

INTERNISTISCHE THERAPIE VON LEBERMETASTASEN COLOREKTALER KARZINOME

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METAANALYSE

IA vs SYST. CHT bei hepat. Met. CRC

- 656 Pat.: ia FUDR vs syst. FUDR oder FU
- Response: 41% vs 14,9%
- Overall Surv.: ns.
(cross over)

Adj. ia CHT nach Resektion hepat.

Metastasen bei CRC

- **LORENZ** 226 Pat. rand: ia FU kont. vs 0 CHT

AnnSurg 98/12 med. surv.: 34,5 Mo vs 40,8 Mo

TTP: 14,2 Mo vs 13.7 Mo

- **KEMENY** 156 Pat. rand: ia FUDR/Dexa + iv FU

Nej 99/12 vs iv FU/Leucovorin

2-y surv: 86% vs 72% p=0,03

med.surv:72,2m vs 53,3m

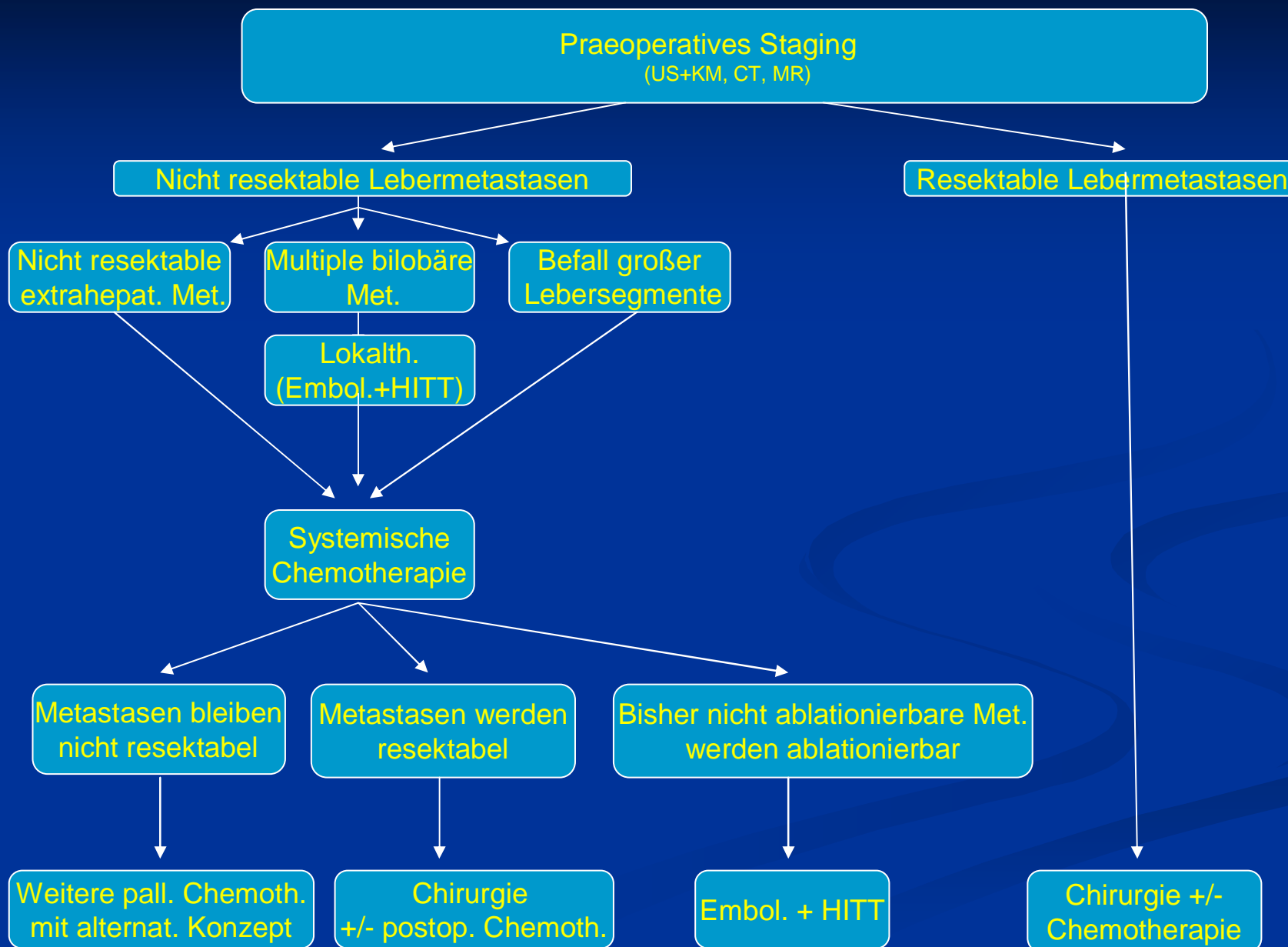
2y-hep.rez.fr.surv:90% vs 60% p=0,001

2y-mort.risk: 2,34 p=0,027

Adj. Intraportale CHT bei resekt. CRC

- **SAKK** 533 Pat. rand: 1periop. Ip CHT vs 0 CHT
Lancet 95/2 Rezid.rate um 21% reduziert
Mort.rate um 26% reduziert
- **EORTC** 235 Pat. rand: ip CHT vs ip Heparin
Eur.J.C 97/7 5y-surv, dis.free surv, TTP ident
- **ROUGIER** 1235 Pat.rand: ip CHT vs 0 CHT
Lancet 98 5y-surv, dis.free surv, TTP ident

MANAGEMENT VON LEBERMETASTASEN BEI COLOREKTALEM CARCINOM



Final results of the EORTC Intergroup randomized phase III study 40983 [EPOC] evaluating the benefit of peri-operative FOLFOX4 chemotherapy for patients with potentially resectable colorectal cancer liver metastases.

	N pts CT	N pts Surgery	% absolute difference in 3-y PFS	HR (CI)	P-value
All patients	182	182	+7.2% (28.1% to 35.4%)	0.79 (0.62-1.02)	P=0.058
All eligible	171	171	+8.1% (28.1% to 36.2%)	0.77 (0.60-1.00)	P=0.041
All resected	151	152	+9.2% (33.2% to 42.4%)	0.73 (0.55-0.97)	P=0.025

