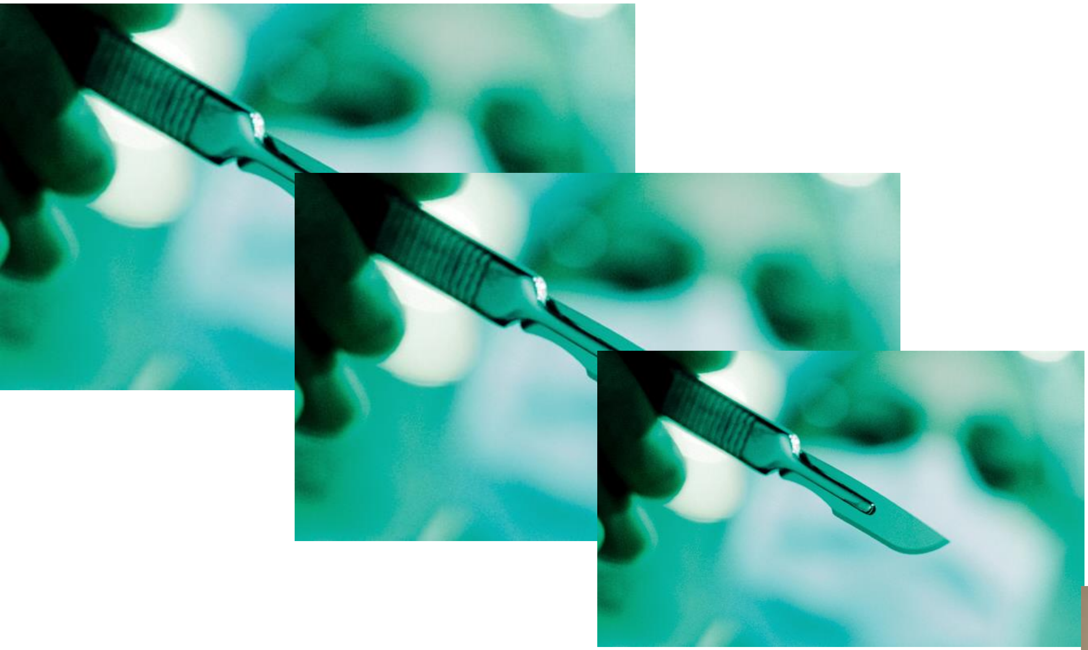
Local ablation for HCC



Pascale Tinguely

8th LIVER INTEREST GROUP Annual Meeting

GF – SSA Dec 2017

Curative treatments for HCC

- Resection, transplantation, ablation
- 5 y Overall Survival 50 – 75 %

- ~ 20 - 27% of patients candidates for surgical treatments
  - Minus 10% when applying restrictive criteria
  - Plus 10-15% with thermal ablation

- Ablation techniques
  - RFA, MWA, PEI, Cryoablation, AAI, IRE, LITT, HIFU

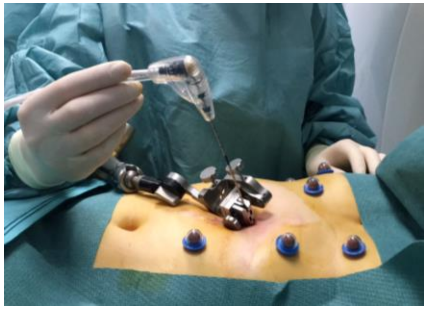
Bolondi et. al, Semin Liver Dis 2012

Ablation techniques

- **Radiofrequency ablation (RFA)**
  - Resistive tissue heating:
  - Alternating electrical current causes oscillation of H_2O molecules (375 to 500 kHz)
  - Dependent on
    - Electrical conductivity
    - Impedance
  - ➢ Temperatures ~ 100° C
  - ➢ Monopolar vs. multipolar devices

- **Microwave ablation (MWA)**
  - Dielectric hysteresis:
  - Electromagnetic field causes continuous rotation of H_2O molecules (0.9, 2.45 GHz)
  - Frictional heating of H_2O-rich tissues
  - ➢ Homogenous distribution of coagulative necrosis
  - ➢ Temperatures ~ 160-180° C in few seconds

- **Irreversible Electroporation (IRE)**
  - High frequency high voltage short electrical pulses
  - Nanopores in cell membrane leading to apoptosis
  - Extracellular matrix speared -> no damage to bile ducts/ blood vessels
  - ➢ Minimal heat production

