PAX2 and PAX8 Expression in Primary and Metastatic Renal Tumors

A Comprehensive Comparison

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Context.—The diagnosis of renal cell carcinoma (RCC) remains problematic, especially in the context of metastasis or small-needle biopsies. PAX2 and PAX8 transcription factors are known to be expressed by several histologic types of renal neoplasms.

Objective.—To evaluate the diagnostic utility of PAX2 and PAX8 relative to one another, which has not been studied.

Design.—Consecutive tissue sections from the archival samples of 243 primary and 99 metastatic renal neoplasms were submitted to PAX2 and PAX8 immunostain.

Results.—Within the primary neoplasms, PAX2 versus PAX8 expression was noted in 90 of 95 (95%) versus 92 of 95 (97%) for clear cell RCC, 29 of 38 (76%) versus 38 of 38 (100%) for papillary RCC, 14 of 25 (56%) versus 22 of 25 (88%) for chromophobe RCC, 3 of 7 (43%) versus 5 of 7 (71%) for collecting duct RCC, 6 of 8 (75%) versus 8 of 8 (100%) for acquired cystic kidney disease–related RCC, and 7 of 13 (54%) versus 11 of 13 (85%) for oncocytoma.

Regardless of histologic subtype, PAX8 staining was noted in more cells and with more intense staining than PAX2. Within the metastatic RCCs, PAX8 expression was more frequently positive than PAX2 expression (88 of 99 cases; 89%; versus 75 of 99 cases; 76%).

Conclusions.—Both PAX2 and PAX8 are diagnostically useful markers for both primary and metastatic renal neoplasms of a large variety of histologic types. However, PAX8 appears to be more sensitive than PAX2 in both primary and metastatic settings. PAX8 can be included in any immunohistochemical panel for the diagnosis of primary renal neoplasms. Adding PAX2 should be optional, but this would gain limited further diagnostic yield. In a metastatic setting, both PAX8 and PAX2 can be included in a panel because a small subset of metastatic RCCs are stained only with PAX2.

abundantly expressed by renal blastemal cells during nephrogenesis, then are noted in only a few renal parenchymal cells in mature kidney, but are identified again in RCC.1,2,6–16 Tissue expression of transcription factor therefore has been used as a specific marker for tumor diagnosis. Several studies, each of which is devoted exclusively to either PAX2 or PAX8, have documented their expression in renal neoplasms.12,14–21 These studies further suggest a similar pattern of expression for PAX2 and PAX8 in these neoplasms, in keeping with their comparable functions in ontogenesis. Nevertheless, a comprehensive direct comparison of these 2 markers is not available, leaving several pertinent diagnostic issues unresolved, such as their comparative diagnostic sensitivity and specificity in primary or metastatic renal neoplasms, and whether both markers or only one, and which one, can be included in a diagnostic panel. These considerations underlie the focus of this study.

**MATERIALS AND METHODS**

This retrospective study included 243 primary (Table 1) and 99 metastatic (Table 2) renal neoplasms. For a direct comparison of

