International Journal of Infectious Diseases 79 (2019) 87–93

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

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

Ex vivo liver resection and autotransplantation versus allotransplantation for end-stage hepatic alveolar echinococcosis

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ARTICLE INFO

Article history:
Received 25 October 2018
Received in revised form 7 November 2018
Accepted 20 November 2018
Corresponding Editor: Eskild Petersen, Aarhus, Denmark

Keywords:
Hepatic alveolar echinococcosis
Ex vivo
Resection
Autotransplantation
Allotransplantation
Immunosuppression

ABSTRACT

Objective: The aim of this study was to compare the clinical outcomes of ex vivo liver resection and autotransplantation (ERAT) with allotransplantation in patients with end-stage hepatic alveolar echinococcosis (HAE).
Methods: From January 2008 to October 2017, 41 of 254 patients with end-stage HAE fulfilled the inclusion criteria (ERAT group, $n = 35$; allotransplantation group, $n = 6$). Each group was assessed for indications and short- and long-term outcomes.
Results: The intraoperative mortality was zero in both groups. Two patients died after ERAT due to intra-abdominal bleeding and acute cerebral hemorrhage. The most frequent postoperative complications were biliary complications, which occurred in six patients (14.6%). Parasite recurrence was recorded in two patients, at 16 months and 52 months after allotransplantation. The survival curve showed a longer survival time in the ERAT group than in the allotransplantation group ($P = 0.028$). In the ERAT group, the 1-, 3-, and 5-year overall survival rates were all 100%. In the allotransplantation group, the 1-, 3-, and 5-year overall survival rates were 100%, 83.3%, and 66.7%, respectively.
Conclusions: This appears to be the first series comparing ERAT with allotransplantation for end-stage HAE. ERAT may be a superior alternative to allotransplantation in some cases, as it requires neither an organ donor nor immunosuppressive therapy.

Introduction

Hepatic alveolar echinococcosis (HAE) is a severe parasitic disease caused by intrahepatic growth of *Echinococcus multilocularis* larvae (Bresson-Hadni et al., 1998). The area endemic for alveolar echinococcosis (AE) is restricted to the Northern Hemisphere, including the central part of Western Europe, parts of the Near East, Russia, the Central Asian Republics, China, Northern Japan, and Alaska (Kern et al., 2017). Although AE is thought to be a benign disease, it is also called 'parasitic cancer' because of its tumor-like features with infiltrative growth (Kern, 2010). If patients are left untreated or are inadequately treated, the mortality rate within 10–15 years after diagnosis is >90% (Brunetti et al., 2010). For these reasons, the World Health Organization (WHO) has listed echinococcosis as a neglected tropical disease (Anon., 2011).

To date, radical surgery combined with antiparasitic drug treatment has been considered the first choice for the treatment of HAE (Brunetti et al., 2010). When the disease progresses to the advanced stage with extensive invasion of the extra- and intrahepatic vasculature, conventional radical resection becomes extremely hazardous because of the potential risk of uncontrollable hemorrhage and long ischemia time. Several unconventional methods have been used to address this complicated situation, including allotransplantation (Sulima et al., 2016) and ex vivo liver resection and autotransplantation (ERAT) (Yang et al., 2018).

Allotransplantation was introduced as an option for patients with unresectable HAE in 1986 (Chapuis et al., 1987). Nevertheless, there are inherent disadvantages of allotransplantation: recurrence of the disease associated with immunosuppressive therapy and the shortage of donors. Recently, other centers, including the present authors' center, have started to use the ERAT technique, in which the entire liver is removed, the parasitic lesions are resected ex vivo, and the remaining liver is returned to the patient (Yang

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https://doi.org/10.1016/j.ijid.2018.11.016

et al., 2018; Wen et al., 2016). In this manner, postoperative immunosuppressive drug treatment can be avoided. The ERAT technique can be used as a rescue modality for large occupying lesions with vascular infiltration. However, in the case of disseminated HAE, ERAT should be ruled out during preoperative assessment, as the remaining liver volume would be insufficient, and intrahepatic conduits may be severely damaged by AE lesions, thus making the consequent reconstruction impossible.

