

Thermothérapie par ultrasons focalisés guidés par IRM



Hervé TRILLAUD

- Hôpital Saint André
- IMOTION (imagerie moléculaire et thérapies innovantes en oncologie)

Une longue histoire.....

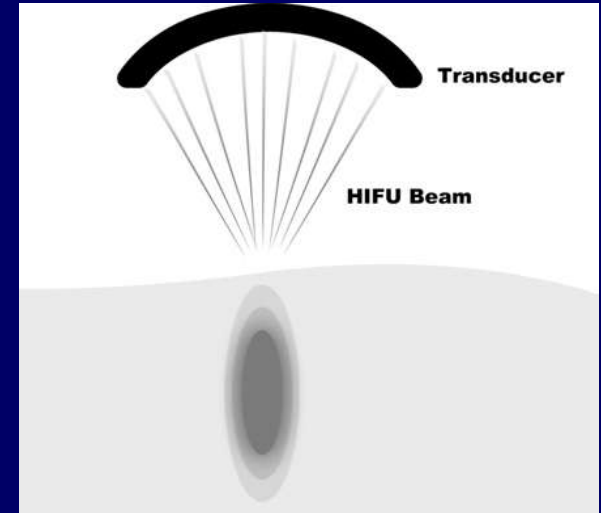
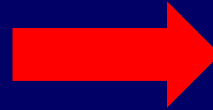
- ◆ Lynn JG et al 1942: les principes
- ◆ Chapelon JY et al 1992: Prostate
- ◆ Madio et al 1998: Thérapie génique
- ◆ Tempany et al 2003: Fibrome
- ◆ Wu et al 2004: Foie
- ◆

Ultrasons focalisés

- ◆ Thermo-ablation Fibrome, prostate, os, seins, foie, pancréas....
- ◆ Monitorage
- ◆ Thermo-modulation
- ◆ Adressage d'agents thérapeutique

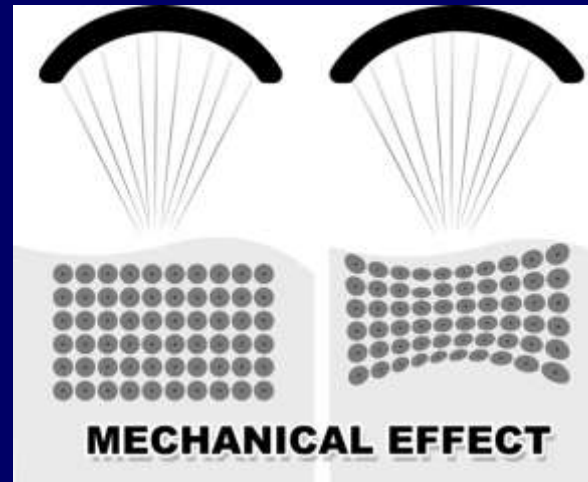
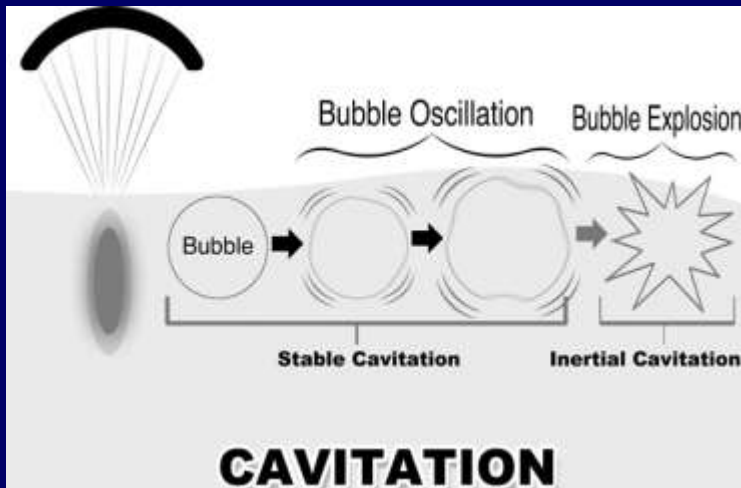
Effet des US

En mode continu à énergie faible ou élevée

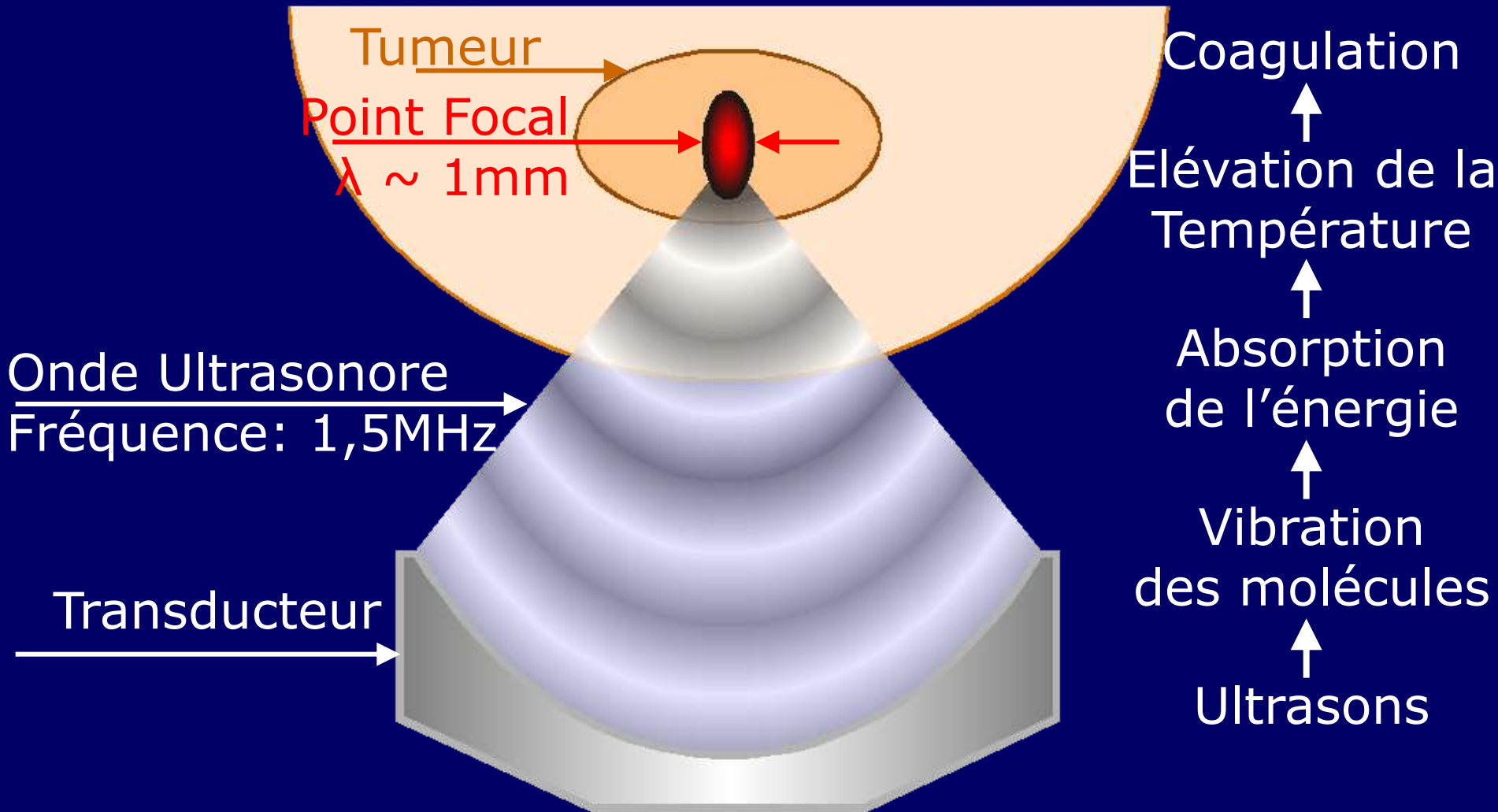


Thermoablation
Thermomodulation

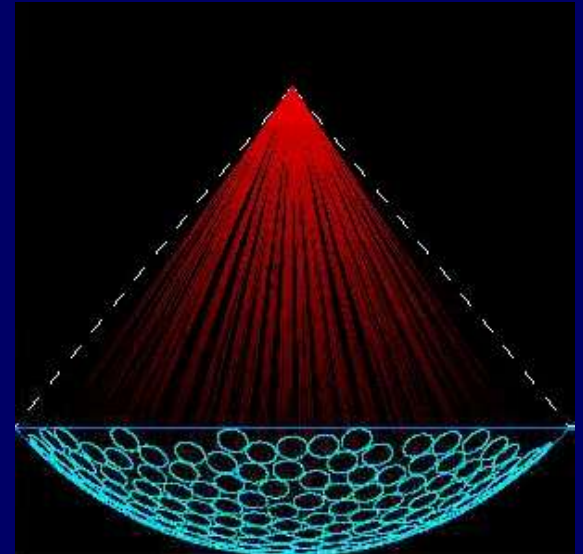
En mode pulsé selon l'énergie:
Histotripsie - Sonoporation



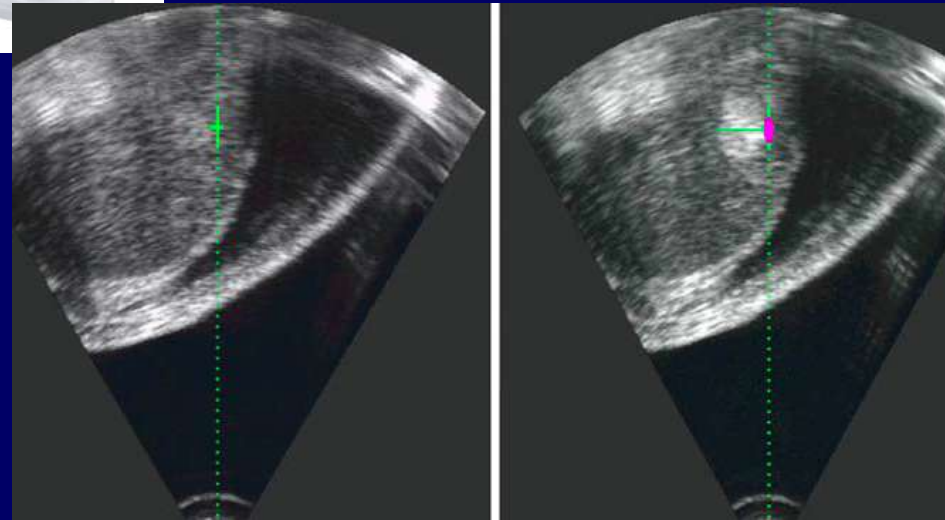
Thermoablation



Transducteur couplé à une sonde d'échographie en son centre: monitorage US

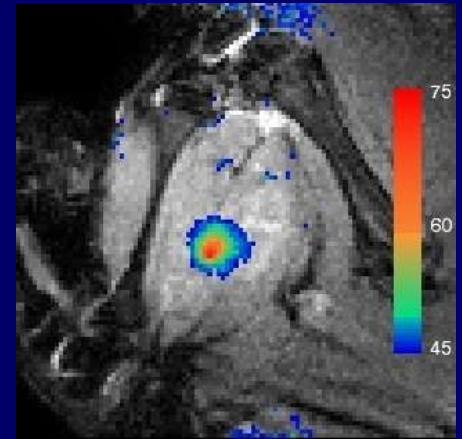


JC focused ultrasound
tumor therapeutic system
Chongqing Haifu Technology Co., Ltd.

