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KIDNEY DISEASES (G CIANCIO, SECTION EDITOR)

Robot-assisted Partial Nephrectomy for Endophytic Tumors

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Abstract Robot-assisted partial nephrectomy (RAPN) has gained increasing popularity in the management of renal masses due to its technical feasibility and shorter learning curve with superior perioperative outcomes compared to laparoscopic partial nephrectomy (LPN). Given the cumulation of surgical experience on RAPN, the indication for RAPN has been extended to more challenging, complex cases, such as hilar or endophytic tumors. Renal masses that are completely endophytic can be very challenging to surgeons. These cases are associated with poor recognition of mass extension, higher risk of inadvertent vascular, or pelvicalyceal system injury. As a result, this can lead to potential positive surgical margin, difficulty in performing renorrhaphy as well as higher perioperative complication rates. There is few evidence of oncologic and functional outcomes of RAPN on treating endophytic masses. Therefore, the objective of this review is to critically analyze the current evidence and to provide a summary on the outcomes of RAPN for endophytic renal masses.

Keywords Robot-assisted partial nephrectomy · Renal mass · Endophytic mass · Nephron sparing surgery

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Introduction

There has been a paradigm shift in the management of renal tumor from radical nephrectomy (RN) to partial nephrectomy (PN) if technically feasible in view of reducing the risk of chronic kidney disease (CKD) and cardiovascular disease [1, 2]. PN has been considered the standard of care in patients with small renal tumors and minimally invasive surgery has gained more popularity due to less pain, shorter hospital stay and morbidity as well as superior cosmesis. Recently, with the advances in robotic technology and availability, there has been and increasing role of robot-assisted partial nephrectomy (RAPN) and it has been established as an alternative treatment modality to open and laparoscopic partial nephrectomy for renal cancers [3]. Initially, RAPN has been performed for exophytic, small renal masses; however, with the increasing experience with RAPN, its application has been expanded toward treating more complex and challenging renal masses [4, 5•]. RAPN for endophytic renal masses is technically very challenging, as the surgeon does not have intraoperative gross visualization of renal mass. Given the technical difficulty with this procedure, there is only limited amount of evidence available with regard to oncological and functional outcomes in this setting. Therefore, this review aims to summarize and analyze the contemporary literature of oncological and functional outcomes of endophytic renal masses treated with RAPN.

Open, Laparoscopic Partial Nephrectomy

PN is regarded as the standard treatment for small renal masses, offering equivalent oncological outcomes compared with radical nephrectomy with the advantage of renal function preservation. Open partial nephrectomy (OPN) has been well established with reliable long-term results [6]. This is particularly true for endophytic or hilar masses and is thought to be due to better access to hilar vessels, cold ischemia, direct compression of the parenchyma, and secure of renorrhaphy. However, LPN has more recently emerged to challenge this belief. It has been shown to be a technically feasible alternative to OPN with the advantages of minimal invasiveness. The complication rates were similar but risk of postoperative bleeding or urinary fistula was higher in some studies [7–9].

With the advent of intraoperative ultrasonography, LPN has become more technically feasible even on highly complex renal masses. It helps to identify tumor to facilitate complete tumor removal with negative margin and identify potential satellite lesions [10, 11•].

Pierro et al. [12] assessed the feasibility and outcomes of LPN for endophytic hilar tumors in patients with masses ≤2 cm and low-intermediate (ASA I-II) risk. They included a total of 11 patients and showed no conversion to radical nephrectomy with warm ischemia time of 24 min and 1 positive surgical margin. They found that LPN is a safe, effective treatment for selected patients with renal hilar masses in experienced hands.

Although the indications for LPN have been increasing for complex renal tumors with improved experience and confidence, it remains associated with technical difficulties and a steep learning curve. The lack of maneuverability and limited external view may explain the potentially increased risk of complications and jeopardize oncological and functional outcomes. Given the technically challenging procedure, RAPN has been developed with much wider applicability.

