Annals of Oncology 23 (Supplement 7): vii65–vii71, 2012
doi:10.1093/annonc/mds227

Renal cell carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

B. Escudier[1], T. Eisen[2], C. Porta[3], J. J. Patard[4], V. Khoo[5], F. Algaba[6], P. Mulders[7] & V. Kataja[8], on behalf of the ESMO Guidelines Working Group*

[1]*Department of Medical Oncology, Institut Gustave Roussy, Villejuif, France;* [2]*NIHR Cambridge Biomedical Research Centre, Cambridge, UK;* [3]*Department of Medical Oncology, IRCCS San Matteo University Hospital Foundation, Pavia, Italy;* [4]*Department of Urology, Bicêtre Hospital, Le Kremlin-Bicêtre, France;* [5]*Royal Marsden NHS Foundation Trust and Institute of Cancer Research, London, UK;* [6]*Department of Pathology, Fundació Puigvert, Universitat Autónoma de Medicina, Barcelona, Spain;* [7]*Department of Urology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands;* [8]*Kuopio University Hospital, Cancer Center, Kuopio, Finland*

incidence and epidemiology

Renal cell carcinoma (RCC) accounts for 2%–3% of all adult malignancies, representing the seventh most common cancer in men and the ninth most common cancer in women [1]. Worldwide, there are ~209 000 new cases and 102 000 deaths per year. The incidence of all stages of RCC has increased over the past several years, contributing to a steadily increasing mortality rate per unit population. Active and passive cigarette smoking is an established risk factor for RCC as well as hypertension. However, anti-hypertensive medications such as diuretics are not independently associated with RCC development. RCC also appears to be more common in patients with obesity, end-stage renal failure, acquired renal cystic disease and tuberous sclerosis.

Approximately 2%–3% of RCC are hereditary and several autosomal dominant syndromes are described, each with a distinct genetic basis and phenotype, the most common one being Von Hippel Lindau (VHL) disease.

diagnosis and pathology/molecular biology

The proportion of small and incidental renal tumors has significantly increased owing to the widespread use of abdominal imaging, e.g. ultrasonography, computed tomography (CT) and magnetic resonance imaging (MRI). More than 50% of RCCs are currently detected incidentally. However, a large number of patients with RCC still present with clinical symptoms, such as flank pain, gross hematuria and palpable abdominal mass (the classical triad); metastatic symptoms such as bone pain or lung nodules; or paraneoplastic syndromes, such as hypercalcemia, unexplained fever, erythrocytosis or wasting syndromes.

Correspondence to: ESMO Guidelines Working Group, ESMO Head Office, Via L. Taddei 4, CH-6962 Viganello-Lugano, Switzerland. E-mail: clinicalguidelines@esmo.org

†Approved by the ESMO Guidelines Working Group: September 2008, last update June 2012. This publication supersedes the previously published version—Ann Oncol 2010; 21 (Suppl 5): v137–v139.

Physical examination alone directs further examinations especially when symptoms and signs mentioned above are present. Suspicion of RCC should prompt laboratory examinations of serum creatinine, hemoglobin, leukocyte and platelet counts, lactate dehydrogenase and serum-corrected calcium, in addition to the other symptom-derived tests [4, B]. Inflammatory syndrome tests such as C-reactive protein (CRP) and erythrocyte sedimentation rate have been suggested. Some of these tests are prognosticators for survival and used for risk assessment (see later).

Most cases of RCC are strongly suspected by imaging. Diagnosis is usually suggested by ultrasonography and confirmed by CT scan which allows for the assessment of local invasiveness, lymph node involvement or other metastases. MRI may provide additional information in investigating local advancement, and involvement of venous tumor thrombus, and in situations where intravenous contrast cannot be used.

For accurate staging of RCC, abdominal and chest CT or MRI is mandatory [3, A]. Chest CT is the most sensitive approach for chest staging [3, A]. Unless there is an indication by clinical or laboratory signs or symptoms, the use of bone scan or CT (or MRI) of the brain is not recommended for routine clinical practice [3, A]. Positron emission tomography is not a standard investigation in the diagnosis and staging of RCC [1, B].

