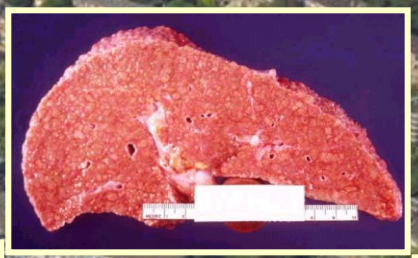
Local treatment of liver tumors – thermoablation



Koert P. de Jong, surgeon

HPB & Liver Transplantation

University Medical Center Groningen

E-AHPBA HPB course, June 3^{d}, 2016

Maastricht

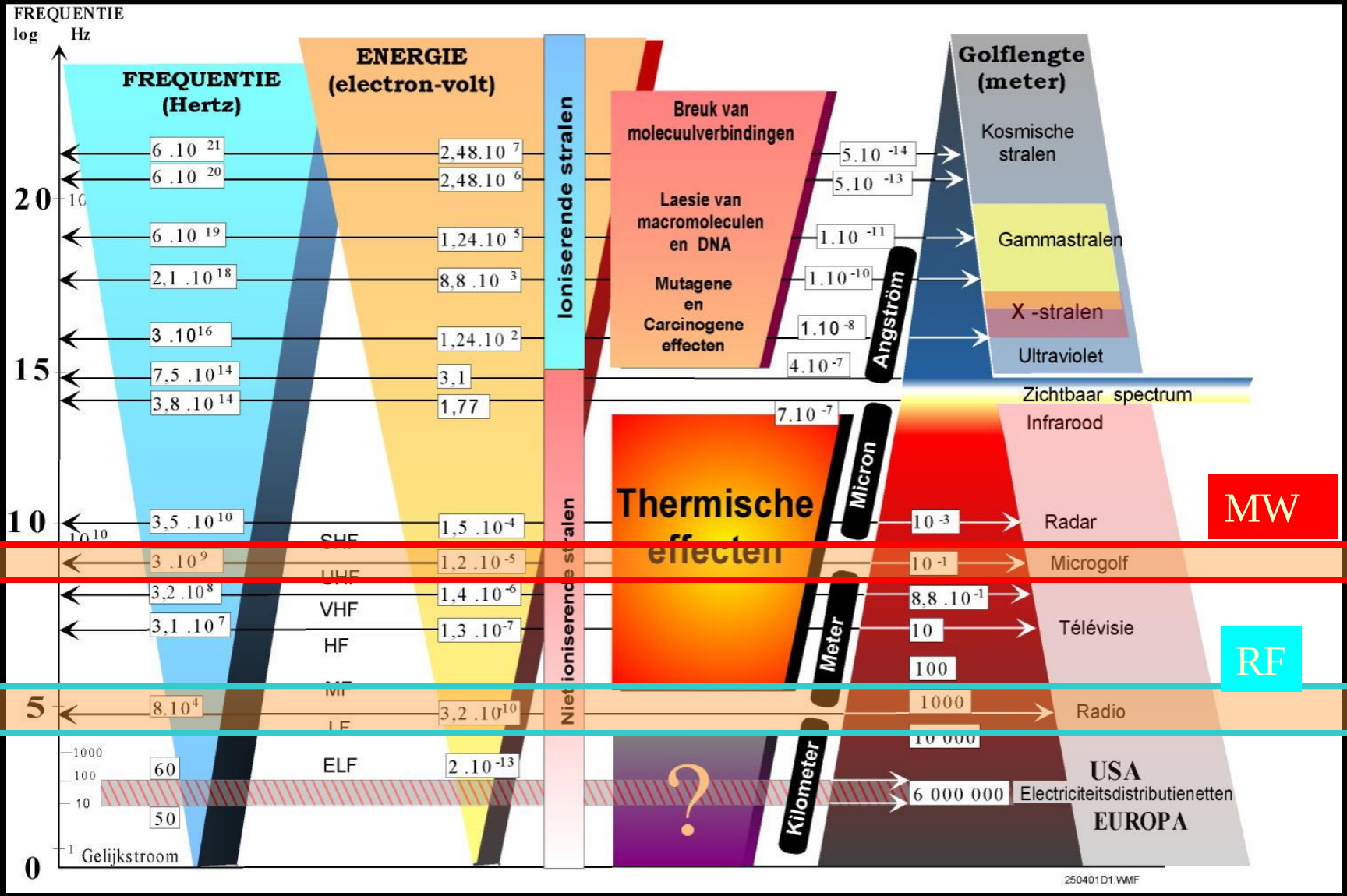
Disclosures

- President of the European Computer Assisted Liver Surgery Society (www.ecalss.org)
- Partner of DEMCON (www.demcon.nl) in Enschede for the development of a Computer Guided Navigation and Needle Positioning System
- Collaboration with University Twente (www.utwente.nl), Enschede
- Member of Center for Medical Imaging (www.cmi-nen.nl)
- Project leader of thermoablation application in patients with liver tumors in the University Medical Center Groningen

- Financial disclosures: none

Radio Frequency Ablation

- Jacques d'Arsonval (1851-1940): "alternating current > 10 kHz harmless to organisms".
  Medical application (urology, brain)
- Launsberry 1961 first application in patient with liver tumor
- 1952 Lortat Jacob: "Hepatectomie droite reglée"
- Radiofrequency: 3 kHz-300 GHz
- Ionic agitation generates frictional heat
- Heat dispersion through tissues
  - Time consuming
  - Dependent on adjacent structures (vessels)
- Microwave more efficient (?)


FREQUENTIE
log Hz
FREQUENTIE (Hertz)
ENERGIE (electron-volt)
Ioniserende stralen
Niet ioniserende stralen
Breuk van molecuulverbindingen
Laesie van macromoleculen en DNA
Mutagene en Carcinogene effecten
Thermische effecten
Golflengte (meter)
Kosmische stralen
Gammastralen
X -stralen
Ultraviolet
Zichtbaar spectrum
Infrarood
Radar
Microgolf
Télévisie
Radio
USA
Electriciteitsdistributienetten
EUROPA
Angström
Micron
Meter
Kilometer
6 .10 21
6 .10 20
6 .10 19
2,1 .10 18
3 .10 16
7,5 .10 14
3,8 .10 14
3,5 .10 10
3 .10 9
3,2 .10 8
3,1 .10 7
8.10 4
60
50
Gelijkstroom
SHF
UHF
VHF
HF
MF
LF
ELF
2,48.10 7
2,48.10 6
1,24.10 5
8,8 .10 3
1,24.10 2
3,1
1,77
1,5 .10 -4
1,2 .10 -5
1,4 .10 -6
1,3 .10 -7
3,2 .10 10
2 .10 -13
5.10 -14
5.10 -13
1.10 -11
1.10 -10
1.10 -8
4.10 -7
7.10 -7
10 -3
10 -1
8,8 .10 -1
10
100
1000
10 000
6 000 000
?
20
15
10
5
0
MW
RF
250401D1.WMF

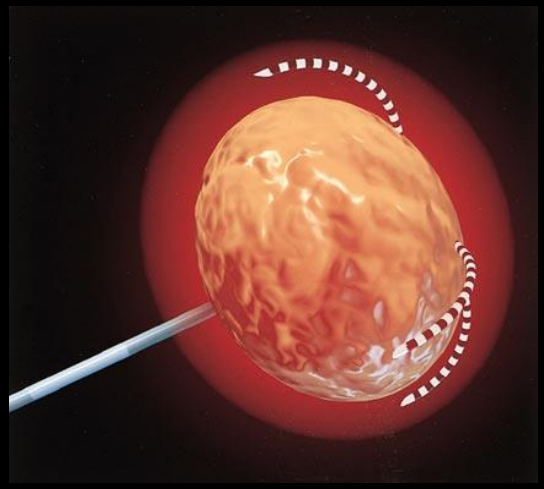
Thermoablation

- Why thermoablation of liver tumors?

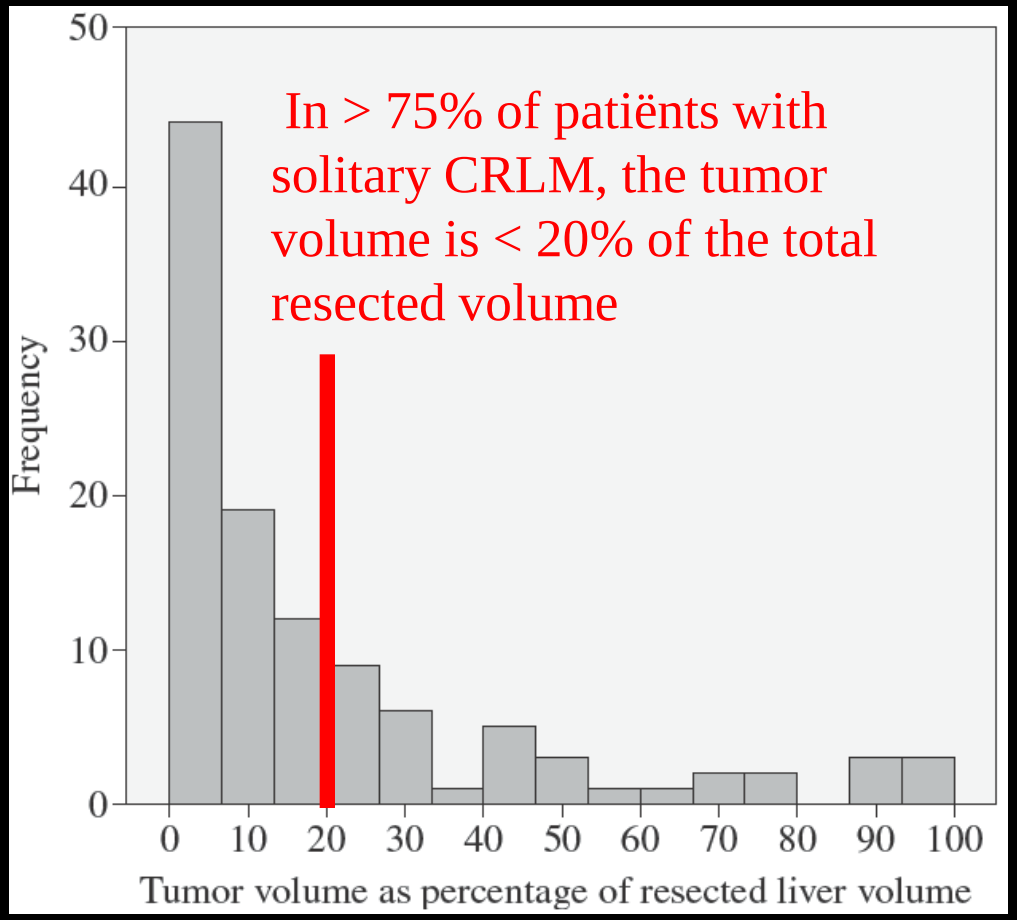
Resection “gold standard”

