

Review Article**Chromophobe renal cell carcinoma: A review of an uncommon entity**Francisco Emilio Vera-Badillo,¹ Esther Conde² and Ignacio Duran^{1,3}¹Department of Medical Oncology, ²Laboratory of Therapeutic Targets, Clara Campal Comprehensive Cancer Center, Madrid Sanchinarro University Hospital, and ³School of Medicine, University CEU San Pablo, Madrid, Spain**Abbreviations & Acronyms**

Akt = protein kinase B
BHD = Birt–Hogg–Dubé
ccRCC = clear cell renal cell carcinoma
chRCC = chromophobe renal cell carcinoma
CI = confidence interval
CSS = cancer-specific survival
CT = computed tomography
DFS = disease-free survival
KIT = tyrosine-protein kinase kit
IFN = interferon
mRCC = metastatic renal cell carcinoma
mTOR = mammalian target of rapamycin
OS = overall survival
PFS = progression-free survival
pRCC = papillary renal cell carcinoma
RCC = renal cell carcinoma
RFS = recurrence-free survival
VEGF = vascular endothelial growth factor

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Abstract: Renal cell carcinoma is the most common neoplasm of the kidney. It is a heterogeneous disease, comprised of different histological variants with a distinct clinical course, genetics and response to treatment. The various subtypes identified include clear cell, papillary and chromophobe, among others. Chromophobe renal cell carcinoma is a rare variant and accounts for 5% of all cases. These tumors are macroscopically larger when compared with other forms and are commonly diagnosed at an early stage. Despite significant advances in renal cell carcinoma therapeutics in the past decade, no standard treatment has been identified for advanced chromophobe renal cell carcinoma. Nevertheless, new molecular insights have recently become available. A familial form of renal cell carcinoma, the Birt–Hogg–Dubé syndrome, has been described and the knowledge obtained has opened research opportunities in the therapeutic arena of chromophobe renal cell carcinoma. The following manuscript will endeavor to provide an overview of this uncommon entity including pathology, epidemiology, genetics, clinical aspects, and current and future treatment options.

Key words: chromophobe renal cell carcinoma, metastatic renal cell carcinoma, mammalian target of rapamycin inhibitors, renal cell carcinoma, tyrosine kinase inhibitors.

Introduction

RCC is the most frequent neoplasm of the kidney. In the USA, over 50 000 new cases were diagnosed in 2010, and approximately 13 000 deaths were related to RCC.¹ This disease accounts for approximately 2–3% of all cancers, most cases being sporadic. Nevertheless, in the past decade, research of familial forms of RCC has provided critical insights into the molecular basis of this neoplasm.

The lifetime risk of developing RCC is estimated to be 1.34%.² Approximately one-third of patients present with advanced disease at diagnosis, and recurrence occurs in 30–40% of cases treated for a localized tumor.^{3,4}

RCC is a heterogeneous disease, comprised of different histological variants with a distinct clinical course, genetic changes and response to systemic treatment. The categorization of RCC is based on the World Health Organization (WHO) classification, which includes different subtypes based on morphology, including clear cell, papillary, chromophobe, granular, spindle cell, cyst-associated, translocation carcinomas and collecting-duct carcinomas.^{5,6} The most common subtype is clear cell, accounting for 75%, papillary follows with 10%, chromophobe 5% and undifferentiated represent approximately 10% of cases.

The systemic treatment of mRCC has evolved drastically during the past decade. A plethora of clinical trials have been carried out targeting the angiogenesis pathway and its different components. The results have led to the approval of a number of drugs for the treatment of mRCC, thus changing the natural history of the disease and doubling the median overall survival of this patient population in comparison with the survival in the cytokine era.^{7–15}

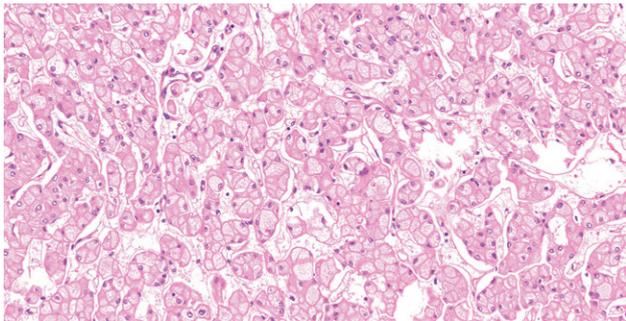


Fig. 1 Large polygonal cells with transparent slightly reticulated cytoplasm with prominent cell membranes in a stone paving pattern (hematoxylin-eosin; magnification: $\times 200$).

