



Review – Kidney Cancer

Renal Cell Carcinoma Guideline

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Abstract

Objectives: The European Association of Urology (EAU) Guideline Group for renal cell carcinoma (RCC) prepared this guideline to help urologists assess the evidence-based management of RCC and to incorporate the guideline recommendations into their clinical practice.

Methods: The recommendations provided in the current guideline are based on a systematic literature search using MedLine, the Cochrane Central Register of Controlled Trials, and publications and review articles.

Results: A limited number of prospective randomised studies are available with high-level evidence. Most publications concerning RCC are based on retrospective analyses, including some larger multicentre validation studies and well-designed controlled studies.

Conclusions: It must be stressed that the current guideline contains information for the treatment of an individual patient according to a standardised general approach. Updated recommendations concerning diagnosis, treatment, and follow-up can improve the clinical handling of patients with RCC.

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1. Introduction

The European Association of Urology (EAU) Guideline Group for renal cell carcinoma (RCC) prepared this guideline to help urologists assess the evidence-based management of RCC and to incorporate the

guideline recommendations into their clinical practice. Detailed information on the level of evidence and grade of recommendations are found at: www.uroweb.nl. Publications concerning RCC are mostly based on retrospective analysis, including some larger multicentre validation studies and

well-designed controlled studies. Only a few prospective randomised studies are available with high-level evidence. Therefore, it is difficult to obtain qualified randomised evidence-based data. The recommendations provided in the current guideline are based on a systematic literature search using MedLine, the Cochrane Central Register of Controlled Trials, and reference lists in publications and review articles. It has to be stressed that the current guideline contains information for the treatment of an individual patient according to a standardised general approach. The information should be considered as providing recommendations without legal implications.

2. Background: epidemiology and etiology

RCC represents 2–3% of all cancers [1], with the highest incidence occurring in the more developed countries. The worldwide and European annual increase in incidence is approximately 2%, though in Denmark and Sweden a continuing decrease has been observed during the last two decades [2]. In 1998, about 30,000 patients were diagnosed with kidney cancer within the European Union and approximately 15,000 died of the disease [1].

RCC is the most frequently occurring solid lesion within the kidney and comprises different RCC types with specific histopathologic and genetic characteristics [3]. There is a 1.5:1 predominance of men over women, with peak incidence occurring between 60 and 70 yr of age. Etiologic factors include lifestyle factors, such as smoking, obesity, and hypertension [2,4]. Cigarette smoking is a definite risk factor for RCC. The roles of obesity and hypertension as risk factors for RCC remain to be definitively clarified. The most important preventive measure for RCC is to eliminate cigarette smoking.

Due to the increased detection of tumours by the use of imaging techniques such as ultrasound and computed tomography (CT), an increasing number of incidentally diagnosed RCCs are found. These tumours are more often smaller and of lower stage [5,6]. Despite the increased incidental detection rate, the mortality from RCC has remained unaffected and parallel to the incidence.

3. Diagnosis and staging

3.1. Symptoms

Many renal masses remain asymptomatic and nonpalpable until late in the natural course of the

disease. Today, >50% of RCCs are detected incidentally using noninvasive imaging for the evaluation of a variety of nonspecific symptom complexes [7]. The classic triad of flank pain, gross haematuria, and palpable abdominal mass is now rarely found (6–10%) [8,9]. Paraneoplastic syndromes are found in about 30% of patients with symptomatic RCC. The most common of these are hypertension, cachexia, weight loss, pyrexia, neuromyopathy, amyloidosis, elevated erythrocyte sedimentation rate, anaemia, abnormal liver function, hypercalcaemia, polycythaemia, etc [7]. A minority of patients present with symptoms directly caused by metastatic disease, such as bone pain or persistent cough [7]. Still, 25–30% of patients are diagnosed due to symptoms associated with metastatic disease.

Physical examination has a limited role in diagnosing RCC, but it may be valuable in some patients, such as those with palpable abdominal mass, palpable cervical lymphadenopathy, nonreducing varicocele, or bilateral lower extremity oedema, which suggests venous involvement. The most commonly assessed laboratory parameters are haemoglobin, erythrocyte sedimentation rate, alkaline phosphatase, and serum calcium [7,10].

