Hereditary Kidney Cancer Syndromes and Surgical Management of the Small Renal Mass

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KEYWORDS

• Hereditary syndrome • Nephron-sparing surgery • Renal cell carcinoma • Multifocal kidney cancer • Germline alterations

KEY POINTS

- Approximately 5% to 8% of all kidney cancers may have a strong hereditary component, and these patients may also present with extrarenal manifestations.
- Nephron-sparing surgery for the small renal mass (and large lesions when feasible) should be the standard of care to preserve long-term renal function and provide excellent oncologic control.
- The "3-cm rule" should be followed as a trigger for surgical intervention in patients with von Hippel-Lindau (VHL), Birt-Hogg-Dube (BHD), and hereditary papillary renal carcinoma (HPRC).
- Aggressive tumors arising in patients with hereditary leiomyomatosis renal cell carcinoma (HLRCC) or succinate dehydrogenase (SDH) should be immediately resected with a wide margin because of a high propensity for early dissemination.

INTRODUCTION

In 2015, there were an estimated 65,000 newly diagnosed cases of kidney cancer, which ultimately resulted in 14,000 deaths.[1] Most of these cases affect elderly patients with an estimated median age of 64 years of age.[2] Although most kidney cancers present spontaneously, it has been increasingly recognized that some patients develop cancer at a younger age because of a hereditary predisposition. Approximately 5% to 8% of all kidney cancers are attributed to a strong hereditary component. However, this approximation is likely a conservative estimate, because familial studies have estimated that up to 58% of patients with renal cell carcinoma (RCC) may have a significant, hereditary influence.[3]

Patients with a known or suspected hereditary syndrome can present a challenge to the clinician who may be less familiar with management strategies for the small renal mass in this population. Although most patients with RCC present with a sporadic, unilateral renal tumor, patients with a hereditary syndrome are often found with bilateral and/or multifocal tumors. Multifocality is subclassified into ipsilateral or contralateral disease, both of which add complexity to management strategy. Bilaterality and multifocality are often synonymous, and studies have shown multifocality to be present in up to 54% of patients with bilateral RCC.[4] In addition to the challenges of multifocality, the tumors in patients with hereditary syndromes may have unusual clinical characteristics/behavior and the

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presence of extrarenal manifestations (eg, gynecologic, ophthalmologic, gastrointestinal, dermatologic).[5] The complexities are further accentuated when considering the higher likelihood of de novo tumor development after treatment.[6] For clinicians who are tasked with managing this unique population, it is important to recognize many of the key clinical features of commonly encountered syndromes and use the appropriate management strategy for affected and at-risk individuals.

For many decades, several hereditary kidney cancer syndromes have been identified and associated with specific germline alterations that can lead to dysfunctional metabolism.[7] Classical hereditary syndromes, such as von Hippel-Lindau (VHL), hereditary papillary renal carcinoma (HPRC), tuberous sclerosis complex (TSC), hereditary leiomyomatosis RCC (HLRCC), succinate dehydrogenase (SDH) kidney cancer, and Cowden syndrome have been described. However, newly discovered hereditary syndromes, including those associated with alterations in *BAP1* (BRCA1 associated protein-1) or *MITF* (microphthalmia associated transcription factor), have only been recently characterized.

KNOWN HEREDITARY KIDNEY CANCER SYNDROMES

Von Hippel-Lindau

Hereditary forms of kidney cancer have been recognized for decades, such as VHL, which was first clinically described in 1926 in familial studies of retinal angiomas and cerebellar hemangioblastomas.[8] Many years later, researchers identified abnormalities in chromosome 3p in VHL-affected patients, later localized to 3p25.1.[9–11] The syndrome is inherited in an autosomal-dominant manner, and its gene product, VHL, performs a role as a tumor suppressor by constitutively regulating levels of hypoxia inducible factors (HIF).[12] As an oxygen sensor, VHL functions as an E3 ubiquitin ligase for HIFs, which promote cell proliferation, angiogenesis, and metastasis.[10,12] Patients with VHL have nearly 100% disease penetrance, including such manifestations as hemangioblastomas of the spine, brain, and retina; endolymphatic sac tumors of the auditory canal (**Fig. 1**); cystadenomas of the epididymis; cysts/cystadenomas and neuroendocrine tumors of the pancreas; bilateral, multifocal renal cysts; clear cell kidney cancer (**Fig. 2**); and pheochromocytoma.[5]

The median age of onset of RCC for patients with VHL is almost two decades younger than those with sporadic renal tumors. One unique aspect of renal tumors with this condition is the appearance of benign cysts that can harbor cancer, rendering the Bosniak scoring system irrelevant for this condition. Patients with VHL disease can have different disease manifestations with a subclassification based on the risk of pheochromocytomas and the particular class of mutation. Patients with type I VHL often contain large gene deletions but have a low risk of pheochromocytomas.[13] Patients with type II VHL most likely

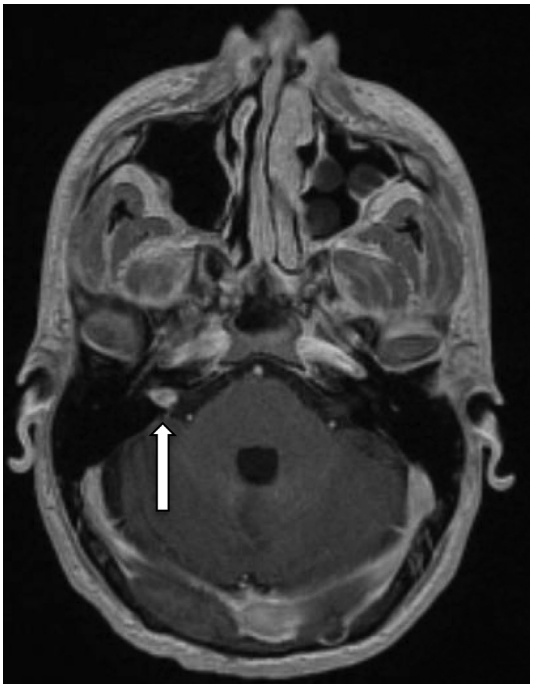

Fig. 1. Axial T1 contrast MRI showing a 9-mm endolymphatic sac tumor in the right internal auditory canal (*arrow*) in a patient with VHL disease.

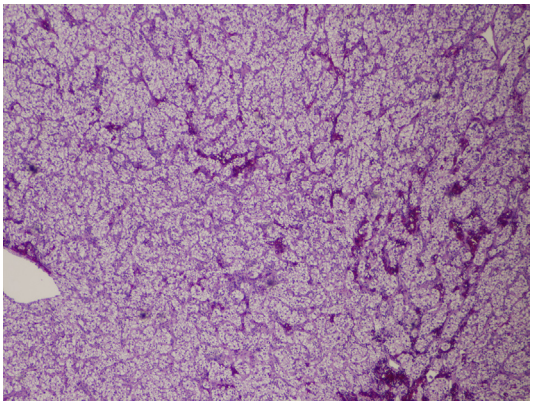

Fig. 2. Image of a patient with VHL that underwent resection of a 3-cm, T1a, Fuhrman grade 2 clear cell RCC tumor demonstrating cells with cytoplasmic clearing arranged in nests (hematoxylin-eosin, original magnification ×5).