UKD Universitätsklinikum Düsseldorf

HEINRICH HEINE UNIVERSITÄT DÜSSELDORF

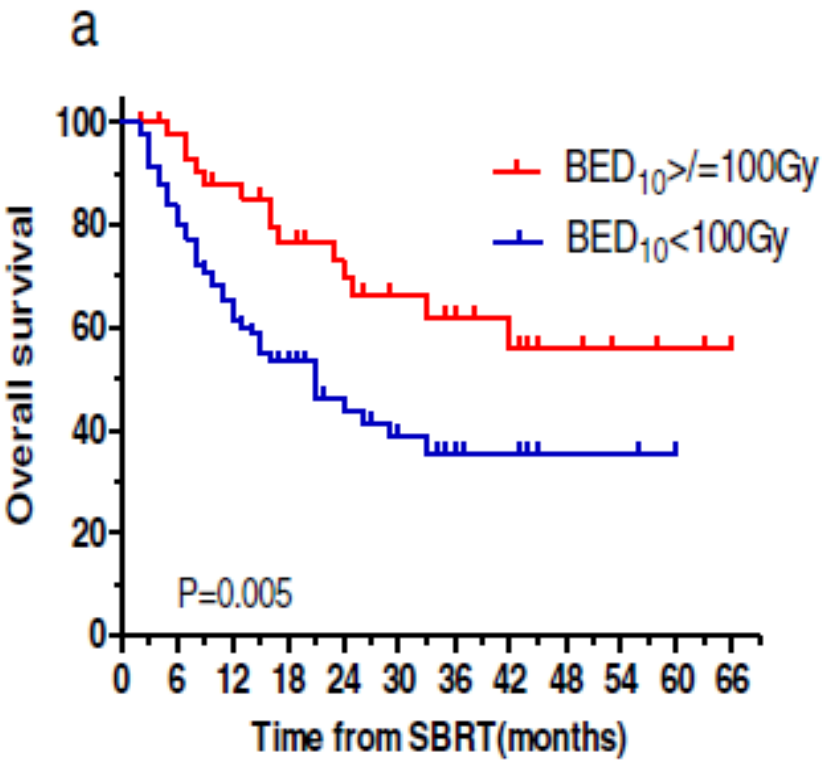
Rolle der SBRT beim HCC

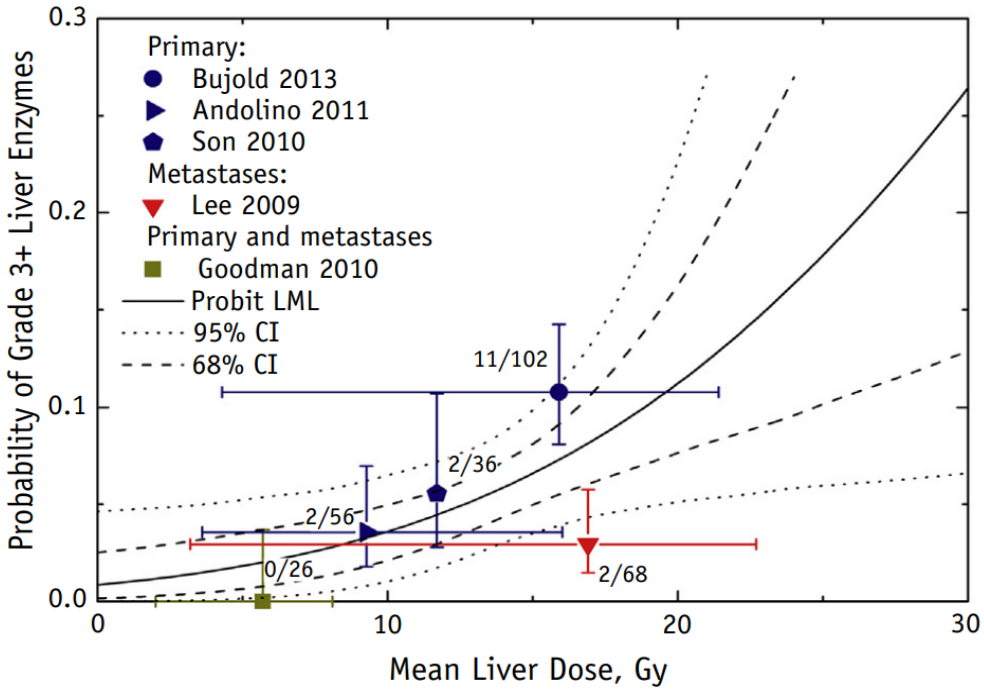
Danny Jazmati, Eleni Gkika, David Krug, Judith Boda-Heggemann, Ricarda von Krüchten, Christiane Matuschek, Oliver Blank, Thomas Brunner

