Histological classification of malignant renal tumours at a time of major diagnostic and therapeutic changes

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Kidney; Malignant tumour; Classification; Histology; Genetics

Abstract Renal cancers account for approximately 3% of adult cancers and the mean age of diagnosis is 65, with men affected two to three times more frequently than women. However, an increase is being seen in kidney tumours also in young adults and in women. The classification of renal tumours includes both benign and malignant tumours, and is currently quite exhaustive, but may be even more extensive in the coming years, particularly for tumours in renal impairment. Except for certain specific entities (such as chromophobe carcinoma), two criteria are required to correctly classify malignant kidney tumours: the Fuhrman grade, and the pTNM stage, defining tumour extension. The stage and grade are applicable in the same way, regardless of the nature of the tumours; for a given group, they are the best prognostic factors.

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Renal cancer accounts for approximately 3% of adult cancers, occurring at a mean age of 65, with male predominance (sex ratio 3/1). In its disseminated form, it is an aggressive tumour (kidney cancer holds the sixth position in the causes of death through cancer).

The histological classification of kidney tumours, updated by the World Health Organisation in 2004, is primarily based on morphological criteria (the appearance of the cells clear or eosinophilic and whether the architecture is papillary or not) [1]. Besides clear cell, papillary and chromophobe renal carcinomas, this classification in addition distinguishes new entities due to their histological appearance, prognosis or genotypic alterations (Boxed text 1 and Table 1).

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Boxed text 1  2004 WHO classification of epithelial tumours of the kidney.

Clear cell carcinoma.
  Multilocular cystic renal cell carcinoma*.
  Papillary carcinoma of the kidney.
  Chromophobe renal cell carcinoma.
  Bellini duct carcinoma.
  Renal medullary carcinoma.
  Carcinoma with Xp11.2 translocation*.
  Neuroblastoma-associated renal cell carcinoma*.
  Low-grade mucinous tubular and spindle cell carcinoma*.
  Unclassifiable carcinoma.
  Papillary adenoma.
  Oncocytoma.
*Entities new to the 2004 classification.

In practice, histological analysis seeks to identify the clear or eosinophilic (oxyphilic) principal cell population and the predominant acinar, papillary or cystic architecture. Immunohistochemical analysis points towards the origin of the cell population responsible for tumour proliferation (Table 2), whereas cytogenetic analysis sets out the principal framework of the major groups of renal tumours (Table 1).

To fully appreciate the risk of progression of these tumours, two histo-prognostic assessments are required. The Fuhrman grade takes into account nuclear size and shape and the size of the nucleoli. It defines the differentiated or non-differentiated character of the tumour cells.

The pTNM stage indicates the extension of the tumour. The Fuhrman grade and pTNM stage are applicable regardless of the nature of the tumours, the value of the Fuhrman grade being however rather more relative for chromophobe carcinomas. For a given group, they are the best prognostic factors [2,3].

For a long time, surgery and immunotherapy (using interferon or interleukin) have been the only available means of treatment in disseminated forms, despite poor efficacy. Understanding the central role played by the VHL gene in the genesis of clear cell carcinoma, the most common form of malignant renal tumour, has revolutionised management of this cancer, with the introduction of targeted anti-angiogenic treatment. In addition to the morphological points of recognition, our objective is to show how understanding the biological and molecular mechanisms involved in the genesis of kidney tumours in adults may modify the histological classification.

Clear cell carcinoma (CCC)

Over 80% of renal carcinomas are of this type, which occurs in the sixth decade of life, more frequently in men [1].

The characteristic macroscopic appearance of CCC is that of a solid or partially cystic, sulphur yellow tumour with haemorrhagic changes (Fig. 1). These small tumours are generally rounded and well-circumscribed. In large tumours or after prolonged development, calcification and possibly ossification may be seen. Necrotic changes are also common.

Table 1  Main genetic alterations observed in renal cell carcinomas.

