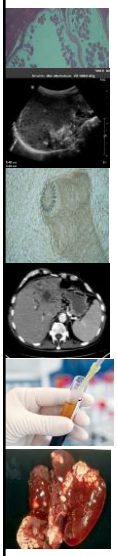

AE at University Hospital of Ulm (UKU)

Diagnosis, treatment and follow up
Data from 280 AE- patients
first presentation from 01.01.2011-31.12.2018

J. Bloehdorn, L. Peters, K. Klein, J. Schmidberger, A. Hillenbrand, T.Gräter , M. Furitsch, T. F. Barth, A. Beer, D. Henne- Bruns, W. Kratzer , and B. Grüner

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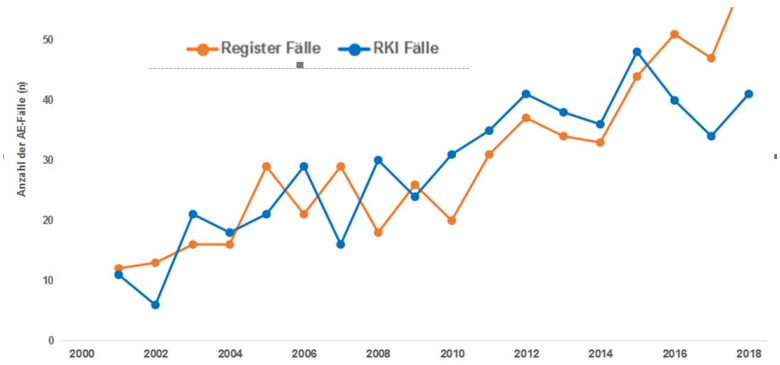
AE Ulm/ Germany: increasing numbers of patients

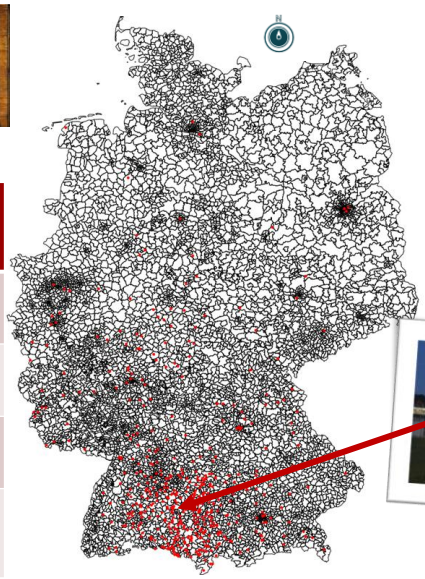


	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
National AE Database Registry		12	13	16	16	29	21	29	18	26	20	31	37	34	33	44	51	47	62
RKI report (IfSG)		11	6	21	18	21	29	16	30	24	31	35	41	38	36	48	40	35	50

Data from: Dr. biol. hum. J. Schmidberger, MPH

Alveolar Echinococcosis in Ulm and around Ulm…

Year	AE-patients at UKU: first presentation
1992-1999 8 yrs.	108
2000-2010 11 yrs.	180
2011-2018 8 yrs.	280
1.1.2019 to Oct. 2019 1 yr.	50



University Hospital Ulm (UKU)→ Located in an endemic area for *E. multilocularis*

Data from: Dr. biol. hum. J. Schmidberger, MPH

Dot Density Map

Long term results of comprehensive AE management 312 patients in Ulm/ Germany 1992- 2011

Grüner B, Kern P, Mayer B, Gräter T, Hillenbrand A, Barth TFE, Muche R, Henne Bruns D, Kratzer W, and Kern P

First admittance in Ulm 01. Jan. 1992 – 31. Dec. 2011. Follow-up until 31. Dec. 2012.
Def. lost-to follow-up: Last contact prior 01. Jan. 2010

Group	A) AE diagnosed < 1999	B) AE diagnosed >2000	Total 01.01.1992-31.12.2011
N (%)	108 (34,6)	204 (65,4)	312
Age at diagnosis [years] (median, range)	48,6(6,6-78,9)	53,0 (10,3-91,7)	51,3
Age at end of follow-up (median, range)	69,7 (18,2-92,9)	59,1 (15,2–97,0)	63,9
Symptoms			
Abdominal symptoms			
- with jaundice	19 (17,6)	16 (7,8)	35 (11,2)
- without jaundice	24 (22,2)	44 (21,6)	68 (21,8)
Other symptoms	22 (20,4)	31 (15,2)	53 (17,0)
None	23 (21,3)	90 (44,1)	113 (36,2)
N. d.	20 (18,5)	23 (11,3)	43 (13,8)

- **Age at diagnosis median 51,3 years./ Male: female ratio 1.29**
- **312 pts. includes (treated UKU Ulm): 108 up to and 204 from 2000**
- **Case definition: 112 confirmed, 73 probable, 19 possible (204 pat.)**
- **17 patients with "aborted" lesions**
- **~50 % of the patients symptomatic , with abd. sy. +/- jaundice and other**
- **Treatment according WHO guidelines**

GMS Infect Dis 2017;5:Doc01
Published: January 6, 2017
2017 Grüner et al.

Long term results of comprehensive AE management 312 patients in Ulm 1992- 2011

Definitions

- **After an STI,** cure was assumed for patients with surgery when parasitic lesions remained undetectable during the 2 years following BMZ interruption.
- **Cases with BMZ treatment alone** were **not** defined as **cured**.
- Structured treatment interruption (**STI)** was a goal for patients with an NoMo status at diagnosis, after surgery and a 2-year BMZ therapy.
- **STI for patients with non-resectable lesions:** all of the following conditions had to be fulfilled for an STI.

Table 1: Preconditions for structured treatment interruption (STI) for patients with non-resectable lesions and no evidence of extrahepatic lesions

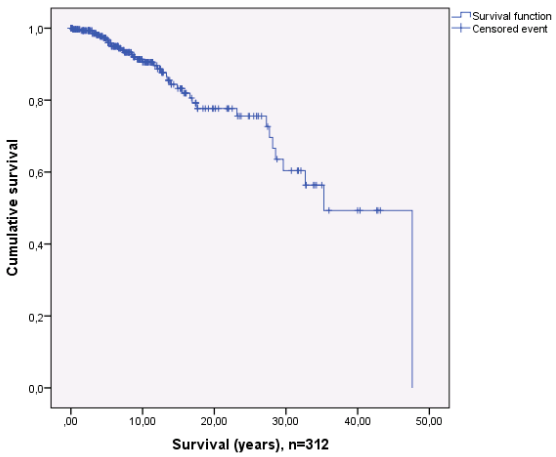
Preconditions
1. marked regression/absence of lesion(s) by imaging AND
2. vanished enrichment of FDG around the AE lesion(s) assessed by FDG-PET/CT scan AND
3. continuous BMZ medication for at least 2 years AND
4. absence of any clinical symptoms or signs of illness AND
5. decrease of specific serology[a]

[a] Consecutive ELISA tests with the same *E. multilocularis* antigen, definitions in [34].
AE = alveolar echinococcosis; BMZ = benzimidazoles; CT = computed tomography; FDG = fluordeoxyglucose; PET = positron emission tomography

GMS Infect Dis 2017;5:Doc01
Published: January 6, 2017,

5

Survival*



5-Years-Survival Rate : 96.8%
10-Years-Survival-Rate : 90.5%

30 patients lived with AE-diagnosis > than 25 years
Longest Survival with AE diagnosis: 47.6 yrs.

