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Endophytic Renal Cell Carcinoma Treated with Robot-Assisted Surgery: Functional Outcomes – A Comprehensive Review of the Current Literature

Keywords

Partial nephrectomy · Robotic surgical procedures · Endophytic mass · Intraparenchymal mass · Renal mass · Glomerular filtration rate

Abstract

Introduction: Robotic surgery for the management of localized renal cell carcinoma (RCC) has gained increasing popularity during the last decade. An endophytic renal tumour represents a surgical technical challenge in terms of identification and resection related to the lack of external visual cues on the kidney surface. **Materials and Methods:** There is little evidence of functional outcomes of robotic surgery on treating endophytic masses. For this reason, we wanted to review the contemporary literature on the functional outcomes of endophytic RCC treated with robotic surgery. **Results:** Many studies investigating robotic partial nephrectomy for totally endophytic RCC confirmed the good functional results of this approach at intermediate follow-up. The greater relative importance of volume loss versus ischaemia duration in predicting long-term renal function after partial nephrectomy is now established, and the robotic technique may facilitate volume preservation. Accurate use of intra-op-

erative ultrasonography, enucleation, and intra-operative techniques using near-infrared fluorescence imaging with indocyanine green dye could minimize excision of the parenchyma and prevent devascularization of adjacent healthy parenchyma. **Conclusions:** Unfortunately, the overall quality of the literature evidence and the high risk of selection bias limit the possibility of any causal interpretation about the relationship between the surgical technique used and functional outcomes.

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Introduction

Surgical management of a localized renal cell carcinoma (RCC) involves balancing cancer removal with an adequate margin, maximizing renal function, and avoiding peri-operative morbidity. Given the lack of cancer-specific survival benefit with radical nephrectomy over partial nephrectomy (PN) [1], the better renal function following nephron-sparing surgery, and the potential cardiovascular benefits with reduced risk of developing chronic kidney disease (CKD) [2, 3], current guidelines recommend prioritizing PN whenever technically feasible [4, 5].

The introduction of robotic technology revolutionized minimally invasive surgery for RCC by overcoming many of the technical challenges of laparoscopy with a shorter learning curve [6]. The robotic platform facilitates precise and efficient execution of excision and renal reconstruction, which has led to its rapid dissemination. The increasing surgical experience in robotic PN (RPN) procedures worldwide gives the opportunity to perform operations in more complex and challenging renal cases [7–9].

Endophytic renal tumours represent a technical challenge due to the difficulties in tumour identification and resection related to the lack of external visual cues on the kidney surface. These difficulties may influence the perioperative outcomes of the procedure with longer warm ischaemia times (WITs), a higher rate of urinary system violation, and more frequent postoperative complications than those reported for standard and smaller tumours. Given its several potential inconveniences, the advantages of RPN for endophytic masses, notably regarding renal function, remain unclear.

This review aims to summarize and analyse the contemporary literature on the functional outcomes of endophytic RCC treated with robotic surgery.

Evidence Acquisition

A non-systematic MEDLINE/PubMed literature search was performed on March 2019 using the terms “Endophytic,” “Intraparenchymal,” “Renal mass,” “Robotic,” “Nephrectomy,” “Functional outcomes,” “Renal function,” and “Functional recovery.” Original articles were included based on their clinical relevance by two authors (Z.-E.K. and B.P.). Additional informative articles were collected by cross-referencing the bibliography of previously selected articles.

Determinants of Functional Outcomes after Partial Nephrectomy: Impact of Patient-, Imaging-, and Surgical-Related Factors

Quantity of Parenchyma Preserved

The proportion of parenchyma preserved seems to be a significant and independent determinant of functional outcome [10, 11]. Several authors have investigated potential methods for predicting the amount of preserved renal parenchyma. Examining pre-operative imaging parameters of a series of 98 PNs, Aertsen et al. [12] showed that loss of healthy renal parenchyma was highest in pa-

tients with renal sinus tumour involvement ($p = 0.003$), tumours with anterior location ($p = 0.006$), and high-grade postoperative complications ($p = 0.001$), but was not significantly correlated with medial/lateral location ($p = 0.940$) or exophytic/endophytic tumour growth ($p = 0.244$).