| Table 1. Comparison of PAX2 and PAX8 Expression in Primary Renal Neoplasms |
|---|---|---|---|---|
| **Tumor Type** | **PAX2** | **PAX8** | **Comparison of PAX2 and PAX8 Expression, No. (%)** |
| **No. Positive/Total No. Cases (%)** | **% of Cells Stained, Mean (SD)** | **Staining Intensity, Mean (SD)** | **No. Positive/Total No. Cases (%)** | **% of Cells Stained, Mean (SD)** | **Staining Intensity, Mean (SD)** |
| **RCC, clear cell** | 90/95 (95) 66.4 (32.7) | 2 (0.7) | 92/95 (97) 76.8 (29.5) | 2.1 (0.7) | 90 (95) 0 (0) | 2 (2) | 3 (3) |
| **RCC, papillary** | 29/38 (76) 62.5 (37.7) | 1.7 (0.7) | 38/38 (100) 65.5 (36.9) | 2.0 (0.7) | 29 (76) 0 (0) | 9 (24) | 0 (0) |
| **RCC, chromophobe** | 14/25 (56) 60.7 (34.7) | 1.7 (0.7) | 22/25 (88) 62.5 (35.3) | 1.8 (0.6) | 14 (56) 0 (0) | 8 (32) | 3 (12) |
| **RCC, collecting duct** | 3/4 (75) 50 (46.5) | 2.4 (0.5) | 5/7 (71) 50 (34.6) | 2.6 (0.5) | 3 (43) 0 (0) | 2 (28.5) | 2.8 (28.5) |
| **RCC, sarcomatoid component** | 2/9 (22) 75 (35.3) | 2.5 (0.7) | 4/9 (44) 100 (0) | 3 (0) | 2 (22) 0 (0) | 2 (22) | 5 (55) |
| **RCC, rhabdoid component** | 0/4 (0) 0 | 0 | 0/4 (0) 0 | 0 | 0 (0) 0 | 0 (0) | 4 (100) |
| **RCC, mucinous tubular and spindle cell carcinoma** | 6/6 (100) 96.6 (8.1) | 1.5 (0.5) | 6/6 (100) 96.6 (8.1) | 2.5 (0.5) | 6 (100) 0 (0) | 0 (0) | 0 (0) |
| **RCC, ACK-related** | 6/8 (75) 100 (0) | 3 (0) | 8/8 (100) 88.7 (31.8) | 2.7 (0.7) | 6 (75) 0 (0) | 2 (25) | 0 (0) |
| **RCC, translocation** | 1/2 (50) 20 (ND) | 2 (ND) | 1/2 (50) 100 (0) | 3 (ND) | 1 (50) 0 (0) | 0 (0) | 1 (50) |
| **RCC, tubulocystic** | 1/1 (100) 90 (0) | 1 (0) | 1/1 (100) 90 (0) | 3 (0) | 1 (100) 0 (0) | 0 (0) | 0 (0) |
| **Metanephric tumors** | 3/3 (100) 90 (0) | 3 (0) | 3/3 (100) 90 (0) | 3 (0) | 3 (100) 0 (0) | 0 (0) | 0 (0) |
| **Mixed epithelial and stromal tumor** | 4/4 (100) 100 (0) | 2.7 (0.5) | 4/4 (100) 100 (0) | 2.7 (0.5) | 4 (100) 0 (0) | 0 (0) | 0 (0) |
| **Cystic nephroma** | 7/7 (100) 90 (0) | 2.1 (0.6) | 7/7 (100) 90 (0) | 2.8 (0.3) | 7 (100) 0 (0) | 0 (0) | 0 (0) |
| **Urothelial carcinoma** | 0/13 (0) 0 | 0 | 0/13 (0) 0 | 0 | 0 (0) 0 | 0 (0) | 13 (0) |
| **Oncocytoma** | 7/13 (54) 55 (36.1) | 1.5 (0.5) | 11/13 (85) 61.8 (35.3) | 1.6 (0.5) | 7 (54) 0 (0) | 4 (31) | 2 (15) |
| **Angiomyolipoma** | 0/8 (0) 0 | 0 | 0/8 (0) 0 | 0 | 0 (0) 0 | 0 (0) | 8 (100) |
| **Total** | **172/243** (71) 78.6 (19.4) | **2.1 (0.5)** | **200/243** (82) 84.8 (20.3) | **2.4 (0.5)** | **172 (71)** 0 (0) | **30 (12)** | **41 (17)** |

Abbreviations: ACK, acquired cystic kidney; ND, not determined (only 1 case); RCC, renal cell carcinoma.

a Staining intensity graded 0–3.

b Type 1, type 2, clear cell, and oncocytic variants.

