New Research on Kidney Cancer: Highlights from Urologic and Oncologic Congresses in 2006

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Abstract

**Objectives:** This paper communicates the major new findings on renal cell cancer (RCC) that were presented at the 2006 annual meetings of the European Association of Urology (EAU), American Urological Association (AUA), and American Society of Clinical Oncology (ASCO), and discussed during a closed meeting in September 2006.

**Methods:** The most relevant new findings were selected by urologic experts in the field of RCC.

**Results:** One basic research study suggested that there might be pathways other than the von Hippel-Lindau/hypoxia-inducible factor-\(\alpha\) pathway involved in RCC tumour angiogenesis. Partial nephrectomy is still relatively uncommon compared with radical nephrectomy, even in small tumours. Overall and cancer-specific 5-yr survival for laparoscopic cryoablation was high, suggesting that it might be suitable for small renal masses. Radiofrequency ablation appears feasible and safe in healthy American Society of Anesthesiologists I and II patients. There were major contributions on angiogenesis inhibitors for metastatic RCC. Sorafenib significantly prolonged progression-free survival (PFS) compared with placebo in patients who failed prior systemic therapy. Sunitinib significantly prolonged PFS compared with interferon (IFN)-\(\alpha\) as first-line treatment of low- and intermediate-risk patients. Temsirolimus significantly increased overall survival compared with IFN-\(\alpha\) as first-line treatment in poor-risk patients.

**Conclusions:** Relevant new data on partial nephrectomy, cryoablation, and radiofrequency ablation are discussed in this paper. New standards are emerging for the treatment of metastatic RCC, which is now based on antiangiogenic drugs.
1. Introduction

Every year with more than 200,000 new cases diagnosed and more than 100,000 deaths occurring worldwide, renal cell carcinoma (RCC) is one of the most lethal urologic malignancies [1,2]. Prognosis for RCC varies considerably, depending on the disease stage at diagnosis. Those diagnosed early with organ-confined tumours have an 80–90% 5-yr survival rate. For patients with locally advanced disease, the 5-yr survival rate is still 50–60%. In contrast, the 5-yr survival rate for patients diagnosed with metastatic disease is only 5–10% [3]. In metastatic patients, factors that are associated with a worse prognosis include poor performance status, elevated serum lactate dehydrogenase, anaemia, hypercalcaemia, and absence of prior nephrectomy [4]. Despite the depressing statistics, there is reason for optimism as significant advances are being made in the diagnosis and treatment of RCC. Particularly the understanding of the genetic and molecular bases of RCC has greatly expanded in the last 5 yr, which has led to the development of novel targeted therapies and new surgical techniques resulting in the initiation of many clinical trials. This manuscript presents the most relevant new data on RCC presented at the European Association of Urology (EAU), the American Urological Association (AUA), and the American Society of Clinical Oncology (ASCO) 2006 annual meetings. These data were selected by urologic experts (the authors of this paper) in the field of RCC and discussed during a closed meeting in Cannes, September 2006. It should be noted that this article gives an overview of what is currently happening in the field of RCC and does not represent the state of the art on RCC.

