

Considerations in the Management of Synchronous Bilateral Multifocal Renal Cell Carcinoma

CASE PRESENTATION

A 66-year-old man presented to the urology clinic for evaluation of recently diagnosed bilateral multifocal renal masses. A renal ultrasound performed for flank pain identified a 5 cm partially cystic mass in the upper pole and a 2.5 cm partially cystic mass in the midpole on the right, as well as a 3.4 cm mass in the parapelvic interpolar region and a 2.5 cm partially cystic mass in the lower pole on the left. There were additional cystic lesions in both kidneys. The flank pain, which was attributed to musculoskeletal strain from golfing, had resolved.

The patient's medical history was significant for hypertension, hyperlipidemia, and nonobstructive coronary artery disease with preserved ejection fraction. There was no family history of kidney cancer or other solid organ malignancy.

Cross-sectional imaging was ordered, which confirmed the findings of the renal ultrasound and showed no evidence of lymphadenopathy or metastatic disease (Figures 1 and 2).

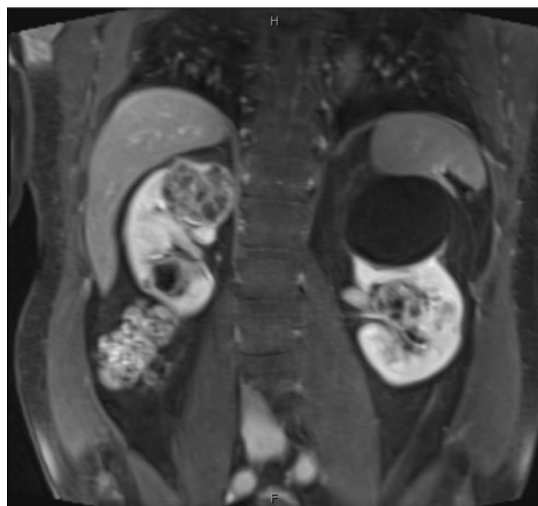


Figure 1

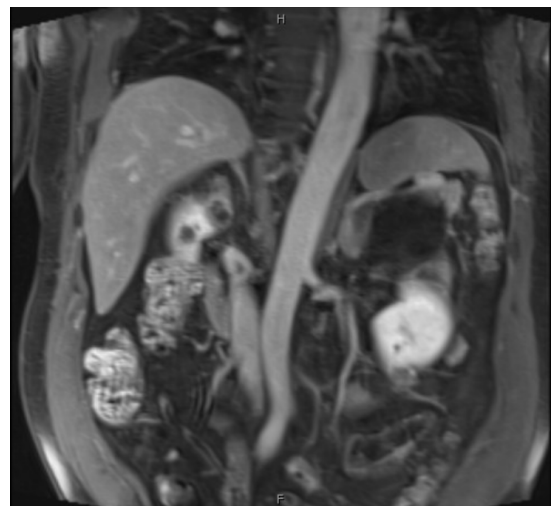


Figure 2

CASE OF THE MONTH

MANAGEMENT

The patient was counseled regarding management options and he elected to proceed with staged nephron-sparing surgeries. He was referred to nephrology to establish care. Genetic testing revealed no mutation for a known hereditary syndrome.

The patient was taken to the operating room for partial nephrectomies of the right side. Intraoperative ultrasound did not demonstrate any solid components of the additional cysts in the right kidney. Both renal masses were clear cell papillary renal cell carcinoma (RCC) limited to the kidney, with negative margins.

The patient recovered without complications, and at 3 months of follow-up his eGFR was 57 mL/min/1.73 m². Repeat imaging showed slight interval growth of the 2 left renal masses but no sign of extra-renal disease. The patient then was taken back for partial nephrectomies on the left, again with intraoperative ultrasound showing no solid components of the additional cystic lesions. Final pathology of both masses revealed clear cell papillary RCC limited to the kidney, with negative margins.

The patient again recovered without complications. At 6 months of follow-up, there was no sign of recurrence and the remaining bilateral renal cysts were stable.

COMMENT

Bilateral synchronous RCC occurs in less than 5% of all cases of RCC.¹ These patients remain a challenge for urologists, with complex diagnostic and management dilemmas. A multidisciplinary approach with careful preoperative planning and conscientious intraoperative techniques can achieve good outcomes.

Multiple synchronous tumors should raise suspicion for an underlying genetic predisposition. Although most patients with bilateral RCC do not have an identifiable hereditary syndrome, these patients are more likely to have familial RCC than are those with a solitary tumor.^{1,2} Evaluation and possible testing for hereditary syndromes are thus important, as management depends on whether and which underlying syndrome exists. For example, enucleation of tumors once they reach 3 cm is safely employed for Von Hippel-Lindau syndrome, whereas hereditary leiomyomatosis and RCC requires early intervention with wide margins even for small tumors.

Preoperative planning may include additional diagnostic studies. Renal mass biopsy is increasingly used. Although the malignant concordance for sporadic bilateral renal masses that occur synchronously is 84% to 95%, the benign concordance is much lower.³ Therefore, a benign pathologic biopsy does not reliably rule out malignancy in the remaining tumor(s), so multiple biopsies may be indicated. Renography to assess split function, such as a MAG3 scan, may also add insight for surgical approach if there is significant differential in function.