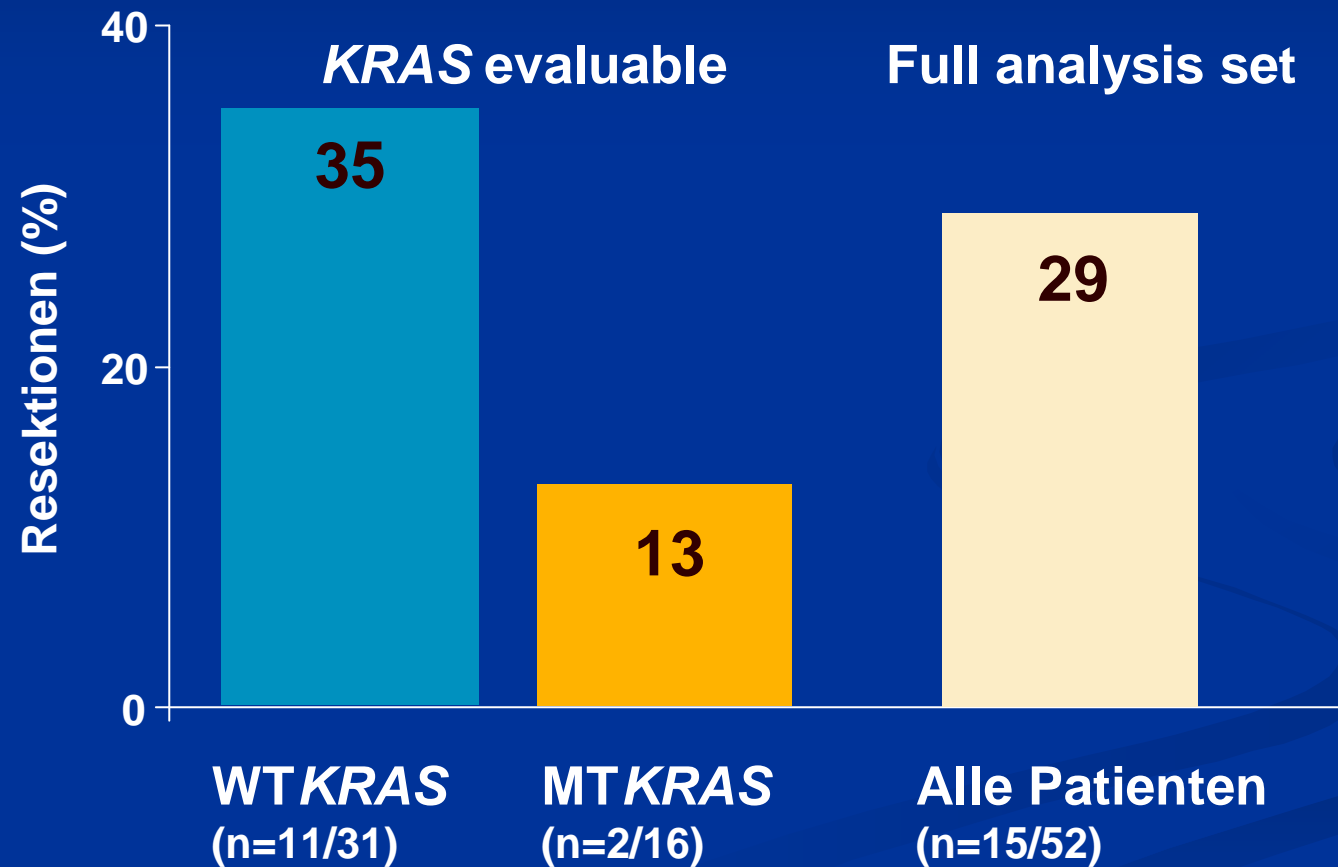
Peri-operative FOLFOX4 chemotherapy improved PFS over surgery alone in patients whose metastases were actually resected. The benefit was slightly diluted when also pts considered resectable on imaging but eventually not resected were taken into account. FOLFOX4 given peri-operatively is safe and does not prevent the pts from undergoing surgery.

Predictive factors for the effect of perioperative FOLFOX for resectable liver metastasis in colorectal cancer patients (EORTC phase III study 40983).

Perioperative FOLFOX is of particular benefit for patients with resectable liver metastases from colorectal cancer when CEA is elevated or when performance status is good (PS 0).

