Irreverssible Electroporation of liver malignancy

A new opportunity of curative treatment for patients not amenable to resection and thermal ablation

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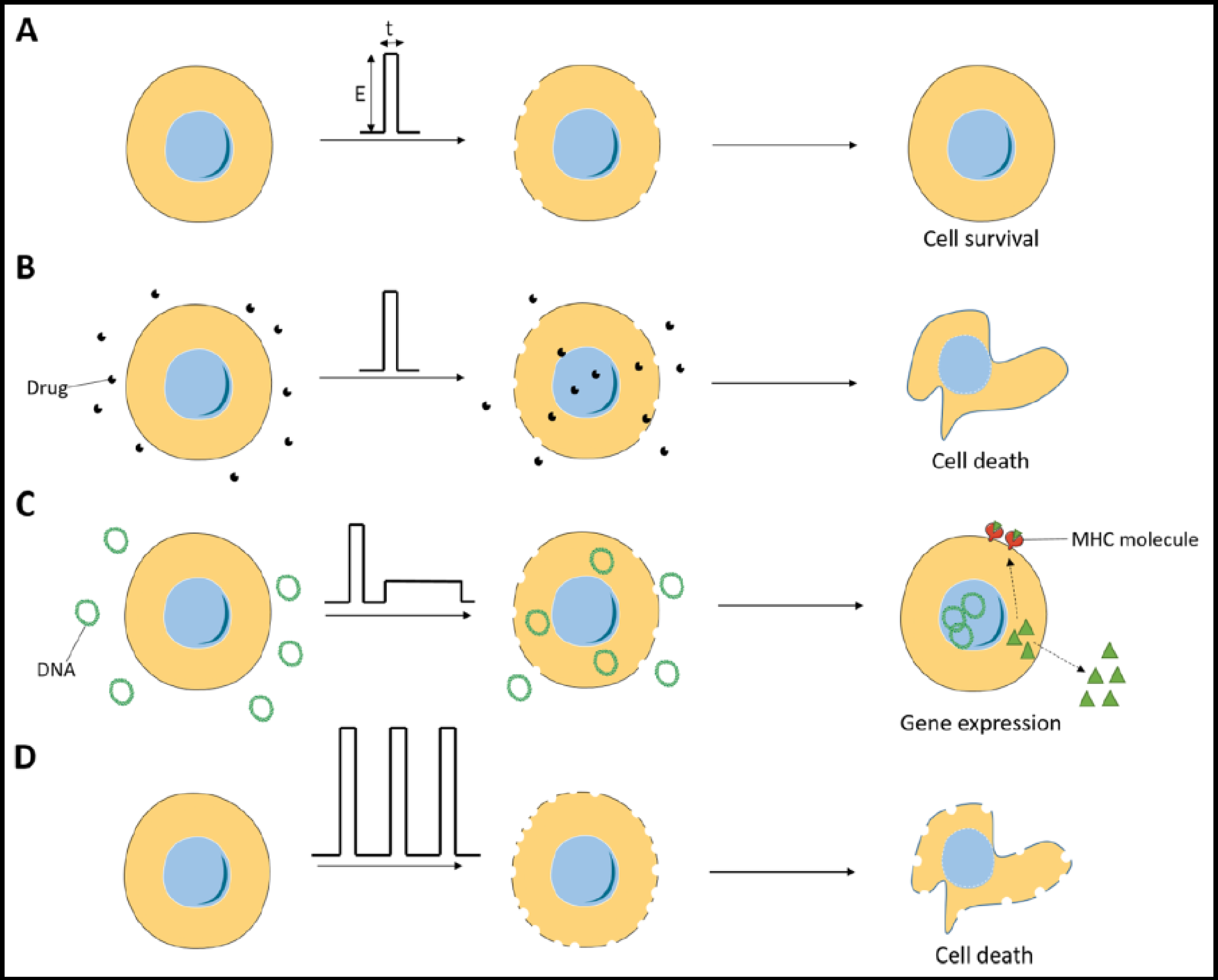
Electroporation : 4 strategies to treat cancer



A/ Basic experiment of cell reversible electroporation (RE)

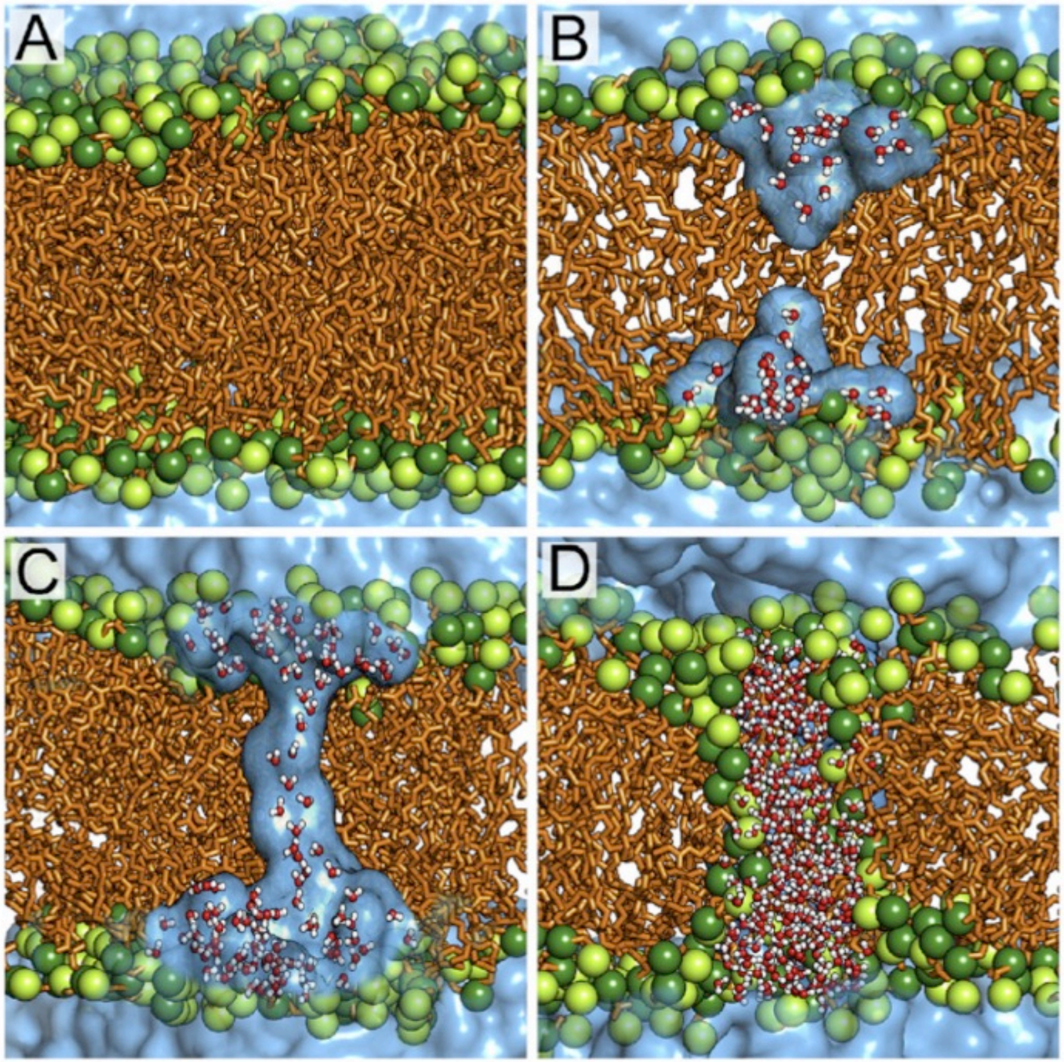
B/ Electrochemotherapy

C/ Electrogenetherapy.

D/ Irreversible electroporation (IRE)

C-Y. Calvet, L-M. Mir
Cancer Metastasis Rev (2016) 35:165–177
DOI 10.1007/s10555-016-9615-3

Pore formation process induced by the ion charge imbalance
(Courtesy of Kristyna Pluhackova)



A/ Intact phospholipid bilayer menbrane.

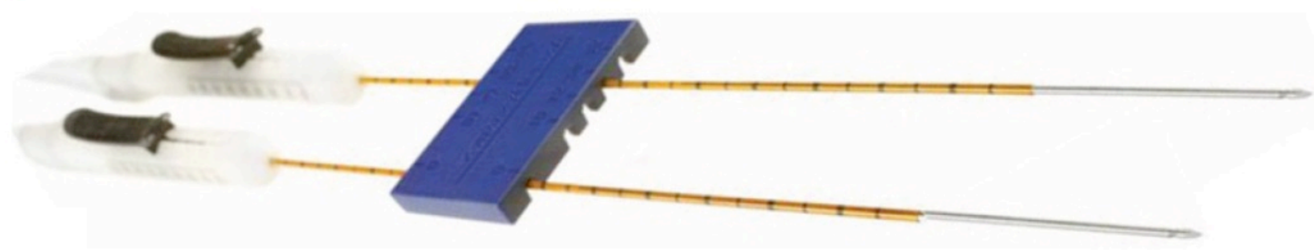
B/ First step, water molecules intrude from both sides of the membrane.

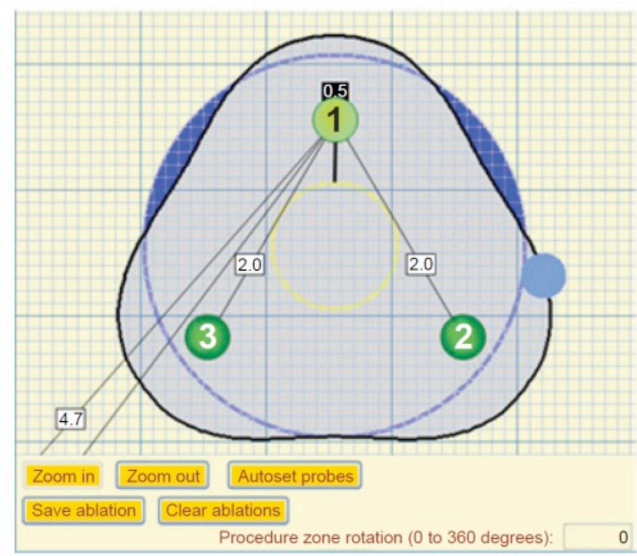
C/ Formation of a water wire with hydrophobic lipid tails lining the pore wall.

D/ Expansion to a larger pore (diameter ≈1 nm) with lipids rearranged in order to stabilize the pore.

