

Current Management of Renal Cell Carcinoma

Mitchell H. Sokoloff, MD

Jean B. deKernion, MD

Robert A. Figlin, MD

Arie Belldgrun, MD

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 trans-

late into slight improvements in survival due to application of operative intervention at an earlier, potentially curable stage.

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 Stauffer 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

Dr. Sokoloff is Chief Resident in the Department of Urology at the University of California, Los Angeles, School of Medicine in Los Angeles, California.

Dr. deKernion is a Professor of Surgery and Urology and Chief of the Department of Urology at the University of California, Los Angeles, School of Medicine in Los Angeles, California.

Dr. Figlin is a Professor of Medicine (Hematology/Oncology) at the University of California, Los Angeles, School of Medicine in Los Angeles, California.

Dr. Belldgrun is a Professor of Surgery and Urology and Director of the Cancer Immunotherapy Program at the University of California, Los Angeles, School of Medicine and Chief of the Division of Urology at Olive View/UCLA Medical Center in Los Angeles, California.

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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

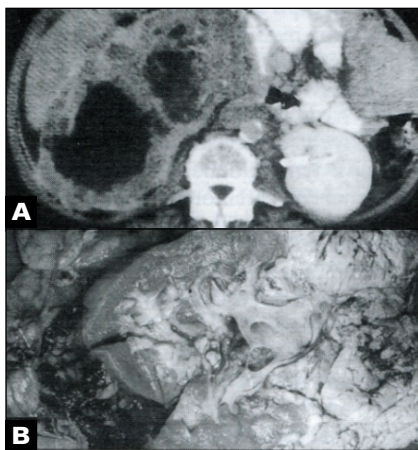


Fig. 1. (A) Computed tomographic scan of large, left renal cell carcinoma. (B) Intraoperative specimen of large, left renal cell carcinoma.

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.

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

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 al³⁴ 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

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

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

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

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. Bell³⁶ 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-

phy and Mostofi¹² showed that three had already metastasized when the lesion was diagnosed. Tsukamoto et al³⁷ demonstrated that 10 percent of tumors measuring less than 6 cm had associated distant metastasis at time of diagnosis. As a general rule, therefore, solid lesions less than 3 cm that are clearly not angiomyolipomas should be excised. In view of their low metastatic potential, however, they can be observed in selected high-risk or elderly patients.

NEPHRON-SPARING SURGERY

The surgical management of small lesions is currently being debated. Although standard treatment with radical nephrectomy has produced good results, at issue is whether a more conservative, nephron-sparing operation would be more appropriate. This procedure was developed for patients who developed tumors in a solitary kidney. The goal is to excise the lesion completely while leaving sufficient renal parenchyma to obviate the need for dialysis. This can almost always be accomplished in situ, but occasionally excision of the kidney for ex vivo workbench surgery followed by autotransplantation is necessary.

The excision of renal cell tumors in solitary kidneys has produced encouraging results. Several series have demonstrated that five-year survival depends on the reason for removal of the contralateral kidney, with improved prognosis when the kidney was excised for benign conditions (70 percent) as compared with neoplasm (50 percent).³⁸ Currently, partial nephrectomy for tumor in a solitary kidney is associated with a five-year survival of about 80 percent. The local recurrence rate is about five percent, but it is almost zero for small, well-differentiated tumors.^{39,40} The patient whose tumor is not amenable to nephron-sparing surgery should be offered a radical nephrectomy followed by dialysis for 18 to 24 months. If no evidence of recurrence or metastasis

is present at that time, transplantation should be considered.