……BUT……

Majority of liver tumors: not resectable



Tumorvolume as % of resected volume



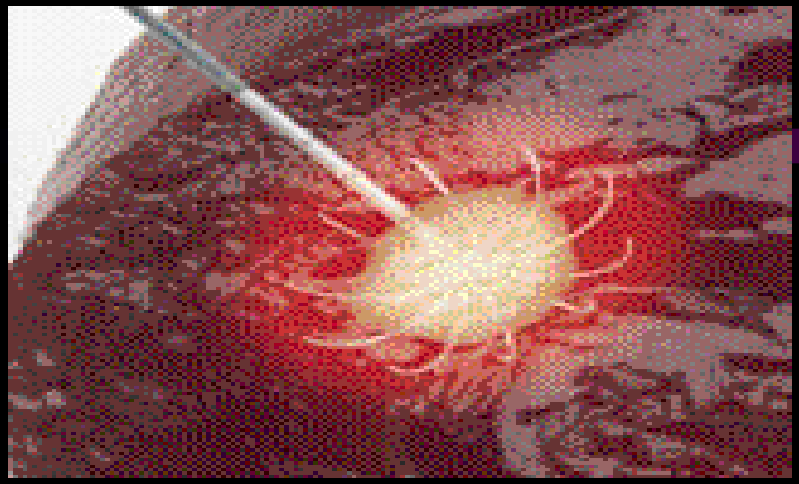
Overshoot ?

Various approaches for tumor destruction

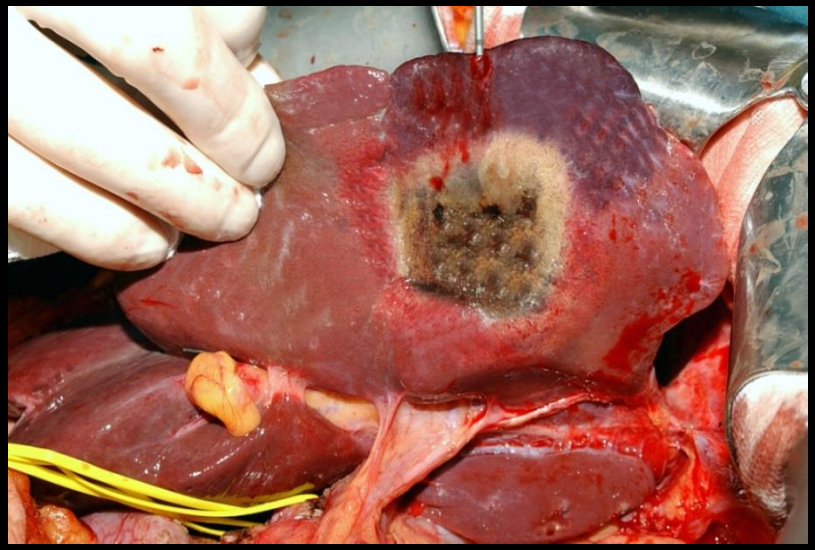
Approach	Tumor destruction	
	Mechanism	**Technique**
Direct puncture	Heat	Radiofrequency ablation
		Microwave ablation
	Cold	Cryo-ablation
	Electrical	Irreversible electroporation
	Chemical	Ethanol injection
Indirect	Ionising radiation	Stereotactic radiotherapy
		Proton radiotherapy
Tumor vasculature	*Embolising*	
	Ionising radiation	Radio-embolisation with beads
	Ischemia	Transarterial embolisation
	Ischemia & drugs	Transarterial chemo-embolisation
	Non-embolising	
Hepatic vasculature	Local drugs	Hepatic artery infusion
	Regional drugs	Isolated liver perfusion

Ontleend aan: S. Kruijff, A.N.A. van der Horst-Schrivers en K.P. de Jong. Liver metastases in thyroid cancer. In: Noncolorectal, Nonneuroendocrine Liver Metastases: Diagnosis and Current Treatment Modalities. Editor: Isidoro Di Carlo. Springer Verlag. 2015. In press.

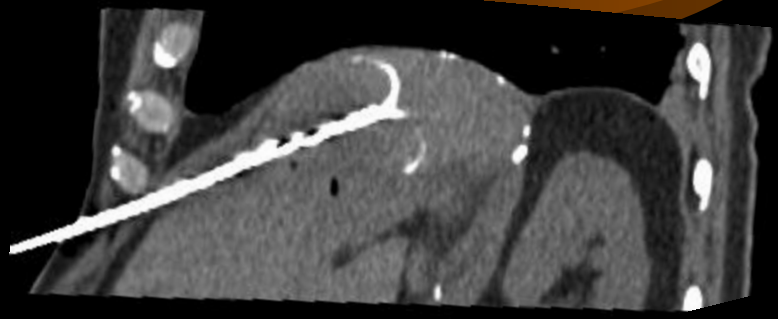
Thermoablation: radiofrequency or microwave

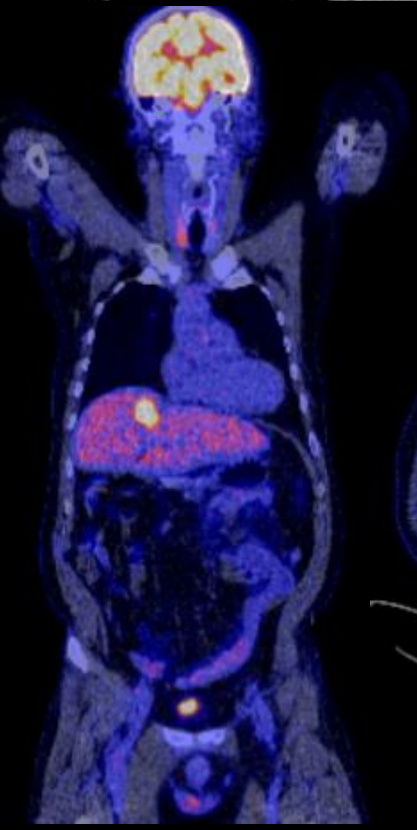


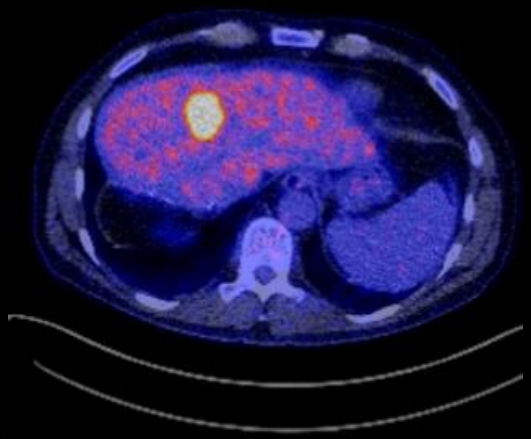
- Changing electromagnetic field
- Ion movements: frictional heat (80°C)
- Tumor and margin
- Preop 3D planning essential