It appears that very few studies have investigated the surgical indications and outcomes of end-stage HAE patients treated by ERAT or allotransplantation. This study was performed to clarify these issues. The short- and long-term outcomes of end-stage HAE patients undergoing ERAT and allotransplantation were compared. Furthermore, the indications for each surgical procedure were also investigated.

Patients and methods

This study was approved by the Ethics Committee of West China Hospital of Sichuan University (No. 2017-38) and was performed in accordance with the Declaration of Helsinki.

Diagnostic criteria and definitions

The diagnosis of HAE was based on clinical findings and epidemiological data, imaging techniques, histopathology and/or nucleic acid detection, and serology (Brunetti et al., 2010). The PNM staging system (P = parasitic mass in the liver, N = involvement of neighboring organs, and M = distant metastasis) was used, which was developed by the WHO (Kern et al., 2006). Postoperative complications were graded according to the Clavien–Dindo classification (Dindo et al., 2004); a major complication was defined as grade III or higher. The cold ischemia time (CIT) was defined as the time from hypothermic perfusion to the reperfusion of the liver graft.

Cohort selection

From January 2008 to October 2017, a total of 254 consecutive HAE patients underwent operations at the West China Hospital of Sichuan University. Of these patients, 41 underwent ERAT or allotransplantation, and these patients comprised the study population. They were divided into two groups: the ERAT group ($n = 35$), consisting of patients who had undergone ERAT; the allotransplantation group ($n = 6$), consisting of two patients who had undergone living donor liver transplantation (LDLT) and four patients who had undergone allotransplantation from donation after cardiac death (DCD) donors. These patients were monitored until October 2018 or their death, and their medical records were analyzed retrospectively.

Preoperative management

Briefly, all patients underwent routine laboratory tests, cardiopulmonary function tests, and serological tests (ELISA, *E. multilocularis* antigens) before surgery. Percutaneous transhepatic cholangial drainage (PTCD) was performed for patients with obstructive jaundice. Preoperative computed tomography (CT) (Figure 1) or magnetic resonance imaging (MRI) was performed to assess lesion size, residual liver volume, infiltration of critical conduit structures, and whether there were metastases. Three-dimensional reconstruction software was used to calculate the residual liver volume and to concretize the anatomical location of the large lesions. Ultrasound of the bilateral great saphenous veins was performed for the candidate of retrohepatic vena cava (RHVC) reconstruction material. The treatment strategy was assessed by a multidisciplinary team including liver surgeons, a vascular surgeon, a physician, a radiologist, and an anesthetist.

Ex vivo liver resection and autotransplantation (Figure 2A, B)

Patients with the following features underwent ERAT: (1) two or more porta hepatis were invaded; (2) involvement of the RHVC was ≥50% of the circumference and ≥3 cm of the longitudinal diameter; (3) infiltration was above the diaphragm and/or extended to the right atrium; (4) the residual liver volume (RLV) was more than 35% of the standard liver volume (SLV); and (5) the total bilirubin value was no more than twice the upper limit of normal for patients with biliary obstruction. Details of the ERAT procedure have been reported previously (Yang et al., 2018).

An artificial vascular graft was applied to temporarily reconstruct the inferior vena cava (IVC), with an additional portal caval shunt for hemodynamic maintenance during the anhepatic time. Another main feature of ERAT was reconstruction of the vessels during the bench resection because of shortness in length, defects in the vessel

