

# Guidelines on Renal Cell Carcinoma

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# 1. INTRODUCTION

The EAU Guideline Group for renal cell carcinoma (RCC) have prepared these guidelines to help urologists assess the evidence-based management of RCC and to help them incorporate the guidelines recommendations into their clinical practice. Publications concerning RCC are mostly retrospective analyses, which include some larger multicentre studies and well-designed controlled studies. As only a few randomised controlled trials are available, there is a lack of data with a strong evidence base.

The recommendations provided in the current guideline are based on a systemic literature search using Medline, the Cochrane Central Register of Controlled Trials, and reference lists in publications and review articles. Where possible a level of evidence (LE) and/or grade of recommendation (GR) have been assigned (1). Recommendations are graded in order to provide transparency between the underlying evidence and the recommendation given (Tables 1 and 2).

There is clearly a need for continuous re-evaluation at regular intervals by the RCC Guideline Group of the information provided in these guidelines. It has to be emphasised that the current guidelines contain 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. A summary of major amendments of the 2009 RCC guidelines update can be found on page 27 of this document.

Publication history information: The Renal Cell Cancer Guidelines were first published in 2000. A partial update was achieved in 2001, followed by a full text update in 2007. The current 2009 version presents a partial update. Additionally, a quick reference guide is available. All texts can be viewed and downloaded for personal use at the society website: <http://www.uroweb.org/professional-resources/guidelines/>.

**Table 1: Level of evidence**

Level	Type of evidence
1a	Evidence obtained from meta-analysis of randomised trials
1b	Evidence obtained from at least one randomised trial
2a	Evidence obtained from one well-designed controlled study without randomisation
2b	Evidence obtained from at least one other type of well-designed quasi-experimental study
3	Evidence obtained from well-designed non-experimental studies, such as comparative studies, correlation studies and case reports
4	Evidence obtained from expert committee reports or opinions or clinical experience of respected authorities

*Modified from Sackett et al. (1).*

**Table 2: Grade of recommendation**

Grade	Nature of recommendations
A	Based on clinical studies of good quality and consistency addressing the specific recommendations and including at least one randomised trial
B	Based on well-conducted clinical studies, but without randomised clinical trials
C	Made despite the absence of directly applicable clinical studies of good quality

*Modified from Sackett et al. (1).*

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# 2. EPIDEMIOLOGY AND AETIOLOGY

Renal cell carcinoma represents 2-3% of all cancers (1), with the highest incidence occurring in Western countries. There is a worldwide and European annual increase in incidence of approximately 2%, though in Denmark and Sweden a continuing decrease has been observed during the last 20 years (2). In 1998, about

30,000 patients were diagnosed with kidney cancer within the EU and approximately 15,000 died of the disease (3).

Renal cell carcinoma is the most common solid lesion within the kidney. It comprises different RCC types with specific histopathological and genetic characteristics (4). There is a 1.5:1 predominance of men over women, with peak incidence occurring between 60 and 70 years of age. Aetiological factors include lifestyle factors, such as smoking, obesity and antihypertensive therapy (2, 5, 6). The most effective prophylaxis is to avoid cigarette smoking.

Due to the increased detection of tumours by imaging techniques, such as ultrasound (US) and computerised tomography (CT), the number of incidentally diagnosed RCCs has increased. These tumours are more often smaller and of lower stage (7-9). However, despite the increased incidental detection rate, after the early 1990s mortality from RCC has stabilized showing a tendency towards decline (10).

## 2.1 Conclusion

A number of aetiological factors have been identified including smoking, obesity and antihypertensive drugs. Cigarette smoking is a definite risk factor for RCC (level of evidence: 2a). The roles of obesity and prolonged intake of antihypertensive medication as risk factors for RCC remain to be definitively clarified (level of evidence: 2a).

### Recommendation

- The most important primary prevention for RCC is to eliminate cigarette smoking and to avoid obesity

GR  
B

GR = grade of recommendation

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## 3. DIAGNOSIS AND STAGING

### 3.1 Symptoms

Many renal masses remain asymptomatic and non-palpable until late in the natural course of the disease (1) (level of evidence: 4). Today, more than 50% of RCCs are detected incidentally using non-invasive imaging to evaluate a variety of non-specific symptom complexes (1) (level of evidence: 4). The classic triad of flank pain, gross haematuria and palpable abdominal mass is now rare (6-10%) (2, 3) (level of evidence: 3).

Paraneoplastic syndromes are found in around 30% of patients with symptomatic RCC, the most common of these being: hypertension, cachexia, weight loss, pyrexia, neuromyopathy, amyloidosis, elevated erythrocyte sedimentation rate, anaemia, abnormal liver function, hypercalcaemia, polycythaemia, etc. (1) (level of evidence: 4).

A minority (25-30%) of patients are diagnosed as a result of symptoms due to metastatic disease, such as bone pain or persistent cough (1) (level of evidence: 4).

#### 3.1.1 Physical examination

Physical examination has a limited role in diagnosing RCC. However, it is valuable in some cases such as:

- palpable abdominal mass
- palpable cervical lymphadenopathy
- non-reducing varicocele
- bilateral lower extremity oedema, which suggests venous involvement.

These findings should initiate radiological examinations.

