

# Renal cell carcinoma

Brian I. Rini<sup>a</sup>, Steven C. Campbell<sup>b</sup> and W. Kimryn Rathmell<sup>c</sup>

## Purpose of review

In this review we will highlight the recent novel contributions to the treatment of renal cell carcinoma in the fields of anti-angiogenesis, immunotherapeutics, and surgical management. In addition, this review will update recent advances in diagnostic and imaging modalities for renal cell carcinoma and dietary and environmental relationships to the epidemiology of this growing disease.

## Recent findings

Advancements in the use of innovative treatment strategies for the management of localized renal cell carcinoma and the introduction of new targeted therapeutics with benefit in the metastatic setting has produced a major impact on the treatment of this disease.

## Summary

The management of metastatic renal cell carcinoma has undergone a revolution in the past year with groundbreaking treatment strategies encompassing a broad range of therapeutic modalities. At the other end of the spectrum, emerging data is beginning to change our perspective about the management of small, localized renal tumors that are being discovered with increasing frequency. This review will update recent findings supporting diet and tobacco exposure as etiologic factors in the development of renal cell carcinoma, the molecular concepts that underlie the disease and the targeted therapeutics designed to inhibit specific kinase activities, and emerging use of minimally invasive therapies for localized disease.

## Keywords

ablative therapies, AG-013736, BAY-43-9006, renal cell carcinoma, SU-11248, vascular endothelial growth factor, von Hippel-Lindau

## Abbreviations

<b>BMI</b>	body mass index
<b>CAIX</b>	carbonic anhydrase IX
<b>CRA</b>	13- <i>cis</i> -retinoic acid
<b>HIF</b>	hypoxia inducible factor
<b>IFN<math>\alpha</math></b>	interferon $\alpha$
<b>PDGF</b>	platelet-derived growth factor
<b>PDGFR</b>	platelet-derived growth factor receptor
<b>RCC</b>	renal cell carcinoma
<b>TTP</b>	time to progression
<b>VEGF</b>	vascular endothelial growth factor
<b>VHL</b>	von Hippel-Lindau

© 2006 Lippincott Williams & Wilkins  
1040-8746

## Introduction

An estimated 36 160 individuals will be diagnosed in the United States with renal cell carcinoma (RCC), and 12 660 will die as a result of RCC in 2005 [1]. These figures reflect a continued trending increase in the incidence of this cancer by 2–3% per year. The factors contributing to this rise remain uncertain. The patterns of this disease, however, have not changed, with approximately 30% of patients presenting with metastatic disease at the outset and a persistent nearly two to one preponderance of males to females afflicted with this disease. RCC is a diagnosis which encompasses a broad spectrum of histologic subtypes, and an appreciation of the unique attributes of each type has become increasingly essential to predicting response to therapy. In essence the disease subtypes include clear cell RCC, papillary RCC, and chromophobe RCC. Although more rare entities such as sarcomatoid RCC are pathologic descriptions still in use, these monikers likely represent variants of the dominant form, clear cell RCC, with divergent genetic features [2]. Although much prognostic value has been placed on these distinctions historically, recent analysis suggests that stage for stage, subtypes of RCC behave with equivalent patterns of relapse and failure [3<sup>••</sup>]. The biology of the subtypes, however, likely predicts distinct therapeutic targets. The molecular events underpinning each of these subtypes, therefore, have been crucial to furthering understanding of molecularly targeted therapy for renal cell carcinoma.

## Epidemiology

Familial RCC accounts for about 3–5% of cases of RCC and includes the von Hippel-Lindau (the familial form of clear cell RCC), familial papillary, hereditary leiomyomatosis, and Birt Hogg-Dube syndromes [4]. Birt Hogg-Dube, in which patients develop cutaneous

Curr Opin Oncol 18:289–296. © 2006 Lippincott Williams & Wilkins.

<sup>a</sup>Department of Solid Tumor Oncology, Cleveland Clinic Taussig Cancer Center, <sup>b</sup>Section of Urological Oncology, Glickman Urological Institute, Cleveland Clinic Foundation, Cleveland, Ohio and <sup>c</sup>Division of Hematology and Oncology, University of North Carolina at Chapel Hill, Lineberger Comprehensive Cancer Center, Chapel Hill, North Carolina, USA

Correspondence to W. Kimryn Rathmell, Division of Hematology and Oncology, University of North Carolina at Chapel Hill, Lineberger Comprehensive Cancer Center, Campus Box 7295, Room 21-237, 247, Chapel Hill, NC 27599-7295, USA  
Tel: +1 919 966 3522; fax: +1 919 843 3160; e-mail: rathmell@med.unc.edu

Current Opinion in Oncology 2006, 18:289–296

fibrofolliculomas, pulmonary cysts, and occasional spontaneous pneumothorax, is unique in that a variety of subtypes of RCC can be observed, including chromophobe RCC, oncocytoma, and a transitional tumor that appears to lie somewhere between these two entities [5]. Hereditary leiomyomatosis, in which patients develop cutaneous leiomyomas and large uterine fibroids (most women with this syndrome have had a hysterectomy by age 30), is unique in that the renal tumors (most commonly type II papillary RCC) are often aggressive and should be managed in a proactive manner. This syndrome is caused by mutations in the fumarate hydratase gene, an enzyme in the Krebs cycle [6]. Accumulation of fumarate leads to activation of hypoxia inducible factor (HIF) $\alpha$ , similar to the key pathogenic steps observed in clear cell RCC, suggesting that this may be a common final pathway for the pathogenesis of RCC.

