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Metastatic Renal Cell Carcinoma: Pathogenesis and the Current Medical Landscape

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Article info

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Abstract

Context: Renal cell carcinoma (RCC) represents a worldwide epidemiologic burden. Patients with metastatic disease usually have poor prognosis, and traditional treatments are often ineffective.
Objective: This review describes the epidemiology and pathogenesis of metastatic RCC (mRCC) and highlights the unmet clinical need for effective, targeted treatments.
Evidence acquisition: Medical literature was retrieved from PubMed during January 2009. Additional relevant articles were included from the bibliographies of retrieved literature.
Evidence synthesis: There were approximately 200 000 new kidney cancer cases worldwide in 2002, and the disease's incidence is increasing in the United States and parts of Europe. The occurrence of RCC can be either sporadic or familial, and risk factors include smoking, obesity, and hypertension. RCC can be asymptomatic, and 25–30% of patients will present with metastatic disease at the time of diagnosis. Patients with mRCC usually have a poor prognosis, and estimates for their 5-yr survival range between 0% and 20%. Traditional therapies—namely, cytokines or chemotherapy—have limited efficacy in the majority of patients. Recently, the emergence of novel targeted therapies has provided new treatment options with increased efficacy. Clinical trials with these agents have highlighted a need to accurately assess activity and efficacy end points such as progression-free survival, which may be a useful surrogate for overall survival.
Conclusions: Despite substantial progress in our understanding and treatment of mRCC in recent years, its incidence is increasing, and the disease is still considered incurable. The increasing accuracy of diagnosis and prognosis and the development of novel targeted agents are vital for the effective management of mRCC.

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1. Introduction

There were approximately 200 000 new kidney cancer cases worldwide in 2002, and renal cell carcinoma (RCC) accounts for approximately 90% of renal tumours [1,2]. Furthermore, 25–30% of patients present with metastatic disease at time of diagnosis [3]. In recent years, there have been a number of breakthroughs in the treatment of metastatic RCC (mRCC). Insights into the biology and genetics of the disease have led to the introduction of several new, targeted therapies. This article discusses the epidemiology and unmet medical need of mRCC as well as addressing some

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of the issues in achieving an accurate prognosis and assessing response to therapy in the context of current management approaches to treatment.

2. Evidence acquisition

Medical literature was retrieved from PubMed during January 2009. Additional relevant articles were included from the bibliographies of retrieved literature.

3. Evidence synthesis

3.1. *Epidemiology*

The worldwide incidence of RCC has increased in the past 3 decades [4], and its frequency is higher in men than in women [3]. In the European Union, there were an estimated 63 300 new cases of kidney cancer and 26 400 kidney cancer–related deaths in 2006 [5], with estimates from the United States for 2008 of 54 390 and 13 010, respectively [6]. However, there has been a decrease in the incidence rate of kidney cancer in some European countries in recent years, and overall mortality rates have also fallen (peak of 4.8 deaths per 100 000 people in 1990–1994 for males compared with 4.1 deaths per 100 000 people in 2000–2004 and 2.1 deaths per 100 000 people in 1990–1994 for females compared with 1.8 deaths per 100 000 people in 2000–2004) [7]. In the United States, mortality rates associated with primary renal cancers have increased considerably since 1973 (Fig. 1), particularly in patients with large tumours. Small tumours are often successfully treated, and 5-yr relative survival rates have improved over time for patients diagnosed with RCC, from 56.4% (diagnosed during 1983–1987) to 68.9% (diagnosed during 1998–2002) [8]. However, total mortality rates in patients with renal tumours increased from 1.5 deaths per 100 000 US population in 1983 to 6.5 deaths per 100 000 US population in 2002, with the greatest increase noted for patients with tumours >7 cm [9]. Although surgical excision is usually the primary treatment for localised renal tumours [2], 20–30% of patients undergoing nephrectomy will experience relapse and develop metastasis [2,10]. In terms of incidence, data specific to mRCC are lacking but can be estimated from findings in non-mRCC (Table 1) [3]. The incidence of RCC and the drastically reduced survival associated with metastatic disease impose a serious worldwide epidemiologic burden [3]. This disease is associated with an economic (resulting from medical, morbidity, and mortality costs) and a quality-of-life (QoL) burden (based on physical, psychological, and social criteria) [3].

