Review

Minimally Invasive Surgery in Pediatric Oncology: Proposal of Guidelines

PRZEMYSŁAW GALAZKA¹, KRZYSZTOF CZYZEWSKI², AGATA MARJANSKA²,
IRENA DANILUK-MATRAS¹ and JAN STYCZYNSKI²

¹Department of General and Oncological Surgery for Children and Adolescents, Jurasz University Hospital, Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Torun, Bydgoszcz, Poland;

²Department of Pediatric Hematology and Oncology, Jurasz University Hospital, Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Torun, Bydgoszcz, Poland

Abstract. *Background/Aim:* The objective of the study was to propose clinical guidelines for the use of minimally invasive surgery (MIS) in pediatric oncology. *Patients and Methods:* Two groups of experts, including pediatric surgeons and pediatric oncologists were created in order to establish strategies of diagnostic and therapeutic surgical management in pediatric oncology. *Results:* On the basis of the analysis of the existing literature, we elaborated guidelines that were graded according to the simple practical clinical system: yes/no. This project was dedicated to the following topics: adrenal tumors including neuroblastoma, renal tumors including Wilms tumor (nephroblastoma), ovarian tumors and pulmonary nodules and metastases (osteosarcoma). *Conclusion:* Although existing data do not allow the recommendation of the use of MIS for all indications, this technique should currently be regarded as a standard of care in several areas of pediatric oncology.

Minimally invasive surgery (MIS), in contrast to open surgery, is a technique that limits the size of incisions that allow access to peritoneal or thoracic cavities, followed by the use of laparoscope or thoracoscope for visualization and precise dissection. The same target operation should be performed *via* an open technique or a minimally invasive approach (1-3).

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Correspondence to: Przemysław Galazka, MD, Ph.D., Department of General and Oncological Surgery for Children and Adolescents, Jurasz University Hospital, Collegium Medicum, Nicolaus Copernicus University in Torun, ul. Skłodowskiej-Curie 9, 85-094 Bydgoszcz, Poland. Tel: +48 525854015, Fax: +48 525854093, e-mail: galazkaprzemek@hotmail.com

Key Words: Minimally invasive surgery, pediatric oncology, neuroblastoma, Wilms tumor, ovarian tumor, lung metastases, review.

The concept of MIS in children with cancer was used for the first time by Holcomb *et al.* (4), who showed laparoscopy and thoracoscopy to be highly accurate with minimal morbidity for the patient. Both modalities were useful for biopsies, assessment of resectability, staging, evaluation of metastatic or recurrent disease, assessing the potential benefit of second-look procedures, and for diagnosis of infectious complications. The development of this technology has been possible with improved visualization of anatomical structures (5). Subsequent studies and analyses confirmed that MIS procedures in pediatric oncology are safe and effective, resulting in earlier administration of adjuvant therapy.

MIS is a developing concept, however in contrast to many areas in adults (6-8), there are no clear guidelines or recommendations in pediatric oncology, mainly due to heterogeneity of clinical diagnoses and small numbers of patients included in the studies. Thus, the aim of this study was to propose clinical guidelines for the use of MIS in pediatric oncology.

Guideline Development Overview

Two initial groups of experts, including pediatric surgeons and pediatric oncologists were created in order to establish strategies of diagnostic and therapeutic surgical management in pediatric oncology. According to our own experience the relevant issues of MIS utilization in pediatric oncology were defined as follow: adrenal tumors including neuroblastoma (NBL), renal tumors including Wilms tumor (WT), ovarian tumors, pulmonary nodules and metastases. The main desired outcome was evidence of a reduction in open surgery, and secondary outcomes included efficacy and safety, expressed as rate of complications. We performed Pub Med searches from 1995 to 2019 to identify potentially relevant English-language studies. The searches included a combination of indexed terms

and free text terms (minimally invasive surgery, laparoscopy, thoracoscopy, AND pediatric, child AND adrenal tumor, retroperitoneal tumor, neuroblastoma, Wilms tumor, ovary, thoracic/lung nodules/metastases). We screened references for other potentially relevant papers. On the basis of these analyses, we elaborated clinical guidelines that were graded according to the simple practical system: yes/no.

Advantages and Disadvantages of MIS

Minimally invasive surgical approach is increasingly used in a variety of pediatric tumor types. So far, there has been no pediatric oncology trial comparing MIS and open approaches. The real challenge in pediatric surgical oncology is that any specific tumor is rare and each subtype usually presents a distinct biologic entity (1). Heterogeneity of tumor types makes a uniform approach difficult and the number of each specific tumor type for most surgeons is small. No single pediatric oncology center is able to diagnose and treat a sufficient number of patients to prepare evidence-based recommendations on surgical approach and operative techniques, while multicenter trials are difficult to organize and control (1, 2).

