Relevance of Regional Lymph Node Invasion in Radical Hepatectomy and Lymphadenectomy for Alveolar Echinococcosis: A Retrospective Cohort Study

Xianwei Yang

Sichuan University West China Hospital

Tao Wang

Sichuan University West China Hospital

Shu Shen

Sichuan University West China Hospital

Wentao Wang (✉ wwtdoctor02@163.com)

Department of Liver Surgery, West China Hospital of Sichuan University, 37 Guoxue Road, Chengdu 610041, P.R.China. <https://orcid.org/0000-0002-6966-2665>

Research

Keywords: Alveolar echinococcosis, Lymph node, Lymphadenectomy, Invasion

Posted Date: August 28th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-67132/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License. [Read Full License](#)

Abstract

Background Hepatic Alveolar echinococcosis (AE) is also known as worm cancer, parasitic cancer, and it often invades the regional lymph nodes of the liver. The present study was to investigate the clinical value of radical hepatectomy and lymphadenectomy in AE patients.

Methods Our study enrolled consecutive AE patients who underwent radical hepatectomy with removal the regional lymph nodes between January 2009 and April 2019. Patients with inflammatory lymph node enlargement was included in group A, and patients with AE lymph node invasion were included in group B. The clinical characteristics, survival and recurrence rates were compared.

Results A total of 103 patients were enrolled group A, and 24 in group B. Preoperative computed tomography showed that the lymph node positivity rate in group B was 70.8% while that in group A was 43.7% ($p=0.017$). The lymph node diameter was 1.8 ± 0.9 cm in group A vs 2.5 ± 1.1 cm in group B ($p=0.004$), and the lymph node number ($p=0.035$) and lymph node location ($p=0.001$). A total of 10 patients (7.9%) had recurrent lesions, and 6 patients (4.7%) died ($P>0.05$).

Conclusions lymph node diameter, number, and distance from the liver were important characteristics for describing lymph node invasion. There was no difference in the long-term efficacy of lymphadenectomy between patients with lymph node enlargement and those with invasion.

Background

Hepatic alveolar echinococcosis (AE), also known as "worm cancer", "parasitic cancer", is a parasitic life-threatening infestation that is caused by the larval stage of *Echinococcus multilocularis* and is found in the majority of the Northern Hemisphere, especially in Tibetan areas of China[1, 2]. Radical hepatectomy is the main way to treat AE, but treating regional lymph nodes before or during surgery is a difficult problem. It is well known that if lymphatic metastasis is found in liver malignancies, the disease is mostly likely in the advanced stage, and the prognosis is poor[3]. Although the biological behavior of AE is similar to that of malignant tumors in that the tumor invades the surrounding organs and tissues, AE invasion is largely a chronic inflammatory response. However, the regional lymph nodes in hepatic AE show inflammatory enlargement, invasion and metastasis. Lymph node invasion and metastasis means that AE fragments can be found in the lymph nodes, but these fragments are not found in inflammatory lymph node enlargement.

In 2006, the WHO-Infomal Working Group on Echinococcosis (WHO-IWGE) proposed the PNM classification[4] (P=parasitic mass in the liver, N=involvement of neighboring organs, and M=metastasis). Lymph nodes were divided into regional lymph nodes and distant lymph nodes, corresponding to N1 and M1, respectively, and interventional treatment/drug therapy was recommended[5]. However, this system does not clearly define "regional" and "distant" lymph nodes or "metastasis" and "involvement", leading to a lack of indications for lymphadenectomy[1, 4]. In addition to intra-abdominal lymph nodes, mediastinal lymphadenopathy[6] and cervical lymph node[7] were observed. The present cases suggested that echinococcosis could be involved in distant organs through the lymphatic system[8]. A previous study[9, 10] by our team found that lymphadenectomy was more common for AE than for malignant tumors, but long-term follow-up observations of large samples of these two conditions have not been reported. Therefore, this study attempts to explain the clinical features of AE lymph node enlargement and invasion and the survival benefits of lymphadenectomy.

Methods

From January 2009 to April 2019, medical records of selected 127 (30.2%) hepatic alveolar echinococcosis patients were reviewed (Figure 1). The Research Ethics Committee of West China Hospital approved this retrospective study, and the Sichuan Province Hydatid Disease Clinical Medicine Research Registration Number (2018-02). Specimens were collected after obtaining informed consent from the patients. This study was performed as per the established national and institutional ethical guidelines regarding the involvement of human subjects and the use of human tissues for research. All procedures were conducted in accordance with the most recent revision of the Declaration of Helsinki.

