Epithelial renal cell tumors comprise a heterogeneous group of neoplasms with diverse biologic potential, different response to therapies, and variable clinical outcomes. In recent years the discovery of new molecular and cytogenetic markers has resulted in the recognition of new tumor entities or subtypes of renal epithelial tumors. Electron microscopy has contributed to the morphological characterization of these new important categories of neoplasms which have become specific clinicopathologic entities that must be recognized by surgical pathologists in order to manage patients appropriately. Surgical pathologists must intelligently select the ancillary diagnostic techniques that will provide the information needed to address the differential diagnosis under consideration in these tumors.

For many years renal cell carcinomas were considered a group of relatively “boring” tumors from the surgical pathologists’ point of view. Only clear and granular cell renal cell carcinomas were recognized and in a significant number of cases both cell types coexisted. This was a very simplistic approach to the categorization of what now we recognize as a rather complex group of neoplasms. More recent classifications have recognized several additional categories of renal carcinomas. Molecular biology and cytogenetics information is being actively incorporated into our understanding of renal neoplasia providing new insights into recognition of new types of neoplasms with specific clinical correlates. Despite all these advances, the clear / granular cell carcinoma category still encompasses the majority (approximately 70%) of the renal epithelial tumors. The role that ancillary diagnostic techniques play in the evaluation of renal neoplasms in the daily practice of pathology remains unclear to most practicing surgical pathologists. Recommendations addressing the proper utilization of adjunct diagnostic techniques are still not well defined. As a result, the temptation is to make the best possible diagnosis using light microscopy and immunohistochemistry. This is rather fast and delivers a diagnosis with “some apparent degree of sophistication”. Because the immunohistochemical profiles of the great majority of renal epithelial tumors are not specific, this approach opens the way for arriving to diagnoses that are not correct which may ultimately adversely affect patients’ management. This approach may also create fertile grounds for legal litigation.

The role of electron microscopy will be highlighted and it should be clearly understood that it still plays an important role in the diagnostic algorithm of these epithelial renal neoplasms in diagnostic laboratories where electron microscopy remains as a viable diagnostic technique.
Electron microscopy is also very helpful in situations where separating primary epithelial renal tumors from metastases is required. Sending difficult cases to regional electron microscopy laboratories should be seriously considered when this technique is not available locally. The use of more than one ancillary diagnostic technique to resolve a difficult case is encouraged.

**DIAGNOSIS AND CLASSIFICATION OF RENAL EPITHELIAL TUMORS- ROLE OF ELECTRON MICROSCOPY**

Renal cell carcinomas are encountered in approximately 10 individuals per 100 000 population. Approximately 15 000 new cases are diagnosed each year and 5 to 7000 deaths occur per year as a result of renal carcinomas. There has not been much improvement in the treatment or management of these patients in the last 10 years. However, our understanding of the biology, morphology, genetics and clinical behavior (prognosis) of these neoplasms has increased markedly.

Approximately 30% of patients with epithelial renal malignancies present with metastatic disease at the time of diagnosis. The clinical and pathological manifestations of renal cell carcinomas can be quite diverse and these tumors are often referred to as the “great mimickers”. This is an area where electron microscopy can be very helpful i.e. determining primary vs. metastatic renal epithelial tumors. There is not an immunocytochemical marker that indicates renal cell origin for a given epithelial neoplasm.

In the AFIP fascicle published in 1975 only clear and granular renal cell carcinomas were recognized. Although oncocytoma was first reported in 1942, the publication by Klein and Valensi in 1976 popularized the concept. The same year papillary renal cell carcinoma became a recognized entity. Fleming and Lewi published the first series of collecting duct carcinomas in 1977. Electron microscopy was an integral part of these seminal publications.

The classification of renal epithelial tumors in 1981 expanded the accepted categories to include conventional (clear cell), papillary, granular cell and sarcomatoid carcinomas but did not include oncocytomas or collecting duct carcinomas. The next attempt at classification of renal epithelial neoplasms was in 1994, and at that time oncocytomas were added. Thoenes and associates in 1985 described and characterized chromophobe renal cell carcinomas and began a revolutionary attempt to redefine the classification of renal epithelial neoplasms, based not only on morphology but also on cytogenetics and molecular information. Merely 14 years ago the first series of metanephric adenomas was published. Electron microscopy played a pivotal role in the recognition of each one of the epithelial tumor categories. In fact their specific definition virtually always carried with it an ultrastructural seal authenticating their separation from other types well recognized at the time a new entity was coined.

Thus the Heidelberg classification of 1997 amalgamated all the information available at the time to generate the latest classification of epithelial renal tumors. However, significant new information has been obtained since and a new classification scheme awaits us all in the near future.

