

Pediatric minimally invasive surgery for malignant abdominal tumor

Single center experience

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Abstract

This study examined the safety and usefulness of minimally invasive surgery (MIS) for malignant abdominal tumors in pediatric patients and analyzed the factors affecting the resection margin, operative time, and hospital stay of neuroblastoma (NBL) patients.

We retrospectively reviewed data of pediatric patients who underwent MIS for malignant abdominal tumors from January 2011 to June 2017 at the Seoul National University Children's Hospital. Sex; age at operation; diagnosis; tumor location; operation-related data, such as operation time and transfusion; and follow-up data were reviewed. We divided patients into an excision group and a biopsy group. Detailed pathologic data were reviewed to analyze factors affecting the resection margin of NBL. Median value and range were calculated for all continuous variables. Mann-Whitney test and χ^2 test were used as appropriate. *P* values of $<.05$ were considered significant.

Thirty-four pediatric patients were included; 21 were boys. The median age was 4 (0.2–18) years. The most common diagnosis was NBL (17 patients; 50.0%). Three patients each were diagnosed with lymphoma, solid pseudopapillary tumor of the pancreas, and teratoma. The median tumor size was 3.4 (0.5–10.2) cm. The median operation time was 108 (55–290) minutes, and the median hospital stay was 5 (2–11) days. The number of conversions to open surgery was 4. There were no postoperative complications or mortality. There were 18 patients in the excision group and 16 in the biopsy group. Diagnosis and the number of patients receiving preoperative chemotherapy differed between the 2 groups. R0 resection of NBL was significantly higher in patients with stage 1 disease and those aged >2 years. There were no clinical factors influencing operative time or hospital stay.

MIS was feasible and safe in pediatric patients with malignant abdominal tumors. R0 resection of NBL was related to age and stage.

Abbreviations: Bx = biopsy, GCT = germ cell tumor, IDRF = image-defined risk factor, INRGSS = International Neuroblastoma Risk Group Staging System, INSS = International Neuroblastoma Staging System, IVC = inferior vena cava, MIS = minimally invasive surgery, NBL = ganglioneuroblastoma, NBL = neuroblastoma, NHL = non-Hodgkin lymphoma, RhMS = rhabdomyosarcoma, SPT = Solid pseudopapillary tumor.

Keywords: abdominal neoplasm, minimally invasive surgical procedure, pediatrics

1. Introduction

In pediatric patients, common malignant solid tumors of the abdomen include neuroblastoma (NBL), Wilms tumor (WT),

non-Hodgkin lymphoma (NHL), germ cell tumor (GCT), and rhabdomyosarcoma (RhMS). In the United States in 2014, 710 NBL cases, 510 WT cases, 620 NHL cases, and 340 RMS cases occurred in patients aged between 0 and 14 years, and 540 GCT cases occurred in patients aged between 15 and 19 years.^[1] NBL is the most common cancer occurring in children under 1 year of age.^[1] With the recent development of novel treatments, the survival rate has increased sharply, and much attention is now being given to minimally invasive surgery (MIS). GCT is histologically diverse and is not responsive to chemotherapy in the case of teratoma; surgery plays an important role in therapy.^[2] Surgery is regarded as initial treatment for RhMS, unless it causes disfigurement or organ function.^[3]

Recently, for treating many pediatric diseases, MIS has been applied for surgical procedures such as appendectomy, cholecystectomy, fundoplication, splenectomy, and nephrectomy.^[4–7] In 1995, Holcomb et al reported the safety of laparoscopic procedures in 25 pediatric cancer patients in 15 institutions.^[8] However, MIS was not introduced for malignant lesions until much later. Several studies have reported on MIS for malignant diseases. Successful resection of NBL in 7 patients was reported in 2012.^[9] A study detailing 9 cases of laparoscopic malignant tumor resection of pediatric malignancies was published, 2 of

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which underwent open conversion.^[10] A multicenter study conducted in Europe reported the result of MIS for 68 adrenal masses, including NBL.^[11] Recently, MIS results according to the image-defined risk factor (IDRF) of the International Neuroblastoma Risk Group Staging System (INRGSS) have been reported.^[12]

To date, no studies have reported the use of the Cochrane Library Systematic Review. This study serves as a bridge study for its use. We investigated pediatric patients who underwent MIS for malignant abdominal diseases and analyzed factors affecting the resection margin, operation time, and hospital stay of patients with NBL resected by MIS.

