Guidelines on
Renal Cell Carcinoma

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1. INTRODUCTION

The EAU Guideline Group for renal cell carcinoma (RCC) have prepared this guideline to help urologists assess the evidence-based management of RCC and to incorporate the guideline recommendations into their clinical practice. Publications concerning RCC are mostly based on retrospective analysis, including some larger multicentre studies and well-designed controlled studies. Only a few randomized studies are available, so that it is difficult to obtain qualified evidence-based data.

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. The level of evidence available for the information given in this guideline (an update of the EAU guidelines on RCC published in 2002) is listed below (Table 1).

There is clearly a need for continuous re-evaluation of the information inherent in the current guideline at regular intervals by the RCC Guideline Group. It has to be emphasized that the current guideline contains information for the treatment of an individual patient according to a standardized general approach. The information should be considered as providing recommendations without legal implications.

Table 1: Levels of evidence and grade of guideline recommendations as used by EAU (1)

Level	Type of evidence
1a	Evidence obtained from meta-analysis of randomized trials
1b	Evidence obtained from at least one randomized trial
2a	Evidence obtained from one well-designed controlled study without randomization
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

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

2. BACKGROUND: EPIDEMIOLOGY AND AETIOLOGY

Renal cell carcinoma represents 2-3% of all cancers (2), 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 (3). In 1998, about 30,000 patients were diagnosed with kidney cancer within the EU and approximately 15,000 died of the disease (4).

Renal cell carcinoma is the most frequently occurring solid lesion within the kidney and comprises different RCC types with specific histopathological and genetic characteristics (5). 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 (3,6,7). The most effective prophylaxis is to avoid cigarette smoking.

Due to the increased detection of tumours by the use of imaging techniques such as ultrasound and computerized tomography (CT), an increasing number of incidentally diagnosed RCCs are found. These tumours are more often smaller and of lower stage (8-10). Despite the increased incidental detection rate, the mortality from RCC has remained unaffected and parallel to the incidence.

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).

2.2 Recommendation

The most important primary prevention for RCC is to eliminate cigarette smoking and to avoid obesity (grade B 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 for the evaluation of 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 rarely found (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 are: 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 of patients present with symptoms directly caused by metastatic disease, such as bone pain or persistent cough (1) (level of evidence: 4). Still, 25-30% of patients are diagnosed due to symptoms associated with metastatic disease.

3.1.1 Physical examination

Physical examination has a limited role in diagnosing RCC, but it may be valuable in some cases such as palpable abdominal mass, palpable cervical lymphadenopathy, non-reducing varicocele or 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 haemoglobin, erythrocyte sedimentation rate, alkaline phosphatase and serum calcium (1,4) (level of evidence: 4).

3.2 Radiological investigations

The majority of 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. It serves to verify the 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), but at least routine chest radiography, as a less accurate alternative, 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). Magnetic resonance imaging is also an option for the evaluation of inferior vena cava tumour thrombus extension and the evaluation of unclassified renal masses (level of evidence: 3). Evaluation of the tumour thrombus can also be performed with Doppler US in such cases (19) (level of evidence: 3).

There is consensus that most bone and brain metastases are symptomatic at the time of diagnosis and that routine bone scan or brain CT are not generally indicated (20,21). If indicated by clinical or laboratory signs and symptoms, other diagnostic procedures may be applied, such as 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 clinical work-up of patients with RCC, but may be considered in selected cases (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). 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).

3.4 Recommendation

In a patient with one or more of these laboratory or physical findings, the possible presence of RCC should be suspected. A plain chest X-ray 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. In high-risk patients for bone metastases (raised alkaline phosphatase or bone pain), further evaluation utilizing an imaging approach should be done (grade A 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 might be a subject for re-classification. The pT1 substratification, introduced in 2002 (1), has been validated by a number of studies (2-4) (level of evidence: 3).

