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KIDNEY DISEASES (G CIANCIO, SECTION EDITOR)

Surgical Treatment of Completely Endophytic Renal Tumor: a Systematic Review

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Abstract

Purpose of Review An endophytic renal tumor represents a special surgical challenge in terms of location and safe removal. For this reason we wanted to review the existing literature on this subject.

Recent Findings In high-activity robotic centers, robot-assisted partial nephrectomy (RAPN) is a safe and efficacious surgical approach for completely endophytic renal tumors. As research innovation, the application of the radio-guided occult lesion localization technique (ROLL) facilitates the location and complete excision of the tumor during surgery.

Summary There are few studies that specifically report the experience with completely endophytic renal tumors. The endophytic tumor is usually smaller than exophytic. Frequently it represents a high complexity value in the different Score systems reported in the last decade. This surgery should be performed by experienced urologists regardless of the surgical approach they prefer (open, laparoscopic, or robotic). It is necessary to develop new techniques for intraoperative easy localization and intraoperative evaluation of surgical margins.

Keywords Endophytic tumor · Intraparenchymal tumor · Open partial nephrectomy · Renal tumor · Surgical treatment · Robotic partial nephrectomy · Laparoscopic partial nephrectomy

Introduction

Kidney cancer is among the ten most common malignant tumors in both men and women accounting for about 3% of all cancer in adults. It has been estimated that 65,340 is the number of new cases of kidney cancer that will be diagnosed in USA along 2018 with 14,970 deaths [1]. The incidental detection of renal masses is increasing every year according to more frequent utilization of CT scans, ultrasound, MRI, and other diagnostic imaging techniques [2, 3]. This circumstance has facilitated that approximately 50% of the new diagnosed tumors have less than 4 cm in diameter, being considered as small renal tumors [SRT] [4]. This fact reveals a progressive decrease in the tumor stage. Despite earlier detection and treatment, paradoxically, it has been described an increasing mortality from renal cell carcinoma (RCC 2). However, this phenomenon—termed "treatment disconnect"—has been refuted showing that cancer-specific survival (CSS) rates remain stable [5].

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Also, we must consider that the chances of a SRT being malignant increase proportionally to its size. Each centimeter rise in diameter means a 16% of increment in aggressiveness [6] and the possibility of being benign is 40% in those who have less than 1 cm, decreasing to 20% in those who have between 1 and 2 cm.

As in tumors larger than 4 cm, surgical removal is the standard indication, in small renal tumors, the treatment options are multiplied and the selection of one or the other depends on small details.

What Is an Endophytic Renal Tumor? A renal tumor is endophytic when it is completely surrounded by non-tumoral renal parenchyma. Therefore, it represents a special challenge for the urologist because it is not detected on the surface and its location and removal are truly complex.

Reasons for a Review on This Type of Tumor

Currently, since the description made by Novick in 1989, nephron-sparing surgery has progressively become the standard surgical option for small tumors [7], but when the kidney tumor is endophytic as well as small, the problem grows and all treatment options must be evaluated in order to choose the most appropriate for the patient. If we choose nephron-sparing surgery for an endophytic tumor, we face a special surgery. For that reason, we wanted to review the existing literature on this subject.

Objectives

Through the systematic review of these articles, it is intended to know:

- Surgical possibilities: open, laparoscopic or robotic surgery and their differences.
- Safety in these surgical treatment options
- Oncological results of this therapeutic approach
- New imaging diagnostic methods to evaluate intraoperatively the tumor.

Materials and Methods

A systematic search was carried out using PubMed, Ovid, and Embase. The search was performed until August 2018, and only articles published in the English language were considered. A hand-search of the reference lists of relevant articles was also conducted. The study was conducted according to the elements of preferred reports for systematic reviews and meta-analyses (PRISMA).

