Systematic Review Methodology for the European Association of Urology Guidelines for Renal Cell Carcinoma (2014 update)

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A: Systematic review on renal biopsy for the diagnosis of renal cell carcinoma

Methods protocol

Lorenzo Marconi (LM), Fabian Hofmann (FH), Saeed Dabestani (SD), Fiona Stewart (FS), Thomas Lam (TL), Alessandro Volpe, Steven Canfield, and the EAU RCC Guideline Panel

Objectives

To conduct a systematic review of the evidence for the diagnostic accuracy and safety of fine needle aspiration cytology (FNAC) or core-needle biopsy for the diagnosis of indeterminate renal masses or metastatic Renal Cell Cancer (mRCC).

Methods
Criteria for considering studies for this review

Types of studies
We included studies containing (primary outcomes):
- Extractable accuracy data on the performance of FNAC or core biopsy for detection of kidney cancer, RCC histologic subtype or RCC Fuhrman grade.
- Adverse events that occurred in the context of FNAC or core biopsy of renal tumour for the diagnosis of primary or mRCC.

The following secondary outcomes will also be considered:
- Impact on patient management or treatment decisions
- Oncological outcomes

For the assessment of the *diagnostic accuracy outcomes* the following study designs were included:
- Direct ("head-to-head") comparison studies (index test(s) and comparator evaluated in the same study population)
    - o Fully paired design (all participants receive all tests as well as the reference standard)
    - o Not fully paired design (Participants receive only a subset of the tests. All test results are verified by the reference standard)
        - Randomized or quasi-randomized (participants randomly allocated to receive Index test or comparator)
        - Non-Randomized
- Indirect comparison studies (The accuracy of the index test is estimated in one set of studies, while the accuracy of the comparator test is estimated in a different set of studies): observational studies, including case series, in which the sample is created by identifying all people presenting at the point of testing.

For the assessment of the *intervention outcomes* we considered the following study designs:

- RCT or quasi-RCT
- Non randomized comparative experimental study
- Comparative observational study
- Single arm case series

The following studies were excluded:
- Reviews, editorials and opinions;
- Case series with fewer than 10 patients with renal mass submitted to biopsy;
- Case series of patients with metastatic disease submitted to biopsy of secondary lesions, if the number of patients with final diagnosis with mRCC is fewer than 10.

Studies were not limited by language, publication type, year of publication, location or setting.

Participants
The participants considered were adult patients with:
- Localized (solid or cystic) renal mass
- Suspected metastatic RCC

Index tests

The following tests were considered:
- Percutaneous fine needle aspiration cytology(FNAC)
- Percutaneous core biopsy

We excluded laparoscopic, endoscopic or ex-vivo FNAC or core biopsies.

We expected studies concerning renal mass FNAC and core biopsy to vary with respect to *sample collection* (needle size, number of passes, clinical background and experience of the aspirator/biopsy technician, use of guidance techniques (ultrasound, CT, MRI, fluroscopy) and immediate onsite assessment of adequacy by a cytopathologist); *sample preparation* (routine staining method, use of special stains, use of immunohistochemical stains, use of cell blocks); *sample interpretation* (number of persons interpreting slides, experience level of pathologists interpreting slides, whether clinical information was available at the time of interpretation, and the diagnostic criteria used for diagnosis). If sufficient data are available we may undertake sensitivity analysis on these variables.

Reference standard
The primary reference standard is definitive histology following radical or partial nephrectomy. Surgery is not usually performed on patients with negative index test results or in patients with positive test results that are unfit for surgery. Thus, clinical follow-up is an alternative reference test for these patients.

Target conditions
We considered the following biopsy target lesions:
- Non-metastatic, indeterminate, solid or cystic renal masses
- Renal masses in the context of metastatic disease of indeterminate origin

- Secondary lesions in the setting of suspected mRCC prior to treatment

Search methods for identification of studies

Studies were identified by searching electronic databases and relevant websites and by the scrutiny of bibliographies of retrieved papers. Highly sensitive electronic searches were conducted to identify randomised controlled trials or non-randomised comparative studies on the use of biopsy in renal tumours. No language or date restrictions were imposed on the search strategy.

The databases searched were MEDLINE (1946 to 30th November 2013), MEDLINE In-Process (9th January 2014), Embase (1974 to 30th November 2013), Cochrane Controlled Trials Register (The Cochrane Library, Issue 1, January 2014) and Latin American and Caribbean Center on Health Sciences Information (LILACS) (11th January 2014). Additionally, systematic reviews and other background information were identified by searching the Cochrane Database of Systematic Reviews (The Cochrane Library, Issue 1, January 2014). Full details of the search strategies used and websites consulted are documented in Appendix A1. Reference lists of all included studies were scanned to identify additional potentially relevant studies.

Data collection and analysis

Selection of studies

Abstract screening: All titles and abstracts retrieved were collected in a reference management file and duplicates were removed. The main review author (LM) examined all abstracts to identify potentially relevant studies using a study screening form (Appendix A2) (*the inclusion and exclusion criteria are stated in the "Criteria for considering studies for this review" section of this protocol*). These abstracts or titles were categorized into 2 groups: conditional inclusion (potentially relevant studies) or exclusion (irrelevant studies). A secondary reviewer (FH) independently screened the abstracts to ensure consistency of results. Disagreements were resolved by discussion, and where no agreement could be reached, an independent third party acted as arbiter (TL).

Full-text screening: After validation of the abstract screening process, we obtained the full text for each potentially relevant study. The main reviewer (LM) assessed the full text of all the potentially relevant studies (conditional included) which were re-categorized into 2 groups (final included or excluded) using the same study screening form used in the abstract screening. A consistency check was performed by a second independent reviewer (TL) and any disagreements were resolved by discussion.

Data extraction and management

A data extraction form was developed by the main reviewer (LM) and piloted by two independent reviewers (FH and SD). We electronically recorded data on study characteristics (title, author, year, institution, biopsy date); study design, selection of participants (inclusion and exclusion criteria), participants characteristics (Age, gender, body mass index, other malignancy status; comorbidities) renal mass characteristics (presentation, prior testing, size, side, cystic/solid); index test and reference standard characteristics; accuracy data for malignancy, histologic subtype and Fuhrman Grade (true positives, false positives, true negatives, false negatives, specificity, sensitivity, positive predictive value, negative predictive value, accuracy);

adverse events, oncological outcomes and influence on clinical decision. The main reviewer (LM) conducted data extraction of English, French, Italian, Spanish and Portuguese studies. Data from other language articles were extracted by other team members with knowledge of the language or by a translator working in conjuction with the main author.

Assessment of methodological quality
Risk of bias in the included studies was assessed by main reviewer (LM) using the QUADAS-2 tool designed to assess the quality of primary diagnostic accuracy studies. It consists of four key domains covering patient selection, index tests, reference standard, and flow of patients through the study and timing of the index test(s) and reference standard.

Statistical analysis and data synthesis
The results of the diagnostic tests were tabulated and sensitivity, specificity, positive and negative predictive values, positive and negative likelihood ratios and diagnostic odds ratios (DORs) calculated for the diagnosis of Renal Cell Cancer, RCC sub-type and Fuhrman Grade. We performed sub-group analysis of the diagnostic test accuracy in small renal masses, cystic vs. solid masses; localized vs. metastatic disease.

For additional non-diagnostic outcomes reported (adverse events, oncological outcomes and impact on managment) where appropriate, meta-analysis will be employed to estimate a summary measure of effect. Where a quantitative synthesis is considered to be inappropriate or not feasible, a narrative synthesis of results will be provided.

Appendix A1: Search strategy for systematic review on renal biopsy for the diagnosis of renal cell carcinoma

Embase 1974 to 2014 January 09
MEDLINE In-Process January 09 2014
MEDLINE (1946 to November Week 3 2013

Ovid multifile search URL: http://shibboleth.ovid.com/

1   Carcinoma, Renal Cell/ use prmz (19997)
2   kidney carcinoma/ use oemezd (39058)
3   ((kidney or renal) adj2 (cancer* or carcinoma* or neoplasm* or tum?or* or mass*)).tw. (88785)
4   or/1-3 (101509)
5   conization/ use prmz (594)
6   ((percutaneous or needle or aspiration or core or tru-cut) adj3 (biops* or sampl$)).tw. (67939)
7   (fna or cytology).tw. (86403)
8   aspiration biopsy/ use oemezd (24714)
9   exp biopsy,needle/ use prmz (49363)
10   percutaneous biopsy/ (2708)
11   or/6-10 (185658)
12   "sensitivity and specificity"/ (427507)
13   roc curve/ (29672)
14   receiver operating characteristic/ use oemezd (24622)
15   predictive value of tests/ (145001)
16   diagnostic errors/ use oemezd (39392)
17   false positive reactions/ use prmz (22965)
18   false negative reactions/ use prmz (15180)
19   diagnostic accuracy/ use oemezd (163098)
20   diagnostic value/ use oemezd (126263)
21   du.fs. use prmz (313521)
22   sensitivity.tw. (1043068)
23   distinguish$.tw. (369632)
24   differentiat$.tw. (1004053)
25   identif$.tw. (3658683)
26   detect$.tw. (3204011)
27   diagnos$.tw. (3421264)
28   (predictive adj4 value$).tw. (138941)
29   accura$.tw. (907336)
30   or/12-29 (10982271)
31   4 and 11 and 30 (2231)
32   Carcinoma, Renal Cell/di [Diagnosis] (9194)
33   kidney carcinoma/di [Diagnosis] (6629)
34   32 or 33 (9194)
35   11 and 34 (640)
36   31 or 35 (2344)
37   exp animals/ not humans/ (5119485)
38   (conference or letter or editorial or comment$).pt. (3943676)
39   36 not (37 or 38) (2054)

40   remove duplicates from 40 (1311)

Cochrane Central Register of Controlled Trials
The Cochrane Library, Issue 1, January 2014

URL: www.thecochranelibrary.com

1   MeSH descriptor Carcinoma, Renal Cell, this term only
2   (metastas* near/5 ((kidney or renal) near/2 (cancer* or carcinoma* or neoplasm* or tum?or* or mass*)))
3   (#1 OR #2)
4   MeSH descriptor Biopsy, Needle explode tree 1
5   MeSH descriptor Conization, this term only
6   ((percutaneous or needle or aspiration or core or tru-cut) near/3 (biops* or sampl*))
7   fna or cytology
8   (#4 OR #5 OR #6 OR #7)
9   (#3 AND #8)

Latin American and Caribbean Health Sciences (LILACS) (January 2014)

URL: http://lilacs.bvsalud.org/en/

1.   (renal cell carcinoma or renal cancer or renal tumour$ or renal tumor$ or renal carcinoma$ or renal neoplasm$ or renal mass$ or kidney cancer or kidney tumour$ or kidney tumor$ or kidney neoplasm$ or kidney mass$)
2.   Pt CLINICAL TRIAL or Pt RANDOMIZED CONTROLLED TRIAL or Pt CONTROLLED CLINICAL TRIAL or random$ or trial$ or compara$ or compare$ or cohort$ or retrospective or prospective
3.   1 and 2

Appendix A2: Study eligibility form for systematic review on renal biopsy for the diagnosis of renal cell carcinoma

Assessor initials: [　　　　　　　　]   Date assessed: [　　　　　　　　]

Study identifier
(surname of first author + year of publication)

Type of study	Yes	Unclear	No
Q1. Is the study design one of the following?			