Nephron-sparing surgery is gradually becoming an accepted method of therapy for the primary treatment of small renal cell carcinomas (less than 3 cm) in patients with a normal contralateral kidney. Licht and Novick⁴⁰ reviewed 241 patients treated in this fashion. The mean cancer-specific survival rate was 95 percent at about three years, and there were only two cases of postoperative local tumor recurrence. At Memorial Sloan-Kettering Cancer Center, partial nephrectomies for renal cell carcinoma with a normal opposite kidney resulted in a recurrence rate of 2.4 percent and a survival rate of 95 percent at three years of follow-up.⁴¹

Those who argue against nephron-sparing surgery cite studies that demonstrate the multifocality of renal lesions in tumor-bearing kidneys.⁴² These are usually microscopic foci, however, and are uncommon except in patients with large tumors. Furthermore, follow-up studies after excision of tumors from a solitary kidney, as mentioned earlier, document an amazing lack of recurrent disease within the involved kidney. For these reasons, most urologists now agree that lesions measuring less than 3 cm in size may be treated by partial nephrectomy or wedge enucleation of the tumor with a rim of normal tissue. Lesions that are centrally located, however, still require a radical nephrectomy.

After radical nephrectomy, follow-up includes laboratory studies, chest radiographs, and physical examinations every six months for up to two years, then annually thereafter.⁴³ Abdominal CT scans are taken every 12 months for two years and every 24 months after that. Recommendations after partial nephrectomy differ by including an additional laboratory and physical examination three months postoperatively and by obtaining abdominal CT scans at one, six, 12, 18, and 24 months and then every year thereafter.

At the University of California, Los Angeles (UCLA), we often substitute ultrasound for CT scans, especially after partial nephrectomy.

Management of Locally Invasive Lesions

Renal cell tumors, even when very large, seldom invade contiguous organs. Instead, they have a tendency to compress and displace adjacent tissues. Nonetheless, occasional direct invasion of the liver, duodenum, large bowel, and perinephric muscle does occur. Such patients usually present with pain, generally from involvement of nerve roots, the abdominal wall, or paraspinous muscles. The outlook for these patients is dismal. Yet when surgical excision is feasible, it should be attempted because no alternative treatment modalities exist. Partial excision (debulking) of a primary lesion is seldom indicated.

Although postoperative adjuvant radiotherapy has been proposed for patients with T3 tumors, no study has demonstrated a distinct survival advantage.⁴⁴ The role of radiotherapy as a primary treatment for locally extensive renal cell carcinoma has failed to show a beneficial effect, although a possible preoperative role to decrease the size of the primary tumor and delay local recurrence after resection does exist.^{44,45}

Renal cell carcinoma has an unusual propensity to extend into the renal vein and vena cava. The extent of the tumor thrombus influences prognosis, and patients with minimal extension to a point below the hepatic veins have a better outlook than those with supradiaphragmatic or atrial extension.⁴⁶ In the absence of any effective alternative therapy, the indications for surgery include patients with vena caval extension at any level, including those with thrombus extending into the right atrium. The results of surgical excision in these patients have been good enough to warrant continued aggressive

surgery, although patients with extension to or above the diaphragm seldom are ultimately cured.^{46,47} Patients with extensive caval tumor thrombus must be placed on vascular bypass and in extreme cases may require cardiopulmonary bypass and hypothermic arrest. For tumors invading into the vena cava wall, resection of the involved vessel is possible with preservation of a sleeve of tissue to accommodate venous drainage.

Management of Metastatic Disease

THE ROLE FOR SURGICAL MANAGEMENT

About one third of patients already have metastatic lesions when diagnosed with renal cell carcinoma. For these patients, five-year survival is less than 20 percent.⁴⁸ Metastasis from renal cell carcinoma is usually multifocal, either within the same organ or to multiple sites. Occasionally (one to three percent of cases) patients will present with solitary metastasis. The five-year survival after excision of such lesions is about 25 percent.⁴⁹

In a study at our institution, aggressive therapy of solitary lesions of the skeleton, central nervous system, and soft tissue produced significant palliation of symptoms and occasionally prolonged survival.⁴⁸ This is a select group of patients, however, and only those with a definite solitary lesion and no lymphatic involvement have any prospect of benefiting from surgical management.

