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Retrospective Study

Computer-assisted three-dimensional individualized extreme liver resection for hepatoblastoma in proximity to the major liver vasculature

Xiu WL *et al*. Extreme liver resection for hepatoblastoma

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Abstract

BACKGROUND

The management of hepatoblastoma (HB) becomes challenging when the tumor remains in close proximity to the major liver vasculature (PMV) even after a full course of neoadjuvant chemotherapy (NAC). In such cases, extreme liver resection can be considered a potential option.

AIM

To explore whether computer-assisted three-dimensional individualized extreme liver resection is safe and feasible for children with HB who still have PMV after a full course of NAC.

METHODS

We retrospectively collected data from children with HB who underwent surgical resection at our center from June 2013 to June 2023. We then analyzed the detailed clinical and three-dimensional characteristics of children with HB who still had PMV after a full course of NAC.

RESULTS

Sixty-seven children diagnosed with HB underwent surgical resection. The age at diagnosis was 21.4 ± 18.8 months, and 40 boys and 27 girls were included. Fifty-nine (88.1%) patients had a single tumor, 39 (58.2%) of which was located in the right lobe of the liver. A total of 47 patients (70.1%) had PRE-TEXT III or IV. Thirty-nine patients (58.2%) underwent delayed resection. After a full course of NAC, 16 patients still had close PMV (within 1 cm in two patients, touching in 11 patients, compressing in four patients, and showing tumor thrombus in three patients). There were 6 patients of tumors in the middle lobe of the liver, and four of those patients exhibited liver anatomy variations. These 16 children underwent extreme liver resection after comprehensive preoperative evaluation. Intraoperative procedures were performed according to the

preoperative plan, and the operations were successfully performed. Currently, the 3-year event-free survival of 67 children with HB is 88%. Among the 16 children who underwent extreme liver resection, three experienced recurrence, and one died due to multiple metastases.

CONCLUSION
Extreme liver resection for HB that is still in close PMV after a full course of NAC is both safe and feasible. This approach not only reduces the necessity for liver transplantation but also results in a favorable prognosis. Individualized three-dimensional surgical planning is beneficial for accurate and complete resection of HB, particularly for assessing vascular involvement, remnant liver volume and anatomical variations.

Key Words: Children; Hepatoblastoma; Surgery; Three-dimensional; Computer-assisted

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Core Tip: Children with difficult hepatoblastoma (HB), characterized by a large size and complex location, pose a clinical challenge, particularly when the tumor remains in close proximity to the major liver vasculature (PMV) even after a full course of neoadjuvant chemotherapy (NAC). We retrospectively collected data from 67 children with HB who underwent surgical resection at our center from June 2013 to June 2023. Sixteen patients still had close PMV after a full course NAC and underwent extreme liver resection. In this process, the use of individualized three-dimensional surgical planning is beneficial for achieving safe and complete resection.

INTRODUCTION

Hepatoblastoma (HB) is the most common primary malignant liver tumor in children, and its incidence is increasing[1,2]. The combination of surgery and chemotherapy, particularly neoadjuvant chemotherapy (NAC), has allowed for the delayed resection of many children initially considered unresectable at diagnosis, resulting in a significant improvement in the survival rate of HB patients from approximately 30%[3,4]. Surgery remains a crucial treatment for HB, as it involves completely removing the tumor and preserving sufficient liver volume[5]. However, there is still no consensus on the optimal diagnosis and treatment plan for difficult cases of HB, which are large in size and complex in location.

Clinically, HB is commonly a large tumor when discovered. Over 50% of HB patients cannot be surgically removed at initial diagnosis according to the PRE-TEXT staging system[6]. These patients require preoperative NAC. After 2 to 4 cycles of NAC, the response to treatment was evaluated using the POST-TEXT staging system. The tumor size of large HB significantly decreases due to its high chemotherapeutic sensitivity, allowing for sufficient future liver remnant volume (FLV) for surgery[7]. At this point, the evaluation of vascular involvement becomes crucial in determining the feasibility of tumor resection.

