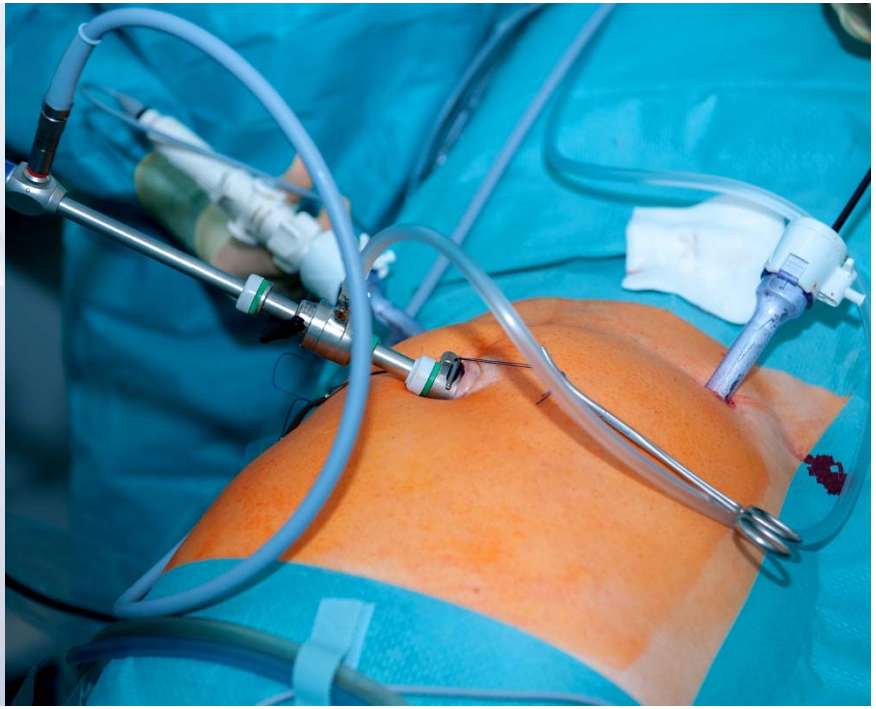
KCE REPORT 253

Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Centre

RENAL CANCER IN ADULTS: DIAGNOSIS, TREATMENT AND FOLLOW-UP



KCE REPORT 253
GOOD CLINICAL PRACTICE

Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Centre

RENAL CANCER IN ADULTS: DIAGNOSIS, TREATMENT AND FOLLOW-UP

NADIA BENAHMED, JO ROBAYS, SABINE STORDEUR, THIERRY GIL, STEVEN JONIAU, NICOLAAS LUMEN, LAURETTE RENARD, SANDRINE RORIVE, DIRK SCHRIJVERS, BERTRAND TOMBAL, BART VAN DEN EYNDEN, GEERT VILLEIRS, SYLVIE ROTTEY

2015 www.kce.fgov.be

COLOPHON

Title:	Renal cancer in adults: diagnosis, treatment and follow-up
Authors:	Nadia Benahmed (KCE), Jo Robays (KCE), Sabine Stordeur (KCE), Thierry Gil (Institut Jules Bordet), Steven Joniau (UZ Leuven), Nicolaas Lumen (UZ Gent), Laurette Renard (Cliniques Universitaires Saint-Luc), Sandrine Rorive (Hôpital Erasme ULB), Dirk Schrijvers (ZNA Middelheim), Bertrand Tombal (Cliniques Universitaires Saint-Luc), Bart Van Den Eynden (Domus Medica), Geert Villeirs (UZ Gent), Sylvie Rottey (UZ Gent)
Project coordinator and Senior supervisor:	Sabine Stordeur (KCE)
Reviewers:	Raf Mertens (KCE), Joan Vlayen (KCE), Hans Van Brabant (KCE)
Stakeholders:	An Claes (Kom op tegen Kanker vzw), Axel Feyaerts (Société Belge d'Urologie), Ward Rommel (Kom op Tegen Kanker vzw), Thierry Roumeguere (Société Belge d'Urologie), Didier Vander Steichel (Fondation Contre le Cancer), Elisabeth Van Eycken (Stichting Kankerregister)
External validators:	Axel Bex (Netherlands Cancer Institute), Sebastien Hotte (Juravinski Cancer Center, Hamilton), Rob Scholten (Universitair Medisch Centrum)
Acknowledgements:	Nicolas Fairon (KCE): information specialist
Other reported interests:	Membership of a stakeholder group on which the results of this report could have an impact: Ward Rommel (Kom op tegen Kanker), Elisabeth Van Eycken (BVRO-VBS), Axel Feyaerts (Société Belge d'Urologie) Consultancy or employment for a company, an association or an organisation that may gain or lose financially due to the results of this report: Axel Bex (Advisory Board Pfizer), Bertrand Tombal (Amgen, Astellas Pharma, Bayer, Sanofi, Ferring Pharmaceuticals) Payments to speak, training remuneration, subsidised travel or payment for participation at a conference: Axel Bex (Pfizer symposium October 2014), Nicolaas Lumen (consultance for Ipsen, Janssen, Lilly and Bayer), Bertrand Tombal (Amgen, Astellas Pharma, Bayer, Sanofi, Ferring Pharmaceuticals), Sylvie Rottey (GSK, Pfizer, Bayer, Novartis), Dirk Schrijvers (post ESMO) Presidency or accountable function within an institution, association, department or other entity on which the results of this report could have an impact: Elisabeth Van Eycken (Kankerregister), Nicolaas Lumen (Board member BAU working group oncology), Geert Villeirs (president Belgische Vereniging voor Radiologie) Participation in scientific or experimental research as an initiator, principal investigator or researcher: Axel Bex (EORTC 30073 Surtime study, partially sponsored by Pfizer), Sebastien Hotte (grant-in-aid for Novartis in a trial using dovitinib for head and neck cancer), Bertrand Tombal (Amgen, Astellas Pharma, Bayer, Sanofi, Ferring Pharmaceuticals), Dirk Schrijvers (studies about renal cell carcinoma)
Layout:	Ine Verhulst, Joyce Grijseels

Disclaimer:	• **The external experts were consulted about a (preliminary) version of the scientific report. Their comments were discussed during meetings. They did not co-author the scientific report and did not necessarily agree with its content.** • **Subsequently, a (final) version was submitted to the validators. The validation of the report results from a consensus or a voting process between the validators. The validators did not co-author the scientific report and did not necessarily all three agree with its content.** • **Finally, this report has been approved by the Executive Board.** • **Only the KCE is responsible for errors or omissions that could persist. The policy recommendations are also under the full responsibility of the KCE.**

Publication date:	5 October 2015
Domain:	Good Clinical Practice (GCP)
MeSH:	Kidney Neoplasms, Practice guidelines
NLM Classification:	WJ 358
Language:	English
Format:	Adobe® PDF™ (A4)
Legal depot:	D/2015/10.273/86

Copyright: KCE reports are published under a “by/nc/nd” Creative Commons Licence http://kce.fgov.be/content/about-copyrights-for-kce-reports.

How to refer to this document?

Benahmed N, Robays J, Stordeur S, Gil T, Joniau S, Lumen N, Renard L, Rorive S, Schrijvers D, Tombal B, Van den Eynden B, Villeirs G, Rottey S. Renal cancer in adults: diagnosis, treatment and follow-up. Good Clinical Practice (GCP) Brussels: Belgian Health Care Knowledge Centre (KCE). 2015. KCE Reports 253. D/2015/10.273/86.

This document is available on the website of the Belgian Health Care Knowledge Centre.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
5FU	5 Fluorouracil
ACI	Adoptive Cellular Immunotherapy
AEs	Adverse events
ASA	American Society of Anaesthesiologist
CBR	Clinical Benefit Rate
CCOG	Cancer Care Ontario Guideline
CPG	Clinical Practice Guideline
CRA	Cis Retinoic Acid
CSS	Cancer specific survival
CT	Computerized tomography
CTSQ	Cancer Therapy Satisfaction Questionnaire
ECOG	Eastern Cooperation Oncology Group
eGFR	Estimated glomerular filtration rate
EGFR	Epidermal Growth Factor Receptor
EORTC	European Organisation for Research and Treatment of Cancer
FACIT-F	Functional Assessment of Chronic Illness Therapy - Fatigue
FACT	Functional Assessment of Cancer Therapy
FKSI-19	Functional Assessment of Cancer Therapy - Kidney Symptom Index
FKSI-DRS	Functional Assessment of Cancer Therapy - Kidney Symptom Index Disease Related Symptoms
HR	Hazard Ratio
HRQoL	Health related Quality of Life
IL-2	Interleukine-2
IQR	Interquartile range
ITT	Intention To Treat
LAK	Lymphokine activated killer
LPN	Laparoscopic partial nephrectomy
MPA	Medroxyprogesterone Acetate
MRI	Magnetic Resonance Imaging

MSKCC	Memorial Sloan – Kettering Cancer Center
mRCC	Metastatic renal cell carcinoma
NSS	Nephron-sparing surgery
OPN	Open partial nephrectomy
ORR	Overall Response Rate
OS	Overall survival
PFS	Progression Free Survival
PS	Performance status
QAS	Quality adjusted survival
QoL	Quality of life
Q-Twist	Quality adjusted Time Without Symptoms or Toxicity
RBP	Retinol-binding protein
RCC	Renal Cell Carcinoma
RECIST	Response Evaluation Criteria in solid Tumours
RFS	Recurrence free survival
RLPN	Retroperitoneal laparoscopic partial nephrectomy
RN	Radical nephrectomy
RPN	Robot-assisted laparoscopic partial nephrectomy
SD	Standard deviation
SMD	Standardized mean difference
SQLQ	Supplementary Quality of Life Questionnaire
SR	Systematic review
SWOG	Southwest Oncology Ontario Guideline
TLPN	Transperitoneal laparoscopic partial nephrectomy
vs	versus
WHO	World Health Organization
WMD	Weighted mean difference
WIT	Warm ischaemia time

SCIENTIFIC REPORT

1 INTRODUCTION

The development of clinical care pathways is one of the main actions described in the Belgian National Cancer Plan 2008-2010 and one of the assignments of the College of Oncology. For many years the Belgian Health Care Knowledge Centre (KCE) has collaborated with the College of Oncology. More precisely, it has provided scientific support in the development of clinical practice guidelines. So far, this collaboration has resulted in the publication of clinical practice guidelines on breast cancer, colorectal cancer, testicular cancer, pancreatic cancer, upper gastrointestinal cancer, cervical cancer, prostate cancer, bladder cancer and lung cancer.

1.1 Background

'Renal cell carcinoma (RCC) represents 2-3% of all cancers, with the highest incidence occurring in Western countries. During the past two decades, there has been an annual increase of about 2% in incidence in Europe, although in Denmark and Sweden a continuing decrease has been observed.'[1]

In 2012, 1 060 cases of renal cancer were registered at the Belgian Cancer Registry corresponding to a crude incidence rate of 19.6 per 100 000 men per year and an age-standardized incidence rate of 15.8 per 100 000 men per year (European standard population). In the female population, 600 cases were registered corresponding to a crude incidence rate of 10.7 per 100 000 women per year and an age standardized incidence rate of 7.5 per 100 000 per year (European standard population). Incidence increases with age, with a peak incidence of 80.3 per 100 000 per year for men between 75 and 80 and 45.2 per 100 000 women per year for women between 80 and 85 (See also http://www.kankerregister.org).

'Renal cell carcinoma is the commonest solid lesion of the kidney and accounts for approximately 90% of all kidney malignancies. It comprises different types with specific histopathological and genetic characteristics. Risk factors include lifestyle such as smoking, obesity, and hypertension.

Having a first-degree relative with kidney cancer is also associated with an increased risk of RCC. Due to the increased detection of tumours by imaging techniques such as ultrasound (US) and computed tomography (CT), the

number of incidentally diagnosed RCCs has increased. These tumours are more often smaller and of lower stage.' [1]

1.2 Scope

During an initial scoping meeting on April 1st 2014 an overview was provided of the available recent high-quality guidelines. During this meeting, the scope of the guideline was delineated to cover the diagnosis, staging, treatment and follow-up of patients with confirmed renal cancer. It does not deal with cost-effectiveness. Screening for and prevention of renal cancer are out of scope.

1.3 Remit of the guideline

1.3.1 Overall objectives

This guideline provides recommendations based on current scientific evidence for the diagnosis, treatment, follow-up and supportive care of patients with renal cancer. Clinicians are encouraged to interpret these recommendations in the context of the individual patient situation, values and preferences. The objective of the present clinical guideline is to reduce the variability in clinical practice and to improve the communication between care providers and patients.

The guidelines are based on clinical evidence and may not always be in line with the current criteria for NIHDI (RIZIV/INAMI) reimbursement of diagnostic and therapeutic interventions. However, we put a warning in the recommendations if a recommended treatment is not currently reimbursed. The NIHDI may consider adaptation of reimbursement/funding criteria based on these guidelines.

1.3.2 Target users of the guideline

This guideline is intended to be used by all care providers involved in the management of patients with renal cancer, including oncologists, surgeons, urologists, radiologists, nuclear medicine specialists, pathologists and nurses). It can also be of interest for patients and their families and for general practitioners. It is however not primarily intended for them.

1.4 Statement of intent

Clinical Guidelines are designed to improve the quality of health care and decrease the use of unnecessary or harmful interventions. This guideline has been developed by clinicians and researchers for use within the Belgian healthcare context. It provides advice regarding the care and management of patients with renal cancer.

The recommendations are not intended to indicate an exclusive course of action or to serve as a standard of care. Standards of care are determined on the basis of all the available clinical data for an individual case and are subject to change as scientific knowledge and technology advance and patterns of care evolve. Variations, which take into account individual circumstances, clinical judgement and patient choice, may also be appropriate. The information delivered in this guideline is not a substitute for proper diagnosis, treatment or the provision of advice by an appropriate health professional. It is advised, however, that significant deviations from the national guideline are fully documented in the patient's file at the time the relevant decision is taken.

1.5 Funding and declaration of interest

KCE is a federal institution funded for the largest part by INAMI/RIZIV, but also by the Federal Public Service of Health, Food chain Safety and Environment, and the Federal Public Service of Social Security. The development of clinical practice guidelines is part of the legal mission of the KCE. Although the development of guidelines is paid by KCE's budget, the sole mission of the KCE is providing scientifically valid information. KCE has no interest in companies (commercial or non-commercial i.e. hospitals and universities), associations (e.g. professional associations, unions), individuals or organisations (e.g. lobby groups) that could be positively or negatively affected (financially or in any other way) by the implementation of these guidelines. All clinicians involved in the Guideline Development Group (GDG) or the peer-review process completed a declaration of interest form. Information on potential conflicts of interest is published in the colophon of this report. All members of the KCE Expert Team make yearly declarations of interest and further details of these are available upon request.

2 METHODOLOGY

2.1 Introduction

This guideline was developed using a standard methodology based on a systematic review of the evidence. Further details about KCE and the guideline development methodology are available at https://kce.fgov.be/content/kce-processes.

Several steps were followed to elaborate this guideline. Firstly, clinical questions were developed in collaboration with members of the Guideline Development Group. Secondly a literature review was conducted (including a search for recent, high quality guidelines). Thirdly, on the basis of the results of the literature review, recommendations were formulated and graded according to the GRADE approach.

2.2 The Guideline Development Group

This guideline was developed as a result of a collaboration between multidisciplinary groups of practising clinicians and KCE experts. The composition of the GDG is documented in Appendix 1. Guideline development and literature review expertise, support, and facilitation were provided by the KCE Expert Team.

The roles assigned to the GDG were:

- To define the clinical questions, in close collaboration with the KCE Expert Team and stakeholders;
- To identify critical and important outcomes;
- To provide feedback on the selection of studies and identify further relevant manuscripts which may have been missed;
- To provide feedback on the content of the guideline;
- To provide judgement about indirectness of evidence;
- To provide feedback on the draft recommendations;
- To address additional concerns to be reported under a section on 'other considerations'.

2.3 Clinical research questions

The selection of research questions was made by the members of the GDG, representatives of professional organizations and patient representatives during an initial stakeholder meeting held at KCE on 01/04/2014. The CPG (Clinical Practice Guideline) addresses the following clinical topics:

2.3.1 Diagnosis and staging

What is the specific role of CT scanning/MRI/US/PET/Bone scan, thorax X-Ray

- in detecting primary tumour?
- in confirming diagnosis?
- for cancer staging (vascular invasion...)?

What is the role of core needle biopsy/fine needle aspiration in confirming the primary tumour / metastatic disease?

Prognosis and prediction of treatment effectiveness:

- Role of biomarkers;
- Role of nomograms and predictive systems.

2.3.2 Treatment of localised disease

Neo-adjuvant treatment

Surgery

- Radical nephrectomy
- Partial nephrectomy

Ablative techniques

- Radiofrequency ablation
- Cryoablation

Additional interventions

- Adrenalectomy
- Lymphadenectomy
- Thrombectomy
- Embolisation

Adjuvant treatment

Active medical surveillance

2.3.3 Treatment of metastatic disease

Role of nephrectomy in metastatic disease

Systemic therapy in first, second and third lines:

- Role of Interleukines;
- Role of targeted therapy;
- Sequencing.

2.3.4 Palliative care

Role of surgery and palliative intervention in incurable disease.

2.3.5 Follow-up

What follow-up is indicated and which techniques need to be used?

Clinical questions were translated into in- and exclusion criteria using the PICO (Participants–Interventions–Comparator–Outcomes) framework (see Appendix 2.2).

2.4 General approach

We first looked for high quality guidelines based on a valid and sufficiently documented systematic search and reporting of the underlying evidence; in some cases, comprehensive guidelines are only based on a systematic review for a part of the clinical questions, as resources often are not sufficient to cover all clinical recommendations. In this case, we only took over recommendations based on a systematic search of the evidence. We mentioned this per clinical question. Recommendations from foreign guidelines were submitted to the GDG to validate their applicability in the Belgian context. If no high-quality, recent guidelines relevant to the research question are available, the general approach began with the search for systematic reviews. In addition to a search in OVID Medline, the National Guideline Clearinghouse and the GIN database were searched to identify relevant guidelines.

For each research question, a search for systematic reviews was conducted in MEDLINE, Embase and the Cochrane Library (Cochrane Database of Systematic Reviews, DARE and HTA database). If a recent high quality systematic review was available, a search for primary studies published after the search date of the review was performed in MEDLINE, Embase and CENTRAL. If more than one systematic review was identified for a particular research question, the focus was on the most complete systematic review. If no systematic review was available, a search for primary studies was performed in those databases. Members of the guideline development group (GDG) were also consulted to identify additional relevant evidence that may have been missed by the search.

For the diagnostic questions, systematic reviews, diagnostic accuracy studies and RCTs were searched; for the other research questions, systematic reviews, RCTs or comparative observational studies (in the absence of RCTs) were searched. Only articles published in Dutch, English and French were included.

To be included a primary study had to:

- be an RCT, an observational study or a diagnostic accuracy study;
- address at least one of the research questions;
- evaluate at least one of the selected (critical and important) outcomes.

If no full-text was available, the study was not taken into account for the final recommendations.

Detailed search strategies per database can be found in Appendix 2.

2.5 Quality appraisal

Critical appraisal of each study was performed by a single KCE expert. In case of doubt, a second KCE expert was consulted.

The AGREE II instrument was used to evaluate the methodological quality of the identified international guidelines (www.agreetrust.org). Based on an overall assessment, 3 high quality guidelines were selected with a general scope. We selected one supplementary guideline that was based on a well documented systematic review of the literature that focused only on follow-up and that we used to formulate recommendations on that chapter.

Selected (systematic) reviews were critically appraised using the AMSTAR checklist[2] (http://amstar.ca/Amstar_Checklist.php).

Retrieved diagnostic studies were assessed for the risk of bias by means of the QUADAS-2 tool.[3]

The quality appraisal of RCTs for therapeutic interventions was performed using the "Cochrane Collaboration's tool for assessing risk of bias".[4] For each criterion the definitions described in the Cochrane Handbook were used. If applicable, risk of bias for the items regarding detection bias and attrition bias were assessed per class of outcomes (e.g. subjective and objective outcomes). At the end, each study was labelled as low risk of bias, unclear risk of bias or high risk of bias according to the criteria described in the Cochrane Handbook.

Study limitations of observational studies were evaluated using a tool developed by KCE, for cohort studies and case control studies (see KCE process book; http://processbook.kce.fgov.be/node/156).

The tools used for the quality appraisal of guidelines, systematic reviews and primary studies and the results of these quality appraisals are sequentially presented in Appendix 3 ([1] diagnostic and follow-up, [2] treatments and [3] evaluation of long term outcomes of partial nephrectomy in comparison with radical nephrectomy).

2.6 Data extraction

For each included CPG the following data were extracted: consulted databases and search terms, search date, publication year, in- and exclusion criteria, quality appraisal, availability of evidence tables, consistency between the evidence and its interpretation, and consistency between the interpretation of the evidence and the recommendations.

For each systematic review, the search date, publication year, included studies and main results were extracted. For RCTs and longitudinal studies, the following data were extracted: publication year, study population, study intervention, and outcomes.

Data extraction was performed by a single KCE expert. In case of doubt, a second KCE expert was consulted.

All evidence tables are reported in Appendix 4.

2.7 Meta-analysis

For each comparison (intervention vs. comparator) separate analyses were done. If a recent systematic review with low risk of bias was available, the results of the review were used and presented in Summary of Findings Tables (Appendix 5). If new RCTs were identified, the existing systematic review and meta-analysis were updated. This was only feasible if the required data in the review were readily available (i.e. the review reports the 2 by 2 Tables of the included studies). If this was not feasible, the results of the newly identified RCTs were summarized and presented in Summary of Findings Tables. If the RCTs served for a new systematic review, meta-analyses were performed and the results were presented in Summary of Findings Tables.

For diagnostic test accuracy, meta-analyses were performed according to the statistical guidelines described in the Cochrane Handbook, (http://srdta.cochrane.org/handbook-dta-reviews) using Stata© software while for treatment, meta-analyses were performed according to the statistical guidelines described in the Cochrane Handbook (http://www.cochrane.org/training/cochrane-handbook) and by the use of Review Manager Software (Review Manager 2011). Heterogeneity was statistically assessed using χ^2 test and I^2 statistic. If heterogeneity was present, a random-effects model was used instead of a fixed-effect model. Possible reasons for heterogeneity were explored post-hoc. Sensitivity analysis was performed by removing outliers from the analysis. Studies that were clinically heterogeneous or did not present the data in sufficient detail to enable statistical pooling were summarized qualitatively. Forest plots are reported in Appendix 6.

2.8 Grading evidence[5-10]

For each recommendation, we provided its strength and the quality of the supporting evidence.[5] According to GRADE, we classified the quality of evidence into 4 categories: high, moderate, low, and very low (Table 1 and Table 2). The quality of evidence reflects the extent to which a guideline panel's confidence in an estimate of the effect was adequate to support a particular recommendation.

GRADE for guidelines was used, meaning that the evidence across all outcomes and across studies for a particular recommendation was assessed. The following quality elements for intervention studies were evaluated: study limitations, inconsistency, indirectness, imprecision and publication bias.

For RCTs, quality rating was initially considered to be of high level (Table 1). The rating was then downgraded if needed based on the judgement of the different quality elements. Each quality element considered to have serious or very serious risk of bias was rated down -1 or -2 points respectively. Judgement of the overall confidence in the effect estimate was also taken into account. We considered confidence in estimates as a continuum and the final rating of confidence could differ from that suggested by each separate domain.[7]

Observational studies were by default considered low level of evidence (Table 1 and Table 2). However, the level of evidence of observational studies with no threats to validity can be upgraded for a number of reasons:

1. Large magnitude of effects: the larger the magnitude of effect, the stronger becomes the evidence. As a rule of thumb, the following criteria were proposed by GRADE:
   a. Large, i.e. RR >2 or <0.5 (based on consistent evidence from at least 2 studies, with no plausible confounders): upgrade 1 level;
   b. Very large, i.e. RR >5 or <0.2 (based on direct evidence with no major threats to validity): upgrade 2 levels.
2. All plausible confounders: all plausible confounding from observational studies or randomized trials may be working to reduce the demonstrated effect or increase the effect if no effect was observed;
3. Dose-response gradient: The presence of a dose-response gradient may increase our confidence in the findings of observational studies and thereby increase the quality of evidence.

The general principles used to downgrade the quality rating are summarized in Table 3.

Due to current methodological limitations of the GRADE system for diagnostic tests, GRADE was not applied to the recommendations on diagnosis.

Table 1 – A summary of the GRADE approach to grading the quality of evidence for each outcome

Source of body of evidence	Initial rating of quality of a body of evidence	Factors that may decrease the quality	Factors that may increase the quality	Final quality of a body of evidence
Randomized trials	High	1. Risk of bias 2. Inconsistency 3. Indirectness 4. Imprecision 5. Publication bias	1. Large effect 2. Dose-response 3. All plausible residual confounding would reduce the demonstrated effect or would suggest a spurious effect if no effect was observed	High (⊕⊕⊕⊕) Moderate (⊕⊕⊕⊖) Low (⊕⊕⊖⊖) Very low (⊕⊖⊖⊖)
Observational studies	Low			

Source: Guyatt GH, Oxman AD, Sultan S, Glasziou P, Akl EA, Alonso-Coello P, et al. GRADE guidelines: 9. Rating up the quality of evidence. J Clin Epidemiol. 2011;64(12):1311-6.

Table 2 – Levels of evidence according to the GRADE system

Quality level	Definition	Methodological Quality of Supporting Evidence
High	We are very confident that the true effect lies close to that of the estimate of the effect.	RCTs without important limitations or overwhelming evidence from observational studies.
Moderate	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies.
Low	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.	RCTs with very important limitations or observational studies or case series.
Very low	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect.	

Source: Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J, et al. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol. 2011;64(4):401-6.

Table 3 – Downgrading the quality rating of evidence using GRADE

Quality element	Reasons for downgrading
Limitations	For each study reporting the selected outcome, possible risk of bias introduced by lack of allocation concealment, lack of blinding, lack of intention-to-treat analysis, loss of follow-up and selective outcome reporting were assessed. Additionally, other limitations such as stopping early for benefit and use of non validated outcome measures were taken into consideration. Level of evidence was downgraded if studies were of sufficiently poor quality. Downgrading was omitted if studies with low risk of bias were available that lead to similar conclusions as the studies with a high risk of bias.
Inconsistency	Downgrading the level of evidence for inconsistency of results was considered in the following situations: point estimates vary widely across studies, confidence intervals show minimal or no overlap, the statistical test for heterogeneity shows a low p-value or the I^2 is large. If large variability in magnitude of effect remained unexplained, the quality of evidence was rated down.
Indirectness	Quality rating was downgraded for indirectness in case the trial population or the applied intervention differed significantly from the population or intervention of interest. Also, the use of surrogate outcomes could lead to downgrading. A third reason for downgrading for indirectness occurred when the studied interventions were not tested in a head-to-head comparison.
Imprecision	Evaluation of the imprecision of results was primarily based on examination of the 95%CI. Quality was rated down if clinical action would differ if the upper versus the lower boundary of the 95%CI represented the truth. In general, 95%CIs around relative effects were used for evaluation, except when the event rate was low in spite of a large sample size. To examine the 95%CIs, the clinical decision threshold (CDT) was defined. When the 95%CI crossed this clinical decision threshold, the quality level was rated down. A relative risk reduction (RRR) of 25% was defined as CDT by default and adapted if deemed appropriate e.g. in case of a low risk intervention. Even if 95%CIs appeared robust, level of evidence could be rated down because of fragility. To judge fragility of results, it is suggested to calculate the number of patients needed for an adequately powered (imaginary) single trial, also called the optimal information size (OIS). If the total number of patients included in a systematic review was less than the calculated OIS, rating down for imprecision was considered. For calculations, a RRR of 25% was used, unless otherwise stated. When the OIS could not be calculated, a minimum of 300 events for binary outcomes and a minimum of 400 participants for continuous outcomes were used as a rule of thumb.
Reporting bias	Quality rating was downgraded for reporting bias if publication bias was suggested by analysis using funnel plots or searching of trial registries. Publication bias was also suspected if results came from small, positive industry-sponsored trials only.

2.9 Formulation of recommendations

Based on the retrieved evidence, the first draft of recommendations was prepared by a small working group (KCE experts and Guideline Development Group members). This first draft was, together with the evidence tables, circulated to the guideline development group 2 weeks prior to the face-to-face meetings (October 10, 2014; March 27, 2015; April 28, 2015). Recommendations were changed if important new evidence supported this change. Based on the discussion meetings a second draft of recommendations was prepared and once more circulated to the guideline development group for final approval.

The strength of each recommendation was assigned using the GRADE system (Table 4). The strength of recommendations depends on a balance between all desirable and all undesirable effects of an intervention (i.e., net clinical benefit), quality of available evidence, values and preferences, and estimated cost (resource utilization). For this guideline, no formal cost-effectiveness study was conducted. Factors that influence the strength of a recommendation are reported in Table 5.

Table 4 – Strength of recommendations according to the GRADE system

Grade	Definition
Strong	The desirable effects of an intervention clearly outweigh the undesirable effects *(the intervention is to be put into practice)*, or the undesirable effects of an intervention clearly outweigh the desirable effects *(the intervention is not to be put into practice)*.
Weak	The desirable effects of an intervention probably outweigh the undesirable effects *(the intervention probably is to be put into practice)*, or the undesirable effects of an intervention probably outweigh the desirable effects *(the intervention probably is not to be put into practice)*.

Source: Andrews JC, Schunemann HJ, Oxman AD, Pottie K, Meerpohl JJ, Coello PA, et al. GRADE guidelines: 15. Going from evidence to recommendation-determinants of a recommendation's direction and strength. J Clin Epidemiol. 2013;66(7):726-35.

