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

B. Escudier1, C. Porta2, M. Schmidinger3, F. Algaba4, J. J. Patard5, V. Khoo6,7, T. Eisen8 & A. Horwich6 on behalf of the ESMO Guidelines Working Group*

1Institut Gustave Roussy, Villejuif, France; 2IRCCS San Matteo University Hospital Foundation, Pavia, Italy; 3Clinical Division of Oncology, Department of Medicine I and Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria; 4Department of Pathology, Fundació Puigvert, Universitat Autònoma de Barcelona, Barcelona, Spain; 5CHU Bicêtre, Université Paris XI, Kremlin Bicêtre, France; 6Institute of Cancer Research and Royal Marsden Hospital, London, UK; 7Monash University, Melbourne, Australia; 8Cambridge Biomedical Campus, Cambridge, UK

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 disease.

In recent years, many new genes associated with RCC have been reported (such as PBRM1, SETD2, BAP1). Their roles in pathogenesis and as prognostic biomarkers are currently under investigation.

diagnosis and pathology/molecular biology

The proportion of small and incidental renal tumours 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, some patients with RCC still present with clinical symptoms, such as flank pain, gross haematuria and palpable abdominal mass (the classical triad); metastatic symptoms like bone pain or lung nodules; or paraneoplastic syndromes, such as hypercalcaemia, unexplained fever, erythrocytosis or wasting syndromes.

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, haemoglobin, leukocyte and platelet counts, lactate dehydrogenase and serum-corrected calcium, in addition to other symptom derived tests [IV, 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 further investigated by CT scan, which allows for assessment of local invasiveness, lymph node involvement or other metastases. MRI may provide additional information in investigating local advancement and venous involvement by tumour thrombus. MRI may also be useful in situations where i.v. contrast cannot be used.

For accurate staging of RCC, abdominal and chest CT or MRI is mandatory [III, A]. Chest CT is the most sensitive approach for chest staging [III, A]. Unless indicated 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 [III, A]. Positron emission tomography is not a standard investigation in the diagnosis and staging of RCC [I, B].

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

Due to a better understanding of the correlation between chromosomal alterations, histological subtypes and molecular pathway abnormalities, researchers now recognize new morphological variants of RCC. The distinct molecular pathway abnormalities demonstrated by these novel variants may provide new therapeutic targets.

In order to classify these novel variants of RCC, the International Society of Urological Pathology (ISUP) coordinated a consensus conference in 2012, which proposed the Vancouver classification [2] (Table 1).

The more important conclusions of the consensus conference are as follows:

refinements of existing WHO (2004) classification

- Clear-cell RCC is the most frequent subtype of sporadic RCC in adults (70%–85%) [3], with loss of 3p and the classical clear aspect of the cells due to glycogen and lipids in their cytoplasm.
- The multi-locular cystic RCC, composed entirely of numerous cysts lined by clear cells, without solid tumoural areas, is considered as a neoplasm of low malignant potential.
- Papillary RCC (7%–15%) shows distribution of malignant cells around capillary cores (papillae) in 50%–70% of the tumour as well as Trisomy 7, 12, 16, 17, 20, loss of Y chromosome but no 3p loss [4]. In 73% of cases, cells have scarce cytoplasm and are classified as type I. In 42% of cases, cells show eosinophilic cytoplasm and are classified as type II. Some pathologists prefer to sub-classify papillary tumours according to nuclear size [5].
- Chromophobe RCC (5%–10%) is made up of typical polygonal cells with a clear delimitation of the cytoplasmic membrane and reticular cytoplasm. The tumour shows loss in chromosomes 1, 2, 6, 10, 13, 17 and 21.
- A hybrid oncocytoma/chromophobe RCC may be present in Birt–Hogg–Dubé syndrome and in sporadic cases.
- Collecting duct RCC (Bellini tumours) constitutes <1% of RCC and derives from the medullary distal nephron or Bellini ducts. The typical morphology of the cells is a high nuclear grade, eosinophilic cytoplasm with predominantly tubular arrangement. Desmoplasia without other RCC subtype or urothelial cell carcinoma is mandatory.
- Medullary RCC shows loss of INI1 and of genes involved in the hypoxia-inducible factor (HIF)1α pathway.
- Microphthalmia-associated transcription (MiT) familial translocation RCC includes translocation of Xp11.2 with TFE3 gene fusion and the t(6;11)(p21;q12) translocation with TFEB gene fusion [6].
- Mucinous tubular and spindle cell carcinoma is a low-grade and indolent tumour which only exceptionally metastasises to lymph nodes.