Studies dealing with differentiation of epithelial renal tumors have arrived to the conclusions that conventional and papillary renal cell carcinomas differentiate along proximal tubular cell lines while oncocytomas and chromophobe carcinomas express distal tubular markers and appear to be closely associated in their genesis to intercalated cells of distal tubules. Finally, medullary and collecting duct carcinomas reflect collecting duct cell differentiating features. Immunohistochemical markers include CD10 for those neoplasms with proximal tubule differentiation while kidney specific cadherin labels tumors differentiating
along distal nephron lines. There is not a good marker for those neoplasms with collecting duct lineage. The combination of several immunohistochemical stains may be used to address the differential diagnosis of these epithelial renal tumors but significant overlap is often present among the reactions observed in different types of neoplasms. Combinations of CK7 and 20 staining have also been used to try to speciate renal epithelial tumor with similar overlap occurring among different groups. Numerous manuscripts have been written (some listed in the references) trying to use immunohistochemical markers to classify renal epithelial tumors and, invariably, the results reported are less than ideal for a diagnostic setting where specificity is crucial. Interestingly, electron microscopy has provided rather specific morphologic markers for neoplasms with proximal and distal nephron differentiation, and even medullary carcinomas, and ultrastructural evaluation is in most instances better than immunohistochemistry when the objective is typing these tumors.

The role that cytogenetics/molecular and gene profiling techniques play in the current assessment of renal epithelial tumors is still not completely defined. This topic will be discussed by one of the speakers in the session and placed in proper perspective.

**PRACTICAL APPLICATIONS**

The various subtypes of renal epithelial neoplasms exhibit rather specific ultrastructural features that permit their accurate diagnosis. The virtual replacement of the cytoplasm of neoplastic cells by mitochondria remains the criterion for a diagnosis of oncocytoma. The finding of coalescent cytoplasmic vesicles in the cytoplasm of an epithelial renal neoplasm is indicative of chromophobe differentiation. The diagnosis of the eosinophilic variant of chromophobe carcinoma can be a source of difficulty to surgical pathologists; this diagnosis can be made with precision ultrastructurally. The presence of certain specific cytoplasmic granules in the cytoplasm of neoplastic cells in a renal neoplasm can define a given renal tumor (i.e. juxtaglomerular cell tumor). These neoplasms can easily be confused with papillary carcinomas. The features and complexity of the microvillous surface in the neoplastic cells can provide indications of either proximal or distal nephron differentiation in a given renal epithelial neoplasm. Diagnosis of a sarcomatoid component in a renal cell carcinoma is generally much easier and accurate using electron microscopy than immunohistochemistry.

The area where electron microscopy findings still remain very broad is in the large category of conventional renal cell carcinomas (granular/clear cell carcinomas). Specific subtypes of these tumors (i.e. Xp11.2- TFEB translocation carcinomas) have been recognized and these share similar ultrastructural features, suggesting that this large category of tumors will be segregated into different clinically significant subtypes in the future. It is likely that in this process ultrastructural evaluation will play a significant role, as it has before in the speciation of other renal epithelial tumors.

As non-surgical therapies (i.e. tumor ablation techniques) and surgical nephron sparing techniques become more sophisticated, it becomes even crucial to properly speciate renal epithelial tumors with small amounts of tissue. Furthermore, the advent of new therapies targeting well defined molecular markers further emphasizes the need for a clinically relevant classification and accurate speciation of these renal epithelial tumors. These newer approaches to treatment are tailored to specific tumor entities. Prior to institution of therapy, confirmation of the diagnosis is needed and a small sample of the tumor is usually obtained, either by fine needle aspiration or surgical biopsy. The pattern of tumor growth that is so important for surgical pathologists to recognize the different varieties of renal epithelial neoplasms may not
be readily recognizable in these less than ideal samples. Furthermore, the material available for evaluation may not be sufficient for performing extended panels of immunohistochemical stains. These specimens become prime candidates for ultrastructural diagnosis. In most instances, a small sample is more than enough for thoroughly characterizing an epithelial renal tumor. The value of electron microscopy is enhanced by the fact that the great majority of renal epithelial neoplasms lack specific reliable immuno histochemical profiles to diagnose subtypes.

It is disappointing that a large percentage of renal tumors remain unclassified. In some series unclassifiable renal neoplasms may account for as many as 5-7% of all tumors. This fact by itself clearly indicates that there is plenty of work ahead to better understand and segregate these tumors into clinically meaningful groups. Incorporating molecular, cytogenetics and morphologic criteria into a unified data bank to be used for diagnostic purposes resulting in sound clinico-pathologic correlates will be the challenge of the future. Electron microscopy will play an important role in the characterization of these currently “unclassifiable” neoplasms.

REFERENCES:


