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Featured Articles

Minimally invasive surgery for pediatric renal tumors: A systematic review by the APSA Cancer Committee

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ABSTRACT

Minimally invasive nephrectomy is performed routinely for adult renal tumors and for many benign pediatric conditions. Although open radical nephroureterectomy remains the standard of care for Wilms tumor and most pediatric renal malignancies, there are an increasing number of reports of minimally invasive surgery (MIS) for those operations as well. The APSA Cancer Committee performed a systematic review to better understand the risks and benefits of MIS in pediatric patients with renal tumors.

Methods: The search focused on MIS for renal tumors in children and followed the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) checklist. The initial database search identified 491 published articles, and after progressive review of abstracts and full-length articles, 19 were included in this review.

Results: There were two direct comparison studies where open surgery and MIS were compared. The remaining studies reported only on minimally invasive nephrectomy. Across all studies, there were a total of 151 patients, 126 of which had Wilms tumor and 10 patients had RCC. 104 patients had MIS, with 47 patients having open surgery. In the two studies in which open surgery and MIS were directly compared, more lymph nodes were harvested during open surgery (median = 2 (MIS) vs 5 (open); mean = 2.47 (MIS) vs 3.8 (open)). Many noncomparison studies reported the harvest of 2 of fewer lymph nodes for Wilms tumor. Several MIS patients were also noted to have intraoperative spill or positive margins. Survival between groups was similar.

Conclusions: There is a lack of evidence to support MIS for pediatric renal tumors. This review demonstrates that lymph node harvest has been inadequate for MIS pediatric nephrectomy and there appears to be an increased risk for intraoperative spill. Survival data are similar between groups, but follow-up times were inconsistent and patient selection was clearly biased, with only small tumors being selected for MIS.

Type of study: Review article.

Level of evidence: III.

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Survival for pediatric renal tumors has improved dramatically over the past several decades. For Wilms tumor, which accounts for nearly 90% of pediatric renal tumors, patient survival was below 50% prior to the initiation of chemotherapy in the early 1960's [1]. The most recent completed Children's Oncology Group (COG) studies show a 5-year overall survival (OS) above 90% [2–5] This improvement in survival has led to a parallel effort to increase quality of life for survivors by decreasing treatment morbidity while continuing to improve outcomes.

A minimally invasive approach to nephrectomy is a potential method to decrease treatment morbidity. Minimally invasive surgery (MIS) offers several well-accepted advantages over open surgery, including decreased postoperative length of stay, decreased pain, and improved cosmesis. [6–15]. An MIS approach to nephrectomy for malignancies is widely practiced in adults, primarily for renal cell carcinoma (RCC), and there are good data to support this practice [16–18]. Conversely, there are no published prospective studies on the use of MIS for renal tumors in children, and we do not yet understand how this approach could affect oncologic outcomes. Despite this lack of evidence, the technique is utilized by some surgeons. A systematic review was performed to better understand the risks and benefits of MIS for definitive resection in pediatric patients with renal tumors.

1. Methods

1.1. Search strategy

The search was conducted by a medical librarian following the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) Checklist from November 2017 to March 2018. The search focused on minimally invasive surgery for renal tumors in children and young adults. The librarian used the MeSH headings "Kidney Neoplasms" and the subheading "surgery" as well as the MeSH term "Laparoscopy" along with natural language terms "laparoscopic approach" and "nephron sparing surgery" to get a broad yet targeted dataset. Published articles, dissertations, and gray literature were searched using Medline, Embase, Web of Science, ProQuest Dissertations, and Clinical Trials. The limiters were humans, "all child" and "young adult", and last 20 years. The resulting abstracts were then reviewed for relevancy and then the associated manuscripts were reviewed by the authors for inclusion in this review [19].

1.2. Study selection

Inclusion criteria for this systematic review were pediatric manuscripts focused on a minimally invasive approach to nephrectomy for renal tumors. Exclusion criteria were nononcologic indication for surgery, open only techniques, and patient age >21 years old. Three members of the review team (JA, TH, MM) performed manual reviews of the identified abstracts. If no consensus was reached on an abstract, it was excluded. Full text review was performed by JA, TH, and MM.

1.3. Data extraction and analysis

The study characteristics and data points extracted from each study include operative details, specifically operative technique (open versus laparoscopic), estimated blood loss, operative time, number of lymph nodes harvested, and incidence of tumor rupture. Also included were the number of patients, patient age, tumor size/dimensions, chemotherapy administration details, tumor histology, tumor stage, postoperative complications, length of stay, length of follow-up, overall survival (OS) and event free survival (EFS). These data were extracted, verified, and analyzed by the authors. The Cochrane risk of bias tool [20], which determines the level of bias as high, low, or unclear based on an assessment of selection, attrition, and reporting, was also utilized.