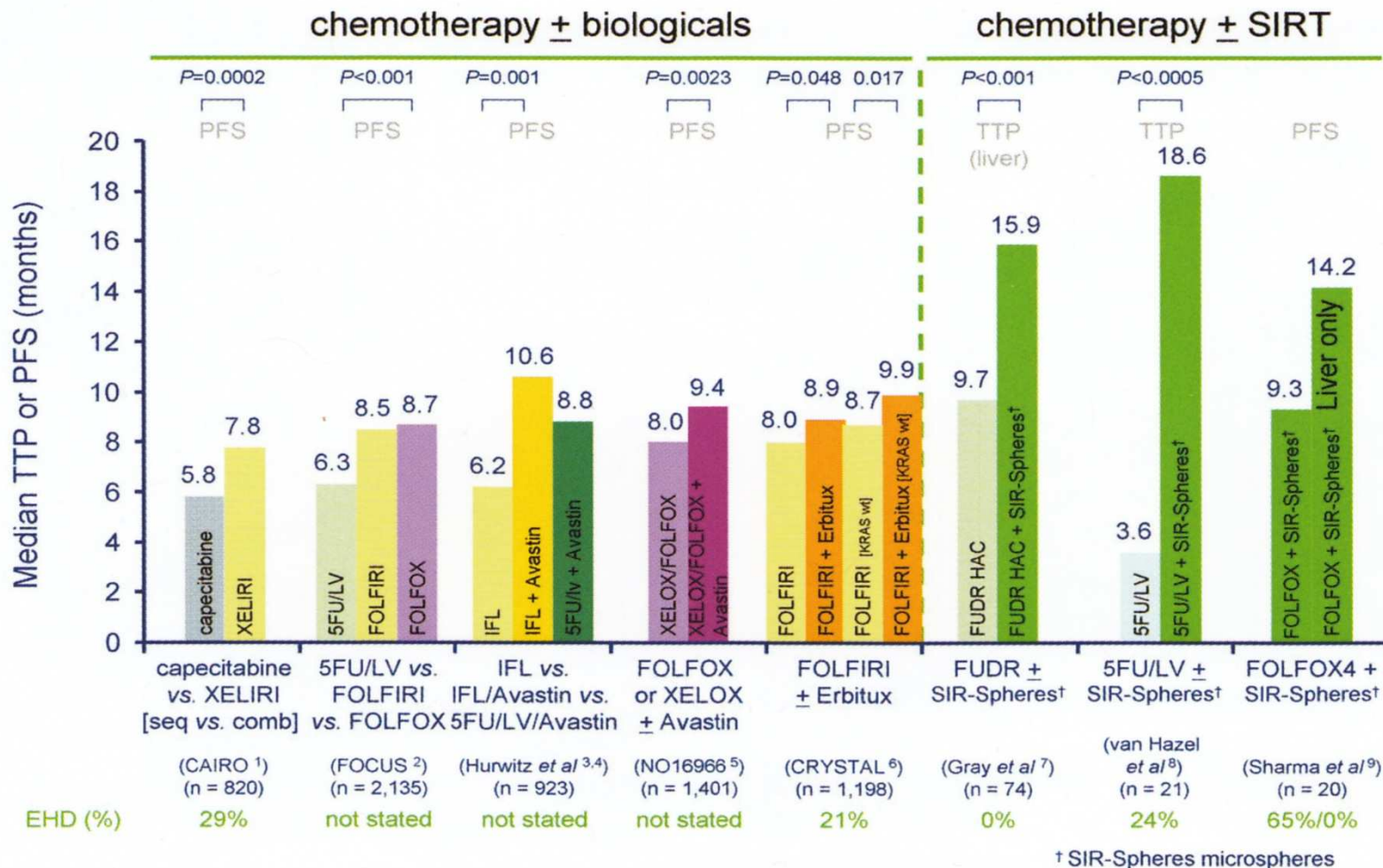
WTKRAS: Panitumumab + FOLFIRI

Overall resections



SIR

First-line Treatment of mCRC: Progression as TTP or PFS



Nicht medikamentöse regionale Therapien hepataler Metastasen

- Chir. Resektion
- Radiofrequenzablation
- Mikrowellenhyperthermie
- Laserkoagulation
- Kryotherapie
- Perkut. sonograph. gezielte Aethanolinstillation
- Stereotaktische Radiatio

Überlebensrate bei colorectalen Lebermetastasen nach Thermoablation

Studie	Jahr	Pat.	1 Jahr %	3 Jahre %	5 Jahre %
Solbiati	1997	29	94	-	-
Lencioni	1998	29	93	-	-
Gillams	2000	69	90	34	-
Solbiati	2001	117	93	46	-
Solbiati	2003	166	96	45	22
Oshowo	2003	25	100	52	-
Abdella	2004	57	92	37	-
Lencioni	2004	423	86	47	24

EORTC 4004 (CLOCC)

prosp. rand. phase II



Background

- Systemic therapy should be considered as the standard of care in patients with unresectable colorectal liver metastases
- Radiofrequency ablation is increasingly used in these patients
- No prospective randomized studies are available proving the efficacy of radiofrequency ablation