Surgical Techniques of RAPN on Endophytic Renal Masses

Robot-assisted partial nephrectomy (RAPN), was initially introduced by Gettman et al. in 2004 [13•]. Surgical techniques, especially on endophytic renal masses, have been developed recently. Careful review of preoperative imaging of CT scan is important. Technical difficulties with endophytic tumor are mostly related to tumor identification. The perirenal fat is removed around renal mass area by opening of the Gerotàs fascia with the aim of exposing endophytic mass area. With the assistance of intracorporeal ultrasonography, the tumor margins and the extent of parenchymal depth involvement are delineated. The renal capsule is scored to guide the tumor resection site with adequate surgical margin.

For tumors that are endophytic or adjacent to the renal hilum, resection is performed usually under warm ischemia under clamping of renal hilum. The assistant clamps the renal hilar vessel using laparoscopic bulldog clamp through the primary 12-mm assistant port. Mannitol (12.5 g) may be administered intravenously prior to clamping. The tumor is resected along the previously scored margin using cold resection with the robotic monopolar scissors. The Maryland bipolar forceps are used to manipulate the tumor for exposure and to aid in dissection. The assistant uses suction to expose and maintain visualization of the resection plane of the tumor. Hemostasis is achieved using a combination of cautery, hemostatic agents, and suturing. Thereafter, the robotic instruments are exchanged for robotic needle drivers. A 3–0 Vicryl suture on an SH needle is used to achieve hemostasis and repair any previously identified entry into the collecting system. Sutures may be secured with either absorbable suture clips or by tying knots. The kidney is placed back on and the hilar clamp is removed by the assistant and a hemostatic agent is applied.

Intraoperative Ultrasonography

Tumor identification during RAPN is necessary for oncologic safety and can be facilitated by intraoperative ultrasonography, especially on endophytic mass. In the era of open partial nephrectomy, Assomos et al. investigated the feasibility of intraoperative ultrasonography in OPN for identification of intraparenchymal tumor mass [14•]. Matin et al. have reported the use of intraoperative ultrasonography in laparoscopic partial nephrectomy for tumor identification for achieving negative surgical margins [10]. Intraoperative ultrasonography improves the identification of renal mass location and facilitates complete tumor excision with negative surgical margins. During RAPN series, Tilepro™, the multi-image display mode of da Vinci® surgical system (Intuitive Surgical, Sunnyvale, CA) was applied to allow view of external images display on surgeon console screen. Tilepro™ for integration of intraoperative ultrasonography image on the console screen simultaneously during surgery facilitates to identify tumor localization, especially in cases of grossly invisible endophytic masses and hilar masses (Fig. 1). Both laparoscopic intraoperative ultrasound and robotic ultrasound probe could be used based on surgeon preference. Several studies demonstrated the comparable perioperative outcomes and surgical margin rates between robotic ultrasound probe and laparoscopic ultrasound probe [15•, 16••]. However, adequate mobilization of the kidney is needed to achieve sufficient identification of renal mass by laparoscopic ultrasound probe. Far edge of tumor site is challenging to achieve adequate angle between probe and kidney, and renal mass on upper pole and posterolateral location is difficult to approach. Also experienced bedside assistant is required for precise evaluation of renal mass. Robotic ultrasound probe can be maneuvered by a console surgeon with

