The Metastatic State of Renal Cell Carcinoma

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1 Epidemiological facts for RCC

Renal cell carcinoma (RCC), tumors of the renal parenchyma that arise from the renal cortex, is considered a heterogeneous group of cancers with regard to its pathological and clinical features. RCC accounts for 2–3% of all adult malignancies and approximately 85–90% of all malignant kidney tumors. Males are more frequently affected (3:2 ratio) with the highest prevalence recorded in the sixth and seventh decade of life with a higher incidence in North America and the Nordic countries. The incidence and mortality of kidney cancer have continuously increased during the last 50 years in the USA and Western Europe (Pantuck et al., 2001). In 2008 approximately 271,000 new cases of renal cancer were diagnosed (Ferlay et al., 2010). The incidence of renal cancer is increasing by around 2% per year, a fact that is mainly attributed to the abundant use of imaging studies and the resultant incidental diagnosis of usually small renal tumors (Ferlay et al., 2007).

In the European Union (EU) countries approximately 88,400 new cases of RCC occurred in 2008, with an almost 2:1 male to female ratio (56,000 male and female 32,000) According to the European Committee of cancer, in 2009 the prevalence of renal cancer was 14.5 (N = 40,395) for men and 6.9 (N = 24,656) for women. The highest prevalence of RCC was observed in countries of the Eastern Europe (Lithuania, Estonia, Latvia, Czech Republic) compared to Western and Northern European countries (Romania, Portugal, Switzerland, Spain, Portugal, Netherlands, Denmark, Sweden, Switzerland) (Levi et al., 2008; Ferlay et al., 2010). Although an increase in RCC has been observed globally during the last decades, in recent years RCC incidence is declining in some European countries, namely, Sweden, Poland, Finland, and the Netherlands (Karim-Kos et al., 2008).

In the USA, RCC is the seventh most common cancer in men. In 2010, 58,000 cases were diagnosed and 13,000 deaths were attributed to renal cancer. The prevalence of the disease in the USA has increased since the ‘70s on average by 30% for the white population and 40% for the African American population (Tripathi et al., 2006). Currently one third of patients are diagnosed with locally invasive or metastatic kidney while another 25% of patients will experience tumor recurrence following what was at the time considered curative radical nephrectomy for localized disease (Gupta et al., 2008; Athar & Gentile, 2008). The median time to relapse after nephrectomy is 15–18 months. Renal cancer has a strong tendency to metastasize following occasionally unpredictable patterns of spread.

RCC has the worst cancer-specific mortality among urologic tumors since more than 40% of the patients with RCC die of the disease, opposite to the 20% mortality observed in prostate or bladder carcinoma (Athar & Gentile, 2008; Pascual & Borque, 2008). Generally patients with metastatic RCC have on average 13 months of survival and the five-year survival rate is under 15% (Cohen & McGovern, 2005; Rini et al., 2009).

2 Diagnosis and Imaging in RCC

The widespread use of cross-sectional imaging during the last years has resulted in great changes in both the diagnosis and management of RCC. Most of the cases of RCC are currently diagnosed due to imaging studies performed for mainly unrelated reasons. As a result, what was once considered the classic the triad of presenting symptoms for renal cancer (hematuria, flank pain, palpable mass) is nowadays a rare finding and is almost exclusively seen in advanced disease (Ng et al., 2006). Other non-specific systemic symptoms of advanced disease include asthenia, weight loss, anorexia, fever and symptoms or conditions
that fall into the category of paraneoplastic syndromes like Stauffer's syndrome, a reversible hepatic dysfunction associated with advanced RCC. Symptoms of metastatic renal cell carcinoma include: pain, stiffness, bruit, and pathologic fracture due to bone metastases; abdominal pain, jaundice, elevations in AST and ALT, and vomiting due to liver metastases, cough, dyspnea, and abnormal chest radiograph in cases of lung metastases. Brain metastases produce diplopia, personality changes, headache, ataxia, vertigo, and seizures. A challenge in renal tumoral imaging is to differentiate benign from malignant lesions but furthermore to have an accurate delineation of the extent of the tumor for optimal treatment planning. The best scanning protocol is the one that include unenhanced CT followed by imaging during the corticomedullary and nephrographic phases of enhancement. The unenhanced images place a baseline from which to measure the amount of enhancement of the lesion. The best stage to detect the renal lesion is the nephrographic but the corticomedullary is more appropriate for imaging the renal veins for possible extension of the tumor and the other organs for potential metastases (Sheth et al., 2001). Several studies confirm a 85 – 90% accuracy in T staging, up to 50% for N stage and approaching 100% for M stage disease (Türkvatan et al., 2009; Liu Y et al., 2012).

3 Histotypes of RCC

The historical Heidelberg classification identified four main histologic subtypes of RCC with distinct characteristics relevant to their microscopic morphology, karyotype and genomic alterations: clear cell RCC (60 – 80%), papillary RCC (10 – 15%), chromophobe (approximately 5%) and collecting duct carcinoma (1 – 2%) (Kovacs et al., 1997) Only recently were other rare subtypes (all composing < 1% of RCC cases) included in this list, mucinous tubular and spindle-type RCC, as well as tubulocystic and translocation-linked carcinomas (Yang et al., 2010; Medendorp et al., 2007; Argani & Ladanyi, 2005).

Clear cell renal cell carcinomas (ccRCC) which comprise the vast majority of RCCs are usually well delineated and centered on the renal cortex. In less than 5% of cases multiple satellite tumor nodules are seen throughout the kidney (Kinouchi et al., 1999). A typical case of clear cell RCC is macroscopically characterized by a solid golden-yellow appearance on cut surface, with a distinct fibrous pseudocapsule sharply separating the tumor from surrounding normal renal parenchyma. Microscopically ccRCC cells are large, with their cytoplasm appearing optically clear to deeply granular. The clear cell appearance of ccRCC cells results from the accumulation of glycogen and fat (Fleming & O’Donell, 2000).

Papillary RCC is the most usual histotype of RCC to arise in patients under chronic dialysis. It is characteristically hypovascular on imaging studies and may exhibit areas of necrosis (Renshaw & Corless, 1995). Although papillary RCC is currently regarded as a distinct subtype, it should not be considered a homogeneous group of tumors since morphologically it comprises of solid variants, variants with rare papillae and variants with clear cell cytoplasm (Renshaw et al., 1997).

Chromophobe RCC is grossly well-circumscribed, with a homogeneous gray to brown cut surface. Microscopically tumor cells are arranged in nests and have sharply defined borders and abundant pale cytoplasm. The pale cytoplasmic appearance is caused by the presence of cytoplasmic vesicles that stain positive for Hale colloidal iron (Bonsib, 1996). Chromophobe RCC has a high tendency for sarcomatoid transformation, probably more than any other RCC subtype (Akhtar et al., 1997). However the most clinically important issue with chromophobe RCC is its close relationship with oncocytoma. Due to the fact that those two tumors have distinctly different prognosis it is imperative that a distinction between them
be attempted. This distinction is possible in the majority of cases based on the different morphologic features coupled with the Hale colloidal iron stain (Cochand-Priollet et al., 1997). The prognosis for chromophobe RCC is better than that of conventional ccRCC, although distant metastases are not uncommon especially in the face of coexistent papillary component or sarcomatoid transformation (Amin et al., 2008).

Collecting duct carcinoma, also known as Bellini’s duct carcinoma is thought to arise from collecting (Bellini) ducts (Rumpelt et al., 1991). This histotype is more common in younger males, usually centers in the medulla and is surrounded by a characteristic desmoplastic reaction. The clinical course is extremely aggressive and prognosis is very poor with the majority of patients having distant metastases at the time of diagnosis (Srigley & Eble, 1998).