Outcome (312 patients)
Progressive Disease: 16 (5,1)
Potentially cured: 49 (15,7)
Stable Disease: 228 (73,1)
"favorable" outcome: 88,8 %

GMS Infect Dis 2017;5:Doc01
Published: January 6, 2017,

UNIVERSITÄTS KLINIKUM ulm

Alveolar Echinococcosis in Germany: Retrospective Analysis of 280 Cases from 2011 to 2018

J. Bloehdorn, L. Peters, K. Klein, J. Schmidberger, A. Hillenbrand, T. Gräter , M. Furitsch, T. F. Barth, A. Beer, D. Henne- Bruns, W. Kratzer , and B. Grüner

Background:
Alveolar echinococcosis (AE) shows a low incidence and controlled clinical studies are hardly feasible. We therefore retrospectively analyzed AE patients with first visit at our center.

Material and methods:
All patients referred to our center between 01.01.2011 and 31.12.2018 (n=280) were analyzed with regard to clinical presentation, disease management and outcome.

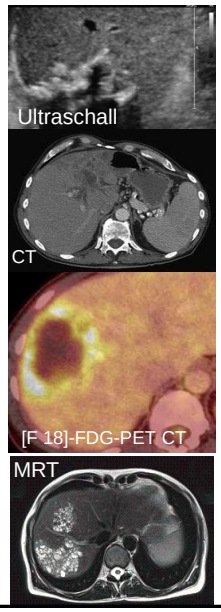
AE at UKU: Assessment at first visit

UNIVERSITÄTS KLINIKUM ulm

1. History/ clinical presentation, circumstances of diagnosis
   data base inclusion, occupational history, AE- risk factors
2. Laboratory examination: blood cell count, clinical chemistry, liver function, +IgE serum level , evtl. Hepatitis screening
3. **E. Serology**: Screening with Echi. IgG (EIA Virion S.) and Em2-18 Elisa (Bordier Aff.)
4. **Imaging**: FDG-PET CT * and ultrasound (+ CEUS), evtl. MRI → PNM Staging, lesion complete resectable?

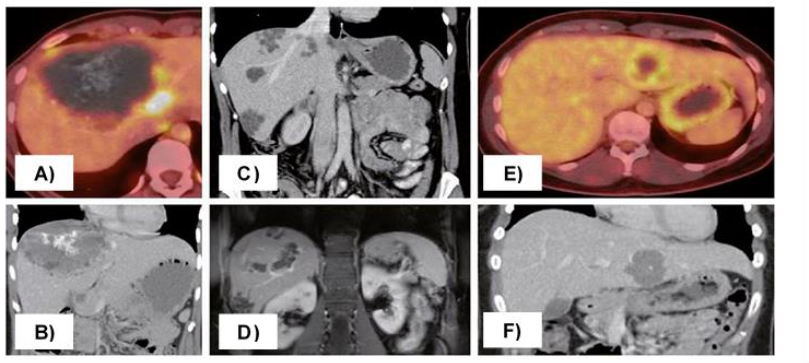
Case definition
Additionally: if AE diagnosis is only „possible":
„more" Serology (Würzburg „whole larvae" GL-Elisa, Em10, AgB)
Liver puncture/ Immunohistochemistry mAb Em2G11/ PCR

* evtl. MRI instead of PET-CT or new consider PET MRI;
- esp. young patients, who had recent CT scan and AE lesion < 2 cm and/ or AE diagnosis is probable/ confirmed, staging done.
- If AE lesion is resectable → no need for a baseline PET

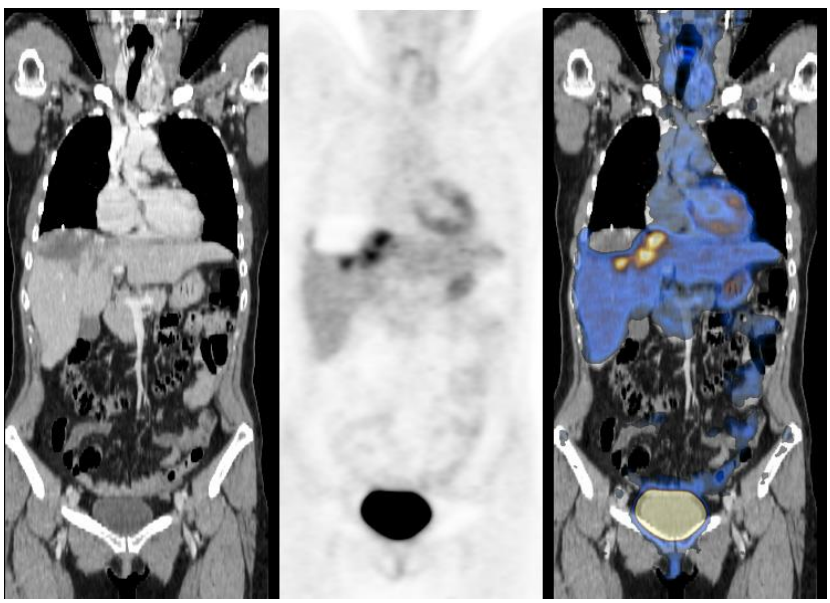


Importance of Imaging

Sturm- und Hagel Muster | Pseudozyste | Hämangiom-lartig | verknöchert | Metastasen-artig



[F18] FDG- PET – CT for Staging



Reuter et al. CID 1999 | Reuter et al. Hepatology 2004 | Reuter et al. Nuklearmedizin 2008

AE treatment UKU

UNIVERSITÄTS KLINIKUM ulm

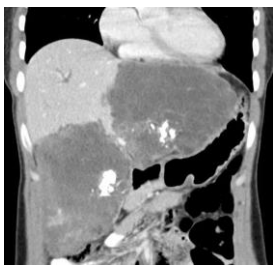
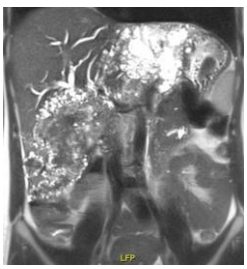
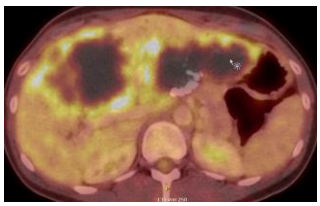
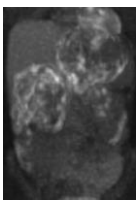
1. Albendazole (ABZ) for **all** patients case defonition probable/ confirmed continuous, long-term (switch to MBZ if indicated)
2. Evaluation if surgery/ complete resection is possible, interdisciplinary → planned surgery (patient under ABZ)
3. Follow up visit after 3 m., than every 6 months (Lab. and imaging)
   Re-Evaluation of surgery, if indicated, with next CT/ MRI-imaging
4. Adjust of ABZ-dosage to plasma level ; ABZ-sulfoxid level 4 hrs. 0,5-1,7 mg/l
1. ABZ interruption „ STI" / stop only

