Immunohistochemical Diagnosis of Renal Neoplasms

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• ***Context.*—Histologic diagnosis of renal neoplasm is usually straightforward by routine light microscopy. However, immunomarkers may be essential in several contexts, including differentiating renal from nonrenal neoplasms, subtyping of renal cell carcinoma (RCC), and diagnosing rare types of renal neoplasms or metastatic RCC in small biopsy specimens.**

***Objective.*—To provide a comprehensive review of the diagnostic utility of immunomarkers for renal neoplasms.**

***Design.*—This review is based on published literature and personal experience.**

***Conclusions.*—The following markers may have diagnostic utility in various diagnostic contexts: cytokeratins, vimentin, α-methylacyl coenzyme A racemase, carbonic anhydrase IX, PAX2, PAX8, RCC marker, CD10, E-cadherin, kidney-specific cadherin, parvalbumin, claudin-7, claudin-8, S100A1, CD82, CD117, TFE3, thrombomodulin, uroplakin III, p63, and S100P. Cytokeratins are uniformly expressed by RCC, albeit in a somewhat limited amount in some subtypes, requiring broad-spectrum anti-CK antibodies, including both low– and high–molecular-weight cytokeratins. PAX2 and PAX8 are sensitive and relatively specific markers for renal neoplasm, regardless of subtype. CD10 and RCC marker are sensitive to renal cell neoplasms derived from proximal tubules, including clear cell and papillary RCCs. Kidney-specific cadherin, parvalbumin, claudin-7, and claudin-8 are sensitive markers for renal neoplasms from distal portions of the nephron, including chromophobe RCC and oncocytoma. CK7 and α-methylacyl coenzyme A racemase are sensitive markers for papillary RCC; TFE3 expression is essential in confirming the diagnosis of Xp11 translocation RCC. The potentially difficult differential diagnosis between chromophobe RCC and oncocytoma may be facilitated by S100A1 and CD82. Thrombomodulin, uroplakin III, p63, and S100P are useful markers for urothelial carcinoma. Together with high–molecular-weight cytokeratins, PAX2, and PAX8, they can help differentiate renal pelvic urothelial carcinoma from collecting duct RCC. A sensitive marker for sarcomatoid RCC is still not available. Immunomarkers are most often used for diagnosing metastatic RCC. Compared with primary RCC, expression of the above-mentioned markers is often less frequent and less diffuse in the metastatic setting. Recognizing the variable sensitivity and specificity of these markers, it is important to include at least CD10, RCC marker, PAX2, and PAX8 in the diagnostic panel.**

(*Arch Pathol Lab Med.* 2011;135:92–109)

More than 90% of the renal cell neoplasms arise from the renal tubules. Renal cell carcinoma (RCC) is divided into 5 main histologic subtypes: clear cell, papillary, chromophobe, collecting duct, and unclassified RCC. Clear cell, papillary, and chromophobe RCCs are the 3 most common types, comprising 70% to 80%, 14% to 17%, and 4% to 8% of all RCCs, respectively. Collecting duct carcinoma is the rarest type of RCC (<1%). Unclassified RCCs include those that do not fit into any of the above 4 subtypes either morphologically or cytogenetically.[1–6] About 7% of the carcinomas of the kidney come from urothelial carcinoma arising from the renal pelvis.[7,8] Approximately 10% of renal tumors belong to one of the several benign entities, most of which are oncocytoma, angiomyolipoma, and papillary adenoma.[6] In the past few years, several new types of RCC have been described, including mucinous tubular spindle cell carcinoma, Xp11 translocation carcinoma, tubulocystic RCC, and clear cell papillary RCC. Most of these tumor types display typical and readily diagnostic morphology. However, overlapping features among renal cell neoplasms are frequent.[9]

For most renal neoplasms, especially for resection specimens, when the entire tumor is available for evaluation, histologic diagnosis and typing is often straightforward by careful examination of hematoxylin-eosin sections. However, immunohistochemistry has become indispensable for diagnosis in several instances including:

1. *Renal Cell Versus Nonrenal Cell Neoplasm*.—Different types of renal cell neoplasms may closely simulate other non–renal cell neoplasms, such as angiomyolipoma, sarcoma, lymphoma, urothelial carcinoma, xanthogranulomatous pyelonephritis, malakoplakia, or metastatic carcinoma.
2. *Histologic Subtyping of RCC*.—Even when the diagnosis of RCC is obvious, its histologic subtypes, upon which the choice among increasingly popular preoperative or postoperative adjuvant therapy regimens may be predicated, may not be obvious from routine light microscopy.

Accepted for publication September 15, 2010.

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The authors have no relevant financial interest in the products or companies described in this article.

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3. *Rare Primary Renal Neoplasms*.—A small subset of renal neoplasms composed of so-called small blue cells, such as lymphoma, synovial sarcoma, neuroblastoma, small cell carcinoma, and primitive neuroepithelial tumor, can occur in the kidney, and their distinctions can be difficult on morphologic examination alone.
4. *Small Biopsy Specimens*.—Fine-needle aspiration biopsy (FNA) or core needle biopsy is now more frequently used for preoperative diagnosis, not only for traditional indications, such as an inoperable tumor or tumors for which surgical resection is contraindicated or ineffective, such as malignant lymphoma or metastatic tumors, but also in response to new therapies, where preoperative diagnosis helps in the choice of treatment (partial versus total nephrectomy, radiofrequency, or cryoablation).[10,11]
5. *Metastatic RCC in distant organs*.—Renal cell carcinoma, particularly the clear cell type, frequently metastasizes, sometime long *before* or *after* the detection of the primary tumor, and the metastasis may involve almost any body site, including odd locations.[12,13] Furthermore, patients sometimes present with a second malignancy together with potential metastatic RCC.[14] An FNA is often performed in this context. In these situations, the amount of tumor tissue available is often quite limited, and ancillary studies, including immunohistochemistry, are needed for initial or confirmatory diagnosis.

There are a few general diagnostic caveats in choosing an appropriate panel of immunohistochemical markers in the diagnostic workup:

1. For each marker, the percentage of tumor cells stained in an individual tumor may vary widely, ranging from a few cells to almost every tumor cell. This should be considered when the FNA produces scant tumor tissue, that is, when positive staining would be helpful, but negative staining would have limited value.
2. The reported immunoprofiles derived from different studies are often variable and most likely result from a selective group of tumors with typical histomorphology. Whether these profiles are faithfully retained in histologically equivocal tumors, where immunohistochemistry is required the most for correct histologic classification, remains largely unanswered.
3. The reported immunoprofiles for most markers are often established for primary tumors. Whether these profiles are retained in the corresponding metastatic tumors has, to our knowledge, been evaluated for only a few markers.[15–21]
4. Several markers that are used for diagnosis because of their expression in renal neoplasms are also expressed by tumors in other organs or tissues. This needs to be considered in diagnosing metastatic renal neoplasms.
5. The general diagnostic approach for a renal neoplasm often includes (1) determining the broad tumor category, such as carcinoma versus sarcoma versus lymphoma; (2) determining RCC versus other tumor types; and (3) determining the histologic type of the RCC. The markers described below have variable utility in relation to these goals. For examples, cytokeratins are a reliable marker for carcinomatous differentiation but have limited utility for the other diagnostic goals; PAX2 and PAX8 can help identify almost all tumors with renal tubular differentiation but do not help with subtyping those tumors; the RCC marker is quite specific for clear cell or papillary RCC but expression can be focal and weak in high-grade tumors.
6. In a healthy kidney, each nephron segment possesses a distinct and specific immunoprofile. Each major type of renal epithelial neoplasm is thought to be derived from a specific nephron segment, and thus, is expected to display an immunoprofile akin to that of the parental nephron segment, for examples, the RCC marker[17] and CD10 for proximal tubules[22] and the corresponding clear cell and papillary RCCs; parvalbumin,[16,23,24] S100A,[25–27] claudins,[28] kidney-specific cadherin for distal portion of the nephron,[29,30] and the corresponding chromophobe RCC and oncocytoma; and high–molecular-weight cytokeratins for the collecting duct and the corresponding collecting duct RCC.[31] Against this background, the reported immunoprofiles of some tumor types, such as clear cell or papillary RCC, are relatively consistent among different studies, but there are greater ranges of variation for other tumor types, especially the more recently described entities (Table 1). These discrepancies may reflect technical vagaries, variable diagnostic criteria, or an intrinsic differentiation of tumor cells along more than one type of renal tubular segments. These discrepancies, regardless of causes, limit the utility of immunoprofile for tumor typing.
7. Large-scale gene profiling and proteomic approaches have revealed newer, tumor-type–specific molecules of renal neoplasms, several of which have been further tested immunohistochemically for diagnostic utility, leading to continuous expansion of potentially useful diagnostic markers.[26,32]

This review will address (1) individual immunohistochemical markers often used in the differential diagnosis of renal neoplasms, (2) immunoprofiles for each major tumor type, (3) application of these profiles in the most common pattern-based differential diagnostic problems, and (4) immunodiagnosis of metastatic RCC.

IMMUNOMARKERS IN THE DIAGNOSIS OF KIDNEY TUMORS

All the antibodies described below are commercially available and provide satisfactory staining in routinely processed tissue. The staining pattern is nuclear for PAX2, PAX8, and TFE3; combined nuclear and cytoplasm stain for S100A and S100P; and cytoplasmic/cell membrane stain for other markers. The immunoprofiles of the better-studied markers, stratified by the major tumor types of the kidney, are summarized in Table 1.

Cytokeratins

All major types of renal tumors express cytokeratin 18 (CK18), whereas CK20 is negative in all of them.[23,31,33–44] Other observations of diagnostic importance are that (1) CK5/6 is positive in 75% of urothelial carcinoma and 15% of collecting duct RCC but not other tumors; (2) CK7 is positive in most papillary RCC, collecting duct RCC, and urothelial carcinoma (87%–100%) but is also positive in a significant percentage of other tumors; (3) High–molecular-weight CKs (detected by the antibody 34βE12) in most collecting duct RCCs (67%) and urothelial carcinoma (100%) but much less frequently in other tumors. Of note, the profile for CKs by the AE1/AE3 antibody, a popular broad-spectrum anti-CK antibody for renal neoplasms, has not been systematically reported. Widely variable

expression was noted for other CKs, limiting their diagnostic utility. Expression of CK by sarcomatoid RCC has not been adequately evaluated.

These observations suggested some diagnostic caveats in the use of CK in diagnosis of renal neoplasms. Frequently, there is a need to confirm the diagnosis of carcinoma, rather than another broad tumor type, even before considering RCC, within the context of limited tissue from an FNA. Use of CK traditionally serves that goal well, and its expression is often evaluated by some broad-spectrum anti-CK antibodies, the most popular of which is, perhaps, the AE1/AE3 antibody.[34] Yet, that antibody lacks the specificity of CK18, a low–molecular-weight keratin, which is expressed by almost all RCCs,[31] perhaps accounting for the negative results in many primary or metastatic RCCs often encountered. Indeed, only 7 of 28 of Xp11 translocation RCCs (25%) were positive for the AE1/AE3 antibody.[45] An antibody against CK18 should be routinely used in this context. Although the popular CAM 5.2 antibody has often been used in conjunction with a broad-spectrum anti-CK antibody, it has specificity against CK8, expressed in most (40%–100%), but not all, RCCs, but it lacks specificity for CK18, expressed in almost all RCCs.[34] The need to confirm the diagnosis of carcinoma is even more pronounced in the case of sarcomatoid RCC. Yet, as mentioned above, the CK profile of sarcomatoid RCC has not been systematically studied.