1.4. Search outcomes

The initial database searches identified 473 published articles. Our manual review of references identified an additional 18 nonduplicate studies for abstract evaluation. Of these 491 studies, we eliminated 452 during abstract review and an additional 17 after full-text review based on the defined exclusion criteria described earlier. The remaining 22 studies serve as the basis for the systematic review. The selection process, based on the PRISMA schema, is detailed in Fig. 1. The level of evidence for each article was recorded, based on the standard definitions (Table 1).

2. Results

2.1. Overview of studies

There were 22 studies that discussed utilizing minimally invasive techniques for definitive resection of a renal tumor [21–42]. After adjusting for duplicates, 19 studies remained. All studies were retrospective reviews, case reports, or case series. There were two studies that directly compared nonrandomized open and minimally invasive nephrectomy, while the rest reported data on only minimally invasive nephrectomies. Two studies included duplicate patients previously

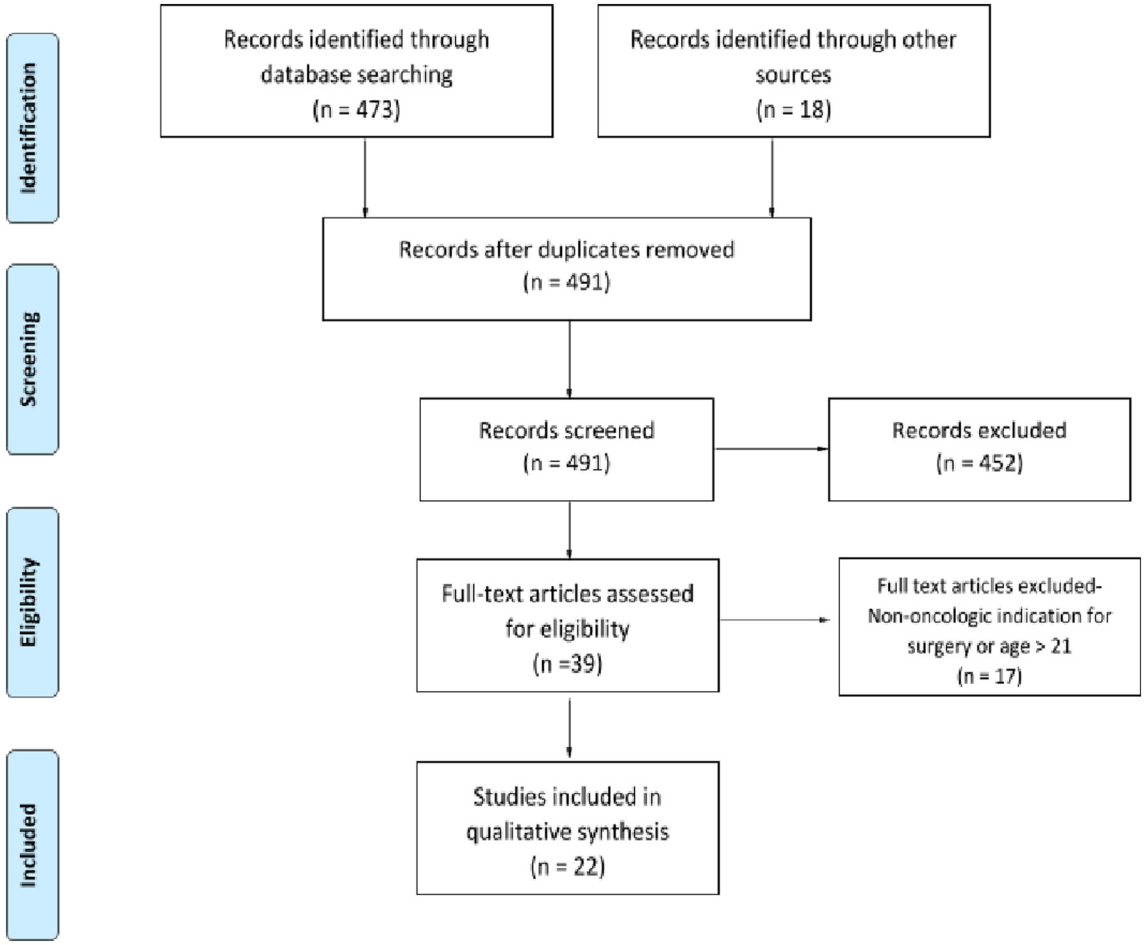

Fig. 1. PRISMA diagram.

discussed in the authors' earlier papers [21–26], so only the most recent study from those groups was included in the analysis. Statistical analyses presented here are those from the individual studies, as the data reporting was not standardized, precluding amalgamation and comparison of data between studies.

