Surgery 165 (2019) 889–896

Contents lists available at ScienceDirect

Surgery

journal homepage: www.elsevier.com/locate/surg

Liver

Vascular infiltration-based surgical planning in treating end-stage hepatic alveolar echinococcosis with ex vivo liver resection and autotransplantation ☆

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ARTICLE INFO

Article history:
Accepted 16 November 2018
Available online 24 December 2018

ABSTRACT

Background: For end-stage hepatic alveolar echinococcosis, insufficient guidance is available regarding surgical treatment, especially for ex vivo liver resection combined with autotransplantation. The indications for this complex surgery require further discussion.

Method: We reviewed 50 cases of patients who underwent ex vivo liver resection combined with autotransplantation from January 2014 to February 2018. A newly developed classification was used to describe vascular infiltration in all patients, who were divided into four groups based on anatomic lesion features and surgical patterns. The surgical planning for ex vivo liver resection combined with autotransplantation is then thoroughly discussed according to the gathered information.

Results: In all patients, the length of the operation and the anhepatic phase were 735 minutes (range, 540-1,170 minutes) and 309 minutes (range, 122-480 minutes), respectively. The median remnant liver volume–to–standard liver volume ratio was 0.58 (range, 0.32-1.11). The rate of complications classified as Clavien-Dindo grade III or higher was 22% (11/50). A total of 3 postoperative deaths occurred. We identified 4 types with distinguished lesion anatomic features. Type I patients required more frequent unconventional reconstruction of the portal vein and bile duct than the other patients. Of the 6 type IV patients, 4 required modification of the surgical protocol according to intraoperative findings.

Conclusion: Vascular infiltration-based classification could improve the anatomic comprehension and, thus, facilitate surgical planning for ex vivo liver resection combined with autotransplantation. Through cautious evaluation of operability, liver function, and residual liver volume, together with delicate operative techniques and careful postoperative management, ex vivo liver resection combined with autotransplantation can achieve good results in the treatment of end-stage hepatic alveolar echinococcosis.

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Introduction

Hepatic alveolar echinococcosis (HAE) is a zoonotic parasitic disease caused by infection with *Echinococcus multilocularis*.[1] Alveolar echinococcosis (AE) is mainly endemic to the northern hemisphere, where its extensive range includes the central part of western Europe, parts of the Near East, Russia, the central Asian republics, China, northern Japan, and Alaska.[2] China bears 90% of the global burden of this long-neglected disease.[3] More than 16,000 cases of AE are primarily diagnosed every year, making AE a major health issue in the eastern part of the Tibet Autonomous Region.[4,5] HAE frequently manifests as an infiltrating growth similar to that of malignant tumors, leading to extensive invasion of multiple intrahepatic structures. Therefore, it is known as "parasitic cancer."[6] Surgery remains the preferred treatment for HAE,[7] but unfortunately only 35% of patients are eligible for conventional radical liver resection.[8] The asymptomatic onset and slow progression of HAE usually result in a delayed diagnosis, leaving many patients without an opportunity for curative treatment. Moreover, palliative surgery, such as lesion reduction surgery or cholangial drainage, has been proven not to be beneficial to patients for long-term survival.[9–11]

☆ Funded by the National Natural Science Foundation of China (No. 81770566) and The New Medical Technology Foundation of West China Hospital of Sichuan University (No. 2016-036).

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https://doi.org/10.1016/j.surg.2018.11.007
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Table 1
Preoperative information.

Variables	Type I ($n=13$)	Type II ($n=4$)	Type III ($n=27$)	Type IV ($n=6$)
Age in years, median (range)	41 (23–57)	32 (25–44)	32 (10–46)	33 (23–49)
Sex (M:F)	4:9	3:1	8:19	3:3
Lesion diameter, cm, median (range)	16 (13.8–20)	16 (11.2–20.1)	16 (10–22)	16 (12.7–19.2)
Extrahepatic lesion, *n*	0	2	5	1
Child-Pugh B, *n*	1	1	2	0
Pre-ERAT PTCD, *n*	4	0	5	0
Pre-ERAT surgery, *n*	5	0	1	0

Multiple unconventional methods have been applied to cope with this predicament. Liver transplantation (LT) is an option for the treatment of end-stage HAE, particularly ex vivo liver resection combined with autotransplantation (ERAT).[12–18] This promising technique comprises several key components, including hypothermic liver perfusion, extracorporeal liver resection, in situ venous-venous bypass, and portacaval shunt, and individualized reconstruction of intrahepatic conduits, and it may be the optimal choice for select patients.[19,20] However, the exact indications for ERAT remain vague.

Currently, the evaluation, planning, and implementation of surgical treatment for complicated HAE remain inconclusive. Predicting treatment outcomes and long-term prognosis is difficult, especially because clinical information regarding this rare disease is rather heterogeneous. Only a few centers worldwide have experience with treating HAE in sophisticated conditions, hampering the establishment of uniform standards and protocols for treatment. For example, the World Health Organization (WHO) parasitic liver lesion infiltration of neighboring organs metastases (PNM) classification of AE, which was proposed in 2006, mainly focuses on the location and extension of primary intrahepatic lesions, the involvement of neighboring organs, and the presence or absence of metastasis.[7] The PNM classification is insufficient for providing guidance in the advanced stage, necessitating the development of a classification exclusively for end-stage HAE.