- Randomised or quasi-randomised trial (quasi-randomised = alternate allocation)
- Non-randomised comparative interventional study
- Comparative observational study
- Single-arm case series

Yes → Go to next question   Unclear / No → **Exclude**

Participants in the study

Q2. Are the tumours of some or all of the participants in the study any of the following?   Yes   Unclear   No

- Any T stage
- Metastatic RCC

Yes → Go to next question   Unclear / No → **Exclude**

If the study involves a mixed population, data must be reported separately for the above groups. If the number of patients is <10, the study has to be excluded.

Diagnostic interventions in the study

Q3. Did some or all the participants receive the following diagnostic interventions for their renal lesion?   Yes   Unclear   No

- Percutaneous core biopsy
- Percutaneous fine needle aspiration cytology

Yes → Go to next question   Unclear / No → **Exclude**

Reference standard used in the study

Q4. Did the study include any of the following reference standards?   Yes   Unclear   No

- CT
- MRI
- PET
- Pathological examination of radical/partial nephrectomy specimen

Yes → **Include**   Unclear   No → **Exclude**

Outcomes in the study

Q4. Does the study report one or more of the following outcomes?   Yes   Unclear   No

- Diagnostic accuracy (e.g. sensitivity, specificity, positive or negative predictive values, false positive or negative rate, area under curve ROC, etc.) based on diagnosis of RCC, histological subtype, or tumour grade
- Adverse events (e.g. bleeding, tumour seedling, etc.)
- Impact on patient management or treatment decisions
- Oncological outcomes (e.g. progression, recurrence, etc.)
- Any other outcomes judged to be relevant by reviewer (please state):

Yes → **Include**   Unclear   No → **Exclude**

Final decision (subject to clarification of 'unclear' points)   **Include Unclear Exclude**

B: Systematic review on systemic therapy for metastatic renal cell carcinoma

Methods protocol

Fabian Hofmann (FH), Saeed Dabestani (SD), Fiona Stewart (FS), Lorenzo Marconi (LM), Temitope Adewuyi (TA), Thomas Lam (TL), Axel Bex (AB), Thomas Powles, Steven Canfield, and the EAU RCC Guideline Panel

Objectives:
To compare the clinical effectiveness and harms of systemic treatments for metastatic renal cell carcinoma.

Methods:

Criteria for considering studies for this review

Type of studies:
Randomised controlled trials or quasi-randomised controlled trials (e.g. alternate allocation).

Types of participants:
Studies reporting on patients with metastatic renal cell cancer are included. Participants may or may not have had prior radical nephrectomy or cytoreductive nephrectomy, or were treatment naïve or received prior systemic treatment.

Types of interventions and comparators:
To be eligible for inclusion, the trial must include one of the pre-specified systemic treatment agents in one of the trial arms. The agents to be considered are as follows:
   a) Axitinib
   b) Bevacizumab
   c) Cancer vaccines
   d) Cytokines (Interleukin, Inferferon alpha)
   e) Everolimus
   f) Pazopanib
   g) Sorafenib
   h) Sunitinib
   i) Temsirolimus
   j) Thalidomide
   k) Dovitinib
   l) Tivozanib
   m) Erlotinib
   n) 5-FU
   o) Other agents identified during search

A valid comparator included:

a. Any of the pre-specified systemic therapy agents

b. Placebo
c. Any other agent judged to be important

Types of outcome measures:
The primary outcome of interest was overall survival.
Secondary outcomes included the following:

Cancer-specific outcomes:
1. Cancer-specific survival
2. Progression-free survival
3. Local tumor control (e.g. stable disease, complete or partial response, progressive disease)
4. Cancer-related symptom control

Other outcomes:
1. Adverse events
2. Quality of life outcomes

Search methods for identification of studies (FS):
Studies were identified by searching electronic databases and relevant websites and by the scrutiny of bibliographies of retrieved papers. Highly sensitive electronic searches were conducted to identify reports of randomised controlled trials of systemic treatment and cytoreductive therapy in metastatic renal cell carcinoma. The search strategy excluded studies published before 2001 and included studies written in any language.

The databases searched were MEDLINE (1946 to 31st October 2013), MEDLINE In-Process (31th October 2013), Embase (1974 to 31st October 2013), Cochrane Controlled Trials Register (The Cochrane Library, Issue 10, October 2013) and Latin American and Caribbean Center on Health Sciences Information (LILACS) (31st October 2013). Additionally, systematic reviews and other background information were identified by searching the Cochrane Database of Systematic Reviews (The Cochrane Library, Issue 10, October 2013). Full details of the search strategies used and websites consulted are documented in Appendix B1. Reference lists of all included studies were scanned to identify additional potentially relevant studies.

Data collection and analysis:
Selection of studies
All abstracts and titles identified by the search were screened and selected for full text screening if matching the defined inclusion criteria. A pre-defined study screening form was used (Appendix B2). Two reviewers (FH and SD) independently performed abstract screening. Full text screening was performed on eligible publications by two reviewers (FH and TL) against pre-defined inclusion criteria specified on the screening form described above. Disagreement was resolved by discussion, and where no agreement could be reached, an arbiter was sought (TL/SD). The identified titles and papers were screened according to the methods described above.

Data extraction and management:
Studies matching the criteria for final inclusion were data abstracted by four reviewers (FH, TA, AB, TL) using a pre-defined data abstraction form. Risk of bias assessment was also performed using this form. Information collected included the following: study identification, methods section, participants eligibility criteria, study characteristics, details on baseline characteristics, and relevant outcomes. Data was collected separately for each arm of the study.

Assessment of risk of bias in included studies:
The risk of bias assessment method was adapted from the Cochrane Handbook (Higgins and Green, eds. 2011, version 5.1.0), marking bias in each domain as high, low or unclear risk. Risk for detection and attrition bias was judged separately for cancer-specific outcomes and adverse events. Any missing information was regarded as unclear risk. Open label studies, lack of blinding and outcome assessment by investigators was considered as high risk. Other risk for bias included industry involvement in several critical parts of the study.

Measures of treatment effect:
Time-to-event data was collected for the primary outcome that was overall survival. Secondary outcomes included abstraction of continuous, dichotomous and ordinal data as well as counts and rates. For data analysis, descriptive statistics were used to summarise baseline characteristics data. The main results were summarized in a summary of findings table. A quantitative synthesis (i.e. meta-analysis) was planned for RCTs wherever appropriate and when clinical and methodological homogeneity is demonstrated. In instances when pooling of data was not performed, where appropriate the results were presented in Forest plots to allow a visual comparison of the effects of interventions between studies. Both fixed effects and random effects models were used to derive the appropriate test statistic. For time-to-event data, hazard ratios and 95% confidence intervals (CIs) obtained directly from studies or indirectly from presented Kaplan-Meier survival curves were used to compare results. In analysing dichotomous outcomes, relative risk with 95% CIs were used, whilst for continuous outcomes, means and standard deviations or median and range were used to summarise the data, and weighted mean difference and 95% CIs were used to compare interventions. Statistical heterogeneity between studies was assessed by visual inspection of plots of the data, the chi-square test for heterogeneity, and the I^2 statistic. Analysis was performed using Cochrane RevMan version 5.2 software. Where meta-analysis was not feasible, a narrative synthesis was provided instead.

Dealing with missing data:
If data was missing in main publications, information was derived from further published articles reporting on follow up data on the specific study.

Appendix B1: Search strategy for systematic review on systemic therapy for metastatic renal cell carcinoma

MEDLINE 1946 to October week 2 2013
MEDLINE In-Process 21st October 2013
Embase 1974 to 21st October 2013

Ovid Multifile search URL: http://gateway.ovid.com

Carcinoma, Renal Cell/ use prmz
kidney carcinoma/ use oemezd
(metastas* adj5 ((kidney or renal) adj2 (cancer* or carcinoma* or neoplasm* or tum?or* or mass*))).tw.
or/1-3
((cytoreduct* or debulk* or metastas* or palliate*) adj4 nephrectom*).tw.
Nephrectomy/
exp nephrectomy/
sorafenib/
sunitinib/
bevacizumab/
axitinib/
pazopanib/
everolimus/
temsirolimus/
interferon/
interleukin 2/
dovitinib/
tivozanib/
erlotinib/
chemotherapy, adjuvant/ use prmz
adjuvant chemotherapy/ use oemezd
cancer chemotherapy/ use oemezd
cytoreductive surgery/ use oemezd
(sorafenib or sunitinib or bevacizumab or axitinib or pazopanib or everolimus or temsirolimus or interferon or interleukin 2 or dovitinib or tivozanib or erlotinib or chemotherapy or radiosurgery).tw.
or/5-24
exp clinical trial/
Randomized Controlled Trials as Topic/
randomized controlled trial.pt.
controlled clinical trial.pt.
randomization/ use oemezd
randomi?ed.ab.
placebo.ab.
drug therapy.fs.
randomly.ab.
trial.ab.
groups.ab.
or/26-36
4 and 25 and 37
exp animals/ not humans/
38 not 39 (8812)
limit 40 to yr="2001 -Current"
 (conference or letter or editorial or comment*).pt.

41 not 42
remove duplicates from 43

Cochrane Database of Systematic Reviews
Cochrane Central Register of Controlled Trials
(The Cochrane Library, Issue 10, October 2013)

URL www.thecochranelibrary.com

MeSH descriptor Carcinoma, Renal Cell, this term only
(metastas* near/5 ((kidney or renal) near/2 (cancer* or carcinoma* or neoplasm* or tum?or* or mass*)))
(#1 OR #2)
(#3), from 2001 to 2012

Latin American and Caribbean Health Sciences (LILACS) (October 2013)

URL: http://lilacs.bvsalud.org/en/

(renal cell carcinoma or renal cancer or renal tumour$ or renal tumor$ or renal carcinoma$ or renal neoplasm$ or renal mass$ or kidney cancer or kidney tumour$ or kidney tumor$ or kidney neoplasm$ or kidney mass$)
Pt CLINICAL TRIAL or Pt RANDOMIZED CONTROLLED TRIAL or Pt CONTROLLED CLINICAL TRIAL or random$ or trial$ or compara$ or compare$ or cohort$ or retrospective or prospective
1 and 2

Appendix B2: Study eligibility form for systematic review on systemic therapy for metastatic renal cell carcinoma

Assessor initials: [   ]   Date assessed: [   ]

Study identifier
(surname of first author + year of publication)

Type of study   Yes   Unclear   No
Q1. Is the study design the following?
- Randomised or quasi-randomised trial (quasi-randomised = alternate allocation)

⬇ Go to next question   ⬇   ⬇ **Exclude**

Participants in the study   Yes   Unclear   No
Q2. Are some or all of the participants in the study any of the following?
- Untreated metastatic RCC
- Metastatic RCC previously treated with cytoreductive nephrectomy
- Metastatic RCC previously treated with first-line systemic therapy

If the study involves a mixed population, data must be reported separately for metastatic RCC.

