Seltene Lebertumoren: vom Hämangioendotheliom bis fibrolamellärem HCC

Dirk Arnold

Asklepios Tumorzentrum Hamburg

AK Altona

Hamburg

ASKLEPIOS TUMORZENTRUM HAMBURG

Declaration of interests

Payment or honoraria for presentations, advisory boards, or educational activities:

- Amgen, Astra Zeneca, Bayer, BMS, Boston Scientific, Eli Lilly, GSK, Gilead, Merck Serono, MSD, Roche, Sanofi, Servier, Seagen, Sirtex, and Takeda

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- Advisory Role and/or PI function: Phanes and Oncolytics

Benigne Lebertumoren

- *Hämangiome:* häufigster gutartiger Lebertumor. Bei bis zu 17% der Autopsien
- *Leberzelladenome* (LZA): epitheloide Lebertumoren, vor allem bei Frauen die Östrogene als Kontrazeptiva verwenden, oder bei Steroiden.
- *Fokale noduläre Hyperplasie*: zweithäufigster gutartiger Tumor der Leber. Bei Frauen etwas häufiger als bei Männern gefunden,
- *Noduläre regenerative Hyperplasie*: diffuse oder herdförmige knotige Veränderung der Leber. Langdauernd Steroide, D. mellitus (?), chron. Entzündung
- *Gallengangsadenome*: Zystadenome, vom kubischem Epithel der Gallengänge ausgehend. Mukoide Zysten. Tendenz zur malignen Entartung.

Maligne Lebertumoren

- *Blastäre Tumoren:* Hepatoblastom
- *Mesenchymale Neoplasien:* zumeist Angiosarkom. Epitheloide Lebertumoren, vor allem bei Gebrauch von Östrogenen, oder bei Steroiden.
- *Hämangioendotheliom*: oft lokal begrenzt. Eher „benigne“
- *Fibrolamelläres Karzinom:* oft fortgeschrittene Erkrankung, aggressiv. Genetisch distinkte Entität
- *„Mischtumoren“:* zwischen HCC und CCC. Genetisch möglicherweise zu differenzieren.

Hepatoblastom

1.6 Fälle pro 1 Mio Kinder in DE. m/f ratio 2:1

1 % aller maligner Erkrankungen im Kindesalter, Auftrittsalter zwischen 6 Monaten und 3 Jahren

Bösartige Tumoren	Hepatoblastom	43 %	Neugeborene, Säuglinge, Kleinkinder
	Hepatozelluläres Karzinom	23 %	Schulkinder, Jugendliche
	Sarkom	6 %	Schulkinder, Jugendliche
Gutartige Tumoren	Hämangiome	13 %	Neugeborene, Säuglinge, Kleinkinder
	Hamartome	6 %	Neugeborene, Säuglinge, Kleinkinder
	Adenome	2 %	Schulkinder, Jugendliche
	Fokale noduläre Hyperplasie	2 %	Schulkinder, Jugendliche

Primäre Lebertumoren
bei Kindern und Jugendlichen

https://www.gpoh.de/kinderkrebsinfo/content/erkrankungen/weitere_solide_tumoren/lebertumoren/index_ger.html

Hepatoblastom

Pathogenese und Risikofaktoren

Frühgeburt mit niedrigem Geburtsgewicht

Frühzeitige Exposition gegenüber einer Hepatitis-B-Infektion

Gallengangsatresie

Genetische Erkrankungen: Beckwith-Wiedemann-Syndrom, FAP, Trisomie 18

Entsteht aus primitiven Vorläuferzellen des Leberparenchyms

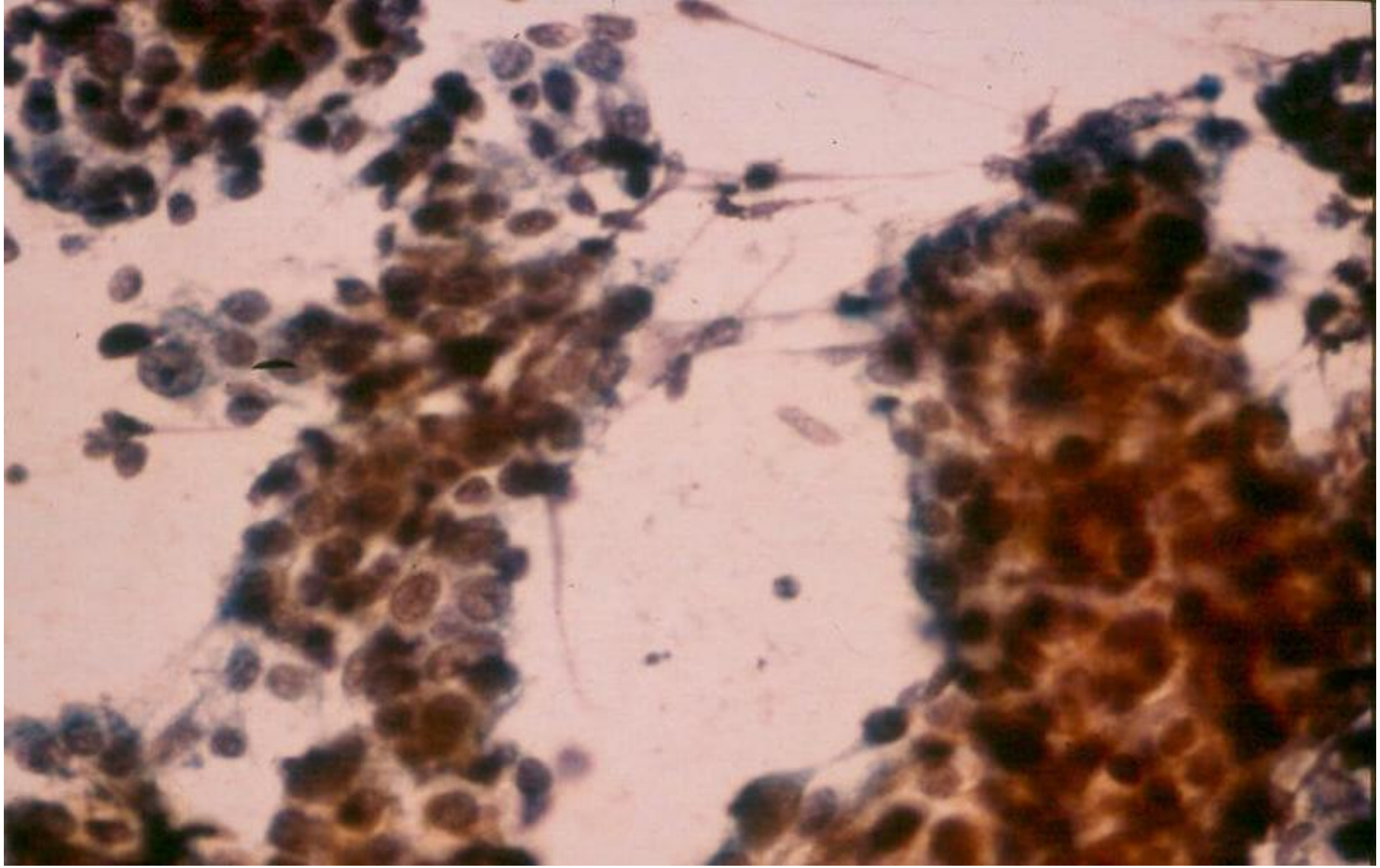
Großer, gut durchbluteter, unifokaler Tumor; bevorzugt im rechten Leberlappen

Bei 40 % der Patient*innen ist die Erkrankung fortgeschritten

(20 % der Fälle mit synchronen Lungenmetastasen)

Alpha-Fetoprotein-Spiegel im Serum sind deutlich erhöht

bei 80-90 % der Patient:innen erhöht, aber: sehr niedriges AFP → aggressives HP mit schlechter Prognose. ß-HCG bei 20%



Kleine, ovale bis spindelförmigen Zelle mit wenig Zytoplasma und ausgeprägten Nukleoli: Maligne Hepatozyten in verschiedenen Reifungsstadien. Verstreute mesenchymale Strukturen

Chang Y, Liver Cancer 2018

Hepatoblastom: Therapie

- Chirurgische Resektion
- Fast immer neoadjuvante Chemotherapie → Polychemotherapie
- Die Gesamtüberlebensrate hat sich in den letzten 4 Jahrzehnten stark verbessert und liegt nun bei 86%.

https://www.gpoh.de/kinderkrebsinfo/content/erkrankungen/weitere_solide_tumoren/lebertumoren/index_ger.html

Epitheloides hepatisches Hämangioendotheliom (EHE)

niedriggradig maligne vaskuläre Neubildung.

„an *(ultra)* rare hepatic vascular tumor“

- zwischen 0.38 - 1 Fälle per 1 Mio.
- Häufiger bei Frauen (m/f ratio 2:3) „in their mid-forties“

Pathologie:

Der Tumor entsteht um mittelgroße Venen.

Gefäßkanäle sind unauffällig; +/- Verkalkungen, Fibrose

Neoplastische Zellen sind plump und oft quaderförmig

Therapie:

Chirurgische Resektion - in den meisten Fällen kurativ

40 % Rezidivrate

20 %–30 % der EHE metastasieren

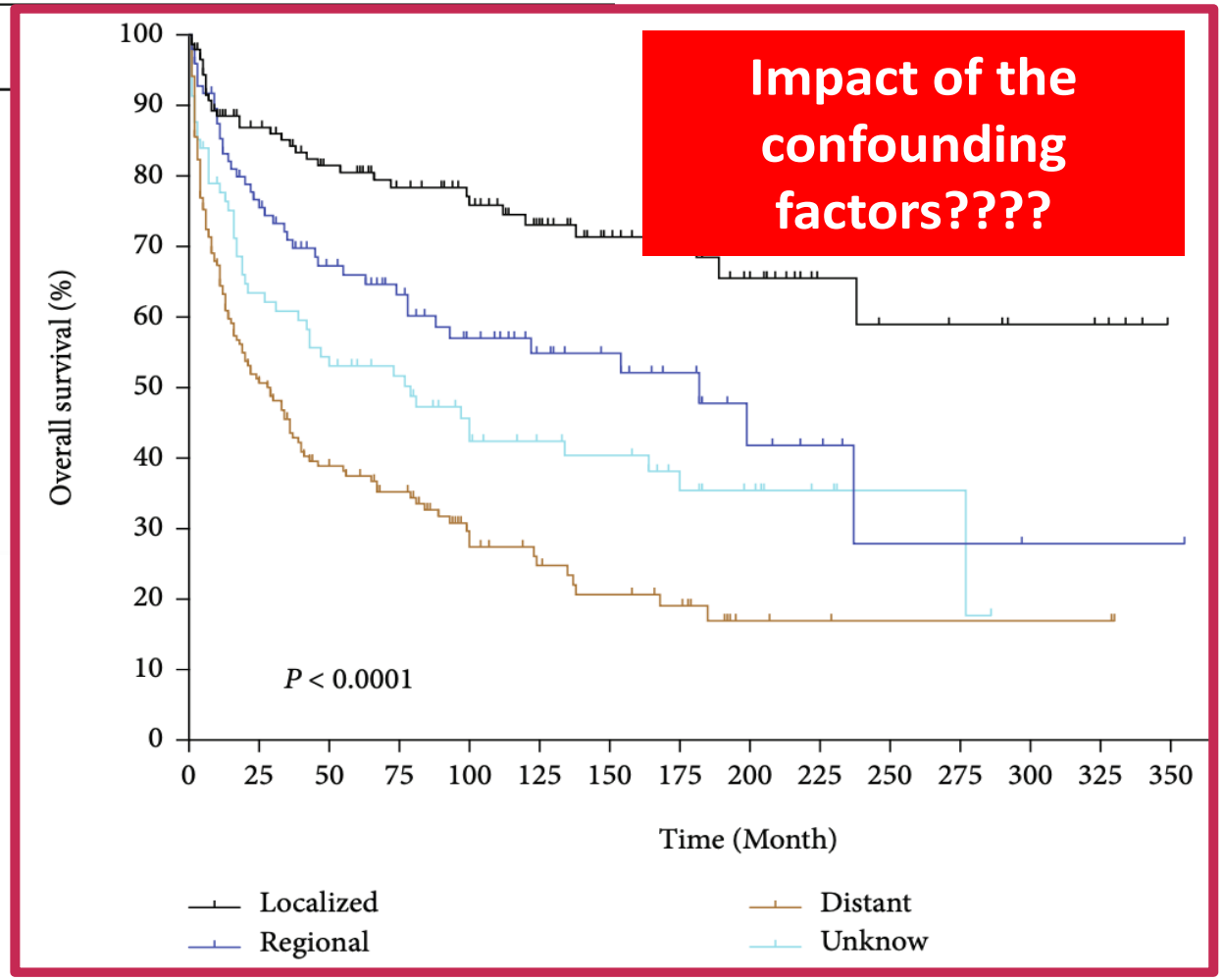
15 % der Patient:innen sterben an ihrem Tumor.

