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Current Management of Renal Cell Carcinoma

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Introduction

Renal cell carcinoma (also called renal adenocarcinoma, hypernephroma, or Grawitz tumor) is the most common malignancy of the kidney and accounts for about three percent of all adult neoplasms.[1] The number of new cases in the United States in 1996 is projected to be 30,600 with an estimated 12,000 deaths.[1] The incidence of renal cell carcinoma is expected to increase slightly, primarily due to enhanced detection of tumors by expanded use of imaging techniques such as computed tomography and ultrasound. The early detection of these tumors, which are generally incurable except by surgical means, should ultimately translate into slight improvements in survival due to application of operative intervention at an earlier, potentially curable stage.

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Clinical Presentation

Symptoms from renal cell carcinoma are generally caused by either invasion of the tumor beyond the confines of the kidney, causing pain, hematuria, or a flank mass, or from the manifestations of metastatic spread, which include weight loss, fever, hypertension, night sweats, and the sudden onset of a varicocele in a male patient.[2] The classic triad of pain, hematuria, and a flank mass is seen in only 10 percent of patients, and usually only those with advanced disease.

About one third of patients with renal cell carcinoma have metastasis at the time of diagnosis,[3] although this number should fall with the increased incidental detection of small renal masses.[4] Paraneoplastic syndromes occur in about 30 percent of patients with renal cell carcinoma and account for such presenting symptoms as hypertension, hypercalcemia, pyrexia, and hepatic dysfunction.[5,6] The last entity, known as Staufer syndrome, can occur in up to 40 percent of patients with renal cell carcinoma and is characterized by hepatosplenomegaly, elevated alkaline phosphatase and serum haptoglobin, and prolonged prothrombin time.[7] After nephrectomy, liver function may return to normal and hepatomegaly may disappear, yet most patients with this

syndrome die within five years.[8] Clearly, renal cell carcinoma patients presenting with any symptoms are at a high risk for having either local extension or metastasis, and those whose tumors are discovered incidentally while still asymptomatic are most likely to be cured.

Staging and Prognostic Factors

Renal cell carcinomas can grow locally into very large masses and invade through the surrounding fascia into adjacent organs. They also metastasize through lymphatic channels to regional and mediastinal nodes or by hematogenous routes primarily to the lungs, bone, and brain, although metastasis has been described in virtually every part of the body.[9] Other than metastasis, the factors that are associated with poor prognosis include tumor size, extension through Gerota's fascia, involvement of contiguous organs, spread to regional or distant lymph nodes, and vena caval involvement.[9-11]

Although the prognostic importance of tumor size is often debated, the propensity for metastasis increases with larger lesions. Metastasis may occur from very small tumors, but the incidence of this is low.[12] Microscopic features (including histologic pattern, cell type, aneuploidy, and nuclear grade) and genetic factors (such as p53 suppressor gene accumulation) also impact on the risk of metastasis and are useful in predicting long-term survival.[13-15] Of special note is chromophobe cell carcinoma, a rare tumor with very low malignant potential despite histologic similarities to renal cell carcinoma.[16]

Two systems have been developed to stage renal cell carcinoma. Historically, Robson's modification of the Flocks and Kadesky system was used.[17] Currently, however, the most commonly employed method is the American Joint Committee on Cancer Staging and End Results Reporting classification (Table 1).[18] This method has advantages over the Robson system in that it more clearly separates the various components of locally invasive tumors and quantifies the extent of lymph node involvement, thereby more explicitly defining the anatomic extent of disease. Regardless of the system used, pathologic stage is the most consistent single prognostic variable that influences survival.

For clinical staging, CT scanning remains the radiologic procedure of choice. For equivocal lesions, angiography can occasionally differentiate pathognomonic malignant and nonmalignant vascular features. If further clarification of venous involvement is necessary, magnetic resonance imaging is extremely sensitive, making venography a seldomly used procedure for documenting and measuring tumor thrombus burden.

