Renal Neoplasms: An Update on Immunohistochemical and Histochemical Features

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Renal Cell Carcinomas

The final two decades of the 20th century witnessed a major evolution in our concept of renal cell carcinomas. The extensive histological variability long noted in renal cell carcinoma (RCC) was shown to reflect the existence of a large number of distinct entities having differing prognoses and often harboring unique cytogenetic abnormalities (1-3). Advancement in understanding the molecular misadventures that result from these genetic abnormalities spurred development of promising targeted therapies for a disease in which surgical approaches were previously the sole option (4, 5).

The emerging therapeutic possibilities have raised the bar for pathologists mandating accurate classification in an increasingly complex arena. Although, histological assessment remains the mainstay of RCC classification, there are immunohistochemical (IH) and histochemical tools that serve as adjuncts to the histologic analysis. However, cautious interpretation of IH data is recommended since experience in the less common and most recently described tumors may be limited. In this brief review we discuss the use of ancillary immunohistochemistry in RCC classification but admit that space precludes fully addressing the myriad of diagnostic permutations that may arise.

Clear Cell Renal Cell Carcinoma

Clear cell RCC is overwhelmingly the most common type of renal cancer accounting for 70% of cases (1, 6). The World Health Organization defines CC-RCC as "a malignant neoplasm composed of cells with clear or eosinophilic cytoplasm within a delicate vascular network" (6). As this definition implies, cytoplasmic clearing may not be present in every cell, or even in every neoplasm. Other types of RCC may have optically clear cytoplasm and appear indistinguishable. Granular cell, or eosinophilic variant of CC-RCC, a term historically applied to tumors with few or no clear cells, is terminology no longer acceptable since several RCC types are characterized by cells having eosinophilic cytoplasm. Since CC-RCC is so common and histologically diverse, most differential diagnoses are driven by comparative features relative to this tumor, a strategy employed below.

Histochemistry of RCCs

The cytoplasmic clearing in CC-RCC results from extraction of abundant intracellular glycogen and lipid by organic solvents during tissue processing (Fig. 1). However, sufficient residual glycogen remains after processing that a PAS stain without diastase is usually positive. Demonstration of lipid by an Oil Red O stain is easily accomplished but requires frozen tissue. Although glycogen and lipid are characteristic findings in CC-RCC, these histochemical stains offer little differential diagnostic power in RCC classification since tumors other than CC-RCC may also harbor appreciable lipid and/or glycogen.

The single differentiating histochemical stain useful in RCC classification is the Hale's colloidal iron (CI) stain (7, 8). The CI stain demonstrates the presence of abundant acid mucosubstances in chromophobe cell (Ch) RCC which are absent in other types of RCC (Fig. 2). The acid
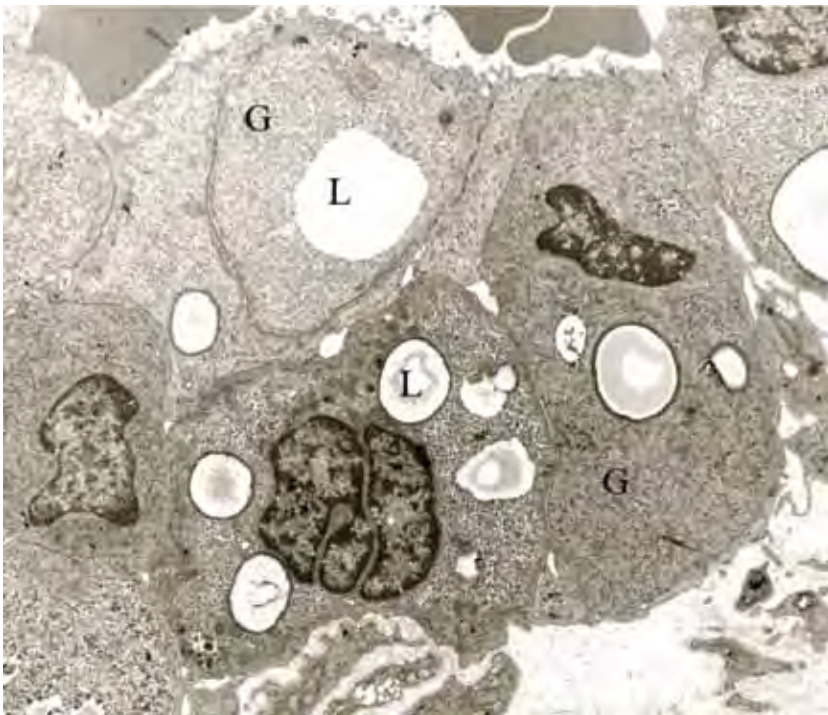
Figure 1. Electron microscopy of a clear cell renal cell carcinoma showing abundant lipid and glycogen. (L- lipid, G- glycogen).