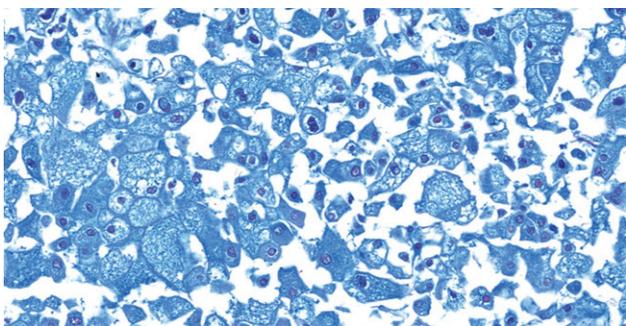


Fig. 2 Hale's colloidal iron stain positivity in the cytoplasm (magnification: $\times 400$).

However, despite these major advances, most of the progress has been in the field of ccRCC providing limited evidence of the impact in the non-clear cell histologies.

The present review will focus on the chRCC subtype. Features such as epidemiology, pathology, genetic alterations and current treatment options will be discussed.

Pathology

Macroscopically, chRCC are well-circumscribed solid neoplasms and highly lobulated. The surface appears homogeneously beige, light tan, brown, mahogany brown or yellow.¹⁶ The median tumor size is 6.0 cm, which is larger than other subtypes.¹⁷

Microscopically, the growth pattern is solid, at times tubulocystic, with broad fibrotic septa. Two types of tumor cells might be present in varying proportions. The first type; pale cells are large, polygonal cells with abundant transparent cytoplasm and prominent cell membranes.¹⁸ Typically, they are admixed with a second population of smaller cells with granular and eosinophilic cytoplasm. The nuclei of both are irregular. Binucleation and perinuclear halos are common¹⁹ (Figs 1,2). The first depiction of a renal chromophobe tumor was in 1985 by Thoenes and Colls. In 1988, the same group reported a series of 32 cases showing a more favorable prognosis.^{20,21}

There are different variants of chRCC according to proportion of cells; classic, eosinophilic and mixed. The eosinophilic variant ($>80\%$ eosinophilic cells) shares certain characteristics with oncocytomas (nested, alveolar or sheet-like architecture with eosinophilic granularity, perinuclear clearing and peripheral accentuation of cytoplasm). This type is often bilateral (11%) and multifocal (22%). The classic type ($>80\%$ pale cells) is associated with necrosis and sarcomatoid changes (aggressive tumors with a high potential for distant metastases). Mixed chRCC have variable architecture.¹⁶

Pathological diagnostic criteria have been described, including Hale colloidal iron and intracytoplasmic microvesicles,¹⁹ which can be seen by electron microscopy. Immunohistochemistry could be helpful to confirm diagnosis of chRCC with positivity in cytokeratin 7 (60–100%), epithelial mesenchymal antigen (75–100%) and parvalbumin (100%).^{22,23}

Oncocytoma, a benign lesion, can frequently be confused with a chRCC, because it consists of a pure population of oncocytes. These are large, well-differentiated, neoplastic cells with intensely eosinophilic granular cytoplasm as a result of a large number of mitochondria.²⁴ The origin of these tumors is the same as chRCC.²⁵ Because of similarities in imaging and cytology findings with chRCC, proper pathological diagnosis of oncocytoma is primarily carried out after surgery. Its potential for metastasis is almost zero. However, a published study of 29 patients described local progression.²⁶

chRCC can also present as a sarcomatoid variant. Spindle-like cells, high cellularity, cellular atypia, commonly associated necrosis and microvascular invasion will be the typical features. This histological form appears more commonly in chRCC than in other RCC subtypes. At presentation, a significant proportion are locally advanced or metastatic and overall have a poor prognosis. Unlike the non-sarcomatoid variants, these tumors tend to respond to chemotherapy. Gemcitabine and doxorubicin have been used in this setting with modest outcomes. More recently, combinations of cytotoxics with targeted agents (i.e. gemcitabine + sunitinib) have shown activity.^{27,28}