<table>
<thead>
<tr>
<th>Histological type</th>
<th>Genetic alteration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clear cell carcinoma</td>
<td>-3 (3p25–26)</td>
</tr>
<tr>
<td>Xp11 translocation carcinoma</td>
<td>t (X;1) (p11.2;q21)</td>
</tr>
<tr>
<td></td>
<td>t (X;17) (p11.2;q25)</td>
</tr>
<tr>
<td></td>
<td>t (X;1) (p11.2;p34)</td>
</tr>
<tr>
<td></td>
<td>inv(X) (p11.2;q12)</td>
</tr>
<tr>
<td></td>
<td>t (X;17) (p11.2;q23)</td>
</tr>
<tr>
<td></td>
<td>t (X;3) (p11.2;q23)</td>
</tr>
<tr>
<td>Carcinoma associating TFEB</td>
<td>t (6.11) (p21;q13)</td>
</tr>
<tr>
<td>Papillary carcinoma (type 1)</td>
<td>+7 +17 −Y</td>
</tr>
<tr>
<td>Mucinous tubular and spindle cell carcinoma</td>
<td>−1 −4 −6 −8 −9</td>
</tr>
<tr>
<td></td>
<td>−11 −13 −14 −15 −22</td>
</tr>
<tr>
<td>Chromophobe carcinoma</td>
<td>−1 −2 −6 −10 −13 −17 −21</td>
</tr>
<tr>
<td>Clear cell papillary carcinoma said to be of end-stage renal disease</td>
<td>None</td>
</tr>
</tbody>
</table>

Table 2  Immunohistochemical profile of the main epithelial tumours of the kidney.

<table>
<thead>
<tr>
<th>Histological type</th>
<th>EMA</th>
<th>CD10</th>
<th>Vim</th>
<th>CK7</th>
<th>AMACR</th>
<th>TFE</th>
<th>CD1117</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clear cell carcinoma</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Papillary carcinoma</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Mucinous tubular and spindle cell carcinoma</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Xp11 translocation carcinoma</td>
<td>−</td>
<td>+</td>
<td>−</td>
<td>+</td>
<td>−</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>Clear cell papillary carcinoma said to be of end-stage renal disease</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Chromophobe carcinoma</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>Oncocytoma</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
</tbody>
</table>
Histological classification of malignant renal tumours

Histologically, CCC is composed of clear or less frequently eosinophilic cells arranged in acini or pseudoalveolar structures or in compact masses within a richly vascularised or myxoid stroma. Sarcomatoid differentiation can be seen, as in other histological types of renal tumour (Fuhrman grade 4). The immunohistochemical profile associating expression of EMA, vimentin and CD10 suggests it originates from the cells of the proximal convoluted tubules. The characteristic vascularisation is explained by the molecular mechanisms involved in the development of the disease affecting the VHL gene (3p25-26) [4]. About 70% of patients with Von Hippel-Lindau disease therefore develop a CCC which is usually multiple and bilateral and appears early, before the age of 40. In the case of sporadic clear cell cancer of the kidney, allelic loss, point mutations or methylation of the VHL gene (3p25-26) promoter are almost constant.

Multilocular cystic renal cell carcinoma

This new entity in the 2004 classification represents 1—4% of kidney carcinomas. It is a purely cystic form of tumour (Figs. 2 and 3). The mean age of discovery, which is often by chance, is 50 years old, and again, it is more frequent in men. With CT scan, the lesion is classified as grade 3 or 4 according to the Bosniak classification with thin septa, which may be calcified, but with no identifiable mass [5]. Size is variable and may reach 15 cm. Macroscopically, it is a tumour forming a single mass divided into many cystic cavities filled with clear serous or haemorrhagic fluid, separated by fibrous septa.

The septa are lined with the same clear cells as those seen in the classic histological form. In addition, in the walls of these cysts there are small nests of analogous clear cells. A sinusoidal type of vascular proliferation can be seen.

The differential diagnosis is with cystic carcinoma and cystic nephroma (multilocular cyst) of the adult, a benign tumour in the REST group (renal epithelial and stromal tumours) (Fig. 4) [6,7].

Figure 1. Clear cell carcinoma with central myxoid changes.

Figure 2. Multilocular cystic renal cell carcinoma: absence of tumour mass.

Figure 3. Histology of the same tumour: fine septa covered by tumour cells.