Table 5 – Factors that influence the strength of a recommendation

Factor	Comment
Balance between desirable and undesirable effects	The larger the difference between the desirable and undesirable effects, the higher the likelihood that a strong recommendation is warranted. The narrower the gradient, the higher the likelihood that a weak recommendation is warranted.
Quality of evidence	The higher the quality of evidence, the higher the likelihood that a strong recommendation is warranted.
Values and preferences	The more values and preferences vary, or the greater the uncertainty in values and preferences, the higher the likelihood that a weak recommendation is warranted.
Costs (resource allocation)	The higher the costs of an intervention, i.e. the greater the resources consumed, the lower the likelihood that a strong recommendation is warranted.

Sources: Schünemann HJ, Jaeschke R, Cook DJ, Bria WF, El-Solh AA, Ernst A et al. An Official ATS Statement: Grading the Quality of Evidence and Strength of Recommendations in ATS Guidelines and Recommendations. Am J Respir Crit Care Med 2006; 174:605–14. – Guyatt G, Gutterman D, Baumann MH, Addrizzo-Harris D, Hylek EM, Phillips B et al. Grading Strength of Recommendations and Quality of Evidence in Clinical Guidelines - Report From an American College of Chest Physicians Task Force. Chest 2006; 129:174-81.

For each set of recommendations the GDG commented on these elements, in order to make more transparent how the recommendation was developed and which considerations were taken into account.

A strong recommendation implies that most patients would want the recommended course of action. A weak recommendation implies that the majority of informed patients would want the intervention, but many would not.[9] Specifically, a strong negative recommendation means the harms of the recommended approach clearly exceed the benefits whereas a weak negative recommendation implies that the majority of patients would not want the intervention, but many would. In the case of a weak recommendation, clinicians are especially required to spend adequate time with patients to discuss patients' values and preferences. Such an in-depth discussion is necessary for the patient to make an informed decision. This

may lead a significant proportion of patients to choose an alternative approach. Fully informed patients are in the best position to make decisions that are consistent with the best evidence and patients' values and preferences.

For policy-makers, a strong recommendation implies that variability in clinical practice between individuals or regions would likely be inappropriate whereas a weak recommendation implies that variability between individuals or regions may be appropriate, and use as a quality of care criterion is inappropriate.[9]

We offer the suggested interpretation of "strong" and "weak" recommendations in Table 6.

Table 6 – Interpretation of strong and conditional (weak)* recommendations

Implications	Strong recommendation	Weak recommendation
For patients	Most individuals in this situation would want the recommended course of action, and only a small proportion would not. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	The majority of individuals in this situation would want the suggested course of action, but many would not.
For clinicians	Most individuals should receive the intervention. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.	Recognize that different choices will be appropriate for individual patients and that you must help each patient arrive at a management decision consistent with his or her values and preferences. Decision aids may be useful helping individuals making decisions consistent with their values and preferences.
For policy makers	The recommendation can be adopted as policy in most situations.	Policy-making will require substantial debate and involvement of various stakeholders.

** the terms "conditional" and "weak" can be used synonymously*
Source: Andrews JC, Schunemann HJ, Oxman AD, Pottie K, Meerpohl JJ, Coello PA, et al. GRADE guidelines: 15. Going from evidence to recommendation-determinants of a recommendation's direction and strength. J Clin Epidemiol. 2013;66(7):726-35.

2.10 External review

2.10.1 Healthcare professionals

The recommendations prepared by the GDG were circulated to professional associations (Table 7). Each association was asked to assign one or two key representatives to act as external reviewers of the draft guideline. All expert referees made declarations of interest.

Globally, 15 experts of the GDG were involved in the evaluation of the clinical recommendations. All invited panellists received the scientific reports for all research questions and were asked to indicate if they agreed or did not agree with the recommendation (the panellists were also able to answer 'not applicable' if they were not familiar with the underlying evidence). If panellists disagreed with the recommendation, they were asked to provide an explanation supported by appropriate evidence. Scientific arguments reported by these experts were used to adapt the formulation or the strength of the clinical recommendations. In Appendix 8.1, an overview is provided of how their comments were taken into account.

Stakeholders meeting was held on 24th of June 2015. Discussions regarding the recommendations are reported in Appendix 8.2.

Table 7 – List of Professional Associations invited

- Belgian Society of Medical Oncology - Belgische Vereniging voor Medische Oncologie - Société Belge d'Oncologie Médicale (BSMO);
- Belgische Vereniging voor Radiotherapie-Oncologie - Association Belge de Radiothérapie-OncoloSgie (BVRO - ABRO);
- Belgian Society of Surgical Oncology (BSSO);
- Royal Belgian Society of Surgery - Koninklijk Belgisch Genootschap voor Heelkunde (KBGH) - Société Royale Belge de Chirurgie (SRBC);
- Belgian Society of Radiology (BSR);
- Belgische Genootschap voor Nucleaire Geneeskunde - Société Belge de Médecine Nucléaire;
- Belgian Society of Pathology - Belgische Vereniging Anatomopathologie - Société Belge d'Anatomopathologie;
- Domus Medica;
- Société Scientifique de Médecine Générale (SSMG);
- Belgische Vereniging voor Urologie (BVU) - Belgian Association of Urology (BAU) - Société Belge d'Urologie (SBU).

2.10.2 Patient representatives

Associations of patient representatives (Fondation contre le Cancer and Kom op tegen Kanker) were contacted to invite patient representatives to take part in both stakeholder meetings (April 1, 2014 and June 24, 2015), from the start of the project. A key role for patient representatives is to ensure that patient views and experiences inform the group's work.

2.11 Final validation

As part of the standard KCE procedures, an external scientific validation of the report was conducted prior to its publication. Such validation process was done on June 12, 2015. The current guideline was reviewed prior to its publication by 3 independent validators (cf. names in the colophon).

3 CLINICAL RECOMMENDATIONS

3.1 Diagnosis and staging

We identified 3 guidelines that dealt with diagnosis and staging of renal cancer.

IKNL[11] gave evidence-based recommendations on all topics whereas the EAU guideline[1] only did a comprehensive search for renal biopsies. The AUA[12] guideline on follow-up of localised renal cancer is based on a comprehensive literature search that, contrary to its title, also covered diagnostic work-up at baseline. We will report the recommendations included in these guidelines in parallel with the underlying evidence.

3.1.1 Patient information

Based on 7 non-comparative studies, IKNL recommends to separate communication of the diagnosis and the thorough discussion of treatment options.
In addition, IKNL advocates that the opportunity to participate in the decision-making process is offered to each patient in a timely manner. This advice is based on 4 non-comparative studies showing, in one hand, that three-quarters of patients want to participate in treatment decisions, and in other hand, that participating in the decision-making process has positive effects on patient satisfaction and disease acceptance.

3.1.2 Role of CT, MRI and ultrasound in the diagnostic work-up

On one hand, the EAU guideline recommends either MRI (Magnetic Resonance Imaging) or CT (Computerized tomography) scan for diagnostic work-up. However, this recommendation was not based on a systematic search of the literature but was consensus-based. On the other hand, IKNL recommends to perform a CT scan, despite the fact that the underlying evidence shows a similar performance between MRI and CT. Reasons for which CT scan is preferred and MRI is finally not recommended are not reported.

The AUA guideline recommends the use of either MRI or CT, based on the fact that there is no proven difference in sensitivity between both diagnostic procedures. Nevertheless, evidence on the side effects of both methods are summarised in the guideline:

- There is some indirect evidence linking exposure to low-level ionizing radiation at doses used in CT to subsequent development of cancer. This includes a study of populations who had received low doses of radiation, including populations who received exposures from diagnostic radiation. Doses received by individuals in whom an increased risk of cancer was documented were similar to doses associated with commonly used CT studies.
- For MRI, which does not involve the use of ionizing radiation, the primary adverse effect to consider is the development of nephrogenic systemic fibrosis due to IV gadolinium administration. Authors report on a study that investigated risk factors for the development of nephrogenic systemic fibrosis in 168 dialysis patients who underwent 559 MR imaging examinations from January 2000 to August 2006. In this study, 12 patients developed nephrogenic systemic fibrosis, all of whom had undergone gadolinium contrast-enhanced MR imaging using a double dose of IV contrast. Four of the 12 patients developed acute renal failure related to hepatorenal syndrome; all four patients underwent liver transplantation within 17 days of MR imaging. It is not clear if these findings are applicable to the diagnosis and staging of renal cancer though.

Both IKNL and AUA report that ultrasound is less sensitive than MRI or CT. The AUA report states that the sensitivity of CT and ultrasonography for detection of lesions 3 cm and less is 94% and 79%, respectively.

We did not perform a primary update of these guidelines, as it is unlikely that more recent studies will alter the conclusions.

Renal biopsies

Three guidelines were retained to discuss renal biopsies, respectively guidelines from EAU, IKNL and AUA.

In preparation of the EAU guideline, an extensive literature search on renal biopsies was performed and published separately; the recommendations are based on this search.

In the EAU guideline,

- Renal tumour biopsy is recommended before ablative therapy and systemic therapy without previous pathology.
- Percutaneous biopsy is recommended in patients in whom active surveillance is pursued.
- Percutaneous renal tumour biopsy should be obtained with a coaxial technique.

These 3 recommendations are based on reports of case series that showed that renal tumour biopsies had an acceptable diagnostic yield and acceptable side effects and complication rates, but the guideline did not publish more details.

The AUA recommended that:

- All patients undergoing ablation procedures for a renal mass undergo a pretreatment diagnostic biopsy.

Authors provide an estimation of the overall accuracy of renal biopsy, which varied slightly according to biopsy technique, specifically core biopsy technique versus fine needle aspiration. The variance was primarily attributed to the difference in non-diagnostic biopsy rate. Importantly, when non-diagnostic biopsies are discarded from the analyses, sensitivity for core versus fine needle aspiration is 99.5% versus 96.5% and specificity is 99.9% versus 98.9%, respectively. When both diagnostic and non-diagnostic samples are considered, core biopsies are more sensitive but less specific than fine needle aspiration, but the difference is not statistically significant for either parameter. Studies suffer from verification bias however, as only a minority of the tested patients proceed to surgery, which should provide the gold standard. They report a complication rate that is low but variable, and an overall estimated risk of needle tract seeding of less than 0.01%.

IKNL formulates similar recommendations based on similar evidence. Authors recommend that:

- Histological needle biopsies should be taken if the indication to perform a nephrectomy is doubtful because the nature of a tumorous process in the kidney is uncertain (for example, in the case of small tumours and/or non-conclusive imaging).

Histological needle biopsies should also be performed in patients with a metastatic or unresectable renal cell carcinoma in order to determine the histological subtype and therefore underpin the choice of systemic therapy. Two to four histological needle biopsies should be taken with a biopsy needle guided by an introducer cannula. The needle biopsy can be

performed under CT guidance as well as ultrasound guidance, depending on local expertise.

We did not do a primary update of the guidelines as we judged it unlikely that studies that are more recent will alter these conclusions.

3.1.3 Bone scintigraphy

Neither EUA, AUA nor IKNL recommends the use of bone scintigraphy for routine use.

- AUA recommended bone scans in patients with an elevated alkaline phosphatase, clinical symptoms such as bone pain, and/or if radiographic findings are suggestive of a bony neoplasm. They base this recommendation on the fact that these factors raise the probability of metastatic spread to a level >5%-10%, leading to an acceptable with a pre-test probability of 5%, a negative post-test probability below 1%, whereas a positive test would raise the post-test probability to 26%, likely necessitating further diagnostic evaluation.
- EAU did not recommend bone scintigraphy, but did not do a systematic review of the evidence.
- IKNL on the contrary advises against the use of bone scan based on the fact that sensitivity remains low and variable, around 60%.

We did not do a primary update of the guidelines as we judged it unlikely that more recent studies will alter the conclusions.

3.1.4 Chest CT or X ray for detection of lung metastases

EAU recommends to perform a chest CT, based on its higher accuracy, but leaves the possibility for an X-ray open. AUA does the opposite. Anyway, there is no evidence for either point of view. We put a recommendation as practice statement, based on consensus.

3.1.5 PET scan and PET/CT

Neither EUA, AUA nor IKNL recommends the use of PET scan at baseline and for follow-up. AUA and IKNL base this negative recommendation on a systematic search that did not yield studies allowing to assess sensitivity and specificity of the PET scan.

As in all these guidelines, it was stated that future research may change the conclusions, especially concerning the detection of extra-renal lesions, we did an update starting from the search date of the AUA guideline (2011).

We found one high quality meta-analysis evaluating the performance of PET scan and PET/CT by Wang et al.[13] Amstar evaluation of the quality of this publication is given in Appendix 3.

3.1.5.1 Results for PET scan

For renal lesions

- The pooled sensitivity was 0.62 (95%CI 0.49 - 0.74) with high heterogeneity; the chi-square value was 11.71 (p=0.0029), and the I- square value was 82.9%.
- The pooled specificity was 0.88 (95%CI 0.47-1.00), with a non- significant chi-square value of 1.02 (p=0.5992) and an I-square value of 0.0%.

For extrarenal lesions

- The pooled sensitivity and specificity were 0.79 (95%CI 0.71 - 0.86) and 0.90 (95%CI 0.82 - 0.95), respectively. Neither of the chi-square scores for the pooled sensitivity and specificity were statistically significant, at 9.00 (p=0.1734) and 7.64 (p=0.2657), respectively. The I-square scores for the pooled sensitivity and specificity were 33.4% and 21.5%, respectively.
- The 3 studies that evaluated the results on a lesion basis were high in heterogeneity. The pooled sensitivity was 0.84 (95%CI 0.75 - 0.91) with a significant chi-square value of 22.22 (p<0.001) and I-square value of 91%.

It is important to note however that heterogeneity as measured by chi- square values and I-square values is usually higher in test validation studies and that these measures are difficult to interpret.

3.1.5.2 Results for PET/CT

For renal lesions, none of the included articles published before 2011 evaluated primary renal lesions in RCC using FDG-PET/CT. By comparing postoperative pathology, one study reported a sensitivity of 46.6%, specificity of 66.6% and accuracy of 50% in 18 cases.
The review found 2 articles that focused on extra-renal lesions in RCC.[14, 15]

- The pooled sensitivity was 0.91 (95%CI 0.84 - 0.96), with a non-significant chi-square score of 0.41 (p=0.5237) and an I-square score of 0.0%.
- The pooled specificity was 0.88 (95%CI 0.77 - 0.94), with a non-significant chi-square score of 0.73 (p=0.3933) and an I-square score of 0.0%.

We updated the review, and found 3 supplementary studies on PET/CT. Results of the QUADAS evaluation about the quality of these diagnostic studies is given in appendix 3.

Bretagna et al.[16] did a retrospective study including 68 patients with renal carcinoma in whom F18-FDG-PET/CT was performed. Sensitivity and specificity, of F18-FDG PET/CT were 82% (69% to 91%), 100% (81% to 100%), respectively.

Fuccio et al.[17] reported on 69 patients (median age = 62 years; range = 36-86 years) affected by clear cell RCC who underwent whole-body F18-FDG PET/CT to restage the disease after nephrectomy for clinical or radiological suspicion of metastases. On a patient basis, 40 patients resulted true positive, 2 patients false positive, 23 patients true negative, and 4 patients false negative. Sensitivity and specificity were 90% (78% to 97%) and 92% (74% to 99%) respectively. On a lesion basis, PET/CT detected 114 areas of abnormal uptake in 42 positive patients of which 112 resulted to be true positive. FDG uptake of the true positive lesions resulted to be high in 83 cases, moderate in 17 lesions, and finally faint in 12 lesions.

Mishra et al.[18] evaluated the role of 18F-Fluorodeoxyglucose (18F-FDG) positron emission tomography-computed tomography (PET/CT) in patients with renal cell carcinoma (RCC) for detection of recurrence, either when suspected clinically on imaging and during routine follow-up. This was a retrospective study. A total of 125 PET/CT were done in 83 patients, suspected for recurrence (n=112) or for routine follow-up (n=13). Seventy nine 18F-FDG PET/CT were positive and 46 were negative for recurrent disease. Seventy three PET/CT were true positive, 43 were true negative, 6 were false positive and 3 were false negative. The sensitivity of 18F-FDG PET/CT was 96% (95%CI: 89% to 99%), specificity 88% (95%CI: 75% to 95%), PPV was 92% (95%CI: 84% to 97%), NPV was 93% (95%CI: 82% to 99%) and accuracy was 93%.

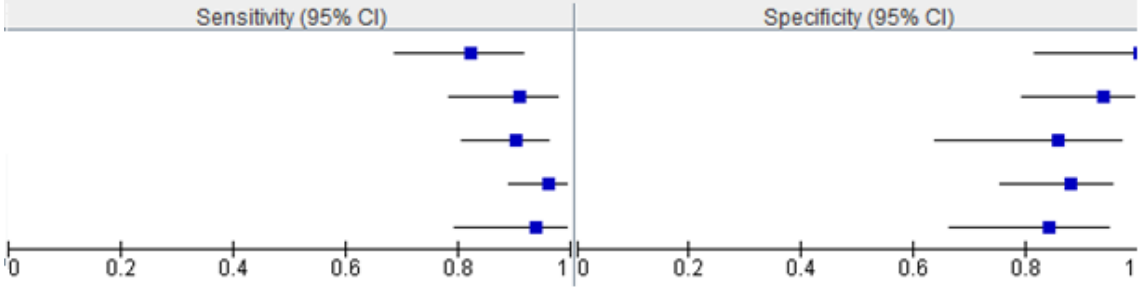
Quality of the studies was low, most of them being retrospective; the studies all mainly suffered from verification bias, especially for negative results, as various methods for verification were used and sensitivity may be overestimated.

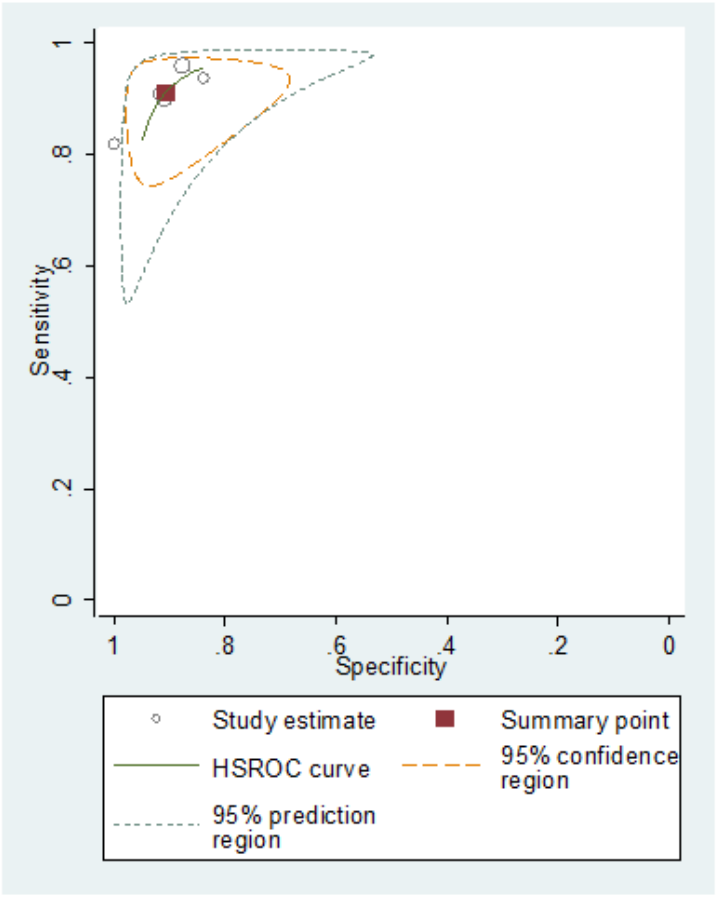
We did a meta-analysis including 5 studies, 2 studies from Wang et al.[14, 15] and the 3 studies found in the update and described above. We did only a per-patient analysis, we did not have all the data for a per-lesion analysis. Both the bivariate model (Reitsma et al.[19]) and the hierarchical summary receiver operating characteristic (HSROC) model (Rutter and Gatsonis 2001[20]) were used; these are different parameterizations of the same model, where a relationship is modelled between sensitivity and specificity. Model was fitted using the metandi command in Stata©.

We found a pooled sensitivity of 91% (95%CI: 85% to 95%) and a pooled specificity of 91% (95%CI: 83% to 95%). Data, forest plot and HSROC curve with confidence region and prediction region are reported in Figure 1.

Figure 1 – Primary data, forest plot and HSROC curve, meta-analysis sensitivity and specificity of PET/CT for detection of recurrences and metastases

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Bretagna et al. 2013	41	0	9	18	0.82 [0.69, 0.91]	1.00 [0.81, 1.00]
Fuccio et al. 2014	40	2	4	30	0.91 [0.78, 0.97]	0.94 [0.79, 0.99]
Kumar et al. 2010	63	3	7	18	0.90 [0.80, 0.96]	0.86 [0.64, 0.97]
Mishra et al. 2012	73	6	3	43	0.96 [0.89, 0.99]	0.88 [0.75, 0.95]
Park et al. 2009	30	5	2	26	0.94 [0.79, 0.99]	0.84 [0.66, 0.95]





Conclusions

- There is no proven difference in sensitivity between MRI and CT to detect renal cancer.
- Ultrasound is less sensitive than MRI or CT to detect renal cancer.
- Core biopsies are more sensitive but less specific than fine needle aspiration, although not statistically significantly different for either parameter. Complication rate is low but variable, and the overall estimated risk of needle tract seeding is less than 0.01%.
- Bone scintigraphy has a low sensitivity to detect bone metastases.
- Validation studies for the use of PET/CT for restaging or detection for recurrence and metastasis showed a pooled sensitivity of 91% (95%CI: 85% to 95%) and a pooled specificity of 91% (95%CI: 83% to 95%). However, the quality of the studies is low, suffering from verification bias, and clinical implications are unclear.

Other considerations

Factor	Comment
Balance between clinical benefits and harms	There is some indirect evidence linking exposure to low-level ionizing radiation at doses used in CT to subsequent development of cancer. For MRI, which does not involve the use of ionizing radiation, the primary adverse effect to consider is the development of nephrogenic systemic fibrosis (NSF) due to IV gadolinium administration. Ultrasound does not generate these problems but is less sensitive. Percutaneous renal biopsies have a low complication rate. This must be balanced against the need for pathological verification before ablation, active surveillance and systemic therapy if no surgery is underwent. The GDG preferred to avoid the recommendation that combines CT and MRI for RCC diagnosis, but to give the opportunity to clinicians to opt for MRI in case of contraindication to iodine contrast injection. The systematic combination of these two diagnostic techniques was considered as an inappropriate overuse. In the original version, we did not formulate a recommendation on the use of X ray or CT for the detection of lung metastases. The GDG preferred to have a risk-adapted recommendation on this issue, based on consensus, since there is no evidence to recommend either X ray or CT. The reasoning behind the recommendation is that for a T1 N0 M0 it is not necessary to search for metastases. Ultrasound has no added value, on condition that a CT or MRI is performed, but the recommendation was seen as confusing, because tumours can be a chance finding in an ultrasound done for other reasons. For bone scan the GDG preferred the position of the AUA, that is clearer: not recommended workup in the absence of skeletal symptoms or elevated alkaline phosphatase. The GDG preferred to add also a recommendation against routine use of brain imaging, as he considered that overuse is a problem in Belgium.
Quality of evidence	A review did not show a difference in diagnostic accuracy between MRI and CT. Evidence on side effects and risks for CT and MRI is indirect and observational. Evidence for renal biopsies comes from diagnostic accuracy studies; they suffer however from verification bias, mainly because test negatives do not undergo further work-up that helps identifying false positives. Evidence on side effects is based on case series. There are credible estimates for PET scan; however, very few data exist for PET/CT for renal lesions. Studies suffer from a similar verification bias as described for renal biopsies though and are of low quality. There is no direct evidence on the impact on patient related outcomes for any of the diagnostic techniques. The GDG considered the evidence in favour of PET as too limited to justify a recommendation on the issue. Role of biopsies in active surveillance is unclear; in small lesions, biopsies are inaccurate, a difference should be made in text between expectance management (in case of co-morbidities) and active surveillance that delay intervention. In case of active surveillance, no biopsy has to be recommended. If the tumour grows, a decision to intervene is to be taken (active surveillance is cancelled). The GDG considered that biopsies are too invasive to be used for active surveillance in patients with comorbidities, compared with their added value.
Resource use	The GDG advised to formulate a recommendation to limit the indications for follow-up, in order to reduce the risk of overuse.

Recommendations
• Contrast-enhanced multi-phasic abdominal CT is recommended for the diagnosis and characterization of patients with a renal mass. In case of contraindication to iodine contrast injection, MRI can be used as an alternative.
• Contrast-enhanced multi-phasic abdominal CT or MRI are the most appropriate imaging modalities for renal mass staging prior to surgery.
• For a tumour ≥ T2 or ≥ N1 or M1 a contrast enhanced CT of the thorax is recommended.
• Bone scan is not routinely recommended in the absence of skeletal symptoms or elevated alkaline phosphatase.
• Brain imaging is not routinely recommended in the absence of symptoms.
• PET/CT is not routinely recommended in the diagnosis, staging and follow-up of renal cell carcinoma.
• Renal tumour biopsy (preferably with a coaxial technique) is recommended before ablative therapy and systemic therapy in the absence of previous pathology.

Best Practices
The use of the current TNM classification system is recommended.
The use of grading systems and classification of RCC subtype is recommended.
The patient must have the opportunity to be fully informed about his condition, the treatment options, and consequences. Information should be correct, communicated in a clear and unambiguous way and adapted to the individual patient. Patient preferences should be taken into account when a decision on a treatment is taken. Special attention should be given to breaking bad news and coping with side effects.
Psychosocial support should be offered to every patient, from diagnosis on.

3.2 Prognosis and prediction of treatment effectiveness

3.2.1 Predictive and prognostic biomarkers for VEGF-targeted therapy

Predictive biomarkers indicate whether a patient will benefit from a given treatment. Prognostic biomarkers provide information about a patient's likely clinical outcomes with or without treatment.

The EAU guideline did not recommend the use of any molecular prognostic marker for routine clinical use. Because this recommendation was not based on a documented search we verified the evidence base of this recommendation with an independent search. We found one high quality systematic review by Funakoshi et al.[21] AMSTAR scores are given in Appendix 3.

They classified biomarkers and their clinical validity and utility following a level of evidence system on the basis of the criteria originally proposed by Hayes et al. and revised by Simon et al.[22, 23] 'According to the scale, Category A represents prospective randomized clinical trials designed and powered specifically to address biomarker questions. Category B represents prospective studies not primarily designed to address biomarker questions, rather archive specimens for retrospective analysis of biomarkers. Category C represents prospective, observational registry studies. Category D represents retrospective, observational studies. Level I evidence is defined as at least one study from Category A, or one or more studies from Category B with consistent results. Level II evidence includes at least one study from Category B or two or more studies from Category C with consistent results.'[21]

'Five predictive biomarkers, such as VEGF, interleukin (IL)-6, hepatocyte growth factor (HGF), osteopontin, single nucleotide polymorphisms in IL-8, satisfied Level II evidence. IL-6 is the most corroborated predictive biomarker based on its consistent predictive value in two different trials. The prognostic value of biomarkers was assessed in 48 studies using the archived specimens from clinical trials, prospective and retrospective observational registries. Three biomarkers, including IL-8, HGF and osteopontin, satisfied Level I evidence for PFS.'[21] They confirm the conclusion of the EAU guideline that no biomarkers are ready yet for use in routine clinical practice.

Also the AUA guideline formulated a recommendation not to use biomarkers in the follow-up, because of the absence of evidence concerning their usefulness.

3.2.2 Prognostic systems and nomograms

The EAU guideline recommended nomograms for metastatic renal cancer but not for localised renal cancer. Because this recommendation was not based on a documented search we verified the evidence base of this recommendation with an independent search.

We found one systematic review of Sun et al.[24] assessing the validity of different prognostic systems. Amstar quality appraisal is given in Appendix 3. We performed an update of that review (search date 2010). We will present the different types of prognostic systems in different subheadings, starting from the review of Sun et al. and present the update of that review.

There is an increasing number of prognostic systems, as many groups seem to prefer to develop their own prognostic system. However, only a minority is externally validated on an independent population. This is very important as it is the only way to evaluate transferability to a setting other than the one on which the prognostic system was developed. Performance is likely to be overestimated when assessed on the same populations that was used to develop the prognostic system. Therefore we only report on systems that have at least one external validation.

3.2.2.1 Metastatic disease

In the review of Sun et al.[24] models were identified that apply exclusively to patients with mRCC. At that moment, models were developed and internally validated on patients undergoing cytokine therapy. None of those was externally validated at that time on patients undergoing targeted therapy.

We did an update of the review, and only considered studies that did external validations (this is a validation on a database that is different from the database on which the prognostic system was developed) on metastatic patients undergoing targeted therapy. We only selected *de novo* models if at least one external validation study was available.

Heng et al.[25] did an external validation comparing the Database Consortium model (commonly denoted as the Heng model) with the Cleveland Clinic Foundation (CCF) model, the International Kidney Cancer Working Group

(IKCWG) model, the French model, and the Memorial Sloan-Kettering Cancer Center (MSKCC) model. They found that all models had a similar concordance index, ranging from 0.640 to 0.668.

Kwon et al.[26] included 106 patients with metastatic renal cell carcinoma who were treated with sunitinib from April 2007 to July 2012 including 35 patients who received systemic treatment before sunitinib and 71 that were naive to systemic treatment. Patients were evaluated using the MSKCC and Heng models. The application of the MSKCC and Heng risk criteria resulted in stratification into 3 groups (favorable, intermediate, and poor risk) with distinctly different overall survival (OS) curves ($p<0.001$ and $p<0.001$, respectively), for the pretreated patients ($p<0.001$ and $p<0.001$, respectively). The Heng model had slightly better discriminatory ability ($chi^2 = 30.82$, Harrell's C = 0.6895) than the MSKCC model ($chi^2 = 25.13$, Harrell's C = 0.6532).

