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Minimally invasive surgery to treat embryonal tumors of childhood

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Abstract

Minimally invasive surgery (MIS) to resect primary and metastatic pediatric embryonal tumors offers the potential for reduced postoperative morbidity with smaller wounds, less pain, fewer surgical site infections, decreased blood loss, shorter hospital stays, and less disruption to treatment regimens. However, significant controversy surrounds the question of whether a high-fidelity oncologic resection of childhood embryonal tumors with gross total resection, negative margins, and appropriate lymph node sampling can be achieved through MIS. This review outlines the diverse applications of MIS to treat definitively pediatric embryonal malignancies, including this approach to metastatic deposits. It outlines specific patient populations and presentations that may be particularly amenable to the minimally invasive approach. This work further summarizes the current evidence supporting the efficacy of MIS to accomplish a definitive, oncologic resection without compromising relapse-free or overall survival. Finally, the review offers technical considerations to consider in order to achieve a safe and complete resection.

Keywords Minimally invasive surgery · Pediatric cancer · Embryonal tumor · Neuroblastoma · Wilms tumor · Rhabdomyosarcoma · Laparoscopy · Thoracoscopy

1 Introduction

A growing body of evidence supports the use of minimally invasive surgery (MIS) to stage and treat adult cancers [1, 2]. However, even in the adult literature, concern remains that a minimally invasive approach produces inferior oncologic outcomes in certain situations [3]. Beyond the need to achieve an adequate oncologic resection, pediatric solid tumors, especially abdominal and thoracic embryonal tumors that will be the focus of this manuscript, pose unique challenges to the surgeon. For example, sporadic embryonal tumors are often quite large at presentation and typically arise in infants and small children. These primitive tumors also tend to encase vessels and nerves and can invade adjacent organs. Although variably, these large tumors can respond significantly to neoadjuvant chemotherapy. Further, a subset of pediatric embryonal tumors arises in the context of a cancer predisposition syndrome, which provides a unique opportunity to intervene early in children that are under surveillance for genetically driven cancers. Some embryonal tumors present with paraneoplastic diseases that afford earlier detection when smaller and more amenable to MIS resection. Intracavitary relapse of embryonal tumors, such as lymphatic, pulmonary, and hepatic, can be managed with MIS in appropriately selected patients as well. Due to disease heterogeneity between embryonal tumor types, no randomized controlled clinical trials have been successfully executed to compare the minimally invasive approach to the open approach for resecting this unique class of pediatric solid malignancies. This review will explore the current evidence as well as technical considerations for achieving a high-fidelity oncologic resection of primary and metastatic pediatric embryonal tumors using a minimally invasive approach.

1.1 Rationale to apply MIS to multimodal treatment of pediatric embryonal tumors

MIS has been shown in the management of many benign surgical conditions to afford a variety of advantages over traditional open procedures. Foremost, postoperative pain tends to be reduced significantly with MIS approaches, which facilitates practicing opioid stewardship. Although MIS techniques often lengthen operative times, given the limitations of working with 5 mm instruments compared to one's hands, the benefits of much smaller incisions and no exposure of intestine to the atmosphere reduce postoperative ileus, which

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promotes earlier return to gastrointestinal function and shortens total length of hospital stays (LOS). Some authors have argued that reducing LOS can lower overall costs and therefore increase the value of care. Other theoretical benefits of MIS include fewer surgical site infections, given again the smaller wounds, and in cancer care, fewer disruptions to treatment algorithms. However, questions about cancer-specific limitations have been raised when applying MIS resection to pediatric embryonal tumors:

1. Are principles of cancer care maintained for each disease type?
2. Among appropriately matched patients, does MIS resection of pediatric embryonal tumors offer valid benefit?
3. Does MIS resection of an in-therapy patient yield earlier return to scheduled treatment and fewer disruptions to overall care?
4. What are size limitations to resect an embryonal tumor without violating principles of cancer treatment?
5. Does insufflation with carbon dioxide enhance distant metastasis of certain embryonal tumors?
6. Is port-site relapse a reality?

A randomized prospective trial is obviously necessary to answer these and other questions. Nevertheless, our group and several others have shown through retrospective analyses (Level III evidence) that MIS resections in appropriately selected patients at best may offer significant advantages over open operations and at worse achieve equivalent outcomes.

1.2 Scenarios to consider MIS to resect pediatric embryonal tumors

1.2.1 Neoadjuvant therapy

Extracranial and intracavitary pediatric embryonal tumors are often massive at initial presentation, related to the high proliferative rate of the "blast" or small round blue cell population characterizing these malignancies. Given this high cellular turnover, embryonal tumors are often chemosensitive at presentation, facilitating complete resection. Occasionally, the response to neoadjuvant therapy can be so dramatic to induce regression of tumors away from invaded organs and previously encased vessels (Fig. 1).

1.2.2 Paraneoplastic syndromes

Neuroblastic tumors, particularly when containing relatively differentiated neural elements, can secrete factors that induce other non-oncologic symptoms. For example, neuroblastoma (NBL) is notorious for causing opsoclonus-myoclonus-ataxia syndrome when secreting anti-Hu antibodies. NBL also can make vasoactive intestinal peptide (VIP) that induces watery diarrhea, dehydration, hypokalemia, and achlorhydria (Fig. 2).

1.2.3 Cancer predisposition syndromes

Embryonal tumors can be associated with unique genetic alterations that predispose to retention of organ progenitors and subsequent malignant degeneration. These genomic alterations are often associated with other congenital anomalies that clue the astute physician to the presence of a cancer predisposing syndrome. These phenotypic presentations have specific patterns that associate with unique embryonal tumors given an overlap in genetic control of organ development. Neuroblastoma is associated with *PHOX2B* alterations that also predispose to congenital central hypoventilation syndrome. *PHOX2B* is a fundamental regulator of the neural crest progenitor population and so associates with Hirschsprung disease, which too is a neurocristopathy. Certain *RAS*-activating mutations give rise to Noonan (e.g., *KRAS* and *RAF1*) and Costello (e.g., *KRAS*) syndromes that both yield characteristic external phenotypes and predispose to NBL. Beckwith-Wiedemann (BWS; e.g., *CDKN1C* and *H19/IGF2*) and neurofibromatosis type I (e.g., *NF1*) both have classic physical exam findings and predispose to NBL development [4].

Wilms tumor (WT) can arise in the context of a variety syndromes that have a common genetic etiology governing kidney and other organ development. For example, BWS (e.g., *H19/IGF2*, also the *WT2* locus at 11p15.5) and hemihypertrophy are both overgrowth syndromes that associate with development of WT. Similarly, genomic alterations in the *WT1* locus have highly specific phenotypes depending on mutation, such as aniridia, genitourinary anomalies, and mental retardation (i.e., WAGR) or disorders of sexual development and renal dysplasia (i.e., Denys-Drash) [5]. Another unique WT predisposing disorder is diffuse hyperplastic perilobar nephrogenic rests (DHPLNR). Although no obvious external phenotype exists with this condition, the discovery of a large abdominal mass with specific renoform characteristics in the kidney on computed tomography (CT) clues the oncologic team to DHPLNR. Treatment approaches follow the principles of other WT-predisposing syndromes.

Similarly, rhabdomyosarcoma (RMS) can arise in the context of BWS. Importantly, Li-Fraumeni (e.g., *TP53*), Costello, and Noonan syndromes also predispose to RMS and again have unique phenotypes [6].

Given specific genotype/phenotype relationships between syndromic anomalies and embryonal tumorigenesis, these affected infants are screened according to specific criteria set forth through multidisciplinary

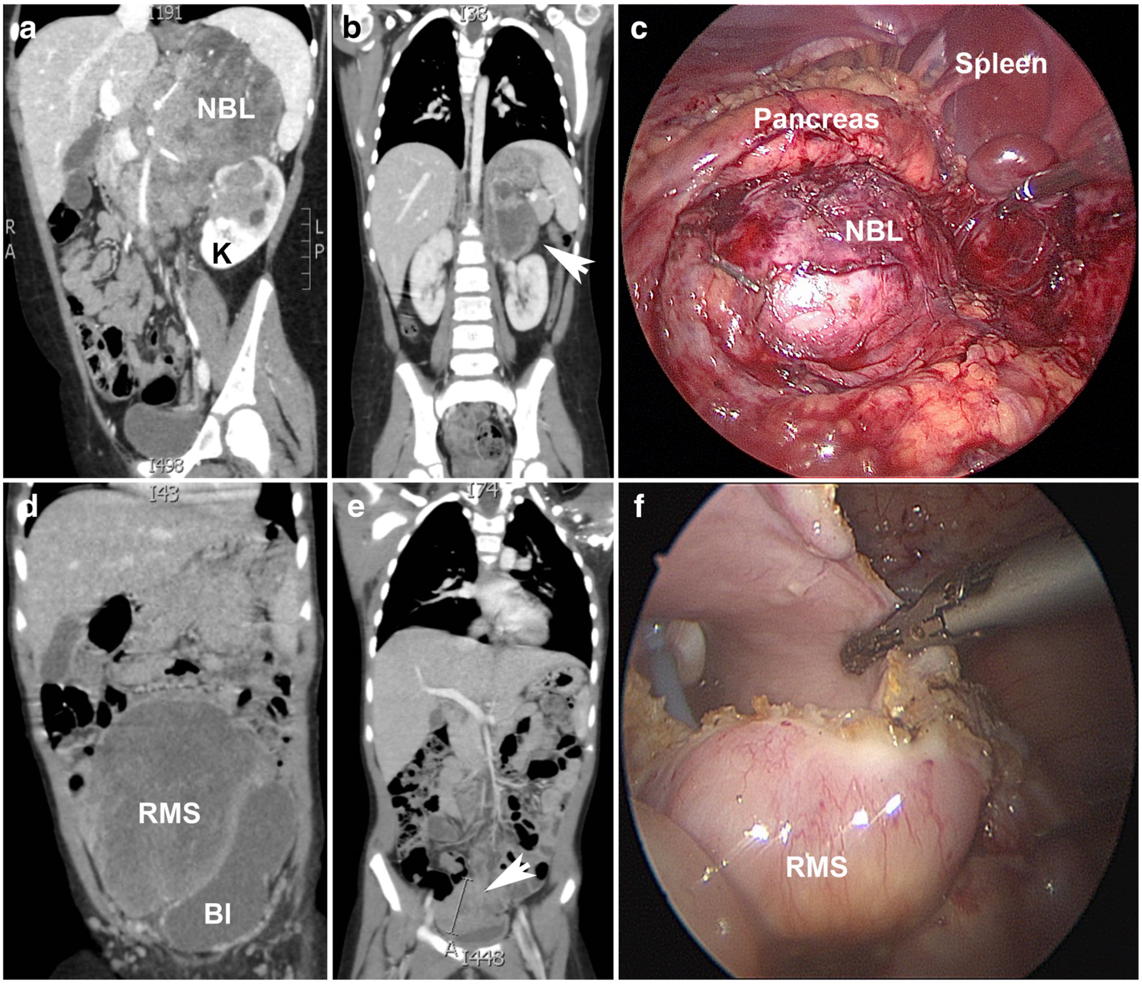

Fig. 1 MIS resection of pediatric embryonal tumors after neoadjuvant therapy. **a** 8-year-old girl who presented with high-risk neuroblastoma (NBL) encasing aorta and visceral vessels, including left renal artery and vein. Tumor also invaded upper pole of left kidney (K). **b** After 4 cycles of neoadjuvant therapy, marked regression of NBL was observed with retraction out of left kidney. Arrowhead denotes residual NBL. **c** MIS resection of NBL. Note dissection away from pancreas, spleen, and kidney and the angiogenic response to neoadjuvant therapy. **d** 3-year-old girl who presented with large rhabdomyosarcoma (RMS) of bladder (Bl). **e** Arrowhead and measuring bar denote residual RMS after neoadjuvant therapy. **f** MIS resection of residual RMS from bladder. Note intravesical Foley catheter and balloon

cooperative groups, such as the Children's Oncology Group (COG) in North America and the Society of International Pediatric Oncology (SIOP). Tumors detected in early stages are potentially amenable to MIS resection and after neoadjuvant therapy, which for WT is protocol-driven to spare renal parenchyma (Figs. 3 and 4).

1.3 Tumor-specific considerations and goals of surgery

1.3.1 Neuroblastic tumors

The primary goal of surgery in treating neuroblastic tumors is to remove as much of the tumor as is safely possible, also known as gross total resection (GTR). However, the benefit of complete resection in high-risk and advanced-stage NBL has not been proven unequivocally. Extent of NBL resection often relies on the surgeon's clinical assessment rather than a detailed imaging review and contributes to uncertainty surrounding whether what extent improves oncologic outcomes in high-risk cases. The most comprehensive report to date that addresses this question concluded that ≥ 90% resection based on the surgeon's intraoperative assessment is associated with higher event-free survival (EFS; 45.9% ± 4.3% vs. 37.9% ± 4.3%, p = 0.04) and improved cumulative incidence of local progression (CILP; 8.5% ± 2.3% vs. 19.8% ± 5.0%, p = 0.01) as compared with < 90% resection [7]. Overall survival (OS), however, was not significantly different based on extent of resection (57.3% ± 4.3% vs. 49.4% ± 7.2%, p = 0.30) [7]. Notably, significant discrepancy was found between a surgeon's intraoperative assessment and central imaging review of resection extent (simple $\kappa = -0.0301$ with concordance for 63% of patients). Nonetheless, differences in CILP, EFS, and

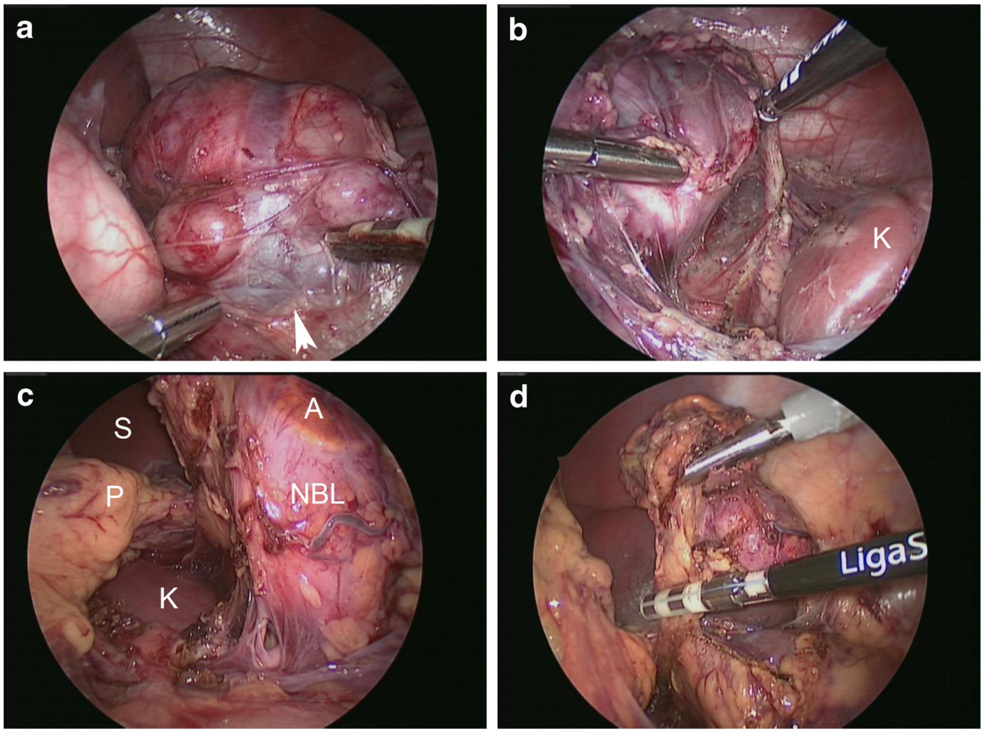

Fig. 2. Upfront MIS resection of neuroblastoma. **a**, **b** Intraoperative photos of a 20-month-old male who presented with watery diarrhea, hypokalemia, and achlorhydria and was discovered to have a left adrenal mass consistent with neuroblastoma that secreted vasoactive intestinal polypeptide. **a** Arrowhead shows confluence of adrenal vein (draped across mass) with left renal vein. **b** Dissection of NBL away from left kidney (K). **c**, **d** 14-month-old infant who presented with opsoclonus-myoclonus-ataxia and was discovered to have a left adrenal mass consistent with neuroblastoma (NBL; A, adrenal gland; S, spleen; P, pancreas; K, kidney). Complete resection with negative margins was achieved in both cases using a bipolar energy vessel sealer

OS were of similar or greater magnitude when resection extent was determined through an independent central imaging review. The association between ≥ 90% resection and improved CILP held with multivariate analysis controlling for tumor biology [7]. However, no significant association between resection extent and EFS or OS was detected on multivariate analysis [7]. Thus, the current evidence supports aggressive and complete surgical resection when possible with the goal of limiting local progression. Formal lymph node sampling is not required, as absolute involvement does not alter treatment intensity. Nevertheless, as much bulky disease, including involved lymph nodes, should be removed to accomplish GTR if safely possible during definitive surgery.

1.3.2 MIS for abdominal and thoracic neuroblastic tumors

The current literature suggests that abdominal neuroblastic tumors are the embryonal tumor most commonly resected with MIS [8]. Table 1 provides cohort information for the key studies commenting on the feasibility and efficacy of MIS to resect abdominal neuroblastic tumors [8–12].These data support the use of MIS to safely achieve GTR of abdominal neuroblastic tumors without adversely affecting relapse-free and overall survival. Similarly, thoracoscopic surgery has been effective in achieving gross total resection of thoracic neuroblastic tumors, both as primary surgery, after neoadjuvant therapy, and relapse [8, 11, 13, 14]. No adverse impact on event-free and overall survival has been reported when using thoracoscopy, as all studies to date have documented an EFS and OS greater than 90% [8, 11, 13, 14].

Our recent in-depth analysis of the oncologic integrity of MIS resections of pediatric embryonal tumors revealed that this less invasive approach was more commonly used to resect NBL in older children having greater body surface and lower stage (stage I/II) tumors without image-defined risk factors [8]. The largest tumor resected with a minimally invasive approach in that study measured approximately 100 ml on imaging (calculated using the formula for an ellipse). Thus, to achieve a direct comparison of the two operative approaches, all tumors with a volume (TV) less than 100 ml either resected open or with MIS were compared. On evaluating oncologic integrity of MIS procedures, we found that margin status did not differ between the open and minimally invasive approaches, with negative margins achieved in 40% (n = 6) of MIS resections and in 35% (n = 12) of open resections of TV < 100 ml (p = 0.916). Given the previously noted

