This review gives an update on selected issues on renal neoplasia with special references to emerging new tumor entities (thyroid-like follicular renal cell carcinoma, succinic dehydrogenase B deficiency–associated renal cell carcinoma, and anaplastic lymphoma kinase [ALK] translocation renal cell carcinoma), tumor grading (the International Society of Urological Pathology grading system), and assessment of tumoral involvement of the renal sinus structures, including the sinus fat, the loose connective tissue, or any sinus-based endothelium-lined space. (Anal Quant Cytopathol Histopathol 2014;36:1–8)

Keywords: emerging new tumor entities, kidney neoplasms, renal cell carcinoma, renal collecting duct carcinoma, renal neoplasia, renal sinus invasion, sarcomatoid renal cell carcinoma, tumor grading.

Although it has been more than 200 years since the report of the first case of renal cancer, it is only in the last 30 years that any real advances have been made in the understanding of the spectrum of renal malignancy.1 In the 1981 edition of the WHO classification of renal tumors there were 9 separate categories of renal neoplasia, as compared to 50 categories in the third edition of the classification published in 2004.2,3 Despite this progress addi-
tional tumor morphotypes continue to be reported, and in a number of instances validation studies have indicated that many of these are worthy of recognition as novel forms of renal cell carcinoma (RCC). In parallel with these developments, a wide variety of prognostic parameters have been investigated with variable success, with much attention being centered upon the importance of features relating to grade and stage.

The aim of this review is to give a contemporary update on selected issues on renal neoplasia with special references to emerging new tumor entities, tumor grading, and assessment of renal sinus invasion. This review refers to the International Society of Urological Pathology (ISUP) 2012 Consensus Conference convened on March 17, 2012, in Vancouver, Canada. The conference made recommendations regarding classification, grading, prognostic factors, staging, and immunohistochemical and molecular assessment of adult renal tumors.

**Emerging and Provisional Tumor Entities**

The ISUP consensus conference suggested modifications to existing WHO 2004 categories. Within the clear cell RCC group, multicystic clear cell RCC is best considered as a neoplasm of low malignant potential. Subtyping of papillary RCC is of value, and the oncocytic variant of papillary RCC should not be considered as a distinct entity. The hybrid oncocytic chromophobe tumor, which is an indolent tumor that occurs in 3 settings, namely Birt-Hogg-Dubé syndrome, renal oncocytosis, and as a sporadic neoplasm, is placed for the time being within the chromophobe RCC category.

Five entities are recognized as new distinct epithelial tumors: tubulocystic RCC, acquired cystic disease–associated RCC, clear cell papillary (tubulopapillary) RCC, the MiT family translocation RCCs (in particular, t(6;11) RCC) (Figure 1), and hereditary leiomyomatosis RCC syndrome–associated RCC.

In addition, there are 3 rare epithelial carcinomas that are considered as emerging or provisional new entities: thyroid-like follicular RCC, succinic dehydrogenase B deficiency–associated RCC, and anaplastic lymphoma kinase (ALK) translocation RCC. Further reports of these entities are required to better understand the nature and behavior of these highly unusual tumors.

While the morphotype of RCCs is usually discernible on examination of the hematoxylin and eosin–stained section, markers are often useful for confirming diagnosis in difficult cases. The main subtypes of RCC (clear cell, papillary, chromophobe and collecting duct RCC) each have typical immunostaining profiles and, as such, immunohistochemistry is of diagnostic utility for these tumors. Immunohistochemistry stains can also be used to distinguish malignant tumors from benign tumors and tumor-like processes and can also be used to determine whether renal tumors are of metastatic origin. In routine clinical practice of genetic studies this was of limited value. Fluorescence in situ hybridization should be undertaken to confirm a diagnosis of translocation carcinoma if the diagnosis is suspected morphologically or if the patient is <30 years of age. Other differential diagnoses for which genetic studies were considered valuable were mucinous tubular spindle carcinoma and papillary RCC with sarcomatoid areas, and clear cell (tubulo)
papillary RCC and either clear cell or papillary RCC.

