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Optimal Strategy of Preoperative Transcatheter Arterial Chemoembolization for Hepatoblastoma

YASUHIRO OHTSUKA, TADASHI MATSUNAGA, HIDEO YOSHIDA, KATSUNORI KOUCHI, TADAO OKADA, and NAOMI OHNUMA

Department of Pediatric Surgery, Graduate School of Medicine, Chiba University, 1-8-1 Inohana, Chuou-ku, Chiba 260-8677, Japan

Abstract

Purpose. To investigate the optimal strategy of preoperative transcatheter arterial chemoembolization (TACE) for hepatoblastoma.

Methods. Between 1992 and 2001, 7 children with hepatoblastoma (aged 9 months to 13 years) underwent preoperative TACE. The chemoembolic agent used was an emulsion of pirarubicin and lipiodol. Four patients without distant metastasis underwent "primary" TACE without systemic chemotherapy. The other 3 with distant metastases underwent "delayed" TACE following systemic chemotherapy. These patients were all examined retrospectively using clinical data.

Results. The average dosage of lipiodol was 0.6 ml per tumor maximal diameter (cm). All the primary cases showed a significant decrease in α-fetoprotein (AFP) and a reduction in the tumor size. They consequently underwent a complete surgical resection and are now disease free. All the delayed cases showed a slight decrease in AFP and underwent complete surgical resection; however, two of them died of lung metastases, and the other died of a second malignancy. Regarding complications, liver dysfunction and pulmonary embolism occurred in one patient each.

Conclusions. For patients without distant metastasis, regardless of the resectability of the primary tumor, TACE may be considered the initial and only preoperative treatment, and it may be repeated. For patients with distant metastases, their complete eradication with systemic chemotherapy prior to TACE is essential.

Key words Transcatheter arterial chemoembolization · Hepatoblastoma · Iodized oil · Lipiodol

Introduction

Pediatric liver tumor (PLT) is the third most common intra-abdominal malignant solid tumor in children after neuroblastoma and Wilms' tumor, and hepatoblastoma (HB) accounts for the vast majority. It is well known that the resectability of the primary tumor is the most important factor for the long-term survival of children with HB, and a complete surgical resection of the primary tumor is absolutely vital to achieve an HB cure.[1–8] However, about half of all children with HB have unresectable tumors at presentation.[3–5] Hepatoblastoma was previously thought to be a chemoresistive tumor similar to hepatocellular carcinoma (HCC). As a result, an extended hepatectomy was therefore frequently attempted to achieve a complete surgical resection of the huge tumor, thus resulting in a high morbidity and mortality.[4,7,9] Since the 1970s, however, HB has been recognized to actually be a highly chemosensitive tumor, and several regimens of intravenous systemic chemotherapy, including doxorubicin (DOX) and cisplatin (CDDP), have been attempted.[9–13] As a result, preoperative systemic chemotherapy successfully reduces the tumor size, converting an initially unresectable tumor into a resectable one, and consequently improving the prognosis of children with HB. However, the toxicity of systemically administered anticancer drugs, especially myelosuppression and DOX-related cardiotoxicity, is sometimes remarkable, and may lead to a delay in performing surgery, thus resulting in tumor regrowth and chemotherapy-related death in the worst cases.[4,9,10,14] In addition, drug resistance[7] and a second malignancy[15,16] induced by the extremely high dosage of anticancer drugs have recently become major

Reprint requests to: Y. Ohtsuka, Department of Surgery, Funabashi Central Hospital, 6-13-10 Kaijin, Funabashi 273-8556, Japan

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problems. To reduce these disadvantages of systemic chemotherapy, an alternative chemotherapeutic modality, namely "targeting therapy," which can maximize the drug uptake of the tumor and minimize drug exposure to the host, is required. In this regard, transcatheter arterial chemoembolization (TACE), a chemotherapeutic modality of percutaneous transcatheter intra-arterial coadministration of anticancer drugs and vascular occlusive agents, may be an alternative to systemic chemotherapy. We have encountered seven patients with HB over the last 10 years and treated them with preoperative TACE in our department. Based on the findings of these patients, we investigated the optimal strategy of preoperative TACE for children with HB.

