



Current status of *ex-vivo* liver resection and autologous liver transplantation for end-stage hepatic alveolar echinococcosis

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Abstract: Hepatic alveolar echinococcosis (HAE) is a cosmopolitan zoonosis distributed widely in the northern hemisphere with high estimated 10-year mortality. Radical resection combined with oral albendazole administration are the major methods for HAE treatment, whereas most patients delayed diagnosis and treatment because which was considered as benign disease. For the cases with end-stage HAE could not be treated through conventional hepatectomy, allograft liver transplantation (LT) was regarded as a life-saving technique previously. However, graft shortage, high recurrence rate and long-term immunosuppressive therapy limited its utilization. Since the *ex-vivo* liver resection and autotransplantation (ERAT) procedure was first used in treating for end-stage HAE in 2011, there are more than 120 HAE cases patients were reported treating in this method up to now. Comparing with LT, ERAT needs neither an organ donor nor long term immunosuppressive therapy, and provide preferable overall survival rates. Based on the conventional ERAT procedure, some modification such as auxiliary partial autologous LT were introduced in the high selected end-stage HAE patients presently. However, the standard procedures for ERAT including surgical details and perioperative management have not been established because of limited reported cases. Also, the present ERAT experience for end-stage HAE treatment are all summarized by the Chinese surgeon groups. For summarizing the knowledge and experience details, we reviewed present opinions about ERAT for end-stage HAE patients, and presented the future perspectives about this topic in this manuscript. We aimed at discussing the feasibility, indications, preparation, technical details, and postoperative outcomes of ERAT for HAE patients.

Keywords: *Ex-vivo* liver resection and autotransplantation (ERAT); hepatic alveolar echinococcosis (HAE); liver transplantation (LT); vascular reconstruction

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Introduction

Alveolar echinococcosis (AE) is a cosmopolitan zoonosis caused by *Echinococcus multilocularis* (1). Hepatic AE (HAE), the main type of AE disease, have a distribution in the northern hemisphere, especially in China, the Russian Federation, continental Europe countries and North

America such as Alaska (2). The untreated HAE patients were estimated have a 10-year mortality rate of 94% (3). Up to now, radical resection combined with oral albendazole are the major methods for HAE treatment (4). However, only 35% of patients are eligible for conventional hepatectomy because of delaying diagnosis and HAE being considered as benign disease (5,6).

As “parasitic cancer”, the AE lesions’ infiltrative growth may involve multi intra-hepatic ducts including biliary ducts, hepatic veins (HVs) or portal vein (PV) branches, which caused difficulty for conventional resection. For the end-stage HAE cases, multiple methods have been applied to cope with this disease which could not be conventionally resected. However, palliative surgery, including lesion reduction surgery or cholangial drainage, has been proved not beneficial for long-term survival (7-9). Allograft liver transplantation (LT) was considered as a life-saving technique for “unresectable” cases previously (10,11), whereas the graft shortage, high recurrence rate and long-term immunosuppressive therapy limited the utilization in end-stage HAE (12-15). Also, HAE patients could not obtain a high enough score to be prior on the transplant list in US (16).

Based on the technique and experience in liver donor LT (LDLT), Wen *et al.* reported the first case showing that *ex-vivo* liver resection and autotransplantation (ERAT) was effective for end-stage HAE patient in 2011 (17). Comparing with allograft LT, ERAT requires neither an organ donor nor long term immunosuppressive therapy, and preferable overall survival rates (18). Up to now, more than 120 end-stage HAE cases have been treated by ERAT approach with ideal effect (19-21). Also, the application of artificial intelligence technique and new preserved solution study were also introduced into this area (22,23). However, the standard procedures of ERAT for end-stage HAE have not been established because of limited reported cases.

Herein, we review the details and discuss the most recent advances of ERAT in the treatment of patients with end-stage HAE, and aim at revealing the future direction of ERAT for this disease.

Ex-vivo liver resection and autotransplantation

ERAT approach was initially used in the advanced hepatic malignant tumors were deemed untreatable conventionally (24). For selected cases with main vascular structures were invaded, ERAT approach is opportunity for radical resection and long disease-free survival (25,26). However, the outcome of ERAT technique for end-stage hepatic carcinoma is depressing because high incidence of unmanageable complications and postoperative recurrence (27-29). This reason is malignant tumor patients conventionally complicated with hypohepatia including cirrhosis and HBV or HCV infections, which may lead to more complication after this giant surgery. Also, the tumor staging is often too late in the selected cases for

ERAT approach, which may lead to rapid recurrence even the surgery completed. Then, this poor prognosis limited the application of ERAT for end-stage hepatic malignant tumors.

