA	NA	1	5	5	5	1	1	5	1
Adjustment	NA	NA	NA	NA	1	5	5	5	1	1	5	1

					*Pre-specified confounders for peri-operative outcomes in non-randomised studies**				*Pre-specified confounders for oncological outcomes and quality of life in non-randomised studies**			
Study, Year, Design, Confounder assessment	**Compa-rison**	**N**	**FU (months) mean (SD), *median [range]**	**Sex Male/ Female**	**Age: Mean (SD), *median [range]**	**Ethnicity**	**Performance status (ASA unless otherwise stated) N or Mean (SD) *median [range]**	**Co-morbidity**	**Clinical Tumour size (cm) Mean (SD), *median [range]**	**Pathological tumour stage**	**Tumour grade (Fuhrman unless stated)**	**Histological cell type**
Nadler 2006,[34] USA	Hand-assisted lap RN	11	Median 20 [0-51]	NR	Mean 61 [42-85]	NR	ASA 2.2 (0.4)	NR	NR	Clinical T1	NR	NR
Q-RCT	Retro lap RN	11		NR	Mean 63 [50-86]	NR	ASA 2.5 [0.5]	NR	NR	Clinical T1	NR	NR
	Trans lap RN	11		NR	Mean 57 [42-58]	NR	ASA 2.1. (0.8)	NR	NR	Clinical T1	NR	NR
Nambirajan 2004,[35] Austria	Rretro lap RN	20	15 [6-26]	M9, F11 (55%)	Mean 66.8 [43-82]	NR	ASA 2.35	NR	4.29 (1.83)	pT1 = 17, pT2 = 0, pT3a = 2, pT3b = 0, benign =1	NR	NR
QRCT	Trans lap RN	20	17 [6-16]	M12, F8 (40%)	Mean 62.2 [41-80]	NR	ASA 2.05	NR	4.58 (1.56)	pT1 = 12, pT2 = 2, pT3a = 2, pT3b = 3, benign =1	NR	NR
O'Malley 2007,[49] USA	Lap cryo-ablation	15	11.9 (7.2)	M 9 (57%), F 6 (43%)	76.1 (4.5)	NR	≥3: 9	>1 comorbid: 7	2.7 (1.3)	All T1	NR	NR
Matched-pair	Lap PN	15	9.83 (8.8)	M 12 (79%) F 3 (21%)	75.7 (4.6)	NR	≥3: 8	>1 comorbid: 7	2.5 (1)	All T1	NR	NR
Precision	NA	NA	NA	NA	1	5	1	1	1	1	5	5
Imbalance	NA	NA	NA	NA	1	5	1	1	1	1	5	5
Adjustment	NA	NA	NA	NA	1	5	1	1	1	1	5	5
Onishi 2007,[41] Japan	Radio-frequency ablation	20	6	M 5 F 15	65.9 [43-85]	NR	NR	NR	2.4 (0.6)	T1a	NR	NR

					*Pre-specified confounders for peri-operative outcomes in non-randomised studies**				*Pre-specified confounders for oncological outcomes and quality of life in non-randomised studies**			
Study, Year, Design, Confounder assessment	**Compa-rison**	**N**	**FU (months) mean (SD), *median [range]**	**Sex Male/ Female**	**Age: Mean (SD), *median [range]**	**Ethnicity**	**Performance status (ASA unless otherwise stated) N or Mean (SD) *median [range]**	**Co-morbidity**	**Clinical Tumour size (cm) Mean (SD), *median [range]**	**Pathological tumour stage**	**Tumour grade (Fuhrman unless stated)**	**Histological cell type**
Prospective cohort	Lap RN	17	6	M 5 F 12	53 [35-75]	NR	NR	NR	2.4 (0.7)	T1a	NR	NR
Precision	NA	NA	NA	NA	1	5	5	5	1	1	5	5
Imbalance	NA	NA	NA	NA	1	5	5	5	1	1	5	5
Adjustment	NA	NA	NA	NA	1	5	5	5	1	1	5	5
Park 2009,[50] Korea **Matched-pair**	Lap single-site RN	9	NR	Matched No data	Matched No data	NR	NR	NR	Matched No data	NR	NR	NR
	Lap RN	18	NR			NR	NR	NR		NR	NR	NR
Precision	NA	NA	NA	NA	5	5	5	5	NA	NA	NA	NA
Imbalance	NA	NA	NA	NA	5	5	5	5	NA	NA	NA	NA
Adjustment	NA	NA	NA	NA	1	5	5	5	NA	NA	NA	NA
Patard 2004,[63] USA, Europe **Database review**	Open or lap PN	379 pT1a; 314; pT1b 65	50.7 (40.3);	M 253 (66.8%); F 126 (33.2%)	59.7 (12.3)	NR	EOCG 1 or more: T1a: 35 (11.1%); T1b: 16 (24.6%)	NR	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%)
	Open or lap RN	1075 pT1a 499; pT1b 576	66.6 (54.2)	M 692 (64.4%); F 383 (35.6%)	60 (12.4)	NR	EOCG 1 or more: T1a: 70 (14.7%); T1b 129 (22.4%)	NR	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%)
Precision	NA	NA	NA	NA	NA	NA	NA	NA	1	1	1	1
Imbalance	NA	NA	NA	NA	NA	NA	NA	NA	1	1	1	1

					*Pre-specified confounders for peri-operative outcomes in non-randomised studies**				*Pre-specified confounders for oncological outcomes and quality of life in non-randomised studies**			
Study, Year, Design, Confounder assessment	**Compa-rison**	**N**	**FU (months) mean (SD), *median [range]**	**Sex Male/ Female**	**Age: Mean (SD), *median [range]**	**Ethnicity**	**Performance status (ASA unless otherwise stated) N or Mean (SD) *median [range]**	**Co-morbidity**	**Clinical Tumour size (cm) Mean (SD), *median [range]**	**Pathological tumour stage**	**Tumour grade (Fuhrman unless stated)**	**Histological cell type**
Adjustment	NA	NA	NA	NA	NA	NA	NA	NA	1	1	1	1
Patard 2008,[51] Europe (multi-institutional)	Open or lap PN	289	Mean 54 overall	NR	59.3	NR	NR	NR	5.47	pT1a: 273 (94.5%), pT2: 16	G1-2: 234 (81%)	NR
Matched-pair	Open or lap RN	257		NR	61	NR	NR	NR	5.5	pT1a: 241 (93.8%) pT2: 16	G1-2: 204 (79.4%)	NR
Precision	NA	NA	NA	NA	NA	NA	NA	NA	1	1	1	5
Imbalance	NA	NA	NA	NA	NA	NA	NA	NA	1	1	1	5
Adjustment	NA	NA	NA	NA	NA	NA	NA	NA	1	1	1	5
Peng 2006,[36] China	Lap RN	27	[6-12]	M 15 F 12	50.67 (15.46)	NR	NR	NR	4.2	T1: 10 T2 :17	NR	clear cell :17
RCT	Open RN	26	[6-12]	M 15 F 11	52.53 (15.12)	NR	NR	NR	4.5	T1 :11 T2: 15	NR	clear cell: 14
Poulakis 2003,[42] Germany **Prospective cohorts**	Open PN	29 (sub-group)	*20 [14-27]	NR	No baseline data for subgroups	NR	NR	NR	NR	NR	NR	NR
	Open RN	22 (sub-group)		NR	No baseline data for subgroups	NR	NR	NR	NR	NR	NR	NR
Precision	NA	NA	NA	NA	NA	NA	NA	NA	5	5	5	5
Imbalance	NA	NA	NA	NA	NA	NA	NA	NA	5	5	5	5
Adjustment	NA	NA	NA	NA	NA	NA	NA	NA	5	5	5	5

					*Pre-specified confounders for peri-operative outcomes in non-randomised studies**				*Pre-specified confounders for oncological outcomes and quality of life in non-randomised studies**			
Study, Year, Design, Confounder assessment	**Compa-rison**	**N**	**FU (months) mean (SD), *median [range]**	**Sex Male/ Female**	**Age: Mean (SD), *median [range]**	**Ethnicity**	**Performance status (ASA unless otherwise stated) N or Mean (SD) *median [range]**	**Co-morbidity**	**Clinical Tumour size (cm) Mean (SD), *median [range]**	**Pathological tumour stage**	**Tumour grade (Fuhrman unless stated)**	**Histological cell type**
Shekarriz 2002,[52] USA **Matched-pair**	Open PN	60	NR	NR	62 [40-76]	NR	NR	NR	3.8 (2.46)	pT1: 13 pT2: 38 pT3a: 9	G1: 14 G2: 31 G3: 13 G4: 2	Clear cell: 92/120 (80%), papillary: 17/120 (14%). Not split by intervention.
	Open RN	60	NR	NR	65 [46-81]				4.2 (1.9)	pT1: 13 pT2; 38 pT3a: 9	G1: 4 G2: 34 G3: 19 G4: 3	
Precision	NA	NA	NA	NA	3	5	5	5	NA	NA	NA	NA
Imbalance	NA	NA	NA	NA	1	5	5	5	NA	NA	NA	NA
Adjustment	NA	NA	NA	NA	1	5	5	5	NA	NA	NA	NA
Simmons 2009,[68] Database review	Lap PN	35	* 44 (27-85)	M 26 (74%) F 9 (26%)	63.5 (12)	NR	2.7 (0.5)	NR	4.6 (4.1-7.5)	pT1b: 29 (83%) pT2: 1 (3%) pT3a: 3 (9%) pT3b: 2 (6%)	Mean (SD): 2.3 (0.6); G 1: 2 (6%); G 2: 20 (57%); G 3: 12 (34%); G 4: 1 (3%)	Clear cell: 23 (66%); Papillary: 12 (33%); Chromophobe: 0; Unspecified: 0
	Lap RN	75	*57 (27-79)	M 39 (52%) F 36 (48%)	63.4 (12)	NR	2.6 (0.6)	NR	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%)
Precision 1	NA	NA	NA	NA	1	5	1	5	1	1	1	1
Imbalance 1	NA	NA	NA	NA	1	5	1	5	2	2	2	2
Adjustment 1	NA	NA	NA	NA	1	5	1	5	5	5	5	5

Soga 2008,[43] Japan **Prospective cohort**	Portless lap RN	14	* 7.1 [2.7, 17.3]	M 8 F 6	57 (13.5)	NR	All WHO <2	NR	3.72 (1.39) [1.6-6.9]	All cT1	NR	clear cell : 12, microtubular spindle: 1, oncocytoma: 1
	Lap RN	15	* 27.2 [19.5, 39.1]	M 11 F 4	53.7 (15)	NR	All WHO <2	NR	3.13 (0.77) [2.4-4.4]	All cT1	NR	no data
Precision	NA	NA	NA	NA	1	5	1	5	1	1	5	5
Imbalance	NA	NA	NA	NA	1	5	1	5	1	1	5	5
Adjustment	NA	NA	NA	NA	1	5	1	5	1	1	5	5
Thompson 2008,[64] USA (Mayo Clinic) **Database review**	Open or lap PN	358 (including 187 who were younger than age 65)	* 67.2 [range 8.4-211.2]	M 253 (70.7%) F 105 (29%)	*64 [26-94	NR	In 558/648 patients: EOCG 0 = 280/307 (91.2%); > 0 = 27/307 (8.8%)	DM: 28/305 (9.2%) Charlson-Romano Index (in 555/648 patients): Median 1 [range 0-8]	* 2.5 [0.2-4]	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 tumour 79 (22.1%)
	Open or lap RN	290 (including 140 who were younger than age 65)	*112.8 [range 1.2-207.6]	M 176 (60.7%) F 114 (39.3%)	*65 [24-85]		In 558/648 patients: EOCG 0 = 218/251 (86.9%); >0 = 33/251 (13.1%)	DM: 13/250 (5.2%) Charlson-Romano Index (in 555/648 patients): Median 1 [range 0-8]	* 3 [0.2-4] P<0.001	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%)
Precision	NA	NA	NA	NA	NA	NA	NA	NA	1	1	5	1
Imbalance	NA	NA	NA	NA	NA	NA	NA	NA	1	1	5	1

					*Pre-specified confounders for peri-operative outcomes in non-randomised studies**				*Pre-specified confounders for oncological outcomes and quality of life in non-randomised studies**			
Study, Year, Design, Confounder assessment	**Compa-rison**	**N**	**FU (months) mean (SD), *median [range]**	**Sex Male/ Female**	**Age: Mean (SD), *median [range]**	**Ethnicity**	**Performance status (ASA unless otherwise stated) N or Mean (SD) *median [range]**	**Co-morbidity**	**Clinical Tumour size (cm) Mean (SD), *median [range]**	**Pathological tumour stage**	**Tumour grade (Fuhrman unless stated)**	**Histological cell type**
Adjustment	NA	NA	NA	NA	NA	NA	NA	NA	1	1	5	1
Thompson 2009,[69] USA **Database review**	Open or lap PN	286	*40.8[0-204]	M 196 (68%)	<65y 164 (57%) ≥65y 122 (43%)	NR	NR	Charleson 0: 113 (45%) >0: 139 (55%)	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%) Benign: 38 (13%)
	Open or lap RN	873	*63.6 [0-228]	M 538 (62%)	<65 422 (48%) 65/> 451 (52%)	NR	NR	Charleson 0: 341 (43%) >0: 459 (57%)	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%)
Precision	NA	NA	NA	NA	NA	NA	NA	NA	1	1	5	1
Imbalance	NA	NA	NA	NA	NA	NA	NA	NA	1	1	5	2
Adjustment	NA	NA	NA	NA	NA	NA	NA	NA	1	1	5	5

					*Pre-specified confounders for peri-operative outcomes in non-randomised studies**				*Pre-specified confounders for oncological outcomes and quality of life in non-randomised studies**			
Study, Year, Design, Confounder assessment	**Compa-rison**	**N**	**FU (months) mean (SD), *median [range]**	**Sex Male/ Female**	**Age: Mean (SD), *median [range]**	**Ethnicity**	**Performance status (ASA unless otherwise stated) N or Mean (SD) *median [range]**	**Co-morbidity**	**Clinical Tumour size (cm) Mean (SD), *median [range]**	**Pathological tumour stage**	**Tumour grade (Fuhrman unless stated)**	**Histological cell type**
Van Poppel 2007,[37] EU, USA, Canada **RCT**	Open PN	268	NR	M 178 (66.4%), F 87 (32.5%), missing 3 (1.1%)	≤60: 117 (43.7%), 61-70: 93 (34.7%), >70: 58 (21.6%)	NR	NR	NR	<4cm: 216 (80.6%) 4.1-5cm: 49 (18.3%) missing: 3 (1.1%)	pT0: 7 (206%) pT1: 123 (45.9%) pT2: 115 (42.9%) pT3: 13 (4.9%) pTx: 4 (1.5%) Missing: 6 (2.2%)	G0: 20 (7.5%), G1-2: 195 (72.8%), G3-4: 21 (7.9%), Gx: 24 (9%), missing: 8 (3%)	Of the malignant RCC tumours (n = 227) Clear cell: 193 (72%), Chromophilic: 25 (9.3%), Chromophobe: 7 (2.6%), Sarcomatiod: 2 (0.7%), Collecting duct: 0
	Open RN	273	NR	M 178 (65.2%), F 91 (33.3%), missing 4 (1.5%)	≤ 60: 123 (45.1%), 61-70: 95 (34.8%), >70: 55 (20.1%)	NR	NR	NR	<4cm: 216 (84.6%) 4.1-5cm: 38 (13.9%) missing: 4 (1.5%)	pT0:10 (3.7%) pT1: 131 (48.0%) pT2: 100 (36.6%) pT3: 15 (5.5%) pTx: 6 (2.2%) Missing: 11 (4.0%)	G0: (8.1%) G1-2: (70.7%) G3-4: 9.6% Gx: 7.3% Missing: 4.4%	Of the malignant RCC tumours (n = 228) Clear cell: 174 (63.7%), Chromophilic: 37 (13.6%), Chromophobe: 13 (4.8%), Sarcomatiod: 2 (0.7%), Collecting duct: 2 (0.7%)

					*Pre-specified confounders for peri-operative outcomes in non-randomised studies**				*Pre-specified confounders for oncological outcomes and quality of life in non-randomised studies**			
Study, Year, Design, Confounder assessment	**Compa-rison**	**N**	**FU (months) mean (SD), *median [range]**	**Sex Male/ Female**	**Age: Mean (SD), *median [range]**	**Ethnicity**	**Performance status (ASA unless otherwise stated) N or Mean (SD) *median [range]**	**Co-morbidity**	**Clinical Tumour size (cm) Mean (SD), *median [range]**	**Pathological tumour stage**	**Tumour grade (Fuhrman unless stated)**	**Histological cell type**
Weight 2010,[65] USA (SEER database) **Database review**	Open or lap PN	524	Median 46 [IQR 25, 75]	M361 (69%), F163	Mean 63 [IQR 53, 71]	NR	NR	Charlson Romano index 0-1 = 386/517 (74.7%), 2 or greater =131/517 (25.3%); missing 7 Solitary kidney 130/524 (24.8%)	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%)

					*Pre-specified confounders for peri-operative outcomes in non-randomised studies**				*Pre-specified confounders for oncological outcomes and quality of life in non-randomised studies**			
Study, Year, Design, Confounder assessment	**Compa-rison**	**N**	**FU (months) mean (SD), *median [range]**	**Sex Male/ Female**	**Age: Mean (SD), *median [range]**	**Ethnicity**	**Performance status (ASA unless otherwise stated) N or Mean (SD) *median [range]**	**Co-morbidity**	**Clinical Tumour size (cm) Mean (SD), *median [range]**	**Pathological tumour stage**	**Tumour grade (Fuhrman unless stated)**	**Histological cell type**
	Open or lap RN	480	Median 50 [IQR 28, 73] (	M295 (61%), F185	Mean 65 [IQR 56, 73]	NR	NR	Charlson Romano index 0-1 = 284/406 (70%), 2 or greater =122/406 (30%); missing 74 Solitary kidney 7/480 (1.5%)	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%)
Precision 1	NA	NA	NA	NA	NA	NA	NA	NA	1	1	1	1
Imbalance 1	NA	NA	NA	NA	NA	NA	NA	NA	1	2	2	1
Adjustment 1	NA	NA	NA	NA	NA	NA	NA	NA	1	1	1	1
Wu 2010, USA,[66] Northwestern University of Feinberg medical school)	Radio-requecy-assisted robot clampless PN	42	25.8 [0.5, 71.5]	M 24 (57%) F 18	56 [27-77]	NR	≥3: 10/41 (24.4%)	NR	2.8 [0.9-12]	NR	NR	RCC: 32 (76.2%) Benign: 10 (23.8%) Other malignancy 0

					*Pre-specified confounders for peri-operative outcomes in non-randomised studies**				*Pre-specified confounders for oncological outcomes and quality of life in non-randomised studies**			
Study, Year, Design, Confounder assessment	**Compa-rison**	**N**	**FU (months) mean (SD), *median [range]**	**Sex Male/ Female**	**Age: Mean (SD), *median [range]**	**Ethnicity**	**Performance status (ASA unless otherwise stated) N or Mean (SD) *median [range]**	**Co-morbidity**	**Clinical Tumour size (cm) Mean (SD), *median [range]**	**Pathological tumour stage**	**Tumour grade (Fuhrman unless stated)**	**Histological cell type**
Database review	Lap PN	36	7.8 [1.0, 18.9]	M 22 (61%) F 14	58 [36-79]	NR	≥3: 11/34 (30.6%)	NR	2 [0.5-3.5]	NR	NR	RCC: 24 (66.7%) Benign: 12 (33.3%) Other malignancy: 0
Precision	NA	NA	NA	NA	3	5	1	5	3	5	5	1
Imbalance	NA	NA	NA	NA	1	5	1	5	2	5	5	1
Adjustment	NA	NA	NA	NA	2	5	1	5	2	5	5	1
Zini 2009a,[53] USA **Matched-pair**	Non-surgical manage-ment	430	*16 [0.1, 146]	M 240 (56%), F 193 (44%), [Unmatched, N = 433]	73 [Un-matched, N = 433]	NR	NR	NR	2.8 [Unmatched, N = 433]	All pT1a	NR	NR
	Surgical manage-ment	1545	*50 [0.1,203]	M 5933 (60%), F 3925 (40%) [unmatched, N = 9858]	61.4 [Un-matched, N = 9858]	NR	NR	NR	2.8 [Unmatched, N = 9858] (p = 0.5)	All pT1a	NR	NR
Precision	NA	NA	NA	NA	NA	NA	NA	NA	2	1	5	5
Imbalance	NA	NA	NA	NA	NA	NA	NA	NA	1	1	5	5
Adjustment	NA	NA	NA	NA	NA	NA	NA	NA	1	1	5	5

					*Pre-specified confounders for peri-operative outcomes in non-randomised studies**				*Pre-specified confounders for oncological outcomes and quality of life in non-randomised studies**			
Study, Year, Design, Confounder assessment	**Compa-rison**	**N**	**FU (months) mean (SD), *median [range]**	**Sex Male/ Female**	**Age: Mean (SD), *median [range]**	**Ethnicity**	**Performance status (ASA unless otherwise stated) N or Mean (SD) *median [range]**	**Co-morbidity**	**Clinical Tumour size (cm) Mean (SD), *median [range]**	**Pathological tumour stage**	**Tumour grade (Fuhrman unless stated)**	**Histological cell type**
Zini 2009b,[54] USA (SEER database) **Matched-pair**	Open or lap PN	1283	*35	M 798 (62.2%), F 485	59.6	NR	NR	NR	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%)
	Open or lap RN	3166	*46	M 1844 (58.2%), F 1322	61.3	NR	NR	NR	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%)
Precision	NA	NA	NA	NA	NA	NA	NA	NA	3	1	1	1
Imbalance	NA	NA	NA	NA	NA	NA	NA	NA	1	1	1	1
Adjustment	NA	NA	NA	NA	NA	NA	NA	NA	1	1	1	1

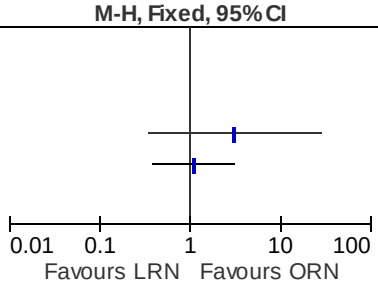
PN = partial nephrectomy; RN = radical nephrectomy; Retro lap RN = retroperitoneal laparoscopic radical nephrectomy; Trans lap RN = transperitoneal laparoscopic radical nephrectomy; Robot RN = robotic radical nephrectomy; Lap RN/PN = laparoscopic radical/partial nephrectomy; NA = not applicable; NR = not reported
For the risk of bias (confounder) assessment scores, see Appendix 5.

