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CLINICAL INVESTIGATION

Preoperative Transcatheter Selective Arterial Chemoembolization in Treatment of Unresectable Hepatoblastoma in Infants and Children

Jia-ping Li · Jian-ping Chu · Jian-yong Yang · Wei Chen · Yu Wang · Yong-hui Huang

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Abstract The purpose of this study was to evaluate the clinical feasibility and efficacy of transcatheter selective arterial chemoembolization (TACE) for unresectable hepatoblastoma in infants and children. The study was performed with the approval of our institutional review board. Sixteen patients (13 boys, 3 girls) with unresectable hepatoblastoma were treated one to three times with preoperative TACE in an effort to improve the surgical and clinical outcome. Their ages ranged from 50 days to 60 months, with a mean age of 20.4 months. All cases were pathologically proved hepatoblastoma by fine-needle biopsy. After an intra-arterial catheter was selectively inserted into the main feeding artery of the tumor, cycles of cisplatin (40 to 50 mg/m^2) and adriamycin (20 to 30 mg/m^2) mixed with lipiodol were given, followed by gelatin foam particles or stainless-steel coils. Tumor response was evaluated according to tumor shrinkage, α-fetoprotein (AFP) levels, and pathological findings. TACE procedure was performed one to three times, depending on the patient's response. Surgical resection was carried out when the tumor volume appeared sufficiently reduced to allow safe resection by either lobectomy or extended lobectomy. A marked reduction in tumor size associated with decreased AFP level occurred after treatment. According to paired-samples test, tumor shrinkage ranged from 19.0% to 82.0%, with a mean value of 59.2%. AFP levels decreased 99.0% to 29.0% from initial levels, with a mean decrease of 60.0%. TACE allowed subsequent complete surgical resection in 13 cases and the other 3 cases underwent partial resection. One patient underwent successful orthotopic liver transplantation after receiving TACE therapy. Pathological examination showed that the mean percentage of necrotic area in the surgical specimens was 87%. Overall survival rate at 1, 3, and 5 years was 87.5%, 68.7%, and 50%, respectively. Correspondingly, event-free survival rate was 75%, 62.5%, and 43.7%, respectively. In addition, there was no marked chemotherapeutic agent-induced toxicity noted during the observation period. We conclude that TACE is feasible, well tolerated, and effective in inducing surgical resectability of hepatoblastoma in pediatric patients, which has become an independent palliative or curative therapeutic option, especially for patients without distant metastasis.

Keywords Hepatoblastoma · Transcatheter arterial chemoembolizaion · Lipiodol

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J.-p. Li · J.-p. Chu · J.-y. Yang · W. Chen · Y. Wang · Y.-h. Huang
Department of Interventional Radiology, First Affiliated Hospital, Sun Yat-sen University, Guangzhou 510080, China

J.-p. Chu (✉)
58 Zhongshan Road 2nd, Guangzhou 510080, China
e-mail: truechu@hotmail.com

Introduction

Hepatoblastoma (HB) is the most common malignancy of the liver in infants and children; complete surgical resection of the primary tumor is absolutely vital to achieve HB cure [1–3]. However, 50% of cases are unresectable at initial presentation due either to local bilobar or porta hepatis invasion or to metastatic spread. In this situation it has traditionally been associated with poor prognosis [3–6]. Preoperative systemic chemotherapy plays a vital role in reducing tumor size and controlling tumor spread to convert an unresectable tumor to a resectable one [7–10]. However, there are several potential risks, including

cardiac and bone marrow damage and adverse effects of hepatic regeneration after delayed operation, and some tumors remain unresectable [11–15]. Therefore, there is a need for new therapeutic methods and alternative treatments that will reduce these disadvantages of systemic chemotherapy and improve the survival rates of these patients. TACE (transcatheter selective arterial chemoembolization) refers to combination transarterial administration of a chemotherapeutic and a vascular occlusive agent in treatment of HB as a potentially independent palliative or an adjuvant preoperative treatment [4–6, 9, 16]. The purpose of our study was to evaluate the feasibility and effectiveness of preoperative TACE for HB that is unresectable because of extensive hepatic involvement and indistinct margins at medical imaging.