However, refinements remain to be performed for pT3 tumours. Firstly, for renal sinus fat invasion only, it has not been established whether this carries the same prognostic information as does perinephric fat invasion (5,6). Secondly, many studies have suggested that adrenal invasion represents a very poor prognostic group.

It has been suggested that these RCCs 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. Additional studies are required to investigate the independent prognostic value of vena caval invasion compared with 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, an accurate pre-operative imaging procedure, which is 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 2: The 2002 TNM staging classification system

T -	**Primary tumour**		
	TX	Primary tumour cannot be assessed	
	T0	No evidence of primary tumour	
	T1	Tumour ≤ 7 cm in greatest dimension, limited to the kidney	
		T1a	Tumour ≤ 4 cm in greatest dimension, limited to the kidney
		T1b	Tumour > 4 cm but ≤ 7 cm in greatest dimension, but not more than 7 cm
	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[1] but not beyond Gerota's fascia
		T3b	Tumour grossly extends into renal vein(s)[2] 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	
N -	**Regional lymph nodes**		
	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

M -	**Distant metastasis**	
	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

[1]*Includes renal sinus (prepelvic fat).*

[2]*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, presence of 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 it is subject to intra- and inter-observer discrepancies, it remains an independent prognostic factor (15) (level of evidence: 3).

According to the WHO classification (16), three major histological subtypes of RCC exist: conventional (clear cell) (80-90%), papillary (10-15%) and chromophobe (4-5%) (level of evidence: 4). 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 of 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, localized symptoms, cachexia, anaemia, platelet count (23-27) (level of evidence: 3).

4.2.4 Molecular factors

There are numerous molecular markers being investigated including: carbonic anhydrase IX (CaIX), vascular endothelial growth factor (VEGF), hypoxia inducible factor (HIF), Ki67 (proliferation), p53, PTEN (cell cycle), E-cadherin, abd 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

Prognostic systems and nomograms that combine independent prognostic factors have been recently developed. It has been suggested that these systems are more accurate than TNM stage or Fuhrman grade alone for predicting survival (29-32) (level of evidence: 3).

4.3 Conclusion

In patients with RCC, TNM stage, nuclear grade according to Fuhrman and RCC subtype (WHO 2004) 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)

4.4 Recommendations for classification and prognosis

The current TNM classification system is recommended since it has consequences for prognosis and therapy. Fuhrman grading system and classification of RCC subtype should be used. The use of integrated prognostic systems or nomograms is not routinely recommended, although these systems provide a rationale for a prognostic prediction useful for including patients in clinical trials. No molecular prognostic marker is currently recommended for utilization in the clinical routine (grade B recommendation).

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5. TREATMENT OF LOCALIZED DISEASE

5.1 Surgery

Radical nephrectomy that includes the removal of the tumour-bearing kidney remains the gold standard curative therapy for patients with localized RCC and offers a reasonable chance of curing the disease (1).

There is no evidence to favour a specific surgical approach. Except in the case of a large upper pole tumour, which is associated with a risk of direct invasion of the adrenal gland, or a tumour of > 7 cm maximum diameter, which is associated with a higher risk of intra-adrenal metastatic spread, there is evidence that a routine adrenalectomy is unnecessary during the surgical treatment of RCC, provided the pre-operative imaging procedures for tumour staging (CT, MRI) reveal negative findings.

5.1.1 Embolization

Indications for tumour embolization include patients with gross haematuria who are not fit for surgical intervention and prior to surgical resection of large paravertebral metastases. There is no benefit in performing tumour embolization before routine radical nephrectomy (level of evidence: 3) (2-8).

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). Lymphadenectomy should be restricted to the perihilar tissue for staging purposes since extended lymphadenectomy does not improve survival (level of evidence: 2b). 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) (9-22).