#### 3.1.2 Laboratory findings

The most commonly assessed laboratory parameters are serum creatinine, haemoglobin, erythrocyte sedimentation rate, alkaline phosphatase and serum calcium (1, 4) (level of evidence: 4). The glomerular filtration rate (GFR) and separate bilateral renal function should be estimated when (5, 6) (level of evidence: 4):

- renal function is of relevant clinical concern, as in patients with a solitary kidney tumour or bilateral tumours
- renal function is compromised, as indicated by an increased concentration of serum creatinine, and in patients at risk for future renal impairment from intercurrent disorders such as diabetes, chronic pyelonephritis, renovascular, stone or renal polycystic disease.

### 3.2 Radiological investigations

Most renal tumours are diagnosed by abdominal ultrasound (US) and CT performed for various reasons (level of evidence: 4).

Detection of a solid renal mass with US should be further investigated with a high-quality CT scan using contrast medium. This will confirm a diagnosis of RCC and provides information on the function and morphology of the contralateral kidney (5) (level of evidence: 3).

- Abdominal CT assesses primary tumour extension with extrarenal spread and provides information on venous involvement, enlargement of locoregional lymph nodes, and condition of adrenal glands and the liver (level of evidence: 3).
- Chest CT is the most accurate investigation for chest staging (6-13) (level of evidence: 3).

However, at the very least, routine chest radiography, as a less accurate alternative to chest CT imaging, must be done for metastatic evaluation (level of evidence: 3).

Magnetic resonance imaging (MRI) can be reserved primarily for patients with locally advanced malignancy, possible venous involvement, renal insufficiency or allergy to intravenous contrast (14-18) (level of evidence: 3). It is also an option for the evaluation of inferior vena cava tumour thrombus extension and unclassified renal masses (level of evidence: 3). Evaluation of the tumour thrombus can also be performed with Doppler US (19) (level of evidence: 3).

In patients with any sign of impaired renal function, a renal scan and total renal function evaluation should be considered in order to optimise the treatment decision, e.g. the need to preserve renal function (6) (level of evidence: 2a).

There is consensus that most bone and brain metastases are symptomatic at the time of diagnosis so that a routine bone scan or brain CT are not generally indicated (20, 21). However, if indicated by clinical or laboratory signs and symptoms, other diagnostic procedures may be applied, such as a bone scan, brain CT or MRI (level of evidence: 3). Renal arteriography, inferior venacavography or fine-needle biopsy (22-24) have only a limited role in the work-up of selected patients with RCC (level of evidence: 3).

### 3.3 Conclusion

In Europe, a large number of patients with RCC are still diagnosed due to clinical symptoms, such as palpable

mass and haematuria, paraneoplastic and metastatic symptoms (level of evidence: 3). However, the number of incidentally detected RCCs is significantly increasing. Accurate staging of RCC with abdominal and chest CT or MRI is obligatory (level of evidence: 3). Chest CT is the most sensitive approach for chest staging. There is no role for routine bone scan or CT of the brain in the standard clinical work-up of asymptomatic patients. There is only a limited indication for fine-needle biopsy (level of evidence: 3).

Recommendations	GR
• In a patient with one or more laboratory or physical findings, the possible presence of RCC should be suspected	A
• A plain chest X-ray can be sufficient for assessment of the lung in low-risk patients, but chest CT is most sensitive	A
• 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	A
• In high-risk patients for bone metastases (raised alkaline phosphatase or bone pain), further evaluation using an imaging approach should be done	A
• Evaluation of renal function is recommended	A

GR = grade of recommendation

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## 4. CLASSIFICATION AND PROGNOSTIC FACTORS

### 4.1 Classification

The 2002 TNM stage classification system is generally recommended for clinical and scientific use (1). It is unclear whether the current TNM classification is optimal for the prediction of survival in patients with RCC and it may require re-classification.

The pT1 substratification, introduced in 2002 (1), has been validated by several studies (2-4) (level of evidence: 3). However, refinements are needed for pT3 tumours. Firstly, it has not been established whether renal sinus fat invasion only carries the same prognosis as does perinephric fat invasion (5, 6). Secondly, many studies have suggested that adrenal invasion is a very poor prognostic factor and that RCCs with this feature should be classified as T4 tumours (7, 8).

Furthermore, it is still not clear whether the stratification of RCCs with venous invasion in T3b and T3c

is accurate. More research is needed to investigate the independent prognostic value of vena caval invasion compared to renal vein invasion (9). More recently, the accuracy of the N1-N2 subclassification has been questioned (10). For adequate M-staging of patients with RCC, accurate pre-operative imaging (currently, chest and abdominal CT) should be performed (11, 12).

## 4.2 Prognostic factors

Factors influencing prognosis can be classified into: anatomical, histological, clinical and molecular (13).

### 4.2.1 Anatomical factors

Anatomical 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 (Table 3).