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| Table 2. Comparison of PAX2 and PAX8 Expression in Metastatic Renal Cell Carcinoma (RCC) |
|---|---|---|---|---|
| **Tumor Type (No. of Cases)** | **Metastatic Sites (No. of Cases)** | **PAX2** | **PAX8** |
| **No. Positive/Total No. Cases (%)** | **% of Cells Stained, Mean (SD)** | **Staining Intensity, Mean (SD)** |
| **Cell RCC** | Lung (30), lymph node (11), bone (6), brain (1), bowel (1), soft tissue (6), pancreas (5), gallbladder (1), adrenal gland (8), liver (2), pleura (2), skin (5), spleen (1), omentum (1) | 64/80 (80) 80.5 (28.1) | 2.3 (0.6) |
| **Papillary RCC** | Lung (4), lymph node (3), bone (1), brain (1), soft tissue (1) | 8/10 (80) 81.2 (26.9) | 2.5 (0.6) |
| **Collecting duct RCC** | Lung (1), liver (1), soft tissue (1) | 2/3 (67) 42.5 (3.5) | 2.5 (0.7) |
| **Chromophobe RCC** | Lung (1) | 0/1 (0) 0 | 0 |
| **RCC, sarcomatoid component** | Bone (2), bowel (1), urethra (1), bladder (1) | 1/5 (20) 100 (ND) | 2 (ND) |
| **All histologic types (99)** | **75/99** (76) 76 (19.5) | **2.3 (0.6)** |

Abbreviation: ND, not determined (only 1 case).

a Lung metastasis.

b Bowel metastasis.
PAX2 and PAX8 expression, consecutive tissue sections of each case were submitted to hematoxylin-eosin stain and immunostain for PAX8 and PAX2.

The tissue sections were subjected to deparaffinization, hydration, and endogenous peroxidase blocking. Antigen retrieval was achieved by Dako Target Retrieval Solution, pH 6 (Dako, Carpinteria, California), 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 an anti-PAX2 polyclonal antibody (1:75; Invitrogen, Carlsbad, California) and an anti-PAX8 polyclonal antibody (1:50; ProteinTech Group, Chicago, Illinois). Detection of the staining reaction was achieved by an enzyme-conjugated polymer complex adapted for automatic stainers from Ventana Medical Systems (Tucson, Arizona). Positive controls included renal carcinoma tissue and lymphoid tissue, which often also served as a built-in control because lymphoid cells were often seen in the evaluated tissue sections. Mesenchymal or epithelial cells in the evaluated tissue sections served as negative controls. For each case, the staining intensity (0, no stain; 1, unequivocal but weak; 2, moderate; 3, strong), and staining extent (estimated percentage of stained cells in 5% increments) was recorded.

RESULTS

PAX2 and PAX8 were successfully detected in routinely processed tissue with appropriate positive and negative controls. The stain was almost exclusively nuclear, with no or negligible cytoplasmic expression.

Primary Neoplasms

Overall, PAX8 expression was more pronounced than that of PAX2 in terms of frequency of positivity (200 of 243 cases; 82% versus 172 of 243 cases; 71%), extent of staining (mean 85% versus 79% of tumor cells), and staining intensity (mean 2.4 versus 2.1) (Table 1). These differences were noted for most histologic subtypes, but were magnified in some histologic subtypes (see below). Seventy-one percent (172 of 243 cases) of the tumors were positive for both markers, and 17% (41 of 243 cases) were negative for both of them. Twelve percent (30 of 243 cases) of the tumors (Figure 1, D through F) were positive only for PAX8. All tumors that expressed PAX2 also expressed PAX8; there was no tumor with only PAX2 expression.

Clear Cell RCC.—The expression of PAX2 and PAX8 was comparable in terms of frequency (92 of 95 cases; 97%; versus 90 of 95 cases; 95%), extent (77% versus 66% of tumor cells), and intensity (2.1 versus 2) (Table 1; Figure 1, A through C). Ninety-five percent (90 of 95 cases) of the tumors were positive and 3% (3 of 95 cases) were negative for both markers. Two percent of the tumors (2 of 95 cases) were positive only for PAX8 (Figure 1, D through F), and there was no tumor with only PAX2 expression.

Papillary RCC.—PAX8 expression was more pronounced than that of PAX2 in terms of frequency (38 of 38 cases; 100%; versus 29 of 38 cases; 76%), extent (66% versus 63% of tumor cells), and intensity (2 versus 1.7) (Figure 1, G through I). Seventy-six percent (29 of 38 cases) of the tumors were positive for both markers. Twenty-four percent (9 of 38 cases) of the tumors were positive only for PAX8, and there was no tumor with only PAX2 expression.