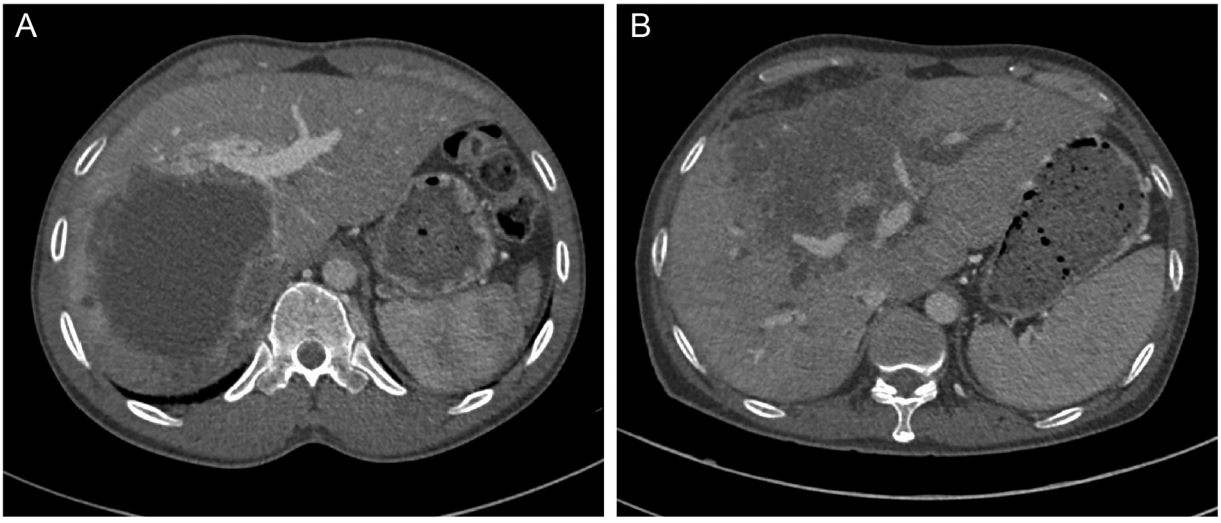

Figure 1. Preoperative assessment of operability. (A) CT scan of a patient underwent *ex vivo* liver resection and autotransplantation revealed a massive lesion invading porta hepatis and retrohepatic vena cava. (B) CT scan of a patient underwent allotransplantation revealed extensive invasion to portal structures, which led to the impracticality of vascular reconstruction.