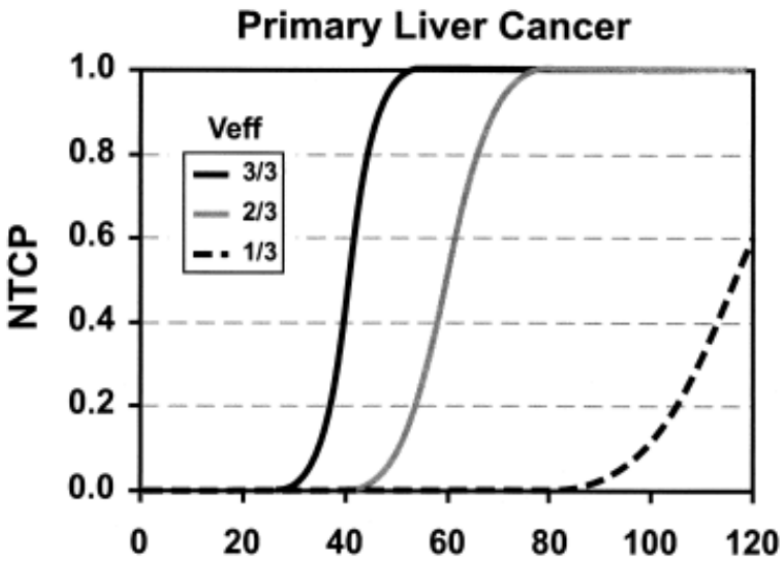
DEGRO
ARBEITSGRUPPE RADIOCHIRURGIE/ STEREOTAXIE

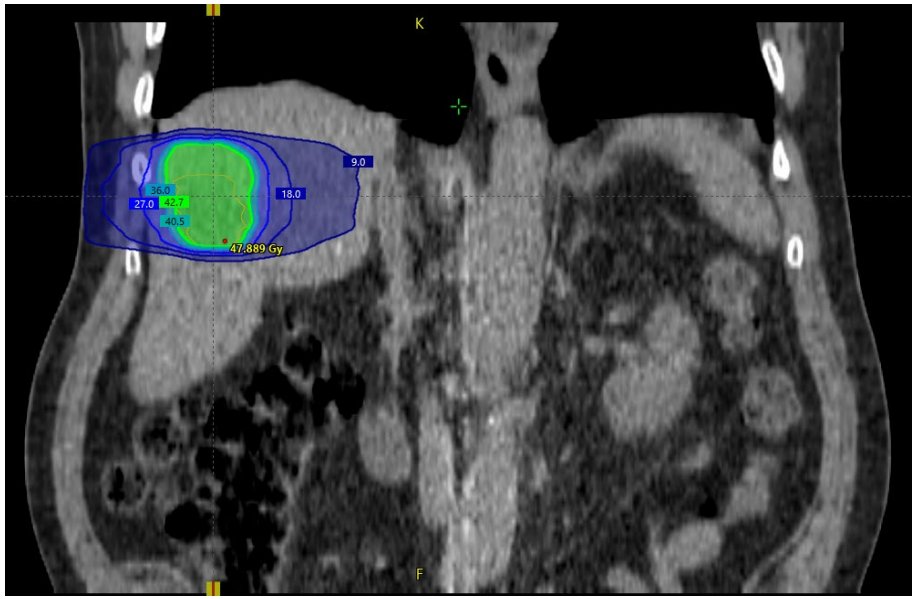
1. Hintergrund SBRT beim HCC
2. Projektvorstellung

Herausforderung .






Primary Liver Cancer
NTCP
1.0
0.8
0.6
0.4
0.2
0.0
Veff
3/3
2/3
1/3
0
20
40
60
80
100
120


K
F
9.0
18.0
36.0
27.0
42.7
40.5
47.889 Gy

Ratio SBRT

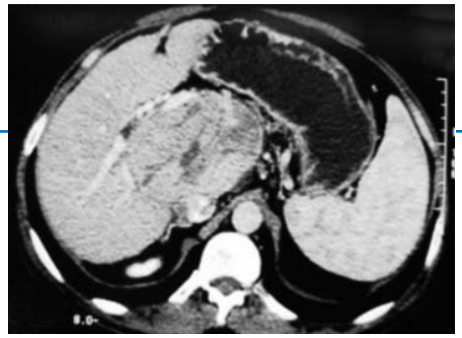
Frühe SBRT-Studien

Study	Year	Design	N	CP	Tumor Size	Dose, Fx	OS, 1yr	LC, 1 yr	Gr≥3 Toxicity
Erasmus	2006	Phase I/II	8	A,B	0.5 – 7.2 cm	25-37.5 Gy, 3-5 fx	75%	75%	12.5%
KIRMS	2012	Phase II	47	A,B	1.3-8 cm	57 Gy, 3 fx	69% (2yrs)	95% (2yrs)	26%
Indiana	2010	Phase I	17	A,B	≤6 cm	36-48Gy, 3-4 fx	75%	100%	18%
PMH	2008	Phase I	31	A	9-1913 ml	26 Gy(24-54), 6 fx	48%	65%	26%
Ibarra, multiple	2012	Pooled	21	A,B	9.5-1494 ml	30 Gy (18-50), 1-10fx	87%	64%	8% RILD
Tokai Univ.	2013	Retrospective	185	A,B	.8 – 5 cm	30-40Gy, 5 fx	95%	99%	13%

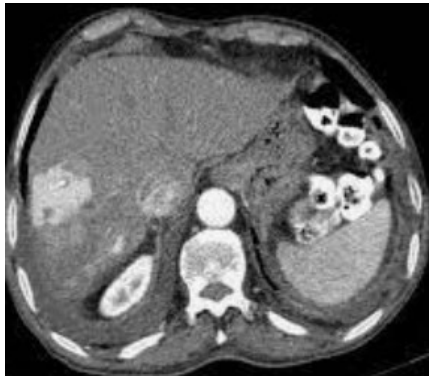
Heterogene Kohorten + Fraktionierung + Study design

=> heterogenes Outcome

UKD Unive
Düsse



HEINRICH HEINE
UNIVERSITÄT DÜSSELDORF



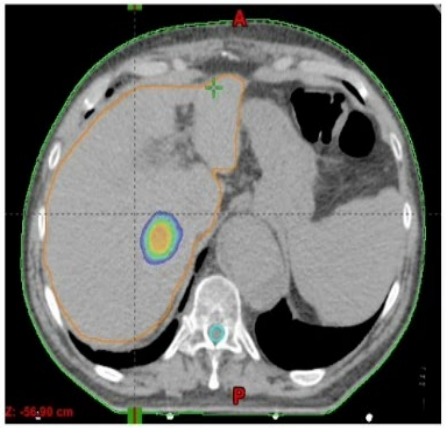
Heterogenes Patientenkollektiv

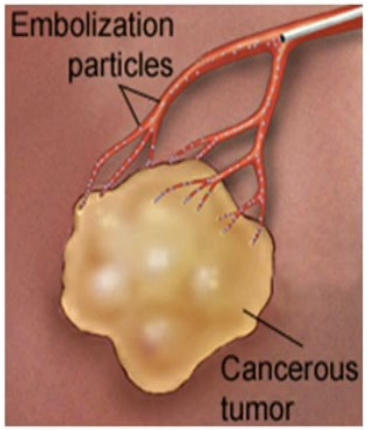
Selection Bias: retro. RT Studien

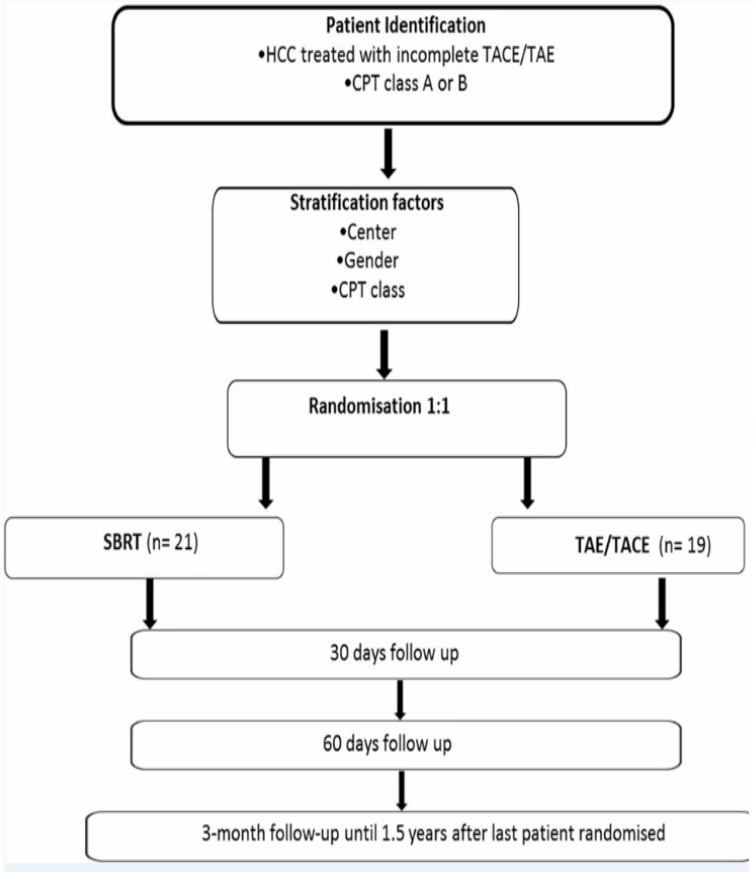
Identifikation von Pat.?

