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Renal cell cancer: overview and immunochemotherapy

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Introduction and epidemiology

Kidney cancer is a relatively common urological cancer, accounting for approximately 2% of all adult cancers. In the UK during 2003, 6683 new kidney cancer cases were registered [1]. Of these 4059 cases were male and 2624 cases were female making it approximately two times more common in males. In the USA, the American Cancer Society predicts that there will be approximately 51 200 new cases of kidney cancer (31 590 in men and 19 600 in women) in 2007 and some 12 890 people will die from this disease [2].

The incidence appears to be rising not only in Western societies owing to a variety of reasons, including the increased use of cross-sectional imaging [3], but also throughout the world [4]. Risk factors for kidney cancer include obesity, smoking, and hypertension [5]. Other implicated factors are environmental exposure to asbestos [6], end-stage renal disease, and hemodialysis. Long-term dialysis may result in acquired renal cystic disease, predisposing to the development of multifocal and bilateral renal cancers [7].

The histological subtypes of kidney cancers are listed in Table 1.1 and discussed in more detail in Chapter 2. This chapter, and indeed most of this book, will concentrate on adult renal cell carcinoma (RCC). Traditionally RCCs were often detected late as they can grow to a relatively large size because of their retro-peritoneal location. Now, with the widespread use of computed tomography (CT) or ultrasound scanning, many more asymptomatic RCCs are being diagnosed, resulting in a downward stage migration of the disease, with smaller and earlier stage tumors. Renal cell carcinomas are usually unilateral but can occur in both kidneys in up to 5% of cases. Renal cell carcinomas also have the tendency to grow into the renal vein, and can further propagate along the inferior vena cava (IVC) into the right atrium in up to 10% of cases with venous invasion [8].

Carcinoma of the Kidney, ed. Uday Patel. Published by Cambridge University Press. © Cambridge University Press 2008.

Table 1.1. WHO subtype classification of renal cell carcinoma (RCC)

RCC Subtype	Resected kidney cancers (%)	5-year DSS[a]	5-year PFS[b]
Clear cell	75	76	70
Papillary	10–12	86	88
Chromophobe	4–5	100	94
Oncocytoma	4–5	–	–
Collecting duct carcinomas	< 1	–	–
Sarcomatous carcinomas and other unclassified subtypes	< 1–2	24–35	18–27

[a] DSS – Disease-specific survival
[b] PFS – Progression-free survival
Source: Delahunt, 2005 [9]; Amin *et al.*, 2002 [12]

Renal cell carcinoma can also be inherited or be associated with familial syndromes. Up to 5% of RCCs fall into this category. This will only be briefly addressed here as it is discussed in detail in Chapter 3. The critical gene involved is located on the short arm of chromosome 3. This is the von Hippel–Lindau (VHL) gene and is involved in the organization of key proteins of cancer initiation and progression. The VHL gene targets the transcription factor hypoxia inducible factor-1 (HIF-1) gene for destruction. Under hypoxic conditions, the VHF gene is not expressed and thus HIF-1 levels increase. This in turn causes the production of several hypoxia response genes including pro-angiogenic factors such as vascular endothelial growth factor (VEGF) and erythropoietin (this process is discussed in greater detail in Chapter 3). The loss of the VHF tumor suppressor gene has been reported to occur in up to 50%–70% of sporadic RCCs [10,11]. This molecular etiology has led to an improved understanding of the development of RCC and the recent development of targeted agents and therapies, currently being clinically investigated.

Prognostic factors

Prognostic factors provide estimations of disease progression and survival, and help guide clinical management. For this, the TNM staging system is extensively used, based mainly on tumor size, nodal status, and presence of metastases

Table 1.2. A summary of the TNM classification of renal tumors

Kidney		Subdivisions	
T1	$\leq$ 7 cm; limited to the kidney	T1a	$\leq$ 4 cm
		T1b	> 4 cm
T2	> 7 cm; limited to the kidney		
T3	Adrenal or perinephric invasion; major veins	T3a	Adrenal or perinephric invasion
		T3b	Renal vein(s); vena cava below diaphragm
		T3c	Vena cava above diaphragm
T4	Beyond Gerota fascia		
N+	Positive nodes	N1	Single node
		N2	More than one node

(Table 1.2). It has limitations if used singularly. Methods used for staging, the TNM classification, and its issues are further discussed in Chapters 4 and 5.

