PAX-2 in the Diagnosis of Primary Renal Tumors

Immunohistochemical Comparison With Renal Cell Carcinoma Marker Antigen and Kidney-Specific Cadherin

Ayhan Ozcan, MD,[1,3,4] Jim Zhai, MD,[1,3,5] Candice Hamilton,[1] Steven S. Shen, MD, PhD,[1,3,5] Jae Y. Ro, MD, PhD,[1,3,5] Bhuvaneswari Krishnan, MD,[2] and Luan D. Truong, MD[1,2,3,5]

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Abstract

The diagnosis of renal cell carcinoma (RCC) remains problematic, especially in the context of metastasis or small needle biopsy specimens. The renal cell carcinoma marker (RCCM) and kidney-specific cadherin (KSC) are considered specific markers for RCC but are expressed preferentially in specific subtypes of RCC of lower grades. This study was aimed at evaluating the usefulness of PAX-2 in the diagnosis of renal tumors and comparing it with that of RCCM and KSC. Immunostaining for PAX-2, RCCM, and KSC was performed on consecutive tissue sections of 130 renal tumors.

PAX-2 was successfully detected in routine tissue specimens. Although PAX-2 seems to be more sensitive than RCCM and KSC, there is significant staining overlap in relation to histologic subtypes, justifying the use of all 3 markers, which helps detect the vast majority of renal neoplasms. PAX-2 seems to have a significant role in renal neogenesis and may represent a novel therapeutic target.

Renal cell carcinoma (RCC) is the most common malignancy among primary renal tumors. The classification of RCC is well established, enabling accurate diagnosis and distinction among different subtypes by routine histologic studies in most cases. However, overlapping morphologic features can create diagnostic problems, including differentiation among chromophobe RCC, oncocytoma, and the granular variant of clear cell RCC and among poorly differentiated clear cell RCC, collecting duct RCC, and high-grade transitional cell carcinoma. This problem is magnified in the context of small biopsy specimens and metastatic disease.

Immunomarkers for the diagnosis of RCC are limited. Several of these markers, such as cytokeratin subtypes, CD10, VHL protein, epithelial membrane antigen, paralbumin, carbonic anhydrase, vinculin, CD24, and hypoxia-induced growth factors, are present not only in RCCs in low frequencies but also in several other tumor types and, thus, are of limited specificity and sensitivity.[1-6] Other markers, including the renal cell carcinoma marker antigen (RCCM) and kidney-specific cadherin (KSC), are more "kidney-specific" and have helped improve diagnostic accuracy.[7-10] However, these markers represent terminally differentiated molecules, ie, RCCM is a component of the brush border of normal proximal tubular cells, whereas KSC is found in the basolateral infolding membrane of normal distal tubular and collecting duct cells. Thus, as expected, they are most often expressed by well-differentiated renal neoplasms, which are usually accurately diagnosed by routine histologic studies alone. They are, however, usually negative in poorly differentiated tumors or tumors differentiating along an unrelated tubular cell line such as collecting duct carcinoma and, thus, are not significantly helpful when immunomarkers are most needed.

Differentiation of embryonic tissue into mature organs is directed by orderly expression of molecules under the control of *organ-specific* transcription factors, which cease to express when differentiation is completed and, thus, are not present in normal mature tissue. Because neoplastic transformation often recapitulates organogenesis in reverse, tumors may express these organ-specific transcription factors, which can serve as sensitive and specific diagnostic markers. Such is the case for colonic carcinoma (CDX-2), Wilms tumor (WT-1), and lung tumor (thyroid transcription factor-1). Because these transcription factors are nuclear protein, as opposed to the cytoplasmic nature of other more traditional immunomarkers, they add an additional morphologic advantage to tumor immunodiagnosis.

Several transcription factors are expressed during nephrogenesis, the best studied of which is probably PAX-2.[11-28] PAX-2 is a member of the paired box family of transcription factors, which is required for development and proliferation of renal tubules from blastema. During this process, PAX-2 is expressed along with mesenchyme-to-epithelium transition but disappears at the onset of terminal differentiation. PAX-2 expression by renal tumors has been described in only a few reports. In the present study, we wanted to comprehensively evaluate PAX-2 expression in renal tumors and compare its expression with RCCM and KSC expression to gain insight into the diagnostic usefulness and the biologic implications of this transcription factor in renal neogenesis.

Materials and Methods

This retrospective study included 130 renal tumors (75 clear cell RCCs, 23 papillary RCCs, 12 chromophobe RCCs, 7 sarcomatoid RCCs, 5 collecting duct RCCs, and 8 oncocytomas). All original slides from each case were reviewed by 3 of us (A.O., S.S.S., and L.D.T.), and the diagnoses were confirmed or revised for each tumor according to the 2004 World Health Organization classification of renal cell neoplasms. A background of clear cell RCC was noted in each of the 7 sarcomatoid RCCs. Of 23 papillary RCCs, 19 were of type 1 and 4 were type 2. Nonneoplastic "normal" kidney tissue was also studied in many of the cases.

Representative and consecutive sections from each tumor were submitted to immunostaining for PAX-2, RCCM, and KSC. Tissue sections were subjected to deparaffinization, hydration, and endogenous peroxidase blocking. Antigen retrieval was done in a similar manner for each of the 3 target antigens: Tissue sections were subjected to DAKO Target Retrieval Solution, pH 6 (DAKO, Carpinteria, CA) in a pressure cooker set at 95°C for 22 minutes followed by gradual cooling for 20 minutes. The tissue sections were incubated for 30 minutes at room temperature with the RCCM antibody (dilution 1:10; Vector Laboratories, Burlingame, CA), a monoclonal antibody against KSC (dilution 1:75; Invitrogen, Carlsbad, CA), or an anti–PAX-2 polyclonal antibody (dilution 1:75; Invitrogen). Detection of the staining reaction was achieved by an enzyme-conjugated polymer complex adapted for automatic stainers from DAKO (EnVision Systems; Dakoautostainer Universal Staining System) and from Ventana (Ventana UltraView; Ventana Benchmark XT; Ventana Medical Systems, Tucson, AZ). Built-in positive control samples included the nonneoplastic kidney tissue adjacent to the tumors. Tumor or nontumor stromal cells were used as negative internal control samples.

