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ORIGINAL ARTICLE

Comparison of long-term prognosis of laparoscopic and open adrenalectomy for local adrenal neuroblastoma in children

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Abstract

Objective To investigate and compare long-term outcomes in children undergoing laparoscopic or open adrenalectomy for local adrenal neuroblastoma.

Methods A retrospective review was conducted of 37 children with local adrenal neuroblastoma treated between January 2005 and December 2013 in our hospital. These patients met inclusion criteria for having adrenal neuroblastoma and undergoing operative resection. All patients were successfully followed up until December 2017.

Results The local adrenal neuroblastoma cases included 25 males and 12 females with an average age of 37.24 ± 37.55 months (range from 5 days to 158 months). Left adrenal lesions were present in 13 cases, the right in 24 cases. According to the INSS staging system, 27 patients were classified as stage I and 10 as stage II. Open adrenalectomy was performed in 24 patients. Laparoscopic adrenalectomy was performed in the other 13 patients, 2 of whom were converted to open surgery because of adhesions to renal vessels and diaphragmatic rupture. Significant differences were observed between the laparoscopic surgery and open surgery groups regarding tumor size ($P = 0.005$). There were two recurrence cases in open surgery, but there was no recurrence in laparoscopic surgery. The average follow-up time was 86.78 ± 24.52 months. The overall 5-year survival rate of open and laparoscopic surgery were 86.2 and 100% ($P = 0.316$).

Conclusions Laparoscopic adrenalectomy for neuroblastoma is feasible and can be performed with equivalent recurrence and mortality rates with open resection. For small tumor size and absence of vascular encasement, the adrenal neuroblastoma may be preferred laparoscopic surgery.

Keywords Laparoscopic surgery · Adrenal neuroblastoma · Prognosis

Introduction

Neuroblastoma is the most common abdominal malignant tumor in children, and the adrenal gland is the main site of occurrence of this tumor. Surgical resection is one of the steps of treatment and the traditional open approach remains the mainstay of treatment, due to the infiltrative nature of neuroblastoma. With the development of minimally invasive techniques, laparoscopic resection of small lesion is increasingly used in adrenal tumor, owing to the smaller wounds and faster postoperative recovery [1]. Although adrenal neuroblastoma may have local invasiveness, application of laparoscopic procedures has become increasingly prevalent due to improvements in surgical techniques and rapid development of imaging technology [2–4]. To date, several literature reports have confirmed the feasibility of laparoscopic adrenalectomy for neuroblastoma and highlighted the safety and rapid postoperative recovery of this approach. However, limited reports are available on tumor recurrence and long-term prognosis after laparoscopic surgery. For the neuroblastoma, the long-term prognosis is the key to establishing the merits of treatment, regardless of surgical approaches. This study reports our experience with a series of 37 patients who underwent laparoscopic adrenalectomy or conventional open surgery for neuroblastoma. The perioperative clinical outcomes and long-term prognosis were analyzed and compared to determine the feasibility of laparoscopic surgery for adrenal neuroblastoma.

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Materials and methods

Clinical data

Primary neuroblastoma confined to the adrenal gland and classified as INSS stage I–II was defined as local adrenal neuroblastoma. Clinical stage was determined according to the International Neuroblastoma staging system (INSS) and International Neuroblastoma Risk Group Staging System (INRGSS), respectively.

A total of 37 patients with local adrenal neuroblastoma treated in the Children's Hospital of Fudan University from January 2005 to December 2013 were included in the current study. Data obtained included tumor location, age at diagnosis, clinical manifestation, results of physical examination and imaging (CT, ultrasound, radionuclide bone scans), tumor markers (24 h urinary VMA, NSE, ferritin), bone marrow aspiration, surgical methods, duration of operation, amount of hemorrhage, pathology, biological factor (MYNC status) and outcomes of follow-up. Follow-up of patients was conducted via mail, telephone, subsequent visits and other approaches, and initiated from the day of discharge after surgery.