Appendix 11: Forest plots

1 Laparoscopic radical vs. Open radical nephrectomy (B1)

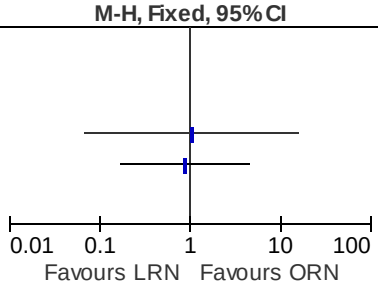
1.1 All cause death

Study or Subgroup	Laparoscopic radical Events	Total	Open radical Events	Total	Risk Ratio M-H, Fixed, 95% CI
1.1.1 RCT					
1.1.2 NRS					
Gratzke 2009	3	36	1	37	3.08 [0.34, 28.28]
Hemal 2007	5	41	8	71	1.08 [0.38, 3.09]



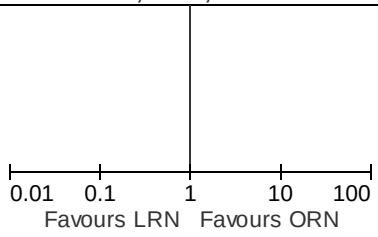
1.2 Cancer-specific death

Study or Subgroup	Laparoscopic radical Events	Total	Open radical Events	Total	Risk Ratio M-H, Fixed, 95% CI
1.2.1 RCT					
1.2.2 NRS					
Gratzke 2009	1	36	1	37	1.03 [0.07, 15.82]
Hemal 2007	2	41	4	71	0.87 [0.17, 4.52]



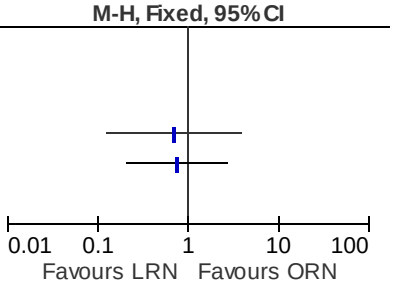
1.3 Local recurrence

Study or Subgroup	Laparoscopic radical Events	Total	Open radical Events	Total	Risk Ratio M-H, Fixed, 95% CI
1.3.1 RCT					
1.3.2 NRS					
Hemal 2007	0	41	0	71	Not estimable



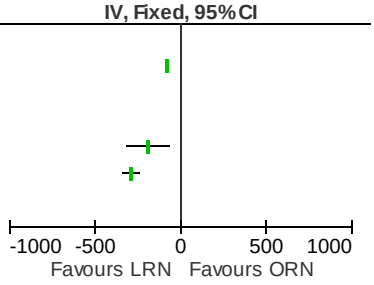
1.4 Distant metastasis

Study or Subgroup	Laparoscopic radical Events	Total	Open radical Events	Total	Risk Ratio M-H, Fixed, 95% CI
1.4.1 RCT					
1.4.2 NRS					
Gratzke 2009	2	36	3	37	0.69 [0.12, 3.86]
Hemal 2007	3	41	7	71	0.74 [0.20, 2.71]



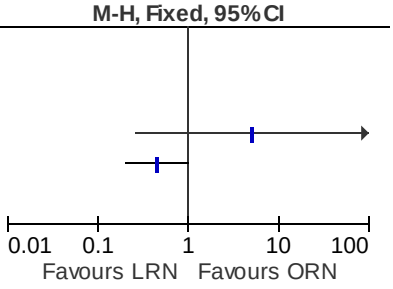
1.5 Blood loss (ml, mean, SD)

Study or Subgroup	Laparoscopic radical Mean	SD	Total	Open radical Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
1.5.1 RCT							
Peng 2006	72.03	19.37	27	154.4	20.42	26	-82.37 [-93.09, -71.65]
1.5.2 NRS							
Gratzke 2009	231	153	36	424	361	37	-193.00 [-319.60, -66.40]
Hemal 2007	245.5	125.13	41	537.3	139.99	71	-291.80 [-342.07, -241.53]



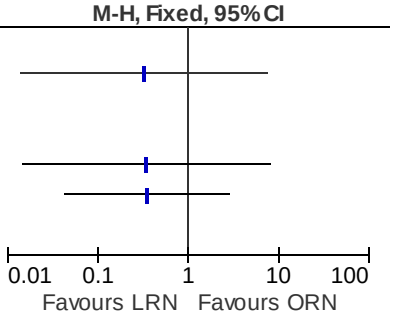
1.6 Blood transfusion (N of patients)

Study or Subgroup	Laparoscopic radical Events	Total	Open radical Events	Total	Risk Ratio M-H, Fixed, 95% CI
1.6.1 RCT					
1.6.2 NRS					
Gratzke 2009	2	36	0	37	5.14 [0.26, 103.39]
Hemal 2007	6	41	23	71	0.45 [0.20, 1.02]



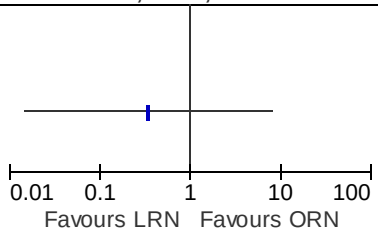
1.7 Surgical site infection

Study or Subgroup	Laparoscopic radical Events	Total	Open radical Events	Total	Risk Ratio M-H, Fixed, 95% CI
1.7.1 RCT					
Peng 2006	0	27	1	26	0.32 [0.01, 7.55]
1.7.2 NRS					
Gratzke 2009	0	36	1	37	0.34 [0.01, 8.14]
Hemal 2007	1	41	5	71	0.35 [0.04, 2.86]



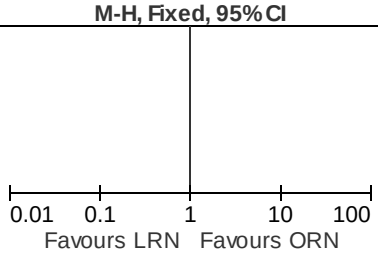
1.8 Pneumonia

Study or Subgroup	Laparoscopic radical Events	Total	Open radical Events	Total	Risk Ratio M-H, Fixed, 95% CI
1.8.1 RCT					
1.8.2 NRS					
Gratzke 2009	0	36	1	37	0.34 [0.01, 8.14]



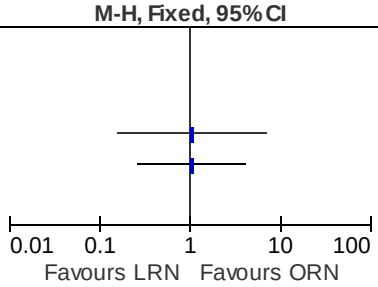
1.9 Deep venous thrombosis

Study or Subgroup	Laparoscopic radical Events	Total	Open radical Events	Total	Risk Ratio M-H, Fixed, 95% CI
1.9.1 RCT					
1.9.2 NRS					
Gratzke 2009	0	36	0	37	Not estimable



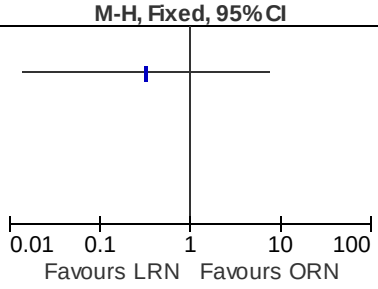
1.10 Haemorrhage

Study or Subgroup	Laparoscopic radical Events	Total	Open radical Events	Total	Risk Ratio M-H, Fixed, 95% CI
1.10.1 RCT					
1.10.2 NRS					
Gratzke 2009	2	36	2	37	1.03 [0.15, 6.91]
Hemal 2007	3	41	5	71	1.04 [0.26, 4.12]



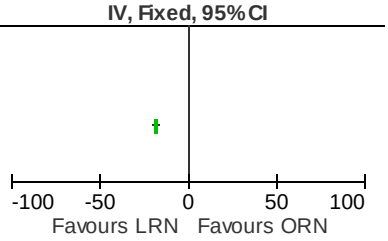
1.11 Post-operative mortality

Study or Subgroup	Laparoscopic radical Events	Total	Open radical Events	Total	Risk Ratio M-H, Fixed, 95% CI
1.11.1 RCT					
Peng 2006	0	27	1	26	0.32 [0.01, 7.55]
1.11.2 NRS					
Gratzke 2009	0	36	0	37	Not estimable



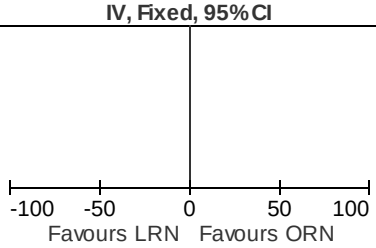
1.12 Analgesic requirement (mg morphine equivalent, mean, SD)

Study or Subgroup	Laparoscopic radical Mean	SD	Total	Open radical Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
1.12.1 RCT							
1.12.2 NRS							
Hemal 2007	16.4	3.35	41	35	8.01	71	-18.60 [-20.73, -16.47]



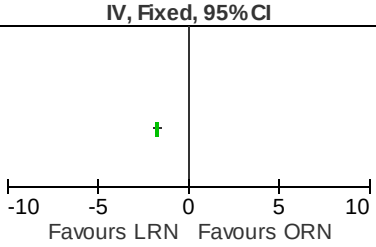
1.13 Analgesic requirement (person time)

Study or Subgroup	Laparoscopic radical Mean	SD	Total	Open radical Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
1.13.1 RCT							
Peng 2006	2	0	27	20	0	26	Not estimable
1.13.2 NRS							



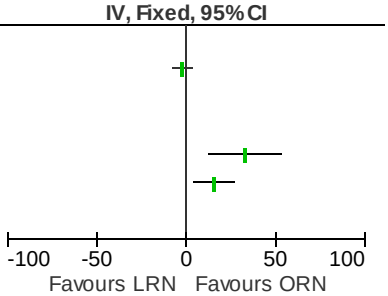
1.14 Convalescence time (Week, mean, SD)

Study or Subgroup	Laparoscopic radical Mean	SD	Total	Open radical Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
1.14.1 RCT							
1.14.2 NRS							
Hemal 2007	1.56	0.5	41	3.3	0.69	71	-1.74 [-1.96, -1.52]



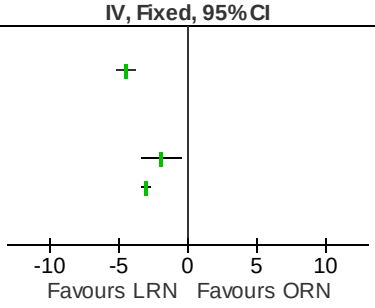
1.15 Duration of operation (minute, mean, SD)

Study or Subgroup	Laparoscopic radical Mean	SD	Total	Open radical Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
1.15.1 RCT							
Peng 2006	66.7	10.37	27	69.08	11.22	26	-2.38 [-8.20, 3.44]
1.15.2 NRS							
Gratzke 2009	146	42	36	113	48	37	33.00 [12.33, 53.67]
Hemal 2007	180.8	21.5	41	165.3	40.9	71	15.50 [3.93, 27.07]



1.16 Length of hospital stay (day, mean, SD)

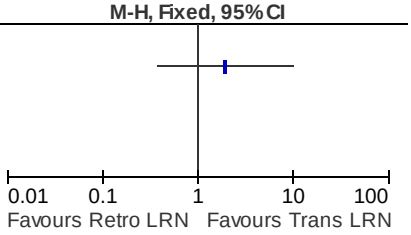
Study or Subgroup	Laparoscopic radical Mean	SD	Total	Open radical Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
1.16.1 RCT							
Peng 2006	6.92	0.96	27	11.42	1.57	26	-4.50 [-5.20, -3.80]
1.16.2 NRS							
Gratzke 2009	7.2	2.9	36	9.1	3.5	37	-1.90 [-3.37, -0.43]
Hemal 2007	3.6	0.79	41	6.6	1.06	71	-3.00 [-3.35, -2.65]



2 Retroperitoneal vs. Transperitoneal laparascopic radical nephrectomy (B2)

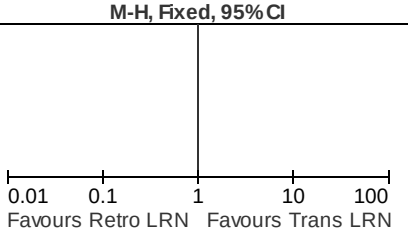
2.1 All cause death (N of patients)

Study or Subgroup	Retropertoneal LRN Events	Total	Transperitoneal LRN Events	Total	Risk Ratio M-H, Fixed, 95% CI
2.1.1 RCT					
Desai 2005a	4	52	2	50	1.92 [0.37, 10.04]
2.1.2 NRS					



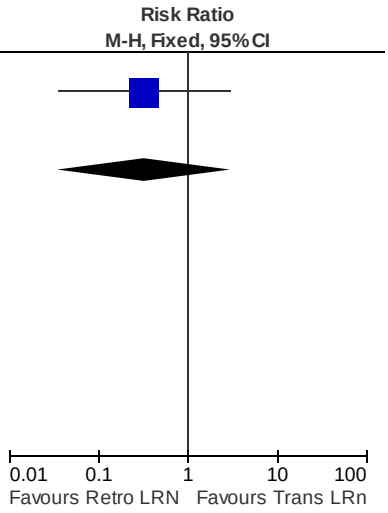
2.2 Cancer specific death (N of patients)

Study or Subgroup	Retropertoneal LRN Events	Total	Transperitoneal LRN Events	Total	Risk Ratio M-H, Fixed, 95% CI
2.2.1 RCT					
Nadler 2006	0	11	0	11	Not estimable
2.2.2 NRS					



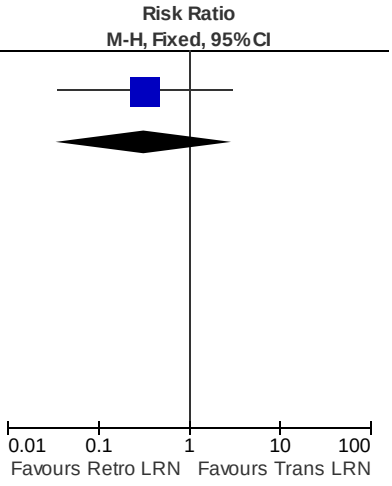
2.3 Local recurrence (N of patients)

Study or Subgroup	Retropertoneal LRN Events	Total	Transperitoneal LRN Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.3.1 RCT						
Desai 2005a	1	52	3	50	100.0%	0.32 [0.03, 2.98]
Nadler 2006	0	11	0	11		Not estimable
Nambirajan 2004	0	17	0	15		Not estimable
Subtotal (95% CI)		**80**		**76**	**100.0%**	**0.32 [0.03, 2.98]**
Total events	1		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.00 (P = 0.32)						
2.3.2 NRS						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						



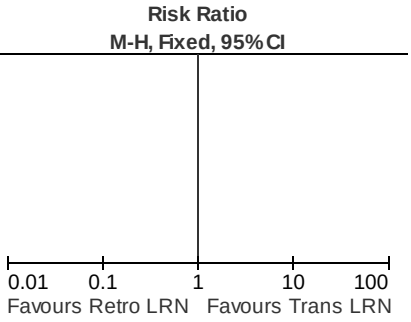
2.4 Incidence of metastasis (N of patients)

Study or Subgroup	Retropertoneal LRN Events	Total	Transperitoneal LRN Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.4.1 RCT						
Desai 2005a	1	52	3	50	100.0%	0.32 [0.03, 2.98]
Nadler 2006	0	11	0	11		Not estimable
Subtotal (95% CI)		**63**		**61**	**100.0%**	**0.32 [0.03, 2.98]**
Total events	1		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.00 (P = 0.32)						
2.4.2 NRS						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						



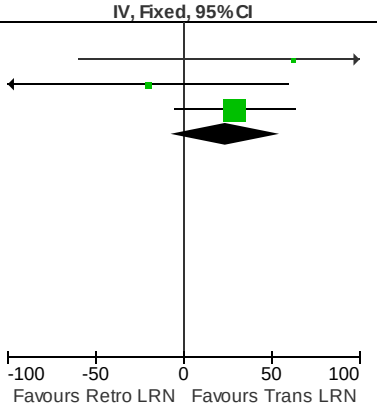
2.5 Postive surgical margin (N of patients)

Study or Subgroup	Retropertoneal LRN Events	Total	Transperitoneal LRN Events	Total	Risk Ratio M-H, Fixed, 95% CI
2.5.1 RCT					
Desai 2005a	0	52	0	50	Not estimable
Nadler 2006	0	11	0	11	Not estimable
Nambirajan 2004	0	20	0	20	Not estimable
2.5.2 NRS					



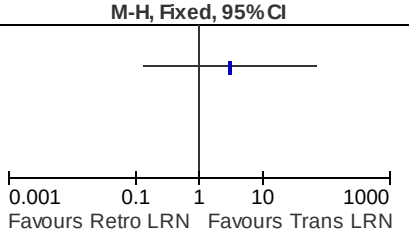
2.6 Blood loss (ml, mean, SD)

Study or Subgroup	Retropertoneal LRN Mean	SD	Total	Transperitoneal LRN Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
2.6.1 RCT								
Desai 2005a	242	402.2	52	179.8	199	50	6.2%	62.20 [-60.24, 184.64]
Nadler 2006	107	103	11	127	88	11	14.6%	-20.00 [-100.06, 60.06]
Nambirajan 2004	208	57	20	179	54	20	79.1%	29.00 [-5.41, 63.41]
Subtotal (95% CI)			**83**			**81**	**100.0%**	**23.91 [-6.70, 54.52]**
Heterogeneity: Chi² = 1.62, df = 2 (P = 0.45); I² = 0%								
Test for overall effect: Z = 1.53 (P = 0.13)								
2.6.2 NRS								
Subtotal (95% CI)			**0**			**0**		**Not estimable**
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								



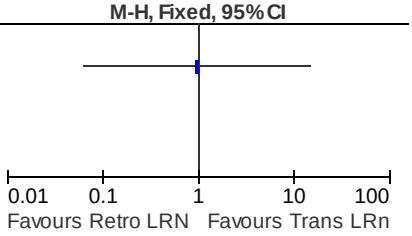
2.7 Blood transfusion (N of patients)

Study or Subgroup	Retropertoneal LRN Events	Total	Transperitoneal LRN Events	Total	Risk Ratio M-H, Fixed, 95% CI
2.7.1 RCT					
Nambirajan 2004	1	20	0	20	3.00 [0.13, 69.52]
2.7.2 NRS					



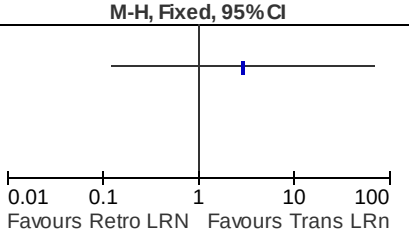
2.8 Infection (N of patients)

Study or Subgroup	Retropertoneal LRN Events	Total	Transperitoneal LRN Events	Total	Risk Ratio M-H, Fixed, 95% CI
2.8.1 RCT					
Desai 2005a	1	52	1	50	0.96 [0.06, 14.96]
2.8.2 NRS					



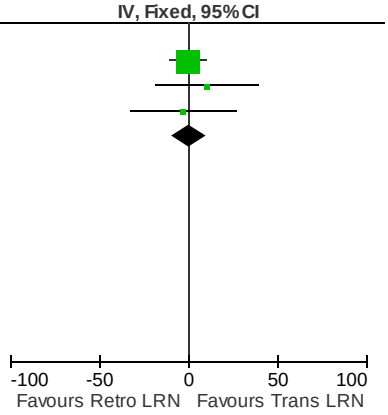
2.9 Deep venous thrombosis (N of patients)

Study or Subgroup	Retropertoneal LRN Events	Total	Transperitoneal LRN Events	Total	Risk Ratio M-H, Fixed, 95% CI
2.9.1 RCT					
Desai 2005a	1	52	0	50	2.89 [0.12, 69.24]
2.9.2 NRS					



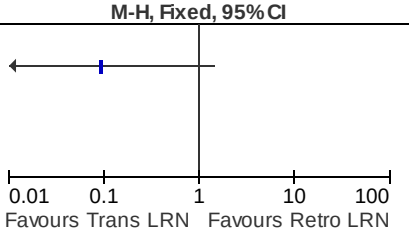
2.10 Analgesic requirement (mg morphine equivalent; mean, SD)

Study or Subgroup	Retropertoneal LRN Mean	SD	Total	Transperitoneal LRN Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
2.10.1 RCT								
Desai 2005a	26.1	18.3	52	26.8	33.8	50	79.3%	-0.70 [-11.31, 9.91]
Nadler 2006	36	46	11	26	17	11	10.6%	10.00 [-18.98, 38.98]
Nambirajan 2004	36	51.69	20	39.4	43.98	20	10.1%	-3.40 [-33.14, 26.34]
Subtotal (95% CI)			**83**			**81**	**100.0%**	**0.16 [-9.28, 9.61]**
Heterogeneity: Chi² = 0.52, df = 2 (P = 0.77); I² = 0%								
Test for overall effect: Z = 0.03 (P = 0.97)								
2.10.2 NRS								
Subtotal (95% CI)			**0**			**0**		**Not estimable**
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								



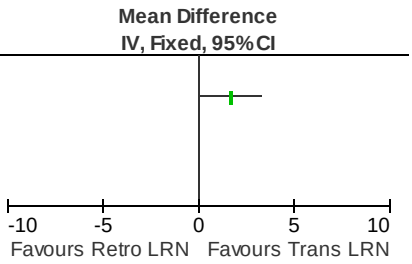
2.11 Return to work at 2 weeks (N of patients)

Study or Subgroup	Retropertoneal LRN Events	Total	Transperitoneal LRN Events	Total	Risk Ratio M-H, Fixed, 95% CI
2.11.1 RCT					
Nadler 2006	0	9	6	11	0.09 [0.01, 1.45]
2.11.2 NRS					



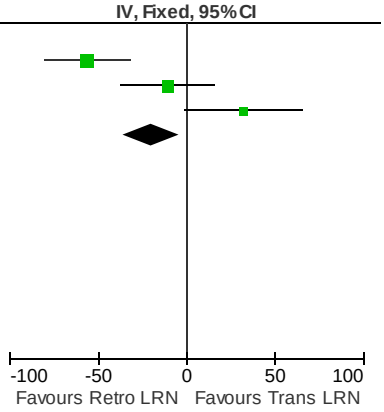
2.12 Convalescence (weeks, mean, SD)

Study or Subgroup	Retropertoneal LRN Mean	SD	Total	Transperitoneal LRN Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
2.12.1 RCT							
Desai 2005a	6	5.5	52	4.3	2.2	50	1.70 [0.09, 3.31]
2.12.2 NRS							



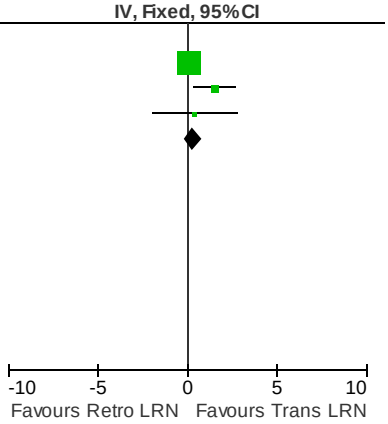
2.13 Duration of operation (minute, mean, SD)

Study or Subgroup	Retropertoneal LRN Mean	SD	Total	Transperitoneal LRN Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
2.13.1 RCT								
Desai 2005a	150	54.3	52	206.5	70.4	50	42.2%	-56.50 [-80.97, -32.03]
Nadler 2006	185	33	11	196	31	11	35.3%	-11.00 [-37.76, 15.76]
Nambirajan 2004	213	54	20	181	54	20	22.5%	32.00 [-1.47, 65.47]
Subtotal (95% CI)			**83**			**81**	**100.0%**	**-20.50 [-36.39, -4.61]**
Heterogeneity: Chi² = 18.25, df = 2 (P = 0.0001); I² = 89%								
Test for overall effect: Z = 2.53 (P = 0.01)								
2.13.2 NRS								
Subtotal (95% CI)			**0**			**0**		**Not estimable**
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								