For each case, the staining intensity (0, no stain; 1+, weak; 2+, moderate; and 3+, strong) and the estimated percentage of stained tumor cells for each of the 3 markers were independently evaluated by 3 of us (A.O., S.S.S., and L.D.T.). The staining pattern (nuclear, cytoplasmic, or membranous) was also noted. PAX-2, RCCM, and KSC expression in tumors was correlated with low (Fuhrman grades 1 and 2) vs high (Fuhrman grades 3 and 4) nuclear grade. This statistical analysis was limited to the clear cell RCCs and the clear cell component of the sarcomatoid RCCs because there were only a few RCCs of other histologic types. The differences between groups were tested for significance by using the χ^2 test with a P value of less than .05 as the cutoff point.

Results

PAX-2

PAX-2 was successfully detected against a background of appropriate positive and negative controls. The staining was predominantly nuclear, but weak cytoplasmic staining was also noted focally.

In normal kidney, PAX-2 nuclear staining was seen in rare cross-sections of distal convoluted tubules, thick Henle loops, and collecting duct. Weak focal cytoplasmic staining was detected in proximal tubular cells. Parietal epithelial cells showed diffuse nuclear staining **Image 1A**. Lymphoid cells, normally present in kidney in small numbers, showed focal nuclear staining. Other cell types were negative.

PAX-2 nuclear staining was detected in 111 (85.4%) of 130 renal tumors, with an equally high frequency in *most tumor types* (clear cell, papillary, chromophobe, and collecting duct RCCs and oncocytomas) but was negative in the sarcomatoid component of all sarcomatoid RCCs **Table 1**. Staining was noted in 5% to 100% of tumor cells (with a mean of about 51%) and the intensity score was 1+, 2+, and 3+ in 16, 47, and 67 cases, respectively. Although homogeneous and diffuse staining was seen in all collecting duct RCCs and oncocytomas, a heterogeneous pattern characterized by more staining in both intensity and extent at the tumor periphery was noted for other tumor types. Cytoplasmic staining was also focally

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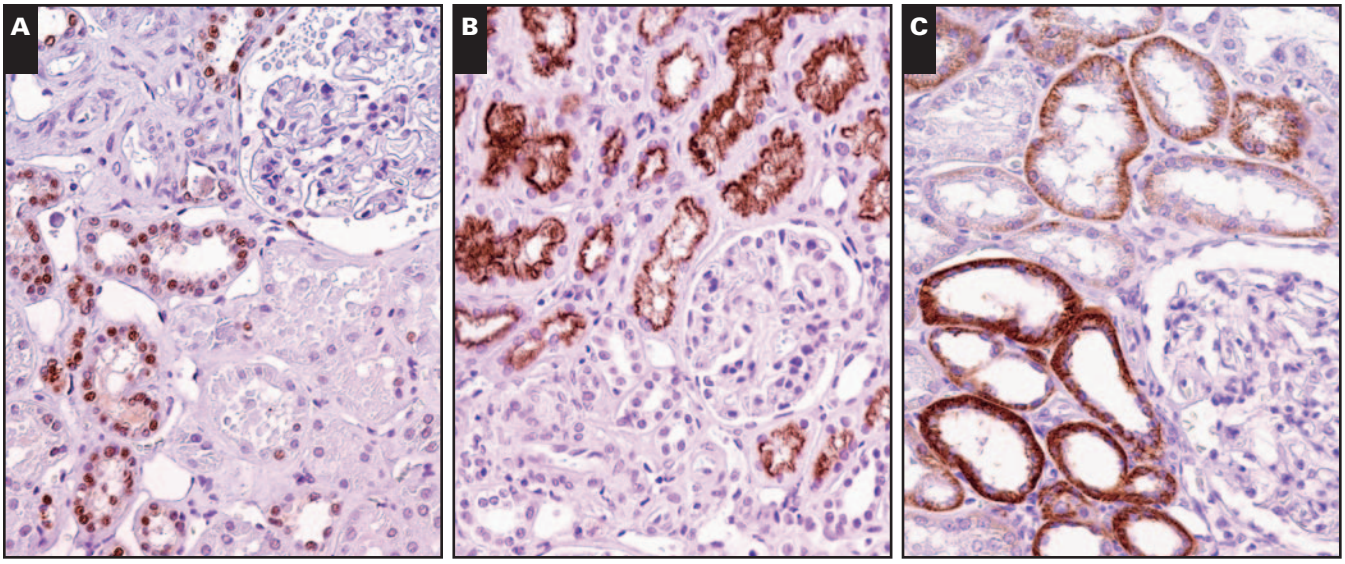

Image 1 The expression of PAX-2 (**A**), renal cell carcinoma marker antigen (**B**), and kidney-specific cadherin (**C**) in nonneoplastic kidney adjacent to tumor (**A**-**C**, ×200).

noted in some of these tumors but was always weak and, in most cases, was associated with nuclear staining.

Among the clear cell RCCs, staining was strong in areas of low nuclear grade **Image 2A** but negative or weak at areas of high nuclear grade of the same tumor **Image 2B**. Although 92% of pure clear cell RCCs (69/75) were positive, the clear cell component of the sarcomatoid RCCs was positive in only 1 (14%) of 7 cases **Image 2C**. Staining was demonstrated in all 8 cystic clear cell RCCs **Image 2D**. Nuclear (and also weak cytoplasmic) staining was seen in both cases of clear cell RCC, granular variant, in which granular cells constituted the bulk of the tumors **Image 2E**. Of 12 chromophobe RCCs, PAX-2 nuclear staining was noted in 10 (10%-100% of tumor cells; intensity scores 1+-3+) **Image 3A**. Of 19 type 1 papillary RCCs, 18 (95%) were positive, and the staining was more pronounced in areas of low nuclear grade **Image 3B**. Among the 4 type 2 papillary RCCs, 2 were negative, whereas the other 2 were weakly positive (about 25% and 10% of tumor cells stained, and intensity scores were 1+ and 3+, respectively). In the remaining 2 tumors, although there was no nuclear staining, cytoplasmic staining was noted in both. All 5 collecting duct RCCs demonstrated strong nuclear staining with weak focal cytoplasmic staining **Image 3C**. Neither nuclear nor cytoplasmic staining was seen in the sarcomatoid component of the 7 sarcomatoid RCCs. Nuclear staining was demonstrated in 7 (88%) of 8 oncocytomas, with focal cytoplasmic staining also **Image 3D**.