Yu et al.[27] did a validation and update of the MSKCC nomogram using patients from a phase 2 sunitinib mRCC study (Renal EFFECT Trial). With comparable patients characteristics and no significant difference in progression-free survival (PFS 8.5 vs. 7.0 months; P=0.070) between the 2 arms of the phase 2 trial, the combined patient population (N=292) was used to validate the existing nomogram. The overall concordance index was 0.615. Based on the decision curve analysis, the existing nomogram has clinical utility when the probability of 12-month PFS exceeds 60%.

We excluded Karakiewich et al.[28, 29] because the test population, that came from an RCT, was a mix of patients receiving targeted therapy and cytokine therapy.

3.2.2.2 Survival and freedom of recurrence before and after nephrectomy

Sun et al.[24] identified 2 models that can predict survival of RCC after nephrectomy. The University of California, Los Angeles (UCLA), devised an integrated staging system (UISS) for the prediction of survival in patients with all stages of RCC. Validation studies reveal concordance indices [c- indices] ranging from 58 to 86%. A multi-institutional collaborative group of European and North American investigators developed two prognostic models that address cancer-specific mortality based on variables that can be obtained either before or after nephrectomy. These two models are commonly known as the pre- and postoperative Karakiewicz nomograms. The Kattan nomogram, the Sorbellini nomogram, and the Leibovich model focus on freedom from recurrence and recurrence free survival.

Tan et al.[30] did a retrospective study on a total of 390 consecutive patients who underwent nephrectomy for sporadic localized RCC in a tertiary institution (1990-2006) with 65 months median follow-up. The Karakiewicz nomogram, the Kattan nomogram, the Sorbellini nomogram and the Leibovich model were compared in predicting survival outcomes (overall survival, cancer-specific survival, and freedom from recurrence). Overall, the Karakiewicz nomogram outperformed the Kattan nomogram, the Sorbellini nomogram, and the Leibovich model, and showed higher adequacy and concordance indices and improved clinical benefit relative to all other nomograms.

Zastrow et al.[31] did an external validation of the postoperative nomogram developed by Karakiewicz et al. for prediction of cancer-specific survival. A total of 1 480 consecutive patients with a median follow-up of 82 months (IQR 46-128) were included into this analysis with 268 RCC-specific deaths. Concordance between predictions of the nomogram and survival rates of the cohort was 0.911 after 12 months, 0.909 after 24 months and 0.896 after 60 months. Comparison of predicted probabilities and actual survival estimates with calibration plots showed an overestimation of tumour-specific survival based on nomogram predictions of high-risk patients, although calibration plots showed a reasonable calibration for probability ranges of interest. Decision curve analysis showed a positive net benefit of nomogram predictions for the patient cohort.

Gontero et al.[32] performed a formal external validation of the preoperative Karakiewicz nomogram for the prediction of cancer-specific survival (CSS) using a large series of surgically treated patients diagnosed with organ-confined or metastatic renal cell carcinoma (RCC). Patient population originated from a series of retrospectively gathered cases that underwent radical or partial nephrectomy between years 1995 and 2007 for suspicion of kidney cancer. The original Cox coefficients were used to generate the predicted risk of CSS at 1, 2, 5, and 10 years following surgery and compared to the observed risk of CSS in the current population. A total of 3 374 patients were identified. Relative to the original development cohort, the current sample population had a larger proportion of patients with localized (40.0 vs. 26.3%, $p<0.001$) and non-metastatic (92.2 vs. 88.1%, $p=0.03$) disease at presentation. Model discrimination for the prediction of

CSS was 87.8% (95%CI, 84.4-91.4) at 1 year, 87.0 % (95%CI, 84.4-89.5) at 2 years, 84.7% (95%CI, 82.3-87.1) at 5 years, and 85.9% (95%CI, 83.2-88.6) at 10 years. The relationship between predicted and observed CSS risk was adequate in the calibration plot.

To assess the accuracy and generalizability of the pre- and postoperative Karakiewicz nomograms for predicting cancer-specific survival (CSS), Cindolo et al.[33] included in a retrospective study 3 231 patients from European and US centres, who were treated by radical or partial nephrectomy for RCC between 1992 and 2010. Prognostic scores for each patient were calculated and the primary endpoint was CSS. Discriminating ability was assessed by Harrell's c-index for censored data. Calibration was graphically explored. The median follow-up (FU) was 49 months. At the last FU, 408 cancer-related deaths were recorded, Kaplan-Meier estimates of CSS (with 95%CIs) at 5 and 10 years were 0.86 (0.84-0.87) and 0.77 (0.75-0.80), respectively. Both nomograms discriminated well. Stratified c-indices for CSS were 0.78 (95%CI 0.75-0.81) for the preoperative nomogram, and 0.84 (95%CI 0.82-0.87) for the postoperative one, with a significant difference between the two values ($P < 0.001$). The calibration plots showed no relevant departures from ideal predictions.

Suzuki et al.[34] measured the predictive accuracy of the Kattan postoperative nomogram for non-metastatic renal cell carcinoma in a Japanese population. A total of 211 patients with stage T1-3 N0 M0 clear renal cell carcinoma who underwent radical nephrectomy or nephron-sparing surgery between 1991 and 2004 were included in this analysis. The concordance index for RFS predicted by the Kattan nomogram was 0.735 (95%CI: 0.734-0.736). There was a slight discrepancy between the RFS predicted by the Kattan nomogram and the likelihood of being recurrence-free at 5 years according to the Cox analysis in the current patient population.

Santiago et al.[35, 36] did a retrospective assessment of the clinical and pathological variables of 305 patients treated with nephrectomy (partial or radical) for renal cell carcinoma. Three models were used to predict RFS (Kattan nomogram, Sorbellini model and Leibovich model), and three ones to predict CSS: the University of California at Los Angeles Integrated Staging System (UISS) model; the Stage, Size, Grade and Necrosis (SSIGN) model and the Karakiewicz nomogram. Survival was estimated using the Kaplan-Meier method. The predictive ability of the different scores was evaluated using the Harrell concordance index. With a median follow-up of 50.7 months, 41 patients (15.1%) died of renal cell carcinoma and in 54 (19.9%) the disease progressed. The 5-years CSS and RFS rates were 84.9% and 77.5%, respectively. The c-indexes for RFS at 5 years were 0.626 for the Kattan nomogram and 0.696 for the Sorbellini model. The Leibovich nomogram presented c-indexes for RFS at 1, 3 and 5 years of 0.807, 0.728 and 0.721 respectively. The c-indexes for CSS were 0.774, 0.773, 0.772, 0.760 and 0.760 at 1, 2, 3, 4 and 5 years respectively for the UISS model, 0.831, 0.819 and 0.795 at 1, 3 and 5 years respectively for the SSIGN nomogram, and 0.752, 0.753 and 0.767 at 1, 2 and 5 years respectively for the Karakiewicz model.

Conclusions

- No biomarkers are ready yet for use in routine clinical practice and have shown added value compared to existing prognostic systems.
- Different prognostic systems for metastatic disease such as the database Consortium model (commonly denoted as the Heng model) with the Cleveland Clinic Foundation (CCF) model, the International Kidney Cancer Working Group (IKCWG) model, the French model, and the Memorial Sloan-Kettering Cancer Center (MSKCC) model have a similar accuracy when validated in an external population.
- The pre- and postoperative Karakiewicz nomograms for predicting cancer-specific survival (CSS) were validated on several large databases.

Other considerations

Factor	Comment
Balance between clinical benefits and harms	Prognostic systems for metastatic disease are used for treatment decisions related to systemic therapy. Clinical added value of prognostic systems for localised disease is less clear, as no treatment decisions are taken on the base of these.
Quality of evidence	Existing prognostic systems were externally validated. For metastatic disease, validation studies did not find important differences in the validity of those nomograms. Pre- and postoperative Karakiewicz nomograms for predicting cancer-specific survival (CSS) were validated on several large databases, their added value compared to TNM stage alone remains uncertain.

Recommendations
• Prognostic systems are recommended in the metastatic disease.
• In localized disease, the use of integrated prognostic systems or nomograms can be considered for prognosis in addition to TNM.
• No molecular prognostic marker is currently recommended for routine clinical use.

3.3 Treatment of localized renal cancer

Localized renal cancer is defined as T1-T2 N0 M0 tumours. However, T3 tumours are included in some recommendations. In such case, we clearly mentioned T3 in the recommendation.

3.3.1 Surgery

First, the value of the surgical management of localized renal cancer (radical or partial nephrectomy) versus nonsurgical management was evaluated in a systematic review (MacLennan et al. 2012)[37] reported by the EAU guideline. This systematic review reported results obtained by a matched-pair population study (Zini et al. 2009)[38] that compared surgical treatment of pT1a patients (n=430) with non-surgical management (observation or active surveillance; n=1 545). According to this study, 5-year cancer-specific mortality was lower in patients with surgical intervention than in those with nonsurgical management (4.4% vs. 12.4%) (very low level of evidence). However, an indication bias weakened this observation, since the surveillance group members were indicated for this intervention and were not randomly allocated to it. Besides, surveillance patients were older (mean age: 73 vs. 61.4 years) and probably more frail and less likely to be suitable candidates for surgery. The median follow-up duration was higher for the non-surgical group (50 months vs. 16 months). Other methodological flaws such as uncertain disease status in the surveillance group (indicated by failing to measure and control for two of the main prognostic confounders, i.e. Fuhrman grade and histologic cell type) make it difficult to draw a definitive conclusion about this comparison.

Update

The additional search did not yield any randomized study on this topic.

Conclusions

- There is some evidence that surgery in localized RCC patients (including T1a patients) leads to a lower 5-year cancer specific mortality than observation or active surveillance.

Recommendation	Strength of Recommendation	Level of Evidence
• Surgery with curative intent is recommended in the patients with localized renal tumour.	Strong	Very low

3.3.1.1 Nephrectomy

Radical nephrectomy vs. partial nephrectomy (nephron-sparing surgery)

In 2010, the IKNL working group stated that radical nephrectomy, as described by Robson[a], is no longer the gold standard for the treatment of small (< 7 cm) renal cell carcinomas (consensus based recommendation). Consequently, IKNL recommended partial nephrectomy for T1a tumours (< 4 cm) including a surgical margin of unaffected tissue (macroscopically normal-appearing parenchyma).

Moreover, IKNL recommended that nephron-sparing treatment is performed (if technically possible) in the case of a (functional) monokidney with renal cell carcinoma. The threshold of 4 cm is not applied here. Their advice is based on one comparative study and 4 case series.

In the same way, the EAU guideline recommended partial nephrectomy in patients with T1a tumours, but also in patients with T1b tumour, whenever technically feasible.

According to the evidence summarized in this guideline, the oncological outcomes following open partial nephrectomy are at least as good as open radical nephrectomy and should be the preferred option when technically feasible.

However, in some patients with localized RCC, partial nephrectomy is not suitable because of:

- tumour growth;
- tumour is in an unfavourable location;
- significant deterioration of a patient's general health.

In these situations, the curative therapy remains radical nephrectomy, which includes removal of the tumour bearing kidney. Complete resection of the primary tumour by either open or laparoscopic surgery offers a reasonable chance of curing the disease.

These recommendations stem from the update of two systematic reviews reporting either oncological outcomes (MacLennan et al. 2012)[37] or perioperative and Quality of Life outcomes (MacLennan et al. 2012).[39] Overall, the body of evidence includes 2 RCTs (Van Poppel et al. 2011, Yu et al. 2010)[40, 41] and 23 comparative studies. The only retrieved RCT, performed by Van Poppel et al. (2011), was a multicentre RCT of partial nephrectomy versus radical nephrectomy for T1–T2 renal cancers.

[a] Including early ligation of the renal veins to prevent the spread of tumour cells via tumour emboli; excision of the kidney, adrenal gland, perirenal tissue, and Gerota's fascia; extensive lymph node dissection with removal of the para-aortal and paracaval nodes, from the crus of diaphragm to the aortic bifurcation (lymphadenectomy).

Unfortunately, the study was impaired by significant limitations (including premature closing of the study due to poor accrual, a change in protocol, and being significantly underpowered) (MacLennan et al. 2012).[37] The results from the intention-to-treat analysis showed a lower overall survival for partial nephrectomy compared with radical nephrectomy, although this difference becomes non-significant when the analysis was restricted to the targeted population of RCC patients and those who are clinically and pathologically eligible. Given such methodological weaknesses and uncertainty, the results from this study should be interpreted with caution (MacLennan et al. 2012).[37] Yu et al. (2010) conducted a study comparing open partial nephrectomy and open radical nephrectomy, obtaining similar oncological outcomes at a minimum of 5 years. The risk of bias of Yu et al (2010) was not evaluated because Chinese was the language of the paper.

Update

The search for the update yielded one systematic review (Kim et al. 2012)[42] and one RCT (Scosyrev et al. 2014).[43]

The review published by Kim et al (2012)[42] compared partial and radical nephrectomy for localized renal tumours. The authors reported three meta-analyses pooling data from 21, 21 and 9 studies for all cause and cancer specific mortality, and severe chronic kidney disease, respectively. In the first meta-analysis, the authors studied all-cause mortality from 21 studies comparing partial nephrectomy and radical nephrectomy. The risk reduction for all-cause mortality was estimated to be 19% in favour of partial nephrectomy (HR=0.81, 95%CI 0.76 to 0.87, I^2=49%, p<0.00001). The second meta-analysis aimed to compare cancer-specific mortality between radical and partial nephrectomy. For the purpose of this comparison, 21 studies were included. Compared to radical nephrectomy, nephron-sparing surgery was correlated with 29% decreased likelihood of cancer-specific mortality (HR=0.71, 95%CI 0.59 to 0.85, I^2=63%, p<0.0002). Finally, 9 observational studies were included to show 61% of risk reduction in severe chronic kidney diseases in patients treated with partial nephrectomy (HR=0.39, 95%CI 0.33 to 0.47, I^2=87%, p<0.00001). These results need to be interpreted with caution due to the low quality of the supportive evidence and the significant heterogeneity across studies. Most groups relied on retrospective institutional data from historical cohort or on case-control study designs. Only one RCT was included (Van Poppel et al. 2011) also suffering from methodological limitations.

Later, Scosyrev et al. (2014)[43] used data from the EORTC randomized trial 30904 (Van Poppel et al. 2011) to evaluate the impact of both surgical interventions on kidney function, using estimated glomerular filtration rates as measure for the outcome. Three levels of renal dysfunction were defined: moderate renal dysfunction (eGFR <60), advanced kidney disease (eGFR <30), and kidney failure (eGFR <15). For each treatment arm, the results were reported on the basis of the lowest recorded follow-up eGFR (intent-to-treat analysis). Authors randomly assigned patients with small renal mass (≤5 cm) and normal contralateral kidney to nephron-sparing surgery group (n=268) or to radical nephrectomy group (n=273). The glomerular filtration rate (eGFR; millilitres per minute per 1.73 m^2) was estimated at a median follow-up of 6.7 years. Moderate renal dysfunction was higher in patients group treated by radical nephrectomy (RN) than those treated by partial nephrectomy (PN) (RN: 85.7% vs PN: 64.7%, p<0.001). No statistical differences were observed between the two groups for the rate of advanced kidney disease (RN: 10.0% vs PN: 6.3%, ns) and kidney failure (RN: 1.5% vs PN: 1.6%, ns). The beneficial impact of nephron-sparing surgery on eGFR did not result in improved survival over a median follow-up of 9.3 years for all-cause mortality.

Conclusions

- There is evidence from observational studies that nephron-sparing surgery is superior to radical nephrectomy in terms of all-cause mortality, cancer-specific mortality and emergence of severe chronic kidney diseases.
- There is evidence from one RCT with methodological flaws that nephron-sparing surgery compared with radical nephrectomy substantially reduced the incidence of moderate renal dysfunction stage (eGFR<60) without impact on the incidence of advanced kidney disease (eGFR <30) or the incidence of kidney failure (eGFR <15). The beneficial impact of nephron-sparing surgery on eGFR did not result in improved survival for all-cause mortality.

Other considerations

Factor	Comment
Balance between clinical benefits and harms	Partial nephrectomy (nephron-sparing surgery) is a more conservative technique than radical nephrectomy offered to patients with RCC. However, there is conflicting evidence regarding the clinical benefits of partial nephrectomy compared to radical nephrectomy. One RCT shows that radical nephrectomy offers higher 10-year overall survival rates (Van Poppel et al. 2011) while the meta-analyses of observational studies concluded that partial nephrectomy was superior.
Quality of evidence	The level of evidence is very low because of the significant limitations of the only one available RCT (including premature closing of the study due to poor accrual, a change in protocol, and being significantly underpowered)[44-47] and the great heterogeneity in pooled studies in the meta-analyses of observational studies. There is conflicting evidence from the RCT and the observational studies. The overall level of evidence is assessed as being of very low quality.

Recommendations	Strength of Recommendation	Level of Evidence
• Partial nephrectomy is recommended in patients with T1a renal tumours.	Strong	Very low
• Partial nephrectomy should be favoured over radical nephrectomy in patients with T1b renal tumour, whenever technically feasible.	Strong	Very low

Long-term outcomes of partial nephrectomy (PN) and radical nephrectomy (RN) in localized tumour RCC

Search results

Long-term outcomes are measured at a follow-up of more than 5 years. Because RCTs do not have a follow-up long enough to answer this question, comparative studies were included whatever the design. The selection of the literature (see Appendix 2.2.3) leads to include 1 RCT and 8 retrospective cohort studies.

Evidence

Overall survival

- 8-year overall survival

Tan et al. (2012)[48] retrospectively analysed a national US database including patients with single renal tumour (≤4 cm) in early-stage (T1a) treated by partial or radical nephrectomy by either an open or laparoscopic approach. The difference in 8-year overall survival was in favour of PN (Δ (95%CI): 15.5 % points (5.0-26.0), p<0.001).

- 10-year overall survival

One RCT[40] and 3 retrospective cohort studies,[38, 49, 50] reported 10-year overall survival. Van Poppel et al.[40] randomly assigned patients with solitary T1-T2 N0 M0 renal tumour (≤ 5 cm) in partial or radical nephrectomy surgical treatment group. The authors found a 10-year survival rate of 75.2 % and 79.5% in PN group and RN group, respectively. Conversely, the three retrospective cohort studies reported a benefit in 10-year survival rate in favour of PN. The retrospective cohort presented by Daugherty et al. (2014) and including localised RCC patients aged from 20 to 44 years with a small tumour size (≤ 4 cm), 10-year overall survival was 94% in patients treated with PN and 89.7% in those treated with RN.[49] Another cohort including

localized pT1-3a RCC patients showed a benefit in 10-year survival rate in patients treated with elective PN in comparison with RN (ePN 74,6% vs RN 67.7%, log rank, p<0.001).[50] There is no more benefit in 10-year survival rate when RN is compared with imperative PN (iPN 57,5% vs RN 67.7%, log rank, p<0.001). Finally a retrospective matched analysis also showed a benefit in 10-year overall survival rate in favour of PN (PN 7.9% vs RN 68.8%).[38] All these retrospective studies suffer from lack of quality in the study design (long period of analysis with change in the surgical techniques, differences in patients characteristics in the compared groups, lack of taking into account of confounding parameters…).

Cancer specific survival

- 10-year cancer specific survival

The previous mentioned cohort of patients by Daugherty et al. (2014)[49] estimated that PN offers a better 10-year cancer-specific survival than RN (PN 100% vs RN 98.3%). This benefit is also shown in cohort from a single institution in Germany including patients with solid renal lesions (PN 95.8% vs RN 84.4%, log-rank test p< 0.05).[51] These two studies present all the bias inherent to retrospective design.

- 15-year cancer specific survival

The last cohort measured additionally 15-year cancer specific survival rate and indicated that the rate is in favour of PN (PN 95.8% vs RN 77.9% (log-rank test p<0.05).

Non-cancer-related mortality

The above retrospective matched analysis also presented advantage in PN when compared with RN in term of 10-year non-cancer-related mortality (PN 27.1% vs RN 30.6%). [38]

Recurrence rate

Stewart et al. (2014) made an evaluation of the National Comprehensive Cancer Network and American Urological Association Renal Cell Carcinoma Surveillance Guidelines.[52] Therefore, the authors retrospectively analysed the occurrence of recurrence in 2 181 low risk patients with M0 sporadic RCC (pT1Nx-0) treated by surgery in one institution. They found RN had significantly higher recurrence rates compared with PN at all locations except for the abdomen (10-year recurrences rate: Any PN 12.4% vs RN 14.5%, p=0.074; Abdomen PN 10.4% vs RN 6.3%, p=0.009, Chest PN 1.1% vs RN 5.3%, p<0.001, Bone PN 0.8% vs RN 2.7%, p<0.001, Other PN 0.8% vs RN 2.5%, p<0.001). However, these results must be interpreted with caution because tumours in the PN group were less aggressive (i.e. more frequent papillary histology, more patients with stage of pT1a, smaller median tumour size and less sarcomatoid differentiation).

Progression rate

Van Poppel et al. (2011) provided an estimation of the 10-year progression rate in favour of RN when compared to PN (rate (95%CI: PN 4.1% (1.7-6.5) vs RN 3.3% (1.2-5.4), Gray's test p=0.48).[40]

Cardiovascular events

A retrospective study including four European tertiary care centres studied the 10-year cardiovascular events rate in 1 331 patients with T1a-T1b N0 M0 and with normal preoperative function.[53] The 10-year cardiovascular events rate was higher in RN group than in PN group (PN 20.2% vs RN 25.9%, p=0.001). Caution is required because the availability for other potential confounders is limited due to the retrospective design and the 2 groups were unbalanced for clinical characteristics and cardiovascular profile.

Conclusions

- There is conflicting evidence between the sole RCT and the eight cohort studies. However, all retrospective studies pointed out that oncological outcomes (survival, recurrence rate, progression rate) and cardiovascular events were in favour of partial nephrectomy. Matched cohort design allows observational study to deal with some confounders. However, other design in observational studies were included raising concerns related to unmeasured confounding effects by indication.
- Long-term outcomes analysis does not allow modifying the recommendation made in the previous sections based on the short and intermediate term outcomes. Therefore, no additional recommendation is put forward.

Techniques of radical nephrectomy

The EAU guideline advocated laparoscopic radical nephrectomy for patients with T2 tumours and localized renal masses not treatable by nephron-sparing surgery to obtain better outcomes such as shorter hospital stay and convalescence time, lower analgesic requirement and lower peri-operative blood loss. The evidence comes from 1 RCT (Peng et al. 2006)[54] and 2 comparative studies (Hemal et al. 2007, Gratzke et al. 2009).[55, 56] Low event rates were reported and no difference in complications was observed. The operation time was significantly shorter in the open nephrectomy arm. The post-operative QoL scores were similar between the two groups. No RCTs assessed oncological outcomes of laparoscopic vs. open radical nephrectomy. However, a prospective cohort study (Hemal et al. 2007)[56] and retrospective database reviews of low methodological quality (Gratzke et al. 2009, Brewer et al. 2012, Sprenkle et al. 2012)[55, 57, 58] found similar oncological outcomes for laparoscopic vs. open radical nephrectomy. Five-year overall survival, cancer specific survival and 5-year recurrence rate did not differ following one or other approach.

Two RCTs (Desai et al. 2005[59], Nambirajan et al. 2004[60]) and quasi-RCT (Nadler et al. 2006)[61] compared transperitoneal versus retroperitoneal laparoscopic radical nephrectomy. Both retroperitoneal and transperitoneal approaches had similar oncological outcomes. During the studies period, no cancer-specific deaths were reported by Nadler et al. (2006)[61] and no difference in all-cause deaths rate between the two approaches was reported by Desai et al. (2005)[59]. No positive surgical margins were recorded in the 3 trials. Metastatic events did not occur in 2 studies (Nambirajan et al. 2004[60] and Nadler et al. 2006[61]) but 4 cases were observed by Desai et al. (2005)[59] respectively 1 of 52 for retroperitoneal group and 3 of 50 for transperitoneal group. No evidence of a difference in intraoperative blood loss (ml) and in analgesic requirement (mg morphine equivalent) was found in the three studies. Between the 2 surgical approaches, Nambirajan et al. (2004)[60] reported no statistically significant difference in the number of patients needed a blood transfusion. Conflicting results related to operative time and length of stay were found. Nambirajan et al. (2004)[60] and Nadler et al. (2006)[61] found no difference in operative time (min) between retroperitoneal and transperitoneal laparoscopic radical nephrectomy while retroperitoneal approach was associated with shorter total operative time in Desai et al. (2005)[59] (respectively, 150 versus 207 minutes, p=0.001). Hospital length of stay was statistically significantly lower using the transperitoneal approach in Nadler et al. (2006)[61] whereas no difference was shown in the 2 other RCTs.

IKNL suggests that the extent, the size of the tumour and the experience of the urologist determined the choice between a transperitoneal and an extraperitoneal (translumbar) radical nephrectomy. This intervention should be preferably performed in a specialised treatment centre. Seven comparative studies and two case series support the recommendations formulated by IKNL.

Update

The additional search did not yield any additional meta-analysis, systematic review or RCTs.

Conclusions

- Laparoscopic radical nephrectomy is associated with shorter hospital stay and convalescence time, lower analgesic requirement and lower peri-operative blood loss compared to open surgery.
- Oncological outcomes (five-year overall survival, cancer specific survival and 5-year recurrence rate) for T1-T2a tumours are equivalent between laparoscopic and open radical nephrectomy.
- Transperitoneal LRN is equivalent to retroperitoneal LRN in terms of length of stay, intraoperative blood loss and analgesic requirement. However, retroperitoneal approach allows a shorter operative time than transperitoneal approach.

Other considerations

Factor	Comment
Balance between clinical benefits and harms	Laparoscopic technique is a less invasive procedure to perform in selected patients who cannot be treated with nephron-sparing surgery. Retroperitoneal RN approach allows lower operative time than transperitoneal approach.
Quality of evidence	Only one RCT compared laparoscopic radical nephrectomy to open surgery. The risk of bias of this RCT is unclear. The 3 RCTs comparing retroperitoneal versus transperitoneal laparoscopic radical nephrectomy showed some limitations, inconsistency and imprecision.

Recommendations	Strength of Recommendation	Level of Evidence
• When partial nephrectomy is not an option for T1 and T2 renal carcinoma, radical nephrectomy should be performed.	Strong	Low
• If technically feasible, laparoscopic technique is preferred above open surgery when radical nephrectomy is required.	Weak	Moderate
• Laparoscopic radical nephrectomy should not be performed in patients with T1 tumours for whom partial nephrectomy is indicated.	Strong	Very low
• Laparoscopic radical nephrectomy is recommended for patients with T2 tumours and localized renal masses not treatable by nephron-sparing surgery.	Strong	Low

Techniques for partial nephrectomy

EAU guideline retrieved nine comparative studies showing that:

- Laparoscopic partial nephrectomy and open partial nephrectomy resulted in comparable progression-free survival and overall survival when performed in centres with laparoscopic expertise.
- Post-operative mortality events were similar whereas the blood loss was generally lower with the laparoscopic approach, which often requires however, a longer operative time.
- Retroperitoneal and transperitoneal laparoscopic partial nephrectomy were found to have similar peri-operative outcomes.

In addition, 2 meta-analyses of small series reported by EAU showed comparable peri-operative outcomes between robotic or pure laparoscopic partial nephrectomy. A shorter warm ischemia time for robot-assisted partial nephrectomy was also reported.

EAU guideline concluded that partial nephrectomy can be performed, either with an open, pure laparoscopic or robotic-assisted approach, based on surgeon's expertise and skills. In line with EAU, IKNL, based on expert opinion, recommended that laparoscopic partial nephrectomy should only be performed in centres with extensive experience and expertise with the relevant treatment.

Update

The update of the evidence yielded three systematic reviews (Zheng et al. 2013, Ren et al. 2014 and Froghi et al. 2013)[62-64] that included non-randomised observational studies (case-control, cohort studies, retrospective studies).

In 2013, Zheng et al. performed a meta-analysis on the available literature on the long-term oncological outcome of laparoscopic (LPN) versus open partial nephrectomy (OPN). Three case control and three cohort studies were included in the meta-analysis including 555 patients operated by LPN and 940 by OPN. There was no significant difference between the two methods in 5-year overall survival (4 studies, OR=1.83, 95%CI 0.80 to 4.19, I^2=32%, p=0.15), 5-year cancer specific survival (4 studies, OR=1.09, 95%CI 0.62 to 1.92, I^2=0%, p=0.75) and 5-year recurrence free survival (5 studies, OR=0.68, 95%CI 0.37 to 1.26, I^2=0%, p=0.22). The authors concluded that there was no difference in long-term oncological outcomes between laparoscopic and open partial nephrectomy for treatment of localized renal tumours.

Ren et al. (2014) selected eight retrospective studies to compare transperitoneal approach vs. retroperitoneal laparoscopic partial nephrectomy. None of the included studies reported recurrence or survival rates. After the pooling of studies, retroperitoneal laparoscopic partial nephrectomy had a lower estimated blood loss (5 studies, SMD =0.403 ml, 95%CI 0.015 to 0.791, I^2=74.9%, p=0.042) and a shorter length of hospital stay (6 studies, WMD =0.94 days, 95%CI 0.61 to 1.26, I^2=46.3%, p<0.001) than transperitoneal approach. There were no significant differences between the two methods in other operative outcomes (operative time, warm ischemia time, serum creatine level), surgical complications (overall complication rate, intra or postoperative complications rate, open conversion rate) or positive margin. Higher heterogeneity in pooled studies must be noted.