⬇ Go to next question   ⬇   ⬇ **Exclude**

- **Interventions in the study**   Yes   Unclear   No
Q3. Did some or all the participants receive:
- Systemic chemotherapy:
  - Sunitinib
  - Sorafenib
  - Axitinib
  - Pazopanib
  - Dovitinib
  - Cabozantinib
  - Tivozanib
  - Erlotinib
  - Bevacizumab
  - 5-FU
  - Other (please state):
- Systemic immunotherapy:
  - IL-2
  - IFA

⬇ Go to next question   ⬇   ⬇ **Exclude**

Outcomes in the study   Yes   Unclear   No
Q4. Does the study report one or more of the following outcomes?
- Overall or cancer-specific survival
- Progression-free survival
- Local tumour control
- Quality of life
- Symptom control
- Toxicity/Adverse events
- Any other outcomes judged to be relevant by reviewer (please state):

⬇ **Include**   ⬇   ⬇ **Exclude**

Final decision (subject to clarification of 'unclear' points)   **Include Unclear Exclude**

Write here if the study is relevant for background information ☞

C: Systematic review on surgical management of T1a renal cell carcinoma

Methods protocol

Lorenzo Marconi (LM), Saeed Dabestani (SD), Fabian Hofmann (FH), Fiona Stewart (FS), Thomas Lam (TL), Alessandro Volpe (AV), Steven Canfield (SC), Markus Kuczyk (MK), Axel Merseburger (AM), Karim Bensalah (KB) and the EAU RCC Guideline Panel

Objectives:

To compare the clinical effectiveness and harms of surgical management for T1a renal cell carcinoma.

The following questions will be addressed:
  i.   What is the best treatment option for T1a renal cell cancers?
  ii.   What is the best way of performing this procedure?
  iii. How do the following interventions compare against each other for small renal masses (i.e. <4cm): partial nephrectomy; cryotherapy or RFA; surveillance?
  iv.   How does cryotherapy compare with RFA for small renal masses?
  v.   What is the best way of performing partial nephrectomy (e.g. laparoscopic vs robotic vs open)?

Methods:

Criteria for considering studies for this review

Type of studies:
Comparative studies only (i.e. study needs to have at least 1 experimental arm and 1 control arm; 3 or 4-arm studies will also be included), including randomised controlled trials, non-randomised comparative studies, cohort studies with matched controls, and database reviews with historical controls.

Types of participants:
Adult men and women (≥18 years of age) with primary RCC (radiological diagnosis acceptable), and clinical stage T1aN0M0 according to latest TNM staging system. Exclusions: Previous surgical treatment, benign tumours, non-RCC malignancies (e.g. oncocytoma, nephroblastoma, etc.).

Types of interventions and comparators:
Any of the following interventions in either or both arms will be included:
  - partial nephrectomy (any approach or type e.g. open, laparoscopic, robotic, etc.)
  - minimally invasive therapy (to include cryotherapy or RFA; any approach or type e.g. percutaneous or laparoscopic)
  - surveillance

Any comparisons between interventions (e.g. partial nephrectomy vs either cryotherapy or RFA; cryotherapy or RFA vs surveillance; etc.) and within interventions (e.g. laparoscopic partial nephrectomy vs robotic partial nephrectomy vs open partial nephrectomy; percutaneous cryotherapy vs percutaneous RFA; laparoscopic cryotherapy vs percutaneous cryotherapy; etc.) will be included.

Types of outcome measures:
The primary outcome of interest was overall survival.

Secondary outcomes included the following:
Oncological outcomes (including cancer-specific survival, recurrence incidence or recurrence-free survival, metastatic incidence);
Perioperative complications, recovery and quality of life;
Renal function (sub-group analysis to include ischaemia time if relevant and if data is available; categorise renal function into eGFR based on CKD classification i.e. $\geq$90/60-90/30-60/15-30/<15ml/min);
Long term outcomes on cardiovascular disease and related events (e.g. myocardial infarction).

<u>Search methods for identification of studies (FS):</u>
Studies were identified by searching electronic databases and relevant websites and by the scrutiny of bibliographies of retrieved papers. Highly sensitive electronic searches were conducted to identify reports of relevant studies of treatment for T1a RCC. The search included studies written in any language.

The databases searched were MEDLINE (1946 to 31st October 2013), MEDLINE In-Process (31th October 2013), Embase (1974 to 31st October 2013), Cochrane Controlled Trials Register (The Cochrane Library, Issue 10, October 2013) and Latin American and Caribbean Center on Health Sciences Information (LILACS) (31st October 2013). Additionally, systematic reviews and other background information were identified by searching the Cochrane Database of Systematic Reviews (The Cochrane Library, Issue 10, October 2013). Full details of the search strategies used and websites consulted are documented in Appendix C1. Reference lists of all included studies were scanned to identify additional potentially relevant studies.

<u>Data collection and analysis:</u>
Selection of studies
All abstracts and titles identified by the search were screened and selected for full text screening if matching the defined inclusion criteria. A pre-defined study screening form was used (Appendix C2). Two reviewers (LM and SD) independently performed abstract screening. Full text screening was performed on eligible publications by two reviewers (LM and SD) against pre-defined inclusion criteria specified on the screening form described above. Disagreement was resolved by discussion, and where no agreement could be reached, an arbiter was sought (TL/AV). The identified titles and papers were screened according to the methods described above.

Data extraction and management:
Studies matching the criteria for final inclusion were data abstracted by five reviewers (LM, SD, FH, TL, AV) using a pre-defined data abstraction form. Risk of bias assessment was also performed using this form. Information collected included the following: study identification, methods section, participants eligibility criteria, study characteristics, details on baseline characteristics, and relevant outcomes. Data was collected separately for each arm of the study.

Assessment of risk of bias in included studies:
Risk of bias (RoB) assessment was planned, using the standard Cochrane Collaboration RoB tool for randomized controlled trials, whilst for non-randomised comparative studies (NRCS), a modified RoB tool was adapted from the Cochrane Handbook (Higgins and Green, eds. 2011, version 5.1.0), marking bias in each domain as high, low or unclear risk. Risk for detection and attrition bias was judged separately for cancer-specific outcomes and adverse events. Any missing information was regarded as unclear risk. Open label studies, lack of blinding and outcome assessment by investigators was considered as high risk. In addition, for NRCS, the main confounders were identified *a priori* by the expert panel, for the primary outcome. A study was considered to be at high RoB if any of the confounders were imbalanced. The main confounders identified included age, comorbidities, performance status, histological subtype, tumour grade, tumour size, pathological stage and presence of necrosis. Each confounder was assessed according to whether it had been considered by the authors (yes/no), whether the confounder was balanced across the groups (high risk/low risk/unclear) and the degree to which adjustment had been made for the confounder (high risk/low risk/unclear).

Measures of treatment effect:
Time-to-event data was collected for the primary outcome that was overall survival. Secondary outcomes included abstraction of continuous, dichotomous and ordinal data as well as counts and rates. For data analysis, descriptive statistics were used to summarise baseline characteristics data. The main results were summarized in a summary of findings table. A quantitative synthesis (i.e. meta-analysis) was planned for RCTs wherever appropriate and when clinical and methodological homogeneity is demonstrated. In instances when pooling of data was not performed, where appropriate the results were presented in Forest plots to allow a visual comparison of the effects of interventions between studies. Both fixed effects and random effects models were used to derive the appropriate test statistic. For time-to-event data, hazard ratios and 95% confidence intervals (CIs) obtained directly from studies or indirectly from presented Kaplan-Meier survival curves were used to compare results. In analysing dichotomous outcomes, relative risk with 95% CIs were used, whilst for continuous outcomes, means and standard deviations or median and range were used to summarise the data, and weighted mean difference and 95% CIs were used to compare interventions. Statistical heterogeneity between studies was assessed by visual inspection of plots of the data, the chi-square test for heterogeneity, and the I^2 statistic. Analysis was performed using Cochrane RevMan version 5.2 software. Where meta-analysis was not feasible, a narrative synthesis was provided instead.

Dealing with missing data:
If data was missing in main publications, information was derived from further published articles reporting on follow up data on the specific study.

Appendix C1: Search strategy for systematic review on surgical management of T1a renal cell carcinoma

MEDLINE 1946 to October Week 4 2013
MEDLINE In-Process 06 October 2013
Embase 1974 to 2013 October 06

Ovid multifile search URL: http://shibboleth.ovid.com/

1. exp Kidney Neoplasms/su
2. ((kidney or renal) adj2 (cancer$ or carcinoma$ or neoplasm$ or tumo?r$)).tw.
3. renal mass$.tw.
4. exp *Kidney Neoplasms/
5. or/2-3
6. 4 and 5
7. ((kidney or renal) adj2 (cancer$ or carcinoma$ or neoplasm$ or tumo?r$)).ti.
8. renal mass$.ti.
9. or/7-8
10. exp *Nephrectomy/
11. (nephrectom$ or nephron sparing surgery).ti.
12. exp *Lymph Node Excision/
13. lymphadenectomy.ti.
14. (Minimally invasive or radiofrequency or cryotherapy or cryoablat* or cryosurg$ or ablation or high intensity focused ultrasound or HIFU or RFA or surveillance or monitor$ or NSS).ti.
15. exp *Ablation Techniques/
16. or/10-15
17. 1 or 6 or 9
18. 16 and 17
19. comparative study/ use prmz
20. follow-up studies/ use prmz
21. Treatment outcome/ use oemezd
22. major clinical study/ use oemezd
23. controlled study/ use oemezd
24. clinical trial/ use oemezd
25. (chang$ or evaluat$ or baseline).tw.
26. (prospective$ or retrospective$).tw.
27. (compara$ or compare$).tw.
28. randomized controlled trial.pt.
29. controlled clinical trial.pt.
30. randomization/ use oemezd
31. trial.ab.
32. random$.tw.
33. or/19-32
34. 18 and 33
35. exp animals/ not humans/
36. 34 not 35
37. 36 not (comment$ or editorial or letter or opinion or note or review).pt.