mucosubstances are located within complex cytoplasmic vesicles demonstrable by electron microscopy, a unique feature of this tumor. The CI is often essential to confirm the diagnosis in Ch-RCC because similar to CC-RCC, Ch-RCC shows histological extremes. Some tumors are composed of cells with somewhat clear, so-called transparent cytoplasm, eliciting the differential diagnosis of CC-RCC. Other Ch-RCCs are composed entirely of cells with eosinophilic cytoplasm, the so-called eosinophilic variant, which elicits the differential of a benign oncocytoma or a CC-RCC with eosinophilic cells.

Immunohistochemical Differential Diagnosis of RCCs with Cytoplasmic Clearing

Although most cases of CC-RCC represent sporadic disease, identical neoplasms may arise in several hereditary and cystic diseases and two tumors are defined by their unique gross or architectural features (Table 1). Family history and presence of extra-renal findings are crucial to establishing the correct diagnosis in these various scenarios because the CC-RCCs that develop may show histological and immunohistochemical identity to sporadic cases.

The most common genetic cystic disease with CC-RCC is von Hippel-Lindau disease (9, 10). In this autosomal recessive syndrome CC-RCC is accompanied by clear cell-lined cysts and extrarenal neoplastic disease. CC-RCC also rarely arises in tuberous sclerosis complex (TSC) especially when associated with polycystic kidney disease, known as the contiguous gene syndrome (11, 12). Finally, there is a very rare non-cystic genetic disease known as constitutional chromosome 3 syndrome, an autosomal dominant syndrome defined by the presence of single or multiple, unilateral or bilateral CC-RCC in patients with a balanced chromosome 3 translocation (13, 14). Only seven families have been identified, each with a different translocation.