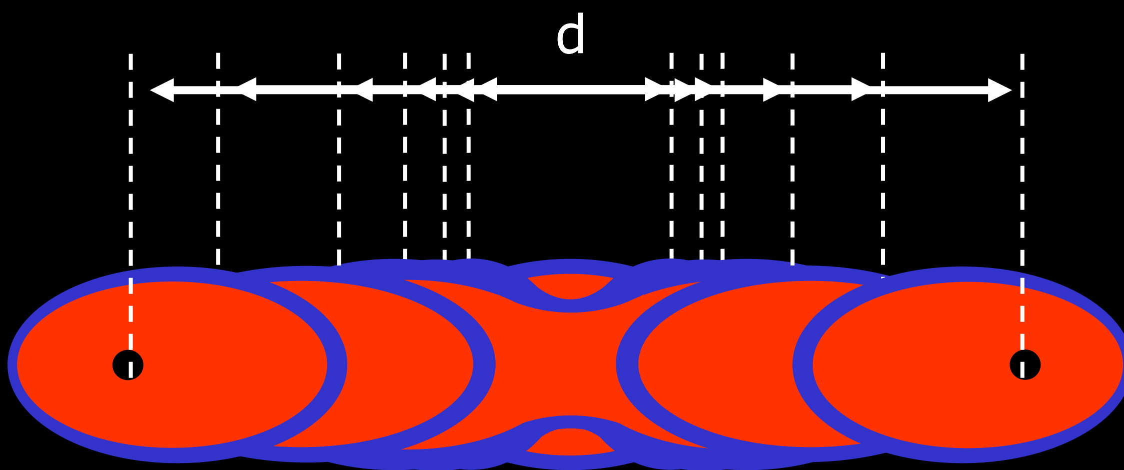
Membrane pore formation in atomistic and coarse-grained simulations
Sonja A. Kirsch, Rainer A. Böckmann
Biochimica et Biophysica Acta 1858 (2016) 2266–2277
http://dx.doi.org/10.1016/j.bbamem.2015.12.031

Only one device currently available for clinical use

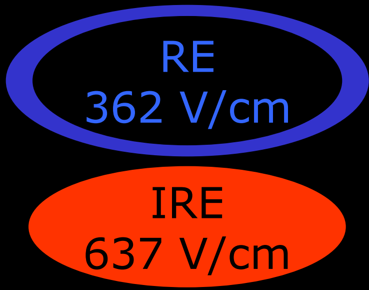




Dosimetry => reversibility/irreversibility



$$\nabla\cdot(\sigma\nabla\Phi)=0$$



σ: local conductivity (S/m)

Φ: local potentiel (V/m)

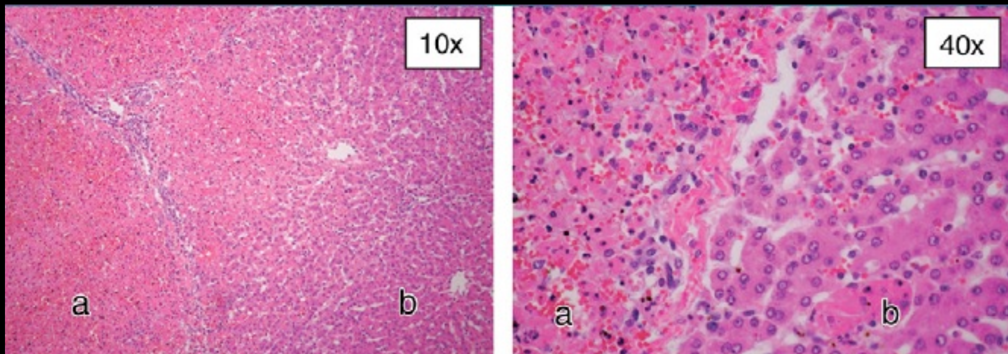
Basic variables in electroporation

- ✓ Pulses magnitude: 1 -> 50 A
- ✓ Pulses duration: 10^{-9} -> 10^{-3} S
- ✓ N of de pulses: 1 -> 120
- ✓ Rate of pulses: 10^{3} -> 10^{-1} Hz