Of these 19 studies, 11 were specific to Wilms tumor (WT), 3 included renal tumors of various histology, 1 was a case report of a renal cell carcinoma (RCC), and 4 studies reported on 1 to 2 patients with other rare renal tumors. In total, the tumor histology presented included 126 WT (87 minimally invasive surgery (MIS), 39 open), 10 RCC (6 MIS, 4 open), 3 cystic nephromas (2 MIS, 1 open), 2 rhabdoid tumors of the kidney (RTK; 1 MIS, 1 open), 2 metanephric adenomas (both MIS), 2 clear cell sarcomas of the kidney (CCSK; 1 MIS, 1 open), and 1 each of the following: reninoma (MIS), extraosseous Ewing's sarcoma (MIS), mesoblastic nephroma (MIS), epithelioid cell tumor (MIS), renal medullary carcinoma (MIS), and undifferentiated sarcoma (open).

All studies in this analysis present a significant risk of bias based on the Cochrane risk of bias tool. There was no attempt at blinding, subjects reported on in each study were not selected randomly, and the studies do not present standardized outcome data.

Table 1
Levels of evidence.

Levels of evidence described:
Level I Evidence from properly conducted randomized controlled trials
Level II Evidence from controlled trials without randomization, or cohort or case–control studies, or multiple time studies.
Level III Evidence from descriptive case series, opinions of expert panels.

2.2. Technical details

Minimally invasive nephrectomy can be performed in several different ways. Fifteen studies described a transperitoneal MIS approach (101 pts), while 3 described the procedure via a retroperitoneal laparoscopic approach (3 pts). Hand-assistance was utilized in one patient. Conversion to an open nephrectomy was required in three patients (3%). A nephron-sparing technique was described in 6 studies for a total of 8 patients, 3 of whom had WT and were predisposed to metachronous tumors. Seventeen studies discussed the technique used for specimen removal. One study described specimen morcellation as their extraction method in 7 patients (5 with WT) [32]. Tumor extraction through an enlarged port (13 patients in 7 studies) or via a Pfannensteil incision (65 patients in 7 studies), or a mix of both (1 study) was the more commonly described technique.

2.3. Operative details

Twelve of the studies reported the estimated blood loss (EBL) for a total of 65 cases (50 laparoscopic, 15 open). Overall, average EBL for laparoscopic operations was 47.2 mL (range 0–180 mL), while the average blood loss for the open operations was 75 mL. For the only study directly comparing laparoscopic to open surgery that described EBL, mean EBL for 15 open cases was 75 mL, while the mean EBL for 24 laparoscopic cases was less than 50 mL [21].

Operative time was reported in 14 studies, totaling 135 patients (88 laparoscopic, 47 open). In total, the average operative time for laparoscopic cases was shorter than that of open cases (192.6 min vs 222.6 min). However, in the two studies which directly compared open to laparoscopic nephrectomy, the laparoscopic cases were slightly longer. Romao et al. [27] reported an average of 263 ± 81 min for 32 open cases, and 282 ± 79 min for 13 laparoscopic cases ($p = 0.5$). Likewise, Duarte et al. [21] noted a mean time of 136.3 ± 16 min for open cases versus 165 ± 27 min for laparoscopic cases ($p = 0.377$).

2.4. Complications

In the two studies that compared open and laparoscopic techniques directly, complications were noted in both groups. Romao et al. [27] reported one small bowel obstruction and one incisional hernia out of 32 open nephrectomy patients and one incisional hernia out of 13 laparoscopic patients. Duarte et al. [22] reported one surgical bed hematoma out of 15 open patients and one incisional hernia out of 24 laparoscopic patients. Other complications noted in the remaining MIS studies include an intraoperative splenic injury necessitating splenectomy [28] and a small bowel perforation [26]. One study noted a positive margin in three of 24 patients undergoing minimally invasive nephrectomy for Wilms tumor, two of which were detected by the surgeon intraoperatively [28]. Rupture within the extraction bag led to the subsequent upstaging of one patient by the managing physicians in an additional study [27]. There were 9 studies (19 patients) that reported no complications, and 7 studies that did not specifically address or mention complications (Table 3). When limiting to studies that reported on complication rates, there were 3 complications out of 47 patients in the open surgery group (6.4%) and 8 complications out of 102 patients in the MIS group (7.8%).