In contrast to malignant tumor, HAE is a relatively benign disease though it’s tumor-like infiltrative growth, and the HAE patients combined with no hepatic hypohepatia conventionally. Also, the HAE lesions growth notable slowly compared with malignant tumor. This characteristic prompt the effect of ERAT technique in end-stage HAE is prior to it’s in malignant hepatic tumors theoretically. To date, there are more than 120 end-stage HAE cases were treated using the ERAT approach (Table 1), and all the reported cases were initiated by Chinese surgeon group where bears 90% of the global burden of this disease.

Candidate

Because of the limited cases, there is no established guideline for ERAT in end-stage HAE patients. Generally, the selected cases for ERAT approach should be the HAE lesions could not be resected conventionally. As the infiltrative growth characteristics, the HAE lesions invaded intra-HVs needing long term for reconstruction. Also, the ERAT procedure should be considered if the giant lesions occupied the space for HVs reconstruction *in situ*. It should be indicated ERAT should be avoided if the patients with multi-organ AE which nether be removed nor controlled by albendazole administration.

The HAE lesion’s “unresectable” using traditional techniques for end-stage HAE including: (I) the hepatocaval region including three HVs were invaded; (II) the retrohepatic vena cava (RHVC) was invaded; (III) the tertiary branches of the PV and portal arteries were invaded needing long time for reconstruction that ischemic time the liver couldn’t tolerate (17,19-21,33). Once the invaded intra- or extra-duct reconstruction could not complete *in situ*, an ERAT approach should be taken into account for radical HAE resection.

Based on the newly published expert consensus on diagnosis and treatment of HAE from China (35), the indications for ERAT included: (I) two or more hilars structure were invaded; (II) the invaded RHVC is more than 3 cm in length, or more than 180° in circumference; (III) the invaded length of RHVC is less than 3 cm, but infiltration above the confluence region of the HVs and below the diaphragm; (IV) obstructive jaundice, or severe first hilars invaded; (V) the ratio of RLV/body weight is

Table 1 Indications and results of ERAT for end-stage HAE from 2011–2020 in PubMed

Year	Authors	N	Indication for ERAT	Follow-up (months), mean [range]	Results
2020	Zhang <i>et al.</i> (30,31)	2	“Unresectability” with conventional hepatic surgery	–	Alived
2020	Aini <i>et al.</i> (32)	1	Auxiliary partial autologous LT: (I) extensive hepatocaval involvement along with three HVs, and (II) RHVC involvement	–	Alived
2018	Aji <i>et al.</i> (19)	69	with or without tertiary vascular branches involvement	22.5 [14–89]	8 patients died
2018	Yang <i>et al.</i> (20)	31	(I) “Unresectable” with traditional techniques, difficulty exposing or removing the lesions, lack of reconstruction techniques and materials; (II) involvement of the hepatocaval region, HVs, RHVC or the PV branches, and PA requiring a complex reconstruction; (III) extra-HAE lesions could be resected or controlled by albendazole	14 [3–42]	2 patients died
2016	Wen <i>et al.</i> (33)	15	(I) “Unresectability” with conventional hepatic surgery; (II) the hepatocaval region, HV, and the RHVC were involved; PV branches and PA were invaded; (III) requiring long ischemic time for complex reconstruction that the liver cannot tolerate	21.6 [N/A]	1 patient died
2015	Lei <i>et al.</i> (21)	1	Involving of the right/middle HV, obstructive jaundice	12 [–]	Alived
2012	Wang <i>et al.</i> (34)	6	(I) End-stage HAE, the lesion was confined to half of the liver; (II) involvement of the IVC	N/A [18–30]	1 patient died
2011	Wen <i>et al.</i> (17)	1	RHVC was obstructed, obstructive jaundice	2 [–]	Alived

ERAT, *ex-vivo* liver resection and autotransplantation; HAE, hepatic alveolar echinococcosis; LT, liver transplantation; RHVC, retrohepatic vena cava; RHIVC, retrohepatic inferior vena cava; PV, portal vein; PA, portal arteries; HV, hepatic veins; IVC, inferior vena cava; N/A, data not available or cannot be counted.

more than 0.75%.

At present, there are some end-stage HAE to be initiated ERAT approach previously could also be radical resected *in situ* with the development of surgical technology. Qiu *et al.* indicated type IV end-stage HAE patients with the opportunity to be operated *in vivo* based on “IHP” vascular infiltrated degree classification (36). For some cases, ante-situm liver resection with inferior vena cava (IVC) replacement procedure replaced ERAT procedure for radical resection for some special location (28,37). And, the continuous pringle maneuver and *in situ* hypothermic perfusion through the inferior mesenteric vein (IMV) may resect the lesion *in vivo*, rather than removing the entire liver for lesion resection *in vitro* (38).