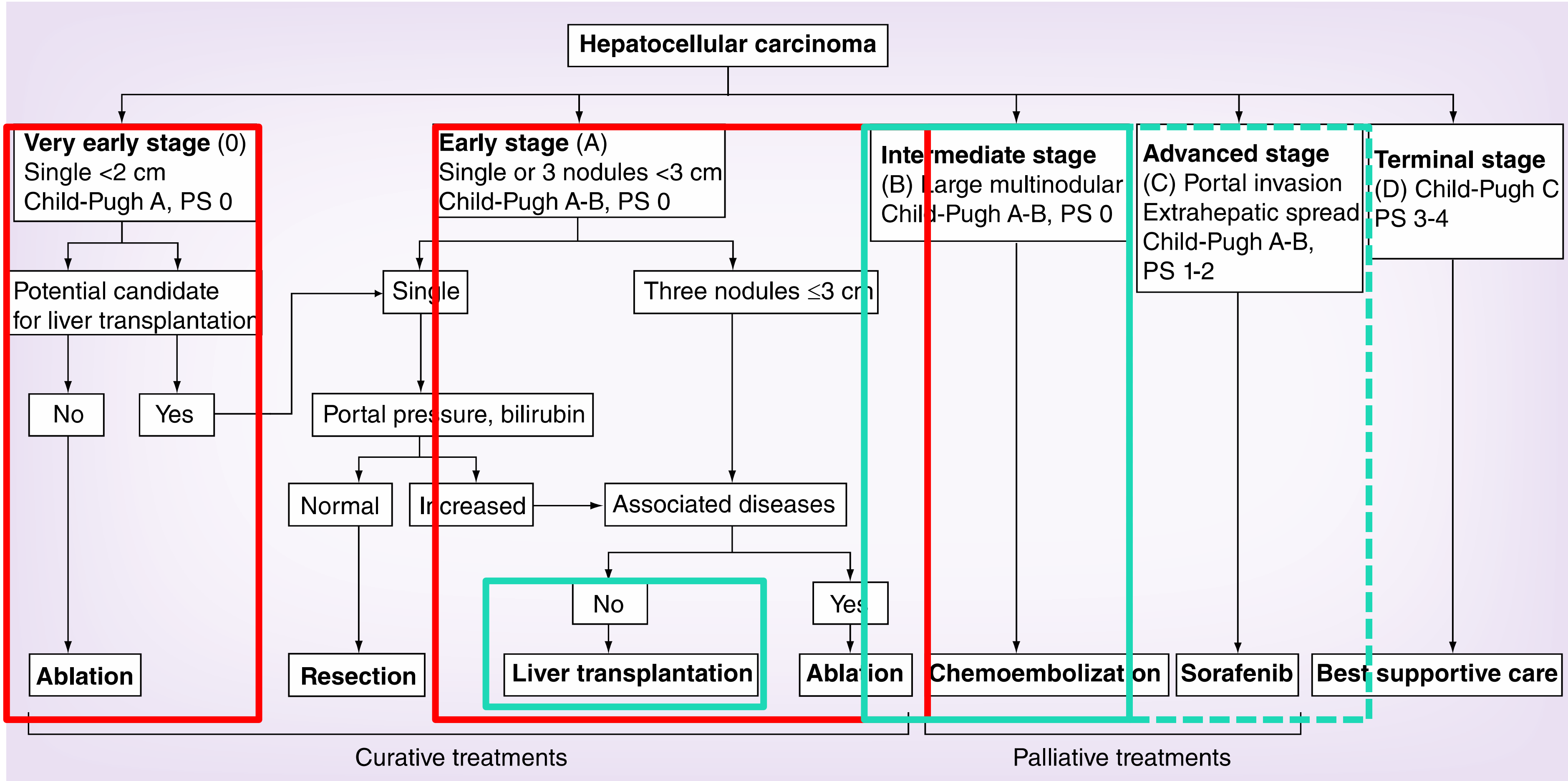


Ablation Techniques

Technology	Potential Advantages	Potential Disadvantages
RFA	• High rates of local control in tumors 3 cm or smaller • Established safety profile • Known limitations • Experience in combination treatments (HCC) • Widely available	• High rates of incomplete ablation in tumors larger than 3 cm • Heat sink effect in perivascular tumors • Potential risk of thermal injury to critical structures • Variability in RFA devices
MWA	• Potential to treat tumors larger than 3 cm more effectively • Less impacted by heat sink effect • Ability to activate multiple probes at the same time • No grounding pads required	• Limited efficacy data (predictability and reproducibility) • Limited safety data • Potential risk of thermal injury to critical structures (and vessels?) • Variability in MWA devices
CRYO	• Ability to activate multiple probes at the same time • Ability to image the ice-ball formation	• Insufficient clinical data • Risk of bleeding • Risk of cryoshock
IRE	• Potential to treat tumors located in the vicinity of critical structures • Heat sink effect not relevant	• Insufficient clinical data • Neuromuscular blockage and cardiac gating required

Lencioni R et al, Liver Cancer 2015

Indications – BCLC/ outside BCLC



Forner A, et al. Hepatocellular carcinoma. Lancet 2012

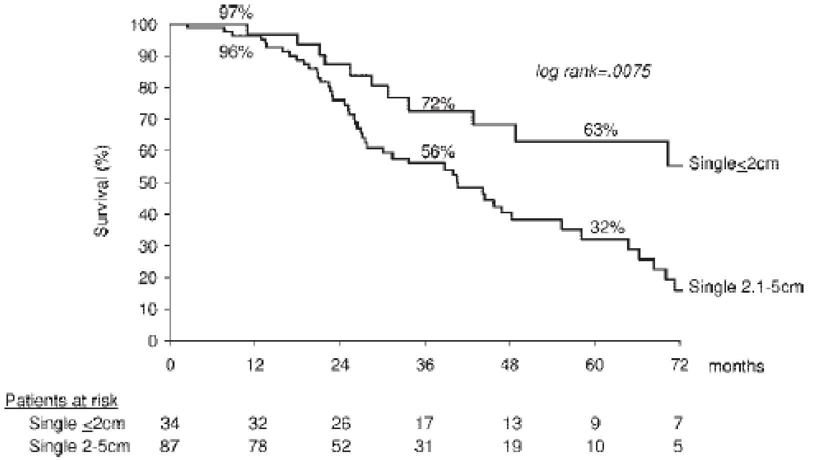
Outcomes of local ablation

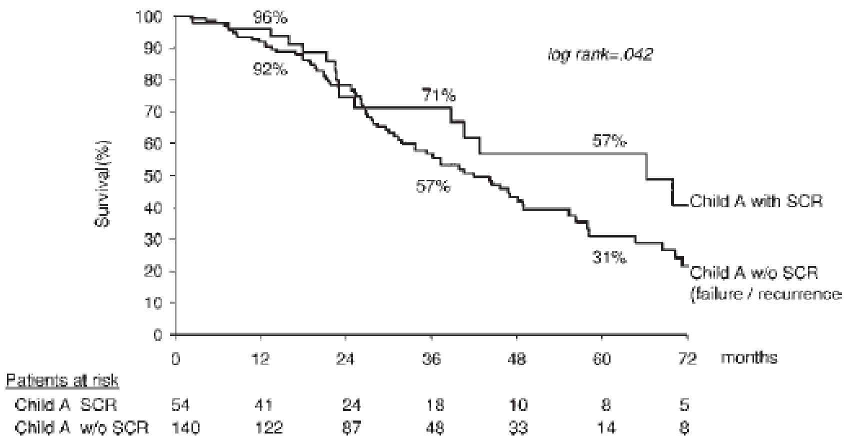
- Strongest prognostic variables:
  - Child Pugh Score
  - No & size of tumors (single, <2cm)
  - Initial complete response

- Local recurrence rates 7 – 24%
- Major complications 4%

➢ 5y OS 40 – 75 %

- !! 80% of the patients develop recurrent disease -> Long-term survival influenced by multiple different interventions





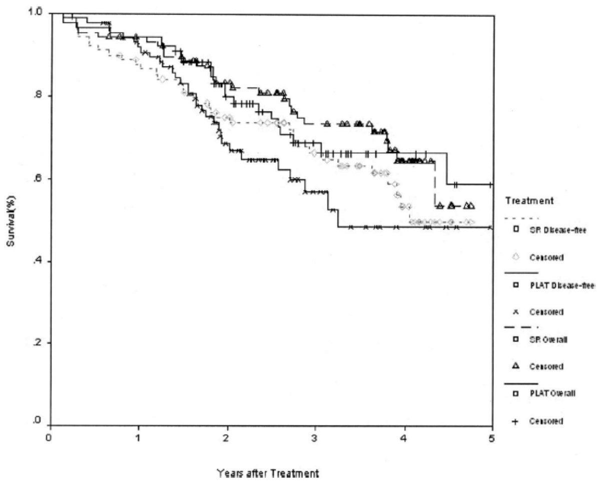
Lencioni et. Al, Hepatology 2010
Sala et. al. Hepatology 2004

Ablation (RFA) versus resection: controversy

- Most data favouring hepatic resection [1,2]
  - Higher OS/ RFS/ DFS

- HOWEVER other data shows [3,4]
  - Resection > RFA regarding local recurrence and DFS
  - No significant differences in 1,3,5 y OS, DFS
  - Some series even for tumors up to 5cm

➢ BUT: lower morbidity/ mortality



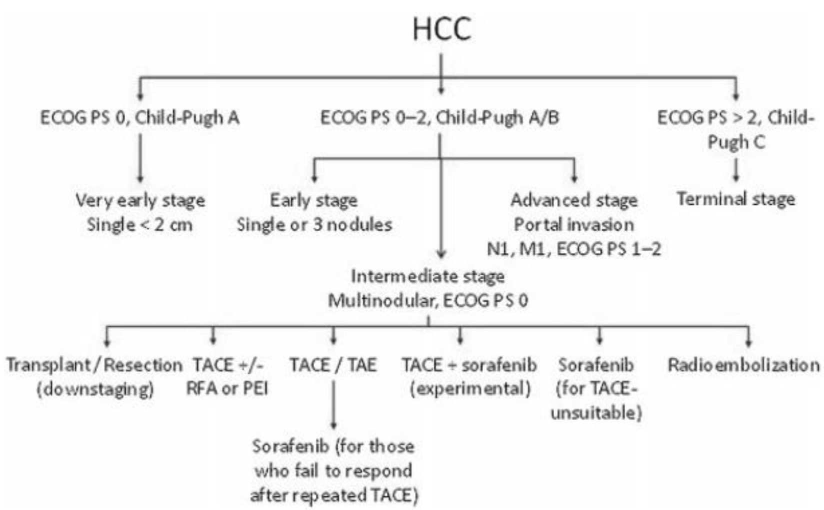
[1] The Cochrane Library 2013
[2] Feng Q, et al. J Cancer Res Clin Oncol 2015

[3] Tiong L, et al. British Journal of Surgery 2011
[4] Chen L et. Al. Ann Surg 2006

Indications beyond BCLC?