The most favorable lesions for resection are solitary pulmonary masses, which occasionally appear more than one year after removal of the primary tumor.⁹ Unfortunately, a metastatic lesion identified at the time of diagnosis of renal cell carcinoma is seldom an isolated lesion, and more clinically evident lesions invariably appear shortly after surgical excision.

In the past, nephrectomy was advocated in the treatment of metastatic disease as a method of both reducing the

Table 2
Phase II Trials of Interleukin-2 for the Treatment
of Metastatic Renal Cell Cancer

Reference	Year	Number of Patients	Response (percent)
West et al ⁸⁶	1987	40	32
Fisher et al ⁸⁷	1988	35	16
Rosenberg et al ⁸⁸	1989	54	22
Bukowski et al ⁸⁹	1990	41	12
Geertsens et al ⁹⁰	1992	30	20
Weiss et al ⁹¹	1992	94	18
Rosenberg et al ⁸³	1992	60	18
Atkins et al ⁹²	1993	71	17
Rosenberg et al ⁸⁵	1994	143	20
Totals		568	19.4

growth of the primary lesion and possibly triggering a spontaneous regression of metastatic disease. Unfortunately, this can be expected to occur in less than one percent of cases, the remissions are extremely short-lived, and the mortality rate from surgery can approach 15 percent, depending on patient selection.¹⁰ This concept has been abandoned as it is now clear that nephrectomy itself seldom, if ever, has any influence on metastatic disease. Therefore, the routine use of adjunctive nephrectomy is unwarranted. Palliation of symptoms is, however, a reasonable rationale for nephrectomy in the face of metastasis, provided the primary tumor can be completely removed without undue morbidity. Patients with perineoplastic syndromes will sometimes benefit from palliative nephrectomy, especially if metastatic sites are not large. Repeated hemorrhage and tumor pain can also frequently be ameliorated by nephrectomy.

The advent of immunotherapy for renal cell carcinoma has once again raised the issue of the role of surgery in patients with metastatic disease. Studies at our institution^{49,50} and elsewhere^{51,52} have documented improved response rates to immunotherapy when given in conjunction with removal of the diseased kidney. Our data indicate that even when considering all the various prognostic factors, patients who receive immunotherapy have a better response rate when nephrectomy is performed prior to treatment. Nonetheless, it is debatable as to whether nephrectomy is best performed before or after immunotherapy, and a randomized study is being performed that will hopefully resolve this question.

Other than for palliation, at UCLA our current philosophy is to perform adjunctive nephrectomies in patients with metastatic renal cell carcinoma only in conjunction with immunotherapy, either to obtain tissue for tumor-infiltrating lym-

Table 3
Phase II Trials of Combination Cytokine Therapy
for Metastatic Renal Cell Cancer

Reference	Year	Number of Patients	Response (percent)
Mittleman et al ⁹⁵	1990	18	22
Kirchner et al ⁹⁸	1990	17	29
Atzpodien et al ⁹⁶	1990	17	36
Hirsch et al ⁹⁷	1990	15	40
Figlin et al ⁹⁴	1992	52	25
Rosenberg et al ⁸³	1992	41	34
Ilson et al ⁹⁹	1992	34	12
Lipton et al ¹⁰⁰	1993	39	33
Bergmann et al ¹⁰¹	1993	30	30
Vogelzang et al ¹⁰²	1993	42	12
Totals		305	27.3

phocytes (TILs) and other experimental protocols or to reduce tumor load in very large primary tumors that are either symptomatic or have a probability of becoming symptomatic in the near future. Conversely, patients with small primary masses and/or multiple small metastatic lesions are first given immunotherapy. Those patients whose metastasis responds to the treatment are then subsequently selected for a nephrectomy.

THE ROLE FOR RADIOTHERAPY

Radiotherapy has been applied to renal cell carcinoma as both an adjuvant to surgical therapy and as a treatment for metastatic lesions. Palliative radiotherapy has been successful in treating painful metastasis and is a powerful tool for pain management. The potential role of preoperative radiotherapy in delaying tu-

mor recurrence and shrinking tumor size has already been discussed as has the lack of success of postoperative adjuvant radiotherapy.