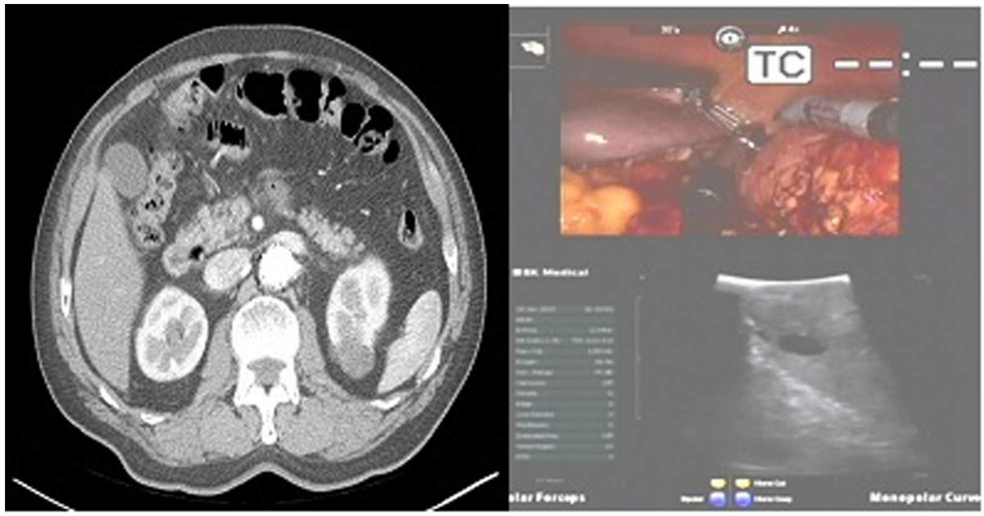

Fig. 1 Preoperative completely endophytic renal mass, and intraoperative image of RAPN on renal mass using intraoperative ultrasonography

maintaining perpendicular contact with the kidney surface of suspicious lesion. This is a feasible tool for identifying complex tumor such as totally endophytic mass and hilar masses.

Additionally, Hyams et al. [17] have reported the feasibility of Doppler ultrasonography techniques to identify renal hilum, aberrant renal vessels, and confirmation of renal ischemia.

Recently, preliminary study of real-time three-dimensional image guidance system by Tilepro™ display is performed [18•, 19••]. Using this system, renal tumor and vascular 3D image navigation has shown on the surgeon console view through Tilepro™, and it facilitated tumor identification with precise dissection, and also for high-order renal artery branches for avoidance of inadvertent vessel injury and also for selective clamp techniques. Furukawa et al. [18•] have investigated total 17 patients who underwent RAPN using real-time 3D image navigation system. The mean warm ischemia time and estimated blood loss were 21.6 min and 25 mL, respectively. There was no positive surgical margin, and eGFR reduction was 8.2, 9.4 mL/min/1.73 m^2 at 1 and 4 weeks, respectively, after RAPN. Given the development of these intraoperative ultrasonography techniques, RAPN on complex renal mass such as completely endophytic, hilar mass could be performed safely with preserving maximal normal parenchyma.

Near-Infrared Fluorescence Imaging Using Indocyanine Green dye

Accurate differentiation of tumor from normal surrounding renal parenchyma is critical to ensure maximal nephron preservation and negative surgical margin. Intraoperative ultrasonography has been widely utilized; however, it is not useful at the time of tumor excision, especially using a minimally invasive technique due to the bulkiness of the instrument and limited maneuverability inside the abdomen. Advanced intraoperative imaging techniques would be beneficial to help maximize renal parenchymal preservation.

The feasibility of the novel intraoperative technique using near-infrared fluorescence imaging (NIRF) with indocyanine green (ICG) dye has been evaluated for improved intraoperative identification of anatomic structures and provided angiographic images. NIRF potentially offers enhanced differentiation of tumor from normal surrounding tissues, as well as monitoring of regional renal ischemia or segmental perfusion deficits after arterial clamping, to minimize blood loss while maintaining perfusion to the remainder of the kidney and simultaneous use in real time during tumor resection.

It is a sterile water-soluble dye that absorbs NIRF and subsequently emits light at slightly longer wavelengths (806 nm). ICG binds to albumin when intravenously injected and therefore remains primarily in the vasculature. It appears to be transported into the proximal tubule of normal renal parenchyma, while malignant tissues do not take up ICG. It is cleared by hepatic metabolism and is not nephrotoxic with minimal adverse reactions making it an ideal agent for PN procedure.

Tobis et al. [20•] investigated that all of 13 malignant lesions were hypofluorescent compared with benign lesions which were iso- or hypofluorescent. The differentiation between tumor and normal kidney was easier to distinguish for more exophytic lesions with less parenchyma overlying them. Thereby, the hypofluorescent nature of the tumor was better appreciated for endophytic ones once resection had commenced. Bjurlin et al. [21••] investigated their experience with 48 patients that the mean warm ischemia time was 17 min and a reduction in eGFR rate was −6.3 %. Forty-eight percent had successful selective clamping.

It is believed that a very promising avenue for further exploration might be the role of NIRF-ICG during selective arterial clamping by improved identification of segmental, tertiary, and quaternary vessels that could significantly make an impact on our approach to RAPN.