A renal tumor core biopsy provides the histopathological confirmation of malignancy with high sensitivity and specificity. The diagnosis with a biopsy should especially be done before the treatment with ablative therapies [3, B]. It is also indicated in patients with metastatic disease before commencing systemic treatment [3, B]. The final histopathological diagnosis, classification, grading and evaluation of prognostic factors are based on the nephrectomy specimen when available.

pathology assessment

Specific genetic alterations have been identified in the various sub-types of RCC (Table 1). Many of these genetic alterations are also found in the more common sporadic forms of RCC.

Table 1. Gene and chromosomal abnormalities associated with RCC

Histological sub-types	Chromosomal abnormalities	Gene abnormalities
Clear cell	3p25–26 (34%–56%) of sporadic carcinomas, 3p14.2 and on 3p12	VHL
Papillary type I	Trisomy or tetrasomy 7, trisomy 17 and loss of the chromosome Y	c MET
Papillary type II	Trisomy or tetrasomy 7, trisomy 17 and loss of the chromosome Y	Fumarate-hydratase
Chromophobe	Chromosomal loss in 1, 2, 6, 10, 13, 17 and 21	Birt–Hogg–Dube
Collecting duct carcinoma	Chromosomal loss in 1q, 6p, 13q, 14, 15, 21q and 22	

VHL, Von Hippel Lindau.

- Clear-cell RCC is the most frequent sub-type of sporadic RCC in the adult (70%–85%) [2]. The typical histological feature is the clear aspect of the cells due to glycogen and lipids in their cytoplasm. They are distributed in tubular and solid areas with a very prominent capillary stroma. The multilocular cystic RCC, composed entirely of numerous cysts lined by clear cells, probably is a variant of low aggressivity of this sub-type.
- Papillary RCC (7%–15%) [3]. Its name arises from the distribution of malignant cells around capillary cores (papillae) in 50%–70% of the tumor [4]. In 73% of cases, they are type I (cells have scarce cytoplasm), and in 42% they are type II (eosinophilic cytoplasm). A strong expression of α-metylacil-CoA racemase is a typical feature.
- Chromophobe RCC (5%–10%). The typical cells are polygonal with a clear delimitation of the cytoplasmic membrane (that gives them the appearance of a plant cell). The pale reticulated cytoplasm (chromophobe) is due to the presence of abundant cytoplasmic invaginated 150–300-nm diameter vesicles. LOH 17 associates this tumor with the Birt–Hogg–Dubé syndrome, c-kit expression is a typical features of the cells.
- Collecting duct RCC (Bellini tumors). Less than 1% of RCC are from the medullary distal nephron or Bellini ducts. The typical morphology of the cells is a high nuclear grade, eosinophilic cytoplasm, predominant tubular arrangement, desmoplasia and expression of high-molecular-weight cytokeratins. Medullary RCC is considered as an undifferentiated collecting duct carcinoma.
- Some other rare histologies include:
  - Translocation RCC. This rare entity, mainly observed in children or young adults is characterised by the translocation of Xp11.2, with the gene-fusion TFE3, or less frequently the translocation t(6;11)(p21;q12) and fusion TFEB [5].
  - Mucinous tubular and spindle cell carcinoma.
  - Tubulocystic RCC composed by packed tubules and cysts lined by cuboidal or hobnail cells with abundant eosinophilic cytoplasm and large nuclei showing prominent nucleoli, may represent a subset of papillary RCC.
  - Clear-cell papillary RCC, often associated with end renal disease.
  - Some RCC still remain unclassified.

Each of these morphological-genetic RCC sub-types can correlate with various pathways, such as:

- The hypoxia-inducible pathway (clear cell, papillary type II through Fumarate gene).
- The mTOR signaling pathway (clear cell and papillary type II).
- The c Met-RAF-MEK-ERK pathway (papillary type I and translocation RCC).
- The c-kit-RAF-MEK-ERK pathway (chromophobe).