Diagnosis

The diagnosis of renal cell carcinoma is usually apparent with modern imaging techniques. As seen on CT, the typical renal cell carcinoma is generally greater than 4 cm in diameter, has a heterogeneous density, and enhances with contrast injection (Fig. 1). Some benign tumors, however, also present as solid renal lesions and may be misdiagnosed as renal cell cancers. The most common of these rare lesions are angiomyolipomas (renal hamartoma) and oncocytomas. Unless very small, angiomyolipomas are usually readily distinguishable from renal cell cancer by the finding of a distinctive fat density on CT scan.[19] Several reports, however, have shown that macroscopic fat can be detected within renal cell carcinomas, and it may no longer be reasonable to dismiss all fat-containing lesions as benign.[20] Unlike angiomyolipomas, oncocytomas do not have a distinct radiologic characteristic. Although they are often solid and are usually without evidence of extensive vascularity or hemorrhage, frequently the diagnosis cannot be made except by surgical excision.[21] Other rare

Table 1
America Joint Committee on Cancer
Staging Classification System for Renal Cell Carcinoma

TNM Clinical Classification	
Primary Tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor 2.5 cm or less in greatest dimension limited to the kidney
T2	Tumor more than 2.5 cm in greatest dimension limited to the kidney
T3	Tumor extends into major veins or adrenal gland or perinephric tissue but not beyond Gerota's fascia
T3a	Tumor extends into adrenal gland or perinephric tissue but not beyond Gerota's fascia
T3b	Tumor grossly extends into renal vein or vena cava
T4	Tumor extends beyond Gerota's fascia
Regional Lymph Nodes (N)	
NX	Regional nodes cannot be assessed
N0	No regional node metastasis
N1	Metastasis in a single node, 2 cm or less in greatest dimension
N2	Metastasis in a single node, more than 2 cm but not more than 5 cm in greatest dimension, or multiple nodes, none more than 5 cm in greatest dimension
N3	Metastasis in a node more than 5 cm in greatest dimension
Distant Metastasis (M)	
MX	Presence of distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Adapted with permission from American Joint Committee on Cancer.[18]

benign and malignant lesions occur in the kidney, but these are seldom distinguishable from renal cell carcinoma preoperatively. The kidney is also a frequent site of metastatic deposits from a variety of solid and hematologic malignancies. Most are discovered at autopsy and are clinically inconsequential. Metastatic or secondary lesions within the kidney rarely produce symptoms, although hematuria and flank pain may occur. The most common metastatic lesions in the kidney oc-

cur from primary lung and breast cancers and should be suspected in patients with these neoplasms.[22]

Management of Clinically Localized Lesions

The mainstay of treatment for primary renal cell carcinoma is surgical excision. It is the only currently known curative therapeutic modality. In the past, the simple nephrectomy had been advocated as adequate treatment. Over the past two decades, however, increases in survival have been documented with the radical nephrectomy, and it is now the surgical procedure of choice for renal cell carcinoma.[23,24] Although defined in various ways, the radical nephrectomy involves complete removal of Gerota's fascia and its contents, including the adrenal glands, kidney, perinephric fat, and, at times, hilar lymph nodes. Implicit in the term radical nephrectomy in many institutions is the inclusion of a regional lymph node dissection.

While the superiority of radical nephrectomy over simple nephrectomy has never been proven in a formal study, the rationale for the complete removal of Gerota's fascia appears sound. Renal tumors frequently impinge on the renal capsule and often may invade into the perinephric fat. A rich plexus of lymphatics drains this area and can potentially diffuse neoplasm throughout Gerota's fascia. Invasion of the perinephric fat is an important determinant of survival, which may be seriously compromised if either microscopic or gross tumor remains.[25] The removal of the adrenal has been advocated not only because it is enclosed within Gerota's fascia, but also because ipsilateral adrenal metastasis occurs in two to 10 percent of most reported series.[26,27] The risk of adrenal metastasis is related to the malignant potential of the primary tumor as well as its size and position. The need for routine ipsilateral adrenalectomy is currently a topic of debate, but certainly patients with large tumors or tumors high in the upper pole are probably better served by a standard radical nephrectomy that includes adrenalectomy.