proposed new epithelial neoplasms

- Tubulocystic RCC is an indolent tumour composed of packed tubules and cysts lined by cuboidal or hobnail cells with abundant eosinophilic cytoplasm and large nuclei showing prominent nucleoli.
- Acquired cystic disease-associated RCC is often diagnosed at an early stage and is composed of eosinophilic cells with cribiform architecture and intra-tumoural oxalate crystals.
- Clear-cell (tubulo) papillary RCC does not demonstrate 3p loss and is unrelated to clear-cell RCC. The papillary growth pattern, expression of CK7 and CAIX and lack of AMACR expression are diagnostic. Published data indicate an indolent evolution.
- Hereditary leiomyomatosis RCC is a papillary RCC with peculiar pseudo-viral nucleoli. It is an entity under debate.

Other emerging entities, which are not yet formally accepted, are the thyroid-like follicular RCC, succinate dehydrogenase B mutation-associated RCC and ALK translocation RCC. Of course some RCCs still remain unclassified.

Each of the most frequent morphological genetic RCC subtypes correlates with a specific molecular pathway. Examples include:

- The hypoxia-inducible pathway (clear-cell, papillary type II through the FH gene).
- The mTOR signalling pathway (clear-cell and papillary type II).
- The c Met-RAF-MEK-ERK pathway (papillary type I and translocation RCC).

new grading system (ISUP)

The 2012 ISUP consensus conference proposed a new grading classification based on the size of the nucleolus [7], which correlates well with prognosis and shows good interobserver reproducibility. The following recommendations were made:

- The nucleolar grading system should be used in clear-cell and papillary RCC.
- In chromophobe RCC, it is only necessary to report sarcomatoid features or the presence of an anaplastic component.

Table 1. Vancouver RCC classification

| Clear-cell renal cell carcinoma | Multi-locular clear-cell renal cell neoplasm of low malignant potential |
| Papillary renal cell carcinoma | Chromophobe renal cell carcinoma | Hybrid oncocytic chromophobe tumour |
| Carcinoma of the collecting ducts of Bellini | Renal medullary carcinoma | MiT family translocation renal cell carcinoma |
| Xp11 translocation renal cell carcinoma | t(6;11) renal cell carcinoma | Carcinoma associated with neuroblastoma |
| Mucinous tubular and spindle cell carcinoma | Tubulocystic renal cell carcinoma | Acquired cystic disease-associated renal cell carcinoma |
| Clear-cell papillary (tubulopapillary) renal cell carcinoma | Hereditary leiomyomatosis-associated renal cell carcinoma | Renal cell carcinoma, unclassified |

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Although some of the novel variants have marked nucleolar atypia, the nucleolar grading system is only recommended for the assessment of anaplastic areas.

**staging and risk assessment**

**staging**

The Union for International Cancer Control tumour–node–metastasis staging system should be used (Table 2).

**risk assessment**

RCC is recognised 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.

**localised disease.** Two systems can be used to assess the risk of progression in localised tumours: the stage, size grade and necrosis (SSIGN) score [9] and the University of California Los Angeles Integrated Staging System (UISS) [10]. These systems are described in Tables 3 and 4. In SSIGN, risk points are accumulated as noted in Table 3 and added up to provide a risk score.

