Natural History and Staging of Renal Cell Carcinoma

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Renal cell carcinoma intrigues both clinician and investigator by its often roguish way of presenting itself. Subtle symptoms, misleading physical and laboratory findings challenge the clinician by mimicking other disorders, rivaling the notoriety of tuberculosis and syphilis. In 30-45 percent of patients, no presenting symptoms are directly related to the primary tumor. The toxic and endocrine effects provide topics for laboratory investigation, while the phenomenon of spontaneous regression or late recurrence demands better understanding of host immune mechanisms.

Our task is to highlight seemingly unrelated clues which, when taken together, will lead to proper diagnosis and earlier treatment of renal cancer. To plan such proper management requires an understanding of the patterns of growth and recurrence. Staging initial extent of tumor helps determine prognosis and most valuable treatment.

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Natural History

It is not yet resolved whether renal cell carcinoma arises de novo from the renal tubule cell or by evolution through adenomatous hyperplasia and renal cortical adenoma. Adenomatous hyperplasia or adenoma have been found in 14 percent of patients with renal cell carcinoma.¹ Time required for a malignant tumor to develop may be deduced from serial biopsies of an easily accessible organ, the uterine cervix. Various studies have shown the duration of the preinvasive phase to be 13-20 years from earliest cellular atypia to the development of cervical carcinoma.² Renal cell carcinoma likely incubates at least this long, considering its often indolent course, the relatively late onset of symptoms which may be misleading, and resulting delay in diagnosis.

Renal carcinoma and simple cyst coexist in two-three percent of patients. Fluid within a cyst containing carcinoma is commonly bloody; cytologic study of the fluid will often show malignant cells. However, tumor cells may be found in the wall of a cyst containing clear fluid.³ In too few instances has accuracy of cyst fluid cytology been confirmed by surgical exploration. In a review of 1,007
cases of cysts or tumors, both were found in only 10 of the 438 cysts, but in none of these patients was the tumor present within the cyst. In the natural history of renal carcinoma, cystic changes within the tumor are relatively common. Central necrosis or marked cystic tumor degeneration represent regression or infarction.

**Modes and Sites of Spread**

Renal cell carcinoma spreads by direct extension or by invasion of intrarenal veins and lymphatics. Approximately one-third of patients already have metastases when the diagnosis of the primary is made. The most common sites of metastases are lungs, lymph nodes, liver and bone. Venous invasion and growth of tumor thrombus into the intrarenal veins is seen in about 30 percent of operative specimens. An unbroken tumor thrombus may extend to the vena cava and even to the right atrium. Tumor emboli thus most likely lodge in the lungs, though they may slip through and be carried anywhere. The lungs are involved in about half of all patients with metastases. These are commonly endobronchial and may cause hemoptysis; occasionally the patient coughs up a plug of tumor. Thus bronchoscopy may allow biopsy of an endobronchial mass and histologic diagnosis of the primary site.

Skeletal metastases seen in about 32 percent of patients dying of renal carcinoma are typically osteolytic, solitary at first, and oval shaped. Tumor cells may enter the vertebral veins (Batson’s plexus) and involve bones of the axial skeleton. The brain and thyroid are involved more often than expected, perhaps due to their proximity to Batson’s plexus.

Hepatic metastases found in 33 percent of autopsied patients may be explained by direct tumor extension to mesenteric veins or by tumor emboli passing through systemic-portal shunts, more dramatically obvious in portal hypertension due to cirrhosis (e.g., esophageal varices, hemorrhoids). Anomalous variations of renal venous drainage are common; venolymphatic connection at the renal level to a tributary of the thoracic duct has been described.

Lymphatic plexuses of the renal parenchyma and perinephric fat communicate freely with each other before draining into the lateral aortic nodes. Most efferents from these nodes drain into the cisterna chyli though some may join the thoracic duct directly. Occasionally the thoracic duct will divide into two branches; the right one then empties into the right subclavian vein. Thus both supraclavicular areas must be examined for suspicious nodes in preoperative staging.

