

RENAL CELL CARCINOMA

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RENAL TUMOURS

Renal cell carcinoma and transitional cell carcinoma constitutes more than 90% of malignant renal tumours. Renal cell carcinoma represents 1.6% of all malignant neoplasms in the UK and 3% of all neoplasm in the USA. The disease is more common in males than in females, 2:1, and the peak incidence is between 5th and 7th decades. In the USA in 1993, an estimated 27,000 new cases were diagnosed and 11,000 deaths were estimated to occur from this disease. In the UK, approximately 3,500 will be diagnosed and over 2,000 deaths from this disease are expected to occur.¹⁻⁵ There are case reports of renal cell carcinoma occurring in children and young adults.^{6,7}

The first accurate gross description dates to 1826 with Konig's observation. In 1855, Robin concluded that renal carcinoma arises from renal tubule or epithelium, also confirmed by Waldyer in 1867. Gravitz (1883) thought that it arose from adrenal rests within the kidney, endorsed by Lubarch in 1894, and the term hypernephroma was used.

Renal cell carcinoma represents a major challenge to surgeons and oncologists alike. Only one third of the patients are cured.

ETIOLOGY

The cause of renal cell carcinoma is unknown. Epidemiological factors may be playing a role. Several studies have shown

a higher risk of renal tumours in smokers.⁵⁻¹⁰ Diuretic use was associated with an increased risk among females, but not among males.⁹ Phenacetin abuse increased the risk, where as acetaminophen did not.

Positive association was found between reproductive factors and risk of renal cell carcinoma.¹¹ Familial cases of renal carcinoma are rare, but still account for 1% of all cases.

Von Hippel Lindau Disease is an autosomal dominant condition and is associated with renal, cerebellar and spinal hemangioblastomas, together with renal cell carcinoma and pheochromocytoma. A translocation between short arm of chromosome 3 and long arm of chromosome 8 has been associated with 87% chance of developing renal cell carcinoma at age 60 years.

Patients suffering from tuberous sclerosis also present with renal cell carcinoma at a younger age than sporadic cases. Patients with acquired cystic disease of the kidney have a 4-9% chance of developing renal cell carcinoma.^{2,3}

PATHOLOGY

Typically, renal cell carcinoma is in the form of a rounded mass from several centimeters in diameter to tumours that fill almost the whole abdomen. There is no true capsule, but a pseudocapsule of compressed renal parenchyma always exists. Haemorrhage, necrosis and cysts may also be found.

Electron microscopy reveals its origin from the proximal convoluted tubules, but some of them do arise from distal convoluted tubules and collecting ducts. George Farrow,⁴ divided renal cell carcinoma into six classes based on morphological and biological characteristics. These are: clear cell (hypernephroid), granular cell (eosinophilic), Chromophobe cells, papillary, collecting duct, and sarcomatoid. With the application of molecular cytogenetic technique, four subtypes have been revealed, with characteristic combination of genetic alternations within the chromosomal and mitochondrial DNA.¹²⁻¹⁴

DIAGNOSIS

The classic presentation of haematuria, pain and flank mass associated with renal cell carcinoma is found in only 10% of cases. Haematuria alone occurs in more than 60% of cases. Pain is the next most common feature. Other features associated with renal tumours are weight loss, fever, hypertension, and hypercalcaemia. Sudden development of varicocele has been reported. Non-metastatic liver dysfunction (Stauffer's Syndrome) is a rare presentation.

Sometimes metastatic disease is discovered before the primary is known. Cutaneous metastasis as the presenting feature has been frequently reported.^{15,16} In 8-30% of cases the diagnosis is incidental for investigations of extra renal symptoms.

TUMOUR MARKERS

Some compounds have been proposed potential tumour markers for renal cell carcinoma. Rising urinary nephrocalcin levels correlate with disease progression in some patients. Neurone specific enolase has been shown to be present in higher concentrations in renal cell carcinoma specimens and in sera of patients suffering from renal cell carcinoma. Serum iron is decreased and serum ferritin increased in renal cell carcinoma, and is proposed as a

possible tumour marker.⁴ Recently serum aldolase A,²⁰ Erythropoietin,²¹ and alpha B-Crystallin has been proposed as useful biomarkers.²²

INVESTIGATIONS/STAGING

Once the clinical suspicion of renal cell carcinoma is established, the diagnosis may be established by a range of imaging techniques. Because most of the patients present with haematuria, intravenous urography is always the preliminary investigation. Intravenous urogram is not a very useful, cheap and non-invasive technique. It can differentiate between solid, cystic and complex lesions.