Surgical technique

Patients were placed in the supine position with a monitor on both sides of the head. Nasogastric tube and catheter were placed prior to the laparoscopic procedure. Initial laparoscopic access is through the umbilicus with 10 mm Trocar, and two additional ports are then placed. at the subcostal anterior axillary line and midclavicular line umbilical level The abdominal cavity is insufflated with carbon dioxide to a pressure of 8–12 mm Hg. Electrocautery or a 5-mm Ultracision (Ethicon, Somerville, New Jersey) harmonic scalpel is used to dissect tissues around the tumor. On the right side, an additional port was placed for liver retraction and retroperitoneum was incised transversely just below the liver to expose the inferior vena cava and adrenal gland.. On the left side, the colon was always mobilized and retroperitoneum was incised along the line of Toldt from the splenic angle to the pelvic brim to completely exposing the adrenal gland. After ligation of the right or left adrenal vein by the clips, the tumor is dissected circumferentially. The specimen is placed in a plastic specimen bag and removed through the umbilical port in a piecemeal fashion. Routine exploration of lymph nodes was performed and suspected lymph nodes were then removed. In cases where the tumor encased important blood vessels or organs or occurrence of tumor rupture, severe hemorrhage, organ damage and other conditions, the laparoscopic procedure was immediately converted to open surgery.

Statistical analysis

Data were analyzed using SPSS18.0 software. Survival analysis was performed using the Kaplan–Meier method, and the log rank method was used to test for significant differences. Data were considered statistically significant at $P < 0.05$.

Results

General information

From January 2005 to December 2013, 37 patients were diagnosed with local adrenal neuroblastoma (including 25 male and 12 female cases) and received surgical treatment in the Children's Hospital of Fudan University. The ages of these patients ranged from 5 days to 158 months, with an average of 37.24 ± 37.55 months. Thirteen patients presented with a left-sided lesion and 24 with a right-sided lesion. According to the INSS staging system, 27 patients were classified as stage I and 10 as stage II. And according to INRGSS staging system, 24 patients were classified as stage L1 and 13 patients as stage L2. Based on the Shimada pathology classification system, 16 cases were categorized as neuroblastoma and 21 cases as ganglioneuroblastoma and amplification of the N-myc oncogene was negative in 36 of the 37 cases. Twenty-two patients underwent surgical resection of their primary tumor without chemotherapy. Only 1 patient received 2 cycles of neoadjuvent chemotherapy, and 15 patients received postoperative chemotherapy. Until December 2017, all patients were successfully followed up, with follow-up 48–141 months (average, 86.78 ± 24.52 months). The 5-year survival rate of all patients was 90.7% (Fig. 1).

Group comparison

All patients were divided into laparoscopic surgery and open surgery groups, and clinical data were compared (Table 1; Fig. 2). A total of 13 laparoscopic adrenalectomies (2 left and 11 right) were performed in 13 children (4 girls and 9 boys). Based on the INSS staging system, 12 patients were classified as stage I and 1 as stage II. According to INRG staging system, 11 patients were classified as stage L1 and 2 patients as stage L2. The average size of the adrenal tumors resected was 3.77 ± 1.35 cm (range 1.98–6.00 cm) and there were no intraoperative or perioperative deaths. The average operative time was 143.85 ± 48.40 min (range 90–240 min), and the average amount of intraoperative hemorrhage was 13.85 ± 12.44 ml (range 10–50 ml). Only one patient received 75 ml blood transfusion. The important blood vessels were infiltrated by tumor only in two cases (15.4%). Two of the 13 procedures were converted to open surgery

