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Original article

Surgical perspectives of primary liver tumors in children: A series of 76 consecutive cases

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Background: Primary liver tumors in children are rare. The objective of this study was to review cases of primary liver tumors in children who underwent tumor removal.
Methods: Children (0 - 15 years old) who underwent surgery for primary liver tumors between 2006 and 2019 were studied. Their clinical data and pathological reports were reviewed. Demographic data, types of procedures, operative time, and post-operative complications were described. Data are expressed as mean ± standard deviation.
Results: There were 76 children (male/female = 39/37), who underwent resection for primary liver tumors. Their average age was 27.9 ± 32.0 months. Asymptomatic abdominal mass was the most common findings. Ultrasonography, computerized tomography (CT) scan or magnetic resonance imaging (MRI) was used to confirm diagnosis and plan for the surgery. The tumors were assessed to be initially unresectable in 57/79 patients (72.2%), and became resectable later following chemotherapy. Types of surgery included 51 hepatectomies (67.1%), 9 trisectionectomies (11.8%), 7 multiple segmentectomies (9.2%), 6 segmentectomies (7.9%), and 3 wedge resections (4.0%). The mean operative time, blood loss, and Intensive Care Unit stay were 204.14 ± 82.08 minutes, 274.1 ± 440.4 ml, and 2.1 ± 3.1 days, respectively. Histopathology revealed 63 hepatoblastomas (82.9%), 4 mesenchymal hamartomas and one of endodermal sinus tumor, mature teratoma, immature teratoma, adenoma, hepatoma, undifferentiated embryonal sarcoma, focal nodular hyperplasia, glomus tumor, and undetermined benign liver tumor. The most common intra-operative complication was massive bleeding in 8 cases, with cardiac arrest in one case. Post-operative complication was found in 16 cases (21.1%) including chylous ascites, atelectasis, intra-abdominal collection, surgical site collection, C-line infection, ileus, gut obstruction, bleeding and bile leakage. Re-operation was required to correct complications in 3 patients. There was one mortality caused by spontaneous rupture of congenital hepatoblastoma.
Conclusions: The most common primary liver tumor in children that requires surgical therapy is hepatoblastoma. Abdominal mass is a common symptom. Serious complications occurred in 20.0% of patients with a small chance of re-operation. Peri-operative mortality is low.

Keywords: Children, hepatoblastoma, liver tumors.

Primary liver tumors are considered relatively rare in pediatric malignancy, representing around 1.0 – 4.0% of all pediatric neoplasm.[1] Malignant hepatic tumors have an incidence about 1 - 1.5 per million children per year.[2, 3] The most common malignant liver tumor in children (about two-thirds of them) is hepatoblastoma.[1] Current management of primary liver tumor is multidisciplinary approach such as surgical resection, chemotherapy, transplantation, etc.[4,5] One of its most important principles is to complete removal of the tumor. Pre-operative chemotherapy is a technique to downstage unresectable tumors to operable ones in order to enable safe tumor resection. In case of unresectable tumors, which

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are multifocal or large solitary or unifocal with centrally located tumor involving hilar, etc., transplantation should be consider. [4] As for the diagnosis, patients usually present with asymptomatic abdominal mass or abdominal distension, including abnormal imaging and laboratory data, such as serum alpha-fetoprotein (AFP). Pre-operative imaging involves ultrasound, computerized tomography (CT) scan or magnetic resonance imaging (MRI), to evaluate size, extension and involvement of tumor. [1, 4] Post-operatively, sepsis, pulmonary congestion, biliary complication, vascular complication, wound infection, etc., have been reported as surgical complications after liver surgery in children.[1, 4, 6, 7]

At present, regarding surgical perspectives together with the advancement of surgical technology, peri-operative outcome of liver resection is generally excellent. [2, 3, 6, 8, 9] Overall perioperative mortality rate was very low.[1, 2, 4, 7, 10] Previous studies from our group (1996 - 2005) demonstrated that, following surgery for primary liver tumors in children, there were significant complications, mostly minor problems and all both minor and major complications were manageable. [7] Since the incidence of primary liver tumors in children is rare, series of its surgical perspectives are not widely reported and receives little attention.

