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Review

EORTC-GU group expert opinion on metastatic renal cell cancer

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ABSTRACT

There is no consensus on the detailed surveillance of renal cell cancer (RCC) patients after radical resection of the kidney. Where relapse is unlikely, one reasonable option would be to confine investigations to chest X-ray and abdominal ultrasound – carried out at 3-month intervals during the first year, but less frequently thereafter. These investigations could be supplemented by annual computerised tomography (CT) of the chest and abdomen. Where risk is intermediate or high, more frequent CT should be undertaken, taking into account the risks of repeated radiation exposure. Since the emergence of new and more effective treatments for metastatic disease, follow-up has tended to become more challenging not only with respect to disease assessment but also for evaluation of toxicity **[Level 5]**.

The diagnostic work-up in metastatic RCC should include a history, physical examination and comprehensive blood screen. In addition, patients to be treated with targeted agents should have a thyroid function test. In patients with a relevant clinical history or who are otherwise at risk, cardiac function should be assessed, and this is also advisable in asymptomatic patients **[Level 2b]**.

Nephrectomy is an important component of the multimodality treatment of mRCC. This procedure induces spontaneous regression of metastases in a small number of patients **[Level 4]**. More generally, it improves the survival of patients who subsequently receive immunotherapy **[Level 1]**. However, it is not yet known whether this benefit is also seen in patients treated with targeted agents **[Level 2b]**.

Certain patients with metastases (even at multiple sites) have lesions that are resectable. Surgery is potentially curative in these cases and can be undertaken prior to use of cytokines or targeted agents **[Level 2b]**.

Vaccine-based therapies may have potential, particularly when disease burden is low **[Level 4]**. The outcome of ongoing trials is awaited.

Metastatic RCC responds, albeit at a low rate, to cytokines. These agents may be helpful for a subgroup of patients. However, for the great majority, and certainly for those with intermediate- or poor-risk disease, cytokines confer no benefit **[Level 1b]**.

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Choice of initial medical management in patients with metastatic clear-cell RCC should be guided by the pivotal, randomised studies. On the evidence available, the first-line therapy in patients with good- or intermediate-risk mRCC should be either sunitinib **[Level 1b]** or bevacizumab plus interferon **[Level 1a]**. In patients ineligible for sunitinib or bevacizumab plus interferon, sorafenib is an option, as is high-dose interleukin 2 if performance status is sufficiently good **[Level 2b]**. In patients with poor prognosis (as defined in the pivotal trial), temsirolimus is recommended **[Level 1b]**. In this group, sunitinib could be an alternative **[Level 2b]**. The role of targeted agents in the treatment of patients with RCC of non-clear-cell histologies remains to be established. In cytokine refractory patients, sorafenib is recommended **[Level 1b]**. Everolimus is the agent of choice when patients have progressed on a tyrosine kinase inhibitor **[Level 1b]**.

1. Introduction

For several decades, metastatic renal cell cancer (mRCC) was stubbornly resistant to therapy. However, recent advances, most notably the introduction of small-molecule inhibitors of intracellular signalling, have substantially improved patients' prospects.[1] Along with an expanding range of possible interventions has come the need to interpret and integrate the wealth of new clinical trial data being generated. The following recommendations have been developed in an attempt to contribute to this process. They relate only to the treatment of mRCC: locally advanced disease is not considered. Except where indicated, recommendations on medical management relate to tumours of clear-cell histology, which comprise approximately 80% of renal cell cancers.[2] Recommendations on surgical management and follow-up are appropriate for renal cell tumours of all histologies. Throughout, recommendations are based on evidence that is published (though, on occasions, only in abstract), and are classified according to the extent and nature of the supporting data (see Table 1).[3]

These recommendations relate to the following areas: the classification of patients post nephrectomy according to risk of recurrence; imaging studies that should be undertaken to detect and investigate relapse; the classification of patients with metastatic disease according to prognostic factors; the role and timing of nephrectomy in patients presenting with metastatic disease; indications for the resection of metastases; the role of non-drug palliation; whether vaccine-based approaches and cytokines should continue to play a role in the era of targeted medical therapies; the sequencing and combination of targeted agents and the classification of patients with metastatic disease according to prognostic factors.