Comparison of robotic and laparoscopic partial nephrectomy for small renal tumours (< 4cm, T1a) was performed by Froghi et al. (2013) using a meta-analysis of 6 recent comparative studies. No statistically significant difference were found between the two techniques in terms of estimated blood loss (WMD =46.13 ml, 95%CI -12.01 to 104.26, I^2=87%, p=0.12), operative time (WMD =0.5 min, 95%CI -24.02 to 25.02, I^2=59%, p=0.97), warm ischemia time (WMD =-5.76 min, 95%CI -15.22 to 3.70, I^2=96%, p=0.23), length of stay (WMD =-0.15 day, 95%CI -0.38 to 0.09, I^2=0%, p=0.22) and overall complications rate (WMD =-0.01, 95%CI -0.05 to 0.06, I^2=0%, p=0.84). The authors concluded to no difference between the two methods despite multiple studies reporting better perioperative outcomes for the robotic partial nephrectomy. However, RCT and long-term oncological data are needed to confirm these results.

Conclusions

- There is evidence that long-term oncological outcomes are comparable between laparoscopic and open partial nephrectomy for localized renal tumours.
- There is some evidence that retroperitoneal LRN is superior to transperitoneal approach in terms of operative time, blood loss and length of stay.
- There is some evidence that robotic partial nephrectomy in patients with small renal tumours is equivalent to LRN.

Other considerations

Factor	Comment
Balance between clinical benefits and harms	Laparoscopic approach offers a less invasive intervention than open surgery. Because no difference in long-term oncological outcomes was observed, laparoscopic partial nephrectomy can be considered as a safe alternative to open partial nephrectomy. All publications concerning the robotic techniques are very recent (from 2008) and do not allow long-term outcomes evaluation. In addition, no RCT on the topic is available. The comparison between off-clamp and complete hilar control during partial nephrectomy is not conclusive in terms of postoperative complication rate and positive margin rate due to the sensitive analysis of the evidence. Better renal function can be obtained by off-clamp procedure but with a higher risk of blood transfusion. This benefit must be interpreted with caution because of inconsistency.
Quality of evidence	The overall level of evidence is low because of a lack of RCTs and the high heterogeneity between studies.

Recommendation	Strength of Recommendation	Level of Evidence
• Partial nephrectomy can be performed, either with an open or laparoscopic approach, the latter being preferably performed in centres with laparoscopic expertise**.**	Strong	Very low

3.3.1.2 Associated procedures

Adrenalectomy

Ipsilateral adrenalectomy is not recommended by the EAU when there is no clinical evidence of invasion of the adrenal gland. This advice is based on one prospective non-randomized study comparing the outcomes of radical or partial nephrectomy with or without ipsilateral adrenalectomy. IKNL also stated that routine removal of the adrenal gland during radical tumour nephrectomy is no longer justifiable. However, IKNL suggested the adrenalectomy may be beneficial in cases of abnormal findings by CT or large, upper-pole tumours. However, it is doubtful whether adrenalectomy improves survival in these settings. Their recommendations stem from 3 pieces of evidence. Firstly, two case series and one comparative study showed an association between adrenal metastases and primary tumours in the upper pole of kidney. Secondly, three comparative studies and three case series support adrenalectomy when suspicious adrenal gland is found by preoperative CT or by macroscopic assessment during the surgery. Finally, three comparative studies and one case series concluded that adrenalectomy has no effect on prognosis for patients with advanced kidney disease.

Update

The additional search yielded one systematic review. Su et al. (2012)[65] performed a meta-analysis on the available literature about the comparison between adrenalectomy and adrenal-sparing radical nephrectomy in RCC treatment. The authors did not find statistically significant differences between the two procedures in overall survival (4 studies; HR=0.89, 95%CI 0.67 to 1.19, I^2=80%, p=0.43), 5-year cancer specific survival (8 studies, OR

=1.06, 95%CI 0.79 to 1.44, I^2=73%, p=0.69) or risk of ipsilateral adrenal metastases in upper pole tumour (9 studies, OR =1.11, 95%CI 0.83 to 1.47, I^2=16%, p=0.50). Results of this meta-analysis must be interpreted with caution because of the lack of RCTs and the great heterogeneity between studies.

Conclusions

- Routine removal of the adrenal gland during tumour nephrectomy does not provide advantage in terms of overall survival or 5-year cancer specific survival.

Other considerations

Factor	Comment
Balance between clinical benefits and harms	Because solitary adrenal metastasis is extremely rare (<1%), adrenalectomy must be limited to patients with clinical evidence. Detection of adrenal metastases by CT or MRI prior surgery is easily feasible (sensitivity of CT and MRI ranges from 88% to 100% and specificity ranges from 40% to 99%).
Quality of evidence	Because of the lack of RCTs and imprecision, the level of evidence is very low.

Recommendation	Strength of Recommendation	Level of Evidence
• Routine removal of the adrenal gland during (partial or radical) nephrectomy is not recommended in the absence of clinical evidence of invasion of adrenal gland.	Strong	Very low

Lymph node dissection

EAU guideline did not recommend lymph node dissection in localized tumours without clinical evidence of lymph node invasion. However, lymph node dissection can be performed for staging purposes or local control in patients with clinically enlarged lymph nodes. These recommendations are based on 1 systematic review (Bekema 2013),[66] 3 narrative reviews and 7 case series. Bekema et al. (2013) retrieved 1 RCT (Blom 2009)[67] and 5 non-randomized studies and concluded that there was no significant difference in adverse events and in 5-year overall survival between radical nephrectomy with or without lymph node dissection in patients with locally advanced RCC cT3–T4 N0 M0. No meta-analysis of trials was performed because of a high heterogeneity between studies.
IKNL recommended that lymphadenectomy should not be performed routinely. In addition, lymphadenectomy has only diagnostic value in patients with renal cell carcinoma. Consequently, it is useful for prognostic purposes only. This advice stems from the same RCT (Blom 2009),[67] 3 comparative studies and 2 case series.

Update

The additional search did not yield any additional meta-analysis, systematic review or RCTs.

Conclusions

- In patients with localized disease and no clinical evidence of lymph node metastases, no survival advantage of a lymph node dissection in conjunction with a radical nephrectomy was demonstrated.
- In patients with localized disease and clinically enlarged lymph nodes, the survival benefit of lymph node dissection is unclear. In these cases, lymph node dissection can be performed for staging purposes.

Other considerations

Factor	Comment
Balance between clinical benefits and harms	Lymph node dissection does not provide advantage to patients with locally advanced RCC cT3–T4 N0 M0.
Quality of evidence	The only RCT included suffers from several methodological limitations (lack of blinding, more than 10% missing data in intervention group). Other included comparative studies and case series provided low quality of evidence for lymph node dissection outcomes.

Recommendations	Strength of Recommendation	Level of Evidence
• Lymph node dissection (lymphadenectomy) should not be performed routinely in patients with a localized renal tumour without clinical evidence of lymph node invasion.	Strong	Low
• In patients with clinically enlarged lymph nodes, lymph node dissection can be performed for staging purposes or local control.	Weak	Low

Embolization

Before a routine nephrectomy, there is no benefit in performing tumour embolization. This technique can be useful in a metastatic setting for palliative purposes (see section 3.5 Palliative care).

Update

The additional search did not yield any additional meta-analysis, systematic review or RCTs.

Recommendation	Strength of Recommendation	Level of Evidence
• Embolization is not routinely recommended before a nephrectomy.	Strong	Low

3.3.2 *Management of RCC complicated with caval thrombus*

EAU guideline recommended excision of the kidney tumour and caval thrombus in patients with non-metastatic RCC. This advice is based on one systematic review including 5 non-comparative retrospective studies to assess different surgical strategies in non-metastatic RCC and 1 case series assessing the opportunity of performing surgery in patients with venous thrombus.

The surgical approach and technique used for the removal of a thrombus of the inferior vena cava is determined by the cranial extent of the tumour thrombus. To ensure optimal care, IKNL advocates that patients with a supradiaphragmatic tumour thrombus are treated in a centre with expertise in cardiopulmonary surgical-technical protocols. This recommendation stems from eight case series and two comparative studies.

Update

The additional search did not yield any additional meta-analysis, systematic review or RCTs.

Conclusions

- Based on limited evidence, thrombectomy must be considered in patients with non-metastatic RCC.

Other considerations

Factor	Comment
Balance between clinical benefits and harms	There is evidence that radical nephrectomy associated with complete thrombectomy reduces the impact of tumour thrombus in renal vein or inferior vena cava on survival.
Quality of evidence	No RCT is available. The body of evidence only consists of comparative studies and cases series leading to a very low level of evidence.

Recommendations	Strength of Recommendation	Level of Evidence
• Excision of the kidney tumour and caval thrombus is recommended in patients with non-metastatic renal cell carcinoma.	Strong	Very low
• To ensure optimal care, patients with a supradiaphragmatic tumour thrombus should be treated in a treatment centre with expertise in cardiopulmonary surgical-technical protocols.	Strong	Very low

3.3.3 *Alternative to surgery*

The incidence of kidney cancer is increasing at a rate of 2-3% per year worldwide.[68] The rising incidence is largely attributable to the increased detection of small renal masses.[69] Nevertheless, small renal masses grow slowly in most cases and only 1 to 2 % of masses progress to metastatic disease.[68, 70] In addition, half of small renal masses are detected in patients older than 65 years of age.[68] Surgical management in patients ≥ 75 years is not associated with a better overall survival[71] because those patients died mostly of a competing cause.[69] For those patients, active surveillance may be considered as a treatment option. Active surveillance is defined as 'the initial monitoring of tumours that show clinical progression during follow-up'. Active surveillance should be distinguished from watchful waiting approach that is a less intensive type of follow-up with fewer tests relying more on changes in patient's symptoms to decide if treatment is needed.[72]

EAU guideline recommended proposing active surveillance in the elderly and/or comorbid patients. The advice stems from nine comparative studies showing that active surveillance offers equal oncological outcome at short and intermediate term in selected patients.

Update

The additional search did not yield any additional meta-analysis, systematic review or RCTs.

Conclusion

- Based on limited evidence, active surveillance of small renal mass in older and/or comorbid patients offers satisfactory oncological outcomes and does not affect mortality rate.

Other considerations

Factor	Comment
Balance between clinical benefits and harms	There is evidence that, in older patients, active surveillance is associated with an overall survival comparable to surgical management.
Quality of evidence	No RCT is available. The body of evidence is composed only of comparative studies leading to a low level of evidence.
Costs (resource allocation)	Active surveillance in patients with small renal mass is a cost-effective alternative to immediate cryoablation.[73]

Recommendation	Strength of Recommendation	Level of Evidence
• Active surveillance of small renal masses can be offered in selected groups patients: frail elderly and/or patients with comorbidity.	Weak	Low

3.3.3.2 Ablative therapy

Cryoablation and radiofrequency ablation

There is no long-term follow-up data (safety) available either for laparoscopic and percutaneous cryoablation nor for radiofrequency ablation.

Due to the low quality of the available data, EAU made no recommendation about the use of radiofrequency ablation and cryoablation in renal cancer. In the elderly and/or comorbid patients with small renal masses and limited life expectancy, radiofrequency ablation and cryoablation can be offered. This advice is based on nine comparative studies and 1 case series.

IKNL recommended cryoablation or radiofrequency ablation in patients with tumours <4 cm for whom partial nephrectomy does not seem technically possible, renal-sparing treatment is necessary and/or when the comorbidity of the patient is a risk factor for other surgery. In addition, cryoablation and radiofrequency ablation should only be performed in centres with extensive experience and expertise with the relevant treatment. These recommendations stem from 3 narrative reviews, 1 comparative study and 1 case series.

Update

The additional search yielded one meta-analysis regarding cryoablation (Klatte et al. 2014)[74] and 1 RCT (Guan et al. 2012)[75] comparing microwave ablation versus partial nephrectomy (retrieved from a systematic review of Katsanos et al. 2014).[76]

Klatte et al.[74] performed a meta-analysis of 13 retrospective, non-randomized, observational studies comparing laparoscopic cryoablation with laparoscopic (robot-assisted) partial nephrectomy. Laparoscopic cryoablation procedure had a significant increased risk of local tumour progression (10 studies, RR =9.39, 95%CI 3.83 to 22.99, I^2=0%, p<0.0001) and metastatic progression rate (10 studies, RR =4.68, 95%CI 1.88 to 11.64, I^2=0%, p=0.001) in comparison with laparoscopic (robot-assisted) partial nephrectomy. However, laparoscopic cryoablation was associated with shorter operative time (12 studies, WMD =35.45 min, 95%CI 17.01 to 53.88, I^2=93.1%, p<0.001), lower evaluated blood loss (12 studies, WMD =130.11ml , 95%CI 94.57 to 165.66, I^2=84.8%, p<0.001), length of stay (12 studies, WMD =1.22 days, 95%CI 0.58 to 1.86, I^2=90.8%, p<0.001) and a lower risk of overall complications (12 studies, RR =1.82, 95%CI (1.22 to 2.72), I^2=59.2%, p=0.003), urological complications (10 studies, RR =1.99, 95%CI 1.10 to 3.63, I^2=45.2%, p=0.024) and non-urological complications (10 studies, RR =2.33, 95%CI 1.42 to 3.84, I^2=6.5%, p=0.001).

In order to compare partial nephrectomy surgery (PN) to microwave ablation (MWA), Guan et al. (2012)[75] included 102 patients with a solitary, unilateral, solid renal mass up to 4 cm. Patients were randomly assigned in PN (open (n=19) or laparoscopic (n=35)) or in MWA (open (n=20) or laparoscopic (n=28)). The median follow-up was 32 months (range: 24-54) and 36 months (range: 25-66) respectively for MWA and PN. Median length of stay (in days (range) MWA 15 (13-26) vs. PN 19 (10-47), p=0.7566) and median operative time (in minutes (range) MWA 148 (117-273) vs. PN 154 (60-277), p=0.0955) were similar in both groups. Estimated blood loss (mean ± SD 138.3±69.4 vs PN 465.9 ± 577.1, p=0.0002) and complication rates (MWA 6/48 vs. PN 18/54, p=0.0187) were significantly lower in the MWA group. Two incomplete ablations were detected in the MWA group on 1-month CT scan. A percutaneous re-ablation was performed in these 2 patients and no evidence of disease was found at last follow-up (41 and 50 months, respectively). For patients with pathologically confirmed RCC, 3-year recurrence-free survival rate did not differ significantly between the 2 groups (PN 96.6% (95%CI: 78.0-99.6) vs. MWA 90.4% (95%CI: 65.3-97.6), p=0.4650). Disease-specific survival was 100% in each group. Renal function was assessed by the serum creatinine concentration and the estimated glomerular filtration rate (eGRF). At follow-up, there was no difference in eGFR (mean ± SD ml/min/1.73 m² MWA: 120.6 ± 28.4 vs PN 107.5 ± 53.4, p=0.13) but a significant lower serum creatinine rate was measured in the MWA group (mean ± SD µmol/l MWA 58.9 ± 9.7 vs PN 90.1 ± 29.2, p<0.0001). The authors concluded that MWA yield to equivalent oncologic, surgical and functional outcomes than PN. Nevertheless, there is a need of additional research with multicentre design, longer follow-up and broader inclusion criteria for patients.

Conclusions

- Despite improved perioperative outcomes, laparoscopic cryoablation leads to worse oncological outcomes such as local tumour progression and metastatic progression.
- Microwave ablation leads to equivalent oncologic, surgical and functional outcomes than partial nephrectomy and offers a gain in terms of estimated blood loss and complication rate.

Other considerations

Factor	Comment
Balance between clinical benefits and harms	Benefits offered by cryoablation in terms of perioperative outcomes are attenuated by the increased risk in oncological outcomes (local tumour progression and metastatic progression).
Quality of evidence	The overall level of evidence for the pooling estimation is low because of heterogeneity, lack of RCT, and imprecision.

Recommendation	Strength of Recommendation	Level of Evidence
• Radiofrequency ablation and cryoablation can be a treatment option in a selected group of patients: frail elderly and/or comorbid patients with small renal masses. For other patients groups, partial nephrectomy is recommended.	Weak	Very low

3.3.4 Adjuvant treatments

3.3.4.1 Search results

EAU guideline did not perform a systematic review for adjuvant treatments. Consequently, we performed a systematic review from 2009. EAU guideline and IKNL (having done a comprehensive search until 2009) were used as source of RCTs for evidence published before 2009.

The systematic search yielded four RCTs[77-80] and 5 RCTs were retrieved from EAU guideline.[81-85] IKNL provided 3 additional RCTs.[86-89] In addition, 2 studies were found by handsearching.[90, 91] As a whole, the retrieved evidence was related to adjuvant treatment of nephrectomy. As adjuvant treatment, 1 RCT considered hormones,[91] 2 RCTs used chemotherapy,[80, 90] 4 other RCTs dealt with immunotherapy[79, 82, 87, 88] and 1 RCT studied adoptive immunotherapy.[83] Combination of both chemotherapy and immunotherapy was studied in two RCTs.[77, 81] Finally, vaccine was included in 4 RCTs.[78, 84, 85, 89]

3.3.4.2 Evidence

Radiotherapy

Radiotherapy was studied as adjuvant therapy to nephrectomy in RCC patients in 5 old RCTs.[86, 92-95] We only report on the most recent RCT because radiotherapy has markedly changed over the time. Moreover, the results of Kjaer et al. must also be interpreted with caution as patients included in this RCT were recruited between 1979 and 1984. No recent RCT was found on the topic.

Postoperative radiotherapy in stage II and III renal adenocarcinoma was tested as adjuvant treatment after nephrectomy *en bloc.*[86] Sixty-four patients were randomized to receive radiotherapy in four fractions per week (target: 50 Gy, 1650 reu, 90 TDF± 15% in 20 fractions of 2.5 Gy) or no further treatment. No benefit in relapse rates and in survival for patients with renal adenocarcinoma was observed when postoperative radiotherapy delivered to kidney bed and regional lymph nodes was used in comparison with observation. In addition, a huge complication rate was reported in the radiotherapy group (44%). Among those, five patients died from Rx-induced complications. Protocol violations and differences in Rx technics between the two participating centres were reported.

Hormones

Adjuvant medroxyprogesterone acetate (MPA) after radically resection of a renal cancer was compared to no adjuvant treatment in 120 Italian patients without metastasis.[91] Hormone therapy (500 mg MPA) was administered during 1 year. No statistically significant difference in 5-year survival rate was reported (treatment with MPA: 67.1% vs control: 67.3%). Therefore, the authors did not support adjuvant MPA to radical nephrectomy in non-metastatic renal cancer.

Chemotherapy

UFT is combination of tegafur (1-[2-tetrahydrofuryl]-5-fluorouracil) and 5-fluorouracil (5-FU) and was tested in 66 low-stage RCC patients as adjuvant therapy after transperitoneal radical nephrectomy in comparison with no adjuvant therapy.[90] No effect on recurrence after 5 years and no improvement of the 5-year cancer specific survival was found.

One small size RCT comparing thalidomide and observation in patients who underwent complete resection of locally advanced RCC was performed in 46 patients (Anderson Cancer Center – Texas – USA).[80] Probabilities of recurrence free survival (RFS) at 2-year and 3-year were in favour of observation group (% (SD) observation vs thalidomide 69.3% (9.7) vs 47.8% (10.4) and 69.3% (9.7) vs 28.7% (9.7), respectively). The 2- and 3-year cancer specific survival were similar in the 2 groups (% (SD) observation vs thalidomide 82.4% (8.0) vs 82.6% (7.9) and 75.5% (9.9) vs 76.7% (9.3), respectively). Dose reduction of thalidomide due to adverse events was needed in 62% of the patients. Number of patients discontinuing the thalidomide treatment because troublesome toxicity was not clearly mentioned in the trial. The authors concluded that adjuvant thalidomide therapy did not improve the 2- and 3-year RFS rates or cancer-specific death rate in high-risk RCC that underwent complete resection nephrectomy.

Immunotherapy and adoptive immunotherapy

Cytokines as adjuvant treatment of nephrectomy in RCC were tested in four trials.[79, 82, 87, 88]

Pizzocaro et al. used rIFN-α2b (recombinant interferon alfa-2b) as adjuvant treatment to nephrectomy in 247 non-metastatic RCC patients (Robson stage II and III or T3 N0 M0, T3b N0 M0 or T2/3 N1-3 M0) in comparison with no adjuvant treatment.[88] The authors found no advantage in 5-year

overall survival (HR (95% IC) = 1.040 (0.671-1.613), log-rank test p=0.861) or in 5-year event-free survival (HR (95% IC) = 1.412 (0.927-2.149), log-rank test p=0.107). In addition, a high toxicity rate was found (55.8% of rIFN-α2b patients group).

The role of adjuvant IFN-α after complete resection of locally extensive RCC was studied in 283 patients randomly assigned in natural lymphoblastoid IFN-α (IFN-α-NL) and observation after surgery.[87] No improvement was found in median survival (IFN-α-NL 7.4 years vs obs. 5.1 years, log-rank p=0.09) or in median recurrence-free survival (IFN-α-NL 3.0 years vs obs. 2.2 years, log-rank p=0.33). The authors of this RCT concluded that IFN-α-NL did not provide a benefit for patients with locally or regionally extensive, completely resected RCC.

The third RCT including 69 patients with a median follow-up of 22 months compared high-dose bolus IL-2 and observation after completely resected advanced RCC at high-risk for recurrence.[82] The trial failed to show any significant advantage to postoperative systemic IL-2 regarding 2-3-year disease free survival (DFS) or overall survival (OS). In addition, a large proportion (88%) of patients treated with IL-2 experienced grade 3 or grade 4 toxicities. For this reason, the study was terminated early leading to underpowered statistical analysis.

Hinotsu (2013)[79] found no improvement in progression-free survival (p=0.456, log-rank test) or in OS (p=0.150, log-rank test) after administration of IFN-α to patients with stage II or III RCC for 1-year after radical nephrectomy in comparison to those only observed. However, the peak hazards of progression free survival might be delayed by about 6 months in IFN-α group. Treatment was suspended in broad large proportion of patients (44/50). Among those, 21 stopped the treatment for adverse events (see evidence table 29). This study however was underpowered (n=100) because of the slow recruitment of patients.

Adoptive immunotherapy refers to “the transfer of anti-tumour reactive cells to the tumour-bearing host which will directly or indirectly mediate the regression of the tumour”.[96] Tumour-Infiltrating Lymphocytes (TILs) are a type of white blood cell found in tumours and implicated in the killing of tumour cells. TILs were used in the 90’s by Figlin et al. as adoptive immunotherapy in metastatic RCC patients previously treated with nephrectomy.[83] The authors failed to demonstrate any improvement in response rate or survival when rIL-2 plus CD8+ (TIL) was used in comparison with rIL-2 plus placebo. The RCT was prematurely terminated because of the lack of efficacy. Moreover, 33 out of 72 patients did not received the TIL treatment due to cell processing failure.

Because both study populations and interventions were very heterogeneous we decided not to pool the results.

Immuno-chemotherapy

Atzpodien et al. (2005)[81] and Aitchison et al. (2014), [71] in two separated RCTs, studied triple combination therapy (5-FU, INF-α and IL-2) as adjuvant therapy after nephrectomy compared to observation. Both studies included patients at high risk of recurrence after surgery (203 and 309, respectively for Atzpodien et al. 2005 and Aitchison et al. 2014). The two trials failed to show any statistically significant benefit for the postoperative adjuvant immune-chemotherapy in terms of DFS or OS. Moreover, the treatment is associated with significant toxicity. No pooling of data was performed because the presentation of the results was too different between the two trials.

Vaccines

Active specific immunotherapy (ASI) is a treatment strategy using a vaccine prepared with patient’s tumour cells. The aim of this vaccination is to attempt to boost the host’s immune response against its own tumour.[84] ASI was tested in 120 patients that have previously underwent radical nephrectomy and staging lymphadenectomy.[84] Patients were randomized to ASI treatment or no adjuvant treatment. ASI treatment did not show any advantage in 5-year DFS or 5-year OS despite an increase in the reactivity to autologous tumour.

Adjuvant autologous renal tumour cell vaccine was also tested by Jocham et al.[85] in 379 patients. At 5-year follow-up, the hazard ratio for tumour progression was 1.58 (95% IC 1.05-2.37) in favour of the vaccine (p=0.0204 long-rank test). In subgroup analysis according to the tumour stage, the advantage of vaccine for 5-year progression-free survival was only noted in T3 tumours (5-year PFS: T2 tumour vaccine 81.3% vs control 74.6%, p=0.216, log-rank test, T3 tumour vaccine 67.5% vs control 49.7%, p=0.039, log-rank test). The 5-year progression-free survival was also in favour of vaccine group (77.4% vs 67.8% for vaccine group and no adjuvant therapy

group respectively, p=0.0204). Quality of life assessed by QLQ-C30 was similar in both groups.

Another type of autologous renal tumour cell vaccine was tested in 118 centres in North America and Europe. Therapeutic vaccine was derived from vitespen (HSPPC-96), a heat-shock protein (glycoprotein 96)-peptide complex purified from tumour cell. Seven hundred-twenty-eight patients at high risk of recurrence after nephrectomy for RCC were randomized to receive this vaccine or to be observed without other treatment. The vaccine did not offer any advantage in terms of recurrence-free survival or OS. Three patients discontinued the treatment because of treatment-related adverse events. Main limitations of the trial were a large implication of the sponsor in trial design and outcome assessment, the fact that eligibility criteria were not accurately checked leading to a large number of dropouts (17%).

The attenuated vaccina virus modified vaccina Ankara (MVA) delivers a tumour antigen 5T4 that is expressed, amongst others, in carcinomas of kidney.[78] A RCT including 732 metastatic clear RCC patients tried to compare MVA-5T4 to placebo in combination with either IL-2 or IFN-α or sunitinib as adjuvant treatment after nephrectomy.[78] This trial was prematurely terminated because there was no prospect of demonstrating a significant survival benefit. The intermediate analysis after a median follow-up of 12.9 months did not show any statistical significant difference in OS, progression-free survival, objective response rate between MVA-5T4 and placebo groups.

Targeted therapy

A very recent published trial (ASSURE) tested sorafenib and sunitinib as adjuvant therapy in patients with locally advanced RCC at high risk of recurrence.[97] The authors concluded that neither sorafenib nor sunitinib offers benefits above or beyond placebo.

Conclusions

- Adjuvant therapies after nephrectomy in non-metastatic RCC such as radiotherapy, chemotherapy, immunotherapy (cytokines or vaccine) or immuno-chemotherapy did not show any improvement in disease free or overall survival.
- Significant toxicity was generally associated with these adjuvant treatments.

Other considerations

Factor	Comment
Balance between clinical benefits and harms	The balance is clearly negative because of the absence of benefit and the significant toxicity of adjuvant treatment.
Quality of evidence	The quality of evidence is very low. One study on the role of vaccines is very underpowered.

Targeted therapy as adjuvant treatment is out-of-scope of the current guideline. However, a recent published trial (ASSURE) tested sorafenib and sunitinib as adjuvant therapy in patients with locally advanced RCC at high risk of recurrence.[97] The authors concluded that neither sorafenib nor sunitinib offers benefits above or beyond placebo.

Recommendation	Strength of Recommendation	Level of Evidence
• Adjuvant therapy is not recommended outside clinical trials.	Strong	Very low

3.4 Treatment of local recurrence/ metastases

3.4.1 Cytoreductive surgery

3.4.1.1 Search results

EAU guideline did not perform a systematic review for the cytoreductive surgery. We performed a systematic review from 2009 to retrieve evidence on this topic. EAU guideline and IKNL were used as sources of RCTs for evidence published before 2009. Based on the systematic search, no RCT related to surgery in RCC patients with local recurrence or metastases was found. IKNL guideline provided 2 RCTs.[98, 99] EAU guideline did not provide any additional trials.

The two trials however had immunotherapy as comparison, which is not the recommended standard of care.

3.4.1.2 Evidence

We found two trials with same eligibility criteria, treatments and design.

Flanigan et al.[98] studied whether prior nephrectomy affects survival in metastatic RCC patients treated with IFNα-2b. Therefore, 241 patients with good SWOG performance status (0 or 1) were randomized in 2 treatment groups (radical nephrectomy + IFNα-2b or IFNα-2b alone). This trial showed that nephrectomy followed by IFNα-2b resulted in longer survival than IFNα-2b alone (median survival (95%CI): nephrectomy + IFNα-2b 11.1 (9.2-16.5) vs IFNα-2b alone 8.1 (5.4-9.5)) and 1-year survival probability nephrectomy 49.7% vs IFNα-2b 36.8%, p=0.012). Response rate was similar in both groups. The two groups were not well balanced for performance status. Performance status of 1 was overrepresented in IFNα-2b alone group. However, the imbalance with respect to performance status did not affect the results.

Eighty-five metastatic RCC patients with good WHO performance score (0 or 1) were randomized to radical nephrectomy + IFNα-2b or IFNα-2b alone.[99] No significant difference in response rate were found between the 2 groups. However, patients that underwent nephrectomy prior immunotherapy had longer time to progression (HR (95%CI): 0.60 (0.36 to 0.97), p=0.04) and longer duration of survival than those that received only IFNα-2b (HR (95%CI): 0.54 (0.31 to 0.94), p=0.03). Median survival improved from 7 months in IFNα-2b alone group to 17 months in nephrectomy prior immunotherapy.

