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ORIGINAL ARTICLE

The trajectory of anti-recEm18 antibody levels determines follow-up after curative resection of hepatic alveolar echinococcosis

Severin Gloor[1], Wanjie Jiang[2], Martin H. Maurer[3,4], Bruno Gottstein[5,6], Alexander Oberli[6], Jürgen B. Hagemann[7], Julian F. Hotz[2,8], Daniel Candinas[1], Anja Lachenmayer[1], Beate Grüner[2] & Guido Beldi[1]

[1]Department of Visceral Surgery and Medicine, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland, [2]Department of Internal Medicine III, Division of Infectious Diseases, University Hospital of Ulm, Ulm, Germany, [3]Department for Diagnostic, Interventional, and Paediatric Radiology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland, [4]Institute for Diagnostic and Interventional Radiology, University Oldenburg, Oldenburg, Germany, [5]Institute of Parasitology, Department of Infectious Diseases and Pathobiology, Vetsuisse Faculty, University of Bern, Bern, Switzerland, [6]Institute for Infectious Diseases, Medical Faculty, University of Bern, Bern, Switzerland, [7]Institute of Medical Microbiology and Hygiene, University Hospital of Ulm, Ulm, Germany, and [8]Department of Medicine I, Division of Infectious Diseases and Tropical Medicine, Medical University of Vienna, Vienna, Austria

Abstract

Introduction: Recurrence after curative resection of hepatic alveolar echinococcosis remains a clinical challenge. The current study tested if assessment of anti-recEm18 allows for postsurgical patient surveillance.

Methods: A retrospective study with patients undergoing liver resection for alveolar echinococcosis (n = 88) at the University Hospital Bern from 2002 to 2020 and at the University Hospital and Medical Center Ulm from 2011 to 2017 was performed. Analysis was directed to determine a potential association of pre- and postoperative values of anti-recEm18 with clinical outcomes.

Results: Anti-recEm18 had a linear correlation to the maximum lesion diameter (R^2 = 0.558). Three trajectories of anti-recEm18 were identified based on a threshold of 10 AU/ml: "Em18-low" (n = 31), "responders" (n = 53) and "residual disease" (n = 4). The decline of anti-recEm18 in "responders" reached a plateau after 10.9 months at which levels decreased by 90%. The only patient with recurrence in the entire population was also the only patient with a secondary increase of anti-recEm18.

Conclusion: In patients with preoperative elevated values, anti-recEm18 confirms curative surgery at 12 months follow-up and allows for long-term surveillance.

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Correspondence

Guido Beldi, Department of Visceral Surgery and Medicine, Inselspital, Bern University Hospital, University of Bern, Freiburgstrasse, 3010 Bern, Switzerland. E-mail: guido.beldi@insel.ch

Introduction

Alveolar echinococcosis (AE) is a severe and potentially lethal zoonotic disease, caused by *Echinococcus multilocularis* infection at the larval stage, i.e. as metacestode. The disease predominantly affects the liver with the proliferation of tumor-like lesions that may result in biliary complications or liver failure.

Complete radical resection (R0) is the only treatment in curative intention to avoid recurrence.[1] Recurrence after resection with margin of 2 cm[2–4] is similar when compared to margins of 1 mm[5,6] ranging between 2% and 11%. Despite complete resection, late recurrences up to 20 years after curative resection have been observed and range from 2% to 16%[2,3,7] indicating the need for long-term surveillance.

Current practices for follow-up after initiation of any type of treatment consisting of watch and wait strategy, pharmacological therapy or surgical resection, include imaging exams and serology. Imaging includes sonography at short intervals and computed tomography (CT), magnetic tomography imaging (MRI) and/or positron-emission-tomography (PET) at longer intervals of 2–3 years.[1,4,5]

Serology, using primarily assessment of antibody levels to e.g. purified *Echinococcus multilocularis* Em2-antigen-ELISA and/or *Echinococcus multilocularis* recombinant Em18 antigen (recEm18)

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ELISA is available for diagnosis and postoperative follow-up.[8,9] For diagnostic purposes, the assessment of anti-recEm18 yielded the best clinical use.[10,11] However, given the limited sensitivity of 80%–94%,[10,11] anti-recEm18 is used only in combination with appropriate imaging procedures[9] and further serologies, such as EgHF-ELISA, purified Em2-ELISA, and especially also EmVF-Westernblot, to serologically prove AE as disease.[12]

Beside its use for the diagnosis of AE, anti-recEm18 has a potential value for the follow-up of AE patients,[6,8,9,13–16] especially after surgical therapy, due to its association with parasite burden and viability.[6,8,13] The predictive value to assess metacestode viability has been shown.[9,13] However, these studies included relatively low numbers of AE patients,[9,14,15] included also cystic echinococcosis[10,11] or were imprecise with regard to time-points for the follow-up,[8,13,16] thus neither allowing to reliably assess a specific postoperative trajectory nor the value for surveillance of anti-recEm18.

Thus, the aim of this study was to determine if recEm18-ELISA is suitable for surveillance of patients who underwent resection for AE and to determine thresholds and time points required to exclude disease recurrence.

