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Nephron-sparing surgery for multifocal and hereditary renal tumors

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Abstract

Purpose of the Review—Despite the controversy surrounding the benefits of nephron sparing surgery (NSS), multiple absolute indications for NSS still exist including the classic indications of hereditary and bilateral kidney tumors.

Recent Findings—Multiple genetic mutations have been identified that lead to hereditary kidney cancer conditions. These are briefly reviewed because the surgical management of hereditary kidney tumors depends on the genetic and histologic subtypes involved. Clear understanding of these hereditary conditions is crucial for proper surgical management of these tumors.

Summary—Complex partial nephrectomy for multiple renal tumors, or multiplex partial nephrectomy, requires not only exceptional surgical skill but expertise of numerous non-surgical methodologies such as hands-on intraoperative ultrasonography and interpretation of multiple imaging modalities. In addition, multi-disciplinary management is crucial for optimal outcomes in patient care. This review evaluates the most advanced surgical techniques and peri-operative management required to successfully care for these challenging cases.

Keywords

renal cell carcinoma; partial nephrectomy; multifocal kidney tumors; hereditary renal tumors; Von Hippel Lindau; Birt-Hogg-Dubé; Hereditary Leiyomyomatosis and Renal Cell Carcinoma

Introduction

Partial nephrectomy is a well-established elective surgical technique for the management of small renal masses (SRMs) and is a mainstay in the care of patients with bilateral multifocal (BMF) renal tumors, solitary kidney or a hereditary renal cancer syndrome. Unique surgical challenges exist in this patient population and these require special care and expertise to successfully navigate. In order to best manage these patients, it is extremely helpful to establish a multi-disciplinary team that includes expert uroradiologists, nephrologists, medical geneticists, anesthesiologists and social workers.

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Defining Multifocal and Bilateral Disease

The vast majority of patients with renal tumors present with a unilateral mass and no family history of renal cell carcinoma (RCC). However, patients who either present with multiple masses or develop them metachronously are not uncommon with an incidence of 4.3–25% in patients who present initially with sporadic ipsilateral renal masses.(1) In patients who present with bilateral renal masses the reported incidence of multifocality may be greater than 50%.(2) Multifocal RCC indicates more than one tumor in a single kidney or in both kidneys. Bilateral kidney cancer specifies that at least one of the multifocal lesions affects each kidney and this may occur simultaneously which is termed synchronous or separately over time which is referred to as metachronous. While multifocality and bilaterality do not define the same clinical scenario, they do often occur together; bilateral renal masses are seen in up to 90% of patients found to meet the definition for multifocality. Moreover, greater than 50% of patients with bilateral tumors will have multifocal RCC.(2–4)

Multiple published series demonstrate that the incidence of synchronous bilateral renal tumors comprises about 2% of patients who are found to have renal masses.(2;4) In addition to this baseline rate of synchronous bilaterality, approximately 1–2% of patients who initially present with a solitary unilateral renal mass will go on to develop a contralateral metachronous tumor.(5–7) In addition, multifocality of renal tumors has been reported to be as high as 25% of patients with a significant percentage of those patients also demonstrating bilaterality.(4;8;9) To further complicate the issue, greater than 75% of multifocal lesions may be missed on preoperative cross-sectional imaging due to the frequent small size of the accompanying “satellite” lesions.(10) As a result, estimated incidence of multifocality ranges from 3–11% clinically whereas pathologically it is estimated to be as high as 25%. (8;11–15) Furthermore, all histologic subtypes of RCC have been shown to a clinically relevant incidence of multifocality although papillary RCC seems to have the highest incidence. (6;7;16;17)

Hereditary Renal Cancer Phenotypes

Hereditary RCC is thought to comprise up to 4% of all renal tumors. Although many hereditary conditions have been well described including von Hippel Lindau (VHL), Birt-Hogg-Dubé (BHD), Hereditary Leiomyomatosis and Renal Cell Cancer (HLRCC), Hereditary Papillary Renal Cell Carcinoma (HPRC); several are only very recently discovered(18–21) and still more have a genetic etiology that has yet to be identified and characterized. These conditions share the common manifestation of bilateral, multifocal RCC; but the tumor histology, prevalence of renal cysts and associated organ manifestations differ dramatically and it is important to understand these differences.

