Renal Cell Carcinoma

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Robert E. Cronin, M.D.

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Renal cell carcinoma is the most frequently occurring malignant tumor involving the kidney (Table 1). It has been called the "internist's tumor" because the presenting symptoms are frequently of a systemic rather than urologic nature. Renal cell carcinoma often remains silent for most of its

Table 1
Primary Malignant Tumors
of the Kidney

Renal Cell Carcinoma	83
Carcinoma of the renal pelvis	8
Transitional cell	
Squamous cell	
Adenocarcinoma	
Nephroblastoma (Wilms' tumor)	6
Sarcoma	3
	100%

course. The classic triad of "flank pain, palpable mass, and hematuria" is a late sign of disease and occurs in only 19% of patients (de Kernion, 1986). Its presence invariably indicates advanced disease. While much has been written about this tumor over the years, it is appropriate to review this tumor at Grand Rounds because of advances in the detection, diagnosis, and therapy of this disorder.

The following cases demonstrate the extremes in presentation of renal cell carcinoma:

Case #1. R.C. was a 63 male was admitted to the VAMC Aug 8, 1988 to evaluate new onset seizures and back pain. Five months earlier, he had been seen in the emergency room because of left testicular pain. Physical examination revealed a left varicocele. Laboratory studies at that time showed a serum creatinine of 0.9 mg/dl and an hematocrit of 56.9%. The seizures work-up included a negative lumbar puncture and head CT. Laboratory studies now showed the serum creatinine had increased to 2.1 mg/dl, hematocrit was 58.5%, serum Ca was 11.1 mg/dl, and parathyroid hormone 3 pg/ml (nl 10-65). Urinalysis was negative. Additional imaging studies demonstrated a 10 cm mass in the upper pole of the left kidney. X-rays of the lumbar spine showed a lytic lesion of the body of L3. On Aug 23, 1988 a fine needle aspiration of the renal tumor showed abnormal cells consistent with renal cell carcinoma. He received radiation therapy to the spinal metastases, but followed a downhill course with worsening mental function, progressive hypercalcemia, and terminally developed deep venous thrombophlebitis of the left lower extremity.

Case #2. B.L. is 58 year old male who was evaluated by the Urology Service because of nocturia 5-6 times nightly and decreased force of stream. In 1983 he underwent transurethral resection of the prostate for benign prostatic hypertrophy. Cystoscopy now showed residual prostate tissue with bladder neck contracture. A routine staging sonogram of the kidneys

showed a large right lower pole renal mass which was confirmed by CT. CT also demonstrated bilateral renal cysts. Laboratory studies were all normal. Bone scan was negative. Radical nephrectomy revealed a 7.5 cm solid mass in the left lower pole and a 7 cm cystic lesion in the left upper pole. One year post nephrectomy he was free of disease.

Demographics.

Renal cell carcinoma accounts for about 3% of all adult cancers and has a 2:1 male to female ratio. The peak incidence is in the fifth to seventh decade of life. Many cases are discovered at autopsy in patients who have died for other causes. Hellsten and colleagues found 350 autopsy cases of renal cell carcinoma at their hospital between 1958-1969 and of these two thirds were unrecognized during life (Hellsten 1981). Of those patients with unrecognized renal cell carcinoma, 24% (56) had metastatic spread and in 21% (49) it was the main cause of death. It is likely that the cases of renal cell carcinoma now being discovered at an increasing rate with newer and more sensitive imaging techniques come from this pool of tumors that might have remained clinically silent for the patient's entire life. Approximately one-fourth of patients with renal cell carcinoma will have distant metastases at the time of diagnosis (Ritchie et al, 1987), with the lungs, bone, skin, liver, and brain being the favored sites.

Paraneoplastic Syndromes.

The normal kidney produces hormones such as erythropoietin, renin, and prostaglandins. Renal cell carcinoma is also capable of producing these same substance as well as other hormones commonly associated with neoplasias (Table 2). Polycythemia occurs in 1-5% of renal cell carcinoma (Nseyo et al, 1986; Murphy et al, 1964). Da Silva and colleagues studied tumor tissue from three

Table 2
Paraneoplastic Syndromes

Tumor-Humoral Syndromes
- Polycythemia
- Feminization
- Masculinization
- Hypoglycemia
- Hypercalcemia

Stauffer's Syndrome

patients with renal cell carcinoma and noted high levels of Epo mRNA in the tumor extracts and the absence of Epo expression in the normal neighboring tissue (Da Silva et al, 1990). They concluded that the kidney carcinoma cells were the source of the erythropoietin, rather than ischemic normal kidney cells. Further, they concluded that Epo production was no longer physiologically regulated since the patients were polycythemic. Chorionic gonadotropins, prolactin, insulin, and parathyroid hormone-related protein (PTHRP) are secreted by renal cell carcinoma (Golde et al, 1974; Turkington, 1971; Pavelic et al, 1981; Burtis et al, 1990; Strewler et al, 1987). Burtis et al (1990) used two sensitive assays for PTHRP in 38 patients with malignant disease and hypercalcemia, including 2 with renal cell carcinoma, and showed that the majority of patients, 30 of 38, had humoral hypercalcemia, as determined by measurement of urinary cAMP excretion and plasma PTHRP. Stauffer's syndrome, characterized by fever, weight loss, deranged liver enzymes, hypoalbuminemia, and focal hepatic necrosis, may be a puzzling presenting finding that only indirectly leads to the diagnosis of renal cell

carcinoma (Boxer et al, 1978). Typically, the liver abnormalities resolve after tumor removal.

Diagnosis.

The most common renal mass lesion is the simple renal cyst. Thus, the aim of the radiology work-up is to differentiate between renal cell carcinoma and a simple cyst (Table 3). Excretion urography had been the primary diagnostic procedure for the initial detection of renal masses, but it

Table 3
Diagnostic Studies for RCC

Excretion Urography
Ultrasonography
Computed Tomography
Arteriography
Cyst Puncture
Magnetic Resonance

is limited in its ability to detect lesions with diameters of less than 2.5 cm, especially when the lesion is in the pole of the kidney. Additionally, visualization of the kidneys with urography may be hampered by poor bowel preparation. Nevertheless, excretion urography still has an important role in the detection of urothelial tumors and in the initial evaluation of hematuria.

