Outcomes After Liver Resection for Hepatic Alveolar Echinococcosis: A Single-Center Cohort Study

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Abstract

Background Switzerland is a region in which alveolar echinococcosis (AE) is endemic. Studies evaluating outcomes after liver resection (LR) for AE are scarce. The aim of this study was to assess the short- and long-term outcomes of AE patients after LR in a single tertiary referral center.

Methods We retrospectively analyzed data pertaining to all patients with liver AE who were treated with LR at our institution between January 1992 and December 2013. Patient demographics, intraoperative data, extent of LR procedures (major vs. minor LR), postoperative outcomes, and negative histological margin (R0) resection rate were recorded in a database. Recurrence rates after LR were analyzed.

Results LR was performed in 59 patients diagnosed with hepatic AE (56 complete surgeries, 3 reduction surgeries). Postoperative morbidity and mortality were observed in 34 % (25 % grade I–II, 9 % grade III–IV) and 2 % of the patients, respectively. R0 (complete) resection rate was 71 % ($n = 42$), and R1/R2 resection rate was 29 % ($n = 17$). Extra-hepatic recurrence occurred in 1 case (lung) after R0 resection. In cases of R1/R2 resection, 7 intra-hepatic disease progressions occurred with a median time of 10 months (IQR 6–11 months). Long-term (more than 1 year) benzimidazole treatment stabilized the disease in 64 % (9/14) of patients with R1 status. The overall survival rate was 97 %.

Conclusions Liver AE can be safely and definitively treated with LR, provided that R0 resection is achieved. In cases of R1 resection, benzimidazole therapy seems to be effective in stabilizing the intra-hepatic disease and preventing extra-hepatic recurrence.

Introduction

Alveolar echinococcosis (AE) is a rare parasitosis due to the larval form of *Echinococcus multilocularis* [1–3]. In Europe, Switzerland is considered to be an endemic region for this parasite, as are France, Germany, or Austria [4].

AE can be compared to a malignant tumor because of its invasiveness and ability to infiltrate not only the liver parenchyma, but also other organs such as lungs or brain. Similar to the TNM classification system used to describe the stages of cancer progression, a PNM classification for AE was developed by the World Health Organization (WHO). This classification is based on the location of the liver lesion, invasion of the vascular/biliary structures (P), the involvement of neighboring organs (N), and the presence of distant metastasis (M) [5]. Since AE mainly affects the liver, symptoms at the time of diagnosis are similar to liver cancer. Patients may have abdominal pain, jaundice, and/or weight loss [6]. If left untreated, approximately 95 % of AE patients will succumb [7].

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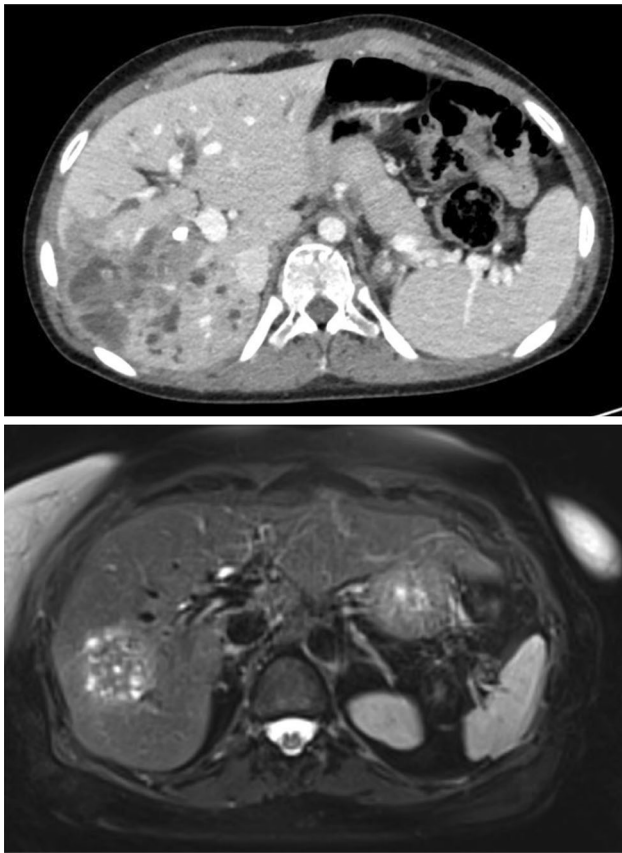
Fig. 1 Typical CT-scan and MRI axial views of hepatic alveolar echinococcosis

Therefore, aggressive therapy including major liver resection (LR) is often necessary to eradicate the totality of the parasites.

