

# Comment on surgical approaches for definitive treatment of hepatic alveolar echinococcosis: results of a survey in 178 patients

## Review

**Cite this article:** Akbulut S, Sahin TT (2020). Comment on surgical approaches for definitive treatment of hepatic alveolar echinococcosis: results of a survey in 178 patients. *Parasitology* **147**, 1408–1410. <https://doi.org/10.1017/S0031182020001390>



Received: 9 May 2020  
Revised: 13 June 2020  
Accepted: 13 June 2020  
First published online: 3 August 2020

### Key words:

Alveolar echinococcosis; *ex vivo* liver resection plus autotransplantation; hepatectomy

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## Abstract

Echinococcus multilocularis causes alveolar echinococcosis which is a chronic, progressive zoonotic disease that mainly affects the liver. Hepatic alveolar echinococcosis is insidious and the patients are asymptomatic most of the time. Generally, it is incidentally found on imaging studies performed for other reasons. Specific symptoms may evolve if the vascular and biliary structures of the liver are affected. Hepatic alveolar echinococcosis shows a similar pattern to malignancies in terms of radiologic and clinical features. For this reason, oncological surgical principles should be applied during the resection of hepatic alveolar echinococcosis. The gold standard surgical treatment is resection with negative surgical margin. However, in patients whose radical resection is not possible other therapeutic options include palliative resection which has no benefit to the patient, and other curative major surgical options such as *ex vivo* liver resection, and autotransplantation and ultimately liver transplantation. The remnant liver volume has paramount importance if resection is going to be performed. For this reason, occasionally, remnant liver volume hypertrophy is induced by employing either two-stage hepatectomy or associating liver partition and portal vein ligation for staged hepatectomy.

## Review and reassessment of previous study

We provide a review and reassessment of data from 178 patients with hepatic alveolar echinococcosis (HAE) originally presented by Yang *et al.* (2019). First, we commend Yang *et al.*, in performing major resection in 67.9% of their HAE patients but wish to make specific reference to their patient D group as their liver transplantation group, for we judge this to be an autotransplantation group. So in order to prevent any further confusion, better terminology such as '*ex vivo* liver resection and autotransplantation' should be used throughout to avoid confusion.

We point out concerns on how they determined their predicted future liver remnant volume (FLRV) cut-off of 40%, as usually this is determined by evaluation of liver function tests and the quality of the liver parenchyma. For this reason, FRLV should be >20% in normal livers, >30% in steatotic livers, and > 40% in the cholestatic liver for a patient to tolerate major liver resection (Guglielmi *et al.*, 2012). Therefore, the cut-off value of >40% determined by the authors in Child A patients, without any history of chemotherapy, is not compatible with literature and our experience of over 2200 donor hepatectomies and 500 major liver resections. Of additional note, they could have better explained why they have included patients under 18 years but excluded the patients >60 years of age which, in our opinion, is important to include P1-4N0-1M0 patients. Patients >60 years of age that fit the inclusion criteria and who underwent successful resection should have been included. Furthermore, although the authors have included patients with FRLV >40%, there were 9 patients that did not meet these criteria and received a two-stage hepatectomy (TSH).

Since benzimidazole treatment was given to the patients for 2 years following the surgery, we observe some patients had a follow-up period of less than 2 years. There is consensus that patients with HAE should receive radical surgical and medical therapy to avoid any invasion of major vasculobiliary structures. Although the radiological tests reported were unequivocal, distant organ metastasis was detected in some patients. Medical therapy of patients with HAE should be in accordance with the PNM classification of the World Health Organization (WHO). According to these guidelines, stage P1-2N0M0 patients who had a successful radical resection should receive benzimidazole therapy for 2 years post-operative. In stage P3-4N0-1M1, patients in whom surgery could not be performed or is suboptimal, benzimidazole therapy should be used indefinitely (Brunetti *et al.*, 2010). For this reason, we believe, nearly half of the patients in the present study should receive benzimidazole treatment indefinitely.