2. Outcome and basic research

Clear-cell RCC (CCRCC) is a highly vascular tumour arising from epithelial elements within proximal tubules of nephrons [5]. von Hippel-Lindau (VHL) disease has provided a model for understanding CCRCC [6]. An early event during the evolution of CCRCC is a loss of function mutation of the VHL gene, which occurs in up to 75% of sporadic RCC [5,6]. The VHL gene encodes a tumour suppressor protein (pVHL) of 213 amino acid residues [6]. pVHL is the substrate recognition component of a ubiquitin ligase complex, which is composed of elongin B, elongin C, and Cul2, and Rbx1 (Fig. 1). This pVHL complex interacts with a protein transcription factor called hypoxia-inducible factor (HIF-1α) for proteolysis. During normoxia, HIF-1α is hydroxylated at two proline residues via an oxygen-dependent enzymatic mechanism [5]. The pVHL complex binds to the hydroxylated HIF-1α and polyubiquinates HIF1-α, leading to proteosome-mediated degradation of HIF-1α. During hypoxia, HIF-1α is not...
hydroxylated and, thus, cannot bind with the pVHL complex. HIF-1α accumulates and binds to HIF-1α, forming the HIF1 complex, which subsequently translocates into the cell nucleus where it binds with hypoxia-responsive element (HRE) in gene promoters and facilitates expression of hypoxia-inducible genes. Similarly, loss of function mutations of VHL prevents ubiquitin-mediated degradation of HIF-1α, resulting in upregulation of hypoxia-inducible genes [5,6]. In short, inactivation of the VHL gene by mutation is responsible for HIF stabilisation and accumulation, and induces upregulation of hypoxia-inducible genes. These genes include vascular endothelial growth factor (VEGF; which stimulates angiogenesis), platelet-derived growth factor (PDGF; which enhances endothelial stabilisation), erythropoietin, carbonic anhydrase IX, and transforming growth factor α (TGF-α, which stimulates cell replication) (Fig. 1). Inactivation of the VHL gene, therefore, can alter intracellular signalling, and lead to increased vascularisation and cell growth. The discovery of the molecular biology of RCC has led to the development of new agents for the treatment of metastatic RCC (mRCC), targeting VEGF, PDGF, and tyrosine kinase receptors. The results of the most recent trials with these agents will be discussed later in this paper.

Basic research remains important in the era of new angiogenesis inhibitors for understanding resistance mechanisms and, therefore, for optimising therapeutic strategy in mRCC [6]. At the ASCO 2006 annual meeting, Fergelot et al [7] presented the results of a prospective study that challenged the concept of the molecular basis of RCC. The aim of the study was to evaluate the relationship between VHL mutation status, tumour VEGF expression, and plasma VEGF measurement in sporadic RCC. Polymerase chain reaction amplification and sequencing of the VHL gene was performed for 70 patients with CCRCC. In 46 of these 70 CCRCC patients (65.7%), a VHL mutation was found. In addition, a significant association was found between VHL mutation and N stage (p = 0.01), Fuhrman grade, symptoms at presentation (p = 0.02), and tumour size (p = 0.007). A VHL mutation was found in 87% of T1 tumours, in 83.5% of low-grade tumours (G1–2), and in 80% of incidental tumours (p < 0.01). Interestingly, VEGF tumour expression and plasma VEGF levels were not significantly different among patients with or without a VHL mutation. The authors concluded that VHL mutations are more frequent in small incidental low-stage or low-grade tumours, suggesting the VHL mutation is an early event in CCRCC tumorigenesis. The lack of an association between VHL mutational status and VEGF tumour expression or plasma VEGF levels suggests that the VHL/HIF/VEGF pathway is not sufficient for explaining the angiogenic phenotype of RCC, but that other pathways may be involved. Further research into the molecular pathways of RCC is therefore needed.

3. Partial nephrectomy and mini-invasive techniques

3.1. Partial nephrectomy

The concept of radical nephrectomy (RN) as a standard of care in localized RCC is increasingly being challenged. In recent years the development of accurate diagnostic tools, such as high-resolution computed tomography (CT) scanning, allowed for a more precise staging of the preoperative tumour. Partial nephrectomy (PN) then became a treatment option for an increasing number of patients. PN was first advocated in selected patients, including those with a single kidney or in those with bilateral RCC [8]. The EAU guidelines recommend that, in small peripheral tumours (<4 cm), PN should be considered a standard of care [9]. During the closed meeting in Cannes, it was discussed that PN is performed by most urologists in tumours <4 cm. However, if the tumour is easily operable, tumours 4–7 cm can also be treated with PN [10].