Materials and Methods

Patients

The study was performed with the approval of our institutional review board, and written informed consents were obtained from all patients' legal guardians. Between 1997 and 2003, 16 cases with HB were enrolled in our study. There were 13 males and 3 females, and their ages ranged from 50 days to 60 months, with a mean age of 20.4 months. All cases were confirmed by computed tomography (CT) or magnetic resonance imaging (MRI) within 2 weeks of study entry. The tumor was considered unresectable because it involved bilobar of the liver or had main hepatic vessels or inferior vena cava invasion. According to the International Society of Pediatric Oncology (SIOP) and PRE-Treatment EXTent of disease (PRETEXT) Grouping System [17, 18], there were four cases with porta hepatis invasion (group III), two cases with multiple pulmonary metastatic lesions at presentation (group IV), seven cases with three liver sectors invasion (group III), and three cases with two liver sectors (group II). All cases were pathologically proven HB by biopsy before TACE. Serum α-fetoprotein (AFP), tumor volume, complete blood and platelet counts, liver function tests, and coagulation profile were obtained within 1 week before TACE and 3 weeks after TACE.

Treatment

Under general anesthesia and aseptic conditions, the femoral artery was catheterized using Seldinger technique. A 4-Fr catheter was introduced percutaneously into the femoral artery. Under fluoroscopy of digital subtraction angiography (DSA), the catheter was manipulated into the celiac axis and superior mesenteric artery. Arteriography was performed to demonstrate the anatomy, identify accessory arteries, and confirm the patency of the portal vein. During the capillary phase, tumor staining was mainly distributed in the right lobe of the liver or, sometimes, the left lobe of the liver or throughout the liver; no intraportal venous thrombosis was found during the venous phase. Through the catheter, a microcatheter was selectively introduced and directed to the artery supplying the tumor. Cisplatin (40 to 50 mg/m^2) and adriamycin (20 to 30 mg/m^2) dispersed in lipiodol were injected into the feeding artery of the tumor within a few minutes, followed by embolic materials using gelatin foam particles (1 × 2 mm) or stainless-steel coils, until near-complete stasis of the blood flow had occurred (Fig. 1). The total volume of the suspension to be administered to achieve stasis varied in each session; however, the total volume injected was not to exceed 10 ml and treatment was to be limited to no more than 70% of the total liver volume. After treatment, patients were hydrated and continued to receive antibiotics

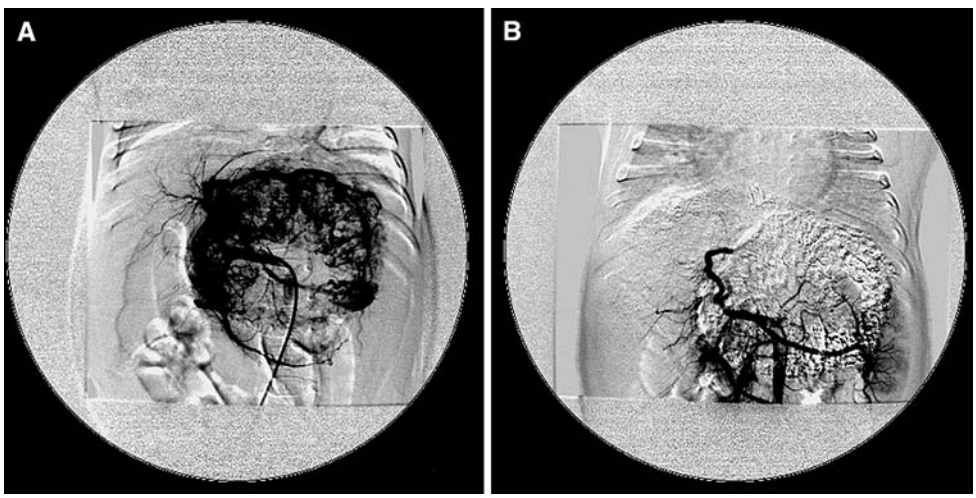

Fig. 1 Pre- and postchemoembolization angiograms. (**A**) Prechemoembolization angiogram via hepatic artery shows a large hypervascular lesion with abundant neovascularity. (**B**) After chemoembolizaion, lipiodol was retained in the tumor, outlining its embolized size

for at least 48 h. Postprocedure pain was managed with parenteral analgesics as needed, and nausea and vomiting were treated with antiemetics. TACE procedure was performed one to three times depending on the patient's response. Subsequent surgical resection was generally carried out at approximately 4-week intervals after last TACE. Surgical resection was carried out when the tumor volume appeared to be sufficiently reduced to allow safe resection by either lobectomy or extended lobectomy. Tumor volume was determined with CT or MR 4 weeks after TACE. Moreover, at least two courses of systemic chemotherapy were appended to all cases. Cycles of cisplatin (20 mg/m^2/day for 3 days) and adriamycin (25 mg/m^2/day for 3 days) were administered every 3 weeks by continuous intravenous infusion.