The RENAL (R – radius, E – exophytic vs. endophytic, N – nearness of tumour to collecting system, A – anterior vs. posterior, L – location relative to polar lines) nephrometry score [13] is a systematic approach designed to characterize renal masses and to develop a standardized reporting but not necessarily to guide clinical decisions [14]. Some teams have found that the RENAL nephrometry score correlates with renal volume loss and postoperative renal function, but groups have failed to identify a similar link [15].

The RENAL score was found to be associated with the pathologically determined non-neoplastic parenchymal volume removed ($\beta = 6.21$, $p < 0.001$) and the renal function decline in patients undergoing RPN. In a multivariate analysis of the RENAL components, the tumour radius ($\beta = 31.9$, $p < 0.001$) and tumour location relative to the polar lines of the kidney ($\beta = 5.26$, $p = 0.036$) were associated with greater non-neoplastic parenchymal volume removal [16].

Using renal scintigraphy in a cohort of 245 patients, Watts et al. [17] assessed the relationship between individual RENAL score constituents on renal function of the surgical kidney in patients undergoing laparoscopic or robotic PN. They found that the endophytic score of the tumour is associated with a significant decrease in split renal function of the surgical kidney at 1 year after surgery but not with overall renal function.

The concept of the surface area of tumour contact with the renal parenchyma (CSA) has also been studied as a predictor of functional outcomes after PN [18]. Early studies suggested strong performance characteristics of CSA can predict functional outcomes after PN [19, 20]. However, a more recent and comprehensive study suggested that the correlations between CSA and functional outcomes were only modest and that CSA was not an independent predictor for endophytic tumours [21].

Finally, Maurice et al. [22] retrospectively reviewed 880 partial nephrectomies to identify predictors of excisional volume loss (EVL) based on pathologic assessment. They observed that open PN (OPN) was associated with 7.8 cm³ more EVL than RPN ($p < 0.01$). In comparison, for every 1-cm increase in tumour size, EVL increased by 7.1 cm³ ($p < 0.01$), and for completely endophytic tumours, EVL increased by 7.8 cm³ ($p = 0.01$).

Ischaemia Time

The subject of ischaemia time to impair renal function remains debatable. Several retrospective clinical studies published in the last decade have evaluated the effect of ischaemia time on postoperative renal function [23–25]. In a study based on a solitary kidney model, Thompson et al. [26] evaluated the effects of WIT and the quantity and quality of kidney preserved on renal functional recovery after PN. They showed that a WIT cut point of 25 min provided the best distinction between patients with and without postoperative acute renal failure and new-onset stage IV CKD (hazard ratio 2.27, 95% CI: 1.00–5.13; $p = 0.049$). In a series of 32 patients, Funahashi et al. [27] quantified ischaemic renal damage using regional ^{99m}Tc -MAG3 uptake in the unaffected section of the surgically treated kidney. They found that a WIT of >25 min was associated with a long-term decrease in regional ^{99m}Tc -MAG3 uptake but that the surgically treated kidney recovered from the ischaemic insult when WIT was ≤ 25 min. In a series of 99 patients, Zargar et al. [28] reported similar findings, but with a threshold of 30 min of ischaemia, whereas Choi et al. [29] drew comparable conclusions in 44 patients, but with a 28-min cut-off time.

In contrast to these studies and based on a host of biomarkers and multiple renal biopsies as surrogates for ischaemic injury, Parekh et al. [30] prospectively studied the tolerance of renal hilar clamping in humans. They found that renal functional changes did not correlate with ischaemia duration and that renal structural changes were much less severe than those observed in animal models that used similar durations of ischaemia. Recently published data by the same group of authors on long-term renal functional outcomes showed no correlation of ischaemia duration with renal function at 1-year follow-up [31]. In another study, Lane et al. [32] took into account the percentage of preserved parenchyma in a multivariate model that sought the predictors of a postoperative decrease in the estimated glomerular filtration rate (eGFR). They demonstrated in their multi-institutional cohort of 660 PNs of solitary kidneys that ischaemia time (warm or cold) was no longer a significant independent predictor of ultimate renal function.