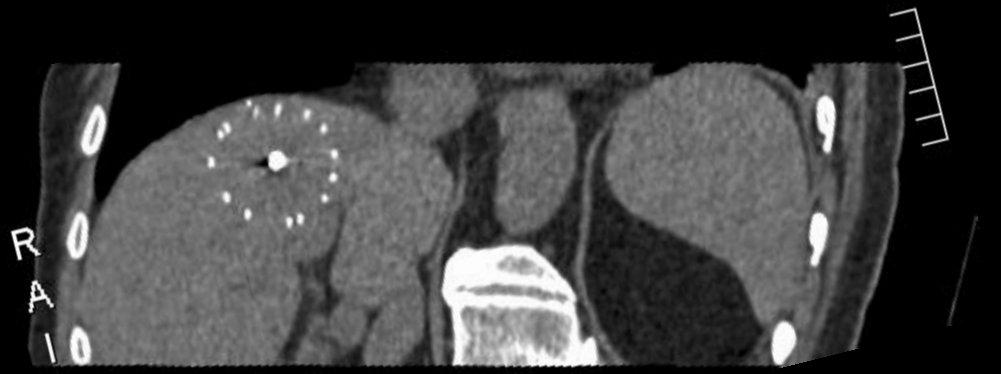


57 year
recurrent CRLM
after right hemihepa and RFA









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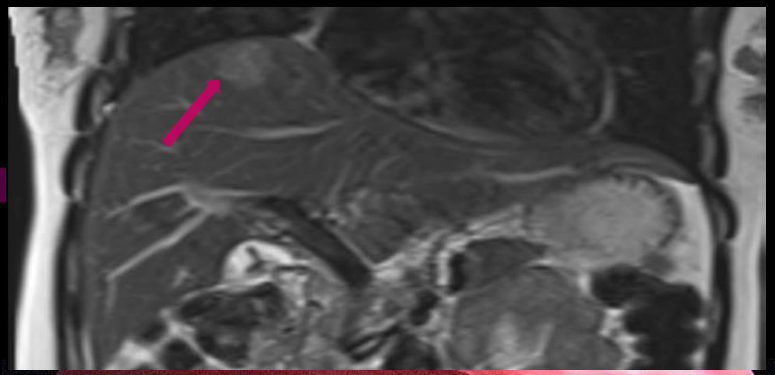
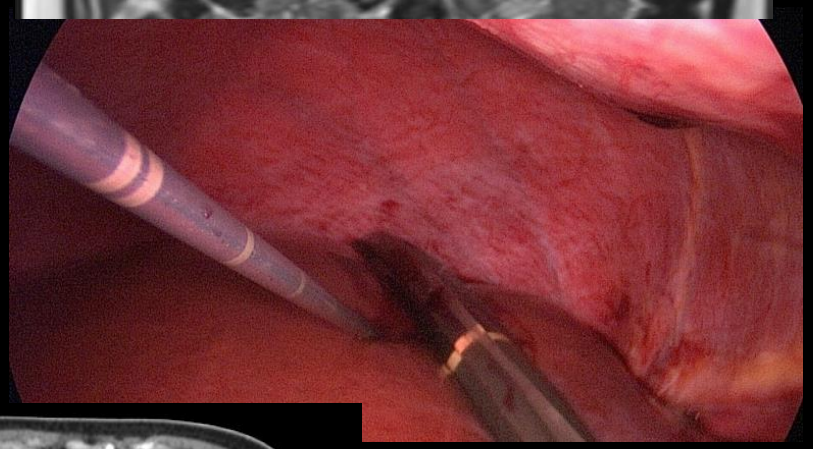
Approach

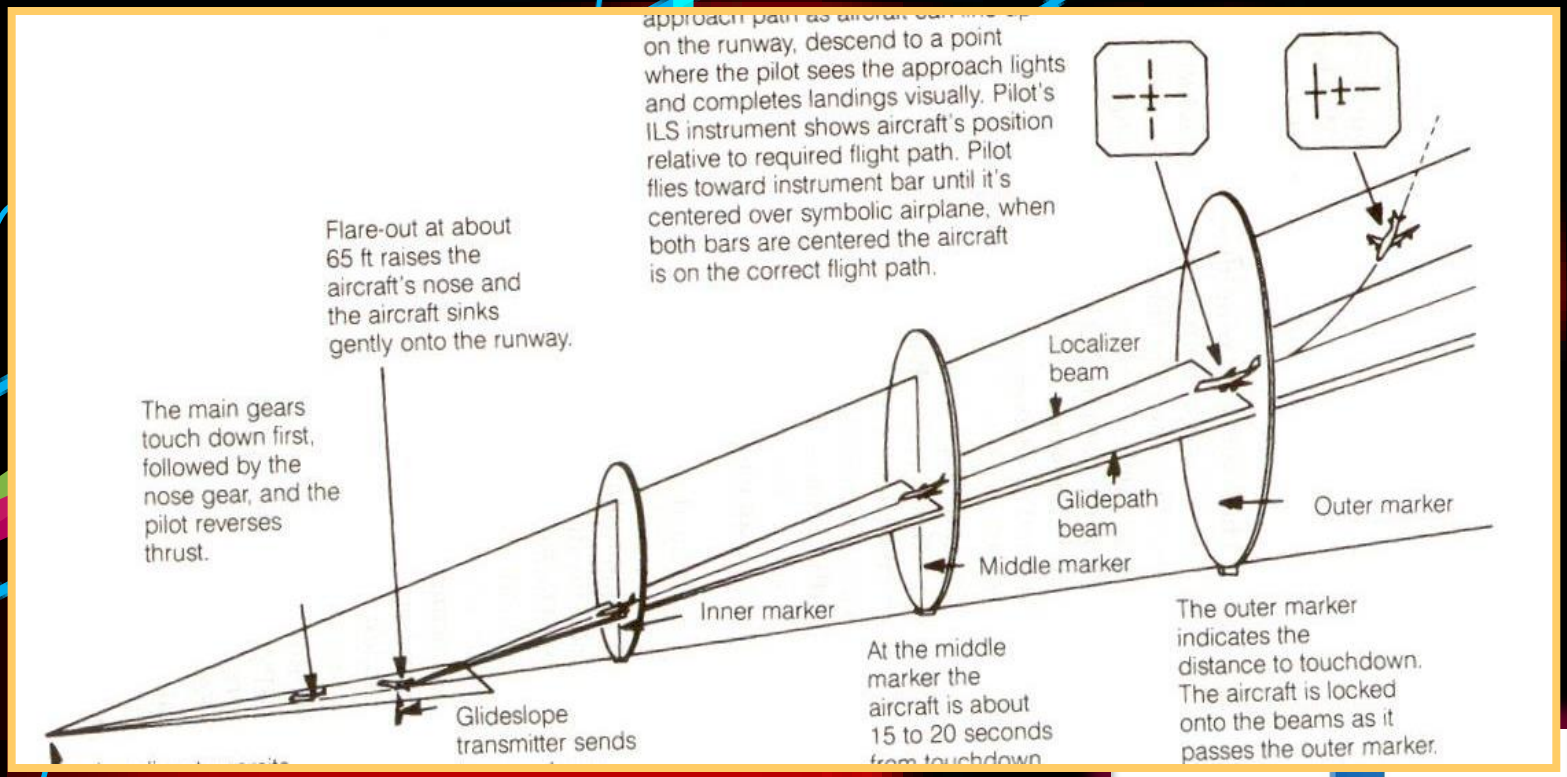


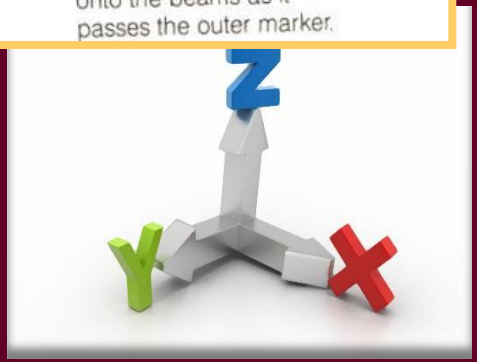


Open
- US guided
- Maximal invasive

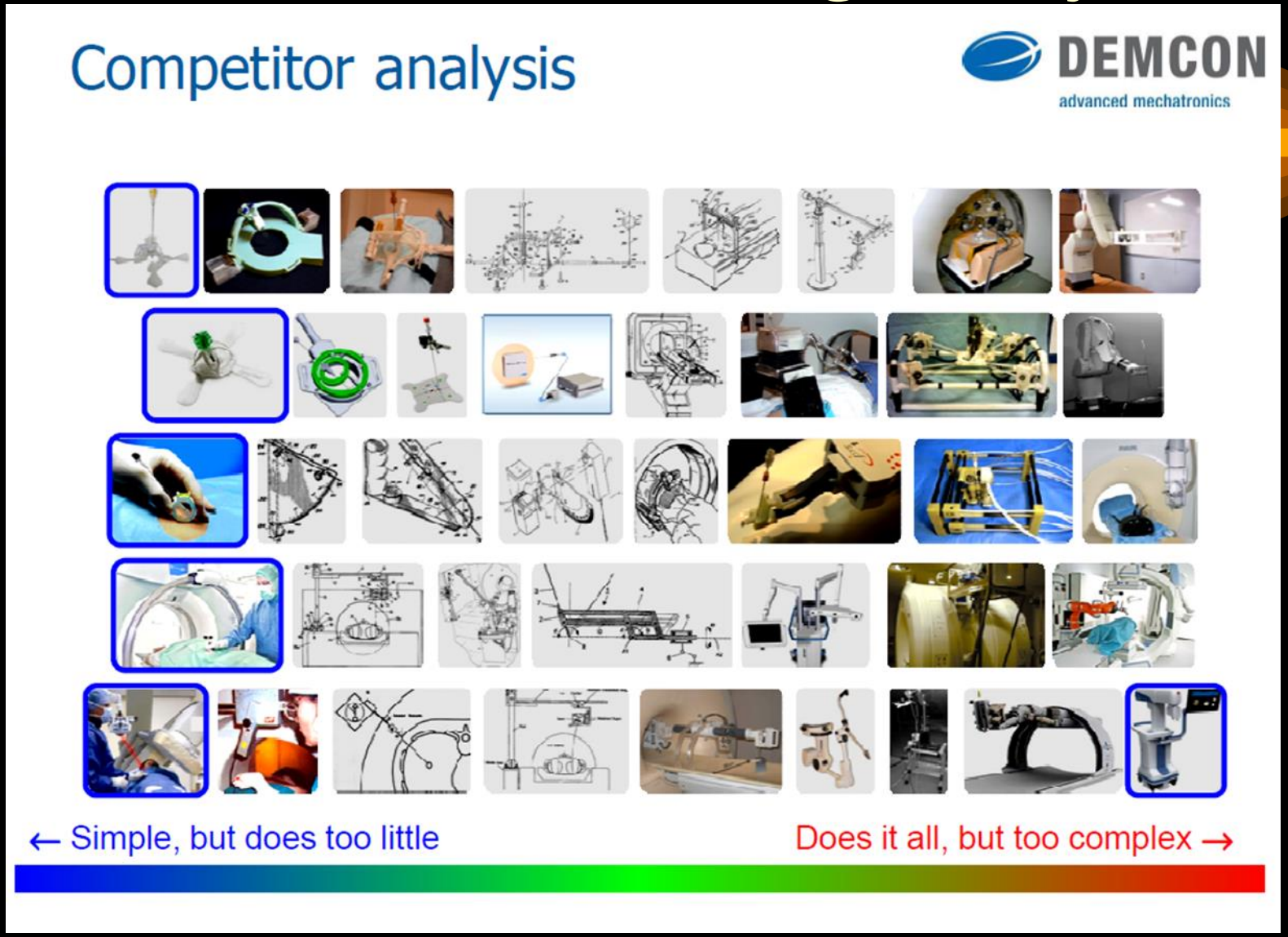
Laparoscopic
- US guided
- Less invasive