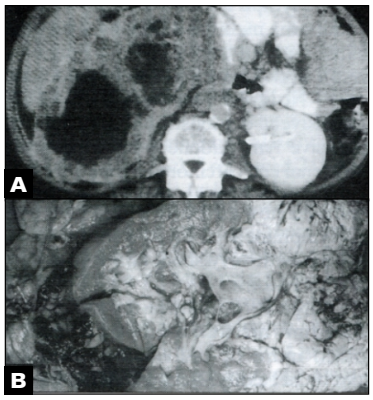

Fig. 1. (A) Computed tomographic scan of large, left renal cell carcinoma. (B) Intraoperative specimen of large, left renal cell carcinoma.

Regional lymph node extension is an important prognostic factor in renal cell carcinoma. Increased survival attributed to removal of involved lymph nodes has prompted the incorporation of regional lymphadenectomy as part of the surgical procedure.[25,28] This too, however, is controversial for several reasons. Even with lymphadenectomy, the survival rate of patients with positive nodes is extremely poor. Likewise, these favorable studies include primarily patients with small-volume metastasis in close proximity to the kidney.

A number of studies have shown that the lymphatic drainage from kidney tumors is not always consistent and may occur anywhere in the retroperitoneum. Furthermore, bloodborne metastasis occurs with at least equal incidence to lymphatic spread, and most patients with

positive lymph nodes eventually acquire bloodborne metastasis. Finally, many patients without metastasis to regional lymph nodes develop disseminated disease.[29] No good randomized study has conclusively demonstrated a benefit of extensive lymphadenectomy in patients with renal cell carcinoma. Nonetheless, it is a valuable staging device, and most urologists now advocate a limited unilateral lymphadenectomy, except for those patients with very small and well-differentiated lesions.

Surgical techniques for radical nephrectomy are well established and are guided more by individual preference than by necessity. Because outcome depends on tumor stage, grade, and histology and because multiple staging systems are used, data comparison is difficult and only broad conclusions on prognosis can be made.[30] After radical nephrectomy for T1 and T2 disease, five-year survival ranges from 60 to 82 percent. This is increased to over 90 percent for incidentally diagnosed tumors.[31] For T3 disease, five-year survival averages 50 percent, although the surgical outcome improves with regional lymphadenectomy.[25]

About one third of patients already have metastatic lesions when diagnosed with renal cell carcinoma.

Management of Incidentally Diagnosed Renal Tumors

Asymptomatic renal cell carcinoma may be incidentally diagnosed on routine physical exam or by abdominal imaging studies obtained for unrelated problems. Tumors identified by CT are often low stage and associated with an excellent prognosis. Careful postmortem studies have documented that a significant number of renal cell tumors are not diagnosed during life. A study of 16,249 autopsies in Sweden revealed that 350 patients had renal cell carcinoma, 235 of which had been previously undetected.[32] In a review of the Greater Los Angeles Tumor Registry, the number of incidental renal masses detected has increased significantly as the use of imaging techniques has expanded.[3] Another series noted that only four percent of asymptomatic tumors were diagnosed in 1976. By 1991, 61 percent were detected.[33] This number continues to increase. In 1988 Smith et al[34] reported that 94 percent of the operable tumors at their institution were discovered incidentally. This is primarily attributed to increased detection by ultrasound and CT imaging.

Incidentally identified renal masses present a significant clinical problem, as the nature of a renal lesion less than 3 cm in diameter is often difficult to determine with current imaging modalities. They are most commonly either early renal cell carcinomas, angiomyolipomas, oncocytomas, or complex cysts. Although CT can often detect small renal cell carcinomas and ultrasound can differentiate solid from cystic components, the diagnosis of these lesions frequently eludes all tests.[35] Likewise, size by itself is not a reliable indicator of malignancy. Our experience suggests that about 50 to 60 percent of these lesions are early renal cell carcinomas, and the others are distributed among the benign lesions mentioned above.

Therefore, the management of these small lesions is problematic. Bell[36] demonstrated a direct correlation between tumor size and malignant potential and noted that lesions less than 3 cm had little propensity for metastasis. In a series of 62 renal tumors less than 3 cm in size, Mur-

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