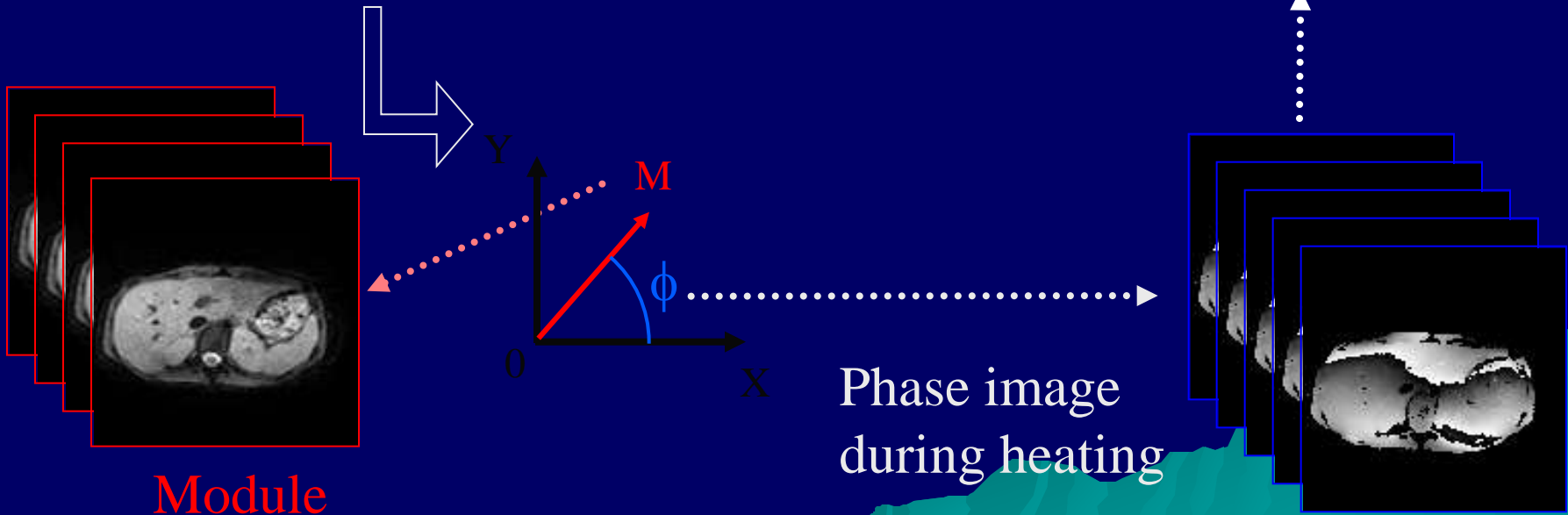


Changement hyperechogène reflétant
les phénomènes de cavitation

MRI: a thermometer!!



Thermal Map
($\Delta T^{\circ} \text{C} + 37^{\circ} \text{C}$)

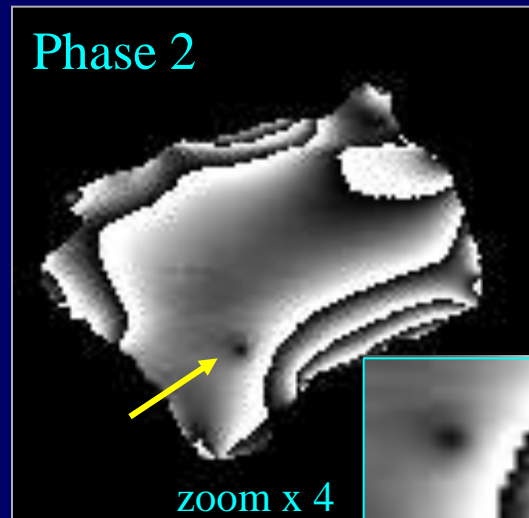
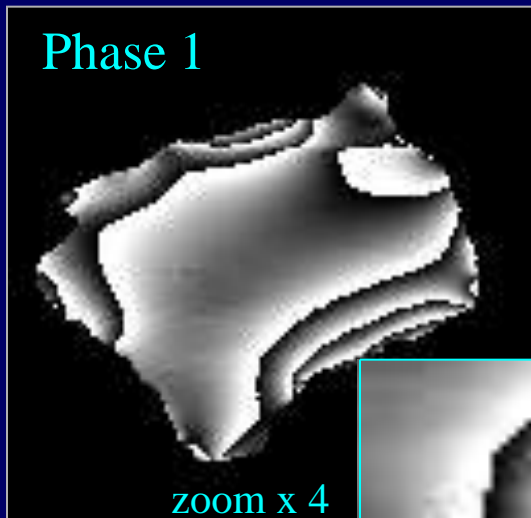


Temperature map based on PRF

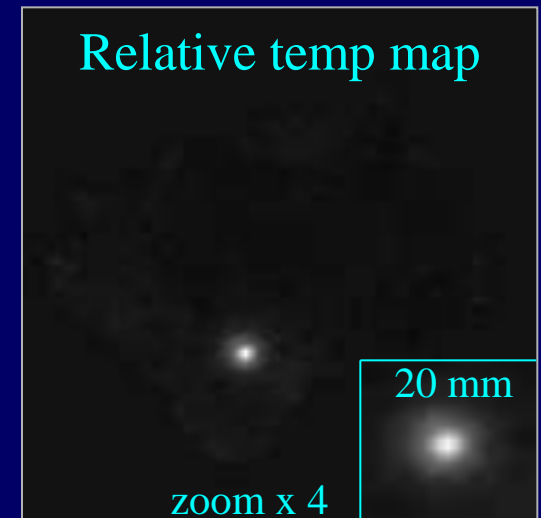
$$d\sigma / dT = \beta = 0.01 \text{ ppm}/^\circ\text{C} \pm 5\% \quad \Delta T = -\Delta\phi / (\beta \cdot \gamma \cdot B_0 \cdot T_E)$$

linear and independent of tissue type

Gradient echo with spoiler



Phase 2 – Phase 1



Comparison of US- and MR-guided FUS

Aspect	US	MR Imaging
Ease and frequency of use	High	Low
Real-time intraprocedural tumor detection	Variable	Generally excellent
Temperature imaging	Limited	Excellent
Cost	Low	High
In clinical use	Extensively outside U.S.	Limited worldwide
Postablative imaging role	Limited	Excellent
Operator dependent	Highly	Moderately

Tempany et al

*Radio*logy: Volume 259: Number 1—April 2011

◆ Système US:

- Le plus simple
- Limite pour le repérage précis de la tumeur
- Limite pour le monitoring avec les US

◆ Système IRM

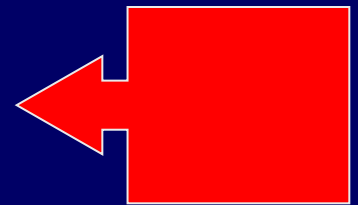
- Image de repérage optimale
- Monitoring du traitement en temps réel
- Rétrocontrôle avec automatisation (sécurité)
- Coût

Therapeutic FUS Companies with Oncologic Applications

Company	Device Trade Name/Guidance (MR or US)	Clinical Application	Status
InSightec, Haifa, Israel	ExAblate 2000/MR	Extracorporeal, fibroids	FDA cleared for fibroid ablation
InSightec, Haifa, Israel	ExAblate 4000/MR	Extracorporeal, bone, brain, breast, transrectal prostate	Clinical and preclinical trials
Misonix/USHIFU Focus Surgery, Indianapolis, Ind	Sonablate 500/US	Transrectal prostate	Clinical and preclinical trials
Phillips Healthcare P.O. Box 10.000, 5680 DA Best, the Netherlands	Sonalleve MR-HIFU/MR	Uterine fibroids	Clinical and preclinical trials
EDAP TMS S.A. Parc d'activités la Poudrette-Lamartine 4, rue du Dauphine, 69120 Vaulx-en-Velin, France	Ablatherm HIFU/US	Transrectal prostate	Approved in Europe, Canada, Russia, Australia, South Korea; Clinical and preclinical trials
Chongqing Haifu (HIFU) Technology 1 Qingsong Road Renhe, Yubei District, Chongqing 401121, China	Haifu/US	Extracorporeal, liver, bone, fibroids, soft tissue sarcomas, kidney, pancreas, and many others	Clinical and preclinical trials
Mirabilis Medica 18706 North Creek Pkwy, Suite 110, Bothell, WA 98011		Extracorporeal fibroids	Clinical and preclinical trials
		Prostate	
Profound Medical, 3080 Yonge Street, Suite 4040, Box 34 Toronto, Ontario, Canada M4N 3N1		Transurethral/prostate	Clinical and preclinical trials
SuperSonic Imagine Les Jardins de la Duranne, Bât E & F, 510 Rue René Descartes, 13857 Aix-en-Provence, France		Brain	
Theraclion Pépinière Paris Santé Cochin, 29 rue du Faubourg Saint Jacques, 75014 Paris, France	TH-One/US	Parathyroid	Clinical and preclinical trials in hyperparathyroidism
Image guided therapy 2, Allée du Doyen Brus, 33600 Pessac, France			Preclinical breast cancer treatment and FUS mediated drug delivery

Fibroids: therapy

- ◆ Hormonal Drug transient effect
 - Progestin
 - Gonadotrophin-releasing-hormone-agonist
- ◆ Conservative approach (\pm mini-invasive)
 - Myomectomy
 - Uterine artery embolization
 - HIFU outpatient procedure
and very short recovery period
- ◆ hystérectomy:
First surgery most for fibroids

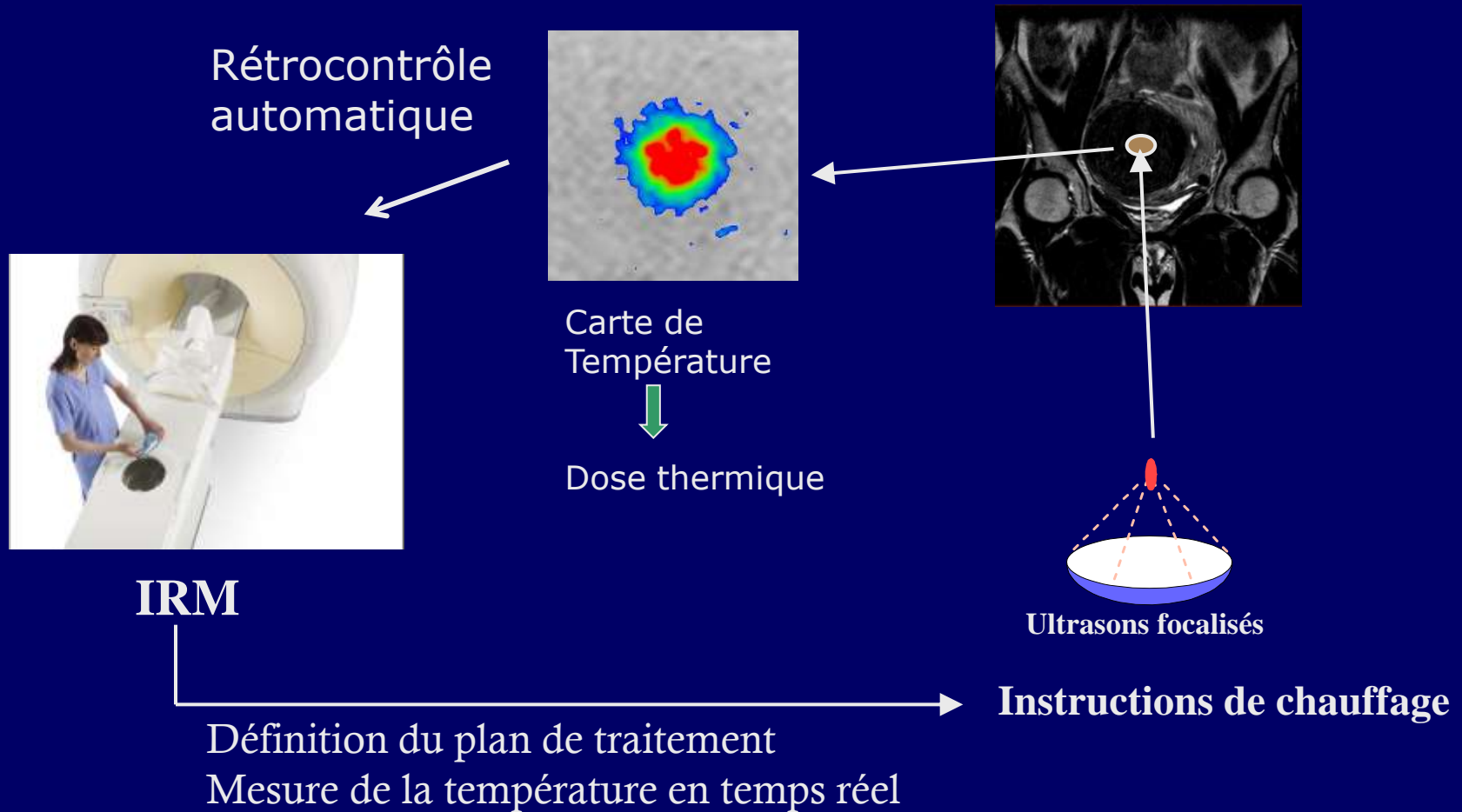


Uterine Fibroids

Comparing treatment options

Treatment Factors	Hysterectomy	Myomectomy	UF Embolization	MR-HIFU
Procedure count (USA, 2007)	250.000	25.000	25.000	> 4.000 (total ww)
Hospital stay	2 – 5 days	1 – 3 days	2 days	0
Complication rate	2 – 50%	2 – 34%	Peri op: 10% Post op: 2%	< 3%
Return to normal activity	28 – 56 days	44 days	10 days	1-2 day
Future fertility	No	yes 50% increased risk during pregnancy	(yes) Possible ovarian embolization	(yes) Exclusion criteria, but encouraging data
Drawbacks/ complications	No future pregnancy, emotional stress	30% recurrence within 5y	effective in 90% of patients at 1 year and 80% at 5 years	effectiveness depends on the NPV long-term monitoring?