Advantages of MIS. This approach, based on better visualization and shorter operative time, results in smaller incisions and lower operative trauma, shorter post-operative course and pain, better cosmesis, earlier post-operative feeding, quicker return to regular activities and earlier initiation of adjuvant chemotherapy. An additional benefit of MIS is less tissue trauma leading to fewer post-operative complications, less bowel adhesion formation, fewer wound complications and immunologic advantages. MIS may cause less pain, scarring, damage to healthy tissue and the patient may have a faster recovery than with traditional surgery (9, 10).

Disadvantages of MIS. Since complete tumor resection is one of the most important factors of survival in pediatric malignancies, the risk of incomplete resection or tumor spillage is a key issue during MIS. In the case of a R1/R2 resection, the prognosis is worse and intensified chemotherapy or radiotherapy might be required in order to minimize the risk of tumor recurrence. Inadequate lymph node sampling will cause errors of staging and risk classification (11).

Unique challenges to MIS in pediatric surgical oncology. Pediatric patients have usually smaller bodies, that imposes a challenge because of restricted working space for large tumors, the need for a larger incision for extraction, difficulty in navigation or limited room for stapler, use of adequate instrumentation, anesthesia difficulties, specificities of thoracoscopy (lung collapse required) and laparoscopy (insufflation, push of diaphragm, hypercapnia),

port site metastases, and risk of visceral injury with trocar placement. Additionally, lack of experience and learning curve might be an issue (12). Apart from possible difficulties in vascular control, the oncologic nature of the disease may cause the risk of dispersion of tumor with insufflation, tumor spillage or incomplete resection within tumor margins. There is also an obvious risk of conversion of MIS approach to open surgery because limited tactile sense or localization or the need of a larger incision to remove the tumor intact.

Pediatric Oncology: Summary of Reported Data

Indications. MIS can be used in pediatric oncology either for diagnosis (biopsy) or treatment (tumor resection). MIS biopsy can be regarded as the management of choice in suspicion of neuroblastoma (NBL), hepatoblastoma (HBL), soft tissue sarcoma (STS) and germ cell tumor (GCT), while the indications for MIS biopsy are questionable in suspicion of Wilms tumor (WT), adrenocortical tumors, and pancreatic tumors. MIS tumor resection can be considered for localized NBL (L1 stage), adrenal tumors, renal tumors and pancreatic tumors, while it might be questionable for ovarian tumors, liver tumors, nephron-sparing surgery (NSS) in Wilms tumors, and soft tissue sarcoma (1, 2, 11, 13-16).

Principles. General considerations for MIS in pediatric oncology require that the basic operative principles of open pediatric cancer surgery should be known and followed: avoiding spill, R0 resection, specimen intact, organ-sparing and optimal lymph nodes sampling. Purpose-specific considerations include proper biopsy, proper staging and proper resection (17). Systematic reviews of larger pediatric studies have been recently presented by Abdelhafeez *et al.* (3) and Phelps *et al.* (2).

Outcome. The summary of 8 studies performed between 2007-2018 aimed at evaluating MIS in tumor resection, including 213 patients, showed gross total resection in 94.3%, with negative margins in 77.0% and a 10.8% (23/213) conversion rate to open surgery, leading to a median overall survival of 100% (range=84-100%) and median event-free survival 95% (range=77-100%) at median follow-up of 28 months (range=16-58 months) (14, 15, 18-24). The conversion rate itself, reported in 14 large studies including >50 patients each, was 15.5% (214/1379) (3, 4, 14, 24-34).

General Considerations on MIS

Because the role of surgical radicality in pediatric oncology can vary from biopsy only to definitive total resection with negative microscopical margins, MIS should be regarded as a potential

approach to achieve a dynamic series of therapeutic objectives. The surgical panels should be prepared for active surgical approaches stratified by tumor size, location, stage, resectability, histology, and available adjuvant therapies. MIS approaches to pediatric tumors should be undertaken with caution simultaneously with traditional open resection approach. During MIS operation, specimens should be placed in a dedicated retrieval bag and removed totally through an enlarged incision, disabling tumor dissemination. The fundamental principles have been outlined by several teams (1, 5).

Recommendations:

- During MIS approach, the operative field should be optimally exposed for surgeon.
- Tumor dissection should proceed from the peripheral to central area and saving division of critical structures until the tumor has been isolated.
- Every attempt should be undertaken by the surgeon to remove the tumor mass without spillage.
- The rescue plan for an intraoperative bleeding should be prepared by the operating surgeon.