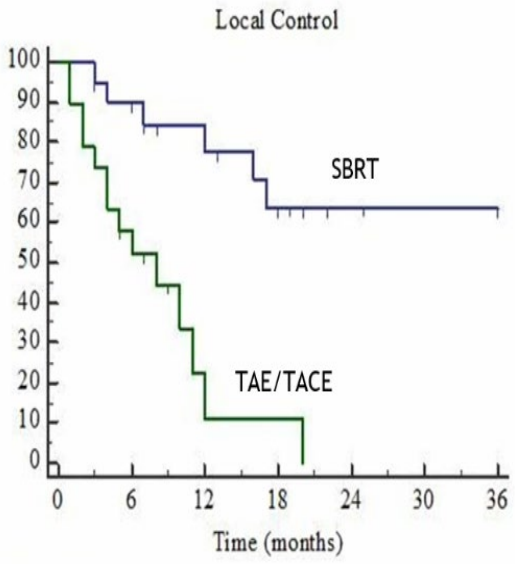
UKD Universitätsklinikum Düsseldorf

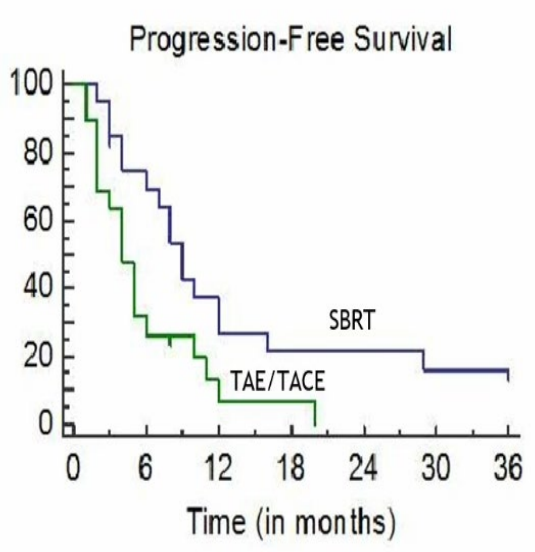
TACE vs. SBRT











Comito et al. (NCT02323360)

frontiers in Oncology

Front Oncol. 2020; 10: 1639.
Published online 2020 Oct 29. doi: 10.3389/fonc.2020.01639
PMCID: PMC7658324
PMID: 33194569

Stereotactic Body Radiotherapy vs. Radiofrequency Ablation in the Treatment of Hepatocellular Carcinoma: A Meta-Analysis

Yang-Xun Pan,[1,2,3] Yi-Zhen Fu,[1,2] Dan-Dan Hu,[1,2] Qian Long,[1,4] Jun-Cheng Wang,[1,2] Mian Xi,[1,5] Shi-Liang Liu,[1,4] Li Xu,[1,2] Meng-Zhong Liu,[1,4] Min-Shan Chen,[1,2] and Yao-Jun Zhang[1,2,*]

2732 Pat. Aus 10 Studien

LC: besser in SBRT
OS: besser in RFA
Tox: vergleichbar

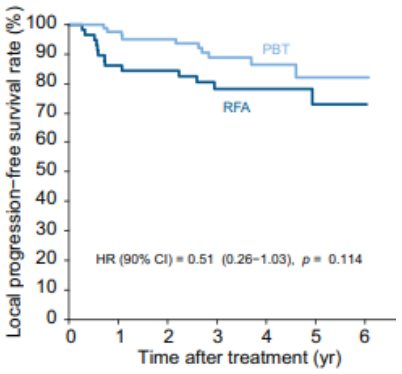
RFA vs. SBRT

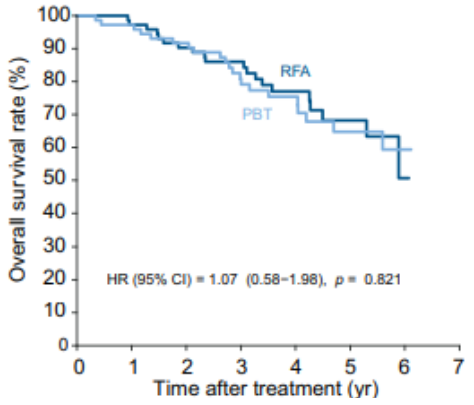
Research Article
Hepatic and Biliary Cancer

JOURNAL OF HEPATOLOGY

Proton beam radiotherapy *vs.* radiofrequency ablation for recurrent hepatocellular carcinoma: A randomized phase III trial

Tae Hyun Kim[1,2,†], Young Hwan Koh[1,3,†], Bo Hyun Kim[1], Min Ju Kim[3], Ju Hee Lee[1,3], Boram Park[4], Joong-Won Park[1,*]





Was ist die beste multimodale Behandlungsstrategie?

Original Investigation

Transcatheter Arterial Chemoembolization Plus Radiotherapy Compared With Chemoembolization Alone for Hepatocellular Carcinoma

A Systematic Review and Meta-analysis

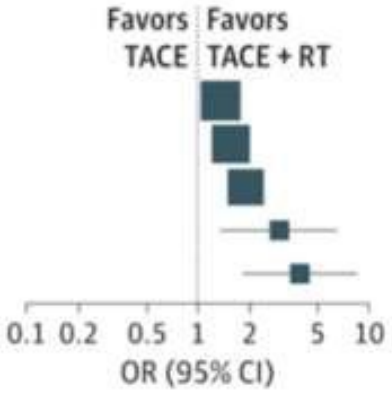
Ya Ruth Huo, BMed, MD; Guy D. Eslick, DrPH, PhD

HEINRICH HEINE
UNIVERSITÄT DÜSSELDORF

25 Studien in 2577 Pat.

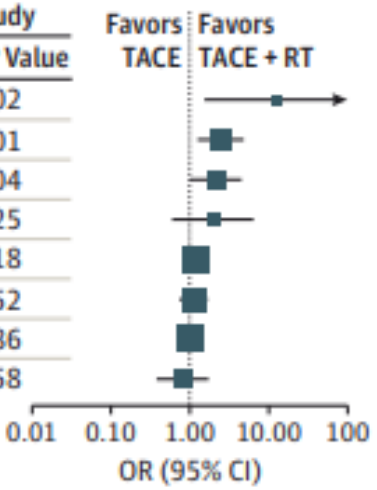
1- to 5-Year Survival

	Statistics for Each Study	
Year	OR (95% CI)	*P* Value
1	1.36 (1.20-1.55)	<.001
2	1.55 (1.30-1.84)	<.001
3	1.91 (1.55-2.35)	<.001
4	3.01 (1.38-6.55)	<.001
5	3.98 (1.86-8.51)	<.001