2. Methods

We performed retrospective chart review of patients under 18 years of age who underwent MIS for abdominal malignancy from January 2011 to June 2017 at the Seoul National University Children's Hospital. Patients without definite major vessel invasion or encasement on imaging study were carefully selected for MIS. Data on sex, age, preoperative diagnosis, tumor location, size, transfusion during surgery, preoperative chemotherapy, and follow-up were collected. To identify factors associated with resection margin, operation time, and hospital stay of NBL patients, the most common malignancy in the pediatric population, pathologic results, and surgery-related data, including operation time and hospital stay, were investigated.

Only patients who had pathologically confirmed malignancy were included. Patients who had previously confirmed malignancy, but had no identified postoperative malignancy, were also included, as were patients who were receiving chemotherapy for suspected recurrent or residual lesions. Tumor size was estimated by the largest diameter through available imaging studies, including computed tomography and magnetic resonance imaging. One pediatric radiologist reviewed all images and determined the IDRF status of each patient.

The pathology results were reviewed by pathologists. The resection margin was defined as follows: R0 resection as the absence of microscopic tumor, regardless of the length of the margin; R1 resection as when the margin had a microscopic tumor and no gross tumor during surgery; and uncheckable margin as when evaluation of margin was impossible. For uncheckable resection margin, the tumor could not be extracted without chopping.

SPSS v. 23 (IBM Corporation, Armonk, NY) was used for statistical analysis. Continuous data are presented as median and range. The Mann-Whitney *U* test was used for comparison of continuous data between 2 groups. Fisher exact test and χ^2 square test were used for assessing differences in categorical data between the 2 groups. *P* values of <.05 were considered significant.

This study was approved by the institutional review board of Seoul National University Hospital (H-1803-101-931).

3. Results

Thirty-four patients underwent MIS for abdominal malignancy during the study period. Twenty-one patients were boys, and the median patient age was 4 (range, 0.2–18) years. Of 34 patients, 18 underwent excision for curative intent (excision group) and 16 underwent incisional biopsy (Bx) for histological confirmation

(biopsy group). The most frequent diagnosis was NBL (17 cases). Solid pseudopapillary tumor (SPT) of the pancreas, lymphoma, and teratoma were each diagnosed in 3 cases. Two, 1, and 1 cases of RhMS, desmoplastic small round cell tumor, and rhabdoid tumor, respectively, were diagnosed. The most common tumor location was around both the kidneys owing to NBL. Other locations included the right psoas muscle, ileum, liver, and presacral, retrovesical, retrocaval, infrapancreatic, and hepato-duodenal ligaments. The median tumor size was 3.4 (0.5–10.2) cm. Fifteen patients received preoperative chemotherapy, and 10 patients received transfusion during surgery. The median operation time was 108 (55–290) minutes, and the median hospital stay after surgery was 5 (2–11) days. Four cases were converted to open surgery during MIS. There was no postoperative complication that led to additional intervention or surgery. No patient in the excision group had a recurrence. The median follow-up period was 24.5 (0–56) months. Two patients died during follow-up (Table 1).

2.1. Incisional Bx group

Diagnosis was more variable in the biopsy group than in the excision group. Most patients in the excision group had NBL (14 patients, 72.2%), but only 4 patients (25.0%) in the biopsy group were diagnosed with NBL. Incisional Bx was performed for patients with lymphoma, teratoma, RhMS, GCT, desmoplastic

Table 1

Clinical characteristics of all patients who underwent minimally invasive surgery for malignancy.

	N=34
Male	21
Age, y	4 (0.2–18)
Preoperative diagnosis	
Neuroblastoma	17
Germ cell tumor	4
Lymphoma	3
Solid pseudopapillary tumor	3
Teratoma	3
Rabdomyosarcoma	2
Desmoplastic small round cell tumor	1
Rhabdoid tumor	1
Purpose	
Excision	18
Incisional biopsy	16
Location of tumor	
Lt. kidney	9
Rt. kidney	6
Paraaortic area	4
Pancreas	3
Peritoneum	2
Iliac vessel	2
Others	8
Size, cm	3.4 (0.5–10.2)
Preoperative chemotherapy	15
Transfusion	10
Operation time, min	108 (55–290)
Hospital stay, day	5 (2–11)
Open conversion	4
Complication	0
Recurrence in excision	0
Follow up period, mo	24.5 (0–56)
Mortality	2

Table 2
Patients' characteristics according to purpose.