Figure 4. Thick-walled, smooth cystic nephroma with no vegetation.

stage, infiltration was seen although proliferation remains limited to the renal parenchyma, with necrotic and haemorrhagic changes.

All the cases reported in the literature had a good prognosis, and the question of the malignant nature of this tumour remains open [8].

Clear cell papillary carcinoma said to be of end-stage renal disease

This histological form has been individualised recently (it was not recognised in the WHO classification of 2004) [9]. First described in end-stage renal disease, 50% of the cases are seen outside of this context. Morphologically, the cells are clear and with a low Fuhrman grade. They have a small central nucleus giving a very homogeneous appearance to proliferation of the tumour (Fig. 5). The immunohistochemical profile of this tumour is also characteristic (Table 2). Like the previous form, it is usually a low-grade tumour, with a good prognosis: no metastatic form has been reported although multifocal forms have been described.

Renal carcinoma associated with XP11.2 translocation with TFE3 expression

This variant of renal cell carcinoma has been identified for a long time in young patients as “juvenile renal cell carcinoma” [10]. It is primarily a tumour of children (second decade) and young adults who are most often female (M/F = 1/1.4). It represents at least 30% of renal carcinomas in children [11]. A few cases have been described in middle-aged adults and even after 60 years of age [12]. In adults, the incidence is probably underestimated, because in the absence of cytogenetic studies the tumour may be considered as a clear cell carcinoma (CCC), which resembles morphologically (Fig. 6). It often presents at an advanced stage, frequently with lymph node metastases at diagnosis.

The architecture is often mixed and confusing, combining areas of clear cell carcinoma with areas of typically papillary structure. This renal carcinoma is characterised by specific cytogenetic abnormalities, with the formation of fusion genes by balanced translocation consistently involving the TFE3 gene located on Xp11.2 and a partner gene, usually the PRCC gene located on 1q21, or the ASPL gene located on 17q25 [13,14].

The differential diagnosis is between it and CCC or a type 2 papillary carcinoma (see below). In young patients, apart from in Von Hippel-Lindau disease, this diagnosis should be considered and investigated through a cytogenetic study on fresh material. In older patients, the diagnosis can be considered when faced with a high grade partially papillary carcinoma of unusual morphology with large eosinophilic and/or clear cells.

The prognosis is favourable in paediatric patients, particularly when there is no lymph node metastasis. The adult forms seem to be more aggressive. A recent study [15] has shown that the presence of metastatic lymph nodes and age over 25 years were factors for a poor prognosis. Nephrectomy is the treatment of choice for localised forms, while anti-angiogenic treatments have proved their efficacy in metastatic forms [16].

Papillary tumours: adenoma and papillary carcinoma [17]

Papillary tumours are the second most common group of kidney tumours (approximately 10%). They also occur more frequently in men in or around their fifties. Macroscopically, papillary carcinomas may be compact or more or less cystic (Fig. 7). Their size is variable, small forms measuring less than 5mm being considered benign (papillary adenomas). They are sometimes multifocal, bilateral tumours where an adenoma-carcinoma association is possible. This group of tumours is defined by the presence of papillary architecture in at least 75% of the tumour proliferation. This is composed of fibrovascular axes with larger or smaller clusters of lipophages (cells loaded with fat). Necrotic changes are more or less marked, with the presence of cholesterol crystals. Cytokeratin expression, in particular of CK7, is an important point in positive diagnosis (Table 2). The presence of small basophilic cells and a large quantity of lipophages characterises type I papillary carcinomas. In the type II
They are whitish-grey in appearance or more rarely brownish. Haemorrhagic or necrotic changes are rare.

Histologically, the architecture is compact, with tubular areas continuing into spindle cell areas which appear to have come about by compression of the tubes. Mitosis is rare. The spindle cell areas can in places be suggestive of proliferation of smooth muscle cells [19].

The differential diagnosis is made with the compact form of papillary carcinoma, metanephric adenomas, sarcomatoid carcinomas or those classed as renal carcinomas with no other indication. The prognosis, according to data in the literature and concurring with the low-grade histological appearance, seems favourable, except where there is sarcomatoid differentiation. For some authors, this group of tumours should be put in the papillary carcinoma group.