Therefore, to confidently confirm the carcinomatous nature of a primary or metastatic renal tumor, a full battery of anti-CK antibodies, including those with broad-spectrum, low–molecular-weight, and high–molecular-weight CK specificities should be used.

Vimentin

Vimentin,[31,36,37,46–48] a broad mesenchymal marker, is expressed by most types of RCC, often in a diffuse fashion. Only a few other types of carcinoma coexpress vimentin, including those from the endometrium, thyroid, and adrenal cortex. This is useful in narrowing down the differential diagnoses of metastatic RCC. Among the primary renal neoplasms, a differential immunoreactivity may facilitate tumor typing because vimentin is expressed in most (87%–100%) clear cell and papillary RCCs but only rarely in chromophobe RCC and oncocytoma. However, in a study of 234 oncocytomas, Hes et al[47] found focal vimentin staining in 73% of cases, albeit often quite focal and with a staining pattern different from other renal neoplasms, leading to the conclusion that vimentin can still aid in the distinction of renal neoplasms, but positive vimentin staining does not completely eliminate the possibility of oncocytoma, especially in small samples.

α-Methylacyl Coenzyme A Racemase

α-Methylacyl coenzyme A racemase (AMACR)[20,37,40,49,50] is a mitochondrial enzyme mediating oxidation of fatty acids. Its normal tissue distribution is limited to hepatocytes and to epithelial cells of the renal proximal tubule, the bronchus, and the gall bladder wall.[49,51]

α-Methylacyl coenzyme A racemase expression has been reported in most papillary RCC,[50] and more recently, it was found expressed in most of the mucinous tubular spindle cell RCC (MTSCC),[30,52] in tubulocystic RCC,[35,41,44,49] in Xp11 translocation RCC,[45] and in up to 68% of clear cell RCC but was found infrequently in chromophobe RCC or oncocytoma.[20,37,49]

α-Methylacyl coenzyme A racemase was initially reported to be a positive marker for prostatic carcinoma and has been described in additional tumor types (7%–92%), including adenocarcinomas of the liver, bladder, lung, colon, stomach, ovary, breast, and endometrium, and in neuroendocrine carcinoma.[20,50,51,53]

Carbonic Anhydrase IX

Carbonic anhydrase IX[54,55] is a transmembrane enzyme that regulates cell proliferation, adhesion, and invasion. It has widespread expression in healthy tissue but is *not* seen in healthy kidney.

Expression of carbonic anhydrase IX in renal neoplasms has been reported in several studies[54,55] and is seen in all clear cell RCC and in many tumor types in variable percentages, including in collecting duct RCC and urothelial carcinomas, but carbonic anhydrase IX is uniformly negative in chromophobe RCC and oncocytoma.

Carbonic anhydrase IX is also expressed by most carcinomas of the endometrium, stomach, cervix, breast, lung, and liver and in brain tumors, neuroendocrine tumors, and mesotheliomas.[54]

PAX2

PAX2[35,55–57] is a nuclear transcription factor essential for fetal development of the kidney, the Müllerian organs, the brain, and the eye. PAX2 is expressed normally in kidney, Müllerian organ epithelium, and lymphoid cells. In the kidney, PAX2 is noted only by podocytes and distal tubular cells in healthy tissues (Figure 1, A) but is neoexpressed by other nephron segments when they are injured (Figure 1, B).

Recently, PAX2 was found to be a good marker for renal tumors.[55–57] This marker offers several diagnostic advantages: (1) the nuclear staining supplements the cytoplasmic staining of other traditional markers for renal tumors, such as CD10 or the RCC marker; (2) it is expressed by a high percentage of renal tumors, regardless of histologic type; and (3) when positive, it often stains a high proportion of tumor cells in both primary or metastatic contexts. For diagnostic purposes, only nuclear staining should be considered a specific and true positive.

Although almost all RCC subtypes express PAX2 (Figure 1, E, F, H, and I), marked decrease in PAX2 expression is noted in high-grade tumors, particularly in clear cell RCC, when comparing them with lower-grade tumors. There has been a marked variation in the frequency of PAX2 expression in oncocytoma (Figure 1, C), chromophobe RCC, and collecting duct RCC, among studies (Figure 2, A and B): All 15 Xp11 translocation RCCs (100%) were negative for PAX2 in the study by Gupta et al,[55] but all the Xp11 translocation carcinomas (100%) in the study by Ross et al[58] were uniformly positive. Sarcomatoid RCC is, however, uniformly negative.

Other tumors, including lymphoma, nephrogenic adenoma, parathyroid tumors, and Müllerian-derived tumors, can express PAX2.

PAX8

PAX8[21,59,60] is a transcription factor that belongs to the same family as PAX2. It is important for fetal development of several organs including kidney, Müllerian organs, brain, eye, and thyroid. Its normal tissue distribution is similar to that of PAX2, except for a strong expression by thyroid follicular cells. Recently found to be a good

marker for renal tumors, PAX8 shares with PAX2 its diagnostic advantages described above.

Staining of consecutive tissue sections for PAX8 and PAX2 showed significant overlapping results.[21] Almost all RCCs were positive for PAX8 (Figures 1, D, G, and J, and 2, A and C). Furthermore, tumors that may be negative or infrequently positive for PAX2, including chromophobe RCC (Figure 2, D and E), oncocytoma, and sarcomatoid RCC, are often positive for PAX8.[21] Most Xp11 translocation RCCs are positive.[58]

PAX8 is also frequently expressed by lymphoma (100%), nephrogenic adenoma (100%), parathyroid tumors (62%), thyroid tumors (100%) and Müllerian-derived tumors (92%).[21]

RCC Marker

The RCC marker[17,37,42,61–63] is a commercial name (Vector Laboratories Inc, Burlingame, California) for a monoclonal antibody directed against a glycoprotein identified in the brush border of healthy renal proximal tubular cells (Figure 3, A).

The RCC marker is positive in almost all papillary and clear cell RCCs but is uniformly negative for collecting duct RCC and oncocytoma (Figure 3, B through F), in keeping with the putative histogenesis of these tumors (proximal origin for the former and collecting duct for the latter). For other renal neoplasms, the stain is widely variable, perhaps reflecting either diagnostic variations or intrinsic differentiation of these neoplasms along more than one renal tubular segment.

Previous studies have shown RCC marker in a small percentage of other neoplasms, including breast carcinoma, testicular embryonal carcinoma, and parathyroid tumors. More recent studies[19,63] suggest a much wider expression (17%–100%) in tumors from the adrenal cortex, colon, breast, prostate, ovary, melanoma, lung, and parathyroid,[63] and in malignant mesothelioma,[19] a surprising and disturbing finding that requires confirmation.

CD10

CD10* (also known as common acute lymphoblastic leukemia or neutral endopeptidase) is a cell surface glycoprotein identified in a large variety of healthy cells and which functions as an enzyme that hydrolyzes peptide bonds, thereby decreasing the cellular response to local peptide hormones. In healthy kidney, CD10 is strongly expressed by podocytes and proximal tubular cell brush borders, similar to the RCC marker antigen (Figure 4, A).

CD10 is strongly and diffusely expressed by clear cell (Figure 4, B), papillary (Figure 4, C), and Xp11 translocation RCCs. Expression of CD10 by other renal epithelial neoplasms is widely variable, which limits its diagnostic use for these tumors.

The wide expression of CD10 in healthy tissue is matched by its expression in a growing list of neoplasms, often with a high percentage (20%–100%) stained, including in cutaneous adnexal neoplasms,[18] malignant mesotheliomas,[19] epithelioid hemangioendotheliomas,[64] ovarian clear cell carcinomas,[33] urothelial carcinomas,[22] prostatic adenocarcinomas, pancreatic adenocarcinomas, hepatocellular carcinomas, colonic adenocarcinomas, malignant melanomas, spindle cell sarcomas, lung carcinomas, ovarian carcinomas, endometrial stromal sarcomas, and pancreatic solid pseudopapillary tumors.[22] These findings suggest caution is needed in the use of CD10 as a marker for metastatic RCC.

E-Cadherin and Kidney-Specific Cadherin

E-cadherin† is a calcium-dependent protein crucial for cell-cell interactions and embryogenesis. It is normally expressed by renal tubular cells and many other cell types. Kidney-specific cadherin is an E-cadherin isoform that is expressed exclusively in the basolateral portion of the cell membrane of the renal distal convoluted and collecting duct cells (Figure 5, A).

Although almost all chromophobe RCCs and oncocytomas (100%) express E-cadherin, its expression has been described in variable percentages in other renal epithelial neoplasms and, thus, is of limited value in histologic typing for RCC. In contrast, kidney-specific cadherin maintains equally high expression in chromophobe RCC and oncocytoma (Figure 5, B through E) but is almost always negative in clear cell and papillary RCCs, in keeping with the putative histogenesis of these tumor types. The pattern of expression of kidney-specific cadherin in other, more recently described, types of renal tumor (66% in Xp11 translocation RCCs and 77% in MTSCCs) carry both diagnostic and histogenetic significance.[42,52]

E-cadherin is noted in several other tumor types, often in high percentages (26%–100%), including lung adenocarcinoma, epithelial mesothelioma, urothelial carcinoma, and breast ductal carcinoma.[67] Expression of kidney-specific cadherin in tumors other than those from kidney has not been reported.

Parvalbumin

Parvalbumin[16,23,24,28] is a calcium-binding protein that regulates cytosolic calcium homeostasis. Tissue types that express this molecule include muscle, brain, neuroendocrine organs. and kidney. In the kidney, parvalbumin is limited to the distal tubular and collecting duct cells, where renal control of calcium flux occurs.

Parvalbumin is strongly expressed in most chromophobe RCC and oncocytoma, but it is essentially negative in other types of RCCs. This limited expression is in keeping with the putative histogenesis of chromophobe RCC and oncocytoma from the distal portion of the nephron and may facilitate in their differential diagnoses.

Parvalbumin expression in nonrenal tumors has not been systematically studied.

Claudins 7 and 8

Claudins 7 and 8[28,68,69] belong to a 20-member family of tight cell junction proteins, which have tissue-limited expression, including in the distal tubule and collecting duct cells of the kidney.

Limited studies on their expression in renal neoplasm showed that most chromophobe RCC and oncocytoma expressed both claudin 7 and 8, but they are seen in no or very few other RCCs. This expression pattern is in keeping with the putative histogenesis of chromophobe RCC and oncocytoma and may facilitate their differential diagnoses.