Patients and Methods

Between 1992 and 2001, 7 patients with PLT were referred to our department and all were treated with 9 courses of TACE (8 for preoperative and 1 for palliative treatment). The patients consisted of 3 boys and 4 girls, ranging in age from 9 months to 13 years (3.5 ± 4.4 years, mean ± SD). The serum α-fetoprotein (AFP) levels at presentation ranged from 265 to 3706000 (a median of 51250) ng/ml. All tumors were diagnosed to be HB (4 well and 3 poorly differentiated types) based on pathological examinations of biopsied or resected specimens, and none were HCC.

Our protocol for the management of PLT is as follows: for patients with abdominal distension, ultrasonography (US) is routinely performed at admission. When a solid liver tumor is revealed by US, the AFP level is quickly examined by blood sampling, and when it is elevated, the diagnosis of PLT is confirmed. Contrast-enhanced computed tomography (CT) is then performed to evaluate the tumor site according to which hepatic segments are occupied by the tumor, the pretreatment extent of disease (PRETEXT),[1] the tumor size measured by maximal diameter on cross-sectional images, the presence or absence of distant metastasis, and the clinical stage according to the staging classification of the Japanese Society of Pediatric Surgeons.[2] At this time, patients without distant metastasis, regardless of the resectability of the primary tumor, enter directly into the TACE protocol without undergoing any systemic chemotherapy; namely, primary TACE. On the other hand, patients with distant metastases initially undergo systemic chemotherapy according to the regimen of the Japanese Study Group for Pediatric Liver Tumor (JPLT)[13] using 80 mg/m^2 of CDDP and 60 mg/m^2 of pirarubicin (THP) until the metastatic lesions have disappeared, and when their disappearance is confirmed with a follow-up CT, they are started on the TACE protocol; namely, delayed TACE. For the purpose of mapping out the precise and detailed anatomy of the hepatic blood supply, all patients routinely undergo diagnostic hepatic angiography prior to surgery, and TACE is performed thereafter.

Our TACE protocol is as follows. Under general anesthesia, the femoral artery is cannulated using the Seldinger technique. A 4- or 5-F sheath with a hemostasis valve is placed in the groin. Initially, superior mesenteric arteriography is performed using a standard 4- or 5-F cobra or hook-shaped catheter (Cook, Bloomington, IN, USA) after the administration of 61% iopamidol (Iopamiron 300; Nihon Schering, Osaka, Japan) at a rate of 0.2 ml/kg per second (for a total of 0.8 ml/kg) to confirm the presence of variations in the hepatic arterial branching and tumor thrombus in the portal vein. Common hepatic arteriography is then performed using a standard 4- or 5-F cobra or hook-shaped catheter after the administration of 61% iopamidol at a rate of 0.15 ml/kg per second (for a total of 0.6 ml/kg) to demonstrate the hepatic arterial branching and tumor stain, and the tumor feeding artery is then identified to determine the injection site. Iopamidol, 30 mg/m^2 of THP, and approximately 1.0 ml per tumor maximal diameter (N) (cm) of iodized oil (Lipiodol (LPD); Laboratoire Guerbet, Roissy Charles de Gaulle, France) are conjugated, and an emulsion is made. A standard catheter is inserted into the injection site (usually the proper, left, or right hepatic artery) using a standard guidewire technique, then the emulsion is slowly injected intra-arterially under fluoroscopic monitoring. For patients with pathologically confirmed HCC, the tumor feeding artery is subsequently embolized with a gelatin sponge (Gelfoam; Upjohn, Kalamazoo, MI, USA). Finally, proper hepatic arteriography is performed to confirm shrinkage of the tumor stain and the concentration of LPD in the tumor. The effects of TACE are evaluated by the AFP level and tumor size measured with a follow-up CT, and surgery is performed as early as possible when tumor resectability is confirmed and the patient's clinical status permits.

Of the nine courses of TACE, the seven initial preoperative courses for each patient were reviewed and examined retrospectively using various clinical data.

Results

The tumor site, PRETEXT, tumor size, and clinical stage at presentation for each patient are shown in Table 1. Two of the seven patients (cases 2 and 3) had distant metastases in the lungs and therefore entered the delayed TACE protocol. In case 1, intra-abdominal tumor dissemination was strongly suspected because the initial presentation of the disease was a tumor rup-

