Renal Cell Carcinoma: Background

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KEYWORDS
RENAL CELL CARCINOMA

Renal cancer accounts for 2 to 3% of all malignant tumors. An estimated 39,000 new cases and 13,000 deaths were predicted for 2006. Renal cancer is diagnosed in patients ranging from 40 to 70 years of age, with a male predominance of 1.6 to 1.0. A comparison of 43,685 cases of renal cancer diagnosed in the period 1973 to 1985 with those diagnosed from 1986 to 1998 (Surveillance, Epidemiology, and End Results [SEER] database) demonstrated a marginal increase in the proportion of localized cancers and a decrease in advanced cases in the latter group. The differences were not significant, and importantly, overall survival was not improved. While increased imaging and laboratory testing may generally explain the increased incidence, other factors may play a role.

Risk factors include smoking (responsible for 24% to 30% of all cases of renal cell carcinoma [RCC]), obesity, sedentary lifestyle, environmental and occupational factors (asbestos, cadmium, polycyclic hydrocarbons, solvents), and long-term use of diuretics or phenacetin-containing analgesics. Patients with end-stage renal disease undergoing dialysis, particularly those with cystic disease, are also more likely to develop RCC than the general population.

Renal cell carcinomas arising from the renal epithelium account for approximately 85% percent of renal tumors. Presentation varies, with most presenting with a solitary lesion, less than 4% presenting with bilateral renal masses, and 33% presenting with locally advanced or metastatic disease. Additionally, 20% to 40% of surgically resected patients may ultimately develop metastatic disease. Historically, patients presented with the classic triad of symptoms including flank pain, hematuria, and a palpable abdominal mass, but currently, increasing numbers of individuals are being diagnosed when asymptomatic with an incidental renal mass found. Advances in imaging and techniques have increased the percent of patients who are eligible for surgical intervention, but a significant number of patients still present with surgically unresectable disease.

Patients with advanced disease may present with symptoms produced by the tumor or resulting from chemical abnormalities, or paraneoplastic syndromes associated with
the neoplasm. Common sites for metastasis include lung, bone, lymph nodes, adrenal gland, liver, soft tissue, and brain.

HISTOLOGY

The importance of histology in predicting the biologic characteristics and clinical behavior of renal cancers was recognized in the last decade. Renal cell carcinoma represents a group of histologic subtypes with unique morphologic and genetic characteristics. The Heidelberg classification of renal cell tumors was developed to subdivide renal cell tumors into benign and malignant subtypes with associated genetic alterations.

Clear cell renal carcinoma is the most common type of renal cancer, accounting for approximately 70% of renal epithelial malignancies and arising from the proximal convoluted tubule. Papillary renal cancer is the second most common type, comprising 10% to 15% of renal tumors. Understanding histologic subtypes and associated gene alterations has provided the opportunity to develop targeted therapeutic agents.

VON HIPPEL-LINDAU (VHL) SYNDROME

Patients with the VHL syndrome provided researchers a unique opportunity to study the development of clear cell tumors and their genetic characteristics. In sporadic renal cancer, both the maternal and paternal VHL alleles are inactivated by acquired mutations whereas in the VHL syndrome the first mutation is inherited. Loss of VHL function may be responsible for approximately 60% of cases of sporadic clear-cell renal carcinomas.

The VHL protein is the product of the VHL gene, functions as a tumor suppressor gene, and is responsible for ubiquitination of hypoxia-inducible factor α (HIF-α), tagging it for degradation. In conditions of hypoxia or abnormal VHL function, HIF-α accumulates and activates the transcription of a variety of hypoxia-inducible genes. These include vascular endothelial growth factor (VEGF), platelet-derived growth factor β (PDGF-β), transforming growth factor α (TGF-α), and erythropoietin (EPO). The VHL gene may enable this process to be controlled through suppressing angiogenesis, but loss of the VHL gene or its function leads to increased secretion of VEGF and PDGF and appears to produce the vascular phenotype associated with this tumor. Blocking VEGF and thus the function of HIF-α is currently the major therapeutic strategy for treatment of advanced renal cancer, replacing immunotherapy with the cytokines interferon and interleukin-2 (IL-2).

SURGICAL MANAGEMENT OF RENAL CELL CARCINOMA

The management of renal cancer is based on the stage at diagnosis, the sites of metastatic disease, and the patient characteristics, including comorbid diseases and functional status. Surgical intervention is determined by tumor size, location, and involvement of the inferior vena cava (IVC), and includes nephrectomy and partial (nephron-sparing) nephrectomy performed through an open abdominal or laparoscopic procedure. Careful case selection allows for surgical resection of renal tumors with vena caval tumor extension and limited metastatic disease using a flank, transperitoneal, transabdominal, or