It is recognised that best practice is evolving rapidly as fresh evidence becomes available and that these recommendations – as with those that have preceded them[4,5] – will need continuous updating based on the accumulation of new information, especially from controlled clinical trials. For many patients with advanced or metastatic RCC, the optimal treatment is still not clear. In such cases, participation in a well-conducted clinical trial is to be encouraged.

Table 1 – Levels of evidence, based on those developed by the Oxford Centre for Evidence-based Medicine.[3]

	Evidence obtained from:
1a	Systematic review of randomised controlled trials (RCTs)
1b	One good quality RCT
2a	Systematic review of cohort studies
2b	One cohort study (or poor quality RCT)
3	Systematic review of case-control studies
4	Case series
5	Expert opinion based on experience, physiology, bench research or first principles

2. Imaging and follow-up of primary RCC

2.1. *Predicting risk of metastasis*

Median 5-year follow-up of a large series of patients who underwent radical nephrectomy for clinically localised clear-cell RCC showed that 29% developed distant metastases.[6] Metastases were discovered at a median of 1.3 years after nephrectomy. Given the possibility of potentially curative surgical intervention, early detection of metastasis is important. However, the ability to detect metastases early enough to have a potential effect on outcome depends heavily on the natural history of the disease and the diagnostic facilities available.

Scoring systems such as that developed at the Mayo Clinic based on tumour stage, regional lymph node status, tumour size, nuclear grade and histologic tumour necrosis predict the risk of metastasis after nephrectomy in patients with clear-cell RCC.[7] Thus, after 3 years, the rate of metastasis-free survival was 97% in the low-risk group, 74% in the intermediate-risk group and 31% in the high-risk group. This system has been used to select patients for trials of adjuvant therapy and can serve as a guide to the appropriate intensity of post-surgical surveillance.

A group at the University of California Los Angeles has also developed an integrated system using stage, Fuhrman grade and ECOG performance status (PS) to stratify patients into five groups with different chances of survival.[8] Other nomograms are being developed and validated as predictors of distant metastases.[9] These may help target post-surgical radiological surveillance towards patients most at risk (Table 2).

Table 2 – Factors to be considered when assessing risk of metastasis following radical nephrectomy for clinically localised RCC.

Size and stage of primary tumour
Extent of regional lymph node involvement, if any
Tumour histology
Presence or absence of necrosis
Presence or absence of vascular invasion

2.2. *Imaging to detect distant metastasis*

There is no consensus on the detail of how surveillance should be conducted after radical resection of the kidney.[10] Where relapse is unlikely, one reasonable option is to confine investigations to chest X-ray and abdominal ultrasound (US). These could be undertaken at 3-month intervals for the first year, four-monthly over years 2 and 3, six-monthly through years 4 and 5, and annually thereafter. These investigations could be supplemented by annual computerised tomography (CT) of the chest and abdomen. Where risk is intermediate or high, more frequent CT of the chest and abdomen could be undertaken, with the frequency left to the physician's discretion, and taking into account the risks of repeated radiation exposure **[Level 5]**.

Given the emergence of new and more effective treatments for metastatic disease, follow-up is becoming more energetic.

PET is not recommended for the routine early detection of mRCC, and its potential needs to be assessed by prospective trials.[11,12] A positive scan should raise the suspicion of malignancy but due to the relatively low sensitivity of the existing techniques, a negative scan does not rule out metastatic disease. However avid the uptake of 18F-FDG by metastases is, the current technology cannot detect lesions of less than around 8mm in diameter.[11] Imaging using monoclonal antibodies to renal tumour antigens may have a useful role in the future but is not yet sufficiently developed to be helpful in routine management.

There are as yet no validated biomarkers for use in the detection of recurrent disease.

2.3. *Diagnostic work-up in metastatic disease*

The diagnostic work-up should include a history, physical examination including blood pressure measurement and comprehensive blood screen (covering ESR, LDH, calcium and haemoglobin, along with lipase, amylase, thyroid function tests and triglycerides if treatment with small molecules is being considered).

Imaging should include chest X-ray and abdominal US as the minimum. Thoraco/abdominal CT is preferred if available. MRI is superior to CT scanning in the case of soft tissue lesions, caval tumour thrombus, and symptomatic spine lesions or visceral lesions that are not clarified by CT. When extensive surgery for metastases is contemplated, there is a case for supplementary PET scanning since the latter is emerging as a useful tool in patients with suspected abdominal and bone metastases[13] **[Level 4]**.