Etiologic factors for the development of sporadic RCC continue to be actively investigated, focusing on obesity, diet, and tobacco as risk factors. Several reviews of cohorts of Norwegian men and women have recently reported on the effect of body mass and diet on the development of RCC. The first report from the Netherlands Cohort Study on Diet and Cancer identified 275 cases of RCC from 120 852 men and women aged 55–69 years who completed a self-administered questionnaire in 1986 [7]. These cases were compared with a cohort of 4779 men and women from the same study pool that did not develop RCC. Body mass index (BMI; calculated as weight in kilograms per meter squared) at baseline was associated with a borderline statistically significant increased risk of RCC (relative risk 1.07;  $P = 0.04$ ). A second report involving this same cohort investigated vegetable and fruit intake associations with RCC development [8]. Total and individual vegetable and fruit consumption were not associated with RCC risk. Also, no association existed for botanical subgroups of vegetables and fruit. A separate report identified 2 001 230 Norwegian men and women aged 20–74 years who had completed questionnaires for various registries and identified 6453 cases of RCC [9]. An increase in RCC risk was observed with increasing BMI across sex and age. This relationship was most pronounced in those who had never smoked. Last, a prospective study of a cohort of 46 572 Swedish women failed to identify a clear relationship between dietary patterns and RCC risk [10,11].

Tobacco exposure affects RCC incidence as in other solid tumors. A recent meta-analysis investigated 24 studies to more precisely define the relationship between tobacco exposure and RCC development. The relative risk for RCC for those who had ever smoked as compared with lifetime never-smokers was 1.38 (95% confidence interval

1.27–1.50) with evidence of a dose-dependent relationship. There was a reduction in risk for those who had quit smoking for more than 10 years as compared with those who had quit for 1–10 years.

These studies add to the growing body of knowledge regarding the epidemiology of RCC. An increase in BMI appears to pose a slightly increased risk for development of RCC, although data regarding risk related to specific dietary intake is less robust. Tobacco exposure poses the greatest relative environmental risk, increasing with amount of exposure and decreasing relative to time since exposure. While the implications for advice to patients regarding avoidance of obesity and tobacco cessation are obvious, further progress in the prevention and treatment of RCC awaits studies to explore the mechanisms of tumorigenesis in such patients and whether such tumors have unique biologic features or therapeutic targets.

### Advances in the molecular biology of renal cell carcinoma

The dominant subtype of RCC (clear cell RCC, comprising 70% of all tumors) bears a strikingly high frequency of mutations in the von Hippel-Lindau (*VHL*) gene which causes constitutive deregulation of the cellular hypoxia response signaling machinery [12–16]. This perturbation, occurring as the result of accumulation of a pair of transcription factors (HIF1 $\alpha$  and HIF2 $\alpha$ ), unleashes a cascade of gene expression normally associated with acute response to anoxic or near anoxic conditions. Genes induced by this mechanism include the vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), transforming growth factor  $\alpha$  (TGF $\alpha$ ), and carbonic anhydrase IX (CAIX/G250) among others, providing a litany of potential targets for novel therapeutics in this disease. Recent investigations have shifted focus onto one of the HIFs (HIF2 $\alpha$ ), as the primary mediator of tumorigenesis in RCC [17]. Other targets of HIF1 $\alpha$  or HIF2 $\alpha$  may contribute to the tumor phenotype without a clear influence on tumorigenesis. HIF1 $\alpha$  expression in a renal carcinoma cell line contributes significantly to the glycolytic phenotype of renal carcinomas, likely as a direct result of induced expression of glycolytic enzymes [18].

### Targeting receptor signaling

The identification of multiple therapeutic targets has spawned a deluge of clinical investigations of receptor targeted tyrosine kinase inhibitors in metastatic renal cell carcinoma. An initial study using a humanized antibody targeting VEGF was promising in delaying time to progression (TTP) in a randomized phase II study [19]. Follow-up has identified no further toxicities, including patients who have continued on therapy without progression for 3–5 years [20].

The current class of receptor tyrosine kinase inhibitors includes BAY-43-9006 (sorafenib; Bayer Pharmaceuticals and Onyx Pharmaceuticals, Inc), SU-11248 (sunitinib; Pfizer Inc) and AG-013676 (axitinib; Pfizer, Inc). These drugs have the distinction of having broad specificity, being referred to as dual action kinase inhibitors for their inhibitory activities on not only VEGF receptor (VEGFR)2, the major pro-angiogenic receptor for VEGF, but also the PDGF receptor (PDGFR)-B [21–23]. One preclinical comparison of the emerging clinical kinase inhibitors assessed binding of a panel of 119 protein kinases to 16 kinase inhibitors approved or pending approval for clinical use [24\*], including VEGFR/PDGFR inhibitors sunitinib and sorafenib. Based on binding affinity, both sunitinib and sorafenib act as potential inhibitors of a broad spectrum of kinases. These promiscuous and non-identical inhibitory profiles may account for observed differences in activity and toxicity.

In clinical analysis, sorafenib was initially investigated in a phase II randomized discontinuation trial in which 202 patients were evaluated. The overall response rate to treatment was 71%, with a progression-free survival advantage of 24 versus 6 weeks ( $P = 0.0087$ ) in the randomized cohort [25]. These data prompted a subsequent 905 patient, placebo-controlled, randomized phase III trial of sorafenib in cytokine refractory RCC. This trial recently reported a progression-free survival advantage in the treatment arm of 24 versus 12 weeks ( $P < 0.000001$ ) (Fig. 1) [26]. Sorafenib recently received US Food and Drug Administration approval for advanced RCC.

Two phase II trials of sunitinib in cytokine-refractory, metastatic RCC have demonstrated a clinical benefit with

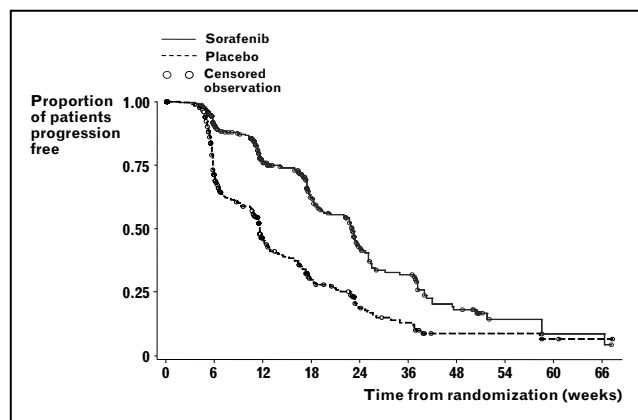
minimal toxicity using this oral agent [27]. The first trial included all histological subtypes and demonstrated an objective partial response in 40% of patients. The second trial restricted eligibility to clear cell RCC, required prior nephrectomy and Response Evaluation Criteria in Solid Tumors (RECIST)-defined progression after prior cytokine therapy. This trial of 106 patients reported a response rate of 39%, including one complete response. Sunitinib recently received US Food and Drug Administration approval for advanced RCC.