Renal Cell Carcinoma Marker

In normal kidney, RCCM was limited to the apical cell membrane of the proximal tubular cells, which probably represented the brush border of these cells **Image 1B**.

Table 1
PAX-2, RCCM, and KSC Expression by Renal Tumors*

	PAX-2	RCCM	KSC
Clear cell (n = 75)	69 (92)	63 (84)	16 (21)
Papillary (n = 23)	20 (87)	20 (87)	1 (4)
Chromophobe (n = 12)	10 (83)	2 (17)	7 (58)
Sarcomatoid (n = 7)†	0 (0)	0 (0)	0 (0)
Collecting duct (n = 5)	5 (100)	0 (0)	0 (0)
Oncocytoma (n = 8)	7 (88)	0 (0)	3 (38)
Total (N = 130)	111 (85.4)	85 (65.4)	27 (20.8)

KSC, kidney-specific cadherin; RCCM, renal cell carcinoma marker antigen.
* Data are given as number (percentage).
† Each of these cases was associated with a clear cell component, and the staining was evaluated for the sarcomatoid component.

RCCM expression was seen in 84% of clear cell RCCs (63/75), 87% of papillary RCCs (20/23), and 17% of chromophobe RCCs (2/12) but not in any collecting duct RCCs, sarcomatoid component of sarcomatoid RCCs, or oncocytomas (Table 1). Staining was noted in a few to all tumor cells with staining of more than 50% of tumor cells in 67% of cases. Both cell membrane and cytoplasmic staining was noted, but there was no nuclear staining. Similar to PAX-2, the staining was more pronounced in low-grade areas **Image 2F** and **Image 2G**. Among the 7 sarcomatoid RCCs, the sarcomatoid component was always negative, but the clear cell component was positive in 4 cases (57%) **Image 2H**. Among the clear cell RCCs, staining was noted in 2 (25%) of 8 tumors of the cystic variant and in 2 (100%) of 2 tumors of the granular variant **Image 2I** and **Image 2J**. Most chromophobe RCCs were negative **Image 3E**, aside from 2 cases that showed a focal weak staining pattern. The staining pattern was similar

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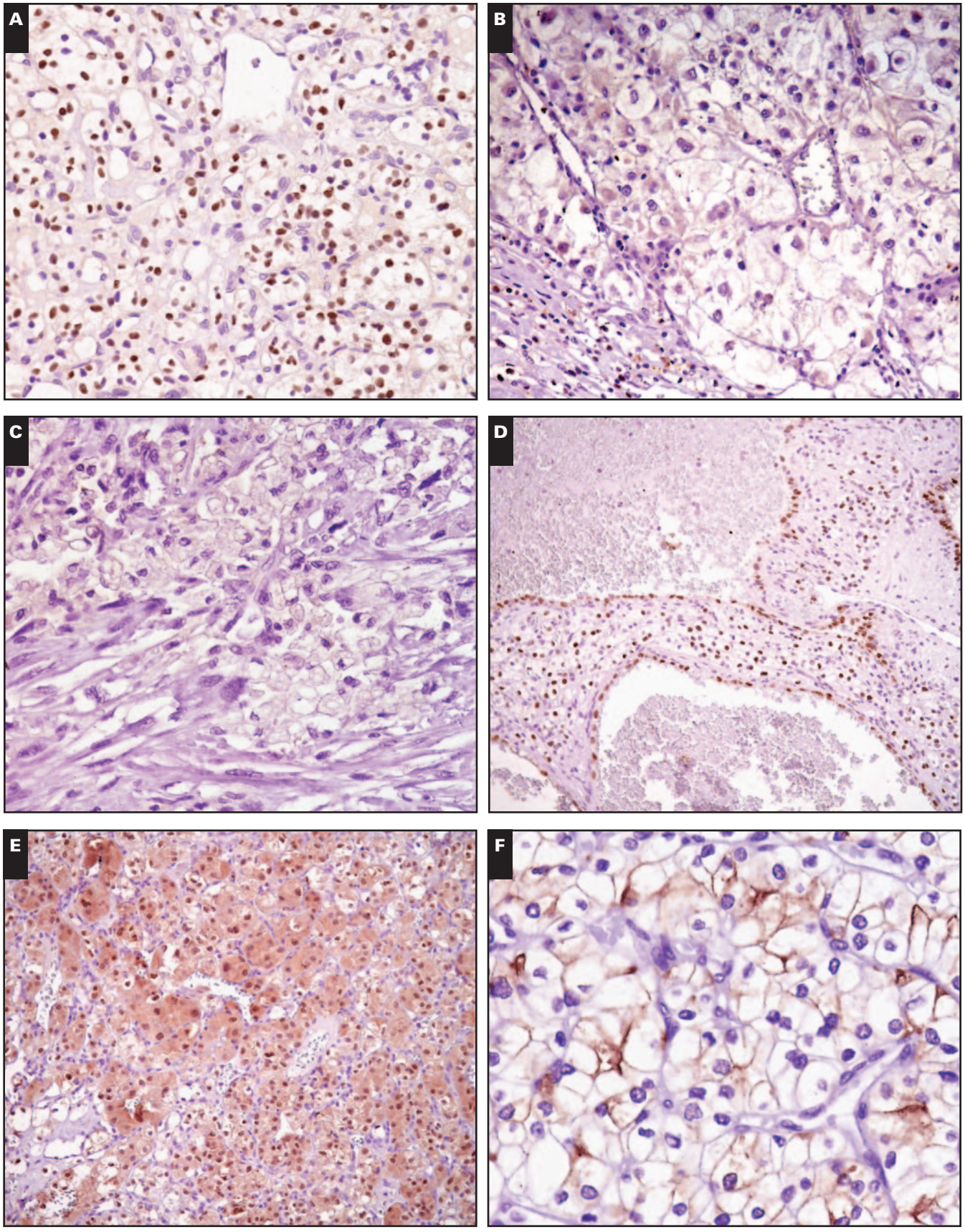

Image 2 The expression of PAX-2 (**A**-**E**), renal cell carcinoma marker antigen (**F**-**J**), and kidney-specific cadherin (**K**-**O**) in low-grade clear cell renal cell carcinoma (RCC) (**A**, **F**, and **K**), high-grade clear cell RCC (**B**, **G**, and **L**), clear cell RCC with a