Von Hippel-Lindau

Von Hippel-Lindau (VHL) is caused by a mutation in the *VHL* tumor suppressor gene found on chromosome 3, locus 3p25.1 and is transmitted via an autosomal dominant inheritance pattern. The renal tumors found in VHL patients are clear cell RCC (ccRCC) and the renal phenotype includes solid tumors, complex cysts and simple cysts. Other clinical manifestations of VHL include retinal angiomas, adrenal pheochromocytomas, cerebellar

and spinal hemangioblastomas, pancreatic cysts and neuroendocrine tumors as well as cystadenomas of the epididymis and mesosalpinx. RCC is found in 25–60% of patients with a germline *VHL* gene mutation and tumors are generally bilateral and multifocal.(22) Prior to the development of rigorous screening guidelines, median survival for VHL patients was around 40 years old and metastatic RCC was the leading cause of death among patients with known germline mutation of the VHL gene.(23;24) In VHL, renal tumors are managed by active surveillance until the largest solid kidney tumor reaches 3 cm at which point surgical intervention is recommended to prevent metastasis.(25)

Birt-Hogg-Dubé

Birt-Hogg-Dubé (BHD) was initially described as a dermatologic disorder when the eponymous authors reported a series of 70 patients with fibrofolliculomas, trichodiscomas and acrochordons.(26) Patients affected with BHD have also found to be at risk for the development of bilateral, multifocal RCC (27) as well as lung cysts and spontaneous pneumothoraces.(28) In 2001, Schmidt et al reported that the gene mutation responsible for the clinical manifestations of BHD had been found on chromosome 17 and was later identified as the folliculin (*FLCN*) gene.(29;30) The incidence of this germline mutation is thought to be approximately 1:200,000(31) and the renal tumor histology tends to be more variable in BHD than is seen in VHL. The most common types of tumors associated with BHD are hybrid oncocytic (50%) and chromophobe RCC (35%) although ccRCC tumors have been seen as well.(32) BHD patients who are found to have renal masses are managed in a fashion similar to those affected with VHL, the renal tumors are followed with active surveillance until the largest tumor reaches 3 cm, at which time surgical intervention is recommended.(32)

Hereditary Papillary Renal Cell Carcinoma

Hereditary papillary renal carcinoma (HPRC) is a highly penetrant autosomal dominant hereditary cancer syndrome in which affected individuals are at risk for the development of bilateral, multifocal type 1 papillary kidney cancers.(33) Unlike many other hereditary kidney cancer conditions, HPRC appears to be associated only with renal tumors, no other physiologic manifestations have been reported to date. The gene coding for the receptor tyrosine kinase, *MET*, found on chromosome 7 at locus 7p31, has been shown to be mutated in the germline of patients affected with HPRC and trisomy 7 has been found in tumors from patients with this condition as well.(34;35) HPRC is truly a rare disease; to date, only about 20 families have been identified. Although an early onset form has been identified,(36) the mean age of onset tends to be later in HPRC than, for example, VHL. HPRC renal tumors are uniformly papillary RCC type 1.(37) Surveillance with cross-sectional imaging is recommended until the largest tumor reaches 3 cm, at which time surgical intervention is recommended.(38)

Cowden Syndrome (CS)

Germline mutations in PTEN have also been linked to an increased risk for renal cancer. (21;39) Phenotypically Cowden's patients are noted for the development of numerous hamartomas, dermatologic manifestations including acral keratosis and facial

trichilemmomas as well as macrocephaly. In addition, CS patients are at an increased risk for breast cancer, endometrial neoplasms and thyroid malignancy. Histologic variation in CS has been reported as well with papillary, chromophobe and ccRCC tumors found in affected patients.(21;39)