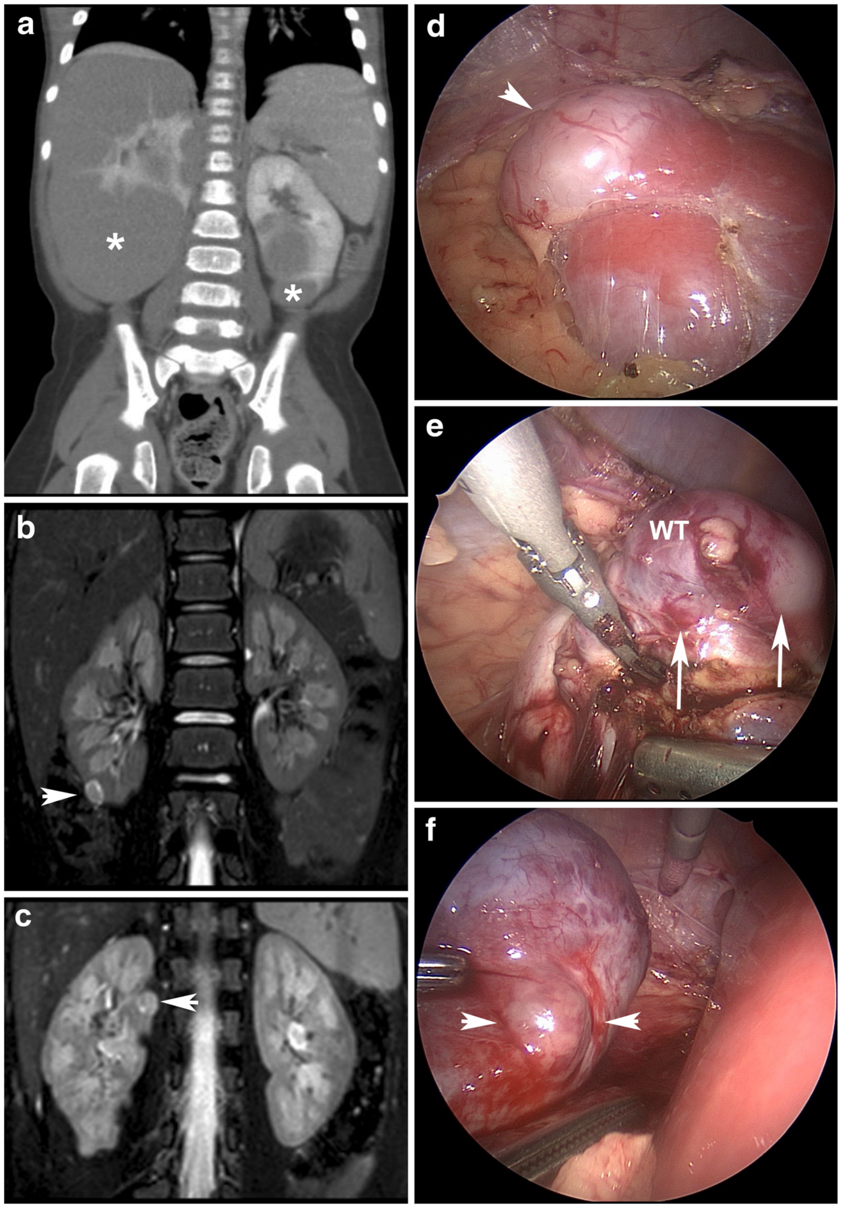

Fig. 3 MIS nephron-sparing resection of Wilms tumor. **a**–**f** 4-year-old girl who presented with a large abdominal mass emanating from right kidney. **a** Computed tomography showed features consistent with diffuse hyperplastic perilobar nephrogenic rests (DHPLNR) involving both kidneys, albeit right more than left (*). Note reniform appearance of both kidneys with effacement of calyces and collecting system, particularly on right. Child was enrolled on AREN0534 and received 12 weeks of neoadjuvant therapy. **b**, **c** Magnetic resonance imaging shows marked regression of DHPLNR in both kidneys, with two residual masses on right (arrowheads) and complete resolution on left. **d**–**f** Intraoperative photographs of nephron-sparing resection of the lower (**d**, **e**) and upper pole (**f**) WTs. Arrowheads show respective WTs, and arrows in **e** show a good but nephron-sparing margin achieved with the ultrasonic scalpel

discrepancy between assessment of gross total resection (GTR) by the operating surgeon and by radiological review, we defined strictly GTR as $\geq$ 98% resection based on measurement of residual tumor on the first post-operative imaging CT scan. Using this definition, GTR was more commonly achieved in patients undergoing MIS as compared with open surgery (p = 0.038), perhaps owing to fewer image-defined risk factors in this group and more patients having paraneoplastic symptoms [8]. Finally, 5-year relapse-free survival was 0.65 (CI 0.47–0.78) after open resection of NBL with TV < 100 ml, while relapse-free survival was 0.88 (CI 0.59–0.97) (p = 0.148) after MIS resection. Five-year overall survival was 0.71 (CI 0.53–0.83) after open resection of NBL with TV < 100 ml, while overall survival was 1.00 (CI 1.00–1.00) after MIS resection (p = 0.021). To account for a greater proportion of lower stage tumors in the MIS group, a stage-by-stage and

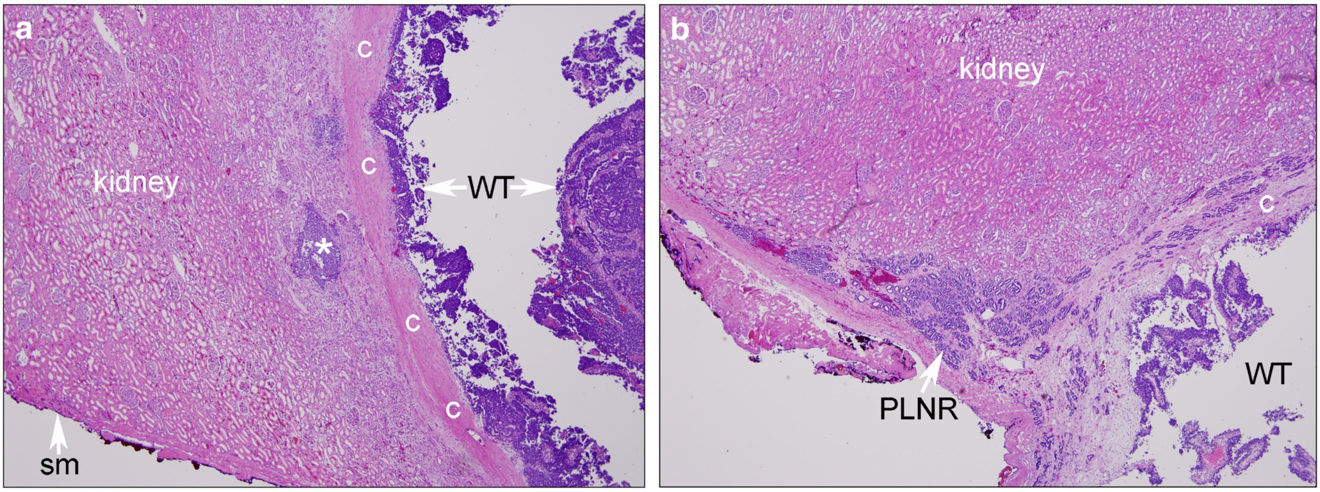

Fig. 4 Histology after MIS nephron-sparing resection of Wilms tumor. **a**, **b** Histology reveals an encapsulated, triphasic WT from both nodules of the DHPLNR patient in Fig. 3. Residual nephrogenic rests (*; PLNR arrow) are visualized in both (**a** and **b**), and note the absence of a capsule (C), which otherwise defines a true WT nodule. The surgical margin (sm) is well-preserved after ultrasonic resection and easily assessed

risk-by-risk analysis of RFS and OS was performed, which demonstrated no significant differences between approaches for any stage or risk group [8].

1.3.3 Paraneoplastic syndromes associated with neuroblastic tumors

Since smaller size and earlier stage tumors tend to lend themselves to a minimally invasive resection, it is important to identify the relevant contexts in which these tumors typically present. In our cohort, several smaller and lower stage tumors were diagnosed in the setting of paraneoplastic syndromes (specifically, opsoclonus-myoclonus ataxia or VIPoma) and discovery on prenatal ultrasonography [15]. Tumors identified in these contexts may be particularly amenable to MIS resection.

