What do local ablative treatments contribute

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COCHRANE analysis 2012

Objective

To systematically review the role of radiofrequency ablation (RFA) in the treatment of CRLM

Conclusion:

- Out of 18 studies, only 1 single RCT could be indentified (EORTC/CLOCC)
- This study showed that PFS was significantly higher in the group that received RFA.

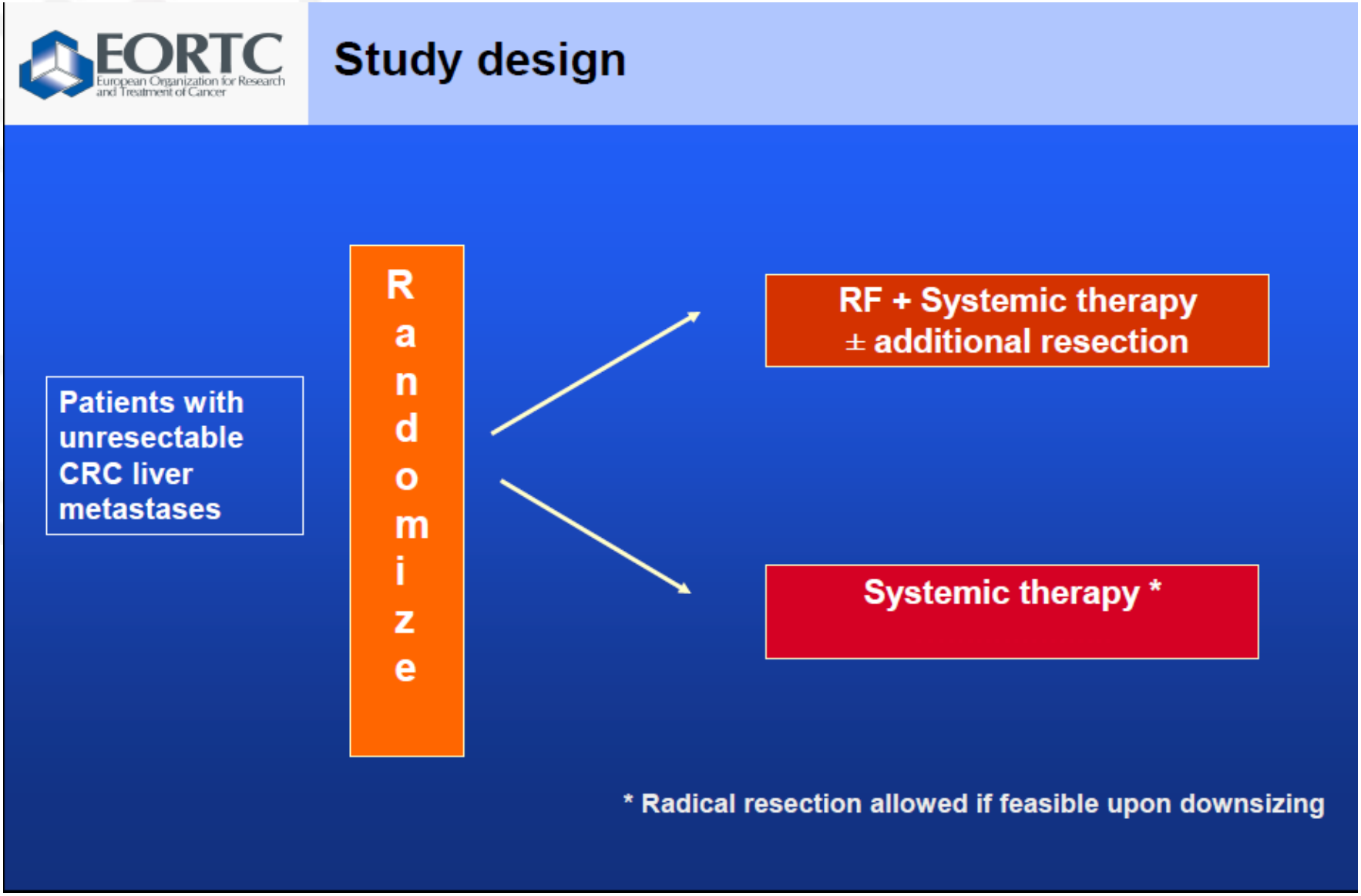
Interpretation of results

	pts	Indication Unresectable disease	number of lesions per pt	Median follow up	Survival
Solbiati Eur J Ultrasound	117	< 4 lesions < 4cm	1.5	24 mo	1 yr 93% 2 yr 69%
Bleicher Ann Surg Oncol	153	1-13 lesions 1-13cm (2.5)	2.9	11 mo	1 yr 61%
Pawlik Ann Surg Oncol	172	2 - 21 lesions 1 – 12 cm	3	21 mo	1 yr 92% 2 yr 72%
Abdalla Ann Surg	57	1-8 lesions 2.5 cm	1	21 mo	2 yr 50% 3yr 38%
Berber J Clin Oncol	135	1-8 lesions 1 – 10 cm (4)	3.2	> 24 mo	2 yr 55% 3 yr 31%

Interpretation of results

18 studies all retrospective or prospective controlled studies: median OS 11 - 40 months

CLOCC Study: EORTC 40004



CLOCC Study: EORTC 40004

EORTC
European Organization for Research and Treatment of Cancer

