



Özgün Araştırma / Original Article

## Challenges, Prognosis and Outcomes of Surgical Resection for Hepatic Alveolar Echinococcosis: A Single Centre Experience

Ahmet Rencuzogulları<sup>1</sup>, Ismail Soner Koltas<sup>2</sup>, Atilgan Tolga Akcam<sup>1</sup>, Abdullah Ulku<sup>1</sup>, Orcun Yalav<sup>1</sup>, Ahmet Gokhan Saritas<sup>1</sup>, Kubilay Dalcı<sup>1</sup>, Ismail Cem Eray<sup>1</sup>

*1 Cukurova University, Faculty of Medicine, Department of General Surgery, Adana, Turkey*

*2 Cukurova University, Faculty of Medicine, Department of Parasitology, Adana, Turkey*

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### Abstract

**Objective:** Alveolar echinococcosis (AE) is an aggressive and potentially fatal infection, which affects the liver primarily and presents as a tumor-like lesion. Outcomes associated with surgical procedures for this infection have been rarely reported. In the present study, we aimed to evaluate long-term surgical treatment outcomes associated with hepatic AE.

**Methods:** Between 2001 and 2013, the management and outcomes of twelve consecutive hepatic AE patients who were considered feasible for complete hepatic resection with/without metastasectomy were described. In all patients, pre-operative diagnosis of AE was based on clinical findings, imaging studies, and serological tests. Antibodies against antigens of *Echinococcus multilocularis* metacestodes were screened as specific markers for the serological diagnosis of AE by Western blot. The oral albendazole protocol was administered for hepatic AE patients who had complete resection.

**Results:** Twelve patients (F/M=7/5) underwent complete resection for pathologically confirmed hepatic AE during the study period. Median follow-up was 82 (32-164) months. The most common initial symptom was abdominal pain (n=9) followed by jaundice (n=4). Four patients had metastasis: Brain, surrenal, splenic and colon. One patient was lost due to massive pulmonary emboli despite appropriate interventions. All other complications that emerged were treated successfully.

**Conclusion:** Long-term favorable outcomes can be achieved by complete surgical resection followed by chemotherapy with albendazole in advanced hepatic AE cases.

**Keywords:** alveolar echinococcosis; hepatic resection; *Echinococcus multilocularis*, tumor-like disease.

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**Yazışma Adresi / Correspondence:** Ahmet Rencuzogullari, Cukurova University, Faculty of Medicine, Department of General Surgery, Balcalı, Sarıcam, 01330, Adana, Turkey e-mail: rencuzdr@gmail.com

## Hepatik Alveolar Ekinokokkoz Cerrahisinde Zorluklar, Prognoz ve Yönetim: Tek Merkez Deneyimi

### Özet

Giriş: Alveolar ekinokokkoz (AE) primer olarak karaciğeri etkileyen ve tümör benzeri davranış gösteren, agresif ve potansiyel olarak fatal bir enfeksiyondur. Bu enfeksiyon için cerrahi prosedürlere ilişkin sonuçlar nadiren raporlanmıştır. Bu çalışmada hepatic AE'in cerrahi tedavisi ile ilişkili olarak uzun dönem sonuçları değerlendirmeyi amaçladık.

Yöntemler: 2001 ve 2013 yılları arasında, metastaz durumuna bakılmaksızın hepatic AE nedeniyle komplet rezeksiyon için uygun bulunan hastaların yönetimi ve sonuçları tanımlandı. Tüm hastaların preoperatif AE tanısı klinik bulgular, görüntüleme teknikleri ve serolojik testlere göre konuldu. Echinococcus multilocularis metastesod antijenine karşı oluşan antikor düzeyleri, Western Blot tekniğiyle elde edilen AE serolojik tanısı için spesifik markırlarlar olarak kullanıldı. Oral albendazol protokolü komplet rezeksiyonun yapılabildiği tüm hastalara uygulandı.

Bulgular: Çalışma periyodu boyunca patolojik olarak hepatic AE olduğu konfirme edilen 12 hastaya (K/E=7/5) komplet rezeksiyon uygulandı. Ortanca takip süresi 82 (32-164) ay idi. En sık başlangıç semptomları karın ağrısı (n=9) ve sarılık (n=4) idi. Beyin, sürrenal, dalak ve kolon olmak üzere 4 hastada metastaz tespit edildi. Alınan uygun önlemlere karşın bir hastada mortalite gözlenirken, gelişen diğer komplikasyonların tamamı başarı ile tedavi edildi.