Percutaneous
- CT guided
- Minimal invasive


on the runway, descend to a point where the pilot sees the approach lights and completes landings visually. Pilot's ILS instrument shows aircraft's position relative to required flight path. Pilot flies toward instrument bar until it's centered over symbolic airplane, when both bars are centered the aircraft is on the correct flight path.
Flare-out at about 65 ft raises the aircraft's nose and the aircraft sinks gently onto the runway.
The main gears touch down first, followed by the nose gear, and the pilot reverses thrust.
Localizer beam
Glidepath beam
Outer marker
Middle marker
Inner marker
Glideslope transmitter sends
At the middle marker the aircraft is about 15 to 20 seconds
The outer marker indicates the distance to touchdown. The aircraft is locked onto the beams as it passes the outer marker.

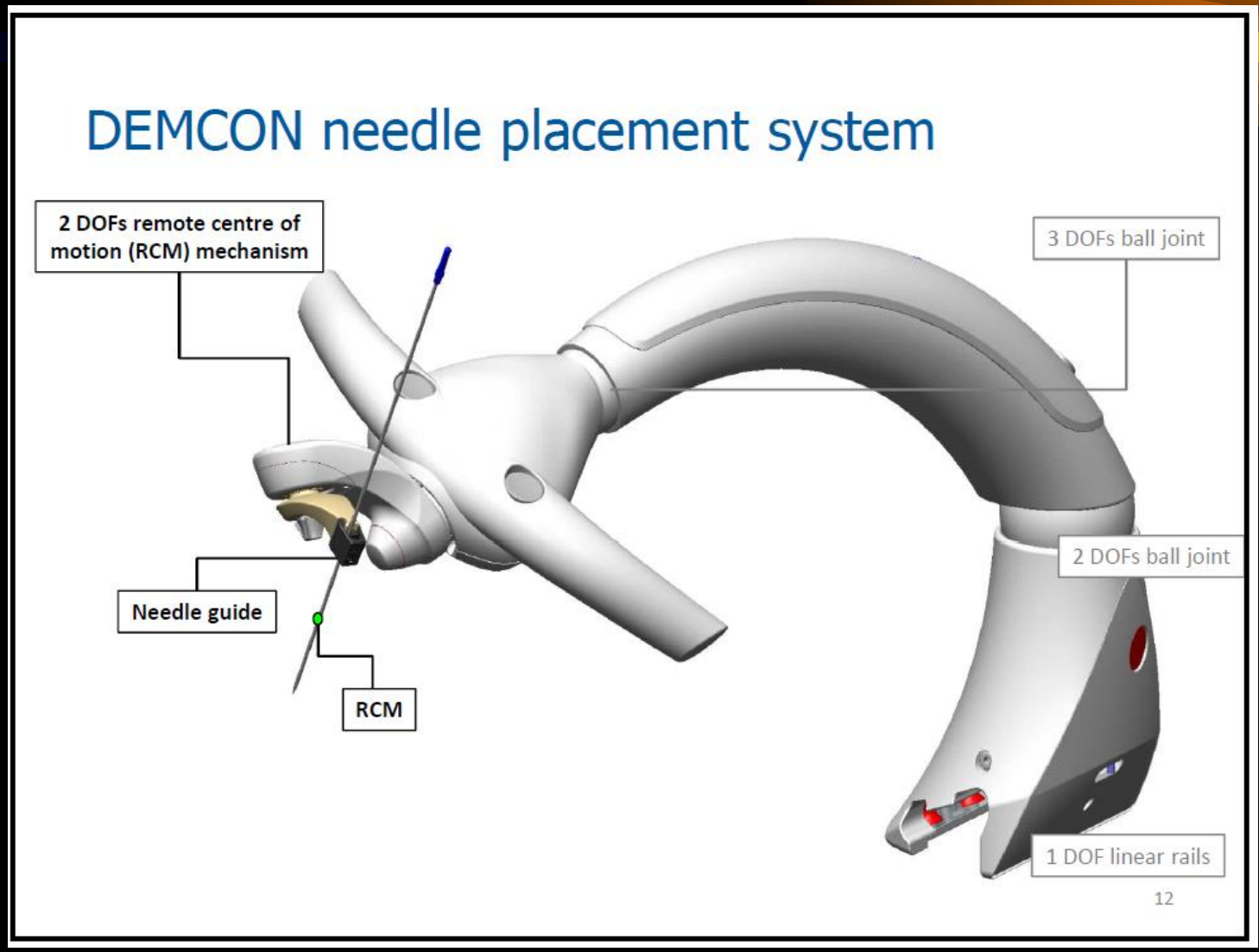

Z
Y
X

Robotic/navigation systems



Courtesy: Michiel Jannink, DEMCON

Currently phantom testing



What about results of RFA for CRLM

Four meta-analyses since 2009

- observational studies
- retrospective studies
- Bias ++
- No information on repeat treatments

OPEN ACCESS Freely available online

2012

PLOS ONE

Radiofrequency Ablation versus Resection for Colorectal Cancer Liver Metastases: A Meta-Analysis

Mingzhe Weng, Yong Zhang, Di Zhou, Yong Yang, Zhaohui Tang, Mingning Zhao, Zhiwei Quan*, Wei Gong*

Department of General Surgery, Xinhua Hospital, School of Medicine, Shanghai Jiaotong University, Shanghai, China

Green: in favour of liver resection

Table 4. Results of the meta-analysis for LR vs RFA in treatment of CLM.

Variables	Time interval	Subgroups	Nsuvival/N_{LR}	Nsuvival/N_{RFA}	LR vs RFA RR (95%CI)	p	I^2	Ref.
Overall survival	3 years	Total	802/1249	269/587	1.377(1.246–1.522)	<0.001	56.6%	26–34
		<3 cm	157/213	33/72	1.680(1.279–2.208)	<0.001	90.0%	26,31
		Solitary	306/481	150/290	1.263(1.109–1.439)	<0.001	64.0%	24,27,29–31,36
		Open	139/280	29/125	2.549(1.801–3.609)	<0.001	73.4%	26,30
		Perc	240/349	55/114	1.143(0.947–1.379)	0.014	48.8%	24,27,28,34,35
	5 years	Total	610/1249	182/587	1.474(1.284–1.692)	<0.001	21.7%	26–36
		<3 cm	123/213	20/72	2.168(1.442–3.260)	<0.001	84.4%	26,31
		Solitary	250/481	119/290	1.209(1.025–1.426)	0.024	0.0%	24,27,29–31,36
		Open	95/280	24/125	2.012(1.321–3.064)	0.001	81.8%	26,30
		Perc	188/349	39/114	1.426(1.062–1.915)	0.018	0%	24,27,28,34,35
Disease-free survival	3 years	Total	539/1171	135/519	1.735(1.483–2.029)	<0.001	65.4%	26–32,34–36
		<3 cm	98/213	18/72	2.238(1.480–3.385)	<0.001	97.7%	26,31
		Solitary	343/653	101/276	1.435(1.212–1.699)	<0.001	61.5%	27–31,36
		Open	117/280	25/125	2.309(1.544–3.453)	<0.001	82.5%	26,30
		Perc	137/329	9/114	3.853(2.065–7.190)	<0.001	6.6%	27,28,34,35
	5 years	Total	456/1171	83/519	2.227(1.823–2.720)	<0.001	71.8%	26–32,34–36
		<3 cm	81/213	17/72	1.104(1.039–1.173)	0.001	97.9%	26,31
		Solitary	324/653	64/276	2.014(1.624–2.499)	<0.001	78.8%	27–31,36
		Open	93/280	4/125	8.477(3.565–20.156	<0.001	70.5%	26,30
		Perc	118/329	5/114	3.763(1.762–8.033)	0.001	41.3%	27,28,34,35

Morbidity & mortality

- Green in favour of RFA

Table 5. Meta-analysis of the safety of liver resection and radiofrequency ablation.