The most important event in the improved survival that has occurred with renal cell carcinoma has been the introduction of ultrasonography (US) and computed tomography (CT) and their ability to distinguish a renal cyst from a renal cancer. These techniques have dramatically improved the detection of small, asymptomatic renal tumors and have a diagnostic accuracy approaching 100%. In the past, renal arteriography was a standard preoperative diagnostic study for renal cell carcinoma; today it is rarely required except in cases where the tumor is exceptionally large or where preoperative infarction is used to reduce the bulk of the tumor (Swanson, 1984). Holmberg et al (1988) compared the reliability of ultrasonography, CT, and angiography in the diagnosis of renal cell carcinoma in 99 patients with a renal mass lesion in which the final diagnosis was confirmed by angiography combined with cyst puncture or surgery (Table 4). Thirty-six of the lesions proved to be simple cysts and 56 were renal cell carcinoma. Eighty-nine percent were diagnosed correctly by US, 98% by CT, and 94% by

Table 4
Renal Mass Lesions

	No.	Average size (cm)
Renal Cell Carcinoma	56	6.2
Simple Cyst	36	4.3
Angiomyolipoma	2	1.8
Cortical Cyst Adenoma	1	-
Renal Hematoma	2	10.3
Extrarenal leiomyoma	1	-
Suprarenal Carcinoma	1	-

angiography (Table 5). The diagnostic accuracy of CT for simple renal cyst was 100% (25 cysts), and only one patient of 42 with renal cell carcinoma could not be correctly diagnosed with CT. Of interest, 29 of the 99 renal masses were incidental findings found in the work-up of other diseases.

Table 5
Diagnostic Accuracy of US, CT, and Angiography

Renal Cell Carcinoma	Definite	Indefinite	False Negative
Ultrasound	89%	7%	4%
CT	98%	2%	-
Angiography	94%	-	6%
Simple Cyst			
Ultrasound	86%	8%	6%
CT	100%	-	-
Angiography	78%	14%	8%

Holmberg et al, 1988

The impact of these imaging techniques is particularly strong for small renal tumors. Smith et al (1989) reviewed their cases of tumors less than 3 cm and noted that only 5.3% of renal cell carcinoma found between 1974 and 1977 were of this size compared with 25.4% found during 1982-1985, a five fold increase (Table 6). In the 1982-1985 group, 96.7% of these small tumors (30 of 31) were incidentally discovered and 77.4% were initially detected with US or CT. Because of their small

Table 6
Detection of RCC = or < 3 cm

Years	No.
1974-1977	4/75 (5.3%)
1982-1985	31/122 (25.4%)

Smith et al (1989)

size at the time of diagnosis, 48.4% were amenable to partial nephrectomy. Of these two techniques, CT is clearly the most sensitive for detection of small tumors. Amendola et al (1988) reported that the sensitivity for detecting renal cell carcinoma of 3 cm or less was 67% for excretory urography, 79% for US and 94% for CT. Another contributor to the increase in detection of renal tumors is the increased use of US and CT to diagnose many abdominal problems. When Smith et al (1989) reviewed the number of abdominal examinations in their institution in which the kidneys were imaged between 1977 and 1985, they noted a four fold increase. Increased detection of silent, small renal cell carcinoma translates into improved survival, since tumor stage is lower in incidentally discovered tumors when compared to tumors whose presence is suspected (Konnak and Grossman, 1985).

Ultrasonography is particularly good for diagnosing simple renal cysts and when the criteria for simple renal cyst are strictly met, the diagnostic evaluation need go no further. For cystic lesions that are not simple or are indeterminate, a CT is recommended, as its ability to distinguish a simple cyst from renal cell carcinoma approaches 100%. CT is the best preoperative staging method for renal cell carcinoma (Levine et al, 1980; Weyman et al, 1980). Percutaneous cyst puncture is rarely indicated as it adds little diagnostic information and the false negative rate is high (Orell et al, 1985).

Magnetic resonance imaging appears to have only a small role in the management of renal cell carcinoma as it has significant limitations in the detection of small tumors (Hricak et al, 1988; Fein et al, 1987). However, since the 5 year survival of renal cell carcinoma depends directly on the extent of tumor spread (Siminovitich et al, 1983), MR can provide useful information about tumor invasion of the renal vein or inferior vena cava, information which can alter the surgical approach. Lastly, the sensitivity

of MR for detecting tumor spread to the axial skeleton, a frequent site of metastasis for this tumor, may assist in the staging and choice of therapy for selected patients (Beltran et al, 1987).

VAMC Experience 1987-1990.

I have reviewed the records of 28 patients given the diagnosis of renal cell carcinoma at the VAMC for the past 2 years with particular attention to features which first brought the diagnosis to light. Table 7 shows the presenting complaint of patients with this diagnosis. Twenty-eight percent of patients

Table 7
VAMC 1987-1990
28 cases of Renal Cell Carcinoma
Presenting Finding

Abdominal pain	7 (25%)
Hematuria, gross or micro	6 (21%)
Tumor incidental finding	8 (29%)
Polycythemia	1 (4%)
Stauffer's syndrome	1 (4%)
Seizure	1 (4%)
W/U rising serum creatinine; proteinuria	2 (8%)
Maxillary sinus metastasis	1 (4%)

had the tumor discovered as an incidental finding during an evaluation for another medical problem (Table 8). Abdominal pain and hematuria were the main clinical problems directly related to

Table 8
Incidental Detection of RCC
VAMC 1987-1990

Routine evaluation of prostate disease	5
Routine pre-hernia workup	1
New onset of seizures	1
Chest CT for pneumonia evaluation	1

the presence of the tumor that lead to the search for a renal tumor. Twenty-one percent of these patients already had a metastatic tumor at the time these presenting symptoms were noted. Paraneoplastic syndromes were present in 7 (25%) of the patients (Table 9). Two patients had a left varicocele, a problem that develops when a tumor in the left kidney invades the left renal vein and

Table 9
VAMC 1987-1990
Renal Cell Carcinoma
Unusual Presenting Findings

Varicocele	2
Polycythemia	2
Stauffer's syndrome	1
Fever	1
Hypercalcemia	1

occludes the spermatic vein. Two patients had polycythemia, but in only one did it prompt a search for the renal cancer. One patient had abnormal liver enzymes and the renal cell carcinoma was discovered while these abnormalities were being evaluated. This collection of findings fits the description of Stauffer's syndrome. One patient presented with fever of unknown origin, flank pain, weight loss, and microhematuria. Finally, Case Report #1 had mild hypercalcemia at presentation.