All of these pathways can represent potential targets for targeted therapies.

staging and risk assessment

staging

The UICC TNM 2009 staging system should be used (Table 2).

Table 2. Staging of RCC (UICC TNM classification of malignant tumors, 7th edition, 2009)

T	Primary tumor
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor ≤7 cm in greatest dimension, limited to the kidney
T1a	Tumor ≤4.0 cm
T1b	Tumor >4.0 cm but ≤7.0 cm
T2	Tumor >7.0 cm in greatest dimension, limited to the kidney
T2a	Tumor >7 cm but ≤10 cm
T2b	Tumor >10 cm, limited to the kidney
T3	Tumor extends to major veins or peri-nephric tissues but not into the ipsi-lateral adrenal gland and not beyond Gerota fascia
T3a	Tumor grossly extends into the renal vein or its segmental (muscle-containing) branches, or tumor invades peri-renal and/or renal sinus fat (peri-pelvic) but not beyond Gerota fascia
T3b	Tumor grossly extends into the vena cava below the diaphragm
T3c	Tumor grossly extends into the vena cava above the diaphragm or invades the wall of the vena cava
T4	Tumor invades beyond Gerota fascia (including contiguous extension into the ipsi-lateral adrenal gland)
N	Regional lymph nodes
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in regional lymph node(s)
M	Distant metastases
cM0	Clinically no distant metastasis
cM1	Clinically distant metastasis
pM1	Pathologically proven distant metastasis, e.g. needle biopsy
Stage grouping	
Stage I	T1 N0 M0
Stage II	T2 N0 M0
Stage III	T3 N0 M0
	T1-3 N1 M0
Stage IV	T4 Any M0
	Any Any M1

risk assessment

RCC is recognized as having a very variable natural history. Risk assessment models have been developed to provide prognostic information for patients and to inform the eligibility and risk stratification designs of clinical trials.

localized disease

Two systems can be used to assess the risk of progression in localized tumors: the stage size grade and necrosis (SSIGN) score [6] and the UCLA Integrated Staging System (UISS) [7]. These systems are described in Tables 3 and 4. In SSIGN, risk points are accumulated as noted in the table below and added up to provide a risk score.

The SSIGN score compared favorably with the UISS score in predictive accuracy in a series of patients who had surgically resected clear-cell RCC. On the other hand, the UISS provides prognostic predictions for both localized and metastatic disease. Further prospective data will be available from the current adjuvant trials for patients with high and intermediate risk RCC.

Table 3. SSIGN score for localized RCC

Feature		Score
Pathological T category of primary tumor (TNM 2002)	pT1a	0
	pT1b	2
	pT2	3
	pT3a-4	4
Regional lymph node status (TNM 2002)	pNx or pN0	0
	pN1 or pN2	2
Tumor size	<10 cm	0
	≥10 cm	1
Nuclear grade	1 or 2	0
	3	1
	4	3
Histological tumor necrosis	No	0
	Yes	1
Scores	Group	5-year metastasis-free survival (%)
0–2	Low risk	97.1
3–5	Intermediate risk	73.8
≥6	High risk	31.2

advanced disease

Prognostic models were first built when immunotherapy was the standard therapy. The Memorial Sloan-Kettering Cancer Center (MSKCC) or Motzer score was the standard system. The MSKCC score has now been validated and updated for use in the current era of targeted therapies as the Heng criteria [8]. Patients are stratified according to the presence of six risk factors:

- Karnovsky performance status (PS) <80%.
- Hemoglobin less than lower limit of normal.
- Time from diagnosis to treatment <1 year.
- Corrected calcium above the upper limit of normal.
- Platelets greater than the upper limit of normal.
- Neutrophils greater than the upper limit of normal.

The number of risk factors present is added up and the risk is stratified as follows:

Number of risk factors	Risk group	Median overall survival (months)	Two-year overall survival (%)
0	Favorable	NR*	75
1–2	Intermediate	27	53
3–6	Poor	8.8	7

*NR, not reported.