Chromophobe RCC.—PAX8 expression was more frequent than that of PAX2 (22 of 25 cases; 88%; versus 14 of 25 cases; 56%), but they were comparable in terms of extent (63% versus 61% of tumor cells) and intensity (1.8 versus 1.7) (Figure 1, J through L). Fifty-six percent (14 of 25 cases) of the tumors were positive for both markers, and 12% (3 of 25 cases) was negative for both of them. Thirty-two percent (8 of 32 cases) of the tumors were positive only for PAX8, and there was no tumor with only PAX2 expression.

Collecting Duct RCC.—PAX8 expression was more pronounced than that of PAX2 in terms of frequency (5 of 7 cases; 71%; versus 3 of 7 cases; 43%) or extent (80% versus 50% of tumor cells), but of comparable intensity (2.6 versus 2.4) (Figure 2, A through C). Forty-three percent (3 of 7 cases) of the tumors were positive for both markers, and 29% (2 of 7 cases) were negative for both of them. Twenty-nine percent (2 of 7 cases) of the tumors were positive only for PAX8, and there was no tumor with only PAX2 expression.

Rhabdoid Component of RCC.—Tumor cells with rhabdoid features, including abundant eosinophilic cytoplasm, paranuclear cytoplasmic inclusion, and large nuclei and nucleoli, were noted in 4 RCCs, all of which were of clear cell type (Figure 2, D through F). These tumor cells were negative for both PAX2 and PAX8, whereas the background RCCs were positive for both markers.

Sarcomatoid Component of RCC.—Sarcomatoid areas characterized by tumor cells with marked nuclear atypia and variable degrees of spindle morphology were noted

<table>
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<tr>
<th>No. Positive/ Total No. Cases (%)</th>
<th>% of Cells Stained, Mean (SD)</th>
<th>Staining Intensity, Mean (SD)</th>
<th>Comparison of PAX2 and PAX8 Expression, No. (%)</th>
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<td>77 (14.3)</td>
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Figure 1. A through C, Clear cell renal cell carcinoma (RCC); diffuse and strong staining for both PAX2 and PAX8. D through F, Clear cell RCC; the tumor cells are negative for PAX2, but positive for PAX8. Renal tubular epithelial cell nuclei are positive for both markers (left). G through I, Papillary RCC; weak focal staining for PAX2, contrasting with strong diffuse staining for PAX8. J through L, Chromophobe RCC; no staining for PAX2, contrasting with diffuse staining for PAX8 (original magnifications ×200).
Figure 2. A through C, Collecting duct renal cell carcinoma (RCC) extending to the liver (upper left); diffuse staining for both PAX2 and PAX8. D, E, and F, RCC with rhabdoid component; no staining of tumor cells for PAX2 or PAX8. Nuclei of atrophic renal tubules incorporated into the tumor tissue (arrows) are positive for both markers. G through I, Metanephric adenoma; strong and diffuse staining for PAX2 and PAX8 of tumor cells. Atrophic renal tubular cell nuclei are also positive for both markers (lower left). J through L, Mucinous tubular and spindle cell carcinoma; the epithelial cell nuclei are diffusely positive for PAX2 and PAX8 (original magnifications ×200).
Figure 3. A through C, Renal cell carcinoma (RCC) with sarcomatoid component; the tumor cells are negative for PAX2 but strongly positive for PAX8. D through F, Clear cell RCC (upper right) with sarcomatoid change (lower left); the tumor cells of both tumor types are negative for PAX2, but positive for PAX8. G and H, Mixed epithelial and stromal tumor; diffuse staining of the epithelial cells for both PAX2 and PAX8. I and J, Oncocytoma; the tumor cells are negative for PAX2, but display focal weak staining for PAX8. The renal tubular cell nuclei are strongly positive for both markers (original magnifications ×200).
in 9 RCCs of usual types. Twenty-two percent of these sarcomatoid areas were positive for both markers. Twenty-two percent of these areas were positive only for PAX8 (Figure 3, A through F), and there was no tumor area with only PAX2 expression.