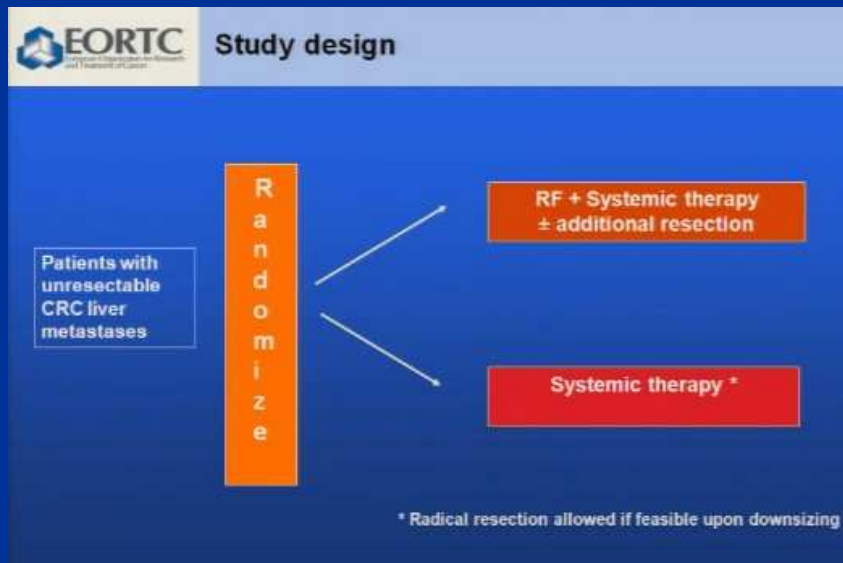


Aim

To assess

Safety and efficacy of radiofrequency ablation in combination with systemic therapy in patients with unresectable colorectal liver metastases.

EORTC 4004 (CLOCC)



EORTC Randomized Phase II trial

Primary objective:
To demonstrate a 30-months OS > 38% in the RF + systemic therapy arm
Fleming design, 1 sided type I error of 10%, power of 90% under the alternative hypothesis of a 30-months OS of 53% in the RF + chemotherapy arm

Secondary objectives:
PFS, OS, Safety, QoL

Sample size:
152 patients (2 x 76)

Study period:
April 2002 - June 2007
Study closed earlier at 119 pts because of reduced accrual, N=119/152 (78.3%)

EORTC 4004 (CLOCC)



Patient characteristics (N=119)

		<i>RF + Chemo</i> (N=60)	<i>Chemo</i> (N=59)
<i>Age Median</i>		64 (31 - 79)	61 (38 - 79)
<i>Sex Male</i>		37 (61.7%)	42 (71.2%)
<i>Number of liver lesions</i>	<i>Median</i>	4.0	5.0
	1	25%	11.9%
	2-5	48.3%	49.1%
	6-9	26.6%	38.9%
<i>Metachronous liver metastases</i>		37 (61.7%)	31 (52.5%)
<i>Prior chemotherapy for metastatic disease</i>		9 (15.0%)	8 (13.6%)
<i>WHO performance PS 0-1</i>	<i>PS 0</i>	47 (78.3%)	47 (79.7%)



Treatment information

<i>Assigned Treatment</i>	<i>Treatment received</i>				
	<i>Folfox</i>	<i>Folfox + bev</i>	<i>RF only</i>	<i>No treatment</i>	<i>Resection</i>
<i>RF + Chemo</i> (N=60)	43 72%	8 13%	6* 10%	3** 5%	
<i>Chemo</i> (N=59)	46 78%	13 22%		0 0%	7 12%

* 6 patients with RF only: progression (2), intercurrent death (1), RF/surgery complications (3)

** 3 patients with no treatment: refusal, no treatment data received, bone metastases at baseline

EORTC 4004 (CLOCC)



Radiofrequency

	RF + Chemo (N=57)
<i>Treatment by</i>	
RF	30 (52.6%)
RF + resection*	27 (47.4%)
<i>RF procedure</i>	
laparotomy	51 (89.5%)
laparoscopically	1 (1.8%)
percutaneously	4 (7.0%)
Unknown	1 (1.8%)
Mean time in hospital	4.8 days