2.14 Length of hospital stay (day, mean, SD)

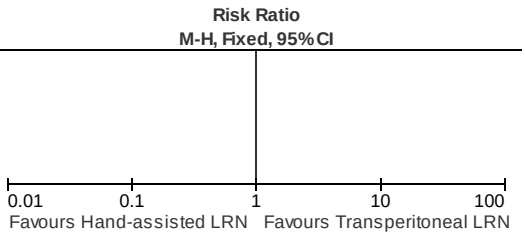
Study or Subgroup	Retropertoneal LRN Mean	SD	Total	Transperitoneal LRN Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
2.14.1 RCT								
Desai 2005a	1.87	1.28	52	1.81	1.43	50	80.4%	0.06 [-0.47, 0.59]
Nadler 2006	3.6	1.9	11	2.1	0.7	11	15.6%	1.50 [0.30, 2.70]
Nambirajan 2004	7.6	4.7	20	7.2	2.7	20	4.0%	0.40 [-1.98, 2.78]
Subtotal (95% CI)			**83**			**81**	**100.0%**	**0.30 [-0.17, 0.77]**
Heterogeneity: Chi² = 4.67, df = 2 (P = 0.10); I² = 57%								
Test for overall effect: Z = 1.24 (P = 0.22)								
2.14.2 NRS								
Subtotal (95% CI)			**0**			**0**		**Not estimable**
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								



3 Hand-assisted vs. Transperitoneal laparospic radical nephrectomy (B3)

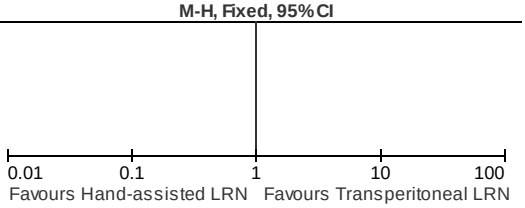
3.1 Cancer specific death (N of patients)

Study or Subgroup	Hand-assisted LRN Events	Total	Transperitoneal LRN Events	Total	Risk Ratio M-H, Fixed, 95% CI
3.1.1 RCT					
Nadler 2006	0	11	0	11	Not estimable
3.1.2 NRS					



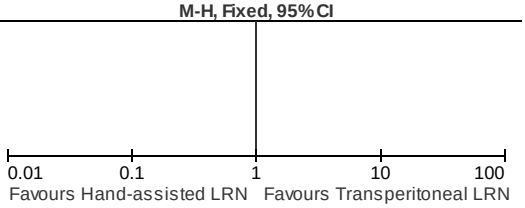
3.2 Incidence of metastasis (N of patients)

Study or Subgroup	Hand-assisted LRN Events	Total	Transperitoneal LRN Events	Total	Risk Ratio M-H, Fixed, 95% CI
3.2.1 RCT					
Nadler 2006	0	11	0	11	Not estimable
3.2.2 NRS					



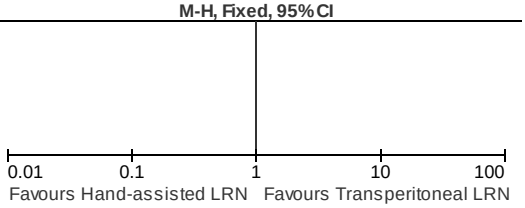
3.3 Local recurrence (N of patients)

Study or Subgroup	Hand-assisted LRN Events	Total	Transperitoneal LRN Events	Total	Risk Ratio M-H, Fixed, 95% CI
3.3.1 RCT					
Nadler 2006	0	11	0	11	Not estimable
3.3.2 NRS					



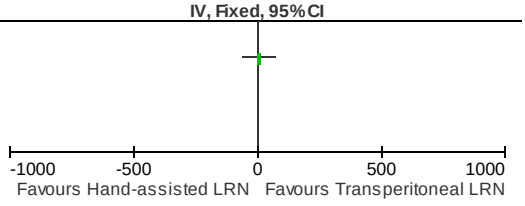
3.4 Postive surgical margin (N of patients)

Study or Subgroup	Hand-assisted LRN Events	Total	Transperitoneal LRN Events	Total	Risk Ratio M-H, Fixed, 95% CI
3.4.1 RCT					
Nadler 2006	0	11	0	11	Not estimable
3.4.2 NRS					



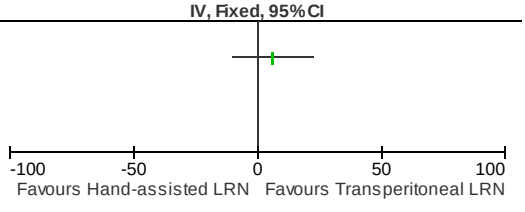
3.5 Blood loss (ml, mean, SD)

Study or Subgroup	Hand-assisted LRN Mean	SD	Total	Transperitoneal LRN Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
3.5.1 RCT							
Nadler 2006	133	75	11	127	88	11	6.00 [-62.33, 74.33]
3.5.2 NRS							



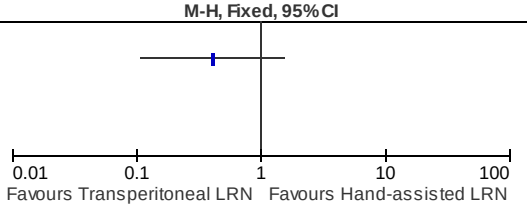
3.6 Analgesic requirement (mg morphine equivalent; mean, SD)

Study or Subgroup	Hand-assisted LRN Mean	SD	Total	Transperitoneal LRN Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
3.6.1 RCT							
Nadler 2006	32	22	11	26	17	11	6.00 [-10.43, 22.43]
3.6.2 NRS							



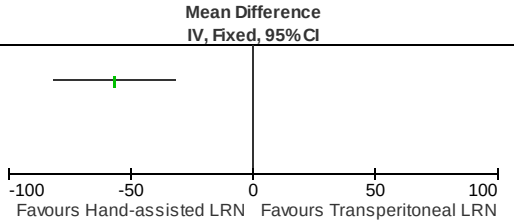
3.7 Return to work at 2 weeks (N of patients)

Study or Subgroup	Hand-assisted LRN Events	Total	Transperitoneal LRN Events	Total	Risk Ratio M-H, Fixed, 95% CI
3.7.1 RCT					
Nadler 2006	2	9	6	11	0.41 [0.11, 1.55]
3.7.2 NRS					



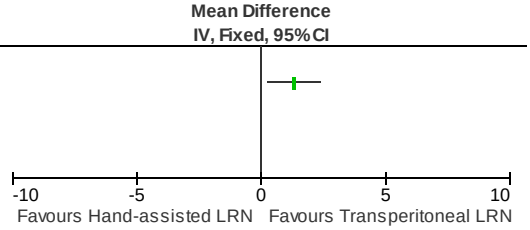
3.8 Duration of operation (minute, mean, SD)

Study or Subgroup	Hand-assisted LRN Mean	SD	Total	Transperitoneal LRN Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
3.8.1 RCT							
Nadler 2006	139	29	11	196	31	11	-57.00 [-82.09, -31.91]
3.8.2 NRS							



3.9 Length of hospital stay (day, mean, SD)

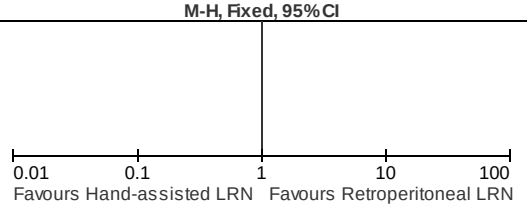
Study or Subgroup	Hand-assisted LRN Mean	SD	Total	Transperitoneal LRN Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
3.9.1 RCT							
Nadler 2006	3.4	1.7	11	2.1	0.7	11	1.30 [0.21, 2.39]
3.9.2 NRS							



4 Hand-assisted vs. Retroperitoneal laparoscopic radical nephrectomy (B4)

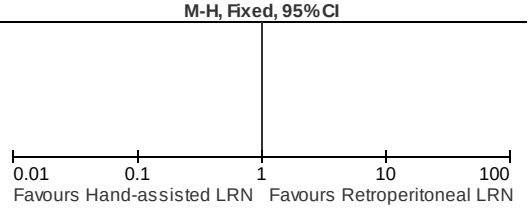
4.1 Cancer specific death (N of patients)

Study or Subgroup	Hand-assisted LRN Events	Total	Retroperitoneal LRN Events	Total	Risk Ratio M-H, Fixed, 95% CI
4.1.1 RCT					
Nadler 2006	0	11	0	11	Not estimable
4.1.2 NRS					



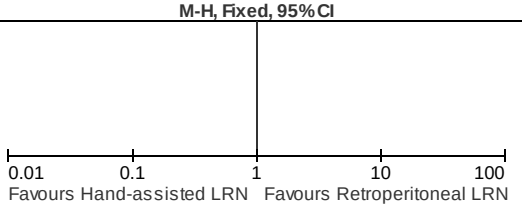
4.2 Incidence of metastasis (N of patients)

Study or Subgroup	Hand-assisted LRN Events	Total	Retroperitoneal LRN Events	Total	Risk Ratio M-H, Fixed, 95% CI
4.2.1 RCT					
Nadler 2006	0	11	0	11	Not estimable
4.2.2 NRS					



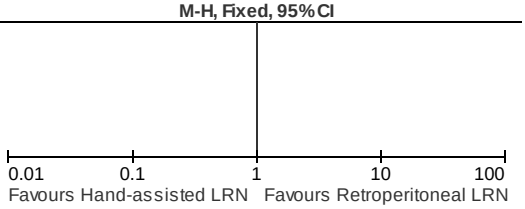
4.3 Local recurrence (N of patients)

Study or Subgroup	Hand-assisted LRN Events	Total	Retroperitoneal LRN Events	Total	Risk Ratio M-H, Fixed, 95% CI
4.3.1 RCT					
Nadler 2006	0	11	0	11	Not estimable
4.3.2 NRS					



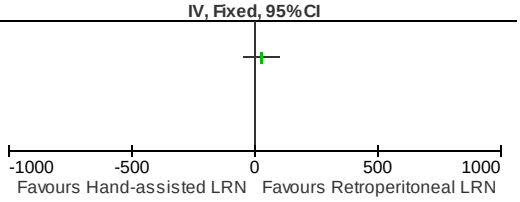
4.4 Postive surgical margin (N of patients)

Study or Subgroup	Hand-assisted LRN Events	Total	Retroperitoneal LRN Events	Total	Risk Ratio M-H, Fixed, 95% CI
4.4.1 RCT					
Nadler 2006	0	11	0	11	Not estimable
4.4.2 NRS					



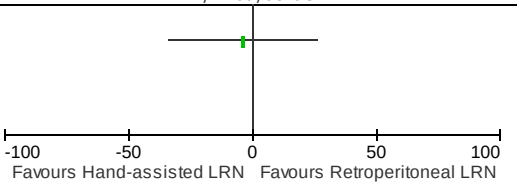
4.5 Blood loss (ml, mean, SD)

Study or Subgroup	Hand-assisted LRN Mean	SD	Total	Retroperitoneal LRN Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
4.5.1 RCT							
Nadler 2006	133	75	11	107	103	11	26.00 [-49.29, 101.29]
4.5.2 NRS							



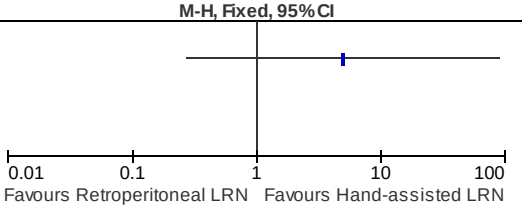
4.6 Analgesic requirement (mg morphine equivalent; mean, SD)

Study or Subgroup	Hand-assisted LRN Mean	SD	Total	Retroperitoneal LRN Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
4.6.1 RCT							
Nadler 2006	32	22	11	36	46	11	-4.00 [-34.13, 26.13]
4.6.2 NRS							



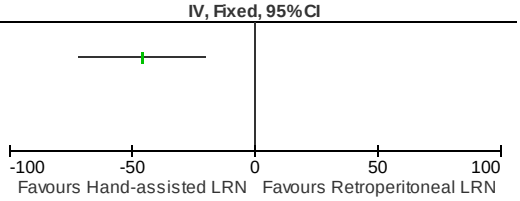
4.7 Return to work at 2 weeks (N of patients)

Study or Subgroup	Hand-assisted LRN Events	Total	Retroperitoneal LRN Events	Total	Risk Ratio M-H, Fixed, 95% CI
4.7.1 RCT					
Nadler 2006	2	9	0	9	5.00 [0.27, 91.52]
4.7.2 NRS					



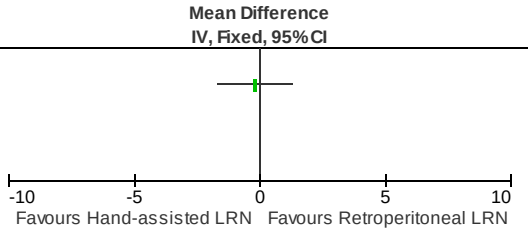
4.8 Duration of operation (minute, mean, SD)

Study or Subgroup	Hand-assisted LRN Mean	SD	Total	Retroperitoneal LRN Mean	SD	Total	Mean Difference IV, Fixed, 95%CI
4.8.1 RCT							
Nadler 2006	139	29	11	185	33	11	-46.00 [-71.96, -20.04]
4.8.2 NRS							



4.9 Length of hospital stay (day, mean, SD)

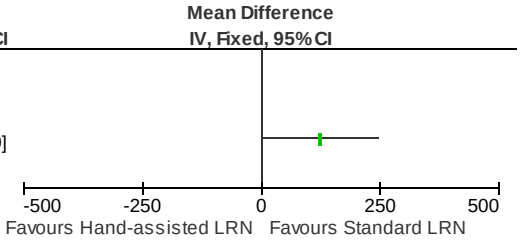
Study or Subgroup	Hand-assisted LRN Mean	SD	Total	Retroperitoneal LRN Mean	SD	Total	Mean Difference IV, Fixed, 95%CI
4.9.1 RCT							
Nadler 2006	3.4	1.7	11	3.6	1.9	11	-0.20 [-1.71, 1.31]
4.9.2 NRS							



5 Hand-assisted vs. standard (transperitoneal or retroperitoneal approach) laparoscopic radical nephrectomy (B5)

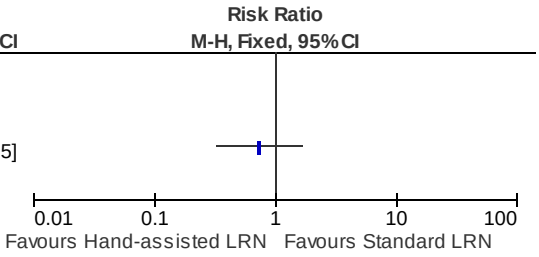
5.1 Blood loss (ml, mean, SD)

Study or Subgroup	Hand-assisted LRN Mean	SD	Total	Standard LRN Mean	SD	Total	Mean Difference IV, Fixed, 95%CI
5.1.1 RCT							
5.1.2 NRS							
Gabr 2009	406	475	108	283	524	147	123.00 [-0.29, 246.29]



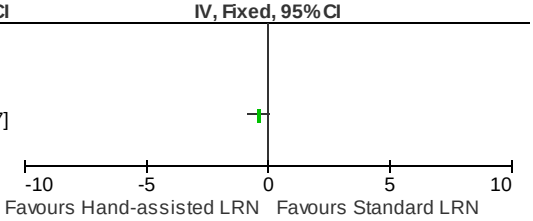
5.2 Blood transfusion (N of patients)

Study or Subgroup	Hand-assisted LRN Events	Total	Standard LRN Events	Total	Risk Ratio M-H, Fixed, 95%CI
5.2.1 RCT					
5.2.2 NRS					
Gabr 2009	8	108	15	147	0.73 [0.32, 1.65]



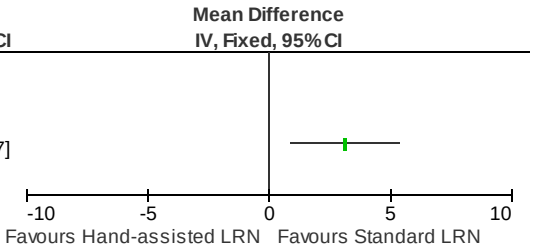
5.3 Pain score at 6 weeks (10-point VAS, mean, SD)

Study or Subgroup	Hand-assisted LRN Mean	SD	Total	Standard LRN Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
5.3.1 RCT							
5.3.2 NRS							
Gabr 2009	1.3	1.7	108	1.7	2.1	147	-0.40 [-0.87, 0.07]



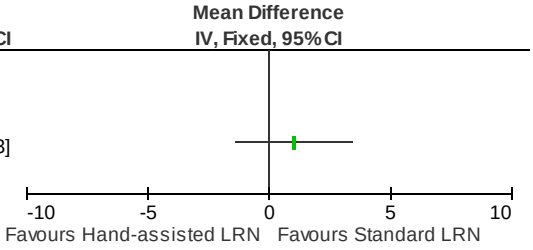
5.4 Time to nonstrenuous activity (days, mean, SD)

Study or Subgroup	Hand-assisted LRN Mean	SD	Total	Standard LRN Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
5.4.1 RCT							
5.4.2 NRS							
Gabr 2009	13	10	108	9.9	7.8	147	3.10 [0.83, 5.37]



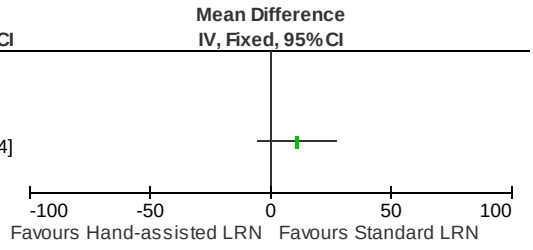
5.5 Time to driving (days, mean, SD)

Study or Subgroup	Hand-assisted LRN Mean	SD	Total	Standard LRN Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
5.5.1 RCT							
5.5.2 NRS							
Gabr 2009	16	9.9	108	15	9.6	147	1.00 [-1.43, 3.43]



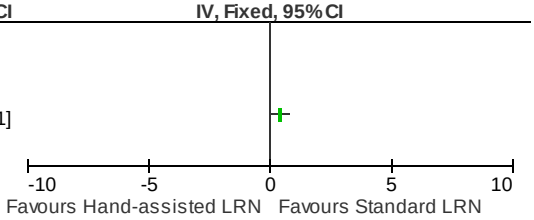
5.6 Duration of operation (minute, mean, SD)

Study or Subgroup	Hand-assisted LRN Mean	SD	Total	Standard LRN Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
5.6.1 RCT							
5.6.2 NRS							
Gabr 2009	220	67	108	209	66	147	11.00 [-5.54, 27.54]



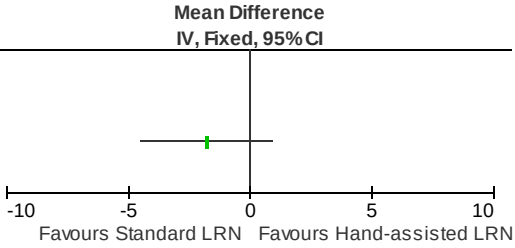
5.7 Length of hospital stay (days, mean, SD)

Study or Subgroup	Hand-assisted LRN Mean	SD	Total	Standard LRN Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
5.7.1 RCT							
5.7.2 NRS							
Gabr 2009	2.8	1.6	108	2.4	1.7	147	0.40 [-0.01, 0.81]



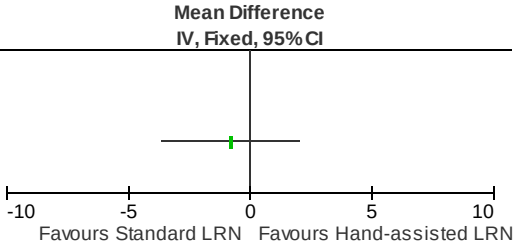
5.8 SF12: mental health score at 6 weeks (change from baseline, mean, SD)

Study or Subgroup	Hand-assisted LRN Mean	SD	Total	Standard LRN Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
5.8.1 RCT							
5.8.2 NRS							
Gabr 2009	4.2	12	108	6	9.3	147	-1.80 [-4.52, 0.92]



5.9 SF12: physical health score at 6 weeks (change from baseline, mean, SD)

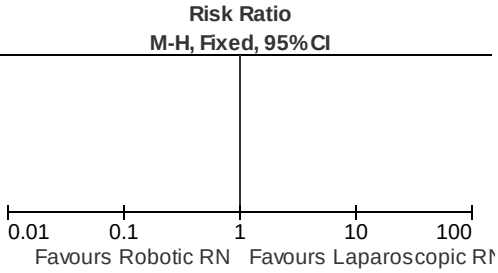
Study or Subgroup	Hand-assisted LRN Mean	SD	Total	Standard LRN Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
5.9.1 RCT							
5.9.2 NRS							
Gabr 2009	-1.3	11	108	-0.5	12	147	-0.80 [-3.64, 2.04]



6 Robotic vs. Laparoscopic radical nephrectomy (B6)

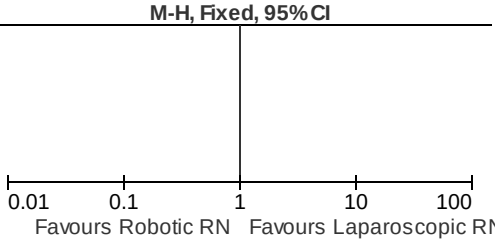
6.1 Local recurrence (N of patients)

Study or Subgroup	Robotic RN Events	Total	Laparoscopic RN Events	Total	Risk Ratio M-H, Fixed, 95% CI
6.1.1 RCT					
6.1.2 NRS					
Hemal 2009	0	15	0	15	Not estimable



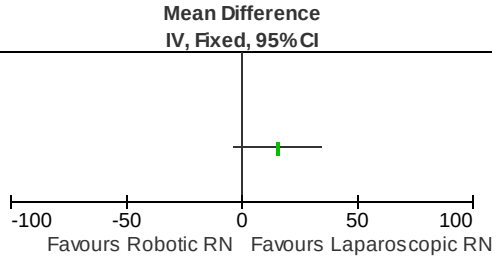
6.2 Distant metastasis (N of patients)

Study or Subgroup	Robotic RN Events	Total	Laparoscopic RN Events	Total	Risk Ratio M-H, Fixed, 95% CI
6.2.1 RCT					
6.2.2 NRS					
Hemal 2009	0	15	0	15	Not estimable



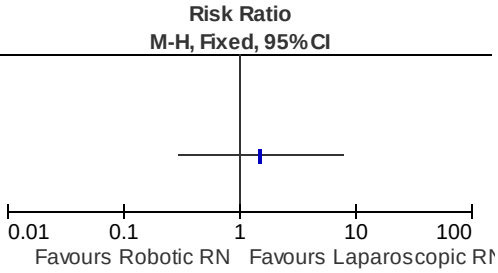
6.3 Blood loss (ml, mean, SD)

Study or Subgroup	Robotic RN Mean	SD	Total	Laparoscopic RN Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
6.3.1 RCT							
6.3.2 NRS							
Hemal 2009	210.3	21.1	15	195	31.3	15	15.30 [-3.80, 34.40]



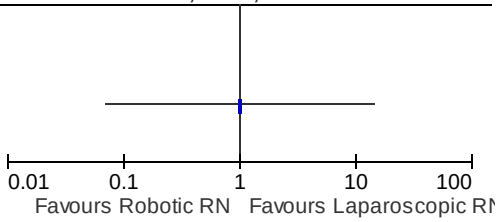
6.4 Blood transfusion (N of patients)

Study or Subgroup	Robotic RN Events	Total	Laparoscopic RN Events	Total	Risk Ratio M-H, Fixed, 95% CI
6.4.1 RCT					
6.4.2 NRS					
Hemal 2009	3	15	2	15	1.50 [0.29, 7.73]



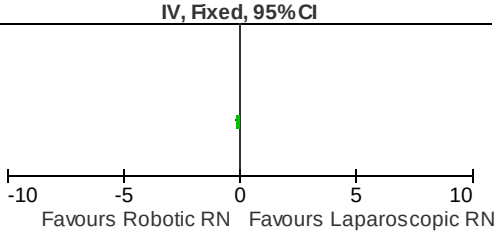
6.5 Surgical site infection (N of events)