All patients underwent abdominal, chest and brain computed tomography (CT) and/or magnetic resonance imaging to evaluate the liver lesions, lymph node characteristics, conduit structures and extrahepatic organ status. For complex liver resection, liver transplantation and liver autotransplantation[11], we created three-dimensional (3D) images to distinguish the anatomical relationships between the AE lesions and neighboring organs. In addition, the remaining liver volume was also estimated. All surgeries were performed by surgeons in the same department, and detailed preoperative multidisciplinary team discussions were conducted. All suspicious lymph nodes were cleared based on the results of preoperative imaging examinations and intraoperative findings (Figure 2). The position, number and diameter of lymph nodes found during the operation were recorded. Immediately after the infected lymph nodes and liver lesions were removed, they were placed in 10% formaldehyde, routinely dehydrated, embedded in paraffin, sliced into 4 μ m sections, and hematoxylin and eosin (HE) and periodic acid-Schiff (PAS) staining was performed.

After conventional HE and PAS staining[12], the diagnosis was based on the presence or absence of small particles of *E. multilocularis* (spems) outside the main lesion under the microscope. If AE structures were found in ≥ 5 fields of vision (X100), the sample was classified as lymph

node invasion and included in group B; otherwise, the sample was included in group A (inflammatory lymph node enlargement). This procedure was performed by 3 blinded independent experienced pathologists. Finally, there were 103 patients in group A and 24 patients in group B (Figure 3).

The diameter of AE lesions was calculated based on preoperative CT. Radical resection refers to a distance of 2.0 cm or more[13]. The largest lymph node diameter was recorded as the diameter. Patients were followed regularly after discharge, at 3 months, 6 months, 1 year, 2 years, etc., and were consecutively observed. Recurrences were defined as any new liver or lymph node lesion on imaging that was highly suspicious of AE recurrence. The appearance of another extrahepatic AE lesion was classified as metastasis. The time and characteristics of the patient's recurrence, metastasis and death were recorded.

Statistical analysis

All quantitative variables that obeyed a normal distribution were reported as the mean $\pm$ standard deviation and were compared using independent Student's t-tests. Categorical variables that did not obey a normal distribution are presented as percentages or/and the median (minimum-maximum) value. Then, the chi-square analysis or Mann-Whitney nonparametric test was used. Survival analysis was performed using the Kaplan–Meier method with a log-rank test for differential analysis. Statistical analyses were performed with SPSS version 13.0 software (IBM, Armonk, New York, USA). $P < 0.05$ was considered statistically significant.

Results

Patient characteristics

A total of 127 patients had abnormal lymph nodes during the operation, while the preoperative CT report found only 62 abnormal lymph nodes (60.2%). The diagnostic accuracy of CT for lymph node invasion was higher than that for lymph node enlargement (70.8% vs 43.7%, $p = 0.017$). There were 122 Tibetan patients (96.1%) and 5 Han patients (3.9%). In group A, the average age was 37 years old, and the body mass index (BMI) was 22.0 kg/m²; in group B, the average was 37.2 years old ($p = 0.79$), and the BMI was 21.8 kg/m² ($p = 0.78$). In total, 58 patients complained of right upper quadrant pain (45.7%), 46 of liver-occupying lesions (36.2%), 14 of jaundice (11.0%), and 9 of abdominal distension (7.1%). Preoperatively, 5 patients had undergone hepatic lobectomy (3.9%), 3 had undergone puncture and aspiration (2.4%), 11 had undergone percutaneous transhepatic cholangial drainage (PTCD) (8.7%), and 2 had undergone portal vein embolization (PVE) (1.6%). Regarding liver lesion location, 53 cases were in the right liver (41.7%), 57 were in the middle liver (44.9%), 9 were in the left liver (7.1%), and 8 were in the caudate lobe (6.3%). There was no difference in liver lesion diameter between the two groups ($p = 0.53$). There were no differences in the number of liver lesions, portal vein invasion, bile duct invasion, inferior vena cava (IVC) invasion, or PNM stage between the two groups ($p > 0.05$). There were no differences in white blood cell count (WBC), total bilirubin, alanine transaminase, aspartate aminotransferase, or prothrombin time before surgery between the two groups ($p > 0.05$). Seventy-five patients underwent right hepatectomy (59.1%), 37 underwent liver transplantation (29.1%), 12 underwent middle liver resection (9.4%), and only 3 underwent left hepatectomy. During the postoperative hospitalization period, 25 patients had grade III complications[14], and no patients died during the postoperative hospital stay. More data are shown in Table 1.

Characteristics of lymph node resection

The diameter of the lymph nodes in group B was larger than that in group A (2.5 ± 1.1 cm vs 1.8 ± 0.9 cm, $p = 0.004$). In group A, the lymph nodes were mainly located around the hepatoduodenal ligament (68.0%) and the perigallbladder region (24.5%), but group B more abdominal lymph nodes (16.7%), apart from around the hepatoduodenal ligament (58.3%). In terms of the distribution of locations, there were differences between the two groups ($p = 0.001$). Group A was dominated by single lymph nodes (61.2%), group B was dominated by multiple lymph nodes (41.7%), and the number of lymph nodes was greater in group B than in group A ($p = 0.035$). All liver lesions were pathologically diagnosed as AE, and regional lymph nodes affected by AE may have either lymph node invasion or lymph node enlargement, or both (Supplementary Figure 1).

