

Diagnosis and Management of Renal Cell Carcinoma

Christina M. Canil, MD, FRCPC, Clinical Research Fellow and Jennifer J. Knox, MD, MSc, FRCPC, Staff Medical Oncologist; Department of Medical Oncology and Hematology, Princess Margaret Hospital, University Health Network, Toronto, ON.

Renal cell carcinoma is more prevalent in older people. The incidence of this cancer is rising secondary to incidental detection on routine imaging. In localized disease, radical nephrectomy is standard therapy; however, options of laparoscopic procedures or surveillance may be appropriate for small tumours. Treatment of advanced or metastatic renal cell carcinoma is limited and the main goal of therapy is palliation of symptoms. Nephrectomy and surgical removal of metastases have been shown to improve survival in patients with good performance status. Results with chemotherapy have been disappointing, but clinical trials of novel systemic agents are underway.

Key words: renal cell carcinoma, kidney cancer, older person, nephrectomy, interferon.

Introduction

Renal cell carcinoma accounts for 3% of all malignancies. In 2003, there will be an estimated 4,100 new cases and 1,470 deaths secondary to kidney cancer in Canada, the vast majority of which are from renal cell carcinoma.¹ Primary treatment for localized disease is surgery. However, once the disease has become locally advanced and/or spread to other organs, prognosis is poor. Many investigational trials are underway to search for new treatments. The peak incidence of renal cell carcinoma is in the seventh decade. In this article, we focus on the diagnosis and treatment of renal cell carcinoma in older people.

Etiology

The etiology of renal cell carcinoma is poorly understood. It has been hypothesized that renal cell carcinoma, along with malignant melanoma, is associated with an unidentified impairment of the immune system. Evidence for this relationship includes a predominance of lymphocytes in cancerous tissue, an increased rate of spontaneous remission (though short-lived) and an increased rate of renal tumours in patients on immunosuppressive therapy for organ transplants. There are no data that clearly demonstrate reduced immunologic

surveillance in older patients as a cause for the increased rates of kidney cancer.² As described later in this article, biological treatments for renal cell carcinoma have focused on enhancement of the immune system. Risk factors for renal cell carcinoma are listed in Table 1.³

Presentation and Diagnosis

Renal cell carcinoma has been referred to as the “internist’s tumour”, as clinical presentation can be variable and is often secondary to paraneoplastic, or hormone-secreting, syndromes (Table 2).^{3,4} The classic triad of hematuria, flank pain and an abdominal mass occurs in less than 10% of patients. Most patients are asymptomatic as retroperitoneal tumours can become large before clinically detected and present in a non-specific manner. In addition, vague symptoms of renal cell carcinoma in the older person may be dismissed as associations with coexisting diseases. To investigate this further, Doherty, *et al.* retrospectively reviewed the charts of 37 patients with renal cell carcinoma to assess whether there was a difference in presentation between patients younger than 69 years of age (27 patients) and patients 70 years and older (10).⁵ The authors found no statistical difference in symptoms (abdominal symptoms, hematuria, loin pain, bone pain, night sweats or

respiratory symptoms) between these two age groups. Locally advanced disease presents in 25% of patients, while 30% of patients present with metastatic spread to the lung, lymph nodes, liver, bone, adrenal, brain or soft tissue.³

There is an increasing trend in incidental diagnoses of kidney cancers with the routine use of ultrasound and computerized tomography (CT).^{6,7} Bretheau, *et al.* found that 50% of renal cell carcinomas were discovered incidentally.⁸ Patients diagnosed in this manner tend to have smaller tumours, less advanced stage and improved survival.^{9,10}

Based on the imaging, radiologists can often identify whether the mass is malignant or benign. However, it is important to differentiate the exact histology of a kidney tumour as it may influence treatment. Transitional cell carcinomas, traditionally seen in the bladder, may occur anywhere along the urothelial lining of the ureters and renal pelvis, and account for 5% of all kidney cancers. Unlike renal cell carcinomas, these tumours are highly sensitive to chemotherapy; therefore, if surgery is not being contemplated, patients who can tolerate chemotherapy should at

Table 1
Risk Factors for Renal Cell Carcinoma

Smoking
Male gender
Older age
Obesity
Hypertension
Chronic dialysis
Family history
Exposure to toxins, such as phenacetin, aniline dyes, asbestos and cadmium

Renal Cell Carcinoma

least have an image-guided biopsy of the mass to confirm the histology.