5.1.1.2 Recommendation

Surgical therapy is the only curative therapeutic approach for the treatment of RCC. In some selected cases with lymph node disease limited to the retroperitoneal space, extended lymphadenectomy might improve a patient's clinical prognosis. In general, extended lymphadenectomy cannot be considered to be the therapeutic standard. 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 the majority of patients (grade B recommendation). Embolization as a palliative approach can be beneficial in patients unfit for surgery with massive haematuria or profound local pain (grade C 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 (localized 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 less than < 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) (23-25).

After nephron-sparing surgery for absolute indications compared with elective indications, both the complication rate and the risk of developing locally recurrent disease appear to be elevated, probably due to the larger tumour size (level of evidence: 3) (26,27). There is some evidence that patients subjected to radical

nephrectomy compared with nephron-sparing surgery for RCC have an increased risk of impaired renal function, resulting in chronic renal insufficiency and proteinuria (level of evidence: 3) (28-30).
In a few series, even patients with a tumour diameter up to 7 cm have been subjected to nephron-sparing surgery, delivering oncological results equivalent to those observed after a radical approach. If the tumour is completely resected, the thickness of the surgical margin does not impact on the likelihood for local recurrence (level of evidence: 3).

5.1.2.2 Recommendation
Nephron-sparing surgery is an established curative approach for the treatment of patients with RCC. Nephron-sparing surgery for the treatment of tumours more than 4-7 cm maximum diameter can be performed in centres with expertize in appropriate cases. A minimal tumour-free surgical margin following partial resection of kidney cancer appears appropriate to avoid the increased risk of local recurrence. If tumours of larger size are treated with nephron-sparing surgery, the follow-up should be intensified due to an increased risk of intrarenal recurrences (grade B 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 has to duplicate established open surgical oncological principles, i.e. early control of the renal vessels before tumour manipulation, wide specimen mobilization external to Gerota's fascia, avoidance of specimen traumatization or rupture, and intact specimen extraction.

In the hands of experienced laparoscopic urological surgeons, and with adherence to the above-mentioned 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).

5.1.3.2 Recommendation
Laparoscopic tumour nephrectomy should be performed in centres with laparoscopic expertize. Laparoscopic tumour nephrectomy can be expected to become a widely distributed treatment option and should be promoted in centres treating kidney tumours (grade B recommendation).

5.1.4 Partial laparoscopic nephrectomy

In experienced hands, laparoscopic partial nephrectomy might be an alternative to open nephron-sparing surgery for very selected patients (31-34). The optimal indication for laparoscopic nephron-sparing surgery is a relatively small and peripheral renal tumour. Although the oncological outcome following laparoscopic partial nephrectomy has been suggested to duplicate that of open techniques of nephron-sparing surgery (35,36), larger studies that would reveal reliable long-term equivalence are not available at present. Suggested disadvantages of the laparoscopic approach are the longer warm ischaemia time and increased intra-operative and post-operative complications when compared with open surgery (37-39).

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

5.1.4.2 Recommendation
Open partial nephrectomy currently remains the standard of care. Laparoscopic partial nephrectomy should be limited to experienced centres (grade C recommendation).

5.2 Alternative treatment

Image-guided percutaneous and minimally invasive techniques, e.g. percutaneous radiofrequency (RF) ablation (40,41), cryoablation (42), microwave ablation, laser ablation and high-intensity focused ultrasound ablation (HIFU) have been suggested as alternatives to the surgical treatment of RCC (level of evidence: 2b) (43).

Potential advantages of these and other techniques might 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 include 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 (44). 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 required to define the oncological success and complications after use 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 patients with reduced health condition, who are otherwise not fit for conventional surgery (level of evidence: 3).

5.2.2 Recommendation

Currently, patients not suitable for open or laparoscopic surgery due to poor performance status with smaller peripheral tumours should be considered for the above-mentioned techniques for RCC treatment (grade B recommendation).

5.3 Adjuvant therapy

Current 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 needs further confirmation regarding the impact on overall survival (level of evidence: 1b) (45-49). Prognostic algorithms might identify patients likely to derive the largest clinical benefit from adjuvant vaccination therapy.