- if not tolerated (GPT/ ALT elevation > 5-10 fold), (first switch to MBZ)
- or after complete surgery and 2 yrs. ABZ treatment
- or small „inactive appearing" lesions (?)
- or in pregnancy/ lactation
- or NoMo stage after >2 yrs. BMZ-treatment **and** PET negative, specific Em Serology negat
- **but not** in large/ central/ extrahepatic lesions
- **And NOT** in immunocompromised patients

MM * 90, f: presented with itching/ Pruritus, 3,5 months after delivery

Hauptdiagnose:
08/2019 Alveoläre Echinokokkose der Leber P4 (V.cava) N1 (organüberschreitend) M01 (pulm. Streuherde) ; WHO Falldefinition "probable"

Therapie und Verlauf:
12.08.2019 Echinokokken-AK:.
Echi. IgG EIA 19.79 U/ml positiv
Ech ELISA positiv; KM Sono Leber: Va AE
22.08.2019 MRT; Ausgeprägter hepatischer Befall bei bek. Echinococcus multilocularis unter Beteiligung der Lebersegmente II, III, IVa, IVb, V und artiell VI." intrahepatische Cholestase rechts bei Tumorbedingter Kompression des prox. DHC, hochgradige Pelottierung der extrahepatischen Pfortader.
28.08.2019 FDG-PET CT; Beginn Albendazol treatment
04.09.2019 Stationäre Aufnahme bei stark erhöhten Leberwerten, L-Tx Listung (prophylaktisch);
28.08.2019 AP 1774 U/l
23.09.2019 Echi.IgG 16.75, Em Elisa pos. IgE 642 IU/ml (fallend), Transaminasenstabil, Bili 20 (normal). ABz Spiegel folgt; ABZ Th. 2x200 mg/Tag weiter, Ursofalk 500 weiter,

Treatment strategy?
Liver Transplant listing?
Go for surgery?
Trust in Albendazole?

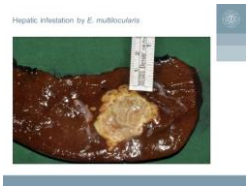
AE Surgery: Role of resection margin

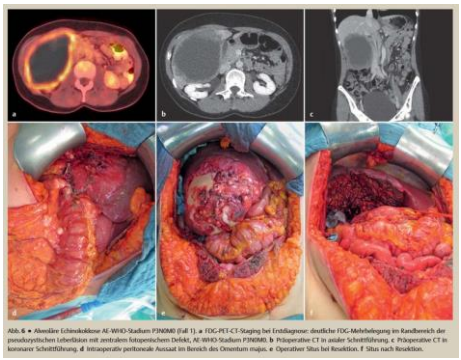
World J Surg (2017) 41:1012–1018
DOI 10.1007/s00268-016-3813-6

ORIGINAL SCIENTIFIC REPORT

Impact of Safe Distance on Long-Term Outcome After Surgical Therapy of Alveolar Echinococcosis

Andreas Hillenbrand[1] · Beate Gruener[2] · Wolfgang Kratzer[2] · Peter Kern[2] · Tilmann Graeter[3] · Thomas F. Barth[4] · Klaus Buttenschoen[5] · Doris Henne-Bruns[1]





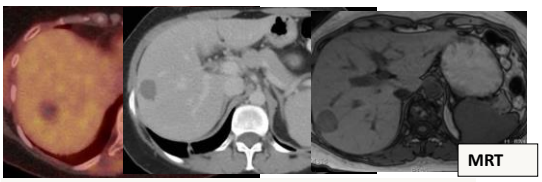
Inclusion 92 AE patients
Surgery at UKU: 41 patients,
Surgery at other clinics: 51 patients

Grading of resection margin
< 1 mm (R1)
1 mm-10 mm (R0)
> 10 mm
> 20 mm

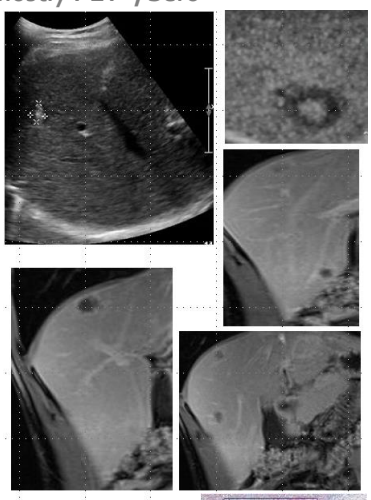
15/ 92 patients with AE-recurrence at resection area; 1-24 J. after surgery
In 13/ 15 pts. Safety margin < 1mm
Conclusion: complete resection with safety margin > 1mm can provide CURE of AE, combined with BMZ- (after) treatment

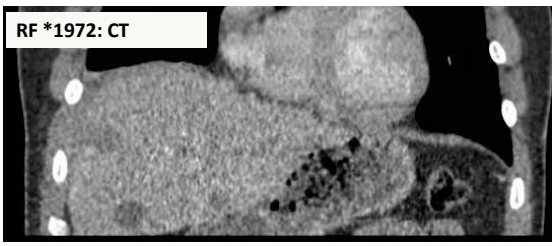
AE : special cases (initial lesions)

EMUC –CT type 4, EMUC-US „ metastasis like", mostly PET- , Sero-



Pat. MR* FDG-PET CT: 2 lesions in the right liver lobe

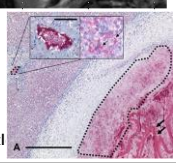




Fremdbefund Institut für Hygiene und Mikrobiologie Würzburg

Untersuchung	Ergebnis	Einheit	Bewertung	Ref.-ber.
ECHINOKOKKOSE				
E. granulosus-HAT	<NWG Titer negativ	<160		
E.multilocularis (Gesamtlarven)-ELISA	negativ			
- E.multil.(GL)-ELISA	Index 0.7	Index negativ	<0.9	

AE Case definition: „confirmed"
Imaging **and** PCR or
Immunohistochemistry mAb Em2G11
??? Best managment?