1. Intermediate stage B?

- 5 y OS within Milan: 41–77% vs. outside Milan: 20–75%[1]
- Highly heterogenous population [2]
  - Tumor burden/ liver function
  - Disease etiology/ comorbidities
- Varying benefits from TACE



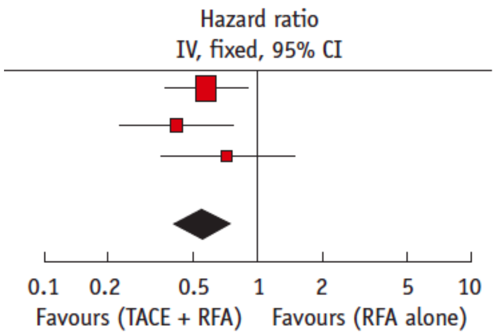
BCLC Sub-Stage	B1	B2	B3	B4
CPT score	5-6-7	5-6	7	8-9*
Beyond Milan and within Ut-7	IN	OUT	OUT	ANY
ECOG (Tumor Related) PS	0	0	0	0-1
PVT	NO	NO	NO	NO
1st option	**TACE**	TACE or TARE		**BSC**
Alternative	LT TACE + ablation	SOR	Research trials TACE SOR	LT**

[1] Tiong L, et al., British Journal of Surgery 2011
[2] Bolondi et. al., Semin Liv Dis 2012

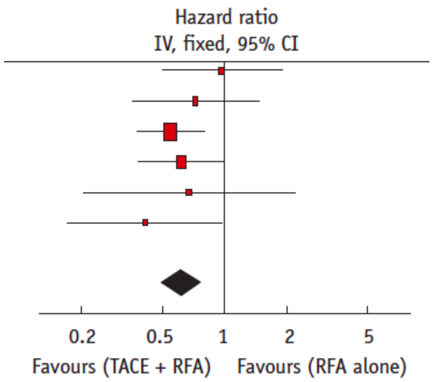
Indications beyond BCLC?

2. Combination therapies ?

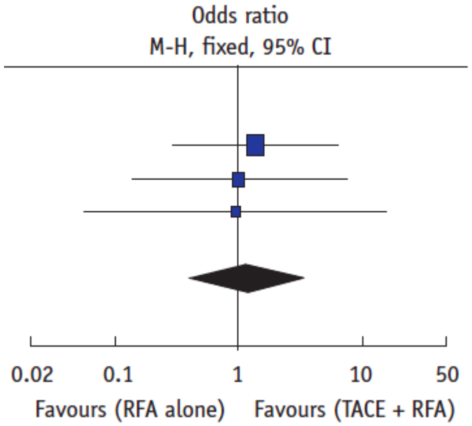
– OS/ DFS (TACE & ablation) > monotherapy
– Synergistic effects of both treatments
– No validated inclusion criteria/ optimal treatment schedule



OS



DFS



Morbidity

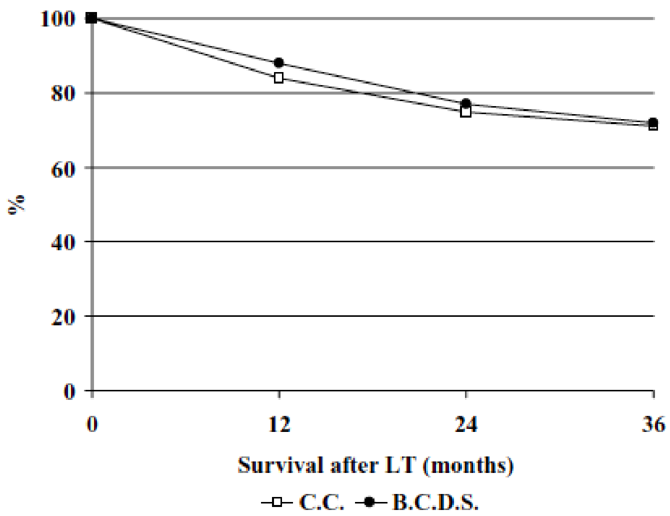
Wang et. al, Korean J Radiol, 2016

Indications beyond BCLC?

3. Bridging/ downstaging?

- EASL: Bridging with ablation (1st choice) or TACE (2nd choice) if waiting times exceed 6 month

- Downstaging of patients initially within Milan versus outside Milan
  - Few data favouring concept
  - EASL: place patient on hold until downstaging is achieved and maintain for 3 month



Lu et. al, Hepatology 2005

Ravaioli et. al, Am J Transplant 2008

Microwave ablation for HCC

- Recent review RFA vs. MWA (3 RCT):
  - Complete response, local recurrence, OS similar
  - Subgroup tumors > 3cm: trend towards MWA> RFA
  - Postintervent. fever: MWA > RFA
  - Local recurrence MWA 14% (n = 480)

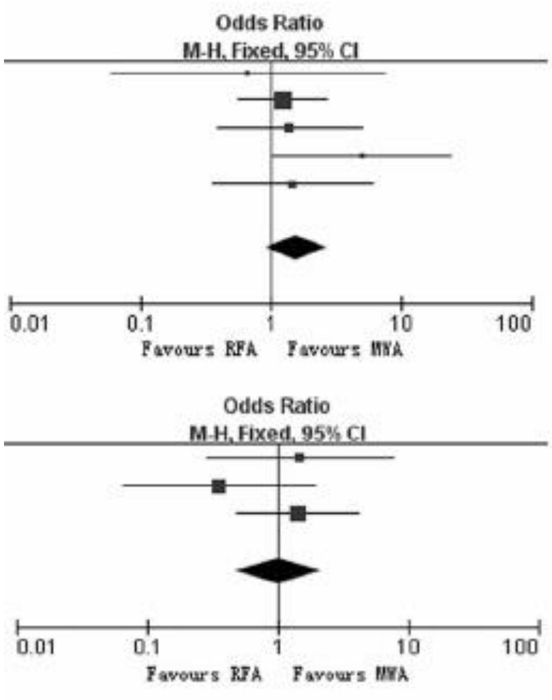


Table 3 Meta-analysis of effects of microwave ablation versus radiofrequency ablation on HCCs

	CTA	1-year SR	3-year SR	OS	LTR	Major complications
Cohort studies	MWA 86.7–100%	MWA 81.6–98%	MWA 49–79%	HR 0.80	OR 0.95	OR 1.23
	RFA 83.9–100%	RFA 67.6–98.7%	RFA 37.6–82.7%	95% CI 0.62–1.04	95% CI 0.64–1.41	95% CI 0.45–3.37
	$P > 0.05$	$P > 0.05$	$P > 0.05$			
	[9–14]	[9–14]	[9–14]	[9–14]	[9–14]	[10–12]
RCT	MWA 89.1–96.1%	NA	NA	HR 0.58	OR 1.19	OR 0.80
	RFA 89.5–95.8%			95% CI 0.22–1.56	95% CI 0.20–7.06	95% CI 0.26–2.49
	$P > 0.05$					
	[15–17]			[15, 17]	[15–17]	[15, 16]

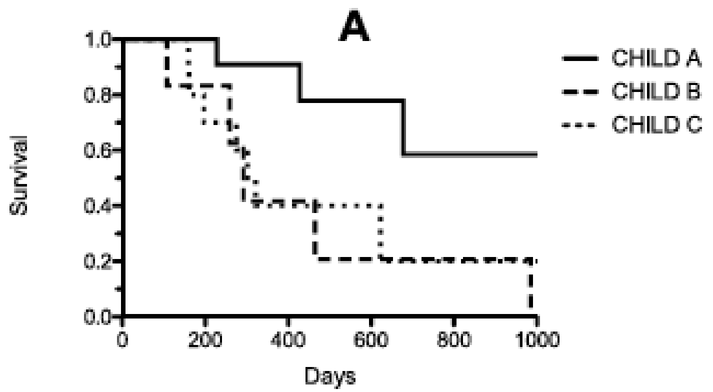
CTA complete tumor ablation, *SR* survival rates, *OS* overall survival, *LTR* local tumor recurrence, *MWA* microwave ablation, *RFA* radiofrequency ablation, *HR* hazard ratio, *RCT* randomized controlled trial, *NA* not applicable. Those in *square brackets* were numbers of references