The SSIGN score compared favourably 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 localised and metastatic disease. Further prospective data will be available from the current adjuvant trials for patients with high and intermediate risk RCC.

**advanced disease.** Prognostic models were first built when immunotherapy was the standard therapy. The Memorial Sloan Kettering Cancer Centre (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 or International Metastatic RCC Database Consortium (IMDC) criteria [11]. Patients are stratified according to the presence of six risk factors:

- Karnofsky performance status (PS) <80%
- Haemoglobin <lower limit of normal
- Time from diagnosis to treatment of <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:

<table>
<thead>
<tr>
<th>Number of risk factors</th>
<th>Risk group</th>
<th>Median overall survival (OS), months</th>
<th>2-year OS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Favourable</td>
<td>43</td>
<td>75</td>
</tr>
<tr>
<td>1–2</td>
<td>Intermediate</td>
<td>27</td>
<td>53</td>
</tr>
<tr>
<td>3–6</td>
<td>Poor</td>
<td>8.8</td>
<td>7</td>
</tr>
</tbody>
</table>

This prognostic model has been recently validated also in second line. It should be noted that work continues to improve risk score models.

**biomarkers.** Although there are many potential biomarkers under investigation, none has yet been validated for general use in the prognostic or predictive assessment of RCC. It is notable that multiple series have suggested that the presence of PBRM1 mutations confer a favourable prognosis, whilst mutations of BAP1 confer a poor prognosis. The small proportion of patients whose tumours exhibited both BAP1 and PBRM1 mutations had the worst survival of all [12].

### management of local/locoregional disease

**T1 tumours (<7 cm)**

Partial nephrectomy is recommended as the preferred option in organ confined tumours measuring up to 7 cm (elective indication). Partial nephrectomy can be performed via open, laparoscopic or coelioscopic robot-assisted approaches. In patients with compromised renal function, solitary kidney or bilateral tumours, partial nephrectomy is also the standard of care, with no tumour size limitation (imperative indication). Laparoscopic radical nephrectomy is recommended if partial nephrectomy is not technically feasible [13].

Radio frequency or cryoablative treatments are options in patients with small cortical tumours (≤3 cm), especially for patients who are frail, present a high surgical risk, and those with a solitary kidney, compromised renal function, hereditary RCC or multiple bilateral tumours. Long-term oncological results are now available with low recurrence rates and excellent cancer-specific survival [14].

Active surveillance is an option in elderly patients, with significant comorbidities, or those with a short life expectancy and solid renal tumours measuring <40 mm with emerging new data about tumour growth rate [15].

**T2 tumours (>7 cm)**

Laparoscopic radical nephrectomy is the preferred option.

### Table 3.

Stage, size grade and necrosis (SSIGN) score for localised RCC

<table>
<thead>
<tr>
<th>Feature</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathological T category</td>
<td></td>
</tr>
<tr>
<td>of primary tumour (TNM 2002)</td>
<td></td>
</tr>
<tr>
<td>pT1a</td>
<td>0</td>
</tr>
<tr>
<td>pT1b</td>
<td>2</td>
</tr>
<tr>
<td>pT2</td>
<td>3</td>
</tr>
<tr>
<td>pT3a–4</td>
<td>4</td>
</tr>
<tr>
<td>Regional lymph node status</td>
<td></td>
</tr>
<tr>
<td>(TNM 2002)</td>
<td></td>
</tr>
<tr>
<td>pNx or pN0</td>
<td>0</td>
</tr>
<tr>
<td>pN1 or pN2</td>
<td>2</td>
</tr>
<tr>
<td>Tumour size (cm)</td>
<td></td>
</tr>
<tr>
<td>&lt;10</td>
<td>0</td>
</tr>
<tr>
<td>≥10</td>
<td>1</td>
</tr>
<tr>
<td>Nuclear grade</td>
<td></td>
</tr>
<tr>
<td>1 or 2</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Histological tumour necrosis</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>0</td>
</tr>
<tr>
<td>Yes</td>
<td>1</td>
</tr>
</tbody>
</table>

**Scores**

<table>
<thead>
<tr>
<th>Group</th>
<th>5-year metastasis-free survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–2</td>
<td>Low risk</td>
</tr>
<tr>
<td>3–5</td>
<td>Intermediate risk</td>
</tr>
<tr>
<td>≥6</td>
<td>High risk</td>
</tr>
</tbody>
</table>

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### Table 4.