Table 1. Characteristics of the patients

Patient no.	Year	Age	Sex	AFP (ng/ml)	Pathology of tumor	Tumor site	PRETEXT	Tumor size (mm)	Clinical stage
1	1992	2y	M	34500	HB (poor)	PAML	IV	125 × 119	IIIB
2	1993	1y	F	51250	HB (well)	LMA	III	89 × 86	IV
3	1993	13y	M	59280	HB (well)	PAL	III	101 × 84	IV
4	1994	5y	F	265	HB (poor)	P	I	20 × 11	I
5	1994	2y	M	567	HB (well)	M	II	63 × 48	I
6	1996	1y	F	673900	HB (well)	PA	II	93 × 86	II
7	2000	9m	F	3706000	HB (poor)	PAM	III	127 × 115	IIIA

y, years; m, months; AFP, α-fetoprotein; PRETEXT, pretreatment extent of disease; HB, hepatoblastoma; poor, poorly differentiated type; well, well-differentiated type; L, lateral segment; M, medial segment; A, anterior segment; P, posterior segment

Table 2. Protocols and effects of transcatheter arterial chemoembolization (TACE)

Patient no.	Method of TACE	Injection site	THP (mg)	LPD (ml)	Characteristic findings	AFP decreasing ratio (%)	Tumor reducing ratio (%)
1	Delayed	PHA	18	5	TT in the IVC	6	12
2	Delayed	LHA	13	6.7	TT in the LPV	42	39
3	Delayed	RHA	30	8	Aberrant RHA[a]	30	21
4	Primary	RHA	20	2	—	70	55
5	Primary	PHA	20	3	—	59	30
6	Primary	RHA	17	4.3	—	35	18
7	Primary	RHA	10	10	—	98	57

THP, pirarubicin; LPD, lipiodol; PHA, proper hepatic artery; LHA, left hepatic artery; RHA, right hepatic artery; TT, tumor thrombus; IVC, inferior vena cava; LPV, left portal vein
[a] Arising from the superior mesenteric artery

ture. He therefore entered the delayed TACE protocol with no distinct sign of distant metastasis; however, after 1 course of systemic chemotherapy, lung metastasis appeared on the follow-up CT. The other four of seven patients had no distant metastasis and therefore entered the primary TACE protocol.

The injection site, dosage of injected THP and LPD, and effects of TACE in each patient are shown in Table 2. The dosage of LPD ranged from 0.4 to 1.0 (a median of 0.75) ml/N. The AFP decreasing ratio until the next therapy in each patient is shown in Fig. 1. All 3 delayed cases showed a slight decrease in the AFP level 1 week after TACE, ranging in ratio from 6% to 42% (a median of 30%); however, they all began to increase 1 week later. On the other hand, all 4 primary cases showed a significant and nearly linear decrease in the AFP levels until the next therapy, ranging in ratio from 35% to 98% (a median of 65%). The reduction ratio of the tumor size was less than the AFP decreasing ratio in almost all of the patients; however, extensive tumor necrosis was revealed by pathological examinations of the resected specimens in all patients.

The complications and clinical courses after TACE for each patient are shown in Table 3. A fever of more than 38.0°C, abdominal pain, and elevated C-reactive protein (CRP), asparate aminotransferase (AST), and

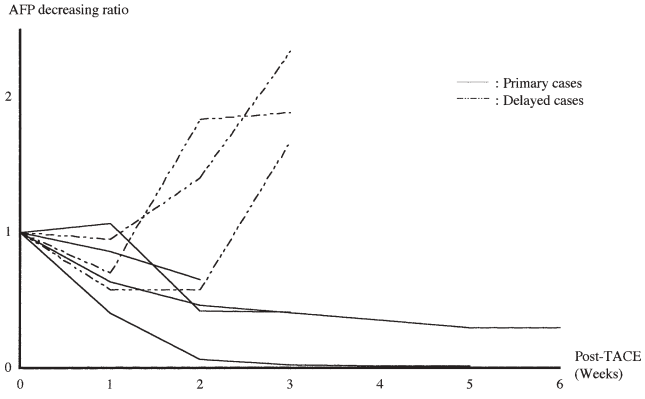

Fig. 1. α-Fetoprotein (*AFP*) decreasing ratio until the next therapy in each patient

alanine aminotransferase (ALT) levels occurred in almost all of the patients, but they were generally minimal and transient. The minimum white blood cell counts after TACE ranged from 1000 to 4100 (a median of 2800)/mm^3, and no patient showed myelosuppression symptoms. No sign of cardiotoxicity was revealed in any of the patients. However, TACE-related major complications occurred in 2 patients. In case 2, severe liver dysfunction occurred 1 day after TACE; however, she recovered well 6 days later with supportive therapies. In