**Table 3: The 2002 TNM staging classification system**

<b>T - Primary tumour</b>	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
T1	Tumour $\leq 7$ cm in greatest dimension, limited to the kidney
T1a	Tumour $\leq 4$ cm in greatest dimension, limited to the kidney
T1b	Tumour $> 4$ cm but $\leq 7$ cm in greatest dimension
T2	Tumour $> 7$ cm in greatest dimension, limited to the kidney
T3	Tumour extends into major veins or directly invades adrenal gland or perinephric tissues but not beyond Gerota's fascia
T3a	Tumour directly invades adrenal gland or perinephric tissues <sup>1</sup> but not beyond Gerota's fascia
T3b	Tumour grossly extends into renal vein(s) <sup>2</sup> or its segmental branches, or the vena cava below the diaphragm
T3c	Tumour grossly extends into vena cava or its wall above diaphragm
T4	Tumour directly invades beyond Gerota's fascia
<b>N - Regional lymph nodes</b>	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single regional lymph node
N2	Metastasis in more than 1 regional lymph node

pN0 lymphadenectomy specimen ordinarily includes 8 or more lymph nodes. If the lymph nodes are negative, but the number ordinarily examined is not met, classify as pN0.

<b>M - Distant metastasis</b>	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

### TNM stage grouping

Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1, T2, T3	N1	M0
Stage IV	T4	N0, N1	M0
	Any T	N2	M0
	Any T	Any N	M1

<sup>1</sup> Includes renal sinus (prepelvic fat).

<sup>2</sup> Includes segmental (muscle-containing branches).

A help desk for specific questions about TNM classification is available at <http://www.uicc.org/tnm>.

### 4.2.2 Histological factors

Histological factors include Fuhrman grade, histological subtype, sarcomatoid features, microvascular invasion, tumour necrosis and collecting system invasion. Fuhrman nuclear grade is the most widely accepted histological grading system in RCC (14). Although affected by intra- and inter-observer discrepancies, it is an

independent prognostic factor (15) (level of evidence: 3).

According to the World Health Organization (WHO) classification (16), three major histological subtypes of RCC exist (level of evidence: 4):

- conventional (clear cell) (80-90%)
- papillary (10-15%)
- chromophobe (4-5%).

Many studies have shown a trend towards a better prognosis for patients with chromophobe, papillary and conventional (clear cell) RCCs, respectively (17, 18). However, the prognostic information provided by the RCC subtype is lost when stratified to tumour stage (18).

Among papillary RCCs, two subgroups with different outcomes have been identified (19):

- Type I are low-grade tumours with a chromophilic cytoplasm and a favourable prognosis.
- Type II are mostly high-grade tumours with an eosinophilic cytoplasm and a great propensity for developing metastases (level of evidence: 3).

The RCC type subclassification has been confirmed at the molecular level by cytogenetic and genetic analyses (20-22).

#### 4.2.3 Clinical factors

Clinical factors include patient performance status, localised symptoms, cachexia, anaemia and platelet count (23-27) (level of evidence: 3).

#### 4.2.4 Molecular factors

Numerous molecular markers being investigated include: carbonic anhydrase IX (CaIX), vascular endothelial growth factor (VEGF), hypoxia inducible factor (HIF), Ki67 (proliferation), p53, PTEN (phosphatase and tensin homolog) (cell cycle), E-cadherin, and CD44 (cell adhesion) (21, 22) (level of evidence: 3). As yet, these markers are not in widespread use. Recently, gene expression profiling has identified 259 genes, which predict survival independent of clinical prognostic factors in conventional RCCs, indicating that genetic information will improve prognostication (28).

#### 4.2.5 Prognostic systems and nomograms

Post-operative prognostic systems and nomograms that combine independent prognostic factors have been developed and externally validated (29-35). These systems may be more accurate than TNM stage or Fuhrman grade alone for predicting survival (level of evidence: 3). A substantial advantage of nomograms is their ability to measure predictive accuracy (PA), which enables objective evaluation of all new predictive parameters. Recently, new pre-operative nomograms with excellent PA have been designed (36, 37).

### 4.3 Conclusion

In patients with RCC, TNM stage, nuclear grade according to Fuhrman and RCC subtype (WHO, 2004; 16), should be performed because they contribute important prognostic information (level of evidence: 2). There are currently no prognostic integrated systems or molecular markers recommended for routine clinical use. Prognostic systems or nomograms can be useful for the stratified inclusion of patients into clinical trials (level of evidence: 2).

Recommendations	GR
• The current TNM classification system is recommended since it has consequences for prognosis and therapy	B
• The Fuhrman grading system and classification of RCC subtype should be used	B
• The use of integrated prognostic systems or nomograms is not routinely recommended, although these systems can provide a rationale for enrolling patients into clinical trials	B
• No molecular prognostic marker is currently recommended for routine clinical use	B

GR = grade of recommendation

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## 5. TREATMENT OF LOCALISED DISEASE

### 5.1 Surgery

Until recently, radical nephrectomy that included the removal of the tumour-bearing kidney was the gold standard for curative therapy for localised RCC and it still offers a reasonable chance of curing the disease (1).

There is no evidence to favour a specific surgical approach. The evidence also indicates that a routine adrenalectomy is not necessary during the surgical treatment of RCC, provided tumour staging is negative according to pre-operative imaging (CT, MRI). There are two exceptions to this general rule, which are:

- a large upper pole tumour, which is associated with a risk of direct invasion of the adrenal gland
- a tumour of > 7 cm maximum diameter, which is associated with a higher risk of intra-adrenal metastatic spread.

Radical lymph node dissection does not improve survival in patients without clinically detectable lymph nodes and distant metastases (2) (level of evidence: 1a). In patients with palpable or CT-detected enlarged lymph nodes, lymph node dissection should still be performed to obtain adequate stage information.