In the electronic databases previously exposed, the search has been carried out with the following Mesh terms: “Endophytic” (“kidney neoplasms” [MeSH Terms] OR (“kidney” [All Fields] AND “neoplasms” [All Fields]) OR “kidney neoplasms “[All Fields] OR (“renal”[All Fields] AND “tumor”[All Fields]) OR “renal tumor”[All Fields]) AND “intraparenchymal” [All Fields]. Study selection inclusion and exclusion criteria of studies were identified before the literature search. All eligible studies were included if they met the following criteria: Studies comparing different surgical approaches for the treatment of endophytic renal tumors; and descriptive studies about total endophytic renal tumors and related articles (Fig. 1). Exclusion criteria were as follows: studies about animal research, non-English language or abstracts of congresses. Study selection was independently performed by two reviewers (JPA, JVSG) and disagreements in this procedure were resolved by consensus. The reviewers independently carried out data extraction by searching the full texts of included studies. The extracted data were: number of cases, *patient characteristics*: Age, gender, comorbidity CCI (Charlson Comorbidity Index), ASA, or solitary kidney (yes/no). *Tumor*: size, R.E.N.A.L, or P.A.D.U.A. scores. *Intraoperative variables*: operative time, ischemia time (Cold/Warm), tumor localization (intraoperative ultrasound or isotopes marking), intraoperative complications (Clavien-Dindo classification), estimated blood loss. *Postoperative variables*: complications, length of stay. *Clinical outcomes*: local recurrence, distal recurrence, glomerular filtration after, early and latest and TRIFECTA criteria.

The search of databases provided a total of 685 citations and four related articles. Of these, 652 studies were discarded because after reviewing the 689 summaries, they did not comply with the PICO (Patient, Intervention, Comparison, and Outcome) question. Three studies were discarded because the full text of the study was not available or it was in a different language from English. The full text of the remaining 34 citations was examined in more detail, but 20 were not associated with the stated objective. Only 14 studies met the inclusion criteria. The general quality of the evidence was evaluated with the GRADE scale.

Results

Fourteen articles were analyzed and a total of 2383 nephrectomies were collected, of which 620 were endophytic tumors. Of these 14 articles, only eight were comparative retrospective studies, six were descriptive (Table 1).

According to the GRADE score, the overall quality of the evidence was low. We only found articles that have been retrospectively analyzed and descriptive articles with very little

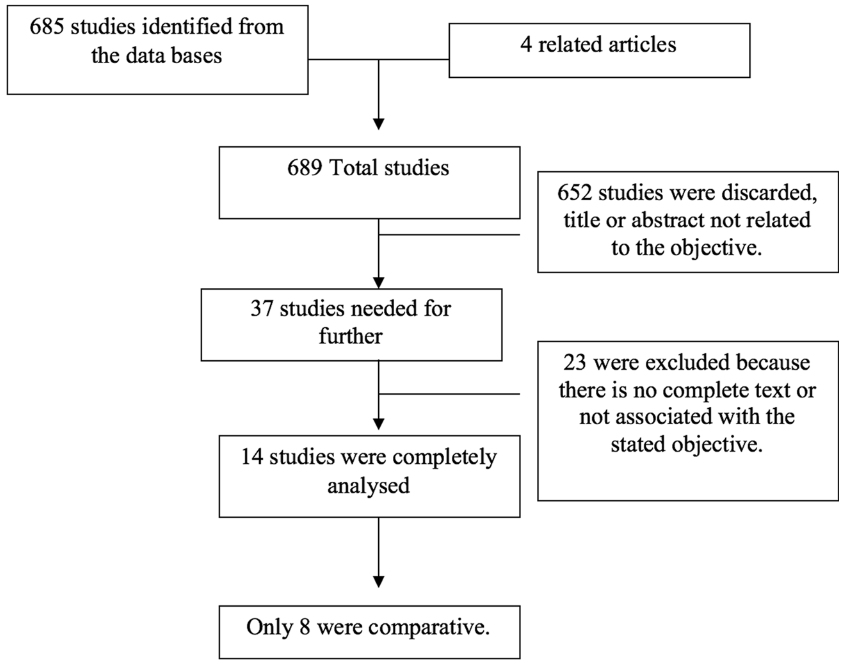

Fig. 1 Flowchart showing screening studies for the systematic review

population. The analysis of the data through a meta-analysis could not be carried out due to the heterogeneity of the information in the different articles.