Science Citation Index (1970 to 7 October 2013)
Conference Proceedings Citation Index – Science (1990 to 7 October 2013)

URL: www.isiknowledge.com

1. TI=((kidney or renal) and (cancer or carcinoma or neoplasm* or tumor* or tumour*))
2. TI=(nephrectom* or nephroureterectom* or nephron sparing or ablation or radiofrequency or cryotherapy or cryoablat* or cryosurgery or ultrasound or vaccine* or adjuvant or surveillance or monitor* or NSS)
3. #2 AND #1
4. TS=(trial* or random* or comparison or compare or comparative)
5. #4 AND #3
6. #5 Timespan=2012-01-01 - 2013-05-07

Cochrane Database of Systematic Reviews : Issue 10 of 12, October 2013
Cochrane Central Register of Controlled Trials : Issue 10 of 12, October 2013

URL: www.thecochranelibrary.com

1. MeSH descriptor: [Carcinoma, Renal Cell] this term only
2. (kidney or renal) near/2 (cancer* or carcinoma* or neoplasm* or tumor* or tumour*)
3. renal mass*
4. #1 or #2 or #3
5. MeSH descriptor: [Nephrectomy] this term only
6. MeSH descriptor: [Lymph Node Excision] this term only
7. MeSH descriptor: [Ablation Techniques] 1 tree(s) exploded
8. Minimally invasive or radiofrequency or cryotherapy or cryoablat* or cryosurg* or ablation or high intensity focused ultrasound or HIFU or RFA or surveillance or monitor* or NSS or lymphadenectom* or nephrectom*
9. #5 or #6 or #7 or #8
10. #4 and #9 from 2011 to 2013

Ongoing trials

ClinicalTrials.gov
www.clinicaltrials.gov

Appendix C2: Study eligibility form for systematic review on on surgical management of T1a renal cell carcinoma

Assessor initials: [   ]   Date assessed: [   ]

Study identifier
(surname of first author + year of publication)

Type of study
Q1. Is the study design one of the following?
- Randomised or quasi-randomised trial (quasi-randomised = alternate allocation)
- Non-randomised comparative study (i.e. study needs to have at least 1 **experimental arm** and 1 **control arm**; 3 or 4-arm studies will also be included)

Yes   Unclear   No

Go to next question   **Exclude**

Participants in the study
Q2. Are some or all of the participants in the study any of the following?
- Adults (≥18 years of age) with primary RCC (radiological diagnosis acceptable)
- T1aN0M0 according to latest TNM staging system; no previous surgical treatment
- Exclusions: benign tumour, non-RCC malignancies (e.g. oncocytoma, nephroblastoma, etc.)

Yes   Unclear   No

Go to next question   **Exclude**

Interventions and Comparisons in the study
Q3. Did some or all the participants receive the following interventions?
- Any of the following interventions in either or both arms:
  - partial nephrectomy (any approach or type e.g. open, laparoscopic, robotic, etc.)
  - minimally invasive therapy (to include cryotherapy or RFA; any approach or type e.g. percutaneous or laparoscopic)
  - surveillance
- Exclusion: Previous surgical treatment for RCC
- To include any comparisons **between** interventions (e.g. partial nephrectomy vs either cryotherapy or RFA; cryotherapy or RFA vs surveillance; etc.) and **within** interventions (e.g. laparoscopic partial nephrectomy vs robotic partial nephrectomy vs open partial nephrectomy; percutaneous cryotherapy vs percutaneous RFA; laparoscopic cryotherapy vs percutaneous cryotherapy; etc.)
- To also include studies with 3 or 4-way comparisons (if appropriate)

Yes   Unclear   No

Go to next question   **Exclude**

Outcomes in the study
Q4. Does the study report one or more of the following outcomes?
- Oncological (including overall survival, cancer-specific survival, recurrence incidence or recurrence-free survival, metastatic incidence)
- Perioperative complications, recovery and quality of life
- Renal function (sub-group analysis to include ischaemia time if relevant and if data is available; categorise renal function into eGFR based on CKD classification i.e. ≥90/60-90/30-60/15-30/<15ml/min)
- Long term outcomes on cardiovascular disease and related events (e.g. myocardial infarction)

Yes   Unclear   No

Include   **Exclude**

Final decision (subject to clarification of 'unclear' points)   **Include Unclear Exclude**

Write here if the study is relevant for background information ☞

D: Systematic review of partial nephrectomy versus radical nephrectomy for T1b and T2a renal cell carcinoma

Methods protocol

Saeed Dabestani (SD), Lorenzo Marconi (LM), Fabian Hofmann (FH), Fiona Stewart (FS), Thomas Lam (TL), Alessandro Volpe (AV), Steven Canfield (SC), Markus Kuczyk (MK), Axel Merseburger (AM), Karim Bensalah (KB) and the EAU RCC Guideline Panel

Objectives:

To compare the clinical effectiveness and harms of partial nephrectomy and radical nephrectomy for T1b and T2a renal cell carcinoma.

The following question will be addressed:
How does partial nephrectomy compare with radical nephrectomy for T1b and T2a renal cell carcinoma?

Methods:

Criteria for considering studies for this review

Type of studies:
Comparative studies only (i.e. study needs to have at least 1 experimental arm and 1 control arm; 3 or 4-arm studies will also be included), including randomised controlled trials, non-randomised comparative studies, cohort studies with matched controls, and database reviews with historical controls.

Types of participants:
Adult men and women (≥18 years of age) with primary RCC (radiological diagnosis acceptable), and clinical stage T1b-T2aN0M0 according to latest TNM staging system. Neoadjuvant chemotherapy/targeted therapy is acceptable for inclusion. Exclusions: Previous surgical treatment, benign tumours, non-RCC malignancies (e.g. oncocytoma, nephroblastoma, etc.).

Types of interventions and comparators:
The following interventions in at least one arm will be included:
- partial nephrectomy (any approach or type e.g. open, laparoscopic, robotic, etc.);
- radical nephrectomy (any approach or type e.g. open, laparoscopic, robotic, etc.).

Any comparisons between interventions (e.g. partial nephrectomy vs radical nephrectomy) and within interventions (e.g. laparoscopic partial nephrectomy vs robotic partial nephrectomy; open radical nephrectomy vs laparoscopic radical nephrectomy; etc.) will be included. Studies with 3 or 4-way comparisons will also be included if appropriate.

Types of outcome measures:
The primary outcome of interest was overall survival.

Secondary outcomes included the following:

Oncological outcomes (including cancer-specific survival, recurrence incidence or recurrence-free survival, metastatic incidence);

Perioperative complications, recovery and quality of life;

Renal function (sub-group analysis to include ischaemia time if relevant and if data is available; categorise renal function into eGFR based on CKD classification i.e. ≥90/60-90/30-60/15-30/<15ml/min);

Long term outcomes on cardiovascular disease and related events (e.g. myocardial infarction).

Search methods for identification of studies (FS):

Studies were identified by searching electronic databases and relevant websites and by the scrutiny of bibliographies of retrieved papers. Highly sensitive electronic searches were conducted to identify reports of relevant studies of treatment for T1b and T2a RCC. The search included studies written in any language.

The databases searched were MEDLINE (1946 to 31st October 2013), MEDLINE In-Process (31th October 2013), Embase (1974 to 31st October 2013), Cochrane Controlled Trials Register (The Cochrane Library, Issue 10, October 2013) and Latin American and Caribbean Center on Health Sciences Information (LILACS) (31st October 2013). Additionally, systematic reviews and other background information were identified by searching the Cochrane Database of Systematic Reviews (The Cochrane Library, Issue 10, October 2013). Full details of the search strategies used and websites consulted are documented in Appendix D1. Reference lists of all included studies were scanned to identify additional potentially relevant studies.

Data collection and analysis:

Selection of studies

All abstracts and titles identified by the search were screened and selected for full text screening if matching the defined inclusion criteria. A pre-defined study screening form was used (Appendix D2). Two reviewers (SD and LM) independently performed abstract screening. Full text screening was performed on eligible publications by two reviewers (SD and LM) against pre-defined inclusion criteria specified on the screening form described above. Disagreement was resolved by discussion, and where no agreement could be reached, an arbiter was sought (TL/AV). The identified titles and papers were screened according to the methods described above.

Data extraction and management:

Studies matching the criteria for final inclusion were data abstracted by five reviewers (LM, SD, FH, TL, AV) using a pre-defined data abstraction form. Risk of bias assessment was also performed using this form. Information collected included the following: study identification, methods section, participants eligibility criteria, study characteristics, details on baseline characteristics, and relevant outcomes. Data was collected separately for each arm of the study.

Assessment of risk of bias in included studies:
Risk of bias (RoB) assessment was planned, using the standard Cochrane Collaboration RoB tool for randomized controlled trials, whilst for non-randomised comparative studies (NRCS), a modified RoB tool was adapted from the Cochrane Handbook (Higgins and Green, eds. 2011, version 5.1.0), marking bias in each domain as high, low or unclear risk. Risk for detection and attrition bias was judged separately for cancer-specific outcomes and adverse events. Any missing information was regarded as unclear risk. Open label studies, lack of blinding and outcome assessment by investigators was considered as high risk. In addition, for NRCS, the main confounders were identified *a priori* by the expert panel, for the primary outcome. A study was considered to be at high RoB if any of the confounders were imbalanced. The main confounders identified included age, comorbidities, performance status, histological subtype, tumour grade, tumour size, pathological stage, presence of necrosis and neoadjuvant systemic or targeted therapy (if appropriate). Each confounder was assessed according to whether it had been considered by the authors (yes/no), whether the confounder was balanced across the groups (high risk/low risk/unclear) and the degree to which adjustment had been made for the confounder (high risk/low risk/unclear).

Measures of treatment effect:
Time-to-event data was collected for the primary outcome that was overall survival. Secondary outcomes included abstraction of continuous, dichotomous and ordinal data as well as counts and rates. For data analysis, descriptive statistics were used to summarise baseline characteristics data. The main results were summarized in a summary of findings table. A quantitative synthesis (i.e. meta-analysis) was planned for RCTs wherever appropriate and when clinical and methodological homogeneity is demonstrated. In instances when pooling of data was not performed, where appropriate the results were presented in Forest plots to allow a visual comparison of the effects of interventions between studies. Both fixed effects and random effects models were used to derive the appropriate test statistic. For time-to-event data, hazard ratios and 95% confidence intervals (CIs) obtained directly from studies or indirectly from presented Kaplan-Meier survival curves were used to compare results. In analysing dichotomous outcomes, relative risk with 95% CIs were used, whilst for continuous outcomes, means and standard deviations or median and range were used to summarise the data, and weighted mean difference and 95% CIs were used to compare interventions. Statistical heterogeneity between studies was assessed by visual inspection of plots of the data, the chi-square test for heterogeneity, and the I^2 statistic. Analysis was performed using Cochrane RevMan version 5.2 software. Where meta-analysis was not feasible, a narrative synthesis was provided instead.

Dealing with missing data:
If data was missing in main publications, information was derived from further published articles reporting on follow up data on the specific study.