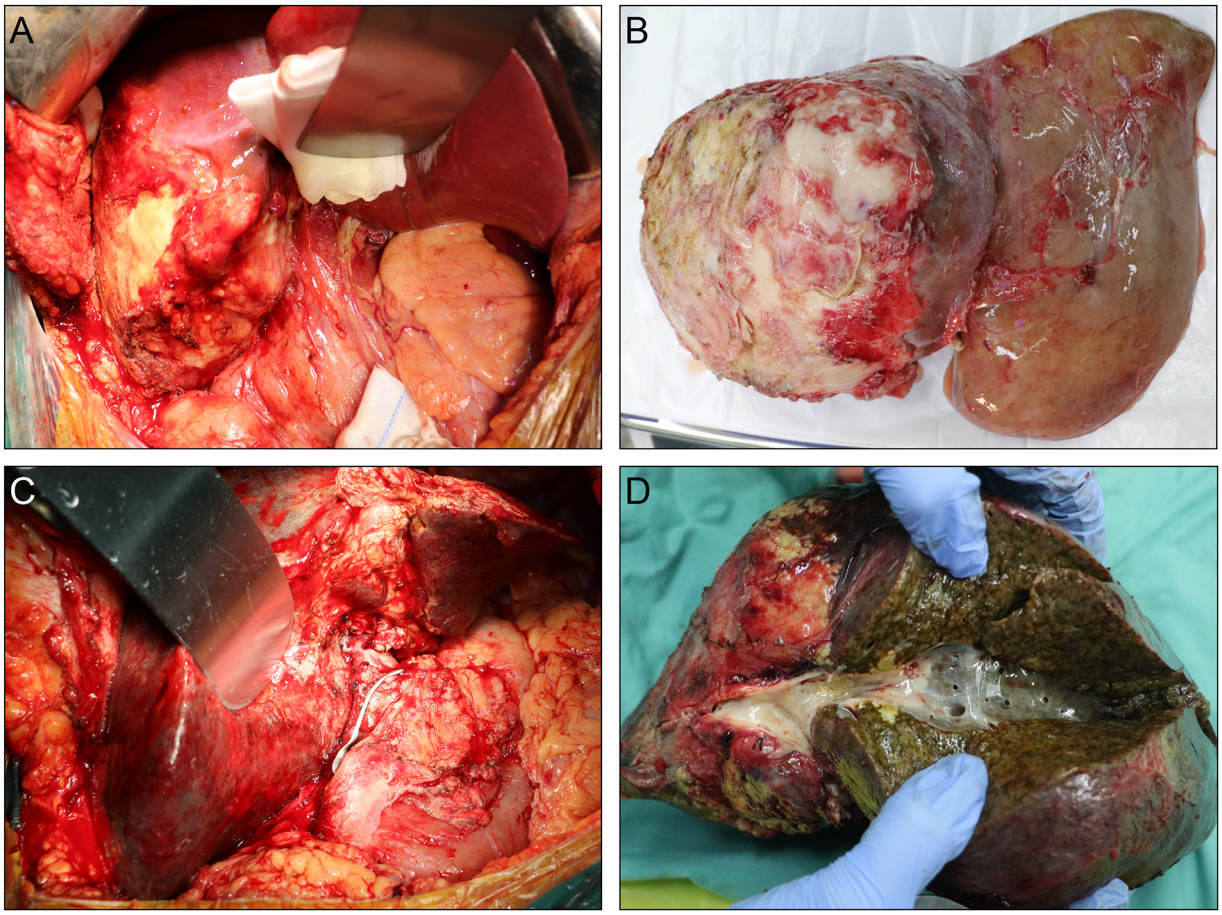

Figure 2. (A & B) From a patient underwent *ex vivo* liver resection and autotransplantation: (A) The intraoperative findings confirmed hilar invasion of alveolar echinococcosis (AE) lesion. (B) The AE-free left lobe was re-implanted after ex vivo resection. (C & D) From a patient underwent allotransplantation: (C) The intraoperative findings confirmed hilar invasion of AE lesion. (D) The AE-free lobe was damaged by sclerosing cholangitis secondary to biliary obstruction, and thus are abandoned.

wall, irregular shape of the orifice, or multiple stumps. The repair procedures included extending the stumps with autologous vascular grafts, repairing vessel defects with patches, and unification of multiple stumps, which were vital for subsequent reconstruction procedures in vivo. A minimum 1.0-cm lesion-free margin was guaranteed by repeated intraoperative frozen biopsy.

Allotransplantation (Figure 2C, D)

Allotransplantation was performed for patients with the following features: (1) lesions widely distributed in both lobes; (2) diffuse invasion of the hilar and intrahepatic conduit structures making ex vivo reconstruction impossible; (3) RLV less than 30% of the SLV; and (4) presence of end-stage liver disease, including secondary sclerosing cholangitis and cholestasis. Details of the procedure have been described in a previous report (Li et al., 2007). The right lobe was used as the donor graft in the two LDLT recipients.

All patients were administrated low-dose immunosuppressive agents including corticosteroids, mycophenolate mofetil, and tacrolimus/cyclosporine A. The immunosuppressive dose was reduced as early as possible, according to the graft function, parasite serology, and drug concentrations.

Follow-up and long-term management

All patients were administered albendazole (15 mg/kg/day) routinely for 2 years after surgery (Anon., 1996). Chemotherapy with albendazole was discontinued or replaced with alternatives if the patient experienced drug-induced liver injury.

Follow-up was routinely performed in the outpatient department. Physical examination, complete blood count, liver function tests, serological tests, ultrasound, and CT/MRI scans were performed every 3–6 months after discharge. Patients undergoing allotransplantation were followed up every 3 months. All follow-up information is available in the China Liver Transplantation Register (http://www.cltr.org/). AE recurrence was determined on the basis of radiographic evidence and/or serological tests.

Statistical analysis

The statistical software package IBM SPSS 22.0 (IBM Corp, Armonk, NY, USA) was used to analyze relevant data. Categorical variables were expressed as numbers and were compared using the Pearson Chi-square test or Fisher's exact test. Continuous variables were expressed as the median and range and were analyzed using the *t*-test or Mann–Whitney *U*-test. Survival rates were calculated using the Kaplan–Meier method and were compared between groups using the log-rank test. *p*-Values of <0.05 were considered significant.