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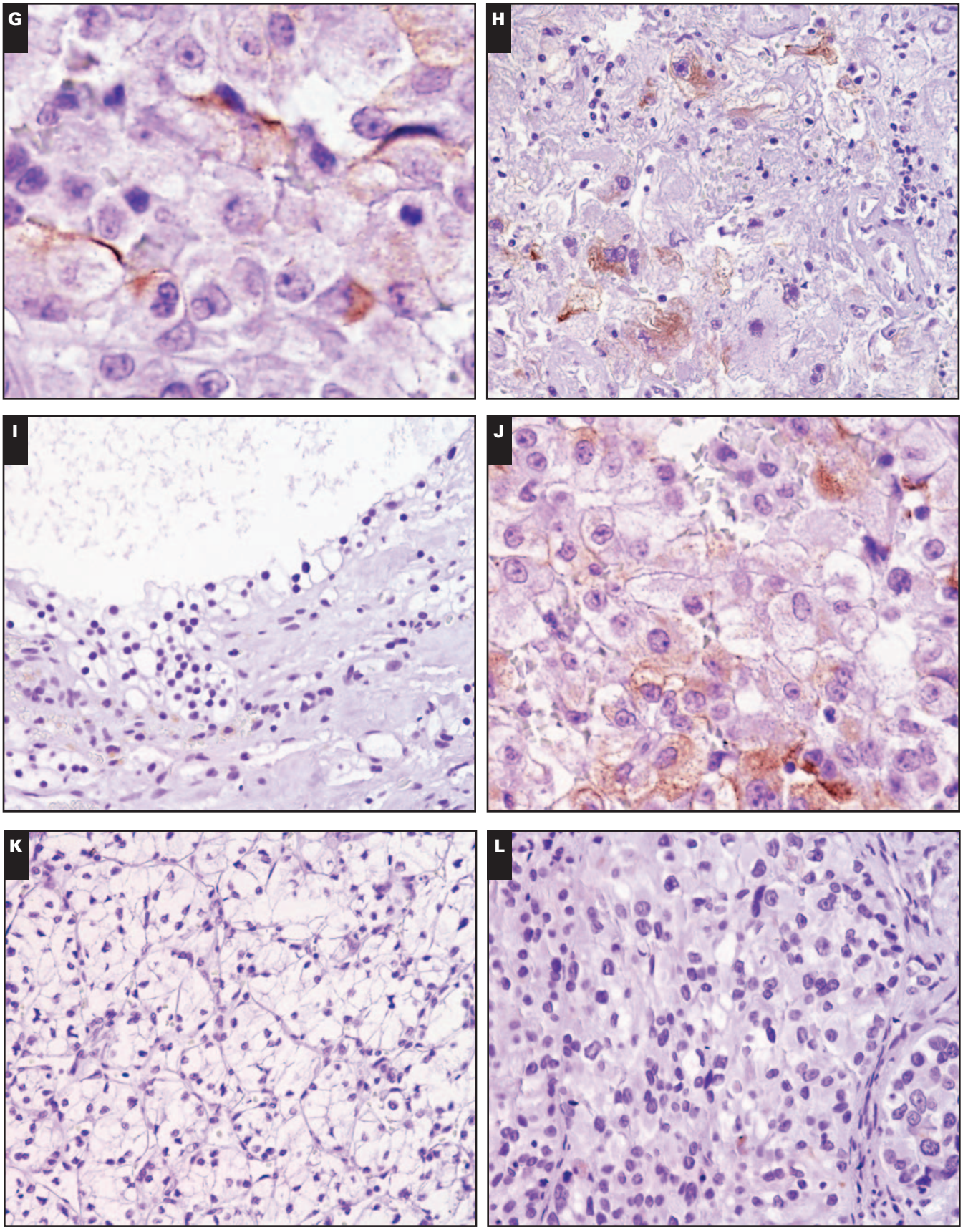

sarcomatoid appearance (**C**, **H**, and **M**), cystic variant clear cell RCC (**D**, **I**, and **N**) and granular variant clear cell RCC (**E**, **J**, and **O**) (×100 for the images of lower magnification; ×400 for the images of higher magnification).

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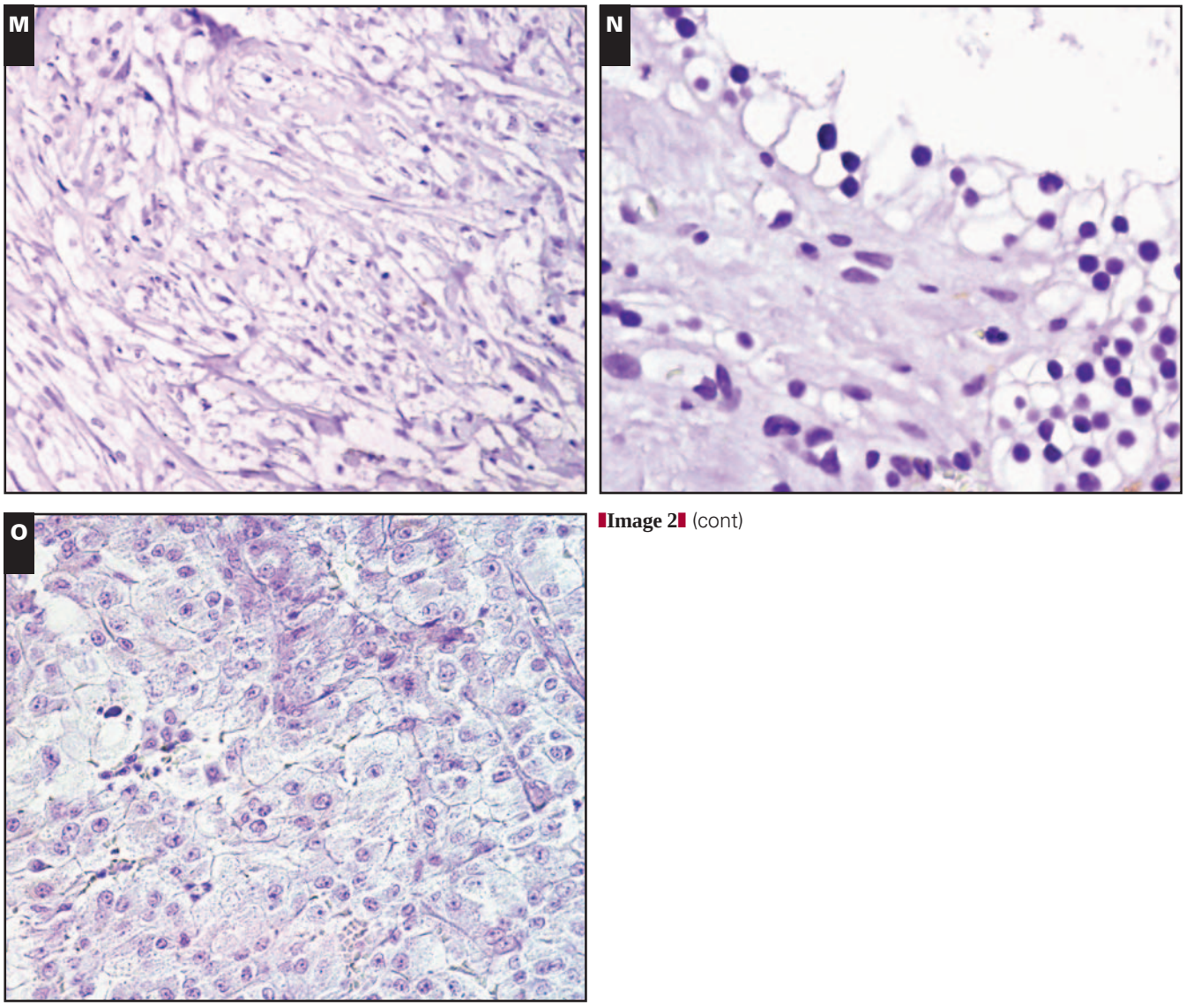