Our center is one of the earliest centers to explore the use of LT[15]and ERAT[19] for the treatment of end-stage HAE, which has helped us accumulate substantial experience in the surgical treatment of this disease. In this report, we present a classification system based on vascular infiltration of intrahepatic HAE lesions and our experiences with ERAT, particularly with regard to the surgical planning and reconstruction techniques for this surgery.

Materials and Methods

Ethics

The study was approved by the Ethics Committee of West China Hospital of Sichuan University, Chengdu, P. R. China (No. 2017-38) and was conducted in accordance with the Declaration of Helsinki. Before the surgery, we communicated fully with the patients and their families in their native language and explained the advantages of surgery and possible complications.

Patients

From January 2014 to February 2018, a total of 50 patients with the following critical features underwent ERAT: (1) “unresectable” advanced HAE as determined, using traditional techniques, because of the difficulty of exposing or removing the lesions and a lack of reconstruction techniques and materials; (2) involvement of the hepatocaval confluence region, three hepatic veins (HVs), and the inferior vena cava (IVC) or invasion of the secondary or tertiary branches of the portal veins (PVs) and hepatic arteries, all of which required complex reconstruction with prolonged ischemic time that the liver could not tolerate; and (3) good physiologic condition with normal liver and kidney function and extrahepatic echinococcosis lesions that could be surgically removed or controlled by albendazole. Furthermore, the serum total bilirubin levels were less than twice the upper limit of the normal value, and the estimated remnant liver volume–to–standard liver volume (RLV/SLV) ratios were at least greater than 0.4.

All patients were divided into four types, based on the classification of vascular infiltration. Baseline data, imaging features, and the medical histories of all patients were collected (Table 1).

The vascular infiltration classification

Based on vascular infiltration and corresponding reconstruction procedures, a classification system was devised to describe the extent of lesion invasion (Fig. 1).

Degree of PV infiltration

P0 indicated no portal vein infiltration. P1 indicated infiltration of the ipsilateral first portal branch of the lesion. P2 indicated infiltration of the main portal vein trunk or the contralateral first portal branch. P3 indicated infiltration of the more distal contralateral second portal branches (segmental or sectoral branches). In addition, patients with severe cavernous transformation of the portal vein (CTPV) were also categorized as P3.

Degree of HV infiltration

H0 indicated no proximal infiltration of the HVs. H1 indicated no involvement of the hepatic outflow of the uninjured side of the liver. H2 indicated involvement of the hepatic outflow of the uninjured side of the liver.

Degree of IVC infiltration

I0 indicated no IVC infiltration. I1 indicated infiltration of the IVC below the hepatocaval confluence region, less than 3 cm longitudinally and less than 180° circumferentially. I2 indicated infiltration of the IVC below the confluence region of the HVs, 3 cm or more longitudinally and 180° or more circumferentially, or infiltration above the confluence region of the HVs but below the diaphragm. I3 indicated infiltration above the diaphragm and even extending to the right atrium.

Four types with distinguished lesion anatomic features were identified: type I ($n=13$) was characterized by the most severe invasion of the first porta hepatis with varying degrees of IVC and outflow tract violations (Figs. 2*A* and *B*), including P3H1I1, P3IH12. Type II ($n=4$) applied to cases in which the IVC was most seriously affected, especially by lesions that extensively violated the diaphragm or even the right atrium (Figs. 2*C* and *D*), including P1H2I3 and P2H2I3. Type III ($n=27$) applied to cases with multiple sites of vascular infiltration, but none of them were extremely infiltrated (Figs. 2*E* and *F*), including P2H1I2 and P2H2I2. Type IV ($n=6$), including P2H1I1 (Fig. 3), is the least invaded with the opportunity to be operated in vivo. Thus, this type could be regarded as a relative indication of ERAT.

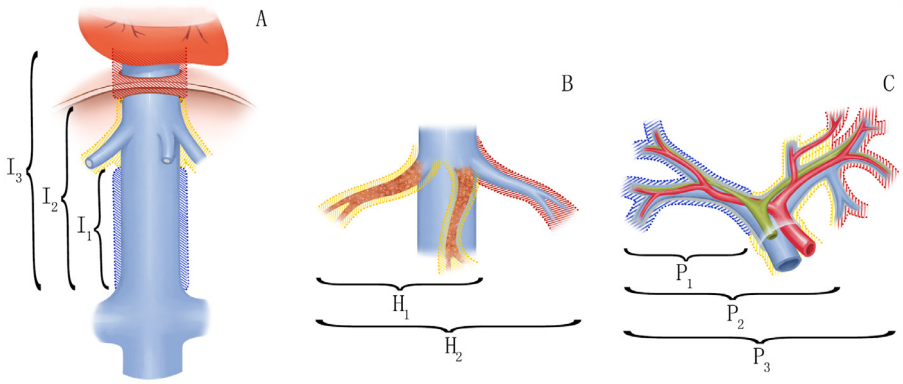

Fig. 1. Classification based on vascular infiltration (when the lesion is located in the right lobe). (*A*) Degrees of inferior vena cava (IVC) infiltration. (*B*) Degrees of hepatic vein (HV) infiltration. (*C*) degrees of portal vein (PV) infiltration.