HORMONAL THERAPY AND CHEMOTHERAPY

Hormonal therapy protocols were based on observations that progestational agents inhibited the growth of renal cell tumors.⁵³ Although early reports were encouraging, no studies have substantiated the initial results, including a study at UCLA in which none of 110 patients treated with progesterone had an objective response.⁴⁸ Other hormonal agents, including tamoxifen, have been equally ineffective.^{54,55}

Although cytotoxic drugs are the cornerstone of therapy for most solid malignancies, the success of chemotherapy

in treating renal cell carcinoma has been poor.⁵⁶ Vinblastine and floxuridine, the most common agents, have response rates of seven percent and 16 percent, respectively. In a review of 72 agents evaluated in phase II trials in over 3,500 patients between 1983 and 1992, an objective response rate of 5.6 percent was noted, which was usually of very short duration. Recent studies with retinoic acid have demonstrated growth inhibition *in vitro*,⁵⁷ and it is currently being investigated as a potential single agent or component of a multiple-agent chemotherapeutic regimen.

IMMUNOTHERAPY

Because of occasional spontaneous regression of renal cell masses, discovery of circulating humoral and cellular elements in such patients, delayed growth of metastatic lesions, and varying tumor doubling times, manipulation of the immune system has been an attractive concept for managing metastatic disease.

Nonspecific Therapies

Initial approaches to immunotherapy used nonspecific stimulators such as xenogeneic RNA-treated lymphocytes, bacillus Calmette-Guérin, *Corynebacterium parvum*, and transfer factor. Despite early enthusiasm, these approaches ultimately yielded no significant improvement in prognosis and are now mainly of historical interest with regard to treating renal cell carcinoma.⁵⁸⁻⁶⁰ With the advent of the modern era of genetic engineering and the mass production of molecular agents, new opportunities have arisen for immunotherapy of renal cell carcinoma.

Biologic Therapy with Cytokines

The isolation, identification, and molecular cloning of interleukin-2 (IL-2) revolutionized the field of cancer immunotherapy and significantly altered the treatment

of metastatic renal cell carcinoma.⁶¹ Other immunostimulatory cytokines have since been identified and purified. The ability to produce large quantities of these cytokines has resulted in their widespread use, and in a relatively short period of time, these agents have become an approved treatment modality for metastatic disease. To date most studies investigating the use of cytokines in the treatment of metastatic renal cell carcinoma have used interferon- α (IFN- α), IL-2, combinations of these cytokines, or adoptive immunotherapy with TILs or lymphokine-activated killer cells (LAKs).

Interferon

Studies of IFN- α for the treatment of metastatic renal cell carcinoma at our and other institutions have documented objective response rates of 16 to 26 percent lasting an average of eight to 10 months.⁶²⁻⁷⁰ Improved response rates to 30 percent and prolongations of this response lasting more than 27 months is seen in a select subset of patients.^{65,69} These patients have had a prior nephrectomy, no previous chemotherapy or radiotherapy, good to excellent performance status, and primarily pulmonary metastasis, although the significance of this last factor has been challenged.⁷¹ Few complete or durable partial responses have been documented, and both cost and toxicity (e.g., fever, chills, myalgia, anorexia, and headache) were significant.