Methods

Patient inclusion criteria

This trial is a bi-centric retrospective analysis of patients diagnosed with AE at the Department of Visceral Surgery and Medicine at Bern University Hospital, Switzerland and at the Clinic of Infectious Disease at University Hospital and Medical Center Ulm, Germany. This study was initiated after obtaining approval from the Ethics Commission of the Canton of Bern (2017-01534), with an amendment for the time frame 2018–2020, and from the Ethics Commission of the Ulm University (420/20). The inclusion criteria were adult patients over the age of 18, who underwent hepatic resection in curative intent for AE and the availability of at least one preoperative, one postoperative value of anti-recEm18 and a follow-up of at least 12 months. Patients with concomitant extrahepatic lesions, which were curatively resectable, were included as well. None of the patients had documented objection to use of healthcare related data.

Among 155 patients who were treated in Bern because of AE between 2002 and 2020, 95 underwent surgery. Excluded were 36 patients with missing preoperative recEm18 values, missing postoperative data or follow-up below one year. Among the 124 patients who were treated in Ulm between 2011 and 2017, 52 underwent surgery. Excluded were 23 patients for the same reasons. Thus, a total of 59 patients from Bern and 29 patients from Ulm who underwent surgery and in whom pre- and postoperative values of anti-recEm18 were available.

The diagnosis of AE was proven by histopathological analysis. Serological data and incidence of disease recurrence were extracted in all 88 patients. Clinicopathological data of the 88 patients from Bern and Ulm were extracted including

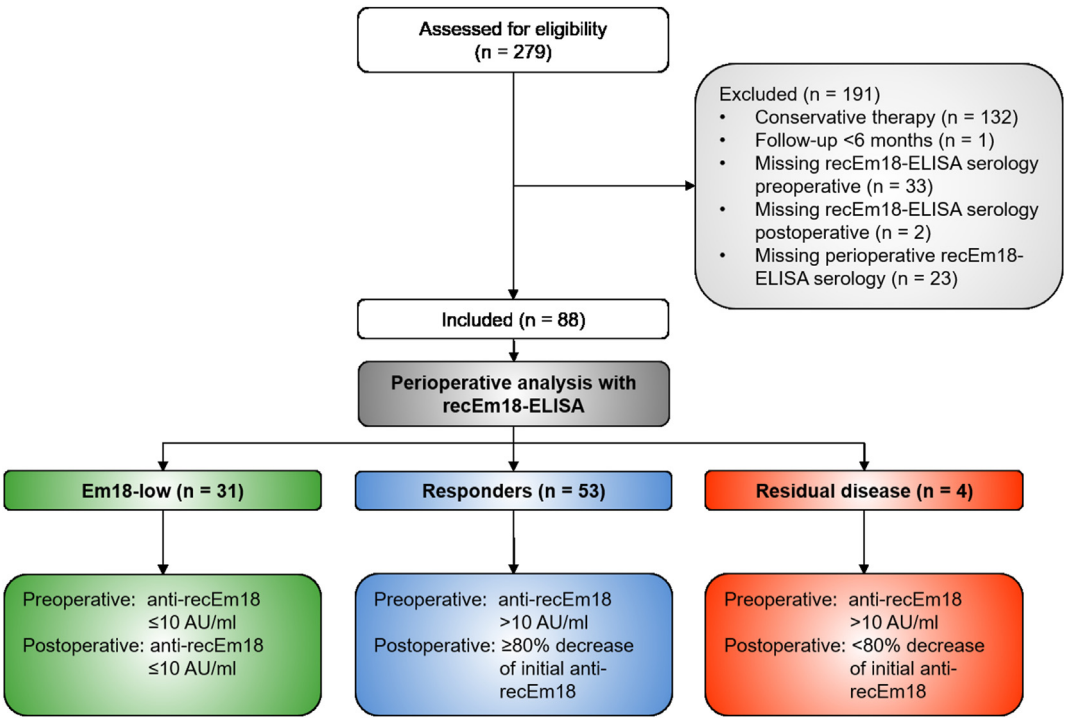

Figure 1 Flow chart with algorithm assigning patients into the three different recEm18-ELISA trajectories