2.5. Direct comparison studies (MIS vs open)

Two studies directly compared laparoscopic to open nephrectomies. Romao et al. [27] retrospectively compared 32 patients undergoing open nephrectomy to 13 patients undergoing laparoscopic nephrectomy over a period of five years. Demographics were similar between patients. Of the 45 tumors resected, 31 (68%) were WT (Table 2). Only 4 open nephrectomy patients and 2 laparoscopic nephrectomy patients underwent preoperative chemotherapy (6/45 patients; 13.3%). The open nephrectomy group had significantly larger tumors than the MIS group (largest dimension 10.99 ± 2.99 cm open vs 6.59 ± 1.88 cm MIS, $p<0.001$). Operative time was similar between cohorts (263 ± 81 min open vs 282 ± 79 min laparoscopic, $p = 0.5$). Open nephrectomy yielded a significantly higher number of lymph nodes with a median of five lymph nodes in open cases (range 2–29) versus two (range 1–14) in MIS ($p = 0.008$). The adrenal gland was spared more often in laparoscopic patients compared to open patients (69% vs 31%, $p = 0.04$). Laparoscopic nephrectomy required a decreased mean duration of narcotics, even with liberal use of epidural anesthesia in open patients (2.15 days MIS vs 3.26 days open, $p = 0.04$). Laparoscopic nephrectomy patients also had a shorter length of stay (2.9 days MIS vs 5.9 days open, $p = 0.002$), and did not require a nasogastric tube (0% vs 56% in open patients for a mean of 1.6 days). EFS was similar in both groups at 87.5% for open surgery patients (median follow-up of 33 months) and 92.3% for MIS patients (median follow-up of 18 months; $p = 1.0$).

The laparoscopic cohort was initially selected based in part on tumor size and presumed feasibility of a minimally invasive approach, with the largest laparoscopically resected tumor measuring 9 cm in diameter. A subgroup analysis was performed to better match patients by the size of their tumor, in which the laparoscopic group was compared to open patients whose tumors were less than 10 cm ($n = 11$). EFS remained similar between groups (92.3% MIS vs 90.9% open, $p = 1.0$). Length of hospital stay (2.92 ± 1.38 days MIS vs 4.5 ± 1.69 days open, $p = 0.02$) and duration of nasogastric tube drainage (0 day MIS vs 2.7 days open, $p<0.001$) remained significantly shorter for laparoscopic nephrectomy patients. Duration of operation did obtain significant difference in this subgroup, with the laparoscopic procedures taking longer (281 ± 82 min vs 214 ± 35 min, $p = 0.01$). Additionally, the difference in mean duration of narcotics was no longer significant.

The other study to directly compare laparoscopic versus open was that by Duarte et al. [21]. As the cohorts in that paper universally had a diagnosis of Wilms tumor, it is discussed in depth in the section on Wilms.

2.5.1. Wilms tumor

Fifteen of the reviewed studies included one or more patients with a diagnosis of Wilms tumor, accounting for 135 unique patients. 96 of these underwent MIS, and 39 underwent open operations. 103 patients (76.3%) received neoadjuvant chemotherapy.

2.6. Direct comparison study

Only one study compared open and laparoscopic nephrectomy solely in patients with Wilms tumor [21]. In this series of patients, collected over a seven-year period, the laparoscopic operation resulted in fewer lymph nodes harvested and longer operative times, but a shorter length of stay (Table 2). The average volume of the tumors in the two groups was significantly different, with the mean volume of the open group 540.07 ± 423.3 mL and the mean volume of the laparoscopic group 217.97 ± 85.05 mL ($p = 0.002$) [21]. The EFS for the two groups was similar, 86.7% (open) compared to 94.1% (laparoscopic) at a median of 4.29 years of follow-up (Table 3).

2.7. Lymph node harvest

Of the 15 studies that were specific to, or included Wilms tumor, 11 included data about lymph node harvest. One study that compared open (32 patients) to laparoscopic (13 patients) nephrectomy for various types of renal tumors showed that open nephrectomy was associated with a significant increase in the number of lymph nodes harvested (median 5; range 2–29) compared to laparoscopic nephrectomy (median 2; range 1–14; $p = 0.008$) [27]. Unfortunately, this study did not specify lymph node numbers by type of tumor, however overall 68.9% of tumors in this study were WT. The other comparison study, which was specific to WT, showed that the average number of lymph nodes obtained was likewise greater for the open surgery group (average 3.8 ± 2.08, range 1–9) compared to the laparoscopic group (average 2.47 ± 2.87, range 1–13, $p = 0.006$) [21]. With their follow-up study in 2017, Duarte et al. [22] examined a larger number of MIS patients (including the original patients from their 2014 paper), and the number of lymph nodes harvested increased slightly (average 2.52 ± 2.57, range 1–13).

The remaining articles examined laparoscopic nephrectomy alone, and the number of lymph nodes harvested (if reported) varied. The two largest noncomparison studies, which included 24 and 17 patients, reported a mean number of lymph nodes obtained of 2.0 (range 0–11) [28] and 3.4, respectively [26]. Other smaller case reports of one or two patients noted lymph nodes ranging between 0 and 7 [29–31,33–35]. Three of these reported taking zero lymph nodes [29–31].

2.8. Outcomes

Overall, 103 patients with WT were followed postoperatively, although the reported follow up time frame varied considerably between studies (Table 3).The range varied from as little as 3 months postoperatively [31] to over 9 years [21]. Looking at all studies, 96 out of 103 patients remained free of disease at follow up, representing an overall EFS of 93.0%. EFS was 94.3% for the laparoscopic patients (83/

Table 2
Patient and operative details.

