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Platinum Priority – Collaborative Review – Kidney Cancer

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Understanding Pathologic Variants of Renal Cell Carcinoma: Distilling Therapeutic Opportunities from Biologic Complexity

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Abstract

Context: Once believed to represent a uniform malignant phenotype, renal cell carcinoma (RCC) is now viewed as a diverse group of cancers that arise from the nephron.
Objective: To review the pathologic characteristics, clinical behavior, molecular biology, and systemic therapy options of recognized RCC histologic subtypes.
Evidence acquisition: A systematic review of English-language articles was performed using the Medline and Web of Science databases. Manuscripts were selected with consensus of the coauthors and evaluated using the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) criteria.
Evidence synthesis: The major findings of the evaluated manuscripts are discussed with an emphasis on the description of the pathologic features, clinical behavior, prognosis, and therapeutic strategies.
Conclusions: Classification schemes for kidney cancer have undergone dramatic changes over the past two decades. Improvements in these classification schemes are important, as pathologic variants differ not only in disease biology, but also in clinical behavior, prognosis, and response to systemic therapy. In the era of genomic medicine, further refinements in characterization of RCC subtypes will be critical to the progress of this burgeoning clinical space.
Patient summary: Kidney cancer can be subdivided into related but different cancers that arise from the kidney's tubules. In this article we review current classifications for kidney cancer, discuss their characteristics, and provide an overview of each subtype's clinical behavior and treatment. We stress that each subtype harbors unique biology and thus responds differently to available treatment strategies.

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1. Introduction

Renal cell carcinoma (RCC) has emerged as one of the most rapidly evolving areas of solid tumor oncology. The past two decades have seen a dramatic change in the clinical landscape that shapes both RCC understanding and treatment. Development of minimally invasive techniques for surgery in the retroperitoneum, emergence of focal therapy, reemergence of percutaneous renal biopsy, introduction of active surveillance strategies, renewed interest in immunotherapy, and the clinical development of targeted therapies for patients with advanced disease have all revolutionized kidney cancer care. Nevertheless, arguably, one of the most significant paradigm shifts in the clinical constructs that shape kidney cancer care is the change in the pathologic classification of RCC (Fig. 1). Efforts aimed at morphologically grouping specific cancers into distinct pathologic subtypes have not only allowed a common descriptive language, but are helping to crystallize the understanding of RCC's molecular origins and its clinical behavior. Indeed, these improved insights into the similarities and differences among RCC variants should offer clinical and therapeutic opportunities to improve patient care.

2. Evidence acquisition

A systematic review of the literature was performed to evaluate the role histologic RCC subtypes have on patient prognosis and response to systemic therapy. The review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) criteria [1]. Searches were carried out on the Medline, Embase, and Web of Science databases using the terms *renal cell carcinoma* in combination with *pathology* or *classification* and *prognosis* or *systemic therapy*. We limited our search to English-language articles published between January 1985 and February 2014. Cited references from selected articles and prior reviews helped identify significant manuscripts not previously included with this search, including important articles outside the time period of the initial search. After exclusion of duplicates and papers outside the scope of this review, we identified a list of 412 relevant manuscripts. The full text of each article was reviewed for level of evidence, sample size, study design, and relevance to the review. Based on these criteria, 112 manuscripts were selected with consensus of the authors and critically assessed. The review is based on evidence synthesis from the interactive peer-review process of the panel.

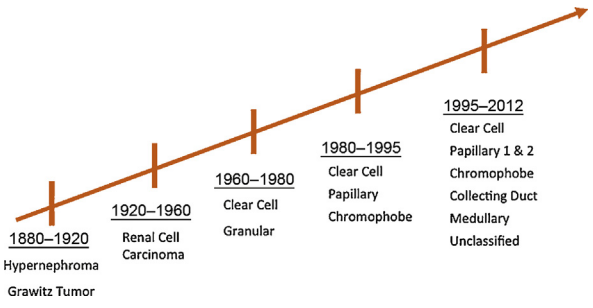

Fig. 1 – Evolution of kidney cancer classification schemes.

3. Evidence synthesis

3.1. History of renal cell carcinoma classification

In the late 1900s, significant disagreement existed in the pathology community over the origins of kidney tumors. Initially, Grawitz, largely due to the similarity in histologic architecture between normal adrenal tissue and clear cell RCC (ccRCC), proposed that these tumors originated from cells of the adrenal gland, a hypothesis that was later supported by Lubarsch [2]. Despite disagreement from other leading pathologists of the early 20th century, the terms hypernephroma or Grawitz tumor were used for many decades and still are occasionally seen in modern pathology reports [3].

Although ccRCC was recognized as the predominant histologic subtype, descriptions of tumors with papillary histologic configuration were also detailed in the early reports [2,4]. Papillary RCC was better characterized in the 1980s, when Kovacs et al. noted that these tumors contained >75% of papillary features and did not have characteristic 3p chromosomal loss on karyotype analysis [5]. Later, it was recognized there were two different classes of papillary tumors [6]. Chromophobe RCC, the third most common RCC subtype, was described in in the mid-1980s by Theones et al. [7]. Additional, rare, histologic subtypes were reported in the 1990s and included collecting duct, medullary RCC, translocation RCC, and mucinous tubular and spindle-cell RCC [8]. Consequently, in 2004, the World Health Organization updated the kidney tumor classification scheme [9]. In 2013, the International Society of Urological Pathology (ISUP) Vancouver Consensus Statement added five more epithelial tumor subtypes: tubulocystic RCC, acquired cystic disease-associated RCC, clear cell tubulopapillary RCC, the micropthalmia (MiT) family translocation RCCs, and hereditary leiomyomatosis–RCC syndrome-associated tumors (Table 1) [10]. Furthermore, this Consensus Statement mentioned three new entities that were given a *provisional* status: thyroid-like follicular RCC, succinate dehydrogenase B deficiency-associated RCC; and anaplastic lymphoma kinase translocation RCC (Table 1) [10].

3.2. General clinical implications stemming from histologic classification of kidney cancer

The importance of robust classification schemes for tumors arising from the kidney cannot be overstated. For instance, up to 20% of enhancing small renal masses are benign and may not need treatment [11]. Tumors such as papillary adenomas, pure oncocytomas, and angiomyolipomas (except a rare epitheloid variant) do not possess metastatic potential. Only if large can these tumors cause local symptoms such as pain or hemorrhage, as is the case for angiomyolipomas >4 cm. Because lipid-poor angiomyolipomas and oncocytomas cannot be easily distinguished