Sarcomatoid RCC is usually an extremely aggressive tumor with a grade IV cytology (Wang et al., 2009). Extrarenal invasion as well as multiple osseous metastases is the rule since the sarcomatoid component of the tumor differentiates in the direction of cartilage and bone. The morphologic appearance of the epithelial component (when present) is usually in keeping with a proximal tubular origin as in ccRCC while some of the cases represent sarcomatoid variants of collecting duct carcinomas, papillary carcinomas, or chromophobe cell carcinomas (Cheville et al., 2004).

4 Aetiology of RCC

There has been considerable discussion on the aetiology of RCC, however there is no evidence to confidently support the presence of a causative factor. Amongst the alleged environmental risk factors, heavy smoking is considered suspicious for an increased risk of RCC (Hunt et al., 2005). Other predisposing factors include genetic predisposition, which will be further discussed in detail, occupational factors (exposure to lead, asbestos, dry cleaning solvents, and cadmium), hypertension, acquired renal cystic disease (ARCD) and dialysis and increased BMI (Label, 2006) (Weikert et al., 2008; Pascual & Borque, 2008; Renehan et al., 2008; Nouh et al., 2010; Ljungberg et al., 2011).

5 Genetic Factors

The risk of RCC for a first degree relative of a patient with RCC is about 2-fold, suggesting a hereditary component. Although the majority of RCC cases (> 95%) are sporadic, there are certain defined types of RCC with a hereditary pattern. Actually there is evidence that all the common histologic subtypes of RCC are caused by different distinct genetic alterations and each corresponds to a specific familiar syndrome (Cohen & Zhou, 2005). As a result, some authors have advocated approaching kidney cancer in terms of a metabolic disease, since each of the identified to date inherited kidney cancer syndromes represent disorders in iron, oxygen, nutrient or energy sensing (Linehan et al., 2010). In contrast to benign renal lesions which show a normal karyotype, all RCC subtypes are characterized by alterations in their genomics. Sporadic clear cell RCCs which originate from the proximal tubule, are characterized by germline mutations of the von Hippel-Lindau (VHL) gene, a tumor suppressor gene, located on chromosome 3p25-26. Mutations in the VHL gene is the commonest alteration related to early onset of usually multiple and bilateral clear cell RCCs (ccRCC). However recent studies on exon sequencing revealed a considerable genetic heterogeneity in ccRCC; suggesting that even though the vast majority of ccRCCs
contain mutated VHL, every tumor has its unique gene signature (Dalgliesh et al., 2010). Under normal circumstances the VHL gene produces a protein that inhibits hypoxia inducible factors (HIFs) and plays a critical role in hypoxia response, including stimulation of angiogenesis. Loss of function leads to accumulation of HIFs and subsequent up-regulation of vascular endothelial growth factor and other factors that promote angiogenesis and tumor growth (Pfaffenroth et al., 2008). Mutations in the VHL gene cause hypoxia inducible factor to stimulate angiogenesis through mainly activation of the vascular endothelial growth factor (VEGF). Other associated alterations include genes implicated in methylation regulation in 15% of cases, underlying the importance of epigenetic modifications, and truncating mutations in chromatin remodelling complex PRMB1 in 41% of cases (Audenet et al., 2012). However recent animal studies have provided evidence suggesting that VHL mutations alone are insufficient for the development of ccRCC implying that additional genetic events are essential (Kapitsinou & Haase, 2008; van Rooijen et al., 2010). The VHL syndrome is a rare condition (1 in 36,000 births) inherited through an autosomal dominant trait (Stolle et al., 1998). The syndrome is characterized by retinal angiomas, which are usually the earlier manifestations of the syndrome, capillary haemangioblastomas of the central nervous system, tumors of the inner ear and islet tumors of the pancreas. Penetrance of each of these manifestations is not complete, for instance RCCs will only develop in 40 – 50% of VHL mutation carriers (Ljungberg et al., 2011). Recent advances in the understanding of the molecular pathways involved in the non-clear cell variants of RCC include the identification of mutations in genes involved in aberrant chromatin remodeling (Singer et al., 2012). Interestingly all these genes are located on chromosome 3, in close proximity to the VHL gene. In contrast to ccRCC, papillary RCC, chromophobe RCC and renal oncocytoma are less dominated by mutations in a single gene. Hereditary papillary RCC type I is associated to activation of the c-met proto-oncogene, which encodes a growth factor receptor, and chromosome 7 alterations (Oosterwijk et al., 2011). A rare but more aggressive type of papillary type II RCC has been associated with alterations in chromosome 1 and an enzyme involved in the Krebs cycle, called fumarate hydratase (Pfaffenroth et al., 2008). Finally, mutations in the Birt-Hogg-Dube gene are associated with the development of familiar chromophobe RCC originating from the collecting ducts although it predisposes to other histologies as well (Cheng et al., 2009; Hasumi et al., 2009).

6 Patterns of Metastatic Spread of RCC

The development of metastatic disease is a sequential process where cancer cells depart from the primary tumor via the blood supply or lymphatic chain and deposit at proximal or distant sites. This metastatic pathway is not always predictable and certainly not for renal cancer, which is notorious for its complex lymphatic drainage. However there is a predilection for certain sites, meaning that these sites are usually the first occupied by cancer cells.

There has been evidence in support of an early dissemination model, where metastasis occurs early in the lifecycle of cancer cells (Oppenheimer, 2006). In an experimental study, engineered untransformed mouse mammary cells were found to express inducible oncogenes transgenes that were able to bypass the primary site and show up at secondary metastatic sites (Podsypanina et al., 2008). In another animal study, Kaplan et al. (2005) also showed that cancer cells in mice models might have instructed bone marrow cells to migrate to pre-selected organs in order to establish a hospitable environment. This event preceded the appearance of cancer cells by four to six days and micrometastatic colonies formed five days later. These studies might explain the unpredictable metastatic pattern of renal tumors and account for the
late appearance of metastatic disease in organs and sites that are considered outside of the “usual” metastatic pathway of RCC (Sountoulides et al., 2011). With regard to RCC, it metastasizes via the hematogenous route through the paravertebral venous plexus. This is an anastomotic network of azygous veins surrounding the bone marrow and vertebrae and is connected with pelvic, intercostal, azygos and cava veins. That allows tumor seeding in both a caudal direction toward the pelvis and a cranial direction to the calotte (Torres Muros et al., 2006).

Once metastases from RCC are present, the lungs are commonly affected by single (30.4%) or multiple metastases (75.6%). Lung metastases are considered a relevant therapeutic challenge. The 5-year survival rate after complete resection of pulmonary metastasis from RCC is up to 60%. (Chen et al., 2008; Russo, 2010). The survival rate is higher after resection of pulmonary metastases than after resection of brain or other extrapulmonary metastases (Volkmer & Gschwend, 2002; Kavolius et al., 1998). In case of lung metastasis, the number and size of nodules to be removed, a long interval between the diagnosis of RCC and the occurrence of metastasis (> 1 year) and a good performance status indicated a favorable clinical setting for pulmonary metastasectomy (Pfannschmidt et al., 2002).