Only a few of the delegates performed PN under laparoscopic conditions; the majority performed PN during open surgery. Because of increasing experience with PN, positive surgical margins after PN are nowadays less common. A US study with 5 yr of follow-up also showed that the recurrence rate of patients with positive surgical margins after PN was very low [11]. It was agreed that patients with positive surgical margins after PN should be closely followed, for example by CT scanning. Although there is obviously increased attention for PN and comparable outcomes have been reported for open PN and open RN [12], a study [13] presented at the AUA showed that PN remains relatively uncommon, even for small renal tumours. This US study used the population-based Surveillance Epidemiology and End Results (SEER) database to evaluate practice patterns for the surgical management of small renal tumours. Between 1988 and 2001, 14,647 patients with a primary tumour ≤7 cm were surgically treated. Overall, 1401 patients (9.6%) were treated with PN versus 13,246 (90.4%) with RN (Fig. 2). For tumours ≤7 cm, the use of PN increased progressively between 1988 and 2001 from 4.6% to 17.6% (p < 0.01; Fig. 3). Despite this trend, PN remained
relatively uncommon even for small tumours. For tumours <2 cm, 14% of patients underwent PN in 1988 versus 42% in 2001 (p < 0.01; Fig. 3). Younger patient age, smaller tumour size, and more recent diagnostic year were independent determinants of the use of PN (all p < 0.05). It was concluded that despite more frequent application of PN over the last two decades, the utilisation of PN remains relatively uncommon even in small tumours. In addition, because of its potentially favourable outcomes associated with preservation of renal parenchyma, PN should be promoted among urologists. It was discussed during the closed meeting that these data may represent only the current situation in the United States and not in Europe. The small number of PNs in the United States may be explained by the legal environment. The fear of law suits in case of disease recurrence or complications after PN may prevent urologists from performing PN. Unfortunately there are no European data on the utilisation of PN. Lack of experience was also advocated as a reason to perform RN instead of PN as was significant comorbidity of the patient. It should also be noted that although PN is becoming a standard surgical option for low-stage renal tumours, particularly in Europe, no prospective study has yet demonstrated that long-term oncologic results are equivalent to those obtained with RN [14].

3.2. Cryoablation

During the urologic congresses there was much interest for minimally invasive therapies such as renal cryoablation (CA) and radiofrequency ablation (RFA). During renal CA, tissue is destroyed by introducing a supercooled probe into the target tissue [12]. Several studies have demonstrated safe and effective treatment of tumours, as documented by radiographic follow-up and/or posttreatment needle biopsy [15–18]. A limitation of these studies was that they were performed in small numbers of patients (range: 15–37 patients) and that all had an intermediate follow-up (range: 3 mo to 3 yr). At the AUA 2006 annual meeting, Hegarty and colleagues [19] presented data on CA from 60 patients with each of them completing at least 5 yr of follow-up. Between September 1997 and September 2005, a total of 168 laparoscopic CAs (LCAs) were performed for small renal tumours. Follow-up included magnetic resonance imaging on postoperative day one, at 3 mo, 6 mo, 12 mo, and annually following LCA. In addition, a needle biopsy was scheduled at 6 mo of follow-up. Of the 60 patients with at least 5 yr of follow-up, the indication for treatment was a solitary sporadic renal tumour in 44 patients (73%). Mean tumour size was 2.3 cm (range: 1–4.5 cm). Median follow-up for all patients was 72 mo. Three patients (6.7%) developed local tumour recurrence, two of which were disease-free on dialysis following nephrectomy. The remaining patient died 10 mo after nephrectomy on dialysis with no evidence of further disease. Overall and cancer-specific 5-yr survival was 82% and 100%, respectively. It was concluded that recurrence rates with LCA are low in patients with solitary sporadic tumours and that 5-yr cancer-specific survival was 100% in these patients. During the meeting in Cannes, it was discussed that a need exists for studies comparing laparoscopic PN with LCA. For the moment laparoscopic or open PN is the most preferred treatment for small tumours. However, for patients who are not suitable for PN, such as those with high comorbidity, CA may be a good alternative.