Therapievorteil für RT+Tace

	Statistics for Each Study	
Complication	OR (95% CI)	*P* Value
Gastric and duodenal ulcers	12.80 (1.57-104.34)	.02
ALT elevation	2.46 (1.30-4.65)	.01
Total bilirubin increase	2.16 (1.05-4.45)	.04
Esophagitis or duodenitis	1.98 (0.62-6.34)	.25
Leukopenia	1.22 (0.91-1.63)	.18
Fever	1.13 (0.78-1.64)	.52
Nausea and/or vomiting	1.03 (0.74-1.44)	.86
Thrombocytopenia	0.81 (0.38-1.72)	.58

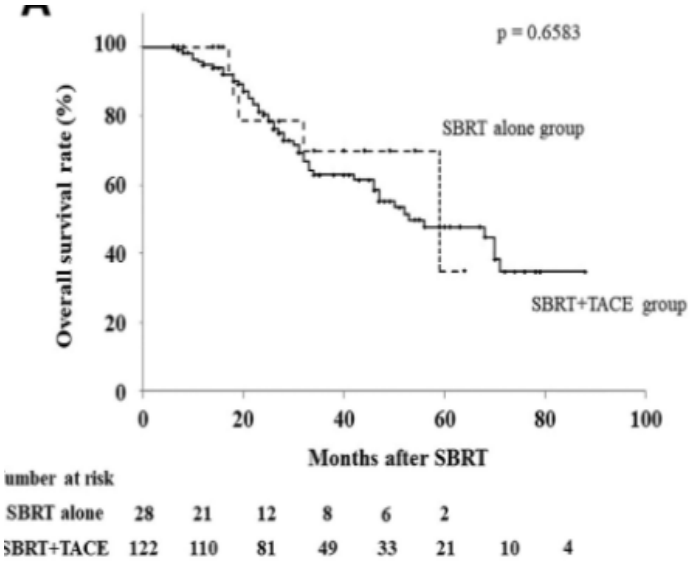


Su et al. BMC Cancer (2016) 16:834
DOI 10.1186/s12885-016-2894-9

BMC Cancer

Comparison of Stereotactic Body Radiation Therapy Combined With or Without Transcatheter Arterial Chemoembolization for Patients With Small Hepatocellular Carcinoma Ineligible for Resection or Ablation Therapies

Tumorgröße < 20 mm (median)

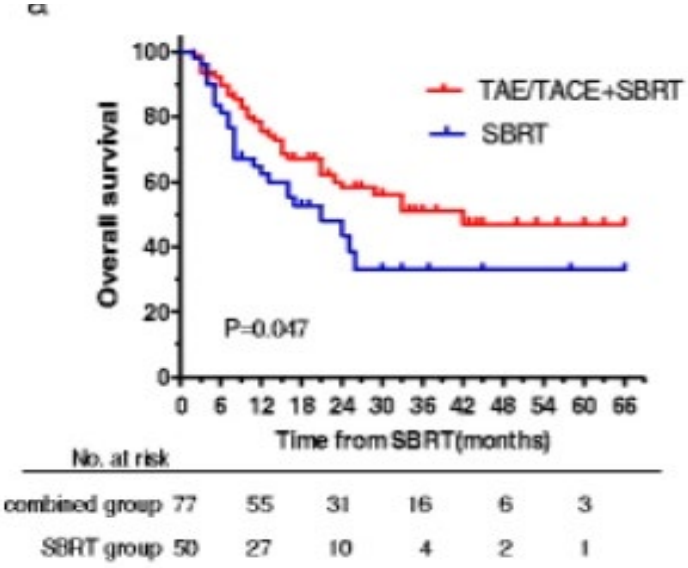


Kein Vorteil

RESEARCH ARTICLE Open Access

Long-term survival analysis in combined transarterial embolization and stereotactic body radiation therapy versus stereotactic body radiation monotherapy for unresectable hepatocellular carcinoma >5 cm