Finally, the current evidence suggests that limited ischaemia time (i.e., ≤ 25 –30 min) has a lower risk of reducing renal function after PN. However, stronger evidence supports greater tolerance of the human renal parenchyma to limited ischaemia. The clinical relevance of these findings in different clinical settings will require further investigation.

Baseline Kidney Function

The quality of the renal parenchyma seems to be a critical determinant of functional recovery after nephron-sparing surgery. Consistent data indicate that the presence of baseline CKD is an important predictor of postoperative renal function after PN either in the single or bilateral kidney setting [26, 33]. Most recent studies indicate that pre-operative eGFR is an independent predictor of a significant decrease in eGFR in solitary kidneys and of the differential contribution of the operated organ in the presence of bilateral kidneys after adjusting for other patient-, tumour-, and surgery-related factors. Preoperative renal function may also have a dominant role over the number of residual nephrons in determining renal function because hyperfiltration of the remaining nephrons may compensate, to a certain degree, for their decreased number [34, 35].

Functional Outcomes of Partial Nephrectomy for Endophytic Tumours in the Literature

There are only a few published studies reporting the results of endophytic tumours resected with robotic surgery (Table 1).

In a series of 140 consecutive patients with completely endophytic tumours, Harke et al. [36] compared the outcomes of RPN and OPN. They showed that warm ischaemia was notably shorter for RPN with a WIT of 13 min compared to open surgery with 18 min, $p = 0.001$, and that there were comparable results for eGFR at discharge for both groups. Autorino et al. [37] reported their experience of RPN in completely intraparenchymal renal tumours. They included 65 patients who underwent RPN and compared the outcomes of endophytic masses with mesophytic and exophytic tumours and stated that they did not detect any differences in terms of surgical complications, positive margin rates, and postoperative changes in eGFR. However, the main limitations of this study included the short follow-up period (mean time was 12.6 months) and that the differences in eGFR were not standardized at established time points. Komninos et al. [38] performed a comparative analysis of 225 patients with renal tumours who underwent RPN, including 45 (40%) completely endophytic tumours, 19 (15.5%) exophytic tumours, and 47 (38%) mesophytic masses. The median follow-up times of the endophytic, mesophytic, and exophytic groups were 48, 43, and 38 months, respectively. They found a significantly higher rate of total artery clamped cases in the endophytic group (82.2%) com-

Table 1. Literature data of endophytic renal tumour outcomes following partial nephrectomy surgery

Reference	Study period	Study design	Study origin	Patients, <i>n</i>	Surgical technique	Tumour size, cm	RENAL score	WIT, min	Follow-up, months	Functional outcomes	LE
Raheem et al. [40], 2019	2005–2015	Retrospective	Korea	89	52 RPN	2.8	8.9	24	59	CKD upstaging occurs in (5.4%)	3
					37 OPN	2.5	8.3	27	53		
Harke et al. [36], 2018	2008–2016	Retrospective	Germany	140	64 RPN	2.5	11	13	—	Latest median% eGFR preservation 72.5 Latest median% eGFR preservation 68.2	3
					76 OPN	2.6	11	18	—		
Kara et al. [39], 2016	2011–2016	Retrospective	USA	143	87 RPN	2.8	9	17.5	15.2	Latest median% eGFR preservation 85.2 Latest median% eGFR preservation 82.9	3
					56 OPN	3.1	9	20.6	18.1		
Komninos et al. [38], 2014	2006–2013	Retrospective	Korea	45	RPN	2.6	9	24	48	Latest median% eGFR change –4.5	3
Autorino et al. [37], 2014	2006–2012	Retrospective	USA	65	RPN	2.6	8.7	21.7	12.6	Latest mean% eGFR change –9.4	3

eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; WIT, warm ischemia time; RPN, robot-assisted partial nephrectomy; OPN, open partial nephrectomy; LE, level of evidence.

pared with the other groups (mesophytic, 72.4% and exophytic, 51.6%; $p < 0.01$). However, they did not find any significant differences among the groups regarding the latest postoperative eGFR and eGFR percentage change. Finally, they concluded that RPN for entirely intraparenchymal masses is a feasible procedure in terms of complication rates and functional and oncologic outcomes during an intermediate-term follow-up period.