Work continues to improve risk score models.

biomarkers

Although there are many potential biomarkers under investigation, none have yet been validated for general use in the prognostic or predictive assessment of RCC.

management of local/loco-regional disease

T1 tumors (<7 cm)

Partial nephrectomy is recommended as the preferred option in organ confined tumors measuring up to 7 cm (elective indication) (Table 5). Partial nephrectomy can be performed via open, laparoscopic or coelioscopic robot-assisted approaches. In patients with compromised renal function, solitary kidney or bilateral tumors, partial nephrectomy is also the standard of care, with no tumor size limitation (imperative indication). Laparoscopic radical nephrectomy is recommended if partial nephrectomy is not technically feasible [9].

Radio frequency or cryo-ablative treatments are alternative approaches [10], especially in patients with small cortical tumors, hereditary RCC and multiple bilateral tumors.

Active surveillance is an alternative option in elderly patients, with substantial co-morbidities or those who have a short life expectancy and solid renal tumors measuring <4 cm [11].

T2 tumors (>7 cm)

Laparoscopic radical nephrectomy is the preferred option.

locally advanced RCC (T3 and T4)

Open radical nephrectomy remains the standard of care even though laparoscopic approach can be considered. Systematic adrenalectomy or extensive lymph node dissection are not recommended when abdominal CT shows no evidence of adrenal or lymph node invasion.

There is no recommended adjuvant treatment, although many adjuvant trials are ongoing. Inclusion of patients with localised disease into clinical trials should be encouraged.

Neo-adjuvant approaches are still experimental, especially for resectable tumors, and should not be proposed outside of clinical trials. Many studies have demonstrated that such approaches are relatively safe, with modest median tumor down-sizing (but more tumor shrinkage in metastatic sites) and no proven efficacy on disease-free survival.

Table 4. UISS (UCLA Integrated Staging System)

Patient group		Prognostic group			
		T stage	Fuhrman's grade	ECOG status	Five-year disease-specific survival (%)
Localised disease (N0, M0)	Low risk	1	1–2	0	91.1
	Intermediate risk	1	1–2	1 or more	80.4
		1	3–4	Any	
		2	Any	Any	
		3	1	Any	
		3	2–4	Any	
	High	3	2–4	1 or more	54.7
		4	Any	Any	
Metastatic disease	Low risk	N_1M_0	Any	Any	32
		N_2M_0/M_1	1–2	0	
	Intermediate risk	N_2M_0/M_1	1–2	1 or more	19.5
			3	0, 1 or more	
			4	0	
	High	N_2M_0/M_1	4	1 or more	0

Risk groups and 5-year disease-specific survival.
NB: This is taken from the Oxford Oncology Library.

Table 5. Recommendations for the treatment of localised and locally advanced RCC

	Level and grade of recommendations
Partial nephrectomy is recommended for the treatment of all T1 tumors if negative margins are obtained and risk of morbidity is acceptable.	III, C
Laparoscopic radical nephrectomy is the preferred option for the treatment of organ-confined RCC (stages T1T2N0N×M0) when partial nephrectomy is not feasible.	II, B
Routine adrenalectomy and lymph node dissection are not required for all radical nephrectomies.	III, C and I, A
Open radical nephrectomy with the goal of obtaining negative margins is still the standard of care for locally advanced RCC.	III, C
Ablative treatments are alternative approaches in elderly patients with small cortical tumors (≤3 cm), hereditary RCC and multiple bilateral tumors.	III, C
Active surveillance is an alternative option in patients ≥75 years, with substantial co-morbidities and solid renal tumors measuring <4 cm.	III, C