1.3.4 Wilms tumor

The primary goal in surgical treatment of WT is complete resection of all visible disease without tumor spillage (i.e., violation of the tumor capsule) and strict lymph node sampling for accurate staging. Intraoperative tumor spillage or a positive surgical margin upstages the tumor, which in turn subjects the child to a more aggressive adjuvant chemotherapy regimen and whole abdomen radiation. Regional lymph node sampling (e.g., renal hilum, iliac, paracaval, and para-aortic nodes) as well as palpation/inspection of the liver and other kidney should also occur at the time of surgery to determine the extent of disease spread and accurate staging. The Children's Oncology Group recommends at least seven lymph nodes should be obtained to provide adequate regional lymph node assessment [16]. Failure to sample lymph nodes puts the patient at risk of under staging. Neoadjuvant chemotherapy followed by a nephron-sparing approach is preferred in bilateral WT or children having predisposition syndromes, in which organ preservation is an additional consideration to prevent late renal insufficiency requiring dialysis and/or kidney transplantation.

1.3.5 MIS for Wilms tumor

The role of MIS to treat Wilms Tumor is less well established than it is for neuroblastoma. Minimally invasive nephron-sparing surgery has been described in the context of bilateral Wilms tumor, as well as WT predisposition syndromes (Figs. 3 and 4) [8, 17, 18]. Complete minimally invasive nephroureterectomy has also been described for WT [19]. Outcomes with the minimally invasive approach have been excellent (Table 1). One report describes peritoneal metastases after laparoscopic nephron-sparing surgery for WT. However, lymph node sampling was not performed at the time of resection nor was adjuvant chemotherapy initiated in a timely manner. The authors of the report suspect that the tumor was not completely removed at the initial operation, underscoring the importance of complete, margin-negative resection in treating this disease [20].

Resecting WT after neoadjuvant therapy is routine in Europe and with any treatment algorithm adhering to SIOP protocols, which call for neoadjuvant therapy for all renal tumors of childhood. In North America, treatment bias in unilateral WT is for upfront resection, which often mandates open radical nephroureterectomy, given bulkiness of this disease in sporadic cases. However, in rare scenarios, WT is unresectable

Table 1 Reports of minimally invasive surgery for resection of pediatric embryonal tumors. Adapted from "Minimally Invasive Surgery in Pediatric Surgical Oncology," originally published in *Children* (Nov 2018) [9]

Study	Number of cases	Conversions	Complications	GTR	Negative margins	Lymph nodes	Median follow-up	Relapse and survival
Abdominal NBL								
Leclair 2008 [9]	45	4	1 bowel obstruction secondary to entrapment in trocar orifice 1 kidney ischemia 1 wound abscess	43/45 (96%)	37/45 (82%)	NR	39 mo	NR
Kelleher 2013 [10]	18	2	None reported	NR	NR	NR	L/I risk: 42 mo H risk: 19 mo	L/I risk: 5-year EFS and OS 100% H risk: numbers too small to calculate, 1 death
Irtan 2015 [11]	19	0	1 renal atrophy	18/19 (95%)	NR	NR	25 mo	5-year EFS and OS: 97.7%*
Phelps 2018 [8]	13	0	No acute complications	9/10 (90%)	5/9 (56%)	4/13 (31%) sampled	58 mo	5-year RFS: 0.90 (CI 0.66–0.97) 5-year OS: 1.00 (1.00–1.00)*
Thoracic NBL								
Malek 2010 [14]	11	0	2 Horner syndrome 1 severe atelectasis	NR	3/7 (43%)	NR	NR	EFS: 90% OS: 100% 1 local relapse
Fraga 2012 [13]	17	0	2 Horner syndrome	17/17 (100%)	17/17 (100%)	NR	16 mo	EFS and OS: 100%
Irtan 2015 [11]	18	2	3 chylothorax	14/18 (78%)	NR	NR	25 mo	5-year EFS and OS: 97.7%*
Phelps 2018 [8]	8	0	No acute complications	7/7 (100%)	1/7 (14%)	2/8 (25%) sampled	58 mo	5-year RFS: 0.90 (CI 0.66–0.97) 5-year OS: 1.00 (1.00–1.00)*
Wilms tumor								
Warmann 2014 [29]	24	0	1 splenic injury	24/24 (100%)	21/24 (88%)	15/24 (63%) sampled	47 mo	EFS: 95.8% OS: 100%
Phelps 2018 [8]	3	0	No acute complications	NR	3/3 (100%)	0/3 (0%) sampled	58 mo	5-year RFS: 0.90 (CI 0.66–0.97) 5-year OS: 1.00 (1.00–1.00)*
Rhabdomyosarcoma								
Phelps 2018 [8]	2	0	No acute complications	NR	0/1 (0%)	NR	58 mo	5-year RFS: 0.90 (CI 0.66–0.97) 5-year OS: 1.00 (1.00–1.00)*

GTR, gross total resection; *NR*, not reported; *mo*, months; *EFS*, event-free survival; *RFS*, relapse-free survival; *OS*, overall survival

*The authors did not specify whether it was an abdominal or thoracic NBL that relapsed and died, so survival numbers represent the combined cohort

