Clinical Management of

Renal Cell Cancer

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Preface

A urologist's or medical oncologist's current perception of progress in the care of the patient with renal cell carcinoma (RCC) is often contradictory. No reliable "breakthrough" has occurred in the treatment of metastatic disease despite tantalizing prospects with biologic response modifier (BRM) therapy. A narrow viewpoint might thus imply that nothing really new is evident with this disease.

However, there truly have been remarkable changes in the diagnosis and treatment of RCC in the 10 to 15 years since the last book on this topic was published in the 1970s. Imaging of the kidney with ultrasonography, computed tomography, and magnetic resonance imaging has not only altered the way that patients are evaluated preoperatively, but has fundamentally changed the manner in which the diagnosis is even established in many cases. We are hopeful that this improved diagnostic ability will ultimately be translated into a survival benefit. There have also been major advances in the technical aspects of partial nephrectomy and inferior vena cava tumor thrombectomy, procedures rarely performed and poorly understood 15 years ago.

This book should assist the urologist, radiologist, and medical oncologist in the diagnosis and treatment of RCC. It is a review designed to allow quick, concise access to the important clinical, imaging, and pathologic differential diagnostic characteristics of RCC. This reflects a practical approach to decision-making and treatment. The present format has not been used previously and we hope it is valuable.

The recommendations for therapy are based to a large degree on experience from the Cleveland Clinic, representing one of the largest series in the world with partial nephrectomy, radical nephrectomy, and inferior vena cava tumor

thrombectomy. A 15-year history of research in the BRM therapy for RCC has culminated in the trials of adoptive immunotherapy with tumor infiltrating lymphocytes and in the study of several new cytokines.

The last decade has been a time of innovation and progress in the management of RCC and we hope that *Clinical Management of Renal Cell Cancer* reflects this progress.

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Introduction

There are several aspects of *Clinical Management of Renal Cell Cancer* that are unique and deserve emphasis. First, as far as we're aware there has not been a major text in English on renal cell cancer in approximately 15 years, and there have been rather marked changes in the diagnosis and treatment of this disease in the intervening period. Thus, the coverage of several aspects of renal cell carcinoma is fragmentary. If an individual needs to know a great deal about the imaging aspects of renal cell cancer and its differential diagnosis, he would have to refer to a radiology textbook (which wouldn't provide information on pathology or clinical situations), to a pathology textbook (which wouldn't provide radiology or clinical information), or to a general urologic oncology textbook (which often has very limited pathology and imaging correlation; when both are present they are often not in the same place). When a clinician sees a patient with a renal mass, he can review the clinical characteristics, which might give a clue to the diagnosis; review the imaging studies, which might provide additional clues; and see how the pathologic findings fit in. Before the publication of *Clinical Management of Renal Cell Cancer,* this has not been available in any other textbook. The clinician can also then proceed to the therapeutic chapters and find specific information on the surgical treatment, adjunctive measures, and specialized surgical treatment, such as partial nephrectomy or inferior vena cava tumor thrombectomy. Even very common conditions, such as incidental renal masses, are presented with very specific treatment approaches. Information is provided on the most current treatments being evaluated for metastatic disease and some of the controversies surrounding the treatments are discussed. The large number of illustrations correlating imaging and pathologic findings constitutes a unique approach.

The individual authors from the Cleveland Clinic are well established and respected individuals in the field of pathology, urology, or medical oncology, and are experts in the field of urologic oncology. The Cleveland Clinic has had one of the largest experiences in the world with RCC and the information in the book has been derived in large degree from that experience, which was obtained by direct patient care. It is our hope that the many lessons that we have learned are transmitted to the reader.

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Part I

Diagnosis

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Epidemiology

J. Edson Pontes, M.D.

It has been estimated that approximately 19,000 cases of renal cell carcinoma (RCC) occur in the United States each year.[1] Approximately 7,000 deaths occur annually as a result of this disease.[1] Despite significant progress in the diagnosis and surgical therapy of RCC, little is known about the epidemiology of this tumor.

