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# Possible treatments for synchronous bilateral small renal masses

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## Abstract

Currently, there is no established consensus on the best treatment approach for patients with bilateral synchronous renal masses (BSRM). The timing and method of managing these cases remain subjects of debate. This review aims to summarize the available literature and explore the ongoing controversies surrounding this topic. Three studies investigated non-surgical treatments within BSRM. Specifically, one study focused on active surveillance (AS) and showed no statistical differences in terms of progression and development of metastatic disease relative to their unilateral counterpart. Two studies investigated ablative techniques showing promising results. Eight papers have been published regarding robot assisted partial nephrectomy (RAPN) for BSRM. All these papers highlighted the safety, feasibility, and efficacy of bilateral RAPN for BSRM. Literature regarding treatments other than surgery such as AS and ablative therapies (ATs) for BSRM is scarce, but promising. Progression, rate of metastases and survival of BSRM are similar to unilateral disease, and AS is a safe option in these cases. Few studies focused on RAPN related outcomes for BSRMs, but all confirmed the safety, feasibility, and efficacy of this procedure. Finally, one step RAPN resulted as feasible as the two staged procedures, especially when selective clamping techniques can be chosen.

**Keywords:** Ablation, active surveillance, bilateral kidney cancer, nephrectomy

## INTRODUCTION

Bilateral kidney cancers account for approximately 3% of renal tumors[1]. Although bilateral renal tumors remain common in patients with genetic renal cell carcinoma (RCC) syndromes [von Hippel-Lindau (VHL) syndrome, tuberous sclerosis, Birt-Hogg-Dubé syndrome] in which a precise DNA related defect can be identified, the majority of bilateral kidney cancer patients showed sporadic, nonfamilial bilateral renal tumors[2,3].

Many factors have contributed to the increase in the prevalence of bilateral renal tumors including the overall growth of kidney cancer incidence rates, early detection due to cross-sectional imaging, increased life expectancy and longer follow-up periods of cancer survivors[4-7].

However, the management and decision-making in these cases are controversial, and both the European Association of Urology (EAU)[8] and the American Urological Association (AUA)[9] Guidelines suggest that patients presenting with bilateral renal masses should undergo genetic counseling and a nephron-sparing approach; however, any standardized disease management is still recommended.

Furthermore, an increasing rate of these patients harboring small renal masses (SRM) at diagnosis has been observed. This reads that along with nephron sparing surgery (NSS) also active surveillance (AS) and ablative therapies (ATs) should be considered.

Regarding AS, sporadic bilateral synchronous renal masses (BSRM) showed no clinically meaningful differences from unilateral SRMs in terms of progression and development of metastatic disease[10-12].

Similarly, ablative techniques provide an alternative to surgery and minimize treatment-related morbidity, particularly for patients with significant comorbidity and pre-existing renal conditions such as chronic kidney disease and/or multiple RCC or genetic RCC related syndrome[13-15]. In this review article, we provide an overview of each possible treatment option for BSRMs.

## PREOPERATIVE MANAGEMENT

The National Cancer Institute proposed an algorithm[16] for the workup and management of patients with bilateral, multifocal, and known or suspected hereditary syndromes.

Pre-treatment characterization is crucial as the rationale of staged surgery focuses on obtaining an accurate surgical anatomy assessment, a definitive histology of one side mass and on the concordance probability between BSRMs. Differently, in order to find the gap of indication for simultaneous surgery, a patient selection must be performed through pre-treatment mass characterization by advanced novel imaging methods [i.e., positron emission tomography (PET)/computed tomography (CT), multiparametric magnetic resonance imaging (mpMRI)], and histogenetic analysis (i.e., biomarkers, biopsy) in order to differentiate as precisely as possible benign from malignant BSRMs. This point of focus will probably be unraveled with the advances and implementation of novel imaging methods and genetic analysis.

Novel imaging methods have been shown to improve the pre-treatment characterization of renal masses, such as mpMRI, molecular imaging, radiomics and artificial intelligence to enhance the interpretation of imaging studies.