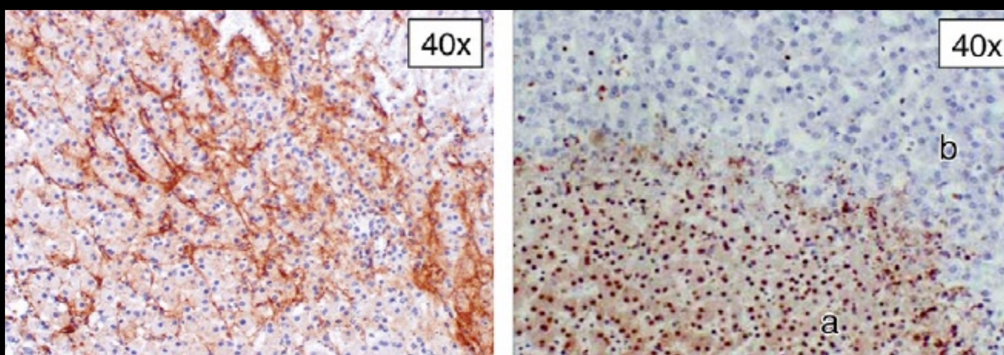
RE -> IRE

Membrane -> Cytoplasme

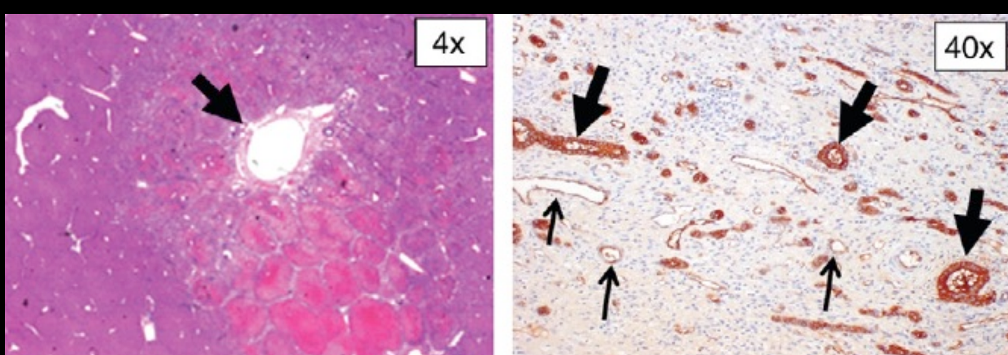
IRE: tissue impact



HES HES



vWF TUNEL



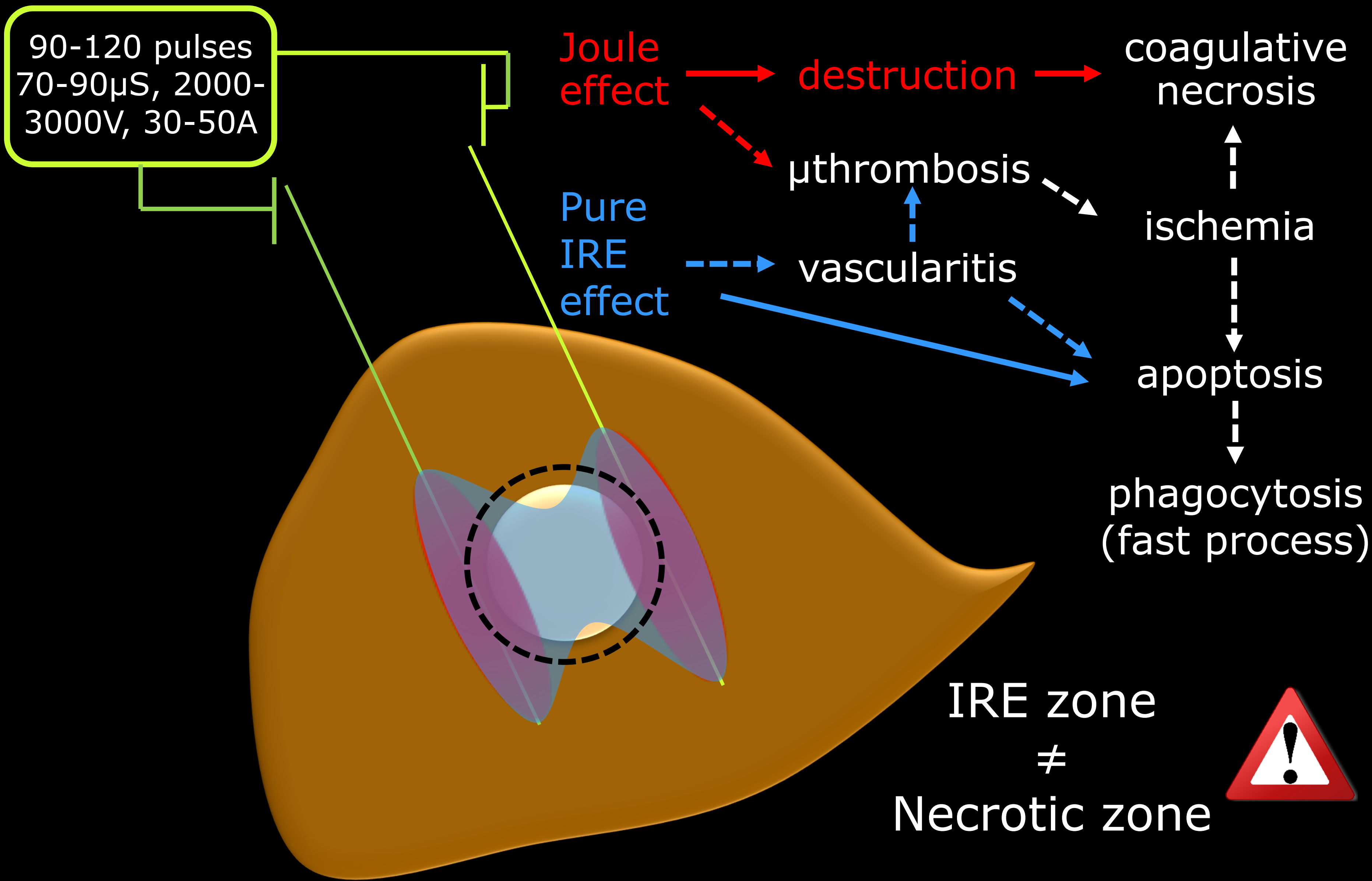
HES vWF

IRE in liver : Lee EW et al. Radiology 2010

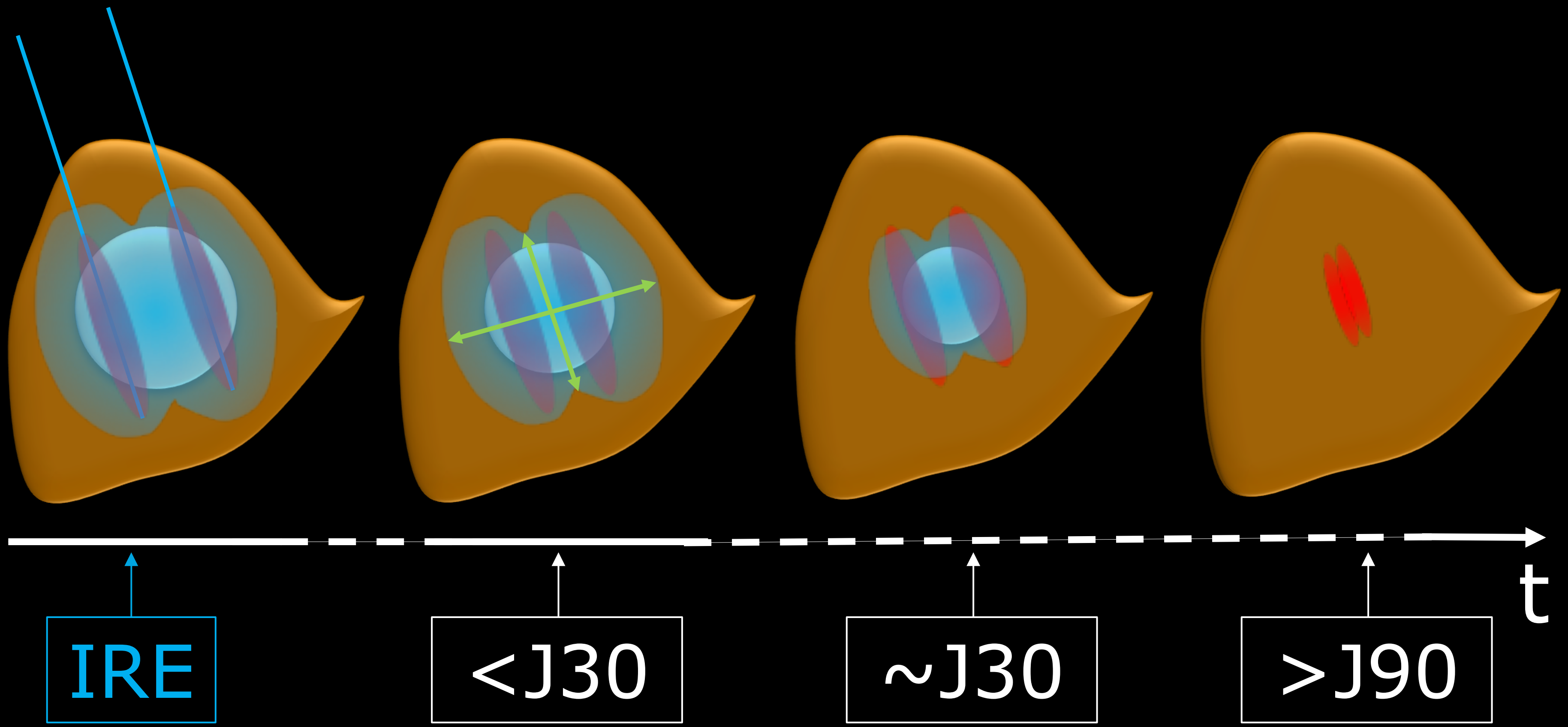
- ✓ **Coagulative necrosis**
  well demarcated
- ✓ **Apoptosis +++**
- ✓ **Vascularitis**

  Lumens of microvessels are still patent +++
- ✓ **Minimal tissue distortion**

IRE pathways of cell death



Practical consequences

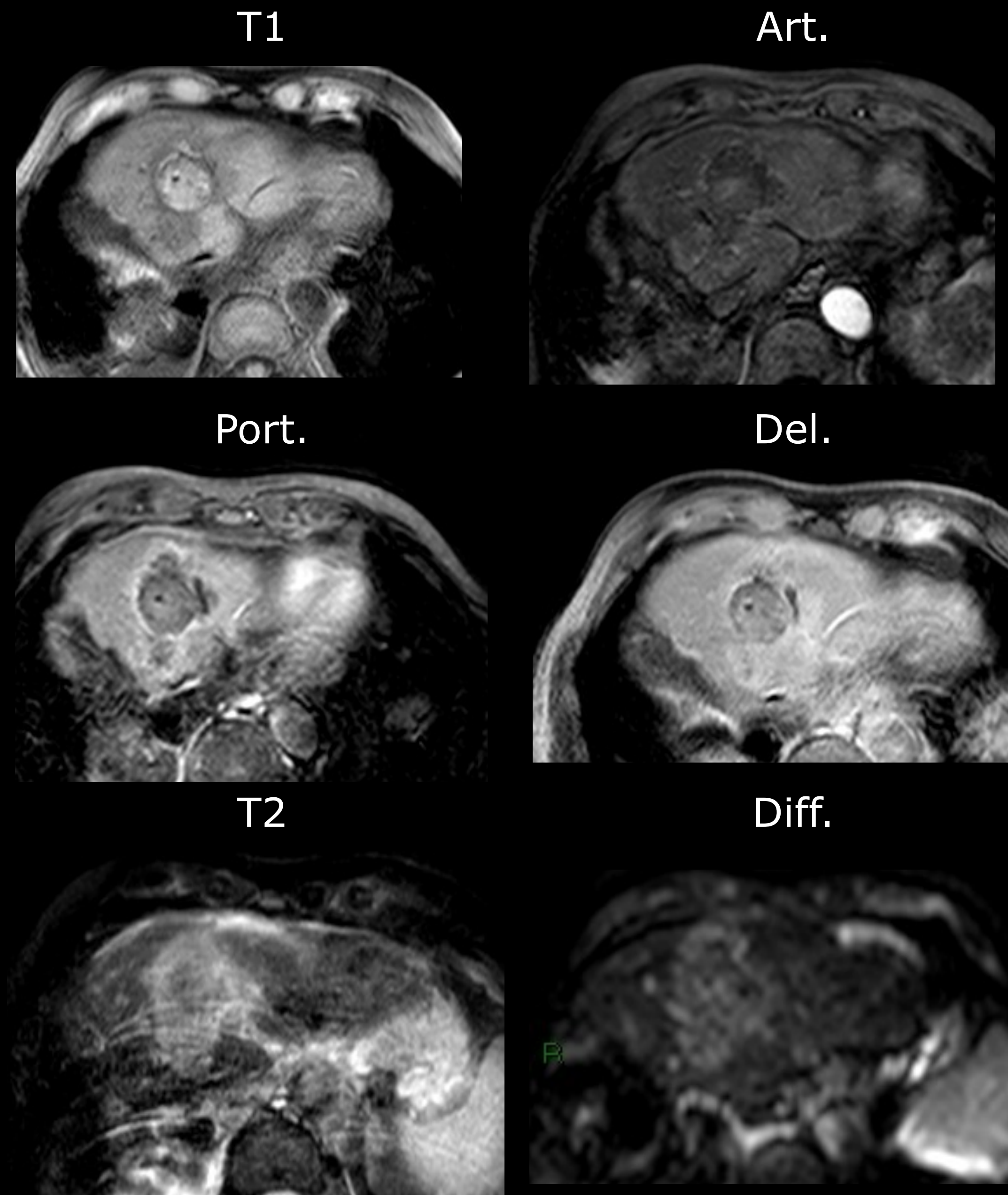


To assess the extent of tissue changes induced by IRE

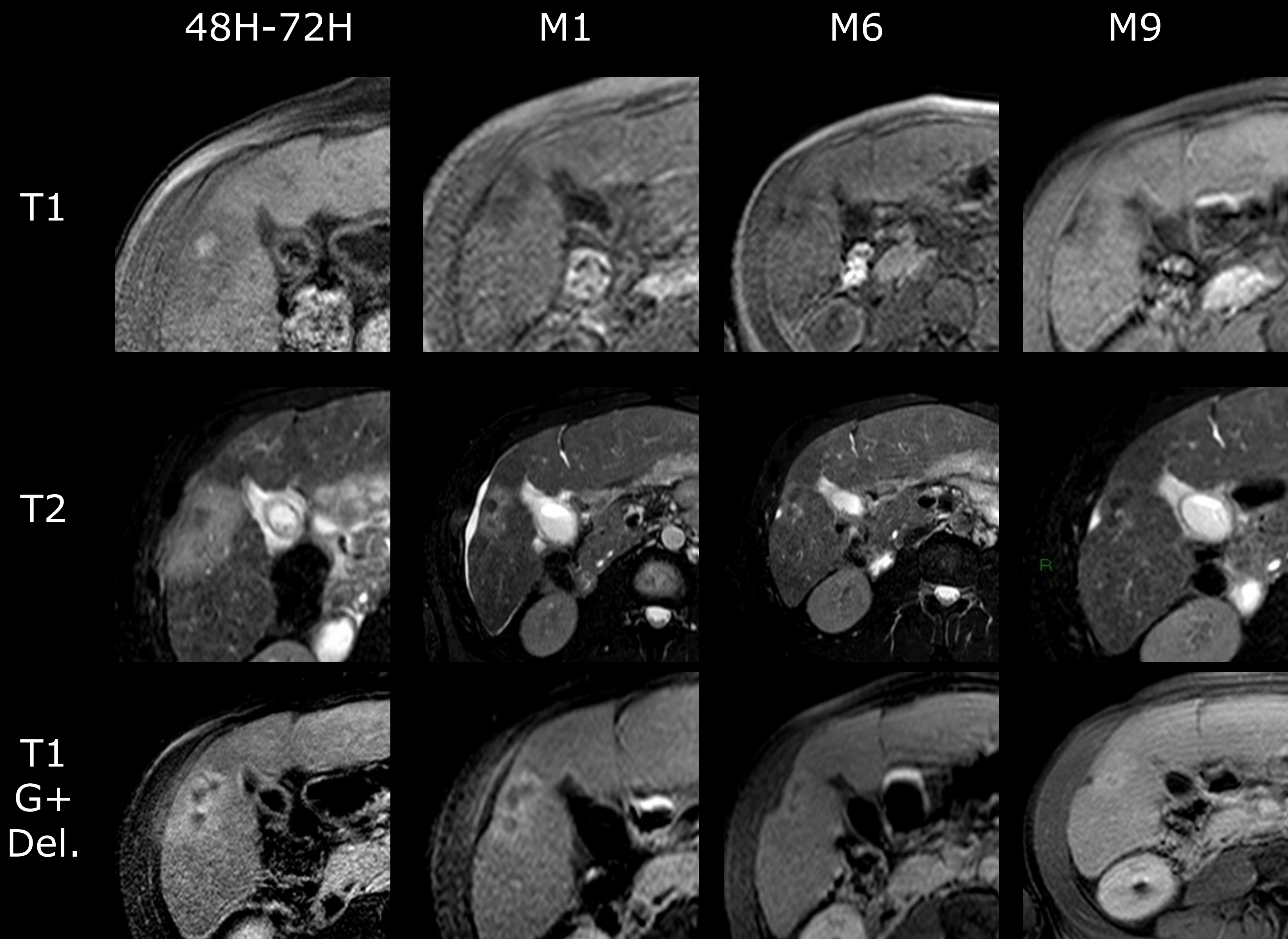
1. Early imaging < 3J is mandatory
2. Can't rely on binary response regarding contrast uptake like for the usual thermal techniques
3. MRI provides the highest natural tissue contrasts

Exemple 1 : 32 mm HCC of segment IV (relapse after hepatectomy). IRE with 5 electrodes 2 cm spaced, 2 cycles of 100 pulses of 70 µs inducing > 30 A.

