Systematic Review Methodology for the European Association of Urology 2013 Guidelines Update

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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), Mari Imamura (MI), Thomas Lam (TL), Alessandro Volpe, Steven Canfield, James N'Dow 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)
    - Fully paired design (all participants receive all tests as well as the reference standard)
    - 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 10th September 2012), MEDLINE In-Process (10th September 2012), Embase (1974 to 10th September 2012), Cochrane Controlled Trials Register (The Cochrane Library, Issue 8, 2012) and Latin American and Caribbean Center on Health Sciences Information (LILACS) (11th September 2012). Additionally, systematic reviews and other background information were identified by searching the Cochrane Database of Systematic Reviews (The Cochrane Library, Issue 8, 2012). Full details of the search strategies used and websites consulted are documented in Appendix A 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 B) (*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 A

Embase 1974 to 2012 September 10
Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present

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 8, August 2012

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)

LILACS

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 B

Study eligibility form: Biopsy for RCC

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 interventional study
- Comparative observational study
- Single-arm case series

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

Participants in the study
Q2. Are the tumours of some or all of the participants in the study any of the following?
- Any T stage
- Metastatic RCC

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.

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

Diagnostic interventions in the study
Q3. Did some or all the participants receive the following diagnostic interventions for their renal lesion?
- Percutaneous core biopsy
- Percutaneous fine needle aspiration cytology

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

Reference standard used in the study
Q4. Did the study include any of the following reference standards?
- 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?
- 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**

Systematic review on local therapy for metastatic renal cell carcinoma

Methods protocol

Saeed Dabestani (SDA), Lorenzo Oliveira Marconi (LOM), Fabian Hofmann (FAH), Mari Imamura, Fiona Stewart (FIS), Thomas B Lam (TBL), Steven Canfield, James N'Dow and the EAU RCC Guideline Panel

Objectives

This systematic review tries to answer the question whether local therapy for metastatic renal cell carcinoma (mRCC) is beneficial and if so, what are the best options.

Methods

Criteria for considering studies for this review

Types of studies

We will include all randomized controlled trials (RCTs), quasi-RCTs and non-randomized comparative studies concerning any type of local therapy for mRCC.

Types of participants

Patients with mRCC to any organ except invasion of ipsilateral adrenal gland or metastases to retroperitoneal lymph nodes will be included. Participants in studies must prior to interventions either have untreated metastatic RCC, metastatic RCC previously treated with cytoreductive nephrectomy (CRN) or metastatic RCC previously treated with systemic therapy (SysT) which includes both chemotherapy and immunotherapy.

Types of interventions

Metastasectomy with or without intended complete macroscopic resection of mRCC to any organ, stereotactic radiosurgery, stereotactic radiotherapy, Cyberknife radiotherapy, hypo-fractionated radiotherapy and no local treatment are the types of interventions what will be considered. Comparators for these interventions will also be any of the above mentioned.

Types of outcome measures

Primary outcomes

Overall survival, cancer specific survival and progression free survival will be considered as primary outcomes.

Secondary outcomes

Local tumour control, quality of life, symptom control and adverse events/toxicity compared will be considered as secondary outcomes.

Search methods for identification of studies

Studies are to be identified by searching electronic databases and relevant websites and by the scrutiny of bibliographies of retrieved papers. Highly sensitive electronic searches are to be conducted to identify reports of RCTs or non-randomised comparative studies of local treatment of metastatic renal cell carcinoma. The search strategy will exclude studies published before 2000 and include studies written in any language.
The databases searched will be MEDLINE (1946 to 31st August 2012), MEDLINE In-Process (10th September 2012), Embase (1974 to 31st August 2012), Cochrane Controlled Trials Register (The Cochrane Library, Issue 8, 2012) and Latin American and Caribbean Center on Health Sciences Information (LILACS) (10th September). Additionally, systematic reviews and other background information will be identified by searching the Cochrane Database of Systematic Reviews (The Cochrane Library, Issue 8, 2012). Full details of the search strategies used and websites consulted are documented in Appendix A. Reference lists of all included studies will be scanned to identify additional potentially relevant studies.