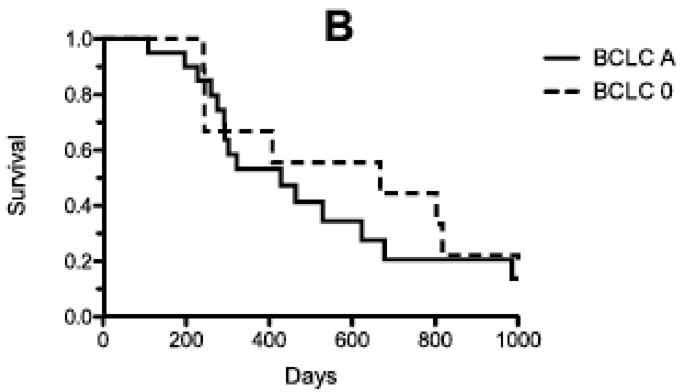
Luo et al. W J Surg Oncol, 2017

IRE for HCC?

Year	Authors	Patients	Tumor	IRE sessions	Tumor size, mm	Voltage, V	Duration, μs	Complete ablation rate		LRFS	
								HCC	Metastases	Rate	Time
2011	Thomson et al[35]	25	N/A	63	10–80	1500–3000	70	.83	.50	N/A	N/A
2012	Kingham et al[36]	28	65	31	5–50	1500–3000	70	N/A	N/A	.93	6 months
2013	Cannon et al[37]	44	44	48	11–110	1500–3000	100	1.00	1.00	.95	6 months
2014	Hosein et al[38]	28	58	36	12–70	N/A	N/A	N/A	.97	.79	2 years
2015	Cheng et al[39]	6	6	6	6–26	1500–3000	90–100	1.00	N/A	1.00	3–17 months
2015	Sugimoto et al[40]	5	6	6	11–28	1500–1800	70	.83	N/A	1.00	244±55 days
2016	Padia et al[41]	20	N/A	N/A	10–33	1500–3000	20–100	.90	N/A	1.00	1 year
2016	Niessen et al [42]	34	65	N/A	2–71	1500	90	1.00	.95	.80	6 months

HCC = hepatocellular carcinoma, IRE = irreversible electroporation, LRFS = local recurrence free survival, N/A = not available.





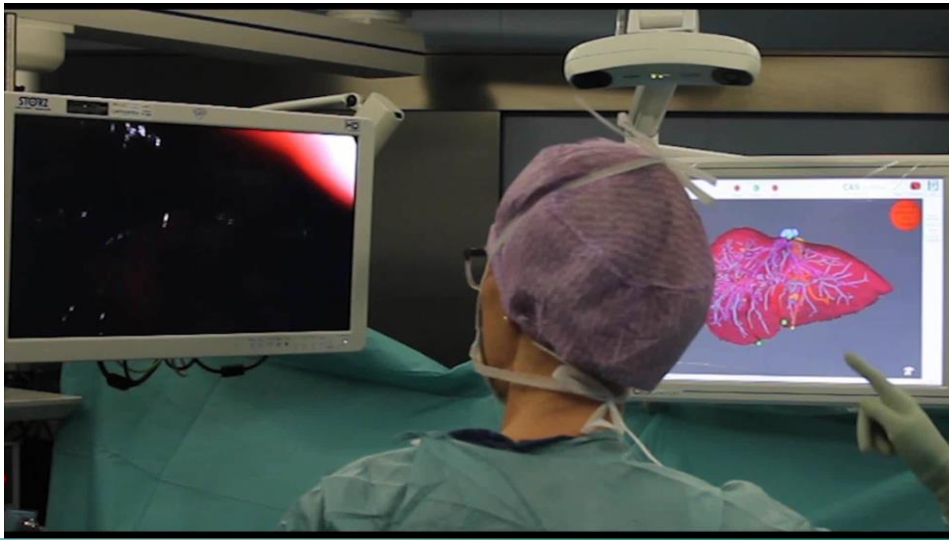
Lyo et. al. Medicine 2017

Niessen et. al. Sci Rep 2017

Image-guidance

- Goal: accurate, complete ablation, 0.5 – 1 cm rim
- Access: open, laparoscopy, percutaneous
- Image-guidance: US, CT, MRI

➢ Stereotactic navigation systems
  - Enhanced localization of intrahepatic lesions
  - Enhanced precision in tumor targeting
    - Targeting trajectories
    - “Vanishing” lesions