Therefore, the objective of this study was to retrospectively review cases of primary liver tumors in children who underwent surgical resection at two university hospitals. The study concentrated on clinical features, types of surgical procedures, pathology, and peri-operative complications.

Materials and methods

Children (0 - 15 years old) who underwent surgery for primary liver tumors between 2006 and 2019 at two university hospitals, including King Chulalongkorn Memorial Hospital and Srinagarind Hospital (SH), were retrospectively studied. The study has been approved by the Institutional Review Board (IRB no. 518/63 and IRB00001189, respectively).

Pre-operatively, demographic data, presenting symptom, and imaging modalities were collected. Intra-operatively, type of surgery, operative time, blood loss, length of intensive care unit (ICU) stays, and pathology were evaluated. Finally, post-operatively, complications, and recurrence within 120 days following surgery were described and analyzed.

Statistical analysis

Data are presented as mean ± standard deviation (SD). Unpaired *t* - tests and Fisher exact tests were used to compare demographic data of patients between the two hospitals. A P – value < 0.05 was considered statistically significant. All statistical analysis was performed by IBM SPSS Statistics version 22.0.

Results

Clinical features

Over the studied period, there were 76 children (male/female = 39/37) who underwent resection for primary liver tumors. At the time of surgery, their average age was 27.9 ± 32.0 months and average weight was 11.7 ± 6.7 kg (Table 1). The most common presenting symptoms were asymptomatic abdominal mass (44/76 or 57.9%), followed by distension and pain, as shown Table 2. Ultrasonography, CT scan or MRI was used to confirm diagnosis and plan for the surgery. The tumors were assessed to be initially unresectable in 57 of 79 (72.2%) patients who then received preoperative chemotherapy and became resectable later, as shown in Table 1. Moreover, there was no difference in terms of gender (P = 0.99), age at surgery (P = 0.74), weight (P = 0.32), co-existing diseases (P = 0.30), and neoadjuvant chemotherapy (P = 0.12) between the two hospitals.

Types of surgical procedures

The types of surgery included 51 hepatectomies (67.1%), 9 trisectionectomies (11.8%), 7 multiple segmentectomies (9.2%), 6 mono-segmentectomies (7.9%), and 3 wedge resections (4.0%). The mean operative time was 204.1 ± 82.1 minutes. The mean intraoperative blood loss was 274.1 ± 440.4 ml. The mean ICU stay was 2.1 ± 3.1 days, as shown in Table 2. There was no difference in terms of blood loss (P = 0.36), ICU stay (P = 0.24), and length of stay (P = 0.84) between the two hospitals, except operative time (P < 0.001).

Pathology of the tumors

Histopathology reports revealed that there were 63 hepatoblastomas (82.9%), 4 mesenchymal hamartomas and one of endodermal sinus tumor, mature teratoma, immature teratoma, adenoma, hepatoma, undifferentiated embryonal sarcoma, focal nodular hyperplasia, glomus tumor, and undetermined benign liver tumor, as shown in Table 3.

As for the cases of the 63 hepatoblastoma, standard hepatectomy was performed in 45 cases, and trisectionectomy in 7 cases. As for the 4 mesenchymal hamartomas, hepatectomy was performed in 2 cases and near total tumor excision with marsupialization of cystic portion was performed in 2 cases. Except for 6 cases of hepatoblastoma, there was no recurrence of either the lesions or symptoms up to 2 years after surgery.

Peri-operative complications

The most common intraoperative complication was massive bleeding in 8 cases, with cardiac arrest in one case. Massive bleeding is defined as blood loss more than 50.0% of total blood volume of patients. Post-operative complication was found in 16 cases (21.1%) including chylous ascites, atelectasis, intra-abdominal collection, surgical site collection, C-line infection, ileus, gut obstruction, bleeding, and bile leakage, as shown in Table 2. Most of these complications were managed non-operatively. Re-operation was required to correct complications in 3 patients. There was one mortality caused by massive bleeding due to spontaneous rupture of congenital hepatoblastoma. Although the baby survived left hepatectomy, mortality occurred 48 hours after surgery due to multiple organ failure. Recurrent hepatoblastoma occurred in 6 cases (6/63 or 9.5%) within 120 days. All 6 cases two out of the 6 recurrent cases had microscopic residual tumors at the resection margin.

Table 1. Demographic data of the patients.