A large study of site-specific disease recurrence following surgery at the Mayo Clinic found metastases in bone in 7% of patients and in the brain in 4%. This compared with abdominal recurrence in 10% and recurrence in the thoracic region in 16%.[7] Given the relatively low risk of CNS metastasis in renal cell cancer, MRI or CT of the brain – in the absence of relevant symptoms – is generally not necessary (although it may be indicated because of possible bleeding risk when bevacizumab is to be used). Similarly, bone scintigraphy is generally not necessary, except in cases of bone pain or abnormal alkaline phosphatase.[11] However, bone scanning is not very sensitive in diagnosing osteolytic metastases and therefore plain X-rays and MRI are the preferred imaging techniques.

In addition to routine clinical and laboratory work-up, patients to be treated with targeted agents should undergo a thyroid function test. In patients with a relevant clinical history or who are otherwise at risk, cardiac function should be assessed, and this is also advisable in asymptomatic patients. In a recently published series, 34% of mRCC patients treated with sorafenib or sunitinib experienced a cardiac event.[14] At least with respect to sunitinib, the rate of cardiac events was higher than that previously reported.[15] Careful monitoring of cardiac function is advisable to detect cardiac changes early. After appropriate treatment, most patients are able to resume using TKIs.

2.4. *Evaluation of response*

Use of RECIST remains standard. However, their appropriateness in evaluating response to targeted therapies – which are more likely to cause stabilisation of disease or central necrosis, rather than tumour shrinkage – is debated.[16] As an indication of the likely advent of more relevant techniques, contrast-enhanced Doppler ultrasound scans showing decreased contrast uptake and stable or reduced tumour volume have been found to predict progression-free and overall survival in patients treated with sorafenib.[17] In assessing the activity of vascular-targeted agents in mRCC, a similar role has been proposed for dynamic contrast-enhanced MRI.[18]

3. Surgical interventions

The options for therapy are nephrectomy plus resection of metastases, nephrectomy plus medical treatment, medical treatment plus nephrectomy or medical therapy alone.

3.1. *Nephrectomy*

Nephrectomy is an important component of the multimodality treatment of mRCC. Two randomised phase III studies – one conducted by the EORTC and the other by the US Southwestern Oncology Group – concluded that patients treated with nephrectomy in addition to IFN-alpha showed significantly longer survival than patients treated with the cytokine alone[19,20] [**Level 1**]. Combining data from these two studies shows that surgery conferred a survival advantage of 5.8 months and a 31% reduction in risk of death.[21] The combined EORTC and SWOG data show a low (1.5%) rate of surgical mortality. A further 5.6% of patients were unable to receive systemic immunotherapy following their operation.

In addition to these phase III trials with interferon, retrospective analysis of a large US series selected according to the criteria used in the SWOG study suggests that nephrectomy followed by IL-2 is also associated with relatively good outcome: median overall survival was 16.7 months, and 19.6% of patients were alive at 5 years[22] **[Level 3]**.

Although the randomised trials showed greatest benefit in patients with the best performance status, nephrectomy prior to cytokine therapy can be recommended in patients who are fit enough to undergo the procedure. Factors that may militate against nephrectomy include comorbidities that increase the risk of surgery, and a high volume of metastatic disease.

In addition to complementing immunotherapy, nephrectomy has been shown to induce spontaneous regression of metastases, especially in the lung, in a small proportion of patients: reported rates range from less than 1% to 7%.[23,24] A further consideration is that the primary tumour is very unlikely to respond to immunotherapy even when metastases prove sensitive.[25] Expert surgeons can now perform even challenging resections using laparoscopic techniques. This development may decrease morbidity and so reduce the delay in delivering systemic treatment.[26]

However, it should be noted that whilst radical nephrectomy offers proven survival advantage when combined with immunotherapy, this benefit has not yet been demonstrated in the case of patients treated with targeted agents such as the small-molecule tyrosine kinase inhibitors.[27] Studies are ongoing.