Clinical outcomes

As of December 2019, the median follow-up duration of the 127 patients was 31 months (7-130 months). AE recurrence in the liver was found in 8 patients (7.86%) in group A and 2 patients (8.33%) in group B during the follow-up, and the disease-free survival (DFS) was not significantly different between the 2 groups ($p = 0.525$). These DFS, OS curve were shown in Figure 4. There were no distant organ metastases, such as brain AE. Six patients died, including 5 patients in group A and 1 in group B, all due to liver failure and multiple organ failure caused by giant AE lesions with liver recurrence. The overall survival (OS) rate was 95.3%, and there was no difference between the two groups ($p = 0.582$).

Discussion

Alveolar echinococcosis is a severely understudied parasitic disease found worldwide, mainly in China[15], Turkey [16], France [17], Germany[18], North America[19], and so on. AE mainly affects the liver, lungs[20], brain, and adrenal glands[21], and radical resection is the main treatment.

Lymph node invasion and metastasis are associated with advanced malignant cancer, but very few studies focus on AE and are ambiguous. Currently, large samples are needed to confirm whether selective lymphadenectomy or extended dissection is effective for AE. The retrospective analysis in this study of data over nearly 12 years found that radical resection for patients with regional lymph node invasion around the liver leads to no survival benefits. Compared with lymph node invasion, inflammatory enlargement of the lymph nodes is more common, and the two pathological states have no difference in long-term outcomes after radical lymph node resection. This study will help surgeons judge the rationality of intraoperative lymph node resection.

AE lymph node changes were mentioned as early as 1984[22, 23] and later written into the WHO guidelines[4] in 2006, which defined lymph node involvement as "N1" or "M1". However, there was no distinction or definition of these two classifications: one was described as regional and distant, and the other was indicated by the pathological evidence of involvement or metastasis. In 2009, Klaus et al[24] confirmed for the first time that a patient with AE had regional lymph node involvement. Subsequently, some cases were gradually reported, but all lacked data regarding the incidence and long-term follow-up conclusions[7, 8, 12, 13, 25] (Table 2). In 2018, a retrospective analysis[26] of 46 patients in this center found that 7 patients had AE lymph node involvement and proposed that lymph node involvement was not associated with recurrent disease. The incidence of infected lymph nodes in that study was comparable to that in our study (16.28% vs 18.90%), and the conclusions were basically consistent, but we observed the patients over a longer period. In contrast, the descriptions of lymph node invasion and metastasis in other studies were ambiguous[7, 12, 13]. However, some animal experiments have also proven the existence of lymph node invasion[27, 28]. Currently, this study is the largest cohort study with the longest follow-up duration of AE regional lymph node resection. Based on the clinical results of 127 patients, there was no difference between inflammatory enlargement of the regional lymph nodes and AE invasion, which were not related to long-term mortality or recurrence rate. However, it is worth noting that resection is the most ethical and effective treatment for enlarged lymph nodes found before and during surgery. Since lymphatic spread has been described, routine removal of regional lymph nodes has been suggested as a curative approach to avoid incomplete resections and reduce the risk of persistent infection.

The hepatoduodenal ligament lymph nodes are still the most commonly affected, followed by the perigallbladder lymph nodes, celiac lymph nodes, mesenteric lymph nodes, and retropancreatic lymph nodes. Lymph node involvement and the inflammatory enlargement of lymph nodes have different localizations. The main reason is that celiac lymph nodes and retropancreatic lymph nodes are important features of invasion. We infer that advanced AE can cross the hilar lymph nodes and directly invade the retropancreatic and abdominal lymph nodes. The hepatoduodenal ligament lymph nodes often act as sentinels to reflect AE inflammatory activity. The enlargement of the perigallbladder lymph nodes is closely related to rich lymphatics. AE lesions involving the gallbladder are rare because of the thick wall of the gallbladder. In addition, infected mesenteric and abdominal lymph nodes may form from repeated stimulation of the worm components that escape from the surface of the liver AE lesion. From an anatomical perspective[29], lymphatic fluid passes through hepatocytes in Disse's space to the sublobular and superficial lymphatic vessels and then to the liver capsule, sublobular region, or into the lymph vessels that lead to the inferior vena cava. Approximately 80% of the hepatic lymph fluid is drained by the portal lymphatic vessels, and the rest flows through the coeliac region, with a small amount reaching the peritoneum and entering the thoracic duct. This is consistent with the distribution probability of our lymph nodes. We speculated that AE can go undetected in the lymph fluid and then colonize the lymph nodes to form lesions. Enlarged inflammatory lymph nodes are only the aggregated effects of inflammatory cells and cytokines. Distant lymph nodes should be above the diaphragm and below the umbilical plane, and it is reasonable to define them as metastases (M1)[30-32].

