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Patient selection and technical aspects for laparoscopic nephrectomy in Wilms tumor

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ABSTRACT

Background: Only limited data exist to define the role of laparoscopic nephrectomy for Wilms tumor. Our aim was to present our experiences with this method with special regard to patient selection and technical aspects.
Methods: Records of patients with Wilms tumor who had been operated on using laparoscopic nephrectomy were reviewed retrospectively. Analyzed data contained patient characteristics, outcome, staging, tumor histology, tumor size, lymph node sampling, lymph node histology, pre- and postoperative chemotherapy, radiotherapy, surgical procedures, and complications.
Results: From 2010 to 2018 laparoscopic Wilms tumor nephrectomy was performed in 9 children (median age 24 months (12.0–57.5)) who did not qualify for nephron sparing surgery and who met internally defined criteria. Each patient received neoadjuvant chemotherapy to which 7 of the tumors responded substantially. Median tumor volume at surgery, maximal diameter, and specimen weight was 74 ml (15–207), 6.5 cm (3.5–9.3), and 125 g (63–310), respectively. No intra- or postoperative complications occurred. Overall survival and event-free survival was 9/9, median follow up was 48 months (24–78). These data were used to propose a patient selection algorithm. Technical aspects derived from our experience include usage of the ureter as leading structure, usage of a transabdominal traction suture around the ureter, and lymph node sampling before tumor nephrectomy.
Conclusion: With increasing expertise of operating surgeons, more complex WT might be a target for minimally invasive surgery, provided that patient selection and technical factors are carefully addressed.

1. Introduction

Treatment of Wilms tumor (WT) is a multidisciplinary effort where the complete surgical resection plays a key role for the outcome [1]. Surgical procedures are described in the protocols of multicenter study groups such as the International Society of Paediatric Oncology (SIOP) or the Children's Oncology Group (COG) as well as in recommendations of national oncological societies [2,3].

Minimally invasive surgery (MIS) procedures are increasingly used for diagnosing and treating solid tumors in children [4–7]. The initiative to perform laparoscopic WT nephrectomies was first taken by single centers or single surgeons, since MIS was not part of general surgical guidelines at the time. Most reports on MIS for WT have small case numbers. However, meanwhile there are already studies of big centers as well as analyzes of international multicenter study cohorts and of a national cancer database [8–18].

Feasibility of laparoscopic WT nephrectomy is basically unquestionable. But currently there is no standardization of the technical approach and of the patient selection. Size and extension of tumors have been identified as critical parameters for performing MIS safely, especially because tumor spillage is of great concern [19]. However, recommendations concerning these parameters differ even if given by the same surgeon, which reflects the growing experience over time [14]. Apart from being feasible, any new surgical procedure should comply with the general principle to improve patient outcome parameters [20–24]. These aspects are important for the upcoming integration of recommendations and guidelines in treatment protocols.

This is a study of a national surgical reference center with special focus on these current issues. We report on our experience with laparoscopic nephrectomy in unilateral WT in 9 children and discuss

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which tumors can be safely removed by MIS. Surgical as well as anesthesiological and radiological aspects of treating patients with WT are described.

2. Methods

The study was approved by the Ethical committee of the University of Tuebingen, Germany (No. 124/2018BO2). Patient records were collected retrospectively and then analyzed.

2.1. Definition of parameters

Calculation of tumor volumes and tumor diameters were performed by using magnetic resonance imaging (MRI) data. Specimen weight including the kidney and adjacent tissue was taken from the pathological report. Determination of the local tumor stage was performed according to the SIOP-2001/GPOH protocol [25].

2.2. Patient selection

All patients received neoadjuvant chemotherapy. Patients were eligible for laparoscopic nephrectomy if they met the selection criteria listed in Table 1. The absolute tumor volume did not influence the indication for minimally invasive surgery.