Data collection and analysis

Selection of studies

All titles and abstracts retrieved will be collected in a reference management file, duplicates will be removed and the remaining titles and abstracts will be reviewed by main reviewer (SDA) using a study screening form created by a secondary reviewer (TL) to determine which studies to include or exclude. The screening form is documented in Appendix B.

Inclusion criteria will be:

Types of studies, participants and interventions as clarified in the "Criteria for considering studies for this review" part of this reviews.

Exclusion criteria will be:

1. Studies dating back before publication year 2000.
2. Review studies.
3. Basic science studies.
4. Genetic or epidemiologic studies.
5. Case reports.
6. Review of prior studies and added case report from authors own institution.
7. Local recurrence of RCC.
8. RCC tumour thrombosis of the Vena Cava.
9. Non-comparative studies, i.e. only descriptive studies.
10. Irrelevant treatment, i.e. regional lymph node recurrence, invasion of ipsilateral adrenal gland, systemic treatment only.
11. Number of participants in any arm (intervention or comparison) less than 10.
12. Localised RCC treatments.

After the abstract screening process is finished it will be rechecked for consistency by a secondary reviewer (LOM) through an additional abstract screening process. This process will be limited to 10% of the full list of titles and abstracts. These 10% will be randomly picked from the full list using randomizing software provided by our information specialist (FIS). Disagreements concerning the rechecked 10 % will be discussed between main author (SDA) and secondary reviewer (LOM) in order to reach consensus. Title and abstract screening will be considered valid if <5% inconsistency is found.

Main reviewer (SDA) will then continue with full text screening of the articles using the previously mentioned study screening form (Appendix B). A consistency check will be performed by secondary reviewer (TL) and any disagreements will be resolved by discussion between main and secondary reviewer.

Finally a list of included articles will be obtained for data extraction.

Data extraction and management

For included studies, a data extraction form will created and used by main reviewer. The data extraction form will collect data on basic study information (author, country, number of centers, recruitment date and type of study), type of intervention and comparator, study inclusion and exclusion criteria, participants characteristics (total number of patients, number of dropouts, reason for dropouts number of participants not yet analysed, age, gender male:female, tumour histology, metastases size, no of metastases, site of metastases treated, Fuhrman grade, performance status as stated by trialist (specified) and ASA Grade), any previous RCC or mRCC treatments and interventions outcomes (overall survival, cancer specific survival, progression free survival, local tumour control, quality of life, symptom control, adverse events/toxicity and other outcomes secondary outcomes judged relevant by reviewer).

Risk of bias assessment will also be included in the data extraction form.

Assessment of risk of bias in included studies

Risk of bias in the included studies will be assessed by main reviewer (SDA) using the Cochrane Collaboration's tools for risk of bias assessment for non-randomised studies. Separate tools will be used for assessing RCTs versus non-randomized studies where predetermined confounders (age, gender, Fuhrman grade, size/volume of metastases, previous treatment prior to local treatment, performance status and different sites treated in same study and tumour histology) will also be assessed. Each of the above specified confounding factors will be assessed on the following four criteria: (a) whether the confounder is considered by the study author, (b) precision of measurement, (c) baseline imbalance between intervention group and comparative group/s and (d) quality of adjustment for imbalance in studies with various treatment sites. The confounders will be scored using a previously used tool with a scoring system of 1 or 5.

1 = The study groups were judged to be balanced at baseline, or the study used statistical methods that attempted to control for the specific confounder.

5 = The specific confounder was either not reported, or was not balanced between the groups at baseline and not adjusted for in the analysis.

Discrepancies will be resolved by discussion with secondary reviewers (TL, LOM, FAH). The following risks of biases will be considered:

Selection bias
Adequate random sequence generation and allocation concealment? High, unclear or low risk.

Performance bias
Blinding of patients and personnel? High, unclear or low risk.

Detection bias
Blinding outcome assessment? High, unclear or low risk.

Attrition bias
Incomplete outcome data? High, unclear or low risk.