Combining accessory agents with IFN- α has been investigated as a means of increasing responsiveness and decreasing toxicity. Studies investigating different combinations of IFN- α with mitomycin-C and 5-fluorouracil therapy demonstrated a response rate of 35 percent.⁷² The combination of IL-2, IFN- α , and 5-fluorouracil increases response rates to over 45 percent and is currently an area of intensive research.^{73,74} The addition of other chemotherapeutic agents, such as vinblastine, doxorubicin, and

Table 4
Phase II Trials of Combination Interleukin-2/LAK Cells
for the Treatment of Metastatic Renal Cell Cancer

Reference	Year	Number of Patients	Response (percent)
Parkinson et al ¹⁰⁸	1990	47	9
Palmer et al ¹¹⁰	1992	102	18
Weiss et al ⁹¹	1992	94	17
Foon et al ¹¹¹	1992	23	26
Thompson et al ¹¹²	1992	42	33
Sznol et al ¹¹³	1992	40	20
Rosenberg et al ¹⁰⁷	1993	72	35
Dillman et al ¹⁰⁹	1993	167	8
Totals		587	20.8

BCNU do not appear to alter the response rate.⁷⁵⁻⁷⁷ While investigations into the use of IFN- γ for the treatment of metastatic renal cell carcinoma have produced results similar to those for IFN- α ,^{78,79} studies combining IFN- α and IFN- γ to stimulate different parts of the immune response are currently under way. The initial results have been disappointing.^{80,81}

Interleukin-2

IL-2 was the first cytokine demonstrated to mediate antitumor effects via the host immune system. Although it has no demonstrable direct antitumor effect, IL-2 activates immune effector cells that then target neoplastic lesions.⁸² The first large studies investigating the therapeutic role of IL-2 in metastatic renal cell carcinoma demonstrated an overall response rate of 18 percent.⁸³ These results have been confirmed in 255 patients for an overall objective response rate of 15 percent lasting almost two years.⁸⁴ Rosen-

berg et al⁸⁵ have recently summarized their experience with high-dose IL-2, confirming an overall response rate of 20 percent. This and other investigations of IL-2 are listed in Table 2.^{82,85-92} Specific patient characteristics are associated with a better response to IL-2 therapy, including good performance scores and either lung; lymph node; or small-volume, extrahepatic abdominal disease.

IL-2 has significant side effects, the most serious of which are prerenal azotemia (with resultant hypotension, pulmonary edema, renal failure, and fluid retention), myocardial infarction, gastrointestinal bleeding and perforation, and death. The high toxicity demands that it be administered only by skilled medical oncologists in an environment in which all of the management team is familiar with the toxicity of this agent. At UCLA we have not experienced any deaths in our series, although national mortality rates range from one to four percent.⁸⁵ These toxicities are dose relat-

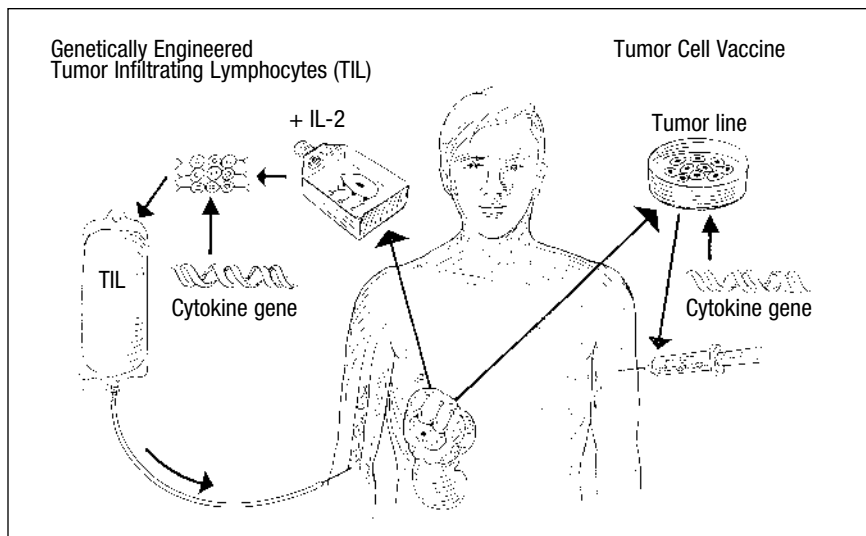


Fig. 2. Schematic diagram of tumor infiltrating lymphocytes (TIL) and vaccine production. (A) left side: TIL production (see text for explanation), (B) right side: tumor cell vaccine (tumor cells are transfected with cytokine genes; these cells, now secreting cytokines, are injected or implanted back into the host to stimulate an antitumor immune response).

ed and largely result from increased membrane permeability and subsequent fluid and colloid loss into viscera and soft tissue.⁸⁵ Other side effects include fever, chills, anorexia, gastrointestinal upset, mental status changes, and tachyarrhythmias and are usually reversible within 72 hours of discontinuing therapy.