**ALK Translocation RCC**

Two cases of RCC harboring a t(2;10)(p23;q22) translocation resulting in a fusion of the gene for the cytoskeletal protein vinculin (VCL) with the ALK gene have been reported. Of note, both cases occurred in young patients (at ages 6 years and 16 years) with sickle cell trait (raising the differential diagnosis of renal medullary carcinoma) and demonstrated distinctive morphology characterized by polygonal to spindle cells with abundant eosinophilic cytoplasm and frequent intracytoplasmic lumina. The findings suggest that VCL-ALK RCCs have distinctive clinical and pathologic features. A recent study from Japan identified 2 further RCCs in adults (ages 36 years and 53 years) associated with ALK fusions involving partner genes (TPM3, EML4) other than VCL. Interestingly, neither of these cases was associated with sickle cell trait, and morphology (papillary and unclassified) was different from that reported for the VCL-ALK fusion. The Mayo Clinic group recently reported 2 additional ALK-positive cases in adults, both of which demonstrated clear cells and papillary architecture and behaved aggressively.

**Succinic Dehydrogenase B Mutation–Associated RCC**

Renal carcinomas have been reported in association with germline succinate dehydrogenase B mutations, the pheochromocytoma/paraganglioma syndrome type IV (PGL4). This syndrome is characterized by a predilection to pheochromocytoma, paraganglioma, so-called type II gastrointestinal stromal tumors (similar to those frequently seen in children and in association with Carney syndrome), and an estimated approximately 14% lifetime risk of renal neoplasia. Fewer than 10 cases of RCC associated with germline succinate dehydrogenase B mutations (SDHB RCC) have been reported. Most have affected young adults, and most cases have been associated with an indolent course on limited follow-up. The exceptions are 2 cases that underwent sarcomatoid change, both of which metastasized and one of which resulted in patient death.

These neoplasms are usually unencapsulated and composed of compact nests of eosinophilic polygonal cells, with entrapped renal tubules at the periphery. The cells may have vacuolated cytoplasm or distinctive pale eosinophilic cytoplasmic inclusions that correspond to giant mitochondria by ultrastructural examination. Loss of SDHB protein by immunohistochemistry is reported to be a sensitive and specific marker for these neoplasms.

While these findings suggest that SDHB RCC may be a distinctive entity, problematic areas remain. First, there is limited experience (fewer than 10 cases published), and some renal neoplasms associated with PGL4 syndrome have been reported as clear cell RCC and oncocytoma, though these have not been illustrated. Second, there is relatively limited experience with SDHB IHC in the kidney (unlike the situation with gastrointestinal stromal tumors). Since SDHB normally localizes to the mitochondria, one should see granular, mitochondrial-pattern staining in cells with eosinophilic cytoplasm and intact SDHB. However, it has been stated that cells with clear cytoplasm (usually reflecting displacement of mitochondria from the cytoplasm and replacement by glycogen or fat) may give a false negative result on SDHB IHC. It is not clear whether there is a minimal size of tumor that needs to be evaluated before loss of SDHB labeling can accurately predict syndromic cases. Some authors have suggested that only whole sections should be evaluated and that tissue microarrays may falsely suggest loss of labeling due to limited tissue size. Finally, mutations in other subunits of succinate dehydrogenase (such as succinate dehydrogenase A, B, C or D) can abrogate SDHB labeling. At this time, SDHB RCC is considered a provisional entity which requires further experience before it can be accepted as a distinctive recognized entity by the ISUP.

**Thyroid-like Follicular RCC**

Thyroid-like follicular RCC is provisionally defined as RCC resembling well-differentiated follicular carcinoma of the thyroid gland. In the fewer than 15 cases reported in the literature, the age range is wide (29–83 years) and there is a slight female predominance. These tumors are well-circumscribed, solid, and generally homogeneous tan-brown in color. At the microscopic level the neoplasms are typically encapsulated and have a macrofollicular and/or microfollicular architecture with associated dense colloid-like material (Figure 2). While cases with a focal papillary architecture have been cited in the literature on thyroid-like follicular RCC, it is thought that this category should be reserved for tumors with a pure follicular architecture. The nuclei are generally round and reg-
ular and contain enlarged nucleoli (nucleolar grade 2 or 3). A solitary case without papillary architecture showed clearing and grooves, which raised the differential diagnosis of a metastasis from the follicular variant of papillary carcinoma. By immunohistochemistry these neoplasms stain negative for thyroid transcription factor–1 and thyroglobulin, allowing their distinction from metastatic follicular thyroid cancer to kidney, which has been more commonly described in thyroid-like follicular RCC. Labeling for cytokeratin 7, PAX2, and PAX8 has been variable. Only limited genetic studies have been performed on this neoplasm, without any distinctive pattern emerging. While the majority of cases have behaved in an indolent fashion, 2 examples of thyroid-like follicular RCC metastatic to regional lymph nodes in 1 example showing metastases to the lung have been described.