Establishment and Validation of a Nomogram Prognostic Model for Epithelioid Hemangioendothelioma

1986 to 2018

SEER-21 database (n=512)

Characteristic	Median (m)
All patients	100
Sex	
Male	97
Female	120
Primary location	
Head and neck	Undefined
Lung	46
Liver	199
Bone (soft tissue)	185
Other	67
Surgery	
No	34
Yes	237
Unknown	17
Chemotherapy	
No	185
Yes	20
Radiotherapy	
No	135



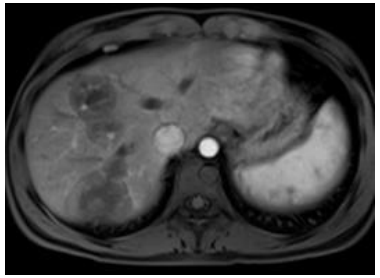
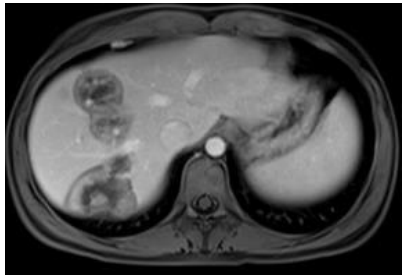
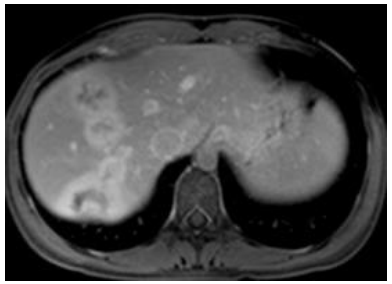
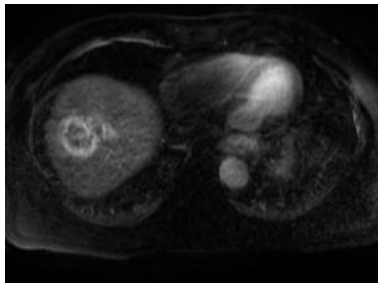
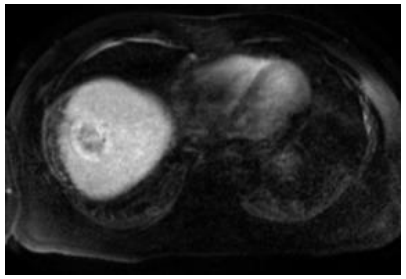
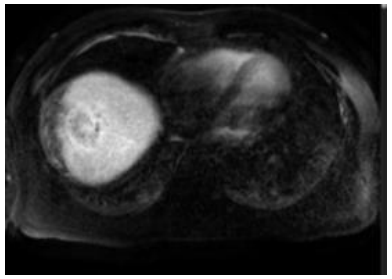
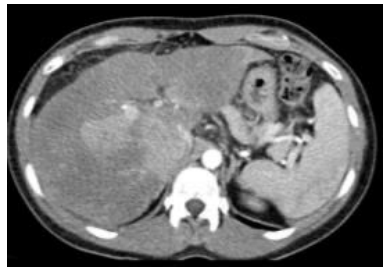
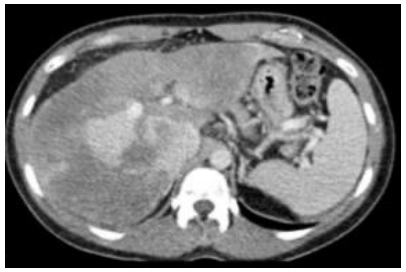
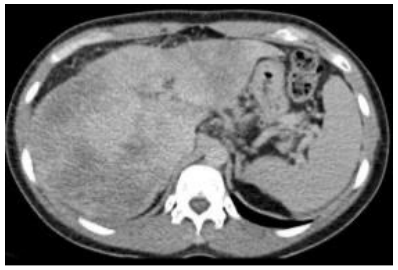
Li et al., J of Oncology 2022

Epitheloides hepatisches Hämangioendotheliom (EHE)

- Ca. 90 % der EHE weisenen eine umschriebene genetische Translokation auf: (1;3)(p36.3;q25) t →*WWTR1-CAMTA1 Fusion*
- Alternative Translokation (X;11)(p11;q22) →*YAP1-TFE3 Fusion.*
- *YAP1-TFE3* Fusionen: früheres Erkrankungsalter

Stacchiotti S et al., Transplantation. 2017

Contrast-enhancement pattern

	Arterial phase	*Portal venous phase*	*Delayed phase*	
Type 1				*Central progression (from hypo to iso-hyperenhancment)*
Type 2				*Stable peripheral without changes*
Type 3				*Persistent minimal uptake through the phases*

Sanduzzi-Zamperelli et al., Digestive and Liver Disease 2020

Epitheloides hepatisches Hämangioendotheliom (EHE)

„The knowledge we have mainly derives from **single or small case series with sub- optimal treatment outcomes...“**

Presenting signs and symptoms ($n = 294$)	No. of patients	%
Asymptomatic	73	24.8
RUQ pain	143	48.6
Hepatomegaly	60	20.4
Weight loss	46	15.6

73%

Mehrabi et al., Cancer 2006; María Reig, ESMO Rare Cancers Symposium 2023

Epitheloides hepatisches Hämangioendotheliom (EHE)

260 cases → **45.4% received treatment**

Table 2 Treatments and prognosis of patients with hepatic epithelioid hemangioendothelioma

Treatment and outcome, *n* = 118	*n* (%)	Mean survival time in months, mean ± SD
LR	35 (29.7)	158.6 ± 20.5
LT	19 (16.1)	147.3 ± 13.8
Palliative treatment	15 (12.7)	4.2 ± 0.8
TACE	12 (10.2)	90.8 ± 13.4
Chemotherapy	13 (11.0)	71.4 ± 23.5
Other treatments	6 (5.1)	55.0 ± 17.0
Antiangiogenic therapy	18 (15.3)	83.1 ± 9.7

LR: Liver resection; LT: Liver transplantation; TACE: Transhepatic arterial chemotherapy and embolization.

Reig et al., World J Clin Cases 2022

REVIEW

Epithelioid hemangioendothelioma, an ultra-rare cancer: a consensus paper from the community of experts

- Active surveillance should be considered only for patients who are not surgical candidates due to the presence of comorbidities or technical challenges.2,5,9,57 [V, A].

- Active surveillance is the initial recommended option in cases presenting with asymptomatic locoregional or systemic metastases53 [V, A].

- The risk of over-treatment appears to outweigh the damage of a delayed treatment start.

Stacchiotti et al., ESMO Open 2021

Epitheloides hepatisches Hämangioendotheliom (EHE)

Treatment and tumor burden					
HEHE characteristics	**LR (n.7)**	**LT (n.4)**	**Systemic therapies* (n.6)**	**No treatment (n.7)**	**All (n.24)**
Bilobar disease n, (%)	3 (42.9)	3 (75)	4 (66.7)	7 (100)	17 (70.8)
Multinodular disease n, (%)	3 (42.9)	3 (75)	4 (66.7)	6 (85.7)	16 (66.7)
Extrahepatic spread n, (%)	1 (14.3)	2 (50)	4 (66.7)	5 (71.4)	12 (50)
Lymph node involvement n, (%)	0	1 (25)	0	0	0
Macrovascular invasion n, (%)	0	0	0	0	0

LR: *Liver Resection****;*** ***LT****: Liver Transplantation*

******Interferon (IFN)* *was the most used first-line therapy in 4 out of 6 patients, followed by* ***IL12*** *(n=1) and paclitaxel monotherapy (n=1).*

Five patients received ***two lines of systemic therapy****, with different regimens used as second-line therapy (n=1 carboplatin/paclitaxel combination; n=1 paclitaxel monotherapy; n=1 cisplatin/etoposide combination; n=1 IFN and n=1 liposomal doxorubicin)*

Palliative radiotherapy was required for local control of a thoracic metastasis in one patient, with symptomatic clinical response.

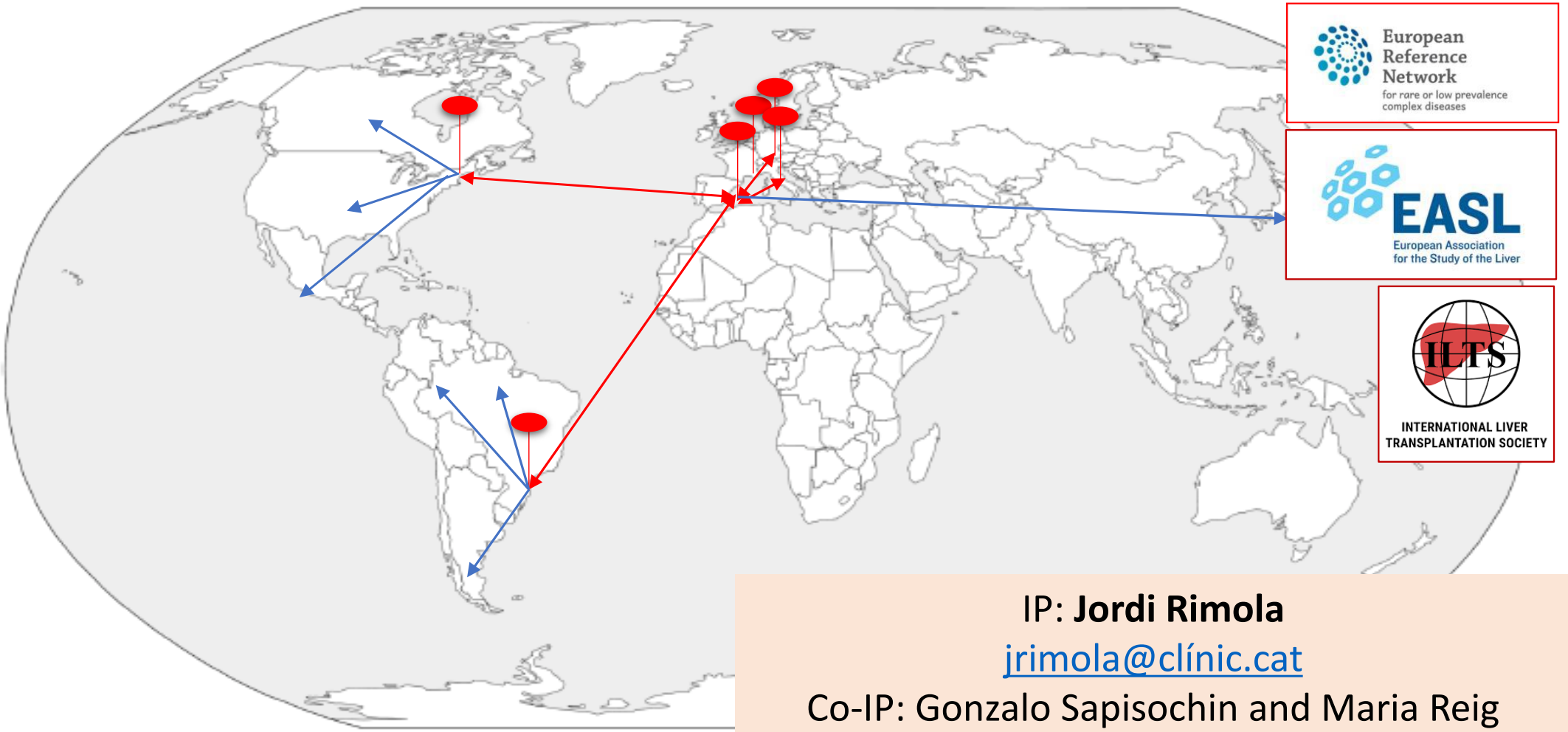
Sanduzzi-Zamperelli et al., Digestive and Liver Disease 2020

Epitheloides hepatisches Hämangioendotheliom (EHE)

NCT03331250	Eribulin in Angiosarcoma and Epithelioid Hemangioendothelioma (EHE	Eribulin	13	May 31, 2025
NCT03148275	A Non-Randomized, Open-Label, Phase 2 Study of Trametinib in Patients With Unresectable or Metastatic Epithelioid Hemangioendothelioma	Trametinib	27	December 31, 2023
NCT05228015	A Phase 1, First-in-Human Study of IK-930, an Oral TEAD Inhibitor Targeting the Hippo Pathway in Subjects With Advanced Solid Tumors	IK-930	158	October 2024
NCT01532687	A Randomized, Double-Blind Phase II, Study of Gemcitabine Alone or in Combination With Pazopanib for Refractory Soft Tissue Sarcoma	Gemcitabine Pazopanib	54	October 31, 2019

www.clinicaltrials.gov

Epithelioid Hemangioendothelioma International Network (EHIN)



European Reference Network
for rare or low prevalence complex diseases

EASL
European Association for the Study of the Liver

ILTS
INTERNATIONAL LIVER TRANSPLANTATION SOCIETY

IP: **Jordi Rimola**
jrimola@clínic.cat
Co-IP: Gonzalo Sapisochin and Maria Reig

Angiosarkom der Leber

Epidemiologie:

Häufigstes Sarkom der Leber, meist ältere Patient*innen (> 60 Jahre alt); Männer > Frauen

Ätiologie:

Risikofaktoren für ca. 25 % der Fälle verantwortlich: Vinylchlorid, Arsen, anabole Steriode, Kontrazeptiva, stattgehabte Bestrahlung

Pathologie:

Morphologie: gut differenzierten Tumoren, die Hämangiomen ähneln, bis hin zu anaplastischen Läsionen.

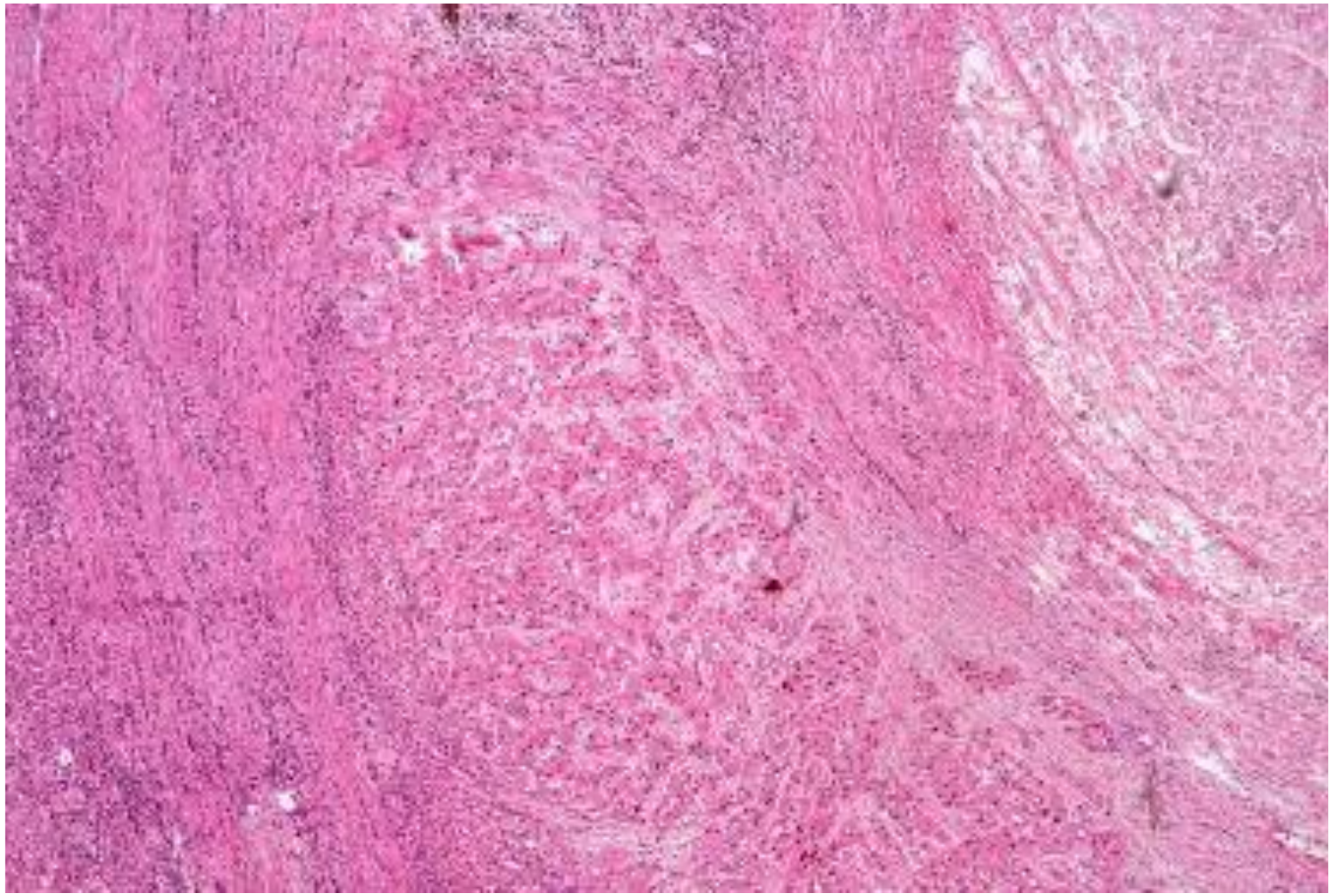
unterschiedlich große hämorrhagische Knötchen; wächst in Sinusoide und Portalvenen ein

IHC-Färbung positiv für vaskuläre Marker

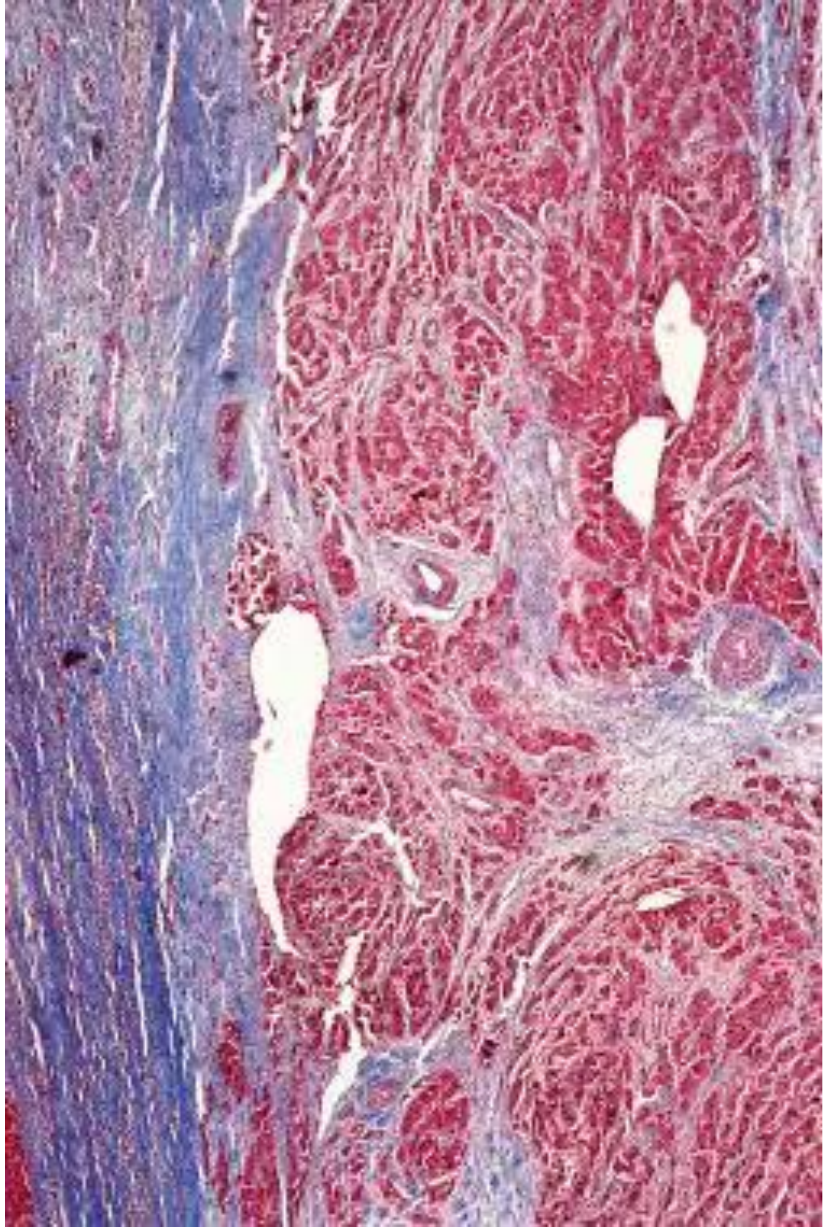
Fibrola....äh... Karzinom

Fibrolamelläres Karzinom

Fibrolamelläres Karzinom

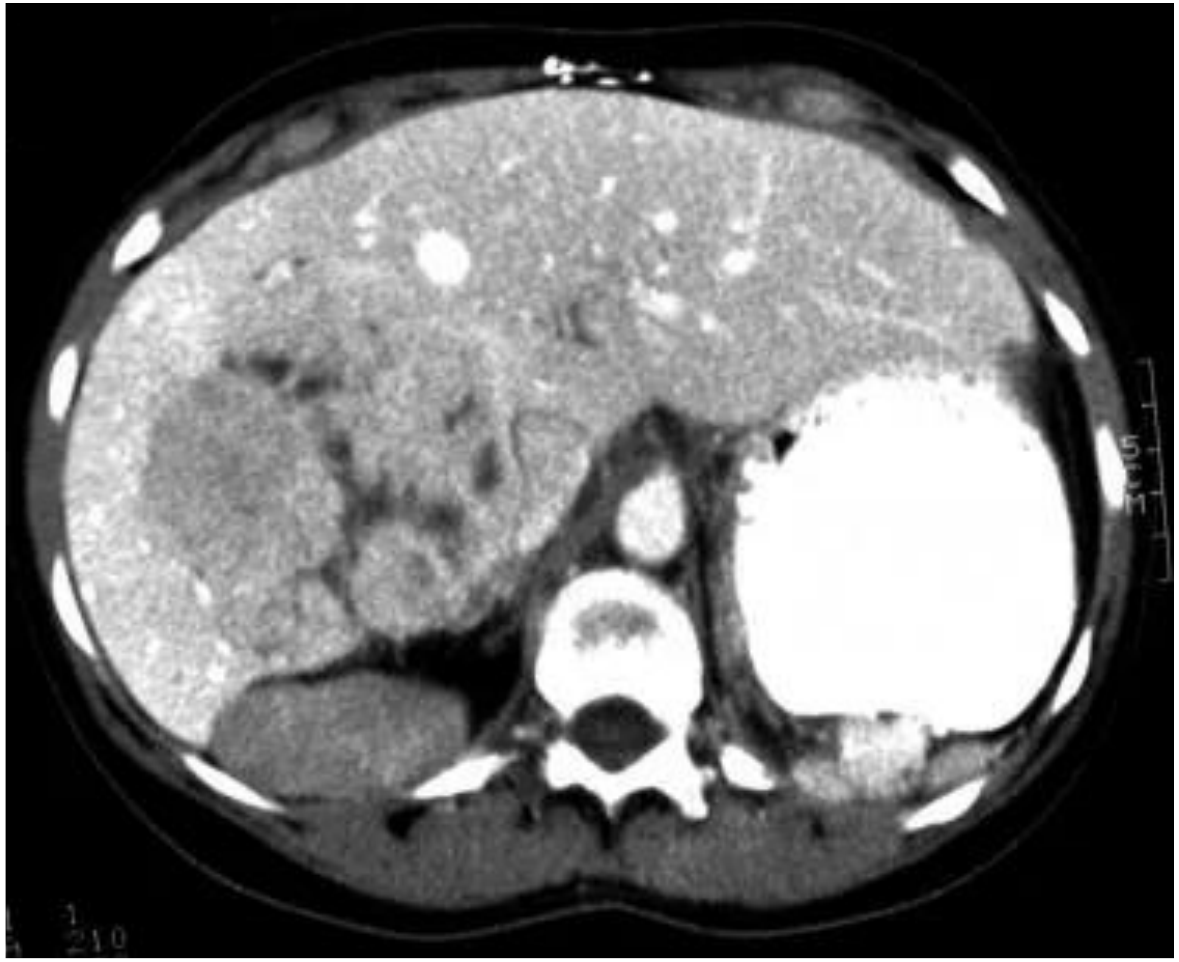


Hematoxylin and eosin stain
Thick fibrous lamellae within the tumor stroma.

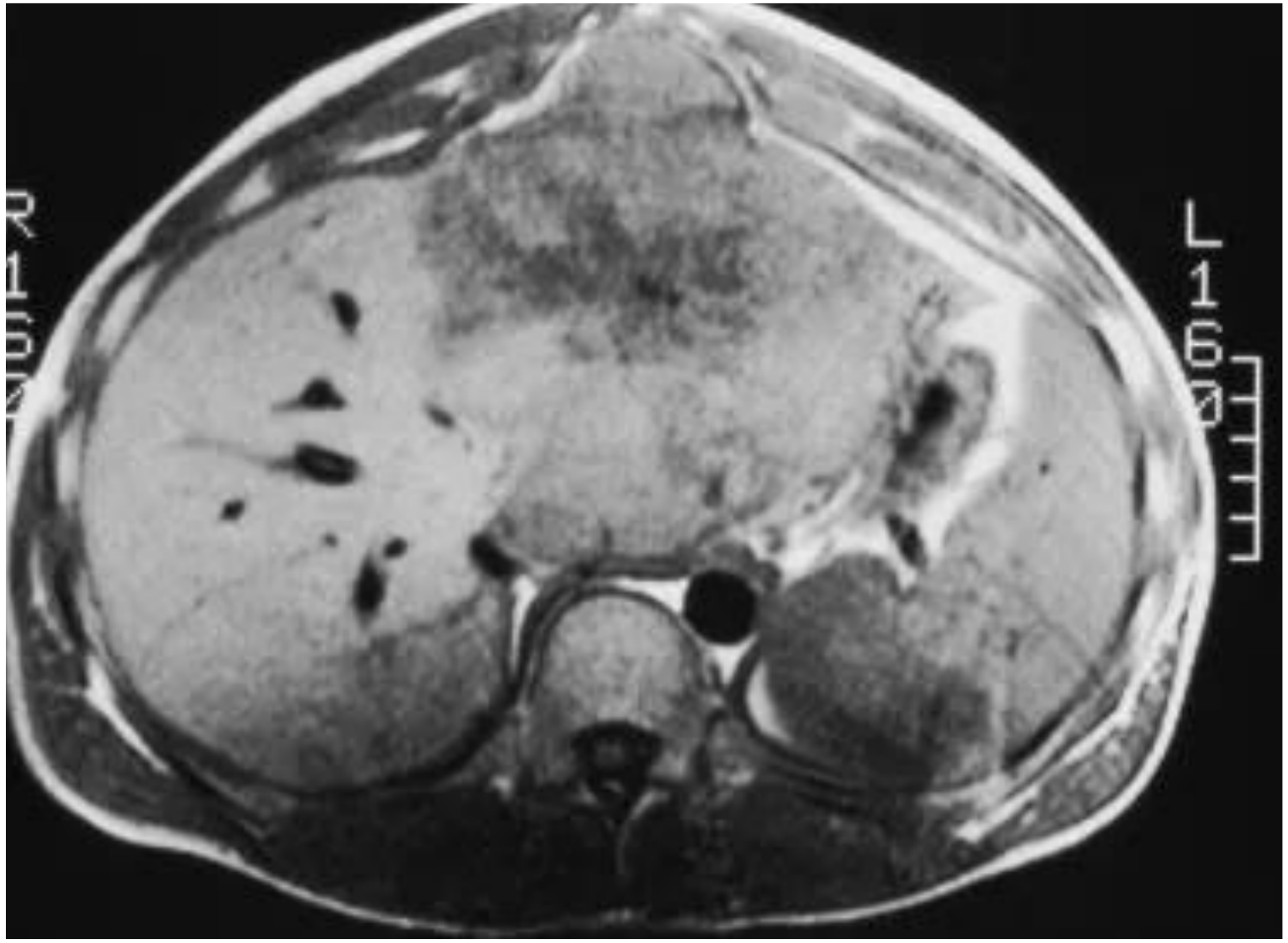


Masson trichrome stain
Collagen-containing lamellae within the stroma

Fibrolamelläres Karzinom

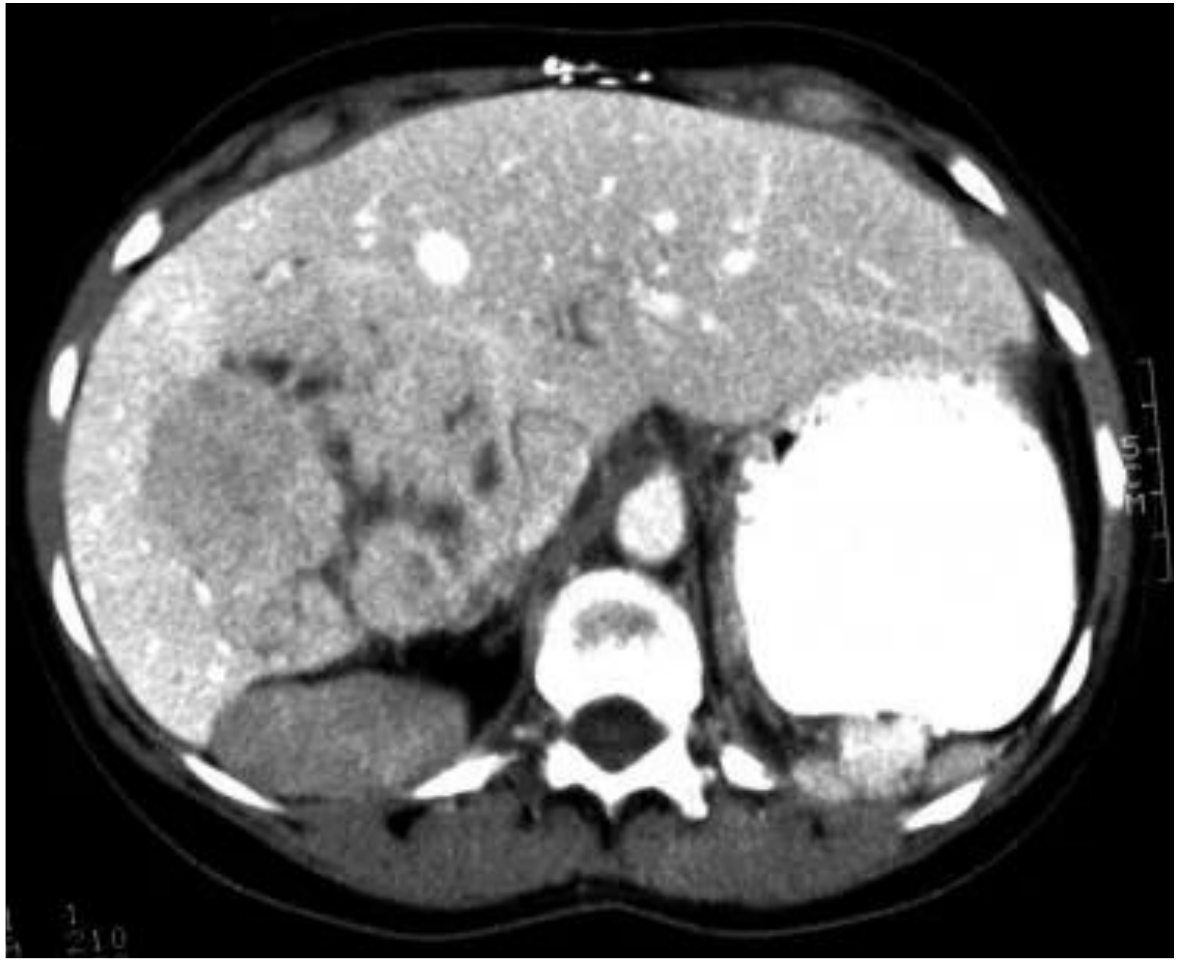


CT scan
with a large stellate central scar.