3.2. Radiologic investigations

The majority of renal tumours are diagnosed by abdominal ultrasound (US) and CT performed for various reasons. Detection of a solid renal mass with US should be further investigated with a high-quality CT scan using contrast medium. The gold standard of diagnosis of RCC, the spiral CT scan, assesses primary tumour extension with extrarenal spread and provides information on venous involvement, enlargement of locoregional lymph nodes, condition of adrenal glands and the liver, and the function and morphology of the contralateral kidney. Chest CT is the most accurate investigation for chest staging [11], but at least routine chest radiography, as a less accurate alternative, must be done for metastatic evaluation. Magnetic resonance imaging (MRI) can be reserved primarily for patients with locally advanced malignancy, possible venous involvement, renal insufficiency, or allergy to intravenous contrast materials [12]. MRI is also an option for the evaluation of inferior vena cava tumour thrombus extension and the evaluation of unclassified renal masses. Doppler US and transoesophageal ultrasonography are also useful in the evaluation of the tumour thrombus [13]. If indicated by clinical or laboratory signs and symptoms, other diagnostic procedures may be applied, such as bone scan and brain CT or MRI. Renal arteriography,

inferior venacavography, or fine-needle biopsy have only a limited role in the clinical work-up of patients with RCC, but may be considered in selected cases.

In summary, it is recommended that in a patient with one or more of these laboratory or physical findings, the possible presence of RCC should be suspected. A plain chest radiograph can be sufficient for assessment of the lung in low-risk patients but chest CT is most sensitive. Abdominal CT and MRI are recommended for the work-up of patients with RCC and are the most appropriate imaging modalities for TNM classification prior to surgery.

3.3. Classification and prognosis

The 2002 TNM stage classification system is generally recommended for clinical and scientific use [14]. It is unclear whether the current TNM classification is optimal for the prediction of survival in patients with RCC and might be subject for reclassification. The pT1 substratification, introduced in 2002 [14], has been validated by a number of studies [15]. However, refinements remain to be performed for pT3 tumours. First, for renal sinus fat invasion only, it has not been established whether this carries the same prognostic information as does perinephric fat invasion [16]. Second, it has been suggested that RCCs with adrenal invasion should be classified as T4 tumours [17]. Furthermore, it is still not clear whether the stratification of RCCs with venous invasion in T3b and T3c is accurate. Additional studies are required to investigate the independent prognostic value of vena caval invasion compared with renal vein invasion. More recently, the accuracy of the N1–N2 subclassification has been questioned [18]. Finally, for adequate M staging of patients with RCC, an accurate preoperative imaging procedure, which is currently chest and abdominal CT, should be performed.

Factors influencing prognosis can be classified into anatomic, histologic, clinical, and molecular. Anatomic factors include tumour size, venous invasion, renal capsule invasion, adrenal involvement, and lymph node and distant metastasis. These factors are commonly gathered together in the universally used 2002 TNM staging classification system.

Histologic factors influencing prognosis include Fuhrman grade, histologic subtype, presence of sarcomatoid features, microscopic vein invasion, tumour necrosis, and collecting system invasion. Fuhrman nuclear grade is the most widely accepted histologic grading system in RCC. Although it is subject to intraobserver and interobserver discrepancies, it remains an independent prognostic factor. According to the World Health Organization

(WHO) classification [19], three major histologic subtypes of RCC exist: conventional (clear-cell; 80–90%), papillary (10–15%), and chromophobe (4–5%). Many studies have shown a trend towards a better prognosis for patients with chromophobe, papillary, and conventional (clear-cell) RCCs, respectively. However, the prognostic information of the RCC subtype is lost when stratified to tumour stage. Among papillary RCCs, two subgroups with different outcomes have been identified [20]. Type I tumours are low-grade with a chromophilic cytoplasm and a favourable prognosis. Type II papillary RCCs are mostly high-grade lesions with an eosinophilic cytoplasm and a great propensity for developing metastases. The RCC type subclassification has been confirmed at the molecular level by cytogenetic and genetic analyses.