Skeletal metastases are relatively common in advanced renal cancer. These are highly osteolytic, destructive lesions leading to debilitating skeletal complications including severe pain, increased fracture rate and spinal cord compression. These lesions pose significant surgical challenges due to the increased risk of life-threatening hemorrhage. The most common locations of bone metastases from RCC are the spine, pelvis, femur, scapula, and the humerus. Solitary osteolytic bone metastasis may present in up to 26% of all mRCC cases and confer a 5-year survival of 11% (Ruiz-Cerda & Jimenez Cruz, 2009; Lin et al., 2007). Althausen reported that those patients with solitary osseous metastasis and the longest interval between the diagnosis of RCC and the diagnosis of the metastasis have a relatively favorable prognosis and they should be treated as radically as possible (Althausen et al., 1997), while Kavolius reported that resection of solitary metachronous RCC metastases from renal cell carcinoma (RCC) is associated with a 5-year survival rate of 35% to 50% (Kavolius et al., 1998). Fortunately, the continuing development of anti-resorptive drugs is revolutionizing the medical management of metastatic bone disease and offers a major advantage on quality of life. The bisphosphonate zoledronic acid appears to yield a significant benefit in terms of reduction in skeletal related events compared to placebo, while the recent release of denosumab, a fully human monoclonal antibody that specifically targets the RANK-ligand offers another promising therapeutic alternative for patients with renal cancer and metastatic bone disease (Wood & Brown, 2012). According to the American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN), patients with bone metastasis should have zoledronic acid, pamidronate, or denosumab (with calcium and vitamin D supplementation) added to their chemotherapy regimen if they have an expected survival of 3 months or longer and have adequate renal function (Iranikhah et al., 2012; Cassinello Espinosa et al., 2012).

7 Lymph Node Involvement

Cancer specific survival is dramatically worse in patients with kidney tumors and regional lymph node involvement. The incidence of lymph node involvement for surgically resected kidney tumors with no evidence of distant metastases at diagnosis ranges from 3 – 14% (Minervini et al., 2011; Blom et al., 1999; Pantuck, et al., 2003). Preoperative imaging using computerized tomography (CT) or magnetic resonance imaging (MRI) has proved inaccurate in positively identifying lymph nodal metastases. A re-
cent study showed that 10% of patients with clinically negative lymph nodes on preoperative imaging had positive lymph nodes for cancer on histology after lymph node removal. This may mean that at least 10% of all renal cell cancers are understaged (Chapman et al., 2008). Accordingly, given the inability of imaging studies to accurately define the lymph node status due to false-negative results, (Terrone et al., 2006; Chapman et al., 2008) lymph node dissection may be key in providing knowledge of the true histology of the renal-associated lymph nodes, thereby improving staging accuracy and consequently effecting the use of adjuvant chemotherapy and the patient’s ultimate prognosis.

However, the concept of lymph node dissection in kidney cancer is still controversial both regarding whether or not lymph node dissection should be performed at all, and as to the extent of the dissection. According to the guidelines of both the UICC/AJCC and the EAU, lymphadenectomy for renal cell cancer has not provided a proven benefit, suggesting that it should be restricted to the perihilar tissue for staging purposes (Ljungberg et al., 2007). It is not uncommon however for pathologists to find “no nodes” in radical nephrectomy specimens, further confounding the problem. Also, the practice patterns of urologists in the United States verify the lack of consensus on the role or even the definition of LND for tumors of the kidney. Results of one survey showed that at the time of radical nephrectomy for a localized renal tumor, 26% of urologists do not perform a formal lymph node dissection, whereas 41% perform a limited node dissection and 33% perform a full retroperitoneal lymph node dissection extending from the crus of the diaphragm to the bifurcation of the aorta or vena cava (Kim et al., 2006).

The absence of an accepted standardized approach to retroperitoneal lymph node dissection contributes to the uncertainty about the benefits of lymph node dissection for renal tumors. In addition, recent evidence of the complex and unpredictable pattern of lymph node drainage of the kidney further contribute to the lack of consensus regarding the template for lymph node dissection. According to findings from studies in cadavers, extensive lymphadenectomy might well need to include the nodes around the celiac artery along with the contralateral paraaortic lymph nodes (Assouad et al., 2006). The potential morbidity of this approach, given the presence of positive nodes in so few patients is far too high to justify a routine or extended node dissection in all patients afflicted with renal tumors.

Removal of all the lymph nodes that drain the kidney is technically demanding, adds hours to the operating time and can be the cause of serious complications. Currently there is no documented survival benefit from lymphadenectomy. More so as it has been shown that as many as 40% of patients with nodal metastases at the time of nephrectomy are alive 5 years after surgery (Karakiewicz et al., 2007). Reasons for this may be that lymphadenectomy is done inconsistently, it is usually only done in patients that already have advanced disease, and there is little consensus on the proper surgical template. Some authors advocate a complete retroperitoneal dissection, while others favor a more limited template in order to reduce morbidity and mortality. Therefore, performing lymph node dissection during radical nephrectomy for RCC is not currently considered the standard of care (Ljungberg et al., 2007). However the role of lymphadenectomy in locally advanced disease is still under question mainly due to the lack of prospective, well-recruited, trials with adequate number of events.

8 Rare Metastatic Sites

8.1 Orbit

Ocular metastases from RCCs are extremely rare and are more likely to involve the iris, ciliary body and choroids, although eyelid, lacrimal sac and orbital metastases have also been described. All the tumors
with a tendency of metastasizing through the blood have a high possibility to metastasize into areas with a great flow of blood. This is why the posterior pole of the oculus, which has higher posterior choroidal blood flow, is the most common localization of those lesions (Galetović et al., 2010). During the last years only 23 cases have been reported. In 7 cases the eye or orbital metastasis was the first manifestation of a previously unknown RCC, while in 14 cases there was a history of nephrectomy for RCC. The diagnosis in most of the cases was done following excision biopsy that revealed metastatic RCC (Galetović et al., 2010; Sabatini & Ducic, 2009; Rodney et al., 2009; Shoaib et al., 2008; Vozmediano-Serrano et al., 2006; Shome et al., 2007; Mudiyanselage et al., 2008; Mancini et al., 2008).

8.2 Parotid Gland

Major salivary gland metastases from distant primary tumors are exceedingly uncommon. An extensive literature search revealed 26 cases of RCC metastatic to the parotid gland. In 14 of these patients, parotid metastasis was the initial sign of the kidney tumor while in the rest, parotid metastasis occurred following nephrectomy. The longest interval from nephrectomy to solitary parotid metastasis was 19 years (Deeb et al., 2012). The most common presenting symptom is that of a palpable parotid mass, while in one case there was facial paralysis. In all cases fine-needle aspiration (FNA) biopsy was diagnostic (Seijas et al., 2005; Spreafico et al., 2008; Dequanter et al., 2005; Kundu et al., 2001; Moudouni et al., 2006). The mechanism by which RCC reaches the parotid gland is, again, via hematogeneous route.

8.3 Nasal and Paranasal Cavities

The nose is another very uncommon site for RCC metastases. Approximately 50 cases of nasal recurrences of RCC have been reported in the literature. The maxillary sinuses are the paranasal sinuses most commonly afflicted by metastatic tumors, followed in frequency by the ethmoid and sphenoid, while there is only one reported case of an isolated metastasis to the nasal septum and one case of metastasis to the frontonasal region 15 years after nephrectomy for RCC (Kumar et al., 2007). The most frequent patients’ complaints are nasal obstruction, swelling and pain, although epistaxis is the most alarming symptom because of the high vascular stroma of these metastatic deposits (Lee et al., 2005; Pereira Arias et al., 2002). In 15 of the cases there was no known history of renal mass, while the rest of them had previously undergone nephrectomy at a time interval ranging from 6 months to 17 years prior to the diagnosis of the metastatic lesion.