These two RCTs were also mentioned in a systematic review dealing with immunotherapy for advanced renal cell cancer[100] and in a combined analysis.[101] Pooling estimation for remission rate did not show any difference between patients who underwent prior nephrectomy and those treated with IFN-α alone [Peto OR (95%CI): 1.45 (0.56 to 3.75), I^2=0.0%, p=0.44].[100] However, the combined analysis presented a lower risk of death in the first year for patients treated with IFN-α combined with nephrectomy than for those without nephrectomy [Peto OR (95%CI): 0.53 (0.34 to 0.83), I^2=0.0%, p=0.006]. [100] The authors concluded than the benefit of nephrectomy is probably larger than the benefit resulting from IFN-α. They also performed a subgroup analysis based on performance status leading that this parameter had greater importance for prognosis than therapy.[100]

Conclusion

- Radical nephrectomy in combination with IFN-α improves the survival at 1 year in patients with mRCC and good performance status.

Other considerations

Factor	Comment
Balance between clinical benefits and harms	There are a proven effect on risk of death and on overall survival but no proven effect on time to progression.
Quality of evidence	There is evidence from two trials of low quality (no allocation concealment) with immunotherapy as comparison group, which is not considered the standard of care anymore. Evidence that cytoreductive treatment is beneficial in the current setting is therefore indirect.

Recommendation	Strength of Recommendation	Level of Evidence
Cytoreductive nephrectomy can be considered in patients with metastatic renal cell carcinoma.	Weak	Low

3.4.2 Local therapy of metastases in mRCC

Authors of EAU guideline performed a systematic review over relevant interventions for local therapy of metastases in mRCC. The interventions taken into consideration were either metastasectomy or various radiotherapy modalities. They found 16 non-randomized comparative studies related to local therapies of RCC-metastases in various organs. The quality of these studies was very low (high risk of bias associated with non-randomization and retrospective design, sample attrition, selective reporting…). Therefore, EAU guideline did not make general recommendation and stated that the decision to resect metastases has to be taken for each site, on a case-to-case basis according to performance status, risk profiles, patient preference and alternative techniques to achieve local control. In addition, the EAU guideline proposed to offer for symptom relief, in individual cases, stereotactic radiotherapy for bone metastases and stereotactic radiosurgery for brain metastases.

Update

The literature search did not yield any additional systematic review, meta-analysis or RCT related to metastasectomy or radiotherapy in adult patients with mRCC.

Conclusions

- Due to the lack of well-designed trial, no recommendation can be made over local therapy of metastases in mRCC.

3.4.3 Systemic treatments

3.4.3.1 Introduction

The systemic treatments such as chemotherapy, immunotherapy, targeted agents or various combinations of these 3 treatments are discussed in this section. Targeted therapy drugs are chemotherapy able to attack specifically cancer cells by acting in the carcinogenesis process.[102] As a result, targeted therapies do less damage to normal cells than usual chemotherapy. Three types of targeted therapies are available: enzyme inhibitors, apoptosis-inducing drugs and angiogenesis inhibitors. Because of their particular mechanism of action, targeted therapies tend to have different (and often less severe) side effects than usual chemotherapy.[102]

EAU guideline[103] no longer considers chemotherapy and immunotherapy as standard systemic treatment for mRCC as it is surpassed by the more powerful targeted therapies. The EAU guideline recommended that

chemotherapy, as monotherapy, should not be considered as effective in patients with mRCC. In addition, the authors stated that monotherapy with IFN-α or high-dose bolus IL-2 should not routinely be recommended as first-line therapy in mRCC. Therefore, evidence related purely to chemotherapy and immunotherapy is only discussed in appendix (see section 7. Additional evidence).

3.4.3.2 Targeted therapy

EAU guideline performed a systematic review (SR) on this topic. However, the material was not retrievable. Therefore, Cancer Care Ontario guideline was used. This guideline, published in 2009, was related to the use of inhibitors of angiogenesis in patients with inoperable locally advanced or metastatic RCC. The authors of the guideline assessed the evidence published between 2009 and 2013 (Cancer Care Ontario guideline update).[104] Therefore we choose to adapt this guideline. During the update, seven SR were identified.[105-111] Only Coppin et al. (2010)[106] is presented in our review because the seven other SRs provided no additional RCTs. From Coppin (2010)[106], 30 publications were identified. Additional 34 papers were found during the updating process of Coppin et al. (2010).[106] Among those, 18 were reported in the Cancer Care Ontario guideline update.[104] Papers related to dose issues were not considered in our review. All these publications together reported 25 RCTs.

Cancer Care Ontario guideline 2009 stated that immunotherapy with or without cytoreductive nephrectomy is no longer the standard of care in patients with inoperable locally advanced or metastatic RCC. They based their advice on evidence of important clinical benefit for agents that inhibit angiogenesis in this patient population. Regarding the tyrosine kinase inhibitors, the authors recommended that:

- Sunitinib is recommended as first-line therapy for appropriate patients with favourable to intermediate-risk disease.
- Sorafenib should be considered as a treatment option in patients who progress following initial immunotherapy.

These recommendations are based on 2 RCTs published as a full text in a peer journal[112, 113] and 1 RCT published as an abstract.[114]

The guideline analysed bevacizumab as monoclonal antibody for renal cancer patients with metastases. Based on 3 RCTs[115-117], they concluded that 'bevacizumab combined with interferon-alpha (IFN-α) reduces the risk of disease progression or death by 35% as first-line therapy in patients with favourable - and intermediate-risk disease'. This benefit appears potentially inferior to the benefit associated with sunitinib, and in light of the associated toxicities of IFN-α therapy, bevacizumab combined with IFN-α was not recommended. Data do not support the use of single-agent bevacizumab, and therefore bevacizumab alone was also not recommended'.

Finally, the guideline addressed the issue of Mammalian Target Of Rapamycin (mTOR) inhibitors. Evidence on temsirolimus and everolimus was retrieved. Based on 1 RCT, the authors recommended temsirolimus as first-line therapy for patients with poor-risk disease.[118] Everolimus was recommended as second- or third-line therapy in patients previously treated with sunitinib, sorafenib, or both (based on Motzer 2008).[119]

The review performed by Coppin (2010) retrieved 16 RCTs related to targeted therapies in RCC patients. These trials are reported in 30 peer reviewed publications (list of publications is available in appendix). The authors concluded that:

- For untreated patients with advanced kidney cancers of the clear-cell subtype
  - o Tyrosine kinase inhibitors

    Compared to IFN-α sc, oral sunitinib caused more frequent major remissions in patients with no prior drug therapy and most with a predicted survival over 12 months. On average, sunitinib was associated with extra 4.6 months of survival. However, sunitinib caused more diarrhoea, high blood pressure, and skin problems than IFN-α whereas IFN-α caused more fatigue.
  - o Monoclonal antibodies

    Oral sunitinib provided similar benefits than bevacizumab IV alternating with IFN-α IV. However, the combined treatment gave more side effects and was less convenient because of the route of administration.

mTOR

- Temsirolimus IV was associated with longer survival and better quality of life than IFN-α in untreated patients with poor predicted survival.
- For patients previously treated with drug therapy

- Following initial IFN therapy

  Compared to placebo, sorafenib improved quality of life and delayed disease growth.

- Following initial targeted therapy with tyrosine kinase inhibitors (sunitinib or sorafenib)

  Compared to placebo, daily oral everolimus delayed cancer growth. No remission or improvement quality of life was observed. Survival seems to be similar but survival interpretation is made difficult because everolimus was latter given to placebo patients.

- For patients with advanced kidney cancers of the non-clear-cell subtypes

  Primary studies regarding tyrosine kinase inhibitors (sunitinib or sorafenib) did not consider non-clear-cell RCC. According one study considering non-clear-cell RCC, temsirolimus may improve survival and progression-free survival in non-clear cell tumours in comparison with interferon.[120]

Update

We give hereafter a short description of the different studies identified in the update. We will then give an overview of the evidence from the different sources for first, second and third line treatment, together with the side effects of the different treatments.

- **Tyrosine kinase**

  SORAFENIB

  - Sorafenib + AMG 386 versus Sorafenib + placebo

    One RCT tested the tolerability and anti-tumour activity of a combination of AMG 386 plus sorafenib with placebo plus sorafenib in 152 previously untreated patients who have clear cell mRCC.[121] AMG 386 is a recombinant peptide Fc fusion that neutralizes the interaction between a receptor (Tie2) and lignad (angiopoietin 1 or angiopoietin 2). Results did not show any advantage in terms of objective response rate or in terms of PFS (HR for AMG + sorafenib versus placebo + sorafenib: 0.88 (95%CI, 0.60 to 1.30; p=0.52)). Serious adverse events (≥ 3 according to the grading using the National Cancer Institute Common Terminology) were observed in 66%, 73% and 86%, respectively in patients group treated with AMG 386 10 mg/kg once weekly or 3 mg/kg once weekly and placebo, respectively. A limitation of the study was the very small sample size due to high discontinuation rates in all arms of the study. Only 19 patients continued the treatment. The most common reasons reported for discontinuation were disease progression and adverse events.

  - Sorafenib versus tivozanib

    Motzer et al. (2013a)[122] compared tivozanib and sorafenib in 517 clear cell mRCC patients. Thirty percent of the included patients were treatment-naïve and 70% received prior treatments as immunotherapy, chemotherapy or hormonal therapy. The authors concluded that tivozanib improved PFS compared with sorafenib (overall PFS HR (95%CI): 0.797 (0.639 to 0.993), p=0.042). During the stratified analysis, the PFS was in favour of tivozanib in treatment-naïve patients, when ECOG Performance Status = 0. No difference in PFS was observed in patients with prior treatment for mRCC, ECOG Performance Status = 1 and when patients were stratified according to MSKCC prognostic group. No differences in objective response rate and overall survival were observed between patients treated with tivozanib and those treated with sorafenib. The proportion of patients with at least one treatment-emergent adverse event was high in both groups (91% in tivozanib arm vs 97% in sorafenib arm) with a different safety profile (hypertension and dysphonia were more common in tivozanib compared with sorafenib and hand-foot syndrome and diarrhoea in sorafenib compared with tivozanib).

  SUNITINIB

  - Sunitib versus pazopanib

    Motzer et al. (2013b)[123] compared pazopanib with sunitinib in 1 110 clear-cell mRCC patients no previously treated with systemic therapy. PFS was not inferior in patients treated with pazopanib compared to those treated with sunitinib [HR (95%CI): 1.05 (0.90 to 1.22)]. Overall response rate was in favour of pazopanib when assessed by independent review committee (pazopanib 31% vs sunitinib 25%, p=0.03). However, the overall survival was similar in

both arms [HR (95%) 0.91 (0.76 to 1.08)]. Safety profile was different between treatment arms (sunitinib provided a higher incidence of fatigue, hand-foot syndrome and thrombocytopenia while pazopanib had a higher incidence of increased levels of alanine aminotransferase). Better quality-of-life was observed in pazopanib patients group than in sunitinib patients group (in 11 of 14 HRQoL domains).

CEDIRANIB

Only one randomized placebo controlled trial in 75 adults with metastatic or recurrent clear cell RCC or adenocarcinoma compared cediranib with placebo.[124] After 12 weeks, mean percentage change from baseline in tumour size was in favour of cediranib (-20%) compared with placebo (+20%, p < 0.0001). Duration of the trial was 12 weeks. After that period, switching to cediranib was allowed leading to caution when interpreting the prolonged PFS in cediranib group [HR=0.45 (95%CI 0.26 to 0.76, p=0.017]. Diarrhoea (74%), hypertension (64%), fatigue (58%) and dysphonia (58%) were most common reported adverse events in cediranib arm.

TIVOZANIB

A discontinued trial compared tivozanib with placebo in inoperable mRCC patients, not treated previously with VEGF pathway-targeted therapy (other systemic treatment were allowed).[125] After 12 weeks, significantly more patients were free of progression with tivozanib compared to those receiving placebo (respectively in 49% vs 21%, p=0.001). PFS was significantly longer in tivozanib arm in comparison with placebo arm (median PFS (95%CI): 10.3 months (8.1 to 21.2) vs 3.3 months (1.8 to 8.0), p=0.01). However, this benefit has to be interpreted with caution since 24/57 patients switched from placebo to tivozanib because of disease progression.

DOVITINIB

Dovitinib was compared with sorafenib in an open-label RCT including 570 clear cell mRCC patients who received one previous VEGF-targeted therapy and one previous mTOR inhibitor.[126] No difference in PFS, OS or Karnofsky deterioration was reported between the two treatment arms. In addition, dovitinib did not provide any benefit in quality-of-life in comparison with sorafenib as third-line targeted treatment.

- **Mammalian target of rapamycin (mTOR)**

TEMSIROLIMUS VERSUS SORAFENIB

Seven hundred and one mRCC patients with progressive disease while receiving first-line sunitinib were randomized to temsirolimus IV or to oral sorafenib.[127] PFS and ORR were not statistically significantly different between the 2 treatment groups. OS was in favour of sunitinib (HR (95%CI): 1.31 (1.05 to 1.63), p=0.01). This advantage was also found in subgroup analyses according to prior nephrectomy, longer duration of prior sunitinib, clear-cell histology, MSKCC intermediate risk, age<65 years, male sex, normal hepatic function, normal baseline lactate dehydrogenase. The authors concluded that temsirolimus did not demonstrate any efficacy advantage compared with sorafenib as second-line therapy after disease progression on sunitinib.

TEMSIROLIMUS + BEVACIZUMAB VERSUS IFN + BEVACIZUMAB

The combination of temsirolimus and bevacizumab was compared with the association of IFN and bevacizumab as first-line therapy in 791 clear cell mRCC patients.[128] Temsirolimus/bevacizumab was not superior to IFN/bevacizumab for PFS (HR (95%CI): 1.1 (0.9 to 1.3), p=0.8) or ORR ($RR_{adjusted}$ (95%CI): 1.0 (0.8 to 1.3), p=1.0) even when stratification by prior nephrectomy, MSKCC prognostic group, age, sex or geographic region. In addition, no benefice was observed in OS (HR (95%CI): 1.0 (0.9 to 1.3), p=0.6) or in quality-of-life (no clinical difference in mean score measured with FKSI-15, FKSI-DRS, EQ-5D, EQ-VAS). The safety profiles are consistent with those observed when agents were used in monotherapy. Hypercholesterolemia, rash, mucosal inflammation, stomatitis, hyperglycaemia and peripheral oedema were significantly (p<0.001) more frequent in temsirolimus/bevacizumab arm while pyrexia, neutropenia and myalgia were significantly (p<0.001) more frequent in IFN/bevacizumab arm.

Overview of evidence

Table 8, Table 9 and Table 10 report the body of evidence according to the first, second and third lines of treatment. When available, acronym of the trial is used to refer to the RCT unless the trial is referred by the first author's name of the primary publication. These tables present the last results published for PFS, OS and ORR. Interim results are therefore not presented. In Appendix 7, we report additional evidence regarding adverse events of targeted therapies (see section 7.3.).

Detailed evidences tables are available in Appendix 5, the review of Coppin et al.[106] or Cancer Care Ontario guideline update[4] according the source of RCT.

- **First-line treatment**

Table 8 presents an overview of main oncological outcomes when targeted therapy are used as first-line treatment.

Table 8 – Overview of progression free survival (PFS), overall survival (OS), overall response rate (ORR) and quality of life (QoL) of targeted therapy in metastatic renal cell carcinoma used as first-line treatment

Study ID	Intervention(s) MSKCC risk score	Comparator(s) MSKCC risk score	Tumour type	Outcomes
1. Targeted therapy vs cytokine				
Escudier 2009a[129]	Sorafenib Low risk: 53.6% Intermediate risk: 45.4% High: 1% Missing: 0%	IFN Low risk: 51.1% Intermediate risk: 47.8% High: 0% Missing: 1.1%	CC mRCC Naïve	**PFS** HR (95%CI)=0.88 (0.61-1.27); p=0.50 **ORR (%)** 5.2 vs 9.7; ns
SUTENT Motzer 2007[113] Cella 2008[130] Castellano 2009[131] Cella 2010[132] Motzer 2009[133] Patil 2012[134] Cella 2014[135]	Sunitinib Low risk: 38% Intermediate risk: 56% High: 6% Missing: 0%	IFN Low risk: 34% Intermediate risk: 59% High: 7% Missing: 0%	CC mRCC Naïve	**PFS** HR (95%CI)=0.54 (0.45-0.64); p<0.001[133] **OS** HR (95%CI)=0.82 (0.67-1.00); p=0.049 (stratified)[133] **ORR (%)** 31 vs 6; p<0.05 **HRQoL** ▪ FKSI-DRS scores: Sunitinib 29.90 vs IFN 27.52; p<0.0001[132] ▪ Subgroup analysis in European population:[131] FKSI-DRS, FKSI, EQ-5D (utility score) FACT-G total score, FACT-G social/family, emotional, functional are in favour of Sunitinib (p<0.05) but no significantly statistically different in FACT-G physical and EQ-VAS **Q-TWiST**[134] ▪ TOX (number of days spent with grade 3 or 4 toxicity): sunitinib 36 vs IFN 9, difference (95%CI): 27 (18-37)

				▪ Twist (number of days spent without symptoms of disease progression or toxicity treatment): sunitinib 317 vs IFN 166, difference (95%CI): 151 (118-180) ▪ REL (mean number of days spent in relapse): sunitinib 269 vs IFN 365, difference (95%CI): -96 (-126–56)
GLOBAL-ARCC Hudes 2007[136] Dutcher 2009[120] Yang 2010[137] Zbrozek 2010[138] Alemao 2011[139] Maroto 2011[140]	Temsirolimus Low risk: 69% Intermediate risk: 31% High: 0% Missing: 0% **or** IFN + Temsirolimus Low risk: 76% Intermediate risk: 24% High: 0% Missing: 0%	IFN alone Low risk: 76% Intermediate risk: 24% High: 0% Missing: 0%	All tumour types Naïve Poor risk	**PFS** ▪ Median progression free survival in months[136] IFN 3.1 (2.2-3.8) Temsirolimus 5.5 (3.9-7.0) IFN + temsirolimus 4.7 (3.9-5.8) Temsirolimus vs IFN; p <0.05 ▪ No result for combination arm[120] Temsirolimus arm, clear cell vs other: 5.5 (CI 3.8-7.1) mo vs 7.0 (CI 3.9-8.9) IFN-a arm, clear-cell vs other: 3.7 (CI 2.5-4.6) mo vs 1.8 (CI 1.6-2.1) mo HR (TEM vs IFN-a) Clear-cell: 0.76 (0.60-0.97) Other: 0.38 (0.23-0.62) **OS** ▪ IFN vs temsirolimus[136] HR (95%CI)= 0.73 (0.58-0.92);p=0.008 IFN vs temsirolimus + IFN HR (95%CI)= 0.96 (0.76-1.20);p=0.70 ▪ No result for combination arm[120] Temsirolimus arm, clear cell vs other: 10.7 (CI 8.5-13.0) mo vs 11.6 (CI 8.9-14.5) mo IFN-a arm, clear-cell vs other: 8.2 (CI 6.6-10.4) mo vs 4.3 (CI 3.2-7.3) mo HR (TEM vs IFN-a) Clear-cell: 0.82 (CI 0.64-1.06) Other: 0.49 (0.29-0.85) ▪ No result for combination arm[139] Overall weighted mean (SD) QAS during PFS: 111.9 (5.3) days in temsirolimus arm, 75.7 (6.3) days IFN-a Difference 36.2 d (p<0.05)

				ORR (%)[136] ▪ Overall ORR IFN 4.8 (1.9-7.8) Temsirolimus 8.6 (4.8-12.4) IFN + temsirolimus 8.1 (4.4-11.8) ▪ Stable ≥ 6 months disease or ORR Temsirolimus 32.1 vs IFN 15.5, p<0.001 IFN + temsirolimus 28.1vs IFN 15.5, p=0.002 **HRQoL** No result for combination arm[137]: Average EQ-5D score significantly higher in TEM vs IFN-a patients: EQ-5D index: 0.10 (p=0.0279) EQ-VAS: 6.61 (p=0.0095) RMME model least-square mean for EQ-5D: 0.590 TEM vs 0.492 IFN-a (p=0.0022) **Q-TWiST** Q-TWiST significantly longer for patients in TEM group vs IFN-a (7.0 quality mo vs 5.6 quality mo, p=0.0015) No significant difference in Q-TWiST between combination and IFNa groups (6.1 vs 5.6 quality mo, p=0.35)
AVOREN Escudier 2007[115] Melichar 2008[141] Escudier 2010[142] Bracarda 2010[143]	Bevacizumab + IFN Low risk: 27% Intermediate risk: 56% High: 9% Missing: 9%	Placebo + IFN Low risk: 29% Intermediate risk: 56% High: 8% Missing: 7%	CC mRCC Naïve	**PFS** HR (95%CI)=0.61 (0.51-0.73); p<0.0001 (stratified) **OS** ▪ HR (95%CI) = 0.86 (0.72-1.04); p=0.13 ▪ Subgroup analysis of patients receiving post-protocol sorafenib, sunitinib or both (Bracarda 2011) HR (95%CI) = 0.80 (0.56-1.13); **ORR (%)** 31 vs 13; p<0.05
CALGB 90206 Rini 2004[144]	Bevacizumab + IFN Low risk: 26%	IFN Low risk: 26%	CC mRCC naïve	**PFS** HR (95%CI)=0.71 (0.61-.83); p<0.0001 **OS**

Rini 2008[145] Rini 2010[146]	Intermediate risk: 64% High: 10% Missing: 0%	Intermediate risk: 64% High: 10% Missing: 0%		HR (95%CI)=0.86 (0.73-1.01); p=0.069 **ORR (%)** 25.5 vs 13.1; p<0.05
2. Targeted therapy vs other targeted therapy				
Motzer 2013b[123]	Pazopanib Low risk: 27% Intermediate risk: 58% High: 12% Missing: 3%	Sunitinib Low risk: 27% Intermediate risk: 59% High: 9% Missing: 4%	CC mRCC Naïve	**PFS** HR (95%CI): 1.05 (0.90-1.22) **OS** HR (95%) 0.91 (0.76-1.08) **ORR** Pazopanib 31% vs sunitinib 25%, p=0.03 **HRQoL** *Difference in mean change from baseline score with pazopanib vs sunitinib* ▪ FACIT-F: 2.32, p< 0.001 ▪ FKSI-19 (total score): 1.41, p=0.02 ▪ CTSQ p < 0.001 excepted in dimension related to expectations of therapy (no difference between arms) ▪ SQLQ p≤0.01 in all dimension
Hutson 2013a[147-149]	Axitinib Low risk: 49% Intermediate risk: 44% High: 4% Missing: 4%	Sorafenib Low risk: 55% Intermediate risk: 42% High: 2% Missing: 1%	CC mRCC Naïve	**PFS** HR (95%CI) 0.77 (0.56-1.05), one-sided p=0.038 **ORR** RR (95%CI) 2.21 (1.31-3.75), one-sided p=0.0006 **QoL** FKSI-15, FKSI-DRS, EQ-5D similar in both groups
3. Combination of targeted therapy and cytokine vs targeted therapy alone				
Jonasch 2010[150]	Sorafenib + IFN Low risk: 52.5% Intermediate risk: 47.5% High: 0% Missing: 0%	Sorafenib Low risk: 50% Intermediate risk: 45% High: 5% Missing: 0%	CC mRCC Naïve	**PFS** HR (95%CI)=0.85 (0.51-1.42); p=0.53 **OS** univariate: HR (95%CI)=1.94 (0.84-4.52); p=0.0764 multivariate: HR (95%CI)= 2.172 (0.92-5.12); p= 0.1219

ROSORC Procopio 2011[148] Procopio 2013[149]	Sorafenib + IL-2 Low risk: 55% Intermediate risk: 41% High: 5% Missing: 0%	Sorafenib Low risk: 55% Intermediate risk: 39% High: 6% Missing: 0%	All tumour types Naïve	**PFS** ▪ Median PFS Sorafenib + IL-2: 33 weeks vs Sorafenib: 30 weeks (p=0.109) ▪ 1-year PFS (95%CI) Sorafenib + IL-2: 30% (20.2-44.6) vs Sorafenib: 22.5% (21.5-45.1) ▪ 2-year PFS Sorafenib + IL-2: 31.1% (14.1-35.9) vs Sorafenib: 11.3 (5.3-23.7) **OS** 5-year OS: Sorafenib + IL-2: 26.3% (CI 15.9-43.5) vs Sorafenib: 23.1% (CI 13.2-40.5)
4. Combination of targeted therapies vs targeted therapy alone				
Bukowski 2007a[151]	Bevacizumab + Erlotinib Low risk: 31% Intermediate risk: 69% High: 0% Missing: 0%	Bevacizumab + placebo Low risk: 36% Intermediate risk: 64% High: 0% Missing: 0%	CC mRCC Naïve	**PFS** 9.9 vs 8.5 months; p=0.58 **OS** 20 months vs not reached; p= 0.16
TORAVA Negrier 2011[152]	Bevacizumab + temsirolimus Low risk: 32% Intermediate risk: 53% High: 14% Missing: 0%	Sunitinib Low risk: 31% Intermediate risk: 59% High: 10% Missing: 0%	All tumour types Naïve	**PFS** At 48 weeks Bevacizumab + temsirolimus: 29.5% (CI 20.0-39.1) Sunitinib: 35.7% (CI 21.2-50.2)
5. Combination of targeted therapy and angiopoietin/Tie2 inhibitor vs targeted therapy alone				
Rini 2012[121]	Sorafenib + AMG 386 arm A: 10 mg/kg qw, arm B: 3 mg/kg qw Low risk: 40% Intermediate risk: 60% High: 0% Missing: 0%	Sorafenib + placebo arm C Low risk: 37% Intermediate risk: 61% High: 2% Missing: 0%	CC mRCC Naïve	**PFS** (months (95%CI)) ▪ Arm A 9.0 (5.4-15.0), arm B 9.0 (5.4-14.4), arm C7.2 (5.4-12.8) ▪ HR for arm A and B combined versus arm C: 0.88 (95%CI, 0.60-1.30; p= 0.52) **ORR** % (95%CI) ▪ Arm A 38 (25-53), arm B 37 (24-52), arm C 25 (14-40)

				▪ Comparison with placebo: arm A (-6.9 to 30.8), arm B (-7.5 to 30.0)
6. Combination of targeted therapies vs combination of targeted therapy and cytokine				
TORAVA Negrier 2011[152]	Bevacizumab + temsirolimus Low risk: 32% Intermediate risk: 53% High: 14% Missing: 0%	Bevacizumab + IFN Low risk: 39% Intermediate risk: 44% High: 17% Missing: 0%	All tumour types Naïve	**PFS** at 48 weeks Bevacizumab + temsirolimus: 29.5% (CI 20.0-39.1) IFN: 61.0% (CI 46.0-75.9)
INTORACT Rini 2014a[128]	Temsirolimus + Bevacizumab Low risk: 31% Intermediate risk: 58% High: 12% Missing: 0%	IFN + Bevacizumab Low risk: 29% Intermediate risk: 61% High: 10% Missing: 0%	CC mRCC Naïve	**PFS** HR (95%CI): 1.1 (0.9 – 1.3), p=0.8 **ORR** RR $_{adjusted}$ (95%CI): 1.0 (0.8-1.3), p=1.0 **OS** HR (95%CI): 1.0 (0.9 – 1.3), p=0.6 **QoL** ▪ FKSI-15, FKSI-DRS, not clinically meaningful difference ▪ EQ-5D, EQ-VAS, ns

CC= clear cell mRCC, PFS: progression free survival, Ps performance status, QoL Quality of life, HRQoL health related QoL, EORTC QLQ-C30 Quality of Life Question-for Cancer Patient developed by European Organisation for Research and Treatment of Cancer, FKSI-DRS FACT Kidney Symptom Index Disease Related Symptoms, mRCC metastatic renal cell carcinoma, CTSQ Cancer Therapy Satisfaction Questionnaire , SQLQ Supplementary Quality of Life Questionnaire, FACIT-F Functional Assessment of Chronic Illness Therapy, OS Overall survival, ORR Overall response rate, Q-Twist Quality adjusted Time Without Symptoms or Toxicity, QAS quality adjusted survival, CBR clinical benefit rate

**subgroup Japanese patients not reported*

$subgroup French patients not reported

Safety and side effects:

Appendix 7.3 presents a comprehensive reporting of adverse events retrieved from the literature. Safety profile is discussed on basis of common adverse events reported in the literature. For the purpose of this report, common adverse events are defined as adverse events observed at least in 10% of the patients.

Targeted therapies may induce a large range of common adverse events. Therefore, prevention and early recognition of common adverse events are crucial to avoid dose reduction.[153] As a matter of fact, the discontinuation rate due to adverse events varies across studies from 4 to 42%. Detailed results are provided in appendix 7.3 (section 7.3.4)

- Tyrosine kinase inhibitors (TIK)

  TIK present similar safety profile. However, slight differences appear according to the molecule considered.

  SOREFANIB causes constitutional symptoms (fatigue, weight loss, decreased appetite), asthenia, hypertension, increased creatine kinase, peripheral oedema, gastrointestinal adverse events (anorexia, diarrhoea, vomiting, nausea, constipation), pain (including back pain and pain in the extremity) and cutaneous adverse events (alopecia, dry skin, hand-foot syndrome, mucositis, rash, stomatitis).

  SUNITINIB produces constitutional symptoms (fatigue, weight loss), increased uric acid, hypermagnesia, gastrointestinal adverse events (diarrhoea, constipation), hematologic adverse events (leukopenia, thrombocytopenia, anaemia, neutropenia, increased ALT, increased AST, increased lipase, increased amylase, increased creatinine, lymphocytopenia, increased alkaline phosphatase, increased LDH, increased blood thyrotropin, hypoalbuminemia, hypoglycaemia), yellow skin and dysgeusia.