3.2. *Metastasectomy*

Certain patients with mRCC (even those with multiple metastases, when the number of lesions is limited) may be treated with radical nephrectomy and resection of the metastatic lesions **[Level 2b]**. A recent study found that metastasectomy was of clinical benefit across the range of prognostic groups and was independently associated with survival.[28] In certain instances, surgery is potentially curative and should therefore be undertaken prior to the use of cytokines or targeted agents. The need to exclude patients with more widespread disease reinforces the importance of adequate imaging studies, such as with PET. There are occasional patients with mRCC in whom sunitinib (for instance) reduces tumour burden to the extent that resection becomes possible, resulting in a durable complete remission[29] **[Level 4]**.

4. Palliative measures

4.1. *Surgery*

Nephrectomy may be indicated to resolve symptoms such as bleeding and pain arising from the primary tumour. Metastasectomy may also provide valuable palliation, particularly in bony disease.

4.2. *Embolisation*

Embolisation can be used to treat inoperable RCC causing pain, haematuria or paraneoplastic symptoms, or metastatic lesions causing symptoms. In rare cases, pre-operative embolisation has been used to facilitate surgical resection by reducing tumour size and vascularisation.[30] Palliative embolisation for haematuria due to inoperable RCC may be offered in cases of short life expectancy, since neo-vascularisation following the procedure can be expected. Several small series have described embolisation for symptomatic relief, but its true value cannot be assessed.[31] Embolisation may also be offered as the sole therapy, or to reduce blood loss during surgery in patients undergoing an operation for intractable metastatic bone pain. However, published series are again small[32,33] **[Level 4]**.

4.3. *Radiotherapy*

If a patient presents with inoperable RCC, which is rare, palliative radiation may be considered. Using stereotactic radiotherapy, Wersäll et al. reported a local control rate of 90–98% in a retrospective series of 50 patients with metastatic and 8 patients with inoperable RCC.[34] Patients who derived the greatest survival benefit from this approach were those with an inoperable tumour, low metastatic burden (1–3 lesions), and local recurrence following radical nephrectomy **[Level 4]**. For patients with brain metastases, there is a possible role for radiosurgery. In a retrospective analysis, O'Neill et al. found no difference in survival between surgical resection and stereotactic radiosurgery: the 1-year survival rates were 62% and 56%, respectively.[35] Interestingly, none of the patients treated with stereotactic radiosurgery had a local recurrence compared to 58% in the neurosurgery group. Stereotactic radiosurgery may also be preferable to whole-brain irradiation for patients with 1–3 metastases. It is an outpatient treatment, minimally invasive and with low rates of local recurrence.[36] In cases of intractable pain due to osseous metastases, radiotherapy is an option if painkillers and bisphosphonates have failed[37,38] **[Level 4]**. Stereotactic radiotherapy may be a good option for patients with metastases of 3 cm or less.

5. Medical management

5.1. *Vaccine approaches*

A variety of vaccine approaches for RCC have been evaluated in animal models, including those involving minimal peptide epitopes, DNA, recombinant viruses, dendritic cells, modified tumour cells and heat shock proteins chaperoning tumour antigens. Vaccines can be autologous (patient-specific) or non-autologous (non-patient-specific), and are administered alone or with adjuvants. All the approaches share the fundamental goal of programming a patient's immune system to attack the patient's cancer by generating an antitumour immune response.

In mRCC, results to date have been mixed and indicate that an approach based on vaccines alone may be insufficient when tumour burden is high.[39,40] Successful development of vaccines in the metastatic setting will probably require a combined approach in which disease is stabilised or (ideally) debulked prior to use of an immune-stimulatory agent, or in which a therapeutic vaccine is used in combination with other agents **[Level 4]**. Positive findings from a

phase II trial of TroVax (MVA 5T4) have led to a phase III trial evaluating this vaccine in combination with cytokine therapy in patients with locally advanced or metastatic RCC.[41] A phase III trial of an adjuvant autologous vaccine (HSPCC-96) recently showed an advantage in recurrence free survival in intermediate-risk patients.[42] There is an ongoing phase III trial with G250.[43]

5.2. *Cytokines*

Metastatic RCC responds, albeit at a low rate, to cytokine therapy.[44] With both interferon (IFN) and IL-2, objective response rates of up to 15% have been reported.[45,46] However, in patients treated with IFN, durable responses are seen only in a small proportion of patients, and these are usually the rare cases in which the treatment has achieved a complete response.