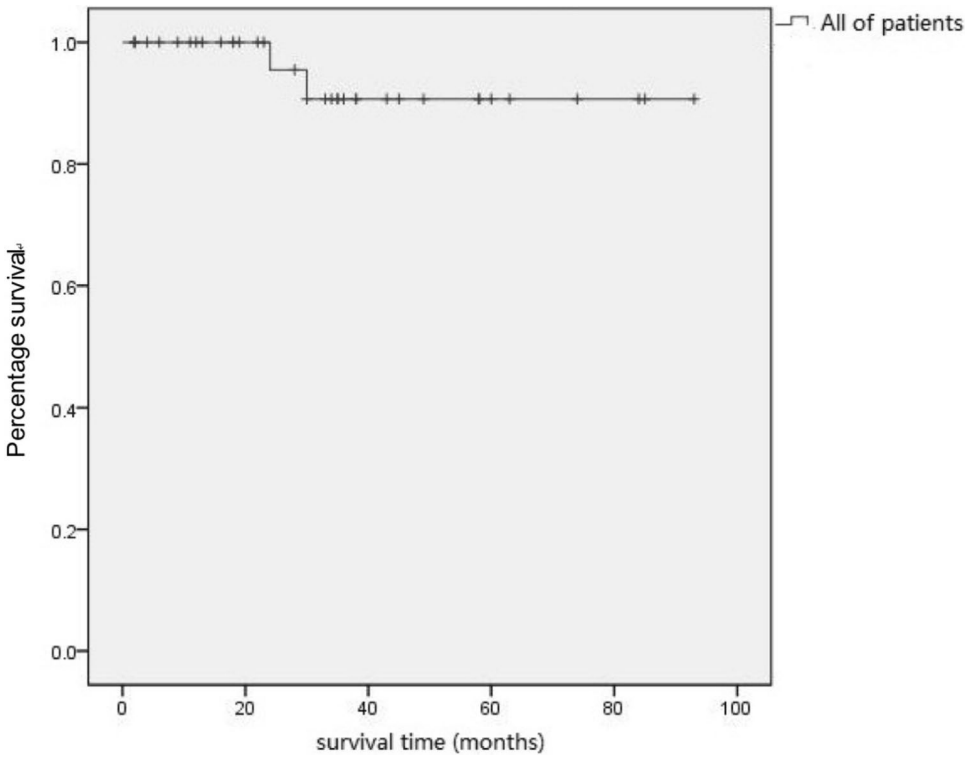

Fig. 1 Overall survival curve of patients with local adrenal neuroblastoma

Table 1 Comparison of the clinical data of the two groups of patients

	The laparoscopic surgery group	The open surgery group	*P* value
Number of patients	15	24	–
Average age (months)	45.15 ± 46.75	32.66 ± 31.81	0.353
Average size of the tumor (cm)	3.77 ± 1.35	5.41 ± 1.70	0.005
Invasion of vital organs or vessels	2 (15.4%)	11 (45.8)	0.064
Average operation time (min)	143.85 ± 48.40	143.13 ± 133.51	0.985
Average amount of hemorrhage during the operation (ml)	13.85 ± 12.44	27.71 ± 28.82	0.109
Number of cases with tumor recurrence	0	2	–
5-year survival rate	100%	86.2%	0.316

due to intraoperative complication. In one case, the tumor partially infiltrated the renal vessels and cannot be dissected by laparoscope. In another case, diaphragm was ruptured when attempting to separate the upper edge of the tumor. In addition to one patient receiving postoperative chemotherapy, the rest of the patients just underwent surgery without chemotherapy. All patients had no amplification of N-myc oncogene. No postoperative tumor recurrence was observed. After a mean follow-up time of 80.38 ± 19.01 months, the 5-year survival rate was 100%.

In the open surgery group, 24 children received laparotomy for resection of adrenal neuroblastoma (16 males and 8 females, 11 left lesions and 13 right lesion cases). Based on the INSS staging system, 15 patients were classified as stage I and 9 as stage II. And according to INRG staging system, 13 patients were classified as stage L1 and 11 patients as stage L2. The average size of the adrenal tumors resected was 5.41 ± 1.70 cm (range 3.23–10.00 cm) and the average operative time was 143.13 ± 133.51 min (range 60–750 min). The average amount of intraoperative hemorrhage was 27.71 ± 28.82 ml (range 10–100 ml), with four cases receiving blood transfusion of 150 ml. In 11 cases (45.8%), important blood vessels were encased by tumor. Only 1 patient received 2 cycles of neoadjuvent chemotherapy, and 14 patients received postoperative chemotherapy. The remaining 10 patients underwent surgery without chemotherapy. In this group, amplification of the N-myc oncogene was positive only in one patient. Tumor recurrence was