Results

Patient characteristics

The baseline characteristics of the patients in both groups are summarized in Table 1. Of the 41 HAE patients undergoing ERAT or

Table 1
Clinical characteristics of patients in the ERAT and allotransplantation groups.[a]

Variable	Total ($n=41$)	ERAT ($n=35$)	Allotransplantation ($n=6$)	p-Value
Age, years	37 (17–57)	33 (17–57)	45 (38–48)	0.006
Sex, male/female	12/29	11/24	1/5	0.804
BMI, kg/m^2	21.8 (16.1–32.3)	21.8 (16.1–32.3)	21.2 (18.7–22.7)	0.523
Maximum lesion diameter, cm	15.6 (11.3–22.0)	15.9 (11.3–22.0)	14.1 (11.8–19.0)	0.122
Solitary lesion	31	27	4	0.970
Albendazole administration	23	21	2	0.441
Preoperative PTCD	12	9	3	0.470
Hepatectomy history	6	5	1	1.000
Child–Pugh classification, A/B/C	34/4/3	33/2/0	1/2/3	<0.001
PNM classification				
IIIb	11	9	2	1.000
IV	30	26	4	–
Associated extrahepatic procedure				
Choledechojejunostomy	16	15	1	0.446
Diaphragm resection	19	16	3	1.000
Adrenalectomy	7	5	2	0.576
Nephrectomy	1	1	0	1.000
Lung lobectomy	3	2	1	0.386
Splenectomy	3	3	0	1.000
Cardiac sac resection	1	1	0	1.000
Intraoperative blood loss, ml	2000 (1000–6000)	1800 (1200–6000)	2000 (1000–2500)	0.504
Red blood cell units transfused	8.0 (0–39.5)	7 (0–39.5)	8.8 (4–14)	0.493
Fresh-frozen plasma transfused, ml	750 (0–6050)	800 (0–6050)	550 (0–1450)	0.481
Cold ischemia time, min	310 (100–730)	309 (180–480)	390 (100–730)	0.438
Anhepatic time, min	304 (42–480)	309 (180–480)	62 (42–75)	<0.001
Operation time, min	720 (240–1170)	750 (563–1170)	405 (240–500)	<0.001

Abbreviations: BMI, body mass index; ERAT, ex vivo liver resection and autotransplantation; PTCD, percutaneous transhepatic cholangial drainage.
[a] Values given are the median (range), or number of patients.

allotransplantation, 29 (70.7%) were female. The median age of the patients was 37 years (range 17–57 years). The PNM stages of the whole cohort were as follows: stage IIIb, $n=11$; stage IV, $n=34$. Twelve (29.3%) patients underwent preoperative PTCD to reduce bilirubin levels and biliary obstructions. One patient in the ERAT group refused PTCD, although she had a total bilirubin level of 174.7 μmol/l. She ultimately underwent ERAT because the duration of the cholestatic jaundice was less than 1 week and the estimated RLV/SLV was 82.9%. One patient in the allotransplantation group and five patients in the ERAT group had a history of previous hepatectomy. Albendazole therapy was administered to 23 (56.1%) patients.

The most common indications for ERAT in this series were two or more porta hepatis invaded and the involvement of the vena cava. Seven patients had severe porta hepatis invasion and secondary portal cavernoma, and two had severe vena cava invasion, extending to the right atrium. In the allotransplantation group, the most common indications were advanced HAE with chronic liver disease: three had secondary sclerosing cholangitis with liver function of Child–Pugh C classification; two had disseminated HAE with intrahepatic conduits severely damaged, thus making consequent reconstruction impossible; and one had hepatic congestion with Budd–Chiari syndrome and portal hypertension.

Operative characteristics

None of the patients in either group underwent extracorporeal shunt. In the ERAT group, the median weight of the graft was 630 (360–1300) g and of the AE lesions was 1722 (1010–4200) g. The RLV/SLV ratio ranged from 32% to 117%, with a median of 61%. The median operative time was 750 (563–1170) min and the median CIT was 309 (180–480) min. The anhepatic time was approximately equal to the CIT in the ERAT group, which was significantly longer than that in the allotransplantation group ($P<0.001$). The median intraoperative blood loss was 1800 (1200–6000) ml. The median transfusion volume of packed red blood cells was 7 (0–39.5) units. Associated extrahepatic procedures were performed to achieve radical resection, including choledechojejunostomy ($n=15$), diaphragm resection ($n=16$), adrenalectomy ($n=5$), nephrectomy ($n=1$), lung lobectomy ($n=2$), splenectomy ($n=3$), and cardiac sac resection ($n=1$). The IVC was reconstructed with an artificial vascular graft ($n=9$), with allograft vessels ($n=2$), or with autologous vessels ($n=23$). Two patients with completely occluded IVCs did not require IVC reconstruction.