Pathology.

Renal cell carcinoma originates from cells of the proximal tubule, probably from the pars recta, or straight portion (Bander, 1987; Terreros et al, 1986). The two primary histological types of tumors are the clear cell and the granular cell type, both of which may be found in the same tumor. The cells may be arranged in different patterns and tumors are variously described as solid, cystic, tubular, or papillary. Whether these descriptions have a clinical utility is unclear as all patterns may exist simultaneously in the same tumor. The predominantly papillary forms are associated with a better prognosis. The least common cellular type is the sarcomatoid variant which has a significantly poorer prognosis (Sella, 1987). Skinner et al (1972) have used a four grade scale: Grade I: nuclei are indistinguishable from normal tubular cells, Grade II: nuclei are often pyknotic and slightly irregular but only slightly enlarged and without abnormal nucleoli, Grade III: nuclei are moderately enlarged, irregular and pleomorphic often with large nucleoli, but there are no bizarre forms. Grade 4: bizarre, giant nuclei are numerous. However, due to the poor correlation with outcome even the prognostic utility of histologic grading systems for renal neoplasms has been questioned (Bretan et al, 1986). Electron microscopic evaluation may give a better picture of a tumor's malignant potential. Joshi et al (1985) noted that mitochondria, lipid, and glycogen content and the amount of rough endoplasmic reticulum is higher in the more malignant tumors. They proposed that renal tumors with a higher malignant potential had a higher rate of intracellular metabolism.

Pathophysiology

Acquired Renal Cystic Disease. Acquired renal cystic disease (ARCD) is a newly described disease. Prior to 1977, the native kidneys of patients with end stage renal disease were generally given little thought other than as a source of renin in a small number of patients with refractory hypertension. In 1977, Dunnill et al (1977) first described acquired cystic disease as a consequence of long standing chronic renal failure. They examined autopsy specimens of 30 patients who had been on chronic hemodialysis and noted that 14 (46%) had developed bilateral cystic disease of the kidney. None of the cases had cystic disease of the kidneys when dialysis was begun. Six of these patients developed renal tumors and one died of metastatic disease. ARCD is estimated to affect 36.5% of patients on long-term hemodialysis (Gardner, 1984). Renal tumors have been found in 25% of patients with ARCD, and 17.5% of these have been renal cell carcinoma (Gardner, 1984; Bretan et al, 1986; Gehrig et al, 1985; Almirall et al, 1989; Ishikawa et al, 1980; Hughson et al, 1986). This occurrence rate for renal cell carcinoma in patients with ARCD is 14 times higher than that observed among patients with chronic renal failure (Table 10)(Gardner, 1984). The pathology of ARCD is characterized by multiple small (0.5 cm) bilateral cysts located predominantly in the renal cortex, but larger cysts (2-3 cm) may be seen and occasionally the cysts are hemorrhagic. Large hematomas may add greatly to

Table 10
Occurrence of Renal Cell Carcinoma

Group	per 1,000
General population	1.3
Azotemic population	1.5
Dialysis population	6.0
Kidneys with cysts	22.8
Dialysis population with ARCD	45.5

Gardner and Evans, 1984

the weight of the kidney. The renal tumors are often bilateral and multifocal with a heterogeneous morphologic pattern and histologic differentiation. In addition to the presence of adenomas and adenocarcinomas, there is a high incidence of renal epithelial proliferation (McManus et al, 1980). Papillary hyperplasia of cyst epithelium is an almost universal finding in the tumors that arise in association with ARCD and seems to be an important factor in the development of the renal tumors (Hughson et al, 1986).

The typical patient with ARCD has chronic glomerulonephritis, but tubulointerstitial nephritis, nephrosclerosis, and diabetes may also be present. There is a 2.9:1 male-to-female ratio (Hughson et al, 1986). The disorder is usually not seen until the patient has been on hemodialysis for 3 years and then the incidence seems to increase directly with time (Bretan et al, 1986). Most patients with ARCD are asymptomatic, but flank, ureteral, or abdominal pain as the result of hemorrhage into the cysts or retroperitoneum can occur (Table 11). When hemorrhagic cysts rupture into the collecting system, painful gross hematuria can occur. Additional symptoms and signs that warrant an

Table 11
Symptoms and Signs of ARCD

Flank pain	Ureteral pain
Abdominal pain	Gross hematuria
Persisting fever	Nephrocalcinosis
Flank mass	Renal enlargement
Kidney shape change	