In fact, approximately 25% of HB patients remain in close proximity to the major liver vasculature (PMV), such as the inferior vena cava (IVC), the main portal vein (MPV), the bifurcation of the portal vein (BPV), and the hepatic veins (HVs), even after undergoing a full course of NAC. This poses a clinical challenge when planning further treatment. While liver transplantation can achieve complete tumor resection, there is increased risk due to the use of living donor livers and the need for lifelong immunosuppressive treatment[8,9]. In recent years, aggressive extreme liver resection has emerged as another viable option, as tumor involvement in blood vessels is no longer considered a contraindication for surgical resection.

The computer-assisted surgery system (Hisense CAS) is capable of performing individualized three-dimensional (3D) reconstruction using traditional two-dimensional (2D) computed tomography (CT) images. This system can provide objective and

comparable 3D information about the liver, tumors and blood vessels, overcoming the limitations of 2D images. Additionally, it can be used to efficiently analyze the complex features and anatomical variations of the liver[10,11]. In this study, we present a case series of HB from a single center and aim to explore the safety of computer-assisted 3D individualized extreme liver resection in HB patients where major liver vasculature is still in close proximity after a full course of NAC.

MATERIALS AND METHODS

Patients and clinical parameters

We retrospectively collected data from children with HB who underwent surgical resection at The Affiliated Hospital of Qingdao University from June 2013 to June 2023. We subsequently analyzed the detailed clinical characteristics and treatment process of HB patients who still had major blood vessels close to the tumor after a full course of NAC. The alpha-fetoprotein (AFP) level and imaging features were monitored during follow-up in all the children. This study was approved by the Ethics Committee of the Affiliated Hospital of Qingdao University (QYFY-WZLL-25776).

Definition and classification of PMV

The PMV is defined according to COG (AHEP0731). In this study, the major liver vasculature of "V" refers to the IVC, all HVs, or both. "P" refers to the MPV, the BPV, or both. The proximity classification was based on the tumor's distance to these vessels: (1) within 1 cm (V0 or P0); (2) touching (V1 or P1); (3) compressing, or encasing (V2 or P2); and (4) presence of a tumor thrombus or cavernous transformation of the MPV (V3 or P3)[2,3].

The procedure for preoperative NAC

Patients who could not undergo upfront resection during the initial diagnosis underwent needle biopsy to obtain a clear pathological diagnosis of HB. Subsequently, they were administered a standardized chemotherapy regimen, which was extensively described in

our previous study[11]. After 2 cycles of chemotherapy, contrast-enhanced CT (CECT) and 3D reconstruction were performed to evaluate the resectability of the tumor. If the tumor remains unresectable, further cycles of chemotherapy and imaging evaluation are continued. The completion of four or more cycles of NAC or tumor enlargement was considered the a full course of NAC.

3D individualized assessment and preoperative planning

Computer-assisted surgery system (Hisense CAS, Qingdao, China) was utilized to conduct 3D reconstruction of the CECT DICOM file. This process allowed for the acquisition of individualized 3D information, including the relationship between the tumor and major blood vessels, as well as the volume of the liver and tumor. The specific steps for this reconstruction have been thoroughly explained in previous reports by our team[9,10]. The PRE-TEXT staging system designed by SIOPEL was used in combination with the individualized 3D model for staging and assessing tumor resectability.

Simulating tumor resection on the 3D model has three modes: (1) Anatomical liver resection, which involves resecting the liver segment invaded by the tumor based on the intrahepatic blood vessel arrangement and vascular domain analysis; (2) tumor dissection, which refers to nonanatomical liver resection. In this mode, a safe resection distance (*e.g.*, 0 mm, 10 mm, *etc.*) is chosen based on the proximity of the tumor to blood vessels, and liver resection is performed along the tumor boundary; and (3) autonomous resection is performed when the tumor is autonomously cut in three dimensions for liver resection based on specific conditions. These three surgical simulation procedures were performed separately to select the best surgical plan.

Surgical resection methods

The incision was made in the upper abdomen, below the costal margin, to access the ligaments around the liver, and the size, location, and relationship of the tumor with nearby organs were examined. The first porta hepatis was dissected, and the intermittent Pringle method was subsequently used to temporarily block hepatic blood flow.