#### 5.1.1 Embolisation

Indications for tumour embolisation include:

- patients with gross haematuria who are not fit for surgical intervention
- prior to surgical resection of large paravertebral metastases.

There is no benefit in performing tumour embolisation before routine radical nephrectomy (level of evidence: 3) (3-9).

#### 5.1.1.1 Conclusion

Radical nephrectomy according to Robson is no longer the gold standard treatment for smaller renal tumours (level of evidence: 2b). Adrenalectomy is not recommended provided the adrenal is normal on pre-operative CT scan (level of evidence: 3). About half of adrenal metastases develop from larger upper pole tumours (level of evidence: 3). Extended lymphadenectomy does not improve survival in patients without clinically detectable lymph nodes and distant metastases and should be restricted to staging purposes in palpable and CT-detected enlarged lymph nodes (2) (level of evidence: 1b). Renal cell carcinomas with tumour thrombi have a higher stage and grade (level of evidence: 2b). Distant or lymph node metastases are twice as common (level of evidence: 3). This increased biological aggressiveness determines the clinical prognosis more than the presence or the cranial extension of intracaval thrombosis (level of evidence: 3) (10-23).

Recommendations	GR
• Surgical therapy is the only curative therapeutic approach for the treatment of RCC. Routine extended lymph node dissection in patients without detectable lymph nodes does not improve survival and can be restricted to staging purposes	A

• Adrenalectomy, together with nephrectomy, except in the case of large upper pole tumours where direct invasion of the adrenal gland is likely, can be spared in most patients .	B
• Embolisation as a palliative approach can be beneficial in patients unfit for surgery with massive haematuria or profound local pain	C

GR = grade of recommendation

### 5.1.2 Nephron-sparing surgery

Standard indications for nephron-sparing surgery are divided into the following categories:

- absolute (anatomical or functional solitary kidney)
- relative (functioning opposite kidney that is affected by a condition that might impair renal function in future)
- elective (localised unilateral RCC with a healthy contralateral kidney).

Relative indications also include patients with hereditary forms of RCC, who are at high risk of developing a tumour in the contralateral kidney in the future.

#### 5.1.2.1 Conclusion

Nephron-sparing surgery for RCC, when performed in patients with a solitary tumour < 4 cm maximum diameter, provides recurrence-free and long-term survival rates similar to those observed after a radical surgical procedure (level of evidence: 2b) (24-26). Nephron-sparing surgery carried out for absolute rather than elective indications has an increased complication rate and higher risk of developing locally recurrent disease, probably due to the larger tumour size (level of evidence: 3) (27, 28).

There is some evidence that radical nephrectomy compared to nephron-sparing surgery carries an increased risk of impaired renal function, resulting in chronic renal insufficiency and proteinuria (level of evidence: 3) (29-31).

In a few series, even patients with larger tumours (up to 7 cm), who have undergone nephron-sparing surgery, have shown oncological outcomes equivalent to those of radical surgery. If the tumour is completely resected, the thickness of the surgical margin does not impact on the likelihood of local recurrence (level of evidence: 3).

Recommendations	GR
• Nephron-sparing surgery is an established curative approach for the treatment of RCC	B
• Nephron-sparing surgery for tumours $\geq$ 4-7 cm maximum diameter can be performed in centres with expertise in selected patients	B
• A minimal tumour-free surgical margin following partial resection of RCC appears appropriate to avoid the increased risk of local recurrence	B
• If tumours of larger size are treated with nephron-sparing surgery, follow-up should be intensified due to an increased risk of intrarenal recurrence	B

GR = grade of recommendation

### 5.1.3 Laparoscopic nephrectomy

Since its introduction, laparoscopic nephrectomy for RCC has become an established surgical procedure worldwide. Whether done retro- or trans-peritoneally, the laparoscopic approach must duplicate established open surgical oncological principles, which are:

- early control of the renal vessels before tumour manipulation
- wide specimen mobilisation external to Gerota's fascia
- avoidance of specimen traumatising or rupture
- intact specimen extraction.

In the hands of experienced laparoscopic urological surgeons, and adhering to these principles of open radical nephrectomy, laparoscopic radical nephrectomy may now be considered a standard of care for patients with T1-2 RCCs. Intermediate outcome data indicate equivalent cancer-free survival rates when compared with open radical nephrectomy.

#### 5.1.3.1 Conclusion

Laparoscopy for radical nephrectomy has a lower morbidity when compared with open surgery (level of evidence: 3). Tumour control rates appear equivalent for T1-2 and possible T3a tumours in experienced hands (level of evidence: 3).

Recommendation	GR
• Laparoscopic tumour nephrectomy should be performed in centres with laparoscopic expertise	B
• Laparoscopic tumour nephrectomy is likely to become a widely distributed treatment option. It can be promoted in specialised centres treating kidney tumours	B

GR = grade of recommendation

#### 5.1.4 Partial laparoscopic nephrectomy

In experienced hands, laparoscopic partial nephrectomy is an alternative to open nephron-sparing surgery for selected patients (32-35). The optimal indication for laparoscopic nephron-sparing surgery is a relatively small and peripheral renal tumour. It has been suggested that the oncological outcome following laparoscopic partial nephrectomy duplicates that of open nephron-sparing surgery (36, 37). However, currently, there are no larger studies able to reveal reliable long-term equivalence.