Ultrasons focalisés en IRM et Système automatisé



MR-HIFU

Traditional ablation concept

- ◆ Point-by-point ablation
- ◆ Challenge #1 – treatment time
 - Ablation speed limit ~1 ml/ min
 - Excessive cooling times
 - Long procedure times 3h+
- ◆ Challenge #2 – tissue properties
 - Local variations in tissue properties
 - Inhomogeneous absorption, attenuation, perfusion, diffusion
 - ◆ Irregular heating patterns
 - ◆ Risk of incomplete coverage



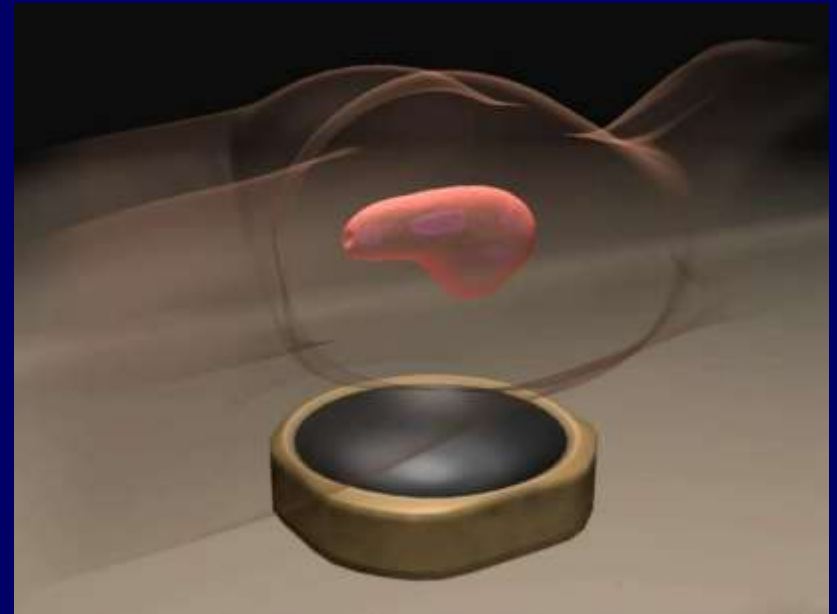
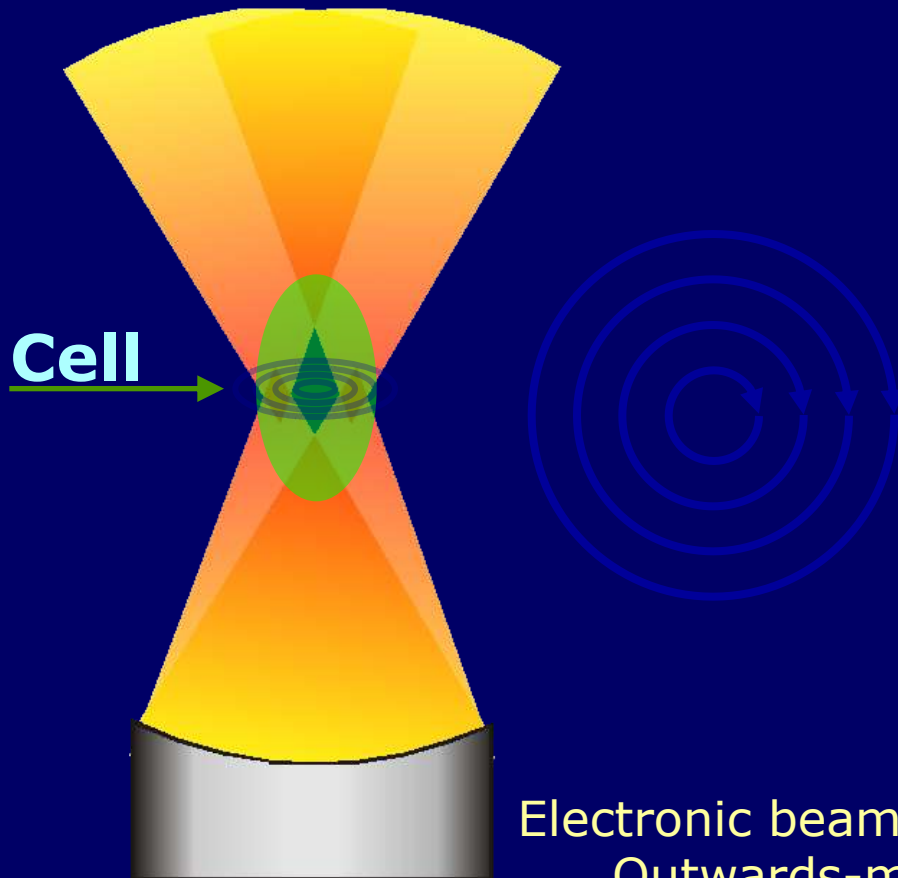
New ablation concept

- ◆ Volumetric heating addressing #1
- ◆ Real-time feedback addressing #2

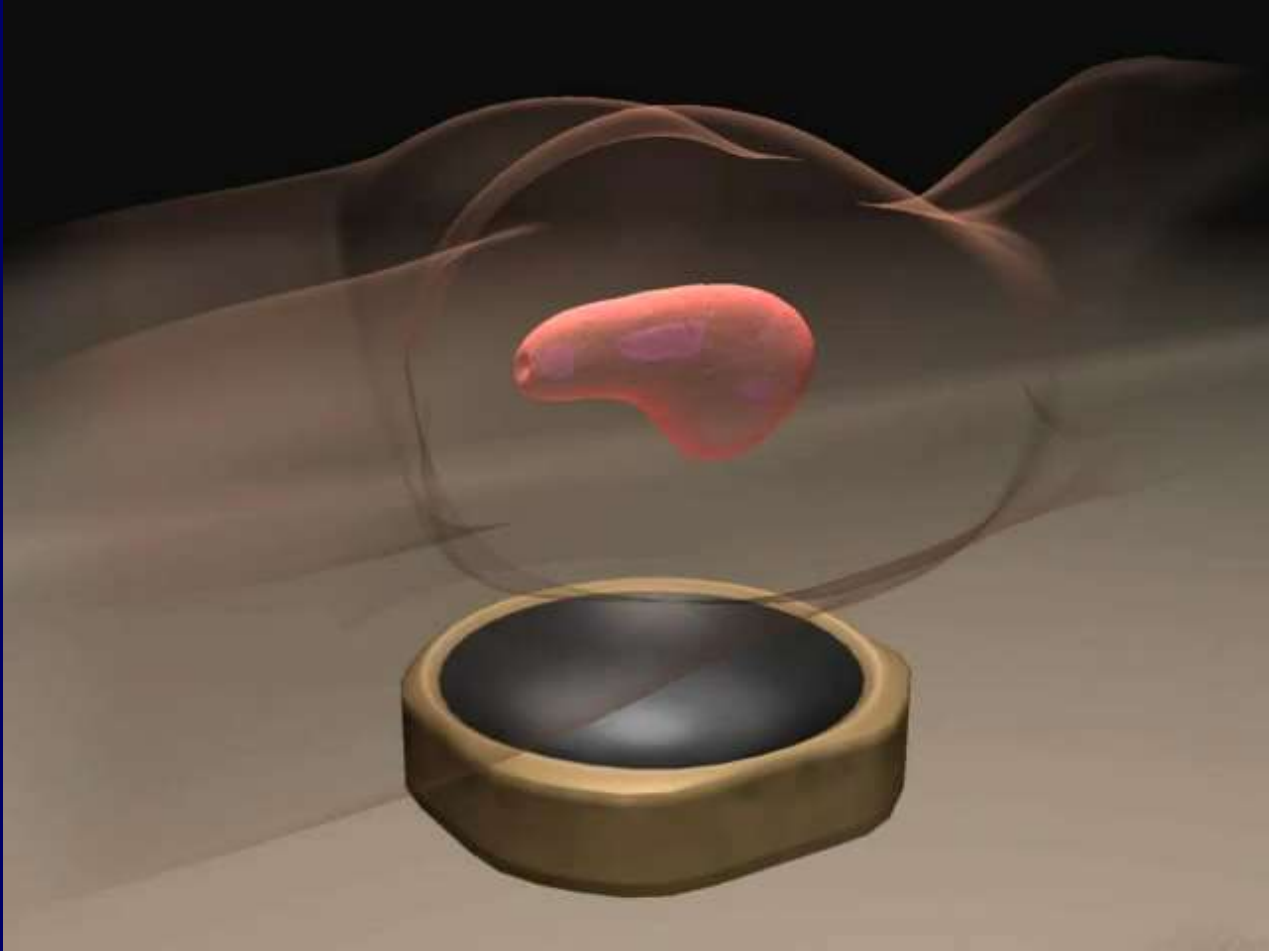
Volumetric ablation

Increased efficiency

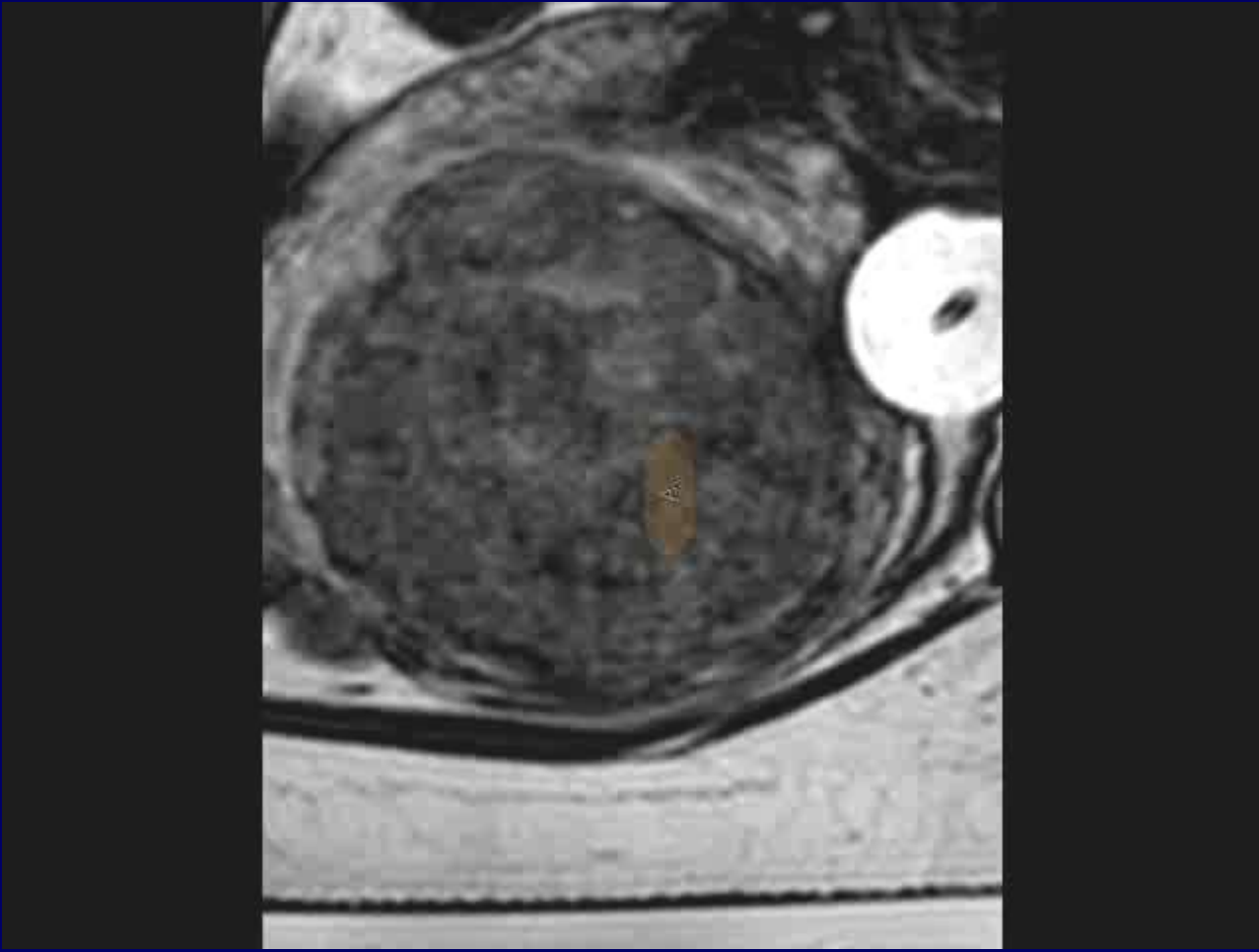
Several volumetric ablation were performed in order to cover the large fibroid volume