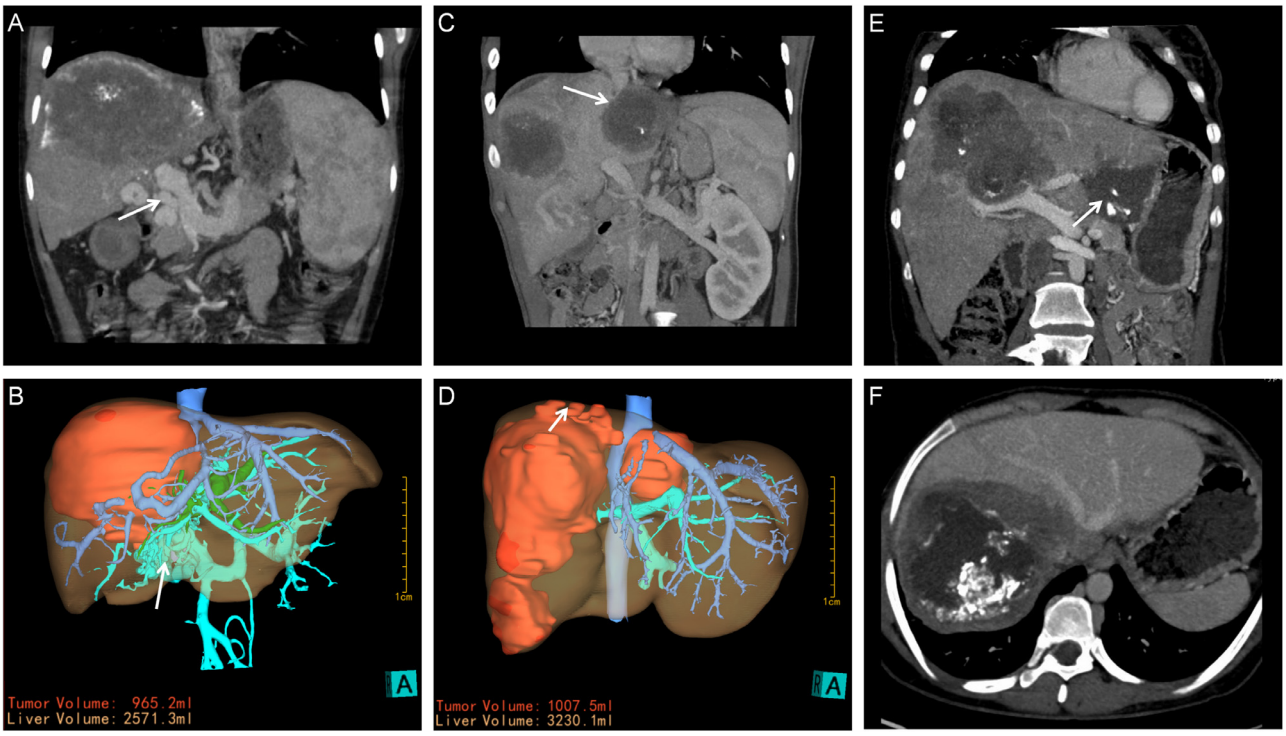

Fig. 2. Preoperative imaging assessments of types I, II, and III. (*A*) Preoperative computed tomography (CT) for a patient classified as P3H2I2, type I attributable to serious cavernous transformation of the portal vein (PV; *white arrow*). (*B*) Three-dimensional reconstruction for the same patient. The cavernous transformation of the PV (*white arrow*) and obvious biliary dilatation (*green vessel*) are presented. (*C*) Preoperative CT for a patient classified as P2H2I3, type II attributable to extensive effects on the diaphragm. The lesion (*white arrow*) had infiltrated above the diaphragm, thus warranting reconstruction of the inferior vena cava (IVC) with direct connection to the right atrium. (*D*) Three-dimensional reconstruction for the same patient. The lesion had widely infiltrated the diaphragm (*white arrow*). (*E, F*) Preoperative CT for a patient classified as P2H1I2, type III, which suggested that the left branch of the PV and the outflow of the uninjured side were intact. An extrahepatic lesion (*white arrow*) was confirmed to be cystic echinococcosis by postoperative histologic examination.

Preoperative assessment

All patients were evaluated using imaging, including magnetic resonance imaging (MRI), computed tomography (CT), and positron emission tomography-computed tomography (PET-CT), to assess the characteristics of the lesions and vascular infiltration and to evaluate whether evidence of extrahepatic metastasis was present. A three-dimensional (3-D) imaging analysis system (CAS; Qingdao Hisense Medical Equipment Co, Ltd, Qingdao, P. R. China)[21] was used to visualize the vascular and biliary tract anatomy and the spatial locations of large masses, conduct virtual resection for surgical planning, and calculate the projected RLV. The SLV was calculated following the experience of Urata et al. and Tongyoo et al.[22,23]

Ultrasonography (US) of the large vessels was performed to assess vascular flow and the presence or absence of "rich collateral circulation." US of the bilateral great saphenous vein (GSV) was performed to evaluate its diameter and length for reconstruction of the IVC. If patients had persistent obstructive jaundice and biliary dilatation before surgery, a radiograph or US-guided percutaneous transhepatic cholangial drainage (PTCD) was performed to alleviate the bilirubin level and biliary obstruction. Patients with cholestatic jaundice were eligible for ERAT if the total bilirubin (TBIL) level was less than twice the upper limit of normal.