CT evaluation can better detect lymph node inflammation than lymph node invasion, which may be related to the larger diameter, larger number, and atypical location of lymph node invasion. We do not recommend lymph node biopsy. If the liver does not have a large primary AE lesion (diameter ≥ 3 cm), the prognosis of the enlarged lymph node and lymph node invasion is also optimistic, and the probability of recurrence or death is very low. If lymph node metastasis is suspected, and puncture should be performed cautiously. EUS-FNA is a good diagnostic tool, but it should be used when the diagnosis is unclear and the patient is from a nonendemic area[8, 25]. Pathological diagnosis is the gold standard. AE in lymph nodes has typical characteristics after HE staining and PAS staining and is very easy for pathologists to diagnose in endemic areas. Combining serum AE IgG antibodies and imaging results is highly useful for diagnosis. New recombinant antibodies, such as Em2 and Em18, are helpful for the diagnosis of AE lymph node invasion, but they are difficult to obtain through commercial channels, and they are also expensive and not suitable for large-scale clinical use. PET has some value in the diagnosis of AE, but it is expensive and imparts great economic pressure on infected individuals in pastoral areas.

Lymph nodes are often an important raw material for studying inflammatory responses, and AE is a chronic inflammation process in response to parasites and hosts. Our study found that a large number of inflammatory cells accumulated on the side of the AE lesion in the lymph nodes, and these cells directly or indirectly participated in the process of chronic inflammation and fibrosis. AE inflammation is similar in liver lesions and lymph nodes and provides a basis for in vitro experiments or animal experiments[33-35].

From our long-term follow-up observations, we found that the recurrence rate and mortality were very low, and there was no difference between lymph node invasion and inflammatory lymph node enlargement. Thus, the treatment guidelines should not recommend regional lymph node resection. If a simple inflammatory enlarged lymph node is found during surgery away from the liver AE lesions, it may not be removed. Lymph

node invasion should be considered a possibility if the lymph nodes are close to the liver AE lesions, a high number (≥ 3) are present, a large diameter (≥ 2.5 cm) is observed, the location is special, etc., and lymph node resection is strongly recommended. Some lymph nodes are located in the hepatoduodenal ligament, around the gallbladder, etc. Although inflammatory reactions are considered empirically, for the convenience of anatomical exposure and liver resection, lymph node resection is recommended. Lymphadenectomy should not be performed for conditions that imitate AE like gastric cancer, pancreatic cancer, or hilar cholangiocarcinoma. The removal of excess normal lymph nodes is not beneficial for long-term outcomes and increases the operative time and risk of surgery. The PNM criteria of the WHO-IWGE for lymph node grouping should be revised. The first revision should distinguish "involvement" as invasion and inflammatory enlargement (N1), and the second revision should define "distant" as the liver hilar and coeliac region, above the diaphragm and below the umbilicus (M1). The corresponding treatment should be administered more cautiously. Finally, because AE has a low probability of lymph node invasion, the disease progresses slowly, and it is difficult to carry out randomized clinical trials; however, we have already started this difficult task. More research is needed to understand the secrets of lymph node invasion, which will provide ideas for elucidating the chronic inflammation mechanism and furthering drug development for AE.

Conclusions

Lymph node diameter, number, and distance from the liver were important characteristics for describing lymph node invasion. There was no difference in the long-term efficacy of lymphadenectomy between patients with lymph node enlargement and those with invasion.

Abbreviations

Alveolar echinococcosis (AE);

Computed tomography (CT);

Hematoxylin and eosin (HE);

Inferior vena cave (IVC);

Periodic acid-Schiff (PAS);

PNM classification, P=parasitic mass in the liver, N=involvement of neighboring organs, and M=metastasis;

Percutaneous transhepatic cholangial drainage (PTCD);

Portal vein embolization (PVE);

Three-dimensional (3D); White blood cell count (WBC)

Declarations

Ethics approval and consent to participate

Patient records were de-identified and anonymized prior to the analysis. The Research Ethics Committee of West China Hospital approved this retrospective study, and the Sichuan Province Hydatid Disease Clinical Medicine Research Registration Number (2018-02).

Consent for publication

Written informed consent was obtained from the patients and/or their legal guardians for publication, and any accompanying images, sex, age of these patients.

Availability of data and material

The data of the article can be obtained from the corresponding author through email consultation.