Image 2 (cont)

for type 1 and type 2 papillary RCCs **Image 3F**. There was no staining in any collecting RCCs **Image 3G** and oncocytoma **Image 3H**.

Kidney-Specific Cadherin

In normal kidney, staining was limited to tubular cells of the thick portion of the Henle loops and distal convoluted tubules in a basolateral membranous and cytoplasmic pattern **Image 1C**.

KSC expression was detected in 21% of clear cell RCCs (16/75), 4% of papillary RCCs (1/23), 58% of chromophobe RCCs (7/12), and 38% of oncocytomas (3/8) but not in collecting duct RCCs or sarcomatoid RCCs (Table 1). Staining was noted in about 20% to 70% of tumor cells with a mean of about 30% of cases. The staining was membranous and cytoplasmic, without nuclear staining. The staining was most frequent in chromophobe RCC (diffuse, strong, and pronounced membranous staining) **Image 3I** and oncocytoma (focal, weak, and less membranous staining) **Image 3L** but was not correlated with nuclear grade, regardless of histologic type. The staining among the clear cell RCCs was weak and focal and among low- and high-grade clear cell RCCs was usually negative **Image 2K** and **Image 2L**. Among the sarcomatoid RCCs, the sarcomatoid and clear cell components were negative in each case **Image 2M**. Among the clear cell RCCs, there was no staining in the cystic or granular cell variants **Image 2N** and **Image 2O**. Most papillary RCCs were negative **Image 3J**, excluding 1 case that had a focal weak staining pattern. All collecting duct RCCs were negative **Image 3K**.

Comparison of PAX-2, RCCM, and KSC Staining

The frequencies of tumor types stratified against various combined staining patterns are summarized in **Table 2**. The following patterns were observed in the 130 specimens: all 3 markers positive, 12 (9.2%); all 3 markers negative, 12

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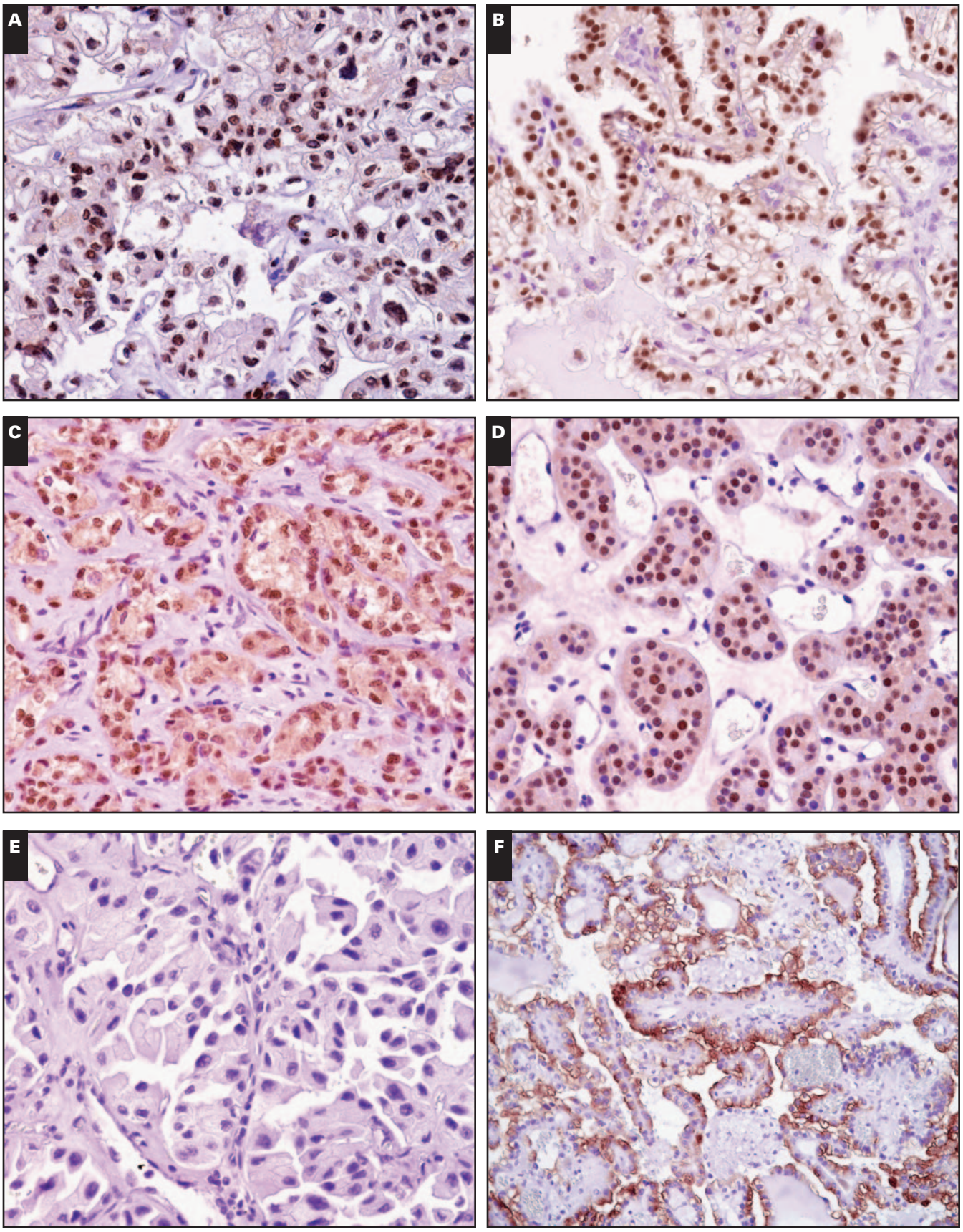