The frequency and durability of response are somewhat better with high-dose bolus IL-2, but this treatment is associated with substantial toxicity.[47–49] Nevertheless, meta-analysis of 52 randomised studies including almost 6000 patients with advanced RCC treated with immunotherapy showed a significant median 3.8-month improvement in survival compared with control arms not treated with immunotherapy[50] **[Level 1a]**.

Randomised studies of the combination of IFN and IL-2 have failed to show survival benefit when compared with administration of one cytokine alone.[51,52] Most recently, the PERCY Quattro trial showed that IFN and IL-2, alone or in combination, failed to improve survival in patients with intermediate prognosis when compared with a control group treated with medroxyprogesterone acetate[53] **[Level 1b]**.

On the evidence available, there is a case for continuing to treat good-risk mRCC patients with high-dose IL-2.[52] However, the trials reviewed below suggest that cytokines can no longer be recommended for patients with intermediate or poor-risk disease[53] **[Level 2b]**.

5.3. *Targeted agents*

In more than 70% of sporadic clear-cell renal tumours, there is inactivation of the Von Hippel-Lindau (VHL) tumour suppressor gene through deletion, mutation or methylation. This leads to increased levels of hypoxia inducible factor (HIF) and mediators of angiogenesis such as vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF).[54,55] Hence, there is a clear rationale for the use of anti-angiogenic agents, and three such drugs have already undergone extensive clinical development in mRCC.

Sorafenib (Nexavar®) and sunitinib (Sutent®) are two oral small-molecule inhibitors of receptor tyrosine kinases (TKIs). Sorafenib targets the VEGF-2 and PDGF-beta receptors and various other tyrosine kinases. Sunitinib is also a multi-targeted inhibitor (with activity against VEGFR-2, PDGF-beta, c-kit and Flt-3 tyrosine kinases), but is not active against RAF. In addition to the multi-targeted TKIs, the anti-angiogenic monoclonal antibody bevacizumab (Avastin®), which targets VEGF itself, also has activity in mRCC.[56]

Renal tumours also frequently demonstrate abnormality in the mammalian target of rapamycin (mTOR) pathway, which is an important regulator of cell growth and proliferation.[55] Inhibitors of mTOR such as temsirolimus (Torisel®) and everolimus should therefore also have an important role in the management of mRCC.

5.4. *First line*

Choice of initial medical management should be guided by the pivotal, randomised studies of first-line therapy. With respect to all the targeted drugs, which may be given long term as maintenance agents, experience of their use and a pro-active approach to the management of toxicities are important in optimising the outcome.

5.4.1. *Sunitinib*

Sunitinib has been compared against interferon in intermediate- and low-risk mRCC patients with no prior medical therapy.[57] In this large phase III trial, 750 patients were randomised to sunitinib 50 mg daily (on a schedule of 4 weeks on treatment, followed by 2 weeks off) or interferon alpha at a dose of 9 MU three times a week.

The primary endpoint of progression-free survival (PFS) showed a clear and highly significant benefit from sunitinib treatment: patients assigned to the TKI had a median PFS of 11 months, compared with 5 months in the interferon group **[Level 1b]**. A nomogram predicting likelihood of PFS at 12 months in patients treated with sunitinib has been developed.[58] On multivariate analysis, these were ECOG PS 0 versus 1; one year or longer time between diagnosis and need for treatment; and corrected calcium of 10 mg/dL or less. Importantly, benefit from sunitinib appears to extend across all subgroups of patients with first-line mRCC.

Recently, data on overall survival have been presented (but not yet subjected to peer review).[59] These show median overall survival (OS) of 26.4 months for patients randomised to sunitinib compared with 21.8 months in the interferon arm. The difference in OS became statistically significant when patients who crossed over from interferon to sunitinib (approximately one-third of those randomised) were excluded from the analysis.

5.4.2. *Sorafenib*

Sorafenib's first-line efficacy was initially shown in a subset of 32 patients in the phase II randomised discontinuation trial, with a PFS of 9.2 months. Based on this, a randomised phase II trial of sorafenib (400 mg bid) against interferon alpha (9 MU three times a week) in intermediate- and low-risk patients was conducted ($n = 189$).[60] The primary endpoint was again PFS. However, in this instance, the PFS in the two arms of the trial was very similar: a median of 5.6 months in patients assigned to interferon and 5.7 months in those randomised to sorafenib.