Ultrasound's sensitivity to diagnose renal vein involvement and local extension is very low. CT scan is the most important modality of imaging techniques for diagnosis and staging. The specificity for diagnosing renal vein and vena cava involvement by CT is over 90%. MRI is very sensitive for renal vein and vena cava involvement.^{23,24} The role of renal artery angiography is decreasing, but is sometimes used in indeterminate cases and in the case of a solitary kidney harboring the tumour, to assess segmental blood supply. Vena cavography is sometimes needed to assess the extent of the thrombus. In unusual cases like metastatic disease or having contraindication to nephrectomy, fine needle aspiration biopsy is very valuable.^{25,26} Bone scan is only indicated when history suggests skeletal involvement. Serum alkaline phosphatase has been found to be a better prognostic indicator than bone scan.²⁷ X-ray chest and routine haematology and biochemistry are also very important. Full blood count, ESR, liver function tests, serum calcium estimation are needed for proper staging.

STAGING

The staging systems most commonly employed are:

a). Robson's System

Stage I. Tumour confined within the parenchyma.

Stage II. Tumour involves the perinephric fat, but is confined within the Gerota's fascia.

Stage III a) Tumours involves the main renal vein or vena cava.

b) Tumour involves the regional lymphnodes.

c) Tumour involves both local vessels and lymphnodes.

Stage IV. a) Tumour involves adjacent organs other than adrenal gland.

b) Distant metastases.

T.N.M. Classification

Primary tumour (T)

T0: No evidence of primary tumors.

T1: Tumours 2.5 cm or less limited to the kidney.

T2: Tumours more than 2.5 cm limited to the kidney.

T3: Tumour extends into major veins or invades adrenal gland or perinephric tissues, but not beyond Gerota's fascia.

T3a: Tumour invades adrenal gland or perinephric tissues, but not beyond Gerota's fascia.

T3b: Tumours grossly extends into renal vein(s) or vena cava.

T4: Tumour invades beyond Gerota's fascia.

Regional Lymphnodes (N)

N0: No regional lymphnodes metastases.

N1: Metastases in a single lymphnode 2 cm or less.

N2: Metastases in a single lymphnode, greater than 2 cm, but not more than 5 cm, or multiple nodes none greater than 5 cm.

N3: Metastases in a lymphnode greater than 5 cm.

Distant Metastases (M)

M0: No distant metastases.

M1: Distant metastases.

PROGNOSTIC FACTORS

The factors that have been associated with poor prognosis in renal cell carcinoma are:

1. Renal vein involvement.
2. Regional lymphnodes involvement.
3. Extension through Gerota's fascia and involvement of contiguous organs.
4. Distant metastases.
5. High grade.

Several recent studies have evaluated these prognostic factors in a large number of cases and confirmed their importance.^{28,29,30,31}

TREATMENT

The definitive treatment for primary renal tumour is surgery. Radical nephrectomy is the most commonly employed method of dealing with the primary tumour. The value of extended lymphnode dissection is controversial and there are studies for and against this procedure.^{32,33} G. Ciancio et al³⁴ and HW Herr³⁵ have shown comparable results of radical versus nephron sparing surgery. Though radical nephrectomy is generally recommended, parenchyma preserving surgery is gaining polarity and due to availability of modern assistance in doing this conservative surgery, with high reliability, the results are quite good.^{36,37} In selected cases laparoscopic enucleation may be useful.³⁸

In case of bilateral tumours, or tumour in a solitary kidney, the options are enucleation of tumour, partial nephrectomy or radical nephrectomy with chronic dialysis and subsequently renal transplantation. Parenchyma preserving surgery is also indicated in Von Hippel Lindau Disease or Tuberous sclerosis, because of the occurrence of multiple tumours in both kidneys. The indication of nephrectomy in face of metastasis are as follows:

1. Large primary tumour associated with small volume of metastatic disease and if it is likely that patient will develop local problem before any symptoms associated with metastasis happen.
2. Large primary tumour associated with severe local symptoms like pain, haematuria, recurrent infections are very well palliated with nephrectomy.
3. Certain experimental protocols, particularly those involving immunotherapy, require patient to have nephrectomy prior to entry into the study.³

In stage-III tumours, involving, renal vein and vena cava, appropriate surgical techniques are required to remove the full tumours thrombus to improve the survival rate.