Claudins 7 or 8 has been reported in carcinoma from several organs, including stomach, esophagus, pancreas, bladder, thyroid, prostate, colon, and breast.[70]

* *References 16, 22, 33, 35–38, 40–42, 61, 62.*

† *References 23, 29, 30, 37, 40, 48, 65, 66.*

Table 1. Immunoprofiles of the Major Renal Neoplasms[a,b]

Source, y	Stain	Clear Cell RCC, Staining (%)	Papillary RCC, Staining (%)
Adley et al,[23] 2006; Skinnider et al,[31] 2005; Bazille et al,[36] 2004; Allory et al,[37] 2008; Liu et al,[38] 2007; Yang et al,[44] 2008	CK7	± (0–37)	+ (80–87)
Skinnider et al,[31] 2005	CK8	+ (40)	+ (87)
Skinnider et al,[31] 2005; Amin et al,[35] 2009	CK18	+ (100)	+ (100)
Skinnider et al,[31] 2005; Ohta et al,[33] 2005; Wasco et al,[39] 2010	CK20	−	−
Skinnider et al,[31] 2005; Ohta et al,[33] 2005; Amin et al,[35] 2009; Kobayashi et al,[40] 2008; Azoulay et al,[41] 2007; Chuang et al,[90] 2007	HMW CKs	± (0–13)	+ (33)
Skinnider et al,[31] 2005	CK5/CK6	−	−
Adley et al,[23] 2006; Skinnider et al,[31] 2005; Ohta et al,[33] 2005; Han et al,[34] 2010; Amin et al,[35] 2009; Bazille et al,[36] 2004; Allory et al,[37] 2008; Liu et al,[38] 2007; Wasco et al,[39] 2010; Kobayashi et al,[40] 2008; Azoulay et al,[41] 2007; Argani et al,[42] 2007; Meyer et al,[43] 2007; Yang et al,[44] 2008	AE1/AE1 CKs	+ (35)	+ (82)
Skinnider et al,[31] 2005; Bazille et al, Allory et al,[37] 2008; Argani et al,[42] 2007; Huang et al,[46] 2009; Hes et al,[47] 2007; Taki et al,[48] 1999	Vimentin	+ (87)	+ (100)
Lin et al,[20] 2004; Allory et al,[37] 2008; Kobayashi et al,[40] 2008; Molinié et al,[49] 2006; Tretiakova et al,[50] 2004	AMACR	+ (4–68)	+ (80–100)
Ivanov et al,[54] 2001; Gupta et al,[55] 2009	Carbonic anhydrase IX	+ (100)	+ (57)
Amin et al,[35] 2009; Gupta et al,[55] 2009; Ozcan et al,[56] 2009; Zhai et al,[57] 2010	PAX2	+ (92)	+ (87)
Ozcan et al,[21] 2011; Tong et al,[59] 2009; Albadine et al,[60] 2010	PAX8	+ (98)	+ (87)
McGregor et al,[17] 2001; Allory et al,[37] 2008; Argani et al,[42] 2007; Avery et al,[61] 2000; Wang et al,[62] 2005; Bakshi et al,[63] 2007	RCC marker	+ (72–85)	+ (87–95)
Martignoni et al,[16] 2001; Chu et al,[22] 2000; Ohta et al,[33] 2005; Amin et al,[35] 2009; Bazille et al,[36] 2004; Allory et al,[37] 2008; Liu et al,[38] 2007; Kobayashi et al,[40] 2008; Azoulay et al,[41] 2007; Argani et al,[42] 2007; Avery et al,[61] 2000; Wang et al,[62] 2005	CD10	+ (94–100)	+ (67–93)
Adley et al,[23] 2006; Shen et al,[29] 2005; Kuehn et al,[30] 2007; Allory et al,[37] 2008; Kobayashi et al,[40] 2008; Taki et al,[48] 1999; Ferlicot et al,[65] 2005; Mazal et al,[66] 2005	E-cadherin	± (0–14)	+ (13–31)
Adley et al,[23] 2006; Shen et al,[29] 2005; Kuehn et al,[30] 2007; Allory et al,[37] 2008; Kobayashi et al,[40] 2008; Taki et al,[48] 1999; Ferlicot et al,[65] 2005; Mazal et al,[66] 2005	Kidney-specific cadherin	± (0–30)	± (0–29)
Martignoni et al,[16] 2001; Adley et al,[23] 2006; Young et al,[24] 2003; Choi et al,[28] 2007	Parvalbumin	± (0–8)	± (0–31)
Choi et al,[28] 2007; Osunkoya et al,[68] 2009; Hornsby et al,[69] 2007	Claudin-7	−	+ (28–35)
Choi et al,[28] 2007; Osunkoya et al,[68] 2009; Hornsby et al,[69] 2007	Claudin-8	NA	NA
Yusenko et al,[26] 2009; Li et al,[27] 2007; Cossu-Rocca et al,[71] 2009	S100A1	+ (57–73)	+ (62–94)
Yusenko et al,[26] 2009; Kauffman et al,[32] 2009	CD82	± (2–23)	−
Kobayashi et al,[40] 2008; Wang et al,[62] 2005; Petit et al,[74] 2004; Zigeuner et al,[75] 2005; Castillo et al,[76] 2004; Pan et al,[77] 2004; Huo et al,[78] 2005; Sengupta et al,[79] 2006; Kruger et al,[80] 2005	CD117	± (0–5)	± (0–13)
Argani et al,[42] 2007; Meyer et al,[43] 2007; Camparo et al,[45] 2008; Ross et al,[58] 2010	TFE3	−	−
Buza et al,[91] 2010; Ordonez,[96] 1997; Ordonez,[97] 1998; Mhawech et al,[98] 2002; Kaufmann et al,[99] 2000	Thrombomodulin	−	NA
Ordonez,[96] 1997; Kaufmann et al,[99] 2000; Ohtsuka et al,[100] 2006; Moll et al,[101] 1993; Higgins et al,[102] 2004	Uroplakin III	0/32 RCCs[c]	−
Wasco et al,[39] 2010; Albadine et al,[60] 2010; Tuna et al,[87] 2009; Comperat et al,[88] 2006; Kunju et al,[89] 2006; Chuang et al,[90] 2007; Buza et al,[91] 2010; Westfall et al,[92] 2009; Houghton et al,[93] 2009	p63	−	−
Tuna et al,[87] 2009; Buza et al,[91] 2010	S100P	−	−
Argani et al,[42] 2007; Camparo et al,[45] 2008	HBM-45	NA	NA
Argani et al,[42] 2007; Camparo et al,[45] 2008	Melan-A	NA	NA

Abbreviations: AE1/AE3 CKs, cytokeratins detected by the antibody AE1/AE3; AMACR, α-methylacyl-coenzyme A racemase; CK, cytokeratin; HMW CKs, high–molecular-weight cytokeratins; MTSCC, mucinous tubular spindle cell carcinoma; NA, data not systematically available; RCC, renal cell carcinoma.

[a] Positive (+), negative (−), or variably positive and negative (±) staining. Percentages represent the percentages of positive cases.
[b] The table includes the more frequent tumor types and those that often cause diagnostic difficulties by routine light microscopy.
[c] Types not specified.

S100A1

S100A1[26,27,71] is 1, among 13 members of the S100 protein family, that is expressed in a large variety of cell types and regulates many cellular functions, including cell cycle and differentiation. Both nuclear and cytoplasmic expression has been described throughout the nephron in adults and is limited to the proximal tubules in fetal kidneys.

S100A1 is expressed in most oncocytomas, but the expression is much less frequent in chromophobe RCC, which may help to differentiate these 2 tumors.

Table 1. Extended

Chromophobe RCC, Staining (%)	Collecting Duct Carcinoma, Staining (%)	Sarcomatoid RCC, Staining (%)	Xp11 Translocation RCC, Staining (%)	MTSCC, Staining (%)	Tubulocystic RCC, Staining (%)	Urothelial Carcinoma, Staining (%)	Oncocytoma, Staining (%)
+ (73–86)	+ (83)	NA	+ (17)	+ (79–100)	+ (62–91)	+ (92)	± (0–10)
+ (53)	+ (83)	NA	NA	−	+ (100)	+ (100)	+ (100)
+ (100)	+ (100)	NA	NA	+ (100)	+ (100)	+ (83)	+ (100)
−	−	NA	NA	−	−	+ (25–68)	−
−	+ (29–67)	NA	NA	+ (15–33)	± (0–67)	+ (100)	+ (10)
−	+ (17)	NA		−	−	+ (75)	−
+ (16)	NA	NA	+ (0–25)	+ (83)	NA	+ (100)	+ (16)
−	+ (100)	NA	+ (65–70)	+ (55–100)	+ (55)	+ (33)	−
± (0–29)	± (0–18)	NA	+ (100)	+ (92–100)	+ (77–100)	+ (20)	+ (2–25)
−	+ (40–100)	NA	+ (40)	−	+ (42)	+ (100)	−
± (0–83)	± (0–100)	−	± (0–100)	+ (75–100)	+ (37–42)	−	+ (88–100)
+ (83)	+ (100)	+ (28)	+ (100)	+ (100)	+ (100)	± (0–8)	+ (87–95)
+ (0–91)	−	+ (0–22)	+ (100)	+ (7–92)	+ (100	−	−
± (0–72)	+ (25)	NA	+ (100)	+ (9–50)	+ (33–100)	+ (50)	+ (12–58)
+ (100)	+ (75)	NA	+ (66)	+ (93)	NA	+ (76–100)	+ (47–100)
+ (86–100)	−	NA	+ (66)	−	+ (71)	−	+ (75–95)
+ (80–100)	NA	NA	NA	NA	NA	NA	+ (47–100)
+ (67–95)	NA	NA	NA	NA	NA	NA	+ (23–73)
+ (27)	NA	NA	NA	NA	NA	NA	+ (88)
± (0–26)	NA	NA	NA	NA	NA	NA	+ (93)
+ (78–87)	NA	NA	NA	NA	NA	NA	± (0–7)
+ (82–100)	± (0–53)	± (4–95)	NA	NA	NA	+ (4–30)	+ (58–100)
−	−	−	+ (87)	−	−	−	−
NA	NA	−	NA	NA	NA	+ (49–100)	NA
−	NA	NA	NA	NA	NA	+ (33–100)	NA
−	+ (0–14)	−	NA	NA	NA	+ (81–100)	NA
−	−	−	NA	NA	NA	+ (71–96)	NA
NA	NA	NA	+ (46)	NA	NA	NA	NA
NA	NA	NA	+ (89)	NA	NA	NA	NA

It is, however, also expressed by clear cell and papillary RCCs.

S100A1 expression in nonrenal tumors has not been systematically studied. It has been reported in 17 out of 18 nephrogenic adenomas (94%).[71]

CD82

CD82[26,32] is known to be a metastasis suppressor gene, which can block one or more steps along the downstream metastatic cascade, without affecting primary tumor growth. Decreased levels of expression have been identified in patients with widespread metastasis. In healthy kidney, CD82 is limited to the cell membrane of the distal portion of the nephron.