**Grading of Renal Neoplasia**

The earliest reports on grading of RCC appeared in 1932 by Hand and Borders and in 1949 by Griffiths and Thackray. These workers were the first to identify an association between tumor differentiation and patient outcome. Over 20 years passed before Skinner et al reported on several observations in the grading of RCC. In a series of cases uniformly treated by nephrectomy and followed for over 6 years, they reported a significant association of 4 grades and 1-5- and 10-year survival rates. Skinner et al defined several histologic parameters in grading RCC that remain in use today. Their study was the first to grade RCC on the basis of nuclear features alone and to define the grade of RCC based on the highest grade area within a tumor. In addition, they were the first to associate cell types with patient outcome. They defined tumors as pure clear, clear and/or granular, and spindle cell (sarcomatoid) and showed that patients with pure clear cell RCC had a significantly better outcome as compared to patients with clear cell/granular tumors, and that both did significantly better than did patients with spindle cell tumors. Although they reported on cell types, they specifically noted that the understanding of RCC types was limited and required further study. Since these studies, several composite grading systems for RCC have been proposed, being based on a variety of morphological features including tumor architecture, mitotic rate, cellular morphology, and nuclear pleomorphism, while more recently novel grading systems have focused upon nuclear features alone.

In 1982 Fuhrman et al reported on 105 patients with RCC treated between 1961 and 1974. Of those 105 patients only 85 had at least 5-year follow-up, and 84 were treated surgically. The grading system used by Fuhrman et al was adapted from the study by Skinner et al. They defined the first 3 grades on nuclear features, and the fourth grade was defined by the presence of nuclear pleomorphism, with the overall grade being based upon the highest grade area. Unlike Skinner et al, who identified survival differences between patients in all 4 of their grades, Fuhrman et al identified only 3 groups that differed in outcome, i.e., patients with grade 1 tumors, patients with grade 2 and 3 tumors, and patients with grade 4 tumors. In their series, patients with grade 2 and 3 tumors comprised over 75% of the entire study population and had a similar outcome. In addition to the small number of patients with limited follow-up and lack of standardized treatment, the study considered RCC a single tumor type and so combined clear cell, papillary, and chromophobe subtypes in the analysis. Despite these major limitations, the Fuhrman grading system has been widely adopted in clinical practice.

As the knowledge of RCC subtypes has expanded, and larger and more rigorous studies have been applied to RCC, issues with the Fuhrman grading system have arisen. In particular, the Heidelberg and Rochester Consensus Conferences defined the 4 major RCC morphotypes, and over time, additional rarer variants of RCC have been defined. As the knowledge of RCC subtypes has grown and larger studies of patients with RCC subtypes have been reported, the prognostic significance of the...
Fuhrman grading system has come under question, and limitations of the system have been better defined. Several problems have been identified with Fuhrman grading. Although nuclear diameter can be objectively assessed, nucleolar prominence is more subjective, while criteria for nuclear pleomorphism are poorly defined. In addition, there is no indication within the system regarding the relative importance of each of these features, and no recommendation is given regarding stratification of parameters in those tumors for which contradictory results are obtained. This problem has been recognized, and there is evidence that pathologists attempt to address this by grading on the basis of nucleolar prominence alone, which does not conform to the grading criteria of the Fuhrman system.

Studies have shown significant variation in the distribution of Fuhrman grades, and the association between grade and outcome also varies, although in the case of clear cell RCC, larger series have reported significant differences in outcome between grades 1 and 2 versus 3 versus 4. Other issues include a lack of definition for the “highest grade area,” while the relevance of Fuhrman grading for chromophobe RCC and other RCC subtypes is uncertain.

Recently, grading systems relying solely on nucleolar prominence have shown a stronger association with patient outcome than Fuhrman grade for clear cell and papillary RCC. In particular, it has been shown that focal or worst nucleolar grade is superior to the other features in the Fuhrman grading criterion for papillary and clear cell RCC, indicating that nucleolar prominence alone is a valid grading system for these tumors. In addition, studies have shown that, given the inherent nuclear atypia of chromophobe RCC, Fuhrman grading is inappropriate. This conclusion is supported by the observation that the distribution of the 4 Fuhrman grades reported in chromophobe RCC varies widely between series. Alternative grading systems have been proposed for this morphotype, although the predictive significance of these have not been independently validated and shown to be independent of stage.