CAUSE

RCC is most common in patients between age 50 and 60 years. These tumors are rare in childhood, and there is a predominance of male patients to female patients of 3:1.[2] There have been only occasional studies in the cause and epidemiology of RCC. Because of the increased incidence in the male population, hormonal factors have been implicated. Experimental studies have shown that gold hamsters that are fed estrogen have developed tumors, and this animal model has been used for the study of this malignancy.[3] Chemical carcinogens have also been implicated with agents such as dimethylamine and lead acetate, which have been used to produce tumors in experimental animals.[4,5]

More recently, studies[6] of familial RCC associated with von Hippel-Lindau disease have pointed to a specific chromosomal translocation. In patients with nonfamilial RCC, we also have recently demonstrated specific nonrandom chromosomal changes involving rearrangements of chromosome 3 in 12 of 27 tumors.[7] Because all break points were clustered from p11 to p21, and two oncogenes (raf-1 and k-ras-1) have been localized in chromosome 3, it is possible that those oncogenes may be associated with the genesis of RCC. Factors responsible for the activation of such a process are presently unknown.

NATURAL HISTORY

The difficulties associated with the study of the natural history of RCC have been addressed previously by Ritchie and Chisholm.[8] The completeness of the registry of clinically presented cases is important, and the registration of unrecognized tumors will depend on the rate of autopsies for patients dying of unrelated causes. In a series reported by Hellsten et al[9] among 16,294 autopsies, 350 cases of RCC were found, 235 of which had not been known clinically. Data also have been collected in Scotland, suggesting that the incidence of RCC has been increasing in the male population as compared with a stable incidence in the female population during the same period of follow-up.[8] One of the difficulties in analyzing the incidence of unsuspected RCC found in autopsy examinations is the difference between adenoma and RCC. Controversy exists over whether the popular definition of the size of lesions less than 2 cm is valid, as some authors believe that renal adenomas are only small RCCs, since on rare occasions those tumors have been shown to be capable of metastasizing.[10,11]

The natural history of RCC is often unpredictable. Although some data are available on the survival of patients with untreated RCC, reporting a 3- and 5-year survival of 4.4% and 2.7%, respectively, reports also are available on the development of metastatic disease 20 years after the removal of the primary and spontaneous regression of metastasis.[8,12] This unusual biologic behavior has given rise to the speculation of the importance of the immune system in this disease and has led to current trials with biologic response modifiers.[13] Despite the curiosity that spontaneous regression has generated among investigators, this occurs infrequently and it has been reported in only about 0.3% to 0.5% of cases.[14,15] Another unusual characteristic of this tumor is its association with paraneoplastic syndromes such as polycythemia, hypercalcemia, hepatic dysfunction, and fever of unknown origin in the absence of metastasis.[8] Despite its unusual characteristics, prognostic factors have been defined on the basis of the extent of the disease, clinical staging, and histopathologic characteristics.[16]

Staging has a distinct correlation with survival, as the presence of either distant metastasis or positive lymph nodes influences the outcome of surgery. Other investigators have looked primarily at the histologic pattern of the disease, which demonstrated that tumors with clear, granular, or oncocytic cells did much better than those containing sarcomatoid patterns.[16] The significance of renal vein involvement has been controversial and appears to relate more to the extent of the primary tumor.[17]

More recently the use of flow cytometry has been added to the histologic characteristics in an attempt to better define prognosis.[18] Although there is a relationship of aneuploidy with high grade tumors, the value of this new technology remains under investigation. In patients with metastatic disease, the natural history of this tumor has been better defined.[19] Because this tumor is resistant to most treatments available, it is easy to determine the natural history of patients with metastatic disease. In a report published by de Kernion,[19] cu-

mulative survival of patients with metastasis was 43% at 1 year, 26% at 2 years, and 13% at 5 years. Survival was better for patients with lung metastasis only than for those with local recurrence. In that series excision of metastatic foci improved survival up to 5 years in contrast to our own experience, which reveals only improvement of survival at 2 years but no advantage at 5 years.[20] Palliative nephrectomy did not appear to influence survival in the de Kernion series, which was similar to other previous reports.[19–21]

In summary, there are no known specific causes, such as environmental factors, responsible for the development of RCC. Nonfamilial genetic markers are now being identified and in the future could shed some light on the cause of this disease.

Although the natural history of RCC is occasionally unpredictable, patients with metastatic disease have a dismal prognosis.

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