Table 3. Complications and clinical courses after TACE

Patient no.	Fever (days)	Max. CRP (mg/dl)	Max. AST (IU/l)	Min. WBC (/mm^3)	Following therapy	Outcome
1	1	0.6	41	2600	Extended right lobectomy, Cx, Rx	PD → died
2	13	5.2	3470	3200	Left lobectomy, Cx, partial resection of the lung	CR → died[a]
3	2	1.7	132	1300	Extended right lobectomy, Cx, TACE, PEI, partial resection of the lung, Rx	PD → died
4	1	1.7	131	4000	Partial resection of the liver, Cx	CR
5	14	0.2	34	2800	Cx, partial resection of the liver, Cx	CR
6	3	1.2	136	4100	Cx, right lobectomy, Cx	CR
7	23	12.6	535	1000	TACE, right lobectomy, Cx	CR

Max., maximum; Min., minimum; CRP, C-reactive protein; AST, asparate aminotransferase; WBC, white blood cell count; Cx, intravenous systemic chemotherapy; Rx, radiotherapy; PEI, percutaneous ethanol injection; PD, progressive disease; CR, complete remission
[a] Died of a second malignancy (myelodysplastic syndrome)

case 7, a symptomatic pulmonary embolism occurred soon after TACE; however, she recovered well with 2 weeks of oxygen inhalation and fluid management. The therapy following TACE was surgery in 4 patients, systemic chemotherapy in 2, and a second TACE in 1, and this began 19–43 (a median of 22) days after TACE. All 3 delayed cases were followed by a complete surgical resection of the primary tumor and then they received postoperative systemic chemotherapy mainly with CDDP (100 mg/m^2) and THP (90 mg/m^2); however, despite aggressive postoperative combination therapies, 2 patients nevertheless died of lung metastases 23 and 27 months after surgery, respectively. The other patient was successfully cured of HB; however, she died of a second malignancy (myelodysplastic syndrome) 57 months after surgery. All 4 primary cases were also followed by a complete surgical resection of the tumor and received postoperative systemic chemotherapy with CDDP (40 mg/m^2) and THP (30 mg/m^2), and are disease-free from 28 to 103 (a median of 83) months after surgery. Of these 4 patients, 1 (case 7) was successfully treated with preoperative repeated TACE, and is shown in Fig. 2.

Discussion

In the late 1970s, TACE was first introduced for the palliative treatment of unresectable HCC in adults, and since the 1980s, TACE has been developed as an effective and useful preoperative chemotherapeutic modality for HCC in adults, especially in Japan.[17–21] The term "chemoembolization" refers to the intra-arterial coadministration of anticancer drugs and vascular occlusive agents,[6] and the most commonly used chemoembolic agent is an emulsion of DOX and iodized oil. In particular, TACE using iodized oil is occasionally known as transcatheter oily chemoembolization (TOCE).[3,20,22] Iodized oil, which was originally an oily lymphographic contrast medium, was found to selectively accumulate and remain in the tumor tissue and to induce microembolization of the tumor vasculature when injected into the tumor feeding artery.[3,4,14,17–21] The selective accumulation of iodized oil in the tumor is considered to be due to the siphoning effect created by increased blood flow in a hypervascular tumor,[17,18] and long-term retention is considered to be due to the lack of reticuloendothelial or lymphatic flow in the tumor which may inhibit the decomposition and absorption of the oil.[17,18] At least some proportion of the injected iodized oil must flow into the normal liver tissue; however, it is washed away by the blood-stream shortly after injection.[3,18] For the purpose of chemoembolization, this iodized oil is conjugated with an anticancer drug such as DOX, and an emulsion is made and injected. The selectively accumulated emulsion releases the anticancer drug slowly and decreases the transit time of the drug through the tumor vasculature, thus resulting in an increased local concentration, local retention time, and tumor contact time of the drug.[14,17–21] Nakamura et al.[20] studied the tissue concentration of DOX in resected tumors and reported that biologically active DOX remained in the tumor tissue for more than 3 weeks after TACE. In addition, microembolization created by the emulsion produces temporary occlusion of the arterial blood supply to the tumor, thus resulting in hypoxic tissue damage and ischemic necrosis.[18,19] Moreover, these features of the emulsion markedly reduce the systemic exposure to the anticancer drugs. Raoul et al.[21] studied the pharmacokinetic and scintigraphic biodistribution of DOX after TACE and reported that the emulsion lowers the peak blood concentration of DOX. Therefore, TACE enables the cytoreductive effects of the anticancer drug to be maximally increased, while the systemic toxicities of the drug are minimally reduced;[14] consequently, it has