Electronic beam steering:
Outwards-moving
concentric circles
4 – 16 mm \varnothing



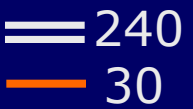
Exemple d'une insonification de 12mm Ø sur un fibro-myome Ut



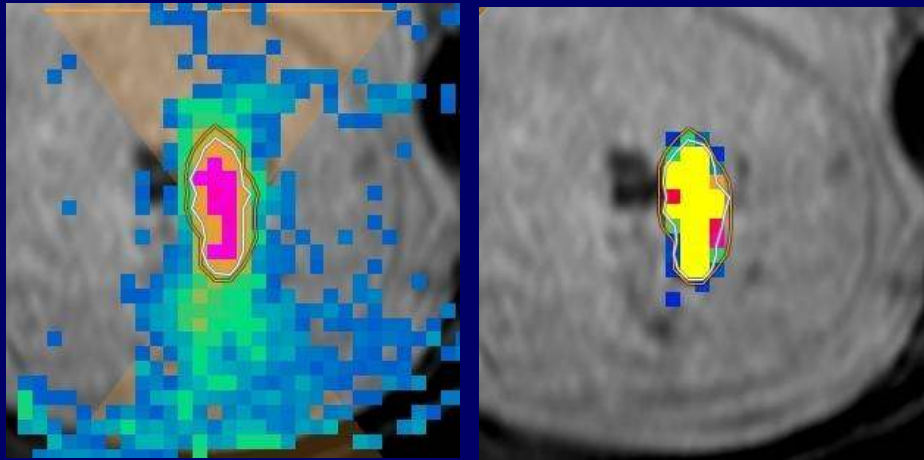
Temp. [° C]



Dose [EM]



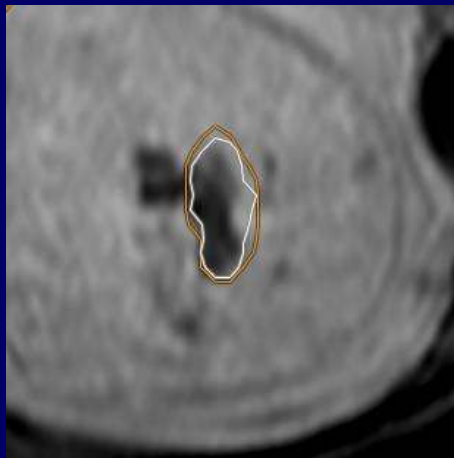
Contrôle automatique de l'ablathermie



Temperature

Dose thermique

STOP



Volume non perfusé

Cartographie de Temperature & Dose
Thermique

Visualisation en temps réel

+

Contrôle automatique

Temp. bord > 54-57° C
ou Dose > 240 EM

Stop HIFU

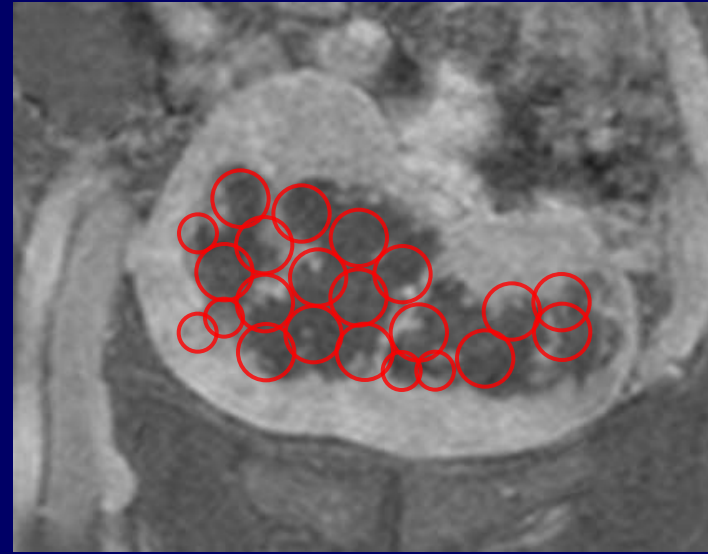
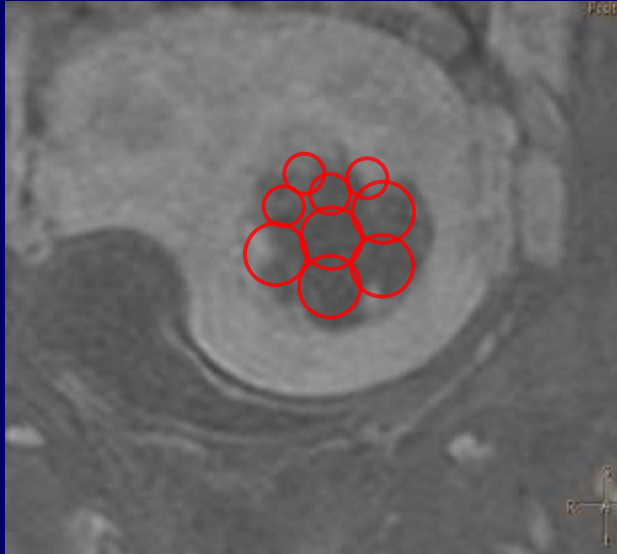
Taille de nécrose attendue

Non perfused volume: good correlation between the ablated volume planned and the NPV

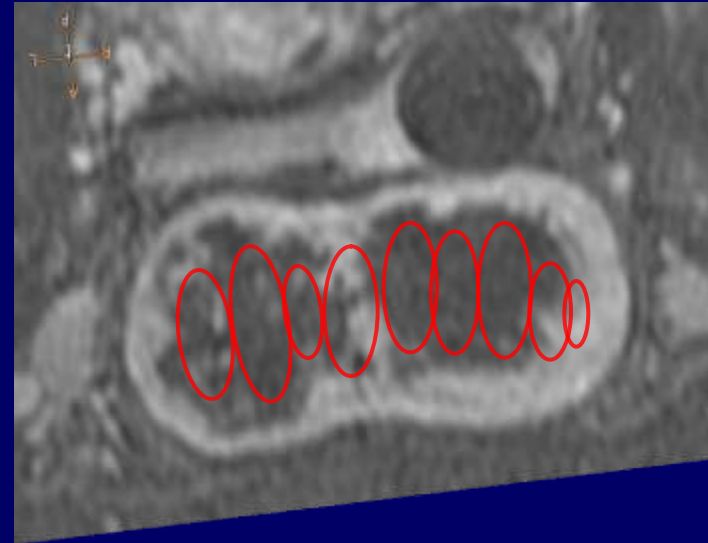
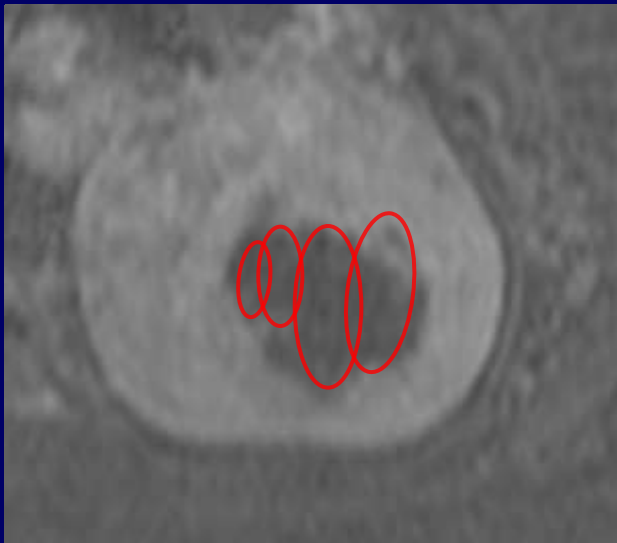
Exemple 1

Exemple 2

CORONAL

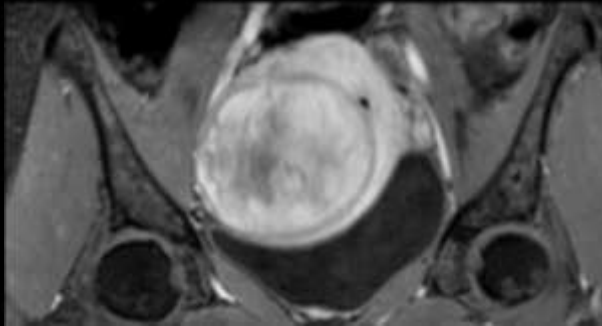
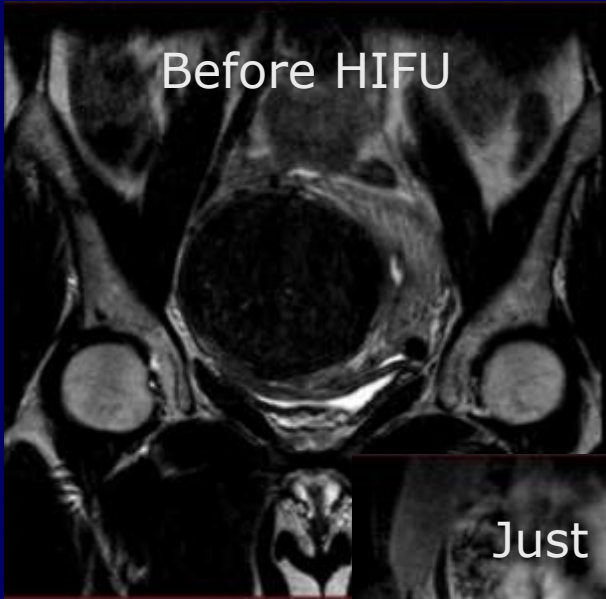