Adrenal Tumors

In case of adrenal tumors, the common histologies include neuroblastic tumors, adrenocortical carcinoma (ACC), and benign adrenal tumors. The goals of surgery for neuroblastic tumors are variable, but R0 resection is not always required. For ACC, complete resection without spillage or positive margins and lymphadenectomy, when nodes are involved is mandatory. Classical indications where MIS is commonly used involve neuroblastic tumors of L1 stage and small, benign adrenal tumors. Controversies include neuroblastic tumors of L2 stage and tumors suspected of being ACC.

Neuroblastoma. The International Neuroblastoma Risk Group staging system (INRGSS) (35) is based on four stages: L1 (localized, no IDRF; image-defined risk factors), L2 (loco-regional, 1 or more IDRF), M (distant metastases (except MS stage)) and MS (with metastases to skin, liver, and bone marrow in patients aged <18 months). Neuroblastic tumor without IDRF and with a tumor volume less than 100 ml is regarded as amenable to MIS resection (2).

MIS approaches in adrenal tumors. Based on a relatively large number of retrospective studies, preference for laparoscopic approach can be given in adrenal tumors in INRGSS stage L1 or INSS stage I/II. Safe resection can be expected for tumors with a diameter of less than 4 cm, and complete tumor resection at the range of 88-100%. Still, conversion rate is 10-15% and surgical complication rate is about 10-30% (2, 5, 10, 36).

Recommendations:

- MIS is recommended for diagnostic biopsy in adrenal tumors.
- Therapeutic MIS resection is recommended for neuroblastic tumor without IDRF and with a tumor volume less than 100 ml.
- The risk of disease- or treatment-related complications is 10-30%.

Renal Tumors

Histologies of pediatric renal tumors include mostly (in almost 90%) Wilms tumor (nephroblastoma) and rarely clear cell sarcoma of kidney, malignant rhabdoid tumor of kidney, renal cell carcinoma (RCC) and mesoblastic nephroma. Goals of surgery are: complete resection with negative margins, no spillage and sampling of lymph nodes, particularly in Wilms tumor. Relatively common indications where MIS is used (at least for adults) is RCC, while there are controversies about Wilms tumor in case small tumors, especially if centrally located, nephron-sparing surgery and sampling of lymph nodes.

Wilms tumor. Total tumor resection after induction chemotherapy is required followed by adjuvant chemotherapy. Usually surgeons have to proceed with large and fragile tumor with a high risk of intra-operative spillage. In most cases open surgery is necessary. The experience with MIS includes a limited number of patients with smaller tumors, and high rate of insufficient lymph node sampling (5, 37-39).

SIOP/RTSG (International Society of Pediatric Oncology/ Renal Tumor Study Group) listed contraindications to MIS in case of: tumor infiltrations on extrarenal structures, tumor extension beyond the border of the spinal column, thrombus in the renal vein or cava vena, tumor without any response to chemotherapy, and lack of experience in laparoscopic urology (20).

According to the SIOP-2001 Nephroblastoma protocol (Societe Internationale D'Oncologie Pediatrique - International Society of Paediatric Oncology), Wilms tumor represents the majority of cases and should be treated with pre-operative chemotherapy without an initial biopsy. Thus, adopted preoperative biopsy is used only in selected cases and imaging-guided core needle biopsy is the preferred technique in these cases (40). With respect to surgical treatment, there is an absolute tendency toward the conventional open tumor nephrectomy as has been reported in a recent survey (40). An additional drawback of the MIS techniques is the issue of inadequate lymph node sampling (20, 41).

Recommendations:

- MIS is not the recommended approach even in selected cases when biopsy is required in renal tumor.
- There is clear expert consensus against laparoscopic tumor nephrectomy.

Ovarian Tumors

Spectrum and goals of surgery in ovarian tumors include: malignant tumor (salpingoophorectomy, inspect other ovary, nodes, omentum, collect ascites) and benign tumor (ovary-sparing tumor excision). Surgical approach largely depends on size, solid nature and serum markers. In all these cases, MIS is commonly used. Other group of indications deals with fertility preservation. Still, there might be some controversies about total intact removal of tumor.

Ovarian tumors. Laparoscopy has a clear role in staging of malignant lesions, inspection of the diaphragm and the other ovary, any sampling from peritoneum can be performed with this technique. The role of MIS in ovarian surgery is not univocal. It has been suggested that tumors with diameter <7.5 cm bring little risk for tumor spillage, so may be approached laparoscopically and removed safely (1, 5). In other cases, there are insufficient data to support the use of laparoscopy in the treatment of ovarian malignancies and an open approach is rather recommended in pediatric oncology (42, 43). MIS approaches that preserve ovarian parenchyma are favored in the treatment of benign adnexal masses and ovarian cysts. However, when compared to an open cystectomy, MIS has been associated with a higher rate of benign cyst rupture (1).