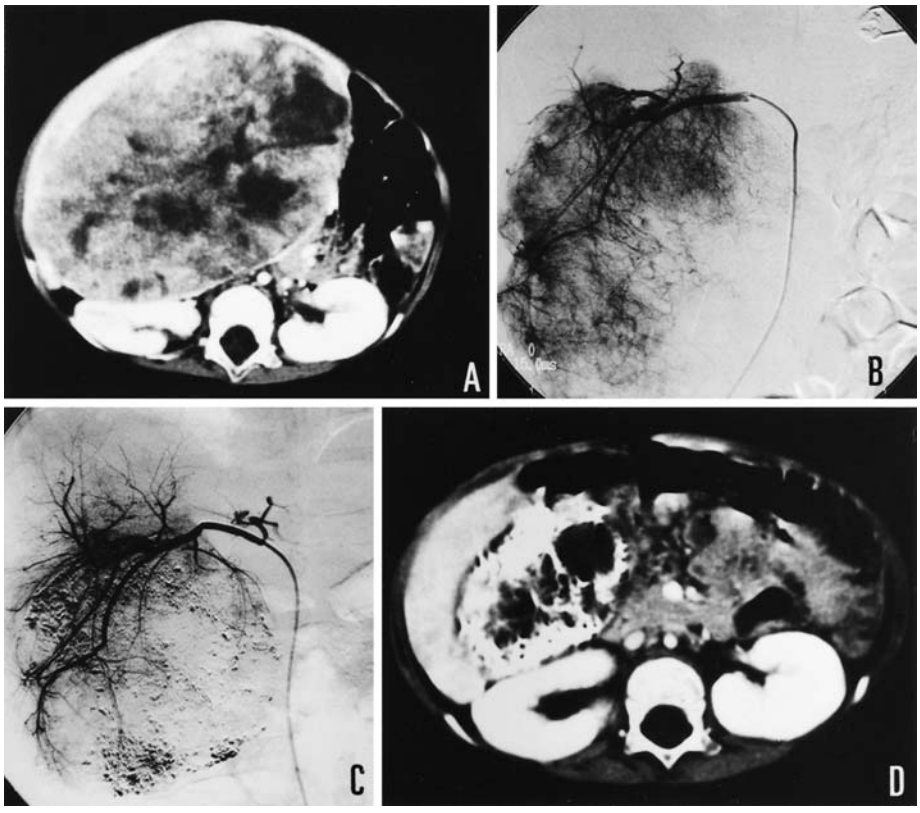

Fig. 2A–D. Case 7. A 9-month-old girl with HB. **A** Contrast-enhanced computed tomography (CT) at presentation revealed a huge liver tumor arising from the right hepatic lobe and spreading in the medial segment. The tumor maximal diameter was 127 mm. **B** Hepatic arteriography at presentation revealed a huge tumor stain in the bilateral hepatic lobes. Transcatheter arterial chemoembolization (TACE) was performed from the right hepatic artery. **C** Hepatic arteriography 5 weeks after the initial TACE revealed a concentration of lipiodol (LPD) in the tumor and a residual tumor stain in the right hepatic lobe. The second TACE was performed from the right hepatic artery. **D** Contrast-enhanced CT 4 weeks after the second TACE revealed a remarkable reduction in tumor size and a concentration of LPD in the tumor. The tumor maximal diameter was reduced to 54 mm

many advantages over systemic chemotherapy and also plays an excellent role as a targeting therapy. Recently, several authors[3–6,23–25] have reported the usefulness of TACE for PLT; however, these reports are sporadic, which may be due to the technical difficulties related to TACE in children. As a result, the optimal strategy for preoperative TACE for children remains controversial.