2.3. Radiological procedure

For local staging, highly resolved ultrasound including color-coded Doppler was carried out at baseline and during treatment. MR imaging (MRI) was performed using a standard protocol at baseline. As our inhouse standard for MRI, the children received general anesthesia allowing acquisition in breath-hold technique especially for high-quality dynamic contrast enhancement (Dyn-CE) sequences and for static excretion MR–urography (MRU). Prior to contrast application the protocol contained navigator-triggered T2 weighted sequences with and without fat suppression and T1 weighted sequences. Diffusion-weighted imaging (DWI) has been added to the protocol since 2011. The same protocol was repeated prior to resection in complicated cases (e.g. large tumor burden with weak response to chemotherapy).

To assess pulmonary metastases a dual-source multidetector computed tomography (MDCT) was carried out using a low radiation dose protocol without contrast medium. Due to the ultrafast acquisition by the high-pitch technique, sedation of the children was not necessary thus also avoiding areas of atelectasis.

2.4. Anesthesiological procedure

A standardized anesthetic technique was applied to all children. Anesthesia was induced with intravenous propofol (2–4 mg/kg), sufentanil (0.3–0.5 μg/kg) and rocuronium 0.6 mg/kg for muscle relaxation. After tracheal tube positioning, patients underwent pressure-controlled lung protective mechanical ventilation (tidal volume 6–8 ml/kg BW) with a low-flow breathing system (Zeus®, Draegerwerk AG & Co. KGaA) and 25–30% oxygen in 70–75% air. Respiration rate was adjusted to achieve an end-tidal CO_2 level of 37–45 mmHg. Anesthesia was maintained with a minimum alveolar anesthetic concentration (MAC) of sevoflurane between 0.7 and 1%. A remifentanil infusion (0.3–0.4 μg/kg/min) was continued to maintain surgical analgesia.

Table 1
Selection criteria for laparoscopic Wilms tumor nephrectomy.

Nephron sparing surgery not possible
Tumor without infiltration of extrarenal structures
Tumor without thrombus in the renal or cava vein
Tumor does not cross the ipsilateral paravertebral line

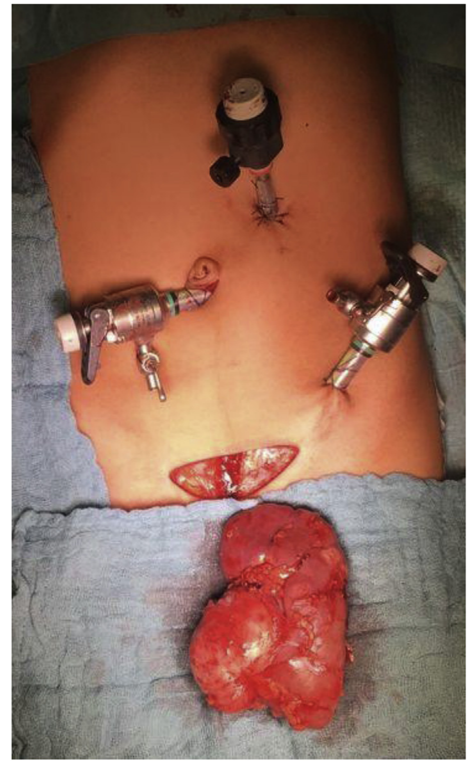

Fig. 1. Trocar placement for left sided tumor nephrectomy. A 5 mm optical trocar and a 5 mm and 3 mm trocar for the laparoscopic instruments were used. The specimen was removed through a Pfannenstiel incision.

2.5. Surgical procedure

All laparoscopic WT nephrectomies were carried out by the senior author of this paper (JF). All cases were operated on by a transperitoneal approach. Usually a 5 mm optical trocar for a 30° optic as well as two 3 or 5 mm trocars for the laparoscopic instruments were placed as indicated in Fig. 1.