Variables	LR	$N_{Morbidity}/N_{LR}$	RFA	$N_{Motality}/N_{RFA}$	RR (95%CI)	p	I^2	Reference
Morbidity	24.10%	220/913	9.98%	47/471	2.495(1.881–3.308)	0.009	60.70%	22,26,28–34
Mortality	0.31%	2/639	0.34%	1/294	1.391(0.306–6.326)	0.407	0.0%	22,26,28–32

LR: liver resection. RFA: radiofrequency ablation.
doi:10.1371/journal.pone.0045493.t005

UMCG results (BJS online)

Outcomes after resection and/or radiofrequency ablation for recurrences after treatment of colorectal liver metastases

J. Hof[1], M. W. J. L. A. E. Wertenbroek[1], P. M. J. G. Peeters[1], J. Widder[2], E. Sieders[1] and K. P. de Jong[1]

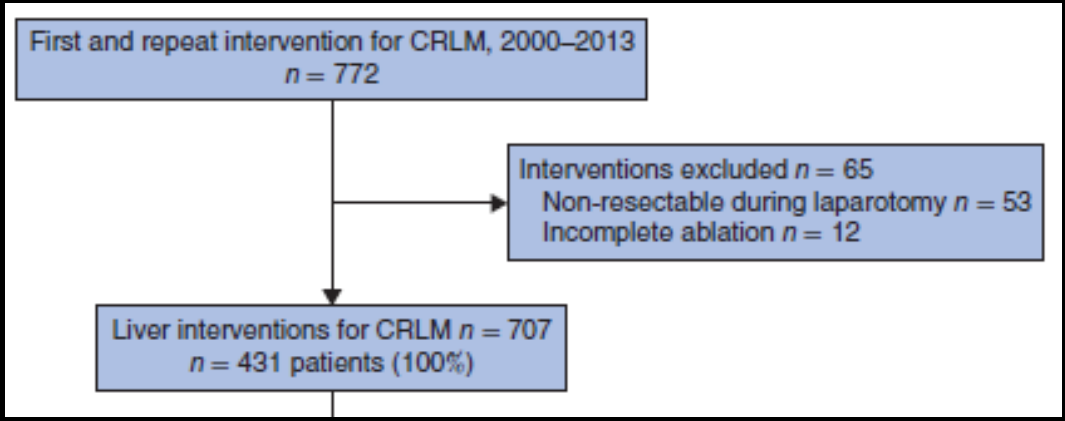


Table 1 Clinicopathological characteristics of all patients at time of first liver intervention

	Total ($n=431$)	Liver resection ($n=261$)	Open RFA ($n=26$)	Percutaneous RFA ($n=75$)	Resection + RFA ($n=69$)	P‡
Patient characteristics						
Age (years)*	62·9(9·4)	63·4(8·9)	60·2(10·8)	65·7(8·5)	59·3(10·4)§	
Sex ratio (M : F)	264 : 167	151 : 110	14 : 12	55 : 20	44 : 25	
Preoperative factors						
Neoadjuvant chemotherapy	138 (32·0)	55 (21·1)	7 (31)	32 (43)	44 (64)	< 0·001
Low CRS (0–2)	285 (66·1)	179 (68·6)	18 (69)	54 (72)	34 (49)	0·018
Synchronous CRLMs	201 (46·6)	107 (41·0)	18 (69)	31 (41)	45 (65)	< 0·001
DFI > 12 months	137 (31·8)	96 (36·8)	4 (15)	23 (31)	14 (20)	0·020
CEA > 200 ng/ml	26 (6·0)	20 (7·7)	0 (0)	2 (3)	4 (6)	
Characteristics of primary tumour						
Rectal site	196 (45·5)	115 (44·1)	13 (50)	34 (45)	34 (49)	
Node-positive disease	261 (60·6)	155 (59·4)	17 (65)	50 (67)	39 (57)	
Characteristics of CRLMs						
Diameter (cm)†	3·5 (2·0–5·0)	4·0 (2·5–5·7)¶	2·2 (1·4–3·0)	2·2 (1·5–3·5)	3·0 (2·0–4·4)	
> 1 CRLM	210 (48·7)	100 (38·3)	12 (46)	29 (39)	69 (100)	< 0·001
Type of resection ($n=330$)						< 0·001
(Extended) hemihepatectomy	183 (55·5)	160 (61·3)	–	–	23 (33)	
(Bi)segmentectomy	70 (21·2)	45 (17·2)	–	–	25 (36)	
Wedge resection	77 (23·3)	56 (21·5)	–	–	21 (30)	

Percut RFA more frequently applied in repeat procedures

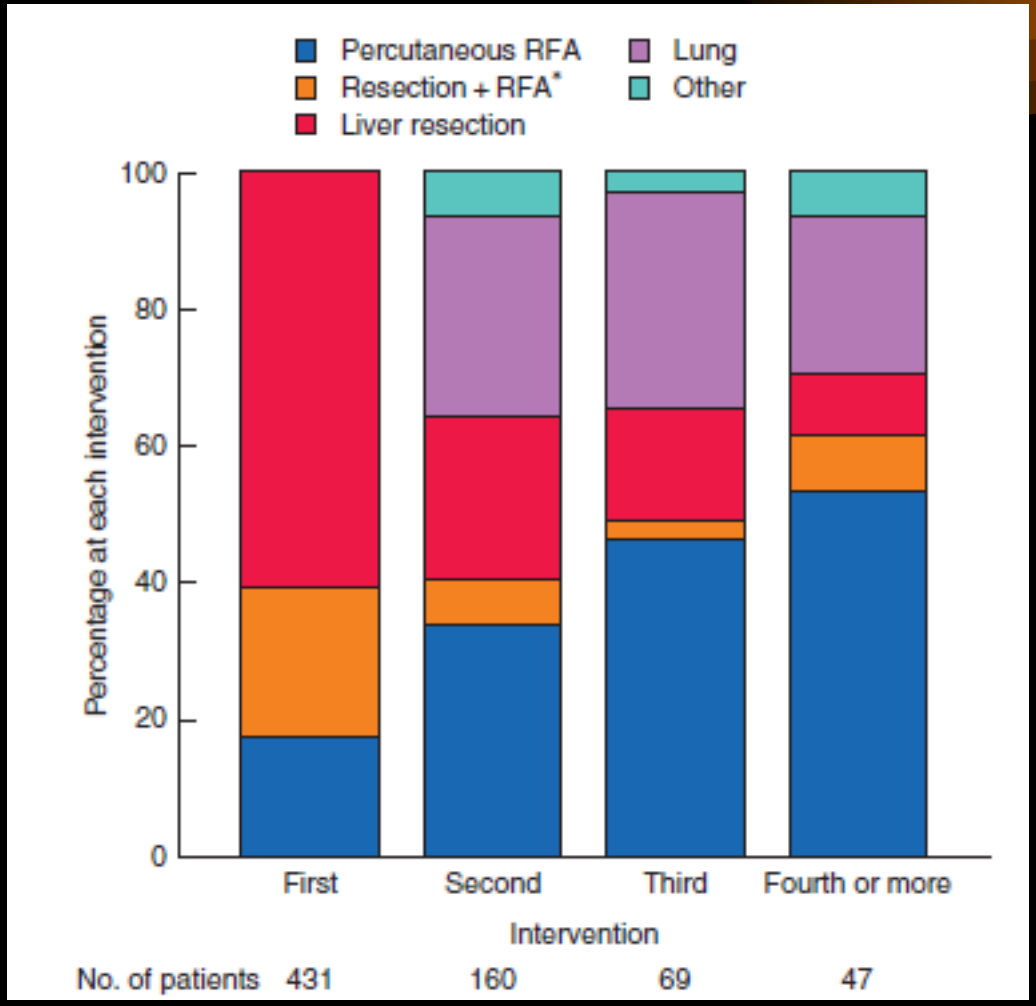
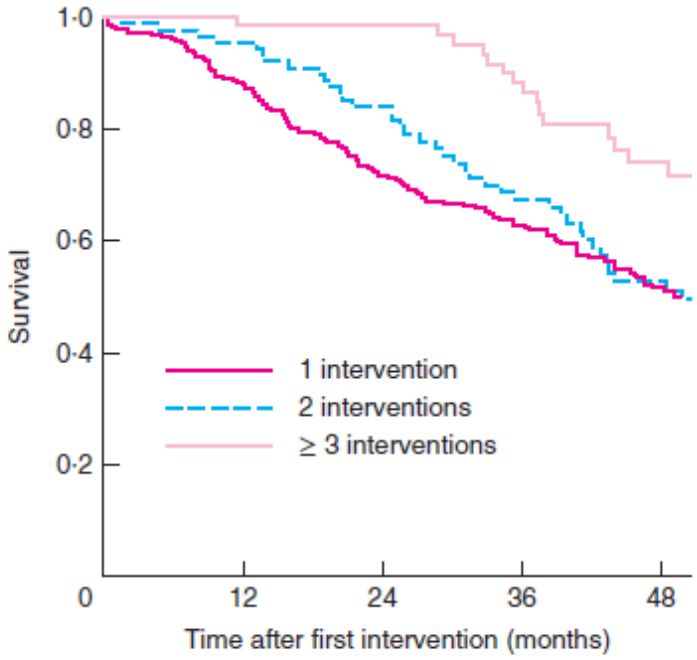
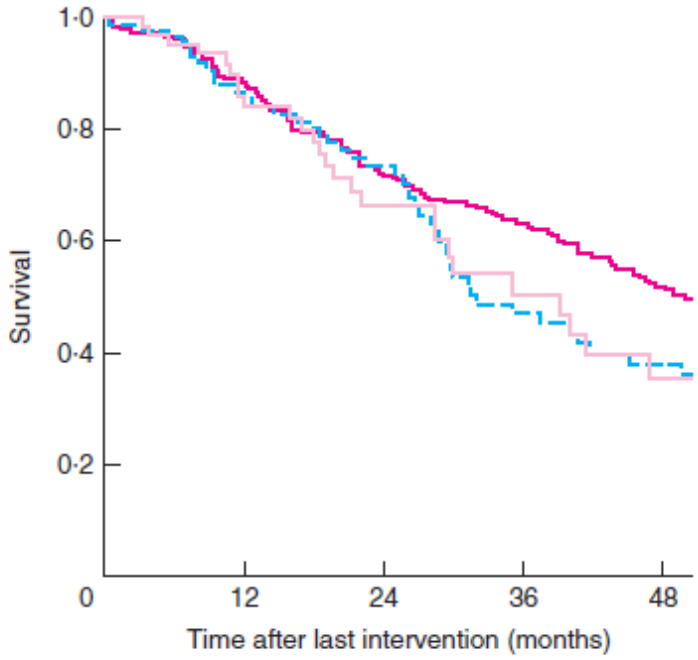