Gardner and Evans, 1984

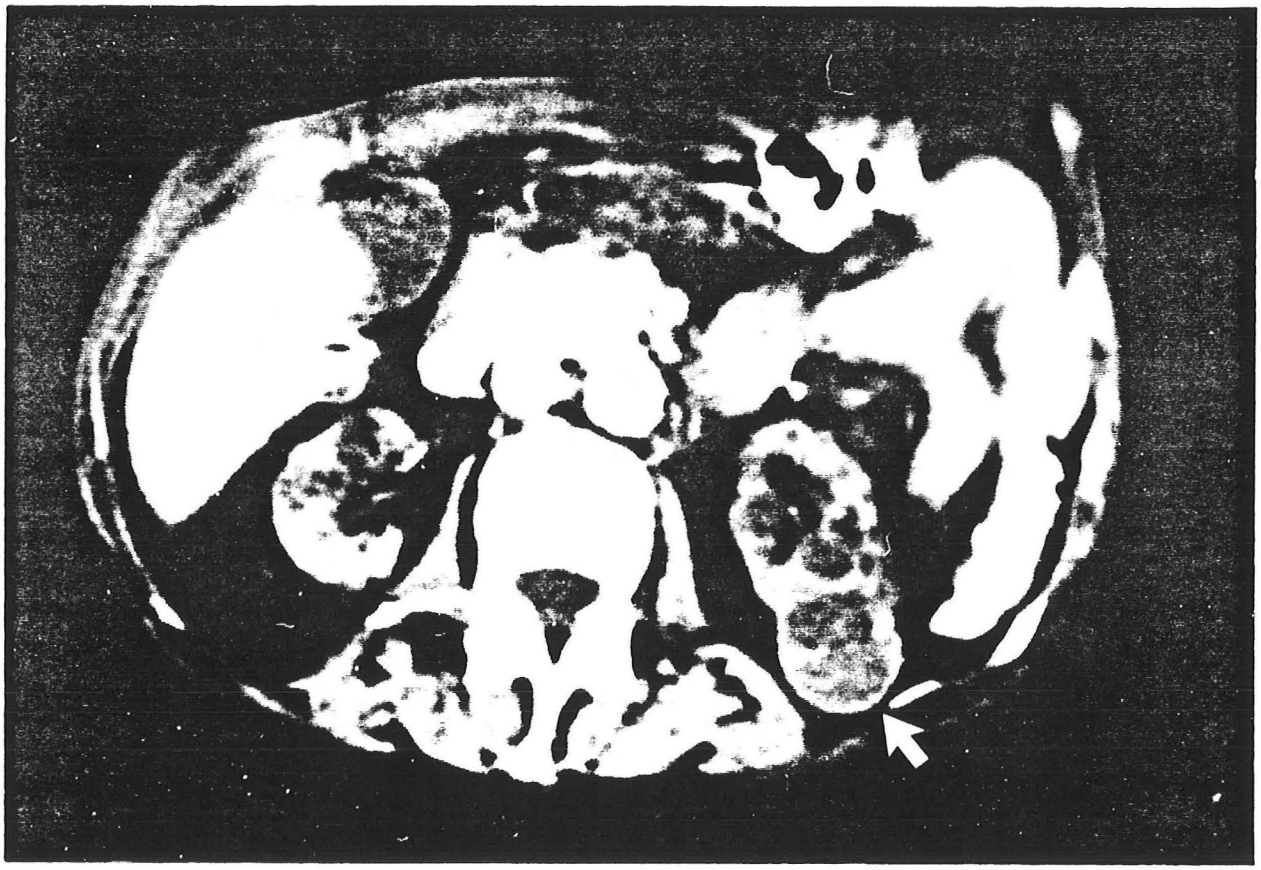
investigation for ARCD include persisting fever, nephrocalcinosis, flank mass, renal enlargement, or change in kidney shape (Gardner and Evans, 1984). Although US will detect the cysts in the 2-3 cm range, CT is the preferred examination for suspected cases as it gives better visualization, particularly of small tumors. While most cases have been reported in patients on chronic hemodialysis and hemodialysis was believed to have a possible etiologic role in its development, (Gardner and Evans, 1984), it has been reported in patients receiving chronic peritoneal dialysis (Trabucco et al, 1990), in native kidneys of patients who have undergone successful renal transplantation (Ishikawa et al, 1983), and in patients with chronic renal failure who have never undergone dialysis therapy (Chung-Park et al, 1983; Bommer et al, 1980; Mickisch et al, 1984). Renal cell carcinoma in patients with ARCD tends to occur at a younger age (average 45 years) versus the general population (average 64 years) (Hughson et al, 1986). There is some controversy about whether the cystic lesions regress following successful renal transplantation, but at least two reports fail to show regression following transplantation (Bommer et al, 1980; Krempien and Ritz, 1980).

The following is a case summary of a patient who has ARCD and is currently on hemodialysis

at the VAMC, Dallas.

Case #3. O.S is a 62 year old white male with ESRD secondary to glomerulonephritis which developed in 1956.He began chronic hemodialysis in 1984. In March 1988 he complained of left flank pain. Renal sonography showed small multicystic kidneys with a prominent complex cystic structure in the left kidney. Additional history indicated a 20 lb weight loss during the preceding 6 months, but no episodes of gross or microscopic hematuria. Abdominal CT confirmed the presence of multicystic renal disease with a suspicious complex solid mass in the left kidney (see photo). In April, a simple nephrectomy was performed. Pathology showed a 7 x 4 x 3 cm multicystic kidney weighing 107 grams containing a 3.5 cm hemorrhagic cyst. No foci of tumor were detected.

Comment: While no foci of tumor was found, there was no way short of nephrectomy to be certain. CT of the remaining kidney is being performed at intervals.



The pathogenesis of ARCD is unknown, but factors that have been suggested include 1) renotropic factors resulting from the reduced nephron population of chronic renal failure, 2) chemicals leached from the dialysis equipment, 3) the accumulation of toxins not excreted by the diseased kidneys, and 4) geographic considerations: ARCD appears to occur more frequently in dialysis patients in Japan (79% of those dialyzed for more than 3 years) (Ishikawa et al, 1980). The uremic environment seems to be important in the pathogenesis of renal cell carcinoma. Penn (1977) noted 12 cases of incidentally discovered renal cell carcinoma in native kidneys of patients who underwent

bilateral nephrectomy prior to receiving a renal transplant. For most of these patients the time on dialysis before transplantation was quite short. Bretan et al (1986) have offered some guidelines for detecting ARCD (Table 12). Patients with ARCD should be considered to have a premalignant condition

Table 12
Monitoring Recommendations for ESRD Patients

1. Baseline abdominal US and/or CT screening
2. Repeat US/CT for:
    a. Gross or microscopic hematuria
    b. Hemodialysis of more than 3 years
    c. Questionable solid renal mass (every 6 mo.)
3. Surgical excision for:
    a. Proven solid renal mass
    b. Increased size of questionable solid mass

Bretan et al 1986

and should undergo yearly CT imaging studies to follow the course of the disease. Since relatively few patients are symptomatic from the cysts and neoplasms and fewer still develop metastatic tumors, it is unclear how exactly to proceed when a patient has a small renal tumor that shows no evidence of enlarging over time. Until more information is available, a conservative approach is probably warranted.