Neuroblastoma-associated renal cell carcinomas

These very rare papillary carcinomas with eosinophilic cells with an oncocytic appearance occur a variable time (often several years) after a neuroblastoma. Apart from their clinical context, they do not have any particular morphological characteristics and are only briefly mentioned here [20].

Oncocytic tumour/chromophobe carcinoma group

A chromophobe carcinoma occurs in approximately 5-7% of cases. Macroscopically, it is a rounded, compact, homogeneous, well-circumscribed, buff coloured tumour (Fig. 9). Necrosis and haemorrhagic changes are exceptional and occur mainly in large tumours. Metastases have been described in about 10% of cases. Aggressive variants, particularly with a sarcomatoid appearance, have been reported [21].

Oncocytoma occurs with similar frequency (5–7%) [22]. Macroscopically, this is a fairly typical, round, buff-brown, compact, well-circumscribed tumour with no haemorrhagic

Low-grade mucinous tubular and spindle cell carcinoma of the kidney (loopoma) [18]

Described for the first time in 1998, this is a tumour of middle-aged adults (in their fifties), occurring more in women (M/F sex ratio = 1/3). These tumours are unusual with less than 80 cases having been reported in the literature. Macroscopically, they occur essentially in the medulla, are well-circumscribed, closed and often homogeneous.

Figure 7. Tumour with a friable and haemorrhagic appearance.

Figure 8. Friable, haemorrhagic tumour destroying much of the kidney. Development from the renal parenchyma but none from the renal pelvis. Differential diagnosis from the macroscopic appearance: urothelial carcinoma.

variant, cell polymorphism is more marked; the cells are more often eosinophilic with a pseudostratified architecture and have a higher Fuhrman grade. This form of carcinoma is considered to be more aggressive. It is usually unifocal (Fig. 8).

The characteristic cytogenetic abnormalities of this tumour group are essentially abnormalities in the number of chromosomes 7 and 17 (Table I).

Figure 9. Buff coloured, multilobed, well delimited tumour, suggesting either an oncocytoma or a chromophobe carcinoma.
or necrotic changes. In 30% of cases, a central fibrous scar is described (Fig. 10). Elsewhere, the appearance may be cystic. An oncocytoma can become very large.

Histologically, an oncocytoma is made up entirely of fairly large, eosinophilic cells with a central round nucleus, which more rarely may be irregular or atypical. The cytoplasm contains many mitochondria. Conversely, chromophobe carcinoma cells often have a wrinkled nucleus with an irregular outline, with a clear perinuclear halo; they also have lighter cytoplasm and a clearly visible membrane, outlining the cytoplasm.

However, it is sometimes difficult to differentiate between oncocytomas and chromophobe carcinomas both from an architectural and a cytological point of view. Hale’s colloidal iron stain shows up diffuse intracytoplasmic microvesicles, in contrast to the oncocytoma where there is focal apical staining. Moreover, expression of E-cadherin and c-kit seem to be more frequent in chromophobe carcinomas.

**Oncocytomatosis [23]**

The presence of many oncocytomas of varying sizes in both kidneys of the same patient is known as oncocyotosis or oncocytomatosis. Clinically, this rare occurrence may be seen at any age. There is usually one or more oncocytoma, possibly measuring several centimetres, that leads to surgery. These lesions can also be unilateral, especially where a kidney is atrophic with parenchymal destruction. Macroscopically, there are multiple nodules measuring centimetres or millimetres, with small cysts.

Histologically, these nodules or cysts are composed of oncocytic cells and small islets of oncocyes are scattered in the parenchyma.

**Birt-Hogg-Dubé syndrome (BHD)**

This is an autosomal dominant genodermatosis with benign skin tumours (trichodiscomas, fibrofolliculomas, acrochord) of the face and trunk that can be associated with tumours of the colon and a pneumothorax. Kidney tumours seem to develop in 15 to 30% of patients, but these tumours can vary histologically (Fig. 11) [24]. The gene responsible for the disease (folliculin: 17p11) acts as a tumour suppressor gene. In practice, if faced with multiple kidney tumours of the chromophobe carcinoma and oncocytoma type, with or without skin lesions, investigation of the family should be offered.