Mediane Tumorgröße = 85 mm

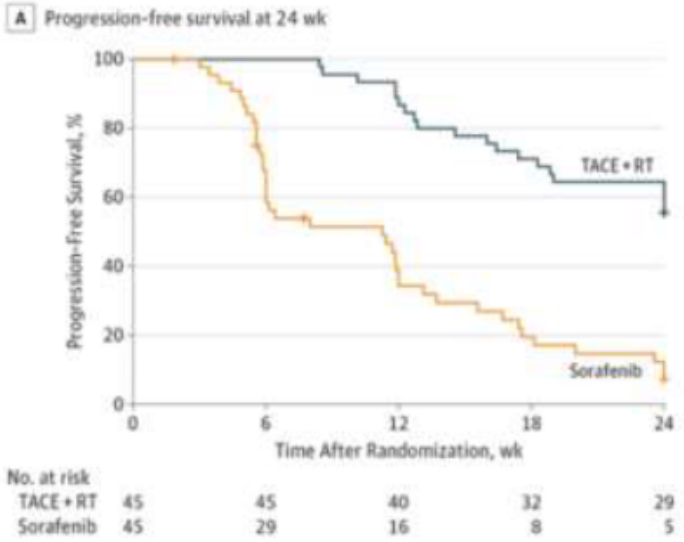


Sig.Vorteil

TACE + SBRT bei großen Tumoren vorteilhaft

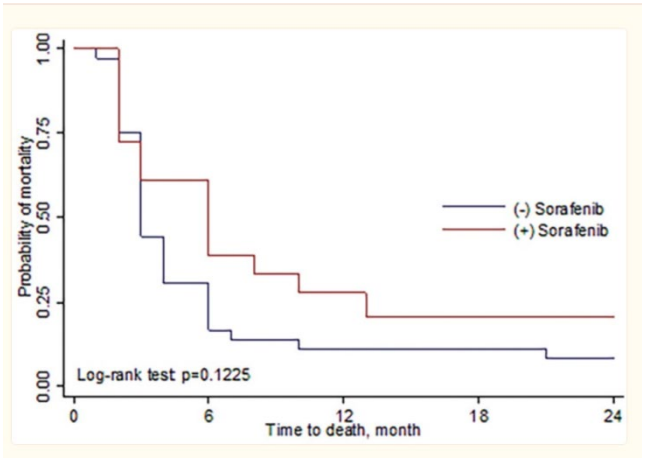
Mikrovaskuläre Invasion

TACE + RT (45 Gy/15-18 fx) vs sorafenib
12 week PFS 86.7% vs 34.3%; *P* < .001



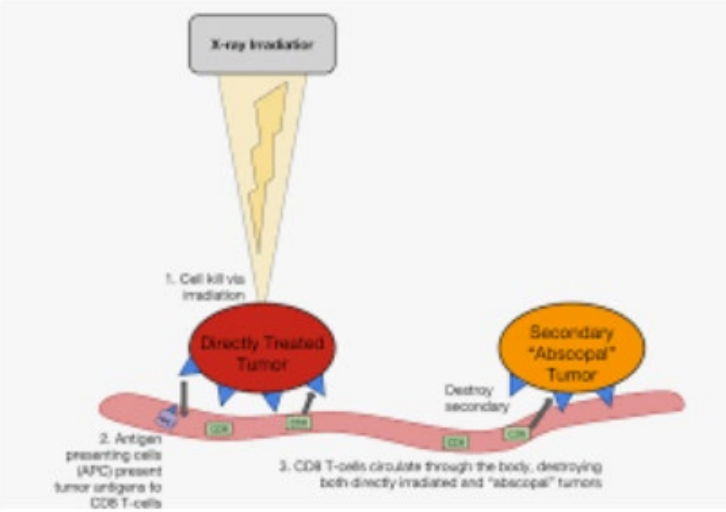
Yoon, JAMA Onc 2018

RT+Sorafenib vs. Sorafenib



Que et al. medicine 2020

Trials (Country)	Type of Disease	Design	Number of Pts	Interventions	Primary Endpoint
NCT04547452 (China)	Stage IV HCC (Liver or lung or any metastatic lesion)	Randomized Phase II	42: SBRT+PD-1 # 42: PD-1 alone	RT: SBRT Drug: Sintilimab (PD-1)	24-week progression-free survival rate
NCT 05396937 (China)	Metastatic HCC (extrahepatic dissemination)	Phase II	42	RT: SBRT Drug: Atezolizumab, Bevacizumab	Objective response rate
NCT04988945 (China)	Tumor size 5–25 cm and number of lesions ≤3	Phase II	33	Procedure: TACE RT: SBRT Drug: Durvalumab, Tremelimumab	Downstaging for hepatectomy
NCT03817736 (China)	Tumor size 5–15 cm or number of lesions ≤3 or segmental portal vein involvement	Phase II	33	Procedure: TACE RT: SBRT Drug: ICI †	Number of Patients Amendable to Curative Surgical Interventions
NCT04857684 (USA)	Resectable HCC	Phase I	20	RT: SBRT Drug: Atezolizumab, Bevacizumab	Proportion of patients with grade 3–4 treatment-related adverse events as assessed by CTCAE v5.0
NCT04913480 (China)	Stage C or earlier HCC based on BCLC * staging Medically fit to undergo surgery as determined by the treating medical and surgical oncology team maximum 10 lesions to be treated, and total tumor diameter to be treated <20 cm	Phase II	37	RT: SBRT Drug: Durvalumab	Progression-free survival at 1 year
NCT05185531 (China)		Phase I	20	RT: SBRT Drug: Tislelizumab (PD-1)	Delay to surgery overall response rate after neoadjuvant SBRT + Tislelizumab
NCT03316872 (Canada)		Phase II	30	RT: SBRT Drug: Pembrolizumab	Overall response rate



› Front Oncol. 2021 Dec 7;11:798832. doi: 10.3389/fonc.2021.798832. eCollection 2021.

Combined Stereotactic Body Radiotherapy and Immunotherapy Versus Transarterial Chemoembolization in Locally Advanced Hepatocellular Carcinoma: A Propensity Score Matching Analysis

Chi-Leung Chiang [1], Keith Wan-Hang Chiu [2], Francis Ann-Shing Lee [3], Feng-Ming Spring Kong [1], Albert Chi-Yan Chan [4]

Was ist die optimale Dosis / Fraktionierung?

CLINICAL INVESTIGATION | VOLUME 109, ISSUE 2, P464-473, FEBRUARY 01, 2021

Dose-Response Relationship in Stereotactic Body Radiation Therapy for Hepatocellular Carcinoma: A Pooled Analysis of an Asian Liver Radiation Therapy Group Study

Nalee Kim, MD • Jason Cheng, MD, PhD • Wen-Yen Huang, MD • ... Victor H.F. Lee, FRCR, MD • Chul Seung Kay, MD, PhD • Jinsil Seong, MD, PhD • Show all authors

HEINRICH HEINE
UNIVERSITÄT DÜSSELDORF

Dosis-Wirkungsbeziehung-
Jedoch in der klinischen Praxis sehr variabele Konzepte

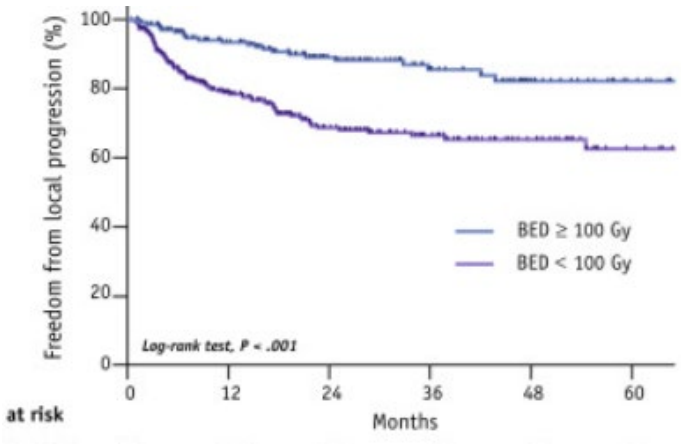


Table 1. Prospective studies of SBRT in early-stage HCC.

Author/Year	Study Design	N	Median Tumor Size	BCLC * Stage C	Previous Treatment	Dose/Fraction (Gy/fr)	Prescription	Local Control	Overall Survival	Toxicity Grade 3≥
Andoliano, 2011, USA [10]	Phase I/II	60 (CPC-A/B #: 36/24)	31 mm	17%	100%	42–60 Gy/3 fr	70–80% isodose	94.6% (2y)	68.7% (2y)	10.7%
Kang, 2012, Korea [11]	Phase II	47 (CPC-A/B: 41/6)	29 mm	N.A. **	N.A. **	24–48 Gy/3 fr	80% isodose	90% (2y)	67% (2y)	25%
Bujold, 2013, Canada [12]	Phase I/II	102 (CPC-A/B: 102/0)	72 mm	65.7%	52%	24- 54 Gy/6 fr	N.A. **	87.0% (1y)	34.0% (2y)	30%
Lasley, 2015, USA [13]	Phase II	CPC-A: 38	N.A.	N.A.	N.A.	48 Gy/3 fr	80–90% isodose	91% (3y)	61% (3y)	11%
		CPC-B: 21	N.A.	N.A.	N.A.	40 Gy/5 fr	80–90% isodose	82% (3y)	26% (3y)	38%
Takeda, 2016, Japan [14]	Phase II	90 (CPC-A/B: 82/8)	23 mm	16%	64%	40 or 35 Gy/5 fr	60–80% isodose	96.3% (3y)	66.7% (3y)	15%
Jang, 2020, Korea [15]	Phase II	65 (CPC-A/B: 64/1)	24 mm	6.2%	100%	42–60 Gy/3 fr	90% isodose	95% (3y)	76% (3y)	2%
Durand-Labrunie, 2020, France [16]	Phase II	43 (CPC-A/B: 37/6)	28 mm	0%	0%	45 Gy/3 fr	80% isodose	94% (2y)	69% (2y)	31%
Kimura, 2021, Japan [17]	Phase II	36 (CPC-A/B: 33/3)	23 mm	0%	0%	40 Gy/5 fr	70% isodose	90% (3y)	78% (3y)	11%

Abbreviations: * BCLC: Barcelona Clinic Liver Cancer, ** N.A.: not available, # CPC-A/B: Child-Pugh class A/B.