Study or Subgroup	Robotic RN Events	Total	Laparoscopic RN Events	Total	Risk Ratio M-H, Fixed, 95% CI
6.5.1 RCT					
6.5.2 NRS					
Hemal 2009	1	15	1	15	1.00 [0.07, 14.55]



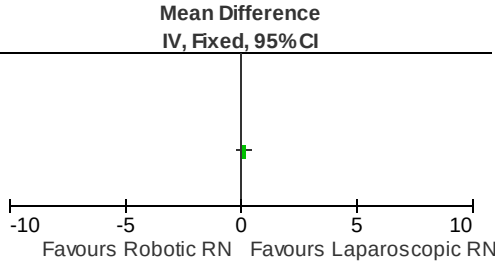
6.6 Analgesic requirement (mg morphine equivalent, mean, SD)

Study or Subgroup	Robotic RN Mean	SD	Total	Laparoscopic RN Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
6.6.1 RCT							
6.6.2 NRS							
Hemal 2009	14.3	0.1	15	14.4	0.2	15	-0.10 [-0.21, 0.01]



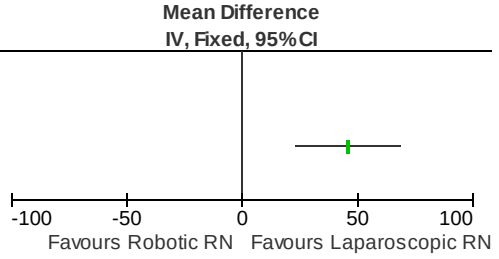
6.7 Convalescence time (weeks, mean, SD)

Study or Subgroup	Robotic RN Mean	SD	Total	Laparoscopic RN Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
6.7.1 RCT							
6.7.2 NRS							
Hemal 2009	2.3	0.5	15	2.2	0.4	15	0.10 [-0.22, 0.42]



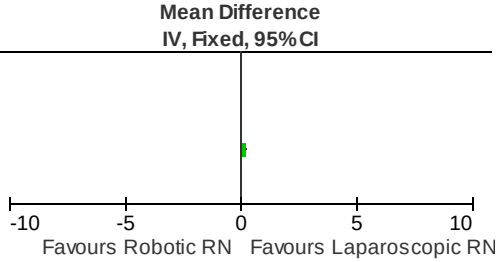
6.8 Duration of operation (minute, mean, SD)

Study or Subgroup	Robotic RN Mean	SD	Total	Laparoscopic RN Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
6.8.1 RCT							
6.8.2 NRS							
Hemal 2009	221	19.1	15	175.3	40.9	15	45.70 [22.86, 68.54]



6.9 Length of hospital stay (day, mean, SD)

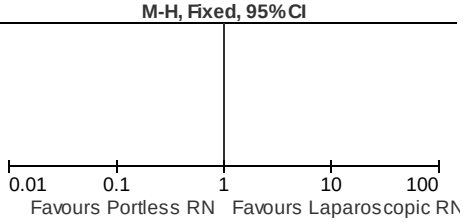
Study or Subgroup	Robotic RN Mean	SD	Total	Laparoscopic RN Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
6.9.1 RCT							
6.9.2 NRS							
Hemal 2009	3.5	0.1	15	3.4	0.2	15	0.10 [-0.01, 0.21]



7 Portless endoscopic vs. Laparoscopic radical nephrectomy (B7)

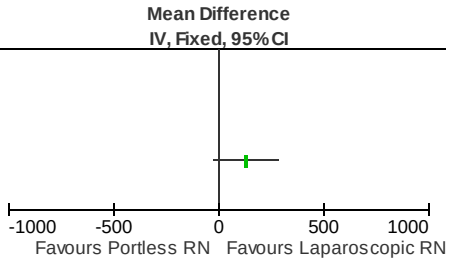
7.1 Local recurrence (N of patients)

Study or Subgroup	Portless endoscopic RN Events	Total	Laparoscopic RN Events	Total	Risk Ratio M-H, Fixed, 95% CI
7.1.1 RCT					
7.1.2 NRS					
Soga 2008	0	14	0	15	Not estimable



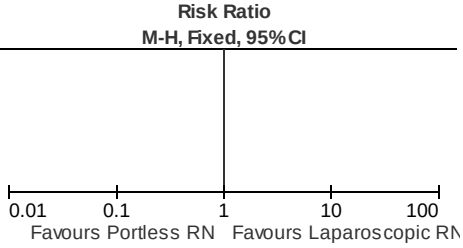
7.2 Blood loss (ml, mean, SD)

Study or Subgroup	Portless endoscopic RN Mean	SD	Total	Laparoscopic RN Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
7.2.1 RCT							
7.2.2 NRS							
Park 2009	158.9	0	9	161.1	0	18	Not estimable
Soga 2008	277	243	14	147	181	15	130.00 [-26.82, 286.82]



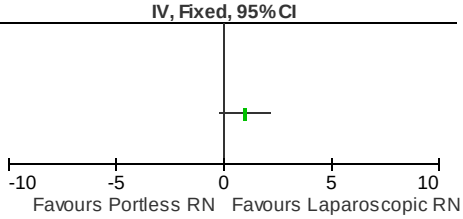
7.3 Blood transfusion (N of patients)

Study or Subgroup	Portless endoscopic RN Events	Total	Laparoscopic RN Events	Total	Risk Ratio M-H, Fixed, 95% CI
7.3.1 RCT					
7.3.2 NRS					
Soga 2008	0	14	0	15	Not estimable



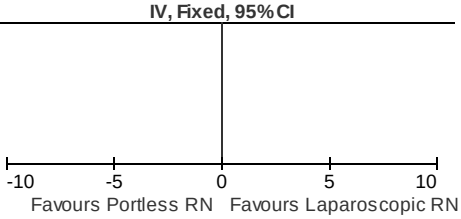
7.4 Analgesic requirement (N of NSAID suppository, mean, SD)

Study or Subgroup	Portless endoscopic RN Mean	SD	Total	Laparoscopic RN Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
7.4.1 RCT							
7.4.2 NRS							
Soga 2008	3.1	1.9	14	2.1	1.3	15	1.00 [-0.19, 2.19]



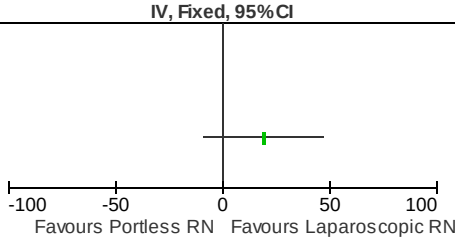
7.5 Pain score at Day 3 (VAS, mean, SD)

Study or Subgroup	Portless endoscopic RN Mean	SD	Total	Laparoscopic RN Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
7.5.1 RCT							
7.5.2 NRS							
Park 2009	2.8	0	9	4.2	0	18	Not estimable



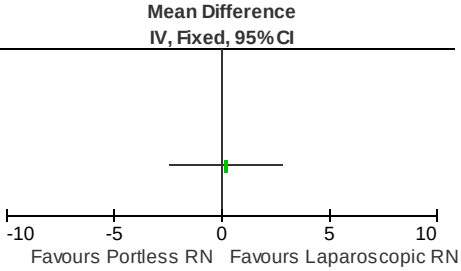
7.6 Duration of operation (minute, mean, SD)

Study or Subgroup	Portless endoscopic RN Mean	SD	Total	Laparoscopic RN Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
7.6.1 RCT							
7.6.2 NRS							
Park 2009	219	0	9	173	0	18	Not estimable
Soga 2008	284	6.78	14	265	55.1	15	19.00 [-9.11, 47.11]



7.7 Length of hospital stay (day, mean, SD)

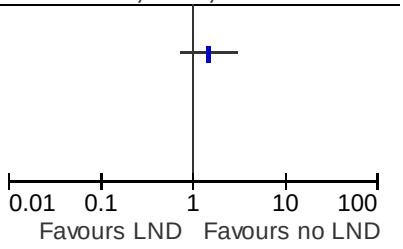
Study or Subgroup	Portless endoscopic RN Mean	SD	Total	Laparoscopic RN Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
7.7.1 RCT							
7.7.2 NRS							
Park 2009	2.7	0	9	3.9	0	18	Not estimable
Soga 2008	9.7	4.5	14	9.5	2.3	15	0.20 [-2.43, 2.83]



8 Radical nephrectomy with lymphadenectomy vs. Radical nephrectomy alone (C1)

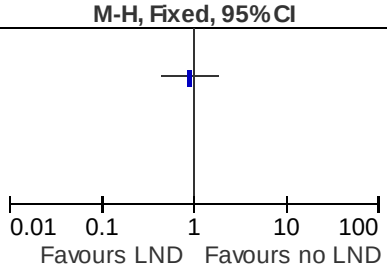
8.1 Bleeding over 1 litre (number of patients)

Study or Subgroup	RN with LND Events	Total	RN without LND Events	Total	Risk Ratio M-H, Fixed, 95% CI
8.1.1 RCT					
Blom 2009	17	253	12	261	1.46 [0.71, 3.00]
8.1.2 NRS					



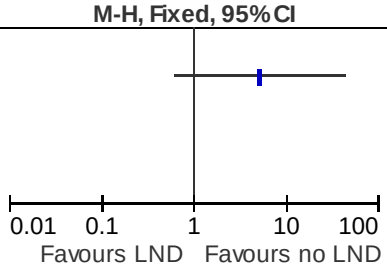
8.2 Infection (number of patients)

Study or Subgroup	RN with LND Events	Total	RN without LND Events	Total	Risk Ratio M-H, Fixed, 95% CI
8.2.1 RCT					
Blom 2009	13	253	15	259	0.89 [0.43, 1.83]
8.2.2 NRS					



8.3 Embolism (number of patients)

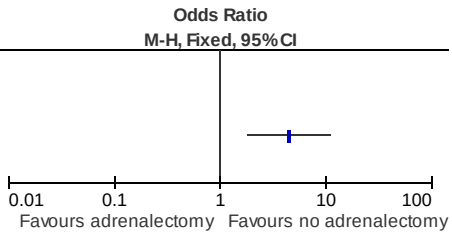
Study or Subgroup	RN with LND Events	Total	RN without LND Events	Total	Risk Ratio M-H, Fixed, 95% CI
8.3.1 RCT					
Blom 2009	5	253	1	260	5.14 [0.60, 43.67]
8.3.2 NRS					



9 Partial nephrectomy with adrenalectomy vs. Partial nephrectomy alone (C2)

9.1 Recurrence (patients with cancer only; benign kidney findings excluded)

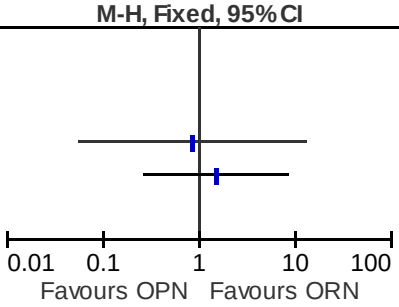
Study or Subgroup	PN with adrenalectomy Events	Total	PN without adrenalectomy Events	Total	Odds Ratio M-H, Fixed, 95% CI
9.1.1 RCT					
9.1.2 NRS					
Lane 2009	6	38	61	1501	4.43 [1.78, 10.98]



10 Open partial vs. Open radical nephrectomy (D1)

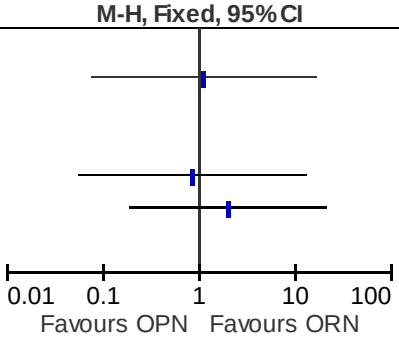
10.1 All cause death

Study or Subgroup	Open partial Events	Total	Open radical Events	Total	Risk Ratio M-H, Fixed, 95% CI
10.1.1 RCT					
10.1.2 NRS					
Gratzke 2009	1	44	1	37	0.84 [0.05, 12.99]
Lee 2007	3	56	2	56	1.50 [0.26, 8.64]



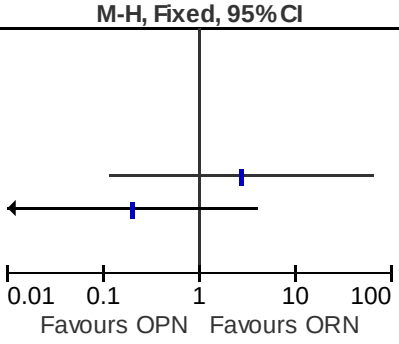
10.2 Cancer specific death

Study or Subgroup	Open partial Events	Total	Open radical Events	Total	Risk Ratio M-H, Fixed, 95% CI
10.2.1 RCT					
D'Armiento 1997	1	19	1	21	1.11 [0.07, 16.47]
10.2.2 NRS					
Gratzke 2009	1	44	1	37	0.84 [0.05, 12.99]
Lee 2007	2	56	1	56	2.00 [0.19, 21.43]



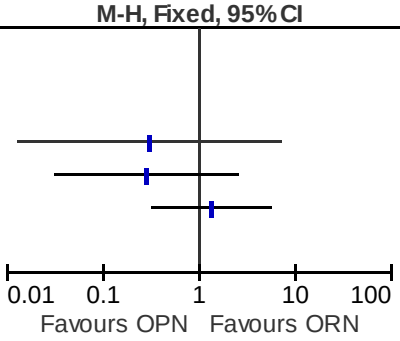
10.3 Local recurrence

Study or Subgroup	Open partial Events	Total	Open radical Events	Total	Risk Ratio M-H, Fixed, 95% CI
10.3.1 RCT					
D'Armiento 1997	0	19	0	21	Not estimable
10.3.2 NRS					
Buttler 1995	1	46	0	42	2.74 [0.11, 65.59]
Lee 2007	0	56	2	56	0.20 [0.01, 4.07]



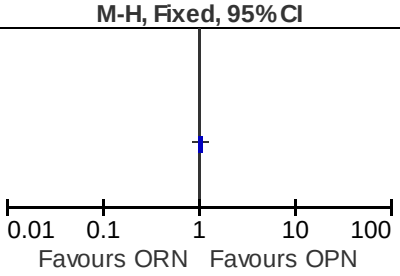
10.4 Incidence of metastasis

Study or Subgroup	Open partial Events	Total	Open radical Events	Total	Risk Ratio M-H, Fixed, 95% CI
10.4.1 RCT					
10.4.2 NRS					
Buttler 1995	0	46	1	42	0.30 [0.01, 7.29]
Gratzke 2009	1	44	3	37	0.28 [0.03, 2.58]
Lee 2007	4	56	3	56	1.33 [0.31, 5.69]



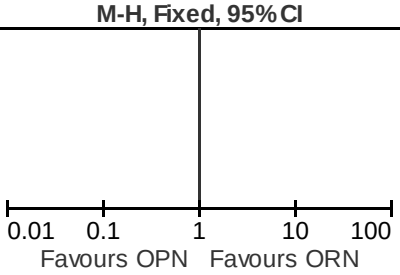
10.5 Disease free rate (N of patients alive and tumour free)

Study or Subgroup	Open partial Events	Total	Open radical Events	Total	Risk Ratio M-H, Fixed, 95% CI
10.5.1 RCT					
10.5.2 NRS					
Buttler 1995	38	46	34	42	1.02 [0.84, 1.24]



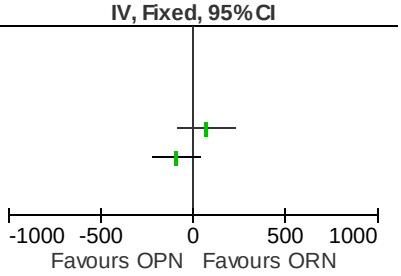
10.6 Postive surgical margin

Study or Subgroup	Open partial Events	Total	Open radical Events	Total	Risk Ratio M-H, Fixed, 95% CI
10.6.1 RCT					
10.6.2 NRS					
Buttler 1995	0	46	0	42	Not estimable



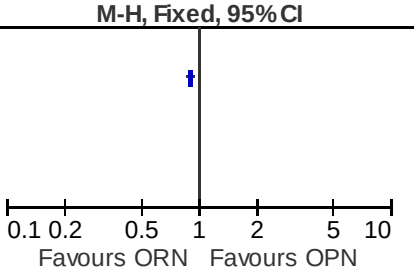
10.7 Blood loss (ml, mean, SD)

Study or Subgroup	Open partial Mean	SD	Total	Open radical Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
10.7.1 RCT							
10.7.2 NRS							
Gratzke 2009	494	360	44	424	361	37	70.00 [-87.62, 227.62]
Shekarriz 2002	415.2	273.5	60	506.9	443.4	60	-91.70 [-223.52, 40.12]



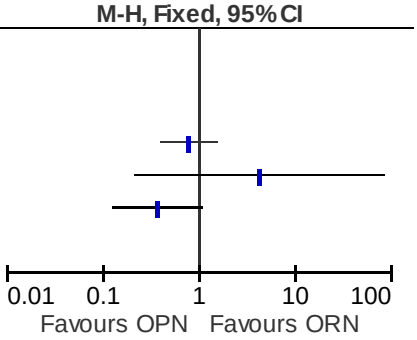
10.8 Blood loss (N of patients with <500 ml)

Study or Subgroup	Open partial Events	Total	Open radical Events	Total	Risk Ratio M-H, Fixed, 95% CI
10.8.1 RCT					
Van Poppel 2007	230	265	254	264	0.90 [0.86, 0.95]
10.8.2 NRS					



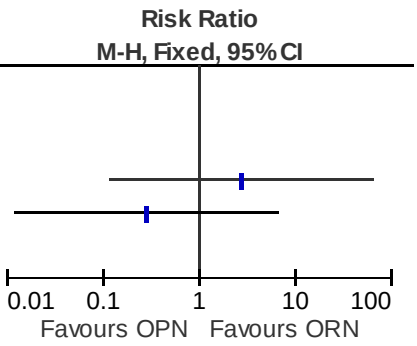
10.9 Blood transfusion (N of patients requiring 1 or more unit)

Study or Subgroup	Open partial Events	Total	Open radical Events	Total	Risk Ratio M-H, Fixed, 95% CI
10.9.1 RCT					
10.9.2 NRS					
Buttler 1995	11	46	13	42	0.77 [0.39, 1.53]
Gratzke 2009	2	44	0	37	4.22 [0.21, 85.27]
Shekarriz 2002	4	60	11	60	0.36 [0.12, 1.08]



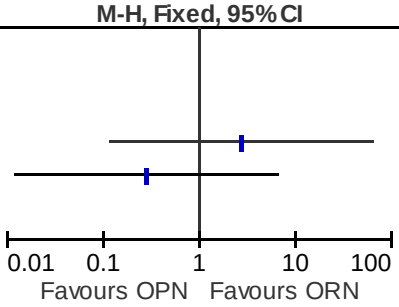
10.10 Surgical site infection

Study or Subgroup	Open partial Events	Total	Open radical Events	Total	Risk Ratio M-H, Fixed, 95% CI
10.10.1 RCT					
10.10.2 NRS					
Buttler 1995	1	46	0	42	2.74 [0.11, 65.59]
Gratzke 2009	0	44	1	37	0.28 [0.01, 6.71]



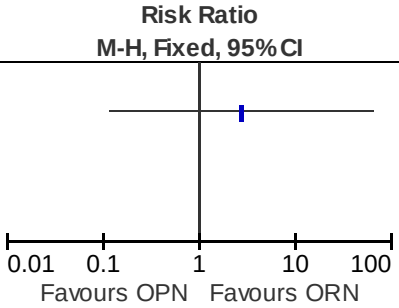
10.11 Pneumonia

Study or Subgroup	Open partial Events	Total	Open radical Events	Total	Risk Ratio M-H, Fixed, 95% CI
10.11.1 RCT					
10.11.2 NRS					
Buttler 1995	1	46	0	42	2.74 [0.11, 65.59]
Gratzke 2009	0	44	1	37	0.28 [0.01, 6.71]



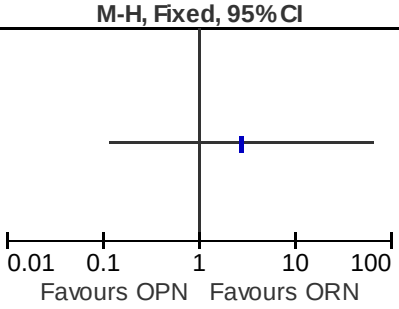
10.12 Urinary tract infection

Study or Subgroup	Open partial Events	Total	Open radical Events	Total	Risk Ratio M-H, Fixed, 95% CI
10.12.1 NRS					
Buttler 1995	1	46	0	42	2.74 [0.11, 65.59]
10.12.2 RCT					



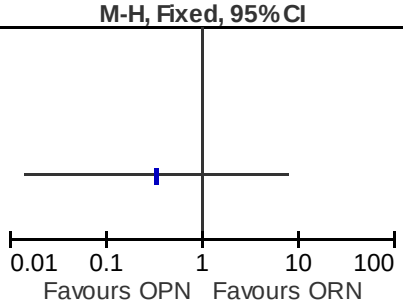
10.13 Deep venous thromosis

Study or Subgroup	Open partial Events	Total	Open radical Events	Total	Risk Ratio M-H, Fixed, 95% CI
10.13.1 RCT					
10.13.2 NRS					
Buttler 1995	1	46	0	42	2.74 [0.11, 65.59]
Gratzke 2009	0	44	0	37	Not estimable



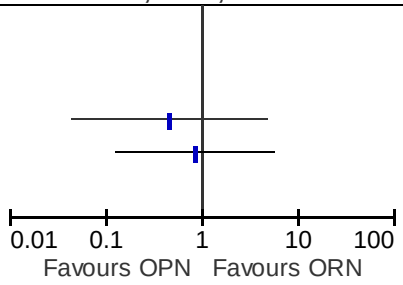
10.14 Pulmonary embolism

Study or Subgroup	Open partial Events	Total	Open radical Events	Total	Risk Ratio M-H, Fixed, 95% CI
10.14.1 RCT					
10.14.2 NRS					
Gratzke 2009	0	44	0	37	Not estimable
Shekarriz 2002	0	60	1	60	0.33 [0.01, 8.02]



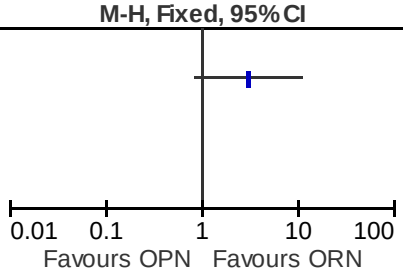
10.15 Haemorrhage

Study or Subgroup	Open partial Events	Total	Open radical Events	Total	Risk Ratio M-H, Fixed, 95% CI
10.15.1 RCT					
10.15.2 NRS					
Buttler 1995	1	46	2	42	0.46 [0.04, 4.85]
Gratzke 2009	2	44	2	37	0.84 [0.12, 5.68]



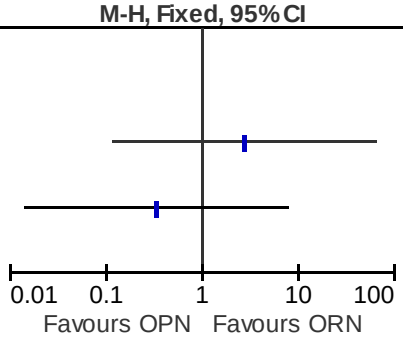
10.16 Severe haemorrhage (N of patients with blood loss >1 litre)