This technology in urology is still in its infancy, but these studies have concluded that this imaging tool could be a useful intraoperative adjunct as angiography to help distinguish tumor margin from normal parenchyma, to confirm selective ischemia, to monitor perfusion deficits of healthy renal parenchyma after the renorrhaphy, especially in the setting of complex hilar or endophytic masses [22•].

Robot-Assisted Partial Nephrectomy for Endophytic Mass

After the initial experiences of RAPN, this procedure has been proved to be a feasible alternative to OPN and LPN [23]. Given the increasing experiences in RAPN worldwide, it offered to perform RAPN in more challenging cases. Complex renal masses such as totally endophytic masses and hilar masses were started to be treated by RAPN techniques. These settings constitute a technically challenging procedure even with robotic assistance due to the difficulty in tumor localization and precise resection, which may have an impact on oncologic safety and perioperative outcomes.

Autorino et al.[24••] have reported the effectiveness and safety of RAPN in completely intraparenchymal renal tumors. The authors included 65 patients who have underwent RAPN, and endophytic group had mean warm ischemia time of 21.7 min, and mean estimated blood loss of 225 mL, and pathology showed 2 (3 %) positive surgical margins. There were no differences in length of stay, intraoperative complications, positive surgical margin rate, and postoperative eGFR change for conclusion that RAPN could be performed for completely intraparenchymal renal tumors safely and effectively in centers with significant robotic expertise. Other groups of Komninos et al. [25••] have also evaluated renal functional outcome and oncologic safety. From a total of 225 patients of RAPN series, 45 patients of completely endophytic masses were compared to other mesophytic and exophytic masses. For the completely endophytic mass group, the median follow-up period was 48 months, and this group showed more malignant and higher tumor complexity based on RENAL nephrometry score. There was no significant difference in complication rates; of 45 patients, there were 2 cases (4.4 %) of radical conversion, 1 case (2.2 %) of urinoma, and 1 case of hydronephrosis (2.2 %). In terms of functional aspect, on the first postoperative date, there was a significant change of eGFR ($P=0.02$); however, after first week of RAPN, there was no significant decrease of eGFR. On oncological analysis, endophytic group showed the tendency of increased positive surgical margin rate compared to mesophytic and exophytic groups with moderate statistical significance ($P=0.06$); however, for an intermediate term of 4 years follow-up, recurrence-free survival rates ($P=0.335$) and overall mortality rates ($P=0.57$) showed no significant difference. Finally, for achievement of trifecta (no complication, negative surgical margin, warm ischemic time <25 min), endophytic mass had a trend of lower rate (37.8 %) compared to mesophytic mass (49.1 %), and exophytic mass (57.8 %) ($P=0.14$).

Curtiss et al. [26••] have investigated 30 patients with completely intrarenal tumors out of 297 patients cohort who underwent RAPN. In a median follow-up of 10.6 months, there was no significant difference in perioperative outcomes between completely intrarenal tumors and exophytic component tumor. Warm ischemic time was same between two groups (17 vs 17 min), and there was no positive surgical margin in the intrarenal group and 5 patients (2.4 %) of positive surgical margin in the exophytic component group ($P=0.74$). Several consideration was suggested that urothelial carcinoma should be kept in mind if the lesion is infiltrative or has atypical appearance. This suspected lesion could be evaluated by diagnostic ureteroscopy and urine cytology. Preoperative ultrasonography could contribute to help identify isoechoic tumor, and tumor that has similar echogenicity which makes it difficult to differentiate from normal renal parenchyma. Therefore, RAPN can be effectively and safely performed in terms of excellent perioperative outcomes including renal function and oncological safety. Robotic assistance in PN in complete intraparenchymal mass offers benefits to a surgeon performing this challenging procedure with flexibility during excision of renal mass and reconstruction of normal renal parenchyma. Perioperative, oncologic, and

Table 1 Summary of perioperative, oncologic, functional outcomes by RAPN on endophytic renal mass

