Management of Advanced Hepatic Alveolar Echinococcosis: Report of 42 Cases

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Abstract. Radical resection is the first choice for hepatic alveolar echinococcosis (HAE). However, many patients with advanced HAE have no chance to be treated with curative resection owing to the long clinical latency. This study aimed to evaluate the necessity of aggressive operations, like palliative resection and orthotopic liver transplantation (OLT), in the management of advanced HAE. A retrospective study analyzed 42 patients with advanced HAE treated with palliative resection ($N = 15$), palliative nonresective procedures ($N = 13$), OLT ($N = 3$), or albendazole therapy alone ($N = 11$). The patients' condition before treatments was comparable among all the four groups. The overall 1-year, 3-year, and 5-year survival rates of the 42 cases were 81.0%, 45.2%, and 23.8%, respectively. No event occurred to end the follow-up during the 5-year observation period except death. The survival time (median $\pm$ standard error) of the palliative resection group (3.6 ± 1.4 years) was longer than that of the palliative nonresective procedures group (1.5 ± 0.2) and the albendazole therapy-alone group (1.0 ± 0.4). The 5-year survival rates after palliative resection and liver transplantation were 40.0% and 66.7%, compared with only 7.7% and 9.1% after palliative nonresective procedures or albendazole therapy alone. Therefore, we concluded that aggressive treatment with a multimodality strategy could contribute to prolonged survival in patients with advanced HAE. Moreover, the prognosis of the patients who received albendazole therapy alone or palliative nonresective procedures is poor.

INTRODUCTION

Hepatic alveolar echinococcosis (HAE) is a serious disease caused by the larvae of *Echinococcus multilocularis* and characterized by tumor-like infiltrative growth,^{1–4} including: destructive tissue growth, invasion of adjacent organs, and metastasis to distant organs.^{1,2,5,6} The natural life cycle of *E. multilocularis* involves a definitive host (foxes, wolves, dogs, etc.) and an intermediate host (mice, other rodents, etc.). In the definitive hosts, the tapeworm attaches to the intestinal mucosa and produces hundreds of eggs, which are dispersed through the feces. The intermediate hosts ingest these eggs through food and water contaminated by the feces of the definitive hosts. Then, oncospheres in the eggs penetrate intestinal wall, and develop into multilocular cysts in liver, lungs, and other organs in the intermediate hosts, which is a prey eaten by the definitive hosts. The oncospheres thus enter the definitive hosts and become sexually mature there to complete the life cycle. Occasionally, humans are infected as intermediate hosts to develop HAE. HAE has a wide distribution throughout the Northern Hemisphere with a broadening trend due to intensified globalization in the past centuries.⁷ Prevalence of alveolar echinococcosis (AE) in humans appear to follow parasite abundance in wildlife.⁸ Individual infection risk is closely linked to hygiene, outdoor activities, contact with definitive host animals such as pet dogs.^{8–10}

The prognosis of HAE is similar to that of liver tumors and the mortality is more than 90% in untreated cases within 10–15 years from diagnosis.^{2,11} The most important factor to improve prognosis of HAE is supposed to be early diagnosis, when complete resection is feasible.¹² Improved overall health in the countries or the regions depending on animal husbandry has contributed to a dramatic decrease in the incidence and the fatality rate of HAE globally.^{13,14} Owing to the long clinical latency, however, there are still some sporadic cases not diagnosed definitely until progressing to an advanced stage when the lesion cannot be resected completely. The advanced stage is characterized by extensive intrahepatic lesions, invasion of caval vein or hepatic hilum, extended invasion of the diaphragm and retroperitoneal space, and distant metastasis, which were the reasons for impossibility of curative resection. The management of advanced HAE, especially the necessity of aggressive operations, like palliative resection and orthotopic liver transplantation (OLT), remains controversial.^{15–17}

METHODS

Patients. In this study, we enrolled 42 patients (Table 1) with advanced HAE who underwent medical and surgical treatments from January 1998 to December 2009. The mean age of the 42 patients with advanced HAE (13 men and 29 women) was 43 (range 26–62). The male-to-female ratio was 0.45:1. This study was conducted in accordance with the ethical principles of the 2008 Declaration of Helsinki and was approved by the Ethics Committee of Affiliated Hospital of Logistics University of Chinese People's Armed Police Forces.