Direct extension to the adrenal occurs within Gerota’s fascia in six to 10 percent of operated patients. Veins in perirenal fat communicate with adrenal veins. Adjacent organs such as colon, liver, spleen and diaphragm are involved in about nine percent of cases.

**Presenting Symptoms and Signs**

Renal cell carcinoma is not often diagnosed early in its course because there are no characteristic early symptoms and signs. The earliest manifestations of renal cell carcinoma are most likely weight loss, weakness and anemia, occurring in about one-third of patients. Thus, nonurologic findings are more common than the “too-late” triad of gross hematuria, flank pain and mass which occurs in only 10-15 percent of patients. Any one of these features is present in only about 65 percent. That the “diagnostic” triad portends advanced disease is confirmed by the finding of metastases in 47 percent of patients on admission. In patients with renal cancer, about 30 percent have metastases when first seen.

Renal tumors have *local effects* (hematuria, pain, mass, etc.), *toxic sys-
temic effects (fever, anemia, hepatopathy, etc.) and endocrine effects (erythrocytosis, hypercalcemia, gonadotrophin production, etc.) The systemic effects are usually nonspecific and may mimic another disease. These are valuable clues because about 30 percent of patients are first seen with mixed findings which may be regarded as systemic effects of the tumor.\(^{14}\) (Table.) These effects often cease after removal of the tumor but may recur if metastases later appear.

Local Effects

- **Hematuria** is caused by tumor growing into the calyces or pelvis and is a late sign. It is usually painless unless brisk enough to cause clotting in the collecting system; such clots are often worm-like casts of the ureter and may cause colic as if a stone were present. Bleeding occurs in about 60 percent of patients and is intermittent. Prompt cystoscopy during a bleeding episode may identify the origin if bloody efflux is seen from one ureter.

- **Loin pain** occurs in about 50 percent of large series of patients. It is usually a continuous dull ache though more severe pain may occur with hemorrhage, necrosis or clot passage. Rather steady severe pain suggests nerve or bone involvement by tumor.

- **Renal mass** is palpable in about one-third of patients. This is a late finding unless the patient is quite thin and the tumor originates in the lower pole. Fixation of the mass is an ominous sign.

- **Acute varicocele** that does not collapse on recumbency indicates obstruction of the internal spermatic vein. Tumor thrombus may block the entry of the left internal spermatic vein into the left renal vein or the tumor may envelop either gonadal vein.

- **Cardiac failure** of high output type may be caused by massive arterial-venous fistulae within the tumor. Hypertension and a continuous to and fro bruit over the tumor are then common. Increased output may return to normal after nephrectomy.\(^{15}\) Arteriovenous fistulae in a metastasis may cause high output failure.\(^{16}\)

| Table. Frequent Systemic Effects with Renal Carcinoma\(^ {14} \) |
|----------------------------------------|----------------|
| **Systemic Reactions**                | **Percent Incidence** |
| Raised E. S. R.                       | 55.6            |
| Anemia                                | 41.3            |
| Cachexia, fatigue, weight loss        | 34.5            |
| Pyrexia                               | 17.2            |
| Abn. liver functions                  | 15.0            |
| Raised alkaline phosphatase           | 10.1            |
| Neuromyopathy                         | 3.0             |
| Amyloidosis                           | 2.1             |
| Hypercalcemia                         | 5.7             |
| Erythrocytosis                        | 3.7             |
| Hypertension > 150/100                | 37.6            |
Toxic Systemic Effects

Malaise, anorexia and weight loss are common to most tumors. While the following effects are nonspecific for renal cell carcinoma, they are seen rather often, singly or together. Most are the result of an immune response to the tumor.

- **Fever**, which is intermittent and of variable degree and pattern, occurs in 17 percent of patients but is thesole presenting symptom in two percent. The fever usually abates when the primary is removed, even in the presence of metastases.\(^7\) A circulating pyrogen has not been shown, perhaps because its concentration is low. Endogenous pyrogen has been clearly demonstrated in renal cell carcinoma tissue taken from febrile patients, while no such pyrogen was found in normal kidney or tumor from an afebrile patient.\(^8\)

- **Anemia** occurs in about 41 percent of patients. Hematuria can rarely be blamed, nor can hemolysis, shortened red cell life or marrow metastases. As in the anemia of chronic renal failure, erythropoietin may be deficient due to renal tissue destruction or the marrow may be depressed by a tumor toxic effect.