Aim

To assess

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

CLOCC Study: EORTC 40004

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Randomized Phase II trial

Primary objective:

To demonstrate a 30-months OS > 38% in the RF + systemic therapy arm

Secondary objectives:

PFS, OS, Safety, QoL

Sample size:

152 patients (2 x 76)

Study period:

April 2002 - June 2007

CLOCC Study: EORTC 40004

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Patient characteristics (N=119)

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

CLOCC Study: EORTC 40004

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Postoperative complications + toxicity

	RF + Chemo n=57	*Chemo n=59*
Post-operative		
Mortality	1 (1.8%)	
Cardiac failure or infarction	3 (5.3%)	
Hemorrhage	2 (3.5%)	
Infection (wound / abscess)	6 (10.5%)	
During chemotherapy		
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%)

CLOCC Study: EORTC 40004

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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)

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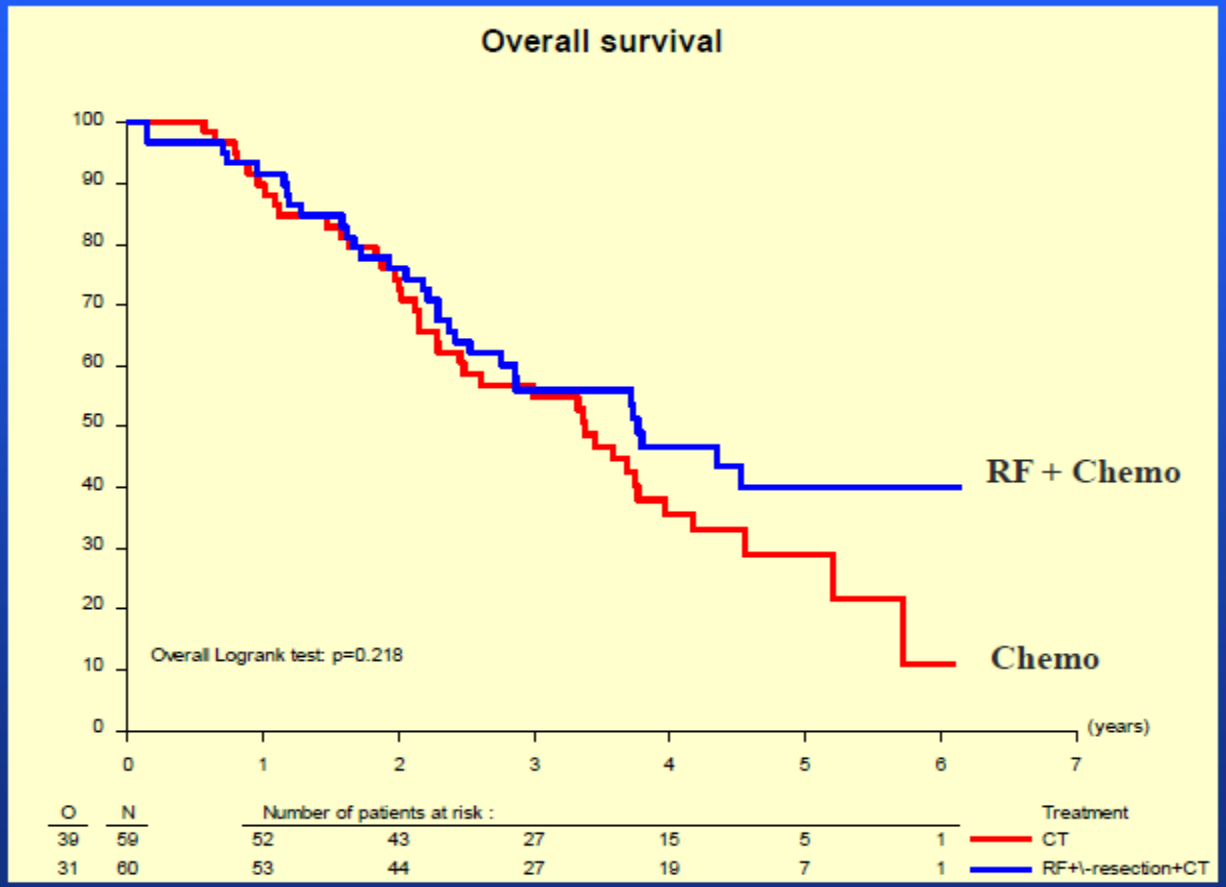
Overall Survival