	Excision (N = 18)	Incision (N = 16)
Preoperative diagnosis		
Neuroblastoma	13	4
Solid pseudopapillary tumor	3	0
Lymphoma	0	3
Teratoma	1	2
Rhabdomyosarcoma	1	1
Germ cell tumor	0	4
Desmoplastic small round cell tumor	0	1
Rhabdoid tumor	0	1
Tumor size, cm	3.4 (1.1–10.2)	1.2 (0.5–5.8)
Preoperative chemotherapy	4 (22.2%)	11 (68.8%)
Transfusion	6 (33.3%)	4 (25.0%)
Open conversion	1 (5.6%)	3 (18.8%)

small round cell tumor, and rhabdoid tumor. Patients with SPT of the pancreas were only found in the excision group, and patients with lymphoma, desmoplastic small round cell tumor, and rhabdoid tumor were found in the biopsy group only. The proportion of patients who received preoperative chemotherapy was higher in the biopsy group (excision 22.2% vs biopsy 68.8%). Open conversion was also higher in the biopsy group (excision 5.6% vs biopsy 18.8%) (Table 2).

2.2. Excision group

Table 3 shows the details of patients who underwent excision. NBL was further subdivided into NBL and ganglioneuroblastoma (GNBL) through pathology. All 3 patients who underwent preoperative chemotherapy in the NBL and GNBL subgroups had distant metastasis and were International Neuroblastoma Staging System (INSS) stage 4. IDRF was negative in all NBL and GNBL patients, including INSS stage 4 patients. The 13 patients

with NBL who underwent excision with curative intent were divided into stages. Six patients had INSS stage 1, 4 had stage 2, and 3 had stage 4. Three patients had M stage according to the INRGSS, and the remaining patients were L1 without IDRF. One patient who underwent surgery for a 1.1-cm RhMS after neoadjuvant chemotherapy (8.7cm before chemotherapy) underwent conversion to open surgery. This patient was the only conversion case in the excision group. We analyzed the factors associated with resection margin, operation time, and hospital stay in NBL and GNBL patients. There were 5 cases of R0 resection, 4 cases of R1, and 4 cases of uncheckable margins. Age of ≥2 years and stage I were significantly associated with positive R0 resection rate (Table 4). There were no clinical factors affecting operation time or hospital stay (Tables 5 and 6).

4. Discussion

MIS is known to have many advantages, such as reduction in postoperative pain and hospital stay, smaller wounds, and reduced surgical complication in adults.^[13,14] The use of MIS in children is increasing, and efficacy similar to that seen in adults has been reported.^[15,16] It is known that vascular control in MIS can be safely achieved with ultrasonic scalpel used in this study.^[17,18] Many procedures have been safely performed through MIS in children with this device^[19,20]; however, long-term safety effect of using this device in children have not been extensively studied (Reviewer #1). The range of MIS applications is now widening, from benign diseases to tumors, and studies on its use for malignant diseases are also being published. In 2016, Oh et al^[21] reported that MIS is safe for the diagnosis and treatment of intraperitoneal tumors, including benign and malignant diseases. In particular, adrenalectomy and nephrectomy have been actively researched,^[11,12,22–26] but there is no confirmed indication for MIS. The INSS, which is widely used for staging NBL, has the disadvantage that staging can only be performed after surgery according to the tumor extent, and accuracy is dependent on the individual surgeon. To overcome

Table 3
Patients who underwent laparoscopic excision.