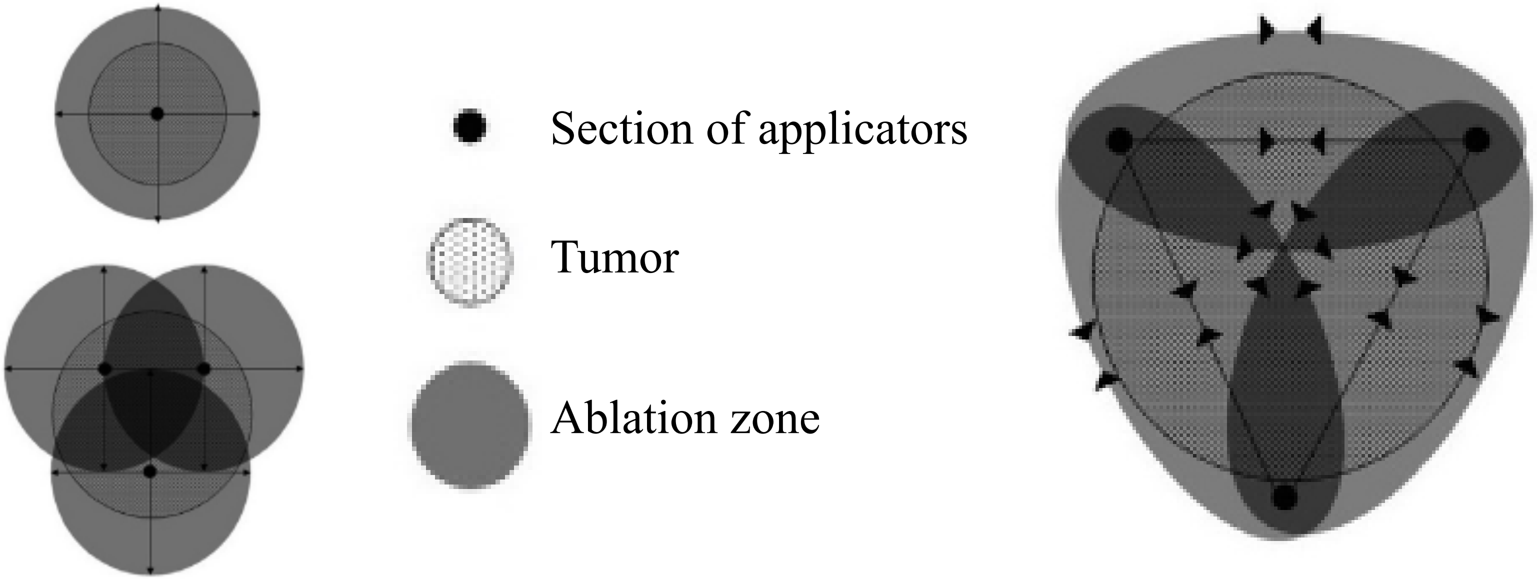
H-48



Exemple 2 : 20 mm HCC of segment V.
Couse of ERI zone up nine months follow-up.



IRE: geometrical arrangement of electrodes



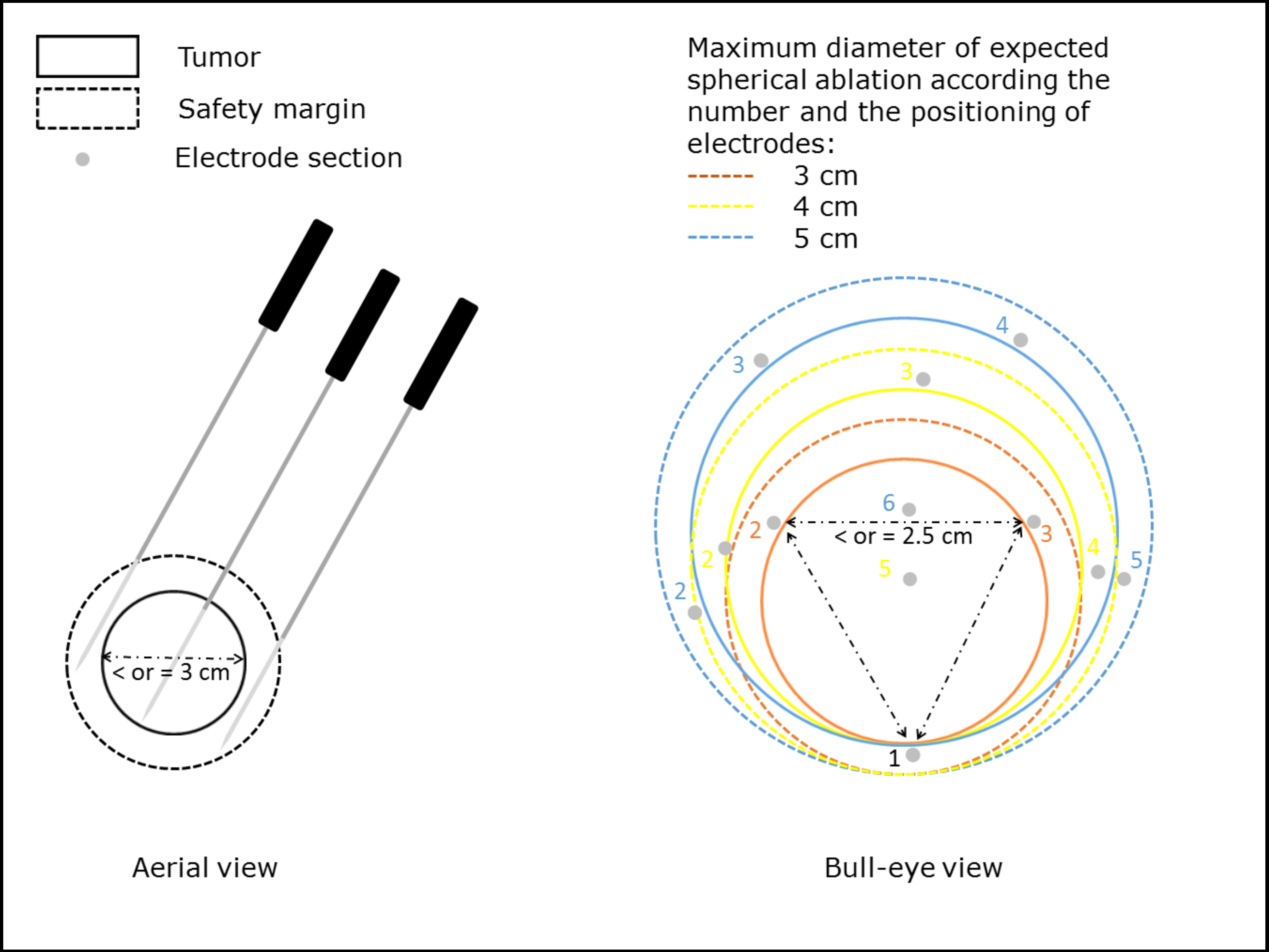
Centrifugal energy radiating devices (1 or X applicators)

- Monopolar RFA
- MWA
- Cryotherapy
- Laser

Centripetal energy deposition devices (2 applicators at least)

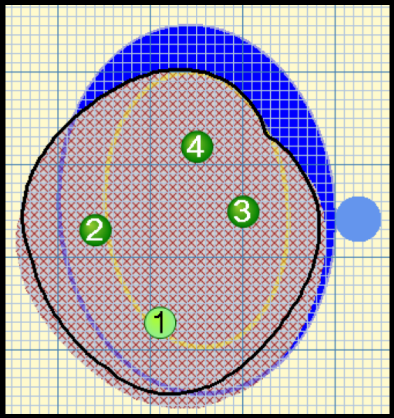
- (Multi) Bipolar RFA
- IRE

Up to which tumour size?