AG-013736 is a substituted imidazole derivative that inhibits the tyrosine kinase portion of all VEGF receptors and PDGFR-B at low nanomolar concentrations (investigator's brochure, December 2002). A phase II trial of AG-013736 was conducted in 52 cytokine refractory RCC patients. A 46% objective response rate was reported with 74% of patients experiencing some degree of tumor shrinkage [28]. Therapy was well tolerated, and median TTP has not been reached at a median follow-up of more than 12 months. Further investigation in sorafenib-refractory RCC is ongoing.

### Therapeutic combinations

Based on preclinical data regarding the additive antiproliferative and differentiation effects of adding 13-*cis*-retinoic acid (CRA) to interferon  $\alpha$  (IFN $\alpha$ ) in addition to high phase II response rates [29,30], a European phase III trial of IFN $\alpha$  with and without CRA was conducted [31]. Three-hundred and twenty patients with metastatic RCC were randomized to IFN $\alpha$  monotherapy, dose-escalated to 9 MU daily or the same dose and schedule of IFN $\alpha$  plus 1 mg/kg/day of CRA. Patients were treated until objective progression or toxicity. The primary endpoint was overall survival, designed to detect a 10% difference in 1-year overall survival from 10% to 20% with an  $\alpha$  value of 0.05 and 80% power. This trial demonstrated a marginally significant improvement in overall survival (17.3 months in the combination arm versus 13.2 months in the IFN $\alpha$  monotherapy arm;  $P = 0.48$ ). TTP was also prolonged in the combination arm (5.1 months versus 3.4 months;  $P = 0.008$ ). This study must be interpreted in light of two other phase III trials that did not demonstrate an overall survival advantage for a cytokine plus retinoid combination [32,33]. In the present trial, 1-year overall survival (59% in the combination arm versus 53% in the IFN $\alpha$  monotherapy arm) did not differ by the 10% stated goal and 1-year survival in both groups was much higher than the original hypotheses. Although well-balanced for many patient characteristics, twice as many patients in the IFN $\alpha$  monotherapy arm had received prior radiotherapy, potentially confounding outcome as evidenced by a very low median TTP in this group compared with historical controls [34]. The authors cite progression-free advantages to the retinoid-containing regimens in the

**Figure 1** Effect on progression-free survival of sorafenib compared with placebo in metastatic renal cell carcinoma



Median progression-free survival for sorafenib, 24 weeks; placebo, 12 weeks. Hazard ratio (sorafenib/placebo), 0.44;  $P < 0.000001$ . Reproduced with permission [26].

previous trials and patient selection features to account for the discrepant overall survival results. Given the activity of newer VEGF-targeted agents, it is unlikely that cytokine/retinoid combinations will be further investigated in large, randomized trials. Investigation of the biologic interaction of IFN $\alpha$  and retinoids and the potential to select patients who would benefit is, however, a reasonable investigative endeavor.

Based on the single agent activity of VEGF-targeted and immune-based therapy, integrated strategies are undergoing active investigation. An intergroup phase III trial investigating the addition of bevacizumab to initial systemic therapy in RCC recently completed accrual [35]. Patients with metastatic clear cell RCC without prior systemic therapy were randomized to either IFN $\alpha$ -2b (Intron A; Schering-Plough, Kenilworth, New Jersey, USA) alone or in combination with bevacizumab. Patients are stratified by nephrectomy status and established prognostic factors to ensure balanced randomization [36–38]. A similarly designed phase III trial is underway in Europe using IFN $\alpha$ -2a (Roferon; Hoffmann-LaRoche, Grenzach-Wyhlen, Germany). Both trials are nearing planned analysis and results are eagerly awaited on the effect of adding bevacizumab to front-line therapy in RCC.

The EGFR/Erb-B receptor pathway is activated in a variety of cancers and thus several small molecule tyrosine kinase inhibitors have been developed for cancer investigations. Furthermore, the ligand which activates this receptor, TGF $\alpha$ , is a target of the hypoxia response pathway and a potential mediator of autocrine tumor growth in RCC [39]. Single agent studies with the anti-EGFR compound erlotinib and gefitinib have demonstrated limited anti-tumor effects [40,41], but in a clinical trial in metastatic RCC with bevacizumab in combination with erlotinib, a 25% partial response rate was reported [42]. A recently completed randomized phase II trial of bevacizumab with or without erlotinib in untreated, metastatic RCC ( $n = 100$ ) has not been formally reported, although a press release from the industry trial sponsor (Genentech) reported a lack of difference between the treatment arms. It is possible that the activity of single-agent bevacizumab has been underestimated, or that the underpowered randomized phase II failed to detect a small but meaningful difference. Further detailed results are needed for full interpretation.

Finally, growth inhibition in RCC cell lines was found to be synergistic between inhibitors of EGFR and mTOR signaling (gefitinib and rapamycin) in a *VHL*-dependent manner [43]. This combination of pathway inhibition remains to be studied in the clinical trial setting.

### Alternative immunological therapy

The evolution of immunotherapy from traditional cytokine-based therapy to more sophisticated and tumor-specific therapy has recently transformed from small single-institution, hypothesis-driven investigations to multi-institutional and industry-sponsored movements toward bringing alternative immunotherapeutic strategies into the mainstream. Recent correlative studies from the earlier vaccine studies have demonstrated the development of tumor specific CD4+ and CD8+ T cell responses following vaccination [44,45]. Internationally, this strategy has gained acceptance as well. In Brazil, a dendritic cell-tumor cell hybrid vaccination strategy achieved objective responses in three of 22 patients (14%), including one complete response, with a median TTP of 5.7 months with no significant toxicities noted [46–48]. In Japan, autologous tumor vaccines primed with granulocyte macrophage colony stimulating factor, similar to those used by Simons *et al.*, were delivered to four patients, with positive conversion of delayed type hypersensitivity responses to irradiated RCC cells in all patients [49–51].