Conflicts of interest

All authors declare no conflicts of interest.

Funding: This research was supported by the Science and Technology Program of Sichuan Science and Technology Department (No. 2019YFS0029, 2019YFS0529), the National Natural Science Foundation of China (No. 81770566). Corresponding author WWT is the guarantor. The funding body financed the costs of the study and contributed to the design of the study, interpretation of data, and revising the manuscript.

Author Contributions

Study conception and design: Xianwei Yang, Wentao Wang

Acquisition of data: Xianwei Yang, Tao Wang, Shu Shen, Wentao Wang

Analysis and interpretation of data: Xianwei Yang, Wentao Wang

Drafting of manuscript: Xianwei Yang

Critical revision: Xianwei Yang, Wentao Wang

Final approval of the version to be submitted: All Authors.

Acknowledgments

I need to thank Wu Zhengru for her help with our illustrations.

References

1. Wen H, Vuitton L, Tuxun T, Li J, Vuitton DA, Zhang W, McManus DP. Echinococcosis: Advances in the 21st Century. CLIN MICROBIOL REV 2019, 32(2).DOI:10.1128/CMR.00075-18
2. Xu K, Ahan A. A new dawn in the late stage of alveolar echinococcosis "parasite cancer". MED HYPOTHESES 2020, 142:109735.DOI:10.1016/j.mehy.2020.109735
3. Benson AR, D'Angelica MI, Abbott DE, Abrams TA, Alberts SR, Saenz DA, Are C, Brown DB, Chang DT, Covey AM *et al.* NCCN Guidelines Insights: Hepatobiliary Cancers, Version 1.2017. J Natl Compr Canc Netw 2017, 15(5):563-573.DOI:10.6004/jnccn.2017.0059
4. Kern P, Wen H, Sato N, Vuitton DA, Gruener B, Shao Y, Delabrousse E, Kratzer W, Bresson-Hadni S. WHO classification of alveolar echinococcosis: principles and application. PARASITOL INT 2006, 55 Suppl:S283-S287.DOI:10.1016/j.parint.2005.11.041
5. Brunetti E, Kern P, Vuitton DA. Expert consensus for the diagnosis and treatment of cystic and alveolar echinococcosis in humans. ACTA TROP 2010, 114(1):1-16.DOI:10.1016/j.actatropica.2009.11.001
6. Issoufou I, Harmouchi H, Efared B, Belliraj L, Ammor FZ, Lakranbi M, Ouadnouni Y, Smahi M. [What contribution for mediastinoscopy in non-tumor specific mediastinal lesions?]. REV PNEUMOL CLIN 2018, 74(4):242-247.DOI:10.1016/j.pneumo.2018.05.003
7. Eser I, Karabag H, Gunay S, Seker A, Cevik M, Ali SZ, Yalcin F, Aydin MS. Surgical approach for patients with unusually located hydatid cyst. ANN ITAL CHIR 2014, 85(1):50-55
8. Moriichi K, Fujiya M, Goto T, Okumura T. Echinococcosis infection diagnosed based on the histological findings of a lymph node involvement obtained by EUS-FNA. ENDOSC ULTRASOUND 2018, 7(3):210-211.DOI:10.4103/eus.eus_90_17
9. Du C, Liu Z, Yang X, Yan L, Li B, Wen T, Yang J, Xu M, Chen Z, Wang W. Hepatectomy for patients with alveolar echinococcosis: Long-term follow-up observations of 144 cases. INT J SURG 2016, 35:147-152.DOI:10.1016/j.ijsu.2016.09.094
10. Yang C, He J, Yang X, Wang W. Surgical approaches for definitive treatment of hepatic alveolar echinococcosis: results of a survey in 178 patients. PARASITOLOGY 2019, 146(11):1414-1420.DOI:10.1017/S0031182019000891
11. Yang X, Qiu Y, Huang B, Wang W, Shen S, Feng X, Wei Y, Lei J, Zhao J, Li B *et al.* Novel techniques and preliminary results of ex vivo liver resection and autotransplantation for end-stage hepatic alveolar echinococcosis: A study of 31 cases. AM J TRANSPLANT 2018, 18(7):1668-1679.DOI:10.1111/ajt.14621
12. Barth TF, Herrmann TS, Tappe D, Stark L, Gruner B, Buttenschoen K, Hillenbrand A, Juchems M, Henne-Bruns D, Kern P *et al.* Sensitive and specific immunohistochemical diagnosis of human alveolar echinococcosis with the monoclonal antibody Em2G11. PLoS Negl Trop Dis 2012, 6(10):e1877.DOI:10.1371/journal.pntd.0001877
13. Kawamura N, Kamiyama T, Sato N, Nakanishi K, Yokoo H, Kamachi H, Tahara M, Yamaga S, Matsushita M, Todo S. Long-term results of hepatectomy for patients with alveolar echinococcosis: a single-center experience. J Am Coll Surg 2011, 212(5):804-812.DOI:10.1016/j.jamcollsurg.2011.02.007
14. Clavien PA, Barkun J, de Oliveira ML, Vauthey JN, Dindo D, Schulick RD, de Santibanes E, Pekolj J, Slankamenac K, Bassi C *et al.* The Clavien-Dindo classification of surgical complications: five-year experience. ANN SURG 2009, 250(2):187-196.DOI:10.1097/SLA.0b013e3181b13ca2
15. Yang GJ, Liu L, Zhu HR, Griffiths SM, Tanner M, Bergquist R, Utzinger J, Zhou XN. China's sustained drive to eliminate neglected tropical diseases. LANCET INFECT DIS 2014, 14(9):881-892.DOI:10.1016/S1473-3099(14)70727-3