Sonuç: İleri evre hepatic AE olgularında uzun dönemdeki olumlu sonuçlar, komplet cerrahi rezeksiyon ile birlikte yapılan Albendazol uygulaması ile elde edilebilir.

Anahtar kelimeler: Alveolar ekinokokkoz, hepatic rezeksiyon, Echinococcus multilocularis, tümör benzeri hastalık

## INTRODUCTION

Alveolar echinococcosis (AE) is a parasitic zoonoses and a major public health issue in endemic areas such as Turkey. Foxes and coyotes are the definitive hosts of Echinococcus multilocularis (E. multilocularis) whereas wolves are the intermediate hosts. Recent reports have described immense concern regarding the significant increase in prevalence and distribution of E. multilocularis in red foxes, in Europe over the past 10-15 years<sup>1</sup>. The disease is aggressive and potentially fatal, since it affects the liver primarily, presents as a tumor-like lesion and metastasizes to any part of the body<sup>2</sup>.

AE is often misdiagnosed as liver cancer and its lesions often metastasize to adjacent or distant organs. Surgery has been regarded as the first treatment modality for the potentially resectable parasitic mass based on the current treatment guidelines. Nevertheless, parasitostatic drugs have been shown to be effective as well<sup>1,3-6</sup>. Despite surgery being the

gold standard for treatment, long-term outcomes associated with surgical procedures for advanced hepatic AE cases have been rarely reported. In the present study, we aimed to evaluate the long-term treatment outcomes associated with AE for patients who underwent complete hepatic resection.

## METHODS

Between 2001 and 2013, hepatic AE patients who were considered feasible for resection and underwent complete resection at the Cukurova University Faculty of Medicine, Balcali Hospital, Adana, Turkey were included in the study. Patient characteristics and initial presentation features were obtained from their medical charts. Radiologic images including ultrasonography (US), triphasic tomography, magnetic resonance imaging (MRI) were retrospectively analyzed. Size and intraoperative localization of the lesions was defined based on Couinaud's anatomical classification<sup>7</sup>. Based on intraoperative findings, stage of the parasitic mass was reported according to the PNM (P=parasitic

mass in the liver, N=involvement of neighbouring organs, and M=metastasis) staging system (18). Surgical procedures performed were documented. Postoperative complications were classified according to the Clavien-Dindo system<sup>8</sup>.

Antibodies against *E. multilocularis* antigens were screened as specific markers for the serological diagnosis of AE by Western blot (WB). Western blot serology was performed on human sera samples using the Echinococcosis WB IgG kit (LDBIO Diagnostics Lyon, France) according to the manufacturer's instructions. The protocol for hepatic AE patients who achieved complete resection was oral administration of 10mg/kg/day albendazole in a treatment cycle of 3 weeks with 1-week breaks for 1 year. The protocol for patients with extra-hepatic dissemination was oral administration of 10mg/kg/day albendazole in the same treatment cycle, and these patients received life-long treatment until they experienced any adverse events. Patients were followed up every six months after discharge with serological tests by WB.

**Table 1.** Patient characteristics and symptoms at index admission

PATIENT	AGE/GENDER	SYMPTOMS (duration,years)
1	38/F	Jaundice,Abdominal pain (2y)
2	42/M	Abdominal pain,fever (5y)
3	37/M	Abdominal pain,nausea,jaundice (3y)
4	15/M	Abdominal pain ,jaundice (2y)
5	54/F	Abdominal pain,fever (3y)
6	52/F	Abdominal pain (2y)
7	65/F	Abdominal pain (1.5y)
8	33/F	Epileptic attack, headache (2y)
9	44/F	Abdominal pain (3y)
10	25/M	Nausea, itching (1y)
11	37/M	Fever, nausea,jaundice (2y)
12	33/F	Nausea,abdominal pain (4y)