Image 3 The expression of PAX-2 (**A**-**D**), renal cell carcinoma marker antigen (**E**-**H**), and kidney-specific cadherin (**I**-**L**) in chromophobe renal cell carcinoma (RCC) (**A**, **E**, and **I**), papillary RCC (**B**, **F**, and **J**), collecting duct RCC (**C**, **G**, and **K**), and oncocytoma (**D**, **H**, and **L**) (×100 for the images of lower magnification; ×400 for the images of higher magnification).

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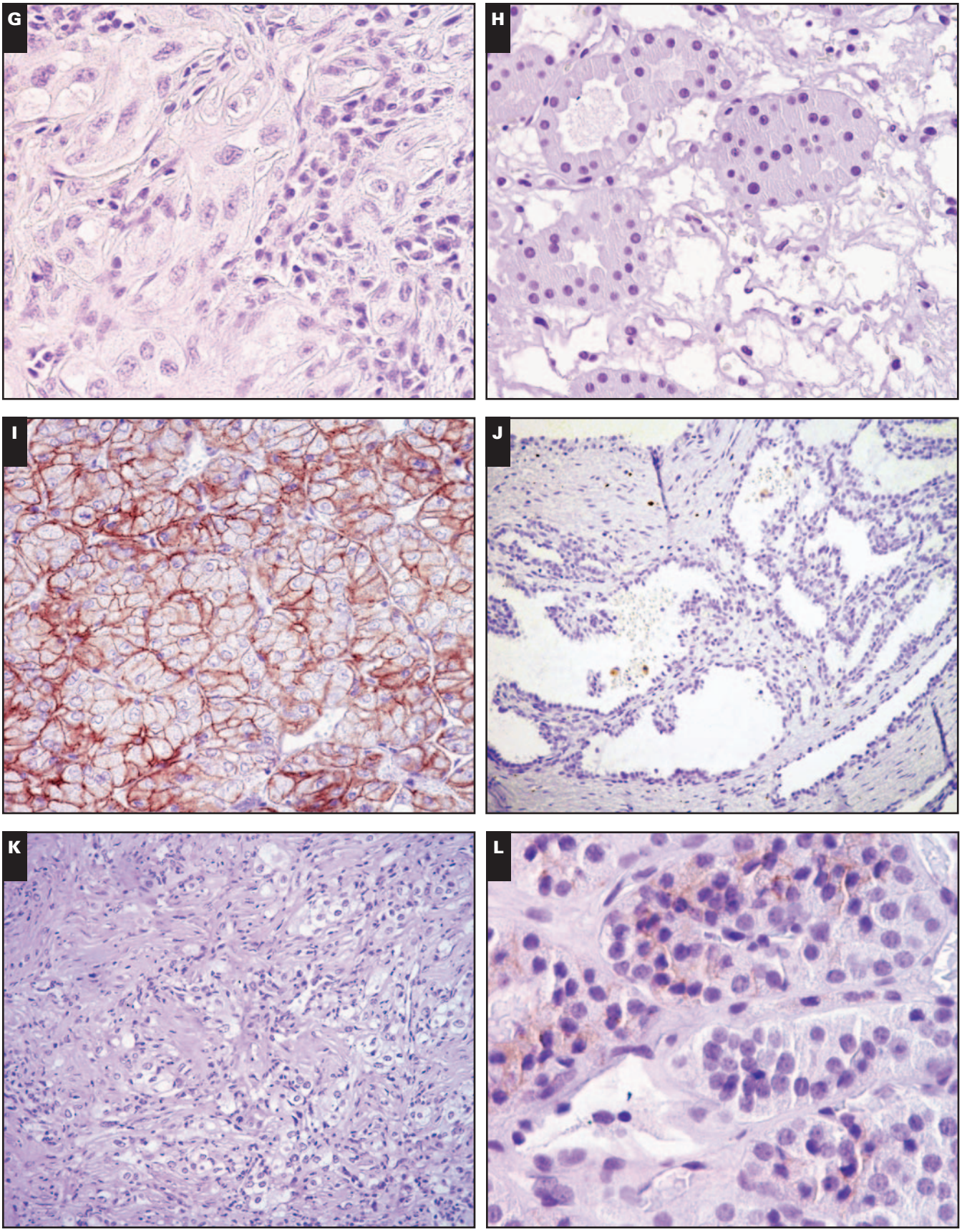

Image 3 (cont)

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Table 2
PAX-2, RCCM, and KSC Expression Among the Histologic Subtypes of Renal Tumors

	PAX-2/RCCM/KSC Expression							
	+/+/+	–/–/–	+/–/–	+/+/–	+/–/+	–/+/+	–/–/+	–/+/–
Clear cell (n = 75)	10	2	7	49	3	2	1	2
Papillary (n = 23)	1	1	2	17	0	0	0	2
Chromophobe (n = 12)	1	1	3	1	5	0	1	0
Sarcomatoid (n = 7)*	0	7	0	0	0	0	0	0
Collecting duct (n = 5)	0	0	4	0	1	0	0	0
Oncocytoma (n = 8)	0	1	4	0	3	0	0	0

KSC, kidney-specific cadherin; RCCM, renal cell carcinoma marker antigen.
* Each of these cases was associated with a clear cell component, in which the clear cell component was positive for PAX-2 in 1 and RCCM in 4, but the sarcomatoid component was negative for all markers.