In the allotransplantation group, the median weight of explanted liver was 2150 (1490–2806) g. The median operative time was 405 (240–500) min and the median CIT was 390 (100–730) min. The anhepatic time was 62 (42–75) min. The median amount of intraoperative blood loss was 2000 (1000–2500) ml and the median transfusion of red blood cells was 8.8 (4–14) units. Associated extrahepatic procedures included diaphragm resection ($n=3$) and adrenalectomy ($n=2$).

Postoperative and follow-up results

The short-term outcomes of the patients in both groups are summarized in Table 2. The intraoperative mortality was zero. There were no differences between the patients in the two groups with respect to postoperative intensive care unit (ICU) stay ($P=0.436$) or hospital stay ($P=0.276$). The most frequent postoperative complications were biliary complications, which occurred in six (14.6%) patients, five patients in the ERAT group and one in the allotransplantation group. Two patients in the ERAT group underwent endoscopic nasobiliary drainage. One patient in the allotransplantation group underwent re-laparotomy and the remaining three patients retained the drainage tube for continued drainage. Twelve (29.3%) patients suffered major complications during the perioperative period. Two patients in the ERAT group underwent re-laparotomy because the jejunojejunostomy revealed hemorrhaging through hematochezia. One patient underwent re-laparotomy because of arterial thrombosis and bile leakage 3 days after DCD allotransplantation. Two patients died after ERAT due to intra-abdominal bleeding originating from the intercostal arteries and acute cerebral hemorrhage.

Table 2
Short-term outcomes of patients in the ERAT and allotransplantation groups.[a]

Variable	Total (n = 41)	ERAT (n = 35)	Allotransplantation (n = 6)	p-Value
Duration of postoperative ICU stay, days	5 (2–15)	4 (2–15)	5 (2–9)	0.436
Duration of postoperative hospital stay, days	19 (4–56)	20 (4–56)	17 (13–20)	0.276
Postoperative complications				
Postoperative bleeding	4	4	0	1.000
Pleural effusion	4	3	1	0.483
Pulmonary infection	4	2	2	0.095
Acute rejection	1	0	1	0.146
Biliary complication	6	5	1	1.000
Vascular complication	5	3	2	0.148
Clavien–Dindo classification				
Grade I/II	8	6	2	0.714
Grade III/IV	10	8	2	0.970
Grade V	2	2	0	1.000

Abbreviations: ERAT, ex vivo liver resection and autotransplantation; ICU, intensive care unit.
[a] Values given are the median (range), or number of patients.

Postoperative pathology showed Echinococcus in all patients. Three patients in the allotransplantation group had secondary biliary cirrhosis, while in the ERAT group, no patient had secondary biliary cirrhosis, but fibrosis was detected in all patients.

With the exception of the patients who died during the perioperative period and the one patient lost to follow-up in the ERAT group, the remaining 38 patients attended long-term follow-up. The median follow-up for the ERAT group patients was 22 (12–55) months, whereas it was 16 (12–120) months for the allotransplantation group patients. During the follow-up period, two patients in the ERAT group developed ascites because of venous outflow stenosis during postoperative months 8 and 12. They were treated with hepatic vein balloon replacement. Two patients underwent biliary reconstruction in the form of hepaticojejunostomy due to biliary stenosis 6 months after LDLT and 16 months after ERAT, respectively.

Two patients died after allotransplantation because of parasite recurrence, while there was no parasite recurrence after ERAT. One patient died due to brain and lung metastases 16 months after DCD allotransplantation. The other patient died due to liver allograft reinfection at 52 months after LDLT. The local recurrence, distant metastasis, and mortality rates in the allotransplantation group were 16.7%, 16.7%, and 33.3%, respectively. The survival curve (Figure 3) showed a longer survival time in the ERAT group than in the allotransplantation group (P = 0.028). In the ERAT group, the 1-, 3-, and 5-year overall survival rates were all 100%. In the allotransplantation group, the 1-, 3-, and 5-year overall survival rates were 100%, 83.3%, and 66.7%, respectively.