## RESULTS

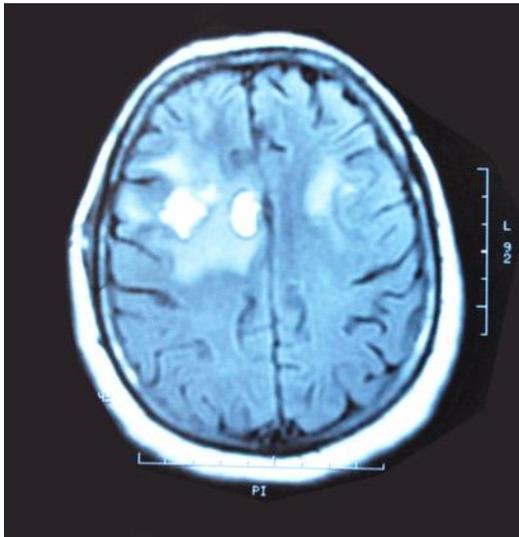
Twelve patients (F/M=7/5) underwent hepatic resection for hepatic AE during the study period. Median follow-up duration was 82 (32-164) months. Patient characteristics and symptoms at index admission are presented in Table 1. The most common initial symptom was abdominal pain in 9 of the patients followed by jaundice (n=4). One particular patient was admitted to the neurosurgery clinic with the complaint of epileptic attacks and headaches (Table 1). Her brain tomography revealed a brain mass (Figure 1) for which she was operated afterwards. She was referred to the general surgery department after pathological and serological examinations of the excised lesions that were located in frontal lobes indicated AE. Further radiologic studies showed that she had a hepatic mass (Figure 2) which invaded the inferior vena cava (Figure 2).

Hepatic AE was demonstrated with US and triphasic tomography. Magnetic resonance angiography was used in five patients for differential diagnosis. Median size of the lesions was 14 cm (range: 6-19 cm). For all patients, completeness of hepatic resections was confirmed by pathological specimens. Distribution of patients according to the PNM staging system is given in Table 2. Out of 12 patients, 2 patients had stage II tumors, 5 patients had stage 3A tumors, 1 patient had stage 3B tumor, and 4 patients had stage IV tumors. Four patients had metastasis; one brain, one surrenal, one splenic and one colon metastasis. The entire patient cohort was seropositive with WB screening test for AE prior to the surgery. The presence of both 16-kDa and 18-kDa bands were interpreted as a positive test for AE (Figure 3).

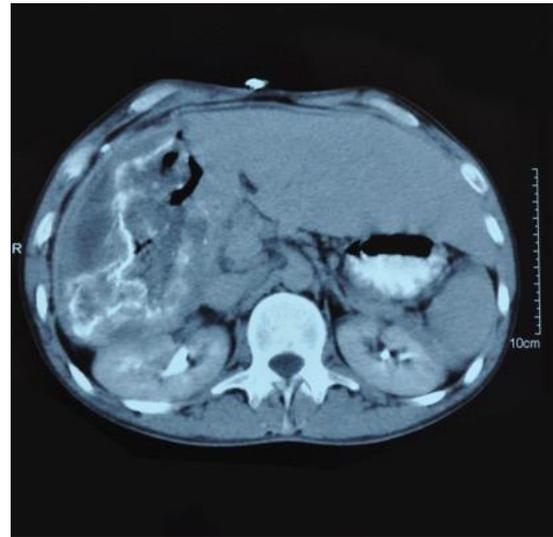
**Table 2.** The size, localization, stage of the tumor, surgical interventions and complications)

Patient	Size/ Localization	pTNM/Stage	Surgery	Complications	Treatment of complications
1	15 cm /Right anterior section. Sg 5, 8 and spleen	P <sub>3</sub> N <sub>0</sub> M <sub>1</sub> stage 4	ERH +splenectomy	Grade I	Conservative
2	8 cm/ left medial section Sg 4	P <sub>2</sub> N <sub>0</sub> M <sub>0</sub> Stage 2	ELH	Grade III-b	R and Y hepatico-jejunostomy
3	12 cm/ left medial section. Sg 4	P <sub>3</sub> N <sub>0</sub> M <sub>0</sub> Stage 3A	ELH, cholecystectomy	Grade V	
4	14 cm/ left lateral section Sg 2, 3	P <sub>3</sub> N <sub>0</sub> M <sub>0</sub> Stage 3A	ELH	Grade III-b	Surgical primary repair
5	19 cm/ right posterior section Sg 6, 7, colon metastasis	P <sub>3</sub> N <sub>0</sub> M <sub>1</sub> Stage 4	ERH+righthemicolecotomy	Grade III-b	Reanastomosis
6	6 cm/ left medial sectionSg 4, 5 cm/ gastrosplenic ligament	extrahepatic	LH+Splenectomy+ mass resection	-	
7	10 cm/ right posterior section Sg 6, 7	P <sub>2</sub> N <sub>0</sub> M <sub>0</sub> Stage 2	ERH	-	
8	19 cm/ right anterior section Sg 5, 8, invasion to the IVC, cerebral metastasis	P <sub>4</sub> N <sub>0</sub> M <sub>1</sub> Stage 4	ERH	Grade IV	Secondary operation for hemostasis
9	15 cm/right posterior section Sg 6, 7	P <sub>3</sub> N <sub>0</sub> M <sub>0</sub> Stage 3A	ERH	-	
10	14 cm/ right anterior section Sg 5, 8, hepatic lobe	P <sub>3</sub> N <sub>0</sub> M <sub>0</sub> Stage 3A	ERH	-	
11	17 cm/ left medial section. Sg 4	P <sub>4</sub> N <sub>0</sub> M <sub>0</sub> Stage 3A	ELH, cholecystectomy	Grade I	Conservative
12	12 cm/right anterior section Sg 5, 8, right surrenal gland	P <sub>3</sub> N <sub>0</sub> M <sub>1</sub> Stage 4	ERH	-	