The multilocular cystic renal cell carcinoma, a relatively common (3-5% of RCCs) RCC and defined by its gross, is a tumor that consists entirely of clear cell lined cysts and cyst septae without solid nodules of tumor cells (15). Clear cell papillary RCC, a recently recognized type of RCC originally identified in patients with end stage kidney disease and acquired cystic kidney disease, is now recognized to also develop in native kidneys. This tumor contains clear cells arranged along papillary fronds with basally oriented nuclei (16-18). The papillary architecture
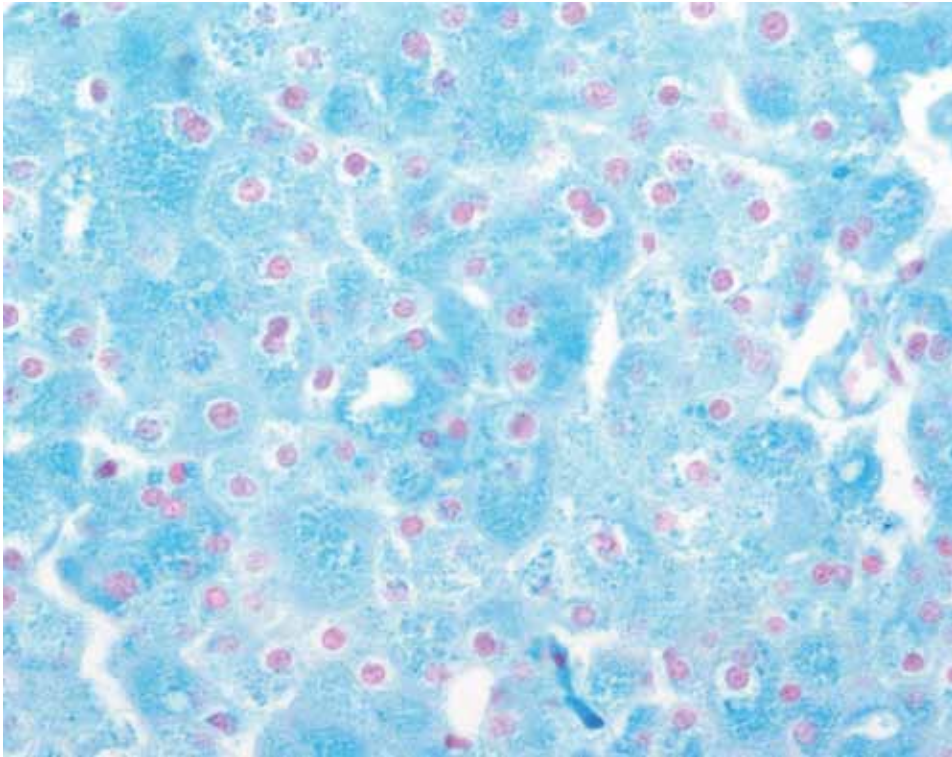
Figure 2. Colloidal iron stain of a chromophobe cell renal cell carcinoma demonstrating intense cytoplasmic staining.
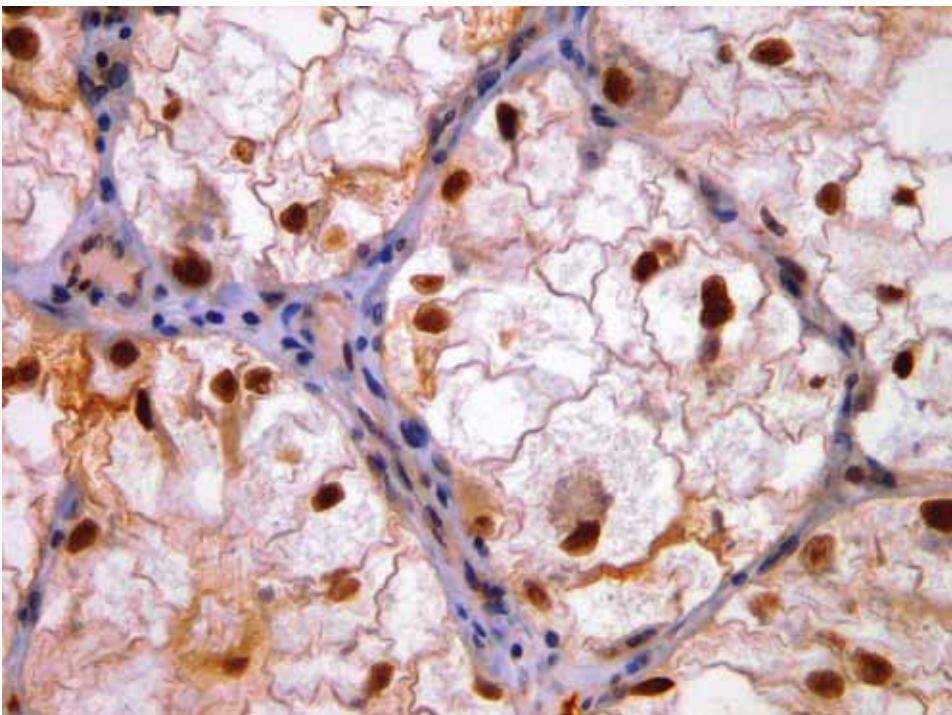

Figure 3. A Xp11.2 translocation carcinoma showing the characteristic TFE3 nuclear staining.

Clear Cell Carcinomas with Defining Gross, Architectural and Additional Features		
Clear Cell Tumor	**Gross or Architectural Features**	**Additional**
von Hippel-Lindau disease	+/- Clear cell lined cysts	Extra-renal neoplastic disease
Tuberous sclerosis complex	+/- Polycystic kidney disease	Angiomyolipomas Extrarenal disease
Constitutional chromosome 3 syndrome	Multiple and/or bilateral CC-RCC	Family history of CC-RCC
Multilocular cystic RCC	Consists entirely of cyst and septae	Renal limited pT1 or pT2
Clear cell papillary RCC	Papillae formation	Often ESKD

Table 1.

is definitional of this entity; conversely true papillary architecture is an exclusionary criterion for CC-RCC.

Many entities with clear and/or eosinophilic cells enter into the differential of RCCs as noted in Tables 2 and 3. The laundry list of antigens provided includes both common and uncommonly employed immunohistochemical analytes. The scope of the differential is smaller with clear cell tumors compared to those with eosinophilic cytoplasm. It includes the two other most common RCCs, papillary RCC, especially when solid, Ch-RCC, translocation carcinomas and urothelial carcinoma which occasionally shows extensive cytoplasmic clearing.