  PAZOPANIB causes fatigue, peripheral oedema, hypermagnesia, gastrointestinal adverse events (constipation, dyspepsia), pain in limb, hyperthyroïdism, hematological adverse events (leukopenia, thrombocytopenia, anaemia, neutropenia, increased ALT, increased AST, increased creatinine, lymphocytopenia, increased alkaline phosphatase, increased bilirubin, increased LDH, increased blood thyrotropin, hypoalbuminemia, hypoglycaemia), cutaneous adverse events (alopecia, hand-foot syndrom, mucosal inflamation, rash, stomatitis, hair colour change) and dysgeusia.

  AXITINIB induces constitutional symptoms (fatigue, decreased appetite, dysphonia), asthenia, hypertension, gastrointestinal adverse events (diarrhoea, nausea), pain (including back pain), hyperthyroidism and cutaneous adverse events (palmar-plantar erythrodysesthesia and rash).

  Discontinuation rate due to adverse events with TIK ranges from 4 to 24% (for detailed results see appendix 7.3 – section 7.3.4).

- Monoclonal antibody

  BEVACIZUMAB induces constitutional symptoms (fatigue, weight loss, pyrexia), asthenia, hypertension, dyspnoea, proteinuria, gastrointestinal adverse events (anorexia, diarrhoea, nausea), headache, hematological adverse events (neutropenia, anaemia, thrombocytopenia), influenza like-illness, depression and bleeding.

  Discontinuation rates due to adverse events with bevacizumab range from 8 to 32% (for detailed results see appendix 7.3 – section 7.3.4).

- mTOR

  TEMSIROLIMUS causes constitutional symptoms (fatigue, weight loss, pyrexia, decreased appetite), asthenia, hypertension, dyspnoea, cough, proteinuria, peripheral oedema, gastrointestinal adverse events (anorexia, nausea, hyperlipidaemia), cutaneous adverse events (stomatitis, mucosal inflammation, and rash) and infection.

  Discontinuation rate due to adverse events with temsirolimus ranges from 7 to 42% (for detailed results see appendix 7.3 – section 7.3.4).

Conclusions

- Chemotherapy and immunotherapy are inferior to targeted therapy in mRCC.
- Sunitinib (TKI) improves PFS and OS in comparison with IFN in CC mRCC patients.
- Sorafenib (TKI) does not improve PFS and ORR in comparison with IFN in low or intermediate risk CC mRCC patients.
- Temsirolimus (mTOR) improves PFS, OS and ORR in comparison with IFN in low or intermediate risk mRCC patients whatever the tumour type.
- The association of bevacizumab (monoclonal antibody) with IFN improves PFS and ORR in CC mRCC in comparison with IFN alone. However, there is no proven improvement in OS.
- Pazopanib does not improve PFS or OS in CC mRCC patients in comparison with Sunitinib. However, pazopanib improves ORR in CC mRCC patients.
- Axitinib does not improve PFS but improves ORR in comparison with Sorafenib in CC mRCC.
- Addition of cytokines (IFN or IL-2) to Sorafenib does not improve PFS or OS in comparison with Sorafenib alone in mRCC whatever the tumour type.
- Bevacizumab (monoclonal antibody) combined with Erlotinib (epidermal growth factor inhibitor) does not improve PFS in comparison to Bevacizumab alone in low to intermediate risk CC mRCC.
- Bevacizumab (monoclonal antibody) combined with Temsirolimus (mTOR) does not improve PFS in comparison with Sunitinib as mono therapy in mRCC whatever the level of risk and the tumour type.
- AMG 386 (Angiopoietin/Tie2 inhibitor) does not improve PFS or ORR when combined with sorafenib in comparison with sorafenib alone in CC mRCC.
- PFS, OS, ORR or QoL are not statistically significantly different when combination of targeted therapies (Temsirolimus + Bevacizumab) is compared with combination of monoclonal antibody (Bevacizumab) and IFN in mRCC whatever the level of risk and the tumour type.
- PFS and response rate are improved in CC mRCC patients treated with pazopanib in comparison to those treated with placebo. However, HRQoL did not improve.
- Tivozanib improves PFS in comparison with sorafenib in a selected patient group with CC mRCC (ECOG PS=0 and favourable MSKCC prognosis).

Other considerations

Factor	Comment
Balance between clinical benefits and harms	Targeted therapies have a proven benefit in term of overall progression free survival, but with numerous side effects.
Quality of evidence	There is high-level evidence that shows the superiority of targeted therapies compared to immunotherapy. In addition, chemotherapy is inferior to immunotherapy. There is moderate evidence based on one study showing that sunitinib is superior to IFN in terms of progression free survival and overall survival. One study comparing pazopanib with sunitinib was downgraded for imprecision because confidence interval did not exclude a clinical important inferiority. There is moderate level of evidence that temsirolimus is superior to IFN based on one study of high quality. There is a high level of evidence that combination of bevacizumab + IFN is superior to IFN alone. However, a publication of Thompson et al. (2009) showed that sunitinib is superior to the combination of bevacizumab + IFN in terms of PFS.[111] Therefore, we downgraded to moderate level of evidence.
Costs (resource allocation)	In the comparison with sunitinib versus bevacizumab plus IFN, sunitinib presents lower cost than bevacizumab plus IFN. [111]

Recommendations	Strength of Recommendation	Level of Evidence
• Cytotoxic agents are not recommended in patients with clear cell metastatic renal cell carcinoma.	Strong	High
• Monotherapy with IFN-α or high-dose bolus IL-2 is not routinely be recommended as first-line therapy in metastatic renal cell carcinoma but can be used in selected patients.	Strong	High
• Sunitinib or Pazopanib is recommended as first-line therapy for clear cell metastatic renal celll carcinoma.	Strong	Low
• Bevacizumab + IFN-α is recommended as first-line therapy for metastatic renal cell carcinoma in favourable-risk and intermediate-risk clear-cell renal cell carcinoma. *Note : the conditions for a reimbursement by the health insurance are:* *1) at least one grade 3 or 4 adverse event due to sunitinib;* *2) the treatment with sunitinib was stopped for at least 4 weeks;* *3) patient has no history of arterial thromboembolic disease or uncontrolled hypertension with standard treatment.* *In addition, the reimbursement rule requires that treatment must be stopped in case of tumour progression assessed by CT-Scan or MRI after 8 weeks of treatment.*	Strong	Moderate
• Temsirolimus is recommended as a first-line treatment in poor-risk renal cell carcinoma patients.	Strong	Moderate

- **Second-line treatment**

Table 9 presents an overview of main oncological outcomes when targeted therapy is used as second-line treatment.

Table 9 – Overview of progression free survival (PFS), overall survival (OS), overall response rate (ORR), clinical benefit rate (CBR) and quality of life (QoL) of targeted therapy in metastatic renal cell carcinoma used as second-line treatment

Study ID	Intervention(s) MSKCC risk score	Comparator(s) MSKCC risk score	Tumour type Previous treatment	Outcomes
1. Targeted therapy vs placebo				
Ratain 2006[154]	Sorafenib Low risk: 41% Intermediate risk: 56% High: 0% Missing: 3%	Placebo Low risk: 42% Intermediate risk: 45% High: 9% Missing: 3%	All tumour types Naïve 16% Systemic anticancer therapy, IL-2, IFN, radiotherapy, nephrectomy, non-diagnostic surgery	**PFS** 5.5 vs 1.4 months; p=0.0087
TARGET Bukowki 2007b[155] Escudier 2007b[112] Eisen 2008[156] Escudier 2009b[157] Antoun 2010[158] Negrier 2010[159] Hutson 2010[160]	Sorafenib Low risk: 52% Intermediate risk: 48% High: 0% Missing: 0%	Placebo Low risk: 50% Intermediate risk: 49% High: <1% Missing: 0%	CC mRCC cytokine or naïve	**PFS** ▪ HR (95%) 0.78 (0.62-0.97, p=0.029)[157] ▪ Elderly patients (age ≥ 70 years and <70 years)[156] ≥ 70 years: HR (95%CI) 0.43 (0.26-0.69) < 70 years: HR (95%CI) 0.55 (0.47-0.66) ▪ Sorafenib > 1 year[160] Time in months 10.9 (9.3-12.8) ▪ Subgroup analysis of patients who received prior cytokine therapy vs cytokine naïve[159] *Prior cytokine therapy*: HR 0.54, CI 0.45-0.64 *No prior cytokine therapy*: *:* HR (95%CI) 0.48 (0.32-0.83) **CBR** ▪ Elderly patients (age ≥ 70 years and <70 years)[156] ≥ 70 years: sorafenib 84.3% vs placebo 62.2% < 70 years: sorafenib 98.6% vs placebo 53.8% ▪ Subgroup analysis of patients who received prior cytokine therapy vs cytokine naïve[159] Prior cytokine therapy:

				sorafenib 83.0% vs placebo 54.3% No prior cytokine therapy: sorafenib 85.7% vs placebo 56.0% **HRQoL**[156] FKSI-15 time to deterioration ▪ ≥ 70 years: HR (95%CI) 0.55 (0.43-1.03) ▪ < 70 years: HR (95%CI) 0.69 (0.59-0.81)
VEG105192 / extension study VEG107769 Sternberg 2010[161] Cella 2012[162] Sternberg 2013[163]	Pazopanib Low risk: 39% Intermediate risk: 55% High: 3% Missing: 3%	Placebo Low risk: 39% Intermediate risk: 53% High: 3% Missing: 4%	CC mRCC Naïve 54% Prior cytokine 46%	**PFS**[161] ▪ All patients HR (95%) =0.46 (0.34-0.62) ▪ First-line treatment: HR (95%) =0.40 (0.27-0.6) ▪ Second-line treatment HR (95%) =0.54 (0.35-0.84) **OS**[163] ▪ ITT analysis HR (95%) =0.91 (0.71-1.16) ▪ Inverse probability of censor weighting HR (95%) =0.50 (0.31-0.76) ▪ Rank-preserving structural failure time HR (95%) =0.43 (0.21-1.39) **Response rate (95%CI)**[161] ▪ All patients Pazopanib 30% (25.1-35.6) vs placebo 3% (0.5-6.4) ▪ First-line treatment: Pazopanib 32% (24.3-38.9) vs placebo 4% (0-8.1) ▪ Second-line treatment Pazopanib 29% (21.2-36.5) vs placebo 3% (0-7.1) **HRQoL**[162] *HR (95%CI) for time to 20% HRQoL deterioration* ▪ EORTC QLQ-C30 global health status/QoL scale All patients 0.77 (0.57-1.03), p= 0.0817 First-line treatment

				0.75 (0.50-1.13), p=0.1698 Second-line treatment 0.75 (0.48-1.18), p=0.2141 ▪ EQ-5D utility index All patients 1.02 (0.73-1.42), p= 0.9279 First-line treatment 1.08 (0.70-1.68), p=0.7274 Second-line treatment 0.91 (0.55-1.53), p=0.7238 ▪ EQ-5D VAS All patients 0.70 (0.51-0.98), p= 0.0350 First-line treatment 0.72 (0.50-1.13), p=0.1037 Second-line treatment 0.66 (0.48-1.18), p=0.1399
Mulders 2012[124]	Cediranib Low risk: 49% Intermediate risk: 49% High: 2% Missing: 0%	Placebo Low risk: 33% Intermediate risk: 56% High: 11% Missing: 0%	All tumour types No VEGF-targeted therapy Only one prior chemotherapy or immune/hormonal therapy	**% change from baseline in tumour size** Cediranib -20% versus placebo +20%, p<0.0001 **Response rate**: ▪ Partial response Cediranib 34% versus placebo 0% ▪ Stable disease Cediranib 47% versus placebo 22% **PFS** HR (95%CI): 0.45 (0.26-0.76)
Nosov 2012[125]	Tivozanib Entire treated population Low risk: 28% Intermediate risk: 60% High: 10% Missing: 0%	Placebo	Inoperable mRCC Systemic treatment but no VEGF pathway-targeted therapy	**PFS**: ▪ Proportion of patients without progression after 12 weeks (95%CI): tivozanib 49% (36-63) vs placebo 21% (11-34), p=0.001 ▪ Median PFS in months (95%CI): tivozanib 10.3 (8.1-21.2) vs placebo 3.3 (1.8-8.0), p=0.01
Yang 2003[117] Elaraj 2004[164]	Bevacizumab 10 mg/kg MSKCC not reported	Bevacizumab 3 mg/kg MSKCC not reported or	CC mRCC II-2	**PFS** *Time to progression of disease* ▪ Bevacizumab 10 mg/kg vs placebo HR 2.55, p<0.001 ▪ Bevacizumab 3 mg/kg vs placebo

		Placebo MSKCC not reported		HR 1.96 p=0.053 *Probability of being progression-free at 4 months* Bevacizumab 10 mg/kg 64%, Bevacizumab 3 mg/kg 39%, and placebo 20% *Probability of being progression-free at 8 months* Bevacizumab 10 mg/kg 30%, Bevacizumab 3 mg/kg 14%, and placebo 5% **OS** p>0.20 for all comparisons **ORR** Partial response rate (% (95%CI)): ▪ Bevacizumab 10 mg/kg: 10% (2.9 - 24.2) ▪ Bevacizumab 3 mg/kg no response ▪ Placebo no response
RECORD-1 Motzer 2008[119] Motzer 2010[165] White 2010[166] Beaumont 2011[167] Tsukamoto 2011[168]* Bracarda 2012[169] Calvo 2012[170] Porta 2012[171] Blesius 2013[172$]	Everolimus Low risk: 29% Intermediate risk: 56% High: 15% Missing: 0%	Placebo Low risk: 28% Intermediate risk: 57% High: 15% Missing: 0%	CC mRCC VEGF-pathway therapy (sunitinib, sorafenib or both), IFN, IL-2, chemotherapy or bevacizumab	**PFS** ▪ HR (95%) 0.33 (0.25-0.43)[165] ▪ Subgroup analysis of 2nd-line vs 3rd line[170] 2nd-line: HR (95%) 0.32 (0.19-0.54) 3rd-line: HR (95%) 0.32 (0.09-0.55) ▪ Subgroup analysis of patients who discontinued previous VEGF-TKI therapy due to AE[169] *All*: HR (95%CI) 0.32 (0.13-0.77) *Intolerance to previous sunitinib:* HR (95%CI) 0.28 (0.07-1.18) *Intolerance to previous sorafenib:* HR (95%CI) 0.29 (0.09-0.91) ▪ Elderly patients (age ≥ 65 years and ≥ 70 years)[171] ≥ 65 years: HR (95%CI) 0.33 (0.21-0.51) ≥ 70 years: HR (95%CI) 0.19 (0.09-0.37) **OS** ▪ HR (95%) 0.87 (0.65-1.15)[165] ▪ Elderly patients (age ≥ 65 years and ≥ 70 years)[171] ≥ 65 years: HR (95%CI) 1.07 (0.69-1.67) ≥ 70 years: HR (95%CI) 0.85 (0.47-1.55) **HRQoL**[167]

				▪ EORTC QLQ_30 Physical functioning Mean difference (SE) -3.0 (2.48), p= 0.229 ▪ EORTC QLQ_30 Global QoL Mean difference (SE) -3.1 (2.48) p=0.210
2. Targeted therapy vs other target therapy				
AXIS Rini 2011[173] Cella 2013[174] Motzer 2013c[175] Ueda 2013[176]* Rini 2014b [177]	Axitinib Low risk: 28% Intermediate risk: 37% High: 33% Missing: 2%	Sorafenib Low risk: 28% Intermediate risk: 36% High: 33% Missing: 3%	CC mRCC One previous systemic first line regimen with a sunitinib, bevacizumab plus IFN-α, temsirolimus, or cytokine	**PFS** HR (95%CI): 0.66 (0.55-0.78) in favour of axitinib[175] **OS** HR (95%) 0.97 (0.80-1.17)[175] **QoL** FKSI-15, FKSI-DRS, EQ-5D, EQ-VAS no statistical difference[174]
TIVO-1 Motzer 2013a[122]	Tivozanib Low risk: 27% Intermediate risk: 67% High: 7% Missing: 0%	Sorafenib Low risk: 34% Intermediate risk: 62% High: 4% Missing: 0%	CC mRCC 30% naïve 70% immunotherapy, chemotherapy or hormonal therapy	**PFS** ▪ Overall PFS (months): HR (95%CI): 0.797 (0.639-0.993), p=0.042 ▪ Stratified PFS by prior systemic therapy ▫ No prior treatment HR (95%CI): 0.756 (0.580-0.985), p=0.037 ▫ Prior systemic treatment for mRCC HR (95%CI): 0.877 (0.587-1.309), p=0.520 ▪ Stratified PFS by ECOG PS ▫ ECOG PS=0 HR (95%CI): 0.617 (0.442-0.860), p=0.004 ▫ ECOG PS=1 HR (95%CI): 0.920 (0.680-1.245), p=0.588 ▪ Stratified PFS by MSKCC prognosis group ▫ Favourable HR (95%CI): 0.590 (0.378-0.921), p=0.018 ▫ Intermediate HR (95%CI): 0.786 (0.601-1.028), p=0.076 ▫ Poor HR (95%CI): 1.361 (0.546-3.393), p=0.504 **OS** ▪ HR (95%CI) 1.245 (0.954-1.624), p=0.105

				ORR (% (95%CI)) ▪ Tivozanib 33.1% (27.4-39.2) vs sorafenib 23.3% (18.3-29.0), p=0.014 **HRQoL:** ▪ No difference between baseline level and 12 months of treatment in both arms
Hutson 2014[127]	Temsirolimus Low risk: 19% Intermediate risk: 69% High: 12% Missing: 0%	Sorafenib Low risk: 17% Intermediate risk: 70% High: 13% Missing: 0%	All tumour types first-line sunitinib	**PFS** HR (95%CI) 0.87 (0.71-1.07), p=0.19 **ORR** Temsirolimus 8% vs sorafenib 8% **OS** ▪ Stratified HR (95%CI) 1.31 (1.05-1.63) in favour of sorafenib ▪ Median OS (95%CI): Temsirolimus 12.3months (10.1-14.8) vs sorafenib 16.6 months (13.6-18.7)
3. Targeted therapy vs other hormones				
Ravaud 2008[178]	Lapatinib Low risk: 41% Intermediate risk: 31% High: 28% Missing: 0%	Hormones Low risk: 37% Intermediate risk: 37% High: 26% Missing: 0%	All tumour types Cytokine	**PFS** HR (95%CI)=0.94 (0.75-1.18); p=0.60 **OS** HR (95%CI)=0.88 (.69-1.12); p=0.29

CC= clear cell mRCC, PFS: progression free survival, Ps performance status, QoL Quality of life, HRQoL health related QoL, EORTC QLQ-C30 Quality of Life Question-for Cancer Patient developed by European Organisation for Research and Treatment of Cancer, FKSI-DRS FACT Kidney Symptom Index Disease Related Symptoms, mRCC metastatic renal cell carcinoma, CTSQ Cancer Therapy Satisfaction Questionnaire , SQLQ Supplementary Quality of Life Questionnaire, FACIT-F Functional Assessment of Chronic Illness Therapy, OS Overall survival, ORR Overall response rate, Q-Twist Quality adjusted Time Without Symptoms or Toxicity, QAS quality adjusted survival, CBR clinical benefit rate

**subgroup Japanese patients not reported*

$subgroup French patients not reported

Safety and side effects:

Appendix 7.3 presents a comprehensive reporting of adverse events retrieved from the literature. Safety profile is discussed on basis of common adverse events reported in the literature. The discontinuation rate due to adverse events varies across studies from 4 to 15%. Detailed results are provided in Appendix 7.3 (section 7.3.4).

- Tyrosine kinase

  SOREFANIB causes constitutional symptoms (fatigue, weight loss, dysphonia), asthenia, hypertension, dyspnoea, cough, gastrointestinal adverse events (diarrhoea, increased lipase, increased amylase, increased ALT, increased AST, nausea, anorexia, constipation), pain (including headache, abdominal pain, arthralgia, myalgia), hematological adverse events (low haemoglobin, hyperglycaemia, hyperuricemia, hypophosphatemia), skeletal loss, dermatological adverse events (alopecia, hand-foot syndrome, stomatitis, dry skin, rash, pruritus, flushing), allergies, haemorrhage and hepatic adverse events.

  PAZOPANIB induces constitutional symptoms (fatigue, weight loss, dysphonia), asthenia, hypertension, gastrointestinal adverse events (diarrhoea, nausea, anorexia, constipation), headache and hematological adverse events (hyperglycaemia, hypophosphatemia, increased ALT, increased AST, hyperbilirubinemia, hypocalcaemia, hyponatremia, hypokalaemia).

  AXITINIB produces increased ALT, increased AST constitutional symptoms (fatigue, weight loss, dysphonia), asthenia, hypertension, gastrointestinal adverse events (diarrhoea, nausea), hematologic adverse events (neutropenia, thrombocytopenia, leukopenia, lymphopenia, anaemia), arthralgia, dermatological adverse events (hand-foot syndrome, stomatitis, dry skin, mucosal inflammation, rash, flushing), and dysgeusia.

  TIVOZANIB engenders constitutional symptoms (fatigue, weight loss, dysphonia), asthenia, hypertension, dyspnoea, hypophosphatemia, proteinuria, gastrointestinal adverse events (diarrhoea, increased lipase, increased amylase, increased ALT, increased AST), headache, and hematological adverse events (neutropenia, thrombocytopenia, low haemoglobin) and dermatological adverse events (palmar-plantar erythrodysesthesia, stomatitis).

  CEDIRANIB engenders fatigue, dysphonia, hypertension, diarrhoea, nausea, constipation, headache, and stomatitis.

  The discontinuation rate due to adverse events of TKI varies across study from 4 to 14%. Detailed results are provided in Appendix 7.3 (section 7.3.4).

- Monoclonal antibody

  Common adverse event reported for BEVACIZUMAB is proteinuria.

  EVEROLIMUS causes constitutional symptoms (fatigue, infection), asthenia, cough, peripheral oedema, stomatitis, diarrhoea, nausea, and hematologic adverse events (haemoglobin decreased, lymphocytes decreased, cholesterol increased, triglycerides increased, glucose increased, creatinine increased, phosphate decreased) and rash.

  The discontinuation rate due to adverse events of everolimus is 10%.[119]

- mTOR

  TEMSIROLIMUS induces constitutional symptoms (fatigue, decreased appetite, pyrexia, weight loss), asthenia, cough, dyspnoea, peripheral oedema, gastrointestinal adverse events (diarrhoea, nausea, constipation, vomiting), hematologic adverse events (anaemia, hypertriglyceridemia, hypercholesterolemia), dermatological adverse events (alopecia, mucosal inflammation, pruritus, stomatitis, rash, epistaxis).

  The discontinuation rate due to adverse events of everolimus is 15%.[127]

Conclusions

- Sorafenib improves PFS and CBR in comparison with placebo in low or intermediate risk mRCC patients. This advantage is also observed in sub-population such as elderly, prior cytokine treated patients. In addition, HRQoL is better rated by CC mRCC patients treated with sorafenib than by those treated with placebo whatever the patients' age (< 70 years vs ≥ 70 years).
- After cytokine treatment or in naïve patients, PFS, response rate are improved in CC mRCC patients treated with pazopanib in comparison to those treated with placebo. However, OS and HRQoL are not improved with this TKI.
- After one prior chemotherapy or immune/hormonal therapy, Cediranib improves PFS, partial response rate, stable disease rate or tumour size in mRCC patients in comparison with placebo.
- After systemic treatment other than VEGF pathway targeted therapy, Tivozanib improves PFS in mRCC patients in comparison with placebo.
- After immunotherapy, chemotherapy or hormonal therapy, improvement by Tivozanib in PFS in mRCC patients in comparison with sorafenib is not statistically significant. Only pooled results (naïve and previous therapy) were reported for OS, ORR and HRQoL.
- After IL-2, Bevacizumab (10 mg/kg or 3 mg/kg) improves PFS and OS in CC mRCC patients in comparison with placebo.
- After VEGF-pathway therapy (sunitinib, sorafenib or both), IFN, IL-2, chemotherapy or bevacizumab, Everolimus improves PFS in mRCC patients in comparison with placebo. This advantage is maintained in elderly and in patients previously intolerant to sorafenib. However, it is not the case for patients previously intolerant to sunitinib. In addition, Everolimus does not improve OS in CC mRCC patients.
- After previous treatment with sunitinib, bevacizumab plus IFN-α, temsirolimus or cytokine, Axitinib improved PFS in comparison with Sorafenib in CC mRCC but no statistically significant difference in OS and QoL is observed.
- After sunitinib, Temsirolimus does not improve PFS, OS or ORR in mRCC patients in comparison with sorafenib.
- After cytokine treatment, there are no statistically significant difference in PFS and OS in patients treated with lapatinib or hormones.

Other considerations

Factor	Comment
Balance between clinical benefits and harms	Targeted therapies have a proven benefit in term of overall progression free survival. However, numerous side effects are reported.
Quality of evidence	There are 2 studies showing superiority of sorafenib in comparison with placebo. The results were not pooled because of difference in the presentation of results on survival. One study comparing pazopanib with placebo showed benefit in terms of PFS and response rate. However, benefit in OS did not reach statistical significance. Therefore, we downgraded the level of evidence to low level of evidence. One study comparing cediranib with placebo showed benefit in terms of PFS and response rate. However, benefit in OS was not reported. One study comparing tivosanib with placebo showed benefit in terms of PFS and response rate. However, benefit in OS was not reported. One study comparing everolimus with placebo showed benefit in terms of PFS. However, benefit in OS did not reach statistical significance. Therefore, we downgraded the level of evidence to low level of evidence. One study comparing axitinib with sorafenib showed benefit in terms of PFS. However, benefit in OS did not reach statistical significance. Therefore, we downgraded the level of evidence to low level of evidence. The patient population is a major source of indirectness, on the one hand, they are partly a mix of naïve and patients on immunotherapy. Moreover, an important part of the first line therapies the patients underwent are not recommended anymore.
Costs (resource allocation)	In the comparison with sunitinib versus bevacizumab plus IFN, sunitinib presents lower cost than bevacizumab plus IFN. [111] Details on reimbursement rules of health insurance for axinitib and for the combination of bevacizumab + IFN-α are provided in Appendix 10. Because Cediranib and tivozanib are not yet approved for the treatment of RCC neither by FDA nor by EMA, no recommendation is provided for these 2 molecules.

Recommendations	Strength of Recommendation	Level of Evidence
• Sorafenib can be considered as second-line treatment in clear cell metastatic renal cell carcinoma.	Strong	High
• Pazopanib, sunitinib or sorafenib can be considered in metastatic renal cell carcinoma patients previously treated with cytokines *(IFN-α, IL-2)*.	Strong	Low
• Everolimus can be considered in metastatic renal cell carcinoma patients previously treated with Vascular endothelial growth factor (VEGF)-pathway targeted therapy *(i.e. bevacizumab, sunitib, sorafenib,…)* or cytokines *(IFN-α, IL-2)*.	Strong	Low
• Axitinib is recommended in metastatic renal cell carcinoma patients previously treated with VEGF-pathway targeted therapy or cytokines. *Note: Axitinib is reimbursed after a failure of first line treatment with TKI or cytokine.*	Strong	Low

- **Third-line treatment**

Table 10 presents an overview of main oncological outcomes when targeted therapy is used as third-line treatment.

Table 10 – Overview of progression free survival (PFS) and overall survival (OS) of targeted therapy in metastatic renal cell carcinoma used as third-line treatment

Study ID	Intervention(s) MSKCC risk score	Comparator(s) MSKCC risk score	Tumour type Previous treatment	Outcomes
Targeted therapy vs targeted therapy				
Motzer 2014[126]	Dovitinib Low risk: 20% Intermediate risk: 58% High: 22% Missing: 0%	Sorafenib Low risk: 21% Intermediate risk: 57% High: 23% Missing: 0%	CC mRCC one VEGF-targeted therapy + one mTOR inhibitor	**PFS** HR (95%CI) 0.86 (0.72-1.04), p=0.063 **OS** HR (95%CI) 0.96 (0.75-1.22) **Median time to definitive worsening of Karnofsky PS** HR (95%CI) 1.12 (0.87-1.45) **Definitive deterioration by 10% of QoL score** ▪ of the EORTC QLQ-C30 HR (95%CI) 1.08 (0.86-1.36) ▪ of the FKSI-DRS HR (95%CI) 1.20 (0.91-1.58)

Safety and side effects:

Appendix 7.3 presents a comprehensive reporting of adverse events retrieved from the literature. Safety profile is discussed on basis of common adverse events reported in the literature. Safety profiles are very similar between the two TKI tested in the only one trial for the third-line treatment.[126]

- Tyrosine kinase

  SORAFENIB engenders constitutional symptoms (fatigue, reduced appetite, pyrexia, dysphonia), asthenia, hypertension, dyspnoea, cough, gastrointestinal adverse events (diarrhoea, nausea, vomiting, constipation), pain (including abdominal pain, back pain, pain in extremity), hematologic adverse events (anaemia, lymphopenia, leukopenia, thrombocytopenia, increased AST, increased ALT) and dermatologic adverse events (rash, alopecia, palmar-plantar erythrodysesthesia, pruritus, stomatitis). The discontinuation rate due to adverse events of sorafenib is 10%.[126]

  DOVITINIB causes constitutional symptoms (fatigue, reduced appetite, pyrexia, dysphonia, and dizziness), asthenia, hypertension, dyspnoea, cough, peripheral oedema, gastrointestinal adverse events (diarrhoea, nausea, vomiting, constipation, dyspepsia), pain (including abdominal pain, myalgia, back pain, pain in extremity), and hematologic adverse events (hypertriglyceridemia, anaemia, lymphopenia, leukopenia, thrombocytopenia, neutropenia, increased AST, increased ALT), dermatologic adverse events (rash, alopecia, palmar-plantar erythrodysesthesia, stomatitis) and dysgeusia. The discontinuation rate due to adverse events of dovitinib is 15%.[126]

Conclusions

- After treatment including VEGF-pathway therapy (sunitinib, sorafenib or both), IFN, IL-2, chemotherapy or bevacizumab, Everolimus improves PFS in mRCC patients in comparison with placebo.
- After treatment with VEGF-targeted therapy and another treatment with mTOR inhibitor, there are no statistically significant differences in PFS, OS, QoL or in performance status in patients treated with Dovitinib in comparison with those treated with Sorafenib.