Genetics of Renal Cell Carcinoma

Familial Renal Cell Carcinoma. Cohen et al (1979) reported detailed karyotyping studies on a family with multiple cases of renal cell carcinoma. Ten members of the family developed renal cell carcinoma (Table 13). Karyotyping was performed on 22 members from 3 generations of this family and in 10 instances they detected a balanced reciprocal translocation between the short arm (p) of the

Table 13
Hereditary Renal Cell Carcinoma

1. 10 members (5 men; 5 women) with RCC
2. 22 members karyotyped
    a. 12 normal
    b. 10 had 46XY (or XX), t(3;8)(p21;q24)
        (1) 5 with RCC
        (2) 1 with renal cyst
        (3) 4 under 35 years of age
3. Median age at detection: 45 yrs
4. RCC bilateral (6/10)
5. RCC multiple sites (8/10)

Cohen et al, 1979

3rd chromosome and the long (q) arm of the 8th chromosome. Of these 10 individuals, 5 had evidence of renal cell carcinoma, 1 had a renal cyst, and 4 were normal. However, the four normal individuals were under 35 years of age, considerably below the median age in this family, 45 years, for presentation of this tumor. In contrast, the median age for sporadic renal cell carcinoma is approximately 60 years (Table 14). Additional findings that distinguished this familial form of renal cell

carcinoma from sporadic renal cell carcinoma was the high frequency of bilaterality and occurrence of

Table 14
Age Distribution Renal Cell Carcinoma

	Cases	Mean Age	SD
Hereditary	51	48	11.2
Sporadic	56	62	11.8

Erlandsson et al (1988)

the tumor in multiple sites in the same kidney. A subsequent report involving this same family showed that the cellular oncogene c-myc is translocated from chromosome 8 to chromosome 3 and the cellular oncogene c-raf is translocated from chromosome 3 to chromosome 8 (Drabkin, 1985). These reports suggested that a small deletion or point mutation on chromosome 3 or 8 predisposed to renal cancer (Figure 1). Pathak et al (1982) described another family with renal cell carcinoma over three generations in which a 3;11 translocation was limited to the tumor tissue. The breakpoint on chromosome 3 was at 3p13 or 14. This 3p14 region is also of interest because small cell carcinoma of the lung has been associated with deletions of the 3p14-3p23 region (Whang-Peng, et al, 1982). There is evidence that a fragile site exists at 3p14 (de la Chapelle and Berger, 1984), and that an association exists among fragile sites, the locations of certain oncogenes, and chromosomal aberrations in various malignant tumors.

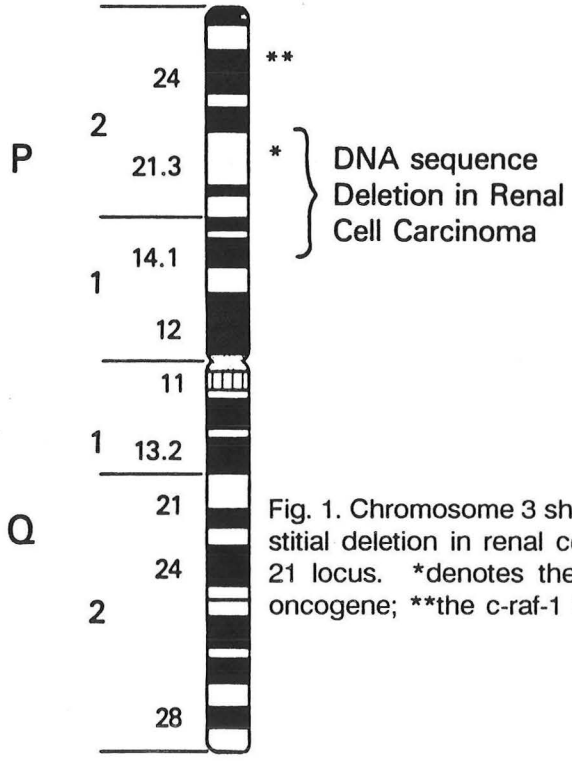


Fig. 1. Chromosome 3 showing the area of interstitial deletion in renal cell carcinoma at 3p14-21 locus. *denotes the site of the c-erb a-2 oncogene; **the c-raf-1 locus.

von Hippel-Lindau Syndrome. Another familial disorder with a propensity to the development of renal cell carcinoma is von Hippel-Lindau syndrome. Here also, chromosome 3 appears to play a central role. von Hippel-Lindau is an autosomal dominant disorder with an inherited susceptibility to various neoplasms including retinal angiomas, hemangioblastomas of the cerebellum and spinal cord,

angiomatous or cystic lesions of the kidneys, liver, pancreas, lung, skin, and epididymis; and adrenal pheochromocytoma (Table 15) (Malek et al, 1987). The ophthalmologist or neurologist is the physician most likely to diagnosed this disorder as only 4 of 37 patients presented with urologic symptoms (Malek