Clear Cell RCC expresses vimentin, a variety of low molecular cytokeratins, EMA, CD10 and RCC MA (19, 20). The latter two have some diagnostic utility when a RCC is considered in a metastatic lesion (Table 2). Notable cytokeratin exceptions in CC-RCC are CK7 and high molecular weight cytokeratins. Cytokeratin 7 coupled with AMACR (a-methylacyl-CoA racemase), is useful when solid forms of Pap-RCCs are encountered (21, 22). Several antigens, some uncommonly stocked in immunopathology laboratories, such as parvalbumin, S100A1, caveolin-1, C-kit, PAX2 and E-cadherin have discriminatory efficacy in separating CC-RCC from Ch-RCC (23-30). However, the first line strategy for Ch-RCC should be to stain for CI. For urothelial carcinoma the presence of high molecular weight cytokeratin, CK 7 and p63 permit confirmation of the diagnosis (32-34).

Xp11.2 translocation carcinomas are a group of neoplasms characterized by a variety of break points at Xp11.2 with translocation to one of several other chromosomes forming fusion genes (35-37). They occur most frequently in children and young adults. Although histologically variable, the most common tumor cell phenotype are clear cells with voluminous cytoplasm and papillary architecture. Intracellular and stromal calcifications provide additional useful clues to the diagnosis. In general the absence of epithelial markers in translocation carcinomas are powerful clues to the diagnosis. However, a positive reaction for the nuclear transcription factor TFE3 is definitive in the absence of cytogenetic confirmation (Fig. 3). Some cases may also stain for melanocytic markers, but this is more common in TFEB positive t(6:11) translocation carcinomas.

Immunohistochemistry in the Differential Diagnosis of RCC with Cytoplasmic Eosinophilia
The differential diagnosis for RCCs comprised entirely or predominately of cells with eosinophilic cytoplasm is broad, as reflected in table 3. Although both the mucinous tubular and spindle cell RCC and tubulocystic carcinoma are listed, their distinctive histology drives the diagnosis rather than immunohistochemical phenotype (38-40). The differential diagnosis in tumors with eosinophilic cytoplasm extends beyond carcinomas to include a benign tumor, oncocytoma, and a RCC mimic, the epithelioid angiomyolipoma (41, 42). Epithelioid AML

| Immunohistochemical and Histochemical Evaluation of Renal Tumors with Eosinophilic Cytoplasm										
Antibody	Oncocytoma	CC-RCC, Eosin Cytoplasm	Chromophobe Carcinoma, Eosinophilic Variant	Epithelioid Angiomyolipoma	Papillary Renal Cell Carcinoma (Pap RCC), Type 2	Translocation Carcinoma t(6;11) t(6;11)	Collecting Duct Carcinoma	Medullary Carcinoma	Tubulocystic Carcinoma	Tubular Mucinous Spindle Cell Carcinoma
CAM 5.2	pos	pos	pos	neg	pos	neg	pos	pos	pos	pos
AE1/AE3	pos	pos	pos	neg	pos	neg	pos	pos	pos	pos
Vimentin	neg	pos	neg	neg	pos	pos	pos	pos	-	pos
EMA	pos	pos	pos	neg	pos	neg	pos	pos	-	pos
CD10	pos/neg	pos	pos/neg	neg	pos	pos	pos/neg	-	pos	pos/neg
RCC Ma	neg	pos	neg	neg	pos/neg	-	-	-	-	neg
CK7	"patchy"	neg	pos	neg	pos	neg	pos	pos	pos	pos
CK20	neg	neg	neg	neg	neg	neg	neg	neg	neg	neg
CK19	neg	neg	neg	neg	neg	pos/neg	pos	pos	pos/neg	pos
34BE12	neg	neg	neg	neg	pos/neg	neg	pos/neg	neg	pos/neg	pos/neg
AMACR	neg	neg	neg	-	pos	pos	neg	-	pos	pos
Parvalbumin	pos	neg	pos	-	neg	-	-	-	pos	-
S100A1	pos	pos	neg	-	pos	-	-	-	-	-
C-kit	pos	neg	pos	neg	pos/neg	-	pos/neg	-	-	neg
E-cadherin	pos	neg	pos	-	pos/neg	pos	pos	-	-	-
Kid sp cad	pos	neg	pos	-	neg	neg	neg	neg	neg	neg
Caveolin-1	neg	-	pos	-	-	-	-	-	-	-
Cathepsin K	neg	neg	neg	-	neg	pos	-	-	-	-
PAX-2	pos	pos	neg	-	pos/neg	neg	neg	-	pos	pos/neg
TFE3	neg	neg	pos	-	neg	pos	-	-	-	-
TFEB	neg	neg	-	-	neg	neg	-	-	-	-
UEA-1	neg	neg	-	-	pos/neg	-	pos	-	pos	-
HMB 45	neg	neg	neg	pos	neg	neg	neg	neg	neg	neg
Melan A	neg	neg	neg	pos	neg	neg	neg	neg	neg	neg
Coll iron	neg	neg	pos	-	neg	neg	neg	neg	neg	neg