Evaluation of Response

Four weeks after TACE, the largest transverse diameter through the tumor center was measured on axial CT images and the tumor volume was calculated by the equation, volume = ½ × length × (transverse diameter)^2 (Fig. 2). Partial response (PR) was defined as a decrease of ≥50% in tumor volume, with no evidence of new lesions or progression in any lesion. Nonresponse (NR) was defined as <25% decrease in tumor volume of all measurable lesions, with no evidence of new lesions or progression in any lesion. For purposes of this article, a decrease between 25% and 50% was also defined as NR. The extent of tumor necrosis was histologically evaluated as the percentage of necrotic or fibrotic area in the largest section of the surgical specimen. We also investigated the clinical symptoms and the serum AFP level before and after TACE on the third day.

Toxicity

Toxicity was assessed after TACE. Cadiac function was monitored by electrocardiography; renal function, by serum electrolytes, urea, creatinine, and creatinine clearance; and liver function, by glutamicoxaloacetic transaminase (GOT), glutamic-pyruvic transaminase (GPT), alkaline phosphatase, γ-guanosine 5′-triphosphate, and bilirubin. Inflammatory reaction was monitored by C-reactive protein (CRP).

Results

Response to TACE

A marked reduction in tumor size associated with a decrease in AFP level occurred after TACE (see Table 1). The tumor volume decreased from 19% to 82%, with a mean value of 59.2%. According to the above PR and NR criteria, 13 cases were considered PRs, while 3 cases were NRs. There was a PR in 81.3% cases (13/16), a minor response in 12.5% of cases (2/16), and stable disease in 6.25% of cases (1/16). AFP levels fell 29% to 99% (mean, 60%) from initial levels. No delay of surgery was encountered and the time interval between TACE and surgical rescection was 28 ± 1.8 days. TACE allowed subsequent safe complete surgical resection in 12 cases (75%), and the other 3 cases (18.7%) underwent partly resection. One patient (6.3%) underwent successful orthotopic liver transplantation (OLT) after receiving TACE therapy. Pathological examination showed massive necrosis in the excisional specimens, and the percentage of necrotic area within the tumor ranged from 18% to 92%, with a mean level of 64.9% (Fig. 3).

Clinical Symptoms

After TACE, all patients presented with fever, and their temperatures ranged from 37.5°C to 39.5°C for 2 to 3 days. Other clinical symptoms, including nausea, vomiting, and poor appetite in 14 cases, dental ulcer in 1 case, and diarrhea in 2 cases, recovered within 5 days under suitable treatment. In addition, there was no marked chemotherapeutic agent-induced toxicity noted during TACE and postoperative systemic chemotherapy.

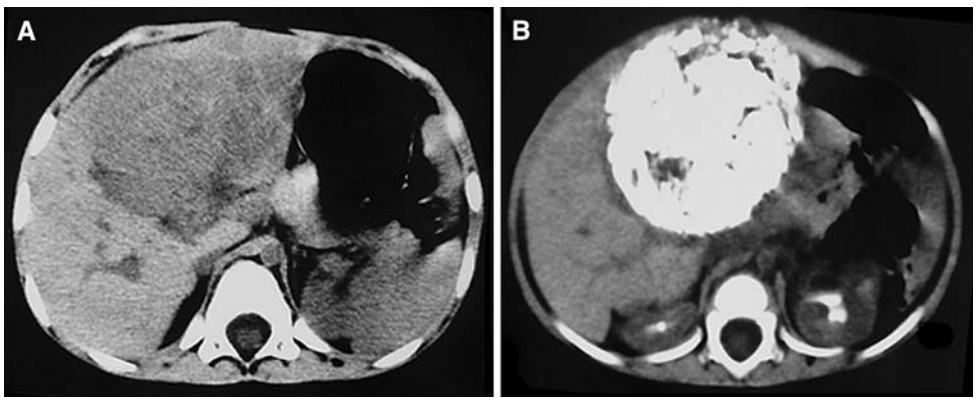

Fig. 2 Pre- and postchemoembolization noncontrast CT. (**A**) Noncontrast CT before TACE demonstrates a large tumor involving almost the entire left lobe. (**B**) After injection of cisplatin and adriamycin dispersed in lipiodol, followed by gelfoam pieces, abundant lipiodol deposits appeared in the left lobe