All patients were arranged in supine position throughout surgery. Depending on age and size of the patients the abdominal insufflation pressure was adjusted to 10–12 mmHg with a flow of 3.5–5 ml/min CO_2. A fourth trocar was used if the liver had to be retracted. After mobilizing the colon on the ipsilateral side, Gerota's fascia was opened. A monopolar hook was used for dissection in order to get a sensory haptic feedback and for an accurate handling of the tissue. After isolation of the ureter, the lower pole of the kidney was dissected. The ureter was used as a leading structure to identify the anatomic structures of the renal pedicle. The ureter was elevated using a transabdominal traction suture in order to facilitate lymph node sampling and management of the renal pedicle (Fig. 2A).

Lymph nodes of the first three patients of our cohort were collected after nephrectomy. We realized that retraction of the organ complicated the identification of the sites of lymph nodes. Therefore, lymph node sampling in the ensuing patients was performed before tumor nephrectomy using the renal vessels, the cava vein and the ureter as leading structures (Fig. 2B and C).

After dissection of the renal vessels, the renal artery was ligated first (Fig. 2D). Then, in order to prevent swelling of the kidney and an increasing risk of tumor rupture, the renal vein was ligated. The dissection was completed with the mobilization of the kidney and ligation of the ureter. The specimen was removed without morcellation through a Pfannenstiel incision.

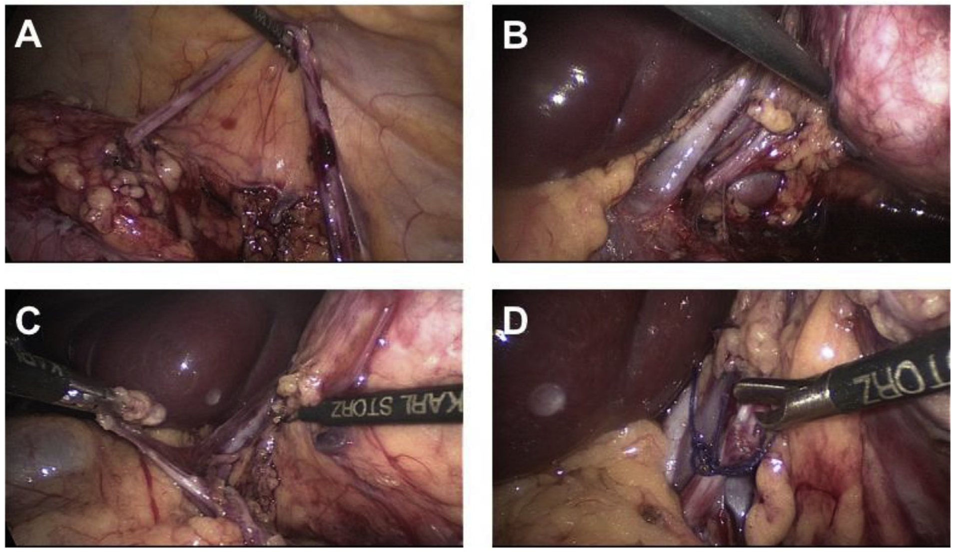

Fig. 2. Surgical procedure. **A**) Transabdominal traction suture around the ureter for a better exposure of the renal pedicle. **B, C**) Lymph node sampling along leading structures before tumor nephrectomy. **D**) Transsection of renal artery prior to ligation of renal vein.

3. Results

3.1. Patient characteristics

MIS WT nephrectomy has been performed in nine children since 2010. At the time of surgery, the patient median age was 24.0 months (12.0–57.5), the median body weight was 17.0 kg (8.0–18.0) (Table 2). Five of the children were females, 4 males; the tumor was on the right side in 6 and on the left side in 3 children.

3.2. Pre- and post-operative chemotherapy

Eight children received neoadjuvant chemotherapy according to the SIOP 2001/GPOH protocol (actinomycin D + vincristine, usually given for 4 weeks). A modification of this scheme was required for patient 9, who was operated on after 2 cycles of the drugs due to a lack of tumor response. Patient 8 received a 3 drug regimen consisting of vincristine + endoxan + epirubicin because of a suspected preoperative tumor rupture. The rupture was suspected on initial imaging. However, it was not confirmed macroscopically during surgery or on pathology. Two out of the 9 patients (patients 1 and 9) showed no response to neoadjuvant chemotherapy. The median weight of the resected specimen was 125 g (63–310); the median largest tumor diameter on preoperative imaging was 6.5 cm (3.5–9.3) (Table 2).