Regarding the population studied in each article, they were patients in general of comparable populations among the studies. They do not have much comorbidity, measured by the Charlson Comorbidity Index or by the ASA classification carried out by the anesthetists. Most studies reported patients with a Charlson index of 1 or 0 or an ASA I or II risk. On the other hand, there seem to be differences in the presence of a solitary kidney, when we talk about the access route, so in two of the eight articles, this difference in favor of the open path is shown, this difference being statistically significant $p < 0{,}01$ [8••, 12••]. Regarding the characteristics of the tumor, the endophytic tumor is usually smaller than exophytic in the reporting studies [9•, 10]. To evaluate the difficulty of the

Table 1 Data presented as mean or rate, of all the studies

STUDY	Patients	Endophytic	Intervention	Study type	Size cm
Kara et al. [8••]	143	143	RAPN 87/OPN 56	Retrospective	2.1 cm (2.1–3.7)
Autorino et al. [9•]	389	65	RAPN endophytic 65/mesophytic 145/exophytic 175	Retrospective	2.6 cm (1,6–3,6)
Chung et al. [10]	800	55	PLN endophytic 55/exophytic 745	Retrospective	2.3 cm (1–4.5)
Hernández et al. [11]	1	1	PLN using TC99	Descriptive	5 cm
Harke et al. [12••]	140	140	RAPN 64/OPN 76	Retrospective	2.5 cm (1.8–3.0)
DI Pierro et al. [13]	11	11	Endophytic PLN	Descriptive	1.6 cm (1.2–2.0)
Zapala et al. [14]	46	17	Retroperitoneal OPN endophytic 17/exophytic 29	Retrospective	2.5 cm (1.1–3.9 cm)
Nadu et al. [15]	443	41	PLN endophytic 41/exophytic 402	Retrospective	2.6 cm (1.8–3.4 cm)
Weight et al. [16]	23	23	PLN with gelatine matrix-thrombin	Descriptive	2.5 cm (1.7–5 cm) range
Dall'Oglio et al. [17]	10	10	OPN	Descriptive	2.3 cm (1.5–3.5)
Komninos et al. [18]	225	45	RAPN endophytic 45/mesophytic 116/64 exophytic transperitoneal	Retrospective	2.7 cm (1.5–3.7)
Mullerard et al. [19]	118	35	OPN endophytic 35/exophytic 83	Retrospective	3.5 cm (1.5–7) range
Black et al. [20]	33	33	OPN	Descriptive	3.8 cm (1.3–7.5) range
Santos et al. [21]	1	1	PLN	Descriptive	2.9 cm

RAPN robot-assisted partial nephrectomy, *PLN* partial laparoscopic nephrectomy, *OPN* open partial nephrectomy procedure, only three articles named the PADUA and the RENAL score, showing a higher RENAL score > 9 for most of patients with endophytic tumor [9•, 18].

About the intraoperative aspects, a greater time of ischemia was observed if we talk about the endophytic tumors, as well as greater bleeding (Table 2). As for the approach, there are contradictory findings, since the studies by Harke et al. [12••] and Kara et al. [8••] contradict each other regarding the surgical technique that produces the most blood loss. Thus, Kara et al. [8••] observe a mean blood loss in RAPN vs OPN (175 vs 341 mL, $p < 0.001$), otherwise Harke et al. [12••] see these differences using the hemoglobin drop grams per deciliter (2.9 vs 2.4, $p = 0.01$). Regarding the location of the tumor intraoperatively, most use ultrasound and palpation if possible with the open approach. The group of Betancourt-Hernández et al. [11] uses radioactive isotopes for pre-operative labeling but there is only one case described, so further studies are needed to confirm this technique. Also one of the articles commented on the possibility of not performing nephrorrhaphy and placing gelatin material of thrombin on the bed, in intrarenal tumors, being this technique safe in a small sample of patients [16].

Considering the complications, there are no statistically significant differences in any of the studies analyzed. A shorter length of hospital stay is exposed in a study, which compares RAPN and OPN 3 vs 5 days, $p < 0{,}001$ [8••]. However due to the poor quality of the studies, most do not make statistical comparisons of them; being unable to find out if this difference is statistically significant.