Hereditary Leiomyomatosis and Renal Cell Cancer

Hereditary leiomyomatosis and renal cell cancer (HLRCC) is an autosomal dominant hereditary cancer syndrome in which affected individuals are at risk for the development of cutaneous and uterine leiomyomas and kidney cancer.(40) Like BHD, HLRCC was originally identified as a dermatologic condition characterized by familial cutaneous lesions, in this case leiomyomas.(41) Subsequently, early onset uterine fibroids and renal tumors were associated with this condition and familial linkage analyses mapped the germline mutation to 1p42 which codes for the Krebs Cycle enzyme fumarate hydratase. However, unlike the other described hereditary conditions, HLRCC is characterized by extremely aggressive papillary type II RCC which has demonstrated the propensity to infiltrate renal parenchyma and metastasize at very small tumor size.(42;43) Consequently, the 3 cm rule does not apply to HLRCC. All at-risk individuals undergo annual visceral imaging to detect renal tumors and early surgical intervention is recommended as soon as any suspicion for a solid renal tumor arises.

Succinate Dehydrogenase B, C, & D Deficiency kidney cancer (SDH-RCC)

Another Krebs cycle enzyme gene mutation that has been linked to hereditary kidney cancer is the *succinate dehydrogenase* (SDH).(44) Like HLRCC, SDH-RCC lesions can be aggressive and may metastasize then the primary tumors are small,(20) and surgical intervention is recommended when renal lesions are detected. *SDH* germline mutations are also associated with pheochromocytoma and paraganglioma and screening for these manifestations is critical in the management of SDHRCC. Familial SDHB-deficient tumors demonstrate an oncocytic histology whereas SDHC and SDHD tumors have been reported as ccRCC.(19) Histologic variation notwithstanding, SDH-related kidney tumors may demonstrate an aggressive metastatic profile. Full phenotypic characterization is ongoing in this recently identified hereditary form of kidney cancer.

Other Hereditary Renal Cancer Conditions

Several other germline mutations have been associated with familial kidney cancer including Bap1 and MITF.(18;45;46) Interestingly, for both Bap1 and MITF germline mutations have been linked not only to RCC but also to melanoma.(47;48) Patients harboring hereditary Bap1 mutations are also at increased risk for mesothelioma.(49) For any patient who presents with bilateral and/or multifocal renal tumors, a family history is obtained in order to identify any previously unrecognized familial component. Even if no known germline cancer syndrome is identified, the presence of bilateral and/or multifocal tumors more than likely increases that patient’s risk for developing future renal tumors. In addition, recent data suggests that early onset RCC before the age of 46 is likely to arise from an unrecognized underlying genetic etiology.(50) Consequently, nephron sparing approaches should be

considered in patients who present at an early age or with bilateral and/or multifocal renal tumors.

Surgical Management of Multifocal and Hereditary Renal Tumors

The goal of surgical therapy in patients with bilateral, multifocal and hereditary renal tumors is not only to prevent metastases but also to maximize and prolong native renal function as long as possible. Secondary aims include minimizing the number of surgical procedures and morbidity whenever feasible. This is a departure from historical approaches which largely consisted of bilateral nephrectomy and hemodialysis.(51) The purpose of historical strategies was to facilitate renal transplantation and this was a common plan of care for patients with VHL for many years.(52–57) However, the combination of better understanding of the natural history of hereditary kidney cancer, increasing skill and application of nephron sparing surgical techniques, and the longstanding shortage of available kidneys for transplant ultimately resulted in a change of the surgical paradigm to primary, repeat and salvage partial nephrectomies. In addition, accumulating data regarding the cardiovascular morbidity and mortality associated with chronic renal insufficiency and hemodialysis further support this change in surgical management.(58;59) Finally, from a heath resource allocation perspective, cost-effectiveness modeling indicates that repeat renal surgery even with a high complication rate not only preserves renal function in the vast majority of patients but is favorable financially less than one year postoperatively compared to nephrectomy, hemodialysis and transplant.(60)