5.3.1 Conclusion

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

5.3.2 Recommendation

Outside controlled clinical trials, there is no indication for adjuvant therapy following surgery (grade A recommendation).

5.4 Surgical treatment of metastatic RCC (tumour nephrectomy)

Tumour nephrectomy is curative only if surgery can excise all tumour deposits. For the majority of patients with metastatic disease, tumour nephrectomy is palliative and other systemic treatments are necessary. In a meta-analysis of two randomized studies, comparing nephrectomy combined with immunotherapy versus immunotherapy only, an increased long-term survival was found in patients subjected to tumour nephrectomy (50). Nephrectomy in patients with metastatic disease is indicated for patients who are both suitable for surgery and have good performance status (51).

5.4.1 Conclusion

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

5.4.2 Recommendation

Tumour nephrectomy is recommended for metastatic RCC patients with good performance status when combined with IFN-alpha (grade A 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) (51-55).

5.5.1 Conclusion

There is a definite role for metastasectomy in patients with RCC in order to improve the clinical prognosis (level of evidence: 3).

5.5.2 Recommendation

In patients with synchronous metastatic spread, metastasectomy should be performed where disease is resectable and the patient has a good performance status. The clinical prognosis is worse in patients who have surgery for metachranous metastases. Metastasectomy should be performed in patients with residual and resectable metastatic lesions previously responding to immunotherapy and/or a limited (solitary lesion) number of metachranous metastases in order to improve the patient's prognosis (grade B 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 (56,57).

5.6.1 Conclusion

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

5.6.2 Recommendation

In individual cases, radiotherapy for the treatment of brain metastases (whole brain irradiation or stereotactic approach) and osseous lesions can induce a relief from symptoms due to mRCC (grade B recommendation) (58,59).

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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).

6.1.2 Recommendation

Chemotherapy as monotherapy should not be considered effective in patients with mRCC (grade B recommendation).

6.2 Immunotherapy

6.2.1 Interferon-alpha

In randomized studies, IFN-alpha has proven superiority for survival over hormonal therapy in patients with mRCC (2). The studies were done using the regimen of IFN-alpha, 10MU, three times per week for 12 weeks. The patients who benefited were of good WHO status (0-1) and were treated for at least 12 weeks and up to 1 year.

6.2.1.1 Conclusion

Immunotherapy with INF-alpha seems beneficial for mRCC patients with a good performance status with an improved survival of several months (level of evidence: 1b).

6.2.1. Recommendation

Interferon-alpha can be considered as standard of care in mRCC patients (grade A recommendation).

6.2.2 Interleukin-2

Interleukin-2 (IL-2) has been used in mRCC since 1985. Several studies have shown responses ranging from 7-27% (3-5). The optimal IL-2 regimen is not clear, but long-term (> 10 years) complete responders have been achieved with high-dose bolus IL-2 (6). However, no randomized study has been done against best supportive care. The toxicity of IL-2 is substantially higher than that of IFN-alpha. It seems that only clear cell type RCC responds to immunotherapy.

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. To date, no superiority has been seen for either INF-alpha or IL-2 treatment in mRCC patients (level of evidence: 1b).

6.2.2.2 Recommendation

Only patients with mRCC, good performance status and with clear cell subtype histology can be treated with immunotherapy IL-2 or IFN-alpha (grade B recommendation).

6.2.3 Combinations

Several randomized studies have been performed to investigate the efficacy of combinations of cytokines. Patient survival was not better than survival achieved with monotherapy regimens (7). No other combinations with cis-retinoic acid or 5FU have shown a clinical significant benefit, although some survival advantage have been seen (8,9).

6.2.3.1 Conclusion

To date, combination therapy has not shown any clinical benefit for mRCC patients (level of evidence: 1b).

6.2.3. Recommendation

The results are awaited from the MRC/EORTC study comparing INF-alpha versus INF-alpha/IL-2/5FU, but so far combination therapy is not advised other than in clinical trials.