Suggested disadvantages of the laparoscopic approach are the longer warm ischaemia time and increased intra-operative and post-operative complications compared with open surgery (38-40).

##### 5.1.4.1 Conclusion

Partial nephrectomy by laparoscopic surgery is technically feasible (level of evidence: 2b).

Recommendations	GR
• Open partial nephrectomy currently remains the standard of care	C
• Laparoscopic partial nephrectomy should be limited to experienced centres	C

GR = grade of recommendation

## 5.2 Alternative treatments to surgery

Suggested alternatives to the surgical treatment of RCC have included image-guided percutaneous and minimally invasive techniques, e.g. percutaneous radiofrequency (RF) ablation (41, 42), cryoablation (43), microwave ablation, laser ablation and high-intensity focused ultrasound ablation (HIFU) (level of evidence: 2b) (44). Possible advantages of these and other techniques include reduced morbidity, outpatient therapy, and the ability to treat high-risk surgical candidates (level of evidence: 2b).

Indications for minimally invasive techniques, including RF ablation, are small, incidentally found, renal cortical lesions in elderly patients, patients with genetic predisposition to multiple tumours, or patients with a solitary kidney, or bilateral tumours (level of evidence: 2b).

Contraindications to the above-mentioned procedures include a poor life expectancy of < 1 year, multiple metastases, or difficulty for successful treatment due to size or location of tumour. In general, tumours > 5 cm or tumours in the hilum, the proximal ureter or central collecting system are not typically recommended for RF ablation (45). Absolute contraindications include irreversible coagulopathies or severe medical instability, such as sepsis.

Although, even in high-risk patients, the reported complication rates are low, greater multicentre experience is needed to define the oncological success and complications of these procedures as an alternative to open or laparoscopic surgery.

##### 5.2.1 Conclusion

The formerly mentioned, minimally invasive approaches currently have the status of experimental treatment options for kidney cancer. Their efficacy should be further evaluated within clinical trials. Their disadvantage is a lack of adequate histopathological evaluation. However, their advantage is decreased invasiveness, enabling treatment of less well patients with a poor performance status and unfit for conventional surgery (level of evidence: 3).

Recommendation	GR
• Currently, patients not suitable for open or laparoscopic surgery due to a poor performance status with smaller peripheral tumours should be considered for non-surgical alternative techniques	B
• These techniques include image-guided percutaneous and minimally invasive techniques, e.g. percutaneous radiofrequency ablation, cryoablation, microwave ablation, laser ablation and high-intensity focused ultrasound ablation	B

GR = grade of recommendation

## 5.3 Adjuvant therapy

There is evidence that adjuvant tumour vaccination might improve the duration of the progression-free survival of selected subgroups of patients undergoing nephrectomy for T3 renal carcinomas. However, further confirmation is needed regarding the impact on overall survival (level of evidence: 1b) (46-50). Prognostic

algorithms might identify patients likely to benefit most from adjuvant vaccination therapy.

### 5.3.1 Conclusion

Adjuvant therapy with cytokines does not improve survival after nephrectomy (level of evidence: 1b).

Recommendation	GR
<ul style="list-style-type: none"> <li>• Outside controlled clinical trials, there is no indication for adjuvant therapy following surgery</li> </ul>	A

GR = grade of recommendation

## 5.4 Surgical treatment of metastatic RCC (tumour nephrectomy)

Tumour nephrectomy is curative only if surgery can excise all tumour deposits. For most patients with metastatic disease, tumour nephrectomy is palliative and other systemic treatments are necessary.

A meta-analysis of two randomised studies comparing nephrectomy + immunotherapy versus immunotherapy only showed that long-term survival increased in patients subjected to tumour nephrectomy (51). Nephrectomy in patients with metastatic disease is indicated for patients who are both suitable for surgery and have a good performance status (52).

### 5.4.1 Conclusion

Tumour nephrectomy in combination with interferon-alpha (IFN-alpha) improves the survival of patients with metastatic RCC (mRCC) and a good performance status (level of evidence: 1b).

Recommendation	GR
<ul style="list-style-type: none"> <li>• Tumour nephrectomy is recommended for metastatic RCC patients with a good performance status A when combined with IFN-alpha</li> </ul>	A

GR = grade of recommendation

## 5.5 Resection of metastases

Complete removal of metastatic lesions contributes to an improvement of clinical prognosis. Immunotherapy, where there has been complete resection of metastatic lesions or isolated local recurrences, does not contribute to an improvement in clinical prognosis (level of evidence: 2b) (52-56).

### 5.5.1 Conclusion

Metastasectomy in patients with RCC has a definite role in improving the clinical prognosis (level of evidence: 3).

Recommendations	GR
<ul style="list-style-type: none"> <li>• In patients with synchronous metastatic spread, metastasectomy should be performed when disease is resectable and the patient has a good performance status</li> </ul>	B
<ul style="list-style-type: none"> <li>• The clinical prognosis is worse in patients who have surgery for metachronous metastases</li> </ul>	B
<ul style="list-style-type: none"> <li>• Metastasectomy should be performed in patients with residual and resectable metastatic lesions previously responding to immunotherapy and/or a limited (solitary lesion) number of metachronous metastases in order to improve the patient's prognosis</li> </ul>	B

GR = grade of recommendation

## 5.6 Radiotherapy for metastases in RCC

Radiotherapy can be used for selected symptomatic patients with non-resectable brain or osseous lesions who do not respond to other conservative treatment approaches (57, 58).