Study or Subgroup	Open partial Events	Total	Open radical Events	Total	Risk Ratio M-H, Fixed, 95% CI
10.16.1 RCT					
Van Poppel 2007	9	265	3	264	2.99 [0.82, 10.92]
10.16.2 NRS					



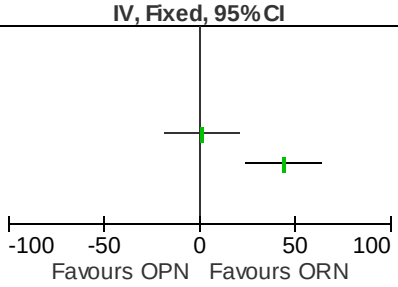
10.17 Post-operative mortality

Study or Subgroup	Open partial Events	Total	Open radical Events	Total	Risk Ratio M-H, Fixed, 95% CI
10.17.1 RCT					
10.17.2 NRS					
Buttler 1995	1	46	0	42	2.74 [0.11, 65.59]
Gratzke 2009	0	44	0	37	Not estimable
Shekarriz 2002	0	60	1	60	0.33 [0.01, 8.02]



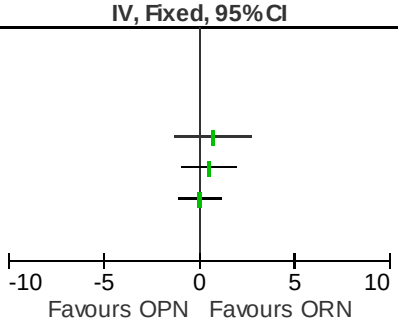
10.18 Duration of operation (minute, mean, SD)

Study or Subgroup	Open partial Mean	SD	Total	Open radical Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
10.18.1 RCT							
10.18.2 NRS							
Gratzke 2009	114	42	44	113	48	37	1.00 [-18.83, 20.83]
Shekarriz 2002	220.1	59.6	60	176	51.6	60	44.10 [24.15, 64.05]



10.19 Length of hospital stay (day, mean, SD)

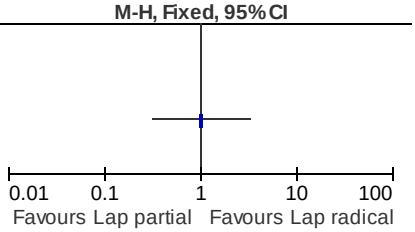
Study or Subgroup	Open partial Mean	SD	Total	Open radical Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
10.19.1 RCT							
10.19.2 NRS							
Buttler 1995	9.2	6.1	46	8.5	3.4	42	0.70 [-1.34, 2.74]
Gratzke 2009	9.6	3.1	44	9.1	3.5	37	0.50 [-0.95, 1.95]
Shekarriz 2002	6.4	3	60	6.4	3.3	60	0.00 [-1.13, 1.13]



12 Laparoscopic partial vs. Laparoscopic radical nephrectomy (D2)

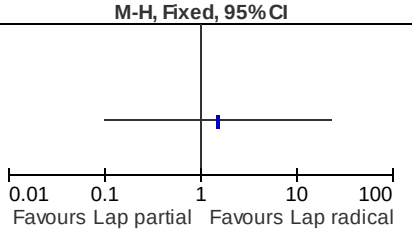
12.1 All cause death (pT1-2 only)

Study or Subgroup	Laparoscopic partial Events	Total	Laparoscopic radical Events	Total	Risk Ratio M-H, Fixed, 95% CI
12.1.1 RCT					
12.1.2 NRS					
Simmons 2008	4	30	6	45	1.00 [0.31, 3.25]



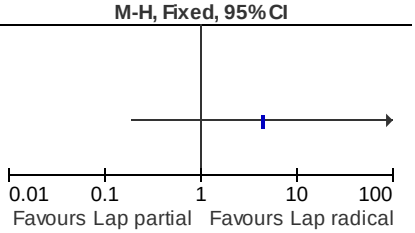
12.2 Cancer specific death (pT1-2 only)

Study or Subgroup	Laparoscopic partial Events	Total	Laparoscopic radical Events	Total	Risk Ratio M-H, Fixed, 95% CI
12.2.1 RCT					
12.2.2 NRS					
Simmons 2008	1	30	1	45	1.50 [0.10, 23.07]



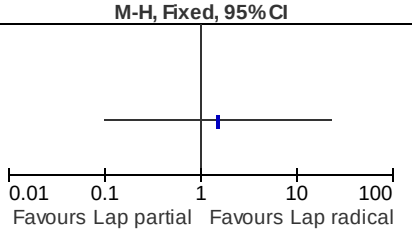
12.3 Local recurrence (pT1-2 only)

Study or Subgroup	Laparoscopic partial Events	Total	Laparoscopic radical Events	Total	Risk Ratio M-H, Fixed, 95% CI
12.3.1 RCT					
12.3.2 NRS					
Simmons 2008	1	30	0	45	4.45 [0.19, 105.77]



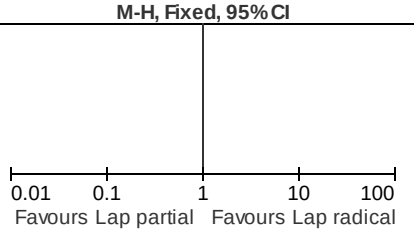
12.4 Systemic recurrence (pT1-2 only)

Study or Subgroup	Laparoscopic partial Events	Total	Laparoscopic radical Events	Total	Risk Ratio M-H, Fixed, 95% CI
12.4.1 RCT					
12.4.2 NRS					
Simmons 2008	1	30	1	45	1.50 [0.10, 23.07]



12.5 Positive surgical margines (pT1-2 only)

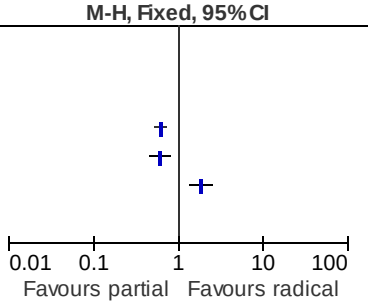
Study or Subgroup	Laparoscopic partial Events	Total	Laparoscopic radical Events	Total	Risk Ratio M-H, Fixed, 95% CI
12.5.1 RCT					
12.5.2 NRS					
Simmons 2008	0	30	0	45	Not estimable



13 Open & lap partial vs. Open & lap radical nephrectomy (D3)

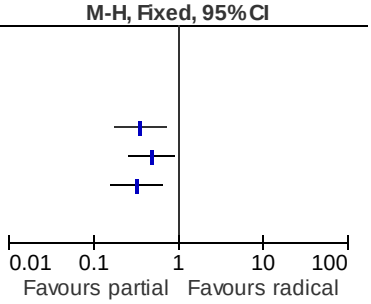
13.1 All cause death (N of patients)

Study or Subgroup	Open and lap partial Events	Total	Open and lap radical Events	Total	Risk Ratio M-H, Fixed, 95% CI
13.1.1 RCT					
13.1.2 NRS					
Huang 2009	110	556	782	2435	0.62 [0.52, 0.74]
Thompson 2008	62	358	84	290	0.60 [0.45, 0.80]
Thompson 2009	55	286	74	704	1.83 [1.33, 2.52]



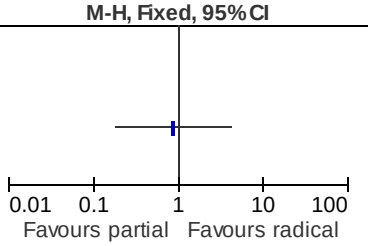
13.2 Cancer specific death (N of patients)

Study or Subgroup	Open and lap partial Events	Total	Open and lap radical Events	Total	Risk Ratio M-H, Fixed, 95% CI
13.2.1 RCT					
13.2.2 NRS					
Huang 2009	8	556	99	2435	0.35 [0.17, 0.72]
Patard 2004	11	379	65	1075	0.48 [0.26, 0.90]
Thompson 2009	8	239	74	704	0.32 [0.16, 0.65]



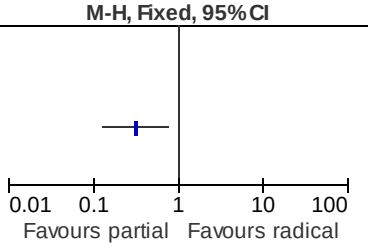
13.3 Local recurrence (N of patients)

Study or Subgroup	Open and lap partial Events	Total	Open and lap radical Events	Total	Risk Ratio M-H, Fixed, 95% CI
13.3.1 RCT					
13.3.2 NRS					
Patard 2004	2	151	6	393	0.87 [0.18, 4.25]



13.4 Distant recurrence (N of patients)

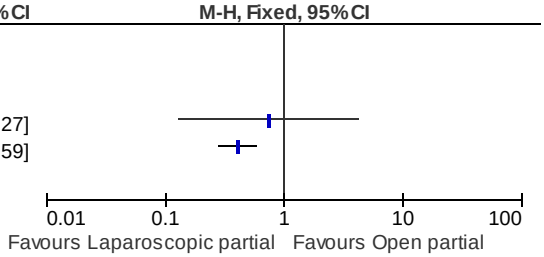
Study or Subgroup	Open and lap partial Events	Total	Open and lap radical Events	Total	Risk Ratio M-H, Fixed, 95% CI
13.4.1 RCT					
13.4.2 NRS					
Patard 2004	5	151	42	393	0.31 [0.12, 0.77]



14 Laparoscopic partial vs. Open partial nephrectomy (D5)

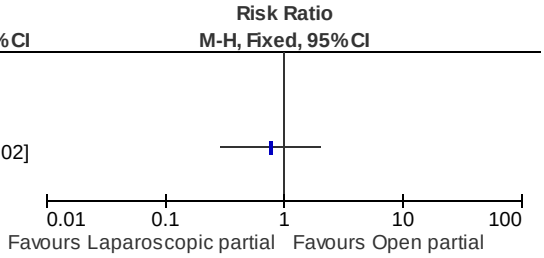
14.1 All cause death

Study or Subgroup	Laparoscopic partial Events	Total	Open partial Events	Total	Risk Ratio M-H, Fixed, 95% CI
14.1.1 RCT					
14.1.2 NRS					
Gong 2008	2	54	3	60	0.74 [0.13, 4.27]
Lane 2010	33	672	115	944	0.40 [0.28, 0.59]



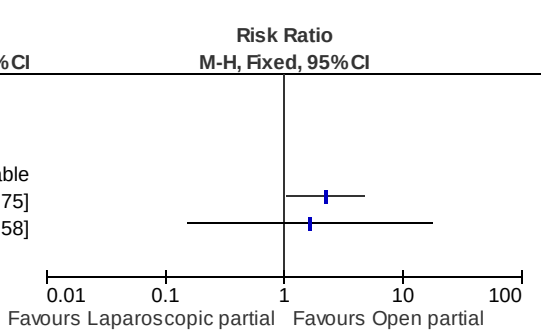
14.2 Cancer-specific death

Study or Subgroup	Laparoscopic partial Events	Total	Open partial Events	Total	Risk Ratio M-H, Fixed, 95% CI
14.2.1 RCT					
14.2.2 NRS					
Lane 2010	6	499	12	762	0.76 [0.29, 2.02]



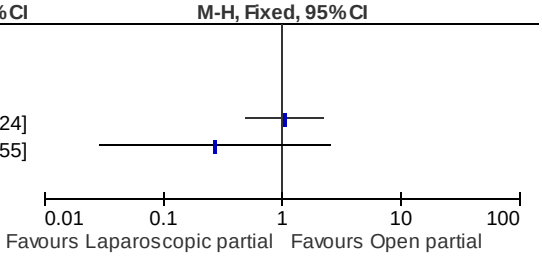
14.3 Local recurrence

Study or Subgroup	Laparoscopic partial Events	Total	Open partial Events	Total	Risk Ratio M-H, Fixed, 95% CI
14.3.1 RCT					
14.3.2 NRS					
Gong 2008	0	76	0	77	Not estimable
Lane 2010	16	499	11	762	2.22 [1.04, 4.75]
Marszalek 2009	2	81	1	66	1.63 [0.15, 17.58]



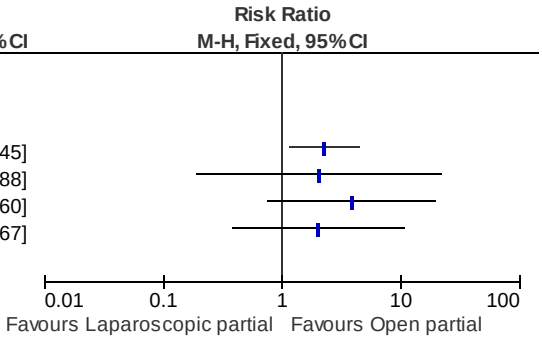
14.4 Incidence of metastasis

Study or Subgroup	Laparoscopic partial Events	Total	Open partial Events	Total	Risk Ratio M-H, Fixed, 95% CI
14.4.1 RCT					
14.4.2 NRS					
Lane 2010	11	499	16	762	1.05 [0.49, 2.24]
Marszalek 2009	1	81	3	66	0.27 [0.03, 2.55]



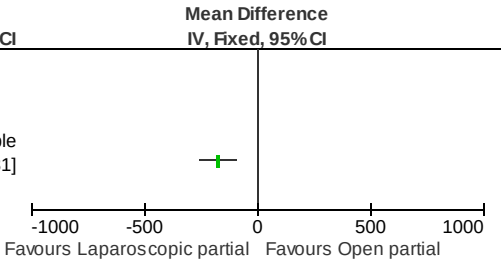
14.5 Postive surgical margin

Study or Subgroup	Laparoscopic partial Events	Total	Open partial Events	Total	Risk Ratio M-H, Fixed, 95% CI
14.5.1 RCT					
14.5.2 NRS					
Gill 2007	22	771	13	1029	2.26 [1.15, 4.45]
Gong 2008	2	76	1	77	2.03 [0.19, 21.88]
Lane 2010	5	499	2	762	3.82 [0.74, 19.60]
Marszalek 2009	4	100	2	100	2.00 [0.37, 10.67]



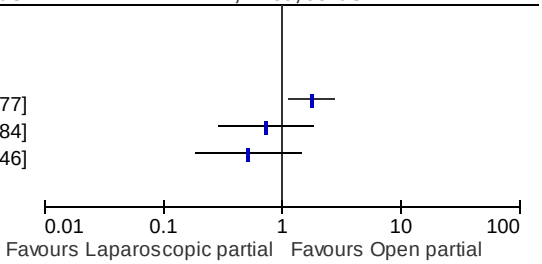
14.6 Blood loss (ml, mean, SD)

Study or Subgroup	Laparoscopic partial Mean	SD	Total	Open partial Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
14.6.1 RCT							
14.6.2 NRS							
Gill 2007	300	0	759	376	0	945	Not estimable
Gong 2008	211.9	251.3	76	385.4	270.3	77	-173.50 [-256.19, -90.81]



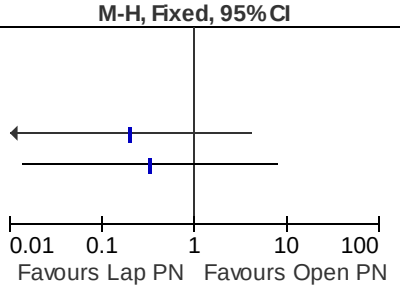
14.7 Blood transfusion (N of patients)

Study or Subgroup	Laparoscopic partial Events	Total	Open partial Events	Total	Odds Ratio M-H, Fixed, 95% CI
14.7.1 RCT					
14.7.2 NRS					
Gill 2007	45	771	35	1029	1.76 [1.12, 2.77]
Gong 2008	9	76	12	77	0.73 [0.29, 1.84]
Marszalek 2009	6	100	11	100	0.52 [0.18, 1.46]



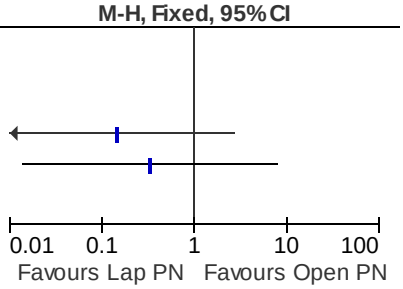
14.8 Wound infection

Study or Subgroup	Laparoscopic partial Events	Total	Open partial Events	Total	Risk Ratio M-H, Fixed, 95% CI
14.8.1 RCT					
14.8.2 NRS					
Gong 2008	0	76	2	77	0.20 [0.01, 4.15]
Marszalek 2009	0	100	1	100	0.33 [0.01, 8.09]



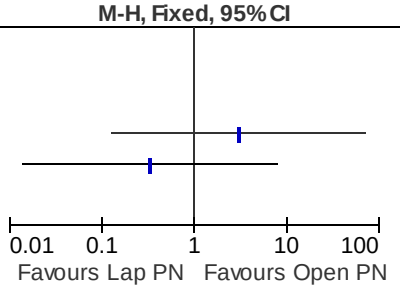
14.9 Pneumonia

Study or Subgroup	Laparoscopic partial Events	Total	Open partial Events	Total	Risk Ratio M-H, Fixed, 95% CI
14.9.1 RCT					
14.9.2 NRS					
Gong 2008	0	76	3	77	0.14 [0.01, 2.75]
Marszalek 2009	0	100	1	100	0.33 [0.01, 8.09]



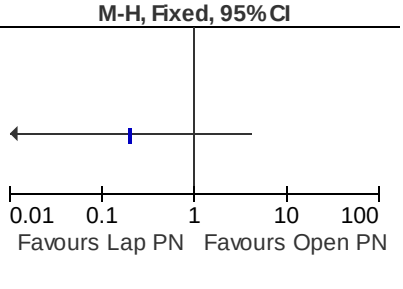
14.10 Urinary tract infection

Study or Subgroup	Laparoscopic partial Events	Total	Open partial Events	Total	Risk Ratio M-H, Fixed, 95% CI
14.10.1 RCT					
14.10.2 NRS					
Gong 2008	1	76	0	77	3.04 [0.13, 73.45]
Marszalek 2009	0	100	1	100	0.33 [0.01, 8.09]



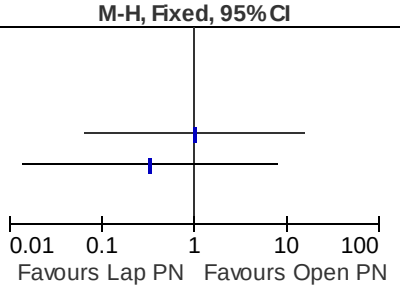
14.11 Deep venous thrombosis

Study or Subgroup	Laparoscopic partial Events	Total	Open partial Events	Total	Risk Ratio M-H, Fixed, 95% CI
14.11.1 RCT					
14.11.2 NRS					
Gong 2008	0	76	2	77	0.20 [0.01, 4.15]



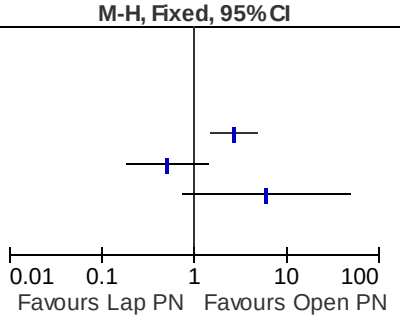
14.12 Pulmonary embolism

Study or Subgroup	Laparoscopic partial Events	Total	Open partial Events	Total	Risk Ratio M-H, Fixed, 95% CI
14.12.1 RCT					
14.12.2 NRS					
Gong 2008	1	76	1	77	1.01 [0.06, 15.91]
Marszalek 2009	0	100	1	100	0.33 [0.01, 8.09]



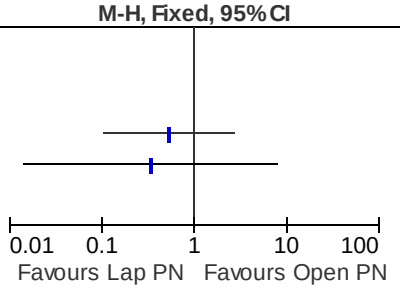
14.13 Hemorrhage

Study or Subgroup	Laparoscopic partial Events	Total	Open partial Events	Total	Risk Ratio M-H, Fixed, 95% CI
14.13.1 RCT					
14.13.2 NRS					
Gill 2007	32	771	16	1029	2.67 [1.48, 4.83]
Gong 2008	5	76	10	77	0.51 [0.18, 1.41]
Marszalek 2009	6	100	1	100	6.00 [0.74, 48.94]



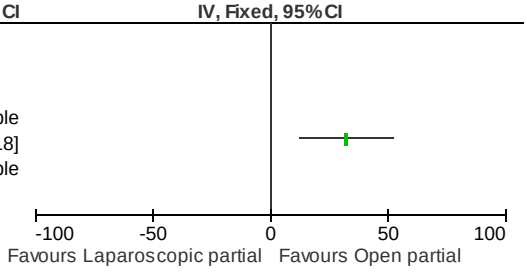
14.14 Post-operative mortality

Study or Subgroup	Laparoscopic partial Events	Total	Open partial Events	Total	Risk Ratio M-H, Fixed, 95% CI
14.14.1 RCT					
14.14.2 NRS					
Gill 2007	2	771	5	1029	0.53 [0.10, 2.74]
Gong 2008	0	76	1	77	0.34 [0.01, 8.16]



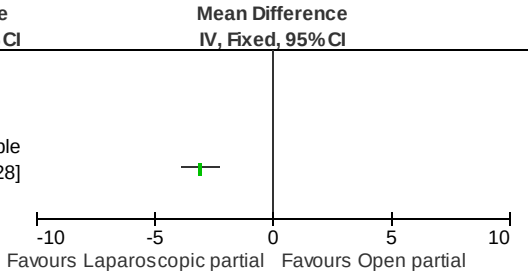
14.15 Duration of operation (minute, mean, SD)

Study or Subgroup	Laparoscopic partial Mean	SD	Total	Open partial Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
14.15.1 RCT							
14.15.2 NRS							
Gill 2007	201	0	680	266	0	449	Not estimable
Gong 2008	225.1	63.8	76	193	62.9	77	32.10 [12.02, 52.18]
Marszalek 2009	0	0	100	0	0	100	Not estimable



14.16 Length of hospital stay (day, mean, SD)

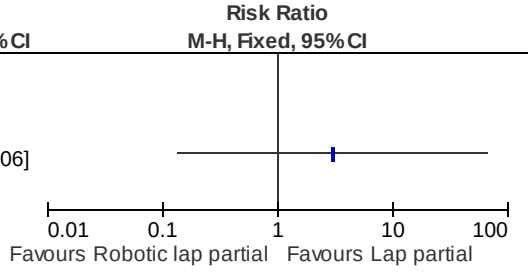
Study or Subgroup	Laparoscopic partial Mean	SD	Total	Open partial Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
14.16.1 RCT							
14.16.2 NRS							
Gill 2007	3.3	0	771	5.8	0	1029	Not estimable
Gong 2008	2.5	2.1	76	5.6	3	77	-3.10 [-3.92, -2.28]



15 Robotic laparoscopic partial nephrectomy vs. Laparoscopic partial nephrectomy (D6)

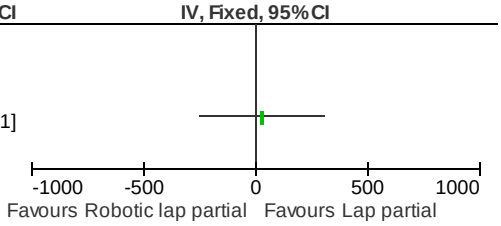
15.1 Postive surgical margin (N of patients)

Study or Subgroup	Robotic lap partial Events	Total	Lap partial Events	Total	Risk Ratio M-H, Fixed, 95% CI
15.1.1 RCT					
15.1.2 NRS					
Aron 2008	1	12	0	12	3.00 [0.13, 67.06]