Preoperative management

Abdominal enhanced computed tomography (CT) and liver magnetic resonance imaging (MRI) is significant for surgical design and lesion volume/future liver remnant (FLR) calculation. Recent years, the application of three-dimensional (3D) imaging analysis system is feasible to

develop a reasonable scheme for liver resection and vascular anastomosis for end-stage HAE, which could effectively improve the success rate of liver ERAT and reduce the risks of surgery (39). Doppler ultrasound was needed to examine the greater saphenous veins’ (GSV) length for potential vascular substitutes, and the digital subtraction angiography (DSA) was also needed to confirm the existence of tangible collateral circulation when total obliteration of RHVC was indicated by imaging studies (19).

The remnant liver volume (RLV) is a significant index for postoperative liver failure in ERAT (40). Based on the experience in LDLT, more than 40% of RLV/standard liver volume (SLV) is critical for the patients’ prognosis (41). However, this index should be extended because there is no cirrhosis for HAE patients commonly. It is also accepted a minimum threshold of 25–30% of the SLV is enough for the functional demand during major resection (42,43). Shen *et al.* revealed the ratio of RLV/SLV below 40% is safe for the end-stage HAE patients undergoing ERAT (44). Gruttadauria *et al.* indicated postoperative liver failure after hepatic resection for patients is highly occurred when the RLV less than 30% (45). Based on this

index (RLV =30%), Shen *et al.* made the surgical plan as whether resect the lesions in one stage or not for multiple giant HAE patients (46). Based on the author's experience, the RLV should be more than 30% for "health" liver before ERAT. If there is HBV or HCV infection, the index should be extended.

As the long germ growing period, the massive lesion may involve the blood supply (PV and/or HA branch) of the resection side, the procedure of hypertrophy for the contralateral hepatic parenchyma is similar to the effect of PV embolization (PVE) or partial associating liver partition and PV ligation for staged hepatectomy (ALPPS) (47,48). Additionally, the HAE patients did not combine with hepatic disease commonly, which enables adequate compensatory function of the disease-free lobe. If the volume of disease-free lobe is still small, the PVE procedure could also be considered aiming to increase the RLV and prevent postoperative hepatic failure (49). Recently, the ALPPS approach were also used in the radical resection for end-stage HAE patients with low RLV when PVE is unsuitable (50).

Some end-stage HAE patients combined with bile duct infiltrated causing obstructive jaundice. Obstructive jaundice or high level of serum bilirubin may critically impair the regenerative ability of the remnant liver (51), a routinely biliary drainage [percutaneous transhepatic cholangio drainage (PTCD) or endoscopic nasobiliary drainage (ENBD)] is needed to alleviate the high bilirubin index and biliary obstruction for an ideal Child-Pugh grade for ERAT. Yang *et al.* indicated the serum total bilirubin index should less than twice the upper limit of normal value before ERAT (20).

Obviously, serum bilirubin is not an isolated index for surgical indication, and some other situations should be taken into account. For example, HAE lesions invading the HVs may cause hepatic edema because of outflow obstruction. Preoperative percutaneous transhepatic HV stent implantation is an effective approach for alleviating hepatic edema and Budd-Chiari syndrome (52). This procedure could improve hepatic function obviously, and sequential ERAT approach may create radical resection opportunities for end-stage HAE patients (30).

Surgical procedure

In contrast to allograft LT, the ERAT procedure need long term for lesion resection and duct reconstruction during the anhepatic phase. An anhepatic phase for 1–1.5 hours without venous bypass is safe for the patient (53), whereas

the term for HVs reconstruction is too long to tolerance. in the biggest series undergoing ERAT, the anhepatic phase is 360 [104–879] minutes (19). For most patients undergoing ERAT, a temporary IVC reconstruction and portosystemic shunt between the PV and hepatic IVC is needed to control hemodynamic stability during anhepatic phase.

A long anhepatic term may affect the hepatic venous reflux leading to internal environment disorder, intoxicants accumulation and hemodynamic changes (54). Shorten the anhepatic term is significant for reducing complications such as pulmonary thromboembolism and post-reperfusion syndrome (55). Based on the experience in LDLT (56,57), the author's group modified the traditional ERAT procedure as resecting the lesions *in vivo* firstly, rather than remove the entire liver for lesion resection *in vitro* directly (31). Once excision plane reached the invaded HVs or RHIVC which could not be dissected from the HAE lesion *in vivo*, it's time for removing the liver into an ice bath for further bench resection. Up to now, Zhang group complete about 30 cases ERAT for end-stage HAE based on the modified procedure. This procedure could shorten the anhepatic term and cold ischemia phase. Also, if the encroached RHIVC range is short and easy to reconstruction *in vivo* based on detection, a halfway *ex-vivo* ERAT maybe enough for lesion resection, which could avoid complex ERAT procedure (34). And, this modified procedure may preserve more functional liver lobe(s) *in situ* (32).