Characteristics of patients	Total (n = 76) (%)
Gender	
Male	39 (51.3)
Female	37 (48.7)
Age at surgery (months)	27.9 ± 32.0
Weight at surgery (kgs)	11.7 ± 6.7
Co-existing diseases	
No	66 (86.8)
Yes[$]	10 (13.2)
Imaging	
Ultrasound	55 (72.4)
Computerized tomography	72 (94.7)
Magnetic resonance imaging	20 (26.3)
Neoadjuvant chemotherapy	57 (75.0)

[$]Co-existing diseases were as follows: Beckwith-Wiedemann syndrome (n = 2), anorectal malformation (n = 1), polycythemia (n = 1), chronic hepatitis B infection (n = 1), thalassemia (n = 3), Kabuki syndrome (n = 1), and congenital heart disease (n = 1)

Table 2. Clinical presentation and peri-operative data of primary liver tumors in children (n = 76).

	Clinical data	N (%)
Clinical presentation	Abdominal mass	44 (57.9)
	Abdominal distension	22 (28.9)
	Abdominal pain	5 (6.6)
	Incidental findings	4 (5.3)
	Prenatal ultrasound	1 (1.3)
Surgical procedures	Right or left hepatectomy	51 (67.1)
	Trisectionectomy	9 (11.8)
	Multiple segmentectomy	7 (9.2)
	Mono-segmentectomy	6 (7.9)
	Wedge resection	3 (4.0)

Table 2. (Con) Clinical presentation and peri-operative data of primary liver tumors in children (n = 76).

	Clinical data	N (%)
Peri-operative data (Mean ± SD)	Operative time (minutes)	204.1 ± 82.1
	Blood loss (ml)	274.1 ± 440.4
	ICU stay (days)	2.1 ± 3.1
	Length of stay (day)	14.1 ± 9.7
Post-op complications	Lung atelectasis	4 (5.3)
	Chylous ascites	4 (5.3)
	C-line infection	2 (2.6)
	Intra-abdominal collection	1 (1.3)
	Gut obstruction	1 (1.3)
	Prolonged bowel ileus	1 (1.3)
	Bile leakage	1 (1.3)
	Bleeding	1 (1.3)
	Wound infection	1 (1.3)

Table 3. Pathological diagnosis of 76 primary liver tumors.

Diagnosis	Number	Percentage
Hepatoblastoma	63	82.9
Mesenchymal hamartoma	4	5.3
Endodermal sinus tumor	1	1.3
Mature teratoma	1	1.3
Immature teratoma	1	1.3
Adenoma	1	1.3
Hepatoma	1	1.3
Undifferentiated embryonal sarcoma	1	1.3
Focal nodular hyperplasia	1	1.3
Glomus tumor	1	1.3
Undetermined benign liver tumor	1	1.3

Discussion

Primary liver tumors in children are rare and account for only 1.0 - 4.0% of all pediatric solid tumors.[2, 3, 11] Patients in this study represent cases from two large pediatric surgery centers in Thailand. Some patients were diagnosed from other hospital and referred to the university hospitals for surgery due to lack of pediatric surgeons. Most children came to the hospitals with asymptomatic palpable abdominal mass or abdominal distension from their caregivers. Another important clinical manifestation was abdominal pain as they could become more serious in ruptured tumors. The patients will present as abdominal pain with anemia or hemorrhagic shock. For some patients, abdominal pain is not related to liver tumors but found accidentally during a physical examination. Prenatal ultrasonography is another modality which can detect liver lesions. Therefore, history taking and careful physical examination in pediatric patients are very important which may reveal critical information.

In this study, the imaging of choice is CT scan. Patients with a strong evidence of palpable mass, some surgeons chose CT scan as their first investigation to determine the nature of the diseases. However, for patients with unclear history taking and physical examination, ultrasonography is still a modality of choice for differential diagnosis. Then CT scan is used to confirm diagnosis and evaluate the extent of disease for staging and respectability. In addition, MRI become more frequently used. Most patients received MRI from private hospitals before referring to our university hospitals for definitive treatment. Re-imaging investigations depend on the preferences of their doctors. Eighteen of 76 cases were considered respectable at diagnosis and received a liver resection.