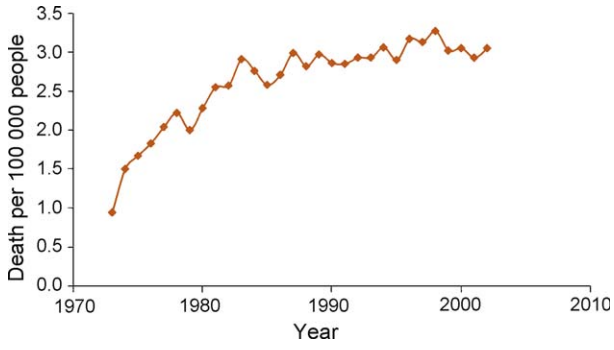

Fig. 1 – Renal cell carcinoma (RCC) mortality rates per 100 000 people in the United States. Patients diagnosed with a first, primary RCC during 1973–2002 were included. Adapted from Chow et al [8], based on data from the nine Surveillance, Epidemiology, and End Results registries.

Table 1 – Global incidence of metastatic renal cell carcinoma (mRCC) in men and women, adapted from Gupta et al [3]. Incidence of mRCC was estimated from the renal cell carcinoma (RCC) data using the assumption that 27.5% of patients with RCC will develop mRCC. Data were derived from the International Agency for Research on Cancer GLOBOCAN 2002 database [1]. Reproduced with permission from Elsevier [3]

Country	Total cases	Male incidence		Female ncidence	
	No.	Cases	Rate*	Cases	Rate*
Europe					
Belgium	311	189	3.8	122	2.3
Denmark	170	105	4	65	2.4
Finland	181	98	3.9	83	3.1
Germany	3026	1883	4.7	1143	2.7
Italy	1919	1302	4.7	617	2.1
Portugal	168	110	2.3	58	1.1
Spain	955	649	3.3	306	1.5
Sweden	273	159	3.7	114	2.6
UK	1495	931	3.2	564	1.9
Australia and Asia					
Australia	584	360	3.7	224	2.3
Japan	2509	1576	2.5	933	1.4
Korea (Republic of)	411	285	1.2	126	0.5
Singapore	51	33	1.6	18	0.9
South America					
Argentina	672	462	2.5	210	1.1
Brazil	966	532	0.6	434	0.5
North America					
Canada	901	573	3.7	328	2.1
Mexico	817	440	0.9	377	0.7
US	8567	5478	3.9	3089	2.1

*Rates indicate the estimated number of new cases per 100 000 people per year.

RCC usually affects individuals aged >50 yr, and cigarette smoking and obesity are identified as the strongest risk factors, with hypertension and family history also contributing to the overall risk profile [11]. In a recent study [12], the association between RCC and smoking was shown to be independent of von Hippel-Lindau (VHL) mutations that are a common early event in sporadic RCC.

3.2. *Histologic subtypes*

The occurrence of kidney cancer can be either sporadic or familial [13], and having a first-degree relative with kidney cancer is associated with an increased risk of RCC [14,15]. Kidney cancer is not a single disease, and cases can be grouped into distinct histologic subtypes: clear cell, papillary (types 1 and 2), chromophobe, collecting duct, and medullary [16]. Clear-cell carcinomas account for the majority (75%) of RCC cases [17].

Approximately 4% of RCCs are inherited; they usually present at an early age and are bilateral. The four main types of hereditary RCC have the following genes associated with them: VHL is associated with the inherited form of clear-cell RCC, the c-Met proto-oncogene with papillary type 1 RCC, the Birt-Hogg-Dubé gene with chromophobe RCC, and fumarate hydratase with papillary type 2 (leiomyomatosis RCC) [16]. The best studied of these inherited forms is clear-cell RCC associated with VHL syndrome. Interestingly, the VHL gene is also mutated in a large proportion of sporadic noninherited RCCs. Novel targeted therapies, directed specifically against molecular components of aberrant signalling pathways associated with specific mRCC subtypes, represent an important advance towards treating this disease [16]. These approaches are particularly relevant in patients for whom surgery may not be an appropriate first-line treatment or when patients undergoing nephrectomy have relapsed after surgery.

3.3. *Unmet medical needs in the treatment of metastatic renal cell carcinoma*

Until recently, few treatment options were available for mRCC. The estimated 5-yr survival for patients with mRCC ranged between 0% and 20%, and the objective response rate (ORR) with chemotherapy was low [18–20]. Higher ORRs were reported with interferon alpha (12%) as well as with high-dose interleukin-2 (19%) [19]. However, in patients who failed to respond to cytokine-based or other systemic therapies, the overall median survival was only 10.2 mo, or 12.7 mo for patients treated after 1990 [21].