For example, the use of mpMRI or 99mTc-sestamibi (SestaMIBI, MIBI) single photon emission computed tomography (SPECT)/CT has shown promising initial results to diagnose clear cell RCC (ccRCC) via a clear cell likelihood score (ccLS) in SRMs[17,18] and for the differentiation between benign and low-grade RCC[19]. This has many clinical implications in the decision-making process as reported in the collaborative review by Roussel *et al.*[20].

Preoperative assessment should also include renal function assessment with renal scintigraphy to better delineate split renal function at baseline which will be helpful for surgical planning, type of access and treatment choice[21,22].

Advancements in imaging technologies, such as mpMRI and 99mTc-sestamibi SPECT/CT, are significantly enhancing the preoperative characterization of renal masses. These technologies aid in distinguishing benign lesions from malignant ones, which can inform the decision-making process regarding whether to pursue AS or surgical intervention. Furthermore, as our understanding of the genetics of RCC progresses - especially concerning hereditary syndromes - genetic testing is becoming an essential aspect of patient management. This shift toward personalized care allows for the development of treatment plans tailored to individual genetic and molecular profiles, which is expected to influence future clinical guidelines. However, despite these advancements, there remains a notable gap in randomized trials that directly compare outcomes between simultaneous and staged surgeries and between surgical and ablative treatments. Long-term studies are still necessary to assess oncological outcomes and the preservation of renal function, which will help refine current treatment protocols.

## TREATMENT STRATEGIES

The EAU guidelines[8] emphasize a nephron-sparing approach in the treatment of BSRMs, especially for patients with predisposing genetic conditions, such as VHL syndrome, Birt-Hogg-Dubé syndrome, or tuberous sclerosis complex. For patients without hereditary conditions, the focus remains on maximizing the preservation of renal function while providing oncological control. Similarly, AUA guidelines[9] support a nephron-sparing strategy and genetic testing for patients with BSRMs.

Preoperative treatment planning is necessary to achieve two important targets: complete tumor resection and the maintenance of renal function adequate to keep the patient off hemodialysis.

Surgeons can choose between a simultaneous or a two-step approach.

Most surgeons prefer a two-different-step approach. The main reason is the contralateral kidney compensation to face a period of transitory unilateral renal insufficiency.

On the contrary, others prefer simultaneous bilateral intervention which could reduce mental and physical stress, require single anesthesia, less medication, less blood loss, shorter hospital stay and convalescence, along with considerable cost savings.

Moreover, the increase of SRM detection as the first presentation of kidney cancer has led to a treatment change. Alongside NSS, AS and AT have been emerging as alternatives in SRM treatment. Scientific data prove that SRMs have little potential for metastasis and disease-related mortality due to their benign or low-grade histology[23-25].

## NON-SURGICAL TREATMENT

In this context, AS and AT are also considered valid options in the treatment of BSRMs[10,12].

### AS

AS is increasingly recognized as a safe option for patients with SRMs, including those with bilateral synchronous renal tumors. Both the EAU and AUA guidelines support AS in patients where surgery is high-risk or unnecessary due to slow tumor growth.

AS should be considered a valid option in both hereditary and sporadic syndromes.

The strategy of combining AS with minimally invasive interventions, especially in hereditary syndromes[26], allows for the preservation of renal function and provides metastasis-free survival based on the assumption that renal tumors less than 3 cm in size show low rate of metastases and progression.

Regarding non-hereditary bilateral synchronous, AS combined with delayed interventions is a valid option as demonstrated by a TUCAN database study[10,12].

They observed 33 patients harboring synchronous SRMs and treated with AS with a mean follow-up of more than six years, comparing their oncological outcomes with their unilateral counterparts.

Specifically, the intervention and growth rate and the development of metastases within BSRM patients were similar, as for metastasis-free, disease-specific or overall survival to those with unilateral SRM. These findings agree with current European and American guidelines[8,9], showing that BSRMs under AS tend to have outcomes similar to unilateral SRMs, with low rates of metastasis and cancer-specific mortality[12,27]. Close monitoring with regular imaging is crucial to detect progression that might necessitate delayed intervention.