For bilateral disease, radical nephrectomy would necessarily render a patient anephric, and this circumstance was one of the earliest accepted indications for partial nephrectomy.⁴ Techniques for nephron-sparing surgery have been refined since the first description in 1890.⁵ Use of nephron-sparing surgery for bilateral tumors shows good prognosis,⁶ and oncologic outcomes are not compromised with use of this approach,⁷ even in the instance of larger multifocal tumors.⁸ However, there are additional important surgical considerations when using partial nephrectomy for bilateral and/or multifocal disease.

CASE OF THE MONTH

A staged or a simultaneous approach may be undertaken, depending on surgeon and institutional practice and patient factors, with many surgeons favoring a staged approach because of concerns about complications, including need for renal replacement therapy after concurrent bilateral renal surgery. Because of the unique surgical challenge of these cases, a uniform single approach may not be appropriate for all patients. For staged surgery, the side with the largest tumor may be approached first, as size is related to oncologic risk. However, approaching the more favorable side first mitigates the risk of performing a nephron-sparing surgery on a solitary kidney, particularly if one side is highly complex.

Unique technical considerations exist because of the not inconsiderable prospect of future operations and greater risk to renal function. Transperitoneal or retroperitoneal open or minimally invasive approaches may be used. Gerota's fascia should be opened in only one location, if possible, to prevent devascularization, and it should be reapproximated over the kidney as able, to facilitate re-exploration and limit adhesion of intraperitoneal structures to the kidney. En bloc hilar control and minimizing hilar dissection may facilitate future vascular control. Examination of the entire kidney is imperative because of the higher risk of multifocality with bilateral disease.⁹⁻¹¹ Meticulous intraoperative ultrasound is critical to identify any additional lesions; this is especially important in patients with cystic phenotypes, where assessment for complexity is mandatory because removing every cyst is not achievable without excessive renal damage.¹²

Maximizing oncologic outcomes can directly challenge renal functional outcomes. However, protecting renal function has added importance when there is risk of significant nephron mass loss and an increased additive lifetime risk of injury. Maintenance of sufficient nephron mass is critical given the poor overall survival of patients requiring dialysis; beyond avoiding radical nephrectomy, techniques to preserve renal function include enucleation, using hypothermia, and minimizing ischemia. The threshold for ischemia is unclear because of the contributions of nonmodifiable factors, although it is generally accepted that longer ischemia times worsen renal functional outcomes,¹³ with authors suggesting limiting warm ischemia to 20 minutes and cold to 35.¹⁴ Methods for minimizing ischemic damage include selective hilar clamping, early unclamping of the hilum, and off-clamp surgery, techniques that may be combined. For example, small or peripheral cortical lesions can be resected off-clamp first, prior to clamping for larger or more complex central tumors, to minimize overall ischemic time. However, off-clamp resection should be weighed against the need to identify margins. With judicious use of partial nephrectomy and conscientious intraoperative techniques, renal replacement therapy usually can be avoided. Risk of progressive renal decline is higher in patients with pre-existing renal dysfunction, and a greater risk of progressive renal decline exists if the new postoperative baseline eGFR is less than 45 mL/min/1.73 m², which may be related to hyperfiltration injury.¹⁵ Nomograms may aid in predicting preoperatively a patient's risk of chronic kidney disease.¹⁶ The rate of progression to end-stage renal disease (ESRD) requiring dialysis in patients with multifocal RCC is reported to be 5% to 10%.^{10,17} Although patients with surgically induced ESRD have better survival than those with medically induced ESRD, these patients still fare poorly, with only 22% surviving 5 years and 3% surviving 10 years after initiation of dialysis, and with only a 4% incidence of renal transplantation.¹⁸ Multidisciplinary care with early nephrology referral is beneficial.¹⁹

CASE OF THE MONTH

Fortunately, good oncologic outcomes can still be achieved in the setting of bilateral RCC, despite the technical challenges. In a multicenter evaluation, patients presenting with synchronous bilateral RCC had a similar prognosis to those presenting with unilateral RCC; with a median follow-up of about 4 years, rates of cancer-specific survival (CSS) for bilateral and unilateral RCC were similar.¹ Although statistical comparison is not always possible because of the low event rate of metastasis or death from RCC, similar overall survival at 10 years has also been reported for small bilateral tumors.¹¹ Even when analysis is limited to patients with sporadic synchronous bilateral RCC (by excluding familial RCC), there is no difference in CSS for clear cell or papillary histology, with no differences in rates of death or distant metastases.¹⁰

An important additional consideration in the case presented here is the multifocality of renal tumors. When hereditary syndromes are included, multifocal RCC has been reported in up to 25% of cases, but a weighted average from a review of the English language literature found multifocal RCC in only 6.8% of cases.⁷ Although unilateral RCC may be multifocal, in patients with synchronous bilateral disease, the rate of multifocality has been reported to be as high as 54% (vs. 16% for unilateral disease).¹ Even when analysis is limited to sporadic cases, about 30% of patients with synchronous bilateral RCC had multifocal disease at presentation.¹⁰ Although multifocality affects treatment approach, several institutional and multi-institutional reviews have found that multifocality, whether unilateral or bilateral, does not affect survival.^{1,20,21}

CONCLUSION

Sporadic bilateral multifocal RCC is both clinically and technically challenging to manage. Despite the complex diagnostic and challenging surgical considerations, good functional and oncologic outcomes can be achieved.

CASE OF THE MONTH

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