Study	Patients (*N*)	Mean tumor size (cm)	Operation time (min)	EBL (mL)	WIT (min)	PSM (%)	Complications (%)	eGFR decrease (mL/min/1.73 m^2)
Abreu et al. 2011 [31•]	7	3.8	237	228.6	0	0	14.2	1.3
Eyraud et al. 2013 [30••]	70	3.9	210	250	27	1.4	33	12.2
Autorino et al. 2014 [24••]	65	2.6	175.8	225.8	21.7	4.6	12.8	12.6
Komninos et al. 2014 [25••]	45	2.6	169	275	(−)	12.5	26.6	3.4
Miyake et al. 2015 [32••]	16	3.0	263	57.5	23	0	8.3	10.4
Curtiss et al. 2015 [26••]	30	2.3	165	100	17	0	6.7	(−)

EBL estimated blood loss, *WIT* warm ischemic time, *PSM* positive surgical margin, *eGFR* estimated glomerular filtration rate functional outcomes by RAPN on endophytic, hilar masses are summarized in Table 1.

Several studies have also been conducted to compare RAPN with OPN. Boylu et al. showed RAPN offers better outcomes in terms of blood loss and length of stay but longer mean operative time and warm ischemia time. They concluded RAPN is a safe and effective minimally invasive alternative to OPN in terms of oncological and functional outcomes, and Ficarra et al. have offered a lower risk of postoperative complications than OPN [27, 28].

Robot-Assisted Partial Nephrectomy for Hilar Mass

Hilar renal tumor poses many challenges to the surgeon, due to close proximity of renal hilum and collecting system and lack of parenchymal margin for adequate renorrhaphy.

Hilar tumor was defined as tumor located in the renal hilum region and the mass is abutting to the renal artery, vein, or both of them [29]. Eyraud et al. [30••] evaluated the effect of hilar location renal mass on perioperative outcomes who underwent RAPN. From a total of 364 patients, 70 patients were in the hilar tumor group. RAPN for hilar tumors was associated with long warm ischemic time (27 vs 17 min, $P<0.001$) and increased EBL (250 vs 200 mL, $P=0.04$). However, positive surgical margin, complication rate, and transfusion rate showed no significant difference between two groups. For functional analysis, immediate postoperative eGFR and last follow-up eGFR showed no significant difference (70.12 vs 74.71 mL/min/1.73 m^2, $P=0.31$), (72.62 vs 75.78 mL/min/1.73 m^2, $P=0.40$). Therefore, clinically relevant changes were minimal despite the complexity of hilar mass; however, increased WIT and higher likelihood of radical conversion were identified in patients of hilar tumors.

For prevention of global ischemia during RAPN, zero-ischemia RAPN was developed even in renal hilar mass series [31•]. Renal vascular microdissection with super-selective clamping of tertiary or higher-order arterial branch was performed, and preoperative 3D reconstructed tumor and renal vasculature of tertiary or quaternary branches supplying hilar mass image was investigated. Color Doppler ultrasonography and neurosurgical micro-bulldogs were used for identification of peritumoral reduction of blood flow, while documentation of preserved perfusion of normal renal parenchyma. Seven patients with renal hilar mass underwent RAPN with super-selective clamping technique, and the median operation time was 222 min, with estimated blood loss of 150 mL, and the median percentage of kidney preservation up to 75 %. The median decrease in eGFR at discharge was 5 mL/min/1.73 m^2. There was no major complication over Clavien grade III, apart from 1 patient who had intraoperative transfusion; all tumor specimen had a negative surgical margin. Super-selective clamp technique in RAPN could be performed safely with optimal preservation of renal function by eliminating global renal ischemia.

Miyake et al. [32••] have compared outcomes of OPN with RAPN for hilar masses. Although there were only 31 patients, they concluded that RAPN is an effective and safe surgical option with less blood loss, similar warm ischemia time, and enhanced recovery for renal hilar tumors.

Conclusions

RAPN proved to be oncologically safe and functionally effective with comparable perioperative complication rates on completely endophytic renal mass. The technically ergonomic features of robotic surgical platform and accurate use of intraoperative ultrasonography and intraoperative technique using NIRF imaging with ICG dye have facilitated this surgery. Further long-term, prospective studies are required for the feasibility of RAPN for endophytic renal masses.

Compliance with Ethics Guidelines

Conflict of Interest Dr. Dae Keun Kim, Dr. Christos Komninos, Dr. Lawrence Kim, and Dr. Koon Ho Rha reported no potential conflict of interest relevant to this article.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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