Two independent studies showed that, in contrast to S100A1, almost all chromophobe RCCs express S100A1, whereas this marker is noted in few or no oncocytomas.[26,32] However, a high percentage of clear cell and papillary RCCs also express this marker. Therefore, a panel, including S100A1 and CD82,

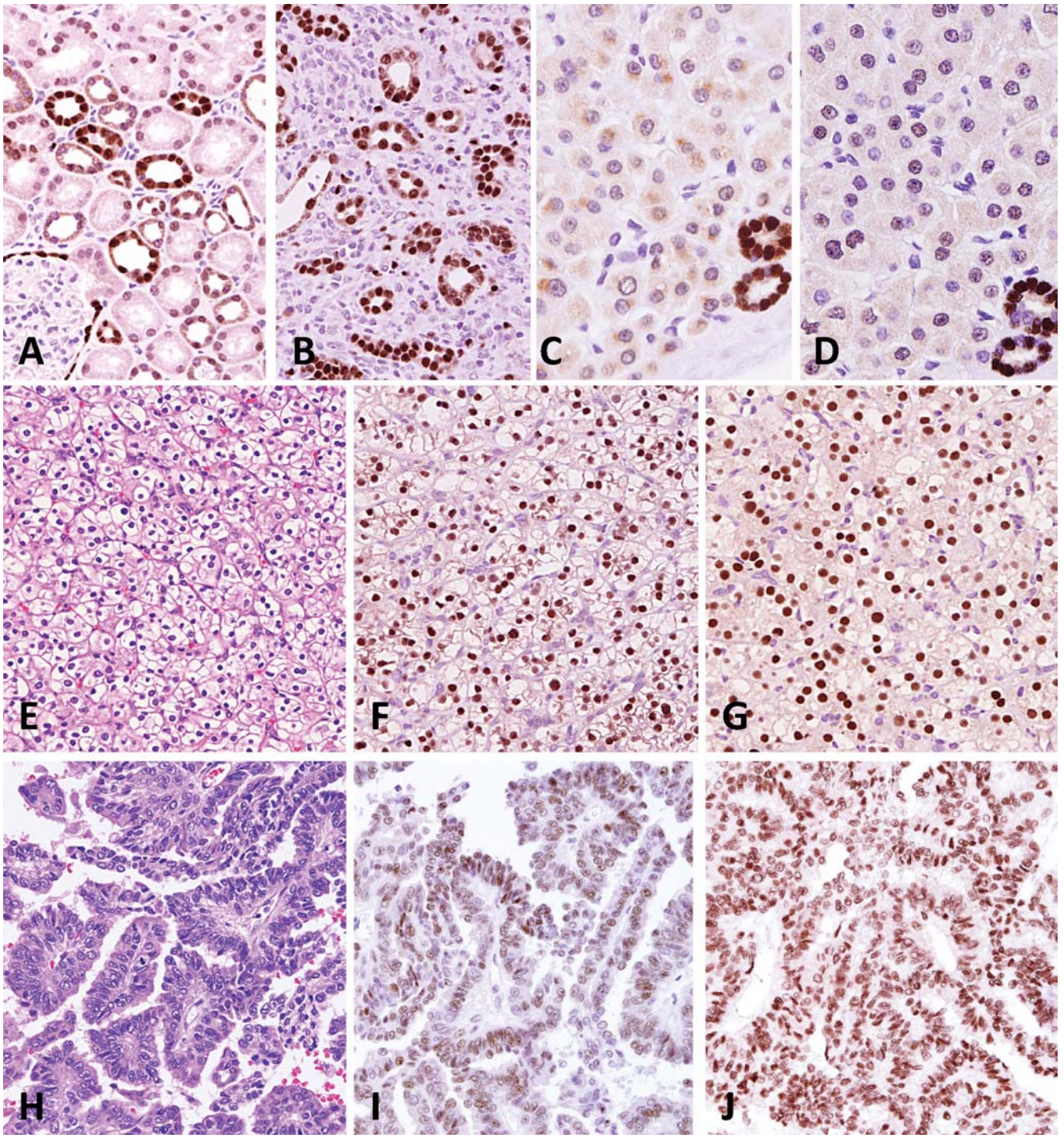

Figure 1. *PAX2 and PAX8: Their staining patterns are very similar. A, Normal kidney: PAX2 staining in distal tubular cells and glomerular visceral epithelial cells. The staining is mostly nuclear, but cytoplasmic staining is also noted, which is usually weak and perhaps nonspecific. Other tubular segments are not stained. B, Atrophic kidney: All atrophic tubules, regardless of nephronic segment, are positive. This is, perhaps, in keeping with the observation that PAX2 is expressed in most types of renal neoplasm regardless of putative nephronic segment of origin. C (PAX2) and D (PAX8): Oncocytoma—Similar staining for PAX2 and PAX8, characterized by weak or nonstaining tumor cells, in contrast with the strong nuclear staining of entrapped renal tubules (lower right). E, F (PAX2), and G (PAX8): Clear cell renal cell carcinoma (RCC)—Diffuse, strong nuclear staining for both PAX2 and PAX8 in consecutive tissue sections. H, I (PAX2), and J (PAX8): Papillary RCC—Diffuse strong nuclear staining for both PAX2 and PAX8 in consecutive tissue sections (original magnifications ×100 [A and B] and ×200 [C through J]).*

may help to differentiate chromophobe RCC from oncocytoma.

CD82 expression in nonrenal tumors has not been systematically studied, but expression has been noted in at least some prostatic or colorectal tumors.[72,73]

C-Kit (CD117)

C-kit (CD117)[40,62,74–80] is a proto-oncogene encoding a tyrosine transmembrane receptor. Its mutation may promote some tumor types, including gastrointestinal

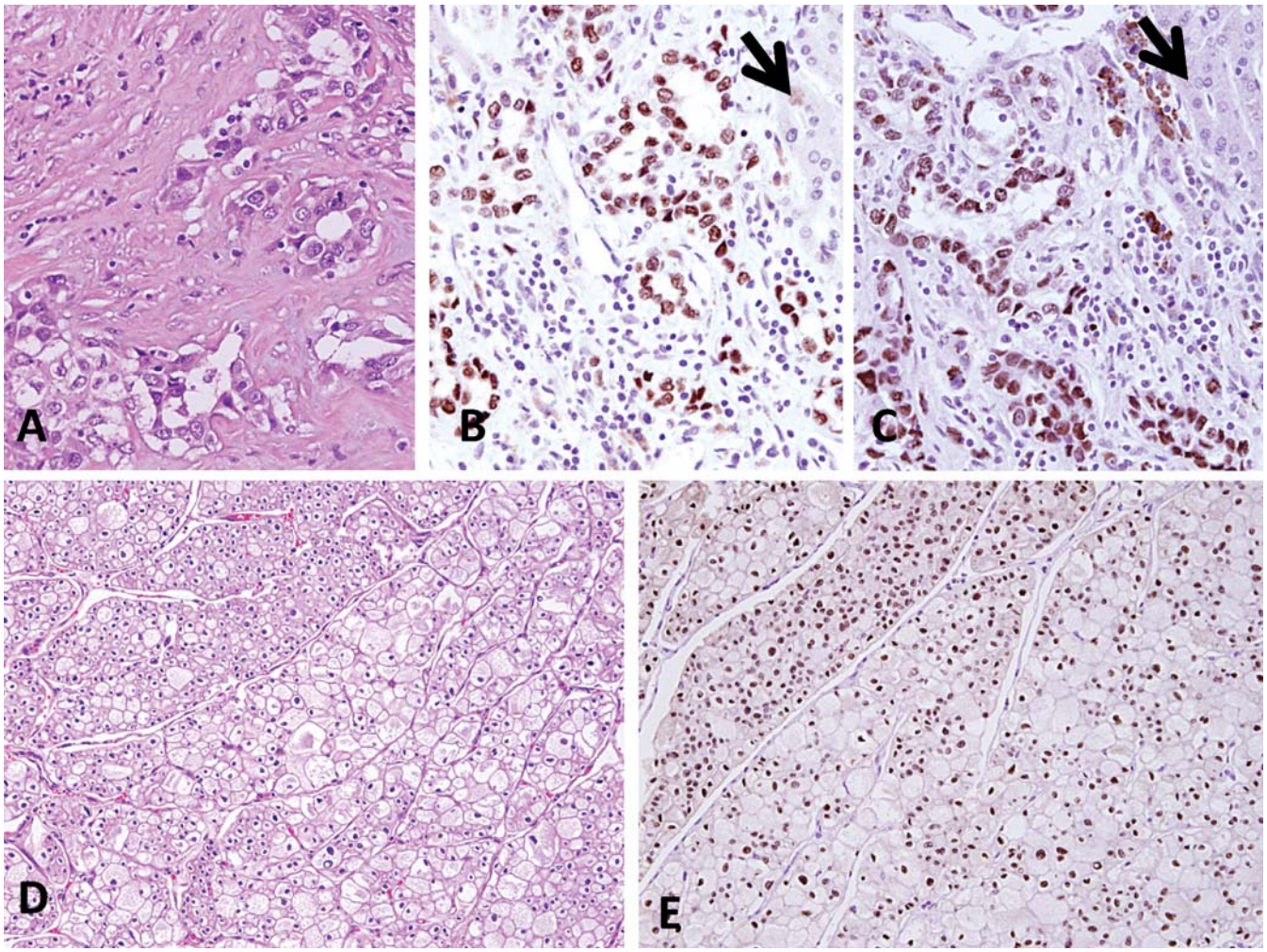

Figure 2. *A, B, and C, PAX2 and PAX8: Collecting duct renal cell carcinoma (RCC)—Strong, nuclear staining for both PAX2 (A and B) and PAX8 (C). The tumor extends to the liver, in which the hepatocytes are negative for both PAX2 and PAX8 (arrows). D and E, Chromophobe RCC—Diffuse staining for PAX8 is shown, which is identical to that of PAX2 staining on a consecutive tissue section (not shown) (original magnifications ×200 [A through C] and ×100 [D and E]).*

stromal tumors and promyelocytic leukemia. Because a CD117 inhibitor can control these 2 tumor types so well, there has been interest in assessing its expression in other tumor types, including renal neoplasms, which may serve as the foundation for anti-CD117 treatment.

Most chromophobe RCC and oncocytoma express CD117, whereas clear cell and papillary RCC findings are almost always negative. CD117 expression was reported in the sarcomatoid component of 94% of sarcomatoid RCC and less frequently in urothelial carcinoma (4%–30%) and in angiomyolipoma (17%–40%). Therefore, CD117 may be useful marker for differential diagnosis in some settings.

In addition to gastrointestinal stromal tumors, CD117 expression has been reported in a large number of other tumor types, such as leukemia, lung carcinoma, mesothelioma, neuroendocrine carcinoma, serous ovarian carcinoma, and melanoma.[67]

TFE3

A subset of RCC is characterized by chromosome translocation involving Xp11.2 resulting in fusion (and activation) of the gene *TFE3* (Figure 6)[42,43,45,58] with at least 6 other genes located in other chromosomes.[58,81,82] All variants of Xp11.2 translocation result in overexpression of TFE3 protein, which can be detected by immunohistochemistry (Figure 6, A and B).[83] The Xp11.2 translocation carcinoma occurs mainly in children and young adults, with an average age of 24.6 years (N = 31) in a recent large series of 31 patients.[45] The protein TFE3 is reported in isolated cases of acquired cystic kidney disease–associated RCC. To be considered a positive finding, the TFE3 should be limited to the nuclei of tumor cells and should not be seen elsewhere in the specimen.

The TFE3 protein has been reported regularly in alveolar soft part sarcoma, which is known to harbor the TFE3 gene translocation and, more recently, in isolated examples of perivascular epithelioid cell tumor.[84,85]

p63

The *p63*[39,60,86–92] gene is a member of the *p53* gene family that regulates several cell functions, including cell cycle, stress adaptation, and signal transduction. It is normally expressed in the basal cell layers of squamous or urothelium (Figure 7, A and B), the basal cells of the breast, the prostate, and the salivary gland, but not in the kidney.