T2-weighted MRI
heterogeneous appearance with a central scar

Fibrolamelläres Karzinom



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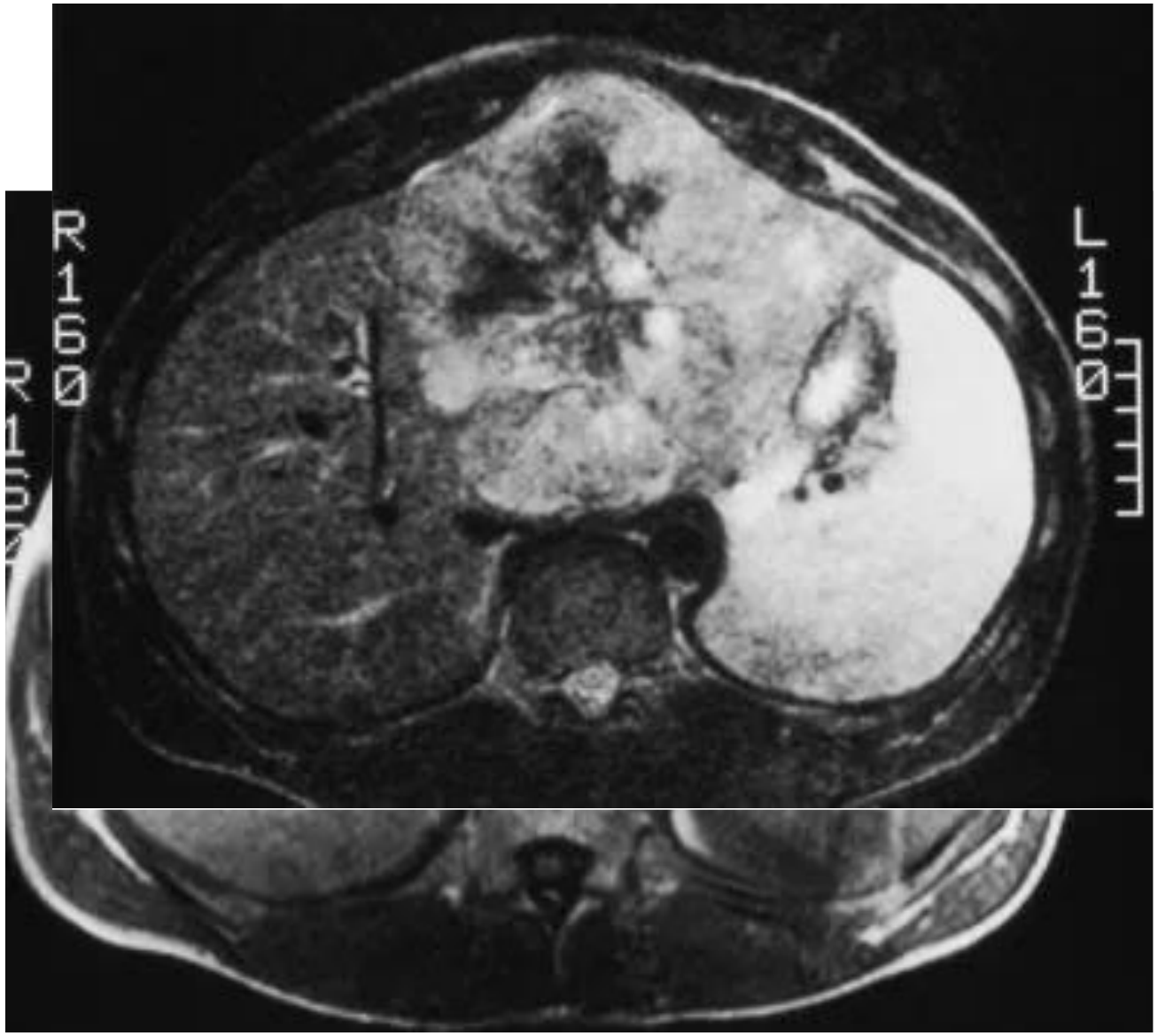

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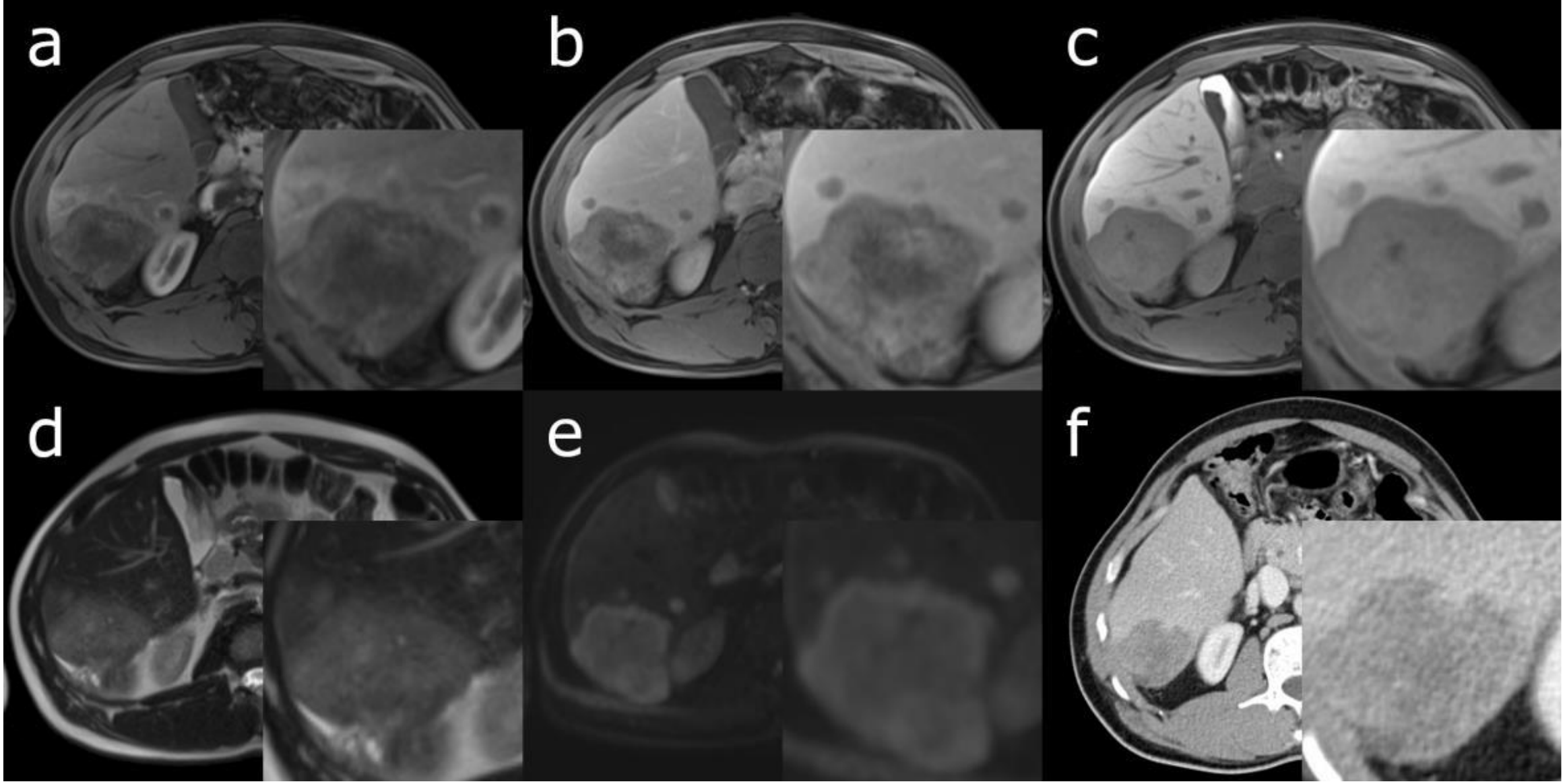
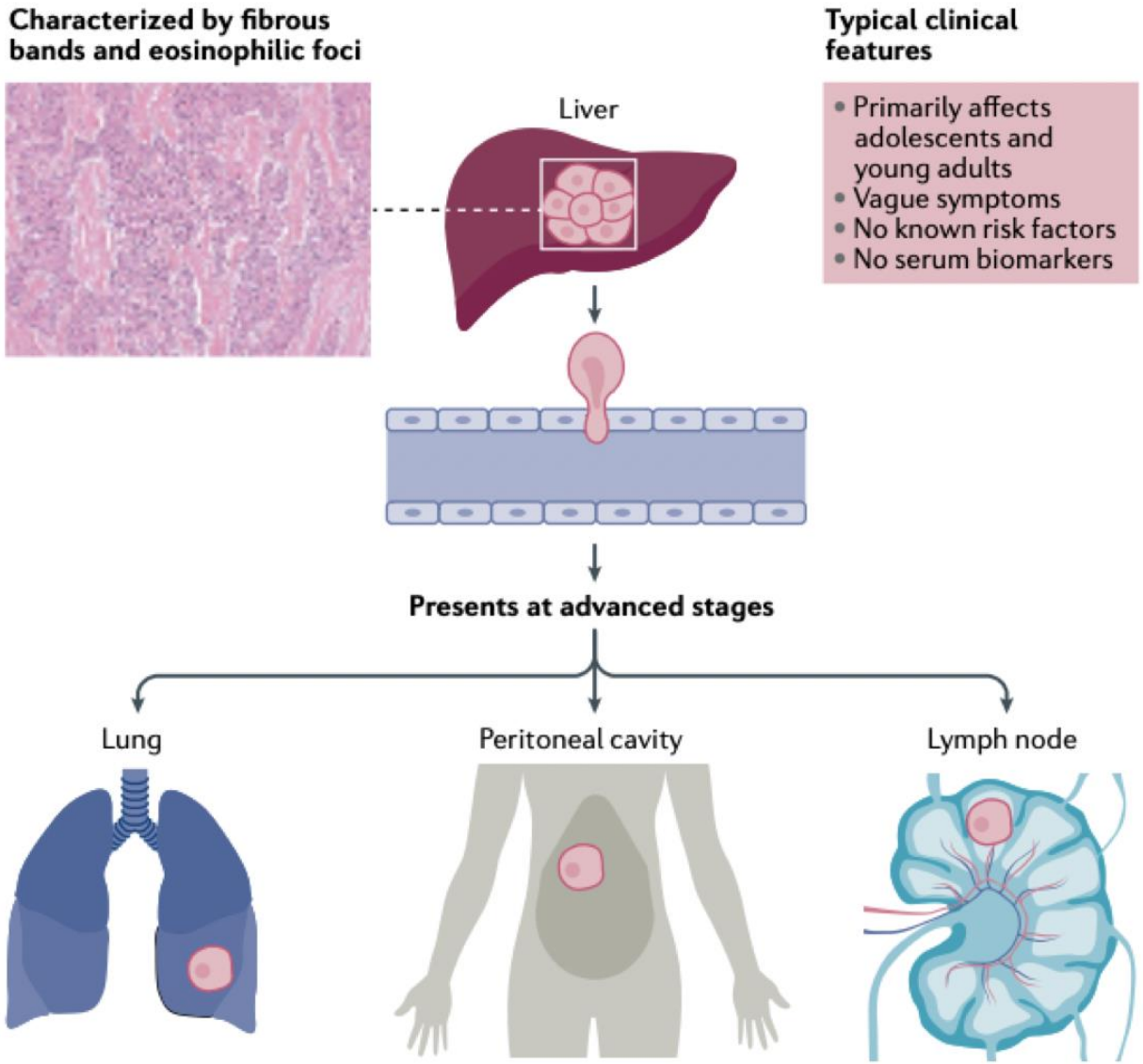


Targetoid enhancement of the primary lesion in arterial phase, whereas the satellite lesions show rim hyperenhancement; hyperintensity in a T2-weighted arterial phase, whereas the satellite lesions show rim hyperenhancement.