Appendix D1: Search strategy for systematic review of partial nephrectomy versus radical nephrectomy for T1b and T2a renal cell carcinoma

MEDLINE 1946 to October Week 4 2013
MEDLINE In-Process 06 October 2013
Embase 1974 to 2013 October 06

Ovid multifile search URL: http://shibboleth.ovid.com/

1. exp Kidney Neoplasms/su
2. ((kidney or renal) adj2 (cancer$ or carcinoma$ or neoplasm$ or tumo?r$)).tw.
3. renal mass$.tw.
4. exp *Kidney Neoplasms/
5. or/2-3
6. 4 and 5
7. ((kidney or renal) adj2 (cancer$ or carcinoma$ or neoplasm$ or tumo?r$)).ti.
8. renal mass$.ti.
9. or/7-8
10. exp *Nephrectomy/
11. (nephrectom$ or nephron sparing surgery).ti.
12. exp *Lymph Node Excision/
13. lymphadenectomy.ti.
14. (Minimally invasive or radiofrequency or cryotherapy or cryoablat* or cryosurg$ or ablation or high intensity focused ultrasound or HIFU or RFA or surveillance or monitor$ or NSS).ti.
15. exp *Ablation Techniques/
16. or/10-15
17. 1 or 6 or 9
18. 16 and 17
19. comparative study/ use prmz
20. follow-up studies/ use prmz
21. Treatment outcome/ use oemezd
22. major clinical study/ use oemezd
23. controlled study/ use oemezd
24. clinical trial/ use oemezd
25. (chang$ or evaluat$ or baseline).tw.
26. (prospective$ or retrospective$).tw.
27. (compara$ or compare$).tw.
28. randomized controlled trial.pt.
29. controlled clinical trial.pt.
30. randomization/ use oemezd
31. trial.ab.
32. random$.tw.
33. or/19-32
34. 18 and 33
35. exp animals/ not humans/
36. 34 not 35
37. 36 not (comment$ or editorial or letter or opinion or note or review).pt.

Science Citation Index (1970 to 7 October 2013)
Conference Proceedings Citation Index – Science (1990 to 7 October 2013)

URL: www.isiknowledge.com

    7. TI=((kidney or renal) and (cancer or carcinoma or neoplasm* or tumor* or tumour*))
    8. TI=(nephrectom* or nephroureterectom* or nephron sparing or ablation or radiofrequency or cryotherapy or cryoablat* or cryosurgery or ultrasound or vaccine* or adjuvant or surveillance or monitor* or NSS)
    9. #2 AND #1
    10. TS=(trial* or random* or comparison or compare or comparative)
    11. #4 AND #3
    12. #5 Timespan=2012-01-01 - 2013-05-07

Cochrane Database of Systematic Reviews : Issue 10 of 12, October 2013
Cochrane Central Register of Controlled Trials : Issue 10 of 12, October 2013

URL: www.thecochranelibrary.com

    11. MeSH descriptor: [Carcinoma, Renal Cell] this term only
    12. (kidney or renal) near/2 (cancer* or carcinoma* or neoplasm* or tumor* or tumour*)
    13. renal mass*
    14. #1 or #2 or #3
    15. MeSH descriptor: [Nephrectomy] this term only
    16. MeSH descriptor: [Lymph Node Excision] this term only
    17. MeSH descriptor: [Ablation Techniques] 1 tree(s) exploded
    18. Minimally invasive or radiofrequency or cryotherapy or cryoablat* or cryosurg* or ablation or high intensity focused ultrasound or HIFU or RFA or surveillance or monitor* or NSS or lymphadenectom* or nephrectom*
    19. #5 or #6 or #7 or #8
    20. #4 and #9 from 2011 to 2013

Ongoing trials

ClinicalTrials.gov
www.clinicaltrials.gov

Appendix D2: Study eligibility form for systematic review of partial nephrectomy versus radical nephrectomy for T1b and T2a renal cell carcinoma

Assessor initials: [   ]   Date assessed: [   ]

Study identifier
(surname of first author + year of publication)

Type of study

Q1. Is the study design one of the following?

- Randomised or quasi-randomised trial (quasi-randomised = alternate allocation)
- Non-randomised comparative study (i.e. study needs to have at least 1 **experimental arm** and 1 **control arm**; 3 or 4-arm studies will also be included)

Yes   Unclear   No

Go to next question   **Exclude**

Participants in the study

Q2. Are some or all of the participants in the study any of the following?

- Adults (≥18 years of age) with primary RCC (radiological diagnosis acceptable)
- T1b-2aN0M0 according to latest TNM staging system; no previous surgical treatment
- Exclusions: benign tumour, non-RCC malignancies (e.g. oncocytoma, nephroblastoma, etc.)

Yes   Unclear   No

Go to next question   **Exclude**

Interventions and Comparisons in the study

Q3. Did some or all the participants receive the following interventions?

- Partial nephrectomy (any approach or type e.g. open, laparoscopic, robotic, etc.) in one arm
- Radical nephrectomy (any approach or type e.g. open, laparoscopic, robotic, etc.) in the other arm
- Exclusion: Previous surgical treatment for RCC; neoadjuvant chemotherapy/targeted therapy is acceptable
- To include any comparisons **between** interventions (e.g. partial nephrectomy vs radical nephrectomy) and **within** interventions (e.g. laparoscopic partial nephrectomy vs robotic partial nephrectomy; open radical nephrectomy vs laparoscopic radical nephrectomy; etc.)
- To also include studies with 3 or 4-way comparisons (if appropriate)

Yes   Unclear   No

Go to next question   **Exclude**

Outcomes in the study

Q4. Does the study report one or more of the following outcomes?

- Oncological (including overall survival, cancer-specific survival, recurrence incidence or recurrence-free survival, metastatic incidence)
- Perioperative complications, recovery and quality of life
- Renal function (sub-group analysis to include ischaemia time if relevant and if data is available; categorise renal function into eGFR based on CKD classification i.e. ≥90/60-90/30-60/15-30/<15ml/min)
- Long term outcomes on cardiovascular disease and related events (e.g. myocardial infarction)

Yes   Unclear   No

Include   **Exclude**

Final decision (subject to clarification of 'unclear' points)   **Include   Unclear   Exclude**

Write here if the study is relevant for background information ☞

E: Systematic review of surgical management of non-metastatic renal cell carcinoma with vena caval thrombus

Methods protocol

Fiona Stewart (FS), Fabian Hofmann (FH), Lorenzo Marconi (LM), Saeed Dabestani (SD), Thomas Lam (TL), Axel Bex (AB), Steven Canfield (SC), Borje Ljungberg (BL) and the EAU RCC Guideline Panel

Objectives:

To systematically review relevant literature comparing the outcomes of different surgical therapies and approaches in treating vena caval thrombus (VCT) from non-metastatic RCC

The following questions will be addressed:
i.   Should patients with non-metastatic RCC and caval thrombus undergo surgery?
ii.   What is the best way of performing this procedure?

Methods:

Criteria for considering studies for this review

Type of studies:
Comparative studies only (i.e. study needs to have at least 1 experimental arm and 1 control arm; 3 or 4-arm studies will also be included), including randomised controlled trials (RCTs), non-randomised comparative studies (NRCS), cohort studies with matched controls, and database reviews with historical controls will be included. Studies with no comparative element (e.g. single-arm case series) will be excluded.

Types of participants:
Adult men and women (≥18 years of age) with non-metastatic RCC with tumour extension into the IVC. Studies in which metastatic disease accounted for greater than 10% of their participants will be excluded. Previous surgery for VCT, recurrent tumours and non-RCC malignancies were also grounds for exclusion.

Types of interventions and comparators:
Studies reporting any kind of surgery for VCT in at least one arm were eligible for inclusion. Eligible comparators were either no intervention or any alternative surgery or treatment. Peri-operative strategies (e.g. IVC filter, thrombus embolization) were also included, as long as thrombectomy was included in one arm.

Types of outcome measures:
The main outcome measures were specified *a priori*, and included overall survival (OS) and cancer-specific survival (CSS). Other oncological outcomes included incidence of recurrence, recurrence-free survival, and incidence of metastatic disease. Additional outcome measures included perioperative complications (including

mortality), process and recovery outcomes (e.g. length of hospital stay, blood loss) and quality of life.

Search methods for identification of studies (FS):

Studies were identified by searching electronic databases and relevant websites. Highly sensitive electronic searches were conducted to identify published and ongoing comparative studies of surgical management of renal cell carcinoma with VCT. Searches were limited to studies published from 2000 onwards up to 31st May 2013. No language restrictions were imposed. The search was complemented by additional sources, including the reference lists of included studies which were hand searched to identify additional relevant studies, and reports identified by an expert panel (European Association of Urology Renal Cell Carcinoma Guideline Panel).

The databases searched were MEDLINE (1946 to 31st October 2013), MEDLINE In-Process (31th October 2013), Embase (1974 to 31st October 2013), Cochrane Controlled Trials Register (The Cochrane Library, Issue 10, October 2013) and Latin American and Caribbean Center on Health Sciences Information (LILACS) (31st October 2013). Additionally, systematic reviews and other background information were identified by searching the Cochrane Database of Systematic Reviews (The Cochrane Library, Issue 10, October 2013), and clinicaltrials.gov and the WHO International Clinical Trials Registry were searched to identify ongoing trials. Full details of the search strategies used and websites consulted are documented in Appendix E1. Reference lists of all included studies were scanned to identify additional potentially relevant studies.

Data collection and analysis:

Selection of studies

All abstracts and titles identified by the search were screened and selected for full text screening if matching the defined inclusion criteria. A pre-defined study screening form was used (Appendix E2). Two reviewers (FS and FH) independently performed abstract screening. Full text screening was performed on eligible publications by two reviewers (FS and FH) against pre-defined inclusion criteria specified on the screening form described above. Disagreement was resolved by discussion, and where no agreement could be reached, an arbiter was sought (TL). The identified titles and papers were screened according to the methods described above.

Data extraction and management:

Studies matching the criteria for final inclusion were data abstracted by three reviewers (FS, FH, TL) using a pre-defined data abstraction form. Risk of bias assessment was also performed using this form. Information collected included the following: study identification, methods section, participants eligibility criteria, study characteristics, details on baseline characteristics, and relevant outcomes. Data was collected separately for each arm of the study.

Assessment of risk of bias in included studies:

Risk of bias (RoB) assessment was planned, using the standard Cochrane Collaboration RoB tool for randomized controlled trials, whilst for non-randomised

comparative studies (NRCS), a modified RoB tool was adapted from the Cochrane Handbook (Higgins and Green, eds. 2011, version 5.1.0), marking bias in each domain as high, low or unclear risk. Risk for detection and attrition bias was judged separately for cancer-specific outcomes and adverse events. Any missing information was regarded as unclear risk. Open label studies, lack of blinding and outcome assessment by investigators was considered as high risk. In addition, for NRCS, the main confounders were identified *a priori* by the expert panel, for the primary outcome. A study was considered to be at high RoB if any of the confounders were imbalanced. The main confounders identified included age, level of thrombus, neo-adjuvant treatment with targeted agents, performance status, and serum albumin level. Each confounder was assessed according to whether it had been considered by the authors (yes/no), whether the confounder was balanced across the groups (high risk/low risk/unclear) and the degree to which adjustment had been made for the confounder (high risk/low risk/unclear).