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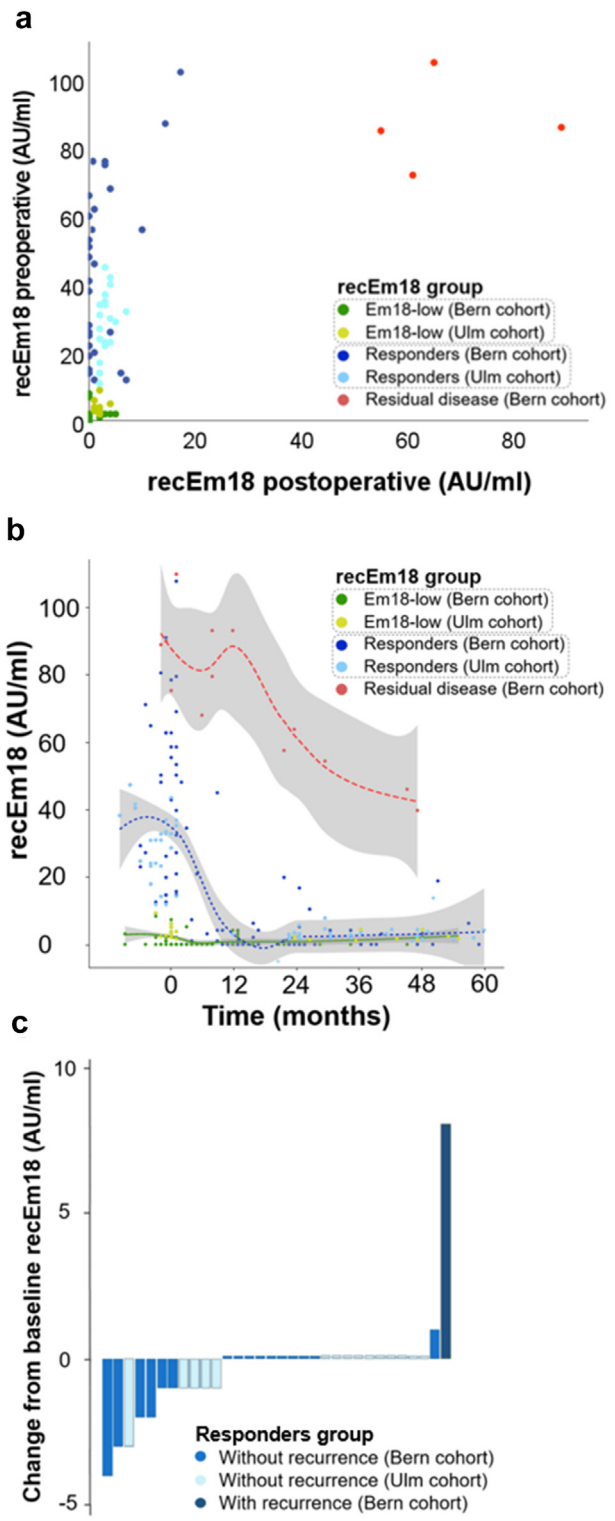

Figure 2 Temporal changes of recEm18-ELISA and different trajectories. Preoperative and postoperative recEm18-ELISA in patients assigned to the different groups in the cohorts from Bern and Ulm (a). Temporal changes of recEm18-ELISA in patients assigned to the different groups (b). The line indicates mean values with 95% confidence interval (grey area). Postoperative changes of anti-recEm18 after reaching baseline-recEm18 under the threshold of 10 AU/ml in patients of the "responders" group with multiple postoperative anti-recEm18 values (c)

demographic, radiological, therapeutic, intraoperative, pathological characteristics, types of surgical procedures and postoperative morbidity.

Serological testing

The recEm18-ELISA at Bern University Hospital was carried out as described previously.[13,17] All serological tests and operating characteristics were run under ISO 17025 certification. The anti-recEm18 measurements at University Hospital and Medical Center Ulm were performed by Bordier recEm18-ELISA.[18] The two different ELISA used were compared by dot-plotting with SPSS® (Fig. S1), ending in a specific conversion factor of 3.72 when calculating recEm18-ELISA out of the Bordier recEm18-ELISA.

Clinical data

In both centers, the recommendation for the individual surgical therapy was made by the weekly multidisciplinary liver board attended by hepatobiliary surgeons, hepatologists, radiologists and pathologists. All patients undergoing surgical therapy due to AE were evaluated preoperatively by experienced hepatobiliary surgeons according to clinical standards (medical history, physical examination, laboratory tests, radiological exams and anesthesia evaluation). Hepatic resection in curative intent was recommended to patients with symptomatic AE lesions or severe side-effects of benzimidazole-therapy when preservation of a sufficient future liver remnant was ensured. In asymptomatic patients, the indication to surgery was made dependent on the localization and the appearance of the lesion. Large, mass-forming lesions were typically resected, whereas in patients with smaller and/or multiple lesions with calcifications rather a watch and wait strategy was performed.

Preoperative imaging was performed mainly by computed tomography (CT) or in a lesser percentage, magnetic resonance imaging (MRI) and PET. Postoperative imaging controls were performed by CT, MRI, PET or sonography. Imaging was analyzed for calcifications and cystic structures. Cystic alterations of hepatic lesions were classified into macrocystic and microcystic lesions. Microcystic were defined by a diameter of less than <1 cm.

Histology was performed on resected specimens, yielding diagnosis of AE and resection margin. R0 resection was defined as complete resection with no laminar layer within 1 mm of the resection margin, R1 resection was defined as microscopic

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Table 1 Demographic and perioperative clinical data in correlation to Em18-low, responders and residual disease group

