

Non–Clear Cell Renal Cancer: Features and Medical Management

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Key Words

Renal cell cancer, non–clear cell, papillary, chromophobe, collecting duct, sunitinib, sorafenib, temsirolimus, c-MET

Abstract

The treatment of metastatic renal cell carcinoma (RCC) has changed dramatically with the introduction of targeted therapies against vascular endothelial growth factor and the mammalian target of rapamycin. Because patients with clear cell histology account for more than 80% of patients with RCC, little evidence is available on treating patients with non–clear cell histologies. Most clinical trials have excluded them from enrollment, except for a randomized study investigating temsirolimus. Many retrospective studies on the use of sunitinib, sorafenib, and temsirolimus in patients with non–clear cell histology have shown response rates ranging from 3.7% to 16%. Prospective studies in non–clear cell histologies are ongoing. Although response rates may not be as high as those in patients with clear cell histologies, targeted therapy may provide a clinically meaningful response. New investigational therapies are on the horizon for papillary RCC—the most-common non–clear cell RCC histology—targeting pathways specific to this histology, such as the c-MET pathway. (*JNCCN* 2009;7:659–665)

The most common renal cell carcinoma (RCC) histology is the conventional clear cell subtype, accounting for more than 80% of all RCCs.¹ Although not as common, the remaining subtypes, papillary (10%–15%), chromophobe (5%–10%), and collecting duct carcinoma (< 1%), represent an important group, and their treatment is a source of clinical controversy (Figure 1). Because novel tyrosine kinase inhibitors (TKIs) and mammalian target of rapamycin (mTOR) inhibitors have changed the armamentarium of treatment options, therapy specific to patients with different histologies is being refined.

Patients with non–clear cell histology RCCs are excluded from most clinical trials. These histologies are rarely encountered in regular practice, and little evidence is available regarding treatment. This article outlines emerging data on the treatment of non–clear cell RCCs.

The Heidelberg classification published in 1997 categorized malignant parenchymal renal cell neoplasms into 4 subtypes:² conventional clear cell, papillary, chromophobe, and collecting duct carcinomas. Metanephric nephradenoma, oncocytoma, and papillary adenoma are benign tumors. Sarcomatoid differentiation is not a histologic subtype on its own but represents a transformation to a higher-grade malignancy. It is generally associated with a poor prognosis.³

Conventional clear cell RCC arises from the proximal convoluted tubule and has clear cytoplasm on routine microscopic sections. The most common genetic alteration is a highly specific deletion of chromosome 3p and a von Hippel-Lindau gene mutation that occurs in most cases.² Metastatic disease occurs more frequently in this subtype; 12% to 21.5% of cases compared with 2.9% to 14.9% of cases in papillary or chromophobe histologies.^{4–6}

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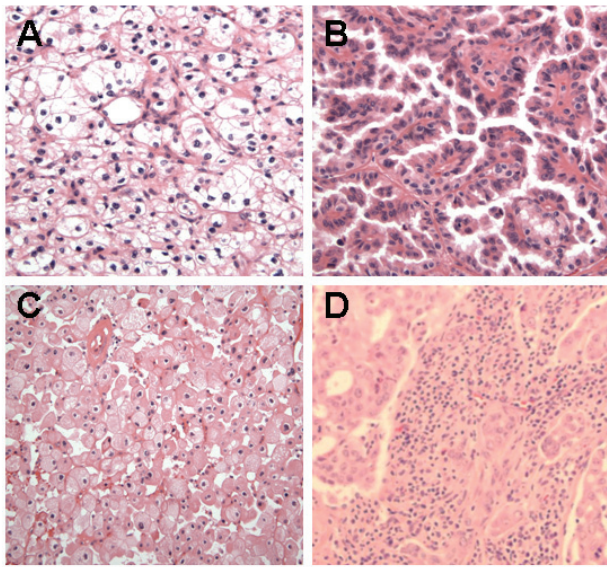