8.4 Tongue and Tonsils

The tongue is a frequent target for RCC metastasis although isolated spread to the floor of the mouth is rare. Lesions in the tongue or floor of the mouth can cause severe pain, bleeding, difficulty eating and even complete oral obstruction. Unfortunately, oral cavity metastasis from RCC is usually a manifestation of widespread disease (Yoshitomi et al., 2011). The literature review revealed 30 cases of RCC metastatic to the tongue. Out of these, only six cases presented initially with tongue metastases before the diagnosis of primary RCC (Azam et al., 2008; Cochrane et al., 2006). Treatment of tongue metastasis is usually palliative and aims to provide patient comfort by means of pain relief while preventing bleeding, infection and breathing difficulties. Surgical excision is recommended as palliative treatment with emphasis on preservation of tongue structure and function (Azam et al., 2008; Cochrane et al., 2006; Basely et al., 2009; Torres-Carranza et al., 2006; Massaccesi et al., 2009; Wadasadawala et al., 2011; Yoshitomi et al., 2011). Only six cases of tonsil metastases from RCC have been reported. All patients had nephrectomy for RCC 6 months to 10 years prior to the tonsil metastasis and two of them were previously diag-
nosed with bone and lung metastasis from RCC (Stańczyk et al., 2006; Massaccesi et al., 2009; García Lozano et al., 1998; Menauer & Issing, 1998).

8.5 Thyroid Gland

Although secondary involvement of the thyroid by RCC is uncommon, more than 150 cases of recognized cases of RCCs metastatic to the thyroid have been reported. Metastatic disease from the kidney to the thyroid gland can occur more than 20 years after nephrectomy, with an average time interval of approximately 7.5 years. Only in five cases were metastases to the thyroid gland the first manifestation of RCC (Bugalho et al., 2006; Nixon et al., 2011; Lee et al., 2007). There are hypotheses that might explain the relatively high incidence of metastases from the kidney to the thyroid gland. The rich blood supply of the thyroid gland is an obvious reason, although some researchers have also suggested that the abnormal thyroid gland is more vulnerable to metastatic growth due to a decrease in oxygen and iodine content alteration (Testini et al., 2008). Metastases to the thyroid can present with symptoms of hypothyroidism, breathing difficulties because of gland enlargement causing airway obstruction, trouble or pain swallowing, and cough due to the vasogastric effect (Garfield et al., 2007). Diagnosis is confirmed by thyroid scintigraphy, thyroid ultrasonography, and cytology of the material obtained through FNA (Bula et al., 2010).

8.6 Heart

There have been rare reports of solitary late metastasis to the heart with the right ventricle being the preferred chamber involved. Isolated metastasis of RCC to the left ventricle of the heart is considered an extremely unique incident. Historically, up to 10% of patients with RCC have tumor thrombus involving the renal vein and inferior vena cava and in up to 1% tumor thrombus extends into the right atrium. There are no more than 25 reports of cardiac metastases of RCC. In 3 cases, a malignant pericardial effusion was the sole evidence of metastatic disease (Zustovich et al., 2008; Tokuyama et al., 2011; Juraszynski et al., 2010). In 3 cases left ventricular metastasis occurred 18 to 23 years after nephrectomy (Talukdera et al., 2010; Bradley et al., 1995; Aburto et al., 2009). In 2 cases there was right ventricular metastasis from RCC, which was incidentally diagnosed after an episode of syncope (Alghamdi & Tam, 2006), and during the evaluation of hematuria (Otahbachi et al., 2009). Finally one case involved metastasis to the interventricular septum which caused cardiac paradox (Faizel et al., 2006).

8.7 Gallbladder

The gallbladder is a very rare metastatic site of RCC with only 33 reported cases of RCC metastatic to the gallbladder (Chung et al., 2012). All cases involved polypoid-like masses that can easily be mistaken with benign gallbladder polyps (Fang et al., 2010). Final diagnosis was made only after cholecystectomy and histopathology examination of the lesions.

8.8 Pancreas

Pancreatic metastases from RCC are relatively rare, with a reported incidence ranging from 1.6% to 11% in large series of patients (Adsay et al., 2004, Washington et al., 1995). Of the primary tumors that can metastasize to the pancreas, renal cell carcinoma (RCC) is the most common, followed by lung cancer, breast cancer, adenocarcinoma, and melanoma. A lot of papers mention that RCC has a high affinity for the parenchyma of the pancreas and an electivity to grow there, but the mechanism has not been extensively explained (Ballarin et al., 2011).
8.9 Skin

Skin metastases of RCC are not easy to diagnose due to the low suspicion index for these skin lesions, both because these lesions mimic common dermatological disorders and due to the usually long interval since nephrectomy. Skin metastases have been reported to occur in around 3% of renal tumors. Several cases of calvarial metastases from clear cell RCC have been reported in the literature (Gaetani et al., 2005; Cohen, 2001; Martínez-Rodríguez et al., 2008), but only one case of papillary RCC with cutaneous metastases (Srinivasan et al., 2010). Skin metastases mainly occur in the head, neck and trunk, in that order. The diagnosis is only made after histopathology examination of the cutaneous lesion. Skin metastases are usually late manifestations of the disease, are associated to synchronous metastases to other sites and carry a poor prognosis (Survival shorter than six months) (García Torrelles et al., 2007; Arrabal-Polo et al., 2009; Jilani et al., 2010; Johnson et al., 2011; Mahmoudi et al., 2012; Terada, 2012; Chauhan et al., 2011).

8.10 Genitalia

Ovarian metastases are found in 0.5% of cases of renal cancer and are thought to occur by retrograde venous embolization through the renal vein to the ovarian vessels. In total only 24 cases of metastasis to the ovaries from RCC have been reported with 6 of the cases initially considered as primary ovarian clear cell cancers (Toquero et al., 2009; Albrizio et al., 2009; Stolnicu et al., 2007; Jalón Monzón et al., 2008; Udoji & Herts, 2012, Guney et al., 2010). With regard to metastatic testicular involvement, the incidence of secondary testicular tumors ranges from 0.3% to 3.6% (Schmorl et al., 2008). To our knowledge only six cases of testicular metastases from RCC have been reported within the last seven years, in one case there was a contralateral chromophobe RCC metastatic to the testis, six years after nephrectomy (Ulbright et al., 2008; Wu et al., 2010).

8.11 Muscle and Joints

Metastatic RCC to muscles is a very rare incident indeed. According to Satake, (Satake et al., 2009) until 2009 only 32 cases of skeletal muscle metastasis from RCC had been reported; our search added another four. Five cases of acute monarthritis secondary to asymptomatic RCC have been described, where the patients were initially diagnosed with septic arthritis. However the finding of hot spots on isotope bone scans and biopsy samples showing secondary neoplasms confirmed the lesions to represent metastatic sites of RCCs. MRI has proven helpful in delineating the features and extent of muscle invasion by the tumor (Picchio et al., 2010; Hur et al., 2007; Placed et al., 2010; Trumm et al., 2011).

9 Management of Metastatic Disease

Metastatic RCC is still considered a non-curable disease state despite the huge efforts in recent years to come up with effective treatment. Thus the best chance of cure lies in the early detection of the disease when the tumor is either organ-confined or locally advanced and therefore amenable to radical surgical excision. At the same time, the constantly changing algorithm of treatment for advanced and metastatic RCC represents the field with the most dramatic changes in oncology in the last few years.