In recent years, basic research into the molecular basis of tumourigenesis in RCC has led to the development of agents, including sorafenib, sunitinib, bevacizumab, temsirolimus, and everolimus (RAD001), that inhibit key proteins involved in angiogenesis, which is a critical driver of tumour progression [22–26]. These novel therapeutic agents provide a valuable alternative to cytotoxic agents or immunotherapies and have demonstrated positive efficacy and tolerability in patients with this notoriously treatment-resistant tumour. These advances are encouraging, but predicting outcomes in RCC remains a daily challenge for treating physicians; in certain subsets of patients, tested algorithms remain unsatisfactory for clinical decision making. New prognostic factors and predictive strategies are still required to ensure that patients receive the best RCC clinical management possible.

3.4. *Diagnosis and prognosis*

Patients with advanced RCC can often present with flank pain, flank mass, and haematuria. Subsequent diagnosis is usually made using ultrasound to image the renal mass, followed by an eventual computed tomography–guided biopsy of the kidney or cytoreductive nephrectomy. Other frequent presenting features may include fatigue, weight loss, or anaemia. RCC can also be asymptomatic, and detection often occurs after a renal mass has been incidentally identified on radiographic or ultrasound examination. Because of the increasing use of these imaging methods in recent years, earlier and incidental detection of RCC has increased, resulting in the detection of smaller tumours. These small-scale tumours are good candidates for precise surgical interventions involving nephron-sparing techniques [2]. Disease stage is closely related to prognosis, and its identification is vital for selecting the most appropriate therapy as well as for effective counselling of patients. Defining the extent of disease by staging for RCC has evolved from the Robson classification system into the TNM system, developed by the International Union Against Cancer and the American Joint Committee on Cancer (AJCC) [27]. The TNM system provides a more defined description of the tumour, area and extent of invasion, and degree of vascular involvement than the original Robson classification [27]. Using these criteria for tumour staging, RCC cases can be grouped into four different stages [2]. Patients with stage I–III tumours will primarily undergo surgical excision, although a subset of elderly or infirm patients with small tumours may be offered less invasive treatments or surveillance alone. Stage IV RCC represents patients who either present with metastasis or in whom metastatic disease later develops. Surgery can still be an option for patients with stage IV RCC, depending on the extent and site of the metastasis, but the outlook for these patients is often dismal. Estimated 5-yr survival rates in patients with RCC presenting with stage I, II, III, and IV disease are 96%, 82%, 64%, and 23%, respectively [2].

3.5. *Prognostic factors*

Numerous prognostic factors associated with clinical outcome in mRCC have been identified during trials with cytokines or chemotherapy, including performance status; time from diagnosis to therapy; number of metastatic sites; liver metastasis; and haemoglobin, serum calcium, and lactate dehydrogenase levels [21,28,29]. Prognostic models derived from these factors have greatly improved prognosis and subsequent patient counselling [28–30]. However, predicting survival for patients with RCC using currently validated models—in particular, the AJCC and the University of California, Los Angeles Integrated Staging System (UISS) [31,32]—has become increasingly difficult as surgical standards of care evolve and treatment options broaden, highlighting the need for modern prognostic alternatives. A nomogram, proposed by investigators in Canada and Europe to address the survival of patients [33], showed an improvement of approximately 3% in the predictive accuracy in an internal comparison with the UISS algorithm for predictions at 2 yr and 5 yr. However, this improved nomogram, while representing an important step forward in reconciling changing practice patterns with strategies for predicting disease-specific survival, continues to be substantially informed by patients treated before the widespread implementation of laparoscopic nephrectomy and targeted therapies.

Inflammation markers have also been identified as prognostic factors for predicting progression-free survival (PFS) in patients treated with nephrectomy or a vascular endothelial growth factor (VEGF)–targeted agent [34,35].

Furthermore, a prognostic nomogram specifically assessing response to treatment with sunitinib in patients with mRCC has been developed based on clinical pretreatment factors [36]. The aim of this and other prognostic nomograms is to assess accurately the probability of successful treatment and eventual tailoring of specific therapies to individual patients. Although these nomograms are based primarily on clinical factors, future prognostic analyses are likely to incorporate the use of biomarkers to help predict survival more accurately, identify patients most likely to benefit from treatment, and assess response to ongoing therapies. In particular, serum levels of VEGF and soluble VEGF receptor-2 and their correlation with response to VEGF-targeted therapy have been measured [37,38].