5.4.3. *Sorafenib and sunitinib compared*

Although there is no head-to-head comparison of sunitinib and sorafenib in this setting, randomised trials of each agent against interferon (which has been considered the appropriate control arm in such studies) indicate that sunitinib is superior to the cytokine while sorafenib is not. Clinical experience suggests that the toxicities associated with sorafenib

and sunitinib are different; and it may be helpful to take this into account in the case of individual patients (such as those who have cardiac risk factors or are elderly).[61] However, given the data available from randomised trials, sunitinib – along with bevacizumab plus interferon (see below) – should be considered the preferred first-line therapy in patients at good and intermediate risk **[Level 1b]**.

5.4.4. *Bevacizumab*

The results of two phase III trials, both showing significant benefit in PFS, justify bevacizumab plus IFN as first-line therapy in intermediate- and good-risk mRCC **[Level 1a]**.

The European study compared bevacizumab plus interferon alpha against placebo plus interferon alpha.[62] In this trial, bevacizumab was given at a dose of 10 mg/kg every 2 weeks, and IFN at 9 MU three times a week. Median duration of PFS was significantly longer in the bevacizumab plus IFN group than in the control arm (10.2 months versus 5.4 months; HR 0.63, 95% confidence interval (CI) 0.52–0.75; $p = 0.0001$). Increases in PFS were seen with bevacizumab plus IFN irrespective of risk group and also when interferon alpha was given at reduced dose. Deaths due to adverse events were reported in eight patients (2%) who received one or more doses of bevacizumab and in seven (2%) of those who did not receive the drug. Three deaths in the bevacizumab arm were considered by the investigators to be possibly related to the drug.

Toxicities were confined to those already known to be associated with the two agents. The most commonly reported grade 3 or worse adverse events were fatigue in 40 patients (12%) in the bevacizumab group versus 25 patients (8%) in the control group. Asthenia was noted in 34 patients (10%) and in 20 patients (7%), respectively. The study's primary endpoint of overall survival has not yet been reached, but a trend favouring the combination of bevacizumab with interferon is evident.

A second phase III study of the combination of bevacizumab plus interferon alpha versus IFN monotherapy, conducted in the United States of America (USA), used the same drug regimens as the European study and also enrolled treatment-naïve patients.[63] Only 10% of the 732 patients accrued were in the poor-risk category by MSKCC criteria. Median PFS was significantly longer in patients treated with IFN plus bevacizumab than in patients treated with IFN alone (8.5 versus 5.2 months). Toxicities such as hypertension, anorexia and fatigue were significantly more common in the combination arm. Data on OS, which was the primary endpoint, are not yet available.

In the absence of a trial comparing the combination of bevacizumab plus IFN against sunitinib, it is not possible to judge the relative merits of these two approaches as first-line therapy.

The potential of single-agent bevacizumab has not been assessed in a large, controlled trial. However, the 8% response rate seen with bevacizumab monotherapy in the phase II study versus erlotinib[64] appears low when compared with the response rate of 31% seen in the phase III trial in combination with interferon. At this stage, it therefore seems inappropriate to treat first-line patients with bevacizumab alone **[Level 4]**.

5.4.5. *Temsirolimus*

The phase III study comparing temsirolimus against IFN differed from the sorafenib, sunitinib and bevacizumab trials in that it was designed specifically to recruit poor-prognosis patients.[65] Selection involved modified MSKCC criteria and included a wider range of patients than would otherwise have been the case. Patients were required to have at least three of the following six predictors of short survival: LDH level more than 1.5 times ULN; Hb less than lower limit of normal; corrected serum calcium greater than 10 mg/dl (2.5 mmol/L); less than 1 year from original diagnosis to development of metastatic disease; Karnofsky PS of 70 or less; metastases in more than one organ. The study did not exclude patients with non-clear cell tumours.

Patients were randomised to one of three arms: weekly temsirolimus 25 mg intravenous (i.v.); IFN escalating to 18 MU given subcutaneously three times a week; or temsirolimus 15 mg i.v. (i.e. a lower dose) plus interferon at 6 MU three times a week. Patients receiving temsirolimus alone enjoyed significantly longer overall survival than the other groups (median 10.9 months versus 7.3 months with interferon monotherapy and 8.4 months in the combination arm). Temsirolimus was also better tolerated than interferon.