University of California Los Angeles Integrated Staging System (UISS) risk groups and 5-year disease-specific survival

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Prognostic group</th>
<th>Prognostic group</th>
<th>Prognostic group</th>
<th>Prognostic group</th>
<th>Prognostic group</th>
<th>Prognostic group</th>
<th>Prognostic group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T stage</td>
<td>Fuhrman’s grade</td>
<td>ECOG status</td>
<td>5-year disease-specific survival (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Localized disease (N0, M0)</td>
<td>Low risk</td>
<td>1</td>
<td>1–2</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>1</td>
<td>1–2</td>
<td>1 or more</td>
<td>80.4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>3–4</td>
<td>Any</td>
<td>4.1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Any</td>
<td>Any</td>
<td>4.1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>1</td>
<td>Any</td>
<td>4.1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>2–4</td>
<td>Any</td>
<td>4.1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>3</td>
<td>2–4</td>
<td>1 or more</td>
<td>54.7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Any</td>
<td>Any</td>
<td>4.1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metastatic disease</td>
<td>Low risk</td>
<td>N1M0</td>
<td>Any</td>
<td>Any</td>
<td>32</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Intermediate risk</td>
<td>N2M0/M1</td>
<td>1–2</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>N2M0/M1</td>
<td>1–2</td>
<td>1 or more</td>
<td>19.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3</td>
<td>0, 1 or more</td>
<td>4.1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>4</td>
<td>0</td>
<td>4.1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>N3M0/M1</td>
<td>4</td>
<td>1 or more</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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 is not recommended when abdominal CT shows no evidence of adrenal or lymph node invasion.

There is no recommended adjuvant treatment, although at least four tyrosine kinase inhibitor (TKI)-based adjuvant trials have been now completed. Results will not be available before 2015.

Neoadjuvant approaches are still experimental, especially for resectable tumours, and should not be routinely proposed outside of clinical trials. Many studies have demonstrated that such approaches are relatively safe, with modest median tumour downsizing and no proven benefit in terms of disease-free survival. See Table 5.

management of metastatic disease

role of surgery

In the era of immunotherapy, cytoreductive nephrectomy was recommended in patients with good PS (I, A) [16]. Whether this recommendation will remain with current targeted therapies is currently being investigated in two prospective trials. In routine practice, cytoreductive nephrectomy is recommended in patients with good PS and large primary tumours with limited volumes of metastatic disease, and for patients with a symptomatic primary lesion. Cytoreductive nephrectomy is not recommended in patients with poor PS.

Metastasectomy can be considered and performed after multidisciplinary review for selected 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 nonrandomised 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 [17]. 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. No systemic treatment is recommended after metastasectomy.

systemic treatment

Recommendations mainly relate to clear-cell histology, since most of the pivotal trials have been done in this common histological subtype (Table 6). In addition, recommendations will differ according to risk stratification (see above). It should be emphasised that many of the pivotal trials (such as Temsirolimus phase 3, RECORD-1 or COMPARZ) have flaws, and have raised questions, but can lead to well-accepted recommendations.

first-line treatment of patients with good or intermediate prognosis. Because some RCC have a very indolent course, a period of observation before starting treatment should be considered, especially in patients with limited tumour burden and few symptoms. Indeed, the outcome of patients who crossed over to an active agent after a brief period of treatment with placebo, within placebo-controlled phase III trials, indirectly supports this option (II, C).