Another reason for parenchymal transection *in vivo* firstly is to reduce potential bile leakage or bleeding after implantation. It's easier to confirm bleeding or bile leakage in the period of blood perfusion *in vivo* rather than U-W or HTK solution perfusion *in vitro*, which could effectively reduce the blood loss after the autograft was replaced *in situ*. One inadequacy is which need to block the first hepatic portal frequently during parenchymal transection *in vivo*. Whereas the remnant liver is commonly disease free, which permit frequent first hepatic portal block without serious hepatic function influence.

The outflow reconstruction of the autologous graft is the surgical difficulty for ERAT. For avoiding graft rejection, autologous vein grafts should be the ideal material for vascular reconstruction. GSV, IMV and non-invaded IVC wall excised from AE lesions is the commonly used materials for outflow reconstruction (10,58). Also, opened ligamentum teres hepatis can also be used as venous patch grafts in LDLT (59). When a long vascular was involved which could not be repaired using limit autologous vein grafts, an artificial vascular is need. The

management of the anhepatic phase is also significant for patients' smooth recovery, a temporary IVC reconstruction should be performed regularly. Also, a temporary porto caval shunt through PV-artificial IVC anastomosis (end to side) were also needed for reducing intestinal congestion. Whether the permanent artificial IVC reconstruction is needed depends on the outflow of the collateral circulation. IVC reconstruction could be avoided in some special cases including vena azygos opening and rich collateral circulation established, non-lower extremity edema, and non-pressure difference between supra- and inferior hepatic vena cava (60-63).

On the other hand, peri-operative PV pressure (PVP) measurement is important for assessment of outflow patency. Ito *et al.* revealed that PVP >20 mmHg is strongly associated with poor survival after LDLT (64). Also, Ogura *et al.* indicated PVP <15 mmHg is a key for successful adult LDLT utilizing smaller grafts than before (65). Based on this experiment in LDLT, we prompt pre-operative RLV and peri-operative PVP measurement is an effective method to evaluate the liver reserve function. For the case with a high pre-operative PVP index whereas which drop down to a low level, it may indicate a fine prognosis. On the contrary, once the PVP didn't drop to an ideal level or even higher after the ERAT procedure finished, it may prompt poor prognosis caused by small-for-size syndrome, PV or reconstructed HV outflow obstruction.

Post-operative management

The post-operative management for ERAT is similarly to LT. As non allograft implanted, the immunosuppressive therapy isn't needed conventionally. Whereas the cold-stored allograft vascular may using as materials for inflow (PV) and outflow (HVs, RHIVC) reconstruction may cause immune reaction similar to the process in solid organ transplantation (66,67). Then, a low dose and short-term immunosuppression therapy may be needed after allograft vascular transplantation for reducing thrombosis formation. Also, the artificial vascular implantation is a reason for thrombosis and even infection. The prophylactic anticoagulant and antibiotic therapy were needed for all patients after ERAT. Yang *et al.* (20) recommend the patients after ERAT should take warfarin sodium tablets for at least half 1 year refers to the international normalized ratio (INR) value is 2.0–3.0. Also, all patients should be administered albendazole (15 mg/kg/day) routinely for 1–2 years after ERAT (68,69).

The most frequently postoperative complications after ERAT for HAE patients is pleural effusion as Aji *et al.* reported, which occurred in 18 cases of total 69 patients (19). The main reason for pleural effusion may be the long surgical time, or long time for RHIVC blocking during the anhepatic phase. Comparing with conventional hepatectomy and allograft LT, the special complication for ERAT is the outflow stenosis which may cause recurrent massive ascites (70). Once the HV-IVC anastomotic stenosis was suspected, the hetophlebography and tentatively stent implantation was needed to deal with the Budd-Chiari syndrome.

Future perspectives

To date, available data on ERAT for end-stage HAE have demonstrated therapeutic efficacy. As an alternative therapy to LT for end-staged HAE patients, ERAT procedure needed neither organ donor nor long-term immunosuppressive agents. However, there are limited cases reported and all the published papers about ERAT in HAE is from China up to now. More cases are needed for evaluating the effectiveness or safety and standardized surgical procedures establishment of ERAT for HAE. Also, the post-operative management procedure needed more cases treatment experience to standardization. For instance, the plan for immunosuppression therapy after allograft vascular used for vascular reconstruction (need or not? and plan) and albendazole administration (1 or 2 years?) is still controversial in different center. And, the experience from non-Asian country is need for future reported.

Conclusions

ERAT procedure is an effective and novel surgical method for end-stage HAE treatment. this method needs neither an organ donor nor long term immunosuppressive therapy and with preferable overall survival rates compared with allograft LT. However, the treated cases are limited up to now, more experience worldwide were need for the standardized management procedures establishment.

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Footnote

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