Given these findings, temsirolimus should be considered standard first-line therapy for mRCC with features associated with poor prognosis **[Level 1b]**. However, the success of the trial validated mTOR as a target in renal cell cancer in general, and FDA approval of the drug does not limit its use to poor-risk patients.

5.4.6. *Metastatic RCC of non-clear cell histology*

Clinical responses occur infrequently in patients with mRCC of papillary or chromophobe histology.[66] However, cases of prolonged progression-free survival have been reported with sunitinib and sorafenib, and further work with these agents is being undertaken.

Recommendation: On the evidence available to date, sunitinib should be the first-line therapy in patients with good- or intermediate-risk metastatic RCC **[Level 1b]**. An alternative would be bevacizumab plus IFN-alpha **[Level 1a]**. Sorafenib is an option for patients ineligible for these agents **[Level 2]**. High-dose IL-2 is an option for selected patients with sufficiently good performance status **[Level 2]**. In patients with poor prognosis according to criteria used in the pivotal trial, temsirolimus is recommended **[Level 1b]**. In this group, sunitinib is an alternative **[Level 2]**.

5.5. *Second-line and combination therapy*

5.5.1. *Cytokine refractory patients*

The most appropriate second-line therapy is sorafenib. This conclusion derives from the TARGET trial showing that PFS with sorafenib 400 mg bid was 24 weeks, compared with only 12 weeks in patients randomised to placebo[67] **[Level 1b]**. Based on these data, placebo patients were allowed to crossover to sorafenib, which confounds analysis of overall survival. However, a pre-planned secondary analysis censoring placebo data showed that sorafenib was associated with significantly prolonged survival **[Level 4]**. Sunitinib is an option in cytokine refractory patients.

5.5.2. *Patients who have failed VEGF(R) inhibitors*

Data from a phase III trial show that patients failing at least one TKI (71% had received sunitinib, 55% sorafenib, and 26% both) enjoy significantly longer PFS when given the oral mTOR inhibitor everolimus (RAD 001), 10 mg daily ($n = 227$), rather than placebo ($n = 138$) (median PFS 4.0 versus 1.9 months).[68] Adverse events led to discontinuation of treatment in 10% of patients on active therapy and in 4% of those receiving placebo. Data on the secondary endpoint of OS are awaited. A good case can now be made for everolimus as standard of care post failure of a TKI **[Level 1b]**. In patients who have been treated with bevacizumab, sunitinib appears able to achieve a partial response or disease stabilisation in a proportion of cases.[69] There are retrospective data suggesting that overall disease control may be longer in patients who are treated first with sorafenib and then with sunitinib, rather than the reverse sequence[70,71] **[Level 4]**. However, such data cannot form the basis for recommendations on sequencing. Information on the relative efficacy of certain sequencing strategies will eventually be provided by the START trial in which patients will receive sunitinib, bevacizumab and temsirolimus in various orders.

5.5.3. *Combinations*

A number of trials combining anti-angiogenic TKIs (those already considered plus agents such as axitinib which are earlier in development) with bevacizumab, EGFR agents, mTOR inhibitors or cytokines have been completed or are in progress. One negative impression that can be arrived at from these early data is that the addition of EGFR agents appears to add little if anything to the VEGF(R) agents,[64] **[Level 5]**. However, there will almost certainly be benefits from combining some agents that act at different levels within the same pathway or simultaneously on different pathways. Only meticulous trial design and interpretation will determine which they are. Additional information should be provided by the BEST Intergroup study in which patients (who may have had a previous cytokine) will receive bevacizumab, temsirolimus/bevacizumab, sorafenib/bevacizumab or sorafenib/temsirolimus.

Conflict of interest statement

Theo M. de Reijke: advisory role Novartis, and GSK.

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Disclaimer

These expert opinions reflect the state of knowledge, current at the time of writing, on effective and appropriate care, as well as clinical consensus judgments when knowledge is lacking. Inevitable changes in the state of scientific information and technology mandate that periodic review, updating, and revision will be needed. These expert opinions do not apply to all patients, and each must be adapted and tailored to each individual patient. Proper use, adaptation, modification or decision to disregard these or other expert opinions, in whole or in part, are entirely the responsibility of the clinician.

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