Figure 1 Renal cell cancer of different histologies under light microscopy with hematoxylin and eosin staining. A) clear cell; B) papillary; C) chromophobe; and D) medullary carcinoma. Courtesy of Sabina Signoretti, MD.

by small cells with pale cytoplasm and low nuclear grade, whereas type II tumors show large nucleated eosinophilic cells of high nuclear grade.⁷

The genetic alterations in papillary carcinoma are different from those of clear cell cancers. Papillary carcinomas typically do not have the chromosome 3p mutation, but rather have trisomy of chromosomes 3q, 7, 8, 12, 16, and 20, and loss of the Y chromosome as the most frequent genetic alterations. Frequently, a duplication of the *c-MET* proto-oncogene occurs on chromosome 7, which encodes the receptor for hepatocyte growth factor.⁷ This may be found in patients with heritable and sporadic disease, thus leading to ongoing clinical trials investigating drugs targeting this pathway. In the hereditary form of type II papillary RCCs, mutations in fumarate hydratase have been detected, although their link to the pathogenesis of these cancers is unknown.⁸

Papillary tumors tend to have a multifocal nature and may present with bilateral kidney involvement. They are also more likely to present with early-stage disease. For example, in a cohort of 157 papillary carcinomas, 85% presented with stage I or II disease and only 6% with metastatic disease.⁵

Implications for Survival

In the setting of localized disease, papillary RCC is associated with an improved overall survival compared with clear cell histologies.^{6,9} In one of the

largest series of 4063 patients with RCC, 5-year survival rates for localized papillary RCC were 79.4% (n = 396) versus 73.2% (n = 3564) for clear cell carcinoma.⁶ In a similar series of 2385 patients with RCC, which included those with metastases (4.1%–4.9% in non-clear cell cancers and 15.8% in clear cell), 5-year survival rates for papillary versus clear cell carcinoma were 87.4% and 68.9%, respectively.⁴

Type I and II papillary cancers may have prognostic differences, as shown in a multivariate analysis reporting 7-year disease-free survival rates of 92% and 44%, respectively (log rank, $P < .001$).¹⁰ More recently, a refinement of the former classification has been proposed based on pathologic and molecular characteristics. The first class consists of type I, low-grade type II, and mixed type I/II. In class I papillary RCC, G1-S checkpoint gene dysregulation is present and *c-MET* continues to be overexpressed. Patients with class I papillary RCC have excellent survival rates, in contrast to those with class II, which consists of papillary type II RCC with high-grade and dysregulation of the G2-M checkpoint gene.¹¹

In patients with metastatic disease, papillary histology seems to portend a poorer prognosis than other histologies.^{12,13} A study of 64 patients with metastatic non-clear cell histologies from a major referral center showed median overall survivals of 29, 11, and 5.5 months for patients with chromophobe, collecting duct, and papillary carcinomas, respectively.¹³ Type I and II papillary tumors were not distinguished. Importantly, most survival comparisons were made in retrospective series in the era of immunotherapy only; the impact of antiangiogenic agents on the prognostic ability of histologic subtyping is unknown.

A retrospective series of 38 patients at the Memorial Sloan-Kettering Cancer Center (MSKCC) with metastatic papillary carcinoma showed a median overall survival of 8 months.¹² These patients were treated in the era of immunotherapy and, of the 12 treated with cytokine therapy, none developed a response and 1 experienced stable disease. However, of 25 patients treated with novel agents on clinical trials, only 1 developed a partial response in her lung, liver, and bony metastases. She was treated with the vascular endothelial growth factor (VEGF) TKI sunitinib and experienced an 8.5-month progression-free interval. This was one of the earliest indications that sunitinib may have activity in papillary RCC.