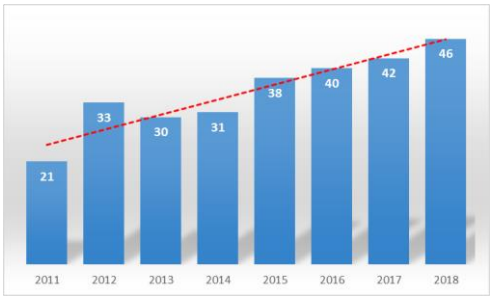
AE- management UKU: Follow up

1. **always** PET- CT (PET-/ MRI) after (1) - 2 yrs. ABZ-treatment: assessment of Treatment Response
2. After surgery→ ABZ for 2 yrs. and PET CT combined with Echi. specific serology (Em2+) before STI
3. Follow up at least 10 yrs. after surgery (Lab/ US/ PET-CT/ MRI)*
4. In non-resectable patients: Evaluation **STI** (localized AE, NoMo, good treatment response, PET negative and Serology negative

*in correlation with primary staging and the resection margin and BMZ- aftertreatment plus age and course of serology, → PET CT vs. (PET)- MRT

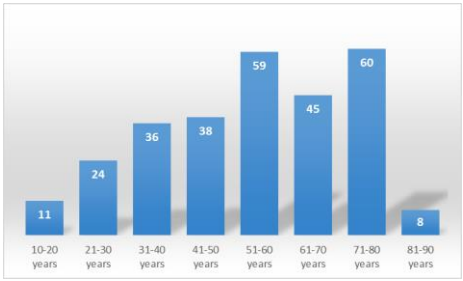
AE at UKU 2011-2018 Results

Increasing numbers of pts.



Demographics

Age at first visit

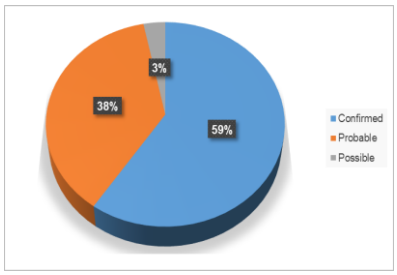


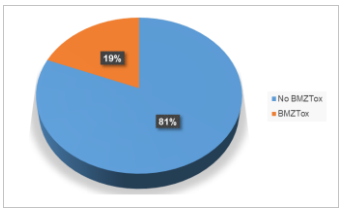
55,4% female
> 50% asymptomatic
14% AE = recognized Occupational disease
Age at first presentation : 11 bis 89 yrs..
Mean 53,7 yrs, Median 55 yrs.
Age at first diagnosis : 11 bis 89, Mean 53,0 yrs., Median 55 yrs.

Primarily farmers

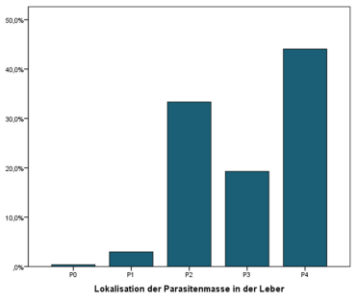
AE at UKU 2011-2018
Results

Case definition
P stage
BMZ toxicity





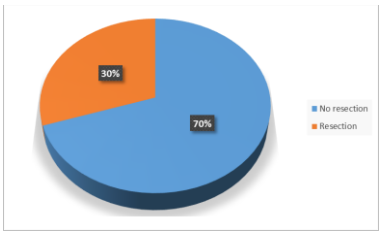
BMZ toxicity



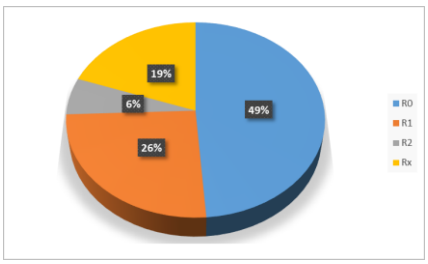
P staging

OUTCOME: AE at UKU 280 patients 2011-2018:

Surgery

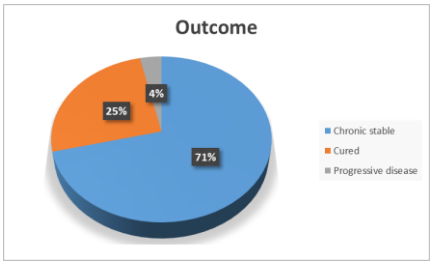


Surgery and resection margin



- Complete resection possible 36,8%
- Complete resection not possible: 57,2%
- Eventually resectable (two stage procedure): 5,9%
- **Surgery done** (in curative intention): 30%

OUTCOME: AE at UKU 280 patients 2011-2018:



Outcome

25 % patients assumed „cured"
71 % chronic stable (incl. all pat. with BMZ treament ,also after resection)
4% Progressive disease PD

STI:

23,3% (resected and medical treated)
9,4% with non resectable- lesions

Outcome

„ crude prognostic variables correlating with negative outcome "

Occupational diseases
Fatigue
Premature termination of STI due to PD
P4 stage
Extrahepatic involvement

Management of AE at UKU: 280 patients from 1.1.2011- 31.12.2018 Results / Conclusion

→ Number of AE- patients is increasing in Germany, and at UKU
→ > 50% of AE- pts. were diagnosed by chance/ without (specific) symptoms
→ In 37 % of patients AE lesions seemed complete resectable
→ ~25% considered cured// ~ 71% chronic stable//~4% progressive disease
→ 20 % pts. immunosupressed and malignancies
→ 19% had BMZ toxicity
→ 40/ 280 (14%) pts. had " initial" lesions (CT type IV/ US metastasis like)

AE at UKU: summary, ideas, questions

- → AE diagnostis is mostly satisfactory, if all diagnostic options can be used
- → Best activity assessment for first diagnosis/ follow up? Role of PET CT?
- → BMZ are effective in most cases, but no treatment options for intolerance.
- → Definition of valid stop criteria. STI→ really a goal for **all** inoperable patients?
- → Assessment of treatment response is sometimes extremely tricky, and non response might be delayed recognized ("Late biliary complications")
- → Overtreatment for small cystoid/ type IV/ metastasis- like lesions ?
- → Undertreatment for immunocomprized ?
- → Rules for surgery: Resection margin > 1 mm enough?
- → Individualization of post. OP ABZ treatment, depending on resection margin?

Vielen Dank für Ihre Aufmerksamkeit!

beate.gruener@uniklinik-ulm.de **Internetpräsenz:** www.fuchsbandwurm.eu

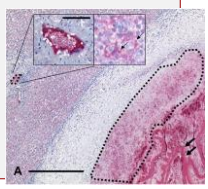
AE Diagnosis and Case definition 2019

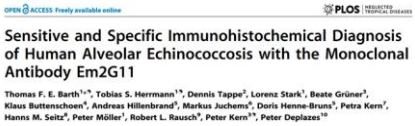
Possible versus probable versus confirmed case*

- **Possible case.**
  Any patient with clinical and epidemiological history and imaging findings or serology positive for AE.