Postoperative chemotherapy consisted of the AV-1 regimen according to the SIOP 2001/GPOH protocol. Patient 8 received actinomycin D + vincristine + doxorubicin and radiotherapy because of the suspected tumor rupture (Table 3).

3.3. Post-operative staging

Local stage I was assigned to six patients, local stage II to patient 1 because of an affection of the peri-renal capsule and to patient 2 because of a central infiltration of the renal vein as observed on pathology, and local stage III to patient 8 due to the suspected preoperative tumor rupture (Table 3). The surgical procedure in this patient No. 8 was started as diagnostic laparoscopy during which the feasibility of application of MIS was confirmed. Therefore, surgery was completed minimally invasively. Pulmonary metastases were detected in 2 children (patients 5 and 8). Patient 5 had bilateral metastases which were diminished by neoadjuvant chemotherapy. At a follow–up visit 26 months after surgery a singular metastasis was suspected in the right middle lobe on CT imaging. The histology of the thoracoscopically removed nodule revealed no malignancy. The pulmonary metastasis of patient 8 located in the right middle lobe completely disappeared after neoadjuvant chemotherapy.

Intraoperative sampling of lymph nodes was performed in all patients. However, pathologists could not identify lymph nodes in the tissue samples of 2 patients. The number of pathologically identified lymph nodes per patient ranged from 0 to 8 (median 2). None of the analyzed lymph nodes was positive (Table 3).

Table 2
Neoadjuvant chemotherapy, patient and tumor characteristics.

Pat. No	Age at surgery (m)	Body weight (kg)	Neoadjuvant chemotherapy	Tumor volume (ml)		Largest tumor diameter (cm)	Specimen weight (g)
				initially	at surgery		
1	15.0	8.8	AV	171	207	8.5	310
2	40.0	14.1	AV	170	58	5.5	157
3	27.5	13.4	AV	170	77	6.5	136
4	57.5	18.0	AV	162	74	7.2	147
5	23.5	10.8	AV	300	15	3.5	63
6	24.0	11.4	AV	376	68	9.3	82
7	12.0	8.2	AV	195	40	7.5	69
8	30.0	13.0	VEnEp	202	59	4.9	125
9	33.0	17.0	AV[a]	47	114	6.5	65

Abbreviations: AV, actinomycin D + vincristine (4 cycles); VEnEp, vincristine + endoxan + epirubicin; AV[a], actinomycin D+ vincristine (2 cycles).

Table 3
Staging, postoperative chemotherapy and follow-up.

Pat. No	Tumor histology	Local tumor stage	Overall stage	LN sampled (n)	LN positive (n)	Postop. chemo-therapy	Postop. radio-therapy	outcome	Follow- up (m)
1	IR (strom.)	II	II	4	0	AV-1	–	NED	78
2	IR (regr.)	II	II	1	0	AV-1	–	NED	61
3	IR (strom.)	I	I	2	0	AV-1	–	NED	57
4	IR (mixed)	I	I	0[a]	–	AV-1	–	NED	53
5	IR (regr.)	I	IV	1	0	AV-1	–	NED	48
6	IR (regr.)	I	I	8	0	AV-1	–	NED	30
7	IR (regr.)	I	I	3	0	AV-1	–	NED	26
8	IR (mixed)	III	IV	0[a]	–	AVD	+	NED	24
9	IR (mixed)	I	I	3	0	AV-1	–	NED	31

Abbreviations: AV-1, actinomycin D + vincristine; AVD, actinomycin D+ vincristine + doxorubicin; IR, intermediate risk; strom., stromal predominant subtype; regr. = regressive type; NED, no evidence of disease.
[a] Sampling documented by surgeon, but no lymph node pathologically identified.

3.4. Outcome

Median time for surgery was 147 min (93–190). No intraoperative or postoperative complications occurred. None of the patients needed a blood transfusion.