Surgical procedure

The technical details of ERAT have been reported elsewhere.[19,20] The operation was divided into three main sections. First, exploratory surgery was performed with procurement of the liver

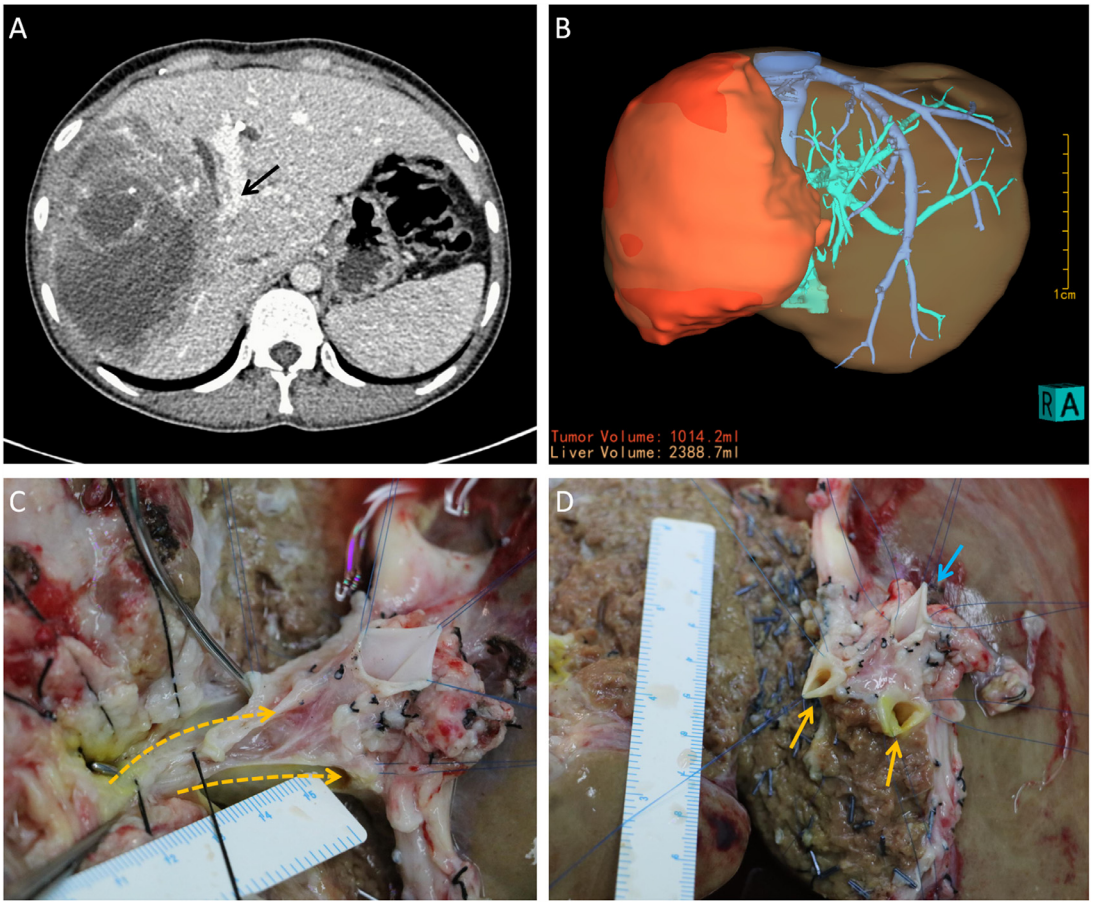

Fig. 3. Preoperative images and intraoperative findings for a patient classified as P2H1I1, type IV. (*A, B*) Preoperative computed tomography (CT) and 3-D reconstruction suggested that the infiltration was confined to the left portal vein (PV) trunk. The sagittal portion of the left portal vein (LPV) was intact (*black arrow*). (*C*) Dissection of the Glisson system of the left lateral lobe is presented. The lesion infiltrated along the left branch and invaded the side wall of the two bile ducts (BDs; *yellow arrow*), which was not detected by preoperative imaging assessment. (*D*) Completion of radical resection is presented. A stump of the PV (*blue arrow*) and two stumps of the BD remain.

graft. Next, a temporary IVC and portocaval shunt were established to maintain hemodynamic stability.

The second part of the operation involved ex vivo resection and repair of vessels. Critical conduit structures were carefully preserved for the subsequent reconstruction. After the lesion was radically removed, some vessel stumps required extra repair because of shortness in length, defects in the vessel wall, irregular shape of the orifice, or multiple stumps. The repair procedures included extending stumps with autologous vascular grafts, repairing vessel defects with patches, and unification of multiple stumps, which were vital for subsequent reconstruction procedures in vivo. An overview of the procedures of the ex vivo operation is presented in Fig. 4.

The third and final section of the operation included reimplantation of the autograft of the liver and reconstruction of the vessels. After the remnant liver was replaced in vivo, all crucial conduits were reconstructed following the order of the HVs (outflow), portal vein, hepatic artery, and bile duct. Reconstruction procedures requiring additional repair in the ex vivo procedures were defined as unconventional reconstructions. The patterns of conduit reconstruction are summarized in Table 2.