Finally, if we talk about the evolution of patients, endophytic or exophytic cases maintain the same survival, according to previously published series, as well as disease-free time (Table 2). The long-term renal function is also maintained. In the first 2 weeks, it seems that there is a fall in glomerular filtration but after 2 months these differences are equalized [18]. The TRIFECTA criteria are also not affected in any of these techniques.

Discussion

There are few studies that analyze in a focused manner the results of the surgical approach in the completely endophytic renal tumor. The advent of classification systems according to size, location, and depth [22, 23] has established an integral system that assesses in a limited way the completely endophytic character of a tumor. If on the one hand they give the maximum score to this characteristic of the tumor, on the other hand, the score of the small tumor is scarce. The original work of the Padua Score [23] reveals that only 8% of the patients included in this study were entirely endophytic.

Surgical options for endophytic renal tumors are changing along the last three decades: open or laparoscopic radical nephrectomy, open or laparoscopic partial nephrectomy, and robot-assisted partial nephrectomy. In the USA, with the availability of robotic surgery, the upward trend towards its use in the removal of endophytic kidney tumors contrasts with the decrease in open or laparoscopic surgery, as observed by the study by Mohapatra et al. [24•].

Open Partial Nephrectomy Four papers are reported in this surgical modality. In 2000, Black et al. [20] reported that between 1969 and 1997, their group performed nephron-sparing surgery on 311 patients, of which 33 (10.6%) had central location. They established that this surgical approach for endophytic tumors is not a standard procedure. They had always the necessary equipment for bench surgery available. They used ultrasound intraoperatively to localize the tumor and rule out multifocality. The renal artery was clamped and slush ice was applied to the surface of the kidney. Tumor was resected via a transparenchymal incision or via exploration from the renal hilum. A transparenchymal approach and blunt dissection were the preferred options preserving the parenchyma and vessels. Four cases were oncocytomas and 19 renal cell carcinomas. Local tumor control was excellent. One patient died postoperatively of heart failure and four patients had complications related to surgery (one hemorrhage and three urinary fistulas). Five years later, Mullerad et al. [19] described a cohort of 118 patients who were operated between 1993 and 2002. Thirty-five patients (29.6%) were localized centrally inside the renal parenchyma (endophytic). Nephron-sparing surgery (NSS) for this kind of tumors demands special surgical expertise and is associated with a greater complication rate compared with peripheral tumors. Two patients required finally nephrectomy due to complications. Twenty five percent were benignant tumors. In 2012, Dall'Oglio et al. [17] described 187 open partial nephrectomies and among them ten patients with endophytic tumors underwent anatrophic nephrotomy. They used ultrasound to identify the tumor borders and depth. The mean pre-operative serum creatinine was 0.88 mg/dL, and the post-operative value was 0.94 mg/dL, measured 2 weeks after surgery. Twenty percent of the tumors were benign. Recently, Zapala et al. [14] compared the evolution of 17 patients with endophytic versus 29 with exophytic tumors who underwent open partial nephrectomy between 2007 and 2012. There were no significant intraoperative, functional, or oncological differences between both groups.

Laparoscopic Partial Nephrectomy In the series reported by Chung et al. [10], it was demonstrated that the laparoscopic approach in 55 endophytic tumors of 800 patients (6.9%) who underwent laparoscopic partial nephrectomy did not highlight differences among the different cohorts studied (endophytic, exophytic, infiltrating of the sinus, non-infiltrating of the sinus) regarding the rates of intraoperative and postoperative complications, rate of positive margins, time of extirpation