In our series, all of the primary cases showed a significant and nearly linear decrease in the AFP levels and a reduction in the tumor size, consequently undergoing complete surgical resection of the tumor with no morbidity, and they are disease-free at this time. In case 7, two courses of TACE were the only preoperative treatment and enabled the initially unresectable tumor to be resected. In addition, in cases 5 and 6, in which TACE was followed by systemic chemotherapy with CDDP (40 mg/m^2) and THP (30 mg/m^2), we should have employed a second TACE treatment instead of systemic chemotherapy. This is because, from our experience with the second malignancy case, total systemic exposure to anticancer drugs should be reduced as much as possible. Therefore, for patients without distant metastasis, regardless of the resectability of the primary tumor at presentation, TACE may thus be considered the initial and only preoperative treatment instead of systemic chemotherapy, and it may be repeated until the tumor becomes resectable. We suppose that preoperative TACE for patients without distant metastasis may contribute to their long-term survival. On the other hand, all the delayed cases showed a response to TACE as demonstrated by the slight decrease in AFP levels 1 week after TACE; however, they all began to increase 1 week later, which might have been due to nonvisualized regrowth of the distant metastatic lesions. Although a complete surgical resection of the primary tumor was successfully performed, their prognoses were poor. Consequently, preoperative TACE for the patients with distant metastases could not improve their prognoses. The effect of TACE is limited to controlling a primary tumor confirmed in the liver,[3,4] which is one of its pitfalls; therefore, the complete eradication of distant metastases with systemic chemotherapy prior to TACE is unavoidable to employ delayed TACE as a preoperative treatment.

In our series, the chemoembolic agent used was an emulsion of LPD and THP, whose anticancer effect is similar to DOX with markedly lower cardiotoxicity,[14] and it is the most recommended. The optimal LPD dosage during TACE for children is still uncertain and further experimental studies and experiences with larger numbers of patients are required. In the literature, Oue et al.[4] used LPD with a constant dosage of

5 ml for all children, but Nakagawa et al.[3] estimated the dosage of LPD individually based on tumor size, with a maximum of 15 ml. We fundamentally decided the dosage of LPD to be approximately 1.0 ml/N; however in fact, except for case 4 whose tumor maximal diameter was only 2 cm, it was decreased to an average of 0.6 ml/N according to the age, tumor size, hepatic angiographic findings, and clinical status of each patient individually, and as a result, a satisfactory TACE effect was obtained. Therefore, we recommend that the optimal dosage of LPD during each TACE is approximately 0.6 ml/N.

Although TACE is an excellent modality, a variety of complications must be considered. A "postembolization syndrome" consisting of fever, abdominal pain, nausea, vomiting, and elevated AST, ALT, and CRP levels occurs in almost all patients,[26] which may be due to the massive necrosis of the tumor,[4] but these symptoms are minimal and transient. However, major complications related to the use of chemoembolic agents such as acute liver failure, liver infarction, liver abscess, tumor rupture, or pulmonary embolism may also sometimes occur.[22,25–28] In our series, severe liver dysfunction and pulmonary embolism occurred in 1 patient each. Major portal vein obstruction is known to be a risk factor for liver infarction after TACE,[26] and in affected patients, such as our case 2 with tumor thrombus in the left portal vein, TACE should be performed cautiously with a reduced amount of iodized oil that is superselectively injected into the tumor feeding artery. In addition, the appearance of iodized oil in the portal vein during TACE also indicates a risk of liver infarction;[28] therefore, careful fluoroscopic monitoring is necessary during TACE. At least some proportion of the injected iodized oil must leave the liver through the normal hepatic vasculature or arteriovenous shunt in the tumor and embolize the peripheral pulmonary arteries,[22] and the amount of iodized oil and the presence of arteriovenous shunt are crucial factors determining whether symptomatic pulmonary embolism may occur.[22,25,26] From our experience with pulmonary embolism in case 7, in which 0.8 ml/N of LPD was used, limiting the dosage of LPD during each TACE to below 0.7 ml/N may be safe. The risk of complications related to the manipulation of a catheter or guidewire such as iatrogenic dissection or perforation of the celiac artery and its branches[26] could be higher in children than adults because of the smaller diameter of each vessel. Needless to say, skillful and careful handling of the appropriate devices under fluoroscopic control is the only way to avoid this risk.

In conclusion, we propose the optimal strategy of preoperative TACE for children with HB to be as follows. For patients without distant metastasis, regardless of the resectability of the primary tumor, TACE may be considered as the initial and only preoperative treatment instead of systemic chemotherapy, and it may be repeated until the tumor becomes resectable. The most recommended chemoembolic agent is an emulsion of THP and LPD, and the total dosage of LPD during each TACE should be 0.6 to 0.7 ml/N to obtain a satisfactory effect and to avoid major complications. For patients with distant metastases, TACE should not be employed unless their complete eradication with systemic chemotherapy has been achieved.

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