- **Probable case.**
  Any patient with clinical and epidemiological history,
  and imaging findings and serology positive for AE with two tests

- **Confirmed case.**
  Suitable imaging findings and 1 out of 3 below
  (1) histopathology compatible with AE and/or
  (2) positive *E. multilocularis* PCR in a clinical specimen
  or (3) positive specific immunohistochemistry using mAbEm2G11




OPEN ACCESS Freely available online PLOS NEGLECTED TROPICAL DISEASES

Sensitive and Specific Immunohistochemical Diagnosis of Human Alveolar Echinococcosis with the Monoclonal Antibody Em2G11

Thomas F. E. Barth[1-3], Tobias S. Herrmann[1,3], Dennis Tappe[2], Lorenz Stark[1], Beate Grüner[1], Klaus Buttenschoen[4], Andreas Hillenbrand[5], Markus Juchems[6], Doris Henne-Bruns[5], Petra Kern[7], Hanns M. Seitz[8], Peter Möller[1], Robert L. Rausch[9], Peter Kern[3,7], Peter Deplazes[10]

* Brunetti et al. / Acta Tropica *114 (2010) 1–16*

Outcome*

Year of diagnosis	<1999	≥2000	All
Outcome at last visit	N=108	N=204	N= 312
Stable	90 (83,3)	138 (**67,6**)	228 (73,1)
Progressive	11 (10,2)	5 (**2,5**)	16 (5,1)
Potentially cured	5 (4,6)	44 (**21,6**)	49 (15,7)
Not evaluable	2 (1,9)	17 (8,3)	19 (6,1)
Death related to AE	12/30 (40%)	3/10 (30%)	15/40 (37,5%)
AE-relapse after surgery +BMZ-treatment	32/55 patients (58,2%)	8/78 patients (**10,3%**)	40/133 patients (30,1%)
AE-progress after or during BMZ-treatment	18/53 patients (34,0%)	10/126 patients (**7,9%**)	28/179 patients (15,6%)

Table 7: State of BMZ therapy at the end of follow-up

Patient group (N, %)	Surgery + BMZ (N=131)	BMZ alone (N=157)	Total (N=288)
BMZ ongoing	53 (40.5)	129 (82.2)	182 (63.2)
STI	68 (51.9)	17 (10.8)	85 (29.5)
Pause due to toxicity	4 (3.1)	7 (4.5)	11 (3.8)
Pause due to non-compliance	6 (4.6)	4 (2.5)	10 (3.5)

BMZ = benzimidazoles; STI = structured treatment interruption

Treatment strategy*

First admittance in Ulm 01. Jan. 1992 – 31. Dec. 2011. Follow-up until 31. Dec. 2012.
Def. lost-to follow-up: Last contact prior 01. Jan. 2010

Group	A <1999	B >2000	Total
N	**108**	**204**	**312**
No treatment			
Aborted lesion at diagnosis	4 (3,7)	11 (5,4)	15 (4,8)
Non-compliance, treatment not started	1 (0,9)	6 (2,9)	7 (2,2)
Treatment	103 (95,4)	187 (91,7)	290 (92,9)
BMZ	48 (44,4)	109 (53,4)	157 (50,3)
Interventions	9 (18,8)	12 (11,0)	21 (13,4)
Liver surgery + BMZ*	55 (50,9)	78 (38,2)	133 (42,6)
Interventions	16 (29,1)	12 (15,4)	28 (21,1)

*For 2 patients BMZ treatment had not begun at the end of follow-up

* Grüner B, Kern P, Mayer B, Gräter T, Hillenbrand A, Barth TFE, Muche R, Henne-Bruns D, Kratzer W and Peter Kern

Outcome*

STI---aim for patients with non-resectable lesions (?)

Table 7: State of BMZ therapy at the end of follow-up

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*** Grüner B, Kern P, Mayer B, Gräter T, Hillenbrand A, Barth TFE, Muche R, Henne-Bruns D, Kratzer W and Peter Kern**

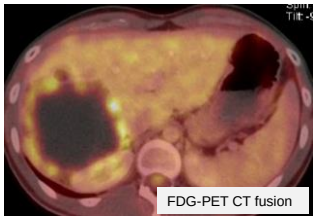
Long term results of comprehensive AE management 312 patients in Ulm/ Germany **1992- 2011**

Conclusion*

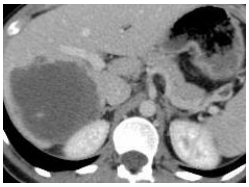
- Patients with AE diagnosed from 2000 onwards had a better outcome:
- with lower relapse and progression rates
- higher rates R0 resections and
- more potentially cured patients (21.6% vs.4,6%)
- Long-term BMZ administration for inoperable cases is (well-) tolerated over many years and keeps parasitic lesions suppressed
- BMZ side effects: out of 290 patients had : 133 (45,9%) no side effects, 122 (42,1%) low or intermediate side effects, 20 (6,9%) severe toxicity→ need for alternative drugs
- In the majority of the patients Alveolar Echinococcosis is a „well controllable" chronic disease, which needs long- term BMZ- therapy and regular follow up`s.
- Around 22 % of the AE patients assumed "Cured" (by surgery + BMZ aftertreatment)
- 10% of not operated patients under "STI" (medical cure ?)

JJ* 23 yrs. male

CT coronar



FDG-PET CT fusion



CT : 5 months ABZ treatment .

Hauptdiagnose:

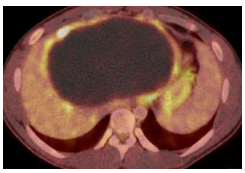
2015	Echinococcus-multilocularis-Infektion [alveoläre Echinokokkose] der Leber; WHO Stadium P4 (Kontakt V.cava) N1 (Lk Leberpforte) M1 (Lunge?); WHO diagnose "probable" : typ. Morphologie, pos. Serologie. (ext.2 pos Tests)

Therapie und Verlauf:

19.05.2015	Echi.Serologie; Extern: Echinococcus Hund ELISA (72 U/ml, Norm < 10), Echinococcus Fuchs-ELISA 408 Index (Norm < 90 Em2+), Echinococcus spp. IHA 1: <32 (negativ).
17.06.2015	Erstvorstellung FDG PET CT: großer aktiver AE-Leberherd rechts max. 20 x 9,4 cm. Echi. Serologie: IHA 1:<32, Em2+ positiv. deutliche IgE Erhöhung 5787 IU/ml; Einleitung Albendazol Therapie: Eskazole 400 mg 1-0-1/Tag mit fetthaltiger Maghlzeit unter regelmässigen Laborkontrollen, Abklärung Operabilität: zunächst Abwarten des Verlaufes unter Eskazole bei Cava-Beteiligung (Re-Evaluation unter 6 monatiger Therapie)
18.06.2015	Beginn Eskazole 2x 1/2 Tbl/Tag,: Laborkontrolle normal (3.7.)
17.07.2015	Erhöhung Eskazole 2x 1 Tbl/Tag (GPT 86 unter 1 Monat 2x1/2 Tbl); 29.7. GPT 98 U/l
14.08.2015	GPT 146 U/l
19.08.2015	Laborko. incl. ABZ Spiegel (4 Std.wert); 1,83 mg/l, GPT 125 U/l, Quick 66%, IgE 5448 IU/ml; zunächst Eskazole 2x1 Tbl weiterhin, WV 25.11. mit CT T/A