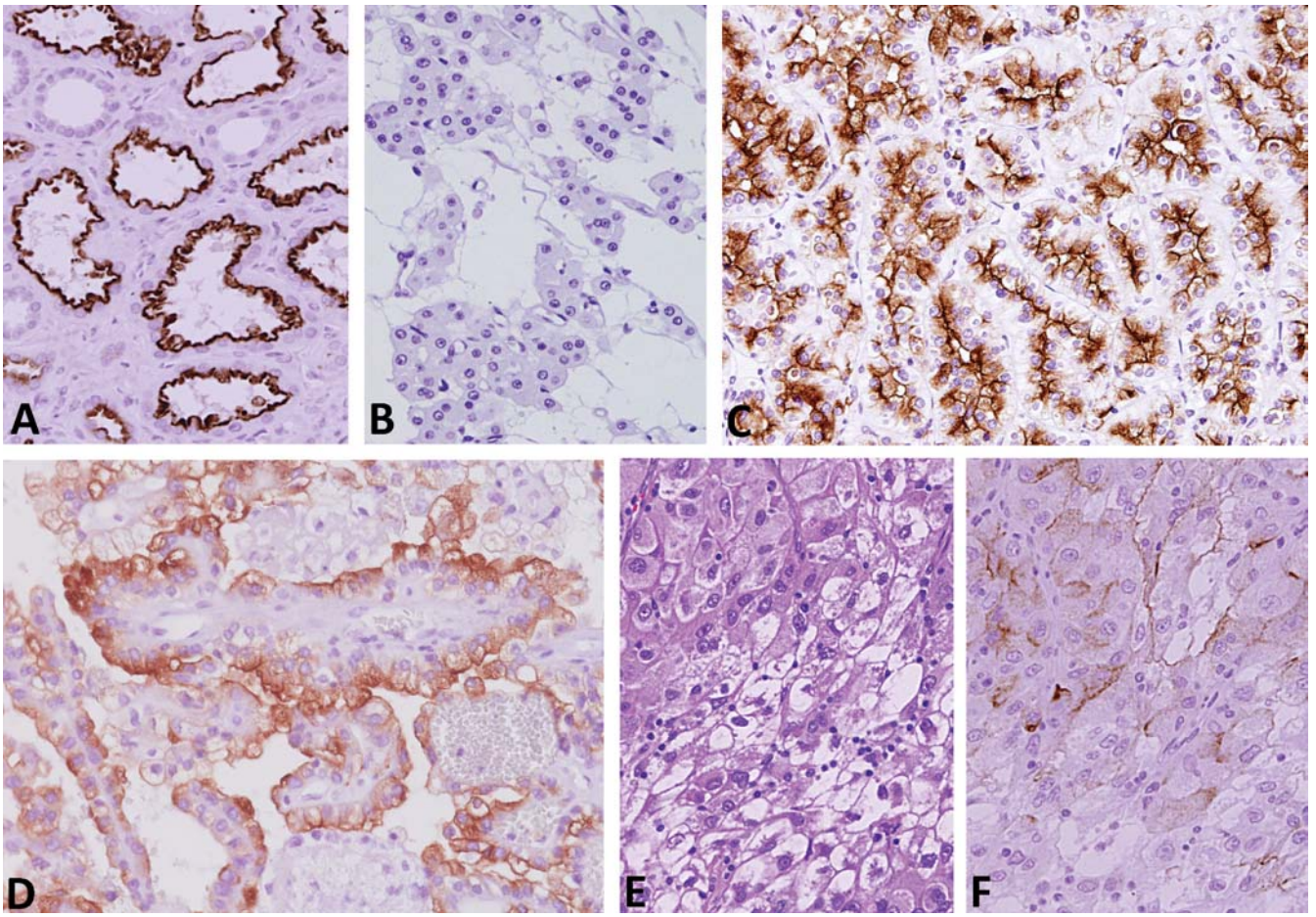

Figure 3. *Renal cell carcinoma (RCC) marker: A, Normal kidney—The staining is limited to the brush border of the proximal tubules. B, Oncocytoma—No staining. C, Clear cell RCC—Diffuse staining predominantly in the luminal side of the cell membrane, replicating the staining pattern of normal renal tubules. D, Papillary RCC—Diffuse staining predominantly in the free surface of the cell membrane. E and F, Xp11 translocation RCC—Displaying focal membranous staining (original magnifications ×200 [A, B, and D through F] and ×100 [C]).*

In urothelial carcinoma, p63 is expressed in a high percentage (70%–100%) of cases, regardless of primary or metastatic sites or grades (Figure 7, D).[90,91] In addition, up to 50% of sarcomatoid urothelial carcinomas stain positive for p63.[92] Its expression is not seen in RCCs,[87] but it was noted in 14% of collecting duct RCC in one study.[60] Thus, p63 may facilitate the often-challenging differentiation of renal urothelial carcinoma from poorly differentiated RCCs, including collecting duct RCC.

In keeping with its usual expression, p63 is noted in a large variety of tumors, including squamous cell carcinoma, urothelial carcinoma of female genital tract, placental trophoblastic tumors,[93] and some breast carcinomas.[94]

Thrombomodulin

Thrombomodulin[90,95–98] is a transmembrane protein that regulates coagulation through activation of the C-reactive protein. Originally described in vascular endothelial cells, it is also noted in several other cell types, including mesothelial cells, platelets, and keratinocytes. Thrombomodulin is found in urothelial cells (Figure 7, C) but not in renal tubular epithelial cells.

Thrombomodulin is expressed by 49% to 100% of urothelial neoplasms, with the lower rate noted in high-grade or metastatic tumors[97] (Figure 7, E). A single study reported no staining in 22 RCCs.[97]

In keeping with its protean expression in healthy tissue, thrombomodulin is seen in several tumor types, including vascular tumors, mesothelioma, squamous cell carcinoma, and adenocarcinoma of the lung, ovary, pancreas, and breast.[67]

Uroplakin III

Uroplakin III[95,98–101] is 1 of the 4 members of the uroplakin family. In healthy tissue, this transmembrane protein is limited to the cell membrane of urothelial cells, especially the superficial ones.

Uroplakin III is expressed in 33% to 100% of urothelial carcinomas of the bladder or renal pelvis, with the lower rates noted in high-grade, invasive, or metastatic tumors. Uroplakin III has not been reported in other tumor types, including 47 RCCs in 2 studies.[99,101] However, collecting duct RCC, which is most often confused with high-grade urothelial carcinoma, was apparently not included in these 2 studies.

A systematic evaluation of uroplakin expression in tumors, other than those in kidney and urinary tract, is not available.

S100P

S100P[86,90] is a member of the S100 protein family that regulates cell cycle and differentiation. Initially identified in placenta (thus S100*P*), widespread expression is later

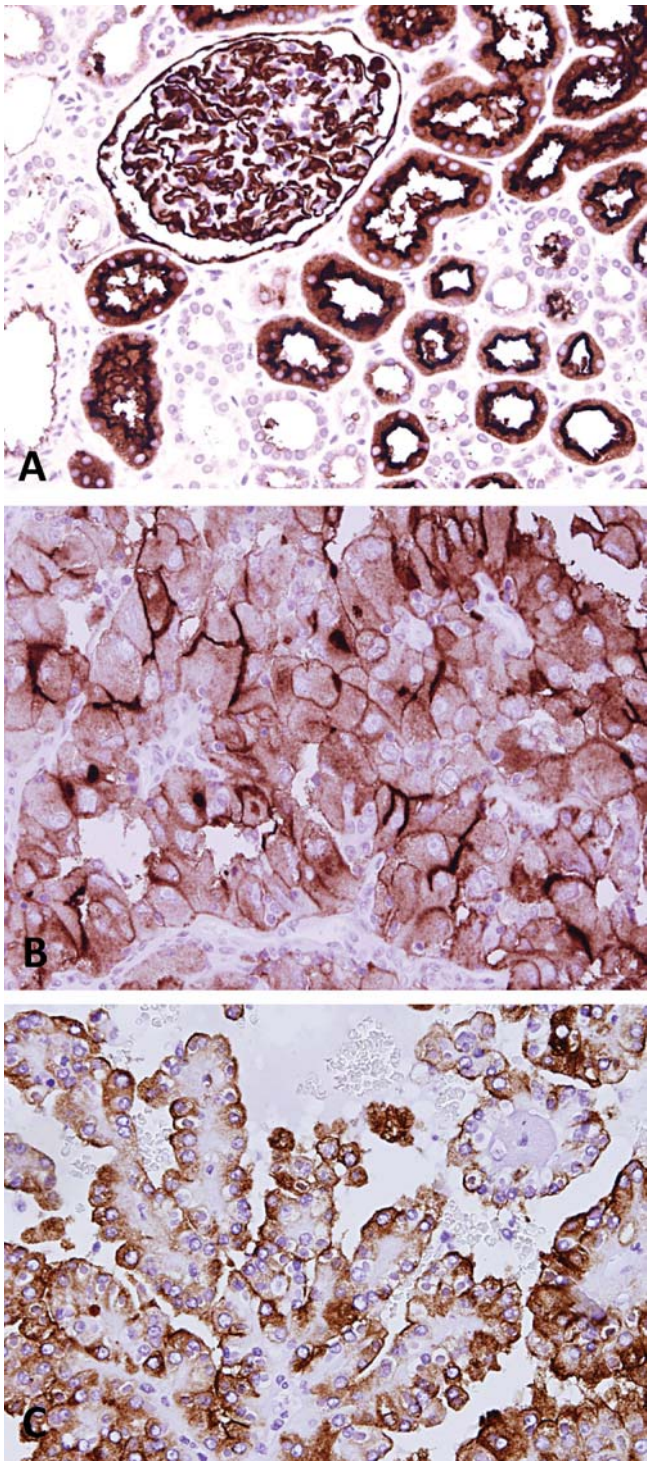

Figure 4. *CD10: A, Normal kidney—Strong staining was shown in proximal, tubular cell brush border and cytoplasm, with accentuation for the former. There is also staining of the glomerular visceral and parietal epithelial cell cytoplasm. B, Clear cell renal cell carcinoma (RCC)—Diffuse cytoplasmic staining with focal, marked cell membrane accentuation, replicating normal renal tubular cell expression. C, Papillary RCC—Diffuse staining of predominantly free surface membrane of the tumor cells (original magnifications ×200 [A through C]).*

noted in the gastrointestinal tract, prostate, leukocytes, and pelvic urothelium, but not in the kidney.[102]

S100P is one of the most recent markers for urothelial carcinoma and is seen in 71% to 96% of urothelial carcinomas, with the lower number (still very significant at 71%) for the higher-grade tumors. A single study of 150 RCCs, including 2 collecting duct and 2 sarcomatoid RCCs, showed negative results.[86] Thus, this marker may facilitate differentiation between urothelial carcinoma and collecting duct RCC.

S100P is described in many types of carcinoma (10%–62%), including those from the gastrointestinal tract, pancreas, liver, lung, and ovary.[103]

Other Antibodies

Other markers not detailed here, including aquaporin-1, MOC31, Ber-EP4, caveolin-1, vinculin, paxillin, progesterone receptor, and aquaporin-6, may have limited diagnostic utility, reflecting single-study data, limited spectrum of evaluated tumors, or failure to provide conclusive differential diagnostic guidance.