### Prognostic factors

The past 5 years have been notable for a substantial advance in our understanding of prognostic factors for patients with RCC that is now impacting clinical decision making and trial design. Current integrative approaches have incorporated tumor stage, grade, performance status, tumor size, and pathologic features such as histologic tumor necrosis to stratify patients with localized or metastatic RCC into low, intermediate, or high risk groups [52,53,54]. Laboratory values such as serum lactate dehydrogenase, calcium, and hemoglobin levels have also proven to have independent prognostic value. A variety of tumor markers, such as CAIX, have also shown great promise and are now being integrated into prognostic algorithms for this disease. Decreased expression of CAIX, which likely reflects *VHL*-independent pathways to tumorigenesis, appears to be a poor prognostic factor for patients with metastatic RCC [55]. Bulky retroperitoneal lymphadenopathy that is seen in about 10–20% of patients with advanced RCC is also now established as a poor prognostic factor [56,57].

### Management of localized renal cell carcinoma

Minimally invasive approaches to radical nephrectomy are now established as a standard of care for the management of localized RCC, with long-term follow-up data suggesting very similar outcomes when compared with open radical nephrectomy. In one recent study 5 and 10-year cancer-free survival was the same (94% versus 94%, and 87% versus 87%, respectively) after either procedure, and there were no port site or local recurrences after laparoscopic surgery [58,59]. Patient selection remains the key issue, with open surgery in general

reserved for patients with large tumors, those that appear to be locally invasive or associated with substantial lymphadenopathy or venous tumor thrombus, or patients who require open surgery for other concomitant medical indications. The contraindications to minimally invasive surgery, however, are relative and continue to evolve. Recent reports document the successful use of laparoscopy for the removal of increasingly larger tumors, occasional RCC with tumor thrombus, and for patients with morbid obesity, prior abdominal surgery, or prior retroperitoneal radiation [60–62]. Minimally invasive approaches are also being used for cytoreductive nephrectomy, although many such tumors may exhibit locally invasive behavior and may be best removed through an open surgical approach [63].

The prevailing trend towards nephron-sparing surgery has also continued, in part fueled by concerns about declining renal function after radical nephrectomy and a greater appreciation that many small renal masses may be benign or of limited malignant potential [64]. Lau and colleagues [65] used a matched analysis to show that the risk of chronic renal insufficiency (serum creatinine level > 2.0 mg/dl) was twice as high after radical nephrectomy when compared with partial nephrectomy (22.4% versus 11.6%). Proteinuria was also found more commonly after radical nephrectomy, and the incidence of dialysis requirement, while admittedly small, was also higher after radical than partial nephrectomy (3.2% versus 1.5%). Elective partial nephrectomy (patients with a normal contralateral kidney, normal renal function, and no chronic illness that can impact upon renal function) is now being performed more frequently, with some centers expanding their indications to include larger tumors between 4 and 7 cm size, which have traditionally been managed with radical nephrectomy. Current data suggest that carefully selected patients with peripherally located tumors may be reasonable candidates for this approach [66,67].

Minimally invasive approaches to partial nephrectomy are also being developed and some centers are now able to replicate all of the essential steps of open partial nephrectomy [68]. The major challenges have been hemostasis, given the extreme vascularity of the kidney, and adequate tumor excision, which was initially more difficult to achieve through a laparoscopic approach. Indeed, this is considered by many authors in the field to be the most difficult application of laparoscopy thus far attempted in urologic oncology. Reflecting this challenge, Gill and colleagues [69,70<sup>\*</sup>] reported three positive margins in their first 100 laparoscopic partial nephrectomies and 19 instances of hemorrhage in their first 200 cases. The latter is most often managed conservatively, but some patients require blood transfusion, postoperative selective embolization, or rarely a nephrectomy.

Increased experience and a number of technical improvements have allowed for greatly improved results, and this group has now had only one positive margin in their next 300 cases, and the total incidence of hemorrhagic complications is now below 3%. Intraoperative ultrasonography to improve localization of the tumor, and the more liberal use of complete vascular occlusion, which allows for optimal tumor excision and renal reconstruction, have facilitated these advances [60,71,72]. Routine use of thrombogenic substances that are incorporated into the capsular closure has also been a contributing factor. Laparoscopic partial nephrectomy can now be performed safely for many relatively small, peripherally located renal tumors, and some centers are now also reporting good results for carefully selected hilar tumors and cystic tumors for which prior concern was related to the risk of cyst rupture during laparoscopic manipulation [73,74].

The experience with thermal ablation for small renal tumors is now beginning to mature, providing a clearer perspective about the role of these minimally invasive modalities. Gill and colleagues [75<sup>\*\*</sup>] recently reported 3-year follow-up after laparoscopic cryoablation in 56 patients, all followed closely with serial magnetic resonance imaging (MRI) and biopsy of the tumor bed at 6 months after treatment [75<sup>\*\*</sup>]. Two patients (3.6%) experienced tumor recurrence in the tumor bed and an additional three patients (5.4%) had de-novo lesions at other sites in the ipsilateral kidney. The total incidence of ipsilateral tumor recurrence was five of 51 patients (8.9%), suggesting that cryoablation approaches, but does not quite reach, the efficacy of surgical excision in this patient population. Morbidity was, however, extremely low, and most would agree that this is a reasonable option for many older patients with small (< 3.5 cm), peripherally located renal masses. The early experience with radiofrequency ablation for renal tumors was less promising with some reports emphasizing a high incidence of tumor persistence after treatment, and the treatment effect is less easy to monitor: there is no 'ice ball equivalent' [76,77]. This technology has, however, evolved substantially and most recent reports rival those of cryoablation [78–83]. This modality is now readily applied through image guided percutaneous approaches at several centers. It is most often reserved for patients that are not good surgical candidates due to comorbid disease or advanced age, patients with a prior history of partial nephrectomy for whom repeat surgery would be challenging, and those with familial RCC that may require multiple treatments through the years.