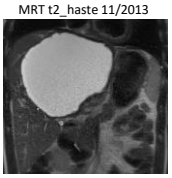
Good response to ABZ (ABZ 2x 800 mg/day), 20 yrs., male

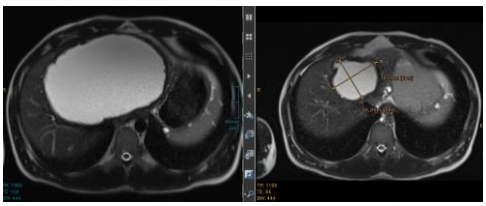
CT 13.02.2013



FDG-PET CT 02/2013

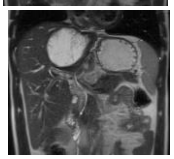
MRT t2_haste 11/2013





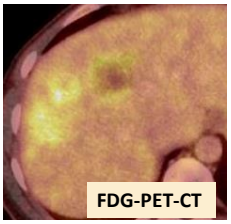
MRT t2_haste 11/2013

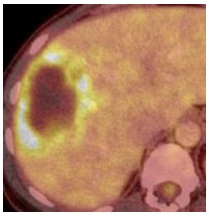
MRT t2_haste 11/2015

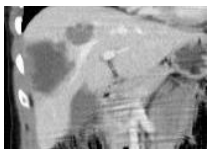


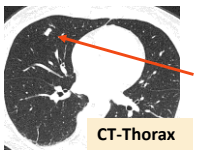
MRT t2_haste 11/2015

KL *1974









Diagnosis Alveolar Echinococcosis (Echinococcus multilocularis Infection)
WHO Stadium P2NoM1 (Pulmo).

Echinokokken-AK:.

Echinococcus spp.	IHA AK	<1:32
Ech ELISA	ELISA IgG	positiv

Mikrobiologische Beurteilung:

Nachweis Echinococcus multilocularis-spezifischer Antikörper. Serologischer Hinweis auf eine Infektion mit Echinococcus multilocularis.

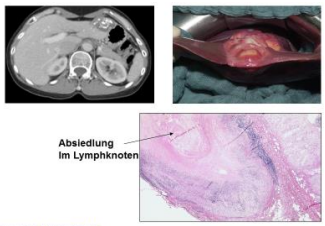
Serologie

C-reaktives Protein	LHeparin	8.2	+	mg/l	< 5.0
IgE	Serum	417.7	+	IU/ml	< 100.0
Serum					
Echinococcus		1.07	+ K1.2	kU/l	< 0.35

Labor

AE treatment UKU: Surgery

Impact of affected lymph nodes on long-term outcome after surgical therapy of alveolar echinococcosis.



Hillenbrand A, Beck A, Kratzer W, Graeter T, Barth TFE, Schmidberger J, Möller P, Henne-Bruns D, Gruener B.

Langenbecks Arch Surg. 2018 Jun16. doi:10.1007/s00423-018-1687-9.

Inclusion 109 (out of 115) AE patients
Surgery between 1.1.2000- 3/2017
56 x surgery UKU, 53 x surgery other clinics

In 43/ 109 patients resection of lymph nodes
In 27/ 43 patients enlarged lymph nodes intra Op

33 / 43 lymph node resections at UKU →histopathology incl. immunohistochemistry
7/43 conventionel histology Em shown, laminated layer.
25/33 showed "SPEMs" with Em2G11 immunohistology staining, tre
3 out of 25 also laminated layer in covent.histological staining

Conclusion: Involvement of lymph nodes in AE is common, more in enlarged lymph nodes.
But no evidence is shown for lymphonodal recurrence.
Recurrance of AE is typical in the region of liver- resection.
Lymphonodal dissection not recommended.
The meaning of lymphonadal involvement, esp. when only immunohistological shown, has to beher evaluated.

Questions in AE-management

???

- BMZ treatment for **all** AE-patients? Initiation immediately?
- What are the best parameters for primary diagnosis & follow up? (delayed PET? Em18?)
- BMZ prior surgery, yes or no? Do we need a safety margin?
- Duration of BMZ treatment after R0, R1 (R2) resection?
- When to start after surgery?
- Stop criteria in longterm treatment setting? (Em18, delayed PET scan, 3hr?)
- Drug of choice in BMZ intolerance or limited response? NEW DRUGS?
- Role of UDCA in cholestatic AE- patients ?
- Better definition of real risk groups? Need for Screening? How?
- Prevention?!

Universitätsklinikum Ulm | AG Echinokokkose

PNM Klassifikation der Alveolären Echinokokkose

P:	**Lokalisation des Parasiten in der Leber**
P X	Beurteilung nicht möglich
P 0	kein Hinweis auf Lebertumor
P 1	peripherer Herd ohne Beteiligung proximaler Gallengänge oder Gefäße
P 2	zentraler Herd mit Beteiligung proximaler Gallengänge oder Gefäße eines Leberlappens*
P 3	zentraler Herd mit Beteiligung hilärer Gallengänge oder Gefäße beider Leberlappen und/oder Beteiligung zweier Lebervenen
P 4	jeder Herd mit Ausbreitung entlang der Gefäße** und Gallenwege
N:	**Extrahepatische Beteiligung von Nachbarorganen**
[Zwerchfell, Lunge, Pleura, Perikard, Herz, Magenwand, Duodenum, Nebennieren, Peritoneum, Retroperitoneum, Brust- oder Bauchwand (mit angrenzenden Muskeln, Haut und Knochen), Pankreas, regionale Lymphknoten, Leberligamente, Niere]	
N X	Beurteilung nicht möglich
N 0	kein Hinweis auf Beteiligung angrenzender Organe oder Gewebe
N 1	Beteiligung angrenzender Organe oder Gewebe
M:	**Fernmetastasen**
[Lunge, Lymphknoten, Milz, ZNS, Orbita, Knochen, Haut, Muskeln, Niere, Peritoneum und Retroperitoneum]	
M X	Beurteilung nicht möglich
M 0	kein Hinweis auf Fernmetastasen***
M 1	Fernmetastasen

* Zur Feststellung der P-Kategorien wird die Leber durch die Ebene zwischen Gallenblase und V. cava inferior in zwei Lappen unterteilt
**Gefäße umfassen V. cava inferior, V. portae, Arterien
***Röntgen-Thorax und Schädel-CT jeweils o.B.