Eschrich J et al., Cancers (Basel) 2023



Dinh TA et al., Nature Rev Gastroenterol Hepatol 2022

Fibrolamelläres Karzinom: eine „junge“ Erkrankung

- SEER des US NCI: Inzidenz 0.2 pro 1 Mio/Jahr (= 1% aller „HCC“)
- Globale Inzidenz: schwer abschätzbar
- In US: überwiegend Kaukasier
- Erkrankungsalter: 25 Jahre (2. Peak >70 Jahre)
- Problem: „sonst gesunde“ Leber

Dinh TA et al., Nature Rev Gastroenterol Hepatol 2022

Fibrolamelläres Karzinom: eine „junge“ Erkrankung

„Fibrolamellar carcinoma (FLC), also known as *fibrolamellar hepatocellular carcinoma*, is a rare liver cancer that primarily occurs in adolescents and young adults who have no history of liver disease...“.

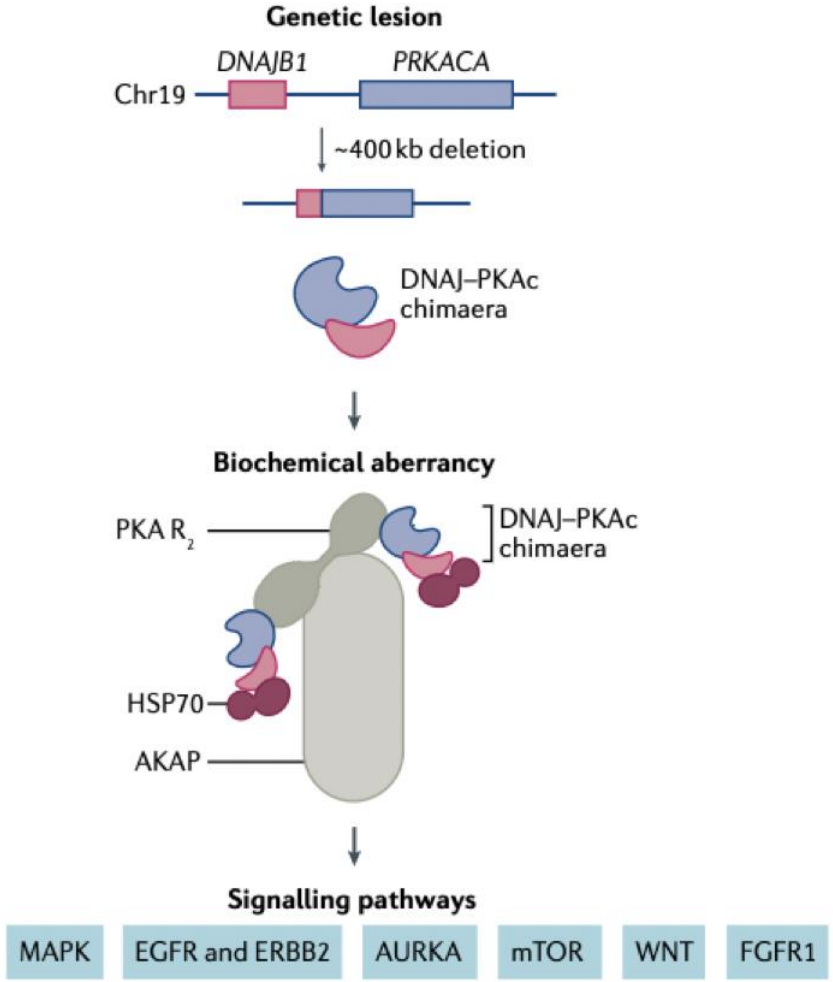
Edmondson et al., AMA J Dis Child 1956; Berman MM et al., Cancer 1980

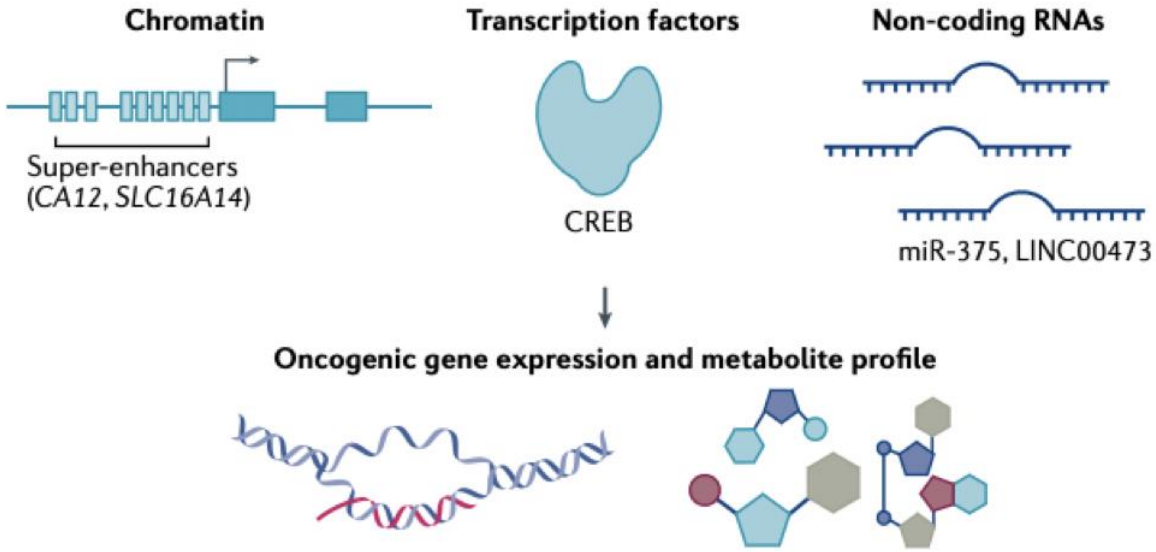
Fibrolamelläres Karzinom: eine „junge“ Erkrankung

- 2014: Honeyman et al.: „novel, chimeric transcript that is present in all studied samples of FLC, *DNAJB1-PRKACA...“*
- Multiple studies confirmed that this mutation is unique to FLC, and support the role of *DNAJB1-PRACA* as a major driver of this tumor and as a key diagnostic and therapeutic target.
- A variant of FLC: mixed fibrolamellar hepatocellular carcinoma (mFL-HCC) and characterized by the presence of both FLC and conventional HCC components within the same tumors, has also been reported. In these rare tumors, the *DNAJB1-PRKACA* fusion transcript is expressed at high levels

Simon SM et al., Nature Rev Cancer 2023

Fibrolamelläres Karzinom: Pathogenese





Dinh TA et al., Nature Rev Gastroenterol Hepatol 2022

Commentary

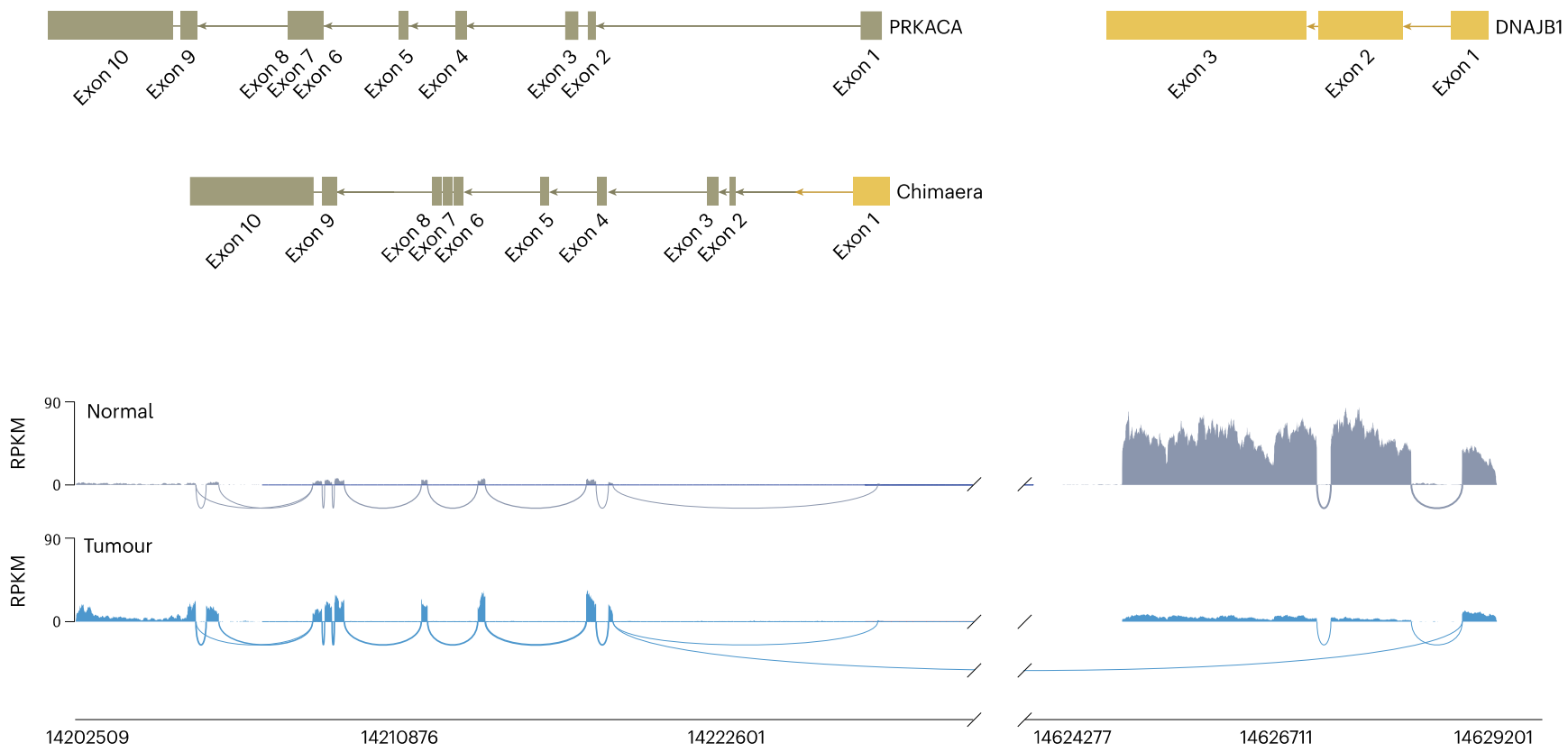
The 2019 WHO classification of tumours of the digestive system

Hepatocellular tumours:

Classification revision based on molecular profiling studies.
Fibrolamellarcarcinoma is defined by *DNAJB1–PRKA CA translocation*

Nagtegaal I et al., Histopathology 2020

Is fibrolamellar hepatocellular carcinoma a single disease?