Dada analysis:
Time-to-event data was collected for the primary outcome that was overall survival. Secondary outcomes included abstraction of continuous, dichotomous and ordinal data as well as counts and rates. For data analysis, descriptive statistics were used to summarise baseline characteristics data. The main results were summarized in a summary of findings table. A quantitative synthesis (i.e. meta-analysis) was planned for RCTs wherever appropriate and when clinical and methodological homogeneity is demonstrated. In instances when pooling of data was not performed, where appropriate the results were presented in Forest plots to allow a visual comparison of the effects of interventions between studies. Both fixed effects and random effects models were used to derive the appropriate test statistic. For time-to-event data, hazard ratios and 95% confidence intervals (CIs) obtained directly from studies or indirectly from presented Kaplan-Meier survival curves were used to compare results. In analysing dichotomous outcomes, relative risk with 95% CIs were used, whilst for continuous outcomes, means and standard deviations or median and range were used to summarise the data, and weighted mean difference and 95% CIs were used to compare interventions. Statistical heterogeneity between studies was assessed by visual inspection of plots of the data, the chi-square test for heterogeneity, and the I^2 statistic. Analysis was performed using Cochrane RevMan version 5.2 software. Where meta-analysis was not feasible, a narrative synthesis was provided instead.

Dealing with missing data:
If data was missing in main publications, information was derived from further published articles reporting on follow up data on the specific study.

Appendix E1: Search strategy for systematic review of surgical management of non-metastatic renal cell carcinoma with vena caval thrombus

MEDLINE 1946 to October Week 4 2013
MEDLINE In-Process 06 October 2013
Embase 1974 to 2013 October 06

Ovid multifile search URL: http://shibboleth.ovid.com/

1. ((thrombus or thrombi or tumo?r$ or neoplas$) adj2 (vena cava or IVC or caval or intravascular or venous)).tw.
2. exp thrombectomy/
3. (((surgery or surgical) adj3 (thrombus or thrombi)) or thrombectomy).tw.
4. or/1-3
5. kidney carcinoma/ use oemezd
6. renal cell carcinoma/ use prmz
7. ((kidney or renal) adj3 (carcinoma$ or cancer$ or tumo?r$ or neoplas$ or mass or masses)).tw.
8. or/5-7
9. comparative study/ use prmz
10. follow-up studies/ use prmz
11. major clinical study/ use oemezd
12. controlled study/ use oemezd
13. clinical trial/ use oemezd
14. (chang$ or evaluat$ or baseline).tw.
15. (prospective$ or retrospective$).tw.
16. (compara$ or compare$).tw.
17. exp clinical trial/
18. randomized controlled trial.pt.
19. controlled clinical trial.pt.
20. randomization/
21. randomi?ed.ab.
22. randomly.ab.
23. trial.ab.
24. groups.ab.
25. or/9-24
26. 4 and 8 and 25
27. exp animals/ not humans/
28. 26 not 27
29. 28 not (comment$ or letter or editorial or case report).pt.
30. limit 29 to yr="2000 -Current"
31. remove duplicates from 30

Cochrane Database of Systematic Reviews : Issue 10 of 12, October 2013

URL: www.thecochranelibrary.com

1. MeSH descriptor: [Carcinoma, Renal Cell] this term only
2. (kidney or renal) near/2 (cancer* or carcinoma* or neoplasm* or tumor* or tumour*)
3. #1 or #2

4. (thrombus or thrombi or tumor* or tumour* or neoplas*) near/2 (vena cava or IVC or caval or intravascular or venous)
5. MeSH descriptor: [Thrombectomy] this term only
6. (surgery or surgical) near/3 (thrombus or thrombi)
7. thrombectomy
8. #4 or #5 or #6 or #7
9. #3 and #8

Science Citation Index (1970 to 23 October 2013)
Conference Proceedings Citation Index – Science (1990 to 23 October 2013)

URL: www.isiknowledge.com

1. TS=((kidney or renal) near/3 (cancer or carcinoma or neoplasm* or tumor* or tumour*))
2. TS=((thrombus or thrombi or tumor* or tumour* or neoplas*) SAME (vena cava or IVC or caval or intravascular or venous))
3. TS=thrombectomy
4. TS=((surgery or surgical) near/3 (thrombus or thrombi))
5. #4 OR #3 OR #2
6. TS=(trial or compara* or random* or compare* or retrospectiv* or prospective*)
7. #1 and #5 and #6. Timespan=2000-2013

ClinicalTrials.gov (October 2013)
www.clinicaltrials.gov

International Clinical Trials Registry (October 2013)
http://apps.who.int/trialsearch/

Appendix E2: Study eligibility form for systematic review of surgical management of non-metastatic renal cell carcinoma with vena caval thrombus

Assessor initials: [   ]   Date assessed: [   ]

Study identifier
(surname of first author + year of publication)

Type of study
Q1. Is the study design one of the following?   Yes   Unclear   No
- Randomised or quasi-randomised trial (quasi-randomised = alternate allocation)
- Non-randomised comparative study (i.e. study needs to have at least 1 **experimental arm** and 1 **control arm**; 3 or 4-arm studies will also be included)

Go to
next question   **Exclude**

Participants in the study
Q2. Are some or all of the participants in the study any of the following?   Yes   Unclear   No
- Adults (≥18 years of age) with primary RCC
- Caval thrombus present (any level)
- No metastatic disease
- Prior neoadjuvant treatment acceptable
- Exclusions: Previous surgery for caval thrombus; recurrent tumours, metastatic disease, non- RCC malignancies

Go to
next question   **Exclude**

Interventions and Comparisons in the study
Q3. Did some or all the participants receive the following interventions?   Yes   Unclear   No
- Surgery for caval thrombus (any approach or type e.g. caval thrombectomy with or without shunt or cardiac bypass) in **at least** one arm
- Systemic therapy alone; or Observation alone; or another type or extent of surgery for caval thrombus in the other arm
- To include any comparisons **between** interventions (e.g. caval thrombectomy vs no thrombectomy or observation or systemic therapy; etc.) and **within** interventions (e.g. caval thrombectomy alone vs caval thrombectomy + systemic therapy; caval thrombectomy with cardiac bypass vs without bypass; different extents or approaches of caval thrombectomy; etc.)
- Use of adjuvant therapy in any arm is acceptable
- If data is available, will attempt to perform sub-group analysis according to level of thrombus (i.e. results analysed according to stage of disease e.g. Novick staging system)

Go to
next question   **Exclude**

Outcomes in the study
Q4. Does the study report one or more of the following outcomes?   Yes   Unclear   No
- Oncological (including overall survival, cancer-specific survival, recurrence incidence or recurrence-free survival, metastatic incidence)
- Perioperative complications (including perioperative mortality), recovery and quality of life

Include   **Exclude**

Final decision (subject to clarification of 'unclear' points)   **Include   Unclear   Exclude**

Write here if the study is relevant for background information ☞

F: Systematic review of lymph node dissection for T2-4N0M0 renal cell carcinoma

Methods protocol

Hanneke Bekema, (HB), Saeed Dabestani (SD), Lorenzo Marconi (LM), Fabian Hofmann (FH), Fiona Stewart (FS), Thomas Lam (TL), Milan Hora, Borje Ljrungberg (BL) and the EAU RCC Guideline Panel

Objectives:
To review the relative clinical effectiveness and harms of lymph node dissection for T2-4N0M0 renal cell carcinoma.

The following question will be addressed:
What are the benefits and harms of lymph node dissection for T2-4N0M0 renal cell carcinoma?

Methods:

Criteria for considering studies for this review

Type of studies:
Comparative studies only (i.e. study needs to have at least 1 experimental arm and 1 control arm; 3 or 4-arm studies will also be included), including randomised controlled trials, non-randomised comparative studies, cohort studies with matched controls, and database reviews with historical controls.

Types of participants:
Adult men and women (≥18 years of age) with primary RCC (radiological diagnosis acceptable), and clinical stage T2-4N0M0 according to latest TNM staging system. Exclusions: Previous surgical treatment, benign tumours, non-RCC malignancies (e.g. oncocytoma, nephroblastoma, etc.).

Types of interventions and comparators:
The following interventions in at least one arm will be included:
- radical nephrectomy (any approach or type e.g. open, laparoscopic, robotic, etc.) **with** lymph node dissection (any extent e.g. limited or extended) in one arm;
- radical nephrectomy (any approach or type e.g. open, laparoscopic, robotic, etc.) **without** lymph node dissection in the other arm;
- or radical nephrectomy (any approach or type e.g. open, laparoscopic, robotic, etc.) with different extents of lymph node dissection between the arms.

Any comparisons between interventions (e.g. lymph node dissection vs no lymph node dissection) and within interventions (e.g. limited lymph node dissection vs extended lymph node dissection) will be included. Studies with 3 or 4-way comparisons will also be included if appropriate.

Types of outcome measures:
The primary outcome of interest was overall survival.

Secondary outcomes included the following:
Oncological outcomes (including cancer-specific survival, recurrence incidence or recurrence-free survival, metastatic incidence);
Perioperative complications, recovery and quality of life.

<u>Search methods for identification of studies (FS):</u>
The review was an update of three systematic reviews published previously (MacLennan et al. 2012, Eur Urol. 2012 May; 61(5):972-93); MacLennan et al. 2012, Eur Urol. 2012 Dec; 62(6):1097-117; Bekema et al. 2013, Eur Urol. 2013 Nov; 64(5):799-810). Studies were identified by searching electronic databases and relevant websites and by the scrutiny of bibliographies of retrieved papers. Highly sensitive electronic searches were conducted to identify reports of relevant studies of treatment for T1a RCC. The search included studies written in any language.

The databases searched were MEDLINE (1946 to 31st October 2013), MEDLINE In-Process (31th October 2013), Embase (1974 to 31st October 2013), Cochrane Controlled Trials Register (The Cochrane Library, Issue 10, October 2013) and Latin American and Caribbean Center on Health Sciences Information (LILACS) (31st October 2013). Additionally, systematic reviews and other background information were identified by searching the Cochrane Database of Systematic Reviews (The Cochrane Library, Issue 10, October 2013). Full details of the search strategies used and websites consulted are documented in Appendix F1. Reference lists of all included studies were scanned to identify additional potentially relevant studies.

<u>Data collection and analysis:</u>
Selection of studies
All abstracts and titles identified by the search were screened and selected for full text screening if matching the defined inclusion criteria. A pre-defined study screening form was used (Appendix F2). Two reviewers (HB and SD) independently performed abstract screening. Full text screening was performed on eligible publications by two reviewers (HB and SD) against pre-defined inclusion criteria specified on the screening form described above. Disagreement was resolved by discussion, and where no agreement could be reached, an arbiter was sought (TL). The identified titles and papers were screened according to the methods described above.