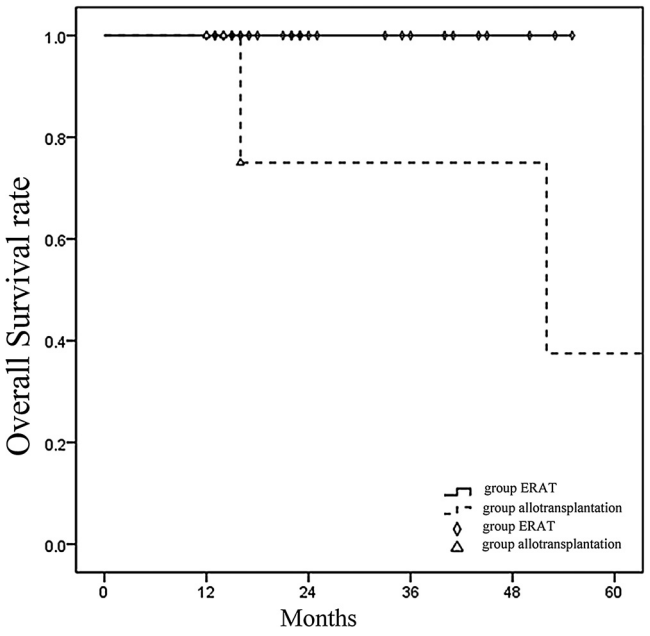

Figure 3. Postoperative survival analysis curve for end-stage HAE patients after ERAT and allotransplantation.

Discussion

HAE is a neglected but deadly parasitic zoonosis, especially in rural China on the Tibetan plateau (Deplazes et al., 2017). Due to the insidious onset and slow progression of AE lesions, many patients are not diagnosed until the very end stages, when the lesions cannot be resected completely by conventional hepatectomy. This may explain why about 20% of HAE patients treated at the West China Hospital of Sichuan University were judged to be beyond resectability. Currently, allotransplantation, ERAT, and palliative albendazole with or without interventional procedures are considered for treatment of the advanced disease (Vuitton et al., 2016). Although long-term albendazole administration appears safest, the outcome is poor, with a 5-year survival of 9.1% (Qu et al., 2017). Unlike cystic echinococcosis, drug therapy has a parasitostatic rather than a parasiticidal effect, with an overall success rate of 55–97% (Reuter et al., 2000). Mandatory life-long treatment with albendazole is costly and carries the risk of potential side-effects in a subgroup of patients (Chauchet et al., 2014). Therefore, the optimal treatment for end-stage disease may be surgical removal of the AE lesions with 2-year postoperative albendazole administration (Bresson-Hadni et al., 2000). The present study was designed to evaluate the indications and short- and long-term outcomes of advanced HAE patients treated by ERAT and allotransplantation.

Prior to the application of ERAT for the treatment of end-stage HAE that was deemed to be untreatable by conventional hepatectomy, allotransplantation provided the only opportunity for radical cure. Since Wen et al. (2011) reported an end-stage HAE patient treated with ERAT, some centers, including the West China Hospital of Sichuan University, have started to use this technique. When both ERAT and allotransplantation are feasible, ERAT should be the first choice, as it requires neither an organ donor nor immunosuppressive therapy. As a result, patients undergoing allotransplantation have decreased dramatically in recent years, as confirmed in the series presented here.

Generally, patients are eligible for ERAT under the following conditions: (1) the IVC, hepatocaval confluence, and/or portal structures are severely infiltrated; (2) uncontrollable hemorrhage is expected during resection or the time required for complex

reconstruction procedures is too long for the liver to tolerate; (3) the RLV/SLV is more than 35% in a patient with normal liver function and no underlying liver disease; and (4) the total bilirubin value is no more than twice the upper limit of normal for patients with obstructive jaundice. To ensure safety and effectiveness, precise indications and meticulous preoperative assessment of the size and quality of the remaining liver are essential. Nevertheless, ERAT should be ruled out during the preoperative assessment if the remaining liver volume would be insufficient; liver function is impaired, as expressed by secondary sclerosing cholangitis, obstructive jaundice, and portal hypertension; and intrahepatic conduits are severely damaged by the AE lesions, thus making consequent reconstruction impossible. Indeed, allotransplantation remains the last resort for the treatment of end-stage HAE.