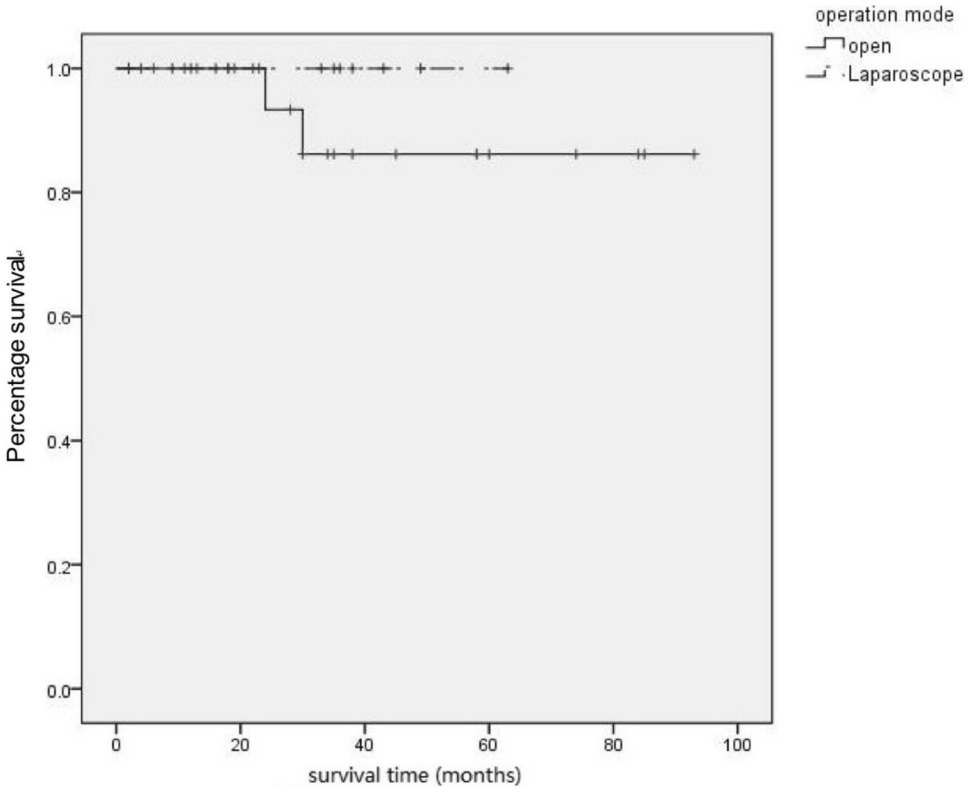

Fig. 2 Comparison of the survival curve of laparoscopic surgery group and open surgery

observed in two cases, both of which were distant metastasis (one bone and one lung metastasis). The average follow-up time was 90.25 ± 26.73 months after surgery, with a 5-year survival rate of 86.2%.

Statistical analysis of data from the two groups

Significant differences were observed between the laparoscopic surgery and open surgery groups regarding tumor size ($P = 0.005$). However, the two groups were comparable in terms of age at operation ($P = 0.353$), operation time ($P = 0.985$), tumor invasion rate of important organs ($P = 0.067$), amount of hemorrhage during surgery ($P = 0.109$) and 5-year survival rate ($P = 0.316$) of patients.

Discussion

With the rapid development of laparoscopic surgery, the application for pediatric adrenal tumors has gradually increased, with satisfactory clinical outcomes [5]. However, the minimally invasive surgical approach is not suitable for all adrenal neuroblastoma, since the choice of operative approach is largely dependent on tumor stage and size as well as its relationship with surrounding organs, which determine whether complete resection is possible. Previously, laparoscopic surgery was thought to be effective only for adrenal neuroblastoma with diameters < 2 cm [6]. With the improvements in operative technology and clinical experience of laparoscopy, its applications have gradually increased. According to the recommendations of the International Pediatric Endoscopic Group [7], laparoscopic surgery can be used to resect adrenal tumor safely with diameters < 6 cm and no peripheral invasion. So we adhere to this criterion study, and the largest size of tumor in this study had no less than 6 cm. No important vessels and organs infiltrated by adrenal tumors were suitable for laparoscopic surgery [8]. To compare the long-term prognosis of different surgical approaches, we used the same INSS staging patients to compare the outcomes. INSS is a postoperative staging system, which has limitations in the choice of surgical approaches. The imaging definition based on risk factors (IDRF) developed in recent years and International Neuroblastoma risk grouping (INRG) allowed determination of tumor stage mainly on the basis of imaging results [9], with emphasis on the relationship between the tumor and surrounding organs, which could guide the choice of surgical approaches for adrenal neuroblastoma. According to the INRG staging system, the proportion of L1 patients in laparoscopic surgery group was significantly higher than that in open surgery group, which implicated that the IDRFs could be used to select patients for laparoscopic surgical treatment.