Reporting bias
Selective reporting? High, unclear or low risk.

Other bias
(judged relevant by reviewer)

Comments to risk assessments will be given by main reviewer where deemed necessary and results will be summarized in a risk of bias summary table.

Measures of treatment effect.

Outcomes measures for ordinal, count and rates data will be assessed as continuous data.

Dealing with missing data

When data cannot be extracted from the text, or statistics are missing this data will not be reviewed but information on type of missing data will be noted in the summary of findings table.

Assessment of heterogeneity

If enough statistical data is available for meta-analysis of included trials, a statistical heterogeneity test will be performed.

Assessment of reporting biases

Small-study bias (publication bias) will be assessed with the funnel plot method only if enough statistical data is available from included trials.

Data synthesis

If enough statistical data is available this will be summarized statistically using Review Manager 5.1.

Subgroup analysis and investigation of heterogeneity

No subgroup analyses will be undertaken. Heterogeneity will be considered if enough quantitative data is available for statistical analyses.

Sensitivity analysis

If there are sufficient included studies, we will conduct a sensitivity analysis to assess the robustness of our review results by repeating the analysis only including studies with an overall medium to low risk of bias.

Appendix A

Details of search strategies and websites consulted
MEDLINE 1946 to 31st August 2012
MEDLINE In-Process
Embase 1974 to 2012 August 31

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 8, August 2012)
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 B

Study eligibility form: Local therapy for mRCC

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

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

Participants in the study
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 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.

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

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

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

Outcomes in the study
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):

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

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

Systematic review on systemic therapy for metastatic renal cell carcinoma

Methods protocol

Fabian Hofmann (FH), Saeed Dabestani (SD), Fiona Stewart (FS), Lorenzo Marconi (LM), Mari Imamura (MI), Thomas Lam (TL), Steven Canfield, James N'Dow 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 August 2012), MEDLINE In-Process (6th September 2012), Embase (1974 to 31st August 2012), Cochrane Controlled Trials Register (The Cochrane Library, Issue 8, 2012) and Latin American and Caribbean Center on Health Sciences Information (LILACS) (6th September 2012). Additionally, systematic reviews and other background information were identified by searching the Cochrane Database of Systematic Reviews (The Cochrane Library, Issue 8, 2012). Full details of the search strategies used and websites consulted are documented in Appendix A. 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 B). 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). An updated search

was performed from September 2012 to the end of November 2012 . 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 the main reviewer (FH) using a pre-defined data abstraction form (Appendix C). 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.

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: A - Search strategies:

MEDLINE 1946 to 31st August 2012 , MEDLINE In-Process, Embase 1974 to 2012 August 31

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

Carcinoma, Renal Cell/ use prmz (19997)
kidney carcinoma/ use oemezd (39058)
(metastas* adj5 ((kidney or renal) adj2 (cancer* or carcinoma* or neoplasm* or tum?or* or mass*))).tw. (6351)
or/1-3 (60749)
((cytoreduct* or debulk* or metastas* or palliate*) adj4 nephrectom*).tw. (1212)
Nephrectomy/ (58819)
exp nephrectomy/ (65485)
sorafenib/ (10490)
sunitinib/ (9241)
bevacizumab/ (22841)
axitinib/ (1212)
pazopanib/ (1640)
everolimus/ (8359)
temsirolimus/ (3940)
interferon/ (68051)
interleukin 2/ (97863)
dovitinib/ (167)
tivozanib/ (108)
erlotinib/ (11890)
chemotherapy, adjuvant/ use prmz (26693)
adjuvant chemotherapy/ use oemezd (20260)
cancer chemotherapy/ use oemezd (144665)
cytoreductive surgery/ use oemezd (4582)
(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. (826086)
or/5-24 (1070251)
exp clinical trial/ (1641522)
Randomized Controlled Trials as Topic/ (102313)
randomized controlled trial.pt. (335371)

controlled clinical trial.pt. (84954)
randomization/ use oemezd (59299)
randomi?ed.ab. (688201)
placebo.ab. (315399)
drug therapy.fs. (1562339)
randomly.ab. (410264)
trial.ab. (594864)
groups.ab. (2690643)
or/26-36 (5790008)
4 and 25 and 37 (8851)
exp animals/ not humans/ (5119485)
38 not 39 (8812)
limit 40 to yr="2001 -Current" (6994)
(conference or letter or editorial or comment*).pt. (3943676)
41 not 42 (5747)
remove duplicates from 43 (4515)