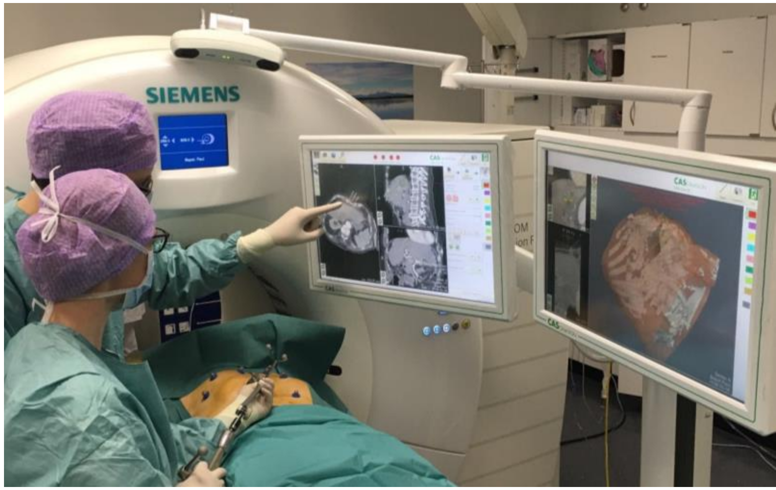
Lencioni R et al, Liver Cancer 2015

Tinguely et. al. Surg Endosc 2017

Stereotactic image-guided procedures

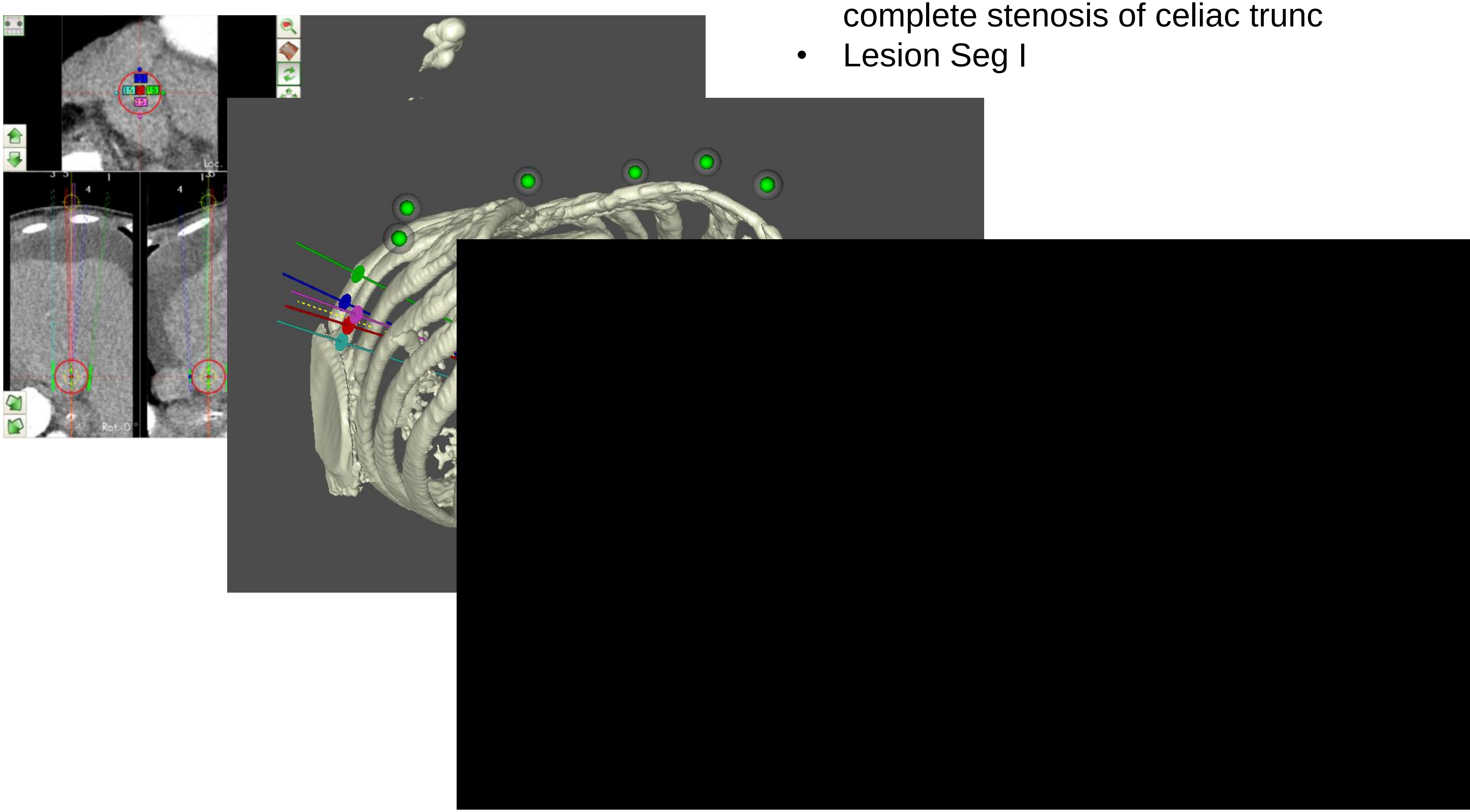
- Percutaneous navigated ablations Bern 2015 -2016
  - 110 patients, 190 malignant liver tumors (97 MWA, 4 IRE)

- 60 HCC patients
  - Target lateral error: 3.4 +/- 2.0 mm
  - Time for probe placement: 8.8 min
  - Complications: 3 % (Grade I/IIIb)
  - LOS 1 day (1 – 13)
  - 6 month follow-up:
    - Local recurrence rate: 15%
      - Not influenced by subcapsular location/ vessel proximity/ BCLC
    - Intrahepatic progression: 43%
  - 8 transplanted (TTT 8.7 month)

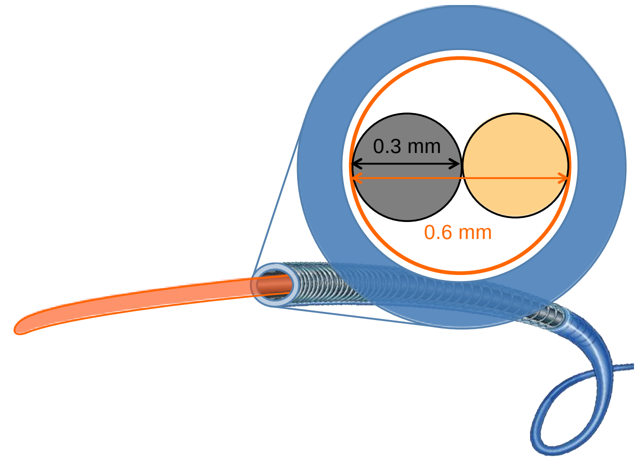


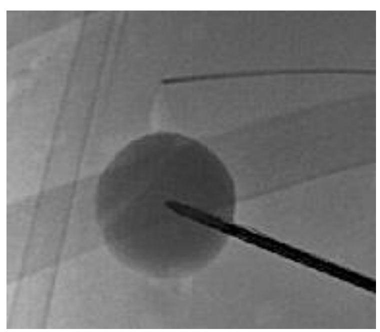
Stereotactic IRE for HCC

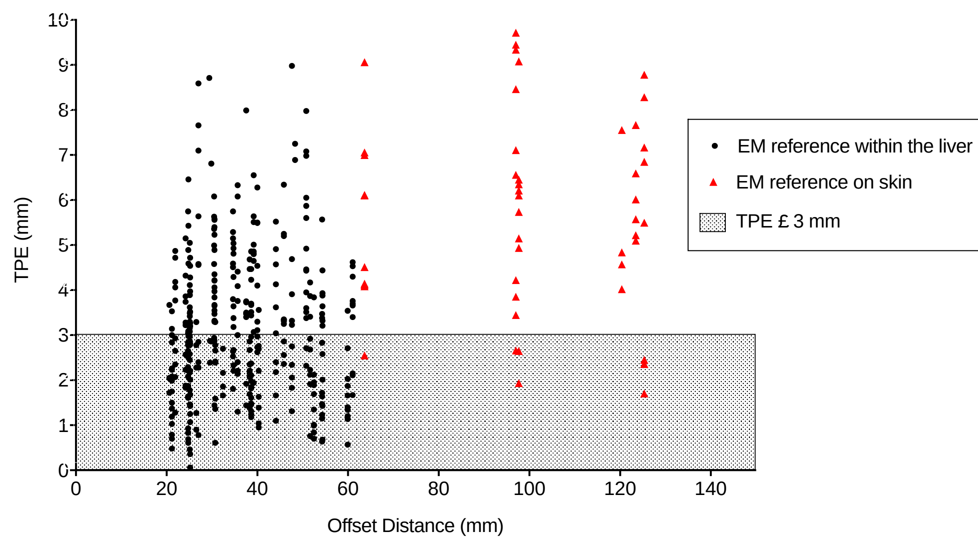
- Multifocal HCC, cryptogenic origin
- Portal hypertension, G2 Varices
- St.p. 3x MWA
- St.p. angiograpy (attempt TACE)-> complete stenosis of celiac trunc
- Lesion Seg I