Table 2 Data presented of the comparative studies

Study	Epidemiology	Tumor	Intraoperative	Postoperative	Clinical outcomes
Kara et al. [8••]	No differences: age, CCI OPN: more in solitary kidneys ($p < 0.001$)	No differences: R.E.N.A.L. or size	Mean blood loss (175 vs 341 mL, $p < 0.001$) and intraoperative transfusion rates (0 vs 7.1%, $p = 0.02$) lower in RALP. No differences: ischemia, complications	RALP lower hospital days (3 vs 5 days, $p < 0.001$)	No differences: recurrence nor eGFR
Autorino et al. [9•]	No differences: CCI, BMI Exophytic: more age $p < 0.001$)	Endophytic: > R.E.N.A.L. < size ($p < 0.001$) no differences: malignant	Less ischemia time in exophytic ($p < 0.001$). No differences: transfusions, complications	No differences: complications (Clavien)	No differences: trifecta, recurrence nor eGFR
Chung et al. [10]	No differences: age, CCI, gender	endophytic: < size ($p < 0.001$)	No differences: transfusions, complications, ischemia time	No differences: complications (Clavien)	No analysis
Harke et al. [12••]	OPN > solitary kidneys < Charlson ($p < 0.001$)	No differences: size, R.E.N.A.L.	Transperitoneal, ischemia time, blood loss < OPN ($p < 0.01$)	No differences: complications (Clavien)	No differences: trifecta, nor eGFR
Zapala et al. [14]	No differences: age, comorbidities (ASA), gender	No differences: size	More clamping in endophytic ($p < 0.01$). No differences: ischemia time	No differences: complications (Clavien)	No differences: trifecta, nor eGFR
Nadu et al. [15]	No differences: age, comorbidities gender	No differences: size	Endophytic > blood loss and radical nephrectomy (risk of bias, multiple tumors)	No differences: complications (Clavien)	No differences: margins, nor eGFR
Komninos et al. [18]	Endophytic < women No differences: age, comorbidities (ASA)	Endophytic > renal No differences: size	More clamping in endophytic ($p < 0.01$) No differences: ischemia time	No differences: complications (Clavien)	Endophytic 2°weeks < eGFR No differences: trifecta, nor glomerular filtration in 3 months
Mullerard et al. [19]	No analysis	No analysis	Endophytic > blood loss, closure of collecting system ($p < 0.05$)	No analysis	Endophytic > local recurrence ($p = 0.04$) but no differences for survival

CCI Charlson Comorbidity Index, *BMI* body mass index, *ASA* American Society of Anesthesiologist, *R.E.N.A.L.* radius, endophytic, nearness to the collecting system or sinus, anterior/posterior, location, *RAPN* robot-assisted partial nephrectomy, *PLN* partial laparoscopic nephrectomy, *OPN* open partial nephrectomy, *eGFR* estimated glomerular filtration rate

or warm ischemia, or blood loss. Evaluation of collecting system entry is performed by administration of indigo carmine through a ureteral catheter. One patient (1.8%) required open conversion. In 15 patients (27%) the tumor was benign. They also presented their initial experience with the robotic and laparoscopic technique of zero ischemia in 15 endophytic tumors, achieving results similar to those of the global series. Santos et al. [21] report a case with incidental renal mass of 2.9 cm, completely endophytic (R.E.N.A.L score 9p) with similar success. Di Pierro et al. [13], in a series of 208 LPNs, found 11 cases of endophytic hilar tumors. They inject indigo carmine intravenously to recognize any collecting system opening. One patient had an oncocytoma and ten had renal cell carcinoma. No conversion to open surgery was required. In the study of Nadu et al. [15], a total of 402 patients who underwent LPN were analyzed, being endophytic tumors 41 (10, 1%). Four patients (9.7%) were converted to radical nephrectomy due to three main reasons: (i) the finding of an additional adjacent tumor abutting the renal sinus; (ii) the inability to correctly locate a small tumor deep in the renal parenchyma; and (iii) the extensive opening of the collecting system in the center of the kidney leaving the upper and lower pole collecting systems almost completely separated. Conversion to RN rate in the control group was lower (5.3%). In other parameters like postoperative complications, there were no significant differences. Positive margin rates were similar, 5.4% in the endophytic group and 6.2% in the control group. It is important to highlight that this group with extensive experience in laparoscopic nephrectomy reveals these last two facts related to the removal of endophytic tumors (conversion rate to radical nephrectomy and margin positivity) that are very close to the reality we have lived.