Table 15
von Hippel-Lindau Syndrome

Retinal angioma
Hemangioblastomas: cerebellum, spinal cord
Angiomas & cysts of:

kidney	liver
pancreas	lung
skin	epididymis

Adrenal pheochromocytomas
Renal cell carcinoma

et al, 1987). Thirty-five percent of patients have renal cell carcinoma, of which 75% will ultimately be bilateral (Malek et al, 1987). Bilaterality among sporadic cases of renal cell carcinoma is much lower at 1.8% (Zincke and Swanson, 1982). Using peripheral white blood cells, von Hippel-Lindau disease has been mapped by linkage with the raf-1 oncogene to the region on chromosome 3 which is associated with renal cell carcinoma (Seizinger et al, 1988). At least three case reports of renal cell carcinoma in von Hippel-Lindau syndrome document that tumor cells show a loss of material from the short arm of chromosome 3 (Goodman et al,1990; King et al, 1987; Decker et al, 1988). Since a similar loss of material from chromosome 3 has been documented in sporadic cases of renal cell carcinoma (Teyssier et al, 1986; Zbar et al, 1987), several investigators have speculated that this loss represents a primary cytogenetic event in renal cell carcinoma and that a tumor suppressor gene may be located in this region (Goodman et al, 1990; Seizinger et al, 1988). Thus, loss of this suppressor gene would result in renal cell carcinoma. Not all renal cell carcinoma show a visible loss of chromosomal material from chromosome 3. However, using the more sensitive technique of restriction length fragment polymorphism, Zbar et al (1987) found evidence for DNA sequence deletion through the use of 3 recombinant probes that have been mapped to the short arm of chromosome 3. Although Cohen et al (1979), reported a constitutional chromosome rearrangement in their cases of familial renal cell carcinoma, the most frequent and consistent abnormality in familial as well as sporadic cases of renal cell carcinoma is a loss of material from the short arm of chromosome 3 in tumor cells without constitutional rearrangement. Other chromosomal abnormalities also have been reported, most commonly extra copies of chromosome 7 (Miles et al, 1988).

These chromosomal defects may in the future be useful predictors of biological behavior of tumors and be helpful in deciding therapy for difficult cases. They also may help in providing genetic counseling to families.

DNA content of renal cell carcinoma. The prognostic criteria for patients with renal cell carcinoma currently in use include clinical and histological staging, histologic grade of the tumor, and nuclear mitotic activity as an index of how aggressive the tumor is. Recent work with measurement of the DNA content of renal cell carcinoma and other tumors suggest that DNA content correlates well with tumor recurrence and long term survival and also may be used as a guide to prognosis. Ljungberg et al (1986) showed that the DNA content of tumor cells generally correlated with the histological grade of the tumor cells (Table 16). With the technique of flow cytometry, normal human diploid cells have

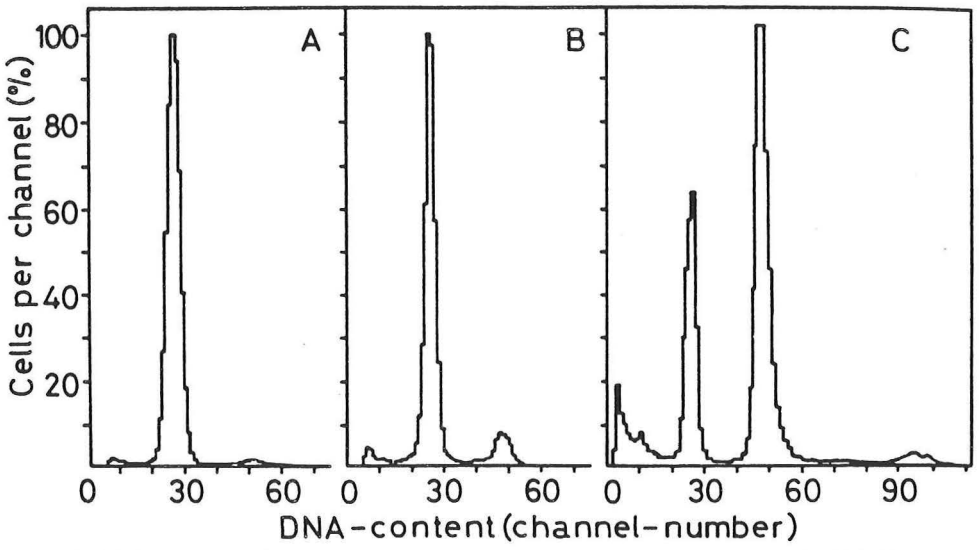
Table 16
DNA Content vs Morphological Grade

DNA Content	Histological Grade 2	3	4
Diploid	2	7	1
Aneuploid	1	6	6

Ljungberg et al (1986)

a DNA index of 1. The DNA index of tumor cells indicates the factor by which DNA content per cell is greater or smaller than that of normal diploid cells (Figure 2). Cells with a DNA content at variance with diploid cells are called aneuploid. Patients with a diploid or near diploid DNA content have a better prognosis when compared with patients with an aneuploid pattern (de Kernion et al, 1989; Otto et al, 1984; Ljunberg et al, 1986). de Kernion et al (1989) performed DNA analysis on fresh tumor specimens

Figure 2



DNA histograms of kidney tissue (A), of a renal carcinoma containing only diploid tumour cells (B), and of a renal carcinoma containing hyperdiploid as well as diploid tumour cells (C).

from 32 patients with renal cell carcinoma. Thirteen of the patients had apparently localized disease while 19 patients had metastases. During the 3 years period of the study, none of the patients free of metastases died and 11 of 13 had a diploid/near diploid pattern. Patients with metastases and a diploid/near diploid pattern had a significantly better survival than those with aneuploid tumors. Otto et al (1984) found that flow cytometry measurements of DNA content of tumor tissue from 68 patients with stage I-III renal cell carcinoma correlated very well with clinical course. Twenty-one per cent of patients with diploid or near diploid tumors had metastases during the 1-4 year follow up period, compared to 89 per cent of those with aneuploid tumors.

Ljungberg et al (1988) examined 26 patients with metastatic renal cell carcinoma and found that 32% had diploid tumors and 68% had aneuploid tumors, with the former having a 5 fold longer survival (Figure 3). Ploidy analysis of the cases with metastases showed a similar correlation with survival. These authors suggested that such DNA analysis of the tumor might be used to determine which patients might be candidates for nephrectomy and excision of solitary metastases.