CLOCC Study: EORTC 40004

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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)
Chemo	59	53	1.00	0.0249	9.92 (9.30, 13.67)	10.65 (4.22, 20.50)
RF +Chemo	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

CLOCC Study: EORTC 40004

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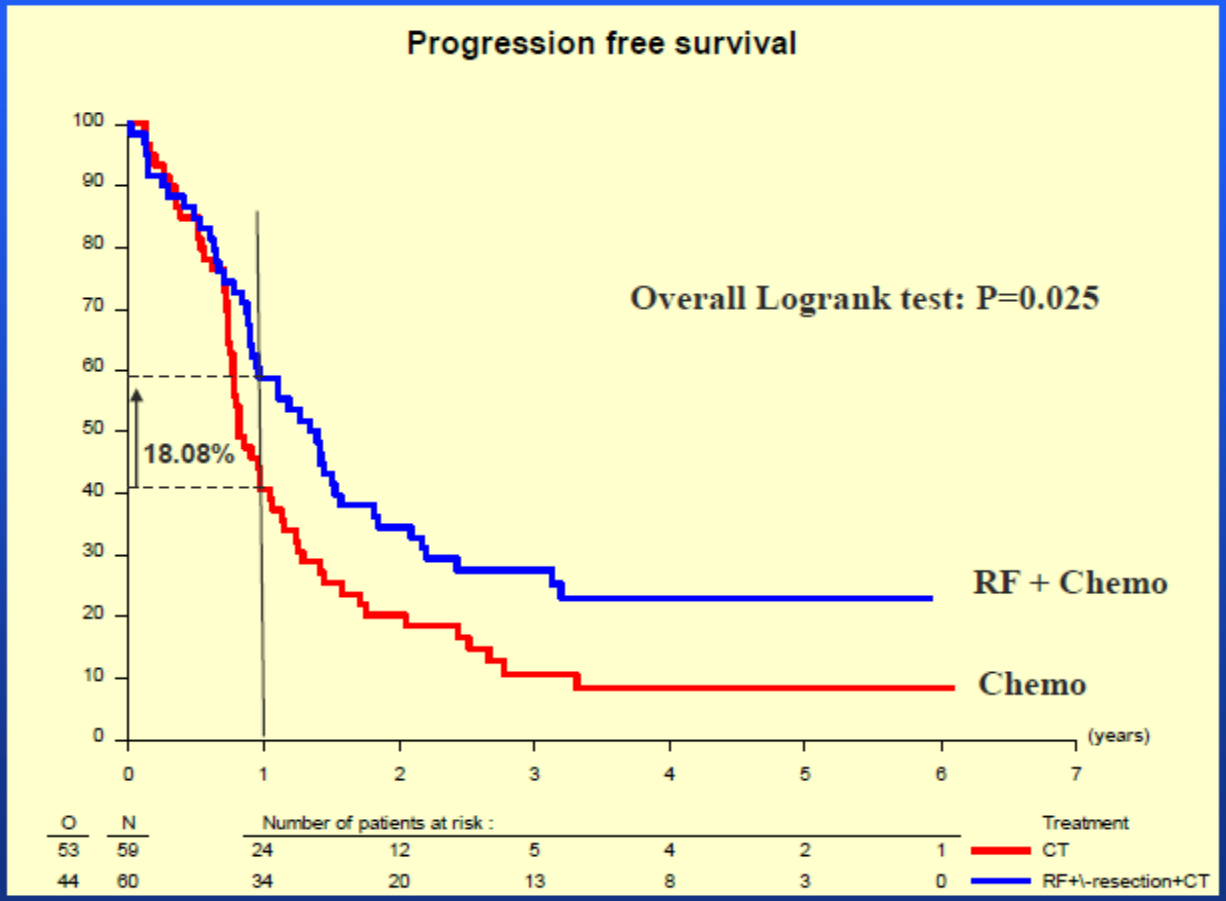
Progression free survival