Natural History

The natural history of renal cell carcinoma is more unpredictable than that of most cancers. The five-year survival for all patients is 40%, but this is dependent on stage or degree of tumour dissemination. There have been well-documented cases of spontaneous tumour regression in the absence of treatment; however, these occurrences are rare and do not lead to long-term survival.¹¹

The growth rate of a primary renal tumour varies and may occasionally remain in a localized form for a number of years. Rendon, *et al.* followed 13 patients with radiologically-detected solitary small renal masses who were unfit for surgery (on the basis of comorbid factors or age) or who refused surgery.¹² The median age was 69 years and the mean lesion volume at diagnosis was 13.6cm³ or 2.95cm in diameter. Patients were followed prospectively with ultrasound or CT scans for a median of 42 months. Five of the 13 patients underwent surgery following a period of surveillance because of tumour enlargement or new onset of symptoms. None of these patients had metastases. Two patients had fast-growing tumours and these were the only two cases in which symptoms developed. When these two patients were excluded from the analysis, the average growth rate was 1.32cm³ per year, which is not significantly different than no growth. The authors concluded that the growth rate of small renal tumour is variable, but tumours that are destined to grow do so early and most small tumours grow at a low rate or not at all. Another study is currently underway to identify radiologic and molecular markers that may prognosticate for slow-growing small renal cancers.

Treatment of Localized Disease

The treatment of localized disease is surgical resection. Radical nephrectomy is the gold standard of treatment and this surgery includes the removal of the kidney, ipsilateral adrenal gland, perinephric fat, renal vein and ureter and Gerota's

fascia (lining around the kidney). The therapeutic benefits of lymph node dissection are not yet proven. Various approaches to nephrectomy exist and technique depends largely on the size and location of the tumour, in addition to the patient's body habitus. For patients with smaller tumours (<7cm), some centres have advocated for partial nephrectomy. In a review by Beldegrun, *et al.*, the outcomes of 146 patients with partial nephrectomy were compared with a matched group of patients treated with radical nephrectomy.¹³ For patients with tumours less than 7cm, there was no difference in survival or complication rates. However, for patients with larger lesions, survival rates were significantly higher with radical nephrectomy versus partial nephrectomy.

In the older patient, a curative open nephrectomy (radical or partial) may not be considered because of concerns regarding operative morbidity. Laparoscopic procedures may be an alternative to the established open surgical procedures.¹⁴ Laparoscopic nephrectomy is a longer procedure that requires expertise, although the patient has minimal post-operative discomfort and a shorter time to recovery. As mentioned previously, current studies are underway that follow small renal tumours with surveillance imaging. This would be reasonable for patients who have competing comorbid factors. Patients who are not candidates for surgery may receive palliation of flank or abdominal pain with external radiation or arterial embolization.

Treatment of Metastatic Disease

The median survival for patients with metastatic renal cell carcinoma is 12–18 months and the five-year survival is less than 10%.³ Treatment of this disease with chemotherapy has been disappointing. In a review by Yagoda, *et al.* of 80 phase II trials, overall response rate for chemotherapy was less than 10%.¹⁵ Motzer and Russo updated this data for systemic therapy trials published between 1990 and 1998 with similar results.¹⁶ The poor response with chemotherapy is probably due to the

Table 2
Presenting Symptoms/Signs or Laboratory Abnormalities in Patients With Renal Cell Carcinoma^{3,4}

Hematuria
Flank or back pain
Abdominal mass
Fatigue
Weight loss
Anemia
Fever
Hypercalcemia
Polycythemia
Non-metastatic hepatic dysfunction (Stauffer's syndrome)

over-expression of the multiple-drug-resistance gene.

Biological therapies have been investigated as a treatment option, as renal cell carcinomas are thought to be associated with an impairment in the immune system. These treatments essentially enhance the immune system's ability to attack the cancer. A minor subset of patients may benefit from immune-stimulating therapy, such as interferon alpha, but the improvement in survival is relatively small and transient.¹⁷⁻¹⁹ Unfortunately, treatment with interferon alpha is accompanied by significant toxicities including headache, fever, myalgias and arthralgias, fatigue and neurocognitive impairments. Treatment with interleukin 2 (IL-2) has similar response rates to interferon alpha; however, 5% of selected patients have a durable, complete remission.²⁰ Administration of IL-2 should only be done in specialized centres and requires monitoring in an intensive care setting, as potential adverse effects include pulmonary edema, arrhythmias, hypotension and even death. Such treatments are highly unattractive for the older patient.