*1 patient with resection only



Postoperative complications + toxicity

	RF + Chemo n=57	Chemo n=59
<i>Post-operative</i>		
Mortality	1 (1.8%)	
Cardiac	3 (5.3%)	
Hemorrhage	2 (3.5%)	
Infection (wound / abscess)	6 (10.5%)	
<i>During chemotherapy</i>		
Gr 3-4 Neutropenia	14 (27.5%)	12 (20.3%)
Gr 3-4 cardiotoxicity	5 (9.8%)	1 (1.7%)
Gr 3-4 diarrhea	10 (19.6%)	10 (16.9%)
Gr 3 neuropathy (no grade 4)	9 (17.6%)	8 (13.6%)

EORTC 4004 (CLOCC)



Primary objective:
30-months Overall Survival

Treatment	Patients (N)	Observed Events (O)	Hazard Ratio (95% CI)	P-Value (Log-Rank)	Median (95% CI) (Years)	% at 30 months (95% CI)
Chemo	59	39	1.00	0.2176	3.38 (2.46, 4.18)	58.56 (44.82, 69.99)
RF+Chemo	60	31	0.74 (0.46, 1.19)		3.78 (2.76, N)	63.83 (50.10, 74.71)

Primary objective: 30-months OS in RF + Chemo >38%

Median follow up time 4.4 years (equal in both arms)



Overall Survival



EORTC 4004 (CLOCC)



Main cause of death

	<i>RF + Chemo</i> N = 60 N (%)	<i>Chemo</i> N = 59 N (%)
Survival status		
<i>Alive</i>	29 (48.3)	20 (33.9)
<i>Dead</i>	31 (51.7)	39 (66.1)
Main cause of death		
<i>PD</i>	28 (46.7)	37 (62.7)
<i>Cardiovascular</i>	1 (1.7)	0
<i>Other</i>	2 (3.3)	1 (1.7)
<i>Missing</i>	0	1 (1.7)



Secondary objective: Progression free survival

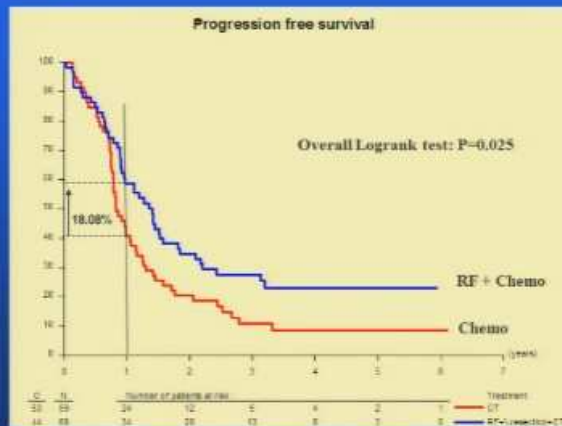
Treatment	Patients (N)	Observed Events (O)	Hazard Ratio (95% CI)	P-Value (Log-Rank)	Median (95% CI) (Months)	% at 3 Year(s) (95% CI)
<i>Chemo</i>	59	53	1.00	0.0249	9.92 (9.30, 13.67)	10.65 (4.22, 20.50)
<i>RF + Chemo</i>	60	44	0.63 (0.42, 0.95)		16.82 (11.66, 22.11)	27.65 (16.91, 39.47)

Median follow up time 4.4 years

EORTC 4004 (CLOCC)



Progression free survival



1st Progression

	<i>RF + Chemo</i> (N=42)	<i>Chemo *</i> (N=53)
Hepatic	27 (64.3%)	45 (84.9%)
local RF site only	5 (11.5%)	
Extrahepatic	15 (35.7%)	7 (13.2%)