Cochrane Database of Systematic Reviews
Cochrane Central Register of Controlled Trials
(The Cochrane Library, Issue 8, August 2012)
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 (#3), from 2001 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

B - Study eligibility form:

Version 1, 01/10/2012

Study eligibility form: Systemic therapy for mRCC

Assessor initials: [ ] Date assessed: [ ]

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

Type of study
Q1. Is the study design the following?
- Randomised or quasi-randomised trial (quasi-randomised = alternate allocation)

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

Participants in the study
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.

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

- **Interventions in the study**

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

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

Outcomes in the study
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):

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

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

Write here if the study is relevant for background information ☞

C- Quality Assessment and Data Extraction Form

Systematic Review – Systemic therapy in mRCC

Quality Assessment and Data Extraction Form

Reviewer : **Date:**

Comparison/Drugs			
Study REF ID			
Type of publication	[] full text paper [] conference abstract		
Country			
METHODS			
No. of Centers	[] single [] multi-centre :		
Type of Center (if single center)			
Type of study	[] RCT [] quasi RCT		
Recruitment period			
Duration of follow-up (months)			
Funding			
Notes:			

PARTICIPANTS	
Inclusion criteria	
Exclusion criteria	

Participants Numbers			**N total**
Number enrolled			
Number randomized			
Number treated			
Number analyzed for - efficacy			
Number analyzed for - safety			
Number of dropouts			
Reason for dropout			

PARTICIPANTS: Characteristics	**n=**	**n=**	**N total**
Age median, years			
Gender M/F			
Prim tumor size			
Clear cell type			
Fuhrman			
Karnovski 80			
Karnovski 90			
Karnovski 100			
MSKCC- favorable			
MSKCC-intermed			
MSKCC- poor			
No. metast sites/patients			
Co-morbidity			
Time to metastases			

Prior target therapy			
Prior immuno therap			
Prior nephrectomy			
Prior radiation			
Prior chemotherapy			
Comments:			

INTERVENTION

Name of intervention

Group 1:

Group 2:

Additional information

Outcomes:

General

	N ana-lyzed	Value	N ana-lyzed	Value	N tot
Overall survival (month) median					
Progression free surv (month)					
Complete resp					
Partial response					
Stable disease					
ORR					

Time to resp

Time to progress

Tumor symptom control

- Hematuria

- Tumour invasion

- Pain

General					
	N ana-lyzed	Value	N ana-lyzed	Value	N tot
FACT					
FKSI					
Dose reduction					
Adverse events					
- Infections					
- Blood (eg low count)					
- Hypothyreosis					
- Elevated BP					
- Hand/foot syndrome					
- Neuropathy					
- Hepatobiliary					
- Gastrointestinal					
Number of people dropping out due to adverse effects					

Other Comments / Notes Regarding Study :

CONTACT AUTHOR

RISK OF BIAS [Adapted from: Cochrane Handbook, Higgins and Green, eds. 2011]	
Selection bias	
Random sequence generation?	[] High [] Low [] Unclear
Allocation concealment?	[] High [] Low [] Unclear
Risk for performance bias	
Blinding of patients to treatment they received.	[] High [] Low [] Unclear
Blinding of personnel to treatment patients received.	[] High [] Low [] Unclear
Risk for detection bias	
Blinding of assessors for cancer specific outcomes.	[] High [] Low [] Unclear
Blinding of assessors for adverse events	[] High [] Low [] Unclear
Risk for attrition bias	
Incomplete reporting of outcome data.	[] High [] Low [] Unclear
Incomplete reporting of adverse events	[] High [] Low [] Unclear
Selective outcome reporting	[] High [] Low [] Unclear

Other risk for bias	