Other considerations

Factor	Comment
Balance between clinical benefits and harms	One study comparing everolimus with placebo showed benefit in terms of PFS. However, benefit in OS did not reach statistical significance. Therefore, we downgraded the level of evidence to low level of evidence. One study comparing dovitinib with sorafenib showed benefit in terms of PFS. However, benefit in OS did not reach statistical significance. Therefore, we downgraded the level of evidence to low level of evidence.
Quality of evidence	We did find a study that showed benefit compared to placebo for Dovitinib.
Costs (resource allocation)	In the comparison with sunitinib versus bevacizumab plus IFN, sunitinib presents lower cost than bevacizumab plus IFN. [111] Dovitinib is not approved the treatment of RCC neither by FDA nor by EMA. Therefore, no recommendation on dovitinib is provided.

Recommendation	Strength of Recommendation	Level of Evidence
• Everolimus or sorafenib can be considered in third-line therapy.	Weak	Very low

3.5 Palliative care

Based on seven comparative studies, EAU concluded that embolization can be a beneficial palliative approach in patients unfit for surgery and suffering from massive haematuria or flank pain. IKNL recommended embolization for the palliative treatment of massive haematuria and marked local pain in patients with inoperable or metastatic renal cell carcinoma, and for patients with poor physical condition. Their recommendations are based on four case series.

Update

The additional search did not yield any additional meta-analysis, systematic review or RCTs.

Conclusions

- Before routine nephrectomy, there is no benefit in performing tumour embolization. However, embolization can control symptoms as gross haematuria or pain in patients who are unfit for surgery or patients with painful bone or paravertebral metastases.

Additional information regarding the overall cancer population can be found in KCE reports (Supportive treatment for cancer – Part 3: Treatment of pain: most common practices)[179] and KCE reports 115B (Organisation of palliative care in Belgium).[180]

Other considerations

Factor	Comment
Balance between clinical benefits and harms	The use of embolization must be limited to palliative patient to control symptoms such as gross haematuria or pain.
Quality of evidence	Low to very low overall level of evidence supported the use of embolization because only comparative studies and case series are available.

Recommendation	Strength of Recommendation	Level of Evidence
• Embolization can be considered for palliative approach in inoperable patients or patients with metastatic renal cell carcinoma who suffer from severe local pain or massive haematuria.	Weak	Low

3.6 Follow-up

The EAU guideline put forward a number of recommendations concerning follow-up of renal cancer. Their recommendations are not based however on a systematic search of the literature.

The AUA guideline on the contrary was based on an extensive and well documented literature search. Authors classified their guideline statements into options, expert opinion statements (based on no evidence but purely on expert opinion, standard of care (based on high level evidence) and recommendations (based on low level evidence). We decided to only retain the standard of care and recommendations, as the other statements are often not very guiding nor clear. Contrary to the EAU that gave a general recommendation whose follow-up should depend on the type of treatment, the AUA formulated specific recommendations separately for follow-up after surgery, after ablation and follow-up for surveillance without treatment. We took over this structure for our recommendations. The evidence was considered weak for all but one statement.

The IKNL guideline did not put forward very specific recommendations on this issue.

3.6.1 Patients with acute neurological signs

The AUA put forward as standard of care that patients with a history of a renal neoplasm presenting with acute neurological signs or symptoms must undergo **prompt** neurologic cross-sectional CT or MRI scanning of the head or spine based on localization of symptomatology.

This recommendation is based on a high diagnostic accuracy of neurologic cross-sectional (CT or MRI) imaging to rule in or rule out metastases of the brain and/or spine, in addition to a high prevalence of underlying management-altering pathology in patients with these symptoms, including but not limited to metastatic disease.

3.6.2 Follow-up after surgery

Both EAU and AUA guidelines stated that there is no proof that intensified follow-up for recurrence and metastases after surgery improves survival. All supporting evidence is considered to be weak.

3.6.2.1 Risk classification

The EAU guideline recommended the use of risk classification systems, but did not review the literature concerning risk classification systems. The AUA guideline recognized the value of risk classification systems, but considered it did not gain sufficient general acceptance, and based the recommendations on the TNM stage (low risk patients: pT1, N0, Nx; moderate to high risk patients pT2-4N0 Nx or any stage N+). We did a review described in point 3.2.2.2 where we showed that a number of the risk classification systems were externally validated but it is not clear that performance is better than that of mere staging.

3.6.2.2 Low risk patients

Neither AUA nor EAU are specific on the intensity or type of follow-up that is recommended for low risk patients.

The AUA recommended that patients with a history of low risk (pT1, N0, Nx) renal cell carcinoma undergo yearly chest x-ray (CXR) to assess for pulmonary metastases for three years and only as clinically indicated beyond that time period. This is however based on very weak evidence, the consideration that CT may give a large number of false positive and require unnecessary additional diagnostic workup.

3.6.2.3 Moderate to high risk patients

The AUA recommended that moderate to high risk patients undergo baseline chest and abdominal scan (CT or MRI) within three to six months following surgery with continued imaging (US, Chest X-Ray, CT or MRI) every six months for at least three years and annually thereafter to year five. This recommendation is largely based on the large recurrence rate in this group, not on estimations of the diagnostic accuracy.

The AUA also recommended site-specific imaging as warranted by clinical symptoms suggestive of recurrence or metastatic spread.

The EAU recommended regular (yearly) follow-up with CT or MRI, they do not see a role for US nor for chest X-ray.

3.6.3 Follow-up after active surveillance

The AUA recommended that patients undergo cross-sectional abdominal scanning (CT or MRI) within six months of active surveillance initiation to establish a growth rate. The AUA further recommended continued imaging (US, CT or MRI) at least annually thereafter. This is based on a systematic review showing that tumours have a linear growth pattern. They argued to balance the higher accuracy of CT/MRI against the risk for radiation or contrast damage. Once a tumour is established with CT/MRI, one study found that US was able to monitor tumour size with similar accuracy. Average tumour size in the study was 4.5 cm though, which may limit the validity of these results.

The AUA recommended that patients on active surveillance with biopsy proven renal cell carcinoma or a tumour with oncocytic features undergo an annual chest X-ray to assess for pulmonary metastases. The choice for chest X-ray is motivated by the fact that the available literature on tumours followed by active surveillance reveal a low metastatic rate (1-2%) during the first few years of surveillance.

Neither the EAU nor the IKNL provided specific recommendations for the follow-up with active surveillance.

3.6.4 Follow-up after ablation

The AUA recommended that patients undergo cross-sectional scanning (CT or MRI) with and without intravenous (IV) contrast unless otherwise contraindicated at three and six months following ablative therapy to assess treatment success. This should be followed by annual abdominal scans (CT or MRI) thereafter for five years. This recommendation is based on evidence from a meta-analysis reporting that thermal ablative techniques are associated with an increased risk of local recurrence compared to extirpative surgery, based on a 5% to 10% failure rate of ablative therapy, which may be underestimated given the lack of pretreatment histological confirmation in most studies, and the 10% to 30% incidence of benign histology in renal masses under 3 cm in surgical series.

The AUA recommended against further radiologic scanning in patients who underwent an ablative procedure with pathological confirmation of benign histology at or before treatment and who have radiographic confirmation of treatment success and no evidence of treatment related complications requiring further imaging. This recommendation is based on the 10% to 30% incidence of benign histology in renal masses mentioned above and the consideration that, given the low biological potential of benign renal masses, routine follow-up scanning after the six month post-procedural mark, other that to confirm treatment success or to monitor complications, should be avoided.

Neither the EAU nor the IKNL provided specific recommendations for the follow-up after ablation.

Conclusions

- There is no information on the impact of follow-up on patient related outcomes.
- Evidence mainly consists of recurrence rates in cohorts of patients.
- Recommendations are largely consensus based.

Other considerations

Factor	Comment
Balance between clinical benefits and harms	Potential harm of CT or MRI should be balanced against the uncertain benefit of intensive follow up.
Quality of evidence	There is no evidence on the impact of follow-up schemes on patient relevant outcomes. Evidence is mainly based on descriptions of cohorts of patients, and gives only an idea of recurrence rates and diagnostic yield. Recommendations are therefore based on a combination of weak evidence and expert consensus. The GDG considered the recommendation of the AUA 'in case of low risk MRI and CT can be used infrequently' as too vague, they want to be more specific. No routine follow-up by imaging is recommended. The GDG asked to mention stage and negative margin in the recommendation (introduce pT1,N0,Nx;R0).
Costs (resource allocation)	The GDG preferred to add also a recommendation to limit the indications for follow-up, as the GDG considered that overuse is a problem in Belgium.

Recommendations
• For low-risk disease (pT1, N0, Nx, M0; R0,) no routine imaging follow up is recommended.
• Moderate to high risk patients should undergo baseline chest and abdominal scanning (CT or MRI) within three to six months following surgery with follow-up imaging (CT or MRI) every six months for at least three years and annually thereafter to year five.
• Patients under active surveillance should undergo cross-sectional abdominal scanning (CT or MRI) within six months of active surveillance initiation to establish a growth rate. Follow-up imaging (US, CT or MRI) at least annually thereafter is recommended.
• After ablative therapy, patients should undergo cross-sectional scanning (CT or MRI) with and without intravenous contrast unless contraindicated at three and six months to assess treatment success. This should be followed by annual abdominal scans (CT or MRI) thereafter for five years.

Best Practice
Patients with a history of a renal neoplasm presenting with acute neurological signs or symptoms must undergo **prompt** (preferably) MRI or CT scanning of the head or spine based on localization of symptomatology.

4 IMPLEMENTATION AND UPDATING OF THE GUIDELINE

4.1 Implementation

Clinical guidelines provide a tool for care providers to consult at different stages of the patient management pathway: screening, diagnosis, treatment and follow-up. KCE formulates recommendations addressed to specific audiences (clinicians, decision-makers, sickness funds, NIHDI, professional organizations, hospital managers,...). KCE is not involved in the decision making process itself, nor in the execution of the decisions.

The implementation of this guideline will be facilitated by the College of Oncology and the professional associations involved in this guideline. The scientific material of this guideline is intended to be disseminated by scientific and professional organisations. They can transform this material into attractive and user-friendly tools tailored to caregivers groups. They will also play a key role by a dissemination that makes use of diverse channels such as websites or sessions of continuing education.

The stakeholders group indicated that MRI is not always available within reasonable time and it is sometimes replaced by CT. This is a comment for the following best practice point: 'Patients with a history of a renal neoplasm presenting with acute neurological signs or symptoms must undergo **prompt** (preferably) MRI or CT scanning of the head or spine based on localization of symptomatology'.

4.2 Monitoring the quality of care

This guideline could be considered as a starting point to develop quality improvement programs that target all caregivers concerned.

It can be used as a tool to support health policies to improve the quality of care, e.g. through the support of actions to increase caregivers' awareness and to improve their practice, or through the development (or revision) of sets of process and outcome quality indicators.

KCE previously recommended to set up an integrative quality system in oncology, covering the development and implementation of clinical practice guidelines, the monitoring of the quality of care with quality indicators, feedback to health care providers and organizations and targeted actions to improve the quality if needed.

Accordingly, supplementing this guideline with an appropriate set of quality indicators would provide an opportunity to systematically assess the quality of renal cancer care delivered in Belgium. However, while quality indicator sets covering the diagnostic and therapeutic options have been developed for other cancer types, this is as yet not the case for renal cancer.

4.3 Guideline update

In view of the rapidly evolving evidence, this guideline should be updated every 5 years. If, in the meantime, important new evidence would become available, this should be taken into consideration.

REFERENCES

1. Ljungberg B, Bensalah K, Canfield S, Dabestani S, Hofmann F, Hora M, et al. EAU Guidelines on Renal Cell Carcinoma: 2014 Update. Eur Urol. 2015.
2. Shea BJ, Hamel C, Wells GA, Bouter LM, Kristjansson E, Grimshaw J, et al. AMSTAR is a reliable and valid measurement tool to assess the methodological quality of systematic reviews. J Clin Epidemiol. 2009;62(10):1013-20.
3. Whiting P, Rutjes AW, Reitsma JB, Bossuyt PM, Kleijnen J. The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. BMC Med Res Methodol. 2003;3:25.
4. Higgins JPT, Altman DG. Assessing risk of bias in included studies. In: Higgins JPT, Green S, editors. Cochrane handbook for systematic reviews of interventions: Wiley 2008. p. 187-241.
5. Balshem H, Helfand M, Schunemann HJ, Oxman AD, Kunz R, Brozek J, et al. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol. 2011;64(4):401-6.
6. Balshem H HM, Schunemann HJ, Oxman AD, Kunz R, Brozek J, et GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol. 2011;64(4):401-6.
7. Guyatt G, Oxman AD, Sultan S, Brozek J, Glasziou P, Alonso-Coello P, et al. GRADE guidelines: 11. Making an overall rating of confidence in effect estimates for a single outcome and for all outcomes. J Clin Epidemiol. 2013;66(2):151-7.
8. Andrews JC SH, Oxman AD, Pottie K, Meerpohl JJ, Coello PA, et al. GRADE guidelines: 15. Going from evidence to recommendation-determinants of a recommendation's direction and strength. J Clin Epidemiol. 2013;66 (7):726-35.
9. Andrews J, Guyatt G, Oxman AD, Alderson P, Dahm P, Falck-Ytter Y, et al. GRADE guidelines: 15. Going from evidence to recommendations: the significance and presentation of recommendations. J Clin Epidemiol. 2013.
10. Schunemann HJ OA, Brozek J, Glasziou P, Bossuyt P, Chang S, et al. GRADE: assessing the quality of evidence for diagnostic recommendations. Evid Based Med. 2008;13(6):162-3.

11. IKNL. Niercelcarcinoom. 2010.
12. Donat SM, Diaz M, Bishoff JT, Coleman JA, Dahm P, Derweesh IH, et al. Follow-up for Clinically Localized Renal Neoplasms: AUA Guideline. J Urol. 2013;190(2):407-16.
13. Wang H.-Y, Ding H.-J, Chen J.-H, Chao C.-H, Lu Y.-Y, Lin W.-Y, et al. Meta-analysis of the diagnostic performance of 18F FDG-PET and PET/CT in renal cell carcinoma. Cancer Imaging. 2012;12(3):464-74.
14. Park JW, Jo MK, Lee HM. Significance of 18F-fluorodeoxyglucose positron-emission tomography/computed tomography for the postoperative surveillance of advanced renal cell carcinoma. BJU Int. 2009;103(5):615-9.
15. Kumar R, Shandal V, Shamim SA, Jeph S, Singh H, Malhotra A. Role of FDG PET-CT in recurrent renal cell carcinoma. Nucl Med Commun. 2010;31(10):844-50.
16. Bertagna F, Motta F, Bertoli M, Bosio G, Fisogni S, Tardanico R, et al. Role of F18-FDG-PET/CT in restaging patients affected by renal carcinoma. Nucl Med Rev Cent East Eur. 2013;16(1):3-8.
17. Fuccio C, Ceci F, Castellucci P, Spinapolice EG, Palumbo R, D'Ambrosio D, et al. Restaging clear cell renal carcinoma with 18F-FDG PET/CT. Clin Nucl Med. 2014;39(6):e320-4.
18. Mishra A.K, Sharma P, Jain S, Bal C.S, Malhotra A, Kumar R. Role of 18F-FDG PET-CT for detecting recurrence in post therapy patients of renal cell carcinoma. Eur. J. Nucl. Med. Mol. Imaging. 2012;39:S188.
19. Reitsma JB, Glas AS, Rutjes AWS, Scholten RJPM, Bossuyt PM, Zwinderman AH. Bivariate analysis of sensitivity and specificity produces informative summary measures in diagnostic reviews. J Clin Epidemiol. 2005;58(10):982-90.
20. Rutter CM, Gatsonis CA. A hierarchical regression approach to meta-analysis of diagnostic test accuracy evaluations. Stat Med. 2001;20(19):2865-84.
21. Funakoshi T, Lee C.-H, Hsieh J.J. A systematic review of predictive and prognostic biomarkers for VEGF-targeted therapy in renal cell carcinoma. Cancer Treat. Rev. 2014;40(4):533-47.
22. Hayes DF, Bast RC, Desch CE, Fritsche H, Jr., Kemeny NE, Jessup JM, et al. Tumor marker utility grading system: a framework to evaluate clinical utility of tumor markers. J Natl Cancer Inst. 1996;88(20):1456-66.
23. Simon RM, Paik S, Hayes DF. Use of archived specimens in evaluation of prognostic and predictive biomarkers. J Natl Cancer Inst. 2009;101(21):1446-52.
24. Sun M, Shariat SF, Cheng C, Ficarra V, Murai M, Oudard S, et al. Prognostic factors and predictive models in renal cell carcinoma: a contemporary review. Eur Urol. 2011;60(4):644-61.
25. Heng DY, Xie W, Regan MM, Harshman LC, Bjarnason GA, Vaishampayan UN, et al. External validation and comparison with other models of the International Metastatic Renal-Cell Carcinoma Database Consortium prognostic model: a population-based study. Lancet Oncol. 2013;14(2):141-8.
26. Kwon WA, Cho IC, Yu A, Nam BH, Joung JY, Seo HK, et al. Validation of the MSKCC and Heng risk criteria models for predicting survival in patients with metastatic renal cell carcinoma treated with sunitinib. Ann Surg Oncol. 2013;20(13):4397-404.
27. Yu C, Kattan M.W, Hutson T.E, Hudes G.R, Yuan J, Valota O, et al. External validation of a sunitinib prognostic nomogram in patients (pts) with metastatic renal cell carcinoma (mRCC). J. Clin. Oncol. 2012;30(15).
28. Karakiewicz P, Sun M, Sneller V, Escudier B. Use of a nomogram to quantify overall survival (OS) benefit in patients with metastatic renal cell carcinoma (mRCC) receiving bevacizumab (BEV) with interferon (IFN) versus IFN alone. J. Clin. Oncol. 2010;28(15).
29. Karakiewicz PI, Sun M, Bellmunt J, Sneller V, Escudier B. Prediction of progression-free survival rates after bevacizumab plus interferon versus interferon alone in patients with metastatic renal cell carcinoma: comparison of a nomogram to the Motzer criteria. Eur Urol. 2011;60(1):48-56.
30. Tan MH, Li H, Choong CV, Chia KS, Toh CK, Tang T, et al. The Karakiewicz nomogram is the most useful clinical predictor for survival outcomes in patients with localized renal cell carcinoma. Cancer. 2011;117(23):5314-24.

31. Zastrow S, Brookman-May S, Von Bar I, Jurk S, Novotny V, Wirth M. Decision curve analysis and external validation of the postoperative Karakiewicz nomogram for the current TNM classification based on a large single-centre study cohort. Eur. Urol. Suppl. 2014;13(1):e316.
32. Gontero P, Sun M, Antonelli A, Bertini R, Carini M, Carmignani G, et al. External validation of the preoperative Karakiewicz nomogram in a large multicentre series of patients with renal cell carcinoma. World J Urol. 2013;31(5):1285-90.
33. Cindolo L, Chiodini P, Brookman-May S, De Cobelli O, May M, Squillacciotti S, et al. Assessing the accuracy and generalizability of the preoperative and postoperative Karakiewicz nomograms for renal cell carcinoma: results from a multicentre European and US study. BJU Int. 2013;112(5):578-84.
34. Suzuki K, Nishiyama T, Hara N, Akazawa K, Takahashi K. Kattan postoperative nomogram for renal cell carcinoma: predictive accuracy in a Japanese population. Int J Urol. 2011;18(3):194-9.
35. Santiago M.C, Sanchez C, Palacin A.M, Golmayo E, Fernandez C, Garcia A, et al. Validation of prognostic models for nonmetastatic renal cell carcinoma after nephrectomy in a Mediterranean Caucasian population. J. Urol. 2011;185(4):e219.
36. Santiago M.D.C, Sanchez C, Olivares J.A, Rodriguez I, Fernandez C, Garcia A, et al. Comparison of predictive accuracy of prognostic models for nonmetastatic renal cell carcinoma after nephrectomy in a Spanish population. Eur. Urol. Suppl. 2011;10(2):137.
37. MacLennan S, Imamura M, Lapitan MC, Omar MI, Lam TB, Hilvano-Cabungcal AM, et al. Systematic review of oncological outcomes following surgical management of localised renal cancer. Eur Urol. 2012;61(5):972-93.
38. Zini L PP, Jeldres C, et al. A population-based comparison of survival after nephrectomy vs nonsurgical management for small renal masses. BJU Int. 2009;103:899-904.
39. MacLennan S, Imamura M, Lapitan MC, Omar MI, Lam TB, Hilvano-Cabungcal AM, et al. Systematic review of perioperative and quality-of-life outcomes following surgical management of localised renal cancer. Eur Urol. 2012;62(6):1097-117.
40. Van Poppel H DPL, AlbrechtW, et al. A prospective, randomised EORTC intergroup phase 3 study comparing the oncologic outcome of elective nephron-sparing surgery and radical nephrectomy for low-stage renal cell carcinoma. Eur Urol. 2011;59:543-52.
41. Yu HY CB, Zhang XJ, et al. A comparative study of nephrectomy and radical nephrectomy for renal cell carcinoma [in Chinese]. Zhonghua Yi Xue Za Zhi. 2010;90:1120-2.
42. Kim S, Thompson RH, Boorjian S, Weight C, Shippee N, Chow G, et al. Comparative effectiveness of partial and radical nephrectomy for localized renal tumors on survival and renal function: A systematic review and meta-analysis. J. Urol. 2012;187(4):e679.
43. Scosyrev E, Messing EM, Sylvester R, Campbell S, Van Poppel H. Renal function after nephron-sparing surgery versus radical nephrectomy: Results from EORTC randomized trial 30904. Eur. Urol. 2014;65(2):372-7.
44. Campbell SC. Re: A prospective, randomized EORTC intergroup phase 3 study comparing the oncologic outcome of elective nephron-sparing surgery and radical nephrectomy for low-stage renal cell carcinoma. Eur. Urol. 2012;62(3):564-5.
45. Ganesamoni R, Mavuduru R, Agarwal MM. Re: Hendrik Van Poppel, Luigi da Pozzo, Walter Albrecht, et al. A prospective, randomised EORTC intergroup phase 3 study comparing the oncologic outcome of elective nephron-sparing surgery and radical nephrectomy for low-stage renal cell carcinoma. Eur Urol 2011;59:543-52. Eur. Urol. 2011;60(2):e9.
46. Kluth LA, Xylinas E, Shariat SF. Re: A prospective, randomised EORTC intergroup phase 3 study comparing the oncologic outcome of elective nephron-sparing surgery and radical nephrectomy for low-stage renal cell carcinoma. Eur. Urol. 2013;63(2):399-400.
47. Taneja SS. A prospective, randomised EORTC intergroup phase 3 study comparing the oncologic outcome of elective nephron-sparing surgery and radical nephrectomy for low-stage renal cell carcinoma. Journal of urology. 2011;185(5):1637-8.
48. Tan HJ, Norton EC, Ye Z, Hafez KS, Gore JL, Miller DC. Long-term survival following partial vs radical nephrectomy among older

patients with early-stage kidney cancer. JAMA. 2012;307(15):1629-35.

49. Daugherty M, Bratslavsky G. Compared with radical nephrectomy, nephron-sparing surgery offers a long-term survival advantage in patients between the ages of 20 and 44 years with renal cell carcinomas (<4 cm): an analysis of the SEER database. UROL. ONCOL. 2014;32(5):549-54.
50. Roos FC, Steffens S, Junker K, Janssen M, Becker F, Wegener G, et al. Survival advantage of partial over radical nephrectomy in patients presenting with localized renal cell carcinoma. BMC Cancer. 2014;14(372).
51. Becker F, Siemer S, Humke U, Hack M, Ziegler M, Stockle M. Elective nephron sparing surgery should become standard treatment for small unilateral renal cell carcinoma: Long-term survival data of 216 patients. Eur Urol. 2006;49(2):308-13.
52. Stewart SB, Thompson RH, Psutka SP, Cheville JC, Lohse CM, Boorjian SA, et al. Evaluation of the National Comprehensive Cancer Network and American Urological Association renal cell carcinoma surveillance guidelines. J Clin Oncol. 2014;32(36):4059-65.
53. Capitanio U, Terrone C, Antonelli A, Minervini A, Volpe A, Furlan M, et al. Nephron-sparing techniques independently decrease the risk of cardiovascular events relative to radical nephrectomy in patients with a T1a-T1b renal mass and normal preoperative renal function. Eur. Urol. 2015;67(4):683-9.
54. Peng B ZJ-H, Xu D-F, Ren J-Z. Retroperitoneal laparoscopic nephrectomy and open nephrectomy for radical treatment of renal cell carcinoma: A comparison of clinical outcomes. Academic Journal of Second Military Medical University. 2006;27:1167-9.
55. Gratzke C SM, Bayrle F, et al. Quality of life and perioperative outcomes after retroperitoneoscopic radical nephrectomy (RN), open RN and nephron-sparing surgery in patients with renal cell carcinoma. BJU Int. 2009 104(4):470-5.
56. Hemal AK KA. A prospective comparison of laparoscopic and robotic radical nephrectomy for T1-2N0M0 renal cell carcinoma. World J Urol. 2009;27(1):89-94.
57. Brewer K OMR, Hayn M, et al. Perioperative and renal function outcomes of minimally invasive partial nephrectomy for T1b and T2a kidney tumors. J Endourol 2012 26(3):244-8.
58. Sprenkle PC PN, Ghoneim T, et al. Comparison of open and minimally invasive partial nephrectomy for renal tumors 4-7 centimeters. Eur Urol. 2012 61(3):593-9.
59. Desai MM SB, Matin SF, et al. Prospective randomized comparison of transperitoneal vs. retroperitoneal laparoscopic radical nephrectomy. J Urol. 2005;173(1):38-41.
60. Nambirajan T JS, Al-Zahrani H et al. Prospective, randomized controlled study: transperitoneal laparoscopic vs. retroperitoneoscopic radical nephrectomy. Urology 2004;65(4):919-24.
61. Nadler RB LS, Clemens JQ et al. A prospective study of laparoscopic radical nephrectomy for T1 tumors--is transperitoneal, retroperitoneal or hand assisted the best approach? J Urol 2006;175(4):1230-3.
62. Froghi S, Ahmed K, Khan MS, Dasgupta P, Challacombe B. Evaluation of robotic and laparoscopic partial nephrectomy for small renal tumours (T1a). BJU Int. 2013;112(4):E322-E33.
63. Ren T, Liu Y, Zhao X, Ni S, Zhang C, Guo C, et al. Transperitoneal Approach versus Retroperitoneal Approach: A Meta-Analysis of Laparoscopic Partial Nephrectomy for Renal Cell Carcinoma. PLoS ONE. 2014;9(3):e91978.
64. Zheng JH, Zhang XL, Geng J, Guo CC, Zhang XP, Che JP, et al. Long-term oncologic outcomes of laparoscopic versus open partial nephrectomy. Chin. Med. J. 2013;126(15):2938-42.
65. Su JR, Zhu DJ, Liang W, Xie WL. Investigation on the indication of ipsilateral adrenalectomy in radical nephrectomy: A meta-analysis. Chin. Med. J. 2012;125(21):3885-90.
66. Bekema HJ MS, Imamura M, et al. Systematic review of adrenalectomy and lymph node dissection in locally advanced renal cell carcinoma. Eur Urol 2013 64(5).
67. Blom JH VPH, Maréchal JM, et al. Radical Nephrectomy with and without Lymph-Node Dissection: Final Results of European

Organization for Research and Treatment of Cancer (EORTC) Randomized Phase 3 Trial 30881. Eur Urol 2009 55(1):28-34.