3.3. Radiofrequency ablation

Radiofrequency ablation (RFA) is another minimally invasive therapy that is currently under investigation. RFA achieves tissue destruction by generating temperatures in excess of 45 °C with the use of a
probe [12]. Several small- and intermediate-term (<1 yr) studies have demonstrated that RFA may be a safe and effective treatment for small tumours [20–22]. A recent study in 78 patients with a mean follow-up of 25 mo showed a cancer-specific survival of 98.5% and an overall survival rate of 92.3% [23]. In most cases, RFA is performed in poor-risk patients such as those with marginal renal function, serious comorbidities, or a high risk of developing additional RCCs (eg, patients with VHL disease) [24,25]. However, at the AUA 2006 annual meeting, Stern et al [26] presented their experience with percutaneous or laparoscopic RFA in 37 healthy American Society of Anesthesiologists (ASA) I and ASA II patients who had at least 12 mo of follow-up. Mean age was 57 yr (range: 20–84 yr), and mean tumour size was 2.2 cm (range: 1–4 cm). Mean follow-up was 27 mo (range: 12–48 mo). There were no incomplete ablations. One patient experienced a recurrence at 24 mo after RFA and underwent salvage RN. This patient was without disease 1 yr later. Four minor complications were observed: three patients with self-limiting neuralgia/paresthesia secondary to RFA and one patient experiencing asymptomatic hydrocalyx 18 mo after RFA. It was concluded that renal RFA is feasible and safe in healthy ASA I and II patients with at least 2 yr of follow-up. These results need to be confirmed in studies with larger patient numbers and longer follow-up.

Some reports have raised concerns about the effectiveness of RFA treatment. A number of studies in which RFA was performed before surgical resection have demonstrated occasional areas of tumours that appear histologically normal and without necrosis after the RFA treatment [12,27–30]. During the AUA 2006 annual meeting, there was much debate about the reliability of RFA. An Austrian study [31] examined the homogeneity and extent of necrosis after RFA in patients with renal tumours smaller than 4 cm. Fifteen patients had laparoscopic RFA followed by immediate PN. Mean resected tumour size was 23 mm (range: 11–49 mm). Pathologic analysis demonstrated incomplete ablation in 31% of tumours treated with RFA. According to the authors, this study shows that, even with state-of-the-art technology, incomplete ablation after RFA for small renal tumours is a problem and makes the technique less reliable. However, at the AUA annual meeting and also during the expert meeting in Cannes, various explanations for these results were given. For instance, immediate pathologic analysis after RFA may be too early because the technique may need some time to exert its effects. In addition, there is the issue of the histologic technique for the pathologic analysis as well as the varying ability of urologists to perform RFA. It was concluded that RFA may be a safe and effective treatment for selected patients; however, more studies with longer follow-up are needed. In addition, randomised controlled trials comparing RFA with PN or LCA are recommended.

4. Systemic treatment

As discussed above, recent advances in the understanding of the molecular biology of RCC have led to the development of several novel agents for the treatment of mRCC [6]. At least five antiangiogenic agents are being investigated intensively: bevacizumab, sorafenib, sunitinib, temsirolimus, and AG013736. These new drugs were initially investigated as second-line treatments in mRCC. Initial results were very promising and show response rates that are much higher than with the standard therapy for advanced RCC and mRCC: cytokine-based immunotherapy [5]. At the ASCO 2006 annual meeting, the results of two exciting phase 3 trials were presented; the trials evaluated the effects of sunitinib and temsirolimus versus cytokine therapy as first-line treatment in advanced RCC and mRCC in respectively good- and intermediate-risk patients, and poor-risk patients (according to the Memorial Sloan-Kettering Cancer Centre [MSKCC] risk group categorisation [32]). In addition, at the EAU the results of a phase 3 trial comparing sorafenib with placebo as second-line therapy were presented.