#### Ablative techniques

For patients unsuitable for surgery or those with genetic syndromes that predispose them to multiple bilateral renal tumors, ATs [e.g., radiofrequency ablation (RFA) and cryoablation (CA)] provide a nephron-sparing alternative. Both the EAU and AUA guidelines support these approaches in appropriate cases. RFA and CA are minimally invasive and can be performed percutaneously or laparoscopically. Studies demonstrate high local control rates (e.g., 93.1% for RFA), with minimal impact on renal function. CA, in particular, has been associated with lower rates of renal function decline compared to partial nephrectomy. However, both methods may require repeat treatments for tumor recurrence or incomplete ablation.

Ablative techniques are fit for patients with kidney cancer genetic syndromes because of the increased likelihood of multiple bilateral renal tumors (VHL syndrome, tuberous sclerosis, and Birt-Hogg-Dubé syndrome). However, also in the treatment of sporadic BSRM, these techniques are a valid option, as reported in two studies[28,29]. According to European and American guidelines, RFA and CA are associated with lower perioperative morbidity compared to surgery and are suitable for patients with small, localized tumors[30,31] or those with high surgical risk[32-34].

Specifically, RFA and CA are the main used ablative techniques for the treatment of BSRM[28,29], both of which could be performed percutaneously, open or via a laparoscopic approach.

Both approaches appear to have acceptable rates of perioperative complications and effects on renal function[28,29].

Concerning RFA, Zhang *et al.* focused on nine patients treated with bilateral RFA through different approaches[29]. During the mean 33 months of follow-up, local tumor control rate was 93.1%, and both the cancer-specific and the overall survival rate were 100%.

Regarding functional outcomes, no statistically meaningful decline in renal function was observed between postoperative and preoperative levels (93.7 ± 13.0 mL/min/1.73 $m^2$ *vs.* 96.9 ± 13.3 mL/min/1.73 $m^2$, respectively; $P > 0.05$).

Regarding CA, Mason *et al.* compared percutaneous CA ($n$ = 13), under either CT or ultrasound (US) guidance, with partial nephrectomy ($n$ = 75 underwent open approach and $n$ = 1 underwent laparoscopic approach) in terms of functional and perioperative outcomes[28].

They found that the median change in estimated glomerular filtration rate (eGFR) from preoperative to the time of discharge was -32% [interquartile range (IQR) -46, -15] for partial nephrectomy (PN) patients and -17% (IQR -33, -3) for percutaneous cryoablation (PCA) patients. After three months, median renal function improved, with changes of -9% (IQR -19, 0) and -8% (IQR -11, 15), respectively, compared with baseline. Thirty-day postoperative complications occurred in 16 (21.6%) PN patients and four (30.7%) PCA patients. This suggests that percutaneous CA has acceptable rates of perioperative complications and effects on renal function.

## SURGICAL TREATMENT

In contrast to hereditary disease, where tumor growth is fast, and SRM is usually managed with AS and multiple minimally invasive ablative procedures, bilateral sporadic SRM can be managed by a single minimally (both laparoscopic or robot assisted) NSS with acceptable morbidity[35-40].

The robotic surgery for large renal mass (ROSULA) collaborative group highlighted the importance of performing NSS in these patients compared to radical surgical treatment[41].

Patients undergoing PN exhibited significantly better preservation of eGFR[41] compared to those undergoing radical nephrectomy (RN). The study concluded that, despite the complexity of the tumor, PN should be prioritized when feasible due to its renal function preservation benefits, especially in patients at risk for long-term renal insufficiency. For bilateral masses, this is particularly relevant, as bilateral RN would almost certainly lead to dialysis dependency, while PN allows for partial preservation of kidney function in both kidneys.

Focusing on the oncological outcomes and perioperative complications associated with PN[42] *vs.* RN in treating complex renal masses, both PN and RN provided excellent oncological control, with no significant difference in cancer-specific survival or recurrence rates between the two approaches, even in cases of large or complex tumors. However, the complication rates were slightly higher in PN due to the technical complexity of preserving renal tissue, particularly for hilar or endophytic tumors. Despite this, the overall morbidity associated with PN was acceptable. These findings support current guidelines[8,9].

that prioritize PN over RN in managing bilateral renal masses to reduce the likelihood of dialysis and maintain long-term renal health, without compromising oncological safety.