Treatment

Pivotal phase III trials have shown that sunitinib,¹⁴ sorafenib,¹⁵ and bevacizumab in combination with interferon therapy^{16,17} provide a progression-free survival (PFS) benefit compared with standard care (either interferon in the first-line setting or placebo in the second-line). Because non-clear cell histologies are limited in number and their biologic differences unclear, all of the aforementioned phase III trials restricted recruitment to patients with clear cell histology. Therefore, the results of these trials are difficult to generalize for all patients with non-clear cell histologies. Table 1 describes retrospective studies examining patients with non-clear cell histologies.

Despite deficiencies in definitive evidence, clinicians have used sunitinib or sorafenib as first-line treatment for patients with non-clear cell histologies because of the lack of more effective therapy. A retrospective analysis of 41 patients with metastatic papillary carcinoma treated with sunitinib or sorafenib was reported by a French group in collaboration with the Cleveland Clinic.¹⁸ The PFS was 7.6 months, with a response rate of 4.8%. The PFS was better than for those treated with sorafenib (11.9 vs. 5.1 months; $P < .001$); patients treated with sunitinib tended to have higher response rates (17% vs. 0%; $P = .08$).

An ongoing phase II study of sunitinib in patients with non-clear cell RCC¹⁹ enrolled 26 patients (13 papillary), of which 9 had progressive disease at or before completion of the first cycle of therapy. No objective responses were seen; however, 8 patients (6 papillary) had stable disease. The response rate and median PFS were not encouraging, but this may be explained by the high percentage of patients ($N = 13$; 50%) with poor-risk features.

The expanded access trials of sunitinib and sorafenib also provide insight into the treatment of non-clear cell histologies. These trials were designed to allow patients with metastatic RCC to be treated with these novel TKIs before they were approved by respective drug administrations in different countries.

Gore et al.²⁰ presented data from the expanded access trial of sunitinib that enrolled 2341 patients. Of these, 87.8% had clear cell, 11.8% had non-clear cell, and 0.4% had missing data about their subtype; the true proportion of patients with papillary histology was unclear. Of 276 patients with non-clear cell histology, the overall response rate was 5.4%; 41.6%

had stable disease; and the PFS was 6.7 months. These values were 9.3%, 43%, and 8.9 months, respectively, for the entire cohort. Although the quality of data obtained from expanded access trials may not be as precise or accurate as from randomized controlled trials, this study certainly shows that patients with non-clear cell histology benefit from sunitinib despite a possibly shorter PFS.

The Advanced Renal Cell Carcinoma Sorafenib (ARCCS) Expanded Access Program²¹ reviewed its data on patients with varying histologies treated with sorafenib. Of the 1871 patients evaluable for response, 118 had papillary carcinoma and 18 had chromophobe histology. The safety profile of sorafenib was similar in patients with clear cell versus non-clear cell histologies. Although the overall response rates among the entire cohort, papillary carcinoma subtypes, and chromophobe subtypes were low at 3.7%, 3%, and 6%, respectively, the proportions of patients with stable disease were 80%, 77%, and 89%, respectively, suggesting disease control. Although the extension phase of this protocol was designed partly to assess PFS in patients with non-clear cell disease, the number of patients with it enrolled was too small ($n = 20$) to provide meaningful estimates of efficacy. A similar expanded access program in the European Union reported PFS for all patients and those with papillary histology, other histologies, and sarcomatoid features of 6.8, 5.8, 4.9, and 4.3 months, respectively.²² Although expanded access trial data must be interpreted with caution, sorafenib does seem to have some clinically meaningful benefit in patients with non-clear cell histologies.

The one exception to other pivotal phase III trials in metastatic RCC that exclude non-clear cell histologies is the trial examining temsirolimus. Temsirolimus is an inhibitor of the mTOR kinase, which is an important intracellular signaling molecule involved in cell proliferation and angiogenesis pathways. This phase III trial²³ included 626 previously untreated patients with poor prognostic criteria and randomized them to temsirolimus, interferon α , or combination.