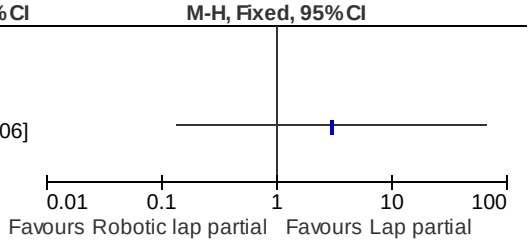
15.2 Blood loss (ml, mean, SD)

Study or Subgroup	Robotic lap partial Mean	SD	Total	Lap partial Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
15.2.1 RCT							
15.2.2 NRS							
Aron 2008	329	315	12	300	384	12	29.00 [-252.01, 310.01]



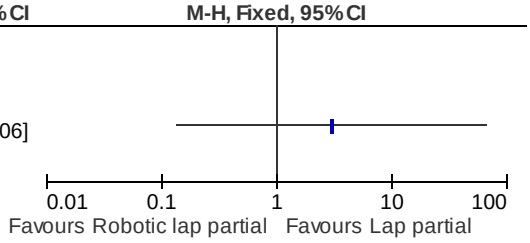
15.3 Pulmoary emblism

Study or Subgroup	Robotic lap partial Events	Total	Lap partial Events	Total	Risk Ratio M-H, Fixed, 95% CI
15.3.1 RCT					
15.3.2 NRS					
Aron 2008	1	12	0	12	3.00 [0.13, 67.06]



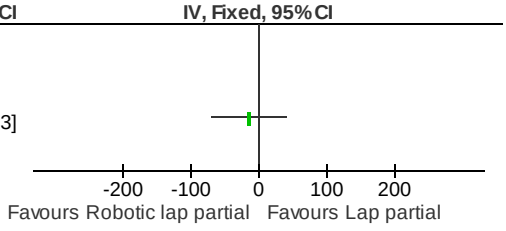
15.4 Haemorrhage, transfused

Study or Subgroup	Robotic lap partial Events	Total	Lap partial Events	Total	Risk Ratio M-H, Fixed, 95% CI
15.4.1 RCT					
15.4.2 NRS					
Aron 2008	1	12	0	12	3.00 [0.13, 67.06]



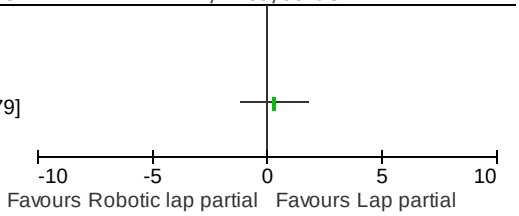
15.5 Duration of operation (minute, mean, SD)

Study or Subgroup	Robotic lap partial Mean	SD	Total	Lap partial Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
15.5.1 RCT							
15.5.2 NRS							
Aron 2008	242	69.2	12	256	70.6	12	-14.00 [-69.93, 41.93]



15.6 Length of hospital stay (day, mean, SD)

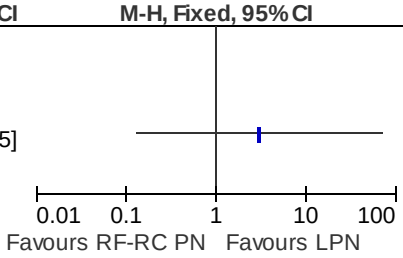
Study or Subgroup	Robotic lap partial Mean	SD	Total	Lap partial Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
15.6.1 RCT							
15.6.2 NRS							
Aron 2008	4.7	2.4	12	4.4	1.1	12	0.30 [-1.19, 1.79]



16 Radiofrequency ablation-assisted robotic clampless partial nephrectomy (RF-RC PN) vs. laparoscopic partial nephrectomy (LPN) (D7)

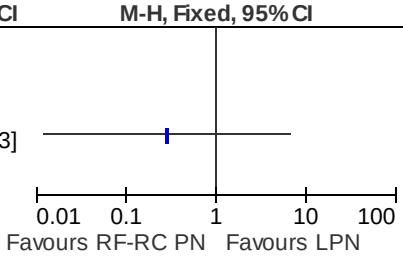
16.1 Local recurrence

Study or Subgroup	RF-RC partial Events	Total	Laparoscopic partial Events	Total	Risk Ratio M-H, Fixed, 95% CI
16.1.1 RCT					
16.1.2 NRS					
Wu 2010	1	34	0	34	3.00 [0.13, 71.15]



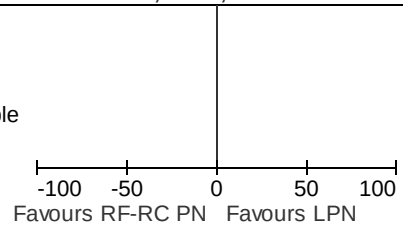
16.2 Positive surgical margins

Study or Subgroup	RF-RC partial Events	Total	Laparoscopic partial Events	Total	Risk Ratio M-H, Fixed, 95% CI
16.2.1 RCT					
16.2.2 NRS					
Wu 2010	0	42	1	36	0.29 [0.01, 6.83]



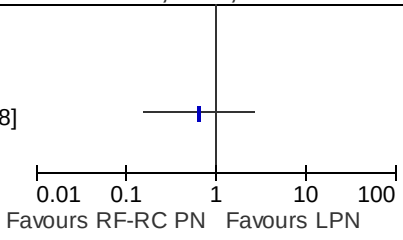
16.3 Blood loss (ml, mean, SD)

Study or Subgroup	RF-RC partial Mean	SD	Total	Laparoscopic partial Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
16.3.1 RCT							
16.3.2 NRS							
Wu 2010	337	0	42	250	0	36	Not estimable



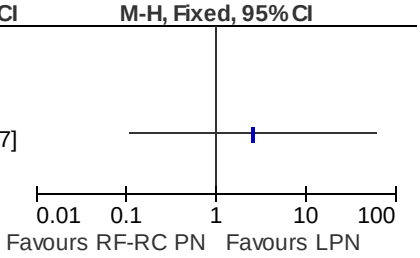
16.4 Blood transfusion (N of patients))

Study or Subgroup	RF-RC partial Events	Total	Laparoscopic partial Events	Total	Risk Ratio M-H, Fixed, 95% CI
16.4.1 RCT					
16.4.2 NRS					
Wu 2010	3	42	4	36	0.64 [0.15, 2.68]



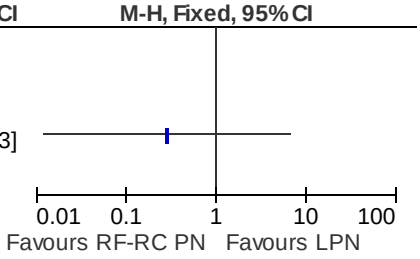
16.5 Superficial wound infection

Study or Subgroup	RF-RC partial Events	Total	Laparoscopic partial Events	Total	Risk Ratio M-H, Fixed, 95% CI
16.5.1 RCT					
16.5.2 NRS					
Wu 2010	1	42	0	36	2.58 [0.11, 61.47]



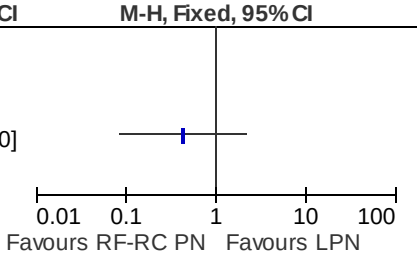
16.6 Pneumonia

Study or Subgroup	RF-RC partial Events	Total	Laparoscopic partial Events	Total	Risk Ratio M-H, Fixed, 95% CI
16.6.1 RCT					
16.6.2 NRS					
Wu 2010	0	42	1	36	0.29 [0.01, 6.83]



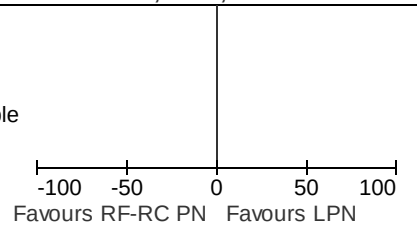
16.7 Hemorrhage

Study or Subgroup	RF-RC partial Events	Total	Laparoscopic partial Events	Total	Risk Ratio M-H, Fixed, 95% CI
16.7.1 RCT					
16.7.2 NRS					
Wu 2010	2	42	4	36	0.43 [0.08, 2.20]



16.8 Duration of operation (minute, mean, SD)

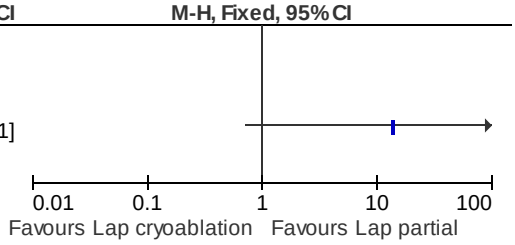
Study or Subgroup	RF-RC partial Mean	SD	Total	Laparoscopic partial Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
16.8.1 RCT							
16.8.2 NRS							
Wu 2010	373	0	42	293	0	36	Not estimable



17 Laparoscopic cryoablation vs. Laparoscopic partial nephrectomy (D8)

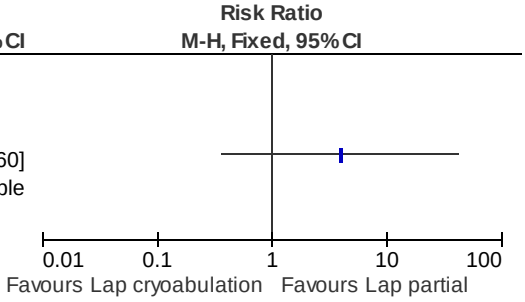
17.1 All cause deaths (N of patients)

Study or Subgroup	Lap cryoabulation Events	Total	Lap partial Events	Total	Risk Ratio M-H, Fixed, 95% CI
17.1.1 RCT					
17.1.2 NRS					
Desai 2005b	3	78	0	153	13.65 [0.71, 260.91]



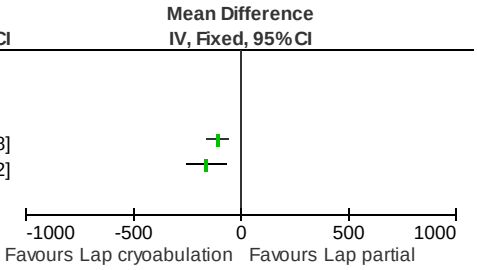
17.2 Local recurrence (N of patients)

Study or Subgroup	Lap cryoabulation Events	Total	Lap partial Events	Total	Risk Ratio M-H, Fixed, 95% CI
17.2.1 RCT					
17.2.2 NRS					
Desai 2005b	2	78	1	153	3.92 [0.36, 42.60]
O'Malley 2007	0	15	0	15	Not estimable



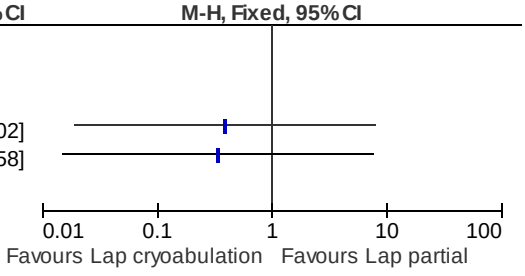
17.3 Blood loss (ml, mean, SD)

Study or Subgroup	Lap cryoabulation Mean	SD	Total	Lap partial Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
17.3.1 RCT							
17.3.2 NRS							
Desai 2005b	100.81	87.72	78	211.39	298.83	153	-110.58 [-161.78, -59.38]
O'Malley 2007	58.7	28.5	15	221.7	182.5	15	-163.00 [-256.48, -69.52]



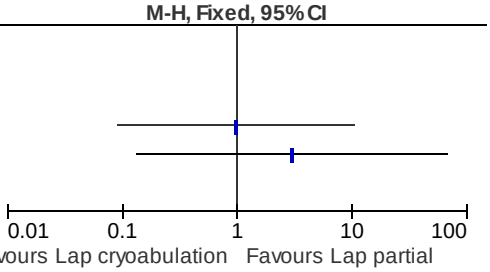
17.4 Blood transfusion (N of patients)

Study or Subgroup	Lap cryoabulation Events	Total	Lap partial Events	Total	Risk Ratio M-H, Fixed, 95% CI
17.4.1 RCT					
17.4.2 NRS					
Desai 2005b	0	78	2	153	0.39 [0.02, 8.02]
O'Malley 2007	0	15	1	15	0.33 [0.01, 7.58]



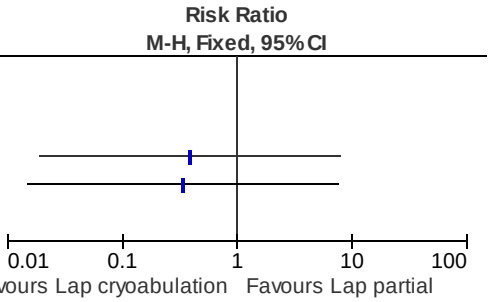
17.5 Pneumonia (N of events)

Study or Subgroup	Lap cryoabulation Events	Total	Lap partial Events	Total	Risk Ratio M-H, Fixed, 95% CI
17.5.1 RCT					
17.5.2 NRS					
Desai 2005b	1	78	2	153	0.98 [0.09, 10.65]
O'Malley 2007	1	15	0	15	3.00 [0.13, 68.26]



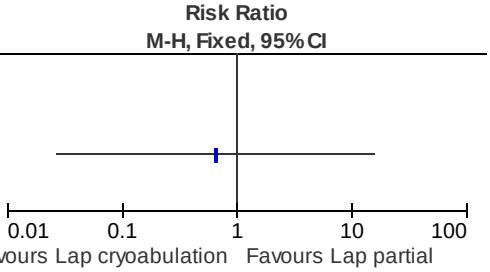
17.6 Deep venous thrombosis (N of events)

Study or Subgroup	Lap cryoabulation Events	Total	Lap partial Events	Total	Risk Ratio M-H, Fixed, 95% CI
17.6.1 RCT					
17.6.2 NRS					
Desai 2005b	0	78	2	153	0.39 [0.02, 8.02]
O'Malley 2007	0	15	1	15	0.33 [0.01, 7.58]



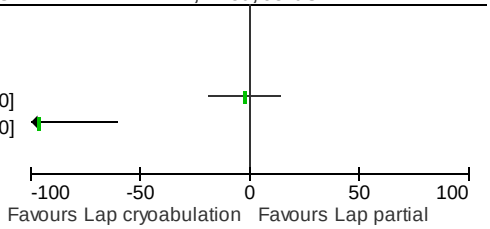
17.7 Pulmonary embolism (N of events)

Study or Subgroup	Lap cryoabulation Events	Total	Lap partial Events	Total	Risk Ratio M-H, Fixed, 95% CI
17.7.1 RCT					
17.7.2 NRS					
Desai 2005b	0	78	1	153	0.65 [0.03, 15.77]



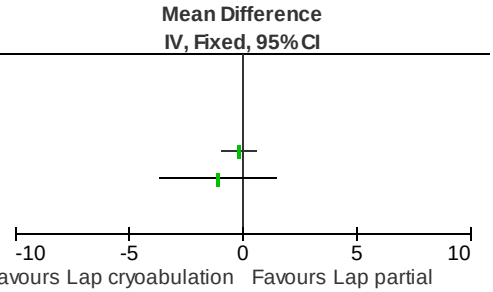
17.8 Duration of operation (minute, mean, SD)

Study or Subgroup	Lap cryoabulation Mean	SD	Total	Lap partial Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
17.8.1 RCT							
17.8.2 NRS							
Desai 2005b	187.77	64.18	78	190.1	51.71	153	-2.33 [-18.76, 14.10]
O'Malley 2007	152.2	37.3	15	248.4	60.1	15	-96.20 [-132.00, -60.40]



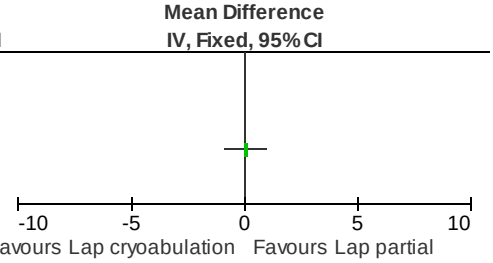
17.9 Length of hospital stay (day, mean, SD)

Study or Subgroup	Lap cryoabulation Mean	SD	Total	Lap partial Mean	SD	Total	Mean Difference IV, Fixed, 95%CI
17.9.1 RCT							
17.9.2 NRS							
Desai 2005b	2.1	2.9	78	2.3	2.8	153	-0.20 [-0.98, 0.58]
O'Malley 2007	3.3	3.3	15	4.4	3.9	15	-1.10 [-3.69, 1.49]



17.10 Convalescence time (weeks)

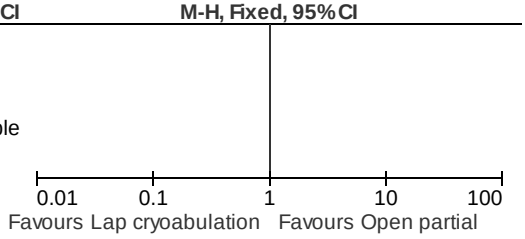
Study or Subgroup	Lap cryoabulation Mean	SD	Total	Lap partial Mean	SD	Total	Mean Difference IV, Fixed, 95%CI
17.10.1 RCT							
17.10.2 NRS							
Desai 2005b	4.45	3.67	78	4.39	3.07	153	0.06 [-0.89, 1.01]



18 Laparoscopic cryoablation vs. Open partial nephrectomy (D9)

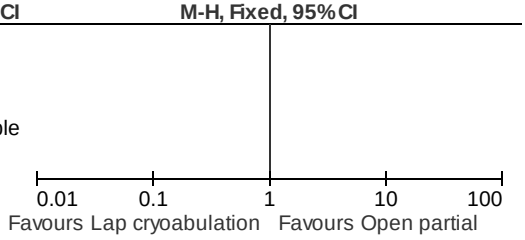
18.1 Local recurrence (N of patients)

Study or Subgroup	Lap cryoabulation Events	Total	Open partial Events	Total	Risk Ratio M-H, Fixed, 95%CI
18.1.1 RCT					
18.1.2 NRS					
Ko 2008	0	20	0	20	Not estimable



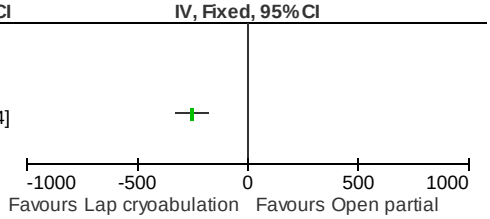
18.2 Incidence of metastasis (N of patients)

Study or Subgroup	Lap cryoabulation Events	Total	Open partial Events	Total	Risk Ratio M-H, Fixed, 95%CI
18.2.1 RCT					
18.2.2 NRS					
Ko 2008	0	20	0	20	Not estimable



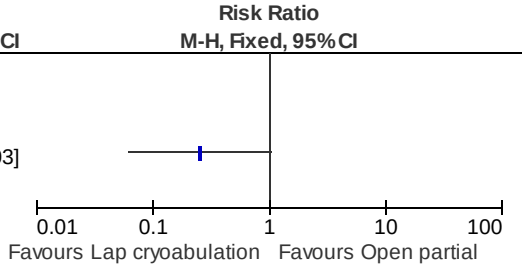
18.3 Blood loss (ml, mean, SD)

Study or Subgroup	Lap cryoabulation Mean	SD	Total	Open partial Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
18.3.1 RCT							
18.3.2 NRS							
Ko 2008	98	87	20	351	147	20	-253.00 [-327.86, -178.14]



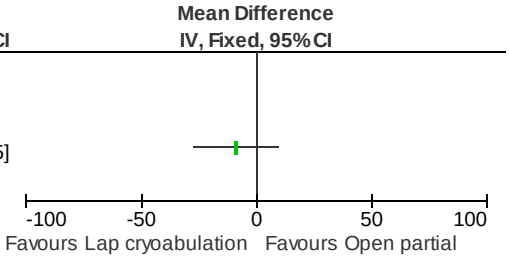
18.4 Blood transfusion (N of patients)

Study or Subgroup	Lap cryoabulation Events	Total	Open partial Events	Total	Risk Ratio M-H, Fixed, 95% CI
18.4.1 RCT					
18.4.2 NRS					
Ko 2008	2	20	8	20	0.25 [0.06, 1.03]



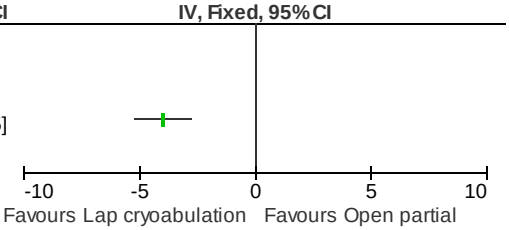
18.5 Duration of operation (minute, mean, SD)

Study or Subgroup	Lap cryoabulation Mean	SD	Total	Open partial Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
18.5.1 RCT							
18.5.2 NRS							
Ko 2008	169	21	20	178	37	20	-9.00 [-27.65, 9.65]



18.6 Length of hospital stay (day, mean, SD)

Study or Subgroup	Lap cryoabulation Mean	SD	Total	Open partial Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
18.6.1 RCT							
18.6.2 NRS							
Ko 2008	4.21	1.5	20	8.2	2.4	20	-3.99 [-5.23, -2.75]



Appendix 12: GRADE profiles

Author(s):
Date: 2011-05-12
Question: Should non-surgical management vs surgical management (A1) be used for localised renal cell carcinoma?
Settings:
Bibliography:

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Non-surgical management	Surgical management (A1)	Relative (95% CI)	Absolute		
Overall survival at 5 years, indicated by proxy outcome of cancer specific deaths at 5 years (follow-up 0.1-203 months[1])												
1	observational studies	serious[2]	no serious inconsistency	very serious[3,4]	no serious imprecision[5]	none	0/430 (0%)[6]	0/1545 (0%)[7]	Not estimable[8]	-	⊕OOO VERY LOW	CRITICAL
Overall survival at 5 years, indicated by proxy outcome of other cause deaths at 5 years (follow-up 0.1-203 months[4])												
1	observational studies	serious[2]	no serious inconsistency	very serious[3,4]	no serious imprecision[5]	none	0/430 (0%)[9]	0/1545 (0%)[10]	Not estimable[11]	-	⊕OOO VERY LOW	CRITICAL
Recurrence at 5 years - not reported												
1	-	-	-	-	-	none	-	-	-	-		CRITICAL
Condition-specific quality of life - not reported												
0	-	-	-	-	-	none	0	-	-	-		CRITICAL
Overall morbidity - not reported												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Time to normal activity - not reported												
0	-	-	-	-	-	none	0	-	-	-		CRITICAL
Analgesic requirement - not reported												
0	-	-	-	-	-	none	0	-	-	-		IMPORTANT
Need for blood transfusion - not reported												
0	-	-	-	-	-	none	-	-	-	-		IMPORTANT

[1] Duration of follow up (months, median, range): non-surgical management 16 [0.1, 146] vs. surgical management 50 [0.1, 203]
[2] Major confounders either not reported, or are not balanced at baseline and not adjusted for in analysis.
[3] Indirect outcome
[4] Duration of follow-up is different between the groups. Also, median follow up is less than 5 years
[5] 95% CI not reported so unable to judge
[6] Reported value 12.4%
[7] Reported value 4.4%
[8] Quote from paper (Zini 2009a: 901): 'In univariate matched competing-risks regression analyses, treatment type was a statistically significant predictor of [cancer-specific] mortality (P<0.001)'.
[9] Reported value 57.4%
[10] Reported value 22.4%
[11] Quote from paper (Zini 2009a: 901): '... the other-cause mortality rates recorded in the NSM group significantly exceeded that of nephrectomy group ....'