Combination Therapy: IL-2 and IFN- α

Combining IL-2 with IFN- α has been investigated as a means of reducing toxicity. Patients with metastatic renal cell carcinoma have had a response rate of 31 percent to this treatment.⁹³ Other studies have investigated this combined approach, with an emphasis on low-dose, outpatient regimens. The results are listed in Table 3.^{83,94-102} These studies have an average response rate of 26 percent. Since 1988 52 patients at UCLA have been treated as

outpatients with the combination IL-2 and IFN- α . The results compare favorably with those achieved with high-dose IL-2 alone. For these patients, the response rate was 25 percent, the median duration of response was 23 months, and the median duration of survival was 34 or more months.⁹⁴ Other studies have confirmed these findings.⁹⁵⁻⁹⁷ The main adverse effects of combination therapy (fever, chills, nausea, anorexia, and hypotension) are less severe than those of high-dose IL-2 and are easily treated on a symptomatic basis.

Adoptive Immunotherapy for Metastatic Renal Cell Carcinoma

Autolymphocyte Therapy

Autolymphocyte therapy relies on activation of memory T lymphocytes in patients with metastatic cancer. These T cells have

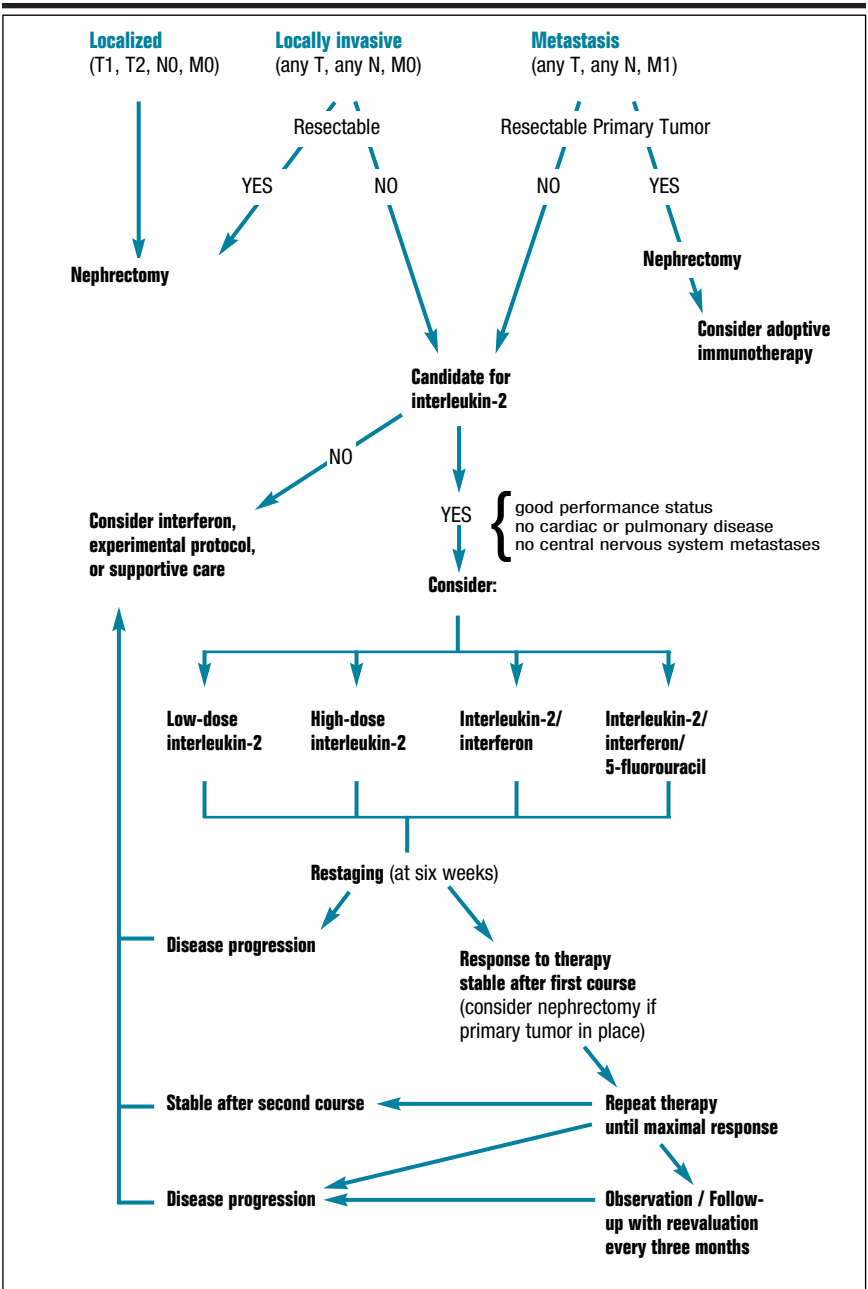


Fig. 3. Algorithm for managing patients with renal cell carcinoma developed at the University of California, Los Angeles.

been exposed *in vivo* to tumor antigens and have the potential for mediating tumor regression following nonspecific activation by incubation with anti-T cell receptor antibodies.^{103,104} Osband et al¹⁰⁵ have reported a response rate of 21 percent in 90 patients with metastatic renal cell carcinoma, achieving a significant survival advantage (21 months versus 8.5 months) and only mild toxicity.¹⁰⁵

Lymphokine-Activated Killer Cell Therapy