CLOCC Study: EORTC 40004

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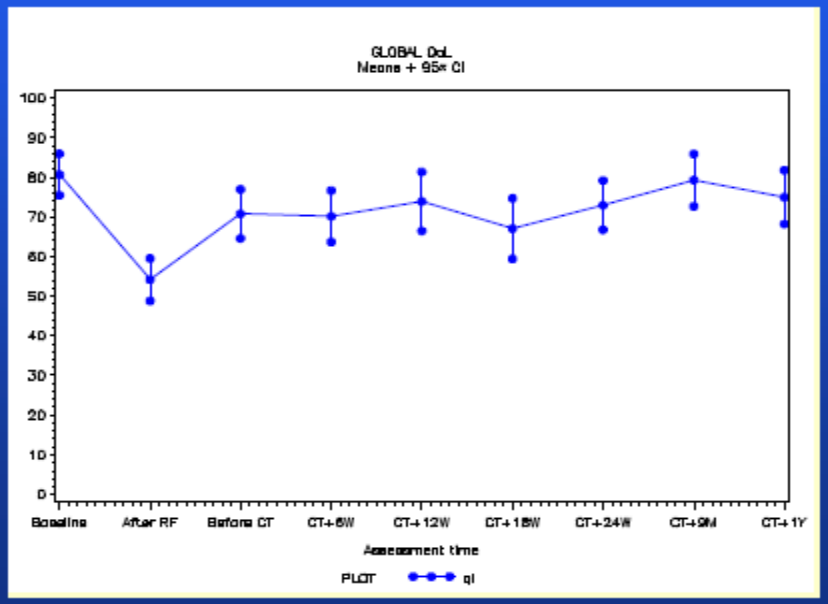
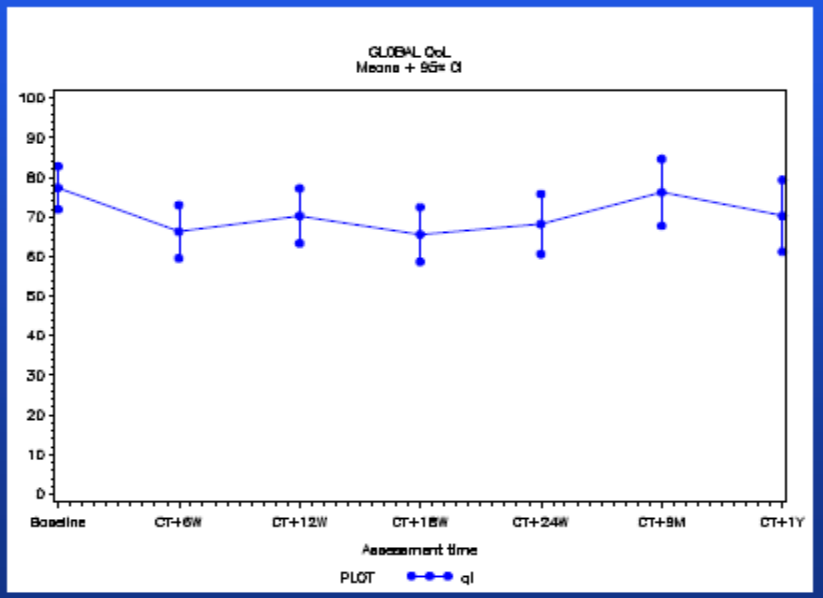
Quality of Life (QoL)