Clinical factors include patient performance status, localised symptoms, cachexia, anaemia, and platelet count. Numerous molecular markers are being investigated including carbonic anhydrase IX (CAIX), vascular endothelial growth factor (VEGF), hypoxia-inducible factor (HIF), Ki67 (proliferation), p53, PTEN (cell cycle), E cadherin, and CD44 (cell adhesion). As yet, these markers are not in widespread use. Recently, gene expression profiling has identified 259 genes that predict survival independent of clinical prognostic factors in conventional RCCs, indicating that genetic information will improve prognostication [21].

The current TNM classification system, the Fuhrman grading system, and the RCC subtype classification are recommended in the clinical work-up because they have consequences for prognosis and therapy. The use of integrated prognostic systems or nomograms is not routinely recommended, but these systems provide a rationale for better prognostic prediction useful for including patients in clinical trials. It is suggested that these nomograms are more accurate than TNM stage or Fuhrman grade alone for predicting survival. No molecular prognostic marker is currently recommended for use in the clinical routine.

4. Treatment

4.1. Treatment of localised disease

Radical nephrectomy that includes the removal of the tumour-bearing kidney remains the only curative therapy for patients with localised RCC and offers a reasonable chance of curing the disease. There is no evidence to favour a specific surgical approach (Table 1) [22].

Table 1 – Primary surgical treatment of renal cell carcinoma according to T stage (TNM 2002)

T1a	Nephron-sparing surgery	Open	Recommended standard
	Nephron-sparing surgery	Laparoscopic	Optional in experienced centres
T1b–T2	Radical nephrectomy		Reasonable in selected patients
	Radical nephrectomy	Open	Adequate (higher morbidity)
T3, T4		Laparoscopic	Recommended standard
	Nephron-sparing surgery		Feasible but generally not recommended
	Radical nephrectomy	Open	Recommended standard for most patients
		Laparoscopic	Feasible in selected patients

Adrenalectomy together with tumour nephrectomy, as recommended by Robson, is no longer the gold standard treatment for smaller renal tumours. Removal of the adrenal gland is not recommended provided the adrenal is normal on preoperative CT scans and a direct invasion of the adrenal by a larger upper pole tumour can be excluded [23,24].

Lymphadenectomy should be restricted to the perihilar tissue for staging purposes because extended lymphadenectomy does not seem to reveal an impact on the patient's long-term survival. RCC with a tumour thrombus on the level of the renal vein or inferior vena cava has a higher grade and stage and an increased likelihood for the development of lymph node metastases. The increased biologic aggressiveness as induced by locally advanced tumour growth together with the presence of metastatic deposits within the regional lymph nodes determines the clinical prognosis more than the presence or cranial extension of intracaval thrombosis. Thrombectomy combined with nephrectomy in patients without distant metastasis is recommended [25].

Embolisation of the primary tumour is indicated in case of gross haematuria or local symptoms such as pain [26]. Additionally, it can be beneficial for patients not fit for resection of the primary tumour as well as before the surgical treatment resection of large skeletal metastases. There is no general benefit in performing tumour embolisation before routine radical nephrectomy.

4.2. Nephron-sparing surgery

Absolute indications for partial nephrectomy are an anatomic or functional solitary kidney as well as bilateral RCC. Relative indications include the presence of a functioning opposite kidney that is affected by a condition that might impair renal function during the future as well as patients with hereditary forms of RCC and an increased risk to develop tumour growth within the contralateral kidney [27,28].

The main elective indication is localised unilateral RCC with a healthy contralateral kidney.

Nephron-sparing surgery is generally recommended for patients with tumours <4 cm in diameter, providing recurrence-free and long-term survival rates similar to those of patients subjected to radical nephrectomy [29,30]. Oncologic results equivalent to those observed after a radical approach have been even reported for patients with a tumour diameter of up to 7 cm [31]. However, nephron-sparing surgery cannot be recommended as a standard procedure in these cases. If the tumour is completely resected, the thickness of the surgical margin (>1 mm) does not correlate with the likelihood for local recurrence. If RCCs of larger size are treated with nephron-sparing surgery, the follow-up should be intensified due to an increased risk of intrarenal recurrent disease.