Journal of Hepatocellular Carcinoma

Dovepress
open access to scientific and medical research

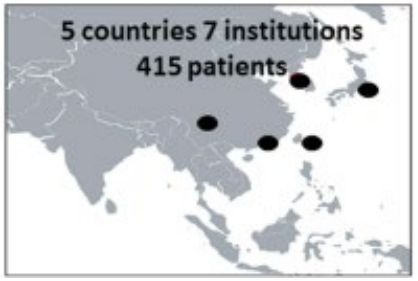
Open Access Full Text Article

ORIGINAL RESEARCH

Does HCC Etiology Impact the Efficacy of Stereotactic Body Radiation Therapy for Hepatocellular Carcinoma? An Asian Liver Radiation Therapy Group Study

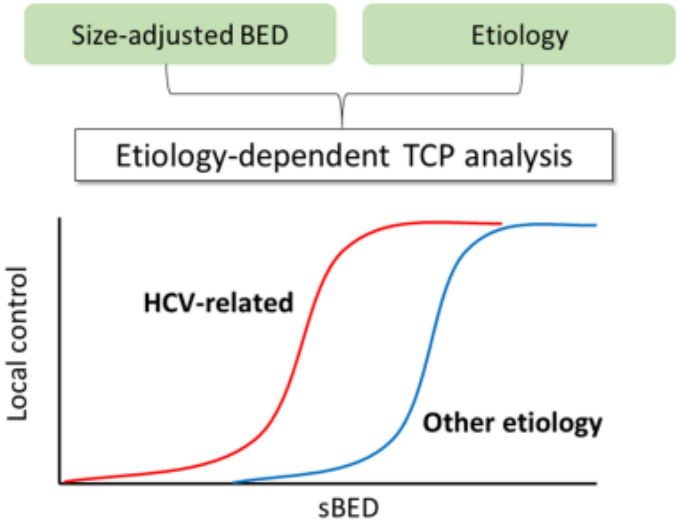
Nalee Kim[1,*], Jason Chia-Hsien Cheng[2,*], Nitin Ohri[3], Wen-Yen Huang[4], Tomoki Kimura[5], Zhao Chong Zeng[6], Victor Ho Fun Lee[7], Chul Seung Kay[8], Jinsil Seong[9]

HEINRICH HEINE



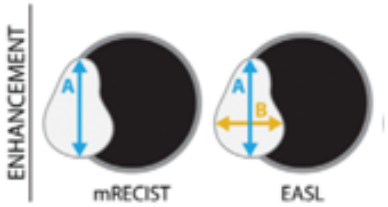
SBRT Schedule / Tumor Diameter	8 Gy × 6 Fractions		10 Gy × 5 Fractions		15 Gy × 4 Fractions	
	HCV-Related	Non-HCV-Related	HCV-Related	Non-HCV-Related	HCV-Related	Non-HCV-Related
2 cm	88%	75%	89%	78%	92%	86%
4 cm	85%	71%	87%	73%	91%	84%
6 cm	83%	66%	85%	69%	89%	80%

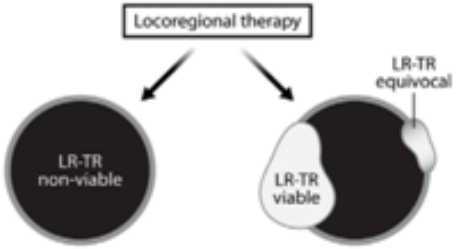
Virus induzierte Tumore mit **weniger Dosis** kontrolliert



Wie können wir den Erfolg der SBRT messen?

Radiologische Klassifizierungssysteme zur Beurteilung des Tumoransprechens





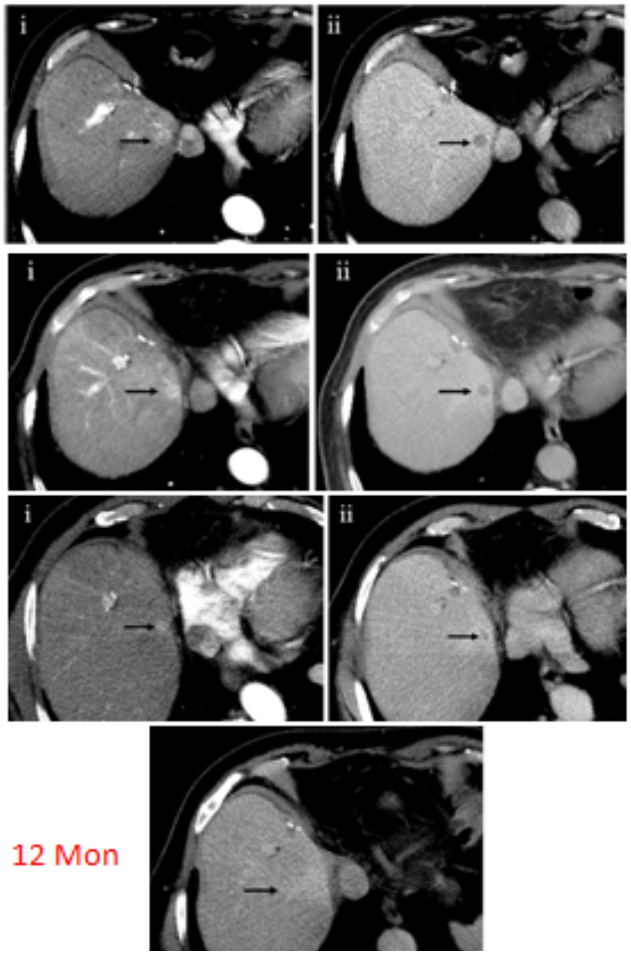
Initial

Arterielles Enhancement: Therapieeffekt oder vitaler Tumor?