Typically, the flow was blocked for 15 to 20 min and then opened for 5 min. The cutting line was determined using electrosurgery based on preoperative planning. During the blocking period, the liver was dissected and separated using cavitational ultrasonic surgical aspiration and vascular forceps to prioritize liver parenchyma resection. Compression and electrocoagulation were used during the opening period to minimize bleeding. The tumor-involved major blood vessels were carefully separated, ligated, and sutured if necessary.

Statistical analysis

The SPSS 26.0 software package was used to organize and analyze the data. Normally distributed data are expressed as the mean ± SD, and nonnormally distributed data are expressed as the median and quartile. The paired-sample *t* test was used for comparisons before and after treatment. A *P* value < 0.05 was considered to indicate statistical significance.

RESULTS

Characteristics of children with HB

Over a 10-year period, a total of 67 children diagnosed with HB underwent surgical resection. The age at diagnosis was 21.4 ± 18.8 months, and 40 boys and 27 girls were included in the study. Of the 67 patients, 52 (77.6%) presented with upper abdominal masses, and the AFP level was 231109.5 [interquartile range (IQR), 39904.8-434407.8] ng/mL. Fifty-nine (88.1%) patients had a single tumor, 39 (58.2%) had a single tumor located in the right lobe of the liver, and 8 (11.9%) had multiple tumors. The majority of patients (47/67, 70.1%) were classified as PRE-TEXT III or IV. The maximum diameter of the tumor was 10.8 (IQR, 8.3-13.1) cm. Following evaluation and planning using Hisense CAS, 28 children with HB underwent upfront resection. On the other hand, 39 patients (58.2%) who were not eligible for upfront surgery underwent 3 (IQR, 2-4) cycles of NAC followed by delayed resection.

Characteristics of children with HB who remain in PMV after a full course of NAC

Children who received a full course of NAC were evaluated preoperatively. Among the 67 patients, 16 (23.9%) still had tumors in the PMV. The detailed clinical characteristics before and after NAC are presented in Table 1. An equal number of boys and girls were included, with a median age at diagnosis of 30.5 (IQR, 17.0-48.5) months. The median AFP level was 414968.5 (IQR, 271680.5-842240.0) ng/mL. There were 10 and 6 patients in PRE-TEXT III and IV, respectively. The maximum diameter of the tumor was 10.9 (IQR, 9.3-14.3) cm, with a tumor volume of 650.1 (IQR, 326.8-1014.9) cm³. The percentage of tumor-free livers was 40.5% (IQR, 31.0%-45.0%).

After chemotherapy, the AFP level decreased to 2437.0 (IQR, 211.3-26512.5) ng/mL. Eight patients with PRETEXT III were downgraded to POST-TEXT II, two patients with PRETEXT IV were downgraded to POST-TEXT II, and three patients with PRETEXT IV were downgraded to POST-TEXT III. However, one patient was upgraded from PRETEXT III to POST-TEXT IV after three courses of treatment. The maximum diameter of the tumor decreased to 6.8 (IQR, 5.7-7.3) cm, with a corresponding tumor volume of 83.1 (IQR, 47.2-99.7) cm³. The percentage of tumor-free livers increased to 86.5% (IQR, 84.0%-89.0%). Except for one case of tumor progression, the tumor volume decreased in the remaining 15 patients, with a median reduction of 90%. Statistical analysis revealed significant differences in the changes in AFP level, tumor diameter and tumor volume before and after NAC ($P < 0.05$). However, there was no significant difference in the change in the tumor-free liver volume ($P = 0.12$).