- Kern P et al: PNM Klassifikation der alveolären Echinokokkose Chemotherapie Journal 4/2002
- Kern P, Wen H, SatoN, Vuitton DA, Gruener B, Shao Y, Delabrousse E, Kratzer W, Bresson-Hadnis S:Parasitology International 55 (2006) 283-287 WHO classifikation of alvolar echonococcosis and apllication

STI---aim for patients with non-resectable lesions ???

Table 1: Preconditions for structured treatment interruption (STI) for patients with non-resectable lesions and no evidence of extrahepatic lesions

Preconditions
1. marked regression/absence of lesion(s) by imaging AND
2. vanished enrichment of FDG around the AE lesion(s) assessed by FDG-PET/CT scan AND
3. continuous BMZ medication for at least 2 years AND
4. absence of any clinical symptoms or signs of illness AND
5. decrease of specific serology[a]

[a] Consecutive ELISA tests with the same *E. multilocularis* antigen, definitions in [34].
AE = alveolar echinococcosis; BMZ = benzimidazoles; CT = computed tomography; FDG = fluordeoxyglucose; PET = positron emission tomography

Alveolar Echinococcosis in Germany: Retrospective Analysis of 280 Cases from 2011 to 2018

J. Bloehdorn1, K. Klein1, J. Schmidberger2, A. Hillenbrand3, T. Gräter4, M. Furitsch5, T. F. Barth6, A. Beer7, D. Henne- Bruns3, W. Kratzer2 , and B. Grüner1

Background:
Alveolar echinococcosis (AE) shows a low incidence and controlled clinical studies are hardly feasible. We therefore retrospectively analyzed AE patients with first visit at our center.
Material and methods:
All patients referred to our center between 01.01.2011 and 31.12.2018 (n=280) were analyzed with regard to clinical presentation, disease management and outcome.
Results:
Throughout the last years we observed a strong increase in patients admitted to our center (2011: n=21; 2018: n=43). Median age at diagnosis was 55 years (range 11-89 years). According to WHO-IWGE n=157 (59%) patients had „confirmed" and n=99 (37%) had „probable" diagnosis of AE. For 31% (n=78) the finding was incidental and 30% (n=74) did not present any specific symptoms. Curative resection of AE lesions was aspired in n=102 patients, with R0 in 16%, R1 in 8%, R2 in 2%, and Rx in 7% of cases reached. According to the WHO guidelines, benzimidazole therapy (BMZT) for ≥ 2 years after resection was recommended. Cases without resection (n=166) received continuous BMZT. BMZT related toxicity was observed in 18% (n=44) of patients. Patients classified as „possible" (4%) did not receive therapy, but regular follow-up. We considered 24% (n=55) of the patients cured (no relapse > 2 years after BMZT, following resection), or prospectively cured (follow-up < 2 years after BMZT, following resection). The majority of patients with 57% (n=131) has been assessed as chronically stable, n=5 (2%) progressed despite BMZT and one patient died. Notably, AE diagnosis was frequently found in patients with immunosuppression and malignomas, accounting for 20% of AE patients.
Conclusions:
Increasing patient numbers mirror rising disease awareness and infection rates. AE mostly requires long-term BMZT. Regarding rising incidences and limited curative options, improved prevention and screening is needed. High AE incidence in patients with compromised immune system points towards common factors inducing diminished resistance.

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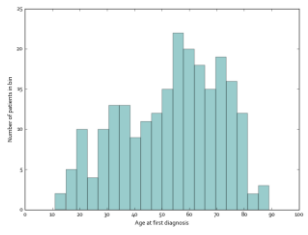
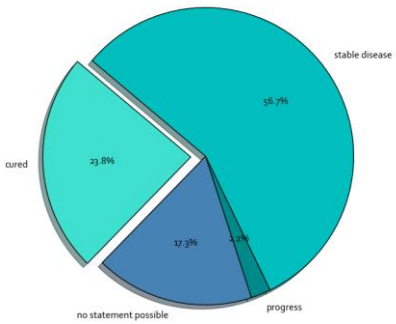
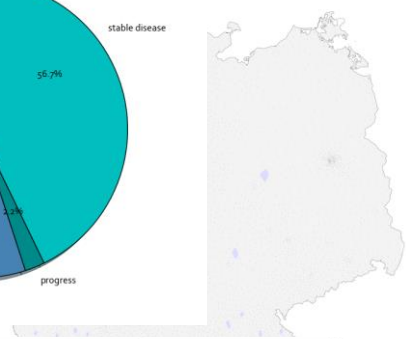
Patienten mit AE Erstvorstellung in Ulm 2011-2017: N= 231





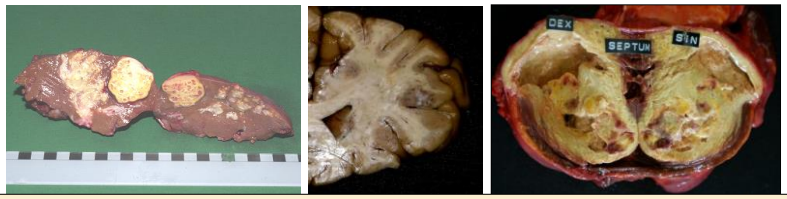


n= 232	Frequency (%)					Case definition		Outcome	
	Occupational disease	*Incidental diagnose*	*BMZ therapy*	*Structured treatment interruption*	*BMZ toxicity*		%		%
Yes	31 (13%)	72 (31%)	214 (92%)	63 (27%)	34 (15%)	**Confirmed**	130 (57%)	**Cured**	53 (23%)
No	188 (81%)	97 (42%)	13 (6%)	140 (60%)	172 (74%)	**Probable**	82 (36%)	**Stable disease**	96 (41%)
No data	13 (6%)	63 (27%)	5 (2%)	29 (13%)	26 (11%)	**Possible**	18 (8%)	**Progress**	5 (2%)
	Mean ± SD; median (range)							**No statement**	78 (34%)
Age at first visit	54,12 ± 18,14; 56,0 (11-89)								

Graph: 229 patients with residency in Germany, according to ZIP codes

Amphotericin B bei alveolärer Echinokokkose

- Reuter S et al. AAChemoth.2003 Feb;47(2):620. **Effect of Amphotericin B on larval growth**
- Reuter et al. AAC. 2003 Nov;47(11):3586. **Salvage treatment with amphotericin B in progressive human alveolar echinococcosis.** AmphoB: 0.5 mg/kg KGW/ Tag laoding 2 Wochen, dann intermit. 2x/Woche (3 Patienten, 2 verstorben)
- Tappe et al. **Limitations of amphotericin B and nitazoxanide in the treatment of alveolar echinococcosis**. Ann.of Tropl Med and Parasit. 2009 Vol. 103 No. 2 pp. 177-181 (1 Patient, verstorben)



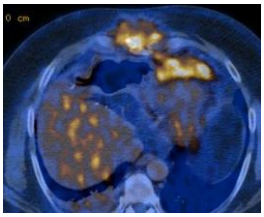
Option als individueller Heilversuch
Limitationen: intravenöse Gabe, Preis, Nephrotoxizität