Three treatments have demonstrated efficacy in pivotal phase 3: bevacizumab combined with interferon-alpha (IFN-α), sunitinib and pazopanib [18–20]. All three drugs have been registered based on improvement of progression-free survival (PFS) over either IFN-α or placebo. More recently, pazopanib has been shown not to be inferior to sunitinib in a large phase III trial [21].

Considering all published trials, the level of recommendation for these three options is considered to be (I, A) for all three regimens.

Sorafenib (II, B), high-dose interleukin-2 (III, C) and low-dose IFN-α combined with bevacizumab (III, A) are options. Single-agent IFN-α, the losing arm of three randomised, controlled trials, should no longer be regarded as a standard option (I, D).

first-line treatment of patients with poor prognosis. Temsirolimus is currently the only drug with level I evidence of activity in this patient population (II, A) [22]. The pivotal trial demonstrated improvement of OS compared with IFN-α or combination of temsirolimus and IFN-α.

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**Table 5. Summary of recommendations for the treatment of localised and locally advanced RCC**

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Level and grade of recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partial nephrectomy is recommended for the treatment of all T1 tumours if negative margins are obtained and risk of morbidity is acceptable.</td>
<td>III, C</td>
</tr>
<tr>
<td>Laparoscopic radical nephrectomy is the preferred option for the treatment of organ confined RCC (stages T1T2N0X:M0) when partial nephrectomy is not feasible.</td>
<td>II, B</td>
</tr>
<tr>
<td>Routine adrenalectomy and lymph node dissection are not required for all radical nephrectomies.</td>
<td>III, D</td>
</tr>
<tr>
<td>Open radical nephrectomy with the goal of obtaining negative margins is still the standard of care for locally advanced RCC.</td>
<td>III, C</td>
</tr>
<tr>
<td>Ablative treatments are options in: patients with small cortical tumours (≤3 cm) and age &gt;70 years, high surgical risk, solitary kidney, compromised renal function, hereditary RCC or multiple bilateral tumours.</td>
<td>III, C</td>
</tr>
<tr>
<td>Active surveillance is an option in patients ≥75 years, with significant comorbidities and solid renal tumours measuring &lt;40 mm.</td>
<td>III, C</td>
</tr>
</tbody>
</table>
Based on subgroup analysis from the pivotal trial as well as expanded access programmes, sunitinib is another reasonable option in this setting [II, B]. Sorafenib based on expanded access programmes is another possible alternative [III, B]. It is clear that, for some poor prognosis patients, best supportive care remains the only suitable treatment option.

**second-line treatment.**

- Evidence that TKIs are active after cytokines has been demonstrated with sorafenib [I, A], pazopanib [II, A] and recently axitinib [I, A] [20, 23, 24]. Sunitinib also has activity in 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 axitinib [I, B] and everolimus [II, A] are active [24, 25]. Both drugs have shown significantly improved PFS over placebo (everolimus) or sorafenib (axitinib), but not OS.
  - Based on recent phase III trials [26], sorafenib can be used as an option [II, A].

**third-line treatment.** Beyond second-line treatment, enrolment into clinical trials is recommended where possible. However, some recent trials have been reported, helping to define two different scenarios:

- 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, sorafenib [I, B] has shown activity [27]. Another TKI or rechallenge with the same TKI is considered as an option [IV, B].

**medical treatment of metastatic disease of non-clear-cell histology.** No prospective randomised data (other than subgroup analyses) are presently available for patients with non-clear-cell renal cancer. For these patients, enrolment into specifically designed clinical trials is recommended. However, in the absence of such trials, recommendations can only be made according to the results of the expanded access programmes 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 treatment with sunitinib, sorafenib or temsirolimus [III, B]. However, in most of these studies, only papillary and chromophobe tumours have been enrolled.