EORTC QLQ-C30: Global health status

RF + Chemo



Chemo



CLOCC Study: EORTC 40004

EORTC
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Conclusions

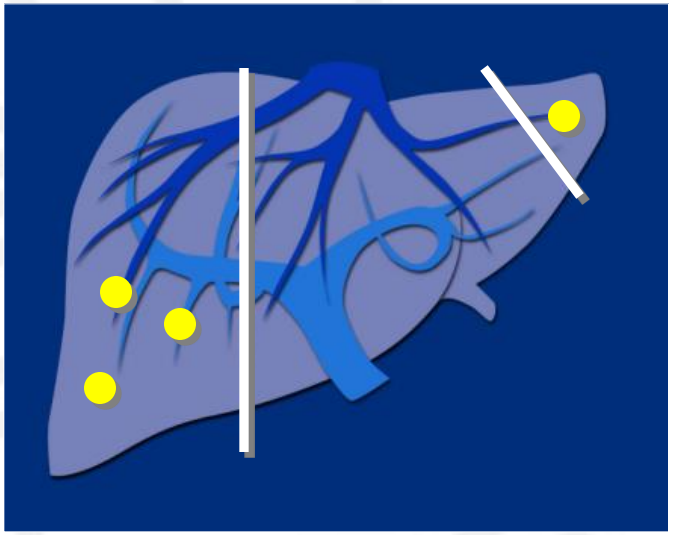
- In patients with unresectable CRLM, RFA + systemic therapy is safe and significantly improves PFS compared to systemic therapy alone

Definition resectability

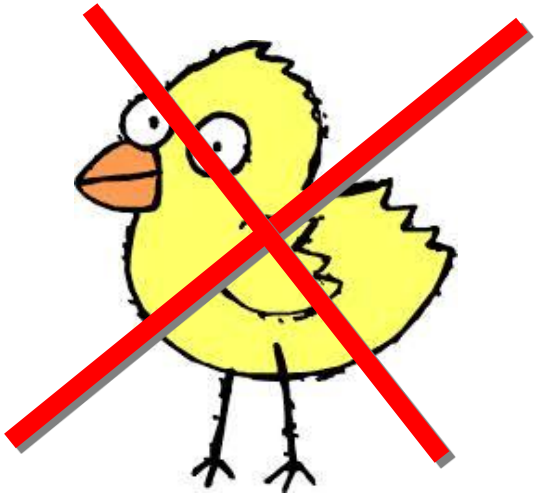
- When all macroscopic disease can be removed with clear (negative) margins

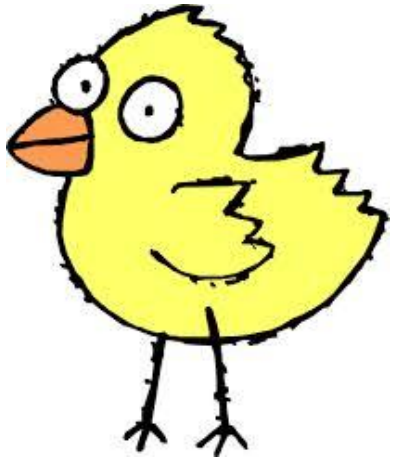
- While leaving sufficient functioning liver tissue

Two clinical cases



Resection





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Route of RFA

Procedure	*n cases*	*n recurrences*	*% recurrences*	*P value*
Open	907	40	4.4%	P < 0.001
laparoscopic	515	30	5.8%	
percutaneous	3002	493	19%	