- **Hepatopathy**, a reversible hepatic dysfunction has been associated with renal cell carcinoma, xanthogranulomatous pyelonephritis and gastrointestinal cancers.\(^9\)\(^{10}\) Hepatosplenomegaly is sometimes present but there is no biopsy evidence of liver metastasis or hepatitis. Abnormal liver function tests include elevated serum alkaline phosphatase, alpha-2-globulin and bromsulphthalein (BSP) retention. Prothrombin time is prolonged. Symptoms do not reflect the chemical abnormalities that usually regress after nephrectomy and, one removal of a lung metastasis.\(^22\)

- **Amyloidosis** occurs in about three to five percent of patients with renal cell carcinoma. The downhill course is accelerated by uremia. In some cases the nephrotic syndrome appears and hepatosplenomegaly may be present. Liver, kidney, spleen and adrenals are most often involved. Tumor removal rarely alters the dismal course of amyloidosis due to renal carcinoma.\(^23\)

- **Neuromyopathy** may be associated with many malignant tumors, most commonly bronchogenic carcinoma. About four percent of patients with renal cell carcinoma present with neurologic complaints which may improve after removal of the tumor. The disorder may resemble peripheral myopathy, polyneuritis or muscular dystrophy. The cause may be an antigen-antibody reaction specifically directed against nerve tissue.\(^24\)

Endocrine Effects

The more interesting, albeit less common, effects are those caused by endocrine activity of the tumor. Many neoplasms, including renal cell carcinoma, produce small amounts of various hormones. These endocrinopathies are being found more frequently as hormone assay techniques are refined.

- **Erythrocytosis** occurs in about four percent of patients. This condition differs from polycythemia vera because splenomegaly is absent, there is no elevation of the leukocyte or platelet count, and the erythrocyte sedimentation rate is elevated. Increased red cell mass is occasionally found in other conditions such as renal cyst, uterine fibroids and hepatic carcinoma. A raised hemoglobin concentration may reflect contracted plasma volume; measurement of red cell mass and plasma volume is advisable. Nephrectomy allows fall in hemoglobin value to normal unless metastases are present. Later rise in hemoglobin may be the first sign of metastases.\(^25\) In benign renal lesions, hypoxia may stimulate erythropoietin release but renal cell carcinoma itself can secrete erythropoietin.\(^26\) Patients with erythrocytosis appear to have a better prognosis. Rarely, a leukemoid reaction has been seen.\(^27\)
Hypertension may occur if renin is released by the ischemic effect of intrarenal artery obstruction or compression of renal parenchyma by the expanding tumor mass within the renal capsule. Pressor substances have been recovered from Wilms’ tumor. There is no report as yet of elevated plasma and tissue renin activity in a patient with renal cell carcinoma whose hypertension has reversed after nephrectomy. Nonetheless, many reported cases present strong circumstantial evidence to support this possibility. Return of hypertension with tumor recurrence has not been reported unless larger arteriovenous shunts are present in the metastasis. The prognosis of hypertensive patients has been downgraded, but they should not be denied a chance for cure.

Hypercalcemia in the absence of bone metastases occurs more commonly with bronchogenic and renal cell carcinomas but may also be associated with carcinoma of the liver, breast, pancreas, and renal pelvis. Nephrectomy has relieved the hypercalcemia of renal cell carcinoma, but high values may recur with development of metastases. Immunoassay of renal carcinoma and of metastases has shown them to be similar or identical to parathyroid hormone. Synthesis and secretion of parathormone-like material by a renal carcinoma has been established.

Enteropathy causing protein loss has been described in a patient with renal carcinoma. Intestinal function and radiographic appearance returned to normal after removal of the kidney tumor, which was shown to be producing glucagon.