3.6. *Efficacy end points*

ORRs, determined by using Response Evaluation Criteria in Solid Tumors, are frequently used as secondary clinical end points in phase 3 trials. However, the gold-standard clinical benefits for patients with cancer are prolongation of life coupled with improvements in QoL. Although the ultimate achievement of increased overall survival (OS) remains the goal for new agents in oncology, the demand for rapid evaluation and early availability of agents that have shown substantial activity in mRCC is increasing. This has led to the incorporation of surrogate end points for OS in clinical trials, which are gaining acceptance in oncology. For example, PFS is becoming an increasingly important end point in oncologic drug development. This is due, in part, to the growing use of "crossover" trial designs that allow patients to switch to the alternate randomised therapy upon disease progression, which can have a serious confounding effect on OS [39]. The confounding effect of allowing patients with mRCC progressing on placebo to cross over to active treatment was demonstrated in trials involving sorafenib, bevacizumab, and everolimus [22,24,40,41]. The use of PFS as a surrogate for OS has gained acceptance in advanced ovarian cancers, especially in the first-line setting [42], but the correlation between disease-free survival (DFS) and OS in adjuvant studies in breast cancer has been inconsistent [43]. In mRCC, recently published phase 3 trials provide reasonable evidence for a potential correlation between PFS and OS that helps support the use of PFS as a potential surrogate end point for OS [23,26,40,44,45]. PFS can be an appropriate measure of clinical outcome in certain settings, and its use is reasonable when ethical considerations require crossover of placebo recipients to the active agent [46].

3.7. *Management strategies for the clinician*

Although several active agents are now available to treat mRCC, they are associated more with disease stabilisation than with durable complete responses; therefore, the majority of patients will require chronic therapy. The clinician must maximise overall therapeutic benefit for each patient by delaying a life-threatening burden of disease for as long as possible while maximising QoL and patient convenience.

Several factors are important in selecting the most appropriate therapeutic agent, namely, proven efficacy for PFS and tumour shrinkage, safety and tolerability, QoL benefits, and characteristics of both the tumour and the patient. Moreover, clinical benefits of any therapy depend on the patient's compliance with the regimen. A subset of mRCC patients has low-volume, slow-growing disease. For these patients, delaying the initiation of systemic therapy may more successfully achieve the overall goal of controlling tumour burden and maximising QoL.

In the management of treatment-related adverse events (AEs), patient education is essential to avoid serious consequences. The newly available targeted therapies for mRCC, being self-administered, empower patients to take control of their own treatment. Therefore, clinicians and other health care providers have a responsibility to ensure that patients are sufficiently educated to be in a position to obtain the optimal benefits from any treatment they receive. Educational materials such as videos and other illustrative aids should be used to reinforce best practice and may also help patients recognise particular AEs, which will hasten their identification and management. Materials should also be tailored to suit a range of educational abilities. Furthermore, patient diaries should be encouraged as a source of information that can help clinicians track and manage AEs and optimise compliance.

Although clinicians now have the chance to offer patients with mRCC a better prognosis than may have been possible only a few years ago, several key issues need to be resolved before clinicians are able to maximise the potential of currently available agents in clinical practice. These include being able to identify those patients who are most likely to derive benefit from multitargeted therapy, understanding how and when to use combination or sequential therapies, and clarifying whether there is a role for novel therapeutic agents as adjuvant therapy.

4. Conclusions

Substantial advances have been made recently in both the biology and clinical science of RCC. However, though advances in the detection and management of mRCC have improved prognosis in recent years, the incidence of RCC continues to increase and, at present, mRCC is still considered incurable. The development and approval of novel targeted agents have revolutionised treatment of mRCC over the past decade by demonstrating clinically useful benefits over the previous standard of care [39]. It will be important to validate surrogate end points such as PFS for determining clinical benefit in RCC patients treated with targeted therapies [47].

Clinicians are continually challenged as to how best to provide patients with the most appropriate therapy for improving the overall therapeutic benefit of different treatments. Key goals include identifying markers of disease, prognosis, and patients' response to treatment.

Conflicts of interest

Professor Bracarda has been an Advisory Board Member for Bayer-Schering Pharma, GlaxoSmithKline, Novartis, Pfizer, Roche, and Wyeth and has received honoraria from Novartis. The author did not receive an honorarium or consultancy fee for writing this manuscript.

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