One final treatment option for patients with localized RCC that is now being reported with increased frequency is active surveillance. Several studies now document that many small renal masses grow slowly and with a relatively low risk of metastatic spread. Thus far only two out of

268 (0.7%) reported patients have developed metastatic disease, and most series report relatively slow growth rates of under 0.3 cm per year. Counterbalancing this provocative data about the natural history of small renal masses is the valid concern that most patients that metastasize cannot be salvaged, and most authors have emphasized that observation should largely be reserved for older patients or those that are not surgical candidates. The availability of minimally morbid procedures such as thermal ablative approaches should also be taken into account when counseling patients about active surveillance.

### Diagnostic imaging

Recent advances in the diagnostic imaging of RCC have centered on the characterization of subtypes of RCC, assessment of risk of malignancy for complex renal cysts, and a critical reappraisal of renal mass biopsy. Recent studies suggest that current generations of computed tomography (CT) may offer the ability to distinguish differences in the degree of enhancement of renal masses that may allow for differentiation between clear cell RCC and other less vascular variants [84,85]. Dynamic contrast CT or MRI may also play a role in monitoring response to anti-angiogenic therapies in the near future due to its ability to reflect subtle differences in neovascularity. A recent update of the Bosniak classification system for complex renal cysts highlighted features thought to be indicative of malignancy (enhancement within a lesion is the most reliable indicator, especially if associated with a nodular component) and those now thought to be benign (calcification of the lesion does not substantially increase the risk of malignancy unless associated with neovascularity) [86,87]. Renal mass biopsy is now being revisited with some recent studies showing relatively reasonable performance characteristics higher than previously reported [88,89]. For instance, in the study from Wunderlich and colleagues [88], a combination of one central and four peripheral biopsies accurately defined the malignant versus benign nature of the tumor in 49 out of 50 cases and tumor grade was accurately defined in 85.7% of cases. Future studies will likely use molecular technologies such as gene arrays to define the malignant potential of small renal tumors based upon the limited material available from percutaneous biopsies. This would substantially improve our ability to counsel and manage patients with small renal masses given the diverse array of management strategies outlined above.

### Conclusion

Recent advances in our understanding of the natural history and molecular genetics of RCC have left this field on the threshold of several major paradigm shifts. General trends in the management of patients with localized disease have included increased use of minimally invasive approaches to reduce morbidity, an increased appreciation of the potential benefits of

nephron-sparing surgery, and the recognition that some elderly patients or those with comorbid disease should be considered for observation or thermal ablative modalities. For patients with advanced RCC, the current generation of molecular targeted therapies has shown great promise with some yielding encouraging response rates and others substantial delays in mean time to progression. Perhaps most exciting of all is the novel perspective that these therapies provide and the renewed enthusiasm for further progress that they have engendered.

### References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 305–306).

- 1 Cancer facts and figures 2005. Atlanta, GA: American Cancer Society Inc.
- 2 Jones TD, Eble JN, Wang M, *et al*. Clonal divergence and genetic heterogeneity in clear cell renal cell carcinomas with sarcomatoid transformation. *Cancer* 2005; 104:1195–1203.
- 3 Patard JJ, Leray E, Rioux-Leclercq N, *et al*. Prognostic value of histologic subtypes in renal cell carcinoma: a multicenter experience. *J Clin Oncol* 2005; 23:2763–2771.
- In this thorough multivariate analysis of 4063 patients stage, Fuhrman grade, and performance status, but not tumor histology were prognostic indicators of survival.
- 4 Linehan WM, Walther MM, Zbar B. The genetic basis of cancer of the kidney. *J Urol* 2003; 170:2163–2172.
- 5 Pavlovich CP, Grubb RL 3rd, Hurley K, *et al*. Evaluation and management of renal tumors in the Birt-Hogg-Dube syndrome. *J Urol* 2005; 173:1482–1486.
- 6 Toro JR, Nickerson ML, Wei MH, *et al*. Mutations in the fumarate hydratase gene cause hereditary leiomyomatosis and renal cell cancer in families in North America. *Am J Hum Genet* 2003; 73:95–106.
- 7 van Dijk BA, Schouten LJ, Kiemeneij LA, *et al*. Relation of height, body mass, energy intake, and physical activity to risk of renal cell carcinoma: results from the Netherlands Cohort Study. *Am J Epidemiol* 2004; 160:1159–1167.
- 8 van Dijk BA, Schouten LJ, Kiemeneij LA, *et al*. Vegetable and fruit consumption and risk of renal cell carcinoma: Results from the Netherlands cohort study. *Int J Cancer* 2005; 117:648–654.
- 9 Bjorge T, Tretli S, Engeland A. Relation of height and body mass index to renal cell carcinoma in two million Norwegian men and women. *Am J Epidemiol* 2004; 160:1168–1176.
- 10 Rashidkhani B, Akesson A, Lindblad P, *et al*. Major dietary patterns and risk of renal cell carcinoma in a prospective cohort of Swedish women. *J Nutr* 2005; 135:1757–1762.
- 11 Rashidkhani B, Lindblad P, Wolk A. Fruits, vegetables and risk of renal cell carcinoma: a prospective study of Swedish women. *Int J Cancer* 2005; 113:451–455.
- 12 Wiesener MS, Munchenhagen PM, Berger I, *et al*. Constitutive activation of hypoxia-inducible genes related to overexpression of hypoxia-inducible factor-1alpha in clear cell renal carcinomas. *Cancer Res* 2001; 61:5215–5222.
- 13 Cockman ME, Masson N, Mole DR, *et al*. Hypoxia inducible factor-alpha binding and ubiquitylation by the von Hippel-Lindau tumor suppressor protein. *J Biol Chem* 2000; 275:25733–25741.
- 14 Maxwell PH, Wiesener MS, Chang GW, *et al*. The tumour suppressor protein VHL targets hypoxia-inducible factors for oxygen-dependent proteolysis. *Nature* 1999; 399:271–275.
- 15 Maxwell PH, Pugh CW, Ratcliffe PJ. The pVHL-hIF-1 system. A key mediator of oxygen homeostasis. *Adv Exp Med Biol* 2001; 502:365–376.
- 16 Mole DR, Maxwell PH, Pugh CW, *et al*. Regulation of HIF by the von Hippel-Lindau tumour suppressor: implications for cellular oxygen sensing. *IUBMB Life* 2001; 52:43–47.
- 17 Kondo K, Kim WY, Lechpammer M, *et al*. Inhibition of HIF2alpha is sufficient to suppress pVHL-defective tumor growth. *PLoS Biol* 2003; 1:E83.