Translocation RCC.—Fifty percent of tumors were positive for both PAX2 and PAX8.

Metanephric Adenoma, Wilms Tumor, and Mucinous Tubular and Spindle Cell Carcinoma.—Both PAX2 and PAX8 were strongly and diffusely expressed in all tumors of these histologic types (Figure 2, G through L).

Cystic Nephroma and Mixed Epithelial and Stromal Tumor.—Both PAX2 and PAX8 were strongly and diffusely expressed in all tumors of these histologic types (Figure 3, G and H). The staining was limited to the epithelial component.

Oncocytoma.—PAX8 expression was more pronounced than that of PAX2 in terms of frequency (11 of 13 cases; 85%; versus 7 of 13 cases; 54%) and extent (62% versus 55% of tumor cells), but was of comparable intensity (1.6 versus 1.3; Figure 3, I and J). Fifty-four percent (7 of 13 cases) of the tumors were positive for both markers, and 15% (2 of 13 cases) were negative for both of them. Thirty-one percent (4 of 13 cases) of the tumors were positive only for PAX8, and there was no tumor with only PAX2 expression.

Urothelial Carcinoma and Angiomyolipoma.—Neither PAX2 nor PAX8 was seen in any tumors.

Metastatic Neoplasms

PAX8 expression was significantly more pronounced than PAX2 expression in terms of frequency (88 of 99 cases; 89%; versus 75 of 99 cases; 76%), but PAX8 and PAX2 were comparable in terms of extent (77% versus 76% of tumor cells) and intensity (2.3 for both) (Table 2; Figure 4, A through I). Seventy-five percent (74 of 99 cases) of the tumors were positive and 7% (7 of 99 cases) were negative for both markers. Sixteen percent (16 of 99 cases) of the tumors were positive only for PAX8, and 2% (2 of 99 cases) was positive only for PAX2. The corresponding primary tumors of the 2 metastases that were positive only for PAX2 were not available for study.

Clear Cell RCC.—PAX8 expression was more pronounced than that of PAX2 in terms of frequency (74 of 80 cases; 93%; versus 64 of 80 cases; 80%), but of comparable extent (88% versus 80% tumor cells) and intensity (2.7 versus 2.3) (Figure 4, A through C). Eighty percent (64 of 80 cases) of the tumors were positive for both markers, and 4% (3 of 80 cases) were negative for both of them. Fifteen percent (12 of 80 cases) of the tumors were positive only for PAX8, and 1% (1 of 80 cases) was positive for only PAX2.

Papillary RCC.—PAX8 expression was more pronounced than that of PAX2 in terms of frequency (9 of 10 cases; 90%; versus 8 of 10 cases; 80%) and extent (90% versus 81% of tumor cells), but of comparable intensity (2.6 versus 2.5) (Figure 4, D through F). Eighty percent (8 of 10 cases) of the tumors were positive for both markers, and 10% (1 of 10 cases) were negative for both of them. Ten percent (1 of 10 cases) of the tumors were positive only for PAX8, and no tumors were positive only for PAX2.

Collecting Duct RCC.—PAX8 expression was similar to that of PAX2 in terms of frequency (2 of 3 cases; 67% for both) and staining intensity (2.5 for both), but with more stained cells (90% versus 43% of tumor cells). Sixty-seven percent (2 of 3 cases) of the tumors were positive for both markers, and 33% (1 of 3 cases) were negative for both of them. Dual staining was noted for each of the positive tumors, with no tumor positive only for either PAX2 or PAX8.

Chromophobe RCC.—The single metastatic chromophobe RCC was positive only for PAX8.

Sarcomatoid Component of RCC.—PAX8 expression was more pronounced than that of PAX2 in terms of frequency (2 of 5 cases; 40%; versus 1 of 5 cases; 20%), but was of comparable extent (100% tumor cells for both) and intensity (2.0 for both). Forty percent (2 of 5 cases) of the tumors were negative for both markers. Forty percent of the tumors (2 of 5 cases) (Figure 4, G through I) were positive only for PAX8, and 20% (1 of 5 cases) were positive only for PAX2 (Figure 4, J through L). No tumors were positive for both markers.