Variable	Em18-low (n = 31)	Responders (n = 53)	Residual disease (n = 4)	*p-value*
Sex, n (%)				*0.997*
Female	15 (48)	26 (49)	2 (50)	
Male	16 (52)	27 (51)	2 (50)	
Age, mean years (SD)	50 (±17)	44 (±16)	67 (±10)	*0.007*
Incidental disease, n (%)	12 (39)	16 (30)	0	*0.362*
PNM-stage, n (%)				*0.200*
1	13 (42)	10 (19)	1 (25)	
2	7 (23)	17 (32)	0	
3a	2 (6)	8 (15)	1 (25)	
3b	6 (19)	12 (23)	1 (25)	
4	3 (10)	6 (11)	1 (25)	
Maximal diameter of lesion, mean cm (SD)	4.8 (±3.1)	8.4 (±3.9)	13.4 (±6.8)	*<0.001*
Cumulative diameter of lesions, mean cm (SD)	6.1 (±3.8)	9.3 (±4.3)	16.4 (±5.0)	*<0.001*
Multifocality of lesions, n (%)	13 (42)	18 (34)	2 (50)	*0.670*
Parasite burden score, mean (SD)	5.8 (±3.2)	8.8 (±4.0)	12.5 (±7.8)	*0.001*
Distant extrahepatic lesions, n (%)	0	0	2 (50)	*0.795*
Immunosuppression, n (%)	12 (39)	6 (11)	2 (50)	*0.008*
Time from diagnosis to operation, mean months (SD)	3.5 (±3.3)	6.2 (±18.0)	9.8 (±13.8)	*0.653*
Type of resection, n (%)				*0.012*
Hemihepatectomy right	5 (16)	18 (34)	0	
Extended hemihepatectomy right	1 (3)	8 (15)	0	
Hemihepatectomy left	1 (3)	8 (15)	1 (25)	
Bisegmentectomy	7 (23)	6 (11)	1 (25)	
Segmentectomy	7 (23)	3 (6)	1 (25)	
Atypical resection	10 (32)	9 (17)	1 (25)	
Other	0	1 (2)	0	
Major resection, n (%)	7 (23)	34 (64)	2 (50)	*0.001*
Laparoscopic approach, n (%)	10 (32)	4 (8)	0	*0.008*
Complications (Clavien-Dindo), n (%)				*0.070*
1	1 (3)	0	0	
2	2 (7)	4 (8)	0	
3a	2 (7)	7 (13)	1 (25)	
3b	1 (3)	4 (8)	0	
4a	1 (3)	1 (2)	2 (50)	
4b	0	0	0	
5	0	0	0	
Major complication (Dindo Clavien ≥3b), n (%)	2 (7)	5 (10)	2 (50)	*0.024*
Length of hospital stay, mean days (SD)	12 (±14)	13 (±10)	16 (±8)	*0.039*
Resection status, n (%)				*0.381*
R0	27 (87)	34 (64)	3 (75)	
R1	4 (13)	8 (28)	0	
R2	0	2 (4)	1 (25)	
Unknown	0	2 (4)	0	

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Table 1 (*continued*)

Variable	Em18-low (n = 31)	Responders (n = 53)	Residual disease (n = 4)	*p-value*
Mean resection margin, cm (SD)	0.6 (±1.0)	0.5 (±0.8)	0.4 (±0.5)	*0.763*
Recurrence, n (%)	0	1 (2)	0	*0.374*
90-day Mortality, n (%)	0	1 (2)	0	*0.674*

SD, standard deviation. *P-value* was analyzed with the Kruskal-Wallis test.

Table 2 Pre- and postoperative recEm18-ELISA findings and data of perioperative benzimidazole-therapy in the Em18-low, responders and residual disease group

Variable	Em18-low (n = 31)	Responders (n = 53)	Residual disease (n = 4)	*p-value*
Mean preoperative anti-recEm18, AU/ml (SD)	2 (±3)	38 (±22)	87 (±145)	*<0.001*
Preoperative treatment with ABZ, n (%)	26 (84)	57 (89)	3 (75)	*0.519*
Mean length of preoperative treatment with ABZ, months (SD)	43 (±105)	30 (±76)	65 (±64)	*0.211*
Mean postoperative anti-recEm18, AU/ml (SD) in a mean time after operation, months (SD)	1 (±1) after 14 (±13)	6 (±12) after 17 (±12)	68 (±15) after 14 (±9)	*<0.001*
Postoperative treatment with ABZ, n (%)	29 (94)	52 (98)	4 (100)	*0.504*
Mean length of postoperative treatment with ABZ, months (SD)	17 (±13)	25 (±19)	24 (±3)	*0.157*

ABZ, albendazole; AU, arbitrary unit; IQR, interquartile range; SD, standard deviation. *P-value* was analyzed with the Kruskal-Wallis test.

Table 3 Univariate and multivariate analysis of characteristics and outcomes between patients who underwent hepatectomy for AE regarding anti-recEm18 levels

	Em18-low (n = 31)	Responders (n = 53)	UV	MV[a]	
			p	*p*	OR (95% CI)
Age >65 years, n (%)	5 (16)	6 (11)	0.531		
Male gender, n (%)	17 (55)	27 (51)	0.732		
Incidental disease, n (%)	12 (39)	16 (30)	0.462		
Immunosuppression, n (%)	12 (39)	6 (11)	0.004	0.055	0.3 (0.1–1.0)
Multiple lesions, n (%)	13 (42)	18 (34)	0.248		
Lesion size (≥7.5 cm), n (%)	8 (26)	25 (47)	0.054		
High PNM (≥3), n (%)	11 (36)	24 (45)	0.382		
Major resection, n (%)	7 (23)	34 (64)	<0.001	0.009	4.3 (1.4–12.7)
Laparoscopic resection, n (%)	10 (32)	4 (8)	0.004	0.242	0.4 (0.1–1.8)
Preoperative treatment with ABZ, n (%)	26 (84)	47 (89)	0.382		
Postoperative treatment with ABZ, n (%)	29 (94)	52 (98)	0.280		
Recurrence, n (%)	0	1 (2)	0.182		

[a] Logistic regression multivariate analysis included all variables with $p < 0.050$ in univariate analysis.

presence and R2 as the macroscopic presence of the laminar layer within the transection line.