Several studies have demonstrated a role for surgery in patients with metastat-

ic disease. Selected patients with solitary or limited numbers of distant metastases can achieve prolonged survival with nephrectomy and surgical resection of metastases, especially in the setting of a long disease-free interval and good performance status. Following resection of solitary metastases from renal cell carcinoma, the five-year survival rate is 35–60%.²¹ For patients who do not have resectable metastases, nephrectomy alone is a reasonable intervention in suitable surgical candidates, as randomized studies have shown a survival benefit in the order of several months.^{22,23}

As treatments for metastatic renal cancer are limited, watchful waiting is an appropriate approach for asymptomatic older patients with comorbidities precluding surgery, especially in light of the variable rate of disease progression. Symptomatic patients may benefit from palliative measures with analgesics, bisphosphonates, embolization or radiation (Figure).

Future Prospects

Given the overall poor results of drug therapy, patients with good performance

status should be considered for clinical trials. Renal cell carcinoma presents an attractive target for anti-angiogenic (prevention of tumour blood vessel formation) therapy, as these tumours are highly vascular and over-express vascular endothelial growth factor (VEGF), a pro-angiogenic peptide. Other therapies under investigation include thalidomide, monoclonal antibodies, tumour vaccines, dendritic cells and low-dose continuous chemotherapy in combination with a COX-2 inhibitor.²⁴ Clinical trials of non-myeloablative allogeneic transplantation, or “mini-transplantation”, are underway; however, this therapy is not appropriate for older people due to severe toxicity.

Conclusions

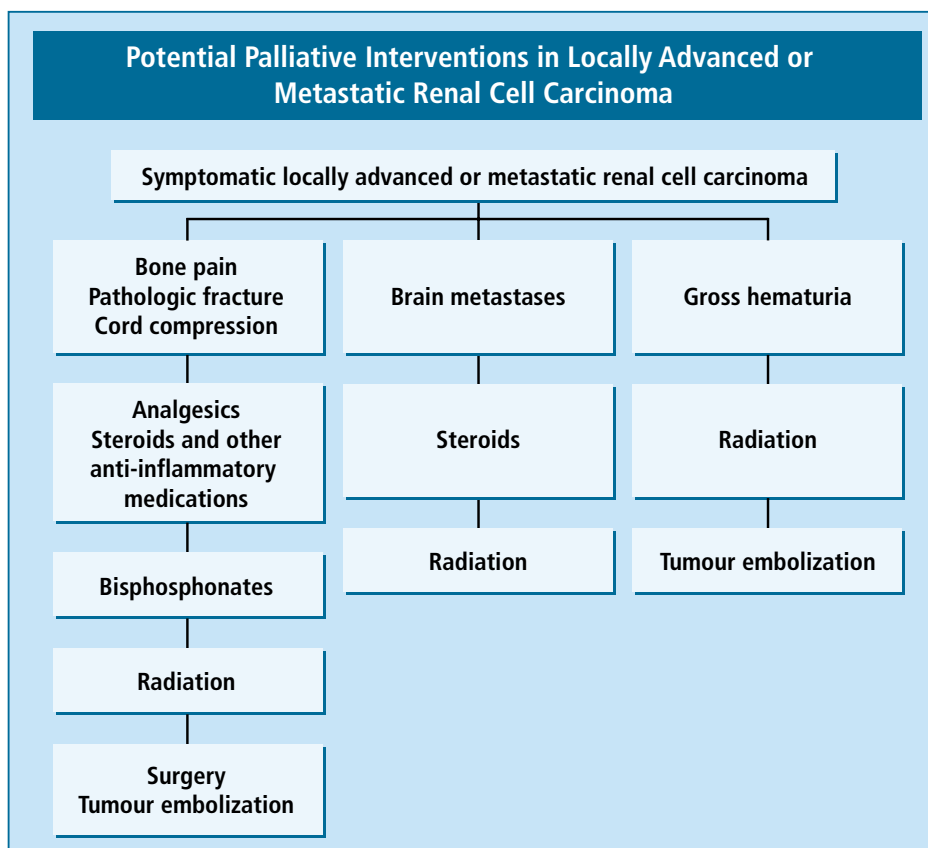
Renal cell carcinoma presents most commonly in older people. The progression of disease is variable. Patients with localized disease and a good performance status should undergo surgery; however, if comorbid factors are of concern, a surveillance approach is reasonable for small tumours. For patients with advanced or metastatic disease, current systemic ther-

apies for renal cell carcinoma are very toxic with minimal gains. Patients with metastatic disease who are fit for surgery should undergo nephrectomy. Asymptomatic patients may be followed or considered for clinical trial, while patients with symptomatic disease benefit from palliative interventions, such as analgesics, bisphosphonates, embolization and/or radiation. ◆

No competing financial interests declared.