management of metastatic disease

role of surgery

- In the era of immunotherapy, cyto-reductive nephrectomy was recommended in patients with good PS [I, A] [12]. Whether this recommendation will remain with current targeted therapies is being investigated in two prospective trials. In routine practice, cyto-reductive nephrectomy is recommended in patients with good PS and large primary tumors, and for patients with a symptomatic primary lesion. Cyto-reductive nephrectomy is not recommended in patients with poor PS.
- Metastasectomy can be considered and performed after multidisciplinary review for select patients with solitary or easily accessible pulmonary metastases, solitary resectable intra-abdominal metastases, a long disease-free interval after nephrectomy or a partial response in metastases to immunotherapy or targeted therapy. Recent retrospective and non-randomized studies of patients with metastatic RCC (mRCC) have demonstrated a prolonged median survival in those with metachronous lung metastases and an interval of at least 2 years [13]. Metastasectomy may provide a possible survival benefit for a select group of patients with lung metastases only, a long metachronous disease-free interval and a response to immunotherapy/targeted therapy before resection.

systemic treatment

Recommendations mainly relate to clear-cell histology, since most of the pivotal trials have been done in this common histological sub-type. In addition, recommendation will differ according to risk stratification (see above) (Table 6).

first-line treatment for patients with good or intermediate prognosis (Figure 1)

Because some RCC have very indolent course, a period of observation before starting treatment should be considered. Three treatments have demonstrated efficacy in pivotal phase 3: bevacizumab (combined with interferon-alpha), sunitinib [I, A] and pazopanib [II, B] [14–16]. All three drugs have been registered based on improvement of progression-free survival (PFS) over either interferon-alpha or placebo. Sorafenib [II, B],

interferon-alpha (I-D) and interleukin-2 (III-C) are alternative options when the other drugs cannot be safely given or in very selected cases. New options, such as tivozanib (based on phase 3 data reported at ASCO 2012 by Motzer et al.) or axitinib might become available for first-line treatment in the near future.

first-line treatment for patients with prognosis

Temsirolimus is currently the only drug with level 1 evidence of activity in this patient population [I, B] [17]. The pivotal trial demonstrated the improvement of overall survival compared with interferon or combination of temsirolimus and interferon.

Based on subgroup analysis from the pivotal trial as well as expanded access programs, sunitinib is another reasonable option in this setting [II, B].

It is clear that, for many prognosis patients, best supportive care remains the only suitable treatment option.

Table 6. Algorithm for systemic treatment in mRCC

Histology and setting	Risk group	Standard	Option
Clear-cell first line	Good or intermediate risk	Sunitinib	Cytokines (including high dose IL2)
		Bevacizumab + IFN	Sorafenib
		Pazopanib	
	Poor prognosis	Temsirolimus	Sunitinib Sorafenib
Clear-cell second line	Post-cytokines	Sorafenib Pazopanib Axitinib	Sunitinib
	Post-TKIs	Everolimus Axitinib	Sorafenib
Clear-cell third line	Post-2 TKIs	Everolimus	
Non-clear-cell histology			Temsirolimus Sunitinib Sorafenib

second-line treatment (Figure 2)

- Evidence for tyrosine kinase inhibitors (TKIs) being active after cytokines have been demonstrated with sorafenib [I, A], pazopanib [II, A] and recently axitinib [I, A] [18, 16, 19]. Sunitinib has also demonstrated activity is this setting (III-A). However, since VEGF-targeted therapy is now the first-line standard of care, the number of patients treated with cytokines is decreasing.
- After first-line treatment with VEGF-targeted therapy, both everolimus [20] and axitinib [19] are active, and can be recommended [respectively II, A and I, B]. Both drugs have shown substantially improved PFS over placebo (everolimus) or sorafenib (axitinib). Shifting from one TKI to another (i.e. from sunitinib to sorafenib or vice versa) showed some activity, in several, mainly retrospective (and thus highly biased), trials [III, B].

third-line treatment

Further to second line, enrollment into clinical trials is recommended where possible. In patients already treated with two TKIs (or a TKI and bevacizumab), everolimus is recommended [II, A]. In patients previously treated with VEGF-targeted therapy and mTOR inhibitor, TKI is a possible treatment [III, B].