A subgroup analysis²⁴ examined the patients with non-clear cell histology. Of the 19% of patients who did not have clear cell carcinomas, 6% had non-clear cell histology and 13% were indeterminant. Of the non-clear cell histologies, 75% were papillary carcinomas. Unfortunately, a central pathology

review was not performed, which is pertinent in an analysis based on histologic subtype. Additionally, whether the patients with indeterminant pathology may have had clear cell or non-clear cell histologies if reviewed by a genitourinary pathologist is unclear. However, the 19% of patients without clear cell histology showed an overall survival hazard ratio (HR) of 0.55 (95% CI, 0.33–0.90) when comparing temsirolimus to interferon. Because of the interest generated by subgroup analyses such as this, future clinical trials should include a central pathology review to ensure quality control and robust comparisons between subtypes.

Temsirolimus is the only novel agent to be included for patients with advanced non-clear cell histology RCC in a randomized controlled trial. Because of its safety and efficacy profile, temsirolimus is frequently considered a first-line option for treating metastatic non-clear cell RCC. However, this must be balanced with differing side effect profiles between temsirolimus and the oral TKIs. Temsirolimus requires weekly intravenous infusions and is associated with rash, peripheral edema, hyperglycemia, and hypertriglyceridemia.²³ The oral TKIs are associated with palmar plantar erythrodysesthesia, diarrhea, hypertension, and hypothyroidism.^{14,15}

Finally, epidermal growth factor receptor blockade has been attempted in papillary RCC based on growth inhibition in non-clear cell RCC-derived cell lines.²⁵ In a study led by SWOG, 45 patients with papillary RCC were treated orally with erlotinib at 150 mg/d.²⁶ The overall response rate was 11% (5/45), median overall survival was 27 months, and toxicities were manageable. Although the RECIST response rate of 11% did not exceed prespecified estimates for further study, single-agent erlotinib yielded encouraging overall survival results.

Chromophobe RCC

The chromophobe subtype arises from the intercalated cells of the kidney and, on staining, shows large solid sheets of cells with pale or eosinophilic cytoplasm.² The most frequent genetic alterations are a combination of loss of heterozygosity in chromosomes 1, 2, 6, 10, 13, 17, and 21 and hypodiploidy. Patients with chromophobe histology also tend to present with early-stage disease, with only 2.9% to 4.9% of patients presenting with metastatic

disease.^{4,6} Patients with Birt-Hogg-Dubé syndrome have a high proportion of RCCs with chromophobe-predominant histology. They possess loss-of-function mutations in the *BHD* gene on chromosome 17p, have prominent cutaneous manifestations, and are predisposed to pneumothoraces.²⁷

Implications for Survival

In localized and metastatic settings, the chromophobe subtype of RCC is associated with the best overall prognosis compared with all other histologic subtypes. In a study of 4063 patients with different subtypes of RCC, the 5-year survival rate for those with chromophobe carcinoma was 87.9% (n = 103) compared with 73.2% (n = 3564) for those with clear cell carcinoma.⁶ The median survival of 12 patients with metastatic chromophobe RCCs at MSKCC was 29 months.¹³

In a Japanese study of gene expression profiling in RCC,²⁸ the *KIT* oncogene was found to be upregulated specifically on the cell membranes of chromophobe RCC. This finding may have the potential to be used as a diagnostic or therapeutic tool. In fact, both receptor TKI sorafenib and sunitinib are known to inhibit *KIT*, which may represent a mechanism of action behind these agents in metastatic chromophobe RCC.

Treatment

The study involving non-clear cell carcinomas treated with targeted therapy identified 12 patients with metastatic chromophobe carcinoma with a PFS of 10.6 months and a 25% response rate to sunitinib or sorafenib. Those treated with sorafenib seemed to have higher response rates and longer PFS (40% vs. 14% and 27.5 vs. 8.9 months, respectively). Because of limited patient numbers, these results were only hypothesis-generating and not statistically significant.