Simon SA et al., Nature Rev Cancer 2023

Fibrolamelläres Karzinom: Therapieprinzipien

- Chirurgie → von „Debulking“ bis Transplantation
- Ablative Therapieverfahren: TACE, SBRT

Fibrolamelläres Karzinom: Therapie

3.82	Evidenzbasiertes Statement	neu 2023
Level of Evidence 5	Für das fibrolamelläre HCC (flHCC) gibt es bisher keine Phase II oder III Studien aus denen Therapieempfehlungen abgeleitet werden können. Individuelle Therapieoptionen ergeben sich lediglich aus retrospektiven Fallserien und Einzelfallberichten.	
	5: Nach ausführlicher Recherche, konnte keine ausreichende Datenlage zur Erstellung einer Empfehlung gefunden werden.	
	Starker Konsens	

Fibrolamelläres Karzinom: Systemtherapie

- Gemcitabin und Oxaliplatin (GEMOX), 5-FU/Oxaliplatin, 5-FU, CAPOX, Irinotecan
- „Beste Einzelsubstanz“: Cisplatin
- auch: Doxorubicin (pegyliert), Mitoxantron
- Interferon und Sorafenib: hier länger anhaltende Stabilisierungen berichtet*
- für pädiatrische Fälle: Orientierung an Hepatoblastom-spezifischen Regimen

* Kim A et al., Cancer Immunol Res 2019; **Simon S et al., Nat Rev Cancer 2023**

Systemic treatment of HCC in special populations

Lorenza Rimassa[1,2,*], Nicola Personeni[1,2], Carolin Czauderna[3,4], Friedrich Foerster[3], Peter Galle[3]

Table 1. Inclusion and exclusion of special populations of HCC patients in phase III trials.

Special population	SHARP[1]	REFLECT[2]	IMbrave150[10]	RESORCE[3]	CELESTIAL[4]	REACH-2[5]	CheckMate 459[9]	KEYNOTE-240[8]
Solid organ transplantation	NO	NO	NO	NO	NO	NO	NO	NO
HIV	NO	NO	NO	NO	NO	NO	NO	NO
Prior or active autoimmune diseases	YES	YES	NO	YES	YES	YES	NO	NO
Significant cardiovascular disease	NO	NO	NO	NO	NO	NO	NO	YES
Diabetes/metabolic syndrome	YES	YES	YES	YES	YES	YES	YES	YES
Fibrolamellar, mixed HCC/CCC, other histological subtypes	NO	NO	NO	NO	NO	NO	NO	NO
Decompensated cirrhosis (Child-Pugh B and C)	YES*	NO	NO	NO	NO	NO	NO	NO
Elderly patients	YES	YES	YES	YES	YES	YES	YES	YES
Significant bleeding history	NO	NO	NO	NO	NO	NO	NO	NO
Haemodialysis	NO	NO	NO	NO	NO	NO	NO	NO
Vascular invasion/portal vein thrombosis	YES	YES**	YES	YES	YES	YES	YES	YES**

Rimassa L et al., J Hepatol 2021

Fibrolamelläres Karzinom: Immuntherapie

- 32 flHCC:
  - Bei 63% eine PD-L1 Expression von Tumorzellen
  - bei 69% bei Tumor-infiltrierenden Immunzellen nachgewiesen
- Retrospektiven Analyse von 19 Patienten:
  - Ansprechen unabhängig vom PD-L1 Status
- Komplettremissionen berichtet mit
  - Nivolumab
  - Nivolumab plus Ipilimumab in PD-L1 neg flHCC mit niedriger Mutationslast (welches interessanterweise nicht auf eine Therapie mit Atezolizumab angesprochen hat)
  - 5-FU, IFN alfa-2b und Nivolumab bei ebenfalls niedriger Mutationslast (mit nachfolgender Lebertransplantation)

Kim A et al., Cancer Immunol Res 2019; Chen K et al., Cancers (Basel) 2022; De Toni et al., Gut 2020

Article

Clinical Outcomes in Fibrolamellar Hepatocellular Carcinoma Treated with Immune Checkpoint Inhibitors

Krista Y. Chen [1,†], Aleksandra Popovic [1,†], David Hsiehchen [2], Marina Baretti [1], Paige Griffith [1], Ranjan Bista [3], Azarakhsh Baghdadi [4], Ihab R. Kamel [4], Sanford M. Simon [5], Rachael D. Migler [5] and Mark Yarchoan [1,*]

Variable	Classification	Overall	Fibrolamellar Registry	Johns Hopkins & UT Southwestern
Number of Patients		19	11	8 (6 JH, 2 UTSW)
Age at Diagnosis (years)		Mean = 22.9 (SD = 6.1)	Mean = 20.7 (SD = 6.0)	Mean = 25.875 (SD = 5.1)
Gender	Male	12 (63.2%)	7 (63.6%)	5 (62.5%)
	Female	7 (36.8%)	4 (36.4%)	3 (37.5%)
FLC Stage at Diagnosis	BCLC A	3 (15.8%)	3 (27.3%)	0 (0%)
	BCLC B	4 (21.1%)	3 (27.3%)	1 (12.5%)
	BCLC C	12 (63.2%)	5 (45.5%)	7 (87.5%)
FLC Stage at ICI Treatment	BCLC A	0 (0%)	0 (0%)	0 (0%)
	BCLC B	1 (5.3%)	1 (9.1%)	0 (0%)
	BCLC C	18 (94.7%)	10 (90.9%)	8 (100%)
Number of Patients Receiving Various Treatments	Prior Systemic Treatment	15 (78.9%)	9 (81.8%)	6 (75.0%)
	Prior Surgery	13 (68.4%)	7 (63.6%)	6 (75.0%)
	Prior Local Radiation	4 (21.1%)	2 (18.2%)	2 (25.0%)
Number of Prior Systemic Treatments		Median = 1 (range 0–8)	Median = 2 (range 0–8)	Median = 1 (range 0–5)
	Prior Sorafenib	9 (47.3%)	9 (81.8%)	0 (0%)

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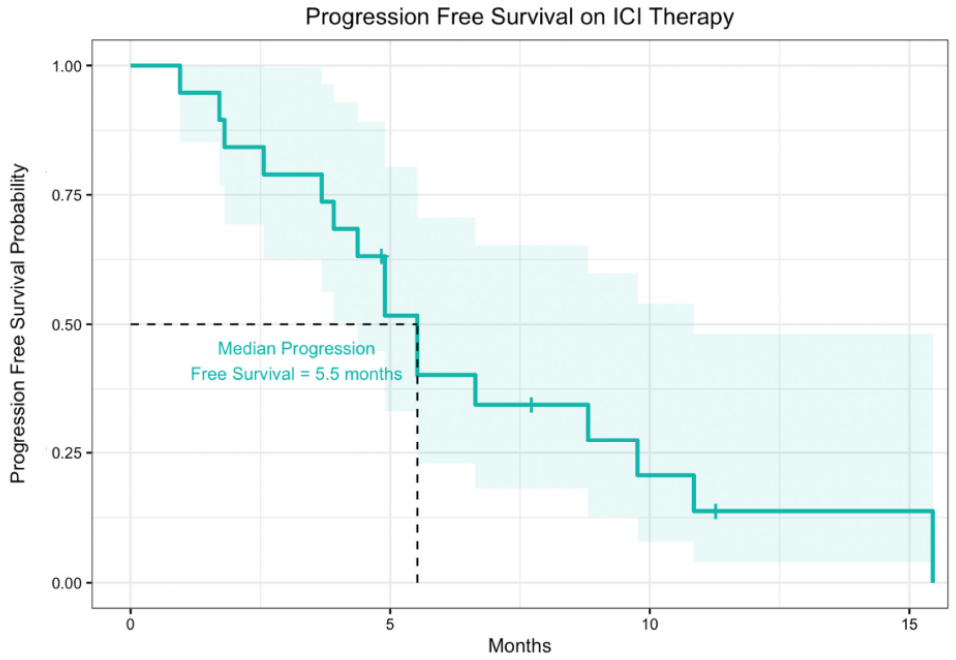
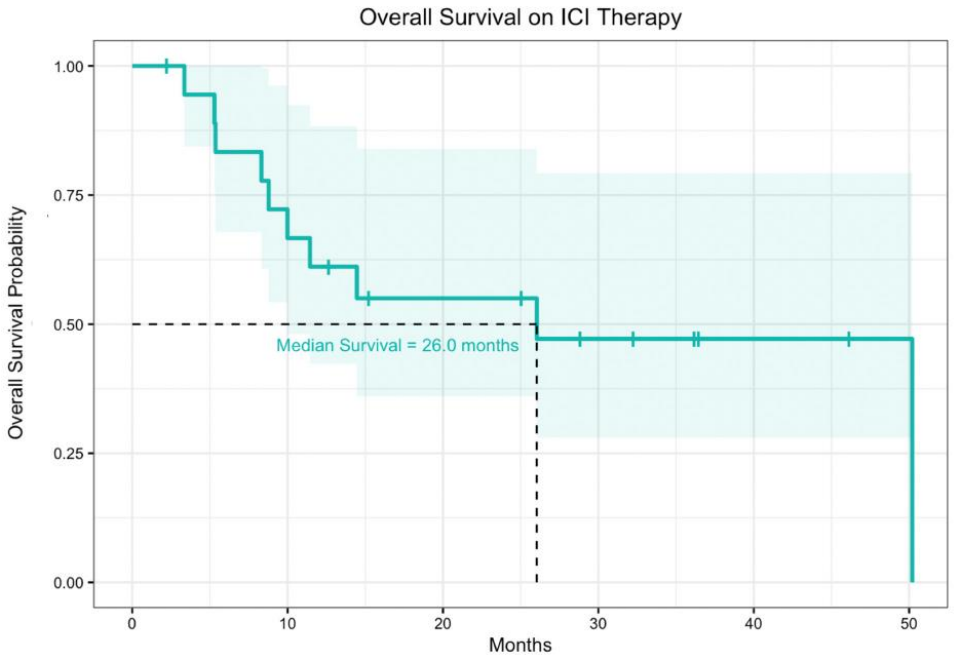