Fertility preservation. MIS approaches can be used for fertility preservation. Surgery leading to ovarian transposition or ovarian cryopreservation are accomplished laparoscopically. This approach is of value in case of planned pelvic irradiation, since already radiation doses of 4-20 Gy may have contributed to loss of ovarian function, thus ovarian transpositions out of the pelvis into paracolic areas can be recommended (44).

Recommendations:

- MIS is recommended in staging of malignant ovarian tumors.
- Tumors with diameter <7.5 cm may be approached and removed laparoscopically.
- MIS technique is of clinical value in fertility preservation procedures.

Lung Nodules and Metastases

Biology of lung nodules is benign in majority (>90%) of pediatric cases (infection, congenital, atelectasis, neoplastic); while cancer lesions from non-pulmonary metastasis and primary lung malignancies in children include <10% and <1% of lung nodules, respectively. Goals of surgery vary and are histology-dependent: *e.g.* diagnostic in Wilms tumor; therapeutic in osteosarcoma. Indications where MIS is

commonly used are diagnosis and therapy, depending on histology, localization and number of nodules. Severe controversies exist with respect to osteosarcoma (OS) metastases.

MIS in thoracic tumors. Thoracoscopic approach is used for biopsy and resection of neurogenic tumors. Gross total resection is combined with a good outcome; conversion rate is at the level of 5-10% and surgical complication rate comparable to open approach (1, 5). In case of malignant immature teratomas, R0 resection without tumor spillage is the most important prognostic factor; it is essential to minimize the risk of disruption of the tumor and its local dissemination including negative margins. MIS approach in these cases should be used only if these principles are secured (5).

Lung metastases. Risk factors influencing decision on selection of surgical technique include: detection of metastases in CT (computed tomography) scan, number of metastases (with variable cut-offs ranging between 5-15), military disease (>25), impalpable metastases, judgement of metastases viability, involvement of vessels or main bronchial branches, or response to previous chemotherapy (45, 46).

Metastatic osteosarcoma. Even though thoracoscopic tumor biopsy is now considered to be the preferred method for obtaining tissue for diagnostic purposes, the MIS approach to metastatic OS is not indicated in pediatric oncology (1). Since the ability to achieve a complete resection of recurrent disease is the most important prognostic factor for relapse, this usually cannot be achieved with MIS. Also, CT is not sufficiently informative about the extent of disease found intraoperatively and more lesions are detected at the time of thoracotomy than identified on preoperative CT (45), so thoracotomy is usually advocated (1). Patients with OS with metachronous metastatic pulmonary disease presenting with a single pulmonary nodule (SPN) on CT frequently require multiple thoracotomies, and two-thirds of patients have a second pulmonary relapse with a significant portion being ipsilateral.

Video-assisted thoracoscopic surgery (VATS) is recommended for SPN with subpleural location and other than OS histology, while the use of thoracoscopy for resection of OS lung nodules is not advocated (47). Manual identification of deeper lesions is difficult for the surgeon during VATS. The majority of SPN can be identified during thoracoscopy by using localizing techniques, including CT-guided radioisotope marking using a gamma probe during VATS or hookwire localization based on injection of methylene blue, or intrathoracoscopic ultrasound (48, 49).

Recommendations:

- MIS is the preferred method for obtaining lung tissue for diagnosis.

- Thoracoscopic approach is recommended for resections in thoracic neurogenic tumors.
- Due to low probability of complete resection of all lesions, MIS approach to lung metastatic osteosarcoma is not recommended.

Future Perspectives

New developments (robotic; virtual methods; 3D MIS; SILS, single-incision laparoscopic surgery; NOTES, natural orifice transluminal endoscopic surgery) will definitively widen the possibilities of pediatric oncological surgery in the future (50, 51). So far robot-assisted solid tumor resections have been used in abdominal, pelvic, thoracic, and neck localization with comparable, to other MIS techniques, rate of conversion to open surgery and tumor spillage (50).

Conclusion

Although existing data do not allow the recommendation of the use of MIS for all indications, this technique should currently be regarded as a standard of care in several areas of pediatric oncology. It is commonly used in suprarenal L1 neuroblastoma, small ovarian teratoma, and thoracic neural tumors. It has limited indications in Wilms tumor and osteosarcoma lung metastases. Existing contraindications include coagulopathy, respiratory insufficiency, and histology of ACC. Still, the success of this approach depends on the technical equipment and the experience of the surgeon.

Conflicts of Interest

The Authors have no conflicts of interest to disclose in regard to this study.

Authors' Contributions

PG, JS - concept/design, data analysis/interpretation, writing article, critical revision of article, approval of article; AM, KC, IDM - data collection, data analysis/interpretation, writing article, critical revision of article, approval of article.

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Received September 26, 2019

Revised October 17, 2019

Accepted October 24, 2019