### 5.6.1 Conclusion

Radiotherapy of metastases from RCC can induce significant relief from symptoms, e.g. reduction of pain from a single bony deposit (level of evidence: 2b).

Recommendation	GR
<ul style="list-style-type: none"> <li>• In individual cases, radiotherapy for brain metastases (whole brain irradiation or stereotactic approach) and osseous lesions can induce relief from symptoms due to mRCC (59, 60)</li> </ul>	B

GR = grade of recommendation

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## 6. SYSTEMIC THERAPY FOR METASTATIC RCC

### 6.1 Chemotherapy

Since RCCs develop from the proximal tubules, they have high levels of expression of the multiple-drug resistance protein P-glycoprotein and are therefore resistant to most chemotherapies. Chemotherapy seems to be effective only if 5-fluorouracil (5FU) is combined with immunotherapeutic agents (1).

#### 6.1.1 Conclusion

Only 5FU in combination with immunotherapy seems to be effective in patients with mRCC (level of evidence: 3).

Recommendation	GR
• Chemotherapy as monotherapy should not be considered effective in patients with mRCC	B

GR = grade of recommendation

## 6.2 Immunotherapy

### 6.2.1 Interferon-alpha monotherapy and combined with bevacizumab

In randomised studies, IFN-alpha has proven superiority for survival over hormonal therapy in patients with mRCC (2). Interferon-alpha provided a response rate of 6-15%, together with a 25% decrease in the risk for tumour progression, and a modest survival benefit of 3-5 months when compared with placebo-equivalent (3, 4). Recently, bevacizumab + IFN-alpha demonstrated increased response rates and progression-free survival in first-line therapy compared to IFN-alpha monotherapy (5, 6). All recent randomised studies comparing anti-angiogenic drugs in a first-line setting to IFN-alpha monotherapy have demonstrated a superiority for either sunitinib, bevacizumab + IFN-alpha or temsirolimus (5-8).

#### 6.2.1.1 Conclusion

Interferon-alpha monotherapy is no longer recommended as first-line therapy for mRCC (level of evidence: 1b).

### 6.2.2 Interleukin-2

Interleukin-2 (IL-2) has been used to treat mRCC since 1985 with response rates ranging from 7-27% (8-10). The optimal IL-2 regimen is not clear, but long-term (> 10 years) complete responders have been achieved with high-dose bolus IL-2 (11). The toxicity of IL-2 is substantially higher than that of IFN-alpha. It seems that only clear cell type RCC responds to immunotherapy. Interleukin-2 has not been validated in controlled randomised studies compared with best supportive care (4).

#### 6.2.2.1 Conclusion

Interleukin-2 has more side-effects than INF-alpha. High-dose IL-2 gives durable complete responders in a limited number of patients. Interleukin-2 remains the only cytokine suitable for monotherapy in selected patients with a good prognosis profile.

Recommendations	GR
• Monotherapy with IFN-alpha can no longer be recommended as a first-line treatment for mRCC.	A
• Bevacizumab + IFN-alpha is recommended as first-line therapy in low- and intermediate-risk patients. Only selected patients with mRCC, revealing a good risk profile, and clear cell subtype histology, show clinical benefit from immunotherapy with IL-2.	B
• Cytokine combinations, with or without additional chemotherapy, do not improve overall survival compared with monotherapy	A

GR = grade of recommendation

## 6.3 Angiogenesis inhibitor drugs

Recent advances in molecular biology have led to the development of several novel agents for the treatment of mRCC (Table 4).

In sporadic clear cell RCC, HIF accumulation due to von Hippel Landau (VHL) inactivation, results in overexpression of VEGF and PDGF (platelet-derived growth factor), both of which promote neo-angiogenesis (12-14). This process substantially contributes to the development and progression of RCC. At present, four targeting drugs have been approved both in the USA and in Europe for the treatment of mRCC:

- sorafenib (Nexavar<sup>®</sup>)
- sunitinib (Sutent<sup>®</sup>)
- bevacizumab (Avastin<sup>®</sup>) combined with IFN-alpha
- temsirolimus (Torisel<sup>®</sup>).

Several other new agents targeting angiogenesis are under investigation, as well as combinations of these new agents with each other or with cytokines.

### 6.3.1 Sorafenib

Sorafenib is an oral multikinase inhibitor with activity against Raf-1 serine/threonine kinase, B-Raf, vascular endothelial growth factor receptor-2 (VEGFR-2), platelet-derived growth factor receptor (PDGFR), FMS-like tyrosine kinase 3 (FLT-3) and c-KIT. A phase III trial comparing sorafenib and placebo after failure of a prior systemic immunotherapy reported a 3-month improvement in progression-free survival in favour of sorafenib (15). Survival seems to improve in patients crossed over from placebo to sorafenib treatment (16).