At the ISUP consensus conference a novel grading system (the ISUP grading system) was proposed (Table I). This grading system should be applied to clear cell RCC (78%) and papillary RCC. Until further data accumulates, chromophobe RCC should not be graded.

### Assessment of Renal Sinus Invasion
Renal sinus fat is the central perinephric fat compartment that is located between the pelvicalyceal system and the renal parenchyma and contains the main lymphovascular supply of the kidney. The importance of renal sinus fat invasion has been initially recognized in staging nephroblastoma, but during the past decade its significance has also been established in adult RCC. These studies have demonstrated that renal sinus invasion is the principal route for extrarenal extension, particularly for clear cell RCC, but also for papillary and chromophobe RCC. In a significant study Bonsib found that over 90% of clear cell RCCs ≥7 cm invaded the renal sinus. In another study Thompson et al reexamined wet tissue from 33 patients with pT1 clear cell RCC who died of their disease. Additional sections from the renal sinus identified renal sinus invasion in 14 (42%) of these cases, in contrast to a matched set of 33 patients not dying of RCC where additional sections of the sinus showed invasion in only 2 (6%). There are also data indicating that renal sinus invasion is associated with a worse prognosis than is perinephric fat invasion. During the last decade the recognition of renal sinus invasion prompted practice changes resulting in direct evaluation and targeted sampling of the renal sinus area in nephrectomy specimens to better identify renal sinus invasion.

Previous studies have presented somewhat varied strategies and recommendation for renal sinus sampling and evaluation. In the original studies of Bonsib, an initial series of 50 cases had the entire tumor-renal sinus embedded; when present, renal sinus invasion was demonstrated in the first few blocks, and the study protocol was revised to a “minimum of 5 blocks” sampled from the interface. In the study by Thompson et al in which previously reported pT1 tumors were re-examined, an additional 10 sections were submitted from the renal sinus. Subsequently other authors

### Table I ISUP Grading System

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<th>Grade</th>
<th>Tumor description</th>
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<tr>
<td>1</td>
<td>Inconspicuous or absent nucleoli at 400 × magnification</td>
</tr>
<tr>
<td>2</td>
<td>Nucleoli distinctly visible at 400 × but inconspicuous or invisible at 100 × magnification</td>
</tr>
<tr>
<td>3</td>
<td>Nucleoli distinctly visible at 100 × magnification</td>
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<tr>
<td>4</td>
<td>Rhabdoid or sarcomatoid differentiation, or containing tumor giant cells or showing extreme nuclear pleomorphism with clumping of chromatin</td>
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have proposed alternate sampling strategies, including a specific number of blocks of the tumor-sinus interface: 1 block/cm tumor-renal sinus interface or 2–3 blocks. If sinus invasion is grossly evident or obviously not present (e.g., small peripheral tumor), only 1 block would be needed to confirm the gross impression that renal sinus invasion is present or absent, respectively.

On histology, renal sinus invasion can be established when the tumor is in direct contact with the sinus fat (100%) or in the loose connective tissue clearly beyond the renal parenchyma (75%). The study by Thompson et al included both of these in their report. In addition, a substantial majority (90%) of participants agreed that involvement of any endothelial lined spaces within the renal sinus, regardless of the size, should also be considered renal sinus invasion (pT3a).

In summary, renal sinus involvement can be diagnosed by tumoral involvement of any renal sinus structures (Figure 3), including the sinus fat, the loose connective tissue or any sinus-based endothelium lined space.

Conclusions
Thyroid-like follicular RCC, succinic dehydrogenase B deficiency–associated RCC, and ALK translocation RCC are rare epithelial carcinomas that are considered as emerging or provisional new entities. Further reports of these entities are required to better understand the nature and behavior of these highly unusual tumors. A wide variety of prognostic parameters have been investigated; however, much attention has centered upon the importance of features relating to both grade and stage. At the consensus conference a novel grading system (the ISUP grading system) was proposed, based on the evaluation of nucleoli. Renal sinus involvement, an important prognostic factor, can be diagnosed by tumoral involvement of any renal sinus structures, including the sinus fat, the loose connective tissue, or any sinus-based endothelium lined space.

References

Figure 3 Renal sinus invasion in a case of clear cell RCC characterized by tumor invading endothelial lined spaces within the renal sinus.


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