Source	No. of patients (*n*)	Average age	Histology	Preop. chemo (*n*)	EBL (mL)	OR time, mean (min)	Average tumor volume (cc) [Largest dimension if vol. not available]	No. of lymph nodes (*n*)	Gross intraop rupture (%)	Average LOS (days)
Romao	45									
Open	32	Median = 3.5 yr. (2 mo.–15 yr.)	Wilms (24) 75% RCC (4) 12.5% Other (4) 12.5%	4	NR	263 ± 81	Largest dimension, avg. (cm): 10.99 ± 2.99 (4.2–18.5)	Median = 5 (2–29)	0	5.9
Laparoscopic	13	Median = 4 yr. (2 mo.–17 yr.)	Wilms (7) 53.85% RCC (4) 30.77% Other (2) 15.38%	2	NR	282 ± 79	Largest dimension, avg. (cm): 6.59 ± 1.88 (3.1–9)	Median = 2 (1–14)	0	2.9
Duarte (2014)[a]	32									
Open	15	47.3 ± 39 mo. (3.6–168.7 mo.)	Wilms (15) 100% All "favorable" histology	15	Mean = 75	136.3 ± 16 (110–162)	540.07 ± 423.3	Mean = 3.8 ± 2.08 (1–9)	0	2–3
Duarte (2017)	24	38.0 ± 23.4 mo. (10–93 mo.)	Wilms (24) 100% Favorable (23) Unfavorable (1)	24	Mean < 50	165 ± 27 (120–195)	211.73 ± 74.3	Mean = 2.52 ± 2.57 (1–13)	0	2.3
Warmann	24	38.7 mo. (14.3–65.4 mo.)	Wilms (24) 100% Intermediate risk (20) High risk (3) No records (1)	24	NR	NR	Median volume = 73.0 (3.8–776)	Mean = 2 (0–11)	0	NR
Varlet (2014)	17	Median age = 26 mo. (5 mo.–11 yrs)	Wilms (15) 88.24% RCC (1) 5.88% Clear cell sarcoma (1) 5.88%	16	NR	Median = 124 (70–210)	Largest dimension (cm) < 5 (*n* = 14), > 5.1 (*n* = 3)	Mean = 3.4	0	Median = 3 (2–10)
Duarte (2006)	8	44.3 mo. (19–70 mo.)	Wilms (8) 100% All "favorable" histology	8	30–50	135 (120–180)	Largest dimension, avg. (cm): 9.7 (5–12.5)	3–12	0	2–3
Liu	7	4.3 yr. (1.5–10 yr.)	Wilms (5) 71.42% (All favorable, 4 low risk, 1 high risk) RCC (1) 14.29% Rhabdoid (1) 14.29%	3	Mean = 13.5 (5–30)	97 (75–150)	Largest dimension, avg. (cm): 6.8 ± 2.5 (4.5–10)	NR	0	Median = 8.5 (6–11) [a]*with inpt. 1st round of chemo*
Varlet (2009)	5	4 yr. (11 mo.–10 yr.)	Wilms (2) 40% Cystic Wilms (1) 20% RCC (1) 20% Clear cell sarcoma (1) 20%	4	0	90 (60–117)	75.25 (55.12–92.45)	Mean = 3 (2–4)	0	Median = 2 (2–3) [a]*not including intest perf patient of 10 d*
Barbancho	4	43 mo. (23 mo.–6y)	Wilms (4) 100%	4	NR	125 (90–160)	446.55 (150.7–502.6)	NR	NR	3 (2–4)
Tanaka	2	9 mo.	Cystic nephroma (2) 100%	No	180 and 100	460, 415	60.46 and 78.26	NR	0	11 (7–15)
Ozden	2	12 yr. (10–14 yr.)	Metanephric adenoma (2) 100%	No	50 and <100	NR	Largest dimension (cm): 2.0 and 6.7	NR	NR	2
Barber	2	14 mo., 16 yr.	Wilms (2) 100% Favorable (1) Anaplastic (1)	No	25 and 300	252, 304	359.0 and 348.16	0 and NR	0	2.5 (2–3)
Duarte (2004)	2	4.5 yr. (4–5 yr.)	Wilms (1) 50% "No viable tumor" (1) 50%	2	50 and 50	120, 180	126 and 260	Mean = 5.5 (4–7)	0	2
Rauth	1	10 mo.	Wilms (1) 100% Favorable histology	1	NR	NR	Largest dimension (cm): 1.0 & 1.6	0	0	2
Xu (2012)	1	15 yr.	Reninoma (1) 100%	No	NR	NR	100	NR	NR	NR
Xu (2013)	1	10 yr.	Wilms (1) 100% Favorable, epithelial predominant histology	No	NR	NR	308	NR	NR	NR
Perer	1	10 yr.	Ewing's sarcoma (1) 100%	1	100	180	Largest dimension (cm): 9.0	NR	NR	NR