For those patients who did not tolerate benzimidazole therapy well and had severe adverse events, alternative treatment options could have been better explored. Whilst the authors discontinued benzimidazole therapy, they did not report how many nor what alternatives were provided. Whilst novel therapeutic agents are being developed or repurposed, administration of liposomal amphotericin B could have been useful. A period of 8-12 weeks should be

**Table 1.** Comparison of all four groups in terms of clinical characteristics and PNM classification (revised authors' Table 1 & 2).

Characteristics	A (n = 87)	B (n = 24)	C (n = 9)	D (n = 58)	p
Sex (Male)	38 (46.9)	15 (18.5)	3(3.7)	25(30.9)	0.310
Symptoms/Findings					
Abdominal Pain	51 (43.6)	24 (20.5)	9 (7.7)	33 (28.2)	<0.001
Nausea/Vomit	12 (44.4)	5 (18.5)	1 (3.7)	9 (33.3)	0.838
Palpable mass	17 (30.4)	23 (41.1)	0 (0)	16 (25.6)	<0.001
Jaundice	14 (35.9)	3 (7.7)	1 (2.6)	21 (53.8)	0.015
Incidental	36 (100)	0 (0)	0 (0)	0 (0)	<0.001
Lesion location					
Right lobe	60 (48.8)	20 (16.3)	0 (0)	43 (35)	<0.001
Left lobe	17 (85)	3 (15)	0 (0)	0 (0)	0.002
Bilobar	10 (29.4)	0 (0)	9 (26.5)	15 (44.1)	<0.001
Number of lesions					
One lesion	41 (43.6)	17 (18.1)	0 (0)	36 (38.3)	0.001
Two lesion	24 (60)	5 (12.5)	0 (0)	11 (27.5)	0.225
Three lesion	15 (62.5)	0 (0)	2 (8.3)	7 (29.2)	0.140
Four or more	7 (35)	2 (10)	7 (35)	4 (20)	<0.001
Invasion features					
HV invasion	44(69.8)	6 (9.5)	1 (1.6)	12 (19)	0.001
PV invasion	16 (45.7)	1 (2.9)	1 (2.9)	17 (48.6)	0.023
HA invasion	0 (0)	0 (0)	0 (0)	25 (100)	<0.001
IVC invasion	0 (0)	0 (0)	0 (0)	53 (100)	<0.001
Diaphragm invasion	3 (6.8)	10 (22.7)	2 (4.5)	29 (65.9)	<0.001
PNM Classification					
P <sub>1</sub> N <sub>0-1</sub> M <sub>0</sub>	27 (100)	0 (0)	0 (0)	0 (0)	<0.001
P <sub>2</sub> N <sub>0-1</sub> M <sub>0</sub>	50 (74.6)	17 (25.4)	0 (0)	0 (0)	<0.001
P <sub>3</sub> N <sub>0-1</sub> M <sub>0</sub>	10 (38.5)	7 (26.9)	9 (34.6)	0 (0)	<0.001
P <sub>4</sub> N <sub>0-1</sub> M <sub>0</sub>	0(0)	0 (0)	0 (0)	58 (100)	<0.001

**Table 2.** Comparison of all four groups in terms of surgical treatment and complication (revised authors' [by Akbulut *et al.*] Table 3).

Characteristics (%)	A (n = 87)	B (n = 24)	C (n = 9)	D (n = 58)	p
Right hepatectomy	49 (75.4)	10 (15.4)	6 (9.2)	0 (0)	<0.001
Left hepatectomy	15 (62.5)	6 (25)	3 (12.5)	0 (0)	0.001
Middle hepatectomy	5 (100)	0 (0)	0 (0)	0 (0)	0.146
Extended right	11 (78.6)	3 (21.4)	0 (0)	0 (0)	0.027
Extended left	7 (58.3)	5 (41.7)	0 (0)	0 (0)	0.005
Autologous LT	0 (0)	0 (0)	0 (0)	58 (100)	<0.001
Mild Complication (I-II)					
Wound infection	6 (66.7)	1 (11.1)	0 (0)	2 (22.2)	0.695
Bile leaks	5 (45.5)	1 (9.1)	1 (9.1)	4 (36.4)	0.891
Residue abscess	2 (40)	2 (40)	1 (20)	0 (0)	0.082
Hydrothorax	3 (18.8)	1 (6.3)	1 (6.3)	11 (68.8)	0.011
Major Complication (IIIa-Vb)					
Septic shock	1 (50)	0 (0)	0 (0)	1 (50)	0.905
Bile leaks	3 (30)	2 (20)	1 (10)	4 (40)	0.616
Pneumonia	2 (28.6)	1 (14.3)	1 (14.3)	3 (42.9)	0.556
Mortality status	2 (28.6)	0 (0)	0 (0)	5 (71.4)	0.149