Table 1 Laboratory results and therapeutic effects of TACE in 16 pediatric patients

No.	Age	Gender	No. of TACEs	Time interval	Tumor size (cm)		AFP value (ng/mL)		Tumor shrink age rate (%)	AFP decrease (%)	Tumor necrosis (%)
					Pre-TACE (first time)	Post-TACE (last time)	Pre-TACE (first time)	Post-TACE (last time)			
1	33m	M	1	25d	18.6 × 14.4	9.2 × 9.8	3,863,208	1,725,300	78	55	90
2	5m	M	1	27d	13.0 × 12.0	10.9 × 7.6	1,577,690	179,566	66	89	69
3	7m	F	1	28d	10.6 × 7.1	6.3 × 4.9	1,927	383	72	80	78
4	50d	M	3	32d	7.0 × 6.0	4.1 × 6.0	839	372	41	56	58
5	23m	M	2	26d	8.0 × 7.3	7.0 × 5.2	156,000	84,000	56	46	39
6	6m	F	1	28d	9.0 × 7.0	7.0 × 5.5	301,000	153,000	52	50	41
7	30m	M	2	29d	10.5 × 6.7	5.8 × 6.3	34,200	4,000	51	89	81
8	19m	M	1	30d	16.0 × 12.0	11.5 × 6.0	24,358	17,400	82	29	18
9	12m	M	2	28d	9.0 × 6.0	6.5 × 4.0	43,442	12,599	68	71	87
10	29m	M	1	28d	12.8 × 7.4	11.0 × 7.2	329,030	201,465	19	39	56
11	30m	M	2	31d	12.0 × 9.0	9.0 × 8.0	348	210	41	40	29
12	8m	M	1	26d	13.5 × 9.5	6.0 × 6.5	66,976	32,240	79	52	74
13	19m	M	3	27d	10.5 × 9.5	9.0 × 7.0	391,478	196,392	53	50	79
14	17m	F	2	28d	8.5 × 7.2	6.0 × 4.8	78,320	19,580	69	75	83
15	27m	M	1	28d	11.5 × 8.5	9.5 × 6.5	107,923	64,754	52	40	65
16	60m	M	1	27d	17.0 × 12.0	11.0 × 8.4	75,000	488	68	99	92
Mean	20.4m	–	–		–	–	464,894.6	168,234.3	59.2	60	64.9

Note: TACE, transcatheter selectively arterial chemoembolization; AFP, α-fetoprotein; m, month; d, day; M, male; F, female

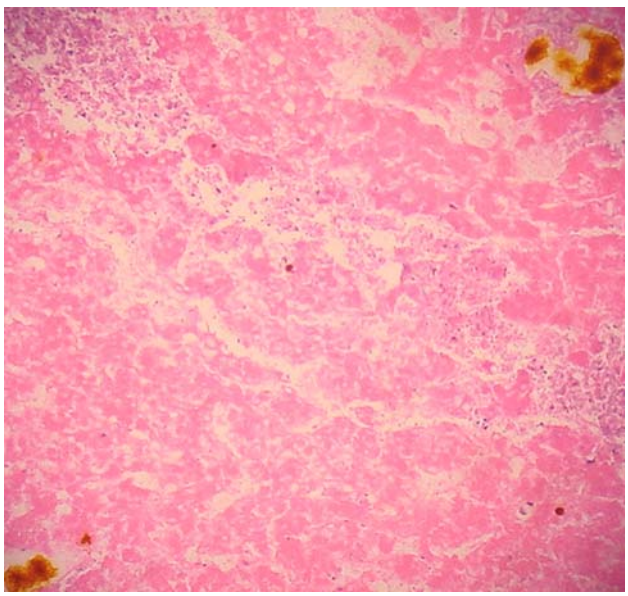

Fig. 3 Pathological slice under microscope. Excisional specimen after transcatheter selective arterial chemoembolization (TACE) indicates extensive necrosis of the tumor cells, and lipiodol is easily detected in the necrotic area

Prognosis

During the average 46-month follow-up, two patients died of extensive lung metastasis, at 2 and 36 months after the operation, respectively. One patient died of liver failure 1 year after TACE. Six patients died of tumor recurrence. The remaining seven cases were doing well and free of disease. At 1, 3, and 5 years, overall survival (OS) was 87.5%, 68.7%, and 50%, and event-free survival (EFS) was 75%, 62.5%, and 43.7%, respectively.