68. Jewett MAS, Mattar K, Basiuk J, Morash CG, Pautler SE, Siemens DR, et al. Active Surveillance of Small Renal Masses: Progression Patterns of Early Stage Kidney Cancer. European Urology 2011;60:39-44.
69. Hollingsworth JM, Miller DC, Daignault S, Hollenbeck BK. Five-Year Survival After Surgical Treatment for Kidney Cancer - A Population-Based Competing Risk Analysis. Cancer. 2007;109(9):1763-68.
70. Smaldone MC, Kutikov A, Egleston BL, Canter DJ, Viterbo R, Chen DYT, et al. Small Renal Masses Progressing to Metastases Under Active Surveillance. A Systematic Review and Pooled Analysis. Cancer. 2012;118(4):997-1006.
71. Lane BR, Abouassaly R, Gao T, Weight CJ, Hernandez AV, Larson BT, et al. Active Treatment of Localized Renal Tumors May Not Impact Overall Survival in Patients Aged 75 Years or Older. Cancer. 2010;116(13):3119-26.
72. American cancer society. Expectant management, watchful waiting, and active surveillance for prostate cance [Web page].2015 [cited 12/05]. Available from: http://www.cancer.org/cancer/prostatecancer/detailedguide/prostate-cancer-treating-watchful-waiting
73. Bhan SN, Pautler SE, Shayegan B, Voss MD, Goeree RA, You JJ. Active surveillance, radiofrequency ablation, or cryoablation for the nonsurgical management of a small renal mass: A cost-utility analysis. Ann. Surg. Oncol. 2013;20(11):3675-84.
74. Klatte T, Shariat SF, Remzi M. Systematic Review and Meta-Analysis of Perioperative and Oncologic Outcomes of Laparoscopic Cryoablation Versus Laparoscopic Partial Nephrectomy for the Treatment of Small Renal Tumors. J. Urol. 2014.
75. Guan W, Bai J, Liu J, Wang S, Zhuang Q, Ye Z, et al. Microwave ablation versus partial nephrectomy for small renal tumors: intermediate-term results. Journal of surgical oncology. 2012;106(3):316-21.
76. Katsanos K, Mailli L, Krokidis M, McGrath A, Sabharwal T, Adam A. Systematic review and meta-analysis of thermal ablation versus surgical nephrectomy for small renal tumours. Cardiovasc. Intervent. Radiol. 2014;37(2):427-37.
77. Aitchison M, Bray CA, Poppel H, Sylvester R, Graham J, Innes C, et al. Adjuvant 5-flurouracil, alpha-interferon and interleukin-2 versus observation in patients at high risk of recurrence after nephrectomy for renal cell carcinoma: Results of a Phase III randomised European Organisation for Research and Treatment of Cancer (Genito-Urinary Cancers Group)/National Cancer Research Institute trial. European journal of cancer. 2014;50(1):70-7.
78. Amato RJ, Hawkins RE, Kaufman HL, Thompson JA, Tomczak P, Szczylik C, et al. Vaccination of metastatic renal cancer patients with MVA-5T4: a randomized, double-blind, placebo-controlled phase III study. Clinical cancer research. 2010;16(22):5539-47.
79. Hinotsu S, Kawai K, Ozono S, Tsushima T, Tokuda N, Nomata K, et al. Randomized controlled study of natural interferon ? as adjuvant treatment for stage II or III renal cell carcinoma. International journal of clinical oncology. 2013;18(1):68-74.
80. Margulis V, Matin SF, Tannir N, Tamboli P, Shen Y, Lozano M, et al. Randomized trial of adjuvant thalidomide versus observation in patients with completely resected high-risk renal cell carcinoma. Urology. 2009;73(2):337-41.
81. Atzpodien J, Schmitt E, Gertenbach U, Fornara P, Heynemann H, Maskow A, et al. German Cooperative Renal Carcinoma Chemo-Immunotherapy Trials Group (DGCIN). Adjuvant treatment with interleukin-2- and interferonalpha2a based chemoimmunotherapy in renal cell carcinoma post tumour nephrectomy: results of a prospectively randomised trial of the German Cooperative Renal Carcinoma Chemoimmunotherapy Group (DGCIN). Br J Cancer 2005 92(5):843-6.
82. Clark JI, Atkins M, Urba W, Creech S, Figlin R, Dutcher J, et al. Adjuvant high-dose bolus interleukin-2 for patients with high-risk renal cell carcinoma: a cytokine working group randomized trial. J Clin Oncol. 2003 21(16):3133-40.

83. Figlin R, Thompson J, Bukowski R, Vogelzang N, Novick A, Lange P, et al. Multicenter, randomized, phase III trial of CD8(+) tumor-infiltrating lymphocytes in combination with recombinant interleukin-2 in metastatic renal cell carcinoma. J.Clin.Oncol. 1999 17(8):2521-9.
84. Galligioni E, Quaia M, Merlo A, Carbone A, Spada A, Favaro D, et al. Adjuvant immunotherapy treatment of renal carcinoma patients with autologous tumor cells and bacillus Calmette-Guerin: five-year results of a prospective randomized study. Cancer 1996 77(12):2560-6.
85. Jocham D, Richter A, Hoffmann L, Iwig K, Fahlenkamp D, Zakrzewski G, et al. Adjuvant autologous renal tumour cell vaccine and risk of tumour progression in patients with renal-cell carcinoma after radical nephrectomy: phase III, randomised controlled trial. Lancet. 2004;363(9409):594-9.
86. Kjaer M, Frederiksen P, Engelholm S. Postoperative radiotherapy in stage II and III renal adenocarcinoma. A randomized trial by the Copenhagen Renal Cancer Study Group. Int.J.Radiat.Oncol.Biol.Phys. 1987 13(5):665-72.
87. Messing E, Manola J, Wilding G, Propert K, Fleischmann J, Crawford E, et al. Messing EM, Manola J, Wilding G, Propert K, Fleischmann J, Crawford ED, Pontes JE, Hahn R, Trump D. Phase III study of interferon alfa-NL as adjuvant treatment for resectable renal cell carcinoma: an Eastern Cooperative Oncology Group/Intergroup trial. J Clin Oncol. 2003;21(7):1214-22.
88. Pizzocaro G, Piva L, Colavita M, Ferri S, Artusi R, Boracchi P, et al. Interferon adjuvant to radical nephrectomy in Robson stages II and III renal cell carcinoma: a multicentric randomized study. J. Clin.Oncol. . 2001;19(2):425-31.
89. Wood C, Srivastava P, Bukowski R, Lacombe L, Gorelov A, Gorelov S, et al. An adjuvant autologous therapeutic vaccine (HSPPC-96; vitespen) versus observation alone for patients at high risk of recurrence after nephrectomy for renal cell carcinoma: a multicentre, open-label, randomised phase III trial. Lancet. 2008;372(9633):145-54.
90. Naito S, Kumazawa J, Omoto T, Iguchi A, Sagiyama K, Osada Y, et al. Postoperative UFT adjuvant and the risk factors for recurrence in renal cell carcinoma: a long-term follow-up study. Kyushu University Urological Oncology Group. Int J Urol. 1997;4(1):8-12.
91. Pizzocaro G, Piva L, Di Fronzo G, Giongo A, Cozzoli A, Dormia E, et al. Adjuvant medroxyprogesterone acetate to radical nephrectomy in renal cancer: 5-year results of a prospective randomized study. J Urol. 1987;138(6):1379-81.
92. Finney R. The value of radiotherapy in the treatment of hypernephroma - a clinical trial. Brit. J. Urol. 1973;45:258-69.
93. Finney R. An evaluation of postoperative radiotherapy in hypernephroma treatment - A clinical trial. Cancer. 1973;32:1332-40.
94. Juusela H, Malmio K, Alfthan O, Oravisto K. Preoperative irradiation in the treatment of renal adenocarcinoma. Scand.J.Urol.Nephrol. 1977;11(3):277-81.
95. Werf-Messing B. Proceedings: Carcinoma of the kidney. Cancer 1973;32(5):1056-61.
96. Chang ED, Sondak VK, Bishop DK, Nickoloff BJ, Mulligan RC, Mule JJ. Clinical Protocol: Adoptive Immunotherapy of Cancer with activated lymph node cells primed in vivo with autologous tumor cells transduced with the GM_CSF Gene. Human gGene therapy 1996;7:773-92.
97. Haas N, Manola J, Ky B, Flaherty K, Uzzo R, Kane C, et al. Effects of adjuvant sorafenib and sunitinib on cardiac function in renal cell carcinoma patients without overt metastases:results from ASSURE, ECOG2805. Clin Cancer Res. 2015;[Epub ahead of print].
98. Flanigan RC, Salmon SE, Blumenstein BA, Bearman SI, Roy V, McGrath PC, et al. Nephrectomy followed by interferon alfa-2b compared with interferon alfa-2b alone for metastatic renal-cell cancer. N Engl J Med. 2001;345(23):1655-9.
99. Mickisch GH, Garin A, Van Poppel H, de Prijck L, Sylvester R, European Organisation fo Research and Treatment of Cancert (EORTC) Genitourinary Group. Radical nephrectomy plus interferon-alfa-based immunotherapy compared with interferon alfa

alone in metastatic renal-cell carcinoma: a randomised trial. Lancet. 2001 358(9286):966-70.

100. Coppin C, Porzsolt F, Autenrieth M, Kumpf J, Coldman A, Wilt T. Immunotherapy for advanced renal cell cancer. Cochrane Database of Systematic Reviews. 2004;Issue 3:Art. No.: CD001425.
101. Flanigan RC MG, Sylvester R, et al. Cytoreductive nephrectomy in patients with metastatic renal cancer: a combined analysis. J Urol 2004 171(3):1071-6.
102. American cancer society. Targeted Therapy [Web page]. 2014 [cited 03/04]. Available from: http://www.cancer.org/acs/groups/cid/documents/webcontent/003024-pdf.pdf
103. B. Ljungberg KB, A. Bex, S. Canfield, S. Dabestani, F. Hofmann, M. Hora, M.A. Kuczyk, T. Lam, L. Marconi, A.S. Merseburger, P.F.A. Mulders, T. Powles, M. Staehler, A. Volpe. Guidelines for Renal Cell Carcinoma. European Association of Urology 2014.
104. Cancer Care Ontario. The use of inhibitors of angiogenesis in patients with inoperable locally advanced or metastatic renal cell cancer: guideline recommendations. 2009.
105. Coppin C, Kollmannsberger C, Le L, Porzsolt F, Wilt TJ. Targeted therapy for advanced renal cell cancer (RCC): A Cochrane systematic review of published randomised trials. BJU Int. 2011;108(10):1556-63.
106. Coppin C, Le L, Wilt TJ, Kollmannsberger C. Targeted therapy for advanced renal cell carcinoma. Cochrane Database of Systematic Reviews. 2008;Issue 2.(Art. No.: CD006017).
107. Duran M, Matheus W, Ferreira U, Clark O. Systematic review and meta-analysis of target terapies for the treatment of metastatic renal cancer. Int Braz J Urol. 2013;39(6):768-78.
108. Leung HW, Chan AL. Multikinase inhibitors in metastatic renal cell carcinoma: indirect comparison meta-analysis. Clin Ther. 2011;33(6):708-16.
109. Liu F, Chen X, Peng E, Guan W, Li Y, Hu Z, et al. VEGF pathway-targeted therapy for advanced renal cell carcinoma: A meta-analysis of randomized controlled trials. J. Huazhong Univ. Sci. Technol. Med. Sci. 2011;31(6):799-806.
110. Thompson Coon J, Hoyle M, Green C, Liu Z, Welch K, Moxham T, et al. Bevacizumab, sorafenib tosylate, sunitinib and temsirolimus for renal cell carcinoma: a systematic review and economic evaluation. Health Technol Assess 2010. Jan;14(2):1-184
111. Thompson Coon JS, Liu Z, Hoyle M, Rogers G, Green C, Moxham T, et al. Sunitinib and bevacizumab for first-line treatment of metastatic renal cell carcinoma: A systematic review and indirect comparison of clinical effectiveness. Br. J. Cancer. 2009;101(2):238-43.
112. Escudier B, Eisen T, Stadler W, Szcylik C, Oudard S, Siebels M, et al. Sorafenib in advanced clear-cell renal-cell carcinoma. N Engl J Med. 2007;356:125-34.
113. Motzer RH, TE , Tomczak P, Michaelson M, Bukowski R, Rixe O, et al. Sunitinib versus interferon alfa in metastatic renal-cell cancer. N Engl J Med. 2007;356:115-24.
114. Szcylik C, Demkow T, Staehler M, Rolland F, Negrier S, Hutson E, et al. Randomized phase II trial of first-line treatment with sorafenib versus interferon in patients with advanced renal cell carcinoma: final results [abstract]. Proc Am Soc Clin Oncol. 2007;25(241s).
115. Escudier B, Pluzanska A, Koralewski P, Ravaud A, Bracarda S, Szcylik C, et al. Bevacizumab plus interferon alfa-2a for treatment of metastatic renal cell carcinoma: a randomised, double-blind phase III trial. Lancet. 2007;370:2103-11.
116. Rini B, Halabi S, Rosenberg J, Stadler W, Vaena D, Ou S, et al. Bevacizumab plus interferon alfa compared with interferon alfa monotherapy in patients with metastatic renal cell carcinoma: CALGB 90206. J Clin Oncol. 2008;26:5422-8.
117. Yang J, Haworth L, Sherry R, Hwu P, Schwartzentruber D, Topalian S, et al. A randomized trial of bevacizumab, an anti-vascular endothelial growth factor antibody, for metastatic renal cell cancer. N Engl J Med. 2003;349:427-34.

118. Hudes G, Carducci M, Tomczak P, Dutcher J, Figlin R, Kapoor A, et al. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. N Engl J Med. 2007;356:2271-81.
119. Motzer RJ, Escudier B, Oudard S, Porta C, Hutson TE, Bracarda S, et al. Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. Lancet. 2008;372:449-56.
120. Dutcher JP, de Souza P, McDermott D, Figlin RA, Berkenblit A, Thiele A, et al. Effect of temsirolimus versus interferon-on outcome of patients with advanced renal cell carcinoma of different histologies. Med Oncol. 2009;26(2):202-9.
121. Rini B, Szczylik C, Tannir NM, Koralewski P, Tomczak P, Deptala A, et al. AMG 386 in combination with sorafenib in patients with metastatic clear cell carcinoma of the kidney: a randomized, double-blind, placebo-controlled, phase 2 study. Cancer. 2012;118(24):6152-61.
122. Motzer RJ, Nosov D, Eisen T, Bondarenko I, Lesovoy V, Lipatov O, et al. Tivozanib versus sorafenib as initial targeted therapy for patients with metastatic renal cell carcinoma: results from a phase III trial. Journal of clinical oncology. 2013;31(30):3791-9.
123. Motzer RJ, Hutson TE, Cella D, Reeves J, Hawkins R, Guo J, et al. Pazopanib versus sunitinib in metastatic renal-cell carcinoma. New Engl. J. Med. 2013;369(8):722-31.
124. Mulders P, Hawkins R, Nathan P, de Jong I, Osanto S, Porfiri E, et al. Cediranib monotherapy in patients with advanced renal cell carcinoma: results of a randomised phase II study. Eur J Cancer. 2012;48(4):527-37.
125. Nosov DA, Esteves B, Lipatov ON, Lyulko AA, Anischenko AA, Chacko RT, et al. Antitumor activity and safety of tivozanib (AV-951) in a phase II randomized discontinuation trial in patients with renal cell carcinoma. Journal of clinical oncology. 2012;30(14):1678-85.
126. Motzer RJ, Porta C, Vogelzang NJ, Sternberg CN, Szczylik C, Zolnierek J, et al. Dovitinib versus sorafenib for third-line targeted treatment of patients with metastatic renal cell carcinoma: An open-label, randomised phase 3 trial. Lancet Oncol. 2014;15(3):286-96.
127. Hutson TE, Escudier B, Esteban E, Bjarnason GA, Lim HY, Pittman KB, et al. Randomized phase III trial of temsirolimus versus sorafenib as second-line therapy after sunitinib in patients with metastatic renal cell carcinoma. J Clin Oncol. 2014;32(8):760-7.
128. Rini BI, Bellmunt J, Clancy J, Wang K, Niethammer AG, Hariharan S, et al. Randomized phase III trial of temsirolimus and bevacizumab versus interferon alfa and bevacizumab in metastatic renal cell carcinoma: INTORACT trial. J Clin Oncol. 2014;32(8):752-9.
129. Escudier B, Szczylik C, Hutson TE, Demkow T, Staehler M, Rolland F, et al. Randomized phase II trial of first-line treatment with sorafenib versus interferon alfa-2a in patients with metastatic renal cell carcinoma J. Clin. Oncol. 2009;27(13):1280-9.
130. Cella D, Li JZ, Cappelleri JC, Bushmakin A, Charbonneau C, Kim ST, et al. Quality of Life in Patients With Metastatic Renal Cell Carcinoma Treated With Sunitinib or Interferon Alfa: Results From a Phase III Randomized Trial. Journal of clinical oncology. 2008;26(22):3763-9.
131. Castellano D, del Muro XG, Perez-Gracia JL, Gonzalez-Larriba JL, Abrio MV, Ruiz MA, et al. Patient-reported outcomes in a phase III, randomized study of sunitinib versus interferon-{alpha} as first-line systemic therapy for patients with metastatic renal cell carcinoma in a European population. Ann Oncol. 2009;20(11):1803-12.
132. Cella D, Michaelson MD, Bushmakin AG, Cappelleri JC, Charbonneau C, Kim ST, et al. Health-related quality of life in patients with metastatic renal cell carcinoma treated with sunitinib vs interferon-alpha in a phase III trial: final results and geographical analysis. British journal of cancer. 2010;102(4):658-64.
133. Motzer RJ, Hutson TE, Tomczak P, Michaelson MD, Bukowski RM, Oudard S, et al. Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. Journal of clinical oncology. 2009;27(22):3584-90.
134. Patil S, Figlin RA, Hutson TE, Michaelson MD, Negrier S, Kim ST, et al. Q-TWiST analysis to estimate overall benefit for patients with metastatic renal cell carcinoma treated in a phase III trial of sunitinib vs interferon-? British journal of cancer. 2012;106(10):1587-90.

135. Cella D, Davis MP, Negrier S, Figlin RA, Michaelson MD, Bushmakin AG, et al. Characterizing fatigue associated with sunitinib and its impact on health-related quality of life in patients with metastatic renal cell carcinoma. Cancer. 2014.
136. Hudes G, Carducci M, Tomczak P, Dutcher J, Figlin R, Kapoor A, et al. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. New Engl. J. Med. 2007;356(22):2271-81.
137. Yang S, De Souza P, Alemao E, Purvis J. Quality of life in patients with advanced renal cell carcinoma treated with temsirolimus or interferon-(alpha). Br. J. Cancer. 2010;102(10):1456-60.
138. Zbrozek AS, Hudes G, Levy D, Strahs A, Berkenblit A, DeMarinis R, et al. Q-TWiST analysis of patients receiving temsirolimus or interferon alpha for treatment of advanced renal cell carcinoma. PharmacoEconomics. 2010;28(7):577-84.
139. Alemao E, Rajagopalan S, Yang S, Curiel RE, Purvis J, Al MJ. Inverse probability weighting to control for censoring in a post hoc analysis of quality-adjusted survival data from a clinical trial of temsirolimus for renal cell carcinoma. Journal of medical economics. 2011;14(2):245-52.
140. Maroto JP, Hudes G, Dutcher JP, Logan TF, White CS, Krygowski M, et al. Drug-related pneumonitis in patients with advanced renal cell carcinoma treated with temsirolimus. J Clin Oncol. 2011;29(13):1750-6.
141. Melichar B, Koralewski P, Ravaud A, Pluzanska A, Bracarda S, Szczylik C, et al. First-line bevacizumab combined with reduced dose interferon-α2a is active in patients with metastatic renal cell carcinoma. Annals of Oncology 2008;19:1470–6.
142. Escudier B, Bellmunt J, Négrier S, Bajetta E, Melichar B, Bracarda S, et al. Phase III trial of bevacizumab plus interferon alfa-2a in patients with metastatic renal cell carcinoma (AVOREN): final analysis of overall survival. Journal of Clinical Oncology 2010;28:2144–50.
143. Bracarda S, Bellmunt J, Melichar B, Négrier S, Bajetta E, Ravaud A, et al. Overall survival in patients with metastatic renal cell carcinoma initially treated with bevacizumab plus interferon-2a and subsequent therapy with tyrosine kinase inhibitors: a retrospective analysis of the phase III AVOREN trial. BJU International 2010;107(2):214-9.
144. Rini BI, Halabi S, Taylor J, Small EJ, Schilsky RL. Cancer and Leukemia Group B 90206: a randomized phase III trial of interferon-a or interferon-a plus anti-vascular endothelial growth factor antibody (bevacizumab) in metastatic renal cell carcinoma. Clinical Cancer Research 2004;10:2584–6.
145. Rini BI, Halabi S, Rosenberg JE, Stadler WM, Vaena DA, S.S. O, et al. Bevacizumab plus interferon alfa compared with interferon alfa monotherapy in patients with metastatic renal cell carcinoma: CALGB 90206. J Clin Oncol. 2008;26(33):5422-8.
146. Rini BI, Halabi S, Rosenberg JE, Stadler WM, Vaena DA, Archer L, et al. Phase III trial of bevacizumab plus interferon alfa versus interferon alfa monotherapy in patients with metastatic renal cell carcinoma: final results of CALGB 90206. J Clin Oncol. 2010;28(13):2137-43.
147. Hutson TE, Lesovoy V, Al-Shukri S, Stus VP, Lipatov ON, Bair AH, et al. Axitinib versus sorafenib as first-line therapy in patients with metastatic renal-cell carcinoma: A randomised open-label phase 3 trial. Lancet Oncol. 2013;14(13):1287-94.
148. Procopio G, Verzoni E, Bracarda S, Ricci S, Sacco C, Ridolfi L, et al. Sorafenib with interleukin-2 vs sorafenib alone in metastatic renal cell carcinoma: the ROSORC trial. British journal of cancer. 2011;104(8):1256-61.
149. Procopio G, Verzoni E, Bracarda S, Ricci S, Sacco C, Ridolfi L, et al. Overall survival for sorafenib plus interleukin-2 compared with sorafenib alone in metastatic renal cell carcinoma (mRCC): Final results of the ROSORC trial. Annals of oncology. 2013;24(12):2967-71.
150. Jonasch E, Corn P, Pagliaro LC, Warneke CL, Johnson MM, Tamboli P, et al. Upfront, randomized, phase 2 trial of sorafenib versus sorafenib and low dose interferon alfa in patients with advanced renal cell carcinoma. Cancer 2010;116:57–65.
151. Bukowski R, Kabbinavar FF, Figlin RA, Flaherty K, Srinivas S, Vaishampayan U, et al. Randomized phase II study of erlotinib combined with bevacizumab compared with bevacizumab alone in

metastatic renal cell cancer. Journal of Clinical Oncology. 2007;25(29):4536–41.

152. Negrier S, Gravis G, Perol D, Chevreau C, Delva R, Bay JO, et al. Temsirolimus and bevacizumab, or sunitinib, or interferon alfa and bevacizumab for patients with advanced renal cell carcinoma (TORAVA): A randomised phase 2 trial. Lancet oncology. 2011;12(7):673-80.
153. Alasker A, Meskawi M, Sun M, Ismail S, Hanna N, Hansen J, et al. A contemporary update on rates and management of toxicities of targeted therapies for metastatic renal cell carcinoma. Cancer Treatment Reviews 2013;39:388-401.
154. Ratain MJ, Eisen T, Stadler WM, Flaherty KT, Kaye SB, Rosner GL, et al. Phase II placebo controlled randomized discontinuation trial of sorafenib in patients with metastatic renal cell carcinoma. Journal of Clinical Oncology 2006;24(16):2505-12.
155. Bukowski R, Cella D, Gondek K, B E. Effects of sorafenib on symptoms and quality of life. Results from a large randomized placebo-controlled study in renal cancer. American Journal of Clinical Oncology 2007;30:220–7.
156. Eisen T, Oudard S, Szczylik C, Gravis G, Heinzer H, Middleton R, et al. Sorafenib for older patients with renal cell carcinoma: subset analysis from a randomized trial. Journal of the National Cancer Institute. 2008;100(20):1454-63.
157. Escudier B, Eisen T, Stadler WM, Szczylik C, Oudard S, Staehler M, et al. Sorafenib for treatment of renal cell carcinoma: Final efficacy and safety results of the phase III treatment approaches in renal cancer global evaluation trial. Journal of clinical oncology. 2009;27(20):3312-8.
158. Antoun S, Birdsell L, Sawyer MB, Venner P, Escudier B, Baracos VE. Association of skeletal muscle wasting with treatment with sorafenib in patients with advanced renal cell carcinoma: results from a placebo-controlled study. Journal of clinical oncology. 2010;28(6):1054-60.
159. Negrier S, Jäger E, Porta C, McDermott D, Moore M, Bellmunt J, et al. Efficacy and safety of sorafenib in patients with advanced renal cell carcinoma with and without prior cytokine therapy, a subanalysis of TARGET. Medical oncology (Northwood, London, England). 2010;27(3):899-906.
160. Hutson TE, Bellmunt J, Porta C, Szczylik C, Staehler M, Nadel A, et al. Long-term safety of sorafenib in advanced renal cell carcinoma: follow-up of patients from phase III TARGET. European journal of cancer (Oxford, England : 1990). 2010;46(13):2432-40.
161. Sternberg CN, Davis ID, Mardiak J, Szczylik C, Lee E, Wagstaff J, et al. Pazopanib in Locally Advanced or Metastatic Renal Cell Carcinoma: Results of a Randomized Phase III Trial. Journal of oncology. 2010;28(6):1061-8.
162. Cella D, Pickard AS, Duh MS, Guerin A, Mishagina N, Antras L, et al. Health-related quality of life in patients with advanced renal cell carcinoma receiving pazopanib or placebo in a randomised phase III trial. Eur. J. Cancer. 2012;48(3):311-23.
163. Sternberg CN, Hawkins RE, Wagstaff J, Salman P, Mardiak J, Barrios CH, et al. A randomised, double-blind phase III study of pazopanib in patients with advanced and/or metastatic renal cell carcinoma: Final overall survival results and safety update European Journal of Cancer. 2013;49:1287– 96.
164. Elaraj DM, White DE, Steinberg SM, Haworth L, Rosenberg SA, Yang JC. A pilot study of antiangiogenic therapy with bevacizumab and thalidomide in patients with metastatic renal cell carcinoma. Journal of Immunotherapy. 2004;27(4):259-64.
165. Motzer RJ, Escudier B, Oudard S, Hutson TE, Porta C, Bracarda S, et al. Phase 3 trial of everolimus for metastatic renal cell carcinoma: Final results and analysis of prognostic factors. Cancer. 2010;116(18):4256-65.
166. White DA, Camus P, Endo M, Escudier B, Calvo E, Akaza H, et al. Noninfectious pneumonitis after everolimus therapy for advanced renal cell carcinoma. American journal of respiratory and critical care medicine. 2010;182(3):396-403.
167. Beaumont JL, Butt Z, Baladi J, Motzer RJ, Haas T, Hollaender N, et al. Patient-reported outcomes in a phase iii study of everolimus versus placebo in patients with metastatic carcinoma of the kidney that has progressed on vascular endothelial growth factor receptor tyrosine kinase inhibitor therapy. Oncologist. 2011;16(5):632-40.

168. Tsukamoto T, Shinohara N, Tsuchiya N, Hamamoto Y, Maruoka M, Fujimoto H, et al. Phase III trial of everolimus in metastatic renal cell carcinoma: subgroup analysis of Japanese patients from RECORD-1. Japanese journal of clinical oncology. 2011;41(1):17-24.
169. Bracarda S, Hutson TE, Porta C, Figlin RA, Calvo E, Grunwald V, et al. Everolimus in metastatic renal cell carcinoma patients intolerant to previous VEGFr-TKI therapy: A RECORD-1 subgroup analysis. Br. J. Cancer. 2012;106(9):1475-80.
170. Calvo E, Escudier B, Motzer RJ, Oudard S, Hutson TE, Porta C, et al. Everolimus in metastatic renal cell carcinoma: Subgroup analysis of patients with 1 or 2 previous vascular endothelial growth factor receptor-tyrosine kinase inhibitor therapies enrolled in the phase III RECORD-1 study. Eur. J. Cancer. 2012;48(3):333-9.
171. Porta C, Calvo E, Climent MA, Vaishampayan U, Osanto S, Ravaud A, et al. Efficacy and safety of everolimus in elderly patients with metastatic renal cell carcinoma: an exploratory analysis of the outcomes of elderly patients in the RECORD-1 Trial. European urology. 2012;61(4):826-33.
172. Blesius A, Beuselinck B, Chevreau C, Ravaud A, Rolland F, Oudard S, et al. Are tyrosine kinase inhibitors still active in patients with metastatic renal cell carcinoma previously treated with a tyrosine kinase inhibitor and everolimus? Experience of 36 patients treated in France in the RECORD-1 Trial. Clinical genitourinary cancer. 2013;11(2):128-33.
173. Rini BI, Escudier B, Tomczak P, Kaprin A, Szczylik C, Hutson TE, et al. Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised phase 3 trial. Lancet. 2011;378(9807):1931-9.
174. Cella D, Escudier B, Rini B, Chen C, Bhattacharyya H, Tarazi J, et al. Patient-reported outcomes for axitinib vs sorafenib in metastatic renal cell carcinoma: phase III (AXIS) trial. British journal of cancer. 2013;108(8):1571-8.
175. Motzer RJ, Escudier B, Tomczak P, Hutson TE, Michaelson MD, Negrier S, et al. Axitinib versus sorafenib as second-line treatment for advanced renal cell carcinoma: overall survival analysis and updated results from a randomised phase 3 trial. Lancet oncology. 2013;14(6):552-62.
176. Ueda T, Uemura H, Tomita Y, Tsukamoto T, Kanayama H, Shinohara N, et al. Efficacy and safety of axitinib versus sorafenib in metastatic renal cell carcinoma: subgroup analysis of Japanese patients from the global randomized Phase 3 AXIS trial. Japanese journal of clinical oncology. 2013;43(6):616-28.
177. Rini BI, Quinn DI, Baum M, Wood LS, Tarazi J, Rosbrook B, et al. Hypertension among patients with renal cell carcinoma receiving axitinib or sorafenib: analysis from the randomized phase III AXIS trial. Targeted Oncol. 2014:1-9.
178. Ravaud A, Hawkins R, Gardner JP, von der Maase H, Zantl N, Harper P, et al. Lapatinib versus hormone therapy in patients with advanced renal cell carcinoma: a randomized phase III clinical trial. Journal of Clinical Oncology 2008;26(14):2285-91.
179. Eyssen M, Benahmed N, Desomer A. Supportive treatment for cancer – Part 3: Treatment of pain: most common practices. Brussels: Belgian Health Care Knowledge Centre (KCE); 2013. Good Clinical Practice (GCP) KCE Reports 211D/2013/10.273/84
180. Keirse E, Beguin C, Desmedt M, Deveugele M, Menten J, Simoens S, et al. Organisation of palliative care in Belgium. Health Services Research (HSR). Brussels: Belgian Health Care Knowledge Centre (KCE); 2009 22/10/2009. KCE Reports 115C (D/2009/10.273/42) Available from: https://kce.fgov.be/sites/default/files/page_documents/d20091027342.pdf