COMMENT

To our knowledge, this is the first systematic and comprehensive study directly comparing PAX2 and PAX8 expression in primary tumors and metastatic tumors of the kidney. PAX2 and PAX8 are cell lineage–restricted transcription factors, with similar tissue expression and ontogenetic function. Both PAX2 and PAX8 are expressed in the primordial tissues of wolffian (nephric) and müllerian ducts.6,9 During organogenesis, these primordial structures give rise to urogenital organs, including kidney, ureter, seminal vesicles, vas deferens, uterus, and fallopian tubes, under the partial control of both PAX2 and PAX8.4,6–9 During nephrogenesis, both PAX8 and PAX2 are expressed very early in the renal blastema and later in collecting duct cells, and all progenitor epithelial cells of the developing nephron. They promote mesenchymal cell proliferation and apoptosis and mesenchymal-epithelial transformation, with formation of immature renal tubules and glomeruli.12–25 Deletion of both PAX8 and PAX2 genes prevents generation of the mesonephric (wolffian) duct and subsequent formation of all three embryonic kidneys (pronephros, mesonephros, and metanephros).6,9 However, inactivation of the PAX8 gene alone does not result in any kidney malformation,8 suggesting an overlapping but differential function of PAX8 and PAX2. Indeed, PAX8 also controls thyroid organogenesis, a function not shared by PAX2. The rather limited cell/tissue-specific expression of PAX2 and PAX8 and the capacity to immunolocalize these transcription factors in routinely processed tissue have promoted the use of PAX2 and PAX8 as diagnostic tumor markers.

PAX2 and PAX8 in Primary Renal Tumors

Previous studies have documented PAX2 expression in various primary renal neoplasms, including 84% to 93% for clear cell RCC, 18% to 87% for papillary RCC, 9% to 83% for chromophobe cell RCC, and 14% to 87% for oncocytoma.1,13,14,19,26 These studies are somewhat limited, either by rather small numbers of cases, lack of some histologic subtypes, or failure to determine the staining extent or intensity. The current study corroborates and expands previous findings. It shows that the majority (172 of 243 cases; 71%) of renal neoplasms of almost all histologic types express PAX2, with variable percentages (22%–100%) depending on tumor types and putative nephronic segment of origin. Thus, all or a high percentage of clear cell RCC, papillary RCC, chromophobe RCC,
Figure 4. A through C, Clear cell renal cell carcinoma (RCC) metastatic to adrenal cortex (upper right); the tumor cells are diffusely positive for both PAX2 and PAX8. The adrenal cortical cells are negative for both markers. D through F, Papillary RCC metastatic to a lymph node. Weak and focal staining of tumor cells for PAX2, contrasting with diffuse staining for PAX8. Lymphoid cells (upper right) are strongly positive for both markers. G through I, RCC with sarcomatoid component metastatic to urethra. Tumor cells are negative for PAX2, but positive for PAX8. The urothelial cells (lower left) are negative for both markers. J through L, RCC with sarcomatoid component metastatic to bowel. Tumor cells are negative for PAX8, but positive for PAX2 (original magnifications ×200 [A through F and J through L] and ×400 [G through I]).
acquired cystic kidney-related RCC, mucinous tubular and spindle cell carcinoma, mixed epithelial and stromal tumor, cystic nephroma, and oncocytoma are positive for PAX2. Of note, all metanephric tumors, which are characterized by an ‘embryonic’ phenotype, display a level of PAX2 expression significantly beyond the already strong staining of other RCC types such as clear cell or papillary RCC, reflecting the pronounced PAX2 expressions during renal embryogenesis. Even tumor types such as collecting duct RCC or sarcomatoid RCC, which are almost always negative for traditional RCC markers such as RCCM, CD10, or kidney-specific cadherin, express PAX2 in 22% to 43% of cases. The staining intensity and extent of staining tend to depend on tumor types and differentiation level, thus accounting for usually less expression in chromophobe RCC and oncocytoma, less expression in less differentiated areas of tumor of any histologic type, and absence of staining in all tumors with rhabdoid features. Urothelial neoplasm and renal mesenchymal tumors such as angiomyolipoma are uniformly negative.