Amphotericin B bei BMZ-Intoleranz: klinisches Benefit

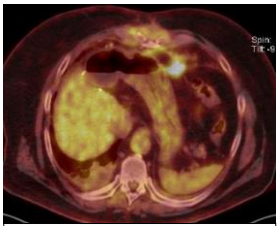
Hauptdiagnose:

1992	Echinococcus-multilocularis-Infektion [alveoläre Echinokokkose] ; WHO-Stadium PxN1M0: ED 1992
Therapie und Verlauf:	
06/1992	Hemihepatektomie links mit Zwerchfellteilresektion und Cholezystektomie
07/1992	Verschluß der post OP biliocutanen Fistel ; endoskop. Papillotomie
10/1998	op Entfernung Echi. multiloc. Rezidiv subcutan/subxiphoidal; Abbbruch der anschließenden Eskazole-Therapie bei ausgeprägtem Transaminasen-Anstieg
12/2000	Rezidiv zwischen Lebervorderrand/vorderer Thoraxwand sowie rechtsseitiger Pleuraerguß
12/2000	Reexpositionsversuch Benzimidazole (Vermox forte, anschl. Eskazole); Reaktion mit ausgeprägter med.-tox. Hepatitis
04/2002-06/2004	Heilversuch mit Amphotericin B; gutes Ansprechen der Erkrankung; Abbruch der Infusionen wegen PortExplantation nach Komplikationen
07.07.2005	Kardio-MRT; Ausschluß kardiasle Beteiligung
08/2005	Abszeß sub/kutal Laparotomie narbe (linslat. Abd.); klinisch V.a. Progress der
28.12.2005-19.04.2006	Alinia (Nitazoxanid): 2x 500 mg/die im Rahmen eines individuellen Heilversuches; Absetzen bei Leberwertanstieg (GPT>20fach, GGT 8fach, keine Cholestase)
03/2007	lipsomoales Amphotericin B (Ambisome) 1x/Woche 400 mg iv
22.06.2015	FDG-PET CT (unter Ambisome 350 mg/Woche): mixed response; jedoch kein Progress im Bereich der perikardialen Herde, 1 neuer Herd rechts subkutan. Echi Serologie IHA 1:1024, Em2+ positiv. Crea 235 , GFR 23 ml/min; stabile Gesamtsituation unter der wöchentlichen AmBisome-Infusion (350 mg absolut, entspricht etwa 3 mg/kg Körpergewicht), Ausweitung des Infusionsabstandes möglich dh Gabe nur noch 2 Wochen empfohlen. Wiedervorstellung in spätestens 18 Monaten incl. FDG-PET-CT

01/2007: CT



01/2008 PET-CT

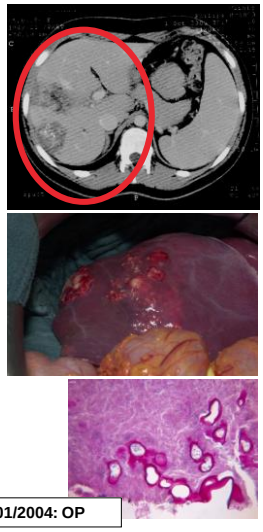


06/2015 PET-CT stabil

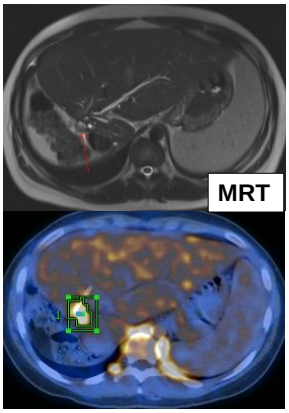
Nitazoxanid bei BMZ-Intoleranz→ bei AE **kein** Benefit

- Stettler et al. **In Vitro Parasiticidal Effect of Nitazoxanide against *Echinococcus multilocularis* Metacestodes.** Antimicrob Agents Chemother. 2003 Feb; 47(2): 467–474. : **in vivo nicht bestätigt**

AE- Rezidiv
post Op. nach NTZ (Jo*86)



01/2004: OP



12/2009 Rezidiv im PET-CT

AE-Rezidiv 4 J. post-OP
(Nachbehandlung
Nitazoxanid)
→ Rezidivtherapie
mit MBZ, später ABZ,
Gutes Ansprechen.
Auslassversuch geplant
Bei Kinderwunsch

Bildnachweis: Prof. K. Buttenschön (Chirurgie)
Prof. Th. Barth, Pathologie Uniklinik Ulm
Prof.M. Beer, Radiologie Uniklinik Ulm
Prof. A. Beer, Nuklearmedizin Uniklinik Ulm

AE at UKU: Imaging→ Ultrasound

Muster	schematische Darstellung	Beispielbild
Sturm- und Hagelmuster		
pseudo-zystisches Muster		
pseudo-hämangiom-artiges Muster		
Verknöche-rungsmuster		
metastasen-artiges Muster		

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ORIGINAL ARTICLE

Retrospective Study

Proposal of an ultrasonographic classification for hepatic alveolar echinococcosis: Echinococcosis multilocularis Ulm classification-ultrasound

Wolfgang Kratzer, Beate Gruener, Tanja EM Kaltenbach, Sarina Ansari-Bitzenberger, Peter Kern, Michael Fuchs, Richard A Mason, Thomas FE Barth, Mark M Haenle, Andreas Hillenbrand, Suemeyra Oeztuerk, Tilmann Graeter

AE at UKU: Imaging→ Computed Tomography

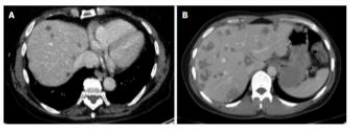

Figure 6 Small-cystoid/metastatic* (A, B): exclusive occurrence of the central calcification* (B).

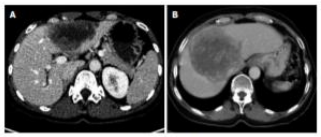

Figure 3 Primarily circumscribed tumor-like with cystoid portion (A); without cystoid portion (B).

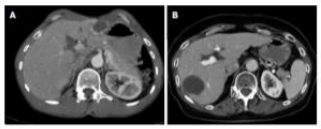

Figure 4 Primarily cystoid - intermediate with more solid portions at the edge (A); without more solid portions at the edge (B).

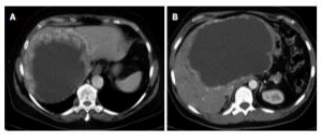

Figure 5 Primarily cystoid - widespread with more solid portions at the edge (A); without more solid portions at the edge (B).

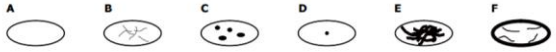

Figure 1 Schematic representation of the calcification patterns. A: Without calcifications; B: With feathery calcifications; C: With focal calcifications; D: With a central calcification; E: With diffuse calcifications; F: With calcifications primarily at the edge.

Figure 7 Mainly calcified.

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