In a cohort of 146 patients with completely endophytic renal tumours, Kara et al. [39] analysed the functional outcomes of RPN and OPN at a median follow-up of 15.2 months. The median percent eGFR preservation was 85.2% (76.4–93.3%), with no significant difference from OPN ($p = 0.22$). More recently, Abdel Raheem et al. [40] reported their experience with the robotic management of totally endophytic renal tumours with RPN. The authors compared the outcomes of endophytic masses managed by OPN or RPN and stated that they did not detect any differences in terms of surgical complications, positive margin rates, and postoperative changes in eGFR. They showed that the median percent eGFR preservation in the RPN group was 88% (80–100%) at a median follow-up of 59 months. The main strengths of this study are the relative long-term functional outcomes and the demonstration of the feasibility, long-term oncologic safety, and renal function preservation of robotic surgery as an effective alternative to open surgery in the treatment of such difficult lesions.

Ways to Optimize the Functional Outcomes of Partial Nephrectomy for Endophytic Tumours

As pre-operative renal function is a non-modifiable factor and there is low-grade evidence to support that limited ischaemia time (i.e., ≤ 25 min) has a lower risk of reducing renal function after PN, the amount of healthy parenchyma preserved appears to be the main potentially modifiable predictor of ultimate renal function.

Improving and Minimizing Excision of Parenchyma

Several intra-operative techniques were developed to help surgeons during RPN, including tumour delineation, tumour differentiation from normal kidney parenchyma, and kidney perfusion during clamping.

Intra-operative ultrasonography is widely used as a real-time intra-operative imaging technique during RPN, especially in cases of totally endophytic tumours. It is used by the assistant during the procedure, and images are projected onto the console screen. Using intra-operative ultrasonography allows the identification of the location, margin, and depth of the endophytic renal tumour before surgery. In addition, the direct contact of the transducer on the kidney capsular surface helps in reducing artefacts and visualization difficulties, detecting additional small renal masses, and characterizing the anatomic relationship of the renal mass to adjacent structures such as the

pelvic/lyceal system, renal sinus, and major blood vessels to determine the best surgical resection site [41–43].

Initially described as an imperative indication, simple tumour enucleation has been proposed as a technique that can maximize the preservation of parenchyma during PN [44–46].

Enucleation is an alternative nephron-sparing technique in which the renal mass is dissected away from the normal parenchyma via an avascular plane along the fibrous tumour pseudocapsule [47]. It is a well-described surgical technique for familial RCC that is increasingly applied to sporadic cases, potentially offering improved volume preservation while obviating the need for formal capsular renorrhaphy.

Enucleation has been used in RPN; however, widespread adoption has been curtailed by concerns about the oncological efficacy. Studies have suggested that tumour enucleation has the potential for maximum parenchymal preservation and optimized functional recovery [45]. A recent meta-analysis showed that tumour enucleation is non-inferior to standard PN regarding positive margin rate and tumour recurrence rates [48]. An alternative to enucleation could be to minimize the rim of the excised adjacent normal parenchyma and to limit devascularization of the adjacent parenchyma during renal reconstruction by optimizing renorrhaphy.

Similar to enucleation, the anatomic “minimal-margin” RPN technique decreases parenchymal loss by leaving minimal parenchymal tissue on the tumour, achieving greater renal parenchymal preservation; however, its oncological safety compared with that of the traditional RPN technique remains to be seen.