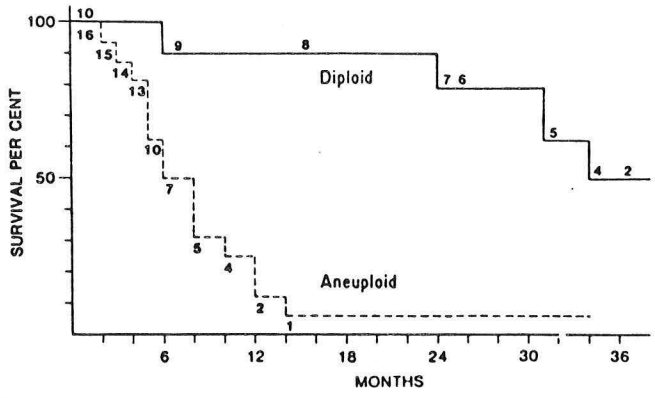


Fig. 3. Survival curves of 26 patients with metastatic renal cell carcinoma, allocated by the DNA content of the primary tumors. The number of patients at risk is indicated at the curves. Ljungberg, 1988.

All investigators have not found this positive relationship of ploidy with clinical course (Frankfurt et al, 1984). Clearly, other factors are involved. A diploid tumor may still contain abnormal chromosomes, such as a balanced translocation (Zbar et al, 1987). Also, the presence of non-malignant cells (having a diploid content of DNA) in the tumor may tend to mask the relatively small number of malignant cells with aneuploid DNA content.

In summary, the data thus far supports the idea that diploid tumors are associated with a better prognosis. Ploidy analysis may improve the prognosis for certain patients with advanced disease.

Growth Patterns.

Clearly not all tumors are the same in their level of aggressiveness. Reports, cited earlier, of asymptomatic tumors found at autopsy, and other credible reports of tumors and metastases which have regressed in conjunction with surgery, and occasionally, spontaneously (Freed et al, 1977; Hellston et al, 1981) indicate that it is difficult to predict the outcome in an individual patient with renal cell carcinoma. However, spontaneous regression of this tumor is not a common event, occurring in only 0.4-0.8% of patients (de Kernion et al, 1978).

The confusion about what to call renal cortical tumors which measure less than three centimeters in diameter seems to have been resolved. Traditionally, these tumors were called adenomas and were believed generally not to metastasize, but a sufficient number of reports document that metastases occur, 6-14% of cases, putting the utility of the term "adenoma" in doubt (Curry et al, 1986; Amendola et al, 1988; Smith et al, 1989; Hellsten et al, 1981). Most pathologists support the view that there are no gross or microscopic features which can truly distinguish a small renal cell carcinoma from the so-called adenoma. It seems prudent to view the small nodule, less than 3 cm, rather as a renal carcinoma of low metastatic potential (Amendola et al, 1988).

Bone metastases are usually lytic and when present tend to preferentially locate in the spine, ribs, pelvis, femur, tibia, and skull (Table 17). Many unusual sites of metastasis have been noted and this is attributed to this tumor's propensity to spread via the hematogenous route. Survival among

Table 17
Organ Distribution of Metastases

	% Single Organ (72 pts)	% Multiple Organ (109 pts)
Lung	72	77
Soft tissue	10	54
Bone	11	26
Liver	5.5	26
CNS	1.4	12
Skin	0	13
Other	0	7

Maldazys and de Kernion, 1986

patients with metastatic renal cell carcinoma is poor (Table 18). Generally less than 20% of

Table 18
Survival in Metastatic Renal Carcinoma

		% Survival		
Ref.	No.	1 yr	2 yr	3 yr
Thompson 1975	65	21.5	9	0
de Kernion 1978	106	42	25	13
Middleton 1967	141	10	-	0
Skinner 1972	77	-	-	8
Montie 1977	77	18	-	-

patients survive 1 year. Hormonal therapy, cytotoxic agents, and experimental procedures such as immunotherapy and the interferons generally do no better than produce a remission in 10-20% of patients. However, some patient groups with metastatic renal cell carcinoma seem to do better than others, particularly those with bone, and lung metastases (Maldazys and de Kernion, 1986).

Clinical Staging

The tumor staging classification proposed by Robson and associates (1969) is a reliable indicator of survival and is still widely accepted. However, Stage III in this classification includes patients with renal vein invasion, inferior vena cava involvement, and metastatic regional lymph nodes, patient groups which appear to have significantly different potentials for metastasis. Siminovitch et al (1983) reexamined 10 years experience with renal cell carcinoma from the Cleveland Clinic Foundation using the TNM classification of the American Joint Committee (Table 19). They found an increase in disease progression in 9 of 80 with tumor contained within the kidney (Stage I), 11 or 44 with

Table 19
Prognostic Indicators of Renal Adenocarcinoma

Category	Robson Stage	5 yr disease-free survival %
Tumor within kidney	I	82
Perinephric extension	II	58
Renal vein	III	31
IVC involvement	III	11
Regional nodes	III	11
Distant metastases	IV	0

Siminovitch et al, 1983

perinephric tumor extension (Stage II), 17 of 35 with renal vein involvement (Stage III), 8 of 11 with inferior vena cava involvement (Stage III), 8 of 9 with regional lymph nodes (Stage III), and 66 of 71 with distant metastases (Stage IV). Other reports have also suggested that renal vein involvement alone provides a better prognosis than when in the presence of IVC extension.

The method of staging tumors used in most institutions is CT which is very useful in showing local invasion of the primary tumor, regional node involvement, and demonstrating metastases in liver and lung.

