



De la recherche aux soins en cancérologie : apport des ultrasons focalisés

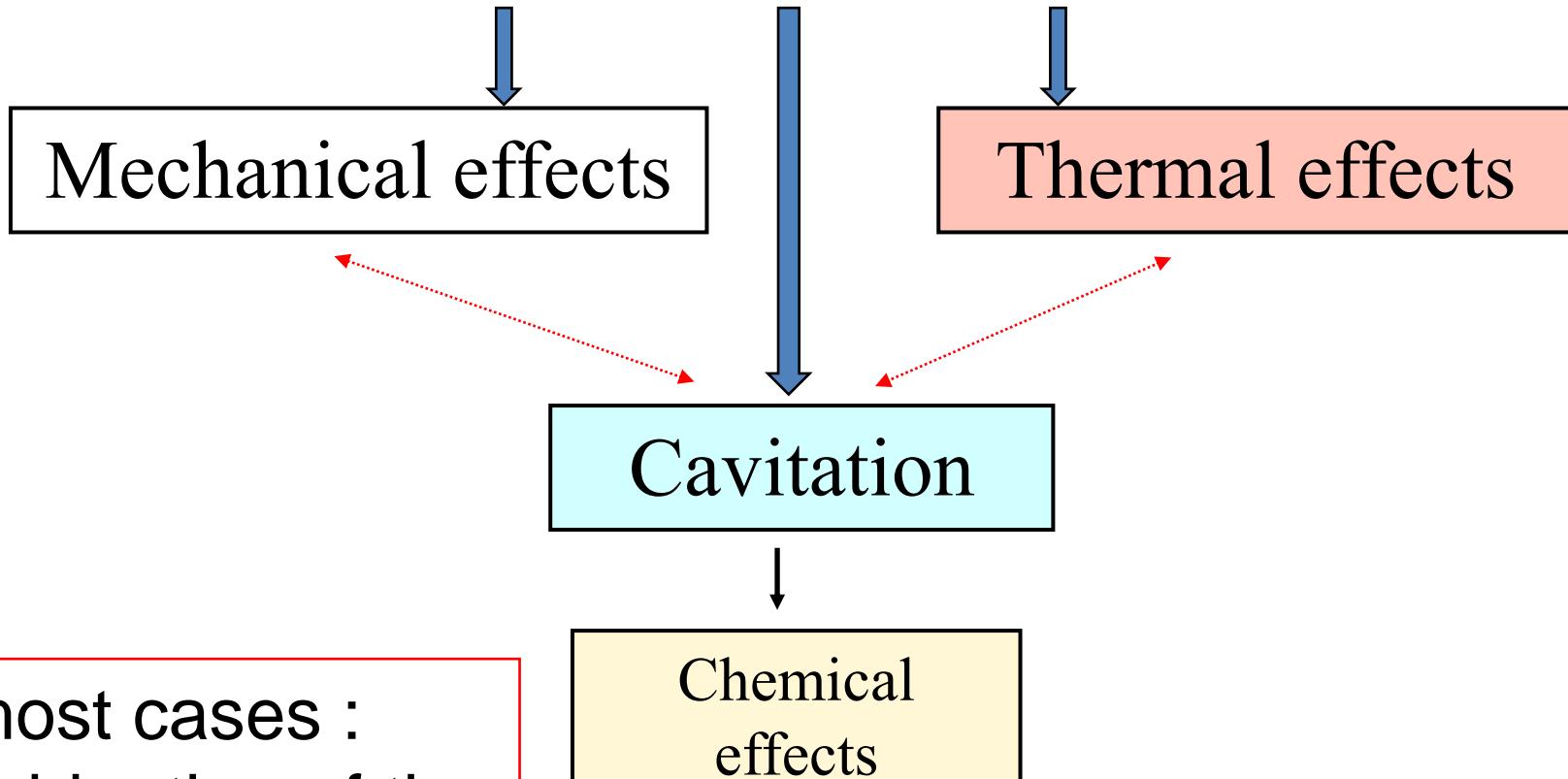
Jean-