SAGITTAL

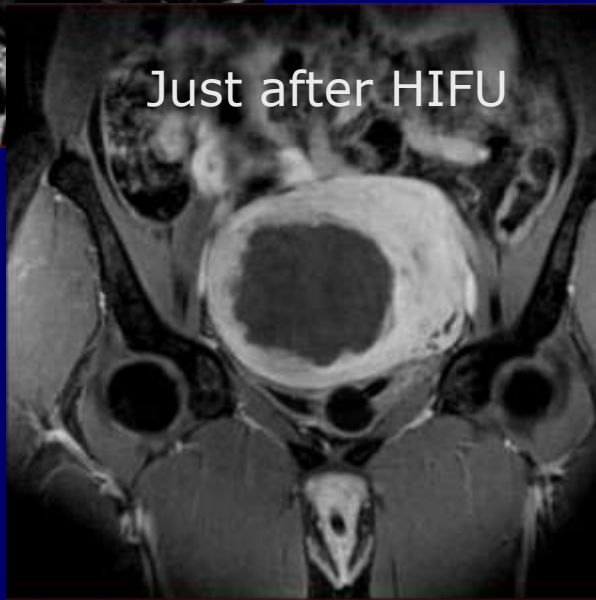


Example of an HIFU treatment outcome

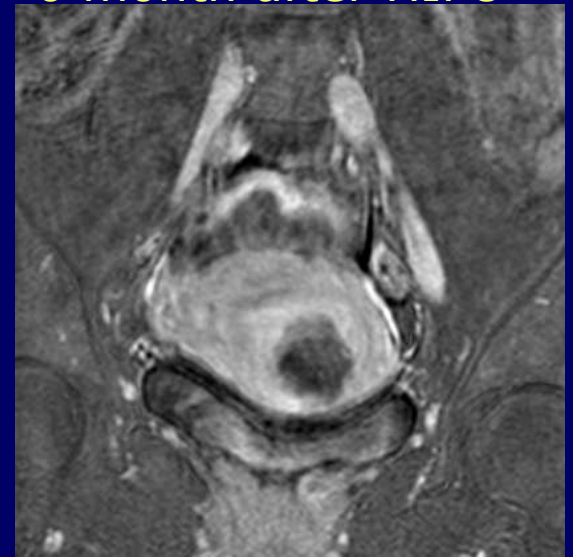
Before HIFU



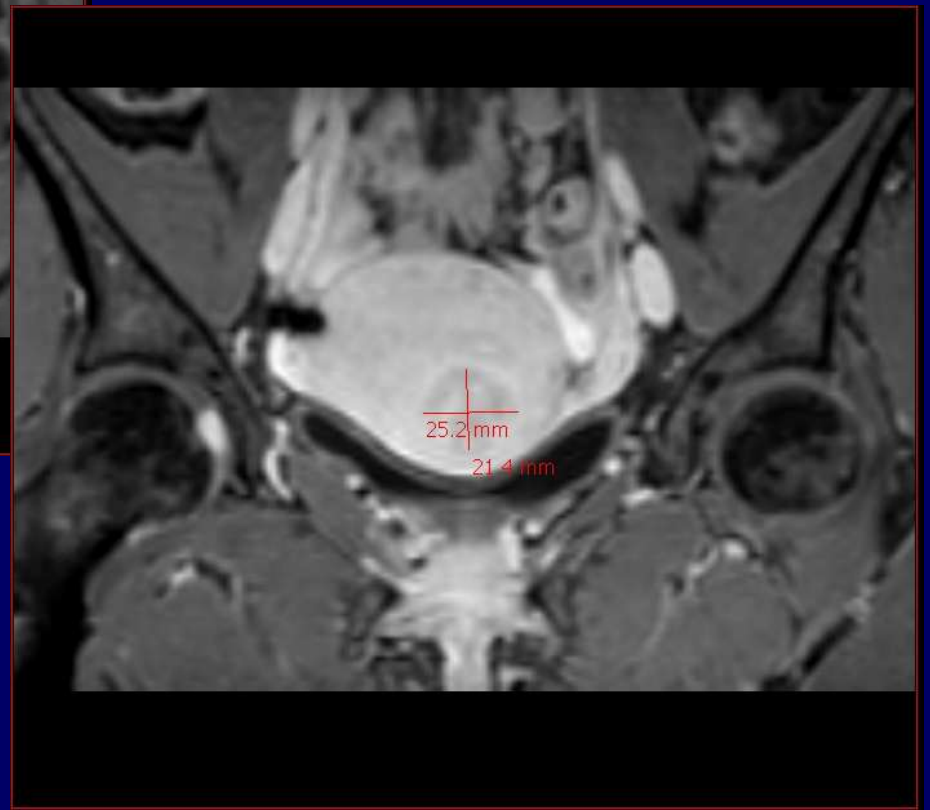
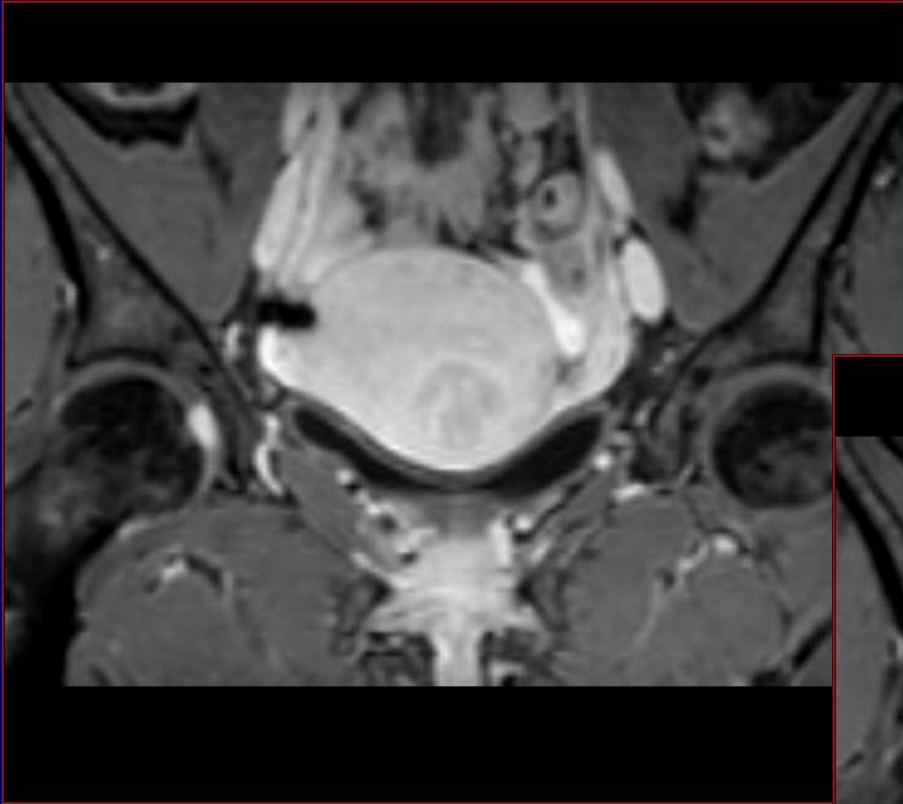
Just after HIFU



6 month after HIFU



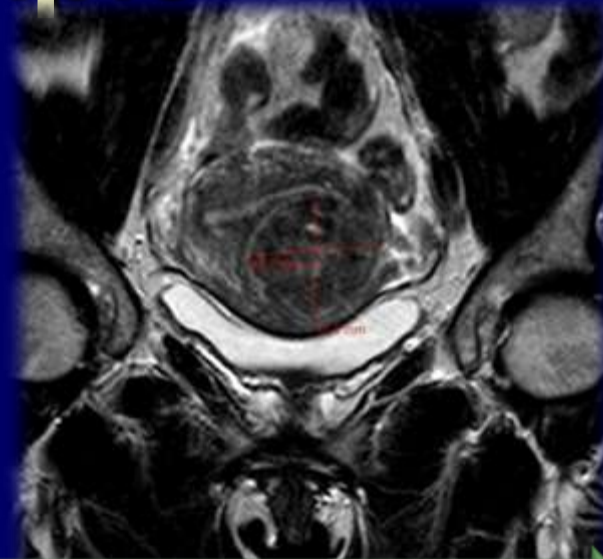
1 year after HIFU



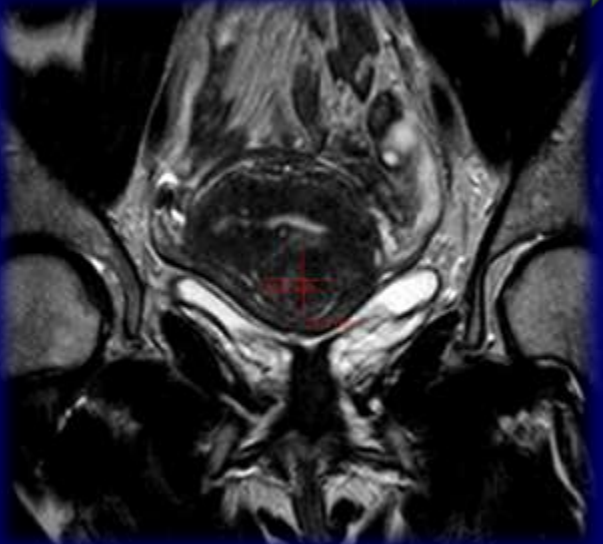
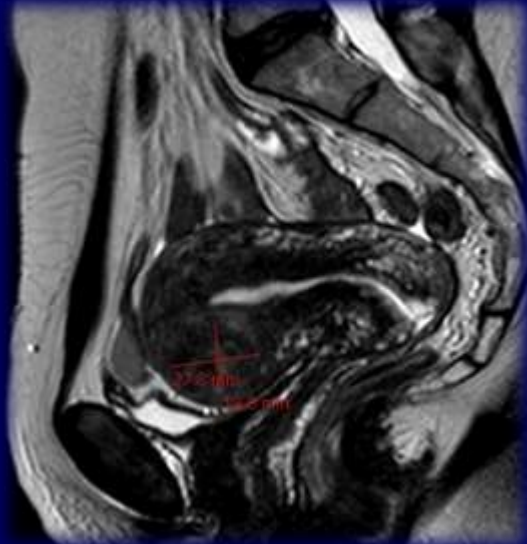
Effet sur le volume : Exemple