6 Mon

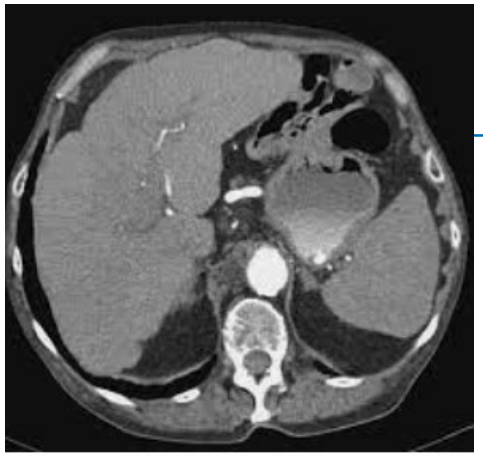
9 Mon

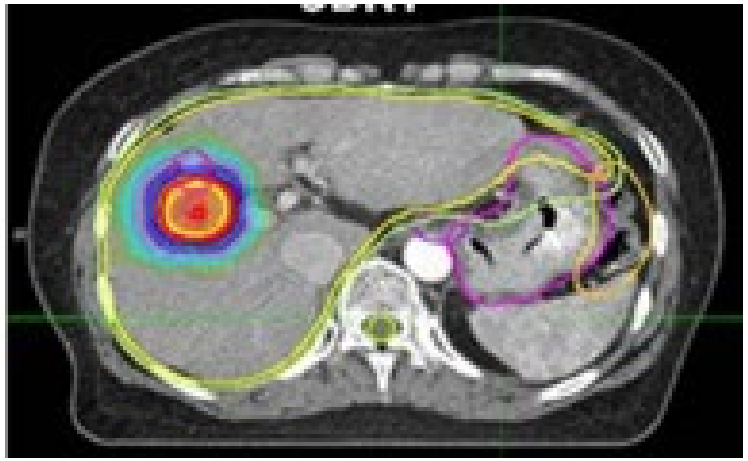
12 Mon

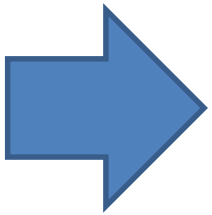


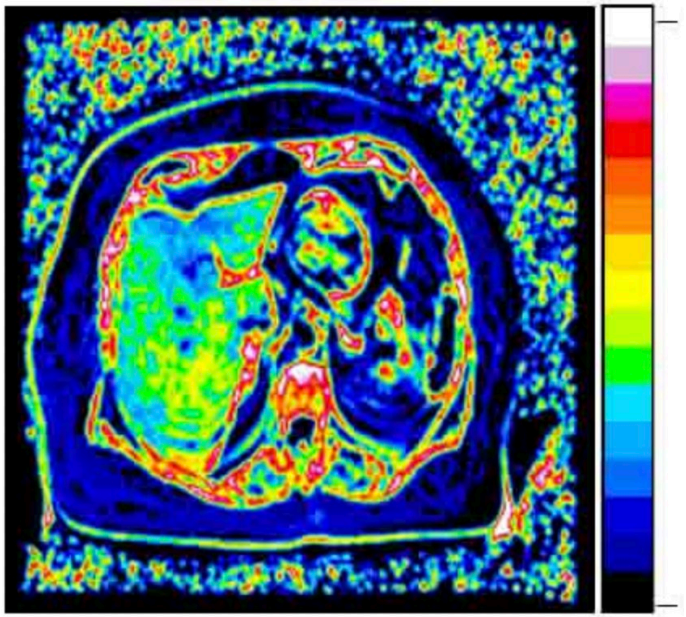
KI-basierte Imaging Features

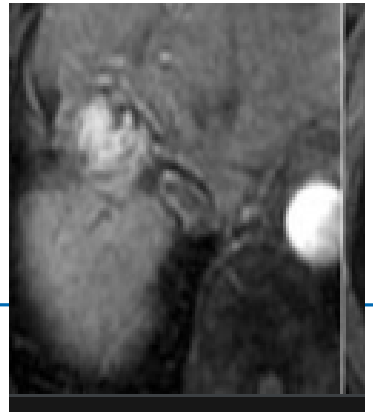

"It is only with the heart
that one can see rightly;
what is essential is invisible
to the eye."





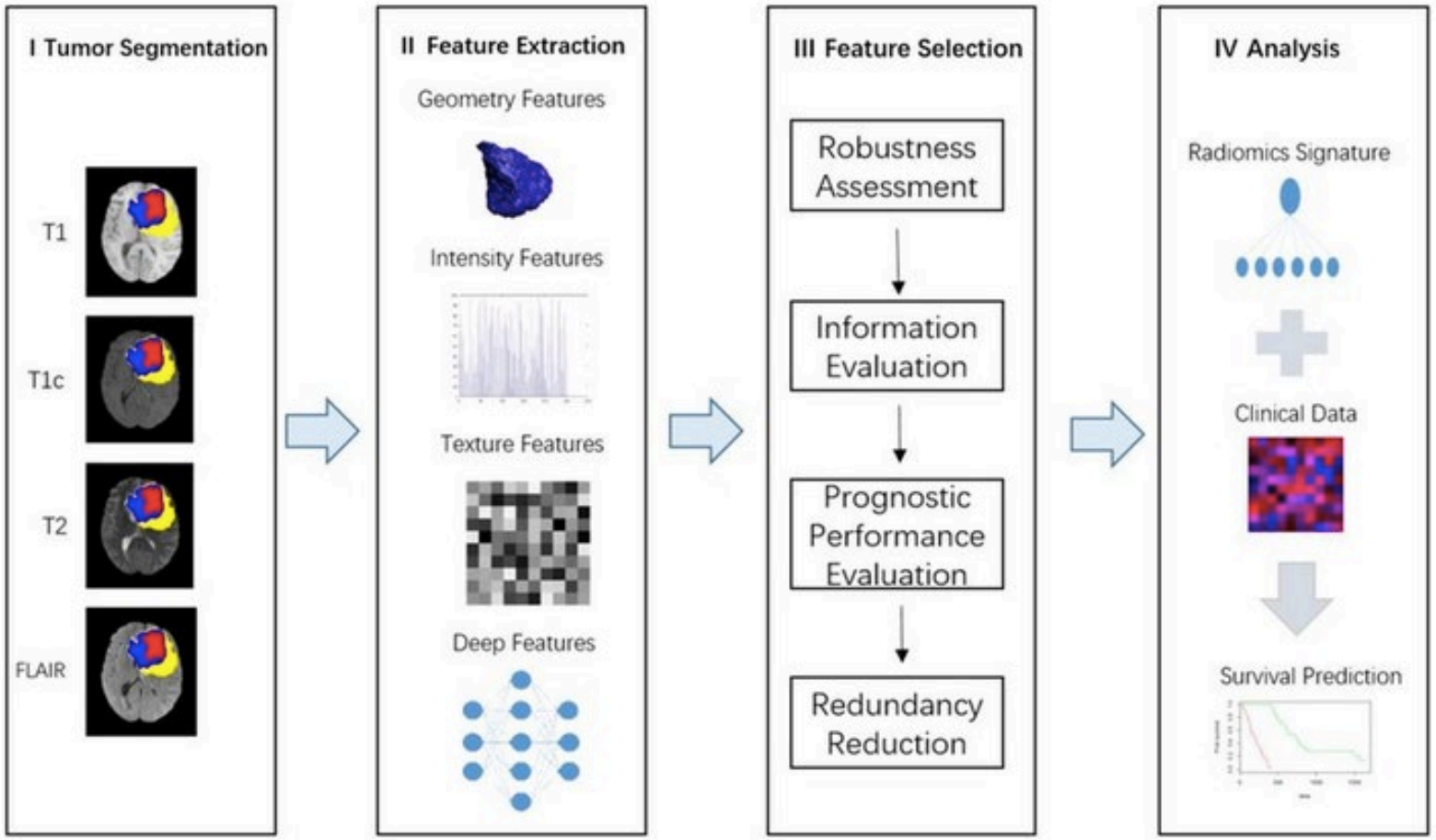






„Functional Liver Mapping“

Etablierte Radiomics Pipeline



1. Identifikation der Patienten
2. Multimodale Therapie
3. Dosis-Wirkungs Beziehung
4. Translationales/ Radiologisches Begleitprojekt zu KI

Studienziel:

1. Bewertung der Rolle der SBRT für die Behandlung vom HCC

2. Optimierung der Empfehlungen zur SBRT in künftigen prospektiven Studien und Leitlinien, um hohe Tumorkontrollraten zu erreichen und die Strahlentoxizität bei Patienten mit Leberzirrhose zu verringern

Zur Beantwortung dieser wichtigen Fragen:

Register für SBRT beim HCC

Studienziele:

1. **Rückfallanalyse** (Muster des Rückfalls) Im Rahmen dieser Studie soll das lokale Rezidivmuster analysiert werden, um Zusammenhänge zwischen Dosis und dem Auftreten von Rezidiven zu identifizieren.

