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

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**incidence**
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. World-wide, annually there are approximately 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 \(\sim 60\) years).

Patients with RCC may present with local or systemic symptoms, although most presentations are incidental owing to the widespread use of abdominal imaging. Local signs and symptoms include hematuria, 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 hypercalcemia, unexplained fever, erythrocytosis or wasting syndromes. Prevalent use of ultrasonography and cross-sectional imaging is now associated with incidental detection of many asymptomatic renal tumors and there has been a stage migration with less presentation of synchronous metastatic disease.

Diagnosis is usually suggested by ultrasonography, and confirmed by CT scan, which allows for assessment for local invasiveness, lymph node involvement or other metastases. Pathology from either the primary tumor or a metastatic site confirms the diagnosis and allows pathological classification. Most common is clear cell cancer, followed by papillary cancer (either type 1 or 2), and then 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) and later validated by investigators at the Cleveland Clinic Foundation (Cleveland, OH) is used widely. In this model, five variables are considered risk factors for short survival: low Karnofsky performance status (<70), elevated lactate dehydrogenase, low serum hemoglobin, 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: favorable (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).

The TNM 2002 staging system should be used (Table 1).

**treatment**

**localized disease**
Current treatment of localized disease is surgery. Nephrectomy, either partial or total according to the size of the tumor, is the standard of care. Minimally invasive techniques are currently under investigation (RFA, cryotherapy).

Adjuvant therapy is investigational.

**metastatic disease**

**surgery.** Cytoreductive nephrectomy appears to benefit many patients with metastatic RCC and should be considered as standard of care, but should not be performed indiscriminately. Metastasectomy may be an option, particularly in patients presenting with solitary metastasis.

Radiotherapy must be considered for palliation, especially in symptomatic bone metastases.

**systemic therapy.** Currently, six drugs have been approved in advanced RCC: interleukin 2 (IL-2), interferon (IFN)-\(\alpha\), sorafenib, sunitinib, temsirolimus and bevacizumab in combination with IFN (IFN and bevacizumab are approved only in Europe) (Table 2).
Clear cell carcinoma: most of the studies have been done in clear cell histology.

First line therapy should use either sunitinib or combination of bevacizumab and IFN as therapeutic options in good and intermediate risk patients, while temsirolimus should be proposed to patients with poor risk features according to the MSKCC classification. The role of high-dose IL-2 remains unclear, but is still an option for selected good risk patients.

Second line therapy for patients who have failed cytokines should be sorafenib, with sunitinib remaining an option based on promising efficacy in phase II. Recently, everolimus has been shown to be active in patients who failed tyrosine kinase inhibitor. However, this drug is not yet approved.

Nonclear cell carcinoma: there are very few data on efficacy of therapy in nonclear 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. Prospective trials are ongoing to determine whether or not these therapies are active in nonclear 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.

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.

literature