(continued on next page)

Table 2 *(continued)*

Source	No. of patients (*n*)	Average age	Histology	Preop. chemo (*n*)	EBL (mL)	OR time, mean (min)	Average tumor volume (cc) [Largest dimension if vol. not available]	No. of lymph nodes (*n*)	Gross intraop rupture (%)	Average LOS (days)
Javid	1	2 yr.	Wilms (1) 100% No evidence of anaplasia, less than 5% viable tumor cells	1	NR	NR	300	5	0	5
Cost	1	14 yr.	Wilms (1) 100% "Favorable" histology, no anaplasia	No	NR	210	105	NR	NR	2
Milhoua	1	13 yr.	Renal medullary carcinoma (1) 100%	No	<50	80	NR	1+	NR	NR
Piche	1	25 mo.	Wilms (1) 100% No anaplasia	1	"Negligible"	180	0.55	1	0	2
Chui	1	2 yr.	Wilms (1) 100% No anaplasia	No	NR	NR	Largest dimension (cm): 10	0	NR	NR

All cases laparoscopic unless otherwise specified. NR = not reported.
[a] Laparoscopic patients in this study are all included in other listed study by same author in 2017.

88) and 86.7% for the open patients (13/15). In the three largest studies examining WT specifically, the median follow-up times were 3.5, 3.9 and 4.29 years, respectively [21,26,28]. OS was inconsistently reported, but ranged from 94% to 100% in the MIS group, and was 100% in the open group [21,26,28]. The study by Romao et al. [27] (31 total WT patients) reported overall EFS of 87.5% (open) and 92.3% (MIS) but did not separate these results by histology or stage. Therefore, outcomes from this study were not included in the Wilms specific data above.

2.8.1. Renal cell carcinoma

Three studies had extractable data for pediatric RCC representing 10 distinct patients [26,27,32]. Of these, four patients underwent an open nephrectomy, while the remaining six underwent a laparoscopic nephrectomy. In the laparoscopic versus open comparison study by Romao et al. [27], there were eight total RCC patients, four in each group. The authors did not report characteristics or outcomes specifically for the RCC patients but did include them in the overall analysis. The remaining RCC patients were either from case reports, or a single patient from a larger series (Tables 2 and 3).

3. Discussion

The majority of operations for pediatric renal malignancies are performed utilizing open techniques. This is especially true for radical nephrectomy. As minimally invasive techniques have become widespread for a diverse range of operations, interest in applying these methods to pediatric renal tumors has increased, driven by reduction in pain and length of stay as well as improved cosmesis [6–15,43,44]. In the adult population, laparoscopic and laparoscopic assisted nephrectomy is common, and is often the treatment of choice for early RCC (T1–3, N0, M0) [16,18,45]. As reports of minimally invasive approaches to pediatric renal tumors have begun to enter the literature, the adoption of less invasive techniques must be judged not only by the perioperative benefits of MIS, but more importantly on oncologic outcomes. We performed this systematic review to evaluate the current literature on MIS for pediatric renal tumors and assess the risks and benefits of this approach.

It is important to emphasize that there are no level I studies that evaluate the use of MIS for pediatric renal tumors, and nearly all publications on the subject present level III data. Further, all studies presented in this analysis present a significant bias, as there was no attempt at blinding, subjects were not randomized, and the studies do not present standardized outcome data, leading to incomplete data and selective reporting.

The major apprehension with MIS for pediatric renal tumors is the concern of an inadequate oncologic operation, specifically, inadvertent tumor spill, or inadequate lymph node sampling. Lymph node sampling is critical to accurate staging and failure to sample LN has been associated with an increased risk for relapse [46–52]. Indeed, the findings of this systematic review support this concern, as the mean number of lymph nodes harvested during MIS nephrectomy for Wilms tumor was less than 3, with 0 nodes harvested in several studies [21–28,30,31,35]. Although the exact number of lymph nodes necessary for proper Wilms tumor staging has not been explicitly determined, most agree that 5–7 lymph nodes should be the target. The nodes should be harvested from the renal hilum and either periaortic or paracaval, depending on tumor laterality [23,50–52]. Upcoming COG renal tumor protocols will attempt to more clearly answer this question.

While the risk of rupture during MIS nephrectomy is not completely clear in this review, the data certainly do suggest that the risk is increased [27,28,31]. Intraoperative spill results in upstaging of local disease to stage III, which necessitates flank radiation and intensified chemotherapy (addition of doxorubicin), along with the associated short- and long-term toxicity of each modality. Specifically, this includes scoliosis, increased risk of secondary malignancies, and cardiomyopathy [53–57]. Although overall survival is typically maintained owing to treatment intensification, these late effects are significant, and monitoring for their incidence will become the most critical measure of a minimally invasive approach to Wilms tumor.