PAX8 expression in renal tumor has been investigated in only a few studies. In these studies, PAX8 was noted in 95% to 98% for clear cell RCC, 90% to 100% for papillary RCC, 82% to 88% for chromophobe cell RCC, 44% to 71% for sarcomatoid RCC, and 61% to 95% for oncocytoma. The current study supports these observations and further illustrates that the majority (200 of 243 cases; 82%) of renal neoplasms of almost all histologic types express PAX8, with variable percentages (44%–100%) depending on tumor types or putative nephrogenic segment of origin.

Direct comparison of PAX2 and PAX8 immunostain in consecutive tissue sections clearly demonstrates that the pattern and topography of their staining and the histologic spectrums of the positive tumors are virtually identical. Nevertheless, PAX8 expression was more pronounced than that of PAX2 in terms of frequency, staining extent, and staining intensity. These differences were noted for most histologic subtypes, but were magnified in some histologic subtypes, such as collecting duct RCC (5 of 7 cases; 71%; versus 3 of 7 cases; 43%), sarcomatoid RCC (4 of 9 cases; 44%; versus 2 of 9 cases; 22%), chromophobe RCC (22 of 25 cases; 88%; versus 14 of 25 cases; 56%), and oncocytoma (11 of 13 cases; 85%; versus 7 of 13 cases; 54%). These observations suggest that both PAX2 and PAX8 may facilitate the diagnosis of the types of renal neoplasms that are often negative for the more traditional markers, and, in this aspect, PAX8 is better than PAX2.

The comparative study also shows that regardless of histologic subtype, when a tumor is positive for PAX2, it is always positive for PAX8. In contrast, 12% (30 of 243) of tumors were positive for PAX8 only, and there was no tumor that was positive only for PAX2. It is noted, however, that there were 2 metastatic RCCs that were positive for PAX2 but negative for PAX8, raising the possibility that their primary tumors would display the same phenotype. The corresponding primary tumors were unfortunately not available for study. These observations suggest that PAX8 can be included in any immunohistochemical panel for the diagnosis of renal neoplasms. Adding PAX2 is optional, but this would add limited further diagnostic yield.

The current study does not directly compare the sensitivity of PAX2 and PAX8 with other traditional markers for renal neoplasms including RCCM, CD10, and kidney-specific cadherin. In previous studies, these traditional markers were detected in 48% to 85%, 81% to 100%, and 0% to 30% of clear cell RCCs; in 63% to 97%, 59% to 95%, and 0% to 13% of papillary RCCs; in 0% to 17%, 0% to 73%, and 58% to 100% of chromophobe RCCs; in 0% to 40%, 40%, and 0% of collecting duct RCCs, and in 0%, 33%, and 38% to 76% of oncocytomas, respectively.

Tickoo et al reported that of the clear cell RCCs, carbonic anhydrase IX was expressed in a majority of the tumors within the epithelial and sarcomatoid components, with more than 85% positive-staining cells in the epithelial and sarcomatoid components of 86% and 68% of the tumors, respectively. They also noted that vascular endothelial growth factor was diffusely presented in 68% of epithelial and 95% of sarcomatoid areas among clear cell RCCs, and in 70% and 92%, respectively, of the non–clear cell RCCs. In the present study, PAX2 and PAX8 expression was noted in 90 of 95 (95%) versus 92 of 95 (97%) of clear cell RCCs, in 29 of 38 (76%) versus 38 of 38 (100%) of papillary RCCs, in 14 of 25 (56%) versus 22 of 25 (88%) of chromophobe RCCs, in 3 of 7 (43%) versus 5 of 7 (71%) of collecting duct RCCs, and in 7 of 13 (54%) versus 11 of 13 (85%) of oncocytomas, respectively. These findings suggest that PAX2 and PAX8 are probably the best among these renal markers.