Preoperative evaluation and simulated liver resection in children with HB in PMV after a full course of NAC

The details of the preoperative evaluation and simulated liver resection in the 16 children who still had tumors close to the major liver vasculature after a full course of NAC are presented in Table 2. Among the patients, two had tumors within 1 cm, 11 had touching, four had compression, and three had tumor thrombus. Thirteen patients had PMV with the IVC, 9 patients with MPV or BPV, and 3 patients with all HVs. Furthermore, there

were 9 cases of tumors involving two lobes of the liver, including three cases of multiple tumors and 6 cases of tumors in the middle lobe of the liver. Additionally, 4 patients (25%) exhibited liver anatomy variations—three with common origins of the middle and left HVs and one with four HVs. Preoperative simulated resection using the Hisense CAS aided in designing individualized surgical plans, with 14 children undergoing simulated anatomical hepatectomy. Ten patients opted for hemihepatectomy (62.5%), 3 chose extended hemihepatectomy, and 1 underwent mesohepatectomy. The simulated FLV was 288.1 (IQR, 177.3-352.0) cm^3, and the FLV-to-TLTV ratio was 51.0% (IQR, 41.0%-57.0%) (Figures 1 and 2).

Intraoperative and postoperative results of children with HB who still had PMV after a full course of NAC

Extreme liver resections were performed following thorough preoperative evaluation and simulated tumor resection. During the operation, the precut lines were drawn based on the preoperative plan, and special attention was given to carefully process the blood vessels around the tumor, particularly those compressed by the tumor and any anatomical variations (Figure 3). The tumors were successfully and completely removed, and the operations were successfully completed (Table 3). The operation time was 247.5 (IQR, 205-282.5) minutes. Hepatic flow occlusion lasted for 22.5 (IQR, 15-27.5) minutes and occurred 2 (ranging from 1 to 4) times. In three patients, reconstruction of the IVC was performed, while reconstruction of the middle HV was conducted in one patient. The amount of blood loss was 50 (IQR, 20-100) mL. One child experienced postoperative intestinal obstruction, which was resolved after loosening of the intestinal adhesions. No other complications, such as postoperative bleeding, biliary damage, or liver failure, were observed in the remaining children. The patient was discharged from the hospital after a median of 13 (IQR, 10-15) days postsurgery. Postoperative pathology revealed 9 cases of the epithelial type (including 6 cases of the fetal and embryonal subtype and three cases of the pure fetal subtype) and 7 cases of the mixed epithelial and mesenchymal type. Following chemotherapy after surgery, the lowest AFP level was 5.48 (IQR, 1.7-265.9)

ng/mL, and the AFP levels of 8 children returned to the normal range. The AFP levels of four children were slightly greater than the normal range but remained stable during long-term follow-up, including the only child with a positive resection margin (R1).

The study included 67 children with HB, and the median follow-up time was 62 months. The 3-year event-free survival (EFS) rate was 88%. Among the 47 children with PRE-TEXT III and IV, the median follow-up time was 58 months, and the 3-year EFS was 85%. Of the 16 children who underwent extreme liver resection, the median follow-up time was 36 months, three patients experienced recurrence, and one patient died due to multiple metastases during the follow-up period.

DISCUSSION

HB is a common malignant solid abdominal tumor in children that accounts for approximately 80% of liver tumors in childhood. The highest incidence is observed in infants and children under 5 years old, and the most common clinical manifestation is an asymptomatic abdominal mass. It has been observed that more than 50% of large HB necessitate NAC followed by delayed surgery due to the inadequate volume of the remnant liver or the involvement of major blood vessels[1,6,10]. Our retrospective analysis revealed that 58.2% of the HB patients underwent delayed resection. However, 23.9% of the HB patients received a full course of NAC; their tumor volume decreased by almost 90%, and the tumor-free liver volume accounted for approximately 85% of the total volume, still remaining close to major blood vessels. Furthermore, simulated surgical resection demonstrated that the remnant liver volume was sufficient (> 30%). This finding indicates that proximity to major blood vessels plays a crucial role in determining surgical resectability and presents a challenge for subsequent management strategies in these children.