Volume

J0



M12

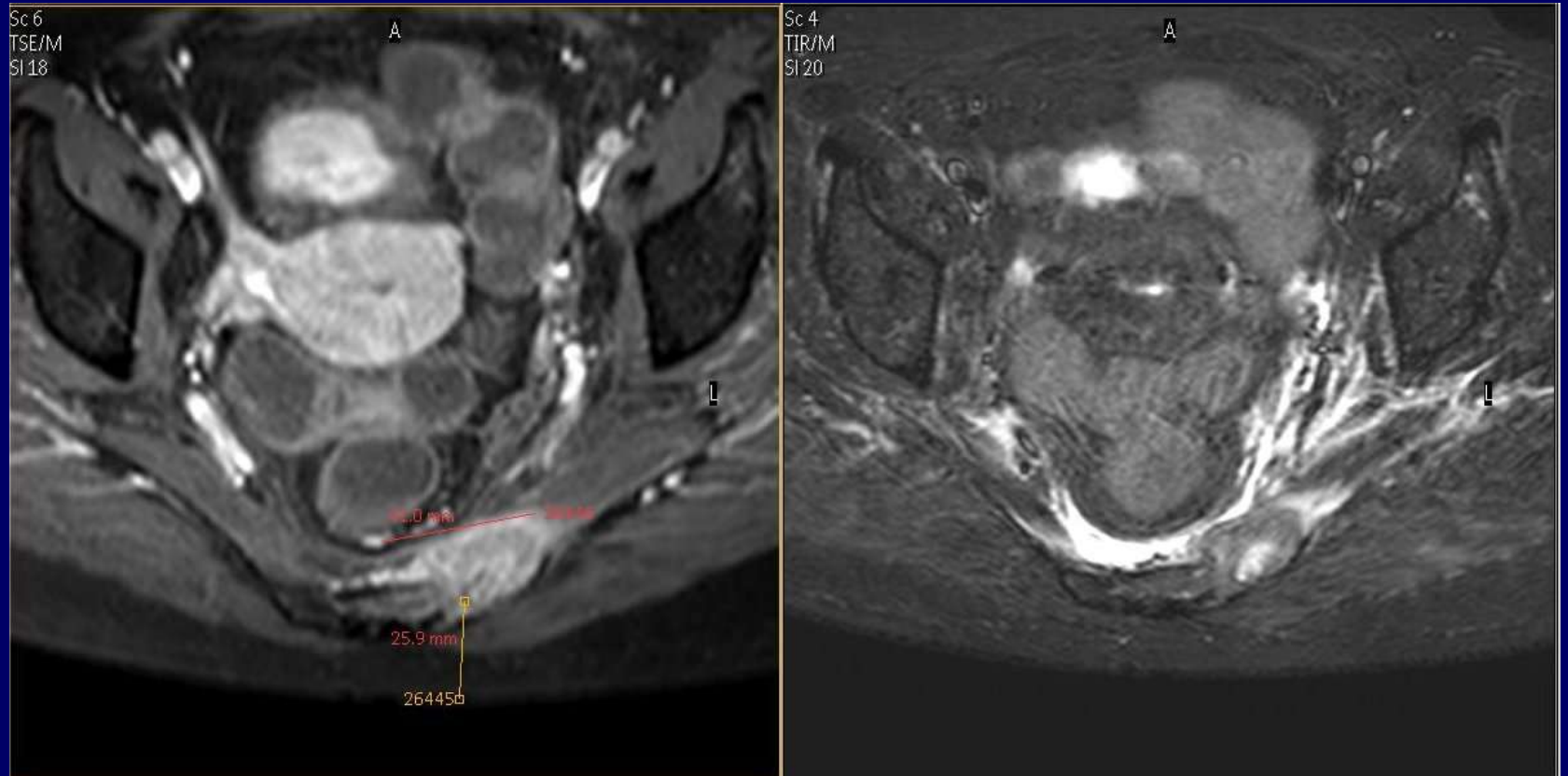


-
70
%

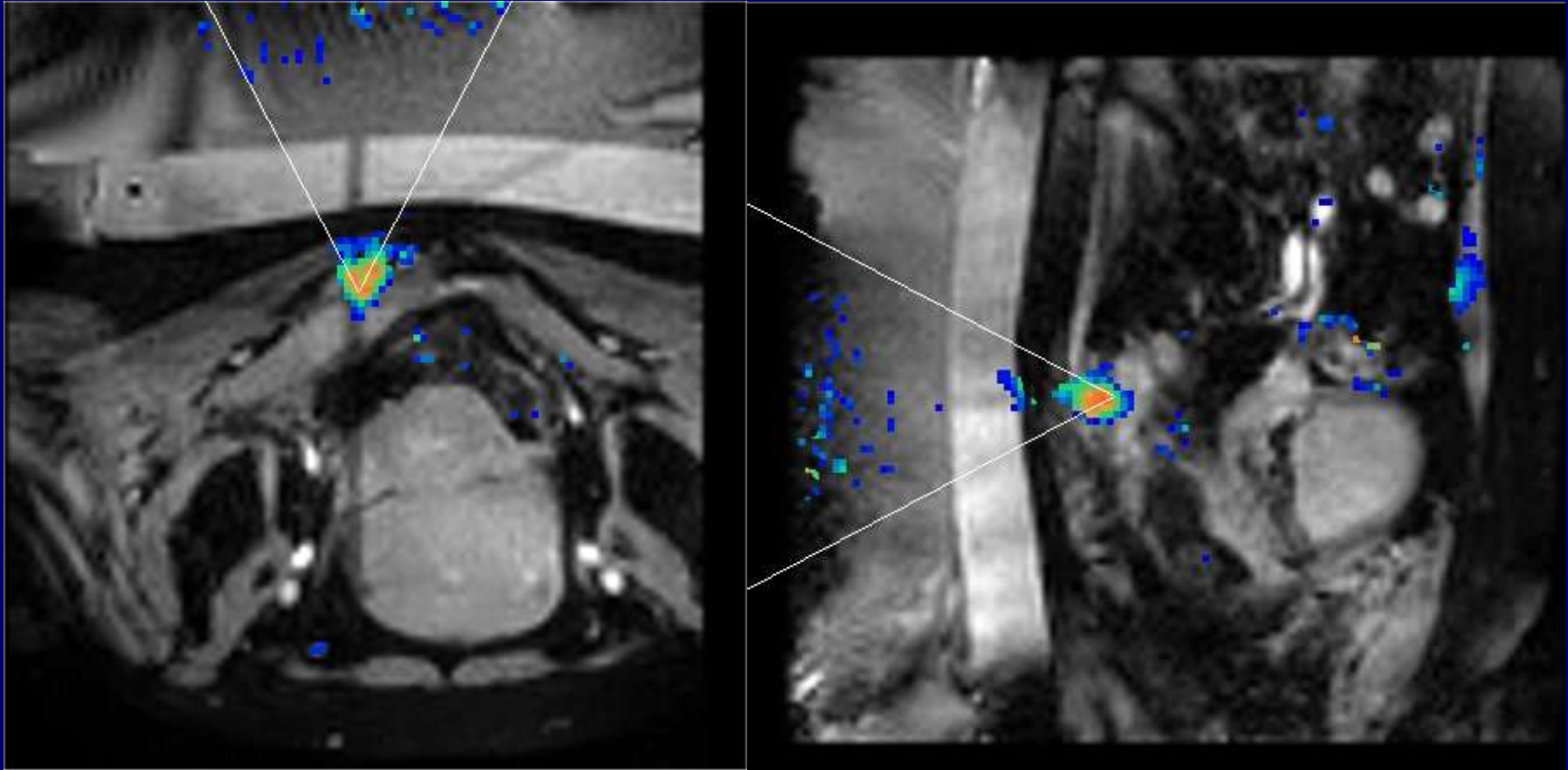
Effacité et Tolérance

	Nb patient	Eff clinique (%)	NPV (%)	%diminution	E secondaire
Voogt	36			22	0
Ikink	46	54	40	30	0
Yoon	60	90	40	30	0
Thiburce	46	74	36	30	0

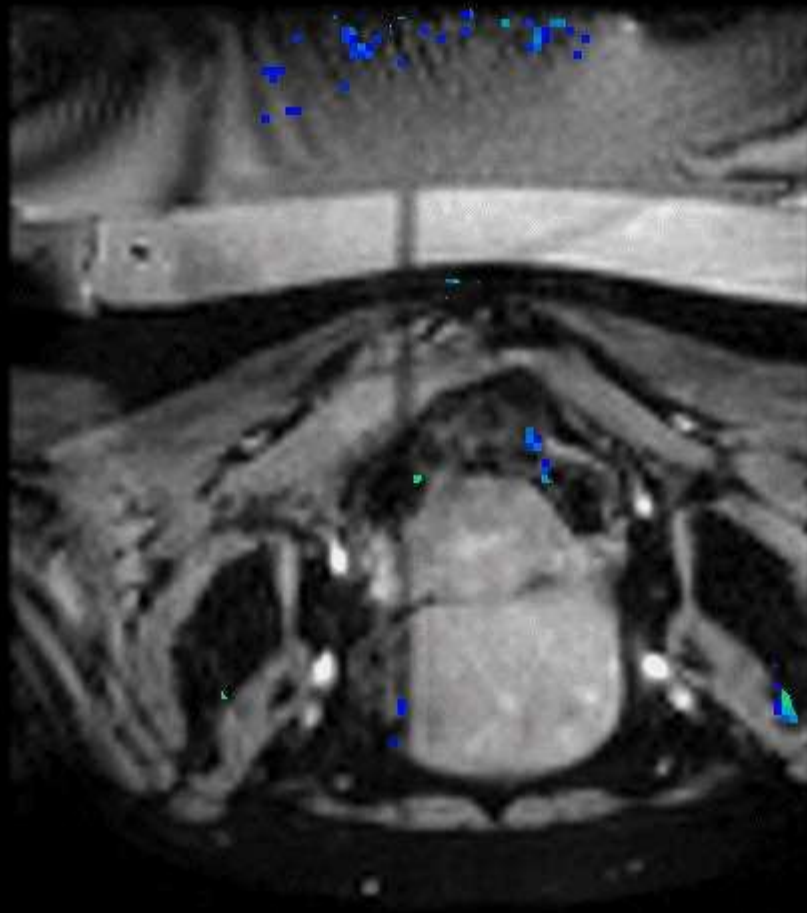
Os

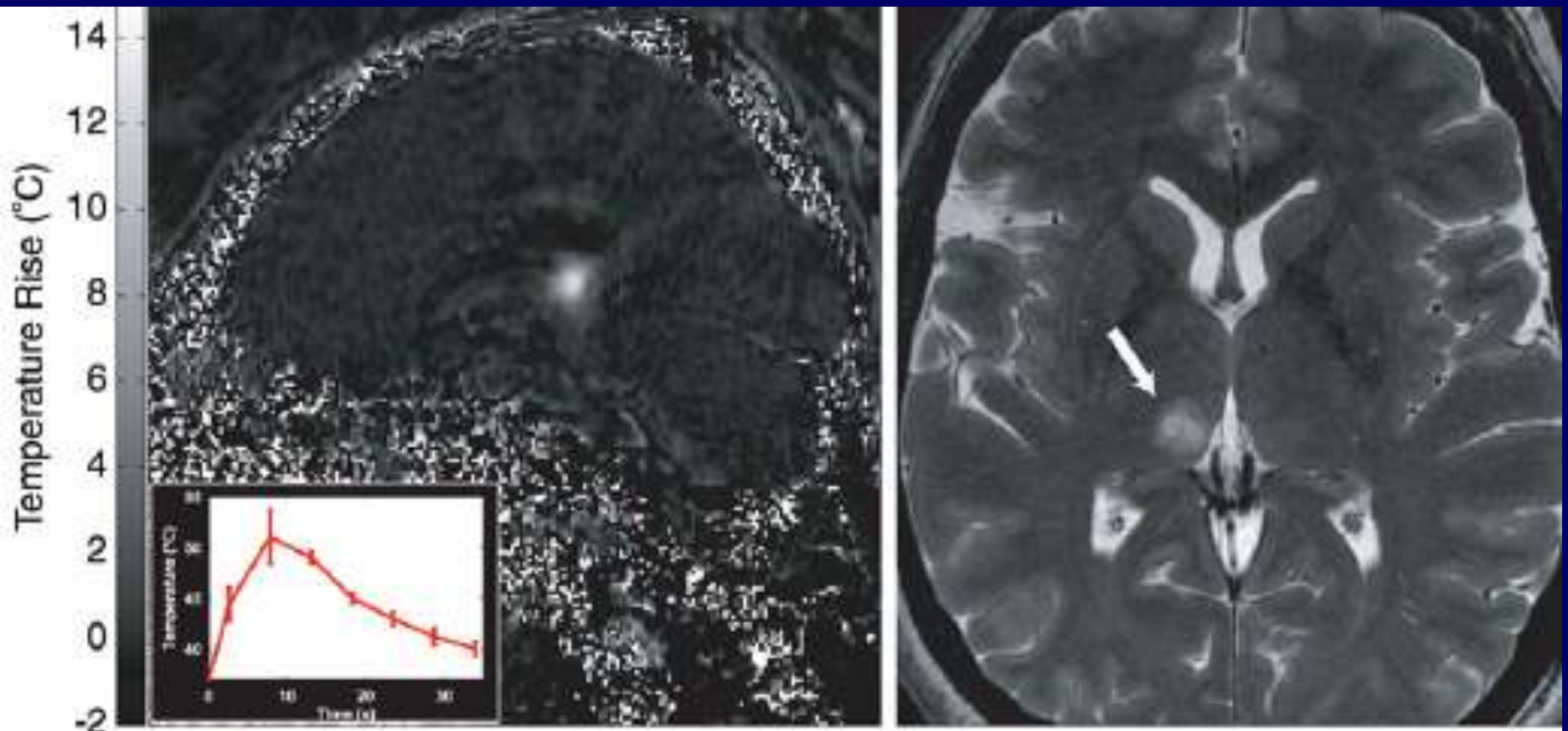


Sonic #7 (12:43:06)



Power=40 W, duration 20.5 sec, $f=1.2\text{MHz}$
Immediately after sonication
with ultrasound cone indicators