LAK cells are generated by cultivating peripheral blood cells with IL-2. They are then infused into the patient along with IL-2.¹⁰⁶ Side effects, therefore, are related to the administered dose of IL-2. Response rates for the treatment of metastatic renal cell carcinoma range from nine to 33 percent (average 23.5 percent) and are summarized in Table 4.^{91,107-113} A single, randomized study has compared the use of IL-2 alone with combined IL-2/LAK treatment. It did not show any superiority for IL-2/LAK therapy over IL-2 alone.¹⁰⁷ This study did, however, document a higher percentage of complete clinical remissions in the IL-2/LAK groups.

Tumor-Infiltrating Lymphocyte Cellular Therapy

The most intriguing application of IL-2 therapy is in conjunction with TILs. These are activated cytotoxic T cells, which show greater specificity for their targets than LAK cells. When given with IL-2, TILs are capable of eradicating advanced and bulky tumors against which LAK cells have been unsuccessful. TILs are isolated from solid tumors and are grown by preparing a single cell suspension of tumor tissue and then culturing these cells with IL-2. After *in vitro* expansion with IL-2, TILs are reinfused in the patient with the hope that they will home to tumor deposits and destroy the neoplastic tissue while leaving normal tissue

unscathed. TILs are 50- to 100-fold more potent than LAK cells in mediating tumor regression.¹¹⁴ The preparation of TILs is schematically diagrammed in Figure 2. Under sterile conditions, radical nephrectomy specimens are mechanically and enzymatically disrupted to obtain single cell suspensions of both lymphoid and tumor cells. These cells are expanded *ex vivo* by incubation with IL-2. This produces a TIL population with antitumor specificity. After five to six weeks in culture, 10 to 100 billion TILs are produced and then infused into the patient along with IL-2.