IMMUNOPROFILES OF COMMON RENAL NEOPLASMS

Clear Cell RCC

In addition to the typical solid and acinar pattern, other growth patterns, such as tubular, cystic, and pseudopapillary, can occur and may even predominate in clear cell RCC. The tumor is composed exclusively of either cells with clear cytoplasm or, more frequently, cells admixed with eosinophilic or granular cytoplasm. The diagnosis is usually straightforward for a primary renal tumor composed of clear cells with abundant vascular network but can be problematic in a metastatic setting because many epithelial neoplasms, and rarely sarcomas, may have prominent cytoplasmic clearing. Clear cell RCC is typically positive for vimentin, AE1/AE3 keratins, CD10, RCC marker, and carbonic anhydrase IX (G250). It is usually negative for CD117, kidney-specific cadherin, and parvalbumin (Table 1).

Papillary RCC

Papillary RCC is characterized by a papillary or tubulopapillary growth, lined with cells of varying cytoplasmic characteristics of abundance and staining features on hematoxylin-eosin section. Other features include solid growth, presence of foamy macrophages within fibrovascular cores, and mucin. Based primarily on the cytologic features, papillary RCCs have been divided into type 1 and type 2. Type 1 papillary RCC is often uniformly positive for vimentin, AE1/AE3 keratins, CK7, AMACR, and RCC marker. It is usually negative for CD117, kidney-specific cadherin, and parvalbumin (Table 1). However, type 2 papillary RCC displays a quite variable immunoprofile.

Chromophobe RCC

Typical growth features of chromophobe RCCs are solid sheets of cells separated by long, curvilinear, sometimes hyalinized vessels. Very helpful diagnostic features for typical chromophobe RCCs include mixed large cells with voluminous, reticulated cytoplasm and smaller cells with granular cytoplasm. The tumor cells display nuclear wrinkling, perinuclear halos, and prominent cell membranes. The immunoprofile is usually quite distinct from those of clear cell and papillary RCCs and is positive for kidney-specific cadherin, parvalbumin, CD117, epithelial membrane antigen, AE1/AE3 keratin, and CK7. It is usually negative for vimentin, carbonic anhydrase IX, and AMACR (Table 1).

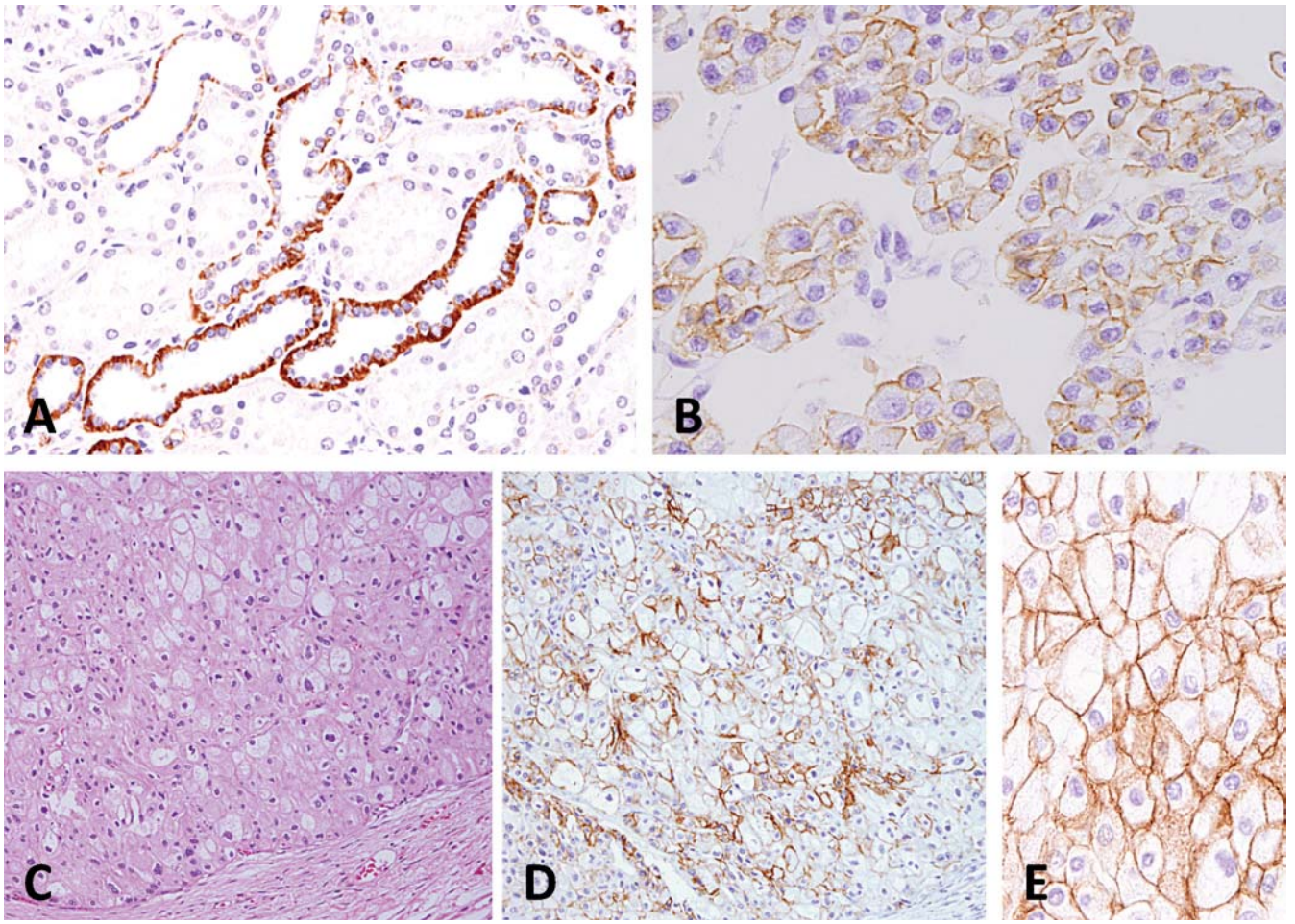

Figure 5. *Kidney-specific cadherin: A, Normal kidney—Staining is limited to the basolateral portion of the distal renal tubular cells. B, Oncocytoma—Diffuse membranous staining. C through E, Chromophobe renal cell carcinoma—Focal (D) or diffuse (E) staining of tumor cell membrane (original magnifications ×400 [A and E], ×200 [B], and ×100 [C and D]).*

Oncocytoma

Oncocytomas are the most-common benign renal neoplasm. Numerous studies[16,17,23–29] have attempted to identify markers that can reliably differentiate oncocytoma from chromophobe RCC. However, the results are largely disappointing. Oncocytoma shares a similar immunoprofile with chromophobe RCC, particularly the eosinophilic variant. This observation may reflect their common cell of origin or differentiation and similar

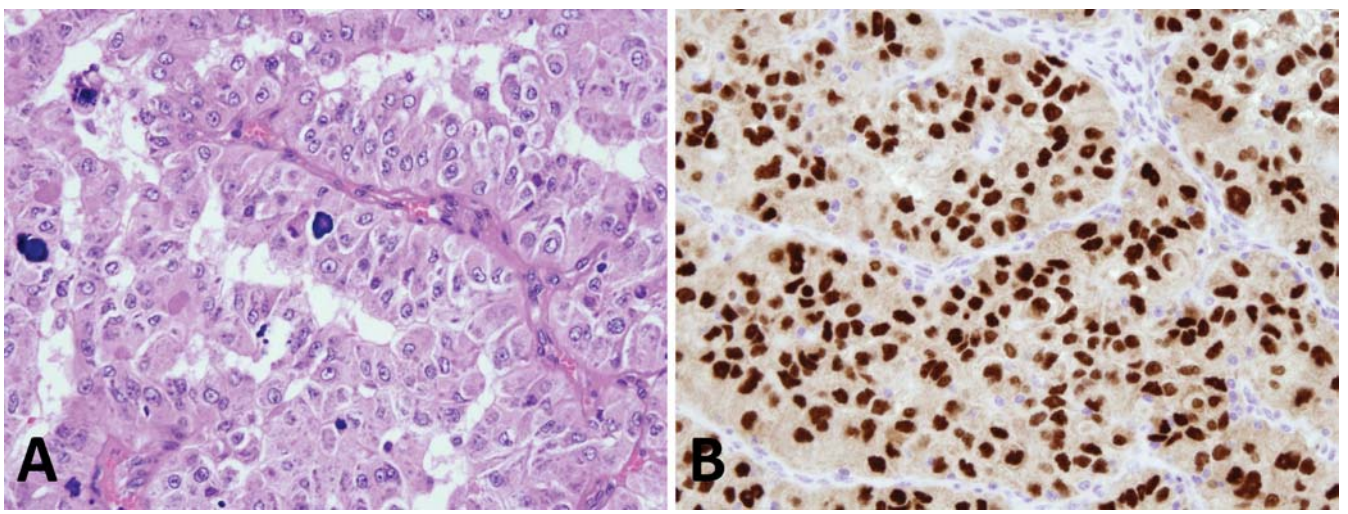

Figure 6. *TFE3: A, Xp11 translocation carcinoma characterized by tumor cells with abundant granular cytoplasm and scattered psammoma bodies. B, The tumor cells show strong and diffuse staining for TFE3, which is limited to the nuclei (original magnifications ×400 [A and B]).*