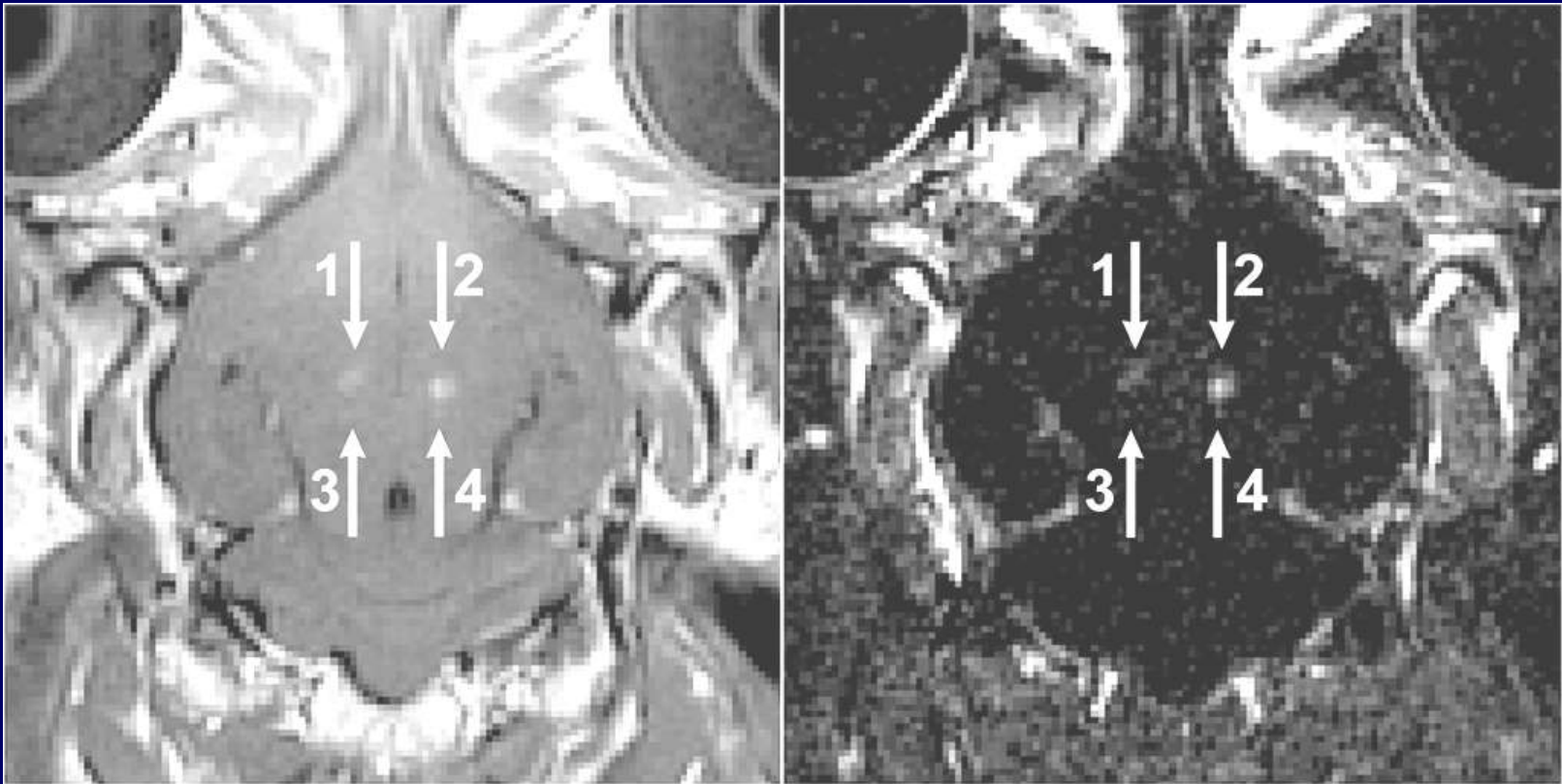




University Children's Hospital, Zurich, Switzerland

Local Drug Delivery via permeability enhancement

Focal BBB Opening using High Intensity Ultrasound in rabbit



T1- weighted contrast enhanced scan

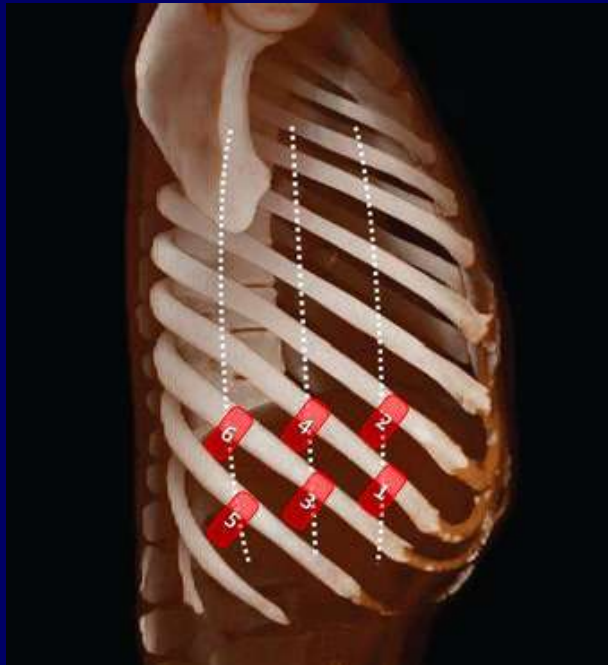
Hynynen et al. Boston

Subtraction Image:

TDI-w: After – Before Contrast Injection

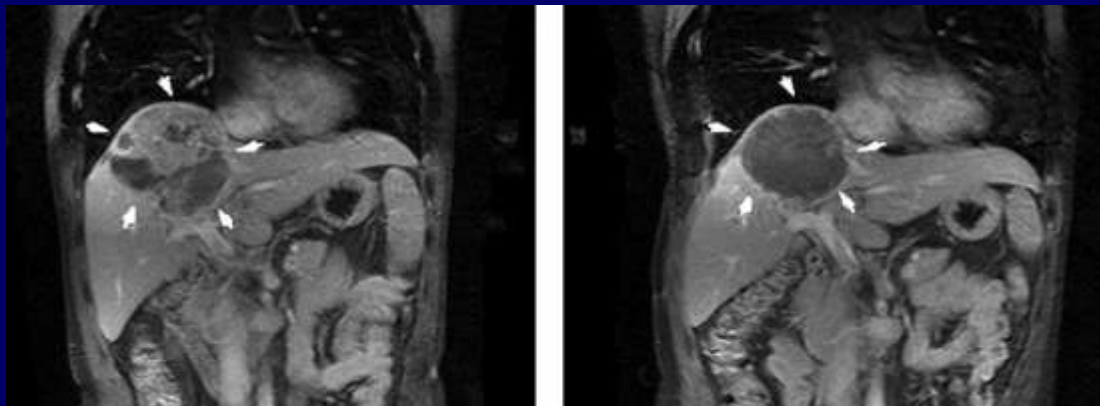
2 problèmes à résoudre pour le foie

- ◆ Les interfaces liées aux côtes
- ◆ Les mouvements respiratoires

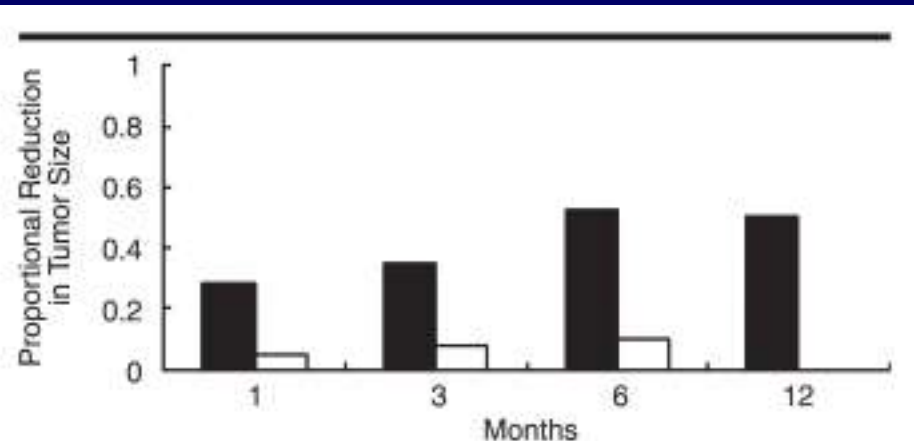
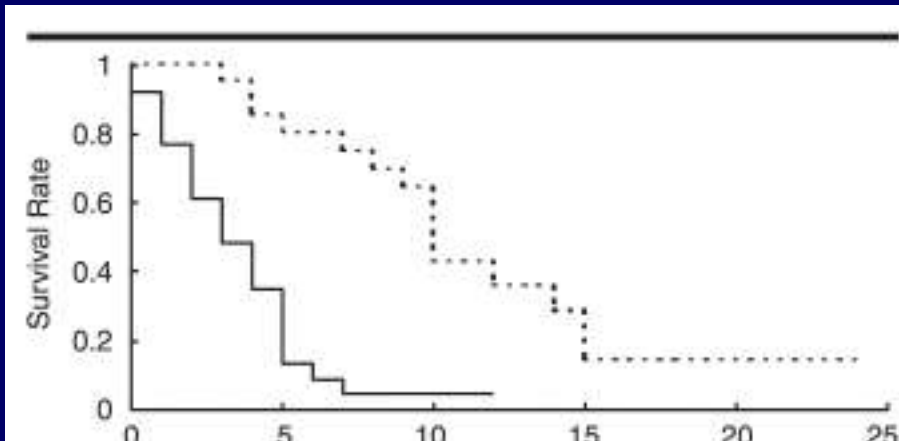


Mouvements respiratoires





*Wu et al Radiology 2005
(n=50-26=24)*



Survie CEL/CEL+HIFU

Pourcentage de réduction tumorale

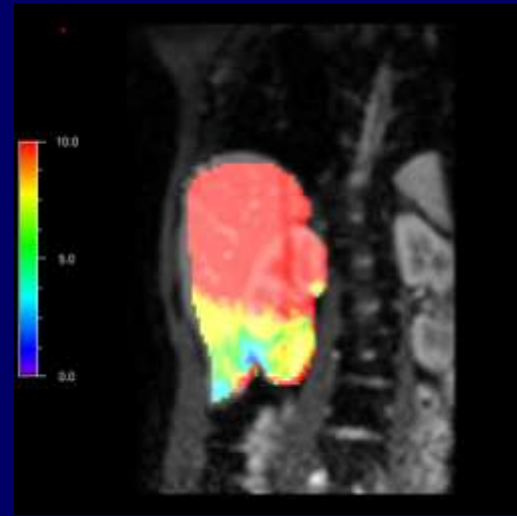
- AG
- 2-8 heure de procédure (moyenne: 4,9 h)
- Nombre de sessions: 1,5

Thermométrie en présence de mouvement : effet de la correction

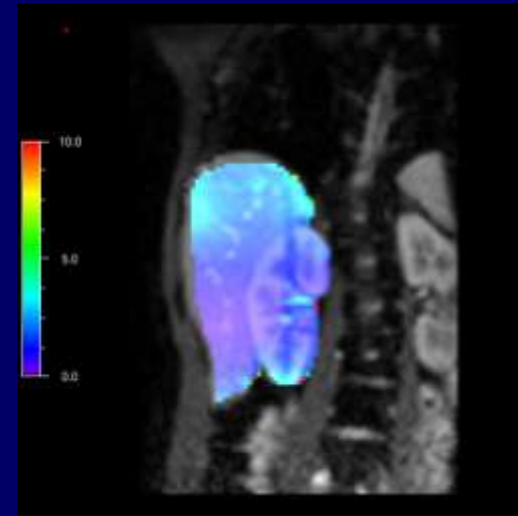
Respiration libre



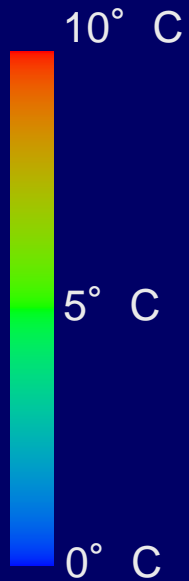
Image anatomique



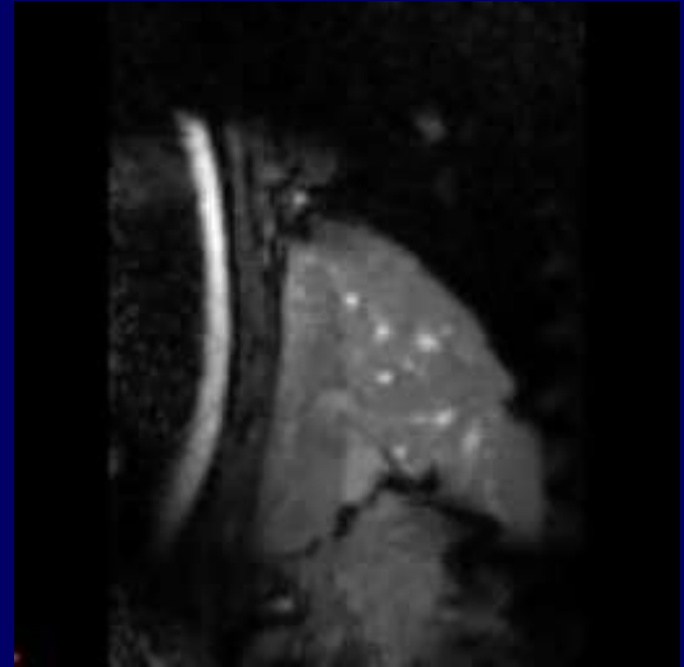
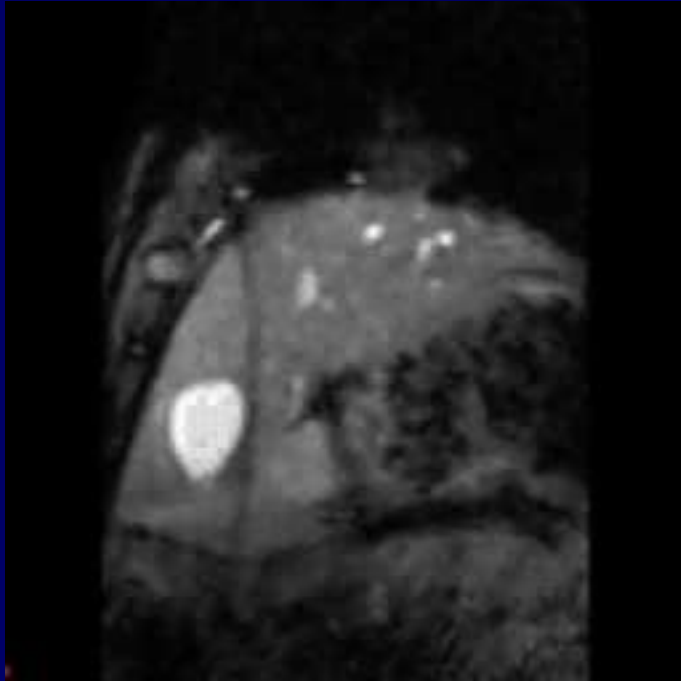
Déviations standards de T
(Sans correction)



