COLLEGE OF ONCOLOGY

National Clinical Practice Guidelines

RENAL CANCER IN ADULTS:

DIAGNOSIS, TREATMENT AND FOLLOW-UP

SUMMARY

Version 2015

Renal Cancer Guideline Development Group (GDG)

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Reference: 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 – Summary. Good Clinical Practice (GCP) Brussels: Belgian Health Care Knowledge Centre (KCE). 2015. KCE Reports 253Cs. D/2015/10.273/85.

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1. INTRODUCTION

'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 male 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 (Source: 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.

2. OBJECTIVES AND SCOPE OF THIS GUIDELINE

The aim of this guideline is to formulate recommendations for health care providers based on the current evidence on diagnosis, treatment and follow-up of adult patients with renal cancer.

This guideline focuses on 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.

3. METHODS

3.1. Systematic review of the literature

A search for clinical guidelines was carried out in several databases and institutional websites (OVID Medline, the National Guideline Clearinghouse and the GIN database). The search for systematic reviews, meta-analyses and primary studies was carried out in OVID MEDLINE, Embase and the Cochrane Library (Cochrane Database of Systematic Reviews, DARE and HTA database). Two independent researchers performed the selection, the quality appraisal and the data extraction of the studies. The analysis followed a hierarchical approach:

1. Extraction of the data from the systematic reviews and meta-analyses; in the absence of high-quality systematic reviews and meta-analyses, clinical guidelines of high quality were considered as a starting point.
2. Search for the most recent primary studies to complete the evidence found in the previous step (randomised and prospective controlled trials).

The search covered the period from 2009 to 2015.

3.2. Formulation and validation of the recommendations

Based on the retrieved evidence, the first draft of recommendations was prepared by a small working group (KCE experts and Guideline Development Group (GDG) 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.

To determine the level of evidence and strength of recommendation, the GRADE methodology was followed (Tables 1 & 2). 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. We did not use GRADE for diagnostic clinical questions because the approach is not mature and there is no consensus on how to apply it for diagnosis-related issues.

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); this was done using an online survey. 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. Patient representatives also played a key role ensuring that patient views and experiences inform the group’s work.

The recommendations prepared by the GDG were circulated to professional associations. 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.

Finally, the current guideline was reviewed prior to its publication by 3 independent validators (cf. names in the colophon).

Declarations of interest were officially recorded.

Table 1 – Levels of evidence according to GRADE[a]

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 estimated is limited: the true effect may be substantially different from the estimate of the effect.	RCTs with 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.	

Table 2 – Strength of recommendations according to GRADEb

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).*

[a] 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.

[b] Guyatt GH, Oxman AD, Kunz R, Falck-Ytter Y, Vist GE, Liberati A, et al. Going from evidence to recommendations.[Erratum appears in BMJ. 2008 Jun 21;336(7658): doi:10.1136/bmj.a402]. BMJ. 2008;336(7652):1049-51.

4. CLINICAL RECOMMENDATIONS

The details of the evidence used to formulate the recommendations and best practice below are available in the scientific report and its supplements. The tables follow the sequence of the chapters of the scientific report.

4.1. Diagnosis

Best practices
The use of the current TNM classification system is recommended.
The use of grading systems and classification of renal cell carcinoma 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.

4.1.1. Contrast-enhanced CT

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.

4.1.2. Bone scan

Recommendation
Bone scan is not routinely recommended in the absence of skeletal symptoms or elevated alkaline phosphatase.

4.1.3. Brain imaging

Recommendation
Brain imaging is not routinely recommended in the absence of symptoms.

4.1.4. PET/CT

Recommendation
PET/CT is not routinely recommended in the diagnosis, staging and follow-up of renal cell carcinoma.

4.1.5. Biopsy

Recommendation
Renal tumour biopsy (preferably with a coaxial technique) is recommended before ablative therapy and systemic therapy in the absence of previous pathology.

4.2. Prognosis and prediction of treatment effectiveness

Recommendations
Prognostic systems are recommended in metastatic disease to evaluate survival.
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.

4.3. Treatment of localized renal cancer

4.3.1. Surgery

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

4.3.2. Management of RCC complicated with caval thrombus

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

4.3.3. Alternative to surgery

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

4.3.4. Ablative therapy

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

4.3.5. Adjuvant treatment

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

4.4. Treatment of local recurrence/ metastases

4.4.1. Surgery

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

4.4.2. Systemic treatments

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 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 cell 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 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 role 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
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	Strong	Low

(*IFN-α, IL-2*).		
Axitinib is recommended in metastatic renal cell carcinoma patients previously treated with VEGF-pathway targeted therapy or cytokines. *Note: Axitinib is only reimbursed after a failure of first line treatment with TKI or cytokine*.	Strong	Low
Everolimus or sorafenib can be considered in third-line therapy.	Weak	Very low

4.5. Palliative care

Additional information regarding the overall cancer population can be found in KCE report 211 (Supportive treatment for cancer – Part 3: Treatment of pain: most common practices) and KCE reports 115 (Organisation of palliative care in Belgium).

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

4.6. Follow-up

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) is recommended at least annually thereafter.
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 Practices
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.