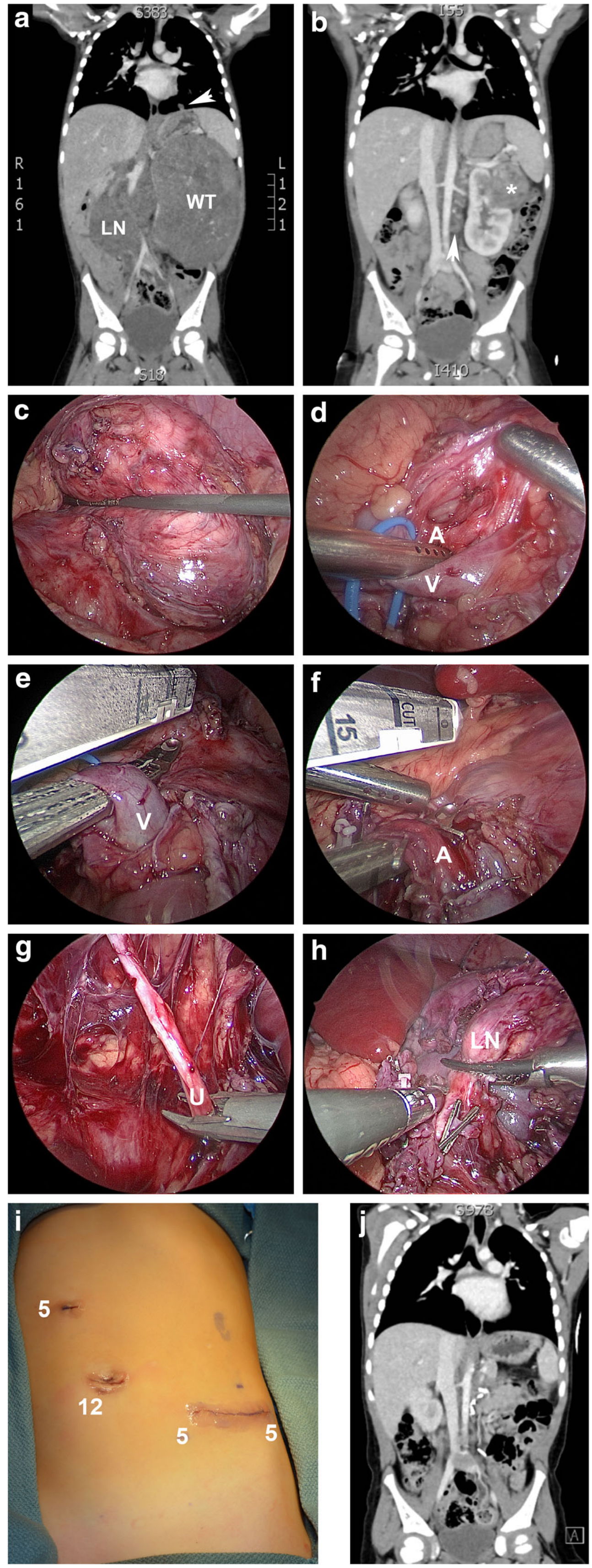

Fig. 5 MIS resection of left Wilms tumor and lymphadenectomy after neoadjuvant therapy. **a** 2-year-old girl who presented with a large abdominal mass that originated from left kidney consistent with WT. She had bulky abdominal lymphatic metastases (LN) and numerous pulmonary metastases (arrowhead). MIS biopsy was performed to confirm diagnosis and to assess histology. A porta-catheter was placed and the child initiated on neoadjuvant therapy. **b** After 12 weeks of therapy, her abdominal disease had regressed remarkably (*), and her pulmonary metastases had resolved on imaging. **c** MIS mobilization of left WT and kidney (note desmoplasia investing WT above and halfway below instrument and involved lower pole of kidney (purple tissue). **d** Identification of renal vessels (V, vein; A, artery). **e** Stapling the left renal vein first to visualize artery posteriorly. **f** Stapling the left renal artery. **g** Clipping (and dividing) the left ureter (U). **h** Excising residual, bulky abdominal lymph nodes (LN). **i** Port placement: 5 mm port in right upper quadrant and two in left lower quadrant that were connected (4 cm total) to deliver specimens. 12 mm port for stapling was placed at umbilicus. **j** Postoperative CT scan shows no residual disease. The clips and staple lines for vessels and ureteral division are seen

upfront and requires neoadjuvant therapy. In those scenarios, MIS radical nephrouretrectomy can be accomplished in highly select cases, as we have performed (Fig. 5).

1.3.6 Predisposition syndromes associated with Wilms tumor

At this point, no established or consensus indications for laparoscopic resection of WT have been standardized. The subset of patients to benefit most from this operation likely consists of those having bilateral disease or with disease arising in the context of a cancer predisposition syndrome such as Beckwith-Wiedemann syndrome, DPHLN (diffuse hyperplastic perilobar nephroblastomatosis), hemihypertropy, WAGR (Wilms tumor, aniridia, genitourinary abnormalities, and mental retardation) that each requires neoadjuvant chemotherapy according to COG AREN0534 [21]. When a WT is detected in a child receiving scheduled surveillance for a cancer predisposition syndrome, it is more likely to be an early stage, small volume tumor. Furthermore, most of these patients will receive neoadjuvant chemotherapy before resection, and a nephron-sparing approach is then favored to preserve as much renal function as possible (Figs. 3 and 4) [8, 17].

1.3.7 Wilms tumor metastases

WT have specific sites of metastasis, principally the lungs and liver. In certain contexts, these metastatic deposits may be amenable to MIS resection as well. Principles surrounding MIS resection of metastases follow those of primary tumors and underscore organ-preservation (Fig. 6). Relapsed intracavitary lymph node deposits may also be amenable to MIS excision when indicated.

2 Other embryonal tumors

2.1 Rhabdomyosarcoma and hepatoblastoma

While neuroblastic tumors and WT are the more common extracranial solid tumors arising in children, respectively, minimally invasive approaches have been used occasionally to resect other solid tumors, particularly rhabdomyosarcoma and more rarely hepatoblastoma [22]. Our previously reported series included two patients who underwent minimally invasive resection of bladder tumors, one via cystoscopy and the other via laparoscopy. The former had positive margins, and the patient died at 77 months from progressive disease. The latter patient had negative margins and survived 5 years from

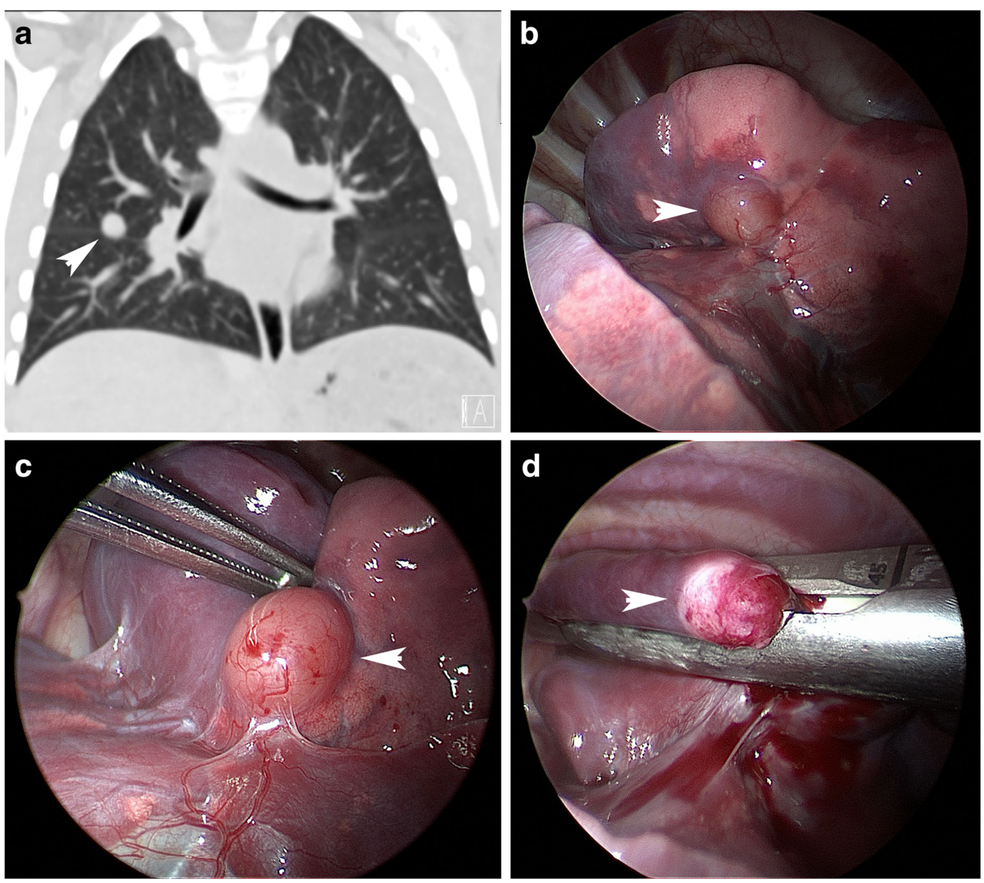

Fig. 6 MIS resection of pulmonary Wilms tumor metastasis. **a** CT scan at end of therapy for a favorable histology WT shows a new right upper lobe mass consistent with metastatic deposit (arrowhead). **b**, **c** Intraoperative photographs of right upper lobe WT metastasis. Note angiogenic response in lesion (arrowheads). **d** Stapling of WT metastasis from right upper lobe. Care must be taken when dividing the lung parenchyma to preserve blood supply and airway to the involved lobe