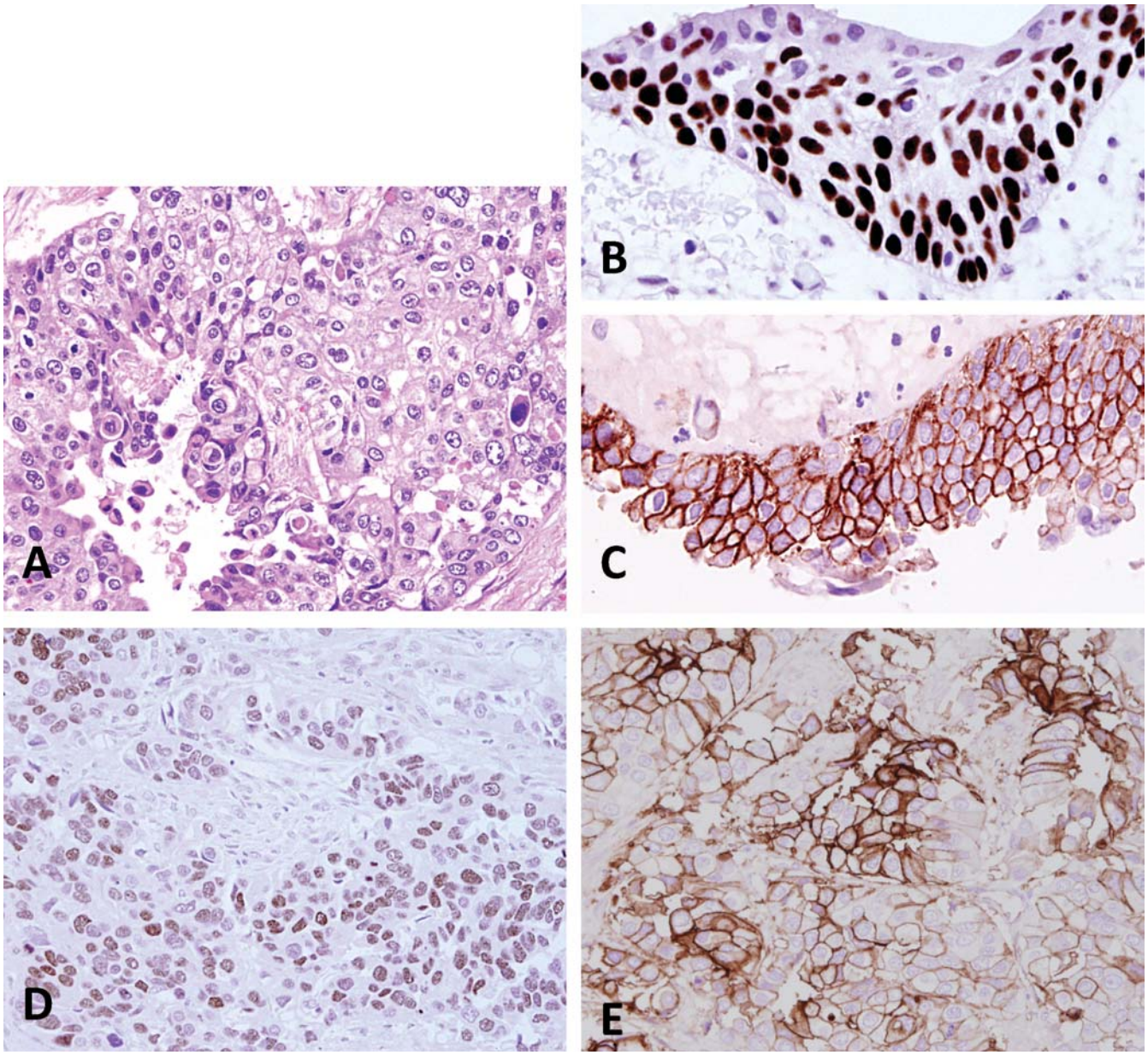

Figure 7. *p63 and thrombomodulin: A, High-grade urothelial carcinoma displaying features that overlap with collecting duct or high-grade clear cell renal cell carcinoma (RCC). B, Normal urothelium with nuclear staining for p63. C, Normal urothelium with cell membrane staining for thrombomodulin. D, Urothelial carcinoma with nuclear staining for p63. E, Urothelial carcinoma with cell membrane staining for thrombomodulin (original magnifications ×200 [A, D, and E] and ×400 [B and C]).*

cytogenetic and molecular profiles. In addition, ample evidence suggests that some tumors may have features of both oncocytoma and chromophobe RCC (the so-called hybrid tumor) as described in patients with Birt-Hogg-Dube syndrome. Sporadic cases of oncocytic tumor with hybrid features have also been described. There have been studies suggesting a differential staining of some markers, such as vimentin, S100A1, and CD82, which may be of help in some situations, but interpretation using these markers must be made cautiously.

Mucinous Tubular and Spindle Cell Carcinoma

The MTSCC tumor typically has a solid and tubular growth pattern. The solid area may show sheets of spindle cells. Stromal mucin can be seen in the stroma or tubules. There are striking, overlapping morphologic features between papillary RCC and MTSCC, including tubules, papillary formation, presence of mucin, and foamy macrophages.[52,104] The immunoprofile of MTSCC is similar to that of papillary RCC and is positive for vimentin, AE1/AE3 keratins, CK7, AMACR, and RCC marker. It is negative for CD117, kidney-specific cadherin, and parvalbumin.

Xp11.2 Translocation Carcinoma

The Xp11.2 translocation tumor type often shows unusual morphologic features, such as clear cells forming papillary or alveolar growths, or large epithelioid tumor cells with voluminous clear to acidophilic cytoplasm. Hyaline nodules with psammomatous calcification are a

frequent finding. Its immunohistochemical profile is similar to that of clear cell RCC (positive for CD10, RCC marker, etc), except for a negative or focal positive staining for pancytokeratin. TEF3 is uniformly expressed in this tumor type, and a positive stain for this surrogate marker for Xp11.2 translocation is required for diagnosis.

Collecting Duct Carcinoma

The collecting duct tumor type is characterized by its infiltrating, nested, glandular, or papillary growth patterns and is composed of often highly atypical cells with prominent desmoplastic stroma. It shares a somewhat similar immunoprofile with that of urothelial carcinoma. Immunopositivity of p63 and uroplakin III may be suggestive of urothelial carcinoma and PAX2 and PAX8 may be helpful for diagnosing collecting duct carcinoma.

Urothelial Carcinoma

The diagnosis of low-grade, papillary urothelial neoplasm that is confined to the renal pelvis is fairly straightforward. However, invasive, high-grade urothelial carcinoma of the renal pelvis often shows infiltrative growth, marked cytologic atypia, and desmoplasia. Therefore, a distinction among high-grade RCC, particularly papillary RCC, collecting duct carcinoma, or unclassified RCC can be quite challenging. The tumor is most often positive for CK7 and p63 (70%) and is usually positive for CK5/6 and CK20. Other relatively specific markers for urothelial carcinoma are uroplakin III, high–molecular-weight CKs, and thrombomodulin. It is typically negative for the common markers for RCC, such as RCC marker, CD10, PAX2, and PAX8.

Myoid-Rich or Epithelioid Angiomyolipoma

Myoid-rich or epithelioid angiomyolipoma is considered an unusual variant of angiomyolipoma and is characterized by cellular spindles or polygonal cells with a paucity, or almost complete absence, of fat tissue or the typical perivascular cuffing by tumor cells. Marked cytologic atypia or cystic changes may be seen in rare cases. This tumor type may closely simulate a high-grade RCC or high-grade sarcomas, particularly at frozen section. The tumor is positive for HMB-45, Mart-1 or Melan-A, microphthalmia transcription factor, tyrosinase, and muscle-specific actin. It is negative for AE1/AE3 keratins, epithelial membrane antigen, CD10, and RCC marker.

APPLICATION OF IMMUNOPROFILES IN PATTERN-BASED DIFFERENTIAL DIAGNOSTIC PROBLEMS

Tumors With Clear Cells

Tumors with clear cells are the most common type of renal neoplasm, with most of them being clear cell RCC. The main differential diagnosis, particularly on frozen sections, is the chromophobe RCC, which is composed of mainly large cells with voluminous reticular cytoplasm. Helpful immunohistochemical markers include vimentin, CK7, carbonic anhydrase IX, kidney-specific cadherin, and CD117. Chromophobe RCC is usually positive for kidney-specific cadherin, CD117, and CK7 but negative for carbonic anhydrase IX and vimentin. Clear cell RCC typically would demonstrate staining patterns that were directly opposite.

A less-likely differential diagnosis could also be angiomyolipoma, particularly at frozen section. Identification of myoid cells and perivascular tumor cell cuffing and positive staining for desmin and HMB-45 would be confirmatory.

A recently defined[105,106] entity, papillary clear cell RCC, can occur either sporadically or be associated with end-stage renal disease. The typical features are that of a low-grade clear cell tumor with focal or extensive papillary growth pattern. Unlike classic clear cell or papillary RCC, this tumor type is strongly positive for CK7 but is negative for AMACR.

Another tumor type with clear and eosinophilic cells forming papillae is Xp11.2 translocation carcinoma. This tumor is typically negative or focally positive for CK and epithelial membrane antigen. Definitive diagnosis can only be made by positive immunostain for TFE3.

Occasionally, an otherwise typical papillary RCC can be focally or predominately composed of cells with clear or foamy cytoplasm. Helpful morphologic features include the presence of foamy macrophages within the fibrovascular cores and areas of classic papillary RCC. Strong, diffuse, positive staining for AE1/AE3 keratins and AMACR is helpful to confirm the diagnosis.

Some invasive urothelial carcinomas can have clear cell changes as well. Usually, other cytomorphologic features and the tumor location will be sufficient for a definitive diagnosis. For difficult cases, the application of an immunostain with a panel of markers may be necessary for a definitive diagnosis. Urothelial carcinoma will be strongly positive for AE1/AE3 keratins, high–molecular-weight CKs, p63, E-cadherin, and CK7 but negative for renal cell markers, such as RCC marker, PAX2, and PAX8.

Tumor With Oncocytic or Granular Cells

Renal neoplasms with granular or eosinophilic cells encompass a variety of neoplasms, including oncocytoma, eosinophilic variant of chromophobe RCC, clear cell RCC with granular cells, papillary RCC type 2, myoid rich/epithelioid angiomyolipoma, and collecting duct carcinoma.

The most frequent differential diagnostic problem is between clear cell RCC with granular cells and oncocytoma/chromophobe RCC. Markers that are often positive for oncocytoma/chromophobe RCC are kidney-specific cadherin, CD117, and CK7, whereas CD10, RCC marker, and carbonic anhydrase IX are positive for clear cell RCC.

Recent studies suggest there might be different expression of S100A1 and CD82 between chromophobe RCC and oncocytoma, which may facilitate their differential diagnosis. However, these findings need verification. Diffuse, strong CK7 expression favors chromophobe RCC, whereas oncocytoma is either negative or focally positive. So far, no markers can reliably distinguish between oncocytoma and chromophobe RCC, particularly the eosinophilic variant.

The papillary RCC type 2 is characterized by papillary tumor with prominent eosinophilic cytoplasm, nuclear stratification, and prominent nucleoli. The immunohistochemical profile of these tumors are quite variable, but most are positive for CK7 and AMACR.

The tumor cells in myoid rich or epithelioid angiomyolipoma often have abundant eosinophilic cytoplasm, which may resemble high-grade RCC. Desmin and HMB-45 are indispensable for confirmation of the diagnosis.

Collecting duct carcinoma may have prominent, eosinophilic cytoplasm, but these tumors are of high grade,

Table 2. Immunoprofiles of "Small Round Cell Tumor" of the Kidney										
	CK	LCA	S100	WT1	Vim	Des	CD99	CD56	Chro	Synp
Nephroblastoma (Wilms tumor)	+	−	−	+	+	+	−	+	−	−
Ewing sarcoma/PNET	Variable	−	−	−	+	−	+	−	−	−
Synovial sarcoma, poorly differentiated	Variable	−	Usually −	−	+	−	+	+	−	−
Lymphoma	−	+	−	−	+	−	−	−	−	−
Small cell carcinoma	+	−	−	−	−	−	−	+	Variable	Variable
Metanephric tumor	+	−	−	+	+	−	−	−	−	−
Congenital mesoblastic nephroma, cellular	−	−	−	−	+	Variable	−	−	−	−
Rhabdoid tumor	Variable	−	−	−	+	−	−	−	−	−
Clear cell sarcoma	−	−	−	−	+	−	−	−	−	−

Abbreviations: Chro, chromogranin; CK, cytokeratin; Des, desmin; LCA, leukocyte common antigen; PNET, peripheral nerve sheath tumor; Synp, synaptophysin.

with marked desmoplasia. They are often positive for high–molecular-weight CKs, p63, and CK7, but usually negative for RCC marker, AMACR, and kidney-specific cadherin.

Spindle Cell/Sarcomatoid Tumors

Low-grade spindle cells can be seen in mucinous tubular spindle cell carcinoma and occasionally clear cell carcinoma. Renal tumors with high-grade spindle cells (sarcomatoid) include all RCC types with sarcomatoid transformation, and primary or secondary sarcomas. Acknowledging that the best "marker" for a correct diagnosis is thorough sampling and careful search for an identifiable low-grade tumor of a specific histologic subtype, immunomarkers can only serve as a diagnostic adjuncts. Markers with relative tissue-specific values, such as RCC marker, PAX2 and PAX8, may be used for confirmation of renal origin.

Tumors With Small Cells

Renal tumors composed of small cells are rare, high-grade malignant tumors and may include Wilms tumor, Ewing sarcoma/primitive neuroectodermal tumor, small cell carcinoma, monophasic synovial sarcoma, and lymphoma. The immunoprofile for these tumors is similar to that of tumors from nonrenal locations (Table 2).