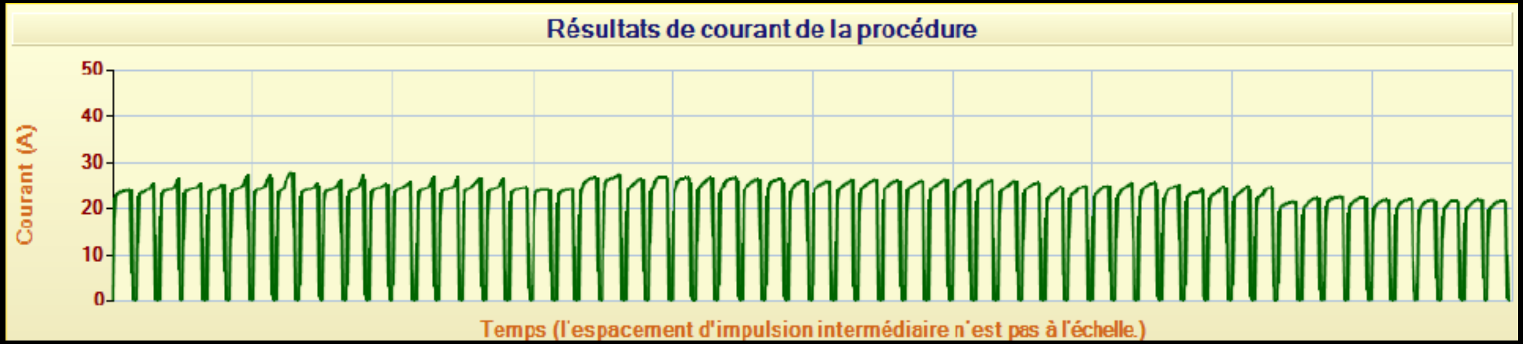
Dynamic setup based on current intensity

1/ Paramétrage

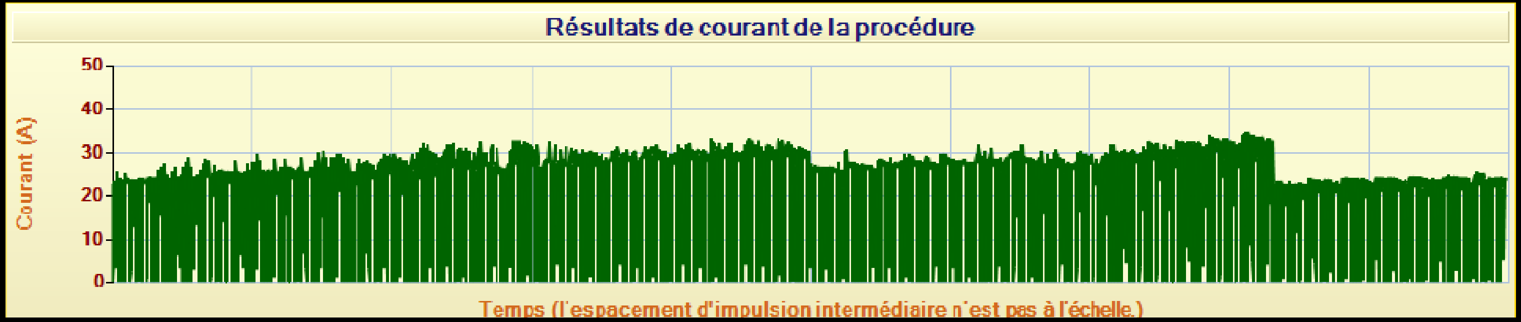


Sondes		Espacement de la sonde (cm)	Volts	Longueur Impulsion	Nombre d'Impulsions
1	2	1.6	3000	70	10
1	3	1.4	3000	70	10
2	3	1.6	3000	70	10
2	4	1.4	3000	70	10
4	1	2.0	3000	70	10
3	4	0.9	2025	70	10

2/ Train of 10 pulses tests : 20A < I < 40A



3/ Completion of treatment with trains of 20 pulses : I↗ car σ↗

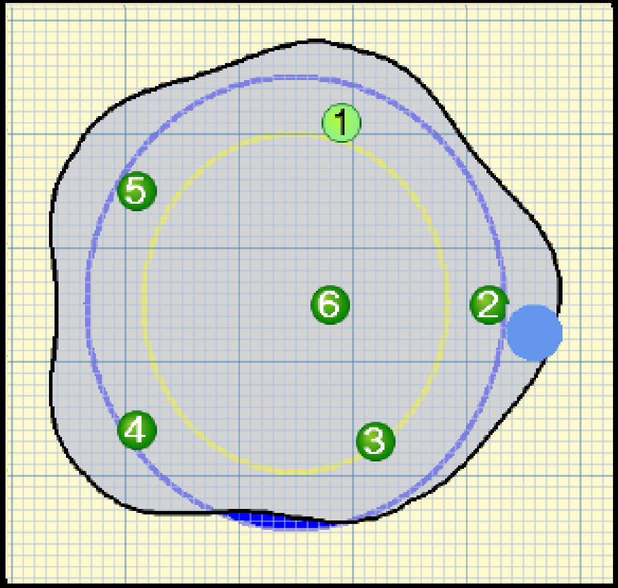


End point of IRE procedure

To delivered between each pairs of electrodes having from 0.5 to 4 cm exposed tips, from 70 to 100 pulses of 90 µs reaching amplitude from 20 to 40 A