Adrenal gland is located at the retroperitoneum with a complex surrounding structure, which makes adrenal

neuroblastoma resection via laparotomy difficult to perform. In contrast, a laparoscope can enlarge the view of the surgeon, leading to clear observation of the local anatomic structure that has obvious advantages over laparotomy [10, 11]. Adrenal neuroblastoma resection via laparoscopic surgery has several other advantages, including less trauma, faster postoperative recovery and reduced hospitalization time [8, 12]. Saad et al. [8] reported six cases of laparoscopic resection for adrenal neuroblastoma with an average operation time of 149.2 min and no complications. Patients could start eating one day after the operation, indicating the superiority of this technique. In our study, operation times for the laparoscopic surgery and open surgery groups were similar. However, the average amount of hemorrhage during operation of the laparoscopic surgery group was half that of the open surgery group, with only one case requiring blood transfusion. Our data indicate that resection of adrenal neuroblastoma via laparoscopic surgery is a safe and reliable approach. Although the patients in the laparoscopic surgery group and the open surgery group had the same staging, the percentage of cases whose tumors surrounded by important blood vessels and organs was significantly higher in open surgery group than that in laparoscopic group (45.8 versus 15.4%), which possibly contributed to the longer operative times and higher levels of hemorrhage.

The complications of adrenal neuroblastoma resection via laparoscopic surgery include hemorrhage interoperation, tumor rupture, damage of important organs, air embolism, and subcutaneous emphysema [13], which depend on the proficiency of the surgeon and whether this approach is suitable for the specific patient. Two patients of the laparoscopic surgery group in our study, the procedure was converted to laparotomy, including one with serious renal vascular adhesion, making it impossible to separate the tumor, and another suffered diaphragmatic rupture during dissecting the tumor. By combining the literature reports with our practical experience, we thought that preoperative imaging examination is essential for successful resection of adrenal neuroblastoma using laparoscopic surgery. As the imaging could not only provide the position and size of tumor and the presence or absence of retroperitoneal lymph node invasion, but also drew more attention of surgeons to the local extension of tumor, including perivascular involvement with arterial encasement, infiltration of adjacent soft tissues and organs, which would facilitate selection of suitable cases for laparoscopic surgery and reduce the incidence of complications.

Resection of adrenal neuroblastoma via laparoscopic operation has been shown to be a safe and reliable approach with satisfactory outcomes [14]. However, neuroblastoma is a malignant tumor, and regardless of the operative approaches performed, ultimately achieving better survival rates is the key to evaluating the effectiveness of treatment. Leclair and co-workers [15] reported that the 5-year event-free survival rate of 45 cases of abdominal neuroblastoma by laparoscopic surgery was 84%. However, limited reports on comparison of laparoscopic surgery and laparotomy in terms of curative effect and tumor recurrence have been documented. The prognosis of neuroblastoma is related to the age, tumor stage, pathological type and biological characteristics of tumor. In our study age of patients, the size of tumor and tumor staging were similar in these two groups, which reduce the influence confounding factors on survival rates in both groups as much as possible. The 5-year survival rate (100%) of the laparoscopic surgery group was slightly higher than that of the open surgery group (86.2%) with no tumor recurrence, indicating that outcome of laparoscopic surgery was similar to that of open surgery and operative approach does not the affect long-term prognosis of neuroblastoma. Laparoscopic surgery is safe and feasible for adrenal neuroblastoma which is suitable for laparoscopy. However, there were a number of limitations in our study. For instance, the tumor invasion rate of adjacent tissues in the open surgery group was greater than 40%, suggesting that tumors in these cases are more invasive with a higher chance of residual tissue leading to recurrence, which would substantially affect prognosis. Second, most laparoscopic surgeries were performed in recent years with a relatively shorter duration of follow-up which also could affect prognosis. Therefore, to validate the treatment outcomes of adrenal neuroblastoma via laparoscopic surgery, clinical trials with larger sample sizes and long-term follow-up are warranted.

In conclusion, resection of local adrenal neuroblastoma using laparoscopic surgery is a safe and feasible option. Compared with open surgery, laparoscopic surgery has similar and satisfactory results in terms of operation time as well as survival rate and long-term prognosis. So laparoscopic surgery may be used as preferred by experienced laparoscopic surgeons for patients with small, well-circumscribed adrenal lesions, without invasive or infiltrative disease.

Compliance with ethical standards

Conflict of interest All authors of this article had no conflict of interest.

Research involving human participants and/or animals All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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