In the expanded access study of sorafenib,²¹ 18 patients had chromophobe histology. The overall response rate (confirmed with follow-up CT scans) for chromophobe subtypes was 6%, with an 89% rate of stable disease.

The phase III trial of temsirolimus and the sunitinib expanded-access studies (described in “Papillary Carcinoma Treatment”) included patients with chromophobe histology. Although the number of chromophobe patients is uncertain and a central pathology review was lacking, these studies contribute to the knowledge that these drugs may also lead to

some clinically meaningful response.

Collecting Duct RCC

Collecting duct carcinomas account for fewer than 1% of all RCCs. They are believed to arise from the collecting ducts within the renal medulla, are characterized by irregular channels lined with atypical epithelium in an inflamed desmoplastic stroma, and have genetic similarities to urothelial cancers.² They can occur at any age but are more common in younger patients. They differ from papillary carcinomas of the renal cortex in their location, lack of multifocality, and higher nuclear grade.²⁹ One third of patients present with metastatic disease, and the median overall survival is 11 months for those patients.¹³ Medullary carcinoma, which is a highly aggressive variant of collecting duct carcinomas, has been associated with the sickle cell trait and develops in young patients.³⁰

Treatment

Because of the rarity of collecting duct carcinomas, few data on treatment efficacy can be found. Certainly, no randomized trials are available, but clinicians tend to treat these with chemotherapy regimens similar to those used for transitional cell carcinomas. In the largest experience to date, a phase II multicenter trial treated 23 patients with metastatic collecting duct carcinoma with a combination of gemcitabine and cisplatin (or carboplatin). Results showed an overall response rate of 26% (including 1 patient with a complete response), a PFS of 7.1 months, and an overall survival of 10.5 months.³¹

Very few patients with collecting duct carcinomas were observed in the sorafenib expanded-access trial.²¹ Although 10 patients were identified, only 5 were evaluated. None experienced a response to sorafenib and 3 (60%) had stable disease. More data in this histologic subtype are required before any clear recommendations can be made.

Sarcomatoid Features

Sarcomatoid differentiation is not a subtype of RCC but an aggressive growth pattern characterized by malignant spindle-shaped histology. With regard to immunohistochemical markers, these tumors are generally positive for AE1/AE3, epithelial membrane

antigen, and vimentin, which supports an epithelial origin. Staining for actin, desmin, and S-100 is usually negative. VEGF, Kit, and S6 kinase have been expressed in most sarcomatoid specimens. Sarcomatoid features can be observed across all RCC subtypes and are associated with a worse outcome compared with RCCs without sarcomatoid features.³

In a retrospective series of 952 RCC cases,³² sarcomatoid features were observed in 8% of conventional (clear cell) renal carcinomas, 3% of papillary renal carcinomas, 9% of chromophobe renal carcinomas, 29% of collecting duct carcinomas, and 11% of unclassified RCC. When adjusted for stage, necrosis, and tumor size, patients with sarcomatoid differentiation had a worse prognosis than those with tumors without sarcomatoid change ($P = .0001$).

In a contemporary series of 43 patients with metastatic RCC containing sarcomatoid features treated with anti-VEGF therapy (sunitinib, sorafenib, bevacizumab), 8 patients (19%) experienced partial responses, 21 (49%) had stable disease, and 14 (33%) had progressive disease as the best response.³³ Partial responses were limited to patients who had underlying clear cell histology and fewer than 20% sarcomatoid elements. The PFS was significantly shorter in those with sarcomatoid elements compared with matched patients without (6.2 vs. 16.3 months; $P < .001$).

These data support the use of targeted therapy in patients with metastatic RCC and sarcomatoid differentiation. Although the response rates and PFS are certainly not as favorable compared with patients without sarcomatoid differentiation, some clinical activity is still seen in those treated with anti-VEGF therapy. Whether this is true of patients treated with mTOR-targeted agents such as temsirolimus remains to be studied.