Table 2.
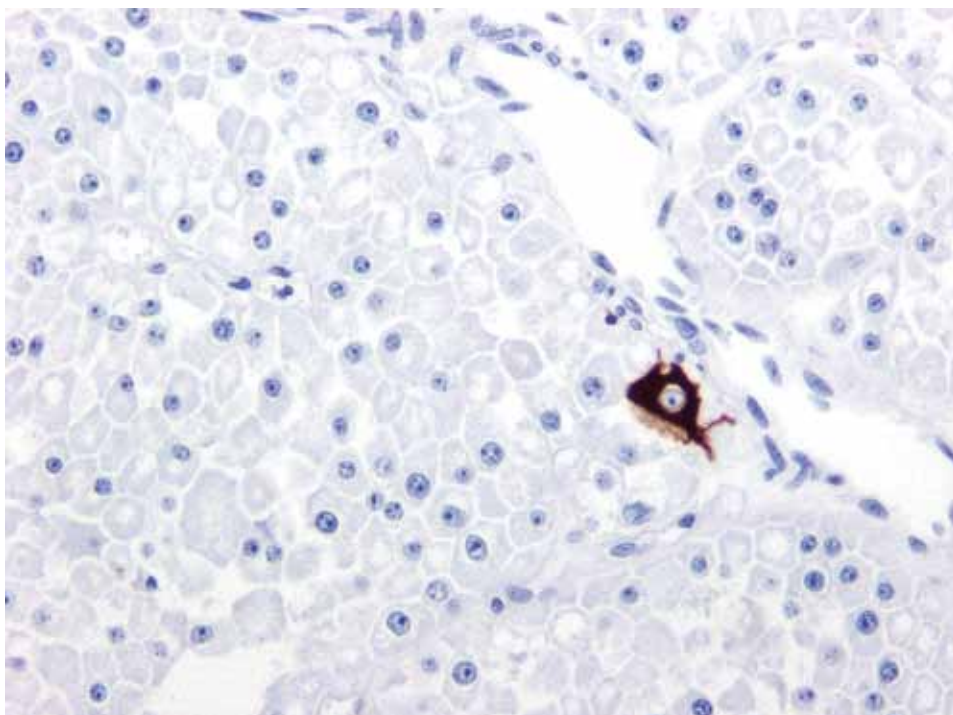
Figure 4. An isolated CK 7 positive cell in an oncocytoma.

(EpAML), although not a carcinoma, demonstrates malignant behavior in 30% of cases and may lead assist in recognition of the hereditary disease, tuberous sclerosis complex.

Most cases of oncocytoma are recognized by their distinctive histology. The presence of mitoses or necrosis should prompt great hesitation in rendering an oncocytoma diagnosis regardless of an otherwise typical histology. Although there are several antigens that can be employed to separate oncocytoma from CC-RCC with eosinophilic cells and the eosinophilic variant of Ch-RCC, because of histogenetic similarity between oncocytoma and Ch-RCC, immunohistochemical stains in these two tumors show substantial overlap. Thus parvalbumin, S100A1, C-kit, caveolin-1, E-cadherin and kidney specific cadherin are usually positive in both (23-30). The CK 7, however, can be very helpful in oncocytoma where most cells are completely negative but a small population of strongly positive cells is invariably present imparting a distinctive staining pattern (Fig. 4). Recently PAX2 has been reported to discriminate between oncocytoma and Ch-RCC (25, 26). When combined with C-kit and CK this profile of three antigens is useful in the separation of the four most common RCCs with eosinophilic cytoplasm as noted in Table 4.