Data extraction and management:
Studies matching the criteria for final inclusion were data abstracted by two reviewers (HB and SD) using a pre-defined data abstraction form. Risk of bias assessment was also performed using this form. Information collected included the following: study identification, methods section, participants eligibility criteria, study characteristics, details on baseline characteristics, and relevant outcomes. Data was collected separately for each arm of the study.

Assessment of risk of bias in included studies:
Risk of bias (RoB) assessment was planned, using the standard Cochrane Collaboration RoB tool for randomized controlled trials, whilst for non-randomised comparative studies (NRCS), a modified RoB tool was adapted from the Cochrane Handbook (Higgins and Green, eds. 2011, version 5.1.0), marking bias in each domain as high, low or unclear risk. Risk for detection and attrition bias was judged separately for cancer-specific outcomes and adverse events. Any missing information was regarded as unclear risk. Open label studies, lack of blinding and outcome assessment by investigators was considered as high risk. In addition, for NRCS, the main confounders were identified *a priori* by the expert panel, for oncological and perioperative outcomes. A study was considered to be at high RoB if any of the confounders were imbalanced. The main confounders for oncological outcomes included histological subtype, tumour grade, tumour size, pathological stage and presence of necrosis. The main confounders for perioperative outcomes were age, comorbidities, performance status, gender, smoking, obesity, ethnicity and hypertension. Each confounder was assessed according to whether it had been considered by the authors (yes/no), whether the confounder was balanced across the groups (high risk/low risk/unclear) and the degree to which adjustment had been made for the confounder (high risk/low risk/unclear).

Measures of treatment effect:
Time-to-event data was collected for the primary outcome that was overall survival. Secondary outcomes included abstraction of continuous, dichotomous and ordinal data as well as counts and rates. For data analysis, descriptive statistics were used to summarise baseline characteristics data. The main results were summarized in a summary of findings table. A quantitative synthesis (i.e. meta-analysis) was planned for RCTs wherever appropriate and when clinical and methodological homogeneity is demonstrated. In instances when pooling of data was not performed, where appropriate the results were presented in Forest plots to allow a visual comparison of the effects of interventions between studies. Both fixed effects and random effects models were used to derive the appropriate test statistic. For time-to-event data, hazard ratios and 95% confidence intervals (CIs) obtained directly from studies or indirectly from presented Kaplan-Meier survival curves were used to compare results. In analysing dichotomous outcomes, relative risk with 95% CIs were used, whilst for continuous outcomes, means and standard deviations or median and range were used to summarise the data, and weighted mean difference and 95% CIs were used to compare interventions. Statistical heterogeneity between studies was assessed by visual inspection of plots of the data, the chi-square test for heterogeneity, and the I^2 statistic. Analysis was performed using Cochrane RevMan version 5.2 software. Where meta-analysis was not feasible, a narrative synthesis was provided instead.

Dealing with missing data:
If data was missing in main publications, information was derived from further published articles reporting on follow up data on the specific study.

Appendix F1: Search strategy for systematic review of lymph node dissection for T2-4N0M0 renal cell carcinoma

MEDLINE 1946 to October Week 4 2013
MEDLINE In-Process 06 October 2013
Embase 1974 to 2013 October 06

Ovid multifile search URL: http://shibboleth.ovid.com/

1. exp Kidney Neoplasms/su
2. ((kidney or renal) adj2 (cancer$ or carcinoma$ or neoplasm$ or tumo?r$)).tw.
3. renal mass$.tw.
4. exp *Kidney Neoplasms/
5. or/2-3
6. 4 and 5
7. ((kidney or renal) adj2 (cancer$ or carcinoma$ or neoplasm$ or tumo?r$)).ti.
8. renal mass$.ti.
9. or/7-8
10. exp *Nephrectomy/
11. (nephrectom$ or nephron sparing surgery).ti.
12. exp *Lymph Node Excision/
13. lymphadenectomy.ti.
14. (Minimally invasive or radiofrequency or cryotherapy or cryoablat* or cryosurg$ or ablation or high intensity focused ultrasound or HIFU or RFA or surveillance or monitor$ or NSS).ti.
15. exp *Ablation Techniques/
16. or/10-15
17. 1 or 6 or 9
18. 16 and 17
19. comparative study/ use prmz
20. follow-up studies/ use prmz
21. Treatment outcome/ use oemezd
22. major clinical study/ use oemezd
23. controlled study/ use oemezd
24. clinical trial/ use oemezd
25. (chang$ or evaluat$ or baseline).tw.
26. (prospective$ or retrospective$).tw.
27. (compara$ or compare$).tw.
28. randomized controlled trial.pt.
29. controlled clinical trial.pt.
30. randomization/ use oemezd
31. trial.ab.
32. random$.tw.
33. or/19-32
34. 18 and 33
35. exp animals/ not humans/
36. 34 not 35
37. 36 not (comment$ or editorial or letter or opinion or note or review).pt.

Science Citation Index (1970 to 7 October 2013)
Conference Proceedings Citation Index – Science (1990 to 7 October 2013)

URL: www.isiknowledge.com

13. TI=((kidney or renal) and (cancer or carcinoma or neoplasm* or tumor* or tumour*))
14. TI=(nephrectom* or nephroureterectom* or nephron sparing or ablation or radiofrequency or cryotherapy or cryoablat* or cryosurgery or ultrasound or vaccine* or adjuvant or surveillance or monitor* or NSS)
15. #2 AND #1
16. TS=(trial* or random* or comparison or compare or comparative)
17. #4 AND #3
18. #5 Timespan=2012-01-01 - 2013-05-07

Cochrane Database of Systematic Reviews : Issue 10 of 12, October 2013
Cochrane Central Register of Controlled Trials : Issue 10 of 12, October 2013

URL: www.thecochranelibrary.com

21. MeSH descriptor: [Carcinoma, Renal Cell] this term only
22. (kidney or renal) near/2 (cancer* or carcinoma* or neoplasm* or tumor* or tumour*)
23. renal mass*
24. #1 or #2 or #3
25. MeSH descriptor: [Nephrectomy] this term only
26. MeSH descriptor: [Lymph Node Excision] this term only
27. MeSH descriptor: [Ablation Techniques] 1 tree(s) exploded
28. Minimally invasive or radiofrequency or cryotherapy or cryoablat* or cryosurg* or ablation or high intensity focused ultrasound or HIFU or RFA or surveillance or monitor* or NSS or lymphadenectom* or nephrectom*
29. #5 or #6 or #7 or #8
30. #4 and #9 from 2011 to 2013

Ongoing trials

ClinicalTrials.gov
www.clinicaltrials.gov

Appendix F2: Study eligibility form for systematic review of lymph node dissection for T2-4N0M0 renal cell carcinoma

Assessor initials: [   ]   Date assessed: [   ]

Study identifier
(surname of first author + year of publication)
Type of study
Q1. Is the study design one of the following?   Yes   Unclear   No
- Randomised or quasi-randomised trial (quasi-randomised = alternate allocation)
- Non-randomised comparative study (i.e. study needs to have at least 1 **experimental arm** and 1 **control arm**; 3 or 4-arm studies will also be included)

Go to next question   **Exclude**

Participants in the study
Q2. Are some or all of the participants in the study any of the following?   Yes   Unclear   No
- Adults (≥18 years of age) with primary RCC
- T2-4N0M0 according to latest TNM staging system (based on pre-operative radiological diagnosis); no previous treatment
- Exclusions: Non-RCC malignancies (e.g. nephroblastoma, etc.)

Go to next question   **Exclude**

Interventions and Comparisons in the study
Q3. Did some or all the participants receive the following interventions?   Yes   Unclear   No
- Radical nephrectomy (any approach or type e.g. open, laparoscopic, robotic, etc.) + lymph node dissection (any extent e.g. limited or extended) in one arm
- Radical nephrectomy (any approach or type e.g. open, laparoscopic, robotic, etc.) alone in the other arm
- Exclusion: Previous surgical treatment for RCC; neoadjuvant chemotherapy/targeted therapy is acceptable
- To include any comparisons **between** interventions (e.g. lymph node dissection vs no lymph node dissection) and **within** interventions (e.g. limited lymph node dissection vs extended lymph node dissection; etc.)
- To also include studies with 3 or 4-way comparisons (if appropriate)

Go to next question   **Exclude**

Outcomes in the study
Q4. Does the study report one or more of the following outcomes?   Yes   Unclear   No
- Oncological (including overall survival, cancer-specific survival, recurrence incidence or recurrence-free survival, metastatic incidence)
- Perioperative complications, recovery and quality of life

Include   **Exclude**

Final decision (subject to clarification of 'unclear' points)   **Include   Unclear   Exclude**

Write here if the study is relevant for background information ☞

G: Systematic review of local therapies for metastases of renal cell carcinoma

Methods protocol

Saeed Dabestani (SD), Lorenzo Marconi (LM), Fabian Hofmann (FH), Fiona Stewart (FS), Thomas Lam (TL), Axel Bex (AB), Steven Canfield (SC), Borje Ljungberg (BL) and the EAU RCC Guideline Panel

Objectives:

To systematically review relevant literature comparing the outcomes of different local surgical therapies for metastases of RCC.

The following questions will be addressed:
i.   Is local therapy for metastatic renal cell carcinoma beneficial?
ii.   If so, what are the best treatment modalities?

Methods:

Criteria for considering studies for this review

Type of studies:
Comparative studies only (i.e. study needs to have at least 1 experimental arm and 1 control arm; 3 or 4-arm studies will also be included), including randomised controlled trials (RCTs), non-randomised comparative studies (NRCS), cohort studies with matched controls, and database reviews with historical controls will be included. Studies with no comparative element (e.g. single-arm case series) will be excluded.

Types of participants:
Adult men and women (≥18 years of age) with metastases from RCC to any organ, except invasion of ipsilateral adrenal gland or metastases to retroperitoneal lymph nodes, will be included. Prior to local interventions to treat metastases, participants must either have untreated metastatic RCC, metastatic RCC previously treated with cytoreductive nephrectomy (CRN), or metastatic RCC previously treated with systemic or targeted therapy. Systemic therapy may include both chemotherapy and immunotherapy. Exclusions: Previous local treatment for metastases, localized RCC, benign tumours, non-RCC malignancies (e.g. oncocytoma, nephroblastoma, etc.), irrelevant treatment (e.g. treatment for regional lymph node disease, invasion of ipsilateral adrenal gland, treatment for caval thrombus, etc.).

Types of interventions and comparators:
The interventions of interest include metastasectomy with or without intended complete macroscopic resection of mRCC to any organ, conformal radiotherapy, stereotactic radiosurgery, stereotactic radiotherapy, Cyberknife radiotherapy, hypo-fractionated radiotherapy and no local treatment. Eligible comparators were the above interventions and their variants, and no local treatment. Any comparisons between interventions (e.g. metastasectomy versus conformal radiotherapy) and within interventions (e.g. different forms of stereotactic radiosurgery) will be included.