- 18 Robey IF, Lien AD, Welsh SJ, *et al.* Hypoxia-inducible factor-1alpha and the glycolytic phenotype in tumors. *Neoplasia* 2005; 7:324–330.
- 19 Yang JC, Haworth L, Sherry RM, *et al.* A randomized trial of bevacizumab, an anti-vascular endothelial growth factor antibody, for metastatic renal cancer. *N Engl J Med* 2003; 349:427–434.
- 20 Yang JC. Bevacizumab for patients with metastatic renal cancer: an update. *Clin Cancer Res* 2004; 10:6367S–6370S.
- 21 Mendel DB, Laird AD, Xin X, *et al.* In vivo antitumor activity of SU11248, a novel tyrosine kinase inhibitor targeting vascular endothelial growth factor and platelet-derived growth factor receptors: determination of a pharmacokinetic/pharmacodynamic relationship. *Clin Cancer Res* 2003; 9:327–337.
- 22 Wilhelm SM, Carter C, Tang L, *et al.* BAY 43-9006 exhibits broad spectrum oral antitumor activity and targets the RAF/MEK/ERK pathway and receptor tyrosine kinases involved in tumor progression and angiogenesis. *Cancer Res* 2004; 64:7099–7109.
- 23 Sun L, Liang C, Shirazian S, *et al.* Discovery of 5-[5-fluoro-2-oxo-1,2-dihydroindol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylaminoethyl)amide, a novel tyrosine kinase inhibitor targeting vascular endothelial and platelet-derived growth factor receptor tyrosine kinase. *J Med Chem* 2003; 46:1116–1119.
- 24 Fabian MA, Biggs WH 3rd, Treiber DK, *et al.* A small molecule-kinase interaction map for clinical kinase inhibitors. *Nat Biotechnol* 2005; 23:329–336.
- This map of kinase domain interactions with the emerging kinase inhibitor pharmacologics is a novel approach to distinguishing the important characteristics of this rapidly evolving class of therapeutics.
- 25 Ratain MJ, Eisen T, Stadler WM, *et al.* Final findings from a phase II, placebo-controlled, randomized discontinuation trial (RDT) of sorafenib (BAY 43-9006) in patients with advanced renal cell carcinoma (RCC). *Proc Amer Soc Clin Oncol* 2005; 23:4544.
- 26 Escudier B, Szczylik C, Eisen T, *et al.* Randomized phase III trial of the Raf kinase and VEGFR inhibitor sorafenib (BAY 43-9006) in patients with advanced renal cell carcinoma (RCC) [abstract]. *Proc Amer Soc Clin Oncol* 2005; 23:4510.
- 27 Motzer RJ, Rini BI, Michaelson MD, *et al.* Phase 2 trials of SU11248 show antitumor activity in second-line therapy for patients with metastatic renal cell carcinoma (RCC). *Proc Amer Soc Clin Oncol* 2005; 23:4508.
- 28 Rini B, Rixe O, Bukowski R, *et al.* AG-013736, a multi-target tyrosine kinase receptor inhibitor, demonstrates anti-tumor activity in a phase 2 study of cytokine-refractory, metastatic renal cell cancer (RCC). *Proc Amer Soc Clin Oncol* 2005; 23:4509.
- 29 Frey JR, Peck R, Bollag W. Antiproliferative activity of retinoids, interferon alpha and their combination in five human transformed cell lines. *Cancer Lett* 1991; 57:223–227.
- 30 Motzer RJ, Schwartz L, Law TM, *et al.* Interferon alfa-2a and 13-cis-retinoic acid in renal cell carcinoma: antitumor activity in a phase II trial and interactions in vitro. *J Clin Oncol* 1995; 13:1950–1957.
- 31 Aass N, De Mulder PH, Mickisch GH, *et al.* Randomized phase II/III trial of interferon Alfa-2a with and without 13-cis-retinoic acid in patients with progressive metastatic renal cell carcinoma: the European Organisation for Research and Treatment of Cancer Genito-Urinary Tract Cancer Group (EORTC 30951). *J Clin Oncol* 2005; 23:4172–4178.
- 32 Motzer RJ, Murphy BA, Bacik J, *et al.* Phase III trial of interferon alfa-2a with or without 13-cis-retinoic acid for patients with advanced renal cell carcinoma. *J Clin Oncol* 2000; 18:2972–2980.
- 33 Atzpodien J, Kirchner H, Jonas U, *et al.* Interleukin-2- and interferon alfa-2a-based immunochemotherapy in advanced renal cell carcinoma: a prospectively randomized trial of the German Cooperative Renal Carcinoma Chemotherapy Group (DGCRN). *J Clin Oncol* 2004; 22:1188–1194.
- 34 Motzer RJ, Bacik J, Murphy BA, *et al.* Interferon-alfa as a comparative treatment for clinical trials of new therapies against advanced renal cell carcinoma. *J Clin Oncol* 2002; 20:289–296.
- 35 Rini BI, Halabi S, Taylor J, *et al.* Cancer and Leukemia Group B 90206: A randomized phase III trial of interferon-alpha or interferon-alpha plus anti-vascular endothelial growth factor antibody (bevacizumab) in metastatic renal cell carcinoma. *Clin Cancer Res* 2004; 10:2584–2856.
- 36 Motzer RJ. Prognostic factors and clinical trials of new agents in patients with metastatic renal cell carcinoma. *Crit Rev Oncol Hematol* 2003; 46 (Suppl):S33–S39.
- 37 Mickisch G, Carballido J, Hellsten S, *et al.* Guidelines on renal cell cancer. *Eur Urol* 2001; 40:252–255.
- 38 Flanigan RC, Salmon SE, Blumenstein BA, *et al.* Nephrectomy followed by interferon alfa-2b compared with interferon alfa-2b alone for metastatic renal-cell cancer. *N Engl J Med* 2001; 345:1655–1659.