PAX2 and PAX8 Expression in Metastatic Renal Tumors

Little is known about PAX2 expression in metastatic RCC. In a few previous studies, PAX2 has been noted in 77% to 86% of metastatic clear cell RCC and 75% to 100% of metastatic papillary RCCs. The current study, which includes the largest number of metastatic RCCs of diversified histologic types, clearly demonstrates that PAX2 is a sensitive marker for metastatic RCC, with an overall detection rate of 76% (75 of 99 cases). Furthermore, this expression is noted in 67% (2 of 3 cases) of metastatic collecting duct RCC and 20% (1 of 5 cases) of metastatic sarcomatoid RCC. This represents a significant diagnostic advantage, in view that both types of RCCs are almost always negative for other more traditional markers for renal neoplasms, and their morphologic features significantly overlap with those of primary tumor of organs other than kidneys.

Even less is known about PAX8 expression in metastatic RCC. Previous studies have shown PAX8 to be noted in 84% to 93% of clear cell RCCs, 100% of papillary RCCs, and 0% to 50% of sarcomatoid RCCs. The current study clearly demonstrates that PAX8 helps recognize the vast majority of metastatic RCCs (88 of 99 cases; 89%), even for diagnostically challenging types such as collecting duct RCC (2 of 3 cases; 67%) or sarcomatoid RCC (2 of 5 cases; 40%).

Studies comparing PAX8 or PAX2 with traditional renal markers in metastatic RCCs are limited, and they have been focused on metastatic clear cell RCC. In these studies, the diagnostic sensitivity of RCCM and CD10 ranges from 27% to 90%,39,40 and 83% to 100%,44,45 respectively; however, CD10 immunoreactivity has also been seen in a wide variety of nonrenal tumors.44 Sangoi et al indeed suggested that PAX2 and PAX8 should replace RCCM and CD10 in the workup for potential metastatic renal neoplasms.

Direct comparison of PAX2 and PAX8 shows that PAX8 is a more sensitive marker for metastatic RCC than PAX2 (88 of 99 cases; 89%; versus 75 of 99 cases; 76%), but with a
similar staining extent and intensity. Although most positive tumors were positive for both markers, 16% (16 of 99 cases) of tumors were positive for PAX8 only. Of note, 2 tumors (1 sarcomatoid RCC and 1 clear cell RCC metastatic to lung and bowel, respectively) were positive for PAX-2 only. These observations suggest that perhaps both PAX8 and PAX2 can be included in a panel for the workup of metastatic RCC.

Several general considerations are pertinent to the diagnosis of metastatic neoplasm. Determination of cellular lineage, an interesting but often diagnostically irrelevant task in the study of primary neoplasms, becomes critical for metastatic tumors, especially for those of unknown primary tumor or those identified against the background of multiple primary tumors. A marker that is strongly and diffusely expressed in a high percentage of primary tumors may display significantly attenuated expression in terms of frequency, extent, and intensity for its metastasis. Tissue for the metastatic workup, often obtained by core or fine-needle aspiration biopsy, is scanty, and thus a marker with a patchy staining pattern would miss the diagnostic cells. Observations from this study suggest that PAX2 and PAX8 may overcome these limitations. This study shows that combined PAX2 and PAX8 helps detect the vast majority of metastatic RCC (92 of 99 cases; 93%). Furthermore, a significant percentage of metastatic tumor cells (77% for PAX8 and 76% for PAX2) are stained with a mean intensity of 2.3 for both markers. These values are comparable to those of primary renal neoplasms and indicate a conserved phenotype at metastasis.

Specificity is an important matter in diagnostic immunohistochemistry. This is even more significant in the context of metastasis, because metastatic disease not infrequently arises in the background of unknown primary tumor or a history of multiple neoplasms. The current study is not designed to evaluate the specificity of PAX2 or PAX8 for primary or metastatic renal tumors. However, previous studies indicate that PAX8 and PAX2 are also expressed in primary müllerian tumors, nephro- genic adenoma, and parathyroid parenchymal lesions. Furthermore, PAX8 but not PAX2 is noted in thyroid tumors of follicular cell origin and well differentiated neuroendocrine tumors. This rather broad expression certainly endorses the diagnostic use of not only PAX8 and PAX2 can be included in a panel for the differential diagnosis of chromophobe cell carcinoma. Am J Clin Pathol. 2007;127(2):225–229.