4.3. Laparoscopic nephrectomy

Laparoscopic radical nephrectomy has become an established surgical procedure with a lower morbidity when compared with open surgery [32]. The laparoscopic approach duplicates established open surgical oncologic principles, that is, with early control of the renal vessels before tumour manipulation, wide specimen mobilisation external to Gerota's fascia, avoidance of specimen trauma or rupture, and intact specimen extraction. Today, laparoscopic radical nephrectomy is recommended as a standard of care for patients with T1–2 RCC, and outcome data indicate equivalent cancer-free survival rates when compared with open radical surgery. Laparoscopic nephrectomy can be expected to become a widely distributed treatment option and should be promoted in centres treating RCC.

In experienced hands, partial laparoscopic nephrectomy is an alternative to open surgery for very select patients [33]. The optimal indications are in patients with a relatively small and peripheral renal tumour. Although the oncologic outcome following laparoscopic partial nephrectomy has been suggested to duplicate that of open techniques, larger studies revealing reliable long-term data are not available. Disadvantages of the laparoscopic approach are the longer warm ischaemia time and

increased intraoperative and postoperative complications when compared with open surgery. Therefore, open partial nephrectomy currently remains the standard of care. Laparoscopic partial nephrectomy should be limited to experienced centres.

4.4. Minimally invasive alternative treatment

Minimally invasive techniques such as percutaneous radiofrequency (RF), cryoablation, microwave therapy, and high-intensity focused ultrasound ablation (HIFU) have been suggested as feasible alternatives to the surgical treatment of RCC. Potential advantages of these techniques might include reduced morbidity, treatment on an outpatient basis, and the ability to treat high-risk patients unfit for conventional surgery due to reduced general health conditions [34,35]. Thus, such experimental approaches might be recommended for selected patients with small and incidentally detected renal cortical lesions in elderly patients, in patients with a genetic predisposition to multiple tumours, or in patients with a solitary kidney, or when bilateral tumour growth is present. The oncologic success rate and complications induced by these procedures have to be further evaluated during clinical trials.

4.5. Adjuvant therapy

Current evidence suggests that adjuvant tumour vaccination may improve the duration of the progression-free survival of selected subgroups of patients undergoing nephrectomy for T3 renal carcinomas, but this study needs further confirmation regarding the impact on overall survival [36]. Prognostic algorithms might identify patients who are supposed to derive the largest clinical benefit from an adjuvant vaccination therapy. However, adjuvant therapy with cytokines does not improve the survival after nephrectomy [37]. Outside controlled clinical trials there is today no recommended indication for adjuvant therapy following surgery. The success of the new tyrosine kinase inhibitors in treating metastatic RCC (mRCC) gave rise to a recommendation to participate in adjuvant clinical trials in risk patients with RCC.

5. Treatment of mRCC

5.1. Surgical treatment of mRCC

Tumour nephrectomy is curative only if surgery can excise all tumour deposits. In a meta-analysis of two

randomised studies including only patients with a high performance status, comparing nephrectomy combined with interferon- α (IFN- α) versus IFN- α immunotherapy only, a median survival benefit of 8.1 mo was found in patients treated also with nephrectomy [38]. Nephrectomy in patients with metastatic disease is in first hand indicated for patients who are both suitable for surgery and have good performance status [38,39].

5.2. Resection of metastases

Complete removal of metastatic lesions can contribute to an improvement of clinical prognosis. Adjuvant immunotherapy in case of the complete resection of metastatic lesions or isolated local recurrences does not contribute to an improvement of the clinical prognosis [37]. In patients with synchronous metastatic spread, metastasectomy should be performed in case of resectable disease and a good performance status, although the clinical prognosis is worse when compared with the occurrence of asynchronous metastases.

5.3. Radiotherapy for metastases in RCC

Radiotherapy can be used for selected symptomatic patients with irresectable brain or osseous lesions who do not respond to other conservative treatment approaches [40,41]. In individual cases, mainly the treatment of brain metastases (whole brain irradiation or stereotactic approach) and osseous lesions can induce a relief from symptoms due to mRCC [41,42].