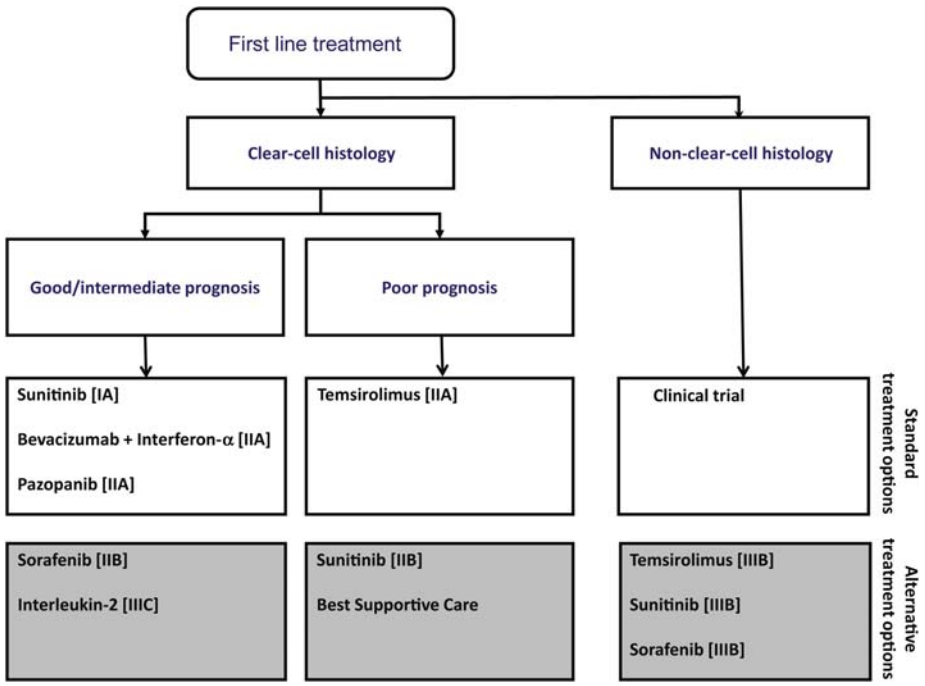

Figure 1 First-line treatment of metastatic RCC.

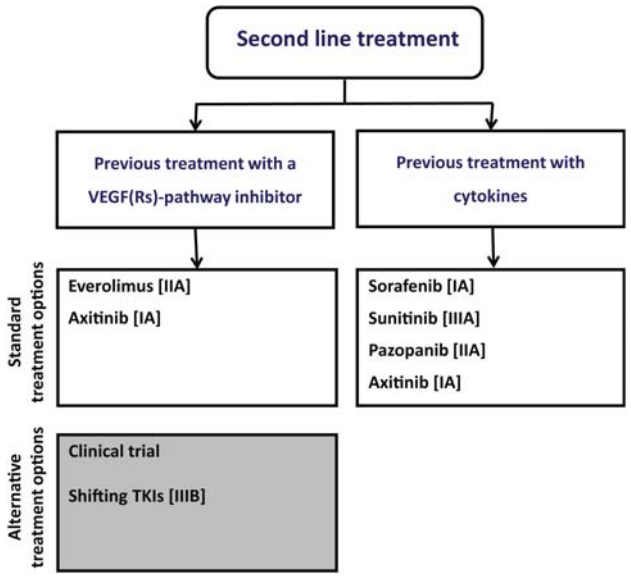

Figure 2 Second-line treatment of metastatic RCC.

medical treatment of metastatic disease of non-clear-cell histology

No prospective randomized data are presently available for patients with non-clear-cell renal cancer. For these patients, enrollment into specifically designed clinical trials is recommended. However, in the absence of such trials, recommendations can only be based on the results of the expanded access programs of sunitinib and sorafenib, of small retrospective studies, and of the subgroup analysis of the temsirolimus registration trial. These studies suggest that patients with non-clear-cell histology may benefit from the treatment with sunitinib, sorafenib or temsirolimus [III, B].

role of radiotherapy and biphosphonates

Radiotherapy has a limited role in the primary management of renal cancer [21]. However, it is utilized in many different clinical situations particularly for unresectable local recurrences and metastatic disease.