A management algorithm for patients with BMF and hereditary RCC has been developed over more than two decades of treating these patients at the National Cancer Institute. At initial presentation, if the patient has an unknown condition, genetic evaluation can be a guide future management. Without obvious evidence of a clinically identifiable hereditary condition, percutaneous renal biopsy of the largest tumors prior to surgical intervention may provide histological data that can direct subsequent genetic testing. Prior to surgery, nuclear Mag-3 renogram is obtained to establish a baseline prior to surgical insult to either renal unit and may help guide the order of surgical intervention if an unexpected disparity in split renal function is identified early. In the setting of synchronous, bilateral renal masses requiring bilateral surgical intervention, the approach is a matter of surgeon and institutional preference. At some institutions, simultaneous bilateral partial nephrectomies are a common strategy in this clinical scenario. At others, a staged approach is preferred over simultaneous partial nephrectomies due to the potential risk of postoperative renal dysfunction requiring hemodialysis as well as the added blood loss and prolonged operative time associated with simultaneous renal surgeries. When a staged surgical strategy is employed, often the kidney with the largest tumor is treated first since the likelihood of high grade malignancy and metastatic potential of large lesions is greater.(25;61;62) However, others perform nephron sparing surgery on the less complicated side; this approach mitigates the likelihood of subsequently performing a complex partial nephrectomy on a solitary kidney if radical nephrectomy is ultimately required for the kidney with the largest tumor.

Nephron Sparing Surgery: Enucleation vs Margins

In order to prolong the interval between ipsilateral renal surgeries, as mentioned previously, the “3cm rule” is applied to many of the known hereditary renal cancer conditions. When the largest solid renal tumor reaches 3cm, nephron sparing surgery with tumor enucleation is the treatment strategy of choice. Surgical margin status in small renal masses is of marginal importance in sporadic RCC and enucleation has been shown safe.(63–66) In patients with a known or suspected germline renal cancer predisposition, the risk of ipsilateral *de novo* tumor recurrence may be higher than for sporadic solitary tumors and, therefore, preservation of unaffected renal parenchyma becomes an even greater clinical imperative. Furthermore it is not technically feasible to achieve a wide margin for every tumor and leave a functional kidney in place in the setting of numerous renal tumors which is very common in this patient population.(67)

The 3 cm rule was developed in the VHL population and has been applied to patients with HPRC, BHD. In HLRCC and SDH-related renal tumor syndromes, active surveillance is not recommended. Surgical intervention and excision with wide margins is recommended as these tumors have a propensity to metastasize very early as well as infiltrate the surrounding renal parenchyma. In HLRCC and SDH-related renal tumors, intraoperative frozen sections are utilized to ensure negative margins. Due to the exceptionally aggressive nature of these tumors, renal biopsy is not recommended in this patient population and tumor violation is avoided at all costs.

The management of hereditary and BMF renal tumors is a delicate challenge for urologists that requires not only excellent diagnostic and surgical skills but also finding the right balance between oncologic control and renal functional preservation. The role of the urologic oncologist is vital to the appropriate care of these patients; despite the dramatic advances in the treatment of metastatic RCC, cures remain largely elusive so the best strategy is to prevent progression to the metastatic disease state if at all possible. Prompt and appropriate surgical intervention is still the optimal treatment approach for bilateral multifocal and hereditary renal cancer patients.