Chemotherapy in patients with metastatic RCC with sarcomatoid differentiation has exhibited modest responses in retrospective series.³⁴ A phase II ECOG trial examined the efficacy of gemcitabine (1500 mg/m²) and doxorubicin (50 mg/m²) with granulocyte colony-stimulating factor support. Of the 38 evaluable patients in this study, 6 (16%) exhibited a response (1 complete response and 5 partial responses).³⁵ Although this regimen was tolerable, 1 treatment-related death occurred and the toxicity profile was not ideal.

Table 1 Response Rates and Progression-Free Survival in Non–Clear Cell Renal Cell Carcinoma Using Sunitinib, Sorafenib, and Temsirolimus

Drug	Study	Non–Clear Cell RCC			
		N	ORR	SD	PFS (mo)
Sunitinib	Gore et al. ²⁰	276	5.4%	41.6%	6.7
	Choueiri et al. ¹⁸	20	16%	N/A	11.9
Sorafenib	Stadler et al. ²¹	136	3.7%	78.7%	N/A
	Choueiri et al. ¹⁸	33	6%	N/A	5.7
Temsirolimus	Dutcher et al. ²⁴	37	N/A	N/A	7.0

Abbreviations: N/A, not available; ORR, overall response rate; PFS, progression-free survival; RCC, renal cell carcinoma; SD, standard deviation.

Mixed Histology

Patients with clear cell RCC may have mixed non–clear cell components. The AVOREN trial of bevacizumab plus interferon versus interferon alone enrolled patients with mixed histologies.³⁶ The PFS of all patients was 10.2 versus 5.4 months (HR, 0.63; $P < .001$) in favor of those treated with bevacizumab plus interferon. Although patients with mixed histology had poorer PFS than those with clear cell, the combination of bevacizumab plus interferon produced better results than interferon alone (5.7 vs. 2.9 months; HR, 0.53; $P < .007$). This finding suggests that any component of non–clear cell carcinoma, even in the background of clear cell–predominant disease, portends a poorer prognosis than pure clear cell carcinomas alone.

Clinical Trials and Future Research

Ongoing clinical trials are assessing the safety and efficacy of sunitinib, sorafenib, and other new investigational agents in patients with papillary RCC or other non–clear cell histologies (NCT00459875, NCT00465179). GSK 089 (formerly XL 880) and ARQ 197 are inhibitors of the c-MET receptor tyrosine kinase, which is mutated in most heritable and some sporadic papillary cancers. Dose-finding phase I studies have been completed.^{37,38}

Preliminary results for GSK 089, a dual VEGFR-2 and met inhibitor, were reported in 25 evaluable patients with papillary RCC, with 4 experiencing a partial response, 20 stable disease, and 1 progressive disease. The median PFS for the entire cohort was 13 months.³⁹ Because antitumor activity was shown for GSK 089, enrollment continues, with the addition of another stratum (80 mg orally, daily).

A phase II study of erlotinib (an epidermal growth

factor receptor antagonist) in patients with papillary RCC showed an 11% response rate.²⁶ To assess this further, a study of ARQ 197 (a c-MET inhibitor) with or without erlotinib is being proposed (Wolfram Samlowski, MD, personal communication).

Clinical trials are also enrolling all subtypes of RCC histology in investigational neoadjuvant, adjuvant, and metastatic settings (NCT00405366, NCT00326898, NCT00098592). Head-to-head comparisons of first-line treatment of metastatic disease with mTOR inhibitors versus TKIs exclusively in non–clear cell histologies are being developed. For example, Armstrong and George from Duke Comprehensive Cancer Center (personal communication) proposed a randomized trial involving patients with papillary or chromophobe histology treated with either an mTOR inhibitor or sunitinib.

Conclusions

The combination of these studies reinforce that targeted therapies used classically in clear cell histologies are safe and have clinically meaningful response rates in patients with non–clear cell histologies. Studies of rational targeted drugs dedicated to non–clear cell histologies are planned and results will help define their role.

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