Epidemiology

chRCC comprises 5–10% of the total cases of RCC. It represents approximately 3000–6000 of new cases of the 61 000 expected new RCC cases in 2011 in the USA.²⁹ The mean age of occurrence is reported in the fifth decade, with a range of 27–86 years, more commonly observed in women (52%) than in men (48%). Most of the cases are diagnosed in stage I or II. Renal vein invasion is seen in approximately 5% of cases and incidence of metastatic disease is 6–7%. The most common sites of metastases are liver (39%) and lung (36%). Typically, chRCC presents as

a large solitary solid compact mass without necrosis or calcification.³⁰

Genetics

The genetics of chRCC have not been explained fully. Non-random loss of chromosomes 1, 2, 6, 10, 13, 17 and 21³¹ could lead to tumor suppressor gene inactivation, promoting tumorigenesis.³² In fact, losses of chromosomes 2, 10, 13, 17 and 21 have been described in 93%, 93%, 87%, 90% and 70% of chRCC, respectively, and can be used as a diagnostic marker when there are doubtful histology findings.³³

New insights are emerging from the description of a familial form of the disease, BHD syndrome, characterized by benign cutaneous lesions (fibrofolliculomas), pulmonary cysts, spontaneous pneumothorax, and bilateral, multifocal RCC.³⁴ Approximately 30% of patients with this familial disease will present with chRCC, 5% with oncocytomas, and 50% will express a mixed pattern of chRCC and oncocytoma.³⁵ BHD syndrome is the consequence of inactivating mutations in the folliculin (*FLCN*) gene. *FLCN* is located on the short arm of chromosome 17,³⁶ and is altered (90% of events) through insertion, deletion or nonsense mutations in the germline of the vast majority of affected individuals. The gene product is folliculin, that in normal conditions forms a complex with two other proteins (FNP1 and FNP2) that bind adenosine monophosphate-activated protein kinase to negatively regulate mTOR activity.³⁷ The majority of germline mutations that have been described in *FLCN* are predicted to truncate the protein. When DNA sequencing was carried out to identify somatic mutations in the wild-type allele of *FLCN* in renal tumors from patients with BHD syndrome, a loss of heterozygosity of the *FLCN* locus was observed in 17% of renal tumors, and sequence alterations were seen in 53%. This supports the view that *FLCN* might be a tumor suppressor gene.

In *FLCN* $-/-$ tumors, there is a mTOR upregulation that activates both mTORC1 and mTORC2 pathways. Furthermore, in animal models with this phenotype, renal tumors and cysts developed,³⁸ and the use of mTOR inhibitors prolonged survival and induced tumor responses, thus unveiling a potential therapeutic field.³⁹ However, one study published by Nagy and Colls involving eight patients with sporadic chRCC reported allelic losses at chromosome 17 in all, but failed to identify any *FLCN* mutations.⁴⁰ Thus, the role of this genetic abnormality in the sporadic tumors remains a matter of debate.

Another mechanism associated with intracellular signal transduction in chRCC is KIT (CD117). It regulates apoptosis, cell differentiation, proliferation, chemotaxis, and adhesion.¹⁹ In the membrane of chRCC cells, an overexpression of KIT has been described in approximately 88–100% of cases.⁴¹ The immunohistochemical detection of KIT might be a modality to support a diagnosis of chRCC. In

addition, KIT can be considered a target of treatment, although this requires further clinical evaluation.

VEGF was reported to be expressed in all subtypes of renal cell carcinomas. However, a correlation between the expression of VEGF and survival time was not shown.⁴²

Clinical presentation

In general, this tumor remains clinically elusive and the triad of hematuria, pain and flank mass is present in only a small percentage of patients, and often indicates advanced disease. Additional signs and symptoms observed can include hypochromic anemia secondary to hematuria or hemolysis (29–88%), pyrexia (20%), cachexia, fatigue and weight loss (33%).⁴³

Individuals affected by BHD syndrome have the following clinical characteristics: benign hair follicle tumors (fibrofolliculoma), pulmonary cysts and bilateral multifocal renal tumors.⁴⁴ Fibrofolliculomas tend to occur on the face and neck, and can be very subtle. Pulmonary cysts are present in 82% of the gene carriers and are best detected by high-resolution lung CT. A subsequent pneumothorax is reported in approximately 32% of patients.³⁴