Postoperative management

The patients were admitted to a special ward for ERAT after the operation. Once postoperative bleeding was excluded, a low-molecular-weight heparin sodium injection (0.4 mL q 12 hours, with the individual dosage adjusted according to the weight of the patient, and the blood international normalized ratio [INR] was administered from the second day after surgery until discharge. All patients were given albendazole (15 mg/kg/d) routinely for 2 years after ERAT.[24] The patients returned for follow-up visits every 3 to 6 months after discharge and were examined by routine CT scan to detect possible recurrence and complications.

Statistical analysis

Patients' clinicopathologic characteristics and short-term surgical outcomes were compared among the four groups. Categorical variables were expressed as numbers and analyzed using the χ^2 test or the Fisher exact test. Continuous variables were expressed as the means (range) and were analyzed, using one-way analysis of variance (ANOVA). The Student-Newman-Keuls test was used when ANOVA results were significant, and the Kruskal-Wallis *H* rank test was used when necessary. All statistical analyses were two-tailed, and *P* values $< .05$ were regarded as statistically significant. All analyses were performed using SPSS v19.0 statistical software (IBM Corp, Armonk, NY, USA).

Results

A total of 50 patients successfully underwent ERAT, including 17 males and 33 females, with a median age of 35 years (range, 10-57 years), and no intraoperative deaths occurred. The preoperative parameters are summarized in Table 1.

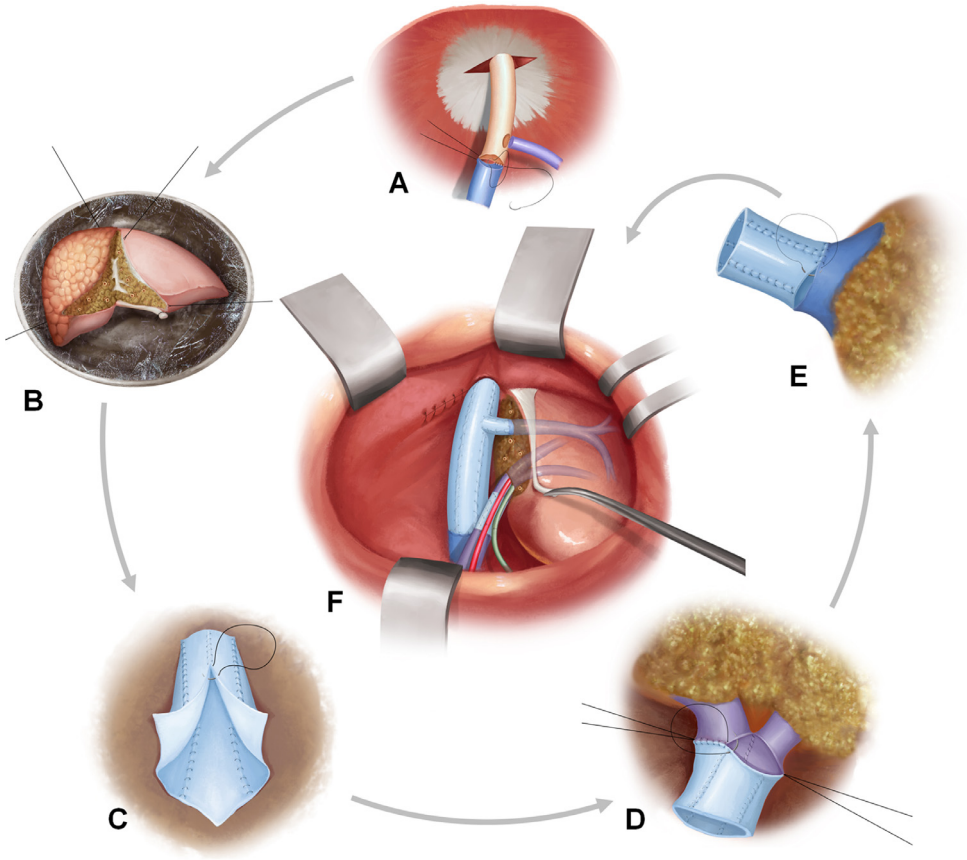

Fig. 4. A brief overview of the ex vivo procedures. (*A*) A temporary inferior vena cava (IVC; prosthetic graft) and portocaval shunt were established. Of note, the incision of the vena cava foramen allowed a direct connection of the temporary IVC to the right atrium. (*B*) Ex vivo liver resection conducted in an ice bath is presented. (*C*) The IVC was reconstructed using the autologous great saphenous vein (GSV). (*D*) Individualized repair of the portal vein is presented. In this particular case, two portal vein (PV) stumps were unified and then extended with a GSV segmental graft. (*E*) Individualized repair of the outflow is presented. In this particular case, the outflow was extended using a GSV segmental graft. (*F*) Reimplantation of the autograft is presented. The vasculature was reconstructed following the order of the hepatic veins, PV, hepatic artery, and bile duct.

Table 2
The vascular infiltration-based classification for guiding conduit reconstruction procedures.