To date, few studies have been published on postoperative outcomes after LR for AE [6, 8–13]. The largest surgical series previously published was a study conducted in Japan, which included a large number of patients with incomplete resection of the hepatic disease [6]. Western series are scarce and these studies include a mixture of debulking strategies, medical treatments, and complete resections [9, 12]. The aim of this study was to evaluate the short- and long-term results of LR for AE in a tertiary referral center located in an area in which AE is endemic. The recurrence rate was analyzed and compared between cases in which negative (R0), positive histological (R1), and positive macroscopic (R2) resection margins were achieved.

Materials and methods

We conducted a retrospective analysis of all consecutive patients surgically treated for liver AE at the University Hospital of Lausanne (CHUV) from 1992 to 2013 based on

prospective patient data. Preoperative patient and lesion characteristics, preoperative treatments, intraoperative data, and postoperative results were analyzed. The study was granted prior approval by the local ethics committee (protocol number 56/14).

Preoperative work-up

Prior to surgery, all patients had a high-resolution contrast-enhanced CT-scan of the chest and abdomen to assess liver volume and vascular anatomy, to measure the extent of the hepatic lesion, and to rule out extra-hepatic disease. In cases where remnant liver volume was going to be less than 30 % of the total volume of the normal liver parenchyma, preoperative portal vein embolization (PVE) was performed according to the standard technique. Patients with preoperative biliary obstruction and jaundice underwent percutaneous or endoscopic drainage prior to surgery. The primary lesions were classified according to the PNM classification system for AE developed by the WHO in 2006 [5]. In this system, the "P stage" defines the liver location of the lesion and indicates whether the vascular/biliary structures have been invaded. The "N stage" concerns the involvement of the neighboring organs, and "M stage" indicates whether any distant metastasis is present [5]. If a suspicious image was found on CT-scan (Fig. 1) and the patient was either living in an endemic area or had other risk factors, then screening for AE was performed. Screening and work-up included serology testing (Western blot, ELISA) and liver MRI (Fig. 1) [14, 15].

Surgical procedure

Major LR was defined as the resection of three or more Couinaud's segments. The surgical procedure consisted of parenchymal transection using an ultrasonic dissector. Intermittent pedicle clamping without preconditioning (Pringle maneuver) was reserved only for cases in which there was bleeding. Hemostasis was achieved with bipolar coagulation, hemoclips, and ligatures. Debulking R2 resection was performed in symptomatic patients where the macroscopic disease could be maximally removed, as determined by preoperative work-up and multidisciplinary discussion.

Postoperative data and patient follow-up

Postoperative complications were graded according to the Dindo–Clavien classification [16]. As AE behaves like a cancer, the resection margins were defined the same as for a LR for hepatocellular carcinoma. R0 resections were defined as those in which the absence of disease was confirmed in the resection margins, and R1 resections were

Table 1 Patient characteristics

	Patients $n = 59$
Age[a]	60 (49–70)
Women	29
Symptoms at diagnosis	39
Metastasis at diagnosis	8
Intent of curative resection	56
Debulking R2 resection	3
Preoperative treatment[b]	20

[a] Median with interquartile range

[b] Radiological, endoscopic, or medical (benzimidazole treatment >6 months before the operation)

Table 2 Preoperative lesion characteristics ($n = 59$)

PNM stage I/II/III/IV	26/3/16/14
Largest liver lesion size[a] (cm)	5.5 (3.9–9.8)
Vena cava invasion	2
Portal vein invasion	8
Hepatic vein invasion	8
Hepatic artery invasion	8
Diaphragm invasion	13
Biliary tree invasion	16

[a] Median with interquartile range

defined as resections with positive histological margins (<1 mm). R2 resections were defined as palliative resections with macroscopic positive margins (debulking). Recurrence was defined as the appearance of intra-hepatic disease at or distant to the resection site after R0 resection, or new extra-hepatic disease. Progression of the disease was defined as intra-hepatic progression observed on radiological studies after a R1 or R2 resection was performed.

Patients were examined at the outpatient clinic 1 month after surgery. Subsequent follow-up was performed either by the patient's general practitioner or by a staff surgeon at our institution. Follow-up included clinical examination, serological tests, and imaging.