MOSCAT for HCC – Endovascular tumor tracking for combined ablation & TACE







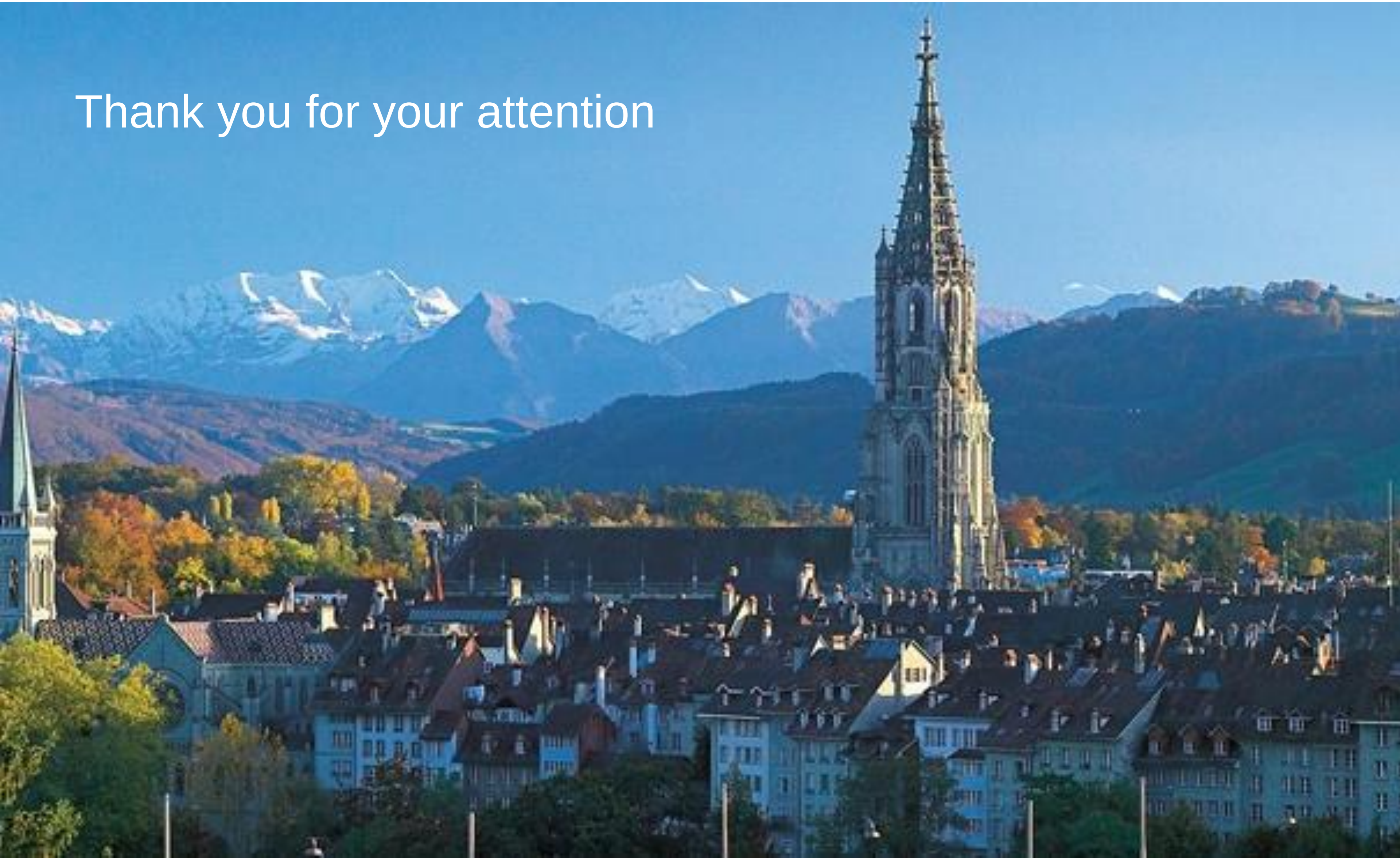
Schwalbe M, Tinguely P et al. MITAT Nov 2017

Tinguely P et al. Under review at PLOS ONE

Conclusion – Local ablation for HCC

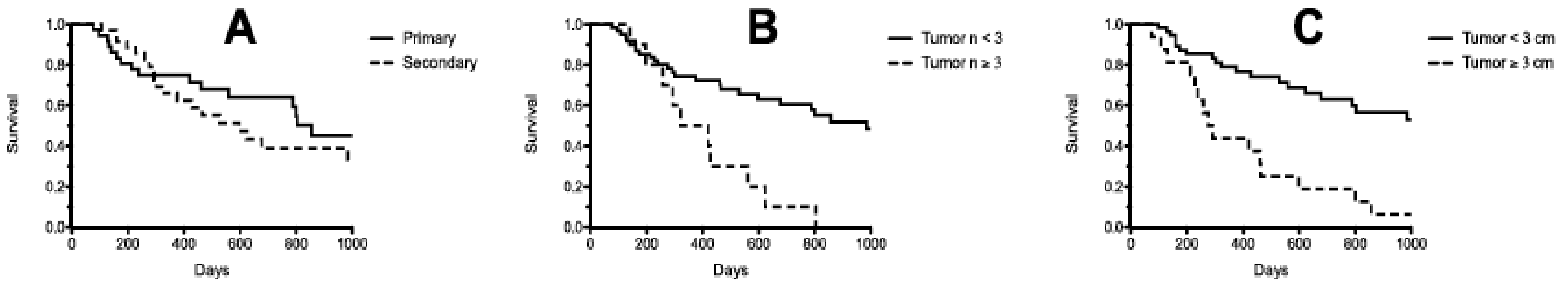
- Tissue-sparing, locally destructive treatment
- Low morbidity, satisfying long-term outcome

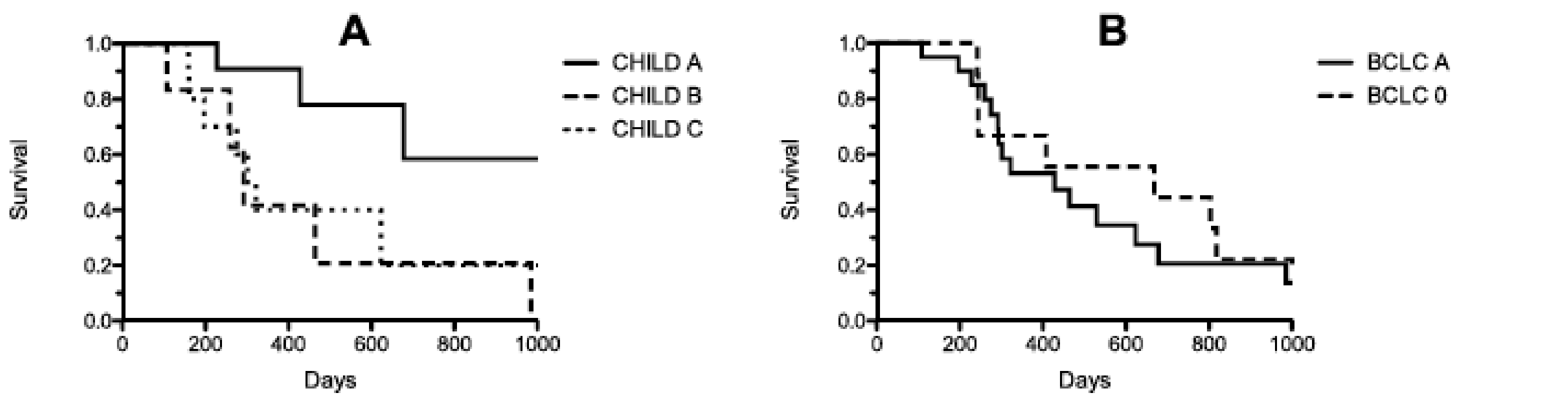
- Challenges -> *aims*
  - Widen boundaries ablation/ combination therapies*-> widen indications for pot. curative therapy*
  - Accuracy of probe positioning to create overlapping ablation zones *-> treatment of larger tumors*
  - Variable ablation zones according to underling liver parenchyma/ tumor characteristics *-> prediction of ablation sizes*
  - Early assessment of completeness of ablation *-> early re-ablation*
  - Validation of advanced technology



Thank you for your attention

IRE for HCC?