Currently, all cooperative trial group institutions recommend complex segmental resection or liver transplantation for HB evaluated for major vascular involvement after chemotherapy. Liver transplantation has traditionally been considered the preferred treatment option for advanced HB, especially for patients with POST-TEXT III and IV

tumors involving the liver hilus[12]. However, recent advancements in imaging evaluation and surgical techniques have led to more studies recommending aggressive surgical resection for advanced HB. This approach can achieve a similar survival rate to liver transplantation while avoiding transplantation-related risks[13,14]. In this study, precise preoperative assessments and surgical simulations were conducted using a computer-assisted surgery system with 3D reconstruction. This approach helps determine the proximity of the tumor to blood vessels and identify the optimal surgical path. Subsequently, intermittent hepatic inflow occlusion was performed using the Pringle maneuver method and the liver parenchyma-first approach were employed based on preoperative planning. These techniques successfully enabled aggressive extreme liver resection in 16 children with HB who still had tumors close to major blood vessels after completing a full course of NAC. Notably, there were no significant complications, such as hemorrhagic shock or bile leakage.

Due to the complex course and anatomical variation of blood vessels in the liver, as well as the limitations of two-dimensional imaging, assessing the surgical resectability of HB can be challenging. Surgeons often rely on their own anatomical knowledge and surgical experience to perform slice selection on cross-sectional CT or MRI images for evaluating staging and vascular involvement[9,15]. However, studies have shown that its accuracy is only 51%, and it tends to overstage[16]. Therefore, as a radiological staging system based on 2D images, the usefulness of this strategy for surgeons is limited, especially when tumors compress the hepatic hilar structure. We propose the use of 3D images to provide a more objective and accurate evaluation of tumor staging and vascular involvement by utilizing 3D spatial position and distance[17-20]. This method is particularly beneficial for patients with multiple tumors, middle lobe involvement, and variations in liver anatomy and has clinical significance.

In addition, the guidelines for HB surgery prioritize anatomical liver resection, which involves removing more normal liver tissue (greater than 1 cm outside the tumor). Nonalcoanatomical resection or segmental resection, such as extended hepatectomy or middle lobectomy, are often considered for advanced HB[21,22]. However, these

procedures make it more challenging to assess the preoperative remnant liver volume. This study utilized three dimensions to track the route of each blood vessel, determine the drainage segment of each vein, and perform the individualized liver segment anatomy. By utilizing 3D volume features, the tumor and liver volume before and after chemotherapy can be objectively calculated, along with the remnant liver volume after simulated surgery. This approach provides overall, comprehensive, and accurate information for liver resection.

With the advancement of chemotherapy, 2 to 4 cycles of NAC for HB have been shown to increase the probability of surgical resection for unresectable HB at diagnosis. However, more than 4 cycles do not further increase the chance of conventional resection and may instead lead to drug resistance and worsening of chemotherapy toxicity[13]. In this study, we attempted to treat three children with 5 cycles and 1 child with 6 cycles of NAC. However, we observed that the tumor volume did not significantly decrease, and the distance from the major blood vessels increased but still involved after 4 cycles. This could be attributed to drug resistance and vascular targeting. Recent studies have indicated that resection margins less than 1 cm and even microscopic positivity do not affect the overall survival rate of children with HB[23,24]. HB exhibits characteristics such as expansile growth within the capsule and the presence of metastatic cancer nests within the chemotherapy regression area that are still contained within the capsule. Furthermore, postoperative chemotherapy may be crucial for eliminating minimal residual tumor tissue and inhibiting occult micrometastases[25-27]. We successfully performed extreme liver resection on HB patients whose major blood vessels were involved, and complete resection was achieved. Postoperative AFP levels decreased significantly, and 12 patients dropped to the normal range, indicating good therapeutic efficacy. However, we did observe recurrence in three children (two with tumor thrombus and one with compression), and 1 child died due to insensitivity to chemotherapy and increased tumor size. These patients were considered to have extremely high risk factors associated with the disease itself. This study was limited by the number of patients and the follow-up

time. Therefore, further research and long-term follow-up data are necessary to validate our findings.

CONCLUSION

Extreme liver resection for HB that is still in close PMV after a full course of NAC is both safe and feasible. This approach not only reduces the necessity for liver transplantation but also results in a favorable prognosis. Individualized 3D surgical planning is beneficial for accurate and complete resection of HB in children, particularly for assessing vascular involvement, remnant liver volume and anatomical variations.

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