In this study, ERAT resulted in acceptable outcomes, although it is a more aggressive surgical procedure with a longer operative time and more complicated conduit reconstruction. The in-hospital mortality rates reported in previous ERAT series are about 30% (Hemming et al., 2013; Oldhafer et al., 2000), much higher than that calculated in the present study. The median RLV/SLV ratio in the ERAT group was 61%, much higher than the threshold of 35%. During the slow progression of AE, the lesions gradually compress one of the portal branches, leading to increased blood inflow and hypertrophy of the residual liver. This process could be considered a natural portal vein embolization. Nine patients in the ERAT group underwent PTCD for preoperative biliary obstruction, but none exhibited biliary cirrhosis according to pathological examination. Another major challenge for ERAT is intrahepatic conduit reconstruction. Based on the authors' experience of 364 cases of LDLT and extensive practice with vascular reconstruction (Zhang et al., 2017), the postoperative biliary and vascular complications in the ERAT group were acceptable, at 14.3% and 8.6%, respectively. During the follow-up period, two patients developed ascites because of venous outflow stenosis at 8 and 12 months after ERAT, respectively. One patient developed biliary stenosis and underwent reoperation 16 months after ERAT. Therefore, patients undergoing ERAT need to be closely monitored in the late period.

Another issue limiting the promotion of allotransplantation for advanced HAE is parasite recurrence, which is mainly seen in the grafted liver, brain, lung, and spleen (Koch et al., 2003; Ozdemir et al., 2015). Furthermore, the emergence of AE in patients with immunosuppressive therapy has contributed to AE occurrence and rapid progression (Chauchet et al., 2014; Vuitton et al., 2015). To prevent recurrence after allotransplantation, the immunosuppressive treatment was reduced as early as possible. Based on the WHO recommendation, allotransplantation should not be performed for patients with metastases (Brunetti et al., 2010). We therefore detected the possibility of metastasis for all patients, but identified no distant metastasis in the allotransplantation group before surgery. On the other hand, albendazole chemotherapy was implemented for at least 2 years after surgery. The side-effects of albendazole in allotransplantation recipients were closely monitored by physicians. However, two patients in this series suffered AE recurrence at 16 and 52 months after allotransplantation. Koch et al. reported that six out of 36 patients had a graft reinfection, and five late deaths were related directly to ongoing AE (Koch et al., 2003). The 5-year survival rate was 71% and the 5-year survival rate without recurrence was 58% in that former study. In comparison to the patients in the former study and the allotransplantation patients in the present study, the results in the ERAT group of patients showed a better survival rate with no AE recurrence despite the short follow-up time.

This study had inevitable limitations. First, it was a retrospective, single-center experience, with a small sample size (only six patients in the allotransplantation group) and a relatively long time span. Second, data regarding various factors that may affect the short-term safety and long-term prognosis associated with ERAT and allotransplantation were lacking; e.g. complex hemodynamic changes during surgery, cold and warm ischemia of the liver grafts, and their impacts on a patient's general condition. Further prospective controlled studies are needed.

In conclusion, surgical intervention for end-stage HAE is effective and feasible, given the severity of the disease. ERAT may be a superior alternative to allotransplantation in some cases, as it requires neither an organ donor nor immunosuppressive therapy. Patient selection and preoperative assessment for size and quality of the remaining liver should be strictly conducted. Patients who have undergone allotransplantation need to be closely monitored for AE recurrence.

Acknowledgement

The authors thank Fang Liu for help collecting the follow-up data.

Funding

This study was supported by grants from the National Natural Science Foundation of China (No. 81770566) and the New Medical Technology Foundation of West China Hospital of Sichuan University (XJS2016004).

Ethics statement

This study was approved by the Ethics Committee of West China Hospital of Sichuan University (No. 2017-38) and was performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from all subjects and/or their legal guardians. All methods used in this study were performed in accordance with the approved guidelines.

Conflict of interest

The authors declare that the work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author contributions

WTW designed the research and approved the submitted manuscript. SS and JJK drafted the manuscript. YWQ and SLZ collected the data. SS and YQ analyzed the data. All authors read and approved the final manuscript.

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