Minimally invasive surgery is the method of choice for treating bilateral sporadic SRM, as it has a comparable prognosis to that for unilateral sporadic SRM[10-12]. However, surgical management of bilateral synchronous SRM is a surgical challenge, because of two different goals: the minimal postoperative renal function loss and the complete eradication of the renal tumor. For this reason, if technically feasible, the preservation of both kidneys through a bilateral NSS would be preferred.

Specifically, robotic approach, thanks to the wide maneuverability and three-dimensional vision, allows a blunt dissection of the tumor pseudocapsule from the healthy parenchyma and an easier suture of the renal parenchyma[43,44] in unilateral SRM.

Additionally, and especially in the case of BSRM, robotic approach could enable simultaneous bilateral procedures maintaining the same position of the robot beside the surgical bed. This results in shorter operative time and cosmetic benefits as the minimal incisions for the trocar ports can be partially used for both sides[30,40].

A recent review[45] addressed the management of complex renal tumors, such as those that are large (cT2-T3), endophytic, hilar, or occur in a solitary kidney. These conditions often pose significant challenges in traditional surgical settings. The findings support RAPN as a viable option in the case of bilateral renal masses, since it maintains oncological control while preserving renal function.

Managing synchronous bilateral renal masses, especially in complex regions such as the renal hilum, could be challenging. RAPN allows surgeons to access difficult-to-reach tumors with greater dexterity and precision, offering better outcomes in complex surgeries compared to traditional laparoscopic or open surgeries, in terms of lower blood loss, shorter hospital stays, and quicker recovery times[46].

In summary, this systematic review underscores the importance of RAPN as a safe and effective surgical option for managing bilateral renal masses, particularly in complex cases where traditional approaches may pose higher risks or complications.

Nevertheless, a lot of questions are still open, mainly regarding the approach of the renal pedicle (unclamping, selective, or main clamping), the optimal timing for surgery (one *vs.* two-step surgeries) and the complication rate.

### Management of the vascular pedicle

Preoperative planning to avoid clamping of the main renal artery is crucial in minimizing renal damage. In a series by Gallo *et al.*, artery clamping was avoided or minimized in many cases, leading to a low warm ischemia time (WIT) and improved renal function over time[47].

Two recently published reviews showed that the data reported in literature regarding renal pedicle management are still not homogenous[48,49].

For example, two studies demonstrated that selective clamping is preferred over total bilateral renal artery clamping, as it could prevent the onset of postoperative acute kidney injury (AKI) in patients[40,47]. On the contrary, two other studies focusing on main clamping RAPN observed postoperative AKI[37,39].

However, due to the lack of data on medium and long-term follow-up, it is not possible to presume that the risk of AKI may overwhelm the benefits of single-stage surgery[37,39].

### The optimal time for surgery

The superiority of either the simultaneous or staged surgical procedure for these patients remains controversial. However, the optimal time for surgery should depend on expertise and surgical complexity. Tailored planning and appropriate patient counseling are important.

Procedure should be staged in patients where there is a high risk of AKI and long hospitalization. Moreover, RENAL nephrometry score should be assessed for each patient[50,51].

On the other hand, simultaneous procedures could decrease the cost in terms of single anesthesia time, shorter overall hospitalization and faster overall recovery than two-step surgeries. Moreover, a single-step strategy might have an impact on oncological outcomes, avoiding delay.

Nevertheless, these advantages could be balanced by the potential risks of AKI increased due to the possibility of bilateral clamping approaches to renal pedicles.

The Mayo Clinic reported that 10.8% of patients undergoing simultaneous bilateral PN experienced AKI, but none required dialysis[28]. Staged procedures are recommended for patients with impaired renal function. Lowrance *et al.* noted that sequential procedures could better preserve renal function and reduce the likelihood of dialysis[52].

However, the only available study comparing simultaneous *vs.* two-step RAPN did not report any significant difference in either functional or oncologic outcomes[39].