Diagnosis. Of 42 patients, 36 originally from the endemic regions were admitted to a local hospital for the disease;

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TABLE 1
Clinical characteristics of the 42 patients with different treatments

Characteristic	Palliative resection (N = 15)	Palliative nonresective procedures (N = 13)	OLT (N = 3)	Albendazole therapy alone (N = 11)	P value
age (year), mean $\pm$ SD	40.53 $\pm$ 7.99	42.00 $\pm$ 9.85	46.33 $\pm$ 5.51	46.64 $\pm$ 4.92	0.225
Sex, n (%)					
Male	6 (40.0)	3 (23.1)	1 (33.3)	3 (27.3)	0.795
Female	9 (60.0)	10 (76.9)	2 (66.7)	8 (72.7)	
Size (cm), mean $\pm$ SD	12.12 $\pm$ 1.95	13.29 $\pm$ 2.07	9.50 $\pm$ 2.39	12.33 $\pm$ 1.81	0.037*
Invasion in hepatic artery, n (%)					
+	2 (13.3)	3 (23.1)	0 (0)	1 (36.4)	0.589
-	13 (86.7)	10 (76.9)	3 (100)	10 (63.6)	
Invasion in hepatic vein, n (%)					
+	6 (40.0)	5 (38.5)	1 (33.3)	3 (27.3)	0.914
-	9 (60.0)	8 (61.5)	2 (66.7)	8 (72.7)	
Invasion in portal vein, n (%)					
+	8 (53.3)	6 (46.2)	2 (66.7)	7 (63.6)	0.818
-	7 (46.7)	7 (53.8)	1 (33.3)	4 (36.4)	
Invasion in bile duct, n (%)					
+	9 (60.0)	5 (38.5)	2 (66.7)	5 (45.5)	0.651
-	6 (40.0)	8 (61.5)	1 (33.3)	6 (54.5)	
Invasion in diaphragm, n (%)					
+	3 (20.0)	4 (30.8)	1 (33.3)	2 (10.6)	0.851
-	12 (80.0)	9 (69.2)	2 (66.7)	9 (89.4)	
Invasion in retroperitoneum, n (%)					
+	5 (33.3)	3 (23.1)	1 (33.3)	4 (36.4)	0.898
-	10 (66.7)	10 (76.9)	2 (66.7)	7 (63.6)	
Distant metastasis, n (%)					
+	3 (6.6)	2 (15.4)	0 (0)	3 (9.1)	0.607
-	12 (93.3)	11 (84.6)	3 (100)	8 (90.9)	
PNM stage, n (%)					
IIIa	1 (6.7)	3 (23.1)	1 (33.3)	1 (9.1)	0.534
IIIb	9 (60.0)	6 (46.2)	2 (66.7)	5 (45.5)	
IV	5 (33.3)	4 (30.8)	0 (0)	5 (45.5)	

+ = positive; - = negative; OLT = orthotopic liver transplantation; PNM = parasite lesion, neighboring organ invasion, metastases; SD = standard deviation.

*When palliative resection group, palliative nonresective group and albendazole therapy-alone group were analyzed separately, $P = 0.267$.

six had history of contacting with dogs from the endemic regions. Symptoms at diagnosis were huge hepatomegaly (29 of 42), jaundice (28 of 42), and upper abdominal pain (42 of 42). None of the patients had a previous history of extrahepatic hydatidosis. Before admitted, only six patients received albendazole therapy irregularly, five of them for 1–5 years, and the remaining one for over 10 years. In all the patients, the diagnosis was confirmed by clinical criteria, serology, and imaging techniques. Fine needle aspiration or true-cut biopsy was used preoperatively or postoperatively for histopathological diagnosis. Liver function tests, serologic tests (enzyme-linked immunosorbent assay, *E. multilocularis* antigens), ultrasonography, computed tomography,^{18,19} and magnetic resonance imaging^{20,21} were used in the diagnosis and follow-up (Figure 1). The parasite lesion, neighboring organ invasion, metastases classification^{22,23} was given in Table 1.