Discussion

Resectability of the primary tumor is the most important factor for the long-term survival of children with HB [1–3]. The cornerstones of successful treatment include total surgical excision and adjuvant chemotherapy. However, more than half of all children with HB have unresectable tumors at presentation due to local bilobar or porta hepatis invasion or to metastatic spread [3–6]. Preoperative systemic chemotherapy plays a vital role in reducing tumor size and converts an unresectable tumor to a resectable one, thus improving prognosis [7–10]. For patients with unresectable or metastatic HB, the Pediatric Oncology Group (POG) moved to a treatment strategy based on intensification of preoperative chemotherapy according to tumor response [19]. However, the associated systemic adverse effects, such as myelosuppression and cardiotoxicity, sometimes lead to delayed surgery and hence tumor regrowth and chemotherapy-related death [11–15]. Moreover, there are the problems of drug resistance [9] and induction of a second malignancy [15] by anticancer drugs. Several reports have described the successful use of intra-arterial injection of tumor agents for unresectable HB in infants.

The rationale of this treatment is the exposure of tumor cells to high concentrations of drugs, which cannot be achieved by systemic administration using the same dose. However, the treatment requires laparotomy for placement of a catheter [20, 21]. To reduce these disadvantages of systemic chemotherapy, an alternative targeting therapy, which can maximize the drug uptake of the tumor and minimize drug exposure to the host, is required.

TACE has been used extensively in hepatocellular carcinoma (HCC) in adults in the last 10 years [22–25]. It has proven to be a valuable method: first, embolization increases the dwell time of the chemotherapeutic agent; second, by occlusion of the blood supply to the tumor, ischemia ensues, followed by hypoxic tissue damage to the tumor. Furthermore, lipodol is effective as an emulsion in chemoembolization when mixed with chemotherapeutic agents, because it is selectively absorbed and retained by emulsification and pinocytosis in hepatic tumor cells [26]. It can provide differentiation between normal parenchyma and tumor as confirmed by CT imaging and pathologic findings. Liovet et al. [25] reported that preoperative TACE could improve survival in patients with unresectable HCC. However, experience with TACE in children is somewhat limited [4–6, 9, 16]. Pediatric interventions differ from adult interventions in that both the setting and the equipment must be adapted to infants and children. Needless to say, another technical challenge is the very small vessel diameter of pediatric vessels, which demands more skill and experience to avoid perforation or dissection. Therefore, the disease processes and the indications for treatment are clearly distinct in this age group. Nowadays, pediatric embolotherapy has become feasible, thanks to the availability of microcatheters and other supplies. There have been several reports in the literature of TACE application in pediatric patients with HB [4–6, 9, 16].

In our series, most patients showed a marked response to TACE, a nearly linear decrease in AFP levels, and a reduction in tumor size. Consequently, 81.3% underwent complete surgical resection of the tumor with no morbidity; the 1-, 3-, and 5-year OS was 87.5%, 68.7%, and 50%, and the EFS was 75%, 62.5%, and 43.7% respectively, values strikingly similar to the results for HB in the POG Phase II study [19]. In that study, 5-year EFS estimates were 59% ± 11% for stage III disease and 27% ± 16% for stage IV disease. In SIOPEL study-1, the long-term (current follow-up is >10 years for all patients), disease-free patient survival was 66% for the whole series [17, 27]. In contrast, 71% of these patients with macroscopic extension into the portal vein and/or the hepatic veins/vena cava were alive and disease-free more than 10 years after liver transplantation [3]. Pathological examination showed pronounced tumor necrosis, 87%, in the excisional specimens. However, whether we can effectively downstage a tumor by producing extensive tumor necrosis will be an area for future study. A "postembolization syndrome" consisting of fever, abdominal pain, nausea, vomiting, and elevated AST, ALT, and CRP levels occurs in almost all patients, but these symptoms are minimal and transient. Serious adverse effects such as myelosuppression, liver dysfunction, and pulmonary embolism did not occur. Moreover, no evidence of tumor growth or spread before operation was noted. TACE may thus be considered the initial preoperative treatment instead of systemic chemotherapy, especially for patients without distant metastasis, and it may be repeated until the tumor becomes resectable. In addition, we noted that the ranges for AFP in primary reports [4–6, 9, 16] were quite different, making it difficult to interpret any true correlation, but AFP level is a useful aid for monitoring response to TACE and disease recurrence after surgery, in our experience. CT does not predict outcome but, more importantly, serves to monitor treatment, rule out complications, and exclude extrahepatic disease [28].