(9.2%); at least 1 marker positive, 118 (90.8%); only PAX-2 positive, 20 (15.4%); only RCCM positive, 4 (3.1%); and only KSC positive, 2 (1.5%). The tumors that were positive for PAX-2 only included 7 clear cell RCCs, 2 papillary RCCs, 3 chromophobe RCCs, 4 collecting duct RCCs, and 4 oncocytomas. The tumors that were negative for all 3 markers included 2 clear cell RCCs (both of high nuclear grade), 1 papillary RCC, 1 chromophobe RCC, 1 oncocytoma, and the sarcomatoid component of all 7 sarcomatoid RCCs.

All 5 collecting duct RCCs were positive for PAX-2, and 1 was also positive for KSC. The sarcomatoid components of all 7 sarcomatoid RCCs were "triple-negative." Almost all tumors with triple positivity were clear cell RCCs (10/12). Chromophobe RCC and oncocytoma displayed similar staining with a characteristic frequency profile (high PAX-2+, low RCCM+, and medium KSC+). Clear cell and papillary RCCs shared the same staining pattern (high PAX-2+, high RCCM+, and low KSC+). Although most clear cell RCCs were positive for RCCM, the rate of positivity was low (2/7) for the cystic variant; yet all 7 cystic clear cell RCCs were positive for PAX-2. Staining for RCCM and PAX-2 was more pronounced in areas of low-grade nuclei for papillary and clear cell RCC.

Correlation of Tumor Grades and Expression Profile

The number of cases adequate for statistic analysis was reached only for clear cell RCC. PAX-2 expression was significantly more frequent in low-grade than in high-grade tumors **Table 3**. A similar trend was noted for RCCM, but the difference did not reach statistic significance. In contrast, KSC expression was significantly less frequent in low-grade than in high-grade tumors.

Table 3
PAX-2, RCCM, and KSC Expression in Clear Cell Renal Cell Carcinomas According to Tumor Grade*

	Low-Grade (n = 45)	High-Grade (n = 37)	*P*
PAX-2	42 (93)	28 (76)	<.05
RCCM	38 (84)	28 (76)	>.05
KSC	3 (7)	14 (38)	<.01

KSC, kidney-specific cadherin; RCCM, renal cell carcinoma marker antigen.
* Low-grade tumors include Fuhrman nuclear grades 1 and 2, and high-grade tumors include Fuhrman nuclear grades 3 and 4. Data are given as number (percentage).

Discussion

The present study suggests that PAX-2 is a sensitive marker for renal tumors, and its expression may have a role in the development of these tumors. PAX-2 is a member of the pair box gene family, which consists of 9 members, each encoding a transcription factor, ie, PAX-1 through PAX-9. These transcription factors are expressed during fetal development and are implicated in proper organogenesis. PAX-2 is known to control the development of the central nervous system, the kidneys,[15,19,20,24] and the müllerian organs.[29-31] During nephrogenesis, PAX-2 appears very early in the renal blastema and promotes mesenchymal cell proliferation and apoptosis and mesenchymal-epithelial transformation, with formation of immature renal tubules and glomeruli. However, maturation of these renal tubules depends partly on the disappearance of PAX-2; thus, in normal adult kidney, PAX-2 is seen only focally in parietal epithelial cells and collecting ducts. In humans and experimental animals, the *PAX*-2 transgene is associated with glomerulosclerosis and renal cystic changes, whereas *PAX*-2 deletion induces renal tubular atrophy.[11-28]

Knowledge about PAX-2 expression by renal tumors is limited. In a study of 56 renal tumors in frozen tissue Daniel et al[22] noted PAX-2 expression in 93.3% of clear cell RCCs and 100% of papillary RCCs and weak staining in chromophobe RCCs and oncocytomas. Mazal et al[28] studied archival microarrays of 202 renal tumors and found PAX-2 expression in 88% of clear cell RCCs, 18% of papillary RCCs, 13% of chromophobe RCCs, and 14% of oncocytomas but not in collecting duct RCCs. In a tissue microarray

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of 91 renal neoplasms, Memeo et al[32] detected PAX-2 expression in 84% of clear cell RCCs, 85% of papillary RCCs, 9% of chromophobe RCCs, and 87% of oncocytomas.

Our study confirms and expands these observations. It demonstrates that PAX-2 can be successfully detected in routinely processed tissue and, thus, is diagnostically relevant. Being a transcription factor, PAX-2 is identified in nuclei. Although cytoplasmic staining is occasionally noted, it is focal and weak and does not interfere with the interpretation of nuclear staining. The significance of cytoplasmic PAX-2 is not clear. It is often seen in cells with abundant eosinophilic cytoplasm, including proximal tubular cells, without accompanying nuclear staining. The explanation for this focal weak cytoplasmic stain is not clear. Although it may represent tissue endogenous avidin binding activity, the use of the enzyme-conjugated polymer complex detection system *without* avidin or streptavidin throughout the present study tends to negate this possibility. It may be related to the nonspecific nature of the secondary antibodies, the polymer complex constructions, or other technical factors relevant to the autostainer systems. In this respect, it is noted that the cytoplasmic staining, albeit always weak, displayed noticeable differences between the 2 staining systems used in the present study, despite the use of the same primary antibody with the same dilution.

In normal adult kidney, PAX-2 is seen only focally in parietal epithelial cells and collecting ducts; however, it is strongly reexpressed during renal neogenesis and may serve as a very sensitive marker for most types of more frequently encountered renal neoplasms, with a detection rate of more than 80%, including oncocytoma (88%) and collecting duct RCC (100%). The latter observations are particularly significant because these 2 types of neoplasms are negative for or only rarely detectable by RCCM and KSC, the 2 most kidney-specific markers thus far. Our study documented more frequent PAX-2 expression by chromophobe RCC (10/12 tumors [83%]) than in the studies by Memeo et al[32] (1/11 tumors [9%]) and Mazal et al[28] (3/24 tumors [13%]). A similar observation was made for collecting duct RCC (all 5 tumors in our study and none of 3 tumors in the study by Mazal et al[28]). These discrepancies probably reflect the observations that our study used regular full-sized tissue sections and a sensitive enzyme-conjugated polymer detection system, whereas microarray tissue sections were used in other studies with a standard avidin-biotin peroxidase complex technique used in one of them. Parenthetically, we have studied PAX-2 expression of metastatic RCCs and confirmed the constant expression of PAX-2 in collecting duct RCC, even in the metastatic context.