this disease. Hepatoblastoma, particularly if discovered at an early stage and small size, as with cancer screening for Beckwith-Wiedemann syndrome, or after good response to neoadjuvant therapy, may indeed be amenable to MIS resection. Occasionally, hepatoblastomas are exophytic or pedunculated from the main liver and too may be approachable with MIS resection [22]. However, larger hepatoblastomas require full mobilization of the liver, which is restricted with MIS and more facile with a standard celiotomy.

2.2 Thoracoscopy and MIS for chest tumors

Several embryonal tumors can arise primarily in the chest cavity or lung (Fig. 7). As discussed above, roughly 20% of neuroblastic tumors arise primarily in the posterior mediastinum. These thoracic neuroblastic tumors may be amenable to MIS resection if appropriate size, either after or without neoadjuvant therapy. These neuroblastic tumors parasitize blood supply from the intercostal arteries, which originate directly from the thoracic aorta, so extreme care and caution must be implemented when resecting a neuroblastoma in this location with MIS. Venous drainage is also via the intercostal arcade but is more easily managed. For tumors arising in the right chest, the intercostal veins can meet confluence with the azygous vein, which if not identified and controlled during dissection can cause significant bleeding.

Extraosseous Ewing sarcoma can arise primarily in the lung and may too be amenable with MIS resection, either with anatomic segmentectomy or lobectomy (Fig. 7). Pleuropulmonary blastoma, a primary embryonal tumor of the lung associated with *DICER1* mutations, originate primarily in the lung and may be approached with MIS lobectomy in highly selected cases [23].

Pulmonary metastatic deposits of pediatric embryonal tumors, as shown for WT above, can be managed with MIS techniques when completely resectable. Thoracic lymph nodes can also be a site for distant metastasis of embryonal tumors and if residual or bulky after therapy may warrant MIS resection (Fig. 7).

3 Pearls and pitfalls

Adapted from "Minimally Invasive Surgery in Pediatric Surgical Oncology" originally published in *Children* (Nov 2018) [12]

3.1 Pearls

1. Identify appropriate patient and cancer type:
   a. Manageable tumor volume
   b. Tumor discovered at early stage during predisposition surveillance
   c. Cases presenting with paraneoplastic symptoms
   d. Tumors discovered in utero
2. Consider MIS for tumors having significant response to neoadjuvant chemotherapy, which facilitates resection when appropriate (e.g., no vascular encasement and manageable tumor volume).
3. Position patient for success.
4. Commit to the challenge of completing the procedure with MIS.
5. Memorize preoperative imaging and location of vascular and other vital structures (and display images during procedure for frequent reference).
6. Must maintain principles of cancer care for the specific tumor type:
   a. Complete or gross total (> 98%) resection of neuroblastoma. *
   b. Complete resection of WT without spill and with adequate lymph node sampling.
7. Have laparoscopic suction in the field for short bursts to aspirate angiogenic bleeding, especially if resecting a tumor after neoadjuvant chemotherapy.
8. Recommend ultrasonic scalpel when excising mass from kidney or liver parenchyma to preserve margin analysis, given minimal thermal spread. Bipolar vessels sealers are adequate as well if greater distance from specimen is permissible and when dividing larger vessels.
9. Surgical clips or vascular staplers are good for dividing larger vessels.
10. Monitor progress regarding time, blood loss, and oncologic integrity. Be willing and prepared to open when necessary.
11. Use specimen bag to remove the tumor.
12. Identify a port location having good cosmesis to deliver specimen in a bag.
    a. Lengthen this port to the narrowest diameter of the tumor and deliver specimen in that dimension.
    b. Advantageous to connect two nearby ports into one incision for specimen delivery.
    c. Pfannenstiel incisions to deliver tumor work nicely too.
13. Port site recurrences after MIS for embryonal tumors do not seem to occur.

*Note: The value of radical surgery for neuroblastoma is controversial. As little as 50% resection is sufficient in patients with low-risk disease. For intermediate-risk disease, the goal is to achieve the most complete resection possible with minimal morbidity. The COG high-risk protocol currently recommends gross total