- 39 de Paulsen N, Brychzy A, Fournier MC, *et al.* Role of transforming growth factor-alpha in von Hippel-Lindau (VHL)(-/-) clear cell renal carcinoma cell proliferation: a possible mechanism coupling VHL tumor suppressor inactivation and tumorigenesis. *Proc Natl Acad Sci USA* 2001; 98:1387–1392.
- 40 Motzer RJ, Amato R, Todd M, *et al.* Phase II trial of antiepidermal growth factor receptor antibody C225 in patients with advanced renal cell carcinoma. *Invest New Drugs* 2003; 21:99–101.
- 41 Dawson NA, Guo C, Zak R, *et al.* A phase II trial of gefitinib (Iressa, ZD1839) in stage IV and recurrent renal cell carcinoma. *Clin Cancer Res* 2004; 10:7812–7819.
- 42 Spigel DR, Hainsworth JD, Sosman JA, *et al.* Bevacizumab and erlotinib in the treatment of patients with metastatic renal carcinoma (RCC): Update of a phase II multicenter trial. *Proc Amer Soc Clin Oncol* 2005; 23:4540.
- 43 Gemmill RM, Zhou M, Costa L, *et al.* Synergistic growth inhibition by Iressa and Rapamycin is modulated by VHL mutations in renal cell carcinoma. *Br J Cancer* 2005; 92:2266–2277.
- 44 Mautner J, Jaffee EM, Pardoll DM. Tumor-specific CD4+ T cells from a patient with renal cell carcinoma recognize diverse shared antigens. *Int J Cancer* 2005; 115:752–759.
- 45 Zhou X, Jun do Y, Thomas AM, *et al.* Diverse CD8+ T-cell responses to renal cell carcinoma antigens in patients treated with an autologous granulocyte-macrophage colony-stimulating factor gene-transduced renal tumor cell vaccine. *Cancer Res* 2005; 65:1079–1088.
- 46 Barbuto JA, Ensina LF, Neves AR, *et al.* Dendritic cell-tumor cell hybrid vaccination for metastatic cancer. *Cancer Immunol Immunother* 2004; 53:1111–1118.
- 47 Dall'Oglio M, Srougi M, Barbuto JA. Complete response of metastatic renal cancer with dendritic cell vaccine. *Int Braz J Urol* 2003; 29:517–519.
- 48 Neves AR, Ensina LF, Anselmo LB, *et al.* Dendritic cells derived from metastatic cancer patients vaccinated with allogeneic dendritic cell-autologous tumor cell hybrids express more CD86 and induce higher levels of interferon-gamma in mixed lymphocyte reactions. *Cancer Immunol Immunother* 2005; 54:61–66.
- 49 Tani K, Azuma M, Nakazaki Y, *et al.* Phase I study of autologous tumor vaccines transduced with the GM-CSF gene in four patients with stage IV renal cell cancer in Japan: clinical and immunological findings. *Mol Ther* 2004; 10:799–816.
- 50 Tani K, Nakazaki Y, Hase H, *et al.* Progress reports on immune gene therapy for stage IV renal cell cancer using lethally irradiated granulocyte-macrophage colony-stimulating factor-transduced autologous renal cancer cells. *Cancer Chemother Pharmacol* 2000; 46 (Suppl):S73–S76.
- 51 Simons JW, Jaffee EM, Weber CE, *et al.* Bioactivity of autologous irradiated renal cell carcinoma vaccines generated by ex vivo granulocyte-macrophage colony-stimulating factor gene transfer. *Cancer Res* 1997; 57:1537–1546.
- 52 Kim HL, Seligson D, Liu X, *et al.* Using tumor markers to predict the survival of patients with metastatic renal cell carcinoma. *J Urol* 2005; 173:1496–1501. This article describes the integration of tumor markers such as CAIX into the prognostic algorithms for RCC.
- 53 Kim HL, Seligson D, Liu X, *et al.* Using protein expressions to predict survival in clear cell renal carcinoma. *Clin Cancer Res* 2004; 10:5464–5471.
- 54 Patard JJ, Kim HL, Lam JS, *et al.* Use of the University of California Los Angeles integrated staging system to predict survival in renal cell carcinoma: an international multicenter study. *J Clin Oncol* 2004; 22:3316–3322.
- 55 Bui MH, Seligson D, Han KR, *et al.* Carbonic anhydrase IX is an independent predictor of survival in advanced renal clear cell carcinoma: implications for prognosis and therapy. *Clin Cancer Res* 2003; 9:802–811.
- 56 Vasselli JR, Yang JC, Linehan WM, *et al.* Lack of retroperitoneal lymphadenopathy predicts survival of patients with metastatic renal cell carcinoma. *J Urol* 2001; 166:68–72.
- 57 Pantuck AJ, Zeng G, Belldegrin AS, *et al.* Pathobiology, prognosis, and targeted therapy for renal cell carcinoma: exploiting the hypoxia-induced pathway. *Clin Cancer Res* 2003; 9:4641–4652.
- 58 Permpongkosol S, Chan DY, Link RE, *et al.* Laparoscopic radical nephrectomy: long-term outcomes. *J Endourol* 2005; 19:628–633. This provides long-term outcomes for laparoscopic radical nephrectomy that are very comparable to open radical surgery.
- 59 Permpongkosol S, Chan DY, Link RE, *et al.* Long-term survival analysis after laparoscopic radical nephrectomy. *J Urol* 2005; 174:1222–1225.
- 60 Desai MM, Gill IS, Ramani AP, *et al.* The impact of warm ischaemia on renal function after laparoscopic partial nephrectomy. *BJU Int* 2005; 95:377–383.
- 61 Steinberg AP, Finelli A, Desai MM, *et al.* Laparoscopic radical nephrectomy for large (greater than 7 cm, t2) renal tumors. *J Urol* 2004; 172:2172–2176.