Nephron Sparing Surgery: Renal Hilar Dissection and Ischemia

Our approach is to rarely employ ischemia of any sort during nephron sparing surgery for BMF and hereditary renal tumors. The vast majority of tumors are removed without hilar occlusion because not only is bleeding substantially reduced with enucleation but also because multiple tumors would require excessively long ischemic periods to remove them completely which is clinically impractical even with cold ischemia. In addition, understanding the increased likelihood of future ipsilateral renal surgeries, we aim to minimize the accumulation of unnecessary insults to the kidney over a lifetime. A single episode of ischemia to a given kidney may confer minimal long term damage almost irrespective of duration.(68–72) However, while the long term combined impact of repeat renal surgeries with repetitive renal hilar occlusion is unknown, we feel that it is likely to result in impaired renal function and is best avoided if possible. Repeat renal hilar clamping of the same kidney is undesirable and is reserved for exceptional situations such as

unexpected and significant hemorrhage. As such, the vast majority of complex partial nephrectomies performed at our institution are completed without hilar occlusion for both open and minimally invasive approaches. During a no-clamp partial nephrectomy, an experience surgical assistant is invaluable to provide adequate suction and retraction to enable enucleation of the tumor rapidly. Arterial bleeding and large caliber venous bleeding is oversewn with 3-0 vicryl sutures once the tumor is removed. Smaller generalized venous oozing is controlled with hemostatic agents such as thrombin-soaked gelatin sponges or oxidized cellulose bolsters. Non-specific suturing along the base of the renal defect may compromise important segmental vascular supply to surrounding parenchyma and is avoided.

Since renovascular occlusion is rare and future reoperation(63) is not uncommon, dissection around the renal artery and vein is kept to a minimum. En bloc hilar dissection allows for an unclamped Cosgrove vascular pedicle clamp to be placed around the renal hilum. Medial mobilization is performed so that the artery pulsation is palpable and the jaws of the Cosgrove clamp can be placed completely across the hilar vessels. The Cosgrove is placed across the hilum but not closed. While this provides the option of rapid hilar control in case uncontrolled bleeding in encountered, in practice it is very rarely deployed. En bloc dissection also minimizes the development of peri-hilar adhesions and scarring which makes future renal mobilization less perilous by reducing the likelihood of renal hilar vascular complications.(73;74)

Nephron Sparing Surgery: Technical Considerations

Before embarking on surgical treatment of BMF renal tumors, it is important to recognize that repeat ipsilateral surgery is likely in the future. While complete removal of Gerota's fascia from the renal capsule is imperative for partial nephrectomy in a patient with hereditary or BMF renal masses, preservation of Gerota's fascia, if possible, is equally important because reapproximating Gerota's fascia after completion of the complex partial prevents adhesion of the kidney directly to other surrounding viscera. In addition, restoring Gerota's fascia provides an additional tissue layer between the multiple renorraphy defects and surrounding structures thus reducing the risk of fistula formation. Therefore, Gerota's fascia is incised in a clamshell fashion and the sub-fascial perirenal fat is mobilized off the renal capsule along the natural crevices within the perirenal fat which minimizes bleeding. This careful incision of Gerota's fascia and mobilization of the peri-renal fat facilitates easier reconstruction of Gerota's fascia when the partial nephrectomy is complete.

Minimally invasive approaches to complex partial nephrectomies may reduce peri-renal and intraperitoneal adhesions in some patients, making subsequent renal surgeries somewhat less challenging and morbid. Both laparoscopic and robotic primary and repeat partial nephrectomies for BMF and hereditary renal tumors have been reported.(75–77) However, it is extremely important to understand that minimally invasive techniques should not be employed at the expense of an oncologically sound nephron-sparing procedure.

For open surgical approaches, our preferred incision is the flank incision, as we attempt to remain extraperitoneal throughout the case if possible. Preserving the integrity of the

peritoneum is helpful in the post-operative period since drain output volumes are not augmented by peritoneal fluid. Furthermore, postoperative urine leaks or bleeding are contained if the surgery is completed extraperitoneally. As noted previously, attempting to preserve Gerota's fascia is important to prevent direct adhesion of the renal capsule and/or renal defects to the surrounding viscera.