RADIOTHERAPY

Post operative radiotherapy has not been routinely employed. Although an attractive concept for sterilizing minimal residual tumour has not been shown to influence overall survival. However, in selected patients, particularly those with invasive tumours or those known to have residual tumour, post operative radiotherapy may retard the progression of the tumour.

Stein M et al³⁹ analysed 147 patients who received post operative radiotherapy and were found to have reduced local recurrence in T3, N0 and M0 tumours. Planning post operative radiotherapy with CT scan, can safely deliver radiation to renal

bed with reduced morbidity and significant improvement in disease free survival rate.⁴⁰ Spontaneous regression of metastasis following low dose palliative radiotherapy of the primary tumour have been reported.⁴¹

TREATMENT OF METASTATIC RENAL CELL CARCINOMA

1. Chemotherapy

The role of chemotherapy in the management of renal cell carcinoma has been unsatisfactory. The overall response has been poor. Several agents have been used as single or in combination without great success. Vinblastine appears to be the most commonly employed single agent, with an overall response of 24%. In 1983, Harris reviewed literature on the use of single agent chemotherapy and reported 38 agents used in 1,011 patients with an overall response rate of 9%. Harris also reviewed 22 combination regimens used to treat 406 patients with cumulative response of 17%.³

The duration of a remission to chemotherapy is short and measured in months. The renal tubular epithelium from which the tumour arise is found to have a multi drug resistant gene, MDRI. Recently, Mickish GH⁴² has studied the role of dexamethasone and concluded that this innovative approach may rationalize the treatment approach.

2. Hormonal therapy

Hormonal manipulation has been used for renal cell carcinoma for several decades. Oestrogen, Progesterone, and Testosterone receptors are found on renal cell carcinoma. Medroxyprogesterone is the most commonly used agent for hormonal therapy. Harris reviewed the literature and found a cumulative response of 10%.³

Tamoxifen in high doses was used to treat progressive renal cell carcinoma and was found to have a response rate of 12%.⁵

Patients with lung metastases do well with hormonal therapy.

3. Immunotherapy

Due to the unusual natural history of renal cell carcinoma, including spontaneous regression, delayed growth of metastatic lesions and varying tumour doubling times have prompted interest in immune modulation of cancer patients.

Several agents have been used for this purpose, including BCG, Coumarine and Cimetidine, with limited success. But, recently the use of interferons and interleukins have been studied extensively with variable success.

i. Interferons

Interferons are a group of proteins classified as alpha, beta, and gamma. Interferons have a wide variety of biological and immunoregulatory activity as well as enhancing cytotoxicity of a variety of leukocytes. Interferons alpha have been used in clinical practice with variable success. Horoszenic and Murphy reviewed 56 published studies in which 1684 patients were treated with interferons. Of the 1112 patients treated with interferon alpha, the overall response rate was 15%. Combination therapy with different types of interferon have been reported in 15 studies with an overall response rate of 19%. Interferons have been used in various doses and routes of administrations, e.g. subcutaneous, intravenous, intramuscular routes have been used. The major toxicities induce flu-like symptoms, lethargy, somnolence, nausea, anorexia and other GI symptoms. Interferon alpha has also been used with other immune modulations and cytotoxic agents, including Cimetidine, medroxyprogesterone acetate, Prednisolone, and Vinblastine. Much attention has been paid to combination of interferon alpha and Vinblastine and a 41% response has been reported. Cumulative data from another 10 studies where 320 patients were treated suggests the response rate only at 17%.³

ii. Interlukin 2

Interlukin 2 is a cytokine that was first identified as T cell growth factor, but has since been shown to have a variety of effects, including induction of the growth of T cell, induction of further lymphokines by T cell, the induction of cytotoxic T cell activity, and stimulation of macrophage cytotoxicity. Interlukin 2 also has a stimulating effect on B cells and when lymphoid cells were incubated with interlukin 2, produced lymphokine activated killer cells, or LAK cells.

Initial clinical studies performed by Rosenberg et al, suggested that the bolus dose of interlukin 2 resulted in an overall response rate of 22% and when combined with LAK cells, the response rate was as high as 35%, and over 10% of patients achieved a complete response.⁴³

Gore ME³ has reviewed the results of published series using interlukin 2, either by continuous infusion or bolus intravenous injection with or without LAK cells. The overall response rates are bolus interlukin 2 with LAK cells: 17%, continuous infusion interlukin 2 without LAK cells: 20%, and bolus interlukin with LAK cells: 24%.