- 62 Viterbo R, Greenberg RE, Al-Saleem T, *et al.* Prior abdominal surgery and radiation do not complicate the retroperitoneoscopic approach to the kidney or adrenal gland. *J Urol* 2005; 174:446–450.
- 63 Finelli A, Kaouk JH, Fergany AF, *et al.* Laparoscopic cytoreductive nephrectomy for metastatic renal cell carcinoma. *BJU Int* 2004; 94:291–294.
- 64 McKiernan J, Simmons R, Katz J, *et al.* Natural history of chronic renal insufficiency after partial and radical nephrectomy. *Urology* 2002; 59: 816–820.
- 65 Lau WK, Blute ML, Weaver AL, *et al.* Matched comparison of radical nephrectomy vs nephron-sparing surgery in patients with unilateral renal cell carcinoma and a normal contralateral kidney. *Mayo Clin Proc* 2000; 75:1236–1242.
- 66 Leibovich BC, Blute ML, Cheville JC, *et al.* Re: nephron sparing surgery for appropriately selected renal cell carcinoma between 4 and 7 cm results in outcome similar to radical nephrectomy. *J Urol* 2004; 172:2483.
- 67 Patard JJ, Shvarts O, Lam JS, *et al.* Safety and efficacy of partial nephrectomy for all T1 tumors based on an international multicenter experience. *J Urol* 2004; 171:2181–2185, quiz 2435.
- 68 Gill IS, Desai MM, Kaouk JH, *et al.* Laparoscopic partial nephrectomy for renal tumor: duplicating open surgical techniques. *J Urol* 2002; 167:469–467; discussion 475–476.
- 69 Gill IS, Matin SF, Desai MM, *et al.* Comparative analysis of laparoscopic versus open partial nephrectomy for renal tumors in 200 patients. *J Urol* 2003; 170:64–68.
- 70 Ramani AP, Desai MM, Steinberg AP, *et al.* Complications of laparoscopic partial nephrectomy in 200 cases. *J Urol* 2005; 173:42–47.  
The authors describe the formidable challenges associated with laparoscopic partial nephrectomy and related complications that can be observed with this procedure.
- 71 Laven BA, Orvieto MA, Chuang MS, *et al.* Renal tolerance to prolonged warm ischemia time in a laparoscopic versus open surgery porcine model. *J Urol* 2004; 172:2471–2474.
- 72 Bhayani SB, Rha KH, Pinto PA, *et al.* Laparoscopic partial nephrectomy: effect of warm ischemia on serum creatinine. *J Urol* 2004; 172:1264–1266.
- 73 Gill IS, Colombo JR Jr, Frank I, *et al.* Laparoscopic partial nephrectomy for hilar tumors. *J Urol* 2005; 174:850–853; discussion 853–854.
- 74 Spaliviero M, Herts BR, Magi-Galluzzi C, *et al.* Laparoscopic partial nephrectomy for cystic masses. *J Urol* 2005; 174:614–619.
- 75 Gill IS, Remer EM, Hasan WA, *et al.* Renal cryoablation: outcome at 3 years. •• *J Urol* 2005; 173:1903–1907.  
This is the first series to provide intermediate follow-up for patients managed with thermal ablative modalities for renal tumors.
- 76 Rendon RA, Kachura JR, Sweet JM, *et al.* The uncertainty of radio frequency treatment of renal cell carcinoma: findings at immediate and delayed nephrectomy. *J Urol* 2002; 167:1587–1592.
- 77 Michaels MJ, Rhee HK, Mourtzinou AP, *et al.* Incomplete renal tumor destruction using radio frequency interstitial ablation. *J Urol* 2002; 168:2406–2409; discussion 2409–2410.
- 78 Jacomides L, Ogan K, Watumull L, *et al.* Laparoscopic application of radio frequency energy enables in situ renal tumor ablation and partial nephrectomy. *J Urol* 2003; 169:49–53; discussion 53.
- 79 Pavlovich CP, Walther MM, Choyke PL, *et al.* Percutaneous radio frequency ablation of small renal tumors: initial results. *J Urol* 2002; 167:10–15.
- 80 Hwang JJ, Walther MM, Pautler SE, *et al.* Radio frequency ablation of small renal tumors: intermediate results. *J Urol* 2004; 171:1814–1818.
- 81 Matsumoto ED, Watumull L, Johnson DB, *et al.* The radiographic evolution of radio frequency ablated renal tumors. *J Urol* 2004; 172:45–48.
- 82 McDougal WS, Gervais DA, McGovern FJ, *et al.* Long-term followup of patients with renal cell carcinoma treated with radio frequency ablation with curative intent. *J Urol* 2005; 174:61–63.
- 83 Varkarakis IM, Allaf ME, Inagaki T, *et al.* Percutaneous radio frequency ablation of renal masses: results at a 2-year mean followup. *J Urol* 2005; 174:456–460; discussion 460.
- 84 Sheir KZ, El-Azab M, Mosbah A, *et al.* Differentiation of renal cell carcinoma subtypes by multislice computerized tomography. *J Urol* 2005; 174:451–455; discussion 455.
- 85 Herts BR, Coll DM, Novick AC, *et al.* Enhancement characteristics of papillary renal neoplasms revealed on triphasic helical CT of the kidneys. *AJR Am J Roentgenol* 2002; 178:367–372.
- 86 Israel GM, Bosniak MA. Calcification in cystic renal masses: is it important in diagnosis? *Radiology* 2003; 226:47–52.
- 87 Israel GM, Bosniak MA. An update of the Bosniak renal cyst classification system. *Urology* 2005; 66:484–488.
- 88 Wunderlich H, Hindermann W, Al Mustafa AM, *et al.* The accuracy of 250 fine needle biopsies of renal tumors. *J Urol* 2005; 174:44–46.
- 89 Neuzillet Y, Lechevallier E, Andre M, *et al.* Accuracy and clinical role of fine needle percutaneous biopsy with computerized tomography guidance of small (less than 4.0 cm) renal masses. *J Urol* 2004; 171:1802–1805.