Benzimidazole therapy

Preoperatively, as soon as the diagnosis of AE was obtained, albendazole treatment was initiated if there was no contraindication. In cases where R0 resection was achieved, albendazole treatment was given for 2 years after the operation. Long-term (life-long) albendazole treatment was pursued when R1 or R2 resections occurred. In cases where albendazole intolerance or hepatic toxicity occurred, mebendazole treatment was given. No benzimidazole

Table 3 Surgical results

Minor resection	24
Major resection	35
Pedicular clamping	9
Vascular resection	7
Diaphragm resection	13
Biliary reconstruction (duct-to-duct or Roux-en-Y anastomosis)[a]	9

[a] Seven cases of AE invading the biliary tree did not need a biliary reconstruction

Table 4 Postoperative results

R0	42	71 %
R1	14	24 %
R2	3	5 %
Complications (Dindo–Clavien)	21	36 %
Minor (I–II)	15	25 %
Major (IIIa–IVb)	5	9 %
Mortality (V)	1	2 %
Overall mortality rate[a]	2	3 %
Recurrences/disease progressions	8	14 %
Intra-hepatic	7	12 %
Extra-hepatic	1	2 %
After R0	1	2 %
After R1	5	9 %
After R2	2	3 %
Follow-up[b] (months)	84	(41–148)
Postoperative benzimidazole treatment	33	56 %
No recurrence after R1/R2 resection	10	17 %
No recurrence after R1 resection	9	15 %
No recurrence after R2 resection	1	2 %

[a] Including the 30 postoperative day mortality
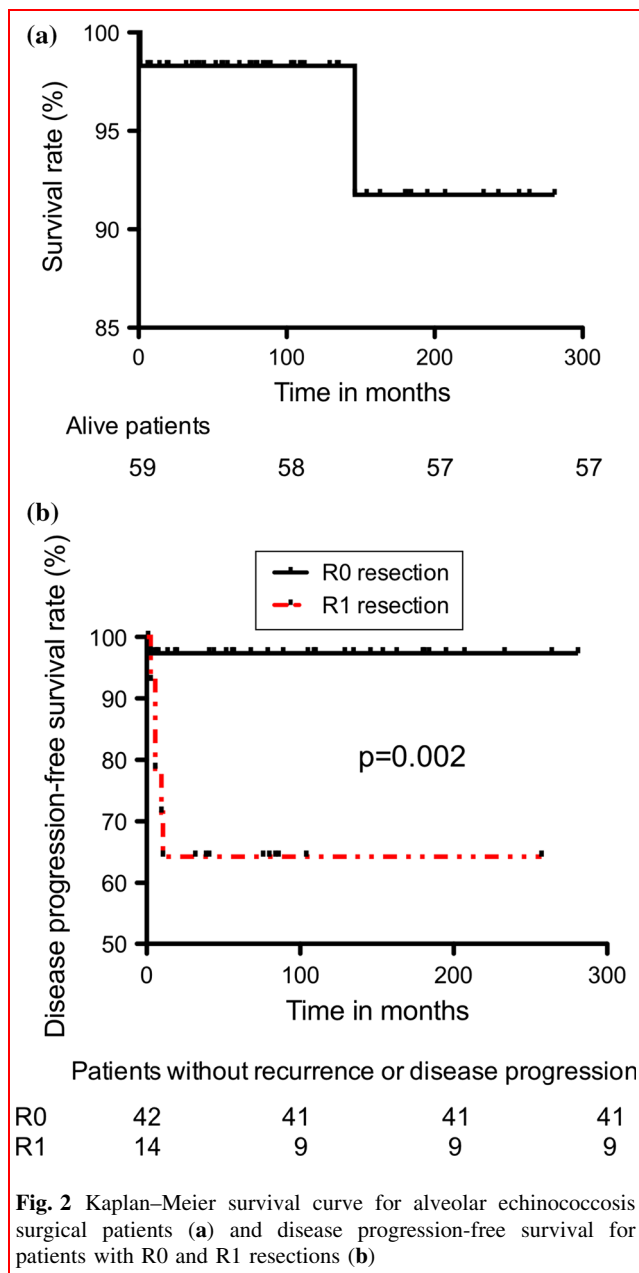
[b] Median with interquartile range

treatment was given if patients experienced allergy, hypersensitivity, intolerance, or during the first trimester of pregnancy. Before 2003, benzimidazole treatment was considered only in case of R1 or R2 resection.

Statistical analyses

All statistical analyses were performed using GraphPad Prism 5 for Mac OS X©. Survival curve calculation was conducted using the Kaplan–Meier technique.