Regarding its medical management, metastatic RCC is considered refractory to treatment with traditional systemic cytotoxic chemotherapies, and until recently management options were limited to immunotherapy and palliative care. RCC has long been considered an immunosuppressive tumor and as
such cytokine therapy had for decades been considered as acceptable therapeutic option albeit with limited long-term disease free survival rates, not exceeding 10 months (Yang et al., 2003; Coppin et al., 2005; Motzer et al., 1999). Recently however the encouraging initial results from clinical trials of targeted therapies which derive their efficacy through affecting angiogenesis, (anti-angiogenic agents and m-TOR inhibitors) signaled a turn in the management of mRCC (Wagstaff, 2006). This paradigm shift in the medical management of metastatic RCC is still evolving and will likely produce more robust results in the future as novel more potent and better tolerated agents are sought and the role of combination and sequential anti-VEGF schemes is defined (Choueiri, 2011).

10 Cytokine Therapy

It was only until recently that immunotherapy, in the form of cytokine therapy, was considered the mainstay of treatment for advanced RCC, even though the somewhat vague term “immunotherapy” comprises a vast array of different therapeutic approaches. Cytokine therapy mainly in the form of interleukin-2 and interferon-α has been used alone and in combination for the treatment of advanced RCC.

Although Interleukin-2 (IL-2) was until 2005 the only drug approved by the Food and Drug Administration (FDA) for the treatment of advanced RCC, significant questions concerning IL-2–based immunotherapy still remain open. Interleukin’s proposed mechanism of action involves both direct effects on cancer cells as well as a general stimulation of the immune system. In more detail, IL-2 acts by stimulating cytotoxic T lymphocytes (CTLs), natural killer (NK) cells and CD8 cells that induce an antitumor immune response (Olencki & Bukowski, 2000). IL-2’s direct effects on cancer cells include cell cycle perturbations and production of cytotoxic reactive oxygen species, e.g., NO (Porta et al., 2007). Although IL-2 probably kills cancer cells with more than one mechanism it also acts, in terms of both activity and toxicity, as completely different drugs depending on the dose and route of administration (Porta et al., 2007). The therapeutic efficacy and safety of high-dose interleukin (HD IL-2) for metastatic RCC has been examined in the setting of large randomized clinical studies. In the study by McDermott et al. (2005) although HD IL-2 showed better response rates compared to low dose (23% versus 10%), no significant difference in progression-free survival or overall survival was observed. Moreover high-dose i.v.IL-2 was associated with significant toxic side effects. Similar results were reached in the study conducted by the National Cancer Institute (NCI) were mRCC patients received either HD or LD IL-2. Overall response rates were 21% for the HD group, versus 13% for the LD group with again a significant price to pay in terms of toxicity, but no difference in overall survival despite the longer duration of responses in patients receiving high-dose IL-2 (Yang et al., 2003). Today HD-IL-2 is considered as first-line treatment option for good risk patients with mRCC (Patard, 2009) (Figure 1). Taken together, overall complete and durable responses with IL-2 have been achieved in no more than 5% of patients. Apart from the disappointing results of IL-2, its administration was associated with a substantial increase in the incidence of grade III-IV toxicities in the high dose group. IL-2 has been linked to the life-threatening capillary leak syndrome and is not indicated in cases of brain metastases, cardiac, pulmonary or renal dysfunction and poor performance status (Fyfe et al.,1995; Yang et al. 2003; McDermott et al., 2005). Interferons (IFNs) are members of a family of regulatory proteins produced by eukaryotic cells in response to viral infections and to several other biologic or synthetic inducers (Porta et al., 2007). The precise mechanisms supporting IFN-induced antitumor activity are still not completely known. IFNs have a broad range of biological effects including immune stimulation, antiangiogenesis, direct antiproliferative
and pro-apoptotic effects as well as effects of cell differentiation that could potentially induce a clinically significant antitumor response in vivo (Lindner, 2002; Nanus et al., 1990, Porta et al., 2007). Interferon-α was the interferon more extensively used for the management of mRCC following early evidence of antitumor activity against RCC and thus became the standard preparation used in clinical practice. The efficacy and the possible survival benefit of interferon for patients with mRCC have been evaluated in clinical trials. Interferon compared to medroxyprogesterone (MPA) demonstrated a significant overall survival advantage with an added median survival time of 2.5 months compared to MPA. The estimated 1-year survival rates were 43% for the interferon arm versus 31% for the MPA arm (no authors, 1999). In another study where 160 patients with mRCC were randomized to either interferon-α2a or vinblastine, overall survival was significantly better for those under interferon (15.8 months versus 8.8 months). Complete response rates, although low, were also in favor of interferon (8.9% versus 1.2%) (Pyrhönen et al., 1999). Cytokines have also been used in combination in order to augment the modest survival benefits of either IL-2 or interferon monotherapies. However clinical studies have shown that the combination of cytokines did not provide with a significant clinical advantage in terms of survival or even quality of life. In other words despite its modest efficacy, cytokine monotherapy is superior to cytokine combination therapy. Negrier et al., (1998) and Atzpodien et al., (1993) and the combined approach is associated with limited efficacy and modest success rates in the majority of mRCC cases (Kruck et al., 2008). Drug-related toxicity is a significant issue with cytokine therapy, high-dose IL-2 in particular can be extremely toxic, requiring inpatient administration with intensive supportive care (Coppin et al., 2005). However, the toxicity of IL-2 can be significantly reduced by subcutaneous administration (Geertsen et al., 2004). A recently published study (PERCY Quattro trial) evaluated both cytokines (interferon alfa-2a, interleukin 2) and the combination of both with regard to their possible survival benefit for a total of 492 intermediate prognosis RCC patients. Although there were no significant survival differences between the interferon-α treated patients or between the interleukin-2 treated patients, grade 3-4 toxicities were significantly more frequent in cytokine-treated patients than in medroxyprogesterone-treated patients. The authors concluded that intermediate risk mRCC patients gain no survival advantage with either interleukin-2 or interferon-α, instead these agents induce a significant risk of toxicity (Negrier et al., 2007). The results of this study were reflected in the recent European Association of Urology guidelines, suggesting that patients with favorable risk profile and clear-cell subtype histology are potential candidates for cytokine therapy (Ljungberg et al., 2010).

11 Molecular Pathways in RCC and Targeted Therapies

The limitations of cytokine treatment intensified research into a more thorough understanding of the underlying molecular biology of RCC. The recent understanding of the fundamentals of kidney cancer biology and the discovery of the implicated pathways, particularly the vascular endothelial growth factor (VEGF) pathway and the mammalian target of rapamycin (mTOR) led to the development of therapies with inhibitory activity against these pathways. As a result, systemic therapy for metastatic renal cell carcinoma (mRCC) that was once limited to interleukin-2 and interferon (IFN)-α, has been recently enriched with the simultaneous emergence of several active compounds that have become available for first- and second-line use.
12 **Molecular Biology**

Under normal conditions, hypoxia inducible factors (HIFs) bind to the von Hippel-Lindau (VHL) protein which is involved in proteolysis as part of an ubiquitin ligase complex and is constantly degraded. In almost all cases of VHL syndrome and in around 70% of sporadic RCC cases the VHL gene is inactivated. The resultant alteration in the VHL proteins leads to disruption of this interaction between the HIF and the VHL protein, impaired degradation of HIF, and accumulation of the HIF transcription factors under normal (non-hypoxic) conditions. HIF accumulation can also result from activation of the mammalian target of rapamycin (mTOR) downstream of cellular stimuli and the PI3-K/Akt pathway (Oosterwijk et al., 2011). Under normal circumstances the mTOR pathway regulates cell growth, and its upregulation in tumors contributes to protein degradation and angiogenesis (Sarbassov et al., 2005). Those accumulated HIFs translocate into the nucleus where they lead to massive transcription of hypoxia inducible genes including vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF). These factors in turn, bind to their corresponding receptors on the surface of endothelial cells and result to neovascularization.