5.4. Systemic therapy for mRCC

5.4.1. Chemotherapy

Because most RCCs develop from the proximal tubules, they have high levels of expression of the multidrug resistance protein P-glycoprotein and are therefore resistant to most chemotherapies. Chemotherapy seems to be effective only if 5-fluorouracil (5-FU) is combined with immunotherapeutic agents but confirming data remain to be reported [43]. Chemotherapy is not recommended in patients with mRCC.

5.4.2. Immunotherapy

In randomised studies, IFN- α has proven superiority for survival over hormonal therapy in patients with mRCC [44]. The patients who benefited were of good WHO status (0-1) and were treated for at least 12 wk and up to 1 yr with an improved survival of several months. Interleukin 2 (IL-2) has been used in mRCC

since 1985 with a substantially higher toxicity than that of IFN- α . Several studies have shown responses ranging from 7% to 27% [45–47]. The optimal IL-2 regimen is not clear, but long-term (>10 yr) complete responders have been achieved with high-dose bolus IL-2 [48]. However, no randomised study has been done against best supportive care. It seems that only clear-cell RCC responds to immunotherapy.

Several randomised studies have been performed to investigate the efficacy of combinations of cytokines. Patient survival was not better than survival achieved with monotherapy [49]. No other combinations with cis-retinoic acid or 5-FU have shown a clinical significant benefit, although some survival advantage has been seen [50,51]. In conclusion, immunotherapy can be beneficial in some good-risk patients with mRCC with clear-cell type of histology.

5.4.3. Angiogenesis inhibitor drugs

Recent advances in the understanding of the molecular biology of RCC have led to the development of several novel agents for the treatment of mRCC. Particularly, VHL inactivation is a common event in sporadic RCC leading to HIF accumulation and therefore to activation of hypoxia-inducible genes including VEGF and PDGF, which are targets for antiangiogenic drugs [52,53]. Recently, two antiangiogenic drugs have been approved both in the United States and in Europe for the treatment of mRCC: sorafenib (Nexavar[®]) and sunitinib (Sutent[®]).

Sorafenib is an oral inhibitor of multiple kinases that has activity against Raf-1 serine/threonine kinase, B-Raf, VEGFR-2, PDGFR, FLT-3, and c-KIT. A phase 3 trial comparing sorafenib and placebo after failure of a prior systemic immunotherapy reported a 24-wk median progression-free survival for sorafenib compared with 12 wk for placebo ($p < 0.000001$). After 3 mo of treatment, 75% of patients taking sorafenib were progression free versus 43% of those taking placebo [54]. Overall survival data have to be awaited, although the crossover use of angiogenesis inhibitors will make the interpretation of survival difficult. Sunitinib is an oxindol tyrosine kinase (TK) inhibitor. It is a small molecule with antitumour and antiangiogenic activity that selectively multi-targets inhibition of PDGFR, VEGFR, KIT, and FLT-3. Two multicentre phase 2 trials with sunitinib as second-line monotherapy in patients with mRCC demonstrated a 34–40% partial response rate and 27–29% of patients had stable disease ≥ 3 mo [55,56]. A phase 3 trial evaluating sunitinib as first-line monotherapy compared to IFN- α has been recently reported.

The median progression-free survival was longer for patients treated with sunitinib (11 mo) than for those treated with IFN- α (5 mo), $p < 0.000001$, suggesting treatment with IFN- α for low- and intermediate-risk patients with mRCC is inferior as first-line therapy compared with sunitinib [57]. Also in this study, overall survival data must be awaited, and the response percentage of only 6% in the IFN- α group is striking.

Temsirolimus, which is a specific inhibitor of mammalian target of rapamycin (mTOR), is also emerging as an important drug in mRCC [53]. A phase 3 trial comparing temsirolimus, IFN- α , and their combination in patients with advanced RCC as first-line therapy has recently been reported. It was clearly demonstrated that temsirolimus monotherapy increases overall survival in poor-risk patients with mRCC compared to IFN- α or combined IFN- α plus temsirolimus treatment [58]. In this study it is confirmed that IFN- α should not be used in poor-risk patients with mRCC because of lack of efficacy [58].