Schoof DD et al have examined the role of LAK cells with interlukin 2 and have found it less toxic than interlukin 2 alone. 42% of patients had tumour regression more than 50%. Survival was found to be dependant on risk factors such as performance status, time from initial diagnosis, number of metastatic sites, recent weight loss and prior cytotoxic chemotherapy.⁴⁴

One of the characteristic toxic effects of interlukin 2 therapy is the vascular capillary leak syndrome, the exact mechanism of which is not known. Other toxicities include fever and chills, pruritus and rash, vomiting, diarrhoea, hyperbilirubinemia, oliguria, with elevation of serum creatinine and significant weight gain, hypertension, leukopenia, and thrombocytopenia have also

been reported. Myocardial infarction and encephalopathy has been reported in 5% of patients.

A number of groups have attempted to combine interferon alpha with interleukin 2. The cumulative data suggests that 28% of patients responded to this combination. However, a randomised study of interleukin 2 and interferon alpha did not show any significant advantage.³

PROGNOSIS

The survival of patients with surgically treated renal cell carcinoma is dependant on tumour stage, grade, renal vein and lymphnode involvement. Distant metastases is also of immense prognostic value.

After radical nephrectomy for stage I disease, 5 years survival ranges from 60-90%. For stage II disease it is 47-80%. For tumours extending outside the capsule (stage-III) treated by radical nephrectomy the survival rate is 20-30%. Patients with lymphnode or distant metastasis (stage-IIIb or IV) have 0-10% 5 years survival rate.

REFERENCES

1. Jean B Dekernion, Arie belldegrum. Renal tumors, Campbell's Urology 6th ed Walsh PC et al. Editors Saunders 1992; 2: 1053.
2. Robert Drecier, Richard D Williams. Renal parenchymal neoplasm, Smith's general Urology, 14th ed. Lange, 1995; 372.
3. ME Gore. Advances in management of renal cell carcinoma, Recent advances in Urology Andrology, WF Hendry, RS Kirby editors. Churchill Livingstone, 1993; 6: 81.
4. Herbert C. Ruckull et al. Renal tumours Current opinion in nephrology and hypertension, 1993; 2: 201.
5. Ken Pittman, Peter Silbvy. The management of renal cell carcinoma, critical reviews in oncology/Haematology, 1994; 181.
6. WH Boykin, et al. Renal tumors in young adults, Urology 1992; 409(6): 503.
7. CC Chen, et al. Renal cell carcinoma in childhood report of one case. Acta Paediatrica Sinica. 1992; 33(6): 450.
8. M Mc Credie, JH Stewart. Risk factors for kidney cancer in New South Wales-I Cigarette smoking. European journal of Cancer. 1992; 12: 2050.
9. N Kreiger, et al. Risk factors for renal cell carcinoma results of a population based study. Cancer causes and control 1993; 4(2): 101.
10. JK Mc Laughlin, et al. International renal cancer study. I. Tobacco use. International journal of cancer. 1995; 60(2): 194.
11. WH Chow, et al Reproductive factors and the risk of renal cell cancer among women. International Journal of cancer. 1995; 60(3): 321.
12. G Kovacs. Molecular differential pathology of renal cell tumors. Histopathology. 1993; 22(1): 1.
13. E van den Berg, et al. Cytogenetic analysis of epithelial renal cell tumors relationship with a new histopathological classification. International Journal of Cancer 1993; 55(2): 64.
14. G Kovacs. The value of molecular genetic analysis in the diagnosis and prognosis of renal cell tumors. Review. World Journal of Urology. 1994; 12(2): 64.
15. John L. Peterson, Metastatic renal cell carcinoma presenting as cutaneous nodule. Journal of Dermatology and surgical oncology. 1983; 215.
16. Daniel H, Connor, et al. Cutaneous metastasis of renal cell carcinoma Achieves of Pathology, 1963; 76: 339.
17. E Nikano, et al. Incidentally diagnosed renal cell carcinoma. Euroean Urology. 1992; 21(4): 294.
18. Y Aso., Y Homma. A survey on incidental renal cell carcinoma in Japan. Journal of Urology. 1992; 147(2): 340.