No.	Diagnosis	Sex/age	Preop CTx	Prev. op	Location	Size, cm	INSS stage	INRGSS stage	IDRF	Resection margin	Op time, min	Open conversion	Open Complication	Follow-up period, mo
1	NBL	M/0.2	No	No	Rt. adrenal	4.4	2	L1	Negative	R1	73	No	No	39
2	NBL	M/0.4	No	No	Lt. adrenal	3.8	2	L1	Negative	R1	210	No	No	48
3	NBL	M/0.8	No	No	Lt. adrenal	2.6	2	L1	Negative	R1	125	No	No	2
4	NBL	M/1.5	Yes	No	Rt. CIA	5.0	4	M	Negative	R1	102	No	No	0
5	NBL	M/1.7	Yes	No	Rt. adrenal	1.5	4	M	Negative	Uncheck	105	No	No	38
6	NBL	M/2.2	No	No	Lt. infrarenal	3.2	1	L1	Negative	R0	105	No	No	43
7	NBL	M/2.6	No	No	Rt. adrenal	4.0	1	L1	Negative	R0	110	No	No	16
8	NBL	F/4.0	Yes	No	Lt. adrenal	4.5	4	M	Negative	Uncheck	185	No	no	29
9	GNBL	F/1.0	No	No	Rt. adrenal	2.0	1	L1	Negative	R0	95	No	No	48
10	GNBL	M/4.0	No	No	Lt. adrenal	3.2	1	L1	Negative	R0	195	No	No	36
11	GNBL	M/4.0	no	No	Prescral	5.0	1	L1	Negative	Uncheck	75	No	No	6
12	GNBL	M/10	No	No	Lt. adrenal	3.0	1	L1	Negative	R0	90	No	No	9
13	GNBL	F/13	No	No	Lt. adrenal	3.5	2	L1	Negative	Uncheck	79	No	No	10
14	SPN	M/8.0	No	No	Pancreas tail	2.4	—	—	—	R0	290	No	No	34
15	SPN	F/14.0	No	No	Pancreas tail	7.7	—	—	—	R0	155	No	No	32
16	SPN	F/14.0	No	Yes	Pancreas body	10.2	—	—	—	R0	185	No	No	21
17	Teratoma	M/3.2	No	No	Rt. retroperitoneum	8.0	—	—	—	Uncheck	135	No	No	4
18	RhMS	F/6.0	Yes	No	Rt. psoas muscle	1.1	—	—	—	Uncheck	220	Yes	No	25

CIA=Common Iliac Artery, CTx=chemotherapy, GNBL=ganglioneuroblastoma, IDRF=image-defined risk factor, INRGSS=International Neuroblastoma Risk Group Staging System, INSS=International Neuroblastoma Staging System, NBL=neuroblastoma, Op time=operation time, Prev. op=previous operation history, RhMS=rhabdomyosarcoma, SPT=solid pseudopapillary tumor.

Table 4
Resection margin and associated variables in neuroblastoma and ganglioneuroblastoma.

	R0	R1	P
Age	1/4	4/0	.04
<2/>2 y			
Sex	4/1	3/1	>.99
M/F			
Diagnosis	2/3	4/0	.16
NBL/GNBL			
Laterality	2/3	2/2	>.99
Rt./Lt/			
Size	4/1	1/3	.20
<3.5/>3.5 cm			
INSS Stage I	5/0	0/4	.01
Yes/no			
INRGSS Stage L1	5/0	3/1	.44
Yes/no			
Transfusion	1/4	2/2	.52
Yes/no			
Op time	4/1	2/2	.52
<120/>120 (minute)			
Hospital stay	4/1	2/2	.52
<5/>5 day			

GNBL = ganglioneuroblastoma, INRGSS = International Neuroblastoma Risk Group Staging System, INSS = International Neuroblastoma Staging System, NBL = neuroblastoma.

this problem, the INRGSS was introduced, and staging is made preoperatively according to the IDRF through imaging results.^[27] Although there are reports that the results of open conversion and bleeding differ dependent on IDRF,^[12,24] they are not used as MIS indications. However, some authors recommend performing MIS if there is no vascular encasement, dumbbell configuration, or infiltration of the main structures.^[24] Several studies, from a case series to multicenter studies for adrenalectomy and a large number of nephrectomies that examined MIS have been

Table 5
Operation time and associated variables in neuroblastoma and ganglioneuroblastoma.

	Mean ± SD, min	P	
Age	118 ± 48	120 ± 50	.94
<2/>2 y			
Sex	119 ± 46	119 ± 56	.88
M/F			
Diagnosis	127 ± 46	106 ± 50	.19
NBL/GNBL			
Laterality	97 ± 14	141 ± 54	.19
Rt./Lt			
Size	119 ± 40	119 ± 56	.57
<3.5/>3.5 cm			
INSS Stage I	112 ± 43	126 ± 53	.72
Yes/no			
INRGSS Stage L1	116 ± 49	131 ± 41	.55
Yes/no			
Transfusion	166 ± 63	98 ± 16	.16
Yes/no			
Port number	131 ± 47	116 ± 49	.55
3/4			

GNBL = Ganglioneuroblastoma, INRGSS = International Neuroblastoma Risk Group Staging System, INSS = International Neuroblastoma Staging System, NBL = Neuroblastoma.