Therefore molecular therapies target these two, essential to the pathophysiology of clear cell RCC, pathways: the hypoxia response pathway associated with inactivation of the VHL tumor suppressor gene and the mTOR signaling pathway. Agents targeting these pathways include inhibitors of multiple tyrosine kinase receptors (TKIs) including VEGF-R and PDGFR (sorafenib, sunitinib, pazopanib, axitinib), antibodies that directly inhibit VEGF (Bevacizumab), and factors that exclusively inhibit the kinase activity of the mTOR complex 1 (temsirolimus and everolimus).

The clinical implementation of targeted molecular therapies has provided encouraging results for patients with mRCC. Molecular-targeted therapies have better efficacy and tolerability than cytokine therapy, and many are administered orally (Hutson, 2011). The administration of these agents (TKIs) has provided with impressive objective response rates as high as 45%, has led to almost doubling of the progression-free survival (PFS) while up to 30% of patients achieve partial remissions (PR) (Staehler et al., 2010; Rini et al., 2009). However, one has to bear in mind that whether these treatments directly target the tumor cells remains uncertain, as at pharmacologically relevant doses of sunitinib no effect on RCC cells was noted (Huang et al., 2010). Furthermore there is evidence in support of growth of tumor cells along large mature vessels, allowing the potential for escaping TKI treatment and evidently progression of cancer despite treatment (Audenet et al., 2012).

13 **Tyrosine Kinase Inhibitors (TKIs)**

Sunitinib (Sutent®, Pfizer Inc., NY, USA) is an orally bioavailable small molecule multi-tyrosine kinase inhibitor of the VEGF receptors (VEGFR-1, -2, and -3), platelet-derived growth factor receptor-a and b (PDGFR-a/b) and c-KIT, FLT-3 and RET (Motzer et al., 2007). Initial phase II trials of administration of 50 mg of sunitinib daily for 4 weeks demonstrated objective partial responses of approximately 40% (Motzer et al., 2006). Sunitinib was compared to IFN-a in a phase III trial of once-daily 50 mg sunitinib versus IFN-a in 750 patients. Sunitinib demonstrated a superior progression-free survival time (11 months vs. 5 months, HR: 0.42; p < 0.000001) The initial report included an increased objective response rate (ORR; 28 vs. 5%), and the final analysis found prolonged OS in the sunitinib group compared with the IFN-a group (26.4 vs. 21.8 months; HR: 0.821; p = 0.051) and final ORRs of 47% for sunitinib and
12% for IFN-a \( (p < 0.001) \) (Motzer et al., 2009). In 2006, sunitinib received approval from the US FDA and the EMA as a first-line therapy to treat advanced mRCC. Sunitinib is now recommended as first-line therapy for good and intermediate risk patients with mRCC and in the second line setting for patients who have failed prior cytokine therapy (Ljungberg et al., 2010; Patard et al., 2011) (Figure 1 and Figure 2) Sorafenib (Nexavar®, Bayer Pharmaceuticals, Berlin, Germany) is a small molecule orally bioavailable multi-kinase inhibitor that decreases tumor cell proliferation by targeting intracellular (Raf-1/B-Raf) and cell surface kinases (VEGFR-1,-2 and -3, FLT-3, PDGF-b, RET, FGFR-1, KIT) (Lyons et al., 2001). In 2006, sorafenib was approved by the EMA for the treatment of mRCC after the failure of IL-2- or IFN-a-based first-line therapy. The recommended dosage of sorafenib is 400 mg twice daily, taken either 1 h before or 2 h after food intake.

Sorafenib was evaluated in a randomized phase III trial in 903 patients with mRCC, the majority (> 80%) of whom had failed previous IL-2- or IFN-a-based first-line therapy (Escudier et al., 2009). Median PFS was significantly improved in patients receiving sorafenib compared with those receiving placebo (5.5 months versus 2.8 months). The first interim analysis of OS showed that sorafenib reduced the risk of death by 28% compared with placebo, while final analysis demonstrated a significant improvement in OS with sorafenib (17.8 vs. 14.3 months; HR: 0.78; \( p = 0.029 \)), after censoring placebo patients who had crossed over to sorafenib (Bukowski et al., 2009). Based on the results of this trial, sorafenib is recommended as a second-line agent in cytokine-refractory or cytokine-unsuitable patients (Patard, 2008; Ljungberg et al., 2010) (Figure 2). Pazopanib (Votrient®, GlaxoSmithKline, London, UK) is a broad spectrum tyrosine kinase inhibitor, inhibiting VEGFR1,-2 and -3, PDGFR-a and -b and c-Kit (Sonpavde & Hutson, 2007). Pazopanib’s efficacy has been recently tested in a phase III trial of both treatment naïve patients and also for patients who failed therapy with cytokines or bevacizumab (Figure 2). In both groups of patients pazopanib achieved significant benefits with regard to PFS compared to placebo (overall: 9.2 vs. 4.2 months; HR: 0.46; \( p < 0.0001 \); treatment-naive (54%): 11.1 vs. 2.8 months; HR: 0.40; \( p < 0.0001 \); and cytokine-pretreated (46%): 7.4 vs. 4.2 months; HR: 0.54; \( p < 0.001 \)). A tumor response rate of 30% for pazopanib was observed, compared to 3% with placebo \( (p < 0.001) \), in 435 treatment naïve and cytokine-pretreated mRCC patients although OS was not positively affected (Sternberg et al., 2010). These results led to pazopanib (800 mg) receiving FDA approval in 2009 for the treatment of advanced mRCC either as a first line treatment regimen or in cases of cytokine failure (Patard et al., 2011). Pazopanib is currently compared to sunitinib for patients with mRCC who have received no prior systemic therapy in an ongoing randomized clinical trial (COMPARZ) (Pazopanib Versus Sunitinib in the Treatment of Locally Advanced and/or Metastatic Renal Cell Carcinoma (COMPARZ), NCT00720941). Axitinib, an inhibitor of VEGFRs 1–3 is administered orally at a dosage of 5 mg twice daily. Axitinib has shown anti-tumor activity with a favorable noncumulative toxicity profile in clinical trials of patients with advanced mRCC previously treated with cytokines, chemotherapy or other targeted agents. For cytokine-refractory advanced RCC axitinib demonstrated an ORR of 44.2%, median time to progression of 15.7 months and median OS of 29.9 months (Rixe et al., 2007). Rini et al. (2009) reported an ORR of 22.6%, a median PFS of 7.4 months, and a median OS of 13.6 months in 62 patients with sorafenib-refractory mRCC. The results of the Phase III AXIS trial comparing axitinib and sorafenib as second-line therapies for mRCC were presented recently (Rini et al., 2011) demonstrating that for patients with disease progression on first line therapy, axitinib has the potential for a standard second-line treatment (Calvo et al., 2012) (Figure 2). Bevacizumab (Avastin®, Roche, Basel, Switzerland) is a humanized monoclonal antibody that inhibits angiogenesis by directly binding the VEGF ligand and neutralizing all forms of circulating VEGFs. The recommended dose is 10 mg/kg bodyweight every 2 weeks.
in combination with IFN-a at 9 MIU three times per week. Bevacizumab was licensed as a first-line therapy in combination with IFN-a for patients with mRCC in 2007 in the EU and in 2009 in the USA.