In the absence of prospective data, genetic considerations may influence treatment decisions: in papillary type I tumours, activation of the c-MET pathway has commonly been reported. Novel agents inhibiting the cMET receptor are currently under investigation. However, as the c-MET receptor and VEGF-receptor were shown to cooperate, VEGF-inhibiting agents may be a reasonable choice. Similarly, there is no evidence for the optimal treatment of papillary type II, which is characterised by inactivation of the fumarate-hydratase gene, fumarate-accumulation and HIF1α up-regulation. Again, VEGF inhibitors may be considered in this context. Patients with chromophobe RCC may benefit from mTOR inhibitors since mutation on chromosome 7 was shown to lead to a loss of the folliculin gene with up-regulation of mTOR. Finally, collecting duct tumours (and also medullary carcinomas) were reported to behave more like aggressive urothelial tumours rather than RCCs and may therefore be considered for chemotherapy. None of these recommendations can be given a grade.

**role of radiotherapy and biphosphonates**

Radiotherapy has a limited role in the primary management of renal cancer [28]. However, it is used in many different clinical situations particularly for unresectable local recurrences and metastatic disease.

- There is no role of radiotherapy in the neoadjuvant or adjuvant setting. This is on the basis of four negative trials with
two preoperative and two adjuvant studies. Despite being randomised trials, there are several major limitations in trial design and methodology that included inappropriate case selection, sub-therapeutic radiotherapy regimes and inadequate patient numbers. Furthermore, treatment morbidity was high and the radiotherapy techniques used then have been superseded by improved modern methods such as 3D conformal or intensity-modulated radiotherapy [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 radiofrequency ablation are not appropriate. There is an emerging biological rationale based on the ceramide pathway that can overcome the apparent radioresistance of renal cancers by the use of high dose per fraction, conveniently delivered by extra-cranial stereotactic radiotherapy [IV, B] [29].

- 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% [I, A].

- For the management of spinal cord compression, an ambulatory status at diagnosis and limited metastatic disease are favourable prognosis 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 [I, A].

- In the management of patients with brain metastases, the use of corticosteroids can provide effective temporary relief from cerebral symptoms. Whole brain radiotherapy between 20 and 30 Gy in 4–10 fractions 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 metastasis due to mRCC [30] and they should be considered for zoledronic acid treatment, weighting the potential benefits of the treatment (supposed benefit in terms of OS) with the potential harms (risk of osteonecrosis of the jaw) [II, A] [31]. Novel agents other than bisphosphonates (e.g. alpharadin 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 localised 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- to 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.

**personalised medicine**

In this disease setting, more research is needed to identify molecular markers which could lead to advances in personalised medicine.

**note**

Levels of evidence and grades of recommendation have been applied using the system shown in Table 7. Statements without grading were considered justified standard clinical practice by the experts and the ESMO faculty.

**conflict of interest**

MS reported honoraria for advisory boards and lectures from Roche, Bayer, Astellas, AVEO, Pfizer, GlaxoSmithKline and Novartis; she is conducting research sponsored by Pfizer and
GlaxoSmithKline. JJP reported consultancy for Pfizer and GlaxoSmithKline; he reported being the principal investigator for a study funded by Pfizer. TE reported holding stock in AstraZeneca; he will take up a post as Vice president Clinical Discovery in AstraZeneca in September 2014; received honoraria for consultancy/lecture from Pfizer, GlaxoSmithKline, Novartis, Astellas/Aveo, Bayer Schering, Boehringer Ingelheim; and research or trial support from Pfizer, Bayer, AstraZeneca. BE reported honoraria for consultancy/lecture from Bayer, Novartis, Pfizer, GlaxoSmithKline, Astellas. CP reported honoraria received for consultancy/lecture from Pfizer, GlaxoSmithKline, Novartis, Astellas/Aveo, Bayer Schering, Boehringer Ingelheim, Pierre Fabre; and research or trial support from Pfizer. AH, FA and VK have reported no potential conflicts of interest.

references