- There is no role of radiotherapy in adjuvant or neo-adjuvant setting (four negative trials) [II, D].
- Radiotherapy can be used to treat unresectable local or recurrent disease with the aim of improving local control. For patients in whom surgery is not possible due to the poor PS or unsuitable clinical condition of the patient, radiotherapy may be used as an alternative if other local therapies such as radio-ablation are not appropriate [IV, B].
- Radiotherapy is an effective therapy for palliation of local and symptomatic metastatic disease or to prevent the progression of metastatic disease in critical sites: bones, brain [I, A]. For symptomatic bone metastasis, local radiotherapy either as a single fraction or fractionated course can provide symptom relief in up to two-third of cases with complete symptomatic responses in up to 20%–25% [1, A].
- For the management of spinal cord compression, an ambulatory status at diagnosis and limited metastatic disease are favorable factors. In those patients able to undergo surgery, the use of surgery and radiotherapy was reported to improve survival and maintenance of ambulation compared with irradiation alone [1, A].
- In the management of patient with brain metastases, the use of cortico-steriods can provide effective temporary relief of cerebral symptoms. Whole-brain radiotherapy between 20 and 30 Gy in 4–10 fractions, respectively, is effective in local control and may be enhanced with stereotactic cranial radiotherapy particularly for the subset of patients with a single unresectable lesion [II, B].

Bisphosphonate therapy with zoledronic acid has been shown to reduce skeletal related events in patients with bone metastatis due to mRCC [22] and is recommended for this patient cohort based on an assessment of expected patient survival time and probability of deriving symptomatic benefit [23] [II, A]. Novel agents other than bisphosphonates (e.g. radium-223 and denosumab) are presently available (or will be available in the near future), but their specific use in kidney cancer is still investigational.

response evaluation and follow-up

There is no evidence that any particular follow-up protocol influences the outcome in early RCC. No standard recommendation can be given for the follow-up in advanced RCC either.

The follow-up scheme for localized RCC following surgery, should be dependent on the therapeutic possibilities upon recurrence. CT scans of thorax and abdomen are routinely performed, with time intervals dependent on risk factors. Long-term follow-up is proposed in some institutions, due to the possibility of late relapse, but its benefit has never been demonstrated.

During systemic therapy in mRCC patients, 2–4 month follow-up schemes with CT scan should be advised to determine response and resistance. Although not perfect, RECIST criteria remain the best method to assess drug efficacy.

conflict of interest

Dr. Escudier has reported: consultancy/honoraria from Pfizer, Bayer, Bristol-Myers Squibb, Aveo Pharmaceuticals, Genentech, Novartis. Prof. Eisen has reported: shareholding: AstraZeneca; advisory boards for Bayer, Pfizer, Roche, GlaxoSmithKline, Aveo Pharmaceuticals; research funding: AstraZeneca, GlaxoSmithKline, Pfizer, Bayer; consultancy: Roche, Bayer, Pfizer, GlaxoSmithKline, Aveo Pharmaceuticals. Dr. Porta has reported: consultant and speakers' bureau for Pfizer Oncology, GlaxoSmithKline, Hoffman La Roche, Bayer-Schering Pharma, Novartis Pharma, Aveo Pharmaceuticals, Astellas, Boehringer Ingelheim, Recordati; Research grants from Bayer-Schering Pharma, Novartis.