### 6.3.2 Sunitinib

Sunitinib is an oxindol tyrosine kinase (TK) inhibitor. It selectively inhibits PDGFR, VEGFR, KIT and FLT-3 and has anti-tumour and anti-angiogenic activity. Phase II trials with sunitinib as second-line monotherapy in patients with mRCC demonstrated a partial response rate in 34-40% of patients and stable disease > 3 months in 27-29% of patients (17).

In a recent phase III trial of first-line monotherapy that compared treatment with sunitinib to IFN-alpha, sunitinib achieved a longer progression-free survival than with IFN-alpha (11 vs 5 months,  $p < 0.000001$ ). Results suggested monotherapy with IFN-alpha was inferior compared to sunitinib in low- and intermediate-risk patients with mRCC (18). Overall survival was 26.4 and 21.8 months in the sunitinib and IFN-alpha arms, respectively ( $p = 0.05$ ) (18). In patients crossed over from IFN-alpha to sunitinib ( $n = 25$ ), median survival times were 26.4 versus 20.0 months for sunitinib and IFN-alpha, respectively ( $p = 0.03$ ). In patients who did not receive any post-study treatment, the median overall survival reached 28.1 months in the sunitinib group versus 14.1 months in the IFN-alpha group ( $p = 0.003$ ).

### 6.3.3 Bevacizumab monotherapy and combined with interferon-alpha

Bevacizumab is a humanised monoclonal antibody that binds isoforms of VEGF-A. Bevacizumab, 10 mg/kg every 2 weeks, in patients refractory to immunotherapy showed an increase in overall response (10%) and in progression-free survival versus placebo (19). A recent double-blind phase III trial ( $n = 649$ ) in mRCC compared bevacizumab + IFN-alpha to IFN-alpha monotherapy (5). The median overall response was 31% in the bevacizumab + IFN-alpha group versus 13% in the IFN-alpha only group ( $p < 0.0001$ ). Median progression-free survival increased significantly from 5.4 months with IFN-alpha to 10.2 months for bevacizumab + IFN-alpha ( $p < 0.0001$ ), but only in low-risk and intermediate-risk patients. No benefit was seen in high-risk patients. No mature data are yet available on overall survival.

### 6.3.4 Mammalian target of rapamycin (mTOR) inhibitors

#### 6.3.4.1 Temsirolimus

Temsirolimus is a specific inhibitor of mammalian target of rapamycin (mTOR) (20). Patients with high-risk mRCC were randomised to receive first-line treatment with temsirolimus or IFN-alpha monotherapy or in combination. In the temsirolimus group, overall survival was 10.9 months versus 7.3 months in the IFN- group ( $p < 0.0069$ ). However, overall survival in the temsirolimus + IFN-alpha group was not significantly improved (7).

#### 6.3.4.2 Everolimus

Everolimus is an oral mTOR inhibitor. A recent phase III study compared everolimus plus best supportive care (BSC) versus placebo plus BSC in patients who had failed previous anti-VEGF-R treatment. Median progression-free survival was 4 months with everolimus versus 1.9 months with placebo ( $p < 0.001$ ) (12, 21).

**Table 4: Updated recommendations for first- and second-line systemic therapy in mRCC**

Treatment	Risk or prior treatment	Recommended agent
• 1st-line therapy	Low- or intermediate-risk	Sunitinib Bevacizumab + IFN-alpha
	High risk	Temsirolimus
• 2nd-line therapy	Prior cytokine	Sorafenib
	Prior VEGFR	Everolimus
	Prior mTOR(-)	Clinical trials

### 6.3.5 Conclusion

Tyrosine kinase inhibitors (TKIs) increase progression-free survival and or overall survival as both first- and second-line treatment of mRCC (level of evidence: 1b). Sorafenib has proven efficacy as second-line treatment after failure of cytokine therapy (level of evidence: 1b). Sunitinib is more effective than IFN-alpha in treatment-naïve, low- and intermediate-risk tumours (level of evidence: 1b). The association between bevacizumab and IFN-alpha is more effective than IFN-alpha in treatment-naïve, low- and intermediate-risk tumours (level of evidence: 1b). Temsirolimus monotherapy in high-risk mRCC patients is more effective than IFN-alpha or temsirolimus + IFN-alpha (level of evidence: 1b). Everolimus prolongs progression-free survival in patients who have failed treatment with TKIs.

The role of the new drugs is still under development and combination studies are ongoing. To date, no data are available indicating the new agents have a curative effect. These agents appear to promise to stabilise mRCC for a prolonged period of time. However, their promise has to be balanced against their toxicity profile and the patient's quality of life (level of evidence: 4).

Recommendations	GR
• Sunitinib is recommended as first-line therapy in low- and intermediate-risk patients	A
• Bevacizumab + IFN-alpha is recommended as first-line therapy in low- and intermediate-risk patients	A
• Sorafenib is recommended as a second-line treatment for mRCC after cytokine failure	A
• Temsirolimus is recommended as first-line treatment in high-risk patients	A
• Everolimus can be recommended as second-line treatment after failure of tyrosine kinase inhibitors	A

GR = grade of recommendation

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## 7. SURVEILLANCE FOLLOWING RADICAL SURGERY FOR RCC

### 7.1 Introduction

Surveillance after radical surgery allows the urologist to monitor or identify:

- post-operative complications
- renal function
- local recurrence
- recurrence in the contralateral kidney
- development of metastases.