Robot-Assisted Partial Nephrectomy (RAPN) The rise of robotic surgery and the increasing experience in minimally invasive nephron-sparing surgery allow highly qualified urologists to perform RPN in especially complex cases as is the situation of endophytic renal tumors. Autorino et al. [9•] in 2013 were the first to report their results of RAPN for 65 patients (16.7%) with complete intraparenchymal renal tumors compared with two groups of mesophytic (145 patients) and exophytic (179 patients) tumors. Regarding surgical technique, they highlight the difficulty related to tumor localization, due to the lack of external visual cues on the kidney surface. Routine use of intraoperative US is the solution to this problem. In experienced hands, RAPN offer functional outcomes comparable with those of LPN for endophytic tumors, but with a significantly lower risk of conversion to radical nephrectomy. There were no differences for intraoperative and postoperative complications or length of hospital stay.

There was no difference in the positive margin rate between the groups. In 2014, Komninos et al. [18] described their results of RAPN in 225 patients. Forty five of them were endophytic. Five patients required conversion to radical nephrectomy, with two of them having endophytic tumors. The endophytic group patients showed higher rates of positive surgical margins in comparison with the mesophytic and exophytic groups (12.5%, 4%, and 2.1%, respectively) but without repercussion on specific and overall survival. Kara et al. [8••] analyzed 87 RAPN and 56 OPN cases performed for completely endophytic renal tumors among 1230 consecutive cases, consisting of 823 RAPNs and 407 OPNs, performed for renal mass between 2011 and 2016. They conclude that for completely endophytic tumors, there was not a difference in complications, oncological outcomes, or functional outcomes between the robotic and open approaches. This year, Harke et al. [12••] report their analysis of a total of 1493 partial nephrectomies performed April 2008 and September 2016. Overall, 140 (12.4%) consecutive patients with completely endophytic tumors were identified. OPN was performed in 76 and RAPN in 64 cases. Conversion from RAPN to robotic radical nephrectomy was necessary in one patient. Positive surgical margins were found in two patients after OPN while the margins generally were negative in the RAPN group. Applying TRIFECTA criteria, good results are achieved. The information available for this review support the use of NSS even for endophytic tumors using the surgeon's preferred approach.

Technical Contributions Weight et al. [16] described an alternative technique of laparoscopic partial nephrectomy (LPN) for selected central tumors that avoid bolstered renorrhaphy. They apply this technique in 23 patients achieving a closure of central LPN defects with a running intrarenal pelvicalyceal suture and gelatine thrombin matrix, avoiding the need for bolstered renorrhaphy, simplifying the technique of LPN. With regard to the location of the endophytic tumor, most of the studies reviewed use ultrasound as an intraoperative system for locating the tumor. Betancourt–Hernández et al. [11] have implemented the application of the Radio-guided Occult Lesion Localization technique (ROLL) from breast tumor surgery in order to make easier the detection of endophytic tumors. Preoperatively and under local anesthesia and ultrasound guided by a central wheal, 10 mCi 99 mTc with macroaggregated albumin is injected. After 20 min, a planar scintigraphy and 2 h after injection a SPECT were performed. During surgery, renal parenchyma is exposed, and a gamma probe and a gamma camera locate the tumor. Laparoscopic partial nephrectomy is performed subsequently as normal but using Tc99 activity guide by gamma probe and gamma camera allowing a correct and complete dissection of the tumor. There is only one case described with this technique and more casuistry is needed to confirm its usefulness to facilitate the location and complete excision of the tumor.

Conclusion

Currently, small tumors represent a high percentage of new diagnosed renal cancers and endophytic tumors, despite being a minority, are more difficult to locate and remove than exophytic tumors. Outcomes for OPN, laparoscopic, and RAPN for endophytic tumors are excellent when performed at high surgical volume centers by experienced surgeons. Therefore, selection of surgery should depend on surgeon experience and comfort with either approach. It is also important to develop methods that facilitate the localization and safe extirpation of these tumors.

Compliance with Ethical Standards

Conflict of Interest Javier Perez-Ardavin, Jose Vicente Sanchez-Gonzalez, Manuel Martinez-Sarmiento, Juan Jose Monserrat-Monfort, Jorge García-Olaverri, Francisco Boronat-Tormo, and César D. Vera-Donoso each declare no potential conflicts of interest.

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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• Of importance

•• Of major importance

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