Gonadotrophin production has been demonstrated. Hemoptysis, gynecomastia, areolar pigmentation and diminished libido in a father of eight children led to the diagnosis of metastatic renal cell carcinoma. Urine and plasma gonadotrophins were elevated. Treatment with estrogens and later androgens reduced plasma luteotropic hormone levels to normal and seemed to halt further growth of tumor.

Spontaneous Regression

Documented regression of the primary tumor and also of metastases (usually pulmonary) has prompted controversy over whether the primary tumor should be removed if multiple metastases are already present. The few cases of spontaneous regression reported (now about 60 world-wide) have been cited so often that the illusion of its frequency gives false substance to hopes rarely borne out. Yet we must examine this facet of the natural history of the disease to ascribe fairly the benefit of various treatments and to understand immunologic factors useful in diagnosis and treatment.

Occasionally a tumor can be seen on films in retrospect, its subsequent behavior showing its natural history. Thus, the true natural history of renal cancer is variable and often capricious. Occasional patients live many years with metastases and even for decades with an unresected primary tumor. Metastases may occur up to 31 years after nephrectomy or may regress without nephrectomy. Thus the surgeon may not always deserve credit for a long-term survival.

Riches has reported a series of 443 untreated patients deemed inoperable because of extent of tumor or another condition precluding operation. The crude survival rate was 4.4 percent at three years and 1.7 percent at five years. This indicates the natural course of patients with advanced disease or in poor general condition.

Spontaneous regression must occur without adequate treatment. Regression usually is temporary and may occur in one area while metastases elsewhere continue to grow. Indolent growth and delayed recurrence also imply host resistance.
Spontaneous Regression

Regression of metastases after nephrectomy in two patients has been presented at the urology department staff conferences, Northwestern University Medical School and Evanston Hospital.

Fig. 1. Case 2. Chest X-ray, November 19, 1970 showing multiple cannonball lesions in both lung fields.

Case 1. A man, age 64, presented with an expanding mass on his right thigh. Biopsy of this mass and tumor satellites showed metastatic renal cell carcinoma. Nephrectomy was performed and the primary renal cell carcinoma was histologically identical to the thigh lesions. One week after nephrectomy the thigh masses were measurably smaller, and at three weeks after nephrectomy, the major metastatic mass was stable but the satellite tumors had begun to enlarge and coalesce. No other metastases were known. Wide resection of the thigh lesions was performed. Histologic section revealed involution of some tumor cells and marked lymphocyte infiltrate around the tumor. Five months later, multiple metastases were found and in six months, he died. (Patient of Dr. Jerome Kaplan, Waukegan, Ill.)
Case 2. A woman, age 57, presented with persistent cough. Chest roentgenogram showed multiple lesions in both lung fields. (Fig. 1.) IVP revealed a right renal mass. Nephrectomy for renal cell carcinoma on December 2, 1970 was followed by marked regression of the pulmonary lesions within five weeks. (Fig. 2.) However, six months later the lung lesions began to grow slowly. Hydroxyprogesterone was begun in August 1972. The lesions continued to enlarge, and testosterone enanthate and cyclophosphamide were started in December 1972. There was essentially no change three months later; no other metastases appeared and she was asymptomatic. This patient died in October 1973 of a cerebral vascular accident. Autopsy confirmed that the lung lesions were indeed metastatic renal carcinoma, but no other metastases were found. (Patient of Dr. Daniel Susmano, Aurora, Ill.)
Everson in 1966 catalogued 31 acceptable cases of spontaneous regression of hypernephroma. Recently, nine more cases of regression of renal cell carcinoma have been reported, and two additional cases are presented here. (Figs. 1 and 2.) Sixteen further cases of spontaneous regression have been found in a recent survey of the British Association of Urological Surgeons by David Wallace. Review of Everson’s series reveals that his cases one and four show necrotic changes of only the primary tumor, a common finding in many tumors as they outgrow their blood supply. Histologic evidence of regression of these primary tumors is equivocal and they should be disregarded. Thus 56 patients are known to have had spontaneous regressions.