Tumor histology

In a single institutional study of 405 consecutive cases, it was reported that routine light microscopic hematoxylin and eosin-based histological sub-typing using the contemporary classification scheme demonstrated prognostic utility [12]. This is summarized in Table 1.1. In this study with a median follow-up of 56 months, multivariate analysis revealed that histological type, Fuhrman's nuclear grade, TNM stage, vascular invasion, and necrosis were all significantly associated with disease-specific survival and progression-free survival rates. More recently, a larger multi-institutional center multivariate analysis of 4063 patients confirmed that TNM stage, Fuhrman grade and ECOG (Eastern Cooperative Oncology Group) performance status, but not histology, were independent prognostic factors [13].

Clinical risk stratification

Other disease characteristics often used to define patient prognosis and likelihood of therapeutic response are performance status, low tumor burden, absence of

paraneoplastic syndromes, and a long disease-free interval. In order to improve prognostic estimations, two systems have been devised by the University of California Los Angeles (UCLA) and Memorial Sloane Kettering Cancer Centre (MSKCC). Both systems include the use of clinical variables and are based on single institutional experience. The UCLA system was based on 670 patients from 24 trials and the MSKCC system used 814 patients in 11 trials. In the UCLA system, five stratification groups were proposed based on the 1997 TNM staging system, Fuhrman grade and ECOG performance status, with projected 5-year survivals of 94% for Group I, 67% for Group II, 39% for Group III, 23% for Group IV, and 0% for Group V [14]. This system was subsequently modified so as to group cases into three different risk groups according to localized or metastatic disease at presentation [15]. The validity of the UCLA system was subsequently assessed in an international multi-institutional analysis of 4202 patients [16]. This analysis revealed that the 5-year survival rates for localized RCC were 92%, 67%, and 44% for low, intermediate, and high risk groups, respectively. For the metastatic RCC group, the 3-year survival rates were 37%, 23%, and 12% for low, intermediate, and high risk groups, respectively. There was an observed trend toward a higher risk of death with increasing risk category. This study confirmed the good concordance of the UCLA system with other institutional databases and that it was an accurate predictor for patients with localized RCC. However, for the metastatic disease group it was less accurate because of patient heterogeneity and variability of treatments.

The MSKCC system for advanced RCC identified five negative prognostic factors by multivariate analysis: Karnofsky performance status $< 80\%$, lactate dehydrogenase levels > 1.5 times normal limits, serum hemoglobin below the normal range, elevated corrected serum calcium levels, and the absence of prior nephrectomy [17]. These factors were used to categorize cases into one of three risk groups, with the best-outcome group having no risk factors; the intermediate risk group having 1–2 risk factors; and the poor risk group having > 2 risk factors. The median survival times for the favorable, intermediate, and poor risk groups were 22, 11.9, and 5.4 months, respectively [18]. In addition, the use of cytokine therapy appeared to double the median survival time regardless of risk category compared to the use of chemotherapy or hormonal therapy [19].

A more recent report of localized non-metastatic RCC reviewed four prognostic models: the Kattan model, the UCLA integrated staging system model, the Yaycioglu model, and the Cindolo model [20]. This study of 2404 patients from six European centers reported that all four models discriminated well for overall survival, cancer-specific survival, and disease recurrence free survival ($P < 0.0001$)

with postoperative models discriminating better than preoperative ones, and the Kattan model being consistently the most accurate. In addition, the Kattan model was also noted to be useful in identifying the intermediate-risk patients described by the UCLA system.

Prognostic biomarkers

Whilst clinical systems are useful, another potential avenue for prognostication and response assessment is the identification of reliable predictive biomarkers. Several biochemical and molecular markers have been proposed including p53, CD-44, CD-95, B7-H4, pAkt, adipose differentiation-related protein, gamma-enolase, IMP3, Ki67, and G250/CAIX. The carbonic anhydrase isoenzyme (CAIX) appears to have a role in cellular adhesion and proliferation via growth factor receptor dependent pathways and has been suggested to be an independent prognostic marker for survival in metastatic RCC, when assessed in a cohort of 321 cases [21]. The predictive value of CAIX could be further enhanced using Ki67 for sub-stratification [22] since an inverse relationship exists between these two factors [22]. Multivariate analysis of 224 cases suggested that the combined use of CAIX and Ki67 can stratify cases in low, intermediate, and high risk groups with median survival times of > 101, 31, and 9 months, respectively ($p < 0.001$). These biomarkers appear promising but need to be validated in clinical trials.