Table 6
Hospital stay and associated variables in neuroblastoma and ganglioneuroblastoma.

	Mean ± SD, day	P	
Age	5.2 ± 2.1	5.0 ± 1.3	.94
<2/>2 y			
Sex	5 ± 1.6	5.5 ± 1.9	.52
M/F			
Diagnosis	5.5 ± 1.9	4.4 ± 0.9	.36
NBL/GNBL			
Laterality	4.8 ± 2.0	5.1 ± 1.6	.55
Rt./Lt			
Size	5.2 ± 1.9	5.0 ± 1.6	.71
<3.5/>3.5 cm			
INSS Stage I	4.8 ± 1.3	5.3 ± 2.0	.82
Yes/no			
INRGSS Stage L1	5.0 ± 1.6	5.3 ± 2.1	.86
Yes/no			
Transfusion	4.8 ± 1.5	5.2 ± 1.8	.58
Yes/no			
Port number	4.3 ± 1.5	5.3 ± 1.7	.34
3/4			

GNBL = ganglioneuroblastoma, INRGSS = International Neuroblastoma Risk Group Staging System, INSS = International Neuroblastoma Staging System, NBL = neuroblastoma.

published, showing that MIS can be safely performed for malignant tumors.^[9,11,22]

NBL, the most common pediatric abdominal solid malignancy, accounted for the largest proportion of patients in the excision group (13/18). SPT of the pancreas, which is common in female adolescents but not in infants and children, was the next most common in the excision group.

NBL in the excision group was treated using a transperitoneal approach, which is achieved by mesocolon dissection. Three or 4 ports were used, and the umbilical port was extended when the specimen was excised. Both Hem-o-lok (Teleflex, Wayne, PA) and Harmonic Scalpel (Ethicon, Blue Ash, OH) Endo bovie and metal clip were used appropriately. In the case of the main vessel, ligation was performed with several Hem-o-lok systems. The number of ports used in MIS is known to affect postoperative pain and recovery. One study reported that the duration of hospital stay was increased by 1.7 days for each port increase.^[11] At our institution, 3 ports are used routinely, but an additional port is inserted when traction is required for optimal visualization.

SPT of the pancreas is a tumor with low-grade malignant potential and good prognosis, and resection is the treatment of choice.^[28] Three patients were diagnosed with SPT of the pancreas, confirmed by pathologic examination, and achieved R0 resection. Two patients had no evidence of high-grade malignancy and 1 patient had perineural invasion. All 3 patients were followed up without chemotherapy, and there was no recurrence in a median 32 months' follow-up. In our patients, distal pancreatectomy included partial omentectomy and pancreatic dissection from the retroperitoneum. The splenic vessel was preserved in our study. Two patients with lesions in the distal pancreas underwent spleen-preserving distal pancreatectomy. One patient with a lesion in the pancreas head underwent tumor excision.

MIS was successfully performed for an 8 × 6.4-cm-sized retroperitoneal mass that dislocated the inferior vena cava

(IVC) and right kidney. The pathologic result confirmed the diagnosis of immature teratoma, Norris grade 1, with nephroblastoma component, which was confirmed as nephroblastoma arising in an immature teratoma. The patient was under close observation and received chemotherapy. One RhMS that was 8.7 cm before chemotherapy was effectively reduced to 1.1 cm by chemotherapy. Invasion to the aorta and right iliac artery was found, and the patient underwent conversion to open surgery. According to a study on MIS safety in NBL patients using the US national database, the open conversion rate was 12.2%.^[23] In this study, there was no open conversion in patients undergoing NBL excision.

There were no conversions because of bleeding among the 6 patients who underwent transfusion during surgery. In this study, 33.3% of patients underwent transfusion, which was higher than the 7.4% seen in a previous study examining MIS for adrenal mass.^[11] In both studies, there were no clear enrollment criteria owing to the retrospective nature, and it was not known whether there was a difference in tumor characteristics. The learning curve of laparoscopic adrenalectomy is known to require 40 to 50 cases.^[29] It is possible that, in some of the cases, the surgeons had not yet reached proficiency. There were no complications or mortality in the excision group.