**Bellini duct carcinoma [25]**

These represent less than 1% of kidney tumours and occur most often in men in their fifties, sometimes earlier, and always have a poor prognosis.

Macroscopically, they are usually hilar tumours and already at the extended stage at the time of the initial diagnosis. They are poorly delimited, show considerable necrotic change and infiltrate the adipose tissue (Fig. 12). From the histological point of view, they are characterised by a very inflamed stroma and atypical eosinophilic carcinoma cell...
masses, forming a vaguely tubular or trabecular architecture.

A very aggressive variant has been found in young people less than 40 years of age with sickle cell trait, known as renal medullary carcinoma. For unexplained reasons, these tumours are more frequently on the right side. Molecular biology studies discuss a similarity with urothelial carcinoma of the renal pelvis. Survival is usually less than 15 weeks [26].

**Angiomyolipomas**

Angiomyolipomas (AML) are benign renal tumours. Their place in this survey may therefore appear strange. However, apart from the fact that some (epithelioid) forms of AML are differential diagnoses for renal carcinomas, the molecular mechanisms underlying their formation justify their inclusion in this topic.

AMLs occur in the kidney either sporadically or as part of tuberous sclerosis (Bourneville’s disease). In patients between 25 and 35 years old with tuberous sclerosis, the incidence of AML is estimated to be 50% [27].

AML occurs four to five times more often in women than in men. When small, they are often located subcapsularly. They may have several extensions into the kidney, which may merge together, or they can extend into the renal fat without invading it (Fig. 13). Some AMLs may merge going so far as to infiltrate the whole kidney. A number of AMLs have been described extending into the lumen of vessels, the renal vein and vena cava, without nevertheless altering their prognosis.

The macroscopic appearance depends on the respective proportions of the three cell types: adipose, muscle and vascular cells. In a pararenal site, it can be very difficult to diagnose an AML, if it is predominantly formed from muscle or fat tissue. The differential diagnosis is between it and a leiomyosarcoma or a liposarcoma. Angiomyolipomas are benign tumours with the exception of a few reported cases of epithelioid angiomyolipoma (an atypical variant that had a fatal outcome).

![Figure 13. Centrally growing angiomyolipoma.](image)

**Renal epithelioid angiomyolipoma**

The epithelioid variant of angiomyolipoma (AML) was described by two teams in 1997 and 1998 [28,29]. The first cases described reported a poor prognosis, in contrast to the usual good prognosis for AML. Recent publications have confirmed this poor prognosis, with the appearance of lymph node or visceral metastases in nearly a third of cases where there is atypia, mitosis and necrosis [30]. It is a renal or pararenal perivascular epithelioid cell tumour (PEComa) with epithelioid morphology, which occurs with equal frequency in men and women, particularly in their forties. More than half of the cases are seen in the context of tuberous sclerosis (TS).

The tumour is usually large (more than 6 cm), compact, greyish white, poorly defined, with haemorrhagic changes. Microscopically, tumour proliferation consists of spindle cells often with abundant clear cytoplasm and large, eosinophilic, epithelial-like, polygonal or ovoid, globular cells (Fig. 14).

The basic differential diagnosis is with eosinophilic renal cell carcinoma. Immunolabelling (HMB45, Melan, A Mitf) is essential here.

![Figure 14. Epithelioid angiomyolipoma: irregular appearance, with giant cells and, at upper right, adipocytes.](image)

**The impact of genetic studies on understanding familial forms and targeted therapy**

**Familial syndromes**

Table 3 sets out the main familial syndromes in which renal tumour involvement is seen, with the genes involved.

**The genetic bases of targeted therapies**

The frequency of alterations to the VHL gene or its product (mutation, deletion, methylation) have made renal tumours a particular area for applying targeted, essentially anti-angiogenic, therapies [31]. As in many other tumoral processes, kidney tumours are characterised by
Table 3 Main genetic syndromes with renal involvement.