The efficacy of bevacizumab in combination with IFN-a as first-line treatment was reported in a randomized study (AVOREN) of 649 previously untreated mRCC patients. Median PFS was significantly longer in the bevacizumab plus IFN-a group compared with the IFN-a alone plus placebo control group (10.2 vs 5.4 months; HR: 0.60; \( p < 0.0001 \)). However, no improvement was reported in OS based on the final analysis conducted after 444 deaths, with a median OS of 23.3 months in the bevacizumab plus IFN-a arm and 21.3 months in the IFN-a plus placebo arm (Rini et al., 2008; Rini et al., 2010). Bevacizumab was also tested in the settings of combination treatment for advanced RCC in the TORAVA trial where 171 untreated mRCC patients were randomized to receive a combination of bevacizumab (10 mg/kg every 2 weeks) and temsirolimus (25 mg weekly), sunitinib (50 mg/day for 4 weeks followed by 2 weeks off), or IFN-a (9 MIU three-times per week). Analysis found a PFS of 29.5% (median: 8.2 months), 35.7% (median: 8.2 months) and 61.0% (median: 16.8 months), respectively. However, 51% of patients treated with the combination of temsirolimus and bevacizumab had to discontinue the scheme due to toxicity (Negrier et al., 2011). Bevacizumab plus IFN-a is recommended as first-line treatment option, for patients with mRCC with favorable or intermediate disease profile offering a prolonged progression free survival (Rini et al., 2008; Escudier et al., 2007, Patard 2009).

14 m-TOR inhibitors

Another pathway involved in RCC development, growth, proliferation, angiogenesis, and potential for metastasis is the mammalian target of rapamycin (mTOR).

Temsirolimus (Torisel®/CCI-779, Pfizer Inc., NY, USA) is an intravenously administered mTOR inhibitor of the PI3K/Akt/mTOR pathway resulting in G1 growth arrest of the treated tumor. Temsirolimus also reduces the level of proangiogenic growth factors HIF-1, HIF-2a, VEGF and PDGF (Kruck et al., 2012). Temsirolimus was approved as a first-line therapy in 2007 for mRCC patients with at least three of six poor prognostic risk factors. The recommended dose for Temsirolimus is 25 mg over a 30–60-min period once a week. Premedication with intravenous antihistamine is recommended to minimize the risk of allergic reactions. Temsirolimus was tested in a randomized phase III trial of temsirolimus (25 mg) monotherapy versus temsirolimus (15 mg) plus IFN-a (6 MIU) in 626 patients with mRCC and poor prognosis. Patients who received temsirolimus alone had significantly longer median PFS compared with those who received IFN-a alone or a combination of temsirolimus and IFN-a. The median OS in the IFN-a, temsirolimus and combination therapy groups was 7.3, 10.9 and 8.4 months, respectively and subgroup analysis found no differences in OS between clear and non-clear-cell renal carcinoma (Hudes et al., 2007) There is recent evidence to support that temsirolimus leads to meaningful improvements in overall survival and thus should be the first-line option for patients with poor risk features (Bullock et al., 2010). Temsirolimus has been recommended as first-line treatment option for treatment-naïve patients with non-clear cell histology and poor MSKCC prognostic factors and prognosis (Patard, 2009; Ljungberg et al., 2010) (Figure 1).

Everolimus (Afinitor®/RAD001, Novartis, Basel, Switzerland) is a synthetic, orally bioavailable analog of the mTOR inhibitor rapamycin that inhibits downstream targets of the PI3K/Akt/mTOR pathway. Everolimus was officially licensed in 2009 by the FDA for the treatment of mRCC and is available in a 5-mg or 10-mg tablet; the recommended dose for advanced mRCC treatment is 10 mg once daily
Everolimus significantly prolonged PFS relative to placebo (4.0 vs. 1.9 months; HR: 0.30; \( p < 0.0001 \)) in patients with mRCC who had progressed with prior anti-VEGF therapy. The final results of the study indicated extended PFS (4.9 vs 1.9 months; HR: 0.33; \( p < 0.001 \) by independent central review and 5.5 vs 1.9 months; HR: 0.32; \( p < 0.001 \) by investigators) (Motzer et al., 2008; Motzer et al., 2010). Everolimus is now the recommended second-line systemic therapy for patients who have progressed on prior VEGF-targeted therapy (Patard, 2008; Patard et al., 2011) (Figure 2). Etafacizumab, Vorinostat, tivozanib, regorfanib, XL880 and Infliximab, antitumor vaccines and checkpoint inhibitors anti-CTLA4 and anti-PD1 are other agents currently under study.

**Figure 1:** Therapeutic options for first-line treatment of mRCC.

**Figure 2:** Therapeutic options for second-line treatment of mRCC.

### 15 Adverse Effects of Molecular Treatments

Molecular therapies for mRCC are often accompanied by potentially serious side effects. Patients treated with tyrosine kinase inhibitors (TKI’s) may experience adverse effects such as fatigue, hypertension, diarrhoea, nausea, proteinuria, cardiac toxicity, hypothyroidism, pancytopenia, hand-foot syndrome, mucosi-
tis and gastrointestinal toxicities. Interestingly, a diastolic blood pressure ≥90 mmHg appears to be associated with a better response to treatment with axitinib and sunitinib (Rini et al., 2011; Rixe, 2007; Escudier et al., 2011). The most commonly reported grade 3 adverse events associated with sorafenib are hypertension (12%), fatigue (11%), diarrhea (9%) and hand–foot syndrome (9%) (Motzer et al., 2007; Motzer et al., 2009). There is evidence that TKI treatment is the cause of alterations of the immune status of RCC patients, as sunitinib is found to inhibit the proliferation of primary human T-cells both from healthy volunteers and from RCC patients (Gu Y et al., 2010). Also the incidence of hematologic adverse events from sunitinib treatment in Japanese patients was higher compared to Western populations, implying a relationship between ethnic origin and frequency of severe treatment toxicity due to different genetic backgrounds (Uemura et al., 2010). The VEGF antibody-cytokine combination presents a different pattern of toxicity, including gastrointestinal perforation, bleeding, thromboembolic events, proteinuria, anorexia and fever. The mTOR’s adverse event profile includes hyperglycemia, hyperlipidemia, asthenia, hematological toxicity, pneumonitis, infections, and mucositis (Kirchner et al., 2010; Bhojani et al., 2008). The most common adverse events observed during everolimus treatment are nausea (38.5%), anorexia (38.5%), diarrhea (30.8%) (Motzer et al., 2008) Due to the increased risk of side effects, it is highly recommended that these treatments be undertaken only under the guidance of oncology specialists with expertise in the toxicity, interactions and monitoring of patients.

16 Sequential and combination therapy

The clinical introduction of novel targeted therapies has shifted research into the evaluation of the optimal drug sequence and also the potential benefits from combination therapy. As more information regarding the underlying molecular mechanisms of RCC becomes available, new targeted agents, and new combinations will be studied with the goal of providing survival advantage with minimal toxicity. Despite the availability of multiple treatment options, several challenges remain: selecting the best first-line or subsequent therapy for a given patient, the optimal sequencing of the various agents available and identifying well tolerated and effective drug combinations.

