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

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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. Worldwide, annually there are ~209 000 new cases and 102 000 deaths.

diagnosis and staging

RCC is a male-predominant (2:1) disease with a typical presentation in the sixth and seventh decades of life (median age ~60 years).

Patients with RCC may present with local or systemic symptoms, although most presentations are incidental owing to the widespread use of abdominal imaging. Prevalent use of ultrasonography and cross-sectional imaging is associated with incidental detection of many asymptomatic renal tumours and thus the incidence of synchronous metastatic disease should decrease in the near future.

Local signs and symptoms include haematuria, flank pain or a palpable abdominal mass, all of which imply negative prognostic features. Systemic symptoms may be due to metastases or paraneoplastic phenomena such as hypercalcaemia, unexplained fever, erythrocytosis or wasting syndromes.

Diagnosis is usually suggested by ultrasonography, and confirmed by CT scan which allows for assessment of local invasiveness, lymph node involvement or other metastases. Pathology from either the primary tumour or a metastatic site will confirm the diagnosis and will allow pathological classification. Most common is clear cell cancer, followed by papillary cancer (either type 1 or 2) and then the rare histologies such as chromophobe, collecting duct, medullary and unclassified.

A four-tiered grading system (Fuhrman system) based on nuclear morphology is a significant prognostic factor in clear cell RCC. Sarcomatoid differentiation is not a distinct histological subtype but is a growth pattern that can occur across all subtypes suggesting an aggressive disease course. Risk assessment models have been created for use in eligibility, stratification in randomization for phase III trials and assessment of outcome. A model derived from data at Memorial Sloan-Kettering Cancer Center (MSKCC, New York, NY, USA) and later validated by investigators at the Cleveland Clinic Foundation (Cleveland, OH, USA) is used widely. In this model, five variables are considered prognosticators for poor survival: low Karnofsky performance status (<70), elevated lactate dehydrogenase, low serum haemoglobin, elevated 'corrected' serum calcium and time from initial RCC diagnosis to start of therapy of <1 year.

Patients are divided into three groups based upon pre-treatment features: favourable (no risk factors, median survival 30 months); intermediate (one or two risk factors, median survival 14 months) or poor (three or more risk factors, median survival 6 months). Because the MSKCC risk model was developed in patients receiving cytokine treatment, new attempts to identify prognostic factors in the era of targeted therapies are ongoing, but still require external validation.

The TNM 2009 staging system should be used (Table 1).

treatment

localized disease

Nephrectomy, either partial or total according to the size of the tumour is the standard of care [I, A]. Laparoscopic radical nephrectomy is now standard procedure for large tumours, and open partial nephrectomy the standard for small tumours (<4 cm) [II, B]. Minimally invasive techniques are currently under investigation (RFA, cryotherapy). Adjuvant and neoadjuvant therapies are investigational, no treatment being currently proved active.

metastatic disease

surgery. Cytoreductive nephrectomy benefits many patients with metastatic RCC and should be considered as standard of care in patients receiving cytokines [I, A]. However, the role of cytoreductive nephrectomy needs to be re-evaluated

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in the present era of molecular targeted therapies. Metastasectomy may be an option particularly in patients presenting with a solitary metastasis [III, A]. Radiotherapy must be considered for palliation especially in symptomatic bone metastases.

systemic therapy (Table 2). Currently, eight drugs have been approved in advanced RCC: interleukin-2 (IL2), interferon-α (IFN), sorafenib, sunitinib, temsirolimus, bevacizumab in combination with IFN, everolimus and pazopanib (only in the USA). Only IFN in the 1990s and temsirolimus more recently (in patients with poor-risk features) have shown statistically significant improvement in overall survival.

Table 1. Staging of renal cell carcinoma (UICC TNM classification of malignant tumours, 7th Edition, 2009)

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 ≤4.0 cm
T1b	Tumour >4.0 cm but ≤7.0 cm
T2	Tumour >7.0 cm in greatest dimension, limited to the kidney
T2a	Tumour >7 cm but ≤10 cm
T2b	Tumour >10 cm
T3	Tumour entends to major veins or perinephric tissues but not into the ipsilateral adrenal gland and not beyond Gerota fascia
T3a	Tumour grossly extents into the renal vein or its segmental (muscle-containing) branches, or tumour invades perirenal and/or renal sinus fat (peripelvic) but not beyond Gerota fascia
T3b	Tumour grossly extends into the vena cava below the diaphragm
T3c	Tumour grossly extends into the vena cava above the diaphragm or invades the wall of the vena cava
T4	Tumour invades beyond Gerota fascia (including contiguous extention into the ipsilateral adrenal gland)
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	Metastases in more than one regional lymph node
M	Distant metastases
M0	No distant metastasis
M1	Distant metastasis

clear cell carcinoma

Most of the studies have been done in clear cell histology.

First-line therapy should utilize either sunitinib or combination of bevacizumab and IFN in good- and intermediate-risk patients, while temsirolimus should be proposed to patients with poor-risk features according to the MSKCC classification [I, A]. Pazopanib will become an option in this setting if approval is granted in Europe, as recommended on 18 February 2010 by the Committee for Medicinal Products for Human Use (CHMP). The role of high-dose IL2 remains unclear but it is still an option for selected good-risk patients.

Second-line therapy for patients who have failed cytokines should be sorafenib [I, A] or pazopanib (if approved), sunitinib remaining an option based on promising efficacy in phase II.

In patients who have failed tyrosine kinase inhibitor, everolimus is the standard of care, as approved in 2009 [I, A].

non-clear cell carcinoma

There are very little data on the efficacy of therapy in non-clear cell histology. Sunitinib and sorafenib are considered as possible options despite limited efficacy, but temsirolimus might be an alternative based on subset analyses from the pivotal phase III study [III, B]. Prospective trials, including new drugs directed to newly recognized targets like the c-met inhibitors, are ongoing to determine whether these therapies are active in non-clear cell histology.

follow-up

There is no evidence that any follow-up protocol would influence the outcome in early RCC.

No standard recommendation can be given for the follow-up procedure in advanced RCC either. The radiological and other examinations should be symptom driven and depending upon the clinical situation.

note

Levels of Evidence [I–V] and Grades of Recommendation [A–D] as used by the American Society of Clinical Oncology are given in square brackets. Statements without grading were considered justified standard clinical practice by the expert authors and the ESMO faculty.

Table 2. algorithm for systemic treatment of renal carcinoma

Histology and setting	Risk group	Standard	Option
Clear cell first line	Good or intermediate	Sunitinib, bevacizumab + IFN (pazopanib)	Cytokines (including high dose IL2)
	Poor	Temsirolimus	Sunitinib
Clear cell second line	Post cytokines	Sorafenib (pazopanib)	Sunitinib
	Post TKIs	Everolimus	
Non-clear cell histology			Temsirolimus Sunitinib Sorafenib

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