16. Emre A, Ozden I, Bilge O, Arici C, Alper A, Okten A, Acunas B, Rozanes I, Acarli K, Tekant Y *et al.* Alveolar echinococcosis in Turkey. Experience from an endemic region. *Dig Surg* 2003, 20(4):301-305.DOI:10.1159/000071695
17. Bresson-Hadni S, Vuitton DA, Bartholomot B, Heyd B, Godart D, Meyer JP, Hrusovsky S, Becker MC, Mantion G, Lenys D *et al.* A twenty-year history of alveolar echinococcosis: analysis of a series of 117 patients from eastern France. *Eur J Gastroenterol Hepatol* 2000, 12(3):327-336.DOI:10.1097/00042737-200012030-00011
18. Buttenschoen K, Carli BD, Gruener B, Kern P, Beger HG, Henne-Bruns D, Reuter S. Long-term experience on surgical treatment of alveolar echinococcosis. *Langenbecks Arch Surg* 2009, 394(4):689-698.DOI:10.1007/s00423-008-0392-5
19. Wilson JF, Rausch RL, Wilson FR. Alveolar hydatid disease. Review of the surgical experience in 42 cases of active disease among Alaskan Eskimos. *ANN SURG* 1995, 221(3):315-323.DOI:10.1097/00000658-199503000-00015
20. Kurt Y, Sucullu I, Filiz AI, Urhan M, Akin ML. Pulmonary echinococcosis mimicking multiple lung metastasis of breast cancer: the role of fluoro-deoxy-glucose positron emission tomography. *WORLD J SURG ONCOL* 2008, 6:7.DOI:10.1186/1477-7819-6-7
21. Babinska A, Peksa R, Swiatkowska-Stodulska R, Sworczak K. The collection of five interesting cases of adrenal tumors from one medical center. *WORLD J SURG ONCOL* 2014, 12:377.DOI:10.1186/1477-7819-12-377
22. Urdiales-Viedma M, Martos-Padilla S, Nogales-Fernandez F, Lopez-Yevenes A. Lymph node changes in echinococcosis. *ARCH PATHOL LAB MED* 1984, 108(7):528
23. Drolshammer I, Wiesmann E, Eckert J. [Human echinococcosis in Switzerland during the years 1956-1969]. *Schweiz Med Wochenschr* 1973, 103(40):1386-1392
24. Buttenschoen K, Kern P, Reuter S, Barth TF. Hepatic infestation of *Echinococcus multilocularis* with extension to regional lymph nodes. *Langenbecks Arch Surg* 2009, 394(4):699-704.DOI:10.1007/s00423-009-0481-0
25. Amano T, Hayashi S, Nishida T, Matsubara T, Takahashi K, Nakamatsu D, Tomimaru Y, Yamamoto M, Nakajima S, Fukui K *et al.* Alveolar Echinococcosis Mimicking a Hepatic Neoplasm with Lymph Node Metastasis: A Case Report. *Case Rep Gastroenterol* 2018, 12(3):587-596.DOI:10.1159/000492461
26. Hillenbrand A, Beck A, Kratzer W, Graeter T, Barth TFE, Schmidberger J, Möller P, Henne-Bruns D, Gruener B. Impact of affected lymph nodes on long-term outcome after surgical therapy of alveolar echinococcosis. *Langenbeck's Archives of Surgery* 2018, 403(5):655-662.DOI:10.1007/s00423-018-1687-9
27. Sakamoto T, Cabrera PA. Immunohistochemical observations on cellular response in unilocular hydatid lesions and lymph nodes of cattle. *ACTA TROP* 2003, 85(2):271-279
28. Eckert J, Thompson RC, Mehlhorn H. Proliferation and metastases formation of larval *Echinococcus multilocularis*. I. Animal model, macroscopical and histological findings. *Z Parasitenkd* 1983, 69(6):737-748
29. Ohtani O, Ohtani Y. Lymph circulation in the liver. *Anat Rec (Hoboken)* 2008, 291(6):643-652.DOI:10.1002/ar.20681
30. Duman U, Yesil C, Gunduz M, Deniz IK. Isolated left supraclavicular hydatid cyst mimicking Virchow's node. *TURK J GASTROENTEROL* 2012, 23(5):612-614
31. Isitmangil T, Toker A, Sebit S, Erdik O, Tunc H, Gorur R. A novel terminology and dissemination theory for a subgroup of intrathoracic extrapulmonary hydatid cysts. *MED HYPOTHESES* 2003, 61(1):68-71
32. Iuliano L, Gurgo A, Poletini E, Gualdi G, De Marzio P. Musculoskeletal and adipose tissue hydatidosis based on the iatrogenic spreading of cystic fluid during surgery: report of a case. *SURG TODAY* 2000, 30(10):947-949.DOI:10.1007/s005950070052
33. Margos MC, Grandgirard D, Leib S, Gottstein B. In vitro induction of lymph node cell proliferation by mouse bone marrow dendritic cells following stimulation with different *Echinococcus multilocularis* antigens. *J HELMINTHOL* 2011, 85(2):128-137.DOI:10.1017/S0022149X10000878
34. Margos M, Gottstein B. Gerbu adjuvant modulates the immune response and thus the course of infection in C56BL/6 mice immunised with *Echinococcus multilocularis* rec14-3-3 protein. *PARASITOL RES* 2010, 107(3):623-629.DOI:10.1007/s00436-010-1907-x
35. Fotiadis C, Sergiou C, Kirou J, Troupis TG, Tselentis J, Doussaitou P, Gorgoulis VG, Sechas MN. Experimental echinococcus infection in the mouse model: pericystic cellular immunity reaction and effects on the lymphoid organs of immunocompetent and thymectomized mice. *IN VIVO* 1999, 13(6):541-546