Degrees of vasculature invasion	Possible reconstruction procedures
P1	PV and BD are reconstructed by end-to-end anastomosis.
P2	PV and BD occasionally warrant unconventional reconstruction.
P3	Unconventional reconstruction is required: PV is extended with segmental grafts or repaired with patch grafts before end-to-end anastomosis. Unification of multiple stumps might be required before hepaticojejunostomy or end-to-end anastomosis.
H1	HV is reconstructed by end-to-side anastomosis.
H2	Unconventional reconstruction is required: HV is extended with segmental grafts or repaired with patch grafts before end-to-end anastomosis.
The HV may be connected to the stump of the superior hepatic vena cava when the IVC is left unconstructed.	
I1	IVC is reconstructed by the uninvaded portion of the original autograft after appropriate repair.
I2	IVC is reconstructed by autologous graft assembled by great saphenous veins, or prosthetic graft.
I3	In addition to the pattern in I2, extensive resection and repair of diaphragm is frequently required. IVC may be directly connected to the right atrium.
The IVC may be left unreconstructed if the collateral circulation was competent.	

HV, hepatic vein; *PV*, portal vein; *BD*, bile duct; *IVC*, inferior vena cava.

In all patients, the length of the operation and the anhepatic phase were 735 minutes (range, 540-1,170 minutes) and 309 minutes (range, 122-480 minutes), respectively. The median RLV was 700 mL (range, 310-1,360 mL), and the corresponding median RLV-to-SLV ratio was 0.58 (range, 0.32-1.11). The rate of postoperative complications classified as Clavien-Dindo grade III or higher was 22% (11/50). The most frequent cause of postoperative morbidity was bile leakage, with an incidence of 18% (9/50). The intraoperative and postoperative parameters and postoperative complications are summarized in Tables 3 and 4, respectively.

Multiple repair procedures were required to facilitate the reconstruction of portal structures in type I patients, who required more frequent unconventional reconstruction of the portal vein (10/13, $P < .05$) and bile duct (BD) (9/11, $P < .05$) than the other patients. Moreover, these patients experienced bile leakage (6/11, $P < .05$) more frequently than the other patients, 3 of 6 patients with bile leakage had an extended drainage, 2 had endoscopic nasobiliary

Table 3
Intraoperative and postoperative parameters.

Variables	Type I ($n = 13$)	Type II ($n = 4$)	Type III ($n = 27$)	Type IV ($n = 6$)
RLV, mL, median (range)	700 (500–1,000)	885 (600–1,360)	700 (310–1,300)	550 (370–950)
RLV/SLV, median (range)	0.63 (0.40–0.94)	0.85 (0.50–1.11)	0.58 (0.35–1.07)	0.45 (0.32–0.77)
Operation time, h, median (range)	800 (563–1020)	720 (660–1170)	743 (580–1020)	645 (540–740)
Anhepatic time, min, median (range)	330 (122–428)	324 (249–455)	306 (180–480)	286 (220–460)
Combined resection, *n*, %	6 (46.2%)	4 (100%)	11 (40.7%)	1 (16.7%)
Autograft volume, g, median (range)	700 (500–1000)	885 (600–1360)	700 (310–1300)	550 (370–950)
Blood loss volume, mL, median (range)	2,500 (1,500–5,000)	3,000 (1,800–3,500)	2,050 (1,200–10,000)	1,500 (1,200–4,750)
Erythrocyte suspension requirement, U, median (range)	10 (0–31)	11 (2–39.5)	6 (0–20)	5 (0–7)
Fresh-frozen plasma requirement, mL, median (range)	1,100 (0–6,050)	825 (0–4,800)	810 (0–2,900)	425 (0–600)
ICU stay, d, median (range)	800 (563–1,020)	720 (660–1,170)	743 (580–1,020)	645 (540–740)
Postoperative hospital stay, d, median (range)	17 (7–41)	15 (4–21)	21 (8–56)	18 (12–31)
Unconventional reconstruction				
Outflow, *n*, %	5 (38.5%)	3 (75%)	12 (44.4%)	1 (16.7%)
Portal vein, *n*, %	10* (76.9%)	1 (25%)	12 (44.4%)	0
Bile duct, *n*, %	9* (69.2%)	2 (50%)	8 (29.6%)	1 (16.7%)

Table 4
Postoperative complications and Clavien-Dindo classification for the 50 patients.

Variables	Type I ($n = 13$)	Type II ($n = 4$)	Type III ($n = 27$)	Type IV ($n = 6$)
Postoperative complication				
None, *n*, %	4 (30.8)	3 (75)	18 (66.7)	4 (66.7)
Biliary leakage, *n*, %	6* (46.2)	0	2 (7.4)	1 (16.7)
Pulmonary infection, *n*, %	1 (7.7)	0	1 (3.7)	0
Pleural effusion, *n*, %	0	0	2 (7.4)	0
Hemorrhage, *n*, %	1 (7.7)	0	1 (3.7)	0
Mild stenosis of outflow, *n*, %	0	0	1 (3.7)	0
Clavien-Dindo Classification				
Grade I, *n*, %	1 (7.7)	0	1 (3.7)	0
Grade II, *n*, %	3 (23.1)	0	4 (14.8)	1 (16.7)
Grade IIIa, *n*, %	2 (15.4)	0	3 (11.1)	1 (16.7)
Grade IIIb, *n*, %	1 (7.7)	0	1 (3.7)	0
Grade IV, *n*, %	0	0	0	0
Grade V, *n*, %	2 (15.4)	1 (25)	0	0