Management of RCC

The median age of patients presenting with RCC is 60 years. At diagnosis, only 30%–40% have localized disease whilst 25%–30% will have metastatic cancer [23]. A further 30%–40% of patients are likely to develop metastatic disease during follow-up and the clinical course can be extremely variable [24]. Metastatic disease can be resistant to conventional forms of systemic therapy such as chemotherapy but spontaneous remissions are possible. These patients can experience substantial morbidity from their metastatic disease. Mortality is approximately 30%–50% and the median survival time of patients with metastatic disease is only about 12 months [25].

Localized RCC: the role of surgery

The gold standard for localized RCC is surgery. Traditionally a radical nephrectomy was the standard procedure and was performed through a variety of surgical

approaches; but in recent times laparoscopic techniques and minimally invasive ablative approaches have radically changed the surgical arena for RCCs. The open surgical approaches are now usually reserved for larger tumors (> 7–8 cm) or tumors that are locally extensive, or have invaded the renal vein or IVC. Following complete resection in a single center series of 1737 T1–3N0M0 cases, the incidence of renal bed recurrence was $< 2\%$; aggressive surgical management of these cases results in long-term disease-free survival [26].

For patients with smaller lesions, laparoscopic nephrectomy or partial (nephron sparing) nephrectomy is becoming the standard of care. It is anticipated that laparoscopic procedures can reduce the length of in-hospital stay, with better recovery for comparable local control and complication rates. Robotic technology is now being used in laparoscopic approaches and its relative value is being assessed. In addition, when surgical approaches are not feasible, minimally invasive ablative methods such as cryotherapy and radiofrequency ablation may be used. The clinical criteria for considering these procedures with their relative merits are discussed in Chapters 8 and 9.

Localized RCC: the role of radiotherapy

Radiotherapy has a limited role in the primary management of RCC. However, it has been considered as either a preoperative or adjuvant measure to reduce the risk of local recurrence following the resection of large and advanced RCCs. Early retrospective studies suggested a survival benefit [27,28,29,30] and two randomized trials have addressed the value of preoperative radiotherapy, and two more randomized trials have assessed adjuvant radiotherapy.

For preoperative radiotherapy, both studies did not demonstrate any difference in 5-year overall survival rates [31,32]. Criticisms of these trials include the small number of patients, the sub-therapeutic radiation dose used, and the inclusion of T1N0 cases where additional local therapy is unlikely to be beneficial. The two randomized trials of adjuvant radiotherapy used more appropriate radiation doses but did not demonstrate any survival benefit [33,34]. At 5 years, the overall survival rate in the UK trial of 100 cases was 36% for the combined therapy arm, compared to 47% with surgery alone [33]; whilst the Danish trial of 65 cases reported a 5-year survival rate of 38% with the combined treatment arm compared to 64% after surgery alone [34]. Other issues with these two trials include the inclusion of early stage cancers, inconsistent reporting, and protocol violations.

It is clear that all these four randomized trials were small – too small to detect any clinically meaningful difference in overall survival. More importantly, there is some concern that the combined therapy arms were associated with a lower survival rate with substantial radiation-related toxicity. Excess toxicity may be caused by the outdated radiotherapy methods, now recognized to be unsuitable for high dose regimes, as well as the little regard paid to bowel irradiation.

Although there are no randomized data to support the use of radiotherapy for unresectable primary disease, postoperative residual disease, or local recurrence following surgery, it is reasonable to consider its use when there are no other treatment options. Radiotherapy may be used as a primary therapy for palliation, or to prevent disease progression or infiltration into surrounding normal tissues or critical adjacent structures. Radiotherapy may also be considered for cases of local recurrence that are unresectable; recurrences that have occurred following a second resection; or those not amenable to other local treatments, with the same intention of preventing severe or troublesome local symptoms from local tumor invasion.

Furthermore, modern radiotherapy techniques can now deliver higher doses with a more acceptable side-effect profile. These new techniques involve the 3D-shaping of the treatment beam (conformal radiotherapy [CFRT]) which tailors the radiotherapy fields to the patient and can substantially reduce the dose to surrounding structures (Figure 1.1). In addition, further advances in radiotherapy technique such as intensity modulation of radiotherapy (IMRT) beams can permit high doses to be "painted" to selected regions of the tumor target. Thus IMRT can better conform the prescribed radiation dose to very irregular or concave shapes compared to CFRT techniques. Other recent advances in radiotherapy include charged particle therapy using protons and light-ions. Particle therapy may provide an improved dose distribution and light-ion therapy may confer a higher biologically effective dose for a better therapeutic ratio. These new techniques are currently being evaluated. Together with the use of image-guided radiotherapy (IGRT), these new techniques may change the place of radiotherapy for the treatment of RCCs, which is otherwise limited.