That the primary tumor itself may regress has been shown satisfactorily. Bartley and Hultquist examined the kidneys of 26 autopsied patients dead of renal cell carcinoma and found regressive changes in 10 of them, consisting of proliferating fibrous connective tissue with plainly evident remains of hypernephroma in the center area. In nine other cases with the same morphological appearance no tumor tissue was seen. Zak reported three “self-healing hypernephromas” in which fibrotic and regressive changes were prominent.

Acceptable regression of metastatic lesions of renal cell carcinoma have now been reported in 40 patients available for analysis. In only three were the regressed metastases nonpulmonary: intestinal, osseous and cutaneous, respectively. The remaining 37 had pulmonary lesions which regressed: following nephrectomy in 28 cases; following irradiation only to the primary tumor (but without nephrectomy) in two; and spontaneously without nephrectomy in one. In six others, the pulmonary shadows appeared after nephrectomy and subsequently regressed.

Histologic proof that the lung lesions were indeed metastatic renal cancer was obtained in only seven of these 37 patients and in all three of the nonpulmonary metastases. Other pulmonary conditions such as sarcoidosis, collagen and fungal diseases may regress too, and can mimic metastatic lesions. Spontaneous regression of renal carcinoma may thus be more scarce than thought, and furthermore has occurred in three patients who did not undergo nephrectomy.

Only five of the 28 patients with regression of lung lesions have been females (sex not recorded for the other nine), and 27 of the 28 have been over the age of 44. Therefore spontaneous regression is most likely to occur in older men with pulmonary metastases.

Possible causes of spontaneous regression of renal cancer have been reviewed by Everson. Endocrine influences are suggested by the preponderance of renal cell carcinoma and regression of metastases in men, especially over the age of 44. Fever and infection have also been associated with regression. However, activation of a host immune response seems to be the most likely explanation for regression.

Delayed occurrence of metastases and prolonged cessation of growth are also instances of biological control of tumor. One patient survived 50 years from the time of diagnosis of renal tumor, the last 10 years of her life demonstrating slowly progressing lung metastases. In Mostofi’s series of 1,247 cases there were 19 patients whose first metastasis appeared more than five years after nephrectomy had been performed.

Evidence is accumulating that some patients with renal cell carcinoma have a specific immunocellular response to their own tumor, as shown by the mixed lymphocyte target interaction test. Tumor-specific antigens were shown to stimulate the patient’s own lymphocytes. A serum factor may also be present; Brendler has shown cytotoxic activity remaining in serum of a patient.
eight years after removal of a mostly necrotic renal cell carcinoma. Systemic symptoms and autoantibodies, as well as toxic and hormonal tumor activity all suggest areas for productive immunological investigation.

Staging of Renal Cell Carcinoma

The chance of cure or control for each patient is assessed preoperatively and the most effective treatment chosen. Surgical and pathologic stages are based on operative findings. When long-term

STAGING OF RENAL CELL CARCINOMA

STAGE I
Tumor within Capsule

STAGE II
Tumor Invasion of Perinephric Fat (Confinned to Gerota’s Fascia)

STAGE III
Tumor Involvement of Regional Lymph Nodes and/or Renal Vein and Cava

STAGE IV
Adjacent Organs or Distant Metastases

Fig. 3. Staging system of Flocks and Kadesky with modifications of Robson. Adapted from G. P. Murphy, personal communication.
survival rates are calculated for a large number of patients treated similarly, variables truly affecting prognosis can be identified and a meaningful staging scheme designed.

Numerous variables interact to determine prognosis: size, weight and number of primary tumors; evidence of vascular and lymphatic invasion; local or distant metastases; and finally pathologic observations of the appearance, differentiation and mitotic activity of the tumor cells. Host resistance factors have already been considered.

Although size alone is not an indication of greater malignancy, larger tumors show a poorer prognosis. Among 45 patients with tumors less than three cm. in diameter, only one had metastases; in 69 patients who had tumors up to five cm. in diameter, five had metastases. In 84 female patients with primary tumors larger than 10 cm., metastases were found in 70. In another series of 58 patients undergoing extensive retroperitoneal lymphadenectomy with nephrectomy, the 21 patients with metastases all had a primary tumor 6.8 cm. in diameter or larger.