C. Niessen, Percutaneous Irreversible Electroporation: Long-term survival analysis of 71 patients with inoperable malignant hepatic tumors. Sci Rep 2017

Strategy of MI navigated ablations of malignant liver tumors

Indication for local ablation

Thermal ablation feasible

Yes

Percutaneous approach feasible

Yes

No, due to
- location next to major portal/ biliary structures
- adjacent to IVC or venous confluens
- status post major liver resection

BUT

- stable, limited disease

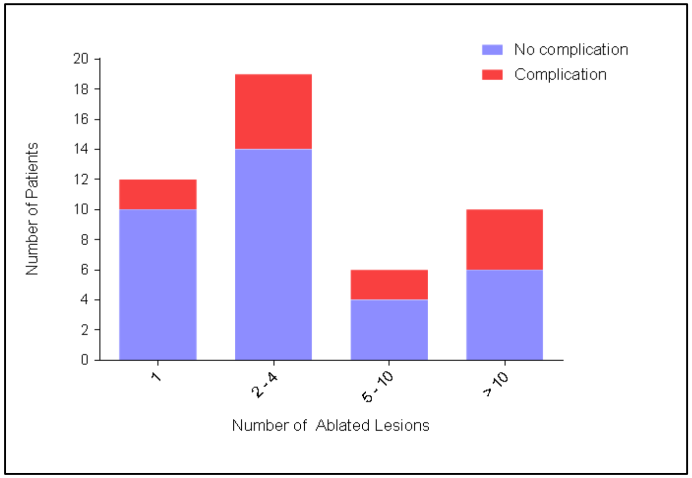
Irreversible Electroporation

No, due to
- need for diagnostic laparoscopy
- lesions in proximity of organs
- multiple lesions (>3-5)
- simultaneous resection of primary
- combined resection and ablation

Laparoscopic approach

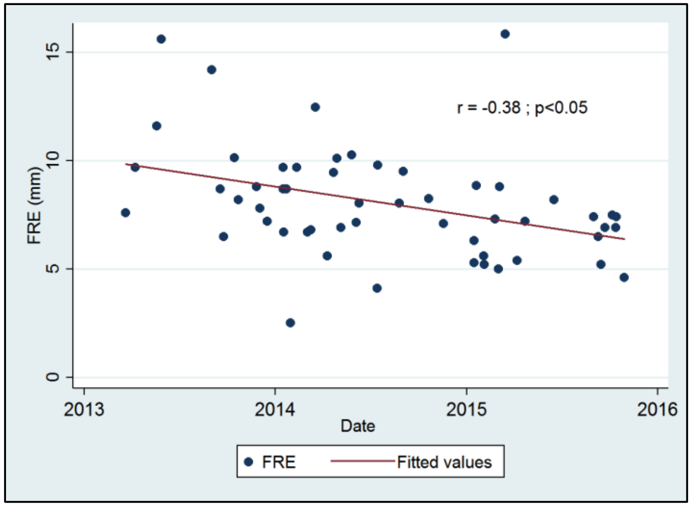
Laparoscopic Navigated MWA 2013 - 2015

- Analysis of 54 patients, 346 tumors
  - Liver-specific complications 5.5%
  - Time for registration/calibration 10min
  - Positive learning curve
  - Local recurrence per lesion at 3 month 9 %
    - Successful re-ablation within 6 month: 75%



➢ Challenges of laparoscopic navigation

  - Limited instrument access
  - Long targeting trajectories
  - Organ deformation



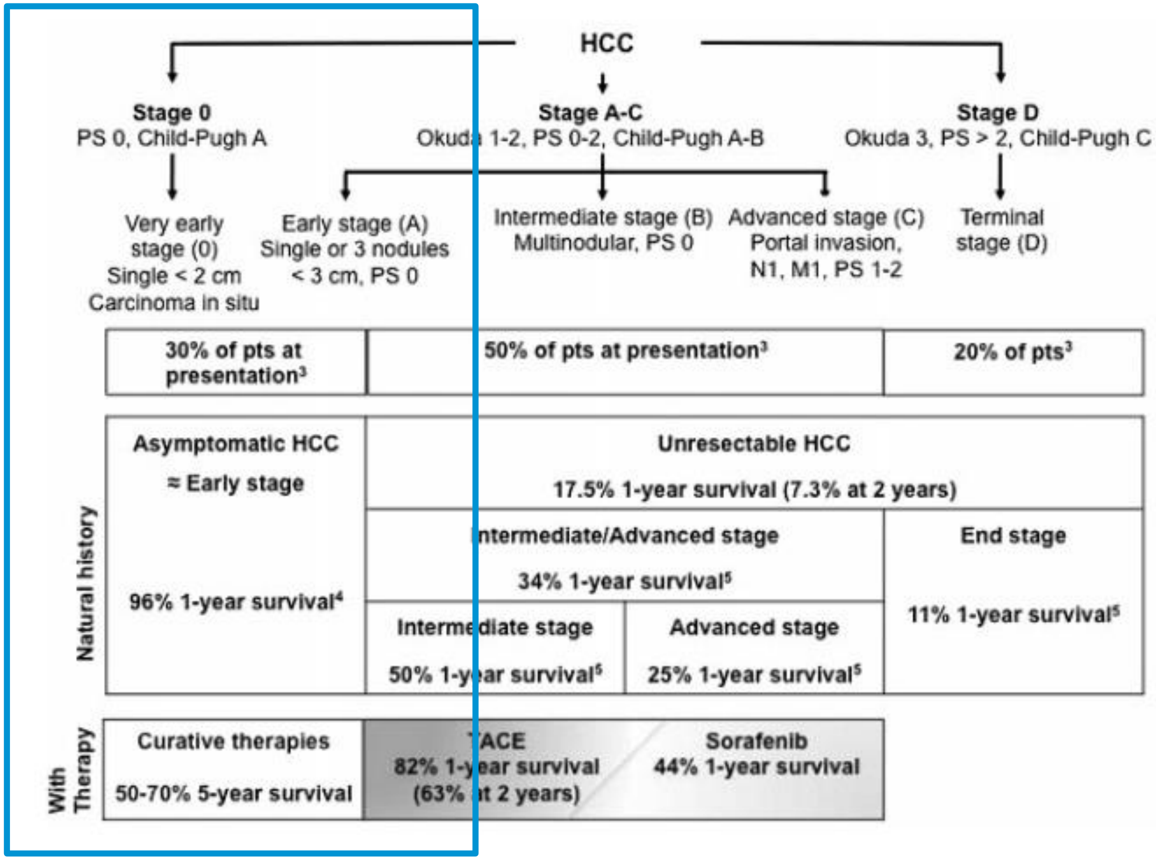
Tinguely P, Fusaglia M, Freedman J et al. Surg Endosc. March 2017

Beyer et al. (2016), Stereotactically-navigated percutaneous Irreversible Electroporation (IRE) compared to conventional
IRE: a prospective trial. PeerJ 4:e2277; DOI 10.7717/peerj.2277

Table 3 Time required for sterile patient preparation; placement of IRE electrodes and total intervention. Data are presented as means and standard deviations.

Conventional or stereotactic	CIRE ($n = 10$)	SIRE ($n = 10$)	t-test
Sterile patient preparation duration—min	17.1 ± 2.8	16.1 ± 3.8	$t(16.4) = 0.67, p = 0.514$
Electrode placement duration—min	87.0 ± 29.9	26.8 ± 7.7	$t(10.2) = 6.2, p < 0.001$
Placement time per electrode—min	18.0 ± 4.2	5.9 ± 2.0	$t(13.0) = 8.1, p < 0.001$
Procedure time until start of the ablation—min	104.1 ± 28.2	55.2 ± 9.3	$t(10.9) = 5.2, p < 0.001$

Curative tretaments for HCC



Bolondi et. al., Semin Liv Dis 2012

Resection vs. local ablation

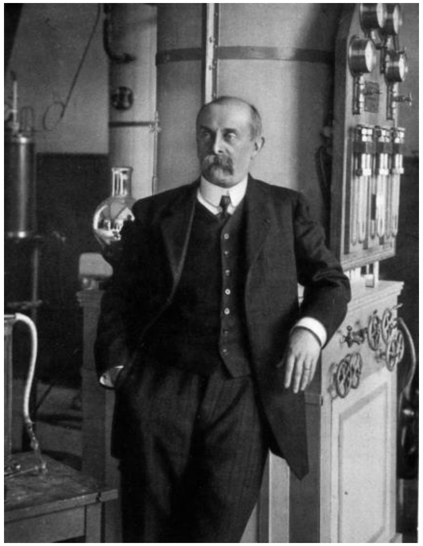
- Hepatic resection is more effective than RFA
  - OS (HR 0.56; 95% CI 0.40 to 0.78)
  - two-year survival (HR 0.38; 95% CI 0.17 to 0.84)
  - event-free survival (HR 0.70; 95% CI 0.54 to 0.91)
  - local progression (HR 0.48; 95% CI 0.28 to 0.82)
  - more complications in resection (OR 8.24; 95% CI 2.12 to 31.95)