*1 site unknown

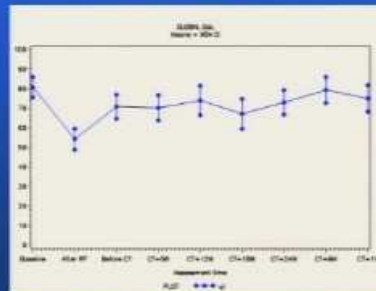
EORTC 4004 (CLOCC)



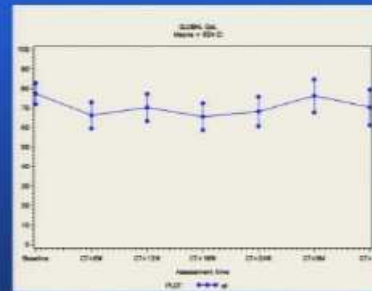
Quality of Life (QoL)

EORTC QLQ-C30: Global health status

RF + Chemo



Chemo



Conclusions

- Primary objective of this randomized Phase II trial (30 months OS > 38%) is reached, *but* also in the systemic therapy alone arm 30 months OS > 38%
- RF + systemic therapy is safe and significantly improves PFS compared to systemic therapy alone

Thermoablation hepat. Meta CRC

Ludwig Boltzmann Institut, Oktober 2011

Table 4.1-5: Overview of included systematic reviews: Single-arm radiofrequency ablation in colorectal liver metastases patients

Author, year, reference number	Wang 2010 [24]	Stang 2009 [24]
Country	US	DE
Funding	None (2 authors had a consultant or advisory role, 2 authors received honoraria)	NR
Indication	CRLM	CRLM
Intervention	RFA	RFA
Comparator	none	none
Study design	Clinical Evidence Review	Systematic Review
Search details	Medline, preMedline, Cochrane Collaboration Library, National Cancer Institute's Physician Data Query, database of clinical trials, National Library of Medicine's ClinicalTrials.gov database	Medline
Time span	January 1990 – April 2007	up to August 2008
Search terms/inclusion criteria	(co)ltheter ablation, radiofrequency ablation, RFA, electrocoagulation, colorectal neoplasm, colonic neoplasm, sigmoid neoplasm, rectal neoplasm, liver neoplasm, cancer, tumor, malignancy, carcinoma, and adenocarcinoma) in English and human patients	colorectal neoplasms AND liver neoplasms AND radiofrequency ablation AND survival OR treatment outcome
Total number of included studies	40	9
ER	0	0
RCT	0	0
NRCT	0	0
Case-series	40	9
Number of pts	NR	875
Age of pts (yrs)	NR	NR
Ratio males:females (%)	NR	NR
Median/mean size of tumor (cm)	1.0 – 5.6	2.2 – 3.9
Duration of follow-up (months)	0 – 33	18 – 38
Critical appraisal of studies by review authors	The heterogeneity of the literature and the limited scope of most of the studies impeded the ability of the authors to develop evidence-based recommendations.	NR
Results		
Overall survival rate in %	1 y: 72.5 – 90 (across 13 studies; 14 NR) 2 y: 50.2 – 80 (across 8 studies; 14 NR) 3 y: 25.1 – 48 (across 10 studies; 14 NR) 4 y: 38 (in 1 study; 14 NR) 5 y: 17 – 31 (across 3 studies; 14 NR)	3 y: 30 – 68 (across 2 studies) 4 y: 20 (in 1 study) 5 y: 18.4 – 34 (across 7 studies)
Disease-free survival rate in %	22 – 90 at 0 – 36 months (across 12 studies; 17 NR)	NR
Recurrence rate in %	Local: 0 – 40 (across 24 studies; 3 NR) Overall: 2.7 – 62.4 (across 12 studies; 17 NR)	Local: 0 – 42 (across 7 studies; 1 NR) Systemic: 43 – 89 (across 7 studies; 2 NR)
Morbidity in %	NR	NR
Mortality in %	NR	NR
Conclusion by review authors	There is a compelling need for more research to determine the efficacy and utility of RFA to increase local recurrence-free, progression-free, and disease-free survival as well as OS for pts with CRLM. Clinical trials have established that SNS can improve OS for pts with resectable CRLM.	RFA offers a complementary option for local treatment of limited CRLM. There is no data to support RFA as an alternative treatment option in surgical candidates with resectable CRLM. However, there is data supportive of RFA as a useful adjunct to surgery and chemotherapy in well-selected pts with unresectable CRLM. Until the clinical benefits are verified in RCTs, the use of RFA for an individual patient should be decided within a multidisciplinary tumorboard.