Metastatic RCC: the role of surgery

The value of nephrectomy in the metastatic setting also continues to generate debate. Two prospective trials randomizing patients to receive immunotherapy alone or post-nephrectomy have been undertaken. Both trials were relatively small.
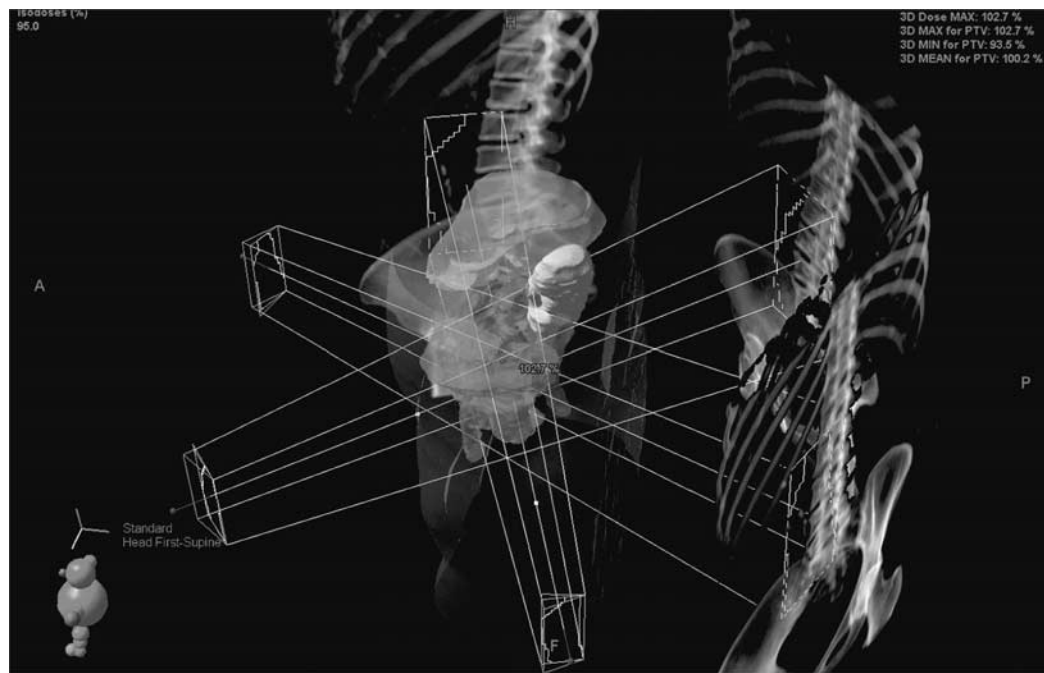
Figure 1.1 Conformal radiotherapy treatment for a postoperative renal bed recurrence. Each treatment beam has been shaped to the profile of the tumor volume within the orientation of the projected treatment beam. This shaped treatment field is then projected onto the outline of the patient's axial skeleton for further illustration of the conformal field shapes. The target volume (near cylindrical shape) is located centrally and is denoted by the pink outline (see also color plate section).

A European trial of 83 patients reported that nephrectomy followed by interferon-alfa-based immunotherapy improved the time to disease progression (5 versus 3 months, hazard ratio 0.60) with better median survival (17 versus 7 months, hazard ratio 0.54) compared to those treated with interferon-alfa alone [35]. In the larger American Southwest Oncology Group (SWOG) study of 241 patients, the median survival time of those undergoing surgery, followed by interferon-alfa therapy, was 11.1 months compared to 8.1 months in those receiving immunotherapy alone ($p = 0.05$) [36]. In this study, the difference in survival was independent of performance status and metastatic site but the median survival times were relatively poor in both study arms, making interpretation more difficult compared to the European study. However, it is generally accepted that a debulking nephrectomy should be considered when the operative risks are acceptable, when palliation from unrestricted growth of the primary tumor is necessary, and if subsequent

immunotherapy is feasible. What is currently uncertain is whether debulking nephrectomy remains of additional benefit in those treated with the novel targeted therapies (discussed below).