Results

Patient characteristics are summarized in Table 1. At the time of diagnosis, two-thirds of the patients had symptoms (mainly abdominal pain) and 14 % (8/59) exhibited distant

Fig. 2 Kaplan–Meier survival curve for alveolar echinococcosis surgical patients (**a**) and disease progression-free survival for patients with R0 and R1 resections (**b**)

metastasis. The main location of extra-hepatic disease was determined to be the lung (5 cases), followed by spleen and peritoneum. Surgery with curative intent was performed in 56 cases; only 3 patients had a debulking R2 resection. Biliary drainage was performed before surgery in 7 cases (5 by endoscopy, 2 percutaneously).

Serology for *Echinococcus multilocularis* was available for 40 patients (68 %). Before surgery, 35 patients had positive tests for *Echinococcus multilocularis* by Western blot (with 5 false-negative tests) and 32 had positive Em2-antigen and EmII/3-10 antigen tests (with 8 false-negative tests). Of note, 12 patients also tested positive for *Echinococcus granulosus* by Western blot.

Table 2 shows the preoperative lesion characteristics. The most frequently observed PNM stage was stage I, followed by stage III, IV, and II, respectively. Forty-four percent of the patients (26/59) exhibited caval/portal/hepatic vein or hepatic artery invasion at the time of diagnosis. Major LR was performed in 35 cases (Table 3). A total of 16 patients presented with biliary invasion, but only 9 of them required bile duct resection with Roux-en-Y reconstruction or with duct-to-duct anastomosis (Table 3). Finally, additional diaphragm resection was necessary in 13 cases due to adjacent AE invasion (Table 3).

Table 4 summarizes the postoperative results. Major complications (grade IIIa–IVb) occurred in 5 cases, and 1 patient died during the postoperative period. The major complications seen included 2 postoperative hemorrhages, 1 case of septic shock due to colon perforation, 1 pulmonary embolism, and 1 biliary leak. The only postoperative death (grade V) was due to colon ischemia complicated by septic shock.

Histopathology showed that there were 71 % R0 (42/59), 24 % R1 (14/59), and 5 % R2 (3/59) resections. During the follow-up (median: 84 months, IQR: 41–148 months), no patient had intra-hepatic recurrence after R0 resection, and only 2 % (1/42) developed lung metastasis 4 months after surgery. After R1 and R2 resections, 41 % (7/17, R1: 5/14, R2: 2/3) of the patients exhibited intra-hepatic disease progression (4 at the resection site, 3 in the biliary tree), and no patient exhibited new extra-hepatic lesion. The median time to disease progression for non-R0 resections was 10 months (IQR 6–11 months). For R1 resections, the median time to disease progression was 6 months (IQR 4.5–10.5 months) and for R2 resections it was 22.5 months (IQR 10–35 months). Three patients underwent a second LR and 1 underwent a Roux-en-Y anastomosis. In 20 cases, benzimidazole therapy was not conducted, but reasons why benzimidazole treatment was not given were missing. Among the remaining 39 patients, postoperative benzimidazole treatment (either 2-year or long-term therapy) was given in 33 cases. One patient declined the postoperative benzimidazole treatment and 5 had contraindications that resulted in discontinued therapy (2 cases of intolerance, 1 of allergy, 1 of hepatic toxicity, and 1 of first trimester of pregnancy). Albendazole was given in 31 cases and mebendazole in 2 cases. Among the R1 cases, benzimidazole treatment stabilized the disease in 9/14 patients (64 %), meaning that 9 cases did not show disease progression after R1 resections and benzimidazole treatment (15 % of all patients, Table 4). After R2 resection, benzimidazole treatment stabilized the disease in 1/3 patients (33 %).

As shown in Fig. 2, the overall survival rate was 97 %. There was 1 death due to a cerebral tumor not related to echinococcosis and 1 death due to septic shock during the

first 30 postoperative days. Patients with R1 and R2 resections had 100 % survival. The survival times observed in the 3 cases with debulking R2 resection were 103, 110, and 132 months.

Discussion

This study shows that LR allows a curative treatment for patients with resectable hepatic AE. The long-term results of R1 and debulking R2 resections are also acceptable provided that patients are treated with adjuvant benzimidazole therapy and closely monitored, as 100 % of patients from this cohort survived after a median follow-up of 7 years.

Due to its low worldwide incidence, data on long-term outcomes after LR for AE are scarce [6, 8–13, 17]. Hepatic AE exhibits a tumor-like behavior with liver invasion, destruction of the parenchyma, and infiltration of adjacent vascular or biliary structures [6]. Most of the symptoms, observed in two-thirds of patients, are related to the infiltrating behavior of this parasitosis [18]. These main symptoms comprise abdominal pain that is most often located in the right upper quadrant, jaundice, weight loss, and vomiting. Postoperative complications occurred in 36 % of patients, mostly minor (i.e., grade I or II). The majority of the complications observed were respiratory, including pulmonary embolism, pneumonia, atelectasis, and pleural effusion. This incidence of common complications is related to the extensive nature of the surgery, as a high rate of major LR was performed in this cohort to obtain curative treatment of the parasitosis.