sufficient to reach adequate functional FLRV values in standard TSH treatment. On the other hand, advanced Associating Liver Partition and Portal vein Ligation for Staged hepatectomy (ALPPS) require 7–10 days to reach optimal FRLV (Selby and Hernandez-Alejandro, 2014; Zhou *et al.*, 2017; Sandstrom *et al.*, 2018).

Current meta-analyses showed that results of ALPPS are superior to TSH (Zhou *et al.*, 2017; Liu *et al.*, 2019). The authors, therefore, should clarify why they chose TSH with long waiting periods instead of performing the ALPPS procedure for waiting 3 months for a definitive complementary resection increases the risk of complications and dissemination of disease. To strengthen their study we have made a statistical comparison of their groups in terms of demographic and clinical parameters by re-analysis of their Table 2 & 3 and have presented our clinical results in Table 1 and Table 2. Although most of the variables are less than 5 in the 4 by 2 crosstable, our analysis shows which groups are broadly different. Briefly, following parameters were statistically different between the groups: abdominal pain, palpable mass, incidental, right lobe, left lobe, bilobar, one lesion, four or more lesion, HV invasion, PV invasion, HA invasion, IVC invasion, diaphragmatic invasion, all PNM classification, right hepatectomy, left hepatectomy, extended right hepatectomy, extended left hepatectomy, autologous liver transplantation, and hydrothorax.

### Topic highlight

- Alveolar echinococcosis is an aggressive zoonotic disease that affects mainly the liver but can be seen at any tissue and organ in the human body. Hepatic alveolar echinococcosis behaves like a neoplastic lesion and tends to invade the liver parenchyma. Although there is no definitive consensus, a clear surgical margin of 10 mm (1–20 mm) is recommended to reduce the postoperative recurrence risk.
- Adjuvant medical therapy including albendazole, mebendazole, praziquantel, nitazoxanide, and amphotericin, is recommended for postoperative 2 years in patients with R0 resection and more than 2 years in patients with R1–2 resection.
- The best surveillance strategy for alveolar echinococcosis after treatment is the use of a combination of serologic (recEm18-ELISA) and radiologic (computed tomography, magnetic resonance imaging) tests.
- The best treatment strategy for the disease is the use of a combination of surgical and medical therapy. The gold standard surgical treatment is radical resection. However, in patients whose radical resection is not possible other therapeutic options include palliative resection which has no benefit to the patient, and other curative major surgical options such as *ex vivo*

liver resection, and autotransplantation and ultimately liver transplantation. The remnant liver volume has paramount importance if resection is going to be performed. For this reason, occasionally, remnant liver volume hypertrophy is induced by employing either two-stage hepatectomy (TSH) or associating liver partition and portal vein ligation for staged hepatectomy (ALPPS).

- Both *ex vivo* liver resection and autotransplantation and liver transplantation are a major surgical procedure that has high morbidity and mortality risk and must be performed in centres that are experienced in hepatobiliary surgery. If liver transplantation is selected for hepatic alveolar echinococcosis then it is recommended that immunosuppressive therapy should be tapered and adjuvant anthelmintic therapy should be performed for at least postoperative 2 years.

**Financial support.** None

**Conflicts of interest.** None

**Ethical standards.** Not applicable

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