* Type I VS the other patients ($P < .05$).

drainage and recovered before discharge, and only 1 received reoperation 16 months after ERAT to treat the biliary stenosis. In type II cases, combined resection of the diaphragm and a portion of the right atrium was required: IVC reconstruction can be extended above the diaphragm, and the IVC can be directly connected to the right atrium. In type III, the most common classification in the series (27/50), unconventional reconstruction procedures were occasionally required for reconstruction of the PV, HVs, and BD. Type IV was the least invaded among all types diagnosed in preoperative assessments and has the feasibility of being operated in vivo. Intraoperatively, however, infiltration is often discovered to be more extensive than initially determined in the preoperative assessment. Extensive infiltration was detected intraoperatively in 4 of the 6 type IV patients, and the surgical procedures were modified from the in vivo to the ex vivo approach.

Three postoperative deaths occurred. One patient died because of intra-abdominal bleeding originating from the intercostal arteries, and another patient died owing to acute cerebral hemorrhage. Only one patient, whose RLV-to-SLV ratio was 0.8 and who had no underlying liver disease, died because of liver dysfunction. Preoperative examination of this patient showed that the right renal vein was invaded and, thus, resection and reconstruction of the right renal vein were performed. During a median of 19 months (6-52 months) of follow-up, no recurrences were noted, and one patient was lost to follow-up.

Discussion

Recent studies have shown that the endemic area of *E. multilocularis* in Europe and central Asia is larger than previously reported and has regionally expanded from rural to urban areas.[24] The unexpected increase in AE may be related to both the increased fox population and infection transmission from dogs. In addition, the emergence of AE in patients receiving immunosuppressive therapy has contributed to its occurrence and rapid progression.[25] To accomplish radical resection of lesions, ERAT has been used for HAE treatment. Compared with LT, ERAT requires neither an organ donor nor any postoperative immunosuppressant and, therefore, exhibits greater potential for use in selected patients. Based on extensive experience with LDLT[14,15] and vascular reconstruction,[26] our center has pioneered ERAT in carefully selected end-stage HAE patients, and the preliminary results have reflected acceptable outcomes.[19,20] Nevertheless, the lack of consensus and guidance regarding the application of ERAT necessitates ongoing discussion and explicit clarification, especially regarding the indications and the arrangement of particular surgical procedures.

End-stage HAE, categorized as P4 by PNM staging,[7] is characterized by heterogeneous lesions that infiltrate crucial intrahepatic conduits, resulting in complex anatomic spatial relationships and complicating surgical planning. Given that HAE often occurs in patients with normal liver function, surgeons tend to perform complex and risky procedures to accomplish radical treatment under the condition that adequate RLV and the feasibility of reconstruction are certain. Therefore, obtaining the anatomic information of lesions and adjacent structures is key to successful surgery. In this study, by analyzing the characteristics of the lesions according to vasculature infiltration based on preoperative two-dimensional (2-D) CT images combined with 3-D reconstruction, we developed the vascular infiltration classification system to improve comprehension of the anatomy of lesions and the vasculature.

Table 5
Major literature (≥3 cases) overview for use of ERAT.

Year	Author	N	Diagnosis	Vascular infiltration	Classification*	Results
2016	Wen et al.[29]	15	Hepatic alveolar echinococcosis	Hepatocaval confluence, retrohepatic vena cava, portal vein	Type I, type III	One died of liver and renal failure in POD 12.
2013	Wen et al.[30]	3	Hepatocellular carcinoma	Hepatocaval confluence, portal vein	Type IV	All 3 patients were alive and survived for 28, 26, and 23 months, respectively. Two patients experienced tumor recurrence 8 months after the operation.
2012	Wang et al.[31]	4	Hepatic alveolar echinococcosis	Hepatocaval confluence, portal vein	Type I, type III	One died of multiple organ failure caused by portal vein thrombosis.
2012	Zhang et al.[32]	3	Hepatic hemangioma, cholangiocarcinoma	Hepatocaval confluence	Type III	One died of liver and renal failure in POD 3.
2011	Malde et al.[33]	6	Hepatocellular carcinoma, colorectal liver metastasis	Hepatocaval confluence, portal vein	Type III	One died in the hospital, the others survived for 5, 5, 76, 29, and 20 months, respectively.
2008	Hemming et al.[34]	4	Hepatic malignancy	Hepatocaval confluence	Type III, type IV	NA†
2000	Oldhafe et al.[35]	22	Metastases of colonic carcinoma, focal nodular hyperplasia	Hepatocaval confluence, portal vein	Type I, type III	Fifteen patients survived the postoperative period. The median survival time of 6 patients who had metastases of colonic carcinoma was 21 months. The 2 patients with benign liver disease are alive 9 and 5 years after ex situ surgery.
2000	Lodge et al.[36]	4	Colorectal metastases	Hepatocaval confluence, portal vein	Type III	One patient died in POD15 because of multiple organ failure, another patient died of renal cell carcinoma after 30 month.

* The classifications were determined according to the description of infiltration in the original reports.
† This report did not report the results of ex vivo resection separately.