Tables

Table 1. Comparison of the clinicopathological factors between patients with and without lymph node changes.

Category	Group A, n=103	Group B, n=24	P
Age	37.9±11.7	37.2±11.3	0.79
Body mass index	22.0±3.1	21.8±3.29	0.78
Sex			
Male	50 (48.5%)	11 (45.8%)	0.81
Female	53 (51.5%)	13 (54.2%)	
Preoperative CT evaluation			
Negative	58 (56.3%)	7 (29.2%)	0.017
Positive	45 (43.7%)	17 (70.8%)	
Lymph node diameter	1.8±0.9	2.5±1.1	0.004
Number of lymph nodes			
One	63 (61.2%)	8 (33.3%)	0.035
Two	19 (18.4%)	6 (25.0%)	
Multiple	21 (20.4%)	10 (41.7%)	
Lymph node location			
Hepatoduodenal ligament	70 (68.0%)	14 (58.3%)	0.001
Perigallbladder lymph nodes	25 (24.3%)	1 (4.2%)	
Mesenteric lymph nodes	3 (2.9%)	2 (8.3%)	
Celiac lymph nodes	3 (2.9%)	4 (16.7%)	
Retropancreatic lymph nodes	2 (1.9%)	3 (12.5%)	
Liver lesion diameter	11.9±4.2	12.5±4.3	0.53
Liver lesion number			
One	51 (49.5%)	11 (45.8%)	0.64
Two	14 (13.6%)	2 (8.3%)	
Multiple	38 (36.9%)	11 (45.8%)	
PNM stage			
P1-2N1-2M0	2 (1.6%)	0	0.36
P3N0M0	42 (40.8%)	7 (29.2%)	
P3N1M0	5 (4.9%)	0	
P4N0M0	21 (20.4%)	3 (12.5%)	
P4N1M0	28 (27.2%)	12 (50.0%)	
P4N1M1	5 (4.9%)	2 (8.3%)	
Portal vein invasion			
Absent	62 (60.2%)	14 (58.3%)	0.87
Present	41 (39.8%)	10 (41.7%)	
Inferior vena cava invasion			
Absent	61 (59.2%)	15 (62.5%)	0.77
Present	42 (40.8%)	9 (37.5%)	
Hepatic vein invasion			
Absent	66 (64.1%)	14 (58.3%)	0.60

Present	37 (35.9%)	10 (41.7%)	
Intrahepatic bile duct invasion			
Absent	69 (67.0%)	13 (54.2%)	0.24
Present	34 (33.0%)	11 (45.8%)	
Clavien-Dindo complications			
None	76 (73.8%)	16 (66.7%)	0.75
I-II	8 (7.8%)	2 (8.3%)	
III	19 (18.4%)	6 (25.0%)	
Follow-up duration in months	31 (8-130)	26.5 (7-95)	0.13

Table 2. An overview of the related literature from 2009 to 2019 obtained from PubMed with the keywords "echinococcosis" and "lymph node" (including this study).