The method and timing of investigation has been the subject of many publications. There is no consensus on surveillance after radical surgery of the kidney.

Post-operative complications and renal function are readily assessed by history, physical examination and measurement of serum creatinine. Repeated long-term monitoring of creatinine levels is indicated if there is impaired renal function before surgery or a post-operative significant increase in the serum creatinine level (1). Local recurrence is rare (1.8%), but early diagnosis is useful since the most effective treatment is

cytoreductive surgery (2, 3). Recurrence in the contralateral kidney is also rare (1.2%) and is related to positive margins, multifocality and grade (4).

The reason for surveillance is to identify metastases early. This is because a greater extension of tumour growth can reduce the possibility of surgical resection, which is considered the standard therapy in cases of resectable and, preferably solitary, metastatic lesions. In addition, within clinical trials, an early diagnosis of tumour recurrence might enhance the efficacy of a systemic treatment if the tumour burden is low.

## 7.2 Which investigations for which patients, and when?

Repeated intensive radiological surveillance for all patients is unnecessary because, for example, the outcome after surgery for small, well-differentiated tumours is almost always excellent. It is therefore reasonable to modify follow-up, taking into account the risk of developing recurrence or metastases. No randomised evidence exists, but there are large studies with long follow-up from which some conclusions can be drawn (level of evidence: 4).

Prognostic factors can be classified into: anatomical (tumour size and stage, venous invasion, adrenal involvement, lymph node status), histological (grade, sarcoma, necrosis and collecting system invasion), clinical (performance status, anaemia, platelet count, cachexia) and molecular (5, 6). Although many molecular markers, using immunotherapy, vaccine, gene and angiogenesis techniques, are being investigated, none are yet in widespread use. Detailed information on molecular markers can be found in Section 4.2 Prognostic factors.

## 7.3 Imaging modalities

Where there is a low likelihood of relapse, chest X-ray and US are appropriate. Where the risk is intermediate or high, the investigation of choice is CT of chest and abdomen, though the significant morbidity of radiation dose with repeated CT scans should be taken into account (7).

Dependent on the availability of new effective treatments, more strict follow-up schedules may be required. A problematic issue is the optimal duration of follow-up. It can be argued that follow-up by imaging is not cost effective after 5 years (8). Late metastases are more frequently solitary and justify more aggressive therapy with curative intent. Also, patients with small tumours in the contralateral kidney (2-3%) can be treated with nephron-sparing surgery. Furthermore, for tumours  $\leq 4$  cm, there seems to be no difference in recurrence between partial and radical nephrectomy (9).

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 tumour recurrence or metastases. The frequency and type of investigation are different for each group (10-13). Examples of these scoring systems are shown in Tables 5 and 6.

**Table 5: Scoring algorithm to predict metastases after nephrectomy in patients with clear cell RCC according to the Mayo Scoring System (13).**

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

Risk groups can be stratified according to the Mayo Scoring System (13) into low-risk, 0-2, intermediate-risk,

3-5, and high-risk, > 6. The use of scoring systems, such as the Mayo System, helps the urologist to select the use of imaging and to appropriately target those patients most in need of intensive surveillance.

**Table 6: Accumulated risk of metastases (%) after nephrectomy in patients with clear cell RCC as defined in risk groups according to the Mayo Scoring System (13).**

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

#### 7.4 Conclusion

In cases with a very low risk for tumour recurrence or systemic tumour progression, CT scans can be omitted as routine follow-up examinations. In these patients, a CT scan is only justified in cases of possible tumour-associated symptoms. 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 (level of evidence: 4).

Recommendation	GR
• The intensity of the follow-up programme for an individual patient should be adapted according to the risk of tumour recurrence or systemic tumour progression, as determined by a risk nomogram developed for risk stratification	C

GR = grade of recommendation

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The current document provides a limited update, with a summary of the amendments provided below.

## 8. Summary of major amendments of the 2009 RCC guidelines update

Prognosis	
•	Prognostic nomograms have been validated and one advantage of nomograms is their ability to measure predictive accuracy.
Treatment	
•	Interferon-alpha (IFN-alpha) is not recommended in a first-line setting as monotherapy in the treatment of metastatic RCC (mRCC)
•	Bevacizumab + IFN-alpha is recommended as first-line therapy in low- and intermediate-risk patients
•	Everolimus can be recommended as second-line therapy after tyrosine kinase inhibitor (TKI) failure

## 9. ABBREVIATIONS USED IN THE TEXT

*This list is not comprehensive for the most common abbreviations*

5FU	5-fluorouracil
BSC	best supportive care
CT	computerised tomography
FLT-3	FMS-like tyrosine kinase 3
HIF	hypoxia inducible factor
HIFU	high-intensity focused ultrasound
IFN-alpha	interferon-alpha
IL-2	interleukin-2
mRCC	metastatic renal cell carcinoma
MRI	magnetic resonance imaging
mTOR	mammalian target of rapamycin
PA	predictive accuracy
PDGF	platelet-derived growth factor
PDGFR	platelet-derived growth factor receptor
RCC	renal cell carcinoma
RF	radiofrequency
TNM	Tumour Node Metastasis
US	abdominal ultrasound
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor
VHL	von Hippel-Lindau
WHO	World Health Organization

### **Conflict of interest**

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