Radiology characteristics

The most commonly used imaging technique for evaluation of renal masses is CT, because it provides information about the tumor itself and the surrounding structures.⁴⁵ Analyzing the dynamic pattern of enhancement can differentiate the different subtypes of renal cell carcinomas. It has been described that ccRCC (84%), pRCC (74%) and collecting duct RCC (100%) tend to show heterogeneous or predominantly peripheral enhancement, whereas chRCC (69%) usually shows homogeneous enhancement. In approximately one-third of the patients (38%) with chRCC, calcifications have been noted, although this is a rare event in ccRCC¹¹. Sensitivity and specificity vary according to the CT phase (corticomedullary or excretory); 74–84% and 91–100%, respectively.⁴⁶

Characterization by imaging of renal cell carcinomas for diagnostic purposes has been attempted using dynamic contrast-enhancement magnetic resonance imaging, showing that chRCC tends to show an intermediate index of enhancement at corticomedullary and nephrographic phases compared with the large index for ccRCC and low index for pRCC.⁴⁷

Treatment

Local disease

chRCC has an overall better prognosis than other subtypes of RCC. The improved prognosis is more evident in local stages, with survival rates approximately 90% at 5 years.^{48–50}

Table 1 RFS and CSS according to T stage and grade in patients with chRCC

T	RFS 5 years (%)	CSS 5 years (%)	Fuhrman grade	RFS 5 years (%)	CSS 5 years (%)
1	91.1	93.3	1	100	100
2	80.3	81.8	2	88.1	90.7
3–4	53.2	85.9	3–4	71.9	84.1

In chRCC, RFS at 5 years for those after surgical resection is 83% and CSS is 89%.⁵¹ (Table 1).

The majority of trials have reported a similar outcome.^{52,53} Patard *et al.* have reported better outcomes compared with ccRCC in cases of localized or high-grade disease.⁵⁴ When controlling for stage and size, chRCC was a significant predictor of DFS compared with ccRCC.¹⁷

Clinical characteristics at diagnosis and DFS of patients with chRCC support an indolent nature of this disease.

When there are recurrences, the sites more commonly involved are the lung, liver and retroperitoneal nodes. Two sites of relapse are frequently observed (66.7%), compared with ccRCC and pRCC, where there is more often solitary recurrence. For chRCC, the liver is the commonest site of recurrence.⁵⁵

Even in the setting of metastatic disease, chRCC has a better prognosis than pRCC, and a similar prognosis to ccRCC, with a median survival of approximately 29 months compared with 5.5 months in pRCC.⁵⁶

Metastatic disease treatment

Despite the great advances achieved in the treatment of advanced RCC over the past 10 years, there is no standard of treatment for chRCC yet.^{8–10,14,57} All the information comes from retrospective studies within expanded access programs or small prospective series.

Current evidence for the different available drugs in advanced RCC will now be summarized:

1 mTOR inhibitors

Two major intracellular pathways, the c-erbB2/HER2 and the mTOR signaling pathway have been shown to be deregulated in chRCC patients in some exploratory analysis of mRNA expression.⁵⁸ Phosphorylation and overexpression of energy pathway genes have also been reported in this population.⁵⁹ Thus, agents targeting the PI3K–Akt–mTOR pathway seem a reasonable option for the treatment of this tumor type.

Unlike the registration studies with tyrosine kinase inhibitors that were restricted to patients with clear cell histology, the pivotal trial of the mTOR inhibitor, temsirolimus, in patients with advanced RCC included up to 18% of patients with non-clear cell histology. This was a phase III, randomized, open-label study comparing IFN alone, temsirolimus

alone and temsirolimus in combination with IFN in patients with previously untreated advanced RCC who had at least three of six protocol-specified risk factors for short survival. The primary end-point was OS.¹⁴ The study was positive, favoring the arm of temsirolimus alone with a median OS of 10.9 months. A recent subgroup analysis of this study aimed to evaluate the effect of temsirolimus in patients with non-clear cell histologies. For the purpose of these analyses, only patients in the single-agent IFN or single-agent temsirolimus arms were compared. Patients' characteristics were balanced for both clear cell and other histologies in the IFN and temsirolimus groups. A total of 170 patients (83%) in the IFN group and 169 (82%) patients in the temsirolimus group had RCC with clear cell histology. A total of 36 (17%) patients in the IFN group and 37 (18%) patients in the temsirolimus groups had other primary histology, non-clear or indeterminate. Among patients treated with temsirolimus, those with tumors of clear cell or other histologies showed comparable median OS (clear cell median 10.7 months, 95% CI 8.5–13.0; other median 11.6 months, 95% CI 8.9–14.5). In contrast, patients with tumors of other histologies treated with IFN showed a shorter median OS than patients with tumors of clear cell histology (clear cell median 8.2 months, 95% CI 6.6–10.4; other median 4.3 months, 95% CI 3.2–7.3). When looking at subtypes, most of the non-clear cell patients were papillary, and just five and seven patients were chRCC in the temsirolimus and IFN arm, respectively. Thus, temsirolimus appears to benefit patients regardless of histology, although the small numbers limit the conclusions. More recent evidence in the literature corresponds to several case reports underlying the efficacy of mTOR inhibitors in these type of patients, normally in the second- or third-line setting, after progressing on other treatment strategies, such as cytokines and/or tyrosine kinase inhibitors.^{60–62}