Metastatic RCC: the role of radiotherapy

Conventionally, RCC has been considered a relatively radio-resistant tumor but clinical experience and retrospective data have demonstrated that a proportion of renal tumors can be radio-responsive. It is particularly effective in the palliation of symptomatic metastatic disease and the prevention of progressive disease in critical sites, such as in the spinal cord and brain. For example, radiotherapy can provide palliation in 67%–77% of patients suffering from symptomatic bony metastases [37,38]. Radiotherapy can be used alone or in combination with surgery.

Metastatic RCC: the role of chemotherapy and hormonal therapies

Renal cell carcinoma remains relatively resistant to both chemotherapy and hormonal therapies. Conventional chemotherapy agents have proved disappointing, with response rates ranging between 6% and 15%. A recent review of over 4000 patients in 83 trials treated with a variety of cytotoxic regimes revealed an overall response rate of only up to 6% [39]. Whilst some durable responses have been reported, in general the median survival times remain unchanged.

Metastatic RCC: the role of immunotherapy

Immunotherapy has been used with more success than conventional cytotoxics but the results are also disappointing. The use of interferon-alfa and high-dose interleukin-2 have been analyzed in a Cochrane review, with a more recent update, in 2007, that identified 58 randomized controlled trials with 6880 patients, comparing immunotherapy with non-immunotherapy controls [40,41]. There are no reported survival data published from randomized studies of high-dose interleukin-2 versus a non-immunotherapy control or interferon-alfa. This issue is currently under evaluation in the UK-led trial RE-04, comparing interferon-alfa alone versus interferon-alfa, interleukin-2 and 5-fluorouracil. This study has just completed recruitment with 1106 patients, and will be reported in the future [42].

The Cochrane reviews outline that immunotherapies provided an overall remission rate of 12.4% compared to only 2.4% in the non-immunotherapy controls,

and 4.3% in the placebo arms [40,41]. Of the remissions, approximately 28% were complete; but the remission did not independently predict for survival. However, the use of interferon-alfa is superior to non-immunotherapy controls, with a pooled hazard ratio (HR) of 0.74 (0.63–0.88), resulting in a weighted average median improvement in survival of 2.6 months. The median survival time was 13 months (range 6–28 months) and the 2-year survival averaged 22% (8%–41%). The Cochrane reviews also noted that the use of either low dose intravenous or subcutaneous interleukin-2 with interferon-alfa did not improve survival compared to interferon-alfa alone. The optimal duration and dose of interferon-alfa remain to be determined.

Metastatic RCC: the role of targeted therapies

Given the modest improvement in survival from immunotherapy, newer approaches have now been directed to potential molecular targets, following the example of the anti-vascular endothelial growth factor (VEGF), bevacizumab, in colorectal cancer [43].

The process of tumor growth and dissemination is reliant on new vascular growth or angiogenesis, and VEGF has an established role as one of the key regulators of this pathway. It has been previously outlined that the HIF-1/VEGF axis is over-expressed in subsets of RCC, particularly in sporadic clear cell RCCs. Thus inhibiting VEGF receptors via their tyrosine kinases has recently been shown to provide substantial anti-tumor activity. One of the first randomized double-blind phase 2 trials comparing bevacizumab versus placebo was stopped early when the trial termination rules were met [44]. This study used two different doses in the active arms of bevacizumab at 3 mg/kg and 10 mg/kg, with the higher dose arm significantly prolonging the time to progression of disease (HR 2.55, $p = < 0.001$). Progression-free survival at 8 months was 30%, 14%, and 5% for the high dose, low dose, and placebo arms respectively, but overall survival was similar between the groups.

Sorafenib (BAY 43–9006) is a small molecule targeted at tyrosine kinase receptor domains including VEGF-2, VEGF-3, FLT3, PDGF, and c-KIT [45]. A recent double-blind, placebo-controlled trial of 903 patients who failed standard therapy, randomized patients to either sorafenib (oral dose of 400 mg twice-daily) or placebo [46]. The first planned interim analysis revealed that sorafenib provided improved median progression-free survival of 5.5 months versus 2.8 months in the placebo group (HR 0.44; CI 0.35 to 0.55; $p < 0.01$) and reduced the risk of death (HR 0.72; CI 0.54 to 0.94; $p = 0.02$). The best responses were partial responses in 10% of