Life-long surveillance was performed postoperatively with repetitive cross-sectional imaging at least annually including serological testing of recEm18-ELISA. Local recurrence was defined when recurrence was observed at the former resection site. One patient died due to concomitant disease. Postoperative medical therapy with albendazole (ABZ) was administered according to the postoperative assessment of the respective multidisciplinary liver board and was not standardized between the two centers. Both centers usually adhered to the recommendations of the World Health Organization (WHO) administering ABZ for at least two years postoperatively.[1] Exceptions were made for patients with adverse events under ABZ-

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treatment, pregnancies or patients with anti-recEm18 under 10 AU/ml and R0 resection status.

Statistical analyses

Quantitative and qualitative variables were expressed as mean (standard deviation) or frequency (percentage). Pre- and postoperative values of recEm18-ELISA were comparatively analyzed and visualized. The threshold for recEm18-ELISA should identify outliers and was set two fold the standard deviation (SD) above this mean. This allows to identify and to remove all outliers outside such 95% confidence interval.[19]

Parasite burden score (PBS) to compare anti-recEm18 antibody levels with multifocal hepatic AE disease was calculated as: $PBS^2 = (\text{Number of liver lesions})^2 + (\text{maximum size of lesion})^2$ according to the methodology used previously to describe the tumor burden score (TBS).[20] Comparisons between groups were analyzed with the Kruskal-Wallis test for variables, as appropriate. $P < 0.05$ was considered statistically significant. Statistical analyses were performed using SPSS® version 25 (IBM, Armonk, New York, USA), R version 3.3.2 (R Core Team, GNU GPL v2 License) and R Studio version 1.3.959 (RStudio, Inc. GNU Affero General Public License v3, Boston, MA, 2016).

Results

Clinical data

Among all patients undergoing hepatic resection in curative intent for AE, 88 patients could be analyzed and clustered into groups as shown in Fig. 1. Clinical details of these three groups are shown in Tables 1 and 2. The overall complication rate of the cohort was 30%, with major complications in 9 (10%) patients.

To determine predictors for the anti-recEm18 trajectory a multivariate analysis was performed (Table 3). The number of major hepatectomies in the "responders" group was higher, potentially indicating that large, mass lesions are associated with increased anti-recEm18. Preoperative imaging was performed in average 1.4 months (SD ± 1.6) prior to surgical resection. Although not being significantly different, the "Em18-low" group contained more patients with immunosuppression and multiple, small lesions.

Temporal changes of serology

Overall, the mean postoperative anti-recEm18 serum antibody level from patients without residual disease was 2 AU/ml (SD ± 4, range 0–19 AU/ml) at 12 months after surgery. Using the twofold standard deviation above this mean, we set a threshold of anti-recEm18 at 10 AU/ml. The patients were clustered into three perioperative recEm18 trajectories as a result of (i) this threshold of anti-recEm18 at 10 AU/ml and (ii) the presence of residual postoperative disease (Fig. 1): An "Em18-low" group (recEm18 pre- and postoperative <10 AU/ml), a "responders" group (recEm18 preoperative over 10 AU/ml with a postoperative decrease of more than 80% of the initial anti-recEm18) and a "residual disease" group (recEm18 preoperative over 10 AU/ml with a postoperative decrease of less than 80% of the initial anti-recEm18 indicating postoperative presence of residual disease). The preoperative and postoperative values are shown in Fig. 2a according to the definition in Fig. 1. There was no difference in anti-recEm18 values between the two centers. The "responders" group had a strong decrease in anti-recEm18 values, while in the "residual disease" group values of anti-recEm18 remained strongly positive.

The trajectories of pre- and postoperative values for the three groups are shown in Fig. 2b and for each patient in Fig. 3a–c. The perioperative decrease of anti-recEm18 was significant ($p < 0.001$)

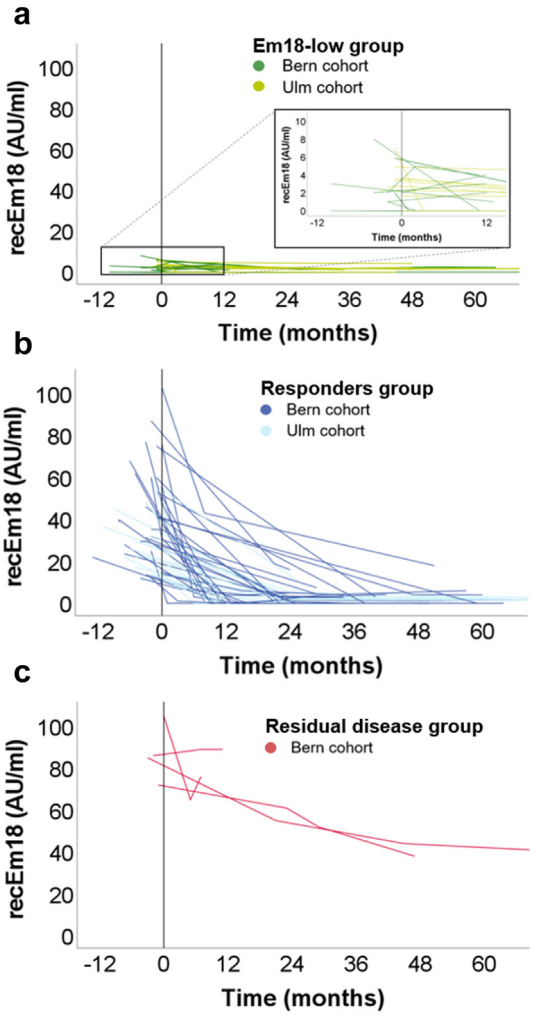

Figure 3 Temporal changes of recEm18-ELISA of each patient for the different groups. The "Em18-low" group remains below recEm18-ELISA 10 AU/ml (a). In the "responders" group recEm18-ELISA decreases rapidly with more than 60% within 6 and 80% within 12 months (b). In the "residual disease" group (only Bern cohort) recEm18-ELISA remain positive during postoperative follow-up (c)