Fig. 3 Survival of patients undergoing one, two and three or more interventions measured from the date of the first, second and last intervention. OS, overall survival; DFS, disease-free survival



No. at risk					
1 intervention	270	230	162	131	94
2 interventions	91	87	70	50	32
≥ 3 interventions	69	68	64	50	31

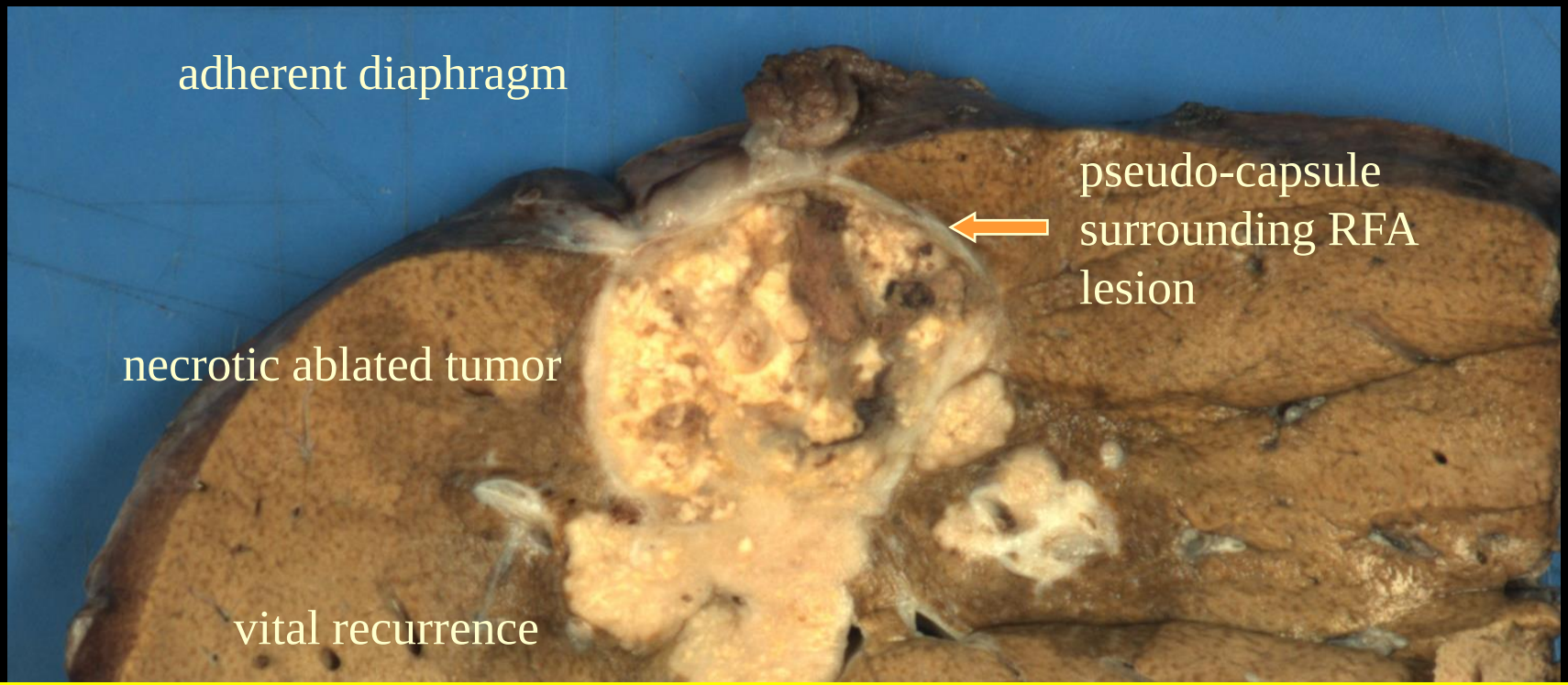
a Overall survival after first intervention



No. at risk					
1 intervention	270	230	162	131	94
2 interventions	90	65	52	27	21
≥ 3 interventions	69	44	27	14	8

b Overall survival after last intervention

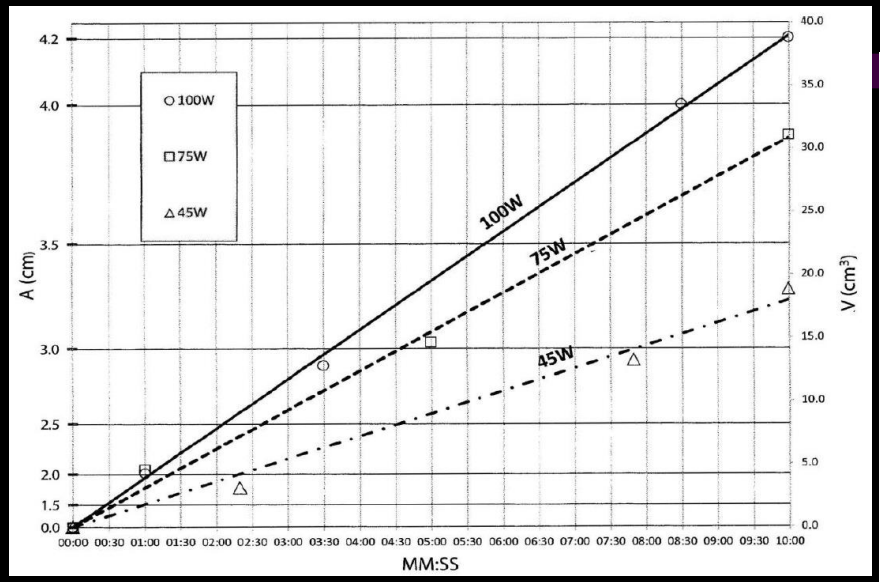
Fig. 4 Kapan–Meier overall survival curves measured from a date of first intervention and b date of last intervention for patients who had one, two, or three or more interventions. a $P = 0{\cdot}212$, b $P = 0{\cdot}043$ (log rank test)