Year	First author	N*	n (n/N×100%)#	Time	Lymph nodes description	Remarks [Ref]	Journal	Region/Country
2009	Klaus Buttenschoen	1	1	None	Lymph node infested by E. multilocularis with a central necrotic zone	Positron emission tomography (PET-CT), hematoxylin-eosin (HE) staining and periodic acid-Schiff (PAS) stain	Langenbecks Arch Surg	Ulm/Germany
2011	Norio Kawamura	188	7 (3.72%)	1984 to 2009	Lymph node metastasis, 3 cases of lymph node resection	In the complete resection group, the 10-, 15-, and 20-year PFS rates were 96.5%, 94.4%, and 94.4%, respectively.	J Am Coll Surg	Norio Kawamura/Japan
2012	Thomas F. E. Barth	49	3 (6.12%)	-1989	Two cases of regional lymph node involvement and 1 case of retropancreatic lymph node involvement, regional lymph nodes with fragments of the laminated layer of E.multilocularis	Immunohistochemistry with the mAb Em2G11 was a new, highly specific and sensitive diagnostic tool.	PLoS Negl Trop Dis	Ulm/Germany
2014	Irfan Eser	367	1 (0.27%)	2005 to 2012	Hydatid cyst, cervical lymph node involvement	Unusual locations of the hydatid cysts from 51 patients.	Ann Ital Chir	Sanliurfa/Turkey
2018	Kentaro Moriichi	1	1	None	A 20 mm necrotic lymph node in the hepatoduodenal ligament, alveolar echinococcosis extending to the lymph nodes	Endoscopic US-guided fine-needle aspiration (EUS-FNA) for lymph nodes; a multilobular lesion in the right lobe of the liver (segment five) .	Endosc Ultrasound	Asahikawa/Japan
2018	Andreas Hillenbrand	43	7 (16.28%)	2000 to 2017	Infected lymph nodes (laminar layer visible, Em2G11 (+), HE and PAS (+))	7 cases of no recurrence, 4 years for patients with infected lymph nodes.	Langenbecks Arch Surg	Ulm/Germany
2018	Takahiro Amano	1	1	None	Retrospectively, a part of Echinococcus was founded in the peripancreatic lymph node specimens	An asymptomatic 17-mm liver mass was slightly enlarged for 5 years, and an abnormal peripancreatic lymph nodes were biopsied by EUS-FNA.	Case Rep Gastroenterol	Toyonaka/Japan
2020	This study	421	127 (30.16%)	2009 to 2019	Lymph node enlargement in 103 patients and lymph node invasion in 24 patients (18.90%)	Hematoxylin-eosin (HE) staining and periodic acid-Schiff (PAS) stain.	This study	XXX/XXX

Notes: N*, All echinococcosis patients; n, refers to patients with lymph node changes and resection who were confirmed to have pathological changes in their lymph nodes.

Figures

Figure 1
Flow chart of the study design.

Figure 2

Preoperative computed tomography evaluation of lymph nodes and intraoperative pathological findings. Notes: A. B. C Preoperative computed tomography evaluations revealed abnormal lymph nodes near the hepatoduodenal ligament (white arrow). D, E, F Abnormal lymph nodes (blue arrows) were found during surgery. The lymph nodes in Figure D were enlarged and soft (group A). Those in E and F were hard and close to the AE lesions in the liver, suggesting lymph node invasion (group B).

Figure 3

Pathological characteristics of lymph node echinococcosis changes. Notes: Panel A was an approximately 2.54 cm×1.25 cm enlarged lymph node found during the operation. Panel B shows granulomatous inflammation of the lymph nodes and a large amount of necrotic material in the lymph nodes (3.10 cm×1.50 cm). Panel C shows a large number of necrotic fibrous tissues in the late stages of AE lymph node invasion (4.20 cm×3.10 cm). PAS staining: Panel D shows a large number of inflammatory cells in the lymph nodes, without worms (D, X100; d, X400); Panels E and F show AE hydatid fragments in the lymph nodes, and the red matrix staining of polysaccharide components was obvious, which was helpful for the diagnosis of lymph node invasion (E/F, X100; e/f, X400).

Figure 4

The disease-free survival and overall survival rates related to AE with lymph node invasion. Notes: Kaplan–Meier plots of disease-free survival (DFS, figure A) and overall survival (OS, figure B) of 127 patients with AE lymph node changes, stratified by the expression of lymph node invasion. The survival data were analyzed by the Kaplan–Meier method and log-rank test. There were no significant differences between group A and group B in DFS and OS (p=0.525 and p=0.582, respectively).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [SupplementaryFigure1.tif](#)