According to the PNM classification, the predominant stage of disease observed in this cohort was stage I. Since Switzerland is one of the major endemic regions of the disease, we adopted a low threshold policy with respect to diagnostic testing, performing AE serology, computed tomography, and/or magnetic resonance imaging in patients with a suspected liver cystic lesion [19]. Consequently, diagnosis was made early in the course of the disease, which allowed curative treatment in up to 71 % of patients.

In this study, extra-hepatic recurrence in the lung appeared in only 2 % of patients, and 7 patients showed disease progression after R1 or R2 resection, with a median time of recurrence of 10 months. These findings support previously published results suggesting that the remaining parasite needs several months to develop sufficiently to induce a recurrence [6, 12]. Interestingly enough, in our cohort, no patient presented a brain metastatic lesion which is one of the most common locations of extra-hepatic alveolar echinococcosis [18].

The only curative treatment for hepatic AE remains surgery, and surgery is curative provided that a R0 resection is achieved [1, 6, 9, 10, 12, 13, 17], in which case a long-term survival up to 97 % is observed. In this study, the level of recurrence after R0 resection was only 2 %, whereas 41 % of patients with R1 and R2 resections showed intra-hepatic disease progression. Alternatives to surgery include benzimidazole drug therapy (albendazole or mebendazole), endoscopic treatment (e.g., biliary drainage), or radiologic treatment (e.g., percutaneous biliary drainage) [20, 21]. In studies assessing benzimidazole treatment alone for hepatic AE, the mortality rates range from 25 to 42 % (with a median follow-up period of 12 years) [12, 20]. Endoscopic treatment of biliary complications related to AE seems to be less effective than for the treatment of hydatic cysts because of the malignant invasion of the parasite into the biliary tree [22, 23]. However, the endoscopic option can be used to treat cholangitis and jaundice prior to surgery. In the present study, 12 % of patients were treated successfully by endoscopy or by percutaneous drainage before surgery. In addition, interventional radiology treatment may be indicated in case of hepatic vein involvement and Budd–Chiari syndrome [24]. Thus, treatment should be tailored for each patient on a case-by-case basis, using a multidisciplinary approach [6]. A WHO working group published, in 2010, treatment recommendations for AE in humans [25].

Hepatic R1 resections and debulking R2 resections in conjunction with postoperative benzimidazole therapy can also yield acceptable results [6, 26]. The survival times of the 3 patients who underwent debulking R2 LR were 103, 110, and 132 months. However, these results have to be taken with caution, since 2 out of the 3 patients with debulking R2 resections showed a disease progression during the study period. In addition, all patients with R1 resection remained alive during the 7-year median follow-up period. Some disagreements exist in the published literature regarding whether or not palliative surgery is advisable. Some previous studies found that it is associated with worse long-term results [12, 13], whereas the current study agrees with other findings [6] that indicate that palliative surgery can improve long-term survival despite the fact that disease progression was 66 % even with benzimidazole therapy.

Western blot tests for *E. multilocularis* gave false-negative results in 13 % of the cases (5/40), while ELISA testing with Em2-antigens and EmII/3-10 antigens gave 20 % false-negative results (8/40). This observation corroborates the conclusions from other studies that the Western blot-based test provides more sensitive detection of *E. multilocularis* than ELISA [18, 27, 28]. Of note, due to cross-reactivity, positive Western blot tests for *E. multilocularis* can give positive results for *E. granulosus* (observed in 12 out of 40 patients) [29]. The use of Em2-and EmII/3-10 antigen ELISA tests coupled to Western blot-

based diagnosis thus increases the sensitivity and specificity of *E. multilocularis* detections in cases of clinical and radiological suspicion [29]. In case of negative *E. multilocularis*-specific serology, some authors advocate the use of ^{18}F-FDG PET-CT to monitor the efficacy of postoperative benzimidazole treatment and to assess the possibility of treatment discontinuation [30].

Surgery remains the treatment of choice of AE if the totality of the parasitic lesions can be removed. LR for hepatic AE is curative with an acceptable morbidity and mortality, provided that a R0 resection can be achieved. R1 resection coupled with benzimidazole adjuvant treatment is associated with acceptable long-term results by controlling microscopic hepatic disease. Debulking R2 resections still are matter of discussion but they can yield acceptable long-term survival even though the risk of disease progression is high.

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