- Until the clinical benefits are verified in RCT's, the use of RFA for an individual patient should be decided within a multidisciplinary tumorboard.

Thermoablation vs. Resektion

Ludwig Boltzmann Institut, Oktober 2011

Tabella 4.1-4: Overview of included systematic reviews: Radiofrequency ablation vs. resection in colorectal liver metastases patients

Author, year, reference number	Gurusamy 2010 [26]	Stang 2009 [24]
Country	UK	DE
Funding	NR	NR
Indication	CRLM	CRLM
Intervention	RFA	RFA
Comparator	SRS	SRS
Study design	Systematic Review	Systematic Review
Search details	The Cochrane Hepato-Biliary Group Controlled Trials Register, Cochrane Central Register of Controlled Trials, Medline, Embase, Science citation Index Expanded, LILACS	Medline
Time span	until September 2009	until August 2008
Search terms/inclusion criteria	only RCTs comparing liver resection versus other treatments (RFA) for hepatic node positive pts with CRLM	'colorectal neoplasms' AND 'liver neoplasms' AND 'radiofrequency ablation' AND 'survival' OR 'treatment outcome'
Total number of included studies	0	5
SR	0	0
RCT	0	0
NRCT	0	5
Coxe-series	0	0
Number of pts	NR	433 (132 RFA, 301 SRS)
Age of pts (yrs)	NR	NR
Ratio males:females	NR	NR
Median/mean size of tumor (cm)	NR	2.0 - 4.0
Duration of follow-up (months)	NR	17 - 68
Critical appraisal of studies by review authors	We were unable to identify any RCT fulfilling the inclusion criteria of this review. We were also unable to identify any quasi-randomized or cohort studies, which could meaningfully answer this important issue.	Factors that determine resectability include comorbidity, disease extent, response to chemotherapy and hepatic reserve. The definition of what constitutes resectability varies largely between analyzed studies and depends on the opinion and experience of the respective centre.
Results		
Overall survival rate in % RFA vs SRS	NR	3 y: 28 - 33 (across 2 studies) vs 33 (in 1 study) 5 y: 19 - 27 (across 3 studies) vs 48 - 71 (across 4 studies)
Disease-free survival rate in % RFA vs SRS	NR	NR
Recurrence rate in % RFA vs SRS	NR	Local: 12 - 37 vs 0 - 0.5 (across 3 studies) Systemic: 41 - 71 (across 3 studies) vs 30 - 60 (across 4 studies; 1 NR)
Morbidity in % RFA vs SRS	NR	NR
Mortality in % RFA vs SRS	NR	NR
Conclusion by review authors	There is no evidence in the literature to assess the role of surgery versus other treatments for patients with CRLM with hepatic node involvement. High quality RCTs are feasible and necessary to determine the optimal management of pts with CRLM with hepatic node involvement.	Our findings support that RFA prolongs time without toxicity and survival as an adjunct to hepatectomy and/or chemotherapy in well-selected pts but not as an alternative to resection.

- Our findings support that RFA prolongs time without toxicity and survival as an adjunct to hepatectomy and/or chemotherapy in well-selected patients, but not as an alternative to resection.

Ode an die Leber

Dort, tief im Innern
Filtrierst und verteilst Du
Teilst und trennst Du
Du schöpfst und erntest den Stoff des Lebens...

Von Dir erhoffe ich Gerechtigkeit:
Ich liebe das Leben: Verrate mich nicht!
Schaffe weiter,
Lass mein Lied nicht sterben.

Pablo Neruda