Follow-up data were available for all patients with a median follow-up period of 48 months (24–78). No patient has had a relapse at the latest follow-up.

4. Discussion

Multimodal treatment concepts for WT have been outlined in the protocols of international multicenter studies and have eventually resulted in survival rates of more than 90% for low stage and low risk patients [3,26]. Surgeons make a major contribution to the management of WT not only because removal of the tumor is a precondition for cure [27] but also because the efficacy of tumor removal and lymph node sampling have an impact on staging and future therapy [28–32]. The minimally invasive surgery of WT should not adversely affect the oncological outcome in comparison to the open procedure and should not be linked to disadvantages. The most critical aspects identified for minimally invasive nephrectomy are tumor resection without spillage and an adequate sampling of lymph nodes [24,33,34].

Laparoscopic removal of the renal tumor and collection of hilar lymph nodes requires an exact exploration of the renal pedicle. A small working space makes a secure exploration very difficult and carries a high risk of bleeding and tumor rupture. In our experience tumors not crossing the ipsilateral paravertebral border can be safely handled, because sufficient exploration of the renal vessels is possible. Additionally, tumor size has to be critically assessed, because it correlates with intraoperative tumor spill [35]. Tumor spillage immediately affects staging and leads to a more aggressive postoperative chemotherapy and radiotherapy with relevant long term side effects [27,36]. Especially large tumors are often very fragile after chemotherapy because of cystic tumor necrosis with a high risk of tumor rupture. Careful movement of the endoscopic instruments reduces the risks linked to the use of instruments of a smaller diameter.

There are differing reports on WT size and extension which can be removed laparoscopically. Duarte et al. found that the largest diameter of tumors resected videolaparoscopically after neoadjuvant chemotherapy amounted on average to 10% of the height of the patients [37]. With increasing experience, they succeeded in the removal of tumors with a largest diameter of 14–16% of the patients' size, the largest tumor they resected had a diameter of 12 cm. They hypothesize that this limit could be extended for older children and with further increase of surgical expertise [14]. Varlet et al. reported on data of a multicenter trial which enrolled children with renal cancer undergoing laparoscopic nephrectomy. Sixteen of the 17 children received neoadjuvant chemotherapy and 15 suffered from WT. The biggest tumor resected had a diameter of 8 cm and reached the midline, eventually requiring conversion to open nephrectomy. Considering their experience, the authors conclude that small tumors under about 8 cm diameter without crossing the ipsilateral edge of the vertebra on the CT scan at the time of surgery can be safely removed by a trained laparoscopic surgeon [11]. Tumors which do not cross the midline are selected for MIS by some centers [13,17,18], in exceptional cases tumors crossing the midline were resected [17]. In our series, we did not define a specific tumor size as limit for MIS; however, we restricted laparoscopic nephrectomy to those cases in which the tumor did not cross the ipsilateral vertebral border. Thus, the largest tumor in our series had a diameter of 9.5 cm.

Recommendations on the size of tumors which have been exposed to preoperative chemotherapy cannot be applied to non-pretreated tumors. Chemotherapy induces the formation of a fibrous capsule which facilitates handling of the tumor and reduces the incidence of tumor spillage [35,38]. Only few cases of minimally invasive nephrectomy in children who have not had preoperative chemotherapy, have been published [8,10]. Romao et al. reported on laparoscopic radical nephrectomy of 7 WT and 6 renal tumors of other origin; two of the 7 WT were exposed to preoperative chemotherapy. The authors of this study recommend careful consideration of this technique for upfront surgery in paediatric renal tumors smaller than 10 cm or after preoperative chemotherapy if tumors have responded significantly [10].

Using the ureter as leading structure to the renal pedicle and a traction suture around the ureter were crucial steps in our procedure. Following the ureter reduces the risk of vascular injury. The traction suture results in an elevation of the kidney and better access to the renal vessels and hilar lymph nodes.