Preliminary observations from our laboratory indicate that PAX-2 is not expressed by tumors that can be confused with collecting duct RCCs, such as poorly differentiated adenocarcinoma or high-grade transitional carcinoma, further highlighting its diagnostic usefulness. We found PAX-2 expression in 92% of clear cell RCCs, and the staining intensity and extent were inversely correlated with tumor grade. These findings confirm the observations of Mazal et al[28] and suggest that PAX-2 expression increases in parallel with better tumor differentiation. However, the clear cell component of sarcomatoid RCC was positive for PAX-2 in only 14% of cases. This discrepancy is, nevertheless, in keeping with the observed correlation between PAX-2 expression and tumor grade because the clear cell components of the sarcomatoid RCCs, as well as the few pure clear cell RCCs with negative PAX-2, in this study were all high nuclear grade. Sarcomatoid tumors often express the transcription factors specific for the tissue or organ from which they derive, but not other more differentiated markers. This is the case for lung-specific thyroid transcription factor-1 or thyroid-specific PAX-8.[33] This expectation, unfortunately, does not materialize for PAX-2, which was not seen in the sarcomatoid component of any sarcomatoid RCCs in this study.

Although PAX-2 seems to be a very sensitive marker for renal neoplasms, its diagnostic specificity for these neoplasms remains to be determined through a yet unavailable systematic study in which a large number of not only renal but also nonrenal tumors are evaluated.[11,14,20-24,28] Nevertheless, PAX-2 expression has been reported in a significant percentage of nephrogenic adenomas,[34] Wilms tumors,[11] and serous ovarian carcinomas.[31] Anecdotal experience suggests an even wider expression that may include regenerative bile duct, endometrioid carcinoma, and lung carcinoma.

The present study confirms the roles and the limitations of RCCM and KSC as renal neoplasm markers. These 2 molecules represent terminally differentiated nephron segment–specific antigens (RCCM for proximal tubule brush border and KSC for distal tubule and collecting duct basolateral infolding). They are, as expected, sensitive markers for tumors that are better differentiated along these specific tubular lineages (RCCM for proximal tubule–derived clear cell and papillary RCCs and KSC for collecting duct–derived chromophobe RCCs and oncocytomas), but they fail to detect less differentiated renal neoplasms such as sarcomatoid and collecting duct RCCs.

On the other hand, staining of PAX-2 in parallel with RCCM and KSC provides insight into the possible complementary diagnostic usefulness of these markers. Our study shows that among these markers, PAX-2 is the most sensitive (overall detection rates of 85.4%, 65.4%, and 20.8% for PAX-2, RCCM, and KSC, respectively) and helps detect a significant number of tumors in which the two other markers fail. Indeed, 15.3% of tumors in this series were detected *only* by PAX-2 (7 clear cell RCCs, 2 papillary RCCs, 3 chromophobe RCCs, 4 collecting duct RCCs, and 4 oncocytomas). These observations indicate that PAX-2 not only

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helps recognize additional cases of clear cell RCC, papillary RCC, and oncocytoma that elude their traditional markers but also, more important, detects all collecting duct RCCs, which are uniformly negative for both RCCM and KSC.

This study suggests that PAX-2 improves the diagnosis of renal tumors, regardless of histologic type. Thus, among the clear cell RCCs, although the positive rates for PAX-2 and RCCM were 92% and 84%, at least 1 marker was detected in 97% (73/75) of these tumors. Among the papillary RCCs, the corresponding percentages were 87% (20/23) for PAX-2, 87% (20/23) for RCCM, and at least 1 marker was detected in 96% (22/23) of these tumors. For chromophobe RCC and oncocytoma, only PAX-2 may be adequate because PAX-2 was positive in 83% and 88% of them, respectively, and, furthermore, all cases that were positive for KSC (58% and 38%, respectively) were also positive for PAX-2. In fact, more than 90% of the tumors included in this study were positive for at least 1 of these 3 markers. The immunodiagnosis of sarcomatoid RCC remains problematic because it consistently fails to express any of these markers. Despite this limitation, the available data suggest the inclusion of PAX-2, RCCM, and KSC as a panel in the diagnostic evaluation of renal neoplasms.

Aside from diagnostic significance, PAX-2 may harbor pathogenic and therapeutic implications for renal tumors. The birth of renal neoplasms remains enigmatic. This process may involve mutations of mature renal tubular cells, during which the oncogenesis recapitulates steps in normal nephrogenesis.[13,26,35,36] Alternatively, putative renal stem cells may undergo uncontrollable growth and subsequently differentiate into tumors of diverse histologic subtypes.[35,36]

PAX-2 seems to have a role in either pathway, as indicated by several observations. PAX-2, which has an essential role in nephrogenesis, is expressed by the majority of renal tumors regardless of histologic subtypes. Putative renal stem cells, with capacity to differentiate into nephronic components in vitro and in vivo, have been isolated from normal human kidney, and these cells express PAX-2.[37,38] PAX-2 promotes cell proliferation and inhibits apoptosis, providing an essential element for oncogenesis.[36] PAX-2 can bind the promoter domain of the *VHL* gene, linking it to the development of clear cell RCC.[27] The oncogenic role of PAX-2 is probably better elucidated along with the understanding of the downstream pathway of this transcription factor, including the repertoire of genes it controls, which is still in its infancy. This limitation withstanding, induction of cultured tumor cells with PAX-2–specific small interfering RNA inhibits growth,[36] thus introducing a novel approach to treat renal tumors.

PAX-2, a kidney-specific transcription factor, can be successfully detected in archival tissue by immunohistochemical techniques. It is expressed with high frequency in most renal tumors, except sarcomatoid RCC, and can serve as a sensitive diagnostic marker. A panel including PAX-2, RCCM, and KSC helps identify renal tumors in the vast majority of cases. PAX-2 seems to have a significant role in renal neogenesis and may represent a novel therapeutic target.

From the Departments of Pathology, [1]the Methodist Hospital and [2]Baylor College of Medicine; and [5]the Methodist Research Institute, Houston, TX; [3]Weill Medical College of Cornell University, New York, NY; and [4]Gulhane Military Medical Academy and School of Medicine, Ankara, Turkey.

Address reprint requests to Dr Ozcan: Dept of Pathology, Gulhane Military Medical Academy, Etlik, Ankara, Turkey, 06018.

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