Tumor With Papillary or Tubulopapillary Growth Pattern

The main tumor of this group is papillary RCC, but many other renal tumor types can have papillary growth patterns as well, such as clear cell papillary RCC, Xp11.2 translocation carcinoma, metanephric adenoma, collecting duct carcinoma, mucinous tubular and spindle cell carcinoma, and chromophobe RCC.

The differential immunoprofiles of these entities are listed in Table 1. α-Methylacyl coenzyme A racemase is often strongly positive for papillary RCC and mucinous tubular and spindle cell carcinoma, whereas clear cell papillary RCC is often negative for AMACR, but strongly positive for CK7. Xp11.2 translocation carcinoma occurs often in children and young adults, and the tumor is typically negative or focally positive for CK but is uniformly positive for TFE3. Metanephric carcinoma is positive for CD57 and WT1. Pseudopapillary clear cell RCC is usually negative for AMACR. Collecting duct carcinoma is rare and often a diagnosis of distinction. Some authors suggest p63 and high–molecular-weight CK might be helpful. Interestingly, MTSCC shares an immunoprofile similar to that of papillary RCC, but the papillary configuration is often very focal and conspicuous.

DIAGNOSING METASTATIC RCC

In the context of diagnosing renal neoplasms, immunohistochemistry is, in our experience, most often used for metastatic RCC (Figure 8). In spite of the availability of several renal markers, the diagnosis of metastatic RCC is often not straightforward for the following reasons: (1) metastatic RCC may precede or follow the primary tumor after a long latent period[12,13]; (2) metastatic RCC may be less differentiated than, and thus appears morphologically different from, its primary tumor; (3) the metastasis may not conform to the known morphologic spectrum of primary RCC; (4) metastatic lesions may develop in patients with a history of both RCC and another primary tumor,[14] and thus, a new tumor in them may represent a new primary tumor, metastatic RCC, or metastasis of the other tumor; (5) although several markers have been described for RCC, many of them are also noted in other types of neoplasm; and (6) within the metastatic context, FNA often results in limited tissue being available.

Among markers for RCC, focus has been directed to the primary tumors, resulting in a lack of information on metastatic lesions. Major studies comparing markers in metastatic and primary RCCs are summarized in Table 3. The tumor type–specific profiles for primary RCCs are largely retained in their metastases, but significant attenuation of both staining frequency and extent may supervene.[17,107] PAX2 seems to be the most useful marker for metastatic RCC, with a frequency and extent of staining similar to those for the primary tumors, that is, up to 74% of cases, including metastatic collecting duct RCC, and often in most of tumor cells, even in the scanty FNA material (Figures 8, C, F, and I).[107] Consecutive sections show that PAX2 and PAX8 have very similar staining for both primary and metastatic RCCs, which suggests only one should be used and adding the other may provide little additional diagnostic yield.[21] The RCC marker displays significantly less-staining frequency and extent for metastatic RCC, compared with the primary tumor.[17] Ozcan et al[107] noted that 28% of metastatic RCCs were detected by PAX2 but not by the RCC marker. Parvalbumin and kidney-specific cadherin detect few

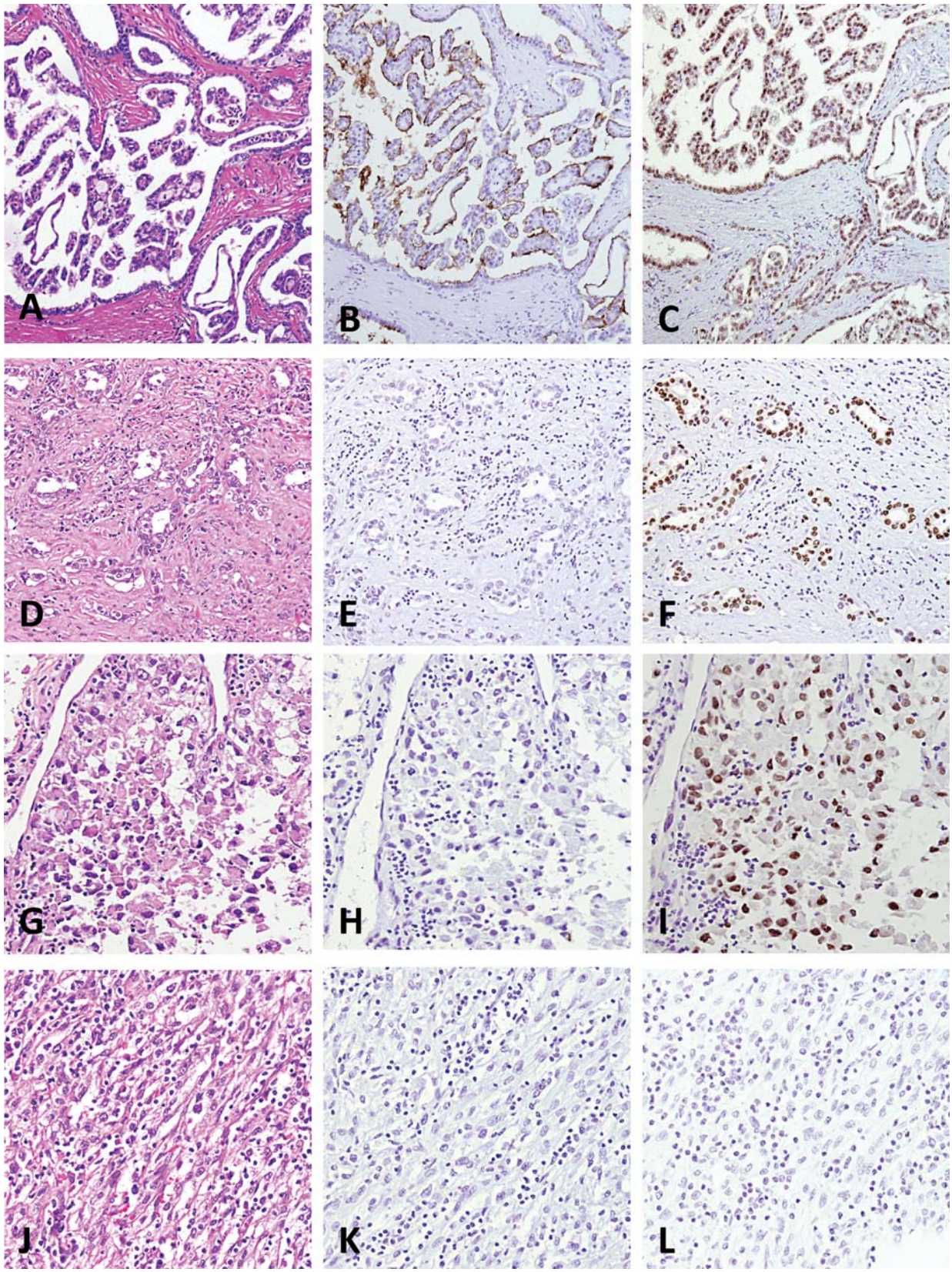

Figure 8. *Metastatic renal cell carcinoma (RCC): A through C, Nodal metastatic papillary RCC—Positive for the RCC marker and PAX2. D through F, Liver metastasis of collecting duct RCC—Negative for the RCC marker and positive for PAX2. G through I, RCC with rhabdoid features metastatic to lung—Negative for the RCC marker and positive for PAX2. J through L, Sarcomatoid RCC metastatic to bone—Negative for the RCC marker and negative for PAX2 (original magnifications ×100 [A through C] and ×200 [D through L]).*

Table 3. Comparison of Metastatic and Primary Renal Cell Carcinomas (RCC)

		Metastasis		Primary	
Source, y	Stain	Positive Cases, %	Staining Extent	Positive Cases, %	Staining Extent
Zhai et al,[57] 2010; Ozcan et al,[107] 2010	PAX2	74	61% of tumor cells (mean)	85	50% of tumor cells (mean)
McGregor et al,[17] 2001; Ozcan et al,[56] 2009	RCC marker	35–46	46% of tumor cells (mean) >50% of tumor cells stained in 17% of cases	85	>50% of tumor cells stained in 72% of cases
Ozcan et al,[107] 2010	Kidney-specific cadherin	2[a]	Rare cells	34[b]	>50% of tumor cells stained in 64% of cases.
Ozcan et al,[21] in press; Tong et al,[59] 2009;	PAX8	Similar to PAX2	Similar to PAX2	Similar to PAX2	Similar to PAX2
Simsir et al,[15] 2005	CD10	100[c]	>50% tumor cells stained in 86% of cases	86	>50% of tumor cells stained in 73% of cases
Martignoni et al,[16] 2001	Parvalbumin	10[d]	Most cells	27[e]	60%–100% of tumor cells
Lin et al,[20] 2004	AMACR	82[f]	>50% of tumor cells stained in 60% of cases	70%	Diffuse staining in most cases
Tretiakova et al,[50] 2004	AMACR	100[g]	Most cells	35%[h]	>90% of cells

Abbreviation: AMACR, α-methylacyl-coenzyme A racemase.

[a] These were metastatic clear cell RCCs; metastatic chromophobe RCC was not present.
[b] Most of these cases are chromophobe RCC.
[c] Only clear cell RCCs were included.
[d] Of 10 metastatic RCCs, 1 was positive (10%), and it was a metastatic chromophobe RCC.
[e] Most positive cases were chromophobe RCC.
[f] Of 28 metastatic RCCs, 23 were positive (82%), and all 28 cases (100%) were clear cell RCCs.
[g] Of 6 cases, all 6 (100%) were papillary metastatic RCC.
[h] There were 35 primary papillary RCCs included, and all of them (100%) were positive.

metastatic RCCs,[16,107] reflecting that these 2 markers are rather specific for chromophobe RCC, and that type of RCC rarely metastasizes, for example, only 18 of 910 metastatic RCCs (2.0%) reported by Hoffmann et al.[108] CD10 helps detect most metastatic RCCs, but only clear cell RCC was included in many studies.[15,18,19] α-Methylacyl coenzyme A racemase was detected[20] in 23 of 28 metastatic RCCs (82%), but all 28 cases were clear cell types. In addition, AMACR was reported[50] in 6 of 6 metastatic papillary RCCs (100%) and 35 of 35 primary papillary RCCs (100%). A few metastatic sarcomatoid RCCs on record were negative for all tested markers,[21,50] thus a marker for metastatic sarcomatoid RCC remains elusive.

As shown above, each RCC marker is also expressed variably by nonrenal tumors, albeit in different percentages. These observations may be irrelevant in diagnosing primary renal neoplasms, but they do matter in metastatic RCC, that is, these markers may be sensitive, but not specific, for metastatic RCC. For example, CD10 detects 100% metastatic clear cell RCC but is also noted in a large variety of primary or metastatic carcinomas,[15,18,19,22,33,64] and in 54% of malignant mesothelioma.[19] α-Methylacyl coenzyme A racemase is expressed in almost all metastatic papillary or clear cell RCCs but is also expressed by many carcinomas; PAX8 detects most metastatic RCCs, but is also seen in most Müllerian tumors.[21]

The available data suggest the panel for evaluating potential metastatic RCC should include PAX2 or PAX8 and the RCC marker or CD10, supplemented by other markers dictated by the affected organ and/or the type of nonrenal tumors that may coexist.

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