References

1. National Cancer Institute of Canada. Canadian Cancer Statistics, 2003, Toronto, Canada, 2003.
2. Heimdal K, Fossa SD. Urologic cancer in elderly patients. *Curr Opin Oncol* 1993;5:568-73.
3. Linehan WM, Zbar B, Bates SE, et al. Cancer of the kidney and ureter. In: Devita VT Jr, Hellman S, Rosenberg SA, editors. *Cancer: Principles and practice of oncology*. Philadelphia: Lippincott, Williams, and Wilkins, 2001:1362-96.
4. Skinner DG, Colvin RB, Vermillion CD. Diagnosis and management of renal cell carcinoma. A clinical and pathologic study of 309 cases. *Cancer* 1971;28:1165-77.
5. Doherty JG, Rufer A, Bartholomew P, et al. The presentation, treatment and outcome of renal cell carcinoma in old age. *Age Ageing* 1999;28:359-62.
6. Smith SJ, Bosniak MA, Megibow AJ, et al. Renal cell carcinoma: earlier discovery and increased detection. *Radiology* 1989;170:669-703.
7. Jayson M, Sanders H. Increased incidence of serendipitously discovered renal cell carcinoma. *Urology* 1998;51:203-5.
8. Bretheau D, Lechevallier E, Eghazarian C, et al. Prognostic significance of incidental renal cell carcinoma. *Eur Urol* 1995;27:319-23.
9. Homma Y, Kawabe K, Kitamura T, et al. Increased incidental detection and reduced mortality in renal cancer: recent retrospective analysis at eight institutions. *Int J Urol* 1995;2:77-80.
10. Thompson IM, Peek M. Improvement in survival with renal cell carcinoma: the role of the serendipitously detected tumour. *J Urol* 1988;140:487-90.
11. Oliver RT, Nethersell AB, Bottomley JM. Unexplained spontaneous regression and alpha-interferon as treatment for metastatic renal carcinoma. *Br J Urol* 1989;63:128-31.
12. Rendon RA, Stanietzky N, Panzarella T, et al. The natural history of small renal masses. *J Urol* 2000;164:1143-7.
13. Belldegrun A, Tsui KH, deKernion JB, et al. Efficacy of nephron-sparing surgery for renal cell carcinoma: Analysis based on the new 1997 Tumor-Node-Metastasis staging system. *J Clin Oncol* 1999;17:2868-75.
14. McDougall EM, Clayman RV. Laparoscopic nephrectomy and nephroureterectomy in the octogenarian with a renal tumor. *J Laparosc Surg* 1994;4:233-6.



Renal Cell Carcinoma

15. Yagoda A, Abi-Rached B, Petrylak D. Chemotherapy for advanced renal-cell carcinoma: 1983-1993. *Semin Oncol* 1995;22:42-60.
16. Motzer RJ, Russo P. Systemic therapy for renal cell carcinoma. *J Urol* 2000;163:408-17.
17. Steineck G, Strander H, Carbin BE, et al. Recombinant leukocyte interferon alpha-2a and medroxyprogesterone in advanced renal cell carcinoma. A randomized trial. *Acta Oncol* 1990;29:155-62.
18. Kriegmair M, Oberneder R, Hofstetter A. Interferon alfa and vinblastine versus medroxyprogesterone acetate in the treatment of metastatic renal cell carcinoma. *Urology* 1995;45:758-62.
19. Pyrhonen S, Salminen E, Ruutu M, et al. Prospective randomized trial of interferon alfa-2a plus vinblastine versus vinblastine alone in patients with advanced renal cell cancer. *J Clin Oncol* 1999;17:2859-67.
20. Fisher RI, Rosenberg SA, Fyfe G. Long-term survival update for high-dose recombinant interleukin-2 in patients with renal cell carcinoma. *Cancer J Sci Am* 2000;6 (Suppl 1):S55-7.
21. Russo P. Renal cell carcinoma: presentation, staging, and surgical treatment. *Semin Oncol* 2000;27:160-76.
22. Flanigan RC, Salmon SE, Blumenstein BA, et al. Nephrectomy followed by interferon alfa-2b compared with interferon alfa-2b alone for metastatic renal-cell cancer. *New Eng J Med* 2001;345:1655-9.
23. Mickisch GH, Garin A, van Poppel H, et al. Radical nephrectomy plus interferon-alfa-based immunotherapy compared with interferon alfa alone in metastatic renal-cell carcinoma: a randomized trial. *Lancet* 2001;358:966-70.
24. Krzyzanowska MK. Renal cell carcinoma. *Oncology Rounds* 2001;3:1-5.