The mortality and recurrence rates are still high in our series. Five-year EFS was only 43.7 %. Two cases were excited multiple pulmonary metastatic lesions. Although complete surgical resection of the primary tumor was successfully performed, the prognoses were poor. One case had right lobectomy and had no recurrence during the follow-up, but still died of chronic liver function failure. Consequently, we strongly recommend superselective catheterization in order to obtain a better efficacy and cause less damage to residual liver. The tumor size, location, number, feeding vessels, pathological typing, and clinical stage should be carefully evaluated before treatment, and suitable strategy planned individually. In the case of embolus in a portal vein, transarterial infusion of antitumor agents can be performed. Embolotherapy should be approached with caution because of ischemia to the normal liver parenchyma. Furthermore, TACE plays an important role in the primary lesion but has little effect on distal metastasis [5, 29]. Two patients died of distal extensive metastasis in this study, which may be explained by pre-existing micrometastasis. Therefore, postoperative systemic chemotherapy should be used in attempts to eliminate micrometastases that may be present at the time of transplant or malignant cells that are shed during surgical manipulation of the tumor.

There is currently no consensus regarding the timing of TACE in relation to surgery. A short interval makes the operation more difficult, owing to obvious liver capsule edema and lack of clear interspace in anatomic structure. In contrast, if the interval is longer than 6 weeks, the tumor will regrow rapidly because of embolized tumor artery recanalization. On the basis of our experience, TACE was performed one to three times, depending on the patient's response. Surgical resection was carried out

when the tumor volume appeared to be sufficiently reduced to allow safe resection by either lobectomy or extended lobectomy under radiologic criteria. The appropriate time interval between last TACE and operation is about 4 weeks.

OLT offers a chance of cure even to patients in whom HB is otherwise unresectable after chemotherapy [27, 30–32]. We agree that multifocal HB and unifocal, centrally located PRETEXT II and III tumors involving main hilar structures or all three main hepatic veins are clear and undisputed indications for liver transplantation, whatever the result of chemotherapy [17, 18]. However, recurrence is a major cause of mortality after OLT for HB [32, 33]. A recent review of the United Network for Organ Sharing [UNOS] database showed that 54% of deaths after OLT for HB were the result of disease relapse rate [34]. TACE has the potential to control tumor growth during the waiting period and to cause tumor necrosis and reduce tumor dissemination during surgery [6, 35]. Arcement et al. [6] suggest that children who do not respond to systemic therapy can eventually be cured by a combination of TACE and OLT. Majno et al. [36] also found that preoperative TACE could improve the 5-year recurrence-free survival rate for patients with larger tumors. In this study, only one case received OLT after TACE. OLT was considered at this stage but it was not appropriate in any of the patients for various reasons, that is, lack of compliance of the family, shortage of donor organs, high costs of and limited access to the transplantation program, and presence of extrahepatic or metastatic disease. The patient who received OLT died of recurrence 1 year later. We agree that, although OLT is a suitable alternative to chemoembolization in most patients with HB, chemoembolization may also be used in the pretransplantation waiting period.

In conclusion, the optimal strategy for preoperative TACE for HB of infants or children remains controversial. It is difficult to reach any definitive conclusions regarding the role of preoperative TACE based on this study because it was not a multicenter, randomized, control study. Optimal management of this disease requires careful liaison among pediatric oncologists, liver surgeons, radiologists, and histopathologists. Although chemoembolization is a minimally invasive and technically demanding procedure requiring general anesthesia, and is associated with potential complications [37, 38], yyour preliminary experience is encouraging and suggests that TACE is feasible, well tolerated, and effective in inducing surgical resectability of unresectable HB in pediatric patients, which has become an independent palliative or curative therapeutic option, especially for patients without distant metastasis during surgical resection and the pretransplantation waiting period. Further experience and follow-up are necessary to validate this approach.

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