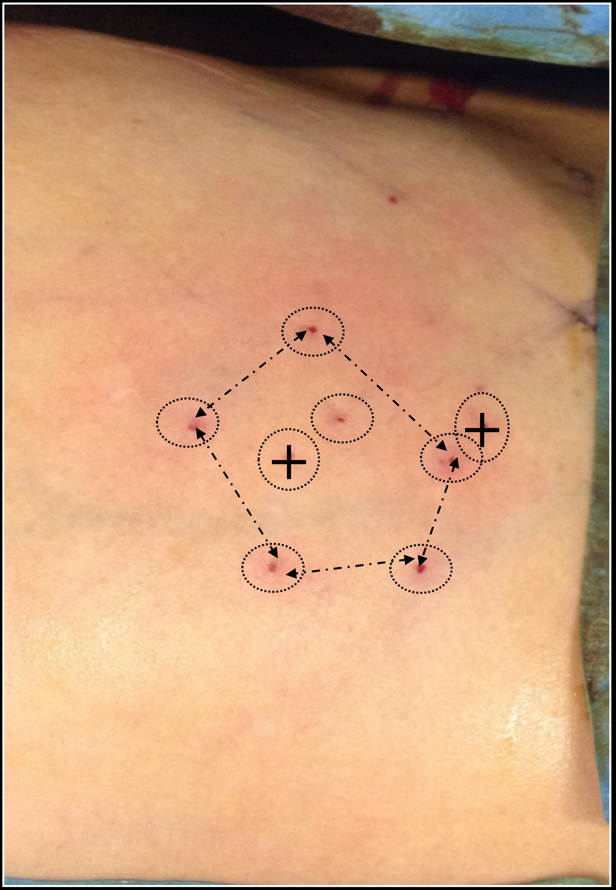
4.5 cm ⇒ 6 electrodes

2D numerical planning

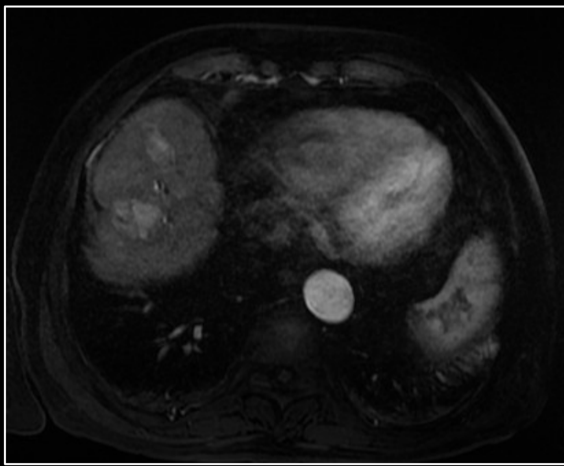


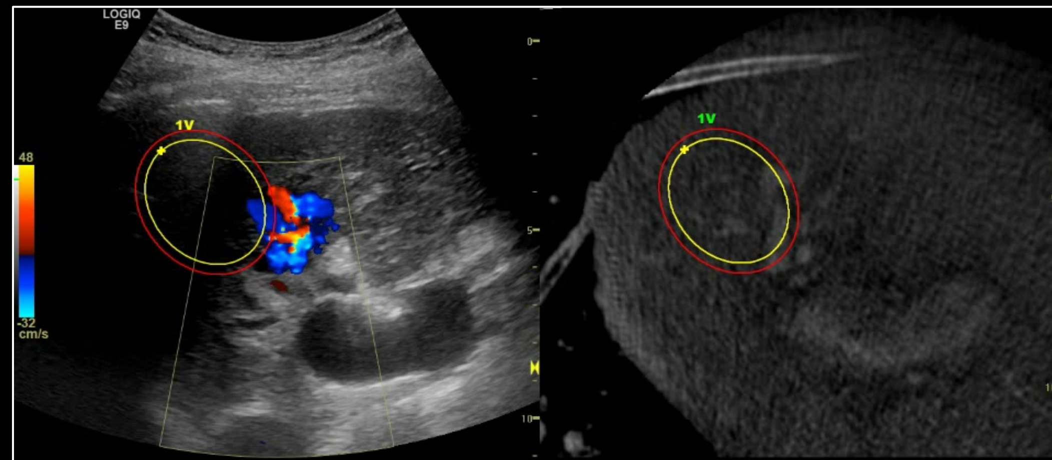
from theory to reality

Do your best

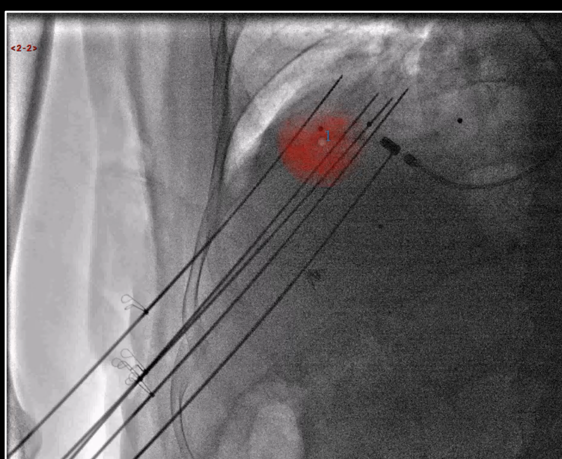


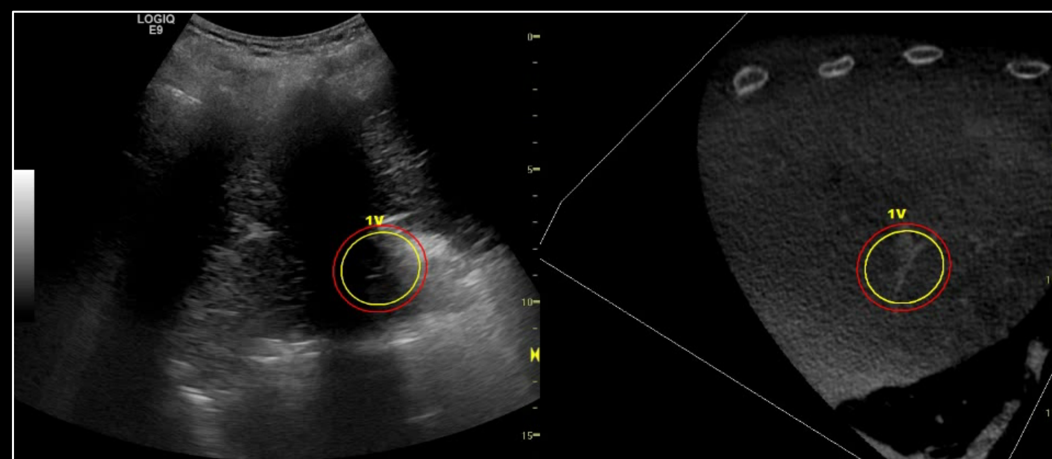
Procedures tricky => Imagerie fusion





IRE sous AG, Fusion automatique US/CBCT

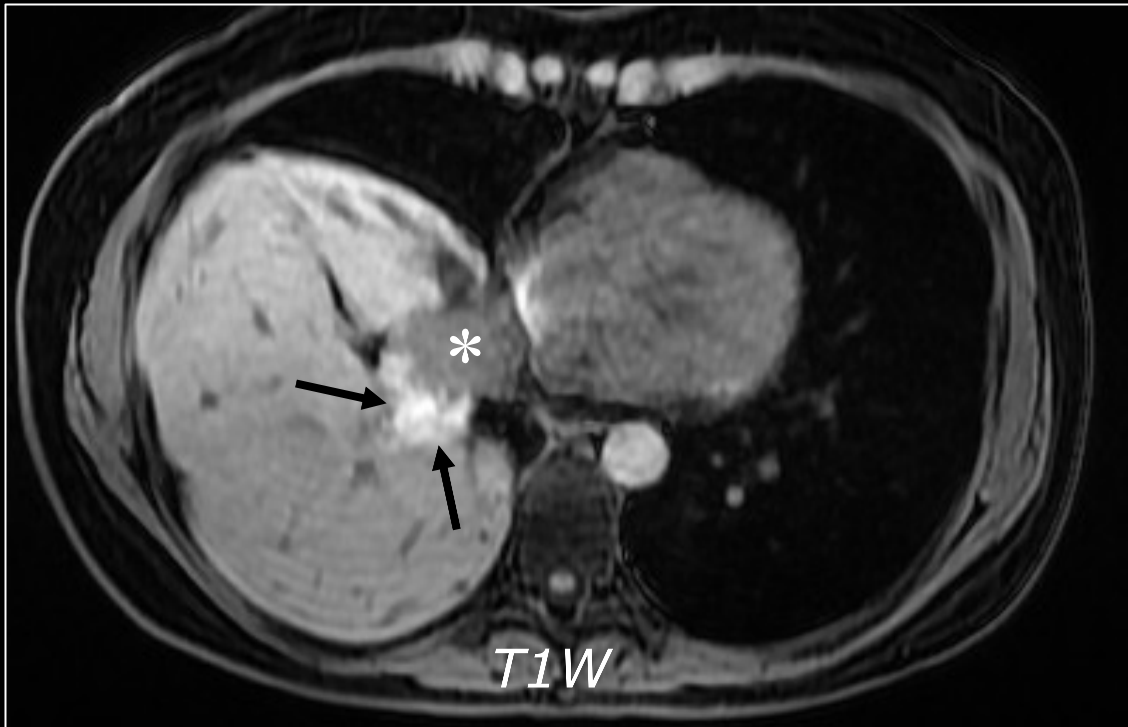


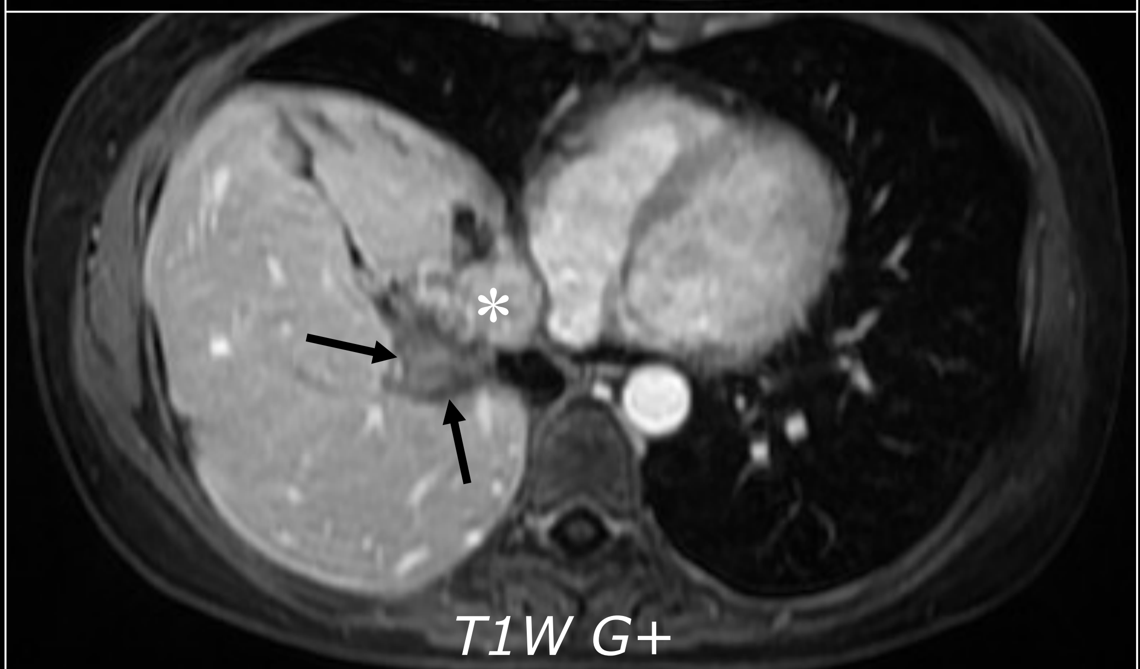


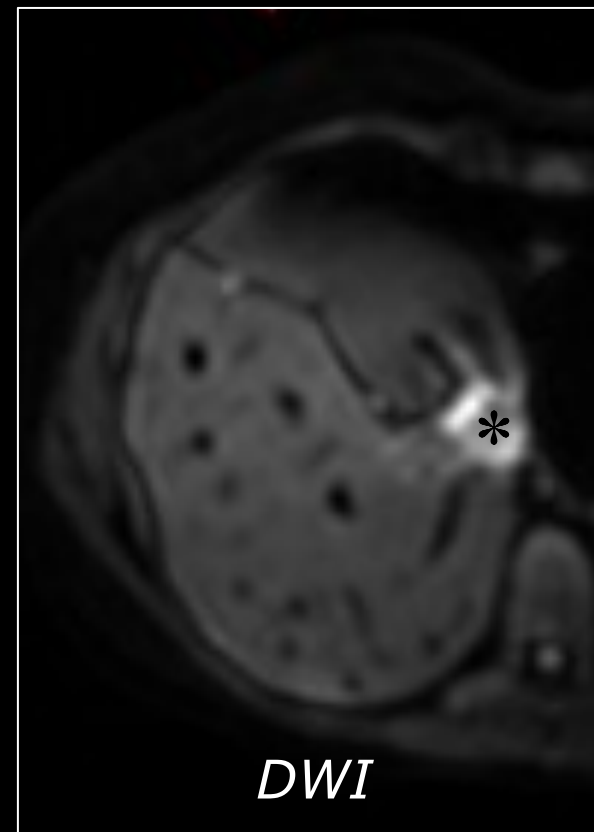
The case

- ✓ Female 47 years old (OMS 0)
- ✓ June 2013: Colorectal cancer pT3N1(3N+/24) resected 2013 + 6 cycles of FOLFOX
- ✓ January 2014: Single liver met in S6 ablated by RF
- ✓ October 2015: New liver met in S4 in precaval location ablated by 2 RF sessions
- ✓ May 2018: Local recurrence of S4 met