Mostofi found that the five- and 10-year survival rates for patients with single tumors were 54 percent and 40 percent respectively, contrasted to 40 percent and 20 percent respectively for those with multiple tumors. Petkovic found that 12 percent of his patients with multiple tumors were alive in contrast to 48 percent of those with single tumors.

Nephrectomy is justifiable in the presence of a resectable solitary metastasis. Of 59 such patients, 34 percent lived five years after resection of both lesions. In another series, 29 percent of 41 such patients lived five years. Despite fairly good initial results, most eventually die of metastases.

Fig. 4. Survival rates of patients according to surgical pathological stage based on Robson's series. 

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SURVIVAL

YEARS AFTER OPERATION

PERCENT SURVIVAL

LYMPH NODES

ADJACENT ORGANS

DISTANT METASTASES

RENAL VEIN

CONFINED TO KIDNEY

PERIRENAL FAT

ATTRITION CURVE AGE 56

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Classifications

Selection of the best treatment for a given patient is based on a survey of likely sites of spread. Preoperative staging based on the TNM classification is of limited value. Accurate pathological staging of regional nodes helps to understand treatment failures. Application of the TNM staging classification to operative staging has been more helpful.

Surgical and pathologic stages based on gross physical characteristics of the tumor have been proposed by Flocks and Petkovic. Neither of these latter two methods of staging is wholly satisfactory. For example, Skinner has shown that renal vein involvement without positive lymph nodes or extension into perinephric fat does not significantly alter the prognosis at either five or 10 years. Positive nodes, however, are an ominous sign. Whitmore was unable to show any difference in survival between Petkovic’s Stage A and B. Rubin’s modification of these two schemes fails to account for the much poorer outlook with nodal than venous invasion.

Robson has proposed a modification of the Flocks and Kadesky staging scheme which best relates survival to surgical and pathologic findings. It is based on his series of 88 patients who underwent radical nephrectomy and removal of para-aortic and paracaval lymph nodes from the aortic bifurcation to crus of the diaphragm. (Fig. 3.)

Robson’s three-, five- and 10-year survival rates based on this rationale are seen in Fig. 4. Comparison of survival rates among various large series shows higher survival rates in Robson’s series.
Histologic Grading of the Primary Tumor

Many investigators have sought to correlate degree of cellular differentiation with prognosis. Skinner\(^3\) has emphasized grading only the nuclear appearance, while Thackray\(^4\) and Robson\(^5\) consider overall impressions of pleomorphism and structural differentiation. Tumor grade is based on the poorest differentiation found. Mostofi has found it difficult to be more precise than to separate the well-differentiated or "good" tumors from the "bad," pointing out that in mixed tumors it is usually the well-differentiated clear cells that invade the renal vein or pericapsular tissue.\(^6\) Most studies show that well-differentiated tumors have a better prognosis than the anaplastic ones.

Those tumors with a predominantly granular cytoplasm appear to have a poorer five-year prognosis, regardless of treatment, but no differences were observed at 10 and 15 years.\(^7\)

In brief, cellular grade, if very undifferentiated, and cellular cytology, if granular, forecast poorer survival. The value of any staging scheme depends upon careful documentation of metastatic disease.\(^8\)

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The Potential for a Disease-free Society

Disease is, fundamentally, unnatural. It is not, in my view, a normal or natural part of the human condition for aging human beings to become paralyzed and idiotic for long years before they finally die, any more than it is for young people to develop acute leukemia. I believe that disease comes, generally, as the result of biologic mistakes; misinterpretations, on the part of cells and tissues, of signals; misuse of information. I believe that the mechanisms of disease are quite open to intelligent intervention and reversal, whenever we learn more about how they operate.—Lewis Thomas, M.D., "The Future Impact of Science and Technology on Medicine," Bulletin of the American College of Surgeons 59:29, 1974.