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in the "responders" group using recEm18-ELISA at Bern University Hospital (Appendix 2) and Bordier recEm18-ELISA at University Hospital and Medical Center Ulm (Appendix 3). Preoperative anti-recEm18 values above 10 AU/ml significantly decreased postoperatively in all but one patient of the "residual disease" group with concomitant distant brain metastasis. Resection status did not influence the postoperative decrease of anti-recEm18 in the "responders" group. The patients with R0 resection in the "responders" group had a mean postoperative anti-recEm18 of 6 AU/ml (SD ± 12) within 16 months compared to the patients with R1 resection with mean postoperative anti-recEm18 of 6 AU/ml (SD ± 12) within 19 months. In the Bern cohort, a drop of anti-recEm18 in the "responders" group below 10 AU/ml was found in 19 patients (58%) at 12 months and in 31 patients (94%) at later time points (mean of 16 months). A mean decrease of 90% was observed at 10.9 months (Fig. 2b). In the Ulm cohort, the 19 patients of the "responders" group had a fast decrease of anti-recEm18 during the first 24 months. Drop of anti-recEm18 in the "responders" group of Ulm below 10 AU/ml was found in 2 patients (11%) at 12 months and 100% (n = 19) at later time points with a mean of 24 months. The decline in the Ulm "responders" group is 90% within 23.3 months, subsequently all values remained low during the long-term follow-up.

In the entire cohort, one recurrence was observed in cross-sectional imaging at 7 years after resection. This patient had a negative anti-recEm18 serology at 16 months after resection that slowly increased up to 8 AU/ml (Fig. 2c, dark blue). One patient died due to concomitant disease, which was not related to AE.

Trajectories in "residual disease"

In the four patients of the "residual disease" group (Fig. 3c), the mean diameter of AE lesions was above 8 cm. This value is higher compared to the other patients in who preoperative anti-recEm18 values was correlated with the size of the largest hepatic AE lesion (Fig. 4a). The PBS that accounts the multifocality of the disease, was not correlated with anti recEm18 values (Fig. 4b). The resection status was R0 in three patients, and R2 in one patient, respectively. Among the patients with R0 resection, one had concomitant pulmonary AE lesions, one had distant peritoneal AE lesions and one had a contralateral hepatic lesion that was treated with simultaneous microwave ablation.

Discussion

This study indicates that anti-recEm18 allows to be used for surveillance in patients with preoperatively elevated anti-recEm18 level. This is based on following findings:

First, the study supports previous smaller studies showing that anti-recEm18 levels may strongly decrease after radical surgery.[8,13,15] The current study adds the identification of different trajectories based on preoperative values (Fig. 1). Also the relevance of anti-recEm18 is shown as one of the studies used Em2^{plus}-ELISA, which may produce false positive values of anti-recEm18, as all wells of the testing plate were coated for both ELISA assays.[15] Conversely, both participating centers avoid cross-reactions of Em2-ELISA and recEm18-ELISA by segregation of the two tests.

Second, the recurrence rate was very low with only one patient (1.1%) developing recurrence. Thus, in two large European centers, recurrence rate is lower compared to published recurrence rates of up to 16% after curative resection indicating a lower pretest probability for surveillance.[2,7] The increase of anti-recEm18 in this patient was concurrent with the detection of a radiological correlate. No significant morbidity was associated with the recurrence indicating that costs and potential side effects of systematic serial radiological investigations need to be critically reevaluated for routine surveillance. The limitation is that the disease severity and/or treatment option may be different in other geographic regions given the different distribution of *Echinococcus multilocularis* strains and the availability of diagnostic and therapeutic options.[21]