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Gene</th>
<th>Chromosome</th>
<th>Renal effect</th>
<th>Other organs involved</th>
</tr>
</thead>
<tbody>
<tr>
<td>VHL (Von Hippel-Lindau)</td>
<td>VHL</td>
<td>3p25</td>
<td>Multiple bilateral renal carcinomas and renal cysts</td>
<td>Haemangioblastomas of the cerebellum and retina, pheochromocytomas, pancreatic cysts and endocrine tumours, tumours of the endolymphatic sac and inner ear, cystadenomas of the epididymis and the broad ligament</td>
</tr>
<tr>
<td>Hereditary papillary carcinoma</td>
<td>C-MET</td>
<td>7q31</td>
<td>Bilateral and multiple type 1 papillary carcinomas of the kidney</td>
<td>Uterine leiomyomas and leiomyosarcomas</td>
</tr>
<tr>
<td>Hereditary leiomyomatosis and carcinomas of the kidney</td>
<td>FH (fumarate hydratase)</td>
<td>1q42</td>
<td>Non type 1 papillary carcinomas of the kidney</td>
<td>Pulmonary cysts, spontaneous pneumothorax, facial fibrofolliculomas</td>
</tr>
<tr>
<td>Birt-Hogg-Dubé</td>
<td>BHD (folliculin)</td>
<td>17p11</td>
<td>Oncocytomas, chromophobe carcinoma, hybrid tumours, bilateral and multiple oncocytic papillary carcinomas Angiomyolipomas, lymphangiomyomatosis, bilateral and multiple renal cysts</td>
<td>Cardiac rhabdomyomas, adenomatoid polypsis of the duodenum and small intestine, pulmonary cysts, cortical tuberosties and subependymal giant cell tumours etc.</td>
</tr>
<tr>
<td>Tuberous sclerosis (TSC syndrome, Bourneville’s disease)</td>
<td>TSC1</td>
<td>9q34</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>TSC2</td>
<td>16p13</td>
<td></td>
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</tr>
</tbody>
</table>

local vascular growth, the function of which is to provide the tumoral process with the oxygen needed to grow. This neoangiogenesis is particularly marked here, as the histological appearance of CCCs shows, due to the involvement of the VHL gene the product of which plays a crucial role in regulating the response to hypoxia. Under hypoxic conditions, HIF1α and HIF1β form a complex that induces the synthesis of VEGF and other growth factors responsible for neovascularisation. In normoxic conditions, the product of the VHL gene prevents the formation of an efficient HIF1αβ complex and thus the synthesis of angiogenic factors. In the case of renal CCC, loss or mutation of the VHL tumour suppressor genes results in the activity of the HIF1 complex being maintained. Local secretion of growth factors leads to stimulation of the PI-3-kinase pathway or targets of the RAS pathway, activating the synthesis of HIF, which in turn results in uncontrolled stimulation of angiogenic factors. While anti-VEGF therapies specifically target the VEGF pathway, being either directly anti-VEGF (bevacizumab) or anti-tyrosine kinase receptors (sunitinib, pazopanib, sorafenib), the mTOR inhibitors (temsirolimus, everolimus) act specifically on cell growth (RAF pathway and PI-3-kinase) [32].

The role of genetic studies in the indication for targeted therapy

The efficacy of these various drugs has been demonstrated in metastatic forms of renal tumours, irrespective of their histological profile. CCCs, as well as translocation carcinomas, papillary carcinomas and mucinous tubular and spindle cell carcinomas are all sensitive to these drugs with similar efficacy.

At present, however, two key issues remain unresolved: which renal tumours with purely local development are likely to develop with a poorer outcome after surgical resection and which metastatic renal tumours will respond best to a specific targeted therapy?

Prognostic criteria

The Fuhrman grade and pT stage are the best prognostic factors known apart from in a few specific morphological types. Clear cell papillary tumours (said to be of end-stage renal disease) and multicystic forms of renal carcinoma (multicystic clear cell carcinoma, tubulocystic carcinoma) usually
have a good prognosis (grade 1). Similarly, chromophobe carcinomas, type 1 papillary carcinomas and mucinous tubular and spindle cell carcinomas have a good prognosis. The Fuhrman grade applied to CCCs and tubulopapillary carcinomas is still the best histo-prognostic factor known. The size of the tumour and especially its extension beyond the limits of the renal parenchyma (pT3 and beyond) are detrimental factors reported in all the major series of patients. To date, no molecular marker or multifactorial molecular model has been demonstrated to have a predictive value [33].