Minimizing Ischaemia

A relatively new development in RCC surgery is intraoperative fluorescence imaging. The most commonly used near-infrared fluorescent (NIRF) dye is indocyanine green (ICG). It is used to differentiate the tumour from normal kidney parenchyma and to confirm adequate ischaemia during selective clamping of renal artery branches. Consequently, it could reduce the proportion of renal parenchyma that is subjected to ischaemia and excision. In the field of robotic surgery, several studies have employed NIR imaging to aid in selective arterial clamping and to limit the proportion of healthy parenchyma during RPN. In 2012, Krane et al. [49] performed the first prospective study comparing 47 patients who underwent RPN with the application of ICG to 47 patients treated previously without. They found that WIT was significantly decreased in the ICG group (15 vs. 17 min, $p =$

0.01). However, there was no significant difference between the groups for percent change in GFR at discharge (-4.6 vs. -7.4% , $p = 0.5$). In another matched-pair analysis, McClintock et al. [50]. found that selective clamping with NIRF was associated with superior kidney function at discharge, as demonstrated by postoperative eGFR (78.2 vs. 68.5 mL/min per 1.73 m²; $p = 0.04$), absolute reduction of eGFR (-2.5 vs. -14.0 mL/min per 1.73 m²; $p < 0.01$), and percent change in eGFR (-1.9 vs. -16.8% , $p < 0.01$). However, the differences did not reach conventional statistical significance (-3.1 vs. -14.6% , $p = 0.07$). In a recent study, Simone et al. [51] evaluated a novel technique for marking pre-operatively endophytic renal tumours with transarterial super-selective intrarenal mass delivery of an ICG-lipiodol mixture. In their cohort of 10 consecutive patients with totally endophytic renal masses, they showed a median percent eGFR decrease at discharge of 11% (10–20%) and a 1-year eGFR percent decrease of 12.2% (5.3–13.7%). However, further research is needed to objectively standardize this technique, and larger series are expected before it is recommended.

Preventing Devascularization of Adjacent Healthy Parenchyma

Initially described as an imperative indication, simple tumour enucleation has been proposed as a technique that can maximize the preservation of parenchyma during PN [44–46].

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ing minimal parenchymal tissue on the tumour, achieving greater renal parenchymal preservation; however, its oncological safety compared with that of the traditional RPN technique remains to be seen.

Improving parenchymal volume preservation through omission or modification of renorrhaphy techniques is still under investigation [52]. During RPN, renorrhaphy typically included a double-layer technique [53]. In a small series of 15 RPN cases performed with a deep suture layer but without cortical renorrhaphy matched 2:1 with traditional two-layered RPN cases, Bahler et al. [54] observed that the non-renorrhaphy group was associated with shorter WITs and decreased parenchymal volume loss (9 vs. 17 cm³, $p < 0.01$) with a trend toward improved GFR preservation. Renorrhaphy techniques using tissue-adhesive sealant have also been described and seem to represent viable alternatives for renorrhaphy that may offer potential decreases in volume loss and consequent improvements in renal function but without a significantly increased risk of complications [55].

Limitations and Perspective

Robotic surgery for completely endophytic RCC presents many surgical challenges: (1) these tumours are not easily identifiable on visual inspection, and (2) the depth of resection is not immediately apparent, which increases the technical difficulty of the surgery and the risk of complications. Regardless of this increased technical complexity, the goals of the surgery remain the same: to achieve oncological control, to avoid complications, and to maximally preserve renal function. The current literature reported that RPN can be effectively and safely performed for endophytic localized tumours in terms of excellent perioperative outcomes, including renal function

and oncological safety. The accurate use of intra-operative ultrasonography and intra-operative techniques using NIRF imaging with ICG dye could facilitate this surgery. However, in terms of comparing functional outcomes, it is difficult to draw strong conclusions based on the data reported due to inherent differences in ischaemia type, resection technique, and the percentage of volume preservation. Moreover, most of these studies are based on two-kidney models and serum creatinine-based assessments of renal function that evaluate global renal function in patients with a contralateral kidney.

In conclusion, robotic surgery is a feasible, safe, and oncologically effective surgical treatment for endophytic RCC. However, the current literature does not provide a major advantage for RPN when compared to standard laparoscopy or open surgery in terms of preserving renal function. Additional studies of high-level evidence are required to confirm these findings.

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Author Contributions

Z.-E.K., B.P., and A.G: conception or design of the work; acquisition, analysis, or interpretation of data; and drafting or revising the work. K.B. and R.M: conception or design of the work; drafting or revising the work; and acquisition of data. G.V. and R.M: conception or design of the work; drafting or revising the work; and interpretation of data.

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