The post-op chemotherapy was dependent on pathological diagnosis. The other 56 of 76 cases were considered unresectable or very dangerous to resect upfront at diagnosis. Then they received neo-adjuvant chemotherapy until follow-up imaging showed that the tumors were respectable.

Surgeons from both university hospitals are experienced pediatric surgeons on hepato-biliary surgery. Factors determining tumor respectability or being dangerous to resect up-front in this study include either PRETEXT-III, PRETEXT-IV, ingrowth vena cava, involvement of all hepatic veins, or ingrowth main portal vein, for instance. [5, 10] Additionally, CT scan or MRI is important for mapping the plan of surgery. Eventually, approximately 80.0% of our patients received standard hepatectomy or trisectionectomy. The rest received segmentectomies or wedge resection.

As liver surgery, especially in children, is a major surgery that can encounter fatal complications, post-operative ICU stay is generally needed in pediatric patients. The minimum length of hospital stay in this study was 7 days. Intra-operatively, massive bleeding is a serious complication and was found in 12 cases in this series. Injury to the inferior vena cava (IVC) is one of the causes of massive bleeding in this study, as it was a major vessel that involved to liver anatomy, and other were found are hepatic vein and portal vein. The injuries to IVC, hepatic artery, portal vein, or hepatic vein usually led to a significant bleeding and sometimes exsanguination. Raw surface or parenchymal bleeding is another common cause of massive bleeding. Several methods including electrical coagulation, bipolar activated devices, ultrasonic system, direct suture ligation, hemostatic agents, and packing are used to stop bleeding. In addition, blood products are used to correct massive bleeding. In one case, intra-operative cardio pulmonary resuscitation was performed due to massive bleeding from IVC injury for 5 minutes. Finally, the patient was return of spontaneous circulation and was discharged without long-term sequelae. Besides vascular injuries, bile duct is another important structure that can be injured. In our series, hepatic duct at its bifurcation was injured in one case. Roux-en-Y hepaticojejunostomy was performed in this patient. Therefore, great care of major vessels and bile duct injuries is mandatory during liver resection.

Post-operative complications in this study were found in 16 case (21.1%). This is consistent with other studies in the literature. [1, 2, 4, 5, 11] Only three cases required re-operation from surgical bleeding, bile leakage and gut obstruction, respectively. Percutaneous drainage for intra-abdominal collection was performed in one case. From many studies, post-operative complication varies from severe to mild complications such as cardiac arrest, massive bleeding, bile leakage, liver failure, intra-abdominal collection, infected wound, lung atelectasis, chylous ascites, bowel ileus, central line infection, gut obstruction and others. [5 - 8, 12] Unfortunately, there was one mortality (1.3%) in this series, caused by the delayed diagnosis of spontaneous rupture of congenital hepatoblastoma. Although rupture of congenital hepatoblastoma is very rare, its fatal consequence cannot be overlooked. At 60 days and 120 days after surgery, recurrence of the lesions was found in 5 cases and 6 cases, respectively. All recurrent tumors are hepatoblastoma. Therefore, around 8.0 – 10.0% of hepatoblastoma experienced recurrence within 120 days after surgery.

When compared to our previously published study [7] of 52 cases between 1996 and 2005, interestingly, there is not much different from our present study in terms of clinical features, tumor respectability rate, types of surgery, pathology, and peri-operative complications except for imaging modalities. Nowadays, we used MRI as a decisive imaging technique more often [13], although CT scan is still the most common imaging of choice due to the easier access of CT scan in the country. Therefore, the markedly increased improvement in long-term overall survival rates for primary malignant liver tumors in children over the last decade is probably due to the advancement in chemotherapy and radiotherapy, not surgery alone.

Conclusions

A 14-year experience of surgery for primary liver tumors in children has been described. The most common primary liver tumor in children that requires surgical therapy is hepatoblastoma. Abdominal mass is a common symptom. Liver surgery is one of the major surgical procedures which can have a serious complication and morbidity. Hepatectomy and trisectionectomy account for approximately 80.0% of all procedures. Serious complications occurred in 20.0% of the patients with a small chance of re-operation. Peri-operative mortality is very low. Experienced team including surgeons, anesthetists, ICU doctors, nurses and advanced hospital facilities are important factors in maintaining good peri-operative outcome.

Conflicts of interest

The authors, hereby, declare no conflict of interest.

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