Author(s):
Date: 2011-04-28
Question: Should laparoscopic radical nephrectomy vs open radical nephrectomy (B1) be used for localised renal cell carcinoma?
Settings:
Bibliography:

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Laparoscopic radical nephrectomy	Open radical nephrectomy (B1)	Relative (95% CI)	Absolute		
Overall survival at 5 years (follow-up 3-80 months[1]; assessed with: Kaplan-Meier estimates)												
1	observational studies	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision[3]	none	0/41 (0%)[4]	0/71 (0%)[5]	Not estimable[6]	-	⊕OOO VERY LOW	CRITICAL
Recurrence at 5 years, indicated by recurrence free survival (follow-up 3-80 months[1]; assessed with: Kaplan-Meier estimates)												
1	observational studies	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision[3]	none	0/41 (0%)[7]	0/71 (0%)[8]	Not estimable[9]	-	⊕OOO VERY LOW	CRITICAL
Condition-specific quality of life - not reported												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Overall morbidity, inferred from length of hospital stay (days) (follow-up 6-12 months; Better indicated by lower values)												
1	randomised trials	serious[10]	no serious inconsistency	serious[11]	serious[3]	none	27	26	-	MD 4.5 lower (5.2 to 3.8 lower)	⊕OOO VERY LOW	CRITICAL
Time to normal activity, inferred from convalescence time (weeks) (follow-up 3-80 months; Better indicated by lower values)												
1	observational studies	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	41	71	-	MD 1.74 lower (1.96 to 1.52 lower)	⊕OOO VERY LOW	CRITICAL
Analgesic requirement (person times) (follow-up 6-12 months; Better indicated by lower values)												
1	randomised trials	serious[10]	no serious inconsistency	no serious indirectness	serious[3]	none	27	26	-	MD 18 lower (0 to 0 higher)[12]	⊕⊕OO LOW	IMPORTANT
Need for blood transfusion (follow-up 3-80 months)												
2	observational studies	serious[2]	serious[13]	no serious indirectness	serious[14]	none	8/77 (10.4%)	23/108 (21.3%)	not pooled	not pooled	⊕OOO VERY LOW	IMPORTANT

[1] Duration of follow-up (months, mean, range): laparoscopic 51.4 [3. 78] vs. open 57.2 [4. 80]
[2] Major confounders are either not reported at baseline, or are not balanced at baseline and are not adjusted for in analysis
[3] Small sample size
[4] Reported KM% 87.8%
[5] Reported KM% 88.7%
[6] Reported p-value = 0.87
[7] Reported KM% 92.6%
[8] Reported KM% 90.1%
[9] Reported p-value = 0.91
[10] The English translation of this Chinese publication was not available at the time of writing so it was unable to to assess risk of bias.
[11] Indirect outcome
[12] Standard deviation not reported and therefore 95% CI not calculated
[13] Opposite direction of effect in the 2 studies
[14] Both studies (not pooled) have wide confidence intervals and cross the line of no effect.

Author(s):
Date: 2011-04-28
Question: Should retroperitoneal laparoscopic radical nephrectomy vs transperitoneal laparoscopic radical nephrectomy (B2) be used for localised renal cell carcinoma?
Settings:
Bibliography:

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Retroperitoneal laparoscopic radical nephrectomy	Transperitoneal laparoscopic radical nephrectomy (B2)	Relative (95% CI)	Absolute	Quality	Importance
Overall survival at 5 years, indicated by number of all cause deaths during study period (follow-up 0.5-24 months[1])												
1	randomised trials	no serious risk of bias	no serious inconsistency	very serious[2,3]	serious[4]	none	4/52 (7.7%)	2/50 (4%)	RR 1.92 (0.37 to 10.04)	37 more per 1000 (from 25 fewer to 362 more)	⊕OOO VERY LOW	CRITICAL
Recurrence at 5 years, indicated by number of recurrences during study period (follow-up 0-51 months[5])												
3	randomised trials	serious[6]	no serious inconsistency	very serious[2,3]	serious[4]	none	1/80 (1.3%)	3/76 (3.9%)	RR 0.32 (0.03 to 2.98)	27 fewer per 1000 (from 38 fewer to 78 more)	⊕OOO VERY LOW	
Condition-specific quality of life - not reported												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Overall morbidity, inferred from length of hospital stay (days) (follow-up 0-26 months; Better indicated by lower values)												
3	randomised trials	serious[6]	serious[7]	serious[8]	serious[9]	none	83	81	-	MD 0.30 higher (0.17 lower to 0.77 higher)	⊕OOO VERY LOW	CRITICAL
Time to normal activity, inferred from convalescence time (weeks) (follow-up 0.5-40 months; Better indicated by lower values)												
1	randomised trials	serious[10]	no serious inconsistency	no serious indirectness	serious[9]	none	52	50	-	MD 1.7 higher (0.09 to 3.31 higher)	⊕⊕OO LOW	CRITICAL
Analgesic requirement (follow-up 0.5-40 months; measured with: mg morphine equivalent; Better indicated by lower values)												
3	randomised trials	serious[6]	no serious inconsistency[11]	no serious indirectness	serious[9]	none	83	81	-	MD 0.16 higher (9.28 lower to 9.61 higher)	⊕⊕OO LOW	IMPORTANT
Need for blood transfusion (follow-up 6-26 months)												
1	randomised trials	serious[12]	no serious inconsistency	no serious indirectness	serious[4]	none	1/20 (5%)	0/20 (0%)	RR 3 (0.13 to 69.52)	-	⊕⊕OO LOW	IMPORTANT

[1] Duration of follow-up (months, mean, range): retroperitoneal 13.5 [0.5, 40] vs. transperitoneal 15 [3. 24]
[2] Short follow up <5 years
[3] Raw data, not censored
[4] 95% CI crosses line of no effect and threshold for appreciable benefit/harm (25%). Small sample size and low event rates.
[5] Duration of follow-up (months): Desai 2005a, mean 13.5 [range 0.5, 40] vs. mean 15 [range 3. 24]; Nadler 2006, median 20 [range 0, 51] for the entire cohort; Nambirajan 2004, mean 15 [range 6, 26] vs. mean 17 [range 6, 16].
[6] One of the three studies is quasi-randomised (Nadler, 2006); allocation concealment unclear in another study (Nambirajan 2004).
[7] Statistical heterogeneity present (I square statitics = 57%)
[8] Indirect outcome measure
[9] 95% CI cross the line of no effect
[10] No blinding
[11] No statistical heterogeneity (I square statistics = 0%)
[12] Methods of randomisation and allocation concealment unclear

Author(s):
Date: 2011-04-28
Question: Should hand-assisted laparoscopic radical nephrectomy vs transperitoneal laparoscopic radical nephrectomy (B3) be used for localised renal cell carcinoma?
Settings:
Bibliography:

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Hand-assisted laparoscopic radical nephrectomy	Transperitoneal laparoscopic radical nephrectomy (B3)	Relative (95% CI)	Absolute	Quality	Importance
Overall survival at 5 years, indicated by proxy outcome of cancer-specific deaths during study period (follow-up 0-51 months[1])												
1	randomised trials	serious[2]	no serious inconsistency	very serious[3,4,5]	serious[6]	none	0/11 (0%)	0/11 (0%)	-	-	⊕OOO VERY LOW	CRITICAL
Recurrence at 5 years, indicated by number of recurrences during study period (follow-up 0-51 months)												
1	randomised trials	serious[2]	no serious inconsistency	very serious[4,5]	serious[6]	none	0/11 (0%)	0/11 (0%)	-	-	⊕OOO VERY LOW	CRITICAL
Condition-specific quality of life - not reported												
0	-	-	-	-	-	none	0	-	-	-		CRITICAL
Overall morbidity, inferred from lenght of hospital stay (days) (follow-up 0-51 months; Better indicated by lower values)												
1	randomised trials	serious[2]	no serious inconsistency	serious[7]	serious[6]	none	11	11	-	MD 1.3 higher (0.21 to 2.39 higher)	⊕OOO VERY LOW	CRITICAL
Time to normal activity, inferred from number of patients who returned to work at 2 weeks (follow-up 0-51 months)												
1	randomised trials	serious[2]	no serious inconsistency	serious[7]	serious[6]	none	2/9 (22.2%)	6/11 (54.5%)	RR 0.41 (0.11 to 1.55)	322 fewer per 1000 (from 485 fewer to 300 more)	⊕OOO VERY LOW	CRITICAL
Analgesic requirement (follow-up 0-51 months; measured with: mg morphine equivalent ; Better indicated by lower values)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[6]	none	11	11	-	MD 6 lower (10.43 lower to 22.43 higher)	⊕⊕OO LOW	IMPORTANT
Need for blood transfusion - not reported												
0	-	-	-	-	-	none	-	-	-	-		IMPORTANT

[1] Duration of follow-up (months, median, range): 20 [0, 51] for the entire cohort
[2] Inadequate sequence generation and allocation concealment (quasi-randomised)
[3] Indirect outcome
[4] Short follow-up <5 years
[5] Raw data, not censored
[6] Small sample size
[7] Indirect outcome measure

Author(s):
Date: 2011-04-28
Question: Should hand-assisted laparoscopic radical nephrectomy vs retroperitoneal laparoscopic radical nephrectomy (B4) be used for localised renal cell carcinoma?
Settings:
Bibliography:

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Hand-assisted laparoscopic radical nephrectomy	Retroperitoneal laparoscopic radical nephrectomy (B4)	Relative (95% CI)	Absolute	Quality	Importance
Overall survival at 5 years, indicated by proxy outcome of cancer specific deaths during study period (follow-up 0-51 months[1])												
1	randomised trials	serious[2]	no serious inconsistency	very serious[3,4,5]	serious[6]	none	0/11 (0%)	0/11 (0%)	-	-	⊕OOO VERY LOW	CRITICAL
Recurrence at 5 years, indicated by number of recurrences during study period (follow-up 0-51 months)												
1	randomised trials	serious[2]	no serious inconsistency	very serious[4,5]	serious[6]	none	0/11 (0%)	0/11 (0%)	-	-	⊕OOO VERY LOW	CRITICAL
Condition-secific quality of life - not reported												
0	-	-	-	-	-	none	0	-	-	-		CRITICAL
Overall morbidity, inferred from length of hospital stay (days) (follow-up 0-51 months; Better indicated by lower values)												
1	randomised trials	serious[2]	no serious inconsistency	serious[7]	serious[8]	none	11	11	-	MD 0.2 lower (1.71 lower to 1.31 higher)	⊕OOO VERY LOW	CRITICAL
Time to normal activity, inferred from number of patients who returned to work at two weeks (follow-up 0-51 months)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[8]	none	2/9 (22.2%)	0/9 (0%)	RR 5 (0.27 to 91.52)	-	⊕⊕OO LOW	CRITICAL
Analgesic requirement (follow-up 0-51 months; measured with: mean mg morphine equivalent ; Better indicated by lower values)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[8]	none	11	11	-	MD 4.0 lower (34.13 lower to 26.13 higher)	⊕⊕OO LOW	IMPORTANT
Need for blood transfusion - not reported												
0	-	-[2]	-	-	-[8]	none	-	-	-	-		IMPORTANT

[1] Duration of follow-up (months, median, range): 20 [0, 51] for the entire cohort
[2] Allocation concealment not adequate (quasi-randomised)
[3] Indirect outcome
[4] Short follow-up <5 years
[5] Raw data, no censoring
[6] Small sample size, low event rates
[7] Indirect outcome measure
[8] Small sample size; 95% CI are wide and cross line of no effect

Author(s):
Date: 2011-05-10
Question: Should hand-assisted laparoscopic radical nephrectomy vs trans- or retro-peritoneal laparoscopic radical nephrectomy (B5) be used for localised renal cell carcinoa?
Settings:
Bibliography:

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Hand-assisted laparoscopic radical nephrectomy	Trans- or retro-peritoneal laparoscopic radical nephrectomy (B5)	Relative (95% CI)	Absolute	Quality	Importance
Overall survival, time to event (follow-up 0.3-114 months[1])												
1	observational studies	no serious risk of bias[2]	no serious inconsistency	no serious indirectness	serious[3]	none	0/108 (0%)	0/147 (0%) 0%	HR 0.407 (0.15 to 1.395)	- -	⊕OOO VERY LOW	CRITICAL
Overall survival at 5 years (follow-up 0.3-114 months[1]; assessed with: Kaplan-Meier estimates)												
1	observational studies	no serious risk of bias[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/108 (0%)[4]	0/147 (0%)[5]	Not estimable[6]	-	⊕⊕OO LOW	CRITICAL
Recurrence, indicated by recurrence free survival, time to event (follow-up 0.3-114 months[1]; assessed with: Kaplan-Meier estimates)												
1	observational studies	no serious risk of bias[2]	no serious inconsistency	no serious indirectness	serious[3]	none	0/108 (0%)	0/147 (0%) 0%	HR 0.384 (0.122 to 1.209)	- -	⊕OOO VERY LOW	CRITICAL
Recurrence at 5 years, indicated by recurrence free survival at 5 years (follow-up 0.3-114 months[1]; assessed with: Kaplan-Meier estimates)												
1	observational studies	no serious risk of bias[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/108 (0%)[7]	0/147 (0%)[8]	Not estimable[9]	-	⊕⊕OO LOW	CRITICAL
Condition-specific quality of life - not reported												
0	-	-	-	-	-	none	-	-	-	-		
Overall morbidity, inferred from length of hospital stay (days) (follow-up 0.3-114 months; Better indicated by lower values)												
1	observational studies	serious[10]	no serious inconsistency	serious[11]	serious[12]	none	108	147	-	MD 0.4 higher (0.01 lower to 0.81 higher)	⊕OOO VERY LOW	CRITICAL
Time to normal activity, inferred from time to non-strenuous activity (days) (follow-up 0.3-114 months; Better indicated by lower values)												
1	observational studies	serious[10]	no serious inconsistency	no serious indirectness	serious[12]	none	108	147	-	MD 3.10 higher (0.83 to 5.37 higher)	⊕OOO VERY LOW	CRITICAL
Analgesic requirement, inferred from pain score at 6 weeks (follow-up 0.3-114 months; measured with: 10 point visual analogue scale; Better indicated by lower values)												
1	observational studies	serious[10]	no serious inconsistency	serious[11]	serious[12]	none	108	147	-	MD 0.40 lower (0.87 lower to 0.07 higher)	⊕OOO VERY LOW	IMPORTANT
Need for blood transfusion (follow-up 0.3-114 months)												
1	observational studies	serious[10]	no serious inconsistency	no serious indirectness	serious[3]	none	8/108 (7.4%)	15/147 (10.2%)	RR 0.73 (0.32 to 1.65)	28 fewer per 1000 (from 69 fewer to 66 more)	⊕OOO VERY LOW	IMPORTANT

[1] Duration of follow-up (months, median, range): 30 [0.3, 114]
[2] Inadequate information on one of the pre-specified confounders (necrosis).
[3] 95% CI cross the line of no effect and threshold for appreciable benefit/harm (25%)
[4] Reported value 74% (95% CI 63 to 85)
[5] Reported value 79% (95% CI 68 to 90)
[6] Reported p-value = 0.6864
[7] Reported value 81.3% (95% CI 72 to 91)
[8] Reported value 76.5% (95% CI 64 to 89)
[9] Reported p-value = 0.8663
[10] Major confounders either not reported, or are not balanced at basline and not adjusted for in analysis
[11] Indirect outcome measure
[12] Wide 95% CI

Author(s):
Date: 2011-04-28
Question: Should robot-assisted laparoscopic radical nephrectomy vs laparoscopic radical nephrectomy (B6) be used for localised renal cell carcinoma?
Settings:
Bibliography:

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Robot-assisted laparoscopic radical nephrectomy	Laparoscopic radical nephrectomy (B6)	Relative (95% CI)	Absolute		
Overall survival at 5 years - not reported												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Recurrence at 5 years, indicated by number of recurrences during study period (follow-up 1-12 months[1])												
1	observational studies	no serious risk of bias[2]	no serious inconsistency	very serious[3,4]	serious[5]	none	0/15 (0%)	0/15 (0%)	-	-	⊕OOO VERY LOW	CRITICAL
Condition-specific quality of life - not reported												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Overall morbidity, inferred from length of hospital stay (days) (follow-up 1-12 months; Better indicated by lower values)												
1	observational studies	serious[6]	no serious inconsistency	serious[7]	serious[5]	none	15	15	-	MD 0.1 higher (0.1 lower to 0.21 higher)	⊕OOO VERY LOW	CRITICAL
Time to normal activity, inferred from convalescence time (weeks) (follow-up 1-12 months; Better indicated by lower values)												
1	observational studies	serious[6]	no serious inconsistency	no serious indirectness	serious[5]	none	15	15	-	MD 0.1 higher (0.22 lower to 0.42 higher)	⊕OOO VERY LOW	CRITICAL
Analgesic requirement (follow-up 1-12 months; measured with: mean mg morphine equivalent ; Better indicated by lower values)												
1	observational studies	very serious[6]	no serious inconsistency	no serious indirectness	serious[5]	none	15	15	-	MD 0.10 lower (0.21 lower to 0.01 higher)	⊕OOO VERY LOW	IMPORTANT
Need for blood transfusion (follow-up 1-12 months)												
1	observational studies	very serious[6]	no serious inconsistency	no serious indirectness	serious[8]	none	3/15 (20%)	2/15 (13.3%)	RR 1.5 (0.29 to 7.73)	67 more per 1000 (from 95 fewer to 897 more)	⊕OOO VERY LOW	IMPORTANT

[1] Duration of follow-up (months, mean, range): robotic 8.3 [1, 12] vs. laparoscopic 9.1 [2, 12]
[2] Inadequate information on one of the pre-specified confounders (necrosis).
[3] Short follow-up <5 years
[4] Raw data, not censored
[5] Small sample size
[6] Major confounders either not reported, or are not balanced at basline and not adjusted for in analysis
[7] Indirect outcome measure
[8] 95% CI crosses line of no effect and appreciable benefit/harm

Author(s):
Date: 2011-04-28
Question: Should single port laparoscopic radical nephrectomy vs laparoscopic radical nephrectomy (B7) be used for localised renal cell carcinoma?
Settings:
Bibliography:

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Single port laparoscopic radical nephrectomy	Laparoscopic radical nephrectomy (B7)	Relative (95% CI)	Absolute		
Overall survival at 5 years - not reported												
0	-	-	-	-	-	none	-	-	-	-		
Recurrence at 5 years, indicated by number of recurrences during study period (follow-up 2.7-39.1 months[1])												
1	observational studies	serious[2]	no serious inconsistency	very serious[3,4]	serious[5]	none	0/14 (0%)	0/15 (0%)	-	-	⊕OOO VERY LOW	CRITICAL
Condition-specific quality of life - not reported												
0	-	-	-	-	-	none	0	-	-	-		CRITICAL
Overall morbidity, inferred from length of hospital stay (days) (follow-up 12.7-39.1 months[6]; Better indicated by lower values)												
2	observational studies	serious[2]	no serious inconsistency	serious[7]	serious[5]	none	23	33	-	not pooled	⊕OOO VERY LOW	CRITICAL
Time to normal activity - not reported												
0	-	-	-	-	-	none	0	-	-	-		CRITICAL
Analgesic requirement (follow-up mean 2.7-39.1 months[1]; measured with: number of nonsteroidal anti-inflammatory drugs (NSAID) suppository ; Better indicated by lower values)												
1	observational studies	serious[2]	no serious inconsistency	no serious indirectness	serious[5]	none	14	15	-	MD 1 higher (0.19 lower to 2.19	⊕OOO VERY LOW	IMPORTANT

										higher)		
Need for blood transfusion (follow-up 2.7-39.1 months)												
1	observational studies	serious[2]	no serious inconsistency	no serious indirectness	serious[5]	none	0/14 (0%)	0/15 (0%)	-	-	⊕OOO VERY LOW	IMPORTANT

[1] Soga 2008. Duration of follow-up (months, median, range) differ between the groups: single port laparoscopic 7.1 [2.7, 17.3] vs. laparoscopic 27.2 [19.5, 39.1].
[2] Major confounders either not reported, or are not balanced at basline and not adjusted for in analysis
[3] Short follow-up <5 years
[4] Raw data, no censoring
[5] Small sample size
[6] Mean follow up from Soga 2008 study; Duration of FU not stated in Park 2009a study
[7] Indirect outcome measure

Author(s):
Date: 2011-04-28
Question: Should radical nephrectomy with lyphadenectomy vs radical nephrectomy (C1) be used for localised renal cell carcinoma?
Settings:
Bibliography:

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Radical nephrectomy with lyphadenectomy**	**Radical nephrectomy (C1)**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Overall survival, time to event (follow-up median 151.2 months)												
1	randomised trials[1]	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	0/271 (0%)	0/288 (0%)	HR 1.096 (0.81 to 1.47)	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Overall survival at 5 years (follow-up 48 to 251 months; assessed with: Kaplan-Meier estimates)												
1	observational studies[1]	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision[4]	none	0/109 (0%)[5]	0/82 (0%)[6]	-	-	⊕OOO VERY LOW	CRITICAL
Overall survival at 10 years (follow-up 48 to 251 months; assessed with: Kaplan-Meier estimates)												
1	observational studies	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision[4]	none	0/109 (0%)[7]	0/82 (0%)[8]	-	-	⊕OOO VERY LOW	CRITICAL
Recurrence at 5 years - not reported												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Condition-specific quality of life - not reported												
0	-	-	-	-	-	none	0	-	-	-		CRITICAL
Overall morbidity - not reported												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Time to normal activity - not reported												
0	-	-	-	-	-	none	0	-	-	-		CRITICAL
Analgesic requirement - not reported												
0	-	-	-	-	-	none	0	-	-	-		IMPORTANT
Need for blood transfusion - not reported												
0	-	-	-	-	-	none	-	-	-	-		IMPORTANT

[1] Subgroup analysis of a randomised trial
[2] 95%CI crosses the line of no effect and threshold for appreciable benefit/harm (25%)
[3] Major confounders either not reported, or are not balanced at basline and not adjusted for in analysis.
[4] 95% CI not calculated so uable to judge
[5] KM estimates 91.6%
[6] KM estimates 81.3%
[7] KM estimates 80.2%
[8] KM estimates 54%

Author(s):
Date: 2011-04-28
Question: Should partial nephrectomy with ipsilateral adrenalectomy vs partial nephrectomy (C2) be used for localised renal cell carcinoma?
Settings:
Bibliography:

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Partial nephrectomy with ipsilateral adrenalectomy**	**Partial nephrectomy (C2)**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Overall survival at 5 years[1] (follow-up median 66-74 months[1]; assessed with: Kaplan-Meier estimates)												
1	observational studies	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	0/48 (0%)[4]	0/2017 (0%)[5]	-	-	⊕OOO VERY LOW	CRITICAL
Overall survival at 10 years[1] (follow-up median 66-74 months[1]; assessed with: Kaplan-Meier estimates)												
1	observational studies	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	0/48 (0%)[6]	0/2017 (0%)	-	-	⊕OOO VERY LOW	CRITICAL
Recurrence at 5 years - not reported[1]												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Condition-specific quality of life - not reported												
0	-	-	-	-	-	none	0	-	-	-		CRITICAL
Overall morbidity - not reported												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL

Time to normal activity - not reported												
0	-	-	-	-	-	none	0	-	-	-		CRITICAL
Analgesic requirement - not reported												
0	-	-	-	-	-	none	0	-	-	-		IMPORTANT
Need for blood transfusion - not reported												
0	-	-	-	-	-	none	-	-	-	-		IMPORTANT