6.3 Angiogenesis inhibitor drugs

Recently, drugs targetted on the angiogenesis axis have been investigated in RCC. Due to the high expression

of angiogenesis proteins in clear cell RCC, clinical efficacy has been observed with antibody inhibition to one of these proteins known as vascular epithelial growth factor (VEGF) (10). In addition, inhibition of downstream tyrosine kinases has shown clinical efficacy (11,12). These studies have reported decreased tumour angiogenesis and a subsequent clinical benefit in both clinical response and survival. The position of these novel agents with regard to primary or secondary treatments of mRCC is still under investigation, as well as combinations of these new agents with each other or with cytokines.

6.3.1 Conclusion

Angiogenesis inhibitors have proven efficacy in mRCC patients for response and survival (level of evidence: 1b).

6.3.2 Recommendation

Angiogenesis-targeted drugs should be considered as first- or second-line treatment of mRCC patients (grade A recommendation).

6.4 REFERENCES

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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 more extended 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 randomized evidence exists, but there are large studies with long follow-up from which some conclusions can be drawn (level of evidence: 4).

Factors influencing prognosis can be classified into: anatomical, histological, clinical and molecular (5,6). Anatomical factors include: tumour size, stage, venous invasion, adrenal involvement and lymph node status. Histological factors include: grade, presence of sarcoma, necrosis and collecting system invasion. Clinical factors include: patient performance status, anaemia, platelet count and cachexia.

There are also numerous molecular markers that are being investigated with respect to future treatments. These markers include immunotherapy, vaccine, gene and angiogenesis techniques, but as yet none of these are in widespread use.

7.3 Imaging modalities

Where the likelihood of relapse is low, chest X-ray and US are appropriate. Where the risk is intermediate or high, CT of chest and abdomen is the investigation of choice, 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. Another problematic issue is the optimal duration of the follow-up. One may argue the follow-up by imaging is not cost effective after 5 years (8). Late metastases are more frequently solitary and these justify more aggressive therapy with curative intent. Also patients with tumors that develop in the contralateral kidney (2-3%) can be treated with nephron-sparing surgery when detected with a small size. Furthermore, for tumors <4cm there seems to be no obvious difference in recurrence in the follow-up after partial or 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 3 and 4.

Table 3: Scoring algorithm to predict metastases after nephrectomy in patients with clear cell renal cell carcinoma according to the Mayo Scoring System (13)

Feature	Score
Primary tumor / T-stage	
T1a	0
pT1b	2
pT2	3
pT3 - pT4	4
Tumor size	
<10cm	0
>10cm	1
Regional Lymph Node status	
pNx/pN0	0
pN1 - pN2	2
Nuclear grade	
Grade 1-2	0
Grade 3	1
Grade 4	3
Tumor necrosis	
No necrosis	0
Necrosis	1

Risk groups can be stratified by the scoring system, characterized into low-risk 0-2, intermediate risk 3-5 and high-risk >6 according to the Mayo Scoring System (13).

Table 4: 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 (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

The use of these scoring systems allows the urologist to be selective in the use of imaging and to appropriately target those patients most in need of intensive surveillance.

7.4 Conclusion

In cases where there is 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).

7.5 Recommendation

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 (grade C recommendation).

7.6 REFERENCES

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8. ABBREVIATIONS USED IN THE TEXT

This list is not comprehensive for the most common abbreviations

5FU	5-fluorouracil
CT	computerized tomography
HIFU	high-intensity focused ultrasound
IFN-alpha	interferon-alpha
IL-2	interleukin-2
mRCC	metastatic renal cell carcinoma
MRI	magnetic resonance imaging
RCC	renal cell carcinoma
RF	radiofrequency
TNM	Tumour Node Metastasis
US	abdominal ultrasound
VEGF	vascular endothelial growth factor
WHO	World Health Organization