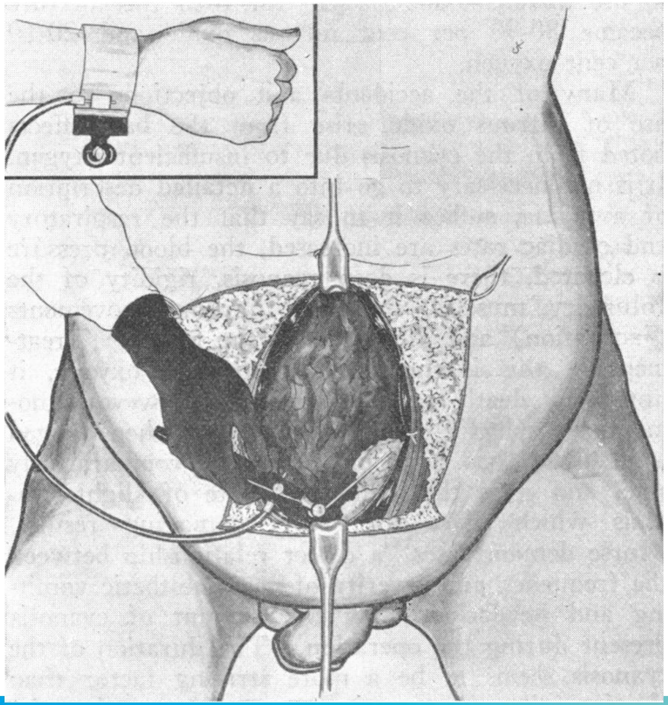
- Surgical resection compared to RFA had
  - a higher overall survival
  - a higher recurrence-free survival
  - a higher morbidity (complication rate)

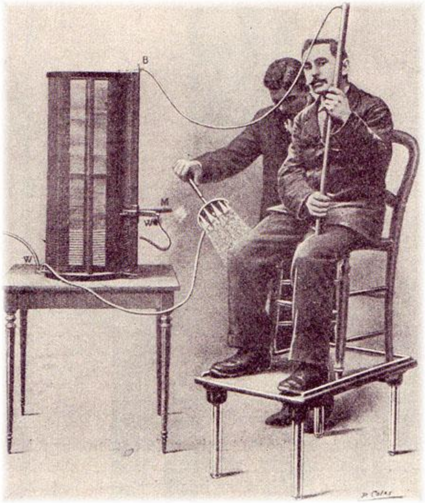
The Cochrane Library 2013, Issue 12
Feng Q, et al. J Cancer Res Clin Oncol 2015;141:

Local ablation
History

available for this purpose, because it is not hemastatic, excepting when the heat of the current becomes sufficient to char the tissues; whereas the bipolar, or D'Arsonval current, is distinctively disorganizing, causing coagulation necrosis and dessication of the tissues. In this process, the fluids of the tissues are cooked, the endothelium of the blood vessels destroyed by the heat of the process of boiling and subsequently dried up. This







Jacques-Arsène d'Arsonva

Macgowan G. Cal State J Med. 1921;19:35

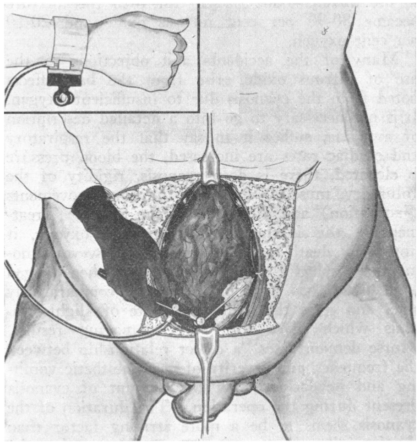
MAVERRIC Trial

Microwave Ablation VErsus Resection for Resectable Colorectal liver metastases

- European multicenter cohort study (Stockholm, Bern, Grøningen)
- Aim: To prove that a strategy of first line local thermal ablation of CRLM is not inferior to liver resection
- *Primary Outcome:* 3-year Overall Survival
- *STUDY GROUP:* Percutaneous navigated CT- guided ablation
- *CONTROL GROUP:* Patients that underwent resection for CRLM
- Propensity score-matched analysis
- Currently: 70 patients included (70%)

Beginning of thermal ablation..

- First reports on coagulative necrosis.. 1981
- First reports on radiofrequency hyperthermia in the liver.. 1983



Surgery. 1983 Oct;94(4):536-42.

Effect of radiofrequency hyperthermia and chemotherapy on primary and secondary hepatic malignancies when used with metronidazole.

Moffat FL, Falk RE, Calhoun K, Langer JC, Dreznik Z, Makowka L, Rotstein LE, Ambus U, Howard V, Campbell A, et al.

Abstract

Hyperthermia is selectively toxic to neoplastic tissue. Since August 1981, 357 patients with incurable tumors in various body areas have been treated with chemotherapy and radiofrequency hyperthermia (RFHT) with adjuvant metronidazole at this center. Of this group, the cases of 102 patients with hepatic tumors are reported here. Patients received one to ten treatment courses, each course consisting of two to five daily RFHT sessions. Systemic temperature rose 0.6 +/- 0.3 degrees C during treatment, and tumor core temperature (measured by percutaneous transhepatic thermistor) reached 39.5 +/- 1.2 degrees C in 38 monitored patients. Results have been encouraging; in particular, among 15 patients with newly diagnosed colorectal metastases limited to the liver (and as yet untreated for their secondary disease), there has been objective partial tumor regression in 66.7%. Side effects have been few. Skin burns and subcutaneous fat necrosis were seen in 3.9% and 13.7% of patients, respectively. Tumor temperature is difficult to measure reliably and does not correlate with machine power or tumor response. A phase III trial is currently underway to determine the efficacy of RFHT and chemotherapy for patients with hepatic metastases from colorectal adenocarcinoma.

Guidelines (EASL/ AASLD)

Local ablation

- Local ablation with radiofrequency or percutaneous ethanol injection is considered the standard of care for patients with BCLC 0-A tumors not suitable for surgery
  (**evidence 2A; recommendation 1B**)
  Other ablative therapies, such as microwave or cryoablation, are still under investigation
- Radiofrequency ablation is recommended in most instances as the main ablative therapy in tumors less than 5 cm due to a significantly better control of the disease
  (**evidence 1iD; recommendation 1A**)
  Ethanol injection is recommended in cases where radiofrequency ablation is not technically feasible (around 10-15%)
- In tumors <2 cm, BCLC 0, both techniques achieve complete responses in more than 90% of cases with good long-term outcome. Whether they can be considered as competitive alternatives to resection is uncertain
  (**evidence 1iA; recommendation 1C**)

Recommendation

1. **The AASLD suggests that adults with Child's A cirrhosis and resectable T1 or T2 HCC undergo resection over radiofrequency ablation.**

   Quality/Certainty of Evidence: Moderate

   Strength of Recommendation: Conditional

Ablation beyond BCLC

Median OS	Within BCLC	Outside BCLC
1 year	96–100 %	78 – 98 %
3 year	53–92 %	33–94 %
5 year	41–77 %	20–75 %

Tiong L, et al., British Journal of Surgery 2011