The exact place of the new drugs is still open for discussion; combination studies will be performed in the future. Currently, no data available show that these new agents will cure any patient but rather they seem to stabilise mRCC for a prolonged period. This has to be balanced with the toxicity profile of the drugs and the quality of life.

6. Surveillance following radical surgery

Surveillance after radical surgery allows the urologist to monitor or identify postoperative complications, renal function, local recurrence, recurrence in the contralateral kidney, and development of metastases. Complications and renal function are assessed by history, physical examination, and serum creatinine determinations. Long-term monitoring of creatinine levels is indicated if renal function is impaired preoperatively or postoperatively. Local recurrence is rare (1.8%), but early diagnosis is useful because the most effective treatment is cytoreductive surgery. Recurrence in the contralateral kidney is also rare (2–3%) and is related to positive margins, multifocality, and grade. One reason for surveillance is to identify metastases early so that surgical excision is possible. In addition, an early diagnosis of tumour recurrence might enhance the efficacy of a systemic treatment if the tumour burden is low.

Intensive radiologic surveillance for patients with small well-differentiated tumours is unnecessary because the outcome after surgery for these tumours is almost always excellent. It is therefore

Table 2 – Scoring algorithm to predict metastases after nephrectomy in patients with clear-cell renal cell carcinoma according to the Mayo Scoring System [62]

Feature	Score
Primary tumour/T stage	
T1a	0
pT1b	2
pT2	3
pT3–pT4	4
Tumour size	
<10 cm	0
>10 cm	1
Regional lymph node status	
pNx/pN0 0	0
pN1–pN2 2	2
Nuclear grade	
Grade 1–2	0
Grade 3	1
Grade 4	3
Tumour necrosis	
No necrosis	0
Necrosis	1

Risk groups can be stratified by the scoring system, characterised into low-risk 0–2, intermediate-risk 3–5, and high-risk >6 according to the Mayo Scoring System [62].

reasonable to modify follow-up according to the risk of developing recurrence or metastases [59].

Where the likelihood of relapse is low, chest radiography and US are appropriate. Where the risk is intermediate or high, CT of the chest and abdomen is the investigation of choice, although the morbidity of the radiation dose with repeated CT scans should be considered. Another issue is the optimal duration of follow-up. One may argue that follow-up is not cost effective after 5 yr, but late metastases are more frequently solitary and these justify more aggressive therapy with curative intent. Patients with tumours that develop in the contralateral kidney can be treated with nephron-sparing surgery provided they are detected early. For tumours <4 cm there is no difference in recurrence after partial or radical nephrectomy [60].

Using many of these variables, several groups have designed scoring systems and algorithms to stratify patients into low-, intermediate-, and high-risk groups for developing recurrence or metastases. The frequency and type of investigation are different for each group [61–64]. Table 2 presents an example of these scoring systems and Table 3 shows the accumulated risk of metastases (%) after nephrectomy in patients with clear-cell RCC according to the Mayo Scoring System [64]. The use of these scoring systems allows the urologist to be selective in the use of imaging and to appropriately

Table 3 – Accumulated risk of metastases (%) after nephrectomy in patients with clear-cell renal cell carcinoma as defined in risk groups according to the Mayo Scoring System [62]

Risk group	Year 1	Year 3	Year 5	Year 10
Low	0.5	2.1	2.9	7.5
Intermediate	9.6	20.2	26.2	35.7
High	42.3	62.9	68.8	76.4

target those patients most in need of intensive surveillance.

In cases where there is a very low risk for tumour recurrence or systemic tumour progression, CT scans can be omitted. In the intermediate-risk group, an intensified follow-up that includes CT scans at regular time intervals should be performed according to a risk-stratified nomogram. In high-risk patients, the follow-up examinations should include routine CT scans. Thus, the intensity of the follow-up programme for an individual patient is recommended to be adapted according to the risk of tumour recurrence or systemic tumour progression, as determined by a risk nomogram developed for risk stratification.

Conflicts of interest

There is no conflict of interest between the authors and commercial interests regarding this review.

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