* Met S4: 35 mm





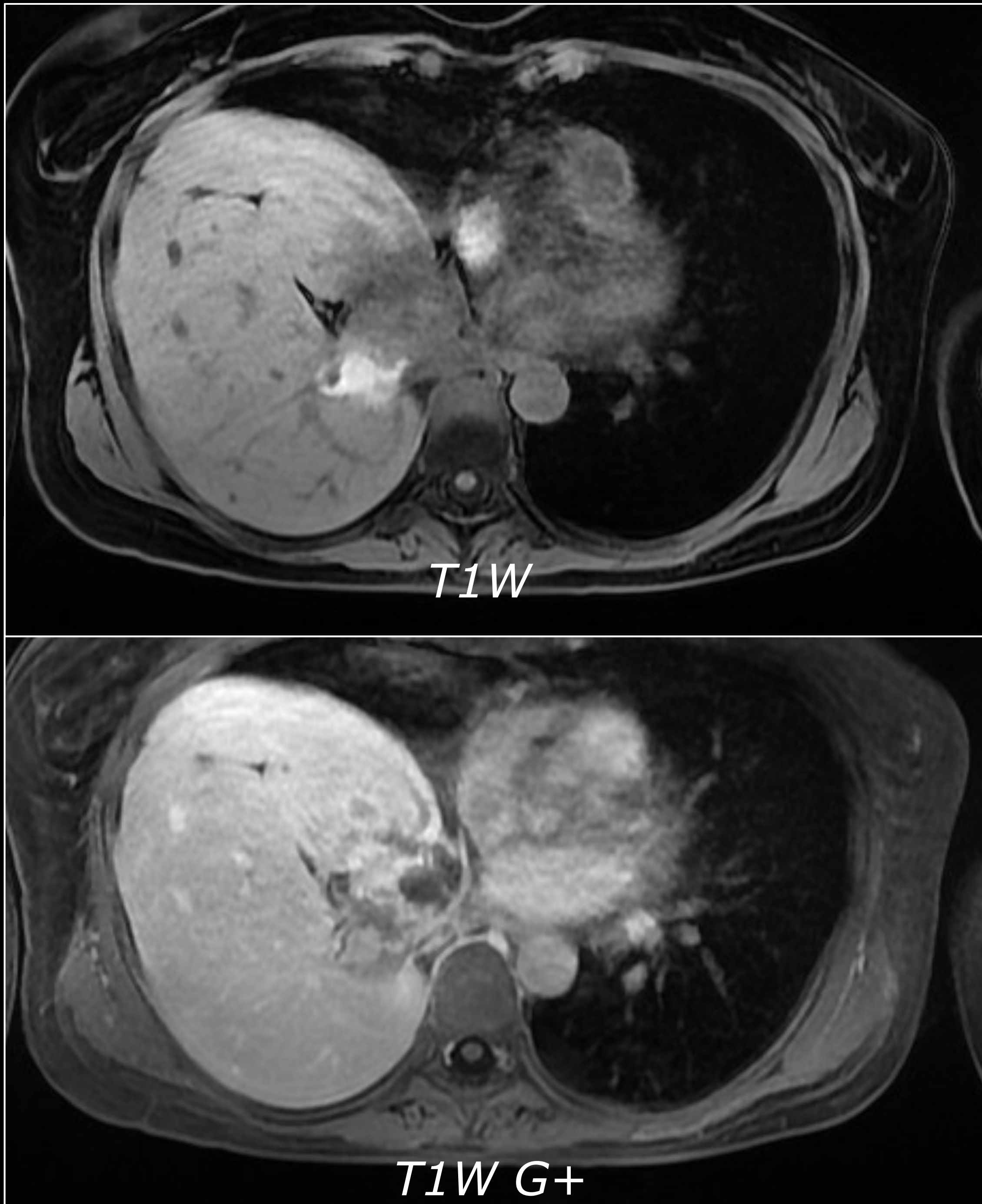


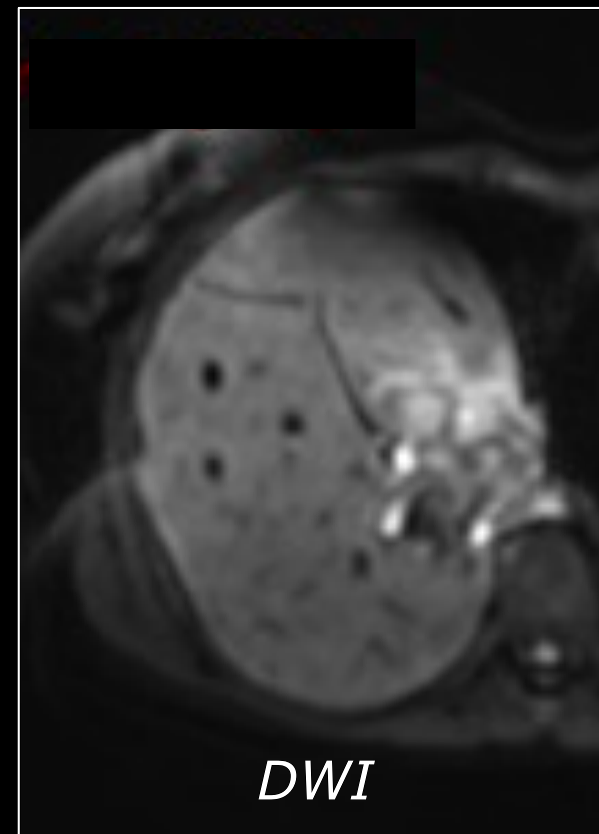
RFA scare

Rational for choosing IRE

- Proximity of critical structures might be damaged is thermal ablative techniques is attempted
- Pre-caval location
- Local recurrence after RFA

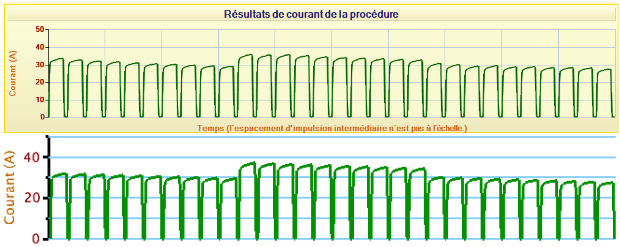
D2 MRI





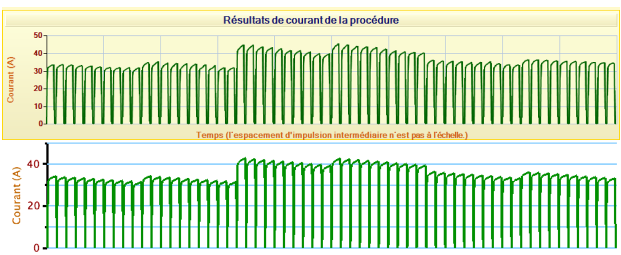
Numerical simulations of IRE

Série 1



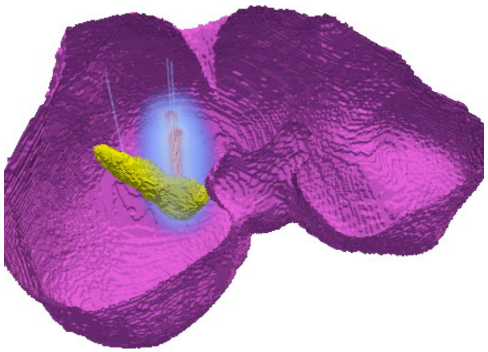
paires 1-2 2-3 1-3

Série 2

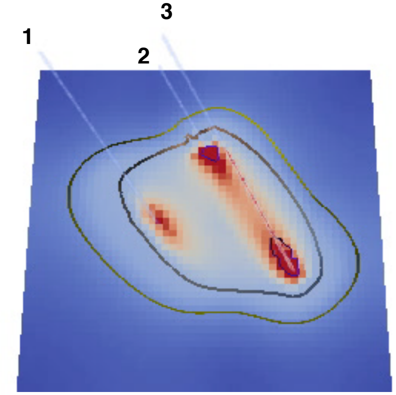


paires 1-2 2-3 1-3

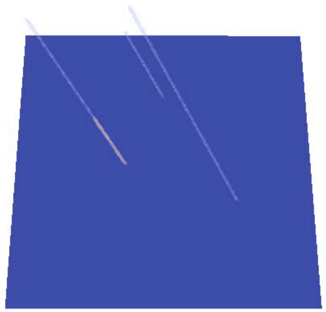
Calibration on chronograms and simulations



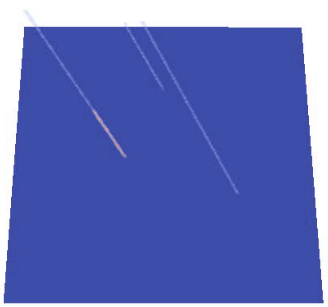
Electric field magnitude

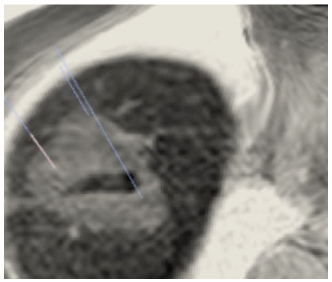


Max applied electric field, with RE / IRE thresholds

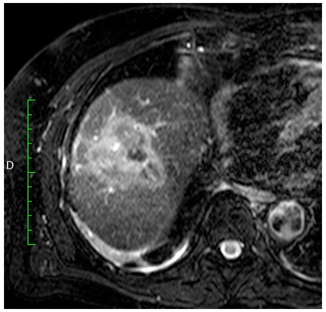


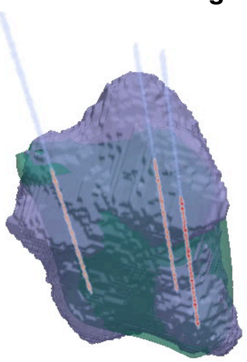
Conductivity





Long term impact area





superimposition
ROI / maxEF simulation

Courtesy of Dr O.Gallinato, C.Poignard, INRIA / University of Bordeaux, NUMEP project

PLAN CANCER 2014-2019
projet NUMEP

Clinical experience with IRE

Author	Organ	N	FU	Results	Level
Martin* 2015	Pancreas LAS (Stage III)	200	29	OS: 24.9 M, Morbidity ≥ III: 18.5%, Mortality: Yes	4
Narayanan 2017	Pancreas LAS (Stage III)	50	-	OS:27 M, Morbidity ≥ III : 20%, Mortality: Yes	4
Scheffer 2017	Pancreas LAS (Stage III)	25	12	OS:17 M, Morbidity ≥ III : 44%, Mortality: No	4
Niessen 2017	Liver HCC/Cmet	71	35.7	OS:26.3 M, Morbidity ≥ III : 7%, Mortality: No	4
Sutter 2017	Liver HCC‡	58	9	PFS: >12 M , Morbidity ≥ III : 5.2%, Mortality: Yes	4
Ricke 2015	Lung NSCLC/Cmet	23	-	PFS: 30%, Morbidity ≥ III : 48%, Mortality: No	4
Trimmer 2015	Kidney	20	9	PFS: 85%, Morbidity ≥ III : 0%, Mortality: No	4
Valerio 2014	Prostate	34	-	PFS: 82%, Morbidity ≥ III : 14.7%, Mortality: No	4

* Open surgical approach, ‡ 10 (13%) patients with portal invasion

Radiology

Safety and Efficacy of Irreversible Electroporation for the Treatment of Hepatocellular Carcinoma Not Amenable to Thermal Ablation Techniques: A Retrospective Single-Center Case Series[1]

Olivier Sutter, MD
Joyce Calvo, MD
Gisèle N'Kontchou, MD
Jean-Charles Nault, MD
Raffik Ourabia, MD
Pierre Nahon, MD, PhD
Nathalie Ganne-Carrié, MD, PhD
Valérie Bourcier, MD
Nora Zentar, MD
Fatna Bouhafs, MD
Nicolas Sellier, MD
Abou Diallo, MD
Olivier Seror, MD, PhD

Radiology. 2017 Sep;284(3):877-886.