Déviations standards de T
(Avec correction)

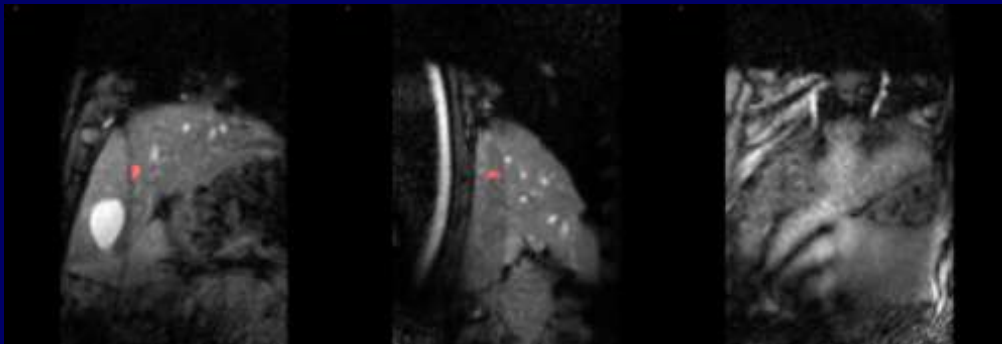
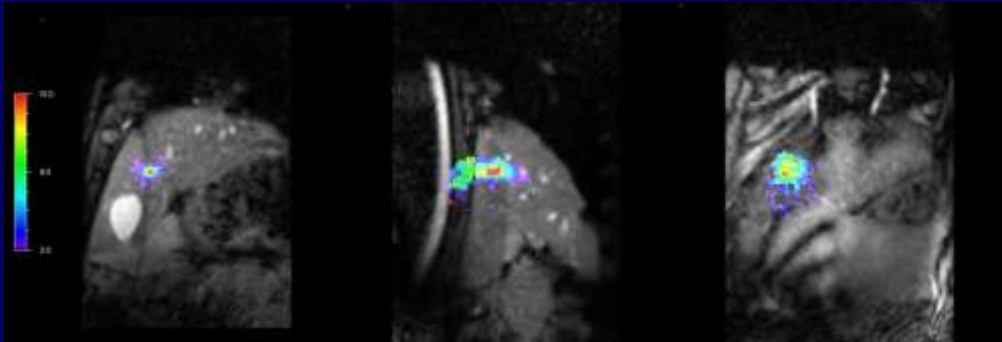


HIFU avec correction de mouvement sur un foie de porc

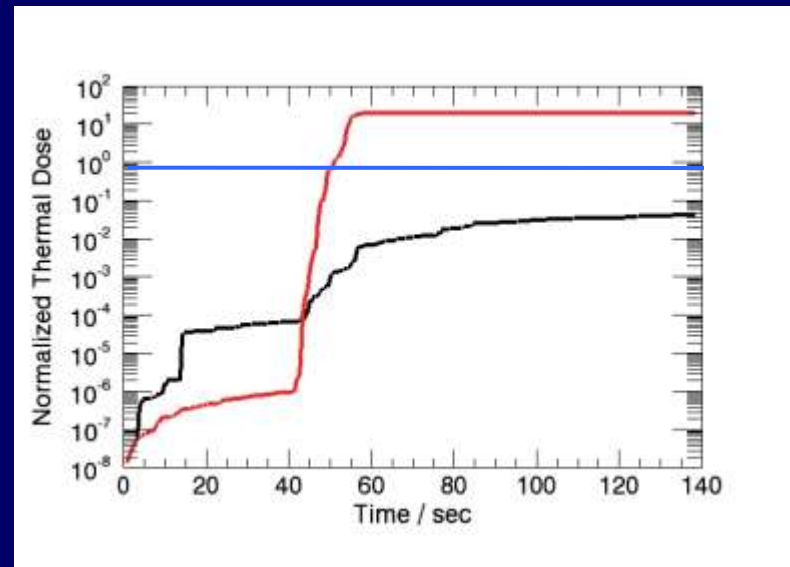
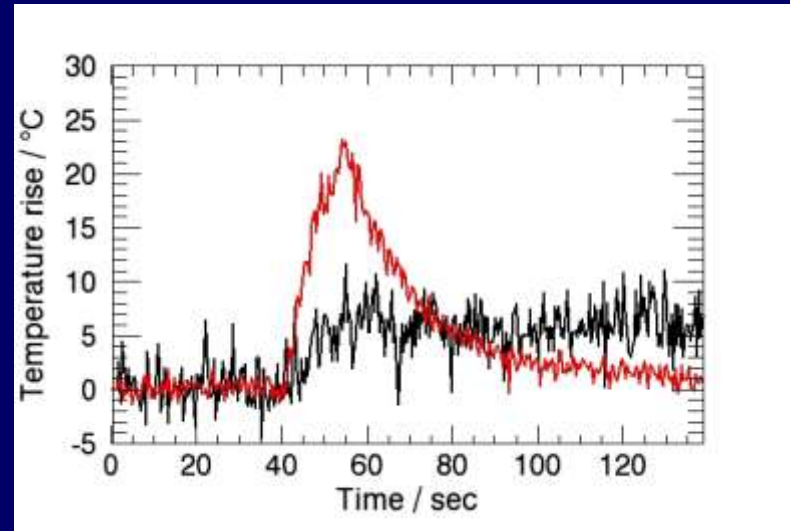


Dose thermique

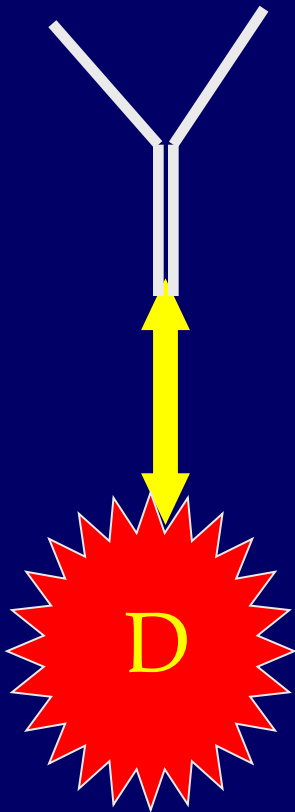
Élévation de température



Dose thermique

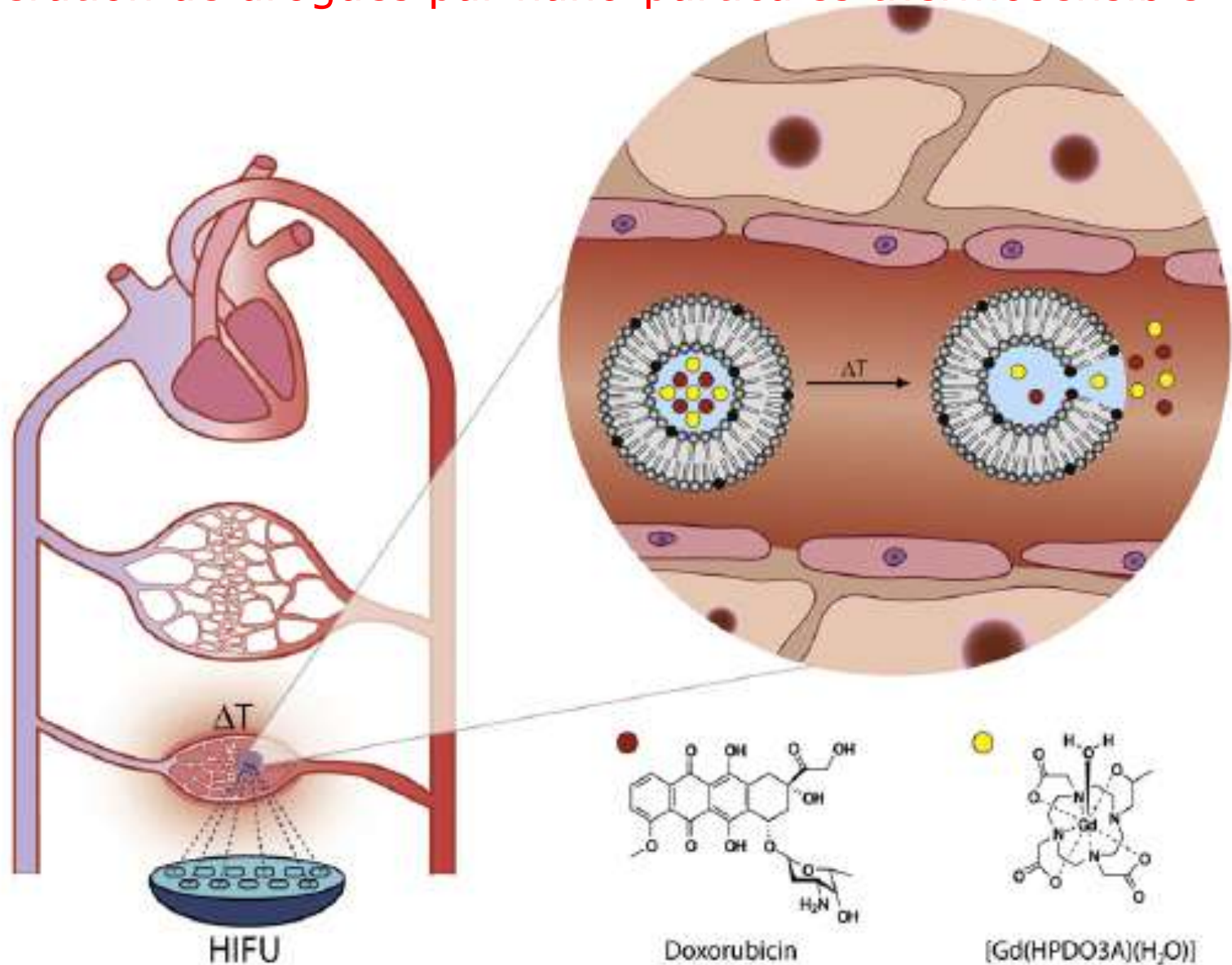


Combinaison pour le diagnostic et la thérapie



- ◆ Cible spécifique
 - Fragments d'Antigène
 - Peptides
 - Aptameres (fragments courts d' ADN/ARN)
- ◆ Liaison sensible à la température (**promoteur thermosensible HSP 70**)
- ◆ **Produit de contraste (multiple)**
 - Gd
 - Particules de fer
 - **Drogues**

Libération de drogues par nano-particules thermosensible



Magnetic resonance imaging of high intensity focused ultrasound mediated drug delivery from temperature-sensitive liposomes: An *in vivo* proof-of-concept study

Mariska de Smet^a, Edwin Heijman^b, Sander Langereis^b, Nicole M. Hijnen^a, Holger Gröll^{a,b,*}

Journal of Controlled Release 150 (2011) 102–110

Conclusion

- ◆ Traitement par ultrasons focalisés
 - Pas d'effraction cutanée
 - Ambulatoire
 - Morbidité faible
 - Combinaisons multiples pour la libération locale de drogues/ADN/ARN

Laboratoire CNRS/Université de Bordeaux/CHU de Bordeaux/labex Trail

- ◆ Franck Couillaud
- ◆ Baudoin Denis de Senneville
- ◆ Nora Frulio
- ◆ Nicolas Grenier
- ◆ Christophe Laurent
- ◆ Mathieu Lepetit Coiffé
- ◆ Crit Moonen
- ◆ Bruno Quesson