Predicting the therapeutic response

The answer to this question is more complex. The main prognostic models in use employ pre-treatment clinical characteristics (performance status, free interval, number of metastases and laboratory variables - serum calcium, haemoglobin and lactate dehydrogenase concentrations). These models are still relevant but are inadequate for determining the response to anti-angiogenic agents. Certain authors have studied the nature of the alterations in the VHL gene and their impact on responses to targeted therapies [34].

For these authors, simple inactivation of the VHL gene (for example, by methylation of its promoter) had no significant impact on the therapeutic response. On the other hand, loss of function by mutation of the reading frame (deletion, insertion, nonsense mutation) was associated with a better therapeutic response.

In parallel to study of Von Hippel-Lindau disease, study of familial forms of papillary carcinoma of the kidney emphasised the role of MET (7q31-34) in the genesis of renal carcinomas. Activation of the MET tyrosine kinase domains, after binding of its HGF (Hepatocyte Growth Factor) ligand, leads to recruitment of intracellular targets (Grb2, SRC etc.) and activation of metabolic pathways (PI3K, Ras/MAPK), involved particularly in cell migration and invasion [35]. Different MET mutations have been identified in the familial forms and in sporadic cases of papillary carcinoma of the kidney [36]. MET could also be involved in the genesis of some forms of translocation carcinoma [37] and the development of the metastatic potential of clear cell carcinomas (Met/β-catenin interactions) [38]. Three therapeutic strategies are being investigated, aiming to inhibit interaction of MET with its ligand, activation of its tyrosine kinase activity or recruitment of its intracellular effectors, alone or in combination with other targeted therapies [35]. Again, the mutation profile of MET appears to play a role in the sensitivity of the tumour to the chemotherapy given [39]. Moreover, some serum or tissue markers may be predictive of a therapeutic response [40].

Other genes are involved in familial forms of kidney cancer (affecting fumarate hydratase in renal carcinomas associated with hereditary leiomyomatosis or folliculin in Birt-Hogg-Dubé syndrome) (Table 3). Their precise role and the therapeutic implications of changes to them are interesting fields for investigation but are still hypothetical [41].

Finally, in addition to the involvement of the mTOR pathway in renal carcinogenesis, we must remember the important role of this pathway in the genesis of renal tumours associated with tuberous sclerosis and sporadic, classic or epithelioid angiomyolipomas [42,43].

Conclusion

The particular place of VHL and the metabolic pathways controlling angiogenesis has made kidney tumours a particularly exciting field of investigation for targeted therapies. Furthermore, the large number of genetic syndromes associated with renal tumours opens promising therapeutic perspectives. However, while the classification of renal tumours has been enriched by new entities, some of which are not yet included in the latest WHO classification, distinction between the various entities making up this group is still based essentially on clinical and histological criteria, supported by the existence of specific immunohistochemical and sometimes cytogenetic profiles. The all-molecular epoch is still hypothetical.

**TAKE-HOME MESSAGES**

General concepts:
- tumour classification contains many variants, which are sometimes difficult to classify, even histologically. The key element is the morphological appearance;
- the two factors for the histological prognosis of a renal cancer are:
  - the Fuhrman grade, which applies, above all, to clear cell carcinomas and less so, to papillary carcinomas,
  - the pTNM stage; since 2009, invasion of the adrenal glands by the cancer is considered to be pT4.

Specific concepts:
- in young subjects, we must consider a renal carcinoma associated with Xp11.2 translocation with TFE3 expression. Often these are large tumours (microcalcifications may be present). In metastatic forms the treatment of choice is chemotherapy after surgery;
- there are many cystic lesions, the largest group being the REST group, followed by multilocular cystic renal cell carcinomas. All of these have a good prognosis;
- many genetic syndromes exist, the most important being the Von Hippel-Lindau (VHL) syndrome. These syndromes must be considered where there are multiple lesions;
- genetic studies have an impact on predicting the response to targeted therapies.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.
References