Although this review does not answer the question of what size tumor would be reasonable to approach laparoscopically, the four largest studies do provide some data. Duarte et al. recommend that the tumor's largest dimension should be less than 10% of the patient's height, although they have performed successful removal of larger tumors with a relationship up to 16% (Duarte 2016). They also recommend preoperative chemotherapy, for its effect on the size of the tumor and the resultant formation of a fibrous capsule, which helps protect against rupture. The mean volume of resected tumors in their study was 211 cm^3 (corresponding to a sphere with a 7.4 cm diameter). Varlet et al. propose criterion of unilateral tumor, absence of thrombus in the renal or caval system, and postchemotherapy tumor size that does not cross the midline [25,26]. 14/17 tumors in their study were less than 5 cm. The mean renal tumor size in the Romao study was 6.59 cm, although not all tumors in that study were Wilms tumor. Finally, the

Table 3
Tumor characteristics and outcomes

Source	No. of patients (*n*)	Complications (*n*)	EFS (%, follow-up time frame)	Histology (*n*, %)	Stage (*n*)	Notes
Romao	45					
Open	32	Small bowel obstruction (1) Incisional hernia (1)	28/32 (87.5%) Median 33 mo. (1–60 mo.)	Wilms (24) 75% RCC (4) 12.5% Other (4) 12.5%	NR	3/4 recurrences were metastatic.
Laparoscopic	13	Incisional hernia (1)	12/13 (92.3%) Median 18 mo. (1–35 mo.)	Wilms (7) 53.85% RCC (4) 30.77% Other (2) 15.38%	Recurrent patient = Stage III Wilms	Recurrent patient upstaged to Stage III owing to rupture within the extraction bag.
Duarte (2014)[a]	32					
Open	15	Surgical bed hematoma (1)	13/15 (86.7%) Median 4.29 yr. (13 mo.–9.22 yr.)	Wilms (15) 100% All "favorable" histology	Stage I (3) Stage II (4) Stage III (4) Stage IV (4)	
Duarte (2017)	24	Incisional hernia (1)	22/24 (91.7%) 6.65 yr.	Wilms (24) 100% Favorable (23) Unfavorable (1)	Stage I (11) Stage II (6) Stage III (3) Stage IV (4)	Relapse patients: One patient with Stage IV relapsed in the lungs. One patient with Stage III involving the liver had delayed radiotherapy owing to social issue.
Warmann	24	Intraoperative splenic injury necessitating splenectomy (1) Tumor rupture (3)	23/24 (95.8%) Median 47 mo. (2–114 mo.)	Wilms (24) 100% Intermediate risk (20) High risk (3) No records (1)	Stage I (14) Stage II (7) Stage III (3)	Stage III pts. had positive margins in all 3 cases. One had + LN. One had preop rupture.
Varlet (2014)	17	Small bowel perforation (1)	15/17 (88.2%) Median 42 mo. (12–77 mo.)	Wilms (15) 88.24% RCC (1) 5.88% Clear cell sarcoma (1) 5.88%	Stage I (8) Stage II (6) Stage III (1)	Stage III owing to presence of vascular tumor thrombus in renal vein margin.
Duarte (2006)	8	0	8/8 (100%) (5–23 mo.)	Wilms (8) 100% All "favorable" histology	Stage I (6) Stage II (1) Stage III (1)	
Liu	7	NR	6/6 (100%) Median 1.9 ± 1.5 yr. (0.3–2.9 yr.); *1 patient lost to follow up*	Wilms (5) 71.42% (All favorable, 4 low risk, 1 high risk) RCC (1) 14.29% Rhabdoid (1) 14.29%	Wilms Stage I (4) Stage IV (1) RCC Stage I (1)	
Varlet (2009)	5	Intestinal perforation (1)	5/5 (100%) Median 18 mo. (12–32 mo.)	Wilms (2) 40% Cystic Wilms (1) 20% RCC (1) 20% Clear cell sarcoma (1) 20%	Wilms Stage I (1) Stage II (1) Stage IV (1)	Stage IV owing to B/L pulmonary metastases.
Barbancho	4	NR	4/4 (100%) Median 3.5 yr.	Wilms (4) 100%	Stage I (2) Stage IV (2)	
Tanaka	2	NR	2/2 (100%) 1 yr.	Cystic nephroma (2) 100%	NR	
Ozden	2	0	2/2 (100%) 6 mo. & 18 mo.	Metanephric adenoma (2) 100%	NR	
Barber	2	0	2/2 (100%) 5 mo. & 16 mo.	Wilms (2) 100% Favorable (1) Anaplastic (1)	Stage II (2)	Stage II owing to involvement of hilar fat and lymphatics.
Duarte (2004)	2	0	2/2 (100%) 5 mo.	Wilms (1) 50% "No viable tumor" (1) 50%	Stage I (2)	
Rauth	1	NR	NR	Wilms (1) 100% Favorable histology	NR	
Xu (2012)	1	0	1/1 (100%) 1 mo.	Reninoma (1) 100%	NR	
Xu (2013)	1	0	1/1 (100%) 1 yr.	Wilms (1) 100% Favorable, epithelial predominant histology	Stage II	Stage II owing to renal sinus extension with vascular involvement.
Perer	1	0	1/1 (100%) 1 yr.	Ewing's sarcoma (1) 100%	NR	
Javid	1	NR	1/1 (100%) 19 mo.	Wilms (1) 100% No evidence of anaplasia, less than 5% viable tumor cells	Stage IV	Presented with B/L pulmonary metastases.
Cost	1	NR	NR	Wilms (1) 100% "Favorable" histology, no anaplasia	Stage II	
Milhoua	1	0	1/1 (100%) 7 mo.	Renal medullary carcinoma (1) 100%	NR	