Before *D2 after T2w* *D2 after art.P*

From March 2012 to June 2015

Parameter	Total	Patients with Tumor in Critical Location (Group 1)	Patients with Poor Liver and General Condition (Group 2)*
Patients			
No. of patients	58 (100)	48 (82.7)	10 (17.3)
Age (y)†	65.4 (41.6–90)	70.8 (42–90)	60 (41.6–70.9)
Age $>$75 y	16 (33.3)	16 (33.3)	0
Male	43 (74)	36 (75)	7 (70)
No previous treatment	24 (41.4)	20 (41.2)	4 (40)
History of decompensation	13 (22)	6 (12.5)	7 (70)
Esophageal varices	36 (62)	28 (58.3)	8 (80)
Ascites‡	20 (34.5)	13 (27.1)	7 (70)
Platelet count $<$75 M/mL	18 (31)	13 (27.1)	5 (50)
Prothrombin activity $<$75%	23 (39.6)	15 (31.2)	8 (80)
Albumin level $<$35 g/L	13 (22.4)	7 (14.6)	6 (60)
Total bilirubin level $>$15 µg/mL	12 (20.7)	8 (16.7)	4 (40)
α-Fetoprotein level (ng/mL)†	29 (2–1662)	52 (2–1662)	6 (3–21)
α-Fetoprotein level $>$100 ng/mL	8 (16.7)	8 (16.7)	0
ECOG performance status $>$1	20 (34.5)	16 (33.3)	4 (40)
ASA score			
1	0	0	0
2	21 (36)	20 (41)	1 (10)
3	37 (64)	28 (59)	9 (90)
4	0	0	0
Nodules			
No. of nodules	75 (100)	60 (80)	15 (20)
Longest diameter (mm)†	24 (6–90)	27 (6–90)	19 (10–45)
Longest diameter $>$30 mm	16 (21.3)	14 (23.3)	2 (13.3)
Location			
Hilar	47 (62.7)	47 (78.3)	0
Peripheral	13 (37.3)	13 (21.7)	0
Infiltrative form	7 (9.3)	7 (11.7)	0
Portal invasion	10 (13.3)	10 (16.7)	0

During the same time …

276 HCCs in 206* patients treated with thermal ablation techniques during the study time.

47 (17%) with MWA

229 (83%) with mbpRFA

- 56 (20%) sub capsular in hepatic dome abutting diaphragm
- 57 (27.5%) sub capsular abutting other critical structures (e.g.: digestive tract, gallbladder)
- 57 (21%) intra paremchymal abutting large (> 3 mm in diameter) normal hepatic vessels (e.g.: portal veins other than Vp4 and Vp3, hepatic veins, inferior vena cava)

Technical Characteristics of 87 IRE Procedures for the Treatment of 75 HCCs

Longest Diameter	No. of Patients Requiring a Pullback Application*	No. of Patients Requiring Repeat Procedure*	Median No. of Electrodes†	Median No. of Pulses†
<30 mm (44 nodules, 59%)	15 (33)	5 (11)	3 (3–6)	105 (30–380)
≥30 to <50 mm (17 nodules, 23%)	9 (50)	5 (27)	4 (3–6)	105 (70–380)
≥50 mm (14 nodules, 18%)‡	9 (64)	2 (14)	5 (3–6)	330 (90–480)

* Numbers in parentheses are percentages.

† Numbers in parentheses are ranges.

‡ Longest diameter of at least 50 mm or infiltrative and or portal invasion.

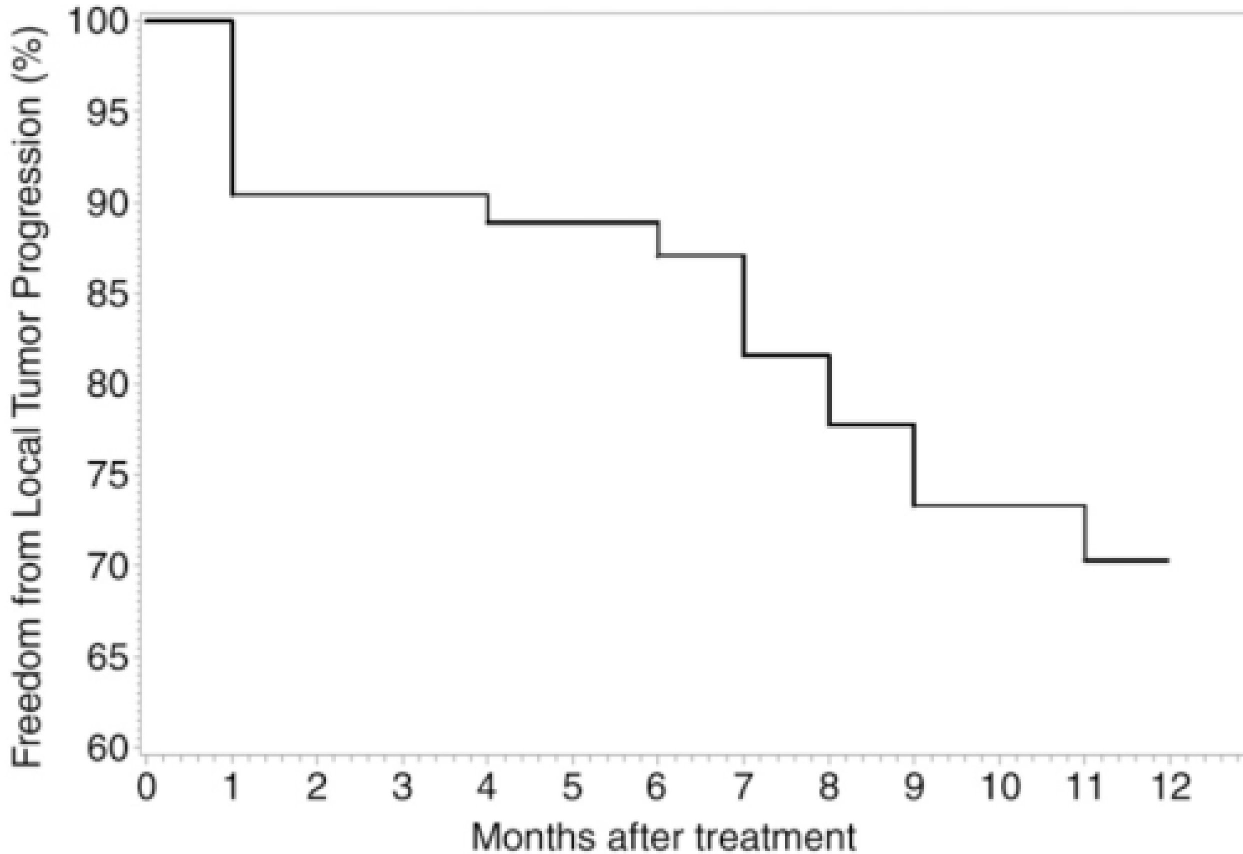
Effectiveness of 87 IRE Procedures for the Treatment of 75 HCCs

Parameter	Complete Ablation after 75 First IRE	Complete Ablation after 9 Second IRE	Complete Ablation after 3 Third IRE	Local Tumor Progression*
Longest diameter				
<30 mm (44 nodules)	36 (81.8)	40 (90.9)	41 (93.2)	7 (15.9)
≥30 to <50 mm (17 nodules)	12 (70.6)	16 (94.1)	17 (100)	2 (11.7)
≥50 mm (three nodules)	3 (100)	...	...	0
Infiltrative or portal invasion (11 nodules)	7 (64)	8 (72.7)	8 (72.7)	6 (54.5)
Total	58 (77.3)	67 (89.3)	69 (92)	15 (20)

Note.—Data are numbers of patients, with percentages in parentheses.

* In cases of complete ablation or failure of initial course of IRE treatment.

Local tumor progression survival



Number of HCC at risk	72	72	49	34	19
Number of patients at risk	56	49	44	30	19
95% confidence limit	81-95	81-95	77-93	60-83	56-81

Complications of 87 IRE Procedures for the Treatment of 75 HCCs in 58 Patients

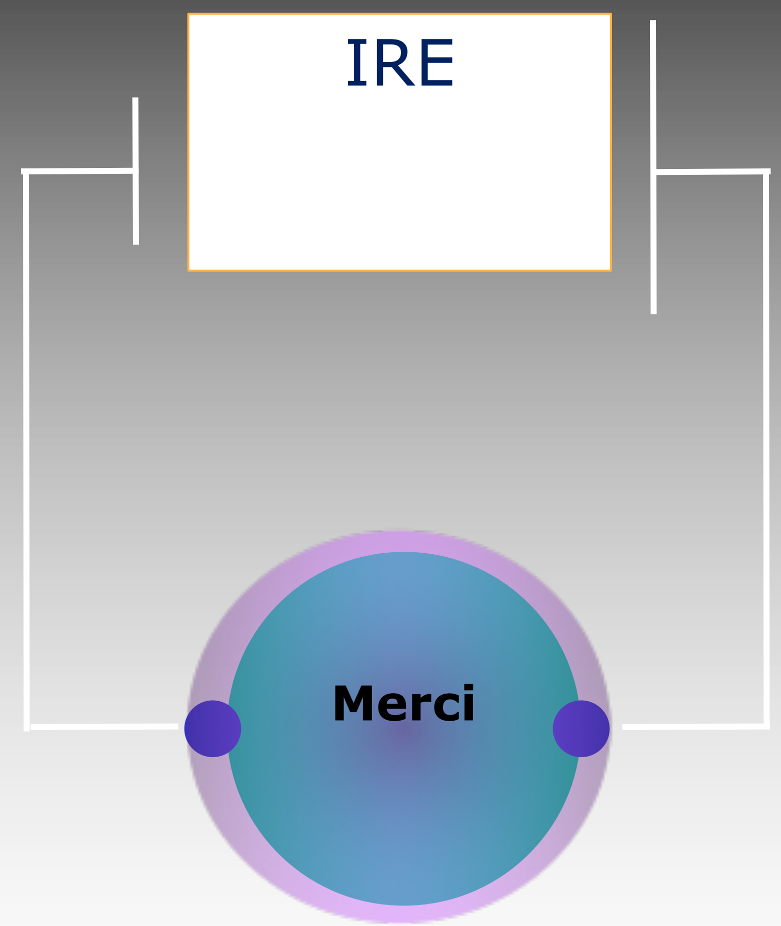
Clavien-Dindo/SIR Grade	Patients with Critical Tumor Location (Group 1) (n = 48)	Patients with Poor Liver Function and/or Poor General Condition (Group 2) (n = 10)
I/B	Pain (n = 1), transient jaundice (n = 1), asymptomatic gastric fistula (n = 1)	...
II/C	Pneumothorax (n = 1), partial portal thrombosis (n = 2), transient encephalopathy (n = 1)	Decompensated chronic bronchitis (n = 1)
IV/D	Liver failure (jaundice and ascites) (n = 1)	Liver failure (jaundice and ascites) (n = 1)
V/F	...	Death (liver failure) (n = 1)

Note.—SIR = Society of Interventional Radiology.

- ✓ Morbidity : 19% (11/58 patients)
- ✓ Major morbidity : 5.2% (3/58 patients)
- ✓ Mortality : 1.7% (1/58 patients)

Key points

- ✓ Because is the sole non thermal ablative method IRE can be unique opportunity of curative treatment for patients not resectable and not ablatable with standard thermal techniques
- ✓ IRE is in infancy and still technically demanding ablative method which requires advanced imaging guidance.
- ✓ In future, numerical simulations are clearly required to improve efficacy and safety of the procedure


IRE
Merci