Local recurrence after open RFA

- Lesions < 4 cm

CLOCC study	*RF performed (lesions N=170)*
Recurrence RF lesion	**11 (6.5%)**

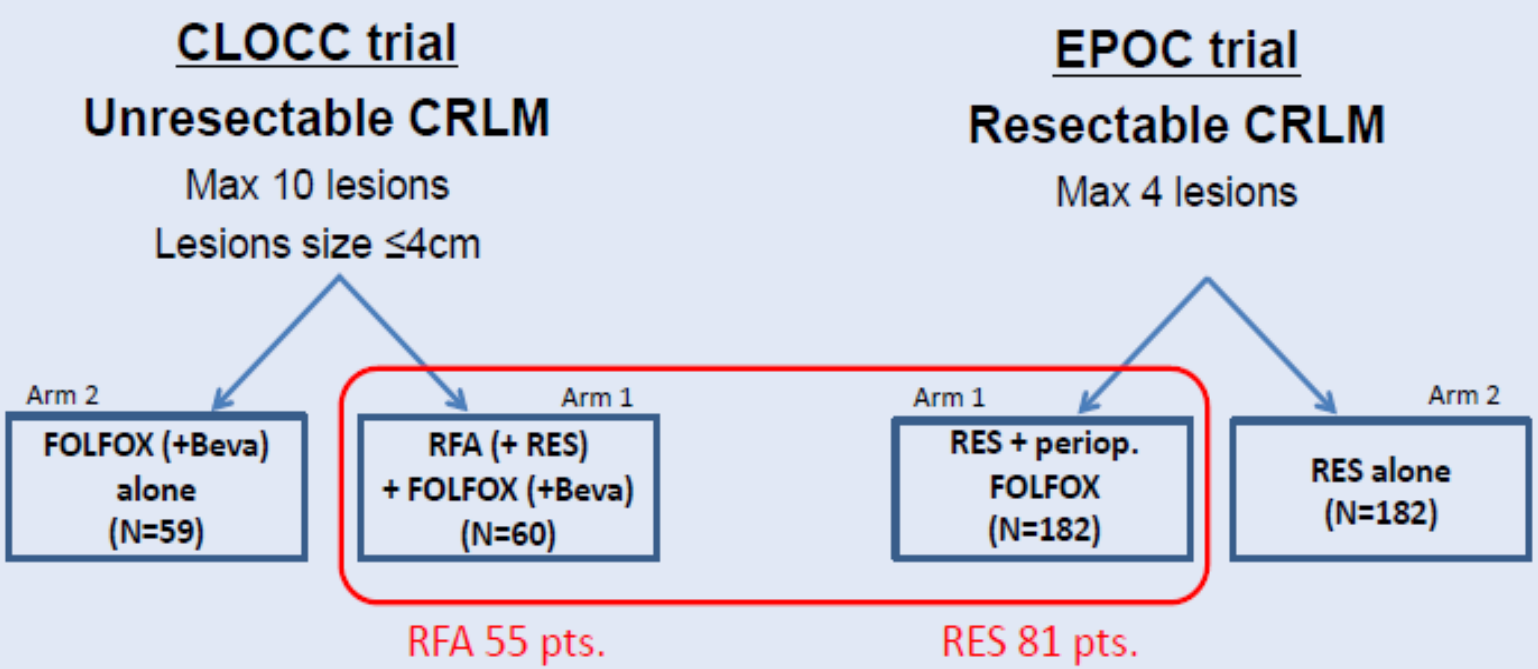
Second EORTC study

AIM OF SECOND STUDY

To describe …

- local tumour control after RFA and resection of CRLM
- for lesions ≤4 cm (max lesion size for RFA)
- in a controlled prospective setting

EORTC TRIALS 40004 (CLOCC) AND 40983 (EPOC)



Patient selection for this study:

- CLOCC arm 1 and EPOC arm 1
- Adequate local treatment
- Lesion size ≤4cm

ENDPOINT OF THIS STUDY

Local recurrence rate on lesion basis after RFA and resection of CRLM

- LR was defined as tumor progression at site of resection / RFA
- All local liver recurrences were confirmed by the local investigator

DEMOGRAPHY

		RFA (±RES) - CLOCC (N=55)	RES - EPOC (N=81)
Age (years) *Median (Range)*		64 (39 – 79)	61 (29-77)
Sex – male *N (%)*		33 (60.0)	58 (71.6%)
ECOG/WHO performance status *N (%)*			
	0	42 (76.4)	61 (75.3%)
	1	13 (23.6)	20 (24.7%)
Metachronous liver metastases *N (%)*		35 (63.6%)	55 (67.9%)
Time to liver metastasis (days) *Median (Range)*		300 (28-1802)	373 (0 - 2837)
Number metastases *Median (Range)*		**4 (1-9)**	**1 (1-4)**
	1-3	27 (49.1%)	74 (91.4 %)
	≥ 4	28 (50.9%)	7 (8.6%)
Diameter largest metastases at baseline (cm) *Median (Range)*		3.0 (1.0-3.9)	2.8 (0.5-4.0)

Lesions **167 RFA** **110 resected**

DISEASE PROGRESSION

First progressions	RFA-CLOCC (N=55)	RES-EPOC (N=81)
Recurrences	38 (69.1%)	48 (59.3%)
Local recurrence per patient		
- Per patient	8 (14.5%)	6 (7.4%)
- Per lesion	10/167 (6.0%)	6/110 (5.5%)
Non-local liver recurrence	17 (30.9%)	18 (22.3%)

IN SUMMARY

- During open RFA local recurrence rate on a lesion basis is similar between RFA and Resection

What do local ablative treatments contribute

EORTC CLOCC Study

- In pt with unresectable CRLM local ablation by RFA results in prolongation of PFS of 7 months

Consequences

- In patients with unresectable CRLM local tumor ablation should be considered