2. **Multimodale Therapie** bewerten?

3. Bewertung der onkologischen Endpunkte und strahlentherapiebedingter Toxizität

4. Untersuchung von FU-Bildgebung, Radiomics und Deep Learning

Studienteilnehmer:

Patienten mit nicht-metastasiertem HCC, die mit SBRT behandelt wurden

Einschlusskriterien:

- Behandlung von HCC mit SBRT
- Frauen und Männer, die mindestens 18 Jahre alt sind

n= 250 im retrospektiven Teil der Studie (HepReg I)
n= 150

UKD Universitätsklinikum Düsseldorf

HEINRICH HEINE UNIVERSITÄT DÜSSELDORF

DEGRO ARBEITSGRUPPE RADIOCHIRURGIE/ STEREOTAXIE

DEGRO WG Radiosurgery and Stereotactic Radiotherapy

Danny Jazmati

Thomas Brunner

David Krug

Eleni Gkika

Ricarda von Krüchten

Christiane Matuschek

Judith Boda-Heggemann

Oliver Blank

UKD Universitätsklinikum Düsseldorf

HEINRICH HEINE UNIVERSITÄT DÜSSELDORF

DEGRO

ARBEITSGRUPPE RADIOCHIRURGIE/ STEREOTAXIE

DEGRO

ARBEITSGRUPPE JUNGE DEGRO

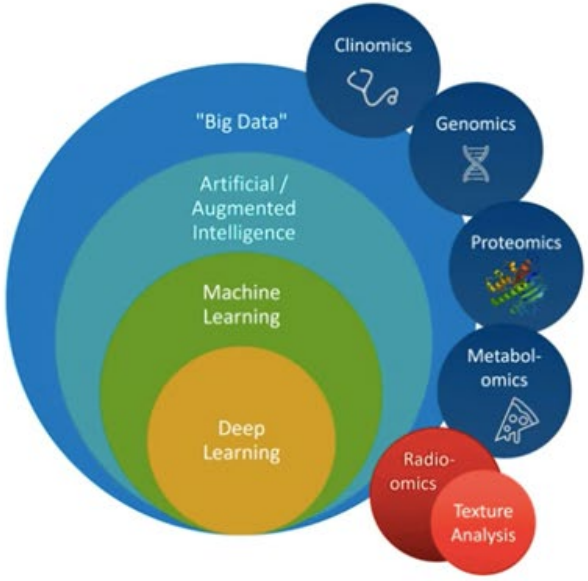
Transnationales Projekt Künstliche Intelligenz

UKD Universitätsklinikum Düsseldorf

UNIVERSITÄTS KLINIKUM FREIBURG

UNIKLINIK KÖLN

UNIVERSITÄTS KLINIKUM FRANKFURT GOETHE-UNIVERSITÄT



AI Working Group

Dr. R. von Krüchten

Dr. Liliane Caldeira

Dr. Marco Reisert

PD Dr. Dr. M.Eisenblätter

PD Dr. D. Pinto dos Santos

Dr. D. Jazmati

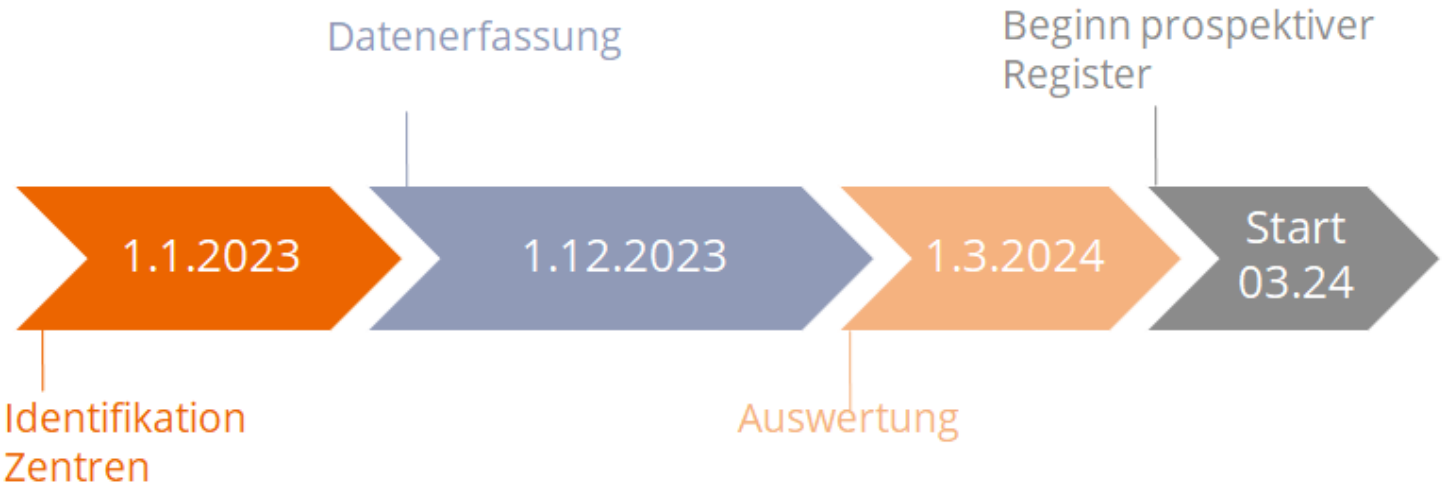
UNIVERSITÄTS KLINIKUM FREIBURG

UNIKLINIK KÖLN

UNIVERSITÄTS KLINIKUM FRANKFURT GOETHE-UNIVERSITÄT

UK OWL UNIVERSITÄTSKLINIKUM OWL der Universität Bielefeld

HepReg I + HepReg II



HepReg I

1. Ermittlung der kooperierenden Zentren (2 M)
2. Identifikation der betreffenden Patienten (2 M)
3. Datenerfassung (6 M)
4. Auswertung (1 M)
5. Zusammenfassung und Publikation (1 M)

Für Rückfragen und bei Interesse zur Teilnahme, stehen wir Ihnen selbstverständlich gerne zur Verfügung:

Danny.Jazmati@med.uni-duesseldorf.de