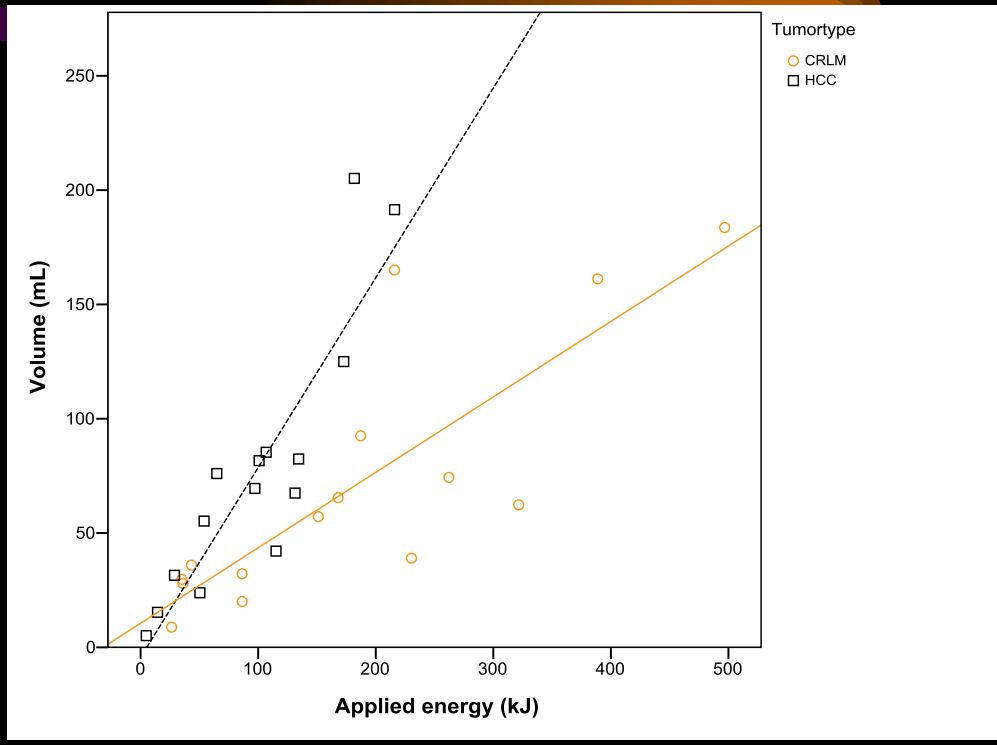


THE *problem of thermoablation: ablation site recurrence (ASR)*

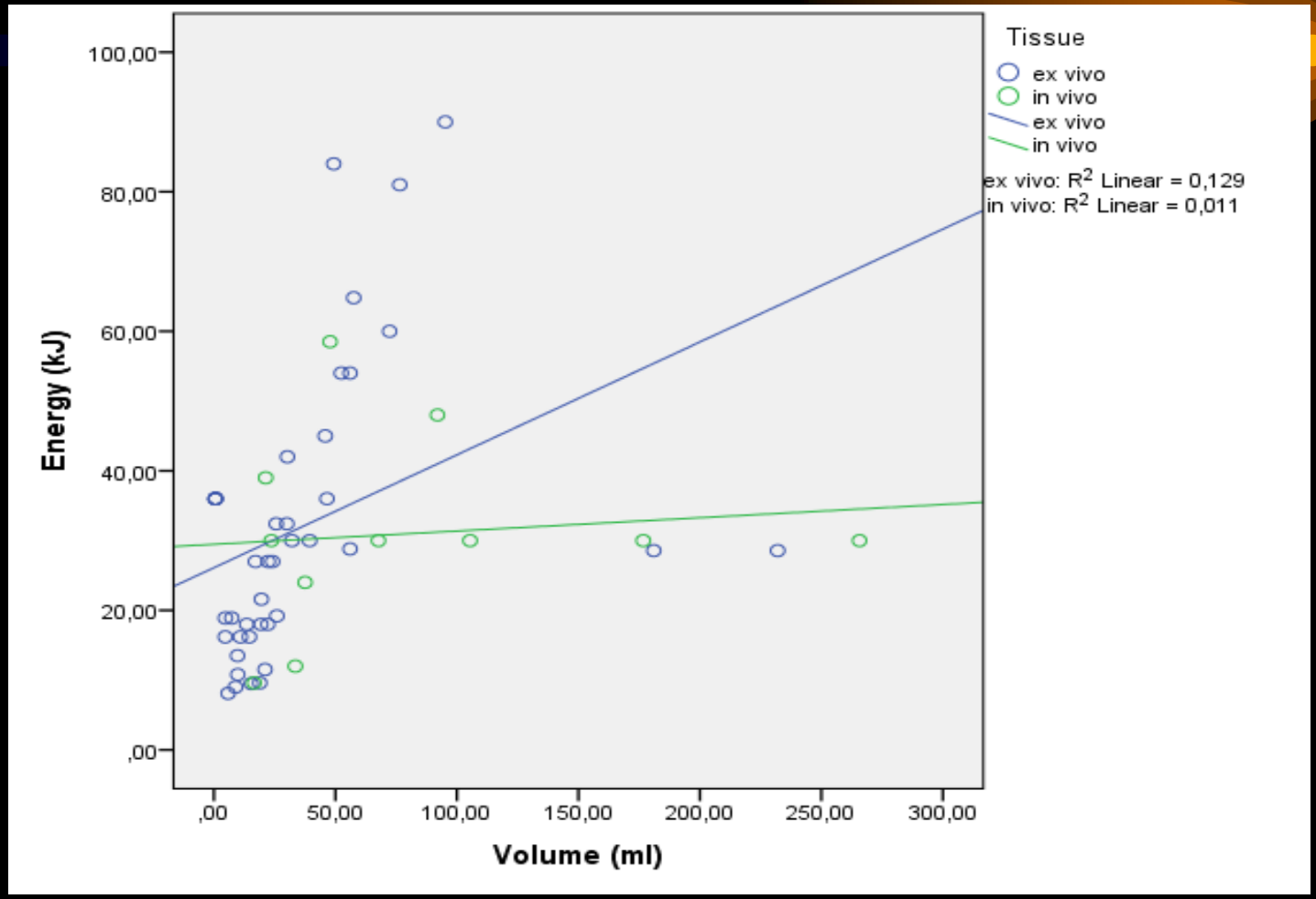
Reported incidence 5 – 42%

Relation applied energy and ablation zone volume in HCC vs CRLM





Relation applied energy and ablation zone volume in bovine/pig liver

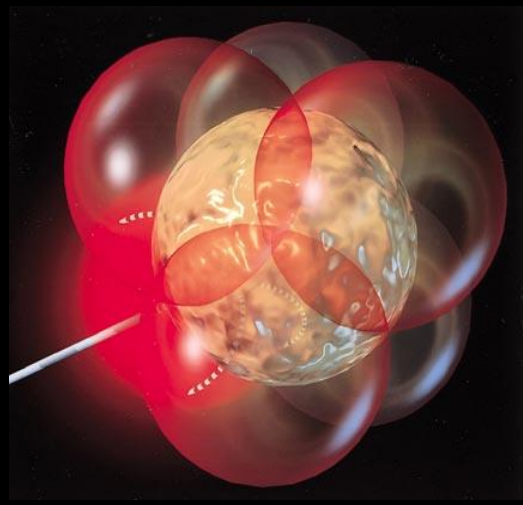


Comparison of PH and percut RFA

	PH	RFA
Admission time	5-10 days	2 days/outpatient
Logistics	1 PH/day	3 RFAs/day
Invasiveness	maximal	minimal
Costs	high	low

How to proceed and improve?

- Collaboration Technical University Twente and UMCG
  - FREENAVI trial
  - OPTISIZE trial
  - OPTIPOS trial: software based algoritm for overlapping positions in larger tumors



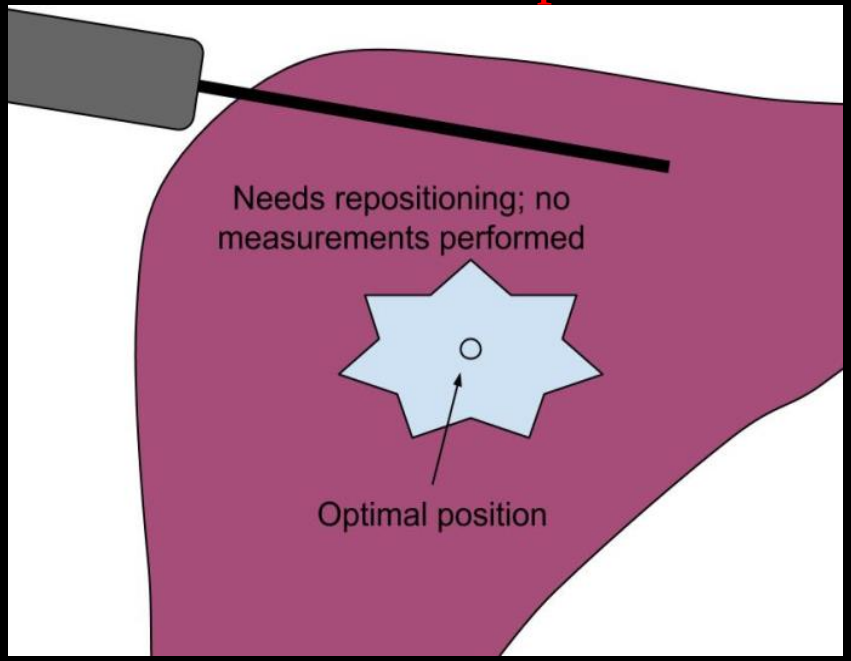
FREENAVI trial:

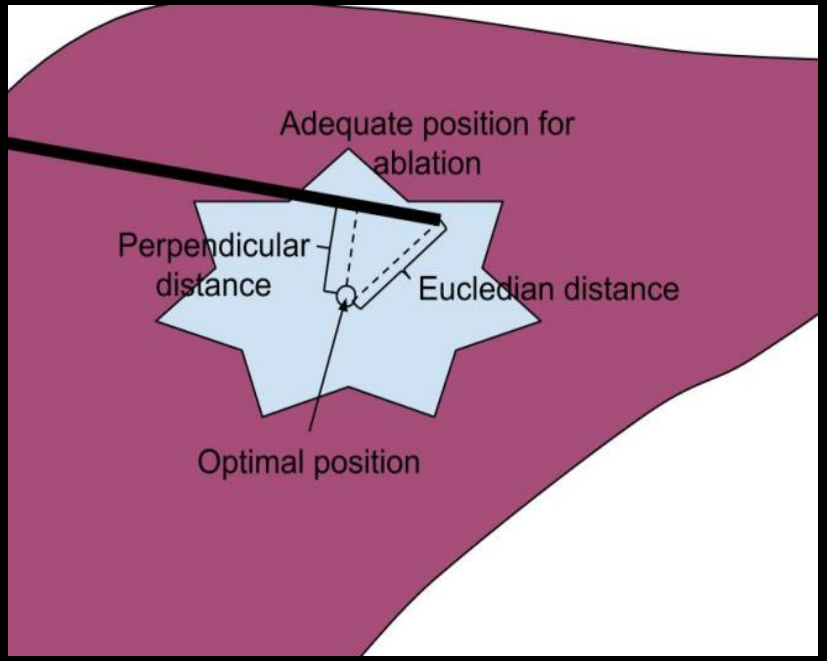
free-hand versus navigation guided needle insertion