Few clinical studies have been undertaken with TIL immunotherapy. The UCLA experience includes 48 patients with an average response rate of 33 percent, a 14-month average response duration, and a mean survival of 22 months.^{114,115} Survival is increased in patients with good performance status, prior nephrectomy, few metastatic sites, and no prior cytotoxic therapy. Bukowski et al¹¹⁶ summarized two Cleveland Clinic series, which culminated in an overall response rate of 25 percent. This is similar to that reported by Topalian et al.¹¹⁷ We have improved our response rates to 40 percent by increasing the proportion of cytolytic cells (CD8+) in the TIL population.¹¹⁸ A multicenter, randomized trial comparing nephrectomy and IL-2 to nephrectomy, IL-2, and CD8+/TILs will begin soon.

Future Directions

In the past two decades, there have been impressive advancements in the application of immunotherapy to renal cell carcinoma. At our institution we have seen a progressive increase in responses to treatment as therapy has evolved from systemic IFN- α administration (16 percent), to combination IFN- α /IL-2 use (25 percent), to the current methods of bulk TILs (33 percent) and CD8+/TILs (40 percent). We have identified patient


characteristics that predict improved responsiveness to therapy and have established treatment protocols that decrease toxicity. The most encouraging results have been the improved rates of complete clinical response, most of which are durable and long lasting. Further refinements in the treatment of renal cell carcinoma with immunotherapy are still needed, yet there is no doubt that current immunotherapeutic protocols have produced changes in the natural history of renal cell carcinoma and have resulted in significant and lasting remissions in select patients.

The roles of the various components of current immunotherapy strategies remain to be clearly defined. However, response rates have been seen with cytokines that exceed those of any other agents. Furthermore, responses in areas other than the lungs, including bone, liver, and lymph nodes, are not infrequent with cytokine therapy. Perhaps most important, complete responses of very long duration, and perhaps "cures," can be attributed to cytokine-based treatments. Much more research is warranted and needed in this area.

Our current focus is on furthering systemic gene therapy modalities and creating tumor vaccines. Modified tumor vaccines using autologous tumor cells transfected with cytokine genes have been applied to animal models and have demonstrated tumor regression and immunologic memory to rechallenge.^{119,120} Such exciting early results have stimulat-

ed a flourish of activity in tumor vaccine research. Current investigations to determine immunogenicity of tumor antigens, increase the potential of the cytolytic T-cell response, and improve host recognition of tumor-specific peptides will result in a better understanding of tumor biology and immunology as well as have broad implications for improvements in the treatment of human malignancies.¹²¹

Conclusion

Renal carcinoma, though not a common malignancy, presents a diagnostic and therapeutic challenge. The increased use of abdominal imaging is detecting many more tumors at a very early stage, and the task will be to improve the differential diagnosis of these lesions to exclude those that do not need surgical therapy. At present, no systemic agent has been proven to be uniformly effective in the management of metastatic or locally advanced renal cell carcinoma. Cytokines, in combination with adoptive immunologic therapies, have produced promising early results, and further manipulations of these methods may improve upon current results. Figure 3 schematically represents our approach to the management of renal cell carcinoma. Obviously, treatment plans must be tailored for each individual patient, yet our algorithm provides a framework through which the most beneficial therapies can be efficiently and effectively applied. 

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UICC Cancer Management Meeting

The International Union Against Cancer (UICC) is organizing its first Cancer Management Meeting in Vienna, Austria, from June 29 to July 1, 1997. The conference will deal predominantly with selected topics where new knowledge has been acquired or progress made in understanding the molecular biology and/or treatment of cancer.

The programs will offer important new information for clinicians and scientists working in oncology as well as for oncology nurses. It will provide an opportunity for direct interaction and exchange of ideas with lecturers of diverse professional backgrounds and for participation in workshops organized in parallel with the meeting.

For further information, contact: Mr. A. J. Turnbull, UICC, 3 rue de Conseil-Général, CH-1205 Geneva, Switzerland. Tel: (+41/22) 809 18 11, Fax: (+41/22) 809 18 10.