Types of outcome measures:
The primary outcomes were overall survival (OS), cancer-specific survival (CSS) and progression-free survival (PFS). Local tumour control, quality of life, symptom control and adverse events or toxicity were considered as secondary outcomes.

Search methods for identification of studies (FS):
Studies were identified by searching electronic databases and relevant websites. Highly sensitive electronic searches were conducted to identify reports of randomized controlled trials (RCTs) or non-randomised comparative studies of local treatment for mRCC. The search strategy excluded studies published before 1st January 2000 and there were no language restrictions.

The databases searched were MEDLINE (1946 to 30th September 2013), MEDLINE In-Process (30th September 2013), Embase (1974 to 30th September 2013), Cochrane Central Register of Controlled Trials (The Cochrane Library, Issue 9, September 2013) and Latin American and Caribbean Center on Health Sciences Information (LILACS) (up to 30th September 2013). The search was complemented by additional sources, including the reference lists of included studies which were hand searched, and additional reports identified by an expert panel (European Association of Urology Renal Cell Carcinoma Guideline Panel). Additionally, systematic reviews and other background information were identified by searching the Cochrane Database of Systematic Reviews (The Cochrane Library, Issue 9, September 2013). Full details of the search strategies used and websites consulted are documented in Appendix G1. Reference lists of all included studies were scanned to identify additional potentially relevant studies.

Data collection and analysis:
Selection of studies
All abstracts and titles identified by the search were screened and selected for full text screening if matching the defined inclusion criteria. A pre-defined study screening form was used (Appendix G2). Two reviewers (SD and FH) independently performed abstract and full text screening against pre-defined inclusion criteria specified on the screening form described above. Disagreement was resolved by discussion, and where no agreement could be reached, an arbiter was sought (TL). The identified titles and papers were screened according to the methods described above.

Data extraction and management:
Studies matching the criteria for final inclusion were data abstracted by three reviewers (SD, FH, LM) using a pre-defined data abstraction form. Risk of bias assessment was also performed using this form. Information collected included the following: study identification, methods section, participants eligibility criteria, study characteristics, details on baseline characteristics, and relevant outcomes. Data was collected separately for each arm of the study.

Assessment of risk of bias in included studies:
Risk of bias (RoB) assessment was planned, using the standard Cochrane Collaboration RoB tool for randomized controlled trials, whilst for non-randomised comparative studies (NRCS), a modified RoB tool was adapted from the Cochrane Handbook (Higgins and Green, eds. 2011, version 5.1.0), marking bias in each domain as high, low or unclear risk. Risk for detection and attrition bias was judged

separately for cancer-specific outcomes and adverse events. Any missing information was regarded as unclear risk. Open label studies, lack of blinding and outcome assessment by investigators was considered as high risk. In addition, for NRCS, the main confounders were identified *a priori* by the expert panel, for the primary outcome. A study was considered to be at high RoB if any of the confounders were imbalanced. The main confounders identified included age, gender, Fuhrman grade, size or volume of metastases, previous treatment prior to local treatment, performance status, different sites treated in the same study and tumour histology. Each confounder was assessed according to whether it had been considered by the authors (yes/no), whether the confounder was balanced across the groups (high risk/low risk/unclear) and the degree to which adjustment had been made for the confounder (high risk/low risk/unclear).

Dada analysis:
Time-to-event data was collected for the primary outcome that was overall survival. Secondary outcomes included abstraction of continuous, dichotomous and ordinal data as well as counts and rates. For data analysis, descriptive statistics were used to summarise baseline characteristics data. The main results were summarized in a summary of findings table. A quantitative synthesis (i.e. meta-analysis) was planned for RCTs wherever appropriate and when clinical and methodological homogeneity is demonstrated. In instances when pooling of data was not performed, where appropriate the results were presented in Forest plots to allow a visual comparison of the effects of interventions between studies. Both fixed effects and random effects models were used to derive the appropriate test statistic. For time-to-event data, hazard ratios and 95% confidence intervals (CIs) obtained directly from studies or indirectly from presented Kaplan-Meier survival curves were used to compare results. In analysing dichotomous outcomes, relative risk with 95% CIs were used, whilst for continuous outcomes, means and standard deviations or median and range were used to summarise the data, and weighted mean difference and 95% CIs were used to compare interventions. Statistical heterogeneity between studies was assessed by visual inspection of plots of the data, the chi-square test for heterogeneity, and the I^2 statistic. Analysis was performed using Cochrane RevMan version 5.2 software. Where meta-analysis was not feasible, a narrative synthesis was provided instead.

Dealing with missing data:
If data was missing in main publications, information was derived from further published articles reporting on follow up data on the specific study.

Appendix G1: Search strategy for systematic review of local therapies for metastases of renal cell carcinoma

MEDLINE 1946 to 30th September 2013
MEDLINE In-Process
Embase 1974 to 2013 September 30

Ovid Multifile search URL: http://gateway.ovid.com

1   Carcinoma, Renal Cell/ (59156)
2   kidney carcinoma/ (39116)
3   (metastas* adj5 ((kidney or renal) adj2 (cancer* or carcinoma* or neoplasm* or tum?or* or mass*))).tw. (6364)
4   or/1-3 (60853)
5   hypofraction* radiotherapy.tw. (769)
6   cyberknife.tw. (1333)
7   stereotactic.tw. (29667)
8   radiosurgery.tw. (14985)
9   radiosurgery/ (15401)
10   metasta?ectom*.tw. (2330)
11   metastasis resection/ (264)
12   Metastasectomy/ (193)
13   ((surgical* or metastas*) adj3 (resect* or excis*)).tw. (120754)
14   ((local* or surg*) adj2 (treat* or managed or manage or management)).tw. (429784)
15   or/5-14 (566628)
16   comparative study/ use prmz (1602428)
17   follow-up studies/ use prmz (454504)
18   time factors/ use prmz (942575)
19   Treatment outcome/ use oemezd (599433)
20   major clinical study/ use oemezd (1994844)
21   controlled study/ use oemezd (3866263)
22   clinical trial/ use oemezd (875485)
23   (preoperat$ or pre operat$).tw. (420834)
24   (chang$ or evaluat$ or reviewed or baseline).tw. (8867611)
25   (prospective$ or retrospective$).tw. (1574002)
26   (cohort$ or case series).tw. (576912)
27   (compare$ or compara$).tw. (5614769)
28   case report/ use oemezd (1890264)
29   case reports.pt. (1593140)
30   or/16-29 (20259993)
31   exp clinical trial/ (1644560)
32   Randomized Controlled Trials as Topic/ (102830)
33   randomized controlled trial.pt. (336587)
34   controlled clinical trial.pt. (85134)
35   randomization/ use oemezd (59354)
36   randomi?ed.ab. (690413)
37   placebo.ab. (316144)
38   drug therapy.fs. (1566011)
39   randomly.ab. (411455)

40   trial.ab. (596761)
41   groups.ab. (2697211)
42   or/31-41 (5803372)
43   exp animals/ not humans/ (5125758)
44   42 not 43 (5264693)
45   4 and 15 and 30 (3679)
46   4 and 15 and 44 (816)
47   45 or 46 (3753)
48   (editorial or letter or comment$ or conference$).pt. (3953821)
49   47 not 48 (3354)
50   limit 49 to yr="2000 -Current" (2441)
51   remove duplicates from 50 (1528)
52   (local* adj2 treat*).tw. (38228)
53   or/5-13,52 (196978)
54   4 and 53 (2558)
55   remove duplicates from 54 (1663)
56   (letter or editorial or comment*).pt. (2417780)
57   55 not 56 (1646)
58   limit 57 to yr="2000 -Current" (1285)
59   51 or 58 (2409)
60   remove duplicates from 59 (1857)

Cochrane Database of Systematic Reviews
Cochrane Central Register of Controlled Trials
(The Cochrane Library, Issue 9, September 2013)
www.thecochranelibrary.com
1   MeSH descriptor Carcinoma, Renal Cell, this term only
2   (metastas* near/5 ((kidney or renal) near/2 (cancer* or carcinoma* or
neoplasm* or tum?or* or mass*)))
3   (#1 OR #2)
1.   MeSH descriptor Radiosurgery, this term only
2.   MeSH descriptor Metastasectomy, this term only
3.   hypofraction* radiotherapy or cyberknife or stereotactic or radiosurgery or
metasta*ectom*
4.   ((surgical* or metastas*) near/3 (resect* or excis*))
5.   ((local* or surg*) near/2 (treat* or managed or manage or management))
6.   (#4 OR #5 OR #6 OR #7 OR #8)
7.   (#3 AND #9)
8.   (#10), from 2000 to 2012

LILACS
http://lilacs.bvsalud.org/en/

1.   (renal cell carcinoma or renal cancer or renal tumour$ or renal tumor$ or renal
carcinoma$ or renal neoplasm$ or renal mass$ or kidney cancer or kidney tumour$ or
kidney tumor$ or kidney neoplasm$ or kidney mass$)
2.   Pt CLINICAL TRIAL or Pt RANDOMIZED CONTROLLED TRIAL or Pt
CONTROLLED CLINICAL TRIAL or random$ or trial$ or compara$ or compare$
or cohort$ or retrospective or prospective
3.   1 and 2

Appendix G2: Study eligibility form for systematic review of local therapies for metastases of renal cell carcinoma

Assessor initials: [   ]   Date assessed: [   ]

Study identifier
(surname of first author + year of publication)

Type of study   Yes   Unclear   No
Q1. Is the study design one of the following?
  • Randomised or quasi-randomised trial (quasi-randomised =
    alternate allocation)   Go to
  • Non-randomised comparative study   next question   **Exclude**

Participants in the study   Yes   Unclear   No
Q2. Are some or all of the participants in the study any of the
following?
  • Untreated metastatic RCC
  • Metastatic RCC previously treated with cytoreductive   Go to
    nephrectomy   next question   **Exclude**
  • Metastatic RCC previously treated with systemic therapy

If the study involves a mixed population, data must be reported
separately for metastatic RCC. If the number of patients in each arm is
<10, the study has to be excluded.

Interventions in the study   Yes   Unclear   No
Q3. Did some or all the participants receive local treatment for
isolated metastases?
  • Metastasectomy: Go to
    - Bone (including vertebra)   next question   **Exclude**
    - Lung
    - Brain
    - Liver
    - Other (please state):
  • Stereotactic surgery
  • Stereotactic radiotherapy
  • Cyberknife radiotherapy
  • Hypo-fractionated radiotherapy
  • No local treatment

Outcomes in the study
Q4. Does the study report one or more of the following outcomes?   Yes   Unclear   No
  • Overall or cancer-specific survival
  • Progression-free survival
  • Local tumour control
  • Quality of life   **Include**   **Exclude**
  • Symptom control
  • Toxicity/Adverse events
  • Any other outcomes judged to be relevant by reviewer (please
    state):

Final decision (subject to clarification of 'unclear' points)   **Include Unclear Exclude**