Therapy

Surgery. Radical nephrectomy is the treatment of choice for renal cell carcinoma (Table 20). This procedure involves early ligation of the renal artery and vein to prevent hematogenous

Table 20
Surgical Therapy

1. Radical nephrectomy
2. Regional lymphadenectomy
3. Partial nephrectomy
4. Partial nephrectomy ex vivo with autotransplantation
5. Complete nephrectomy with chronic dialysis
6. Palliative nephrectomy
7. Resection of solitary metastasis

dissemination of the tumor during the en bloc dissection and removal of the kidney and surrounding Gerota's fascia and its contents, including the adrenal gland. Regional lymphadenectomy is frequently done in addition to radical nephrectomy and offers primarily prognostic information. For patients with Stage I disease confined to the pole of the kidney and in whom preservation of non-tumor bearing kidney is important (e.g. tumor in a solitary kidney or in the presence of chronic renal insufficiency), partial nephrectomy may be indicated. Usually this can be accomplished in situ, but ex vivo "bench" surgery to remove the tumor and autotransplantation of the remnant kidney has also been successful (Calne, 1973). In some institutions, partial nephrectomy or enucleation of small renal cell carcinoma has replaced radical nephrectomy, particularly when the lesions are in one of the poles or are superficial

patient has a renal cell carcinoma in a solitary kidney or has diminished overall renal function. This technique is preferred as an alternative to dialysis therapy. However, whether it should be used in patients with a normal opposite kidney is controversial (Montie and Novick, 1988). For patients with renal cell carcinoma in a solitary kidney in whom partial nephrectomy is not feasible, total nephrectomy with institution of chronic hemodialysis has been successful. The success of renal transplantation for young patients with Wilms' tumor has lead to its use in a few patients with renal cell carcinoma who have been left anephric following surgery for tumor in a solitary kidney (Stroup et al, 1974).

A problem arise when deciding what to do with hereditary renal cell carcinoma, as the tumor tends to be bilateral and multifocal. The desire to maintain normal renal function in these patients who are on average 15 years younger than patients with sporadic disease, must be balanced by the well documented and high likelihood that these patients will have bilateral disease. Partial nephrectomy remains an option, but the chance of multifocal disease in the same kidney is high, and suggests that for most patient this will prove to be of only temporary benefit. Unilateral nephrectomy with regular CT evaluation of the remaining kidney would seem to be the most conservative approach once the presence of tumor in one kidney has been established. Chronic hemodialysis has been successful in prolonging life in patients with hereditary forms of renal cell carcinoma.

Preoperative arterial embolization of large renal cell carcinomas has been used to decrease blood loss and reduce the bulk of tumor (Goldstein et al, 1974). Since it can be associated with several serious complications and is seldom complete, its use should be reserved for selected patients.

Palliative nephrectomy is sometimes performed on patients with metastatic disease, especially when pain, hemorrhage, or tumor-humoral syndromes are clinically prominent problems (Freed et al, 1987). The small number of cases (0.8% of 474 patients) of regression of metastatic renal cell carcinoma after removal of the primary tumor is too low to support the use of palliative nephrectomy solely on the chance of achieving spontaneous regression of a metastatic lesion (Freed et al, 1977). Nonetheless, nephrectomy and resection of a solitary metastasis occasionally will produce some longterm survivors. O'Dea et al (1978) reported that of patients who underwent nephrectomy and later developed metastases, 23% survived more than 5 years after removal of the metastatic lesion.

Radiotherapy. Renal cell carcinoma, with few exceptions, is a radioresistant tumor. Large studies of its use in the preoperative or postoperative setting have shown little promise (Van der Werf-Messing, 1973). However, irradiation of metastatic renal cell carcinoma does seem to provide palliation, especially for bone metastases (Halperin and Harisiadis, 1983).

Hormonal and Chemotherapy. Hormonal therapy and chemotherapy, alone, have offered little hope in the therapy of renal cell carcinoma with response rates of 5% and 16%, respectively, when large series have been reviewed (Garnick and Ritchie, 1988).

Immunotherapy. Immunotherapy for advanced renal cell carcinoma has included the use of autologous and homologous vaccines (Rauschmeier, 1988), alpha and gamma interferon alone (Gebors et al, 1988; Swanson and Quesada, 1988), or interferon in combination with chemotherapy (Fossa, 1988). These interventions have had little effect on the growth of the tumor. However, recent experimental studies (Table 21) with lymphokine activated killer (LAK)-cell-mediated adoptive immunotherapy has raised the possibility that the prognosis for patients with advanced renal cell

Table 21
Adoptive Immunotherapy

1. 4-5 days of IV IL-2 every 8 hours
2. 2-day rest
3. 4-5 daily leukophoresis for lymphocytes
4. Lymphocytes cultured with IL-2 to produce LAK cells
5. LAK cells and IL-2 reinfused IV

carcinoma may some day improve. Interleukin-2, a lymphokine produced by T-helper lymphocytes, not only supports the growth of T cells in vitro, but also enhances tumor cell cytotoxicity by both T cells and natural killer (NK) cells. LAK cells are prepared from patient mononuclear cells which have been activated in 4-5 day culture with IL-2. These LAK cells, along with recombinant interleukin-2, are then administered systemically. Rosenberg et al (1985) demonstrated partial regression of pulmonary metastases in four patients with renal cell carcinoma using (LAK) cells. Interleukin-2 has a number of side effects including fever, nausea, vomiting, diarrhea, erythroderma, hypotension, fluid retention, pulmonary edema, confusion, and acute renal failure (Rosenberg et al, 1985; Belldegrun et al, 1987). Fortunately, most of these side effects are reversible with withdrawal of the drug. Rosenberg et al (1985) recently reported (Table 22) on a further use of adoptive immunotherapy by giving a combination of tumor-infiltrating lymphocytes and interleukin-2 to patients with metastatic malignant melanoma with

Table 22
Tumor-infiltrating Lymphocytes

1. Lymphocytes grown from tumor with IL-2
2. TIL cells, IL-2, cyclophosphamide
   reinfused IV

objective regression of tumor in 60%. The feasibility of using this technique for human renal cell carcinoma has recently been demonstrated (Beldegrun et al, 1988) and a pilot study is underway (Topalian et al, 1988). It is still unclear whether these therapies will ultimately prolong life. Further, these research techniques are laborious and expensive and will require much refinement and simplification before they can be adapted to the clinical care of patients.

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