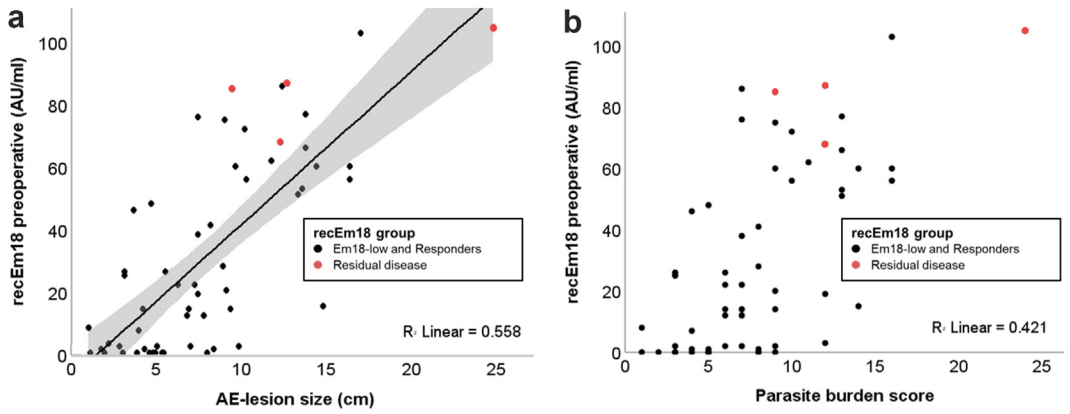

Figure 4 Correlation of preoperative recEm18-ELISA to the size of hepatic AE-lesion. Association of preoperative recEm18-ELISA values with (a) the size of the largest hepatic AE-lesion and (b) parasite burden score (PBS^2 = (Number of liver lesions)^2 × (Maximum size of lesion)^2). The line indicates mean values with 95% confidence interval (grey area)

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Third, persistent disease was strongly associated with persistent elevated levels of anti-recEm18 in all four patients. Indicating that elevated levels are sufficient to detect disease persistence in patients with preoperative elevated anti-recEm18 levels.

Even though our study has limitations due to its retrospective design, follow-up upon determination of recEm18 antibody concentration showed valuable results in this rare disease. Despite the mean follow-up time of 45 months, longer periods of observation would be desirable, because AE may develop recurrence even after 20 years after curative resection.[3,4] Even if time-points of follow-up in the cohort of Ulm were set rather later compared to the Bern cohort, trajectories of anti-recEm18 are similar and decrease occur mainly during the first 12 months after curative liver resection. Another limitation of our study is the lack of data on PET findings, which can assess parasite activity in combination to serology,[16] or immunohistochemical staining of the specimen to assess differences in histology.[22] PET examination that is not regularly reimbursed in Switzerland was replaced by anti-recEm18 measurements that have been shown to be sufficient for postoperative assessment of disease activity.

There are immediate clinical consequences of these findings, which include both pre- and postoperative management. Preoperatively, anti-recEm18 may indicate the relevance of surgical management by representing the extent of parasite burden and parasite activity. The present evidence shows that preoperative anti-recEm18 is associated with hepatic AE lesion size and may therefore be a parameter of the intrahepatic parasite load. We have introduced the PBS, to account for the multifocality of the disease. Mainly maximum size (R^2 = 0.558) rather than PBS (R^2 = 0.160) correlate with anti-recEm18 levels. This finding is partially supported by a recent study in 29 patients, where recEm18 correlates to lesion size but conversely to our cohort also with the number of lesions.[16]

Postoperative management may depend on anti-recEm18 levels by directing the onset of anti-recEm18-based surveillance. The results indicate that one measurement before 12 months postoperatively may indicate success of surgery if anti-recEm18 levels drop compared to preoperative values. The strong association of recurrence with secondary increase of anti-recEm18 indicates that surveillance by recEm18-ELISA alone may be sufficient. But, as soon as there is a serological suspicion of recurrence, this should subsequently be checked by imaging.