4.1. Sunitinib

Sunitinib is an oxindol tyrosine kinase inhibitor. It is a small molecule with antitumour and antiangiogenic activity that selectively multitargets inhibition of PDGFR, VEGFR, KIT, and FLT3 [6]. Two multicentre phase 2 trials [33,34] with sunitinib as second-line monotherapy in patients with mRCC have been reported. A total of 34–40% of patients had a partial response, and 27–29% of patients had stable disease ≥ 3 mo. Time to progression was 8.3–8.7 mo. The phase 3 trial presented at the ASCO 2006 annual meeting concerned the first study evaluating sunitinib as first-line monotherapy [35,36]. A total of 750 untreated, good- and intermediate-risk patients (according to the MSKCC risk group categorisation [32]) with metastatic CCRCC were randomised to sunitinib (6-wk cycles: 50 mg orally once daily for 4 wk, followed by 2 wk off) and interferon-α (IFN-α; 6-wk cycles: subcutaneous injection 9 MU three times weekly). The median progression-free survival (PFS) was longer for patients treated with sunitinib (11 mo)
than for those treated with IFN-α (5 mo), with a hazard ratio (HR) of 0.415, \( p < 0.000001 \). The objective response rate was also statistically significantly higher for patients treated with sunitinib (37%) versus those treated with INF-α (9%). Sunitinib was well tolerated: Only 8% of patients taking sunitinib withdrew from the study because of adverse events (AEs) versus 13% of patients taking INF-α. This study suggests that sunitinib is significantly better as first-line therapy of mRCC than the current standard treatment with IFN-α for low- and intermediate-risk patients with mRCC.

### 4.2. Temsirolimus

Temsirolimus is a specific inhibitor of mammalian target of rapamycin (mTOR), a serine/threonine kinase that plays a key role in cell-cycle regulation [6]. In a phase 2 study [37] including 111 patients with mRCC who had failed prior treatment, temsirolimus showed an objective response rate of 7%. The overall clinical benefit was 51%, median time to progression was 5.8 mo, and median survival time was 15 mo. The study that was presented at the 2006 ASCO annual meeting concerned a direct-comparative, phase 3 trial between temsirolimus, INF-α, and their combination in patients with advanced RCC as first-line therapy [35,38]. Primary end point of the study was overall survival. Patients with stage IV or recurrent RCC who met at least three of the following poor prognosis criteria were enrolled: (1) less than 1 yr from initial diagnosis to randomisation; (2) Karnofsky performance status of 60 or 70; (3) haemoglobin less than normal limit of normal; (4) corrected calcium higher than 10 mg/dl; (5) lactate dehydrogenase higher than 1.5 times the upper limit of normal; and (6) more than one metastatic disease site. A total of 626 patients were randomised to IFN-α (up to 18 MU subcutaneously 3 times weekly; \( N = 207 \)), temsirolimus (15 mg/wk; \( N = 209 \)), or combined therapy (temsirolimus 15 mg/wk and INF-α 6 MU 3 times weekly; \( N = 210 \)). Median survival was 7.3 mo with IFN-α, 10.9 mo with temsirolimus, and 8.4 mo with combined treatment. These findings translate into a 49% increase in median survival with temsirolimus monotherapy compared with IFN-α monotherapy, with the difference between treatments being statistically significant (HR = 0.73, \( p < 0.007 \)). There was no statistically significant difference in median survival between IFN-α and combined therapy (\( p = 0.69 \)). Objective responses occurred in 7%, 9%, and 11% of patients in the IFN-α, temsirolimus, and combination arms. Temsirolimus was well tolerated: AEs leading to withdrawal from the study occurred in 7%, 14%, and 22% of patients on temsirolimus, IFN-α, and combined therapy, respectively. It was concluded that temsirolimus monotherapy increases overall survival in poor-risk patients with mRCC compared with IFN-α or combined IFN-α + temsirolimus treatment.