(continued on next page)

Table 3 *(continued)*

Source	No. of patients (*n*)	Complications (*n*)	EFS (%, follow-up time frame)	Histology (*n*, %)	Stage (*n*)	Notes
Piche	1	0	1/1 (100%) 8 mo.	Wilms (1) 100% No anaplasia	Stage I	
Chui	1	NR	0/1 (0%) 3 mo.	Wilms (1) 100% No anaplasia	NR	Patient presented with recurrence.

All cases laparoscopic unless otherwise specified. NR = not reported. B/L = bilateral.
[a] Laparoscopic patients in this study are all included in other listed study by same author in 2017.

mean size of the tumors in the SIOP study was 5 cm. To summarize, the maximum size that would seem to be supported by all four studies is 5 cm. It is important to note that a majority of these patients received preoperative chemotherapy.

3.1. Outcomes

The four-year survival rate for unilateral WT patients with favorable histology is 90%–94% EFS and 98%–100% OS for stage I, 86% EFS and 98% OS for stage II, 88%–91% EFS and 97% OS for stage III, and 76%–85% EFS and 86%–96% OS for Stage IV [58–61]. In the current review, the length of follow-up was variable between studies, but the combined, reported EFS was 93.0% and 94.3% in the open and laparoscopic patients, respectively. Of the studies that reported detailed tumor histology, the vast majority were favorable histology. The group with the largest experience in MIS radical nephrectomy reports an EFS of 86.7% for open nephrectomy and 94.1% for laparoscopic nephrectomy at a median of 4.29 years of follow-up. [21]. Although the EFS and OS seem similar between groups and in-line with expected outcomes, it is difficult to interpret the significance of these findings owing to the selection bias in choosing smaller tumors for the MIS approach and also owing to inconsistent and often short follow-up intervals in most of the reviewed studies. It is also important to note that over 75% of patients that underwent MIS nephrectomy for Wilms tumor received preoperative chemotherapy in order to decrease tumor size. This would be a shift from standard Wilms therapy in North America, as upfront nephrectomy is the standard approach on COG protocols.

3.2. Advantages of MIS

Several studies did show statistically significant improvements in a number of postoperative metrics using laparoscopic techniques. Most notably, Romao et al. [27] directly compared open and MIS nephrectomy and demonstrated that MIS was associated with a shorter length of stay (2.9 vs 5.9 days), decreased use of postoperative nasogastric tubes, and decreased duration of narcotic use (2.15 vs 3.26 days). Comparing all open and MIS patients, neither the estimated blood loss nor the operative time showed significant differences between the open and minimally invasive methods. These perioperative data are consistent with previously published results comparing laparoscopic to open nephrectomies for adult RCC, [62,63] and for benign disease in the pediatric population [64].

3.3. Recommendations

This review of MIS for pediatric renal tumors demonstrates a lack of evidence to formally endorse routine MIS techniques for all renal tumors. Based on the literature to date, the following recommendations should be considered:

1. The surgeon must have expertise in minimally invasive surgery within the retroperitoneum.
2. Standard oncologic procedure avoiding intraoperative spill and including adequate lymph node sampling must be followed.
3. Extraction in a specimen bag via a Pfannensteil incision or enlarged port site are both acceptable. Tumor morcellation as an extraction technique is absolutely contraindicated as valuable histopathological information is lost and the risk of tumor spill with subsequent upstaging of disease is increased.
4. There are insufficient data to state whether a transperitoneal or retroperitoneal approach is superior. The surgeon's approach should be based upon his/her own technical skills and in-depth knowledge.
5. MIS should be considered only in small Wilms tumors (≤5 cm), but the surgeon MUST balance any perceived advantage of the MIS approach against the risk of upstaging the patient, particularly because this group of patients has excellent long-term outcomes with an open approach and, if stage I, may only require a nephrectomy for treatment.

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