### Complications

Similar intraoperative and postoperative complication rates were reported after RAPN for unilateral or bilateral RAPN[53,54]; furthermore, any conversion to open surgery was described in all the papers included in the two most recent published reviews[48,49].

Pandolfo *et al.* reported postoperative complication rates during simultaneous bilateral RAPN, including renal hemorrhage, in 25.9% of cases, with major complications being rare (3.7%) and PSM rate of 3.7%, comparable to unilateral procedures[45].

The authors concluded that simultaneous bilateral PN is feasible in expert hands with good functional and oncologic outcomes[45].

Table 1 summarized the complications and the oncological outcomes in patients with synchronous bilateral renal masses treated with surgery, AS, or AT.

Simultaneous bilateral PN offers high cancer control rates with no progression to metastasis, though there is a risk of AKI. Long-term renal function is generally preserved, with only a minimal decline in eGFR.

AS is an effective approach for BSRMs, providing outcomes comparable to those seen in unilateral cases, with no significant impact on renal function.

**Table 1. Surgical *vs.* non-surgical treatment: oncological and functional outcomes**

| Study | Treatment type | Sample size and FU | Survival rates | Recurrence rates | Complications |
|---|---|---|---|---|---|
| Sheikh *et al.*, 2018[12] | AS | 70, 72 months | 5-year OS 100%<br>5-years CSS 95%<br>MFS 100% | 4% | 15% (major complications) |
| Mason *et al.*, 2018[28] | Bilateral PN or PCA, FU not reported | 76 PN and 13 PCA | NR | NR | 20% (mostly minor) |
| Zhang *et al.*, 2018[29] | RFA and open RN | 3 one-stage RN and RFA and 9 one-stage RFA, 33 months | 5-year CSM 100%<br>5-year OS 100% | NR | 33% (only minor) |
| Hillyer *et al.*, 2011[36] | One-stage RAPN *vs.* two-stage LPN | 18 RAPN *vs.* 32 LPN, 7.5 months | NR | NR | 11% RAPN *vs.* 12.5% LPN (2 patients with major complication in LPN group) |
| Di Maida *et al.*, 2022[40] | One *vs.* two-stage OPN or RAPN or RN | 41 patients, 42 months | DFS 90.2%<br>CSM 7.3% | Local 2.4%<br>Systemic 7.3% | CD II 7.3%<br>CD III 4.9% |
| Lowrance *et al.*, 2010[52] | One-stage OPN, one-stage ORN, RN followed by PN, PN followed by RN | 73 patients, of those 32 one-stage OPN, 38 months | 5-year OS 85% | 13% | 15% (major complications) |

FU: Follow up; AS: active surveillance; OS: overall survival; CSS: cancer specific survival; MFS: metastases free survival; PN: partial nephrectomy; PCA: percutaneous cryoablation; NR: not reported; RFA: radiofrequency ablation; RN: radical nephrectomy; CSM: cancer specific survival; RAPN: robot assisted partial nephrectomy; LPN: laparoscopic partial nephrectomy; OPN: open partial nephrectomy, DFS: disease free survival; CD: clavine Dindo; ORN: open radical nephrectomy.

RFA achieves excellent local tumor control while minimizing effects on renal function, with cancer-specific and overall survival rates similar to surgical treatments.

CA yields comparable oncological outcomes to RFA, with a slight advantage in preserving renal function when compared to partial nephrectomy.

A two-step bilateral PN also offers high oncological control but better preserves renal function than simultaneous surgery, particularly for patients at higher risk of AKI.

## CONCLUSIONS

Current guidelines from both the EAU and AUA emphasize the importance of a nephron-sparing approach for BSRM, with PN being the preferred treatment when feasible. AS and AT are valuable alternatives, particularly for patients with small tumors or significant comorbidities. The decision between simultaneous and staged surgery should be individualized based on patient-specific factors, with the aim of maximizing oncological control while preserving renal function. Emerging imaging modalities and genetic profiling are expected to further refine treatment strategies for these patients.

## DECLARATIONS

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Literature research, writing and editing: Pecoraro A
Literature research writing: Diana P

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