[1] Duration of follow up (months, median, IQR): adrenalectomy 74.4 [26.4, 105.6] vs. no adrenalectomy 66 [34.8, 108]
[2] Major confounders either not reported, or are not balanced at basline and not adjusted for in analysis.
[3] 95% CI for risk difference not calculated so uable to judge.
[4] 82.3%
[5] 85.3%
[6] 72.4%

Author(s):
Date: 2011-04-28
Question: Should open partial nephrectomy vs open radical nephrectomy (D1) be used for localised renal cell carcinoma?
Settings:
Bibliography:

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Open partial nephrectomy**	**Open radical nephrectomy (D1)**	**Relative (95% CI)**	**Absolute**		
Overall survival at 5 years (follow-up mean 37-66 months[1]; assessed with: Kaplan-Meier estimates)												
2	observational studies	serious[2]	serious[3]	serious[4]	no serious imprecision[5]	none	0/100 (0%)[6]	0/93 (0%)	not pooled	not pooled	⊕OOO VERY LOW	CRITICAL
Recurrence at 5 years, indicated by number of recurrences during study period (follow-up mean 70 months[7])												
1	randomised trials	serious[8]	no serious inconsistency	serious[9]	serious[10]	none	0/19 (0%)	0/21 (0%)	-	-	⊕OOO VERY LOW	CRITICAL
Condition-specific quality of life (follow-up 14-27 months[11]; measured with: EORTC QLQ-C30; Better indicated by lower values)												
1	observational studies	serious[2]	no serious inconsistency	no serious indirectness	serious[5,10]	none	29	22	-	MD 0 higher (0 to 0 higher)	⊕OOO VERY LOW	CRITICAL
Overall morbidity, inferred from length of hospital stay (days) (follow-up 11-71 months[12]; Better indicated by lower values)												
3	observational studies	serious[2]	no serious inconsistency	serious[13]	serious[14]	none	150	139	-	not pooled	⊕OOO VERY LOW	CRITICAL
Time to normal activity - not reported												
0	-	-	-	-	-	none	0	-	-	-		CRITICAL
Analgesic requirement - not reported												
0	-	-	-	-	-	none	0	-	-	-		IMPORTANT
Need for blood transfusion (follow-up 11-71 months)												
3	observational studies	serious[2]	serious[15]	no serious indirectness	serious[14]	none	17/150 (11.3%)	24/139 (17.3%)	not pooled	not pooled	⊕OOO VERY LOW	IMPORTANT

[1] Duration of follow-up (months, mean, SD): Butler 1995, 40 (26) vs. 66 (30); Lee 2007, 37.1 (26.1) vs. 39 (20.37)
[2] Major confounders either not reported, or are not balanced at basline and not adjusted for in analysis
[3] The direction of effect appears inconsistent.
[4] Duration of follow-up is different between the groups in one study (Butler 1995).
[5] 95% CI not reported so difficult to judge
[6] Reported values (open partial vs. open radical): Butler 1995, 75% vs. 80%, p-value not statistically significant; Lee 2007, 98.2% vs. 88.8%, p = 0.63.
[7] Duration of follow-up (months): mean 70 (max. 98) vs. mean 70 (max. 97)
[8] Allocation concealment unclear
[9] Raw data, no censoring
[10] Small sample size
[11] Duration of follow-up (months): Gratzke 2009, mean 22 [range 11-71] for both groups; Poulakis 2003, median 20 [range 14-27] for both groups.
[12] Range taken form they study by Gratzke et al.; mean only given for Butler 1995 and duration of follow up not reported in Shekarriz 2002;
[13] Indirect outcome measure
[14] 95% CI of individual studies (not pooled) cross line of no effect.
[15] Inconsistent direction of effects

Author(s):
Date: 2011-04-28
Question: Should laparoscopic partial nephrectomy vs laparoscopic radical nephrectomy (D2) be used for localised renal cell carcinoma?
Settings:
Bibliography:

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Laparoscopic partial nephrectomy**	**Laparoscopic radical nephrectomy (D2)**	**Relative (95% CI)**	**Absolute**		
Overall survival at 5 years, indicated by overall survival at 80 months (follow-up 27-85 months[1]; assessed with: Kaplan-Meier estimates)												
1	observational studies	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/35 (0%)[3]	0/75 (0%)[4]	Not estimable[5]	-	⊕OOO VERY LOW	CRITICAL
Recurrence at 5 years, indicated by recurrence free survival at 80 months (follow-up 27-85 months[1]; assessed with: Kaplan-Meier estimates)												
1	observational	serious[2]	no serious	serious	no serious	none	0/35	0/75	Not	-	⊕OOO	CRITICAL

	studies		inconsistency		imprecision		(0%)[6]	(0%)[7]	estimable[8]		VERY LOW	
Condition-specific quality of life - not reported												
0	-	-	-	-	-	none	0	-	-	-		CRITICAL
Overall morbidity - not reported												
0	-	-	-	-	-	none	0	-	-	-		CRITICAL
Time to normal activity - not reported												
0	-	-	-	-	-	none	0	-	-	-		CRITICAL
Analgesic requirement - not reported												
0	-	-	-	-	-	none	0	-	-	-		IMPORTANT
Need for blood transfusion - not reported												
0	-	-	-	-	-	none	-	-	-	-		IMPORTANT

[1] Duration of follow-up (months, median, range): 44 [27, 85] vs. 57 [27, 79]

[2] Downgraded for group imbalance at baseline, or lack of case-mix adjustment, or inadequate information, on more than 2 pre-specified confounders (clinical tumour size, pathlogical tumour stage, tumour grade, histological cell type and necrosis).

[3] Reported value 74% (95% CI 67 to 76)

[4] Reported value 72% (95% CI 67 to 76)

[5] Reported p-value = 0.660

[6] Reported value 81% (95% CI 74 to 87)

[7] Reported value 77% (95% CI 74 to 79)

[8] Reported p-value = 0.495

Author(s):
Date: 2011-04-28
Question: Should open or laparoscopic partial nephrectomy vs open or laparoscopic radical nephrectomy (D3) be used for localised renal cell carcinoma?
Settings:
Bibliography:

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Open or laparoscopic partial nephrectomy**	**Open or laparoscopic radical nephrectomy (D3)**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Overall survival, time to event (follow-up 0-228 months[1]; assessed with: Kaplan-Meier estimates)												
4	observational studies	no serious risk of bias[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/2649 (0%)	0/6954 (0%)	not pooled	not pooled	⊕⊕OO LOW	CRITICAL
Overall survival at 10 years (follow-up 0-204 months[3]; assessed with: Kaplan-Meier estimates)												
2	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision[4]	none	0/1470 (0%)[5]	0/3306 (0%)	not pooled	not pooled	⊕⊕OO LOW	CRITICAL
Overall survival at 5 years (follow-up median 35-50 months[6]; assessed with: Kaplan-Meier estimates)												
3	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision[4]	none	0/2363 (0%)[7]	0/6081 (0%)	not pooled	not pooled	⊕⊕OO LOW	CRITICAL
Recurrence at 5 years, indicated by number of recurrences during study period (follow-up mean 54 months[8])												
1	observational studies	serious[9]	no serious inconsistency	serious[10]	serious[11]	none	2/151 (1.3%)	6/393 (1.5%)	RR 0.87 (0.18 to 4.25)	2 fewer per 1000 (from 13 fewer to 50 more)	⊕OOO VERY LOW	CRITICAL
Condition-specific quality of life - not reported												
0	-	-	-	-	-	none	0	-	-	-		CRITICAL
Overall morbidity - not reported												
0	-	-	-	-	-	none	0	-	-	-		CRITICAL
Time to normal activity - not reported												
0	-	-	-	-	-	none	0	-	-	-		CRITICAL
Analgesic requirement - not reported												
0	-	-	-	-	-	none	0	-	-	-		IMPORTANT
Need for blood transfusion - not reported												
0	-	-	-	-	-	none	-	-	-	-		IMPORTANT

[1] Duration of follow-up (months): Huang 2009, mean 43 overall and 48 in patients alive at last follow-up; Thompson 2009, median 40.8 [range 0, 204] vs. 63.6 [0, 228]; Weight 2010, median 46 [IQR 25, 75] vs. 50 [IQR 28, 73; Zini 2009b, median 35 vs. 46

[2] Inadequate information on one of the pre-specified confounders (necrosis).

[3] Duration of follow-up (months): Thompson 2009, median 40.8 [range 0, 204] vs. 63.6 [0, 228]; Zini 2009b, median 35 vs. 46

[4] 95% CI not reported so unable to judge

[5] Reported value (partial vs. radical): Thompson 2008, 93% vs. 82%; Zini 2009b, 70.9% vs. 68.8%

[6] Duration of follow-up (months): Huang 2009, mean 43 overall and 48 in patients alive at last follow-up; Weight 2010, median 46 [IQR 25, 75] vs. 50 [IQR 28, 73; Zini 2009b, median 35 vs. 46

[7] Reported value (partial vs. radical): Huang 2009, 74% vs. 68%; Weight 2010, 85% (95% CI 81.4 to 88.6) vs. 78% (95% CI 73.7 to 82.3); Zini 2009b, 88.9% vs. 85.5%

[8] Duration of follow-up: mean 54 months for the entire cohort

[9] Major confounders are imbalanced at baseline and not controlled for in analysis

[10] Raw data, not censored (downgrade by 1). Not downgraded further for duration of follow-up, as although maximum follow-up is not reported, mean follow-up is close to 5 years.

[11] 95% CI crosses line of no effect and threshold for appreciable benefit/harm (25%)

Author(s):
Date: 2011-04-28
Question: Should radiofrequency ablation vs laparoscopic radical nephrectomy (D4) be used for localised renal cell carcinoma?

Settings:
Bibliography:

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Radiofrequency ablation	Laparoscopic radical nephrectomy (D4)	Relative (95% CI)	Absolute		
Overall survival at 5 years - not reported												
0	-	-	-	-	-	none	-	-	-	-		
Recurrence at 5 years - not reported												
0	-	-	-	-	-	none	-	-	-	-		
Condition-specific quality of life - not reported												
0	-	-	-	-	-	none	0	-	-	-		CRITICAL
Overall morbidity - not reported												
0	-	-	-	-	-	none	0	-	-	-		CRITICAL
Time to normal activity - not reported												
0	-	-	-	-	-	none	0	-	-	-		CRITICAL
Analgesic requirement - not reported												
0	-	-	-	-	-	none	0	-	-	-		IMPORTANT
Need for blood transfusion - not reported												
0	-	-	-	-	-	none	-	-	-	-		IMPORTANT

Author(s):
Date: 2011-04-28
Question: Should laparoscopic partial nephrectomy vs open partial nephrectomy (D5) be used for localised renal cell carcinoma?
Settings:
Bibliography:

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Laparoscopic partial nephrectomy	Open partial nephrectomy (D5)	Relative (95% CI)	Absolute		
Overall survival, time to event (follow-up median 48-68.4 months[1]; assessed with: Kaplan-Meier estimates)												
1	observational studies	no serious risk of bias[2]	no serious inconsistency	no serious indirectness	serious[3]	none	0/499 (0%)	0/762 (0%)	HR 0.69 (0.45 to 1.02)	-	⊕OOO VERY LOW	CRITICAL
								0%		-		
Overall survival at 5 years (follow-up 12-117.6 months[4]; assessed with: Kaplan-Meier estimates)												
1	observational studies	serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/81 (0%)[6]	0/66 (0%)[7]	Not estimable[8]	-	⊕OOO VERY LOW	CRITICAL
Recurrence at 5 years, indicated by recurrence free survival at 5 years (follow-up 12-117.6 months[4]; assessed with: Kaplan-Meier estimates)												
1	observational studies	serious[9]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/81 (0%)[10]	0/66 (0%)[11]	-	-	⊕OOO VERY LOW	CRITICAL
Recurrence at 5 years, indicated by local recurrence rate at 3 years (follow-up 0-91.2 months[12]; assessed with: Kaplan-Meier estimates)												
1	observational studies	serious[9]	no serious inconsistency	serious[13]	no serious imprecision[14]	none	0/514 (0%)[15]	0/676 (0%)[16]	-	-	⊕OOO VERY LOW	CRITICAL
Condition-specific quality of life - not reported												
0	-	-	-	-	-	none	0	-	-	-		CRITICAL
Overall morbidity, inferred from length of hospital stay (days) (follow-up 0-91.2 months; Better indicated by lower values)												
2	observational studies	serious[5]	no serious inconsistency	serious[17]	serious[18]	none	847	1106	-	not pooled	⊕OOO VERY LOW	CRITICAL
Time to normal activity - not reported												
0	-	-	-	-	-	none	0	-	-	-		CRITICAL
Analgesic requirement - not reported												
0	-	-	-	-	-	none	0	-	-	-		IMPORTANT
Need for blood transfusion (follow-up 0-117.6 months[19])												
3	observational studies	serious[5]	serious[20]	no serious indirectness	serious[21]	none	60/947 (6.3%)	58/1206 (4.8%)	not pooled	not pooled	⊕OOO VERY LOW	IMPORTANT

[1] Duration of follow up (months, median, IQR): 48 [39.6, 81.6] vs. 68.4 [46.8, 87.6]
[2] Inadequate information on one of the pre-specified confounders (necrosis).
[3] 95% CI crosses the line of no effect and threshold for appreciable benefit/harm (25%)
[4] Duration of follow-up (months, mean, range): 44.4 [19.2, 110.4] vs. 42 [12, 117.6]
[5] Major confounders either not reported, or are not balanced at baseline and not adjusted for in analysis.
[6] Reported value 96% (95% CI 92 to 99)
[7] Reported value 85% (95% CI 79 to 92)
[8] Reported p-value = 0.1
[9] Major confounders not balanced at baseline or controlled for in analysis.
[10] Reported value 97% (95% CI 94 to 99)
[11] Reported value 98% (95% CI 95 to 100)
[12] Duration of follow-up (months, median, range): 14.4 [0, 84] vs. 33.6 [0, 91.2]
[13] Estimates are for <5 years
[14] 95% CI not reported so unable to judge
[15] Reported value 1.4% (95% CI 0 to 2.8)
[16] Reported value 1.5% (95% CI 0.4 to 2.6)
[17] Indirect outcome measure
[18] One of the 2 studies did not report standard deviation so unable to judge

[19] Duration of follow-up (months): Gill 2007 (median, range) 14.4 [0, 84] vs. 33.6 [0, 91.2]; Gong 2008 (mean, SD) 21.7 (25.6) vs. 20.6 (23.1); Marszalek 2009 (mean, SE, range) 44.4 (2.4) [19.2, 110.4] vs. 42 (2.4) [12, 117.6]
[20] Inconsistent direction of effect between studies
[21] 95% CI crosses line of no effect and appreciable benefit/harm in 2/3 studies (not pooled)

Author(s):
Date: 2011-04-28
Question: Should robotic partial nephrectomy vs laparoscopic partial nephrectomy (D6) be used for renal cell carcinoma?
Settings:
Bibliography:

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Robotic partial nephrectomy	Laparoscopic partial nephrectomy (D6)	Relative (95% CI)	Absolute	Quality	Importance
Overall survival at 5 years - not reported												
0	-	-	-	-	-	none	-	-	-	-		
Recurrence at 5 years - not reported												
0	-	-	-	-	-	none	-	-	-	-		
Condition-specific quality of life - not reported												
0	-	-	-	-	-	none	0	-	-	-		CRITICAL
Overall morbidity, inferred from length of hospital stay (days) (follow-up mean 7.4-8.5 months; Better indicated by lower values)												
1	observational studies	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	12	12	-	MD 0.3 higher (1.19 lower to 1.79 higher)	⊕OOO VERY LOW	CRITICAL
Time to normal activity - not reported												
0	-	-	-	-	-	none	0	-	-	-		CRITICAL
Analgesic requirement - not reported												
0	-	-	-	-	-	none	0	-	-	-		IMPORTANT
Need for blood transfusion - not reported												
0	-	-	-	-	-	none	-	-	-	-		IMPORTANT

[1] Major confounders either not reported, or are not balanced at baseline and not adjusted for in analysis.
[2] Indirect outcome measure
[3] Small sample size; wide 95% CI crossing line of no effect

Author(s):
Date: 2011-04-28
Question: Should radiofrequency-assisted robotic clampless partial nephrectomy vs laparoscopic partial nephrectomy (D7) be used for localised reanl cell carcinoma?
Settings:
Bibliography:

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Radiofrequency-assisted robotic clampless partial nephrectomy	Laparoscopic partial nephrectomy (D7)	Relative (95% CI)	Absolute	Quality	Importance
Overall survival at 5 years - not reported												
0	-	-	-	-	-	none	-	-	-	-		
Recurrence at 5 years, indicated by number of recurrences during study period (follow-up 0.5-71.5 months[1])												
1	randomised trials	serious[2]	no serious inconsistency	serious[3,4]	serious[5]	none	1/34 (2.9%)	0/34 (0%)	RR 3.00 (0.13 to 71.15)	-	⊕OOO VERY LOW	CRITICAL
Condition-specific quality of life - not reported												
0	-	-	-	-	-	none	0	-	-	-		CRITICAL
Overall morbidity - not reported												
0	-	-	-	-	-	none	0	-	-	-		CRITICAL
Time to normal activity - not reported												
0	-	-	-	-	-	none	0	-	-	-		CRITICAL
Analgesic requirement - not reported												
0	-	-	-	-	-	none	0	-	-	-		IMPORTANT
Need for blood transfusion (follow-up 0.5-71.5 months[1])												
1	observational studies	serious[2]	no serious inconsistency	no serious indirectness	serious[5]	none	3/42 (7.1%)	4/36 (11.1%)	RR 0.64 (0.15 to 2.68)	40 fewer per 1000 (from 94 fewer to 187 more)	⊕OOO VERY LOW	IMPORTANT

[1] Duratin of follow-up (months, mean, range): 25.8 [0.5, 71.5] vs. 7.8 [1.0, 18.9]
[2] Major confounders either not reported, or are not balanced at baseline and not adjusted for in analysis.
[3] Short follow-up <5 years. Duration of follow-up is also different between the groups.
[4] Raw data, not censored
[5] 95%CI crosses the line of no effect and threshold for appreciable benefit/harm (25%)

Author(s):
Date: 2011-04-28
Question: Should laparoscopic cryoablation vs laparoscopic partial nephrectomy (D8) be used for localised cell carcinoma?
Settings:
Bibliography:

Quality assessment							No of patients		Effect			
								Laparoscopic				

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Laparoscopic cryoablation	partial nephrectomy (D8)	Relative (95% CI)	Absolute	Quality	Importance
Overall survival at 5 years, indicated by number of all cause deaths during study period (follow-up median 1-60 months[1])												
1	observational studies	serious[2]	no serious inconsistency	very serious[3,4]	serious[5]	none	3/78 (3.8%)	0/153 (0%)	RR 13.65 (0.71 to 260.91)	-	⊕OOO VERY LOW	CRITICAL
Recurrence at 5 years, indicated by number of recurrences during study period (follow-up 1-60 months[6])												
2	observational studies	serious[7]	no serious inconsistency	very serious[3,4]	serious[8]	none	2/93 (2.2%)	1/168 (0.6%)	not pooled	not pooled	⊕OOO VERY LOW	CRITICAL
Condition-specific quality of life - not reported												
0	-	-	-	-	-	none	0	-	-	-		CRITICAL
Overall morbidity, inferred from length of hospital stay (days) (follow-up 1-60 months[6]; Better indicated by lower values)												
2	observational studies	serious[2]	no serious inconsistency	serious[9]	serious[10]	none	93	168	-	not pooled	⊕OOO VERY LOW	CRITICAL
Time to normal activity, inferred from convalescence time (weeks) (follow-up 1-60 months[6]; Better indicated by lower values)												
1	observational studies	serious[2]	no serious inconsistency	no serious indirectness	serious[10]	none	78	153	-	MD 0.06 higher (0.89 lower to 1.01 higher)	⊕OOO VERY LOW	CRITICAL
Analgesic requirement - not reported												
0	-	-	-	-	-	none	0	-	-	-		IMPORTANT
Need for blood transfusion (follow-up 1-60 months)												
2	observational studies	serious[2]	no serious inconsistency	no serious indirectness	serious[11]	none	0/93 (0%)	3/168 (1.8%)	not pooled	not pooled	⊕OOO VERY LOW	IMPORTANT

[1] Duration of follow-up (months, mean, range): 24.6 [1, 60] vs. 5.8 [1, 36]

[2] Major confounders either not reported, or are not balanced at baseline and not adjusted for in analysis.

[3] Duration of follow-up is different between the groups and is <5 years in one of them.

[4] Raw data, not censored

[5] 95% CI crosses the line of no effect and threshold for beneficial benefit/harm (25%)

[6] Duration of follow-up (months): Desai 2005b, mean 24.6 [range 1, 60] vs. mean 5.8 [range 1, 36]; O'Malley 2007, mean 11.9 (SD 7.2) vs. mean 9.83 (SD 8.8)

[7] Downgraded for group imbalance at baseline, or lack of case-mix adjustment, or inadequate information, on 2 or more pre-specified confounders (tumour grade, histological cell type, and necrosis).

[8] Small sample size, low event rates. Of the two studies, one study (Desai 2005b) is associated with RR of 3.92 (95% CI 0.36, 42.60). Here 95% CI crosses the line of no effect and threshold for appreciable benefit/harm (25%). The other study (O'Malley 2007) reported that there were no incidents of recurrence during the study period.

[9] Indirect outcome measure

[10] Small sample size; wide 95% CI crossing line of no effect

[11] 95% CI of both studies (not pooled) cross the line of no effect and threshold for appreciable benefit/harm (25%)

Author(s):
Date: 2011-04-28
Question: Should laparoscopic cryoablation vs open partial nephrectomy (D9) be used for localised renal cell carcinoma?
Settings:
Bibliography:

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Laparoscopic cryoablation	Open partial nephrectomy (D9)	Relative (95% CI)	Absolute	Quality	Importance
Overall survival at 5 years - not reported												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Recurrence at 5 years, indicated by number of recurrences during study period (follow-up mean 27-28 months[1])												
1	observational studies	no serious risk of bias[2]	no serious inconsistency	very serious[3,4]	serious[5]	none	0/20 (0%)	0/20 (0%)	-	-	⊕OOO VERY LOW	CRITICAL
Condition-specific quality of life - not reported												
0	-	-	-	-	-	none	0	-	-	-		CRITICAL
Overall morbidity, inferred from length of hopsital stay (days) (follow-up mean 27.3 months; Better indicated by lower values)												
1	randomised trials	serious[6]	no serious inconsistency	serious[7]	serious[5]	none	20	20	-	MD 3.99 lower (5.23 to 2.75 lower)	⊕OOO VERY LOW	CRITICAL
Time to normal activity - not reported												
0	-	-	-	-	-	none	0	-	-	-		CRITICAL
Analgesic requirement - not reported												
0	-	-	-	-	-	none	0	-	-	-		IMPORTANT
Need for blood transfusion (follow-up mean 27.8 months[1])												
1	observational studies	serious[6]	no serious inconsistency	no serious indirectness	serious[5]	none	2/20 (10%)	8/20 (40%)	RR 0.17 (0.03 to 0.92)	332 fewer per 1000 (from 32 fewer to 388 fewer)	⊕OOO VERY LOW	IMPORTANT

[1] Duration of follow up (months, mean, SD): 27.3 (10.8) vs. 28.7 (14.9)

[2] Inadequate information on one of the pre-specified confounders (necrosis).

[3] Short follow-up <5 years

[4] Raw data, not censored

[5] Small sample size

[6] Major confounders either not reported, or are not balanced at baseline and not adjusted for in analysis.

[7] Indirect outcome measure