Other authors have reported no potential conflicts of interest.

references

1. Rini B, Campbell S, Escudier B. Renal cell carcinoma. Lancet 2009; 373(9669): 1119–1132.

2. Patard JJ, Leray E, Rioux-Leclercq N et al. Prognostic value of histologic subtypes in renal cell carcinomas: a multicenter experience. J Clin Oncol 2005; 23: 2763–2771.
3. Algaba F, Akaza H, Lopez-Beltran A et al. Current pathology keys of renal cell carcinoma. Eur Urol 2011; 60: 634–644.
4. Delahunt B, Eble JN. Papillary renal cell carcinoma: a clinicopathologic and immunohistochemical study of 105 tumors. Mod Pathol 1997; 10: 537–544.
5. Argani P, Lal P, Hutchinson B et al. Aberrant nuclear immunoreactivity for TFE3 in neoplasms with *TFE3* gene fusions. A sensitive and specific immunohistochemical assay. Am J Surg Pathol 2003; 27: 750–761.
6. Leibovich BC, Blute M, Cheville JC et al. Prediction of progression after radical nephrectomy for patients with clear cell renal cell carcinoma: a stratification tool for prospective clinical trials. Cancer 2003; 97: 1663–1671.
7. Patard JJ, Kim HL, Lam JS et al. Use of the University of California Los Angeles integrated staging system to predict survival in renal cell carcinoma: an international multicenter study. J Clin Oncol 2004; 22(16): 3316–3322.
8. Heng DY, Xie W, Regan MM et al. Prognostic factors for overall survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor-targeted agents: results from a large, multicenter study. J Clin Oncol 2009; 27(34): 5794–5799.
9. MacLennan S, Imamura M, Lapitan MC et al. UCAN Systematic Review Reference Group; EAU Renal Cancer Guideline Panel. Systematic review of oncological outcomes following surgical management of localised renal cancer. Eur Urol 2012; 61(5): 972–793.
10. Best SL, Park SK, Yaacoub RF et al. Long-term outcomes of renal tumor radio frequency ablation stratified by tumor diameter: size matters. J Urol 2012; 187 (4): 1183–1189.
11. Mason RJ, Abdolell M, Trottier G et al. Growth kinetics of renal masses: analysis of a prospective cohort of patients undergoing active surveillance. Eur Urol 2011; 59(5): 863–867.
1.2. Flanigan RC, Mickisch G, Sylvester R et al. Cytoreductive nephrectomy in patients with metastatic renal cancer: a combined analysis. J Urol 2004; 171: 1071–1076.
13. Karam JA, Rini BI, Varella L et al. Metastasectomy after targeted therapy in patients with advanced renal cell carcinoma. J Urol 2011; 185(2): 439–444.
14. Escudier B, Pluzanska A, Koralewski P et al. Bevacizumab plus interferon alfa-2a for treatment of metastatic renal cell carcinoma: a randomised, double-blind phase III trial. Lancet 2007; 370: 2103–2111.
15. Motzer R, Hutson TE, Tomczak P et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. N Engl J Med 2007; 356(2): 115–124.
16. Sternberg CN, Davis ID, Mardiak J et al. Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. J Clin Oncol 2010; 28(6): 1061–1068.
17. Hudes G, Carducci M, Tomczak P et al. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. N Engl J Med 2007; 356(22): 2271–2281.
18. Escudier B, Eisen T, Stadler WM et al. Sorafenib in advanced clear-cell renal-cell carcinoma. N Engl J Med 2007; 356(2): 125–134.
19. Rini BI, Escudier B, Tomczak P et al. Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised phase 3 trial. Lancet 2011; 378(9807): 1931–1939.
20. Motzer RJ, Escudier B, Oudard S et al.; for the RECORD-1 Study Group. Everolimus for advanced renal cell carcinoma. Lancet 2008; 372(9637): 449–456.
21. Khoo VS, Pyle L. Radiotherapy and supportive care. In Eisen T, Christmas T (eds), Clinical Progress in Renal Cancer. Oxford: Informa UK Ltd 2007; 191–201. ISBN 10–1–84184-604-X.
22. Lipton A, Zheng M, Seaman J. Zoledronic acid delays the onset of skeletal-related events and progression of skeletal disease in patients with advanced renal cell carcinoma. Cancer 2003; 98(5): 962–969.
23. Aapro M, Abrahamsson PA, Body JJ et al. Guidance on the use of bisphosphonates in solid tumors: recommendations of an international expert panel. Ann Oncol 2008; 19(3): 420–432.