Collection of lymph nodes is essential for the exact staging and for defining the adjuvant therapy. Adequate lymph node sampling is often not realized during open radical nephrectomy [16,29–31] or during MIS [10–12,14,16]. Insufficient lymph node sampling would be a substantial disadvantage for MIS. The data available so far do not allow drawing a final conclusion. A most recent retrospective review of the National Cancer Data Base and the analysis of the data by a propensity matching methodology revealed that lymph node sampling was performed more frequently (81.8% vs 66.7%) and more lymph nodes were harvested (median 4 vs 2) in open surgery. However, the difference did not reach statistical significance [16]. The authors conclude that lymph node sampling requires further examination in prospective randomised trials.

Absence of lymph node sampling has been shown to increase the risk of tumor recurrence [28]. Data on the impact of lymph node sampling on survival are not consistent. The number of lymph nodes collected has previously been correlated to survival [30]. However, this was not confirmed by another study which suggests that collecting at least 7 lymph nodes increases the possibility of detecting a metastasis but does not affect event free survival [31]. A recent analysis revealed that collecting 7 or more lymph nodes is more important for patients with neoadjuvant chemotherapy than for patients with upfront surgery [32].

In our experience lymph node sampling before transsecting the renal vessel and removing the tumor is a key step for a sufficient sampling. It allows sampling to be performed along the correct anatomical structures without the tissue being retracted and is associated with a reduced probability of vascular injury. We collected lymph nodes in the first 3 patients of our cohort after tumor removal like in open tumor nephrectomy. Identification of the sites of lymph nodes proved difficult because of tissue retraction. Therefore, we changed the procedure to early removal of lymph nodes in the following patients.

In two patients, no lymph nodes were identified by the pathologist although intraoperative collection of lymph nodes in these patients had been performed. It is well described and conceivable that the number of lymph nodes noted as intraoperatively excised and identified pathologically might differ [28,39]. It has been shown that separate collection of lymph nodes in addition to those in a resected specimen adjacent to the tumor could increase the number of collected lymph nodes [39]. Our procedure to collect lymph nodes before resecting the tumor realizes a separate sampling of tumor specimen and lymph nodes.

No relapse occurred during the follow-up period which comprises more than 5 years for two patients and 78 months at the maximum. Our data show that MIS is a technique which can be safely performed in children suffering from unilateral WT without affecting the long term outcome. There are few comparative data of MIS and open surgery on surgical outcome. A retrospective matched propensity analysis of the National Data Base revealed comparable oncological outcomes after MIS and open surgery. Because of the bias linked to register data and the retrospective nature of the analysis the authors suggest performing prospective randomised trials [16]. Additionally, as most of these patients may have not received preoperative chemotherapy, data may not be representative for preoperatively treated patients. Therefore, further studies are necessary to investigate the effect of MIS on the oncological outcome in these patients.

In addition to our above listed criteria for laparoscopic WT nephrectomy (Table 1), the SIOP-RTSG protocol guidelines contain two more aspects. First, there should be a clear response to the pre-operative chemotherapy in order to reduce the risk of tumor spillage. Second, operating surgeons should have sufficient expertise with surgery of the upper urinary tract.

Our group has a wide experience with laparoscopic procedures of the upper urinary tract including surgery in over 150 infants below one year of age [40,41]. Also, as members of the national and international SIOP steering committees for renal tumors (RTSG) we were actively involved in the development of surgical and MIS guidelines in the new SIOP Umbrella Protocol.

5. Conclusion

Key steps for minimally invasive WT nephrectomy in addition to a careful selection of patients are the usage of the ureter as a leading structure, the usage of a traction suture around the ureter for a better exploration of the renal pedicle, and performance of lymph node sampling before tumor nephrectomy. Appraising the data published on laparoscopic radical nephrectomy in WT management including our own, one has to conclude that there clearly is a need for further data to eventually classify any guidance as based on the principle of evidence based medicine. These data however can be collected only in multicenter studies. MIS has been introduced in the new RTSG umbrella protocol and will be assessed based on the gathered experiences [42].

Declarations of interests

None.

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Appendix A. Supplementary data

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