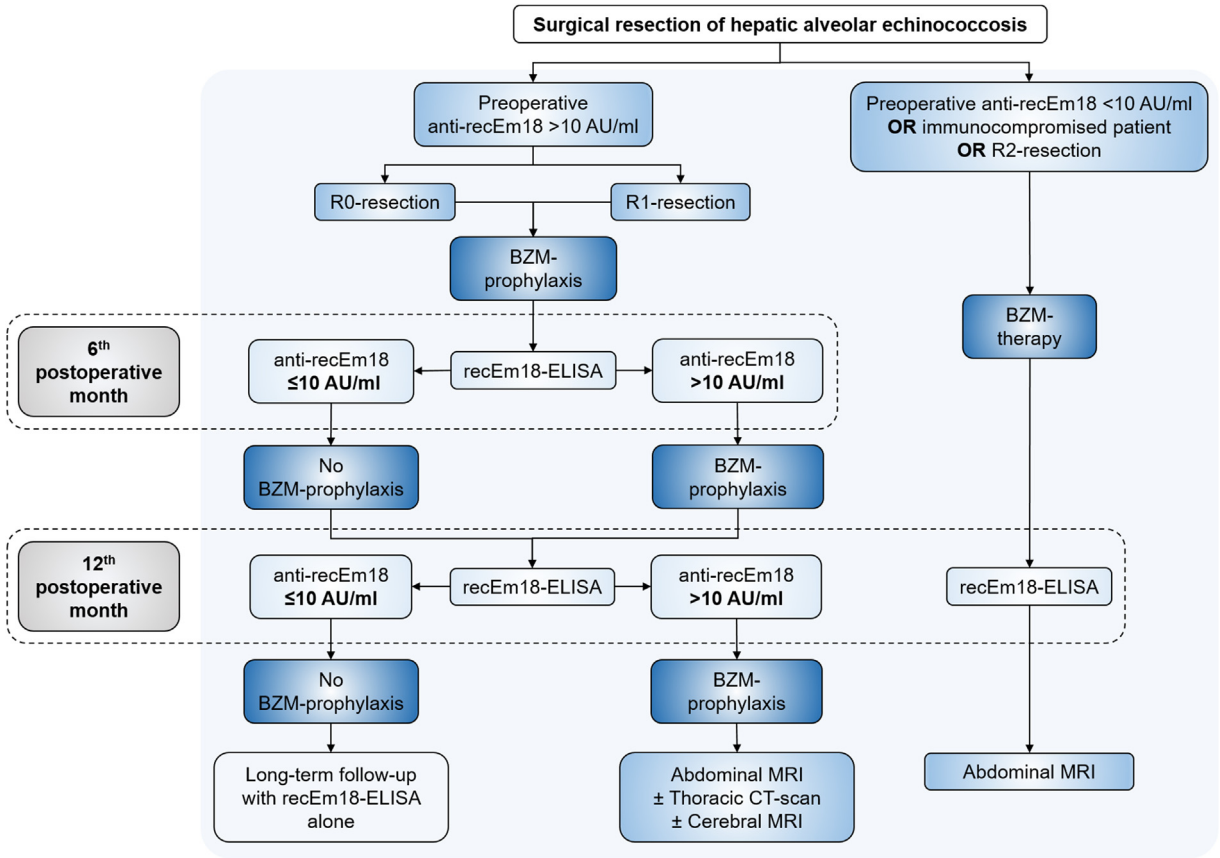

Figure 5 Postoperative short-term follow-up algorithm of the first year for treatment of immunocompetent patients with hepatic alveolar echinococcosis. A stop of BZM-prophylaxis in patients should be evaluated, when an anti-rec-Em18 ELISA of <10 AU/ml is given and especially in patients with a R0-resection. AU, arbitrary units; BZM, benzimidazole; MRI, magnetic resonance imaging

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Primarily, an abdominal MRI would be recommended to exclude a recurrence of hepatic involvement and, depending on the findings, a further search by means of a thoracic CT-scan or cerebral MRI. Nevertheless, the association of anti-recEm18 with disease activity may allow avoiding unnecessary postoperative radiological exams (e.g. CT-scans, abdominal MRI or PET) or therapy with benzimidazoles in responders to reduce potential adverse medical side effects.[23–25] Future studies may address if response to preoperative anti-recEm18 could guide the duration of BZM treatment pre- and post-operatively therapy and also determine the optimal timing of cross-sectional imaging.

These suggested clinical pathways do not apply in patients with preoperative anti-recEm18 antibody levels below 10 AU/l or in immunocompromised patients. In such patients, preoperative workup to secure the diagnosis of AE needs to firmly establish the diagnosis by other serological markers such as purified Em2 antibody or by westernblotting. Furthermore, in these patients neither response to surgery nor surveillance can be performed using anti-recEm18 alone. In immunocompromised patients, preoperative anti-recEm18 was lower, potentially because of a decreased capacity for immunoreaction against recEm18. Similarly, postoperative surveillance in immunocompromised patients may need to incorporate imaging in addition to anti-recEm18 measurements. However, postoperative follow-up of patients with preoperative low anti-recEm18 and in immunocompromised patients should be performed in combination with sonography on yearly intervals.[1,5] In particular, because of the lifelong follow-up and the inter-individual differences, there is no harmonized approach to the methods used.

Persistent elevated values of recEm18 antibody levels indicate persistent disease. Most likely high anti-recEm18 are the consequence of circulating Em18-antigens metabolized by still active lesions, which may be extrahepatic as well. In all of these patients a long-term postoperative ABZ medication was given.

According to these findings Fig. 5 shows the algorithm of the first year for treatment of immunocompetent patients with hepatic alveolar echinococcosis. Cornerstones for decision making are the hepatic resection status and the threshold of anti-recEm18 of 10 AU/ml. The time point of 6 months is used for decision making as at this time points a possible significant decrease of anti-recEm18 will be visible. Based on the WHO recommendation all patients should be treated with adjuvant BZM-therapy until this time point. This therapy may be stopped in patients, when an anti-rec-Em18 of <10 AU/ml is given, especially in patients with a R0-resection.

Conclusion

Taken together, these results indicate that recEm18 antibody levels can be used for postoperative surveillance in immunocompetent AE patients with preoperatively elevated anti-recEm18 levels. We propose that the trajectory of anti-recEm18, integrating preoperative and postoperative values identifies patients at high or low risk for recurrence. In patients with elevated preoperative anti-recEm18 values, measurement of anti-recEm18 after 6 and 12 months and annually thereafter is sufficient for long-term follow-up.

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Data availability statement

All data supporting the findings of this study are available within the paper and its supplementary information.

Authors' contributions

The study was designed by Severin Gloor, Anja Lachenmayer and Guido Beldi. Severin Gloor, Daniel Candinas, Anja Lachenmayer and Guido Beldi cared for the Bern patients. Beate Grüner cared for the Ulm patients. Severin Gloor, Wanjie Jiang, Martin Maurer and Julian Frederic Hotz made data acquisition. Bruno Gottstein, Alexander Oberli and Jürgen Benjamin Hagemann cared for serological testing. Severin Gloor wrote the manuscript and made statistical analysis. Wanjie Jiang, Martin Maurer, Bruno Gottstein, Alexander Oberli, Jürgen Benjamin Hagemann, Julian Frederic Hotz, Daniel Candinas, Anja Lachenmayer, Beate Grüner and Guido Beldi revised the manuscript critically for important intellectual content. All authors read and approved the final manuscript.

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Conflict of interest

None to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.hpb.2023.10.007.

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