There were fewer patients in the biopsy group, and they tended to have a different diagnosis than patients in the excision group. There were also more patients who received chemotherapy before surgery. This is probably because incisional biopsy may be performed for diagnostic intent in suspected recurrence after chemotherapy. Lymphoma is not usually cured by surgical treatment. We had one case of lymphoma that underwent surgery, which had been diagnosed as an intussusception with a leading point. Lymphoma was suspected on preoperative CT, and pathologic results indicated Burkitt lymphoma. The patient received chemotherapy. There were 3 open conversions in the incision group; two were NBL, and one was GCT. One NBL case underwent conversion due to severe adhesion and the other due to difficult identification of the lesion. The GCT case had adhesion to a dangerous site (the aorta). The two NBLs had a previous operative history. The two NBL tumors were 5.8 cm and 1.0 cm, respectively, and the GCT was 4.1 cm. It was difficult to identify the 1.0-cm NBL lesion. Two deaths were observed during the follow-up period, but we did not observe any surgery-related mortality. Two patients died of refractive NBL that did not respond to chemotherapy: one had multiple metastases and the other had brain metastasis. NBL is a heterogeneous tumor, from mature ganglioneuroma to immature NBL, depending on the degree of differentiation.^[30] Tissue Bx is required for risk evaluation before treatment.^[31,32] Incisional Bx with MIS can be safely performed to attain sufficient tissue with the advantages of small wound and fast recovery. Care should be taken in cases of previous surgery or in adhesion to major vessels.

IDRF was not used as a criterion for enrollment of patients in this study. No death was observed at a median follow-up of 24 months. It is possible that there were no deaths because the follow-up period was not long enough or the stages were rather low.

Resection margin could be evaluated in 9 cases of excised NBL. Five of 9 were R0 and 4 were R1. Although size is considered to be associated with resection margin, we found that only INSS stage 1 and age were related to R0 resection. Although a recent study reported that positive margins in NBL do not significantly affect local control,^[33] residual lesions play an important role in

determining future chemotherapy administration. In patients younger than 2 years, all tumors were IDRF-negative and located around the right and left kidneys, and all were resected as R1. Age should be considered when NBL patients are scheduled to undergo MIS. The INSS stage was thought to be closely related to the resection margin because of the staging system. All patients were IDRF-negative, so comparison with positive patients was impossible.

A previous study reported an increase in operation time in patients with bilateral tumors and vascular invasion during MIS surgery, and an increase in hospital stay with symptomatic patients, bilateral tumors, and increase in port number.^[11] In our study, there were no cases of bilateral tumors or vascular invasion. There was no significant difference in the number of ports, sex, age, or laterality. In the transfusion group, the average operation time was 166 minutes, whereas it was 98 minutes in the nontransfusion group. There was no statistically significant difference in operative time between the 2 groups. However, the statistical power will increase if the number of enrolled patients increases.

MIS in malignant abdominal tumors in the pediatric population is gaining popularity. However, more research should be performed. This study showed that MIS could be successful for incisional Bx, even though the number of patients included was smaller than in previous studies. We were unable to perform comparative analysis with IDRF-positive and -negative patients. Nevertheless, this study analyzed patients with only malignant cases and included tumors other than NBL.

Although it is a retrospective study in which the number of patients is small, this study showed that MIS can be performed safely for malignant abdominal tumors in children. Patients should be carefully selected, considering the invasiveness of the tumor, size, age, and oncologic safety, such as IDRF. A prospective study for procedure-related safety, oncologic outcome, and MIS indication is needed.

5. Conclusions

Among the 18 excisions, 1 RhMS case, which was reduced in size by preoperative chemotherapy, required open conversion (5.6%). Blood transfusion was performed in 6 cases (33.3%). Excision and Bx can be performed safely and applied to various malignancies. In patients older than 2 years who underwent MIS surgery for NBL and GNBL, the rate of R0 resection was significantly higher than that in patients under 2 years of age. Age should be considered when determining which patients should undergo MIS for NBL and GNBL.

Author contributions

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