Primary endpoint: number of needle repositionings

Sec endpoints: accuracy, targeting time, radiation dose, technical succe
rate

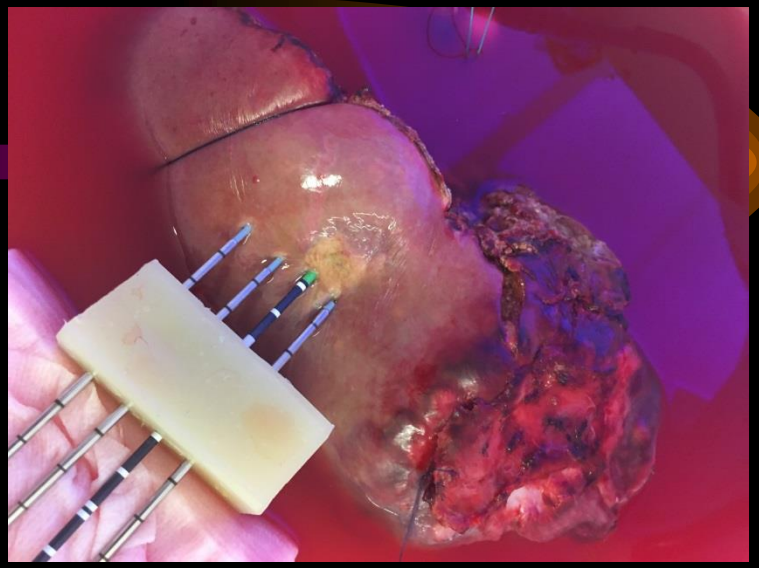
Evaluation at end procedure & 1-week CE CT scan

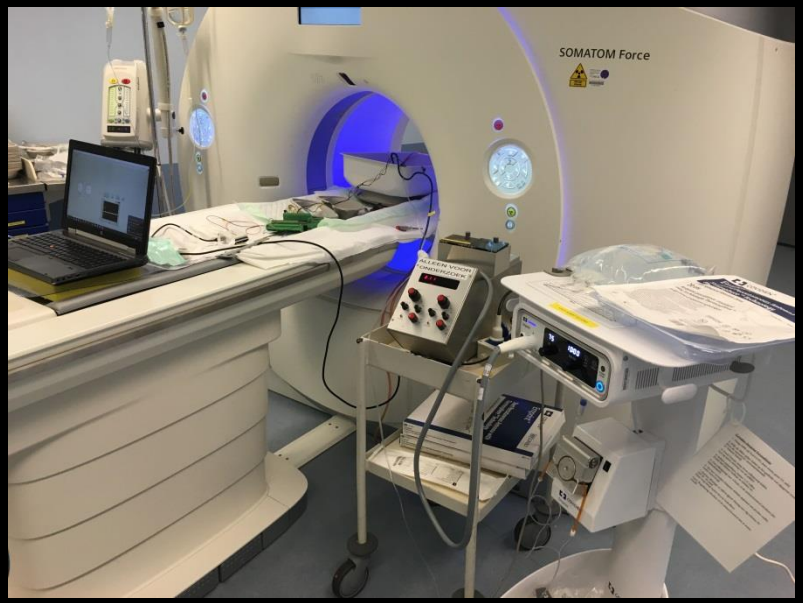




OPTISIZE study:

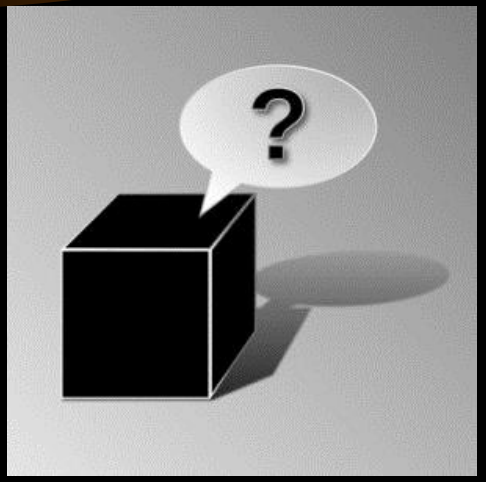
resected human liver specimens: various perfusion flowrates





Conclusions

- Ablation not inferior to liver resection in selected patients:
  - Intensive imaging follow up
  - Low treshhold fo repeat intervention if incomplete
  - Dedicated team of surgeon AND radiologist
- No RCTs: still needed?
- To Do:
  - more basic research
  - MRI compatible ablation systems
  - Flexibele MWA naalden (endoscopic approach)
  - Temperature monitoring at the border of the AZ
  - Tumor type and parenchyma type based algortims



Moor fire (Veenbrandje)

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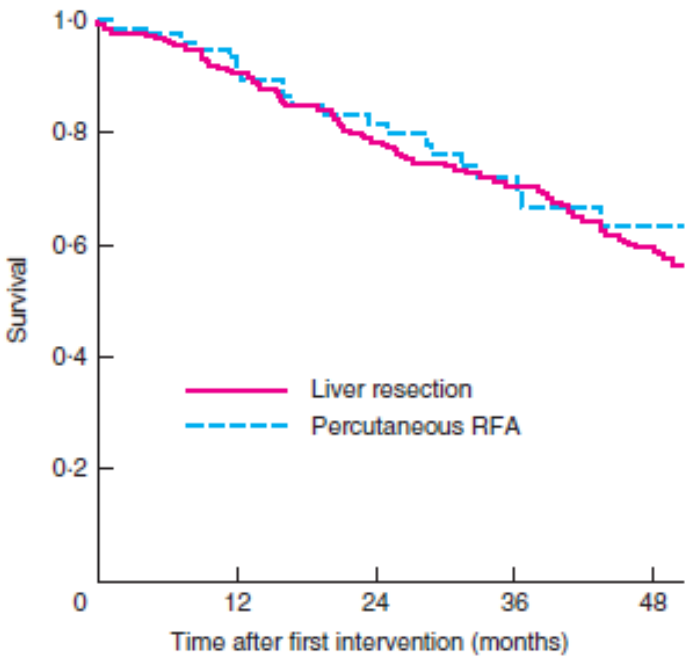
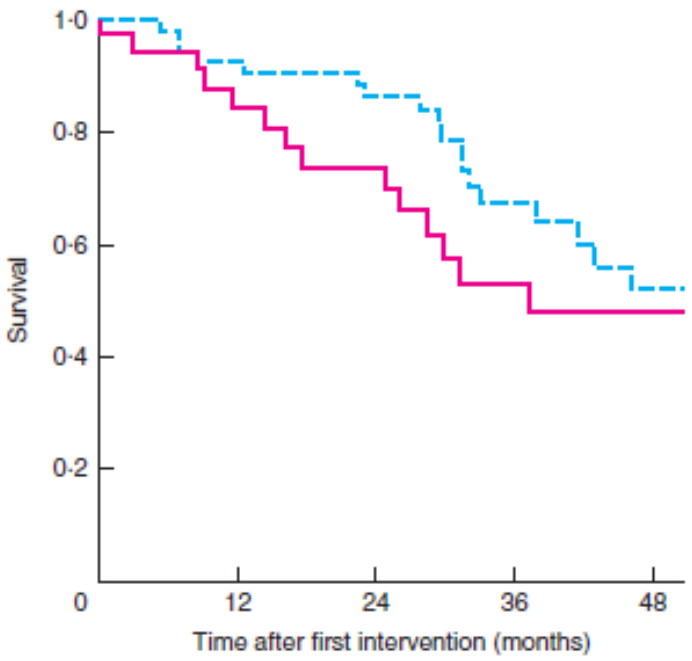


No. at risk

Resection	261	231	177	151	109
RFA	75	68	48	29	16

a Overall survival after first intervention



No. at risk

Resection	37	24	19	11	9
RFA	54	47	40	22	13

b Overall survival after second intervention

Fig. 5 Kapan–Meier overall survival curves **a** after liver resection *versus* percutaneous radiofrequency ablation (RFA) as first intervention and **b** after liver resection *versus* first percutaneous RFA as second intervention for first recurrence of metastatic colorectal cancer. **a** $P = 0{\cdot}979$, **b** $P = 0{\cdot}704$ (log rank test)

Table 2 Prognostic factors associated with overall survival identified by univariable and multivariable Cox regression analysis at the time of the first intervention in patients who had first and repeat interventions

	Univariable analysis		Multivariable analysis	
	Hazard ratio	*P*	Hazard ratio	*P*
Patient factors				
Age > 60 years	1·09 (0·83, 1·44)	0·539	–	–
Male sex	0·89 (0·67, 1·17)	0·397	–	–
Clinical risk score				
Node-positive disease	1·37 (1·03, 1·82)	0·033	1·40 (1·03, 1·90)	0·030
DFI < 12 months	1·24 (0·92, 1·66)	0·158	–	–
> 1 CRLM	1·58 (1·20, 2·07)	0·002	1·53 (1·12, 2·09)	0·007
CEA > 200 ng/ml	2·20 (1·36, 3·60)	0·001	1·89 (1·11, 3·22)	0·020
Size of CRLM > 5 cm	1·57 (1·17, 2·10)	0·001	1·54 (1·09, 2·17)	0·014
Primary tumour				
Rectal location	1·01 (0·77, 1·34)	0·923	–	–
Synchronous CRLMs	0·92 (0·70, 1·21)	0·549	–	–
Treatment				
Neoadjuvant chemotherapy	1·28 (0·95, 1·71)	0·100	1·07 (0·76, 1·52)	0·685
Liver resection only	0·78 (0·59, 1·04)	0·087	0·74 (0·54, 1·03)	0·071
Percutaneous RFA	0·91 (0·60, 1·35)	0·651	–	–
> 1 intervention	1·19 (0·90, 1·58)	0·226	–	–

Values in parentheses are 95 per cent confidence intervals. DFI, disease-free interval between primary tumour treatment and detection of colorectal liver metastases (CRLMs); CEA, carcinoembryonic antigen.