Sg: Segment ,ERH: Extended right hepatectomy, ELH: Extended left hepatectomy

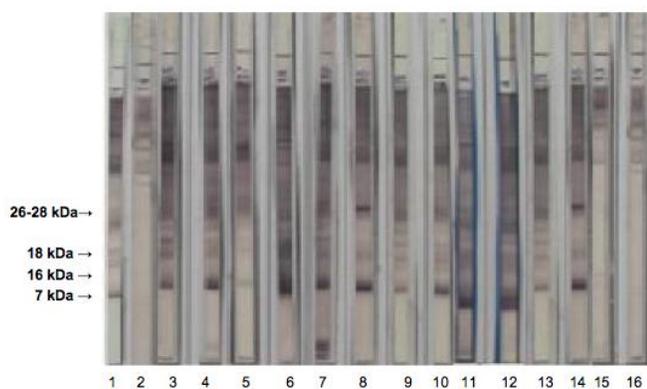


**Figure 1.** Well defined, contoured cystic lesions in the right frontoparietal lobe, in the parafalcine region, involving the subcortical white matter, with surrounding edema and focal edema in the white matter in the left frontal lobe.



**Figure 2.** Wide lesion in segment 5-6 of the liver, invading vena cava inferior (arrow) with curvilinear calcifications and air pockets.

Surgical resection was the choice of treatment in all patients. Two patients who had surrenal and splenic metastasis had splenectomy and unilateral surrenalectomy, respectively. The patient who had colonic invasion underwent a right hemicolectomy. In five patients, there were no complications during surgery or follow-up. Two patients had a minor postoperative complication [Clavien-Dindo I & II], whereas six had major (Clavien-Dindo  $\geq$ III) complications (massive ascites, biliocutaneous fistula, evisceration, leak from ileocolic anastomosis, bleeding and pulmonary emboli resulted in mortality) (Table 2). Only one patient, who had initially presented with a brain metastasis, still had WB seropositivity for AE after surgery.



**Figure 3.** Western blot analysis of 12 patients sera using Echinococcus WB IgG kit. The lines represent: 1- positive *E. multilocularis* control, 2-negative control, 3-14 sera with confirmed AE patients preoperation (positive 16 kDa-18 kDa bands), 15-16 AE patients postoperation. (Presence on the strip of a band at 7 and/or 26-28 kDa; diagnosis of the genus *Echinococcus* and 16-18 kDa; diagnosis of the species *Echinococcus multilocularis*)

No mortalities were recorded except for one patient who had massive pulmonary emboli despite appropriate precautions. That patient had undergone left hepatectomy and cholecystectomy for a 12 cm large left hepatic AE but died on postoperative day 9 in the intensive care unit. All other complications

were managed successfully with re-operation (n=4) or conservative treatment (n=2).

Out of 4 patients who were diagnosed with metastatic disease, complications were observed in 3 patients and managed successfully (n=1 conservative, n=2 reoperation). Follow-up radiological evaluation did not show any case of new or recurrent hepatic lesion.

## DISCUSSION

The current study shows that long-term favorable outcomes can be achieved by complete surgical resection followed by chemotherapy with albendazole even in advanced hepatic AE cases. Highly advanced cases, such as those in which adjacent organs are involved and those in which metastasis are identified, can be treated with complete hepatic resections with acceptable complication rates.

AE is found in the northern hemisphere and is a potentially fatal disease. The infectious eggs of the parasite are transmitted via feces of foxes. The liver is almost always affected<sup>4,5</sup>. Recently published reports have demonstrated rural-to-urban regionally expanding endemic areas in regards to *E. multilocularis*<sup>3,9,10</sup>. If this trend continues, it is possible that human AE will become an emergent zoonosis in some regions of Europe and Eurasia. Improvements in diagnostic and treatment approaches are being investigated<sup>1</sup>.