Chen KY et al., Cancers (Basel) 2022

ASKLEPIOS TUMORZENTRUM HAMBURG

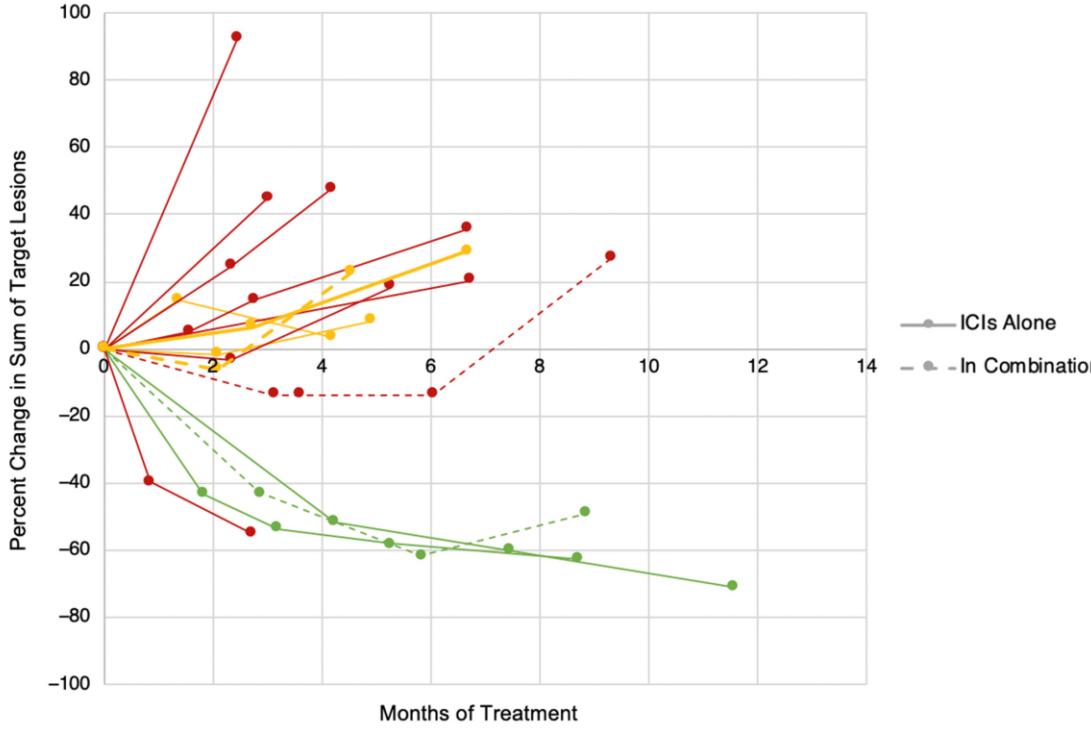
Article

Clinical Outcomes in Fibrolamellar Hepatocellular Carcinoma Treated with Immune Checkpoint Inhibitors

N=19

Krista Y. Chen [1,†], Aleksandra Popovic [1,†], David Hsiehchen [2], Marina Baretti [1], Paige Griffith [1], Ranjan Bista [3], Azarakhsh Baghdadi [4], Ihab R. Kamel [4], Sanford M. Simon [5], Rachael D. Migler [5] and Mark Yarchoan [1,*]

Variable	Classification	N (%)
Immune Checkpoint Inhibitor	Nivolumab monotherapy	9 (47.4%)
	Nivolumab + 5FU + IFN	1 (5.9%)
	Nivolumab + regorafenib	1 (5.9%)
	Nivolumab + gemcitabine-based chemotherapy	1 (5.9%)
	Nivolumab + ipilimumab	2 (11.8%)
	Pembrolizumab monotherapy	4 (23.5%)
	Atezolizumab + bevacizumab	1 (5.3%)
Time on Therapy (months)		Median = 5.1 (range 0–36.5)
Any ICI Regimen	Progressive Disease	12 (63.2%)
	Stable Disease	4 (21.1%)
	Partial Response	3 (15.8%)
	Complete Response	0 (0%)
ICI Alone Subset (i.e., anti-PD1 +/− CTLA4)	Progressive Disease	10 (66.7%)
	Stable Disease	3 (20%)
	Partial Response	2 (13.3%)
	Complete Response	0 (0%)



Chen KY et al., Cancers (Basel) 2022

ASKLEPIOS TUMORZENTRUM HAMBURG

Fibrolamelläres Karzinom: Systemtherapie, US-Perspektive

Notable immunotherapy combination treatments ....for FLC include:

- **Nivolumab, plus 5-fluorouracil (5-FU) and interferon alpha-2b**. Many fibrolamellar patients have already been prescribed this “triple therapy” at some institutions.
- **Ipilimumab plus nivolumab** (approved in 2020 for the treatment of HCC).
- **Atezolizumab plus bevacizumab** (approved in 2020 for the treatment of HCC).
- **Nivolumab plus lenvatinib**.

Fibrolamelläres Karzinom: (kausale) Therapieansätze

- DNAJB1-PRKACA Fusion Kinase Peptide Vaccine Combined With Nivolumab and Ipilimumab for Patients With Fibrolamellar Hepatocellular Carcinoma (Baltimore, MD) https://www.clinicaltrials.gov/study/NCT04248569.
- FusionVAC22_01: Fusion Transcript-based Peptide Vaccine Combined With Immune Checkpoint Inhibition (FusionVAC22)(Tübingen, Germany) https://clinicaltrials.gov/study/NCT05937295.
- Nivolumab, Fluorouracil, and Interferon Alpha-2B for the Treatment of Unresectable Fibrolamellar Cancer (Houston, TX) https://www.clinicaltrials.gov/study/NCT04380545

Rare variants of primary liver cancer: Fibrolamellar, combined, and sarcomatoid hepatocellular carcinomas

Henning Wege [a,b,*], Kornelius Schulze [a], Johann von Felden [a], Julien Calderaro [c,d], Maria Reig [e], for the rare liver tumors working group of the European Reference Network on Hepatological Diseases (ERN RARE-LIVER)

	Fibrolamellar HCC	Combined HCC-CCA	Sarcomatoid HCC
Rate among primary liver cancers	• 2%	• 2–5% • Recent studies 1%	• 2%
Patient characteristics	• Pediatric, adolescent or young adults • Both genders (1:1) • Mostly no underlying liver disease	• Could have the same risk factors as classic HCC • Cirrhosis in at least 50% • Mostly males	• Cirrhosis as underlying disease • Mostly males
Diagnosis	Histopathology		
Imaging	• Large tumors (10–15 cm) • Central scar • 50% with calcification • No Angioinvasion	• Discrepancy between imaging (HCC or CCA) and tumor marker (CA19-9 or AFP) • Features of both HCC and CCA	• Large nodules with satellites • Cystic or necrotic regression, mixed density
Histopathology profile	• Strands of lamellar fibrosis • Eosinophilic polygonal cells with prominent nucleoli, • *DNAJB1-PRKACA* gene fusion	• Hepatocytic and cholangiocytic differentiation in one nodule • HepPar1, glypican 3, CK19, CK7, EpCAM, CD133 • Nestin overexpression in 80%	• Epithelial (HCC) and mesenchymal (sarcoma) features • Cells spindle shaped with a clear nucleolous and acidophilic attributes • Cytokeratin and vimentin
Primary treatment reported in literature	• Surgical resection • Regional lymphadenectomy	• Surgical resection • Regional lymphadenectomy	• Surgical resection
Systemic treatment	• No evidence-based regimen	• No evidence-based regimen • Mostly according to leading entity HCC or CCA, respectively	• No data from specific trials

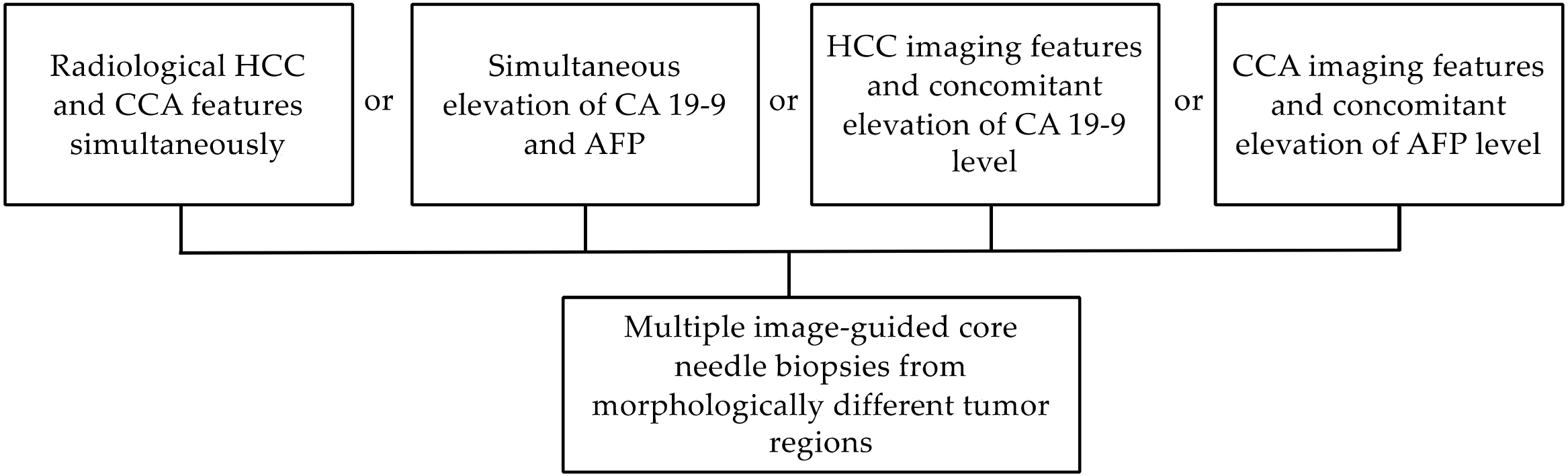
Wege H et al., Eur J Med Genetics 2021

„Mischtumoren“: HCC/CCA

3.83	Evidenzbasiertes Statement	neu 2023
Level of Evidence 5	Für die HCC / CCA Mischtumoren (combined or mixed HCC and CCA; cHCC-CCA) gibt es bisher keine Phase II oder III Studien, aus denen Therapieempfehlungen abgeleitet werden können. Individuelle Therapieoptionen ergeben sich lediglich aus retrospektiven Fallserien und Einzelfallberichten.	
	5: Nach ausführlicher Recherche, konnte keine ausreichende Datenlage zur Erstellung einer Empfehlung gefunden werden.	
	Starker Konsens	

3.84	Konsensbasierte Empfehlung	neu 2023
EK	In einer palliativen Situation bei Patienten mit ECOG 0 – 1 sollte bei der Diagnose eines cHCC-CCA eine molekulare Charakterisierung des Tumors und Vor-stellung in einem Interdisziplinären/Molekularen Tumorboard erfolgen.	
	Starker Konsens	

„Mischtumoren“ HCC/CCC: diagnostisches Vorgehen



Eschrich J et al., Cancers (Basel) 2023

„Mischtumoren“ HCC/CCA: Molekularpathologie

Combined Hepatocellular-Cholangiocarcinoma	Hepatocellular Carcinoma	Intrahepatic Cholangiocarcinoma
TP53 (45.3–80%) TERT promoter (23–70%) IDH1 or IDH2 (0–11.8%) AXIN1 (10%) CTNNB1 (6–10%) KMT2D (9%) KRAS (0–7.5%) FGFR2 (0–3%) BAP1 (0–3%)	TERT promoter (44–54%) TP53 (13–31%) CTNNB1 (6–31%) ALB (13–%) AXIN1 (6–8%)	IDH1 or IDH2 (9–30%) TP53 (5–22%) FGFR2 (6–20%) KRAS (5–19%) BAP1 (10–12%)

Eschrich J et al., Cancers (Basel) 2023

Fighting rare cancers: lessons from fibrolamellar hepatocellular carcinoma

- The fight against **rare cancers** faces myriad challenges, including missed or wrong diagnoses, lack of information and diagnostic tools, too few samples and too little funding.
- Yet many advances in cancer biology, such as the realization that there are tumour suppressor genes, have come from studying well-defined, albeit rare, cancers.
- From the paucity of data, it was not known whether FLC was one cancer or a collection with similar phenotypes, or whether it was genetically inherited or the result of a somatic mutation.
- A personal journey through a decade of work reveals answers to these questions and a road map of steps and missteps in our fight against a rare cancer.

Simon S et al., Nat Rev Cancer 2023