Intraoperative ultrasound is utilized to enable a thorough partial nephrectomy in patients with BMF and hereditary renal tumor conditions. Frequently the ultrasound probe, when placed directly on the renal surface, will identify many more tumors than are seen on standard cross-sectional imaging modalities. Particularly for VHL and other BMF conditions that are associated with renal cysts, intraoperative ultrasound is critical for detecting complexity within cysts that predict occult malignancy. In patients with cystic-predominant renal phenotypes, ultrasound is the primary tool used to determine which lesions are resected and which are simple or hemorrhagic cysts that have a low likelihood of becoming tumors. Use of intraoperative ultrasound is invaluable as in many of these kidneys it is not feasible to remove every simple cyst without excessive damage to the remaining renal parenchyma. In our experience with HLRCC, intraoperative ultrasound has been critical for identifying small complex cysts and sub-centimetric solid tumors that are not seen on preoperative high resolution imaging. A meticulous ultrasound survey of the entire kidney both the anterior and posterior surface is invaluable for the successful conduct of these extremely challenging cases.

Long Term Outcomes

The renal functional and oncologic outcomes for patients managed at the NCI using the techniques described above have been published over the past decade. For patients with BMF or hereditary renal tumors undergoing repeat or salvage renal surgery, the percentage of patients requiring permanent hemodialysis was 3% or less.(73;74) More encouraging, no patients who required 20 or more tumors removed during a single surgery required dialysis during followup.(67) In 2011, Singer *et al* reported a cohort of 128 patients with BMF renal tumors who had undergone a median of 3 operations each and all had bilateral renal surgery with a minimum follow up of 10 years.(78) Nearly 70% needed repeat renal surgery at a median of 6.2 years. Yet, overall survival and metastasis-free survival was 88% and RCC-specific survival was 97% at a median follow up of 16 years. The median estimated glomerular filtration rate for the entire group was 57mL/min/1.73m2 at most recent follow up. Less than 5% of the patients progressed to dialysis during follow up indicating that this approach provides excellent oncologic and renal functional outcomes for patients with BMF and hereditary renal cancer conditions.

Conclusion

The clinical incidence of bilateral and multifocal renal masses is not uncommon. Surgical management of BMF and hereditary kidney cancer is both technically and clinically challenging and the complexity of management strategies is increasing as new genetic alterations are being identified and characterized. Knowledge of hereditary renal cancer syndromes is provides the clinician with the ability to quickly and accurately distinguish

among them and apply appropriate surgical techniques to provide optimal care. Careful clinical decision making and surgical techniques are required to manage HLRCC and SDH-related tumors. When appropriately applied, these strategies can be associated with a long life expectancy with long term maintenance of renal function for most patients with bilateral, multifocal and hereditary RCC.

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ABBREVIATIONS

NSS	nephron sparing surgery
VHL	Von Hippel Lindau
BHD	Birt-Hogg-Dubé
HPRC	Hereditary Papillary Renal Cell Carcinoma
HLRCC	Hereditary Leiyomyomatosis and Renal Cell Carcinoma
BMF	Bilateral MultiFocal
SRM	small renal mass
RCC	renal cell carcinoma

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KEY BULLET POINTS

- Hereditary RCC comprises 4% of all renal tumors whereas multifocal renal tumors are found in 3–11% of patients clinically and up to 25% pathologically.
- The “3cm rule” developed for managing VHL patients can also safely be applied to patients with BHD, HPRC.
- The “3cm rule” is NOT appropriate for patients with suspected renal masses and known germline HLRCC or SDH mutations.
- Enucleation of tumors is appropriate for VHL, BHD and HPRC; wide margins are required for HLRCC and SDH-related kidney tumors.
- Long term oncologic control and renal functional preservation is excellent at more than 10 years follow up using this approach.