In addition to describing anatomic information, the classification of vascular infiltration also facilitates the planning of reconstruction procedures. Patients categorized as H2, with invasion of the outflow of the residual liver, generally required additional repair procedures to facilitate outflow reconstruction because of excessive removal of the HVs during ex vivo radical resection. For P2 patients, unconventional reconstruction was occasionally required for the portal vein or bile duct under the condition that the infiltration detected intraoperatively was more extensive than initially determined preoperatively. In P3 patients, the most grievous situation of porta hepatis infiltration frequently warrants additional repair procedures because of the destruction of secondary or tertiary portal structures. Of note, the cavernous transformation of the portal vein, which is included in the P3 category, is a unique condition secondary to obstruction caused by a huge lesion. This particular manifestation substantially increased the complexity of hilar dissection and identification of the portal vein trunk, bile duct, and arteries. In brief, surgeons can determine the preliminary schedule of reconstruction by obtaining P, H, and I grades from preoperative images and finalize the schedule according to intraoperative findings.

In this study, ERAT resulted in acceptable outcomes; however, it is a challenging type of liver surgery. To ensure safety and effectiveness, we thoroughly discussed the indications for ERAT from the aspects of "operability, quantity, and quality." Generally, patients are eligible for ERAT under the following conditions: (1) the IVC, hepatocaval confluence, or portal structures are severely infiltrated and (2) uncontrollable hemorrhage is expected during resection, or the time required for complex reconstruction procedures is too long for the liver to tolerate. The purpose of forming types from the vascular infiltration classification is to concisely summarize the characteristics of cases and facilitate the discussion on the indication of ERAT. Type I is characterized by the most severe porta hepatis infiltration and requires additional repair procedures to reconstruct the PV and BD, which ultimately results in a surgical duration that is substantially longer than the liver can tolerate. Moreover, extensive infiltration of the PV precludes prolonged liver tolerance via in situ hypothermic perfusion. In type II, infiltration of the IVC extends above the diaphragm or even the left atrium. Therefore, the vena cava foramen must be dissected and expanded to expose the surgical area above the diaphragm, which is very difficult using conventional approaches (in situ) because of interference by the liver. Extensive resection and repair of the infiltrated diaphragm further increases the complexity of the operation. In type III, both the porta hepatis and RHVC are invaded, requiring excision and reconstruction of the PV, outflow, and IVC, the time for which obviously exceeds the tolerance of the liver. Type IV applies to the lowest extent of infiltration, according to preoperative assessment, compared with the other three types. Thus, these patients have the opportunity of an in vivo approach. However, more extensive infiltration is often found intraoperatively, and the surgical plans are converted to the ex vivo approach because of the discovery of more extensive perihepatic adhesions and more bleeding than expected preoperatively. Taken together, both necessity and operability characterized the selected patients of all four types presented in this study, and they therefore qualified for ERAT.

For the "quantity" of the liver in ERAT, the RLV-to-SLV ratio should be at least greater than 0.4.[27] According to our experience, four patients successfully underwent ERAT with an RLV-to-SLV ratio less than 0.4. One patient had an RLV-to-SLVof 0.32. Therefore, the RLV-to-SLV can be relaxed to 0.35 when a patient has normal liver function and no underlying liver disease. For the requirement of "quality," ex situ liver surgery should be avoided in patients with cholestasis because a high level of serum bilirubin or obstructive jaundice may critically impair the regenerative ability of the remnant liver.[28] Patients with obstructive jaundice in whom the serum total bilirubin level can be reduced to less than twice the upper limit of the normal value through PTCD are still eligible for ERAT. Compared with our other reports, the new indications reflect the anatomic information of lesions in more detail, according to the newly established classification system, which facilitates easier operability assessments.

Many studies have reported the application of ERAT for both malignant and benign hepatic pathologies (Table 5).[29–36] Most of these studies focused on the technical aspects of ERAT rather than on the indications for the procedure and did not include systematic descriptions of the lesions. The common feature of infiltrating extension in these reports was invasion of the hepatocaval confluence and IVC, which has traditionally been considered impossible to resect. Moreover, we want to emphasize the significance of invasion of the porta hepatis, which increases the necessity of adopting ERAT. Under the condition that lesions are confined to the hepatocaval confluence, in vivo approaches combined with hypothermic perfusion[37,38] or the ante situm technique[39,40] can also be applied. As summarized in Table 5, most ERAT procedures for malignant tumors resulted in unsatisfactory outcomes, especially because preventing recurrence was difficult. Therefore, we believe that the presence of benign hepatic tumors, such as alveolar echinococcosis, is the best indication for ERAT.

The present study had inevitable limitations. As a case series, the sample size of this study was relatively small, no control group was included, and the follow-up time was relatively short. In addition, information regarding various factors that may affect the short-term safety and long-term prognosis associated with ERAT was lacking. Complex hemodynamic changes during surgery, cold and warm ischemia of the liver graft, and their impacts on a patient's general condition also warrant more clinical or experimental exploration.

In conclusion, vascular infiltration-based classification could improve the anatomic comprehension, thus facilitating surgical planning for ERAT. Through cautious evaluation of operability, liver function, and residual liver volume, together with delicate operative techniques and careful postoperative management, ERAT can achieve good results in the treatment of end-stage HAE.

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