19. RA Mevorach, et al. Renal cell carcinoma incidental diagnosis and natural history review of 235 cases. Review. *Urology* 1992; 39(6): 519.
20. M Tekashi, et al. Elevated levels of serum aldolase A in patients with renal cell carcinoma. *Urological Research*. 1992; 20(4): 307.
21. B Ljunberg, et al. Erythropoietin in renal cell carcinoma evaluation of its usefulness as a tumor marker. *European Urology* 1992; 21(2): 160.
22. SE Pinter, et al. The expression of alpha B-crystallin in epithelial tumors a useful tumors marker. *Journal of Pathology*. 1994; 174(3): 209.
23. DA Kallman, et al. Renal vein and inferior vena cava tumor thrombus in renal cell carcinoma, CT, US, MRI and venacavography. *Journal of Computer Assisted Tomography*. 1992; 16(2): 240.
24. PJ Fritzsche, C Millar. Multimodality approach to staging renal cell carcinoma. *Urologic Radiology*. 1992; 14(1): 3.
25. H Saleh, et al. Unsuspected metastatic renal cell carcinoma diagnosed by fine needle aspiration biopsy a report of four cases with immunocytochemical contributions. *Acta Cytologica*. 1994; 38(4): 554.
26. J Niceforo, BF Coughlin. Diagnosis of renal cell carcinoma value of fine needle aspiration cytology in patients with metastases or contraindications to nephrectomy. *AJR American Journal of Roentgenology*. 1993; 161(6): 1303.
27. I Atlas, et al. Value of serum alkaline phosphatase and radionuclide bone scans in patients with renal cell carcinoma. *Urology*. 1991; 38(3): 220.
28. T Strohhmeyer, R Ackermann. Classic and modern prognostic indicators in renal cell carcinoma. Review of literature. Review. *Urologia Internationalis*. 1991; 47(4): 203.
29. B Delahunt, et al. Renal cell carcinoma in New Zealand. A national survival study *Urology*. 1994; 43(3): 300.
30. JB Thrasher, DF Paulson. Prognostic factors of renal cell cancer. *Urologic clinics of North America*. 1993; 20(2): 247.
31. JU Roosen, et al. Renal cell carcinoma prognostic factors. *British Journal of Urology*. 1994; 74(2): 160.
32. A Herrlinger, et al. What are the benefits of extended dissection of the regional lymphnodes in the therapy of renal cell carcinoma. *Journal of Urology*. 1991; 146(5): 1224.
33. L Hulten, et al. Occupance and localization of lymph node metastasis in renal cell carcinoma. *Scand Journal of Urology and Nephrology*. 1969; 3: 129.
34. G Ciancio, et al. Renal Parenchymal sparing surgery as conservative treatment of renal cell carcinoma. *British Journal of Urology*. 1994; 74: 422.
35. HW Herr. Partial Nephrectomy for incidental renal cell carcinoma. *British Journal of Urology*. 1994; 74: 431.
36. V Moll, et al. Kidney preserving surgery in renal cell tumors indications, techniques and results in 152 patients. *Journal of Urology*. 1993; 150(2): 319.
37. RS J Taylor. Case for nephron sparing surgery in managing renal cell carcinoma. Review. *Seminars in Urology*. 1993; 11(2): 104.
38. RC Luciani, et al. Laproscopic enucleation of renal cell carcinoma. *Surgical Endoscopy*. 1994; 8(11): 1329.
39. M Stein, et al. The value of postoperative irradiation in renal cell cancer. *Radiotherapy and Oncology*. 1992; 24(1): 41.
40. GD Kao, et al. Locally advanced renal cell carcinoma low complication rate and efficacy of post nephrectomy radiation therapy planned with CT. *Radiology*. 1994; 193(3): 725.

41. MP MacManus, et al. Spontaneous regression of metastatic renal cell carcinoma following palliative irradiation of the primary tumor. Irish journal of Medical Science. 1994; 163(10): 461.
42. GH Mickisch. Chemoresistance of renal cell carcinoma. Review. World Journal of Urology. 1994; 12(4): 214.
43. SA Rosenberg, et al. Experience with high dose on Interlukin 2 in treatment of 652 cancer patients. Ann Surg 1989; 210: 474.
44. DD Schoof, et al Survival characteristics of metastatic renal cell carcinoma patients treated with Lymphokine activated killer cell plus Interlukin 2 Urology. 1993; 41(6): 534.