Treatments. Although the treatment strategies were made mainly according to the patients' condition, we believe that the individual wishes and economic status also played an important role in the strategy selection. Of 42 patients, not randomized, 15 received palliative resection (Table 2) and three received OLT. Immunosuppressive after OLT included cyclosporine or tacrolimus, mycophenolate mofetil, and corticosteroids. Thirteen patients underwent palliative nonresective procedures (Table 3). Eleven patients were treated with albendazole therapy alone. All patients received long-term albendazole therapy regularly. The chemotherapy protocol comprised albendazole administered orally in a daily dose of 15 mg/kg in a treatment cycle of 30 days with

10-day drug-free intervals. There were no major adverse reactions of discontinuing the chemotherapy of albendazole.

Statistical analysis. The survival rates were calculated using the Kaplan–Meier method and compared between groups using the log-rank test. P values were calculated by χ^2 analysis for enumeration data and one-way analysis of variance for measurement data. All statistical analyses were performed using the SPSS statistical package (Los Angeles, CA). A P value less than 0.05 was considered to be statistically significant.

RESULTS

We first analyzed the comparability of the conditions of the patients who underwent different treatments. Generally, no significant difference was found in the basic conditions of four groups. The overall 1-year, 3-year, and 5-year survival rates of the 42 patients with advanced HAE were 81.0%, 45.2%, and 23.8%, respectively. At the end of the follow-up period, 32 patients died of liver failure and its complications. No event occurred to end the follow-up during the 5-year observation period except death. All the survival rates of the 42 patients with different treatments were given in Table 4.

Palliative resections were performed in 15 patients (Table 2). The overall 1-year, 3-year, and 5-year survival rates were 86.7%, 53.3%, and 40.0%, respectively. Two of the 15 patients were treated with hemihepatectomy, concomitant pulmonary involvement necessitated pulmonary resection. Twelve of 15 patients experienced medical or

FIGURE 1. Imaging examinations of advanced hepatic alveolar echinococcosis in several representative cases. (A) Computed tomography for a patient with stage IV and P4N1M1. (B) Angiography using 64-slice spiral computed tomography for the same patient in A. (C) Enhanced computed tomography scanning (arterial phase) for a patient with stage IIIb and P3N1M0. (D) Computed tomography for a patient with stage IIIb and P2N1M0.

surgical complications: liver failure (two cases), bile leakage (four cases), hepatic artery thrombosis (one case), and pulmonary infection (five cases). Two patients with liver failure died on the 51st day and the 64th day, respectively, post-operatively. Five patients with bile leakage were treated by percutaneous transhepatic cholangial drainage. One patient experienced hepatic artery thrombosis on the 12th day was treated by hepatic artery reanastomosis and died of encephalorrhagia 3.6 years after surgery. Five patients with pulmonary infection were cured by anti-infection therapy. Six patients died of progressive HAE (postoperative 1.8, 2.5, 2.7, 2.8, 2.9, 4.9 years, respectively). No deaths could be attributed directly to surgical technique. Histopathological analysis of the hepatectomy specimens confirmed HAE in all the 15 patients. The mean duration of hospital stay was 45 days (range 35–73 days). The median survival time of the palliative resection group was 3.6 years.

Three patients underwent OLT because of advanced HAE with chronic liver disease: one had secondary sclerosing cholangitis; one had hilum invasion related to parasitic involvement of the porta hepatis after a palliative hepatectomy; one had obstructive jaundice with biliary tract fistula after multiple operations on the biliary tract. Major post-operative complications, such as liver failure, biliary leakage, and major bleeding did not develop. One patient died 4.8 years after OLT because of AE recurrence in brain. Two survived without diseases up to now. Histopathological analysis of the hepatectomy specimens disclosed echinococcus in all the three patients at the time of OLT.

Most patients of the palliative resection group and transplantation group achieved prolonged survival (5 years, so far, in our patients) and good quality of life, though the procedures carries a high postoperative complication rate (66.7%, 12/18).

TABLE 2
Operative procedures in palliative resection group

Procedure	Palliative resection (N = 15)	
	N	%
Left lateral sectionectomy + PTCD	3	20.0
Right posterior sectionectomy + PTCD	2	13.3
Right posterior sectionectomy + lesion partial resection + cyst puncture drainage	1	6.7
Right hemihepatectomy + pneumoresection	2	13.3
Left hemihepatectomy	2	13.3
Lesion partial resection + cyst puncture drainage	5	33.3

PTCD = percutaneous transhepatic cholangial drainage.

TABLE 3
Palliative nonresective procedures

Procedure	Palliative nonresective procedures group (N = 13)	
	N	%
PTCD guided by ultrasound	5	38.5
Cholangiojejunostomy	2	15.4
Modified Longmire procedure	4	26.7
Surgical drainage	2	15.3

PTCD = percutaneous transhepatic cholangial drainage.

Because of cholestatic jaundice and liver abscess, we performed palliative nonresective procedures on 13 patients: biliary diversion in six patients (segment III cholangiojejunostomy in two patients, modified Longmire procedure in four patients) and external drainage in seven patients (Table 3). Twelve patients died of progressive HAE including distant metastasis in lung and brain (postoperative 0.5, 1.1, 1.1, 1.2, 1.3, 1.3, 1.5, 1.6, 1.7, 3.0, 3.1, 3.2 years, respectively). The overall 1-year, 3-year, and 5-year survival rates of the 15 patients with palliative nonresective procedures were 92.3%, 30.8%, and 7.7%, respectively.

Eleven patients were treated with long-term albendazole therapy alone and 10 patients died of liver failure and its complications in the follow-up period (0.2, 0.3, 0.5, 0.5, 0.6, 1.0, 1.2, 3.0, 3.4, 3.9 years, respectively). The overall 1-year, 3-year, and 5-year survival rates of the 11 patients with albendazole therapy alone were 54.5%, 36.4%, and 9.1%, respectively.

The survival curve (Figure 2) showed longer survival time of the palliative resection group (3.6 ± 1.4 years) than that of the palliative nonresective procedures group (1.5 ± 0.2) and the albendazole therapy-alone group (1.0 ± 0.4). The results were given in Table 4.

DISCUSSION

Although the radical resection was regarded as the first choice for HAE, due to the long clinical latency, many cases were not diagnosed until at advanced stage when the lesion had no chance to be resected completely. The treatment of the advanced HAE, especially the necessity of aggressive operations, is disputed.¹⁵⁻¹⁷ In the retrospective study, we analyzed 42 patients with advanced HAE treated with palliative resection, palliative nonresective procedures, OLT, or albendazole therapy alone. These patients were not randomized and that treatments were based on disease presentations, individual wishes, and physician choices as

well. We concluded that palliative resection might be more beneficial for the advanced HAE patient than palliative nonresective procedures and albendazole therapy alone.

Chemotherapy with albendazole is commonly recommended for the HAE patient, but its role alone in advanced HAE remains unknown. Although there is no doubt that the first choice for treatment of HAE is surgical resection,^{1,2,24,25} even after curative resection, recurrence can occur.²⁴⁻²⁶ It seems to be related to invisible remnant parasitic tissue in the liver. Therefore, 2-year chemotherapy with albendazole is recommended for most HAE patient even after curative resection.^{2,24,25} Nevertheless, the chemotherapy alone seems little effective in a long run, especially for those with advanced HAE.²⁷⁻²⁹ In our series, long-term albendazole therapy was used alone in 11 cases with advanced HAE, and had no remarkable successful (complete response) results according to the modified World Health Organization criteria.³⁰ The survival time of the advanced HAE patient with albendazole alone (1.0 ± 0.4 years) was significantly less than that of those with palliative resection (3.6 ± 1.4 years, $P = 0.045$). These results suggest that albendazole alone were not beneficial for the advanced HAE patient, especially for those who were surgical candidates.