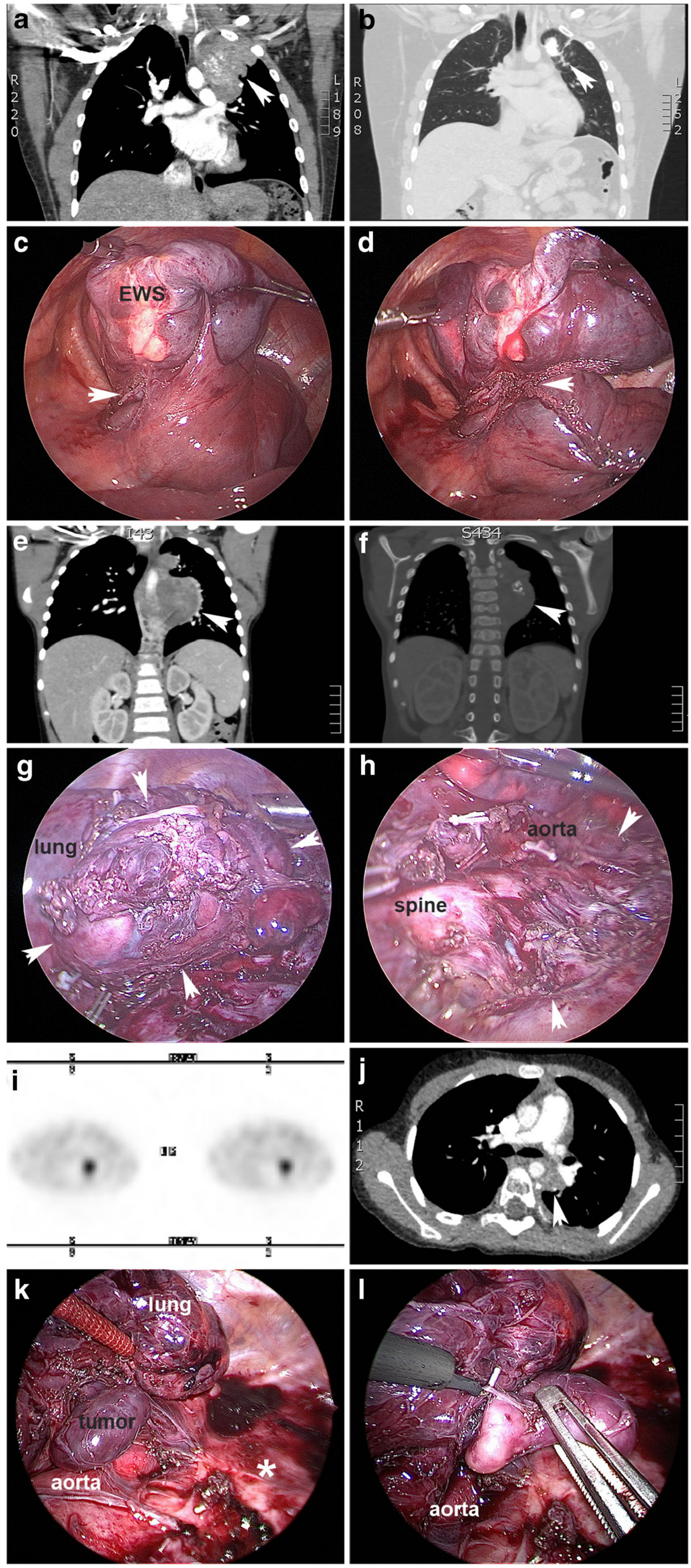

Fig. 7 MIS resection in the chest of pediatric embryonal tumors and relapse. **a**–**l** Minimally invasive surgery (MIS) resection of thoracic pediatric embryonal tumors. **a**–**c** Adolescent male who was diagnosed with a primary Ewing sarcoma (EWS) of the left upper pulmonary lobe (**a**; arrowhead). Marked regression of primary lesion was observed after neoadjuvant therapy (**b**; calcified nodule and arrowhead). **c** Thoracoscopic view of superior segment of left upper lobe and mass (EWS). Arrowhead denotes staple line after dividing segmental artery to mass. **d** Completing the segmentectomy with a linear stapler. Arrowhead denotes resection staple line. **e**–**h** Four-year-old girl who presented with a large left-sided thoracic neuroblastoma (NBL). **e**, **f** CT imaging of mass before and after neoadjuvant therapy (arrowheads). **g**, **h** Thoracoscopic resection of large thoracic NBL. **g** Borders of the mass after mobilization are depicted with arrowheads. Collapsed lung is labeled. Note the profound angiogenic nature of the NBL and desmoplastic response after neoadjuvant therapy. **h** Tumor bed after complete resection. Arrowheads depict cephalad and caudal borders of tumor bed. Clips are on intercostal arteries originating from aorta. Vertebrae of spine are visible. **i**–**l** Three months after completing therapy, MIBG-avidity of a hilar lymph node persisted (**i**; dark spot). Arrowhead denotes mass in left pulmonary hilum on CT scan (**j**). **k**, **l** Repeat thoracoscopic approach to resect hilar "tumor" 12 months after initial operation. Tumor, lung, and aorta are labeled. Asterisk denotes primary tumor bed free of local relapse (**k**). **l** Hook cautery dissection of vessels feeding the dumbbell-shaped hilar mass that is visible within atraumatic grasper

resection with removal of locoregional disease, despite conflicting evidence of the role of surgery in high-risk neuroblastoma [24]. Regardless, resection extent should not be sacrificed in favor of a minimally invasive approach.

3.2 Pitfalls

1. Inappropriate patient selection:
   a. Excessively large tumors.
   b. Vascular encasement.
   c. Limited tactile feedback, or haptics, with MIS instruments to appreciate large vessels, so must have good visualization of critical structures.
2. Not mentally committing to the MIS approach. These procedures are challenging.
3. Not positioning the patient appropriately.
4. Tissue planes are difficult after neoadjuvant chemotherapy (desmoplasia is challenging to dissect) and if angiogenic bleeding is persistent.
5. Not recognizing feeding and draining vessels (i.e., difficult to control large, anatomic vessels with MIS, so need to know location precisely).
6. Not sampling lymph nodes adequately.
7. Not completing the appropriate oncologic resection for a given tumor type.
8. Recommend using a specimen bag.
9. Do not morcellate tumor to deliver specimen—it must remain intact for pathologic analysis.
10. Effect of pneumoperitoneum to facilitate dissemination of tumor cells remains to be proven or refuted.

4 Conclusion

Minimally invasive resection of pediatric embryonal tumors is an appealing alternative to open resection to achieve the same benefits that MIS carries with benign surgical diseases: less pain, improved cosmesis, fewer wound complications, lower rates of post-operative ileus or small bowel obstruction, shortened hospital stays, and earlier return to activity. Unique to cancer patients, MIS may offer earlier initiation of (or return to) chemotherapy after surgery. Indeed, our study found a near-significant difference in time to initiation of post-operative chemotherapy after a minimally invasive resection versus an open resection (12.5 days [7.5, 19.5] vs. 19.5 [14, 26]; $p = 0.051$) [8]. Alternatively, recent studies in Japan suggest that delaying surgery until after completion of chemoradiation therapy may be an effective treatment option for high risk NBL [25, 26]. Maximizing medical management in this way could provide additional opportunities to employ MIS. Port site relapse does not seem to be an issue with MIS and should not differ from open wound recurrence in theory. Limitations of MIS to resect embryonal tumors in young children are that large tumors need to be mobilized in a small space. Vascular control during MIS can prove to be more difficult with the limited ability to expose large vessels adequately and the restraints of smaller laparoscopic instruments to clamp a bleeding structure. Further, maintaining pneumoperitoneum while aspirating typical bleeding encountered with any dissection can limit visibility too. Some have raised concern that the pneumoperitoneum may facilitate distant metastasis and local relapse, although we have found no clinical or reported evidence that MIS increases these risks [27, 28]. Finally, an individual surgeon's comfort level and experience with MIS is another important factor in determining the ultimate success of this less invasive approach. The surgeon must also have expert command of the oncologic principles and surgical guidelines protocolized for each embryonal tumor.

The studies highlighted in this review offer preliminary evidence for the safety and efficacy of the minimally invasive approach to resect pediatric embryonal tumors. Neither in our experience nor in the literature have we found evidence that MIS alters the biology unfavorably or increases the risk for local relapse or disseminated disease progression. We offer pearls and pitfalls for the operating surgeon to consider when employing the minimally invasive approach. The most important consideration, however, is not to compromise the oncologic integrity of the operation in favor of a minimally invasive approach. The data presented in this review suggest that at a minimum no apparent negative impact on relapse-free and overall survival arises when using MIS to resect pediatric embryonal tumors. As the technique is adopted by more surgeons, there will be greater opportunity to assess both surgical and oncologic outcomes after a minimally invasive resection. We suggest that certain patient populations may invite a minimally invasive surgical approach, including those with excellent response to neoadjuvant therapy, predisposition syndromes or paraneoplastic symptoms.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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