### 4.3. Sorafenib

Sorafenib is an oral multikinase inhibitor that has activity against Raf-1 serine/threonine kinase, B-Raf, VEGFR-2, PDGFR, FLT-3, and c-KIT [6]. Phase 2 trials have established the antitumour activity of sorafenib. In a phase 2 trial including 41 patients with mRCC receiving sorafenib as second-line or third-line therapy, 30% of patients had stable disease and 40% had responded (>25% reduction) after 12 wk of treatment [39]. A phase 3 trial [40] comparing sorafenib and placebo after failure of a prior systemic therapy has been completed recently, and the results were presented at the EAU 2006 annual meeting. A total of 905 patients with advanced CCRC were randomised to receive continuous oral sorafenib 400 mg twice daily or placebo added to best supportive care. Median PFS was 24 wk for sorafenib and 12 wk for placebo, with an HR sorafenib/placebo of 0.44, \( p < 0.000001 \). After 3 mo of treatment, 75% of patients taking sorafenib were progression-free versus 43% of those taking placebo. It was concluded that sorafenib significantly prolongs PFS compared with placebo in patients with previously treated advanced RCC. A trial comparing sorafenib and IFN-α as first-line treatment is currently ongoing.

### 5. Conclusions

Many interesting data were presented on RCC at the urologic and oncologic congresses in 2006. SEER data from the United States show that PN is still relatively uncommon compared with RN even in small tumours. Lack of experience with the technique or fear of surgical-related morbidity seems to be the major reason for keeping urologists from performing PN. Therefore, increased attention should be paid to the training of urologists in PN techniques. There was also much attention on minimally invasive techniques. Data from a large study with 5 yr of follow-up showed that LCA had a high overall and cancer-specific 5-yr survival, suggesting that it is a suitable technique for patients with small renal tumours. Although RFA is commonly reserved for patients who are not suitable for PN/RN, data with 2 yr of follow-up now suggest that it is also feasible and safe in healthy ASA I and II patients. However,
more long-term studies with adequate patient numbers are needed.

In the past few years, major progress has been made in understanding the molecular basis of RCC, suggesting a leading role for the VHL/HIF-α/VEGF pathway. However, one study presented at the ASCO annual meeting showed that VHL mutations are more frequent in small, incidental, low-grade or low-stage tumours, and failed to show an association between VEGF and VHL mutation status. It was suggested that there also may be pathways other than the VHL/HIF-α pathway involved in the vascular phenotype of RCC.

The understanding of the molecular pathway of RCC has led to the development of several novel agents for mRCC such as sorafenib, sunitinib, and temsirolimus. At the ASCO 2006 annual meeting there were two major contributions in this respect. It was demonstrated that sunitinib has a statistically significant longer PFS than the current standard therapy for metastatic RCC patients. In addition, it was demonstrated that temsirolimus statistically significantly increases overall survival compared with IFN-α as first-line treatment in low- and intermediate-risk mRCC patients. Next to these important new data, a phase 3 study presented at the EAU confirmed the role of sorafenib as second-line therapy in mRCC.

It is clear that we now have new drugs that are more effective than cytokines in mRCC. We are in a position to change the natural history of this disease by transforming mRCC into a chronic disease. However, further improvements are still necessary because no complete response is usually obtained with antiangiogenic drugs. Therefore, for achieving complete remission in mRCC patients, it is likely that we will have to combine drugs acting on both tumoral cells and endothelial cells. As most of the new drugs for mRCC are prescribed by oncologists, the treatment of mRCC will have to take place in a multidisciplinary team involving both urologists and oncologists. Urologists therefore will have to learn from oncologists and keep up to date with the rapid progress that is being made in the area of RCC. In addition urologists will have to be strongly involved in further clinical trials with these new drugs, particularly in adjuvant and neoadjuvant settings.

References