2 c-Kit inhibitors

chRCC tumors express CD117 (KIT), a membrane receptor that plays an important role in signal transduction. However, mutations have not been detected in this population in contrast with the findings in other tumor types, such as gastrointestinal stromal tumors. KIT inhibitors, such as imatinib, dasatinib or nilotinib, could be effective in this type of renal cell cancer, but no hard data are yet available.¹⁹

3 Tyrosine kinase inhibitors

Both sorafenib and sunitinib have been evaluated in patients with advanced chRCC.⁶³ In North America, the expanded access program of sorafenib included 20 patients with chRCC, and one achieved a partial response (5%).⁶⁴ Choueiri *et al.* reported their experience with non-clear cell patients, and among the 12 chRCC patients included, seven were treated with sunitinib and five were treated with sorafenib. Two patients treated with sorafenib and one patient treated with sunitinib achieved a partial response, corresponding to a response rate of 25% (three of 12 patients). PFS for chRCC patients was 10.6 months. Sorafenib-treated patients tended to have a more prolonged median PFS (27.5 months).⁶⁵

Characteristics of this research (retrospective, non-randomized) and the limited number of patients evaluated argue against a definitive conclusion in the treatment of this subgroup of patients. Even when the number of patients included for evaluation is small, this retrospective analysis is the largest to report treatment outcomes for patients with chRCC.

Sunitinib was evaluated in an expanded access program driven mainly in European hospitals; inclusion of non-clear RCC was allowed and a total of 588 (13%) patients were included for evaluation. Unfortunately, distribution by subtypes was not carried out. Objective responses were reported in 11% of patients (<1% complete responses and 11% partial responses), stability for >3 months was described in 57% of patients. Median progression-free survival and median overall survival were 7.8 months and 13.4 months, respectively; for ccRCC after cytokine therapy, the median progression-free survival and median overall survival were 11.1 months and 18.1 months, respectively.⁶⁶ It shows that sunitinib is an active treatment option. Case reports have also been reported to discuss efficacy and sequencing of treatment.⁶²

Ongoing studies

Multiple studies are ongoing in this patient population. Two of them are investigating sunitinib, either as a single arm phase II study (NCT00465179) or as a randomized phase II trial versus temsirolimus (NCT00979966; <http://clinicaltrials.gov/ct2/search>).

Conclusion

chRCC is a rare variety of kidney neoplasm that has recently been better characterized from a molecular and genetic perspective. Overall, it is considered to have a better prognosis, and is associated with earlier stage tumors and longer overall survival compared with ccRCC. When advanced, conflicting data exist regarding its prognosis.

This tumor variety has been scarcely represented in the large randomized studies that have changed the standards in RCC therapy in recent years. To date, no standard of treatment has been established and most of the evidence is from small retrospective series or anecdotal cases.

However, new insights about its genetics and molecular biology have opened a new and promising research field. The PI3K–Akt–mTOR pathway seems to play a relevant role in this tumor type in preclinical models, and this could explain some activity observed with mTOR inhibitors. Current studies are testing drugs directed at this intracellular pathway and its main regulators.

Other potential targets are KIT, and the VEGF receptor family and their ligands/effectors. Yet, the scarce data in this setting preclude any definitive conclusions.

In the future, these patients should not be excluded from the very intense research effort in the field of RCC therapeutics. Only prospective trials will give us the appropriate information to guide treatment decisions in this population. More importantly, a greater knowledge about the molecular basis of this disease is required to guide future drug development in this setting.

Conflict of interest

None declared.

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