There is recent clinical evidence to suggest that targeting different pathways through sequential therapy may offer an advantage in terms of overcoming resistance to individual agents (Moreno Garcia et al., 2012; Escudier et al., 2009). Sequential treatment with targeted therapies is currently considered the standard of care for patients with metastatic renal cell carcinoma (mRCC). This stepwise approach initially involves the administration of a first-line vascular endothelial growth factor receptor-tyrosine kinase inhibitor (VEGFr-TKI). In the event of disease progression under first line treatment there are studies suggesting that failure to a previous anti-VEGF therapy might not preclude failure to a VEGFR agent with a different mechanism of action and molecular target, given that the targets are overlapping but not identical (Stein & Flaherty, 2007). In many cases of disease progression during TKI therapy, switching to a different TKI can bring the disease under control again. Therefore sequence therapy with tyrosine kinase inhibitors is an effective alternative to the TKI/mTOR inhibitor sequence. Several trials have shown substantial clinical benefits from a TKI–TKI sequence including sunitinib, sorafenib and axitinib in mRCC patients failing treatment with prior VEGFr-targeted TKIs (Eichelberg et al., 2008; Sablin et al., 2009; Dudek et al., 2009). Patients with mRCC who will experience disease progression during initial VEGF-TKI therapy may alternatively switch to treatment with everolimus or axitinib (Motzer et al., 2008). Sequential treatment with multiple targeting agents provides disease control and additional PFS.
Clinical guidelines recommend the use of everolimus, an mTOR inhibitor, in patients with VEGFr-TKI-refractory mRCC (Patard et al., 2011). Recent positive results of the phase III AXIS trial led to recent approval in the United States of the VEGFr-TKI axitinib for use in patients with mRCC who failed one previous therapy (Figure 2). Ongoing studies comparing first-line everolimus followed by second-line sunitinib versus the opposite sequence (RECORD-3 study) and comparing the optimal sequence of sorafenib given prior or after sunitinib (SWITCH trial) are awaited with interest. Currently there is not sufficient evidence for a clear recommendation for second-line alternatives after disease progression under mTOR inhibitors. In contrast to the first-line setting based on large Phase III studies, insufficient data are available to determine the optimal sequence after single or multiple systemic treatment failures in advanced RCC (Kruck et al., 2012). Antiangiogenic drug combination has been recently proposed in a theoretical effort to enhance the positive effects of monotherapy and overcoming drug resistance by either inhibiting several steps of the same pathway (vertical blockade) or by targeting in parallel two different pathways (horizontal blockade) (Sosman & Puzanov, 2009). A variety of drug combinations, (bevacizumab + sunitinib, bevacizumab + sorafenib, sunitinib or sorafenib + IFN-a-2b, temsirolimus + bevacizumab) have been tested in phase I studies (Feldman et al., 2009; Gollob et al., 2007; Azad et al., 2008; Patnaik et al., 2007). In general results were not encouraging due to either lack of synergistic or additive efficacy of the drugs or due to severe drug-related toxicity precluding the use of certain drug combinations (Feldman et al., 2009; Patnaik et al., 2007). Expert opinion considers antiangiogenic drug combinations investigational and not currently recommended outside the context of clinical trials.

Beyond overall survival and progression free survival, it is also fundamental to distinguish which therapies offer a major benefit in terms of quality of life. There are some studies reporting an advantage in quality of life when VEGFR inhibitors (sunitinib and sorafenib) are administered (Cella et al., 2008; Escudier et al., 2009), however no placebo-controlled trial has reported a health-related quality of life benefit according to a recent systematic review of randomized trials (Coppin et al., 2012). Since durable complete responses still remain elusive, improving overall survival is the main challenging objective although this effort is to an extent hampered by the lack of biomarkers predictive of response to treatment (Audenet et al., 2012). Cytoreductive nephrectomy was considered to be beneficial in terms of survival prolongation compared to cytokine therapy alone according to two randomized studies (Mickisch et al., 2001) (Flanigan et al., 2001) and is the current standard of care for mRCC. In the era of molecular targeted therapies such studies have not yet been conducted, although the vast majority of patients in the sunitinib and sorafenib trials underwent nephrectomy (Escudier et al., 2007; Motzer et al., 2007). There is evidence supporting that standard cytoreductive nephrectomy should probably be reconsidered at least for poor prognosis patients according to MSKCC criteria (Bex & Powles, 2012; Logan et al., 2008). Current practice patterns in this issue are based on individual clinical indications while results from ongoing studies (CARMENA trial, SURTIME trial) are eagerly awaited.

17 Prognostic Factors in mRCC

In general, pathologic prognostic features that have been proposed in RCC include nuclear grade, histologic subtype, and molecular biomarkers. Since the impact of histologic subtype on prognosis has been addressed previously the role of molecular markers will be discussed in more detail. The association of particular molecular markers with progression and outcome means that certain markers can be used to
identify the likelihood for progression and can be incorporated into nomograms for patient counseling and for patient stratification in clinical trials. Molecular biomarkers that have been investigated in RCC prognostics include carbonic anhydrase IX (CA-IX), p53, p21, PTEN, Vimentin, pAKT, IMP3, B7H1/B7H4, Hif-1α and Survivin. Genetic biomarkers include VHL mutation, deletion, and/or hypermethylation.

The prognostics for the metastatic state of RCC are somewhat different from early stage disease. For instance although nuclear grade has been recognized as an independent predictor of survival in early stage disease, it has not been shown to correlate with survival in the metastatic setting (Patard et al., 2005; Frank et al., 2002). Prognostic molecular biomarkers have been identified by both DNA microarray and tissue array techniques. In a study on 150 metastatic clear cell RCC cases, using tissue array techniques investigators isolated CAIX, p53, PTEN, and vimentin as independent prognostic factors for survival. Increased immunohistochemical staining of p53 and vimentin was predictive of poor survival, while increased staining with CAIX and PTEN were associated with more favorable outcomes (Kim et al., 2005). Increased CAIX tumor expression has also been found to be an independent predictor of prolonged survival in mRCC patients treated with IL-2, (Atkins et al., 2005) while other investigators believe that CAIX expression as a predictive marker requires additional investigation (Leibovich et al., 2007). Tumor expression of the insulin-like growth factor-II mRNA binding protein, IMP3, has been linked to poor outcome perhaps due to its association with poor prognostic features including tumor necrosis and sarcomatoid differentiation. Hoffmann et al. found a 42% increased risk of death from RCC in patients whose tumor IMP3 expression was positive (Hoffmann et al., 2008). With regard to genetic markers, loss of heterozygosity (LOH) of chromosomes 8p, 9p and 14q have been associated with higher grade and stage in clear cell RCC and papillary RCC (Beroud et al., 1996). LOH of chromosome 9p has been correlated with progression in locally advanced clear cell RCC and papillary RCC (Moch et al., 1996; Schraml et al., 2000). Finally on genetic biomarkers, although alterations in the VHL gene (mutations, deletions, hypermethylation) have been identified in 60% of patients with clear cell RCC, the question whether VHL loss correlates with survival has received variable answers (Patard et al., 2008; Choueiri et al., 2008).

18 Conclusions and Future Directions

Metastatic RCC is known to be an aggressive, potentially lethal and highly resistant disease. Nevertheless, the introduction of new targeted therapies based on an improved understanding of RCC tumor biology has produced encouraging outcomes with substantial improvement on overall survival for patients with advanced RCC. However despite some dramatic initial responses, targeted treatment rarely cannot be considered curative as advanced cancers become resistant to VEGF and mTOR agents in the long term.

The future holds promise that the genomic approach to RCC classification, will allow the identification of prognostic markers and predictive indicators of response to treatment while technological developments, such as large-scale analysis and high-speed sequencing, will allow the systematic screening of tumors to fully determine the somatic genetic architecture of RCC (Audenet et al., 2012; Wright & Kapoor A, 2011). Metastatic RCC represents a field of constant and rapid development and progress during the last few years. Today patients with RCC have several alternative treatment options that warrant survival prolongation with acceptable morbidity. Still, certain issues need further refinement. Among
those is the place for cytoreductive nephrectomy in the era of targeted molecular treatments, the timing and ideal sequencing of targeted therapies, the optimal combination of these agents and the understanding of the mechanisms of drug resistance. What ongoing research on RCC allows us to expect from the future is the possibility of personalized treatment for renal cancer patients.

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