Identification of a translocation carcinoma as previously described is facilitated by negative cytokeratin stains and EMA stain. The presence of a positive melanocytic marker is helpful, but a positive stain for the nuclear transcription factor TFEB or TFE3 is required for confirmation. Although, EpAML like translocation carcinomas is negative for cytokeratin and EMA stains and positive for melanocytic markers, its distinctive histology with large ganglion-like cells should permit recognition (40, 41). In uncertain case TFEB and TFE3 stains should be employed.

When collecting duct carcinoma (CDC) is considered the histologic features of a high grade tubulopapillary tumor with desmoplastic stroma and infiltrating growth among native nephron elements is characteristic and markedly distinct from all other renal cancers except for urothelial carcinoma (42, 43). The presence of high molecular weight cytokeratin and positive reaction for UEA-1 stain distinguish CDC from other RCCs. A related carcinoma, renal medullary carcinoma (RMC), is recognized by its mucinous or mucoid stroma and infiltrating inflammatory cells. Since development of RMC to date has been limited to patients with sickle cell trait or SC disease, this laboratory feature must be present to support the diagnosis. Immunohistochemistry rarely plays a role.

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Immunohistochemical and Histochemical Evaluation of Renal Tumors with Clear Cytoplasm					
Antibody	Clear Cell RCC	Papillary RCC, Type 1	Chromophobe RCC	Translocation Carcinoma	Urothelial Carcinoma
CAM 5.2	pos	pos	pos	neg	pos
AE1/AE3	pos	pos	pos	neg	pos
Vimentin	pos	pos	neg	pos	pos
EMA	pos	pos	pos	neg	pos
CD10	pos	pos	pos/neg	pos	pos
RCC Ma	pos	pos	neg	pos	pos
CK7	neg	pos	pos	neg	pos
CK20	neg	neg	neg	neg	neg
CK19	neg	neg	-	neg	neg
34BE12	neg	neg	neg	neg	pos
Parvalbumin	neg	neg	pos	-	-
S100A1	pos	pos	neg	-	-
C-kit	neg	neg	pos	neg	neg
AMACR	neg	pos	neg	pos	neg
E-cadherin	neg	-	pos	pos/neg	neg
Kid sp cad	neg	neg	pos	neg	-
Cathepsin K	neg	neg	neg	pos	-
PAX-2	pos	pos	neg	neg	neg
TFE3	neg	neg	neg	pos	neg
TFEB	neg	neg	neg	neg	neg
HMB 45	neg	neg	neg	neg	neg
Melan A	neg	neg	neg	neg	neg
Coll iron	neg	neg	pos	neg	neg
P63	neg	neg	neg	-	pos

Table 3.

> "Demonstration of lipid by an Oil Red O stain is easily accomplished but requires frozen tissue."

Discussion

The classification of RCC has blossomed in recent years with the description of many new entities. The 20th century acceptance of an astounding degree of morphologic diversity within a single nosologic entity RCC has been replaced by a broad menu of diagnostic choices that the pathologist must consider. One member, CC-RCC, remains the most common of RCC. Although CC-RCC is usually sporadic, similar appearing tumors can arise in patients with several genetic cystic diseases. Furthermore, CC-RCC is histologically diverse and may resemble several other cytogenetic and prognostically different tumors. Therefore, the pathologist, must have pertinent history and be well versed in histological nuances of renal tumor classification.

Histology remains the cornerstone for diagnosis; immunohistochemistry serves as a useful adjunct to the diagnosis in selected circumstances. When considering immunohistochemistry in differential diagnosis, profiles of antigens are required since any type of RCC may not fully express the IH profiles listed in the tables provided where positive entries do not indicate 100% incidence, nor do negative entries indicate 0% incidence of reaction.

Selected Immunohistochemical Profile For The Four Most Common Renal Neoplasms			
Antibody	CK 7	C-Kit	PAX2
Clear cell RCC	neg	neg	pos
Chromophobe cell RCC	pos	pos	neg
Papillary RCC	pos	neg	pos
Oncocytoma	neg	pos	pos

Table 4.

The IH profiles although useful are not a substitute for careful histologic assessment. In a practical sense, more blocks of tissue are often more cost effective than immediate initiation of IH. Lastly, do not feel obligated to place every tumor within a currently defined category. Renal cell carcinoma, unclassified is a valid designation and should account for several percent of RCC diagnoses rendered. It is from this category that new entities may emerge of academic interest that may demonstrate differing biologies with important prognostic or therapeutic implications.

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