AE is recognized by intrahepatic tumor-like multi-vesicular primary lesions with its infiltrating features. Early diagnosis of AE is made by considering characteristic symptoms, imaging techniques, serology, histopathological examination or molecular analysis of biopsied material<sup>4,9,11</sup>. Asymptomatic chronic *E. multilocularis* infection lasting up to 15 years represents the greatest proportion of infected cases. Diagnosis of AE is often difficult and can sometimes be only possible in the later stages of the disease. Recently developed and

improved serological tests for AE have been shown to be reliable but they are rarely available in most urban areas. Consequently, failure to diagnose AE or its misdiagnosis leads to presentation in advanced stages, making treatment challenging and prognosis poor<sup>11,12</sup>. Symptoms depend on the involved organs. In metastatic cases patients may be referred to other clinics based on the metastasis related symptoms. In this series, abdominal pain was the most common symptom with jaundice. Patients were referred to our clinic at least two years after the symptoms began. None of them could be diagnosed in stage 1. In one patient who had brain metastasis; the only symptoms were epileptic attacks and headache.

Imaging techniques of hepatic involvement by AE commonly reveal an ill-defined lesion of the liver parenchyma and contrast computer tomography (CT) and MRI are considered to clearly demonstrate infiltrative structure and extension of the parasitic tumor to adjacent structures<sup>3,13,14</sup>. According to current treatment guidelines, cure can be achieved by surgical treatment once the parasitic mass is predicted as resectable<sup>3,4,6,11</sup>. In advanced cases, organs neighboring the liver can be infiltrated by the organisms, whereas distant organs such as lungs and brain can be affected hematogenously. For liver cases where resection is not feasible, or complications develop, a liver transplant can be a lifesaver. Liver transplantation, as treatment option for AE cases, is technically difficult because of the history of prior surgery, interventional radiological procedures, and mass size<sup>3,15</sup>. Moray et al. reported two cases of advanced AE, which invaded both lobes and the inferior vena cava. Both cases were treated successfully with liver transplantation. The authors suggested transplantation as a lifesaving treatment of choice in patients who did not have any other medical or surgical options<sup>16</sup>. Ayifuhan et al analyzed 50 cases of hepatic AE who were treated with radical or conservative surgery. In

their retrospective analysis, mortality and recurrence were significantly higher in a palliative group. They concluded that radical resection appears to be best treatment of hepatic AE and palliative operation may cause a series of severe complications leading to death<sup>17</sup>.

It has been previously reported that, if left untreated > 95% of AE patients will die within 10 years following diagnosis<sup>18</sup>. As described here, surgery can be used even for late stage AE cases, but this attempt may be problematic because of the difficulty in removing all of the parasitic lesions. To improve survival for patients with non-resectable lesions or for which complete resection is not feasible, chemotherapy should be used in combination with surgery. Due to high and well-known efficacy against AE, albendazole should be used before surgical procedure, together with regular patient follow-up post-treatment<sup>10,11,19,20</sup>. Despite remarkable improvement of long-term patient survival after the introduction of anti-helminthic drug treatment, this therapeutic modality proved to be mostly parasitostatic. Therefore, surgical resection represents the therapy of choice for patients with operable lesions of AE<sup>3,11,21</sup>.

Metastatic AE is a special challenge. The lesions may spread to the thyroid, bone, vertebra, scrotum, spleen, ovary, heart, kidney, peritoneum, lymph nodes, rectus muscle, knee, lacrimal sac and occasionally the nervous system<sup>22,23</sup>. Cerebral occurrence in AE is approximately 1%, and considered to be fatal. Treatment involves chemotherapy with benzimidazole derivatives (albendazole, mebendazole) and surgery for accessible lesions. Cure is achieved only if the lesion is completely resected followed by chemotherapy that may prolong the patient's survival time. We had four cases of metastatic AE who were all treated successfully with resection of the invaded organ. Decrease in antibody levels was observed in all cases where curative resections

could be performed. In these patients, antibody levels began to decrease at 6, 12 and 18 months after surgery in 4, 6, and 1 patients, respectively. Only one patient had WB seropositivity for AE after discharge with serological tests by WB. As shown in our series, albendazole treatment combined with complete curative resections may be responsible for satisfying long-term outcomes and sustained low antibody levels.

As a conclusion, this report represents our surgical experience in advanced AE cases. Based on literature and our findings, we suggest that early diagnosis and radical resection combined with antihelminthic drug therapy is the life saving and associated with favorable long-term outcomes in AE even in advanced cases. Yet; there is need for more, larger and prospective studies.

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