The effect of palliative resection for the advanced HAE was encouraging in a retrospective study by Kawamura and others.¹⁵ They reported the reduction surgery group ($N = 63$) had higher 10- and 15-year overall survival (97.1% and 92.8%) than that of the drainage or exploratory laparotomy group ($N = 6$) (50.0% and 33.3%). In our series, the 5-year survival rates of the palliative resection group were 40.0%, higher than that of the palliative nonresective procedures group (7.7%). The survival time of the palliative resection group (3.6 ± 1.4 years) was also higher than that of the nonresective procedures group (1.5 ± 0.2 , $P = 0.016$). Although a reduction surgery carried a higher postoperative complication rate, the overall survival was improved significantly. Thus, palliative resection may be beneficial for patients who have lost the chance of radical resection but can tolerate the surgery. Compared with malignant tumor, the more positive effect of debulking operation may derive from the benign nature of HAE without genetic canceration, even though behaving like a slow-developing liver cancer with subsequent invasion of liver tissues and metastatic dissemination.

OLT may offer the only opportunity for survival and cure for the patient with progressive advanced HAE, which is usually marked by a succession of biliary tract infectious episodes, obstructive jaundice, liver abscesses, septicemia,

TABLE 4
Survival rates and median survival time of the 42 patients with different treatments during 5-year follow-up period

Treatment	N	Survival rates			Median (years)			
		1-year survival rate % (n)	3-year survival rate % (n)	5-year survival rate % (n)	Estimate	Standard error	95% confidence interval	
							Lower bound	Upper bound
Palliative resection*†	15	86.7 (13)	53.3 (8)	40.0 (6)	3.600	1.353	0.949	6.251
OLT	3	100.0 (3)	100.0 (3)	66.7 (2)	N/A	N/A	N/A	N/A
Palliative nonresective*‡	13	92.3 (12)	30.8 (4)	7.7 (1)	1.500	0.180	1.148	1.852
Albendazole therapy alone†‡	11	54.5 (6)	36.4 (4)	9.1 (1)	1.000	0.385	0.245	1.755
Total	42	81.0 (34)	45.2 (19)	23.8 (10)	N/A	N/A	N/A	N/A

N/A = not available; OLT = orthotopic liver transplantation. Median survival time: * $P = 0.016$, † $P = 0.045$, ‡ $P = 0.791$.

FIGURE 2. Cumulative survival rates of patients with different treatments. Green line, palliative resection; red line, orthotopic liver transplantation (OLT); blue line, palliative nonresective procedures; black line, albendazole therapy alone.

recurrent cholangitis, bleeding caused by portal hypertension, and chronic Budd–Chiari syndrome. Although some³¹ considered that surgery including OLT should be restricted to patients at an early stage of HAE, others argued that complications during the terminal illness could be relative indications for OLT.³² In our series, three advanced HAE patients underwent OLT because of severe complications survived longer (one for 4.8 years, two for more than 5 years) than expected. The result suggests OLT may benefit the advanced HAE patients with parasitic Budd–Chiari syndrome or when resection techniques have been exhausted and those with end-stage functional disorders caused by secondary biliary cirrhosis, secondary sclerosing cholangitis, and postnecrotic cirrhosis.^{33–37}

In summary, our study suggests aggressive treatment with a multimodality strategy could result in prolonged survival in patients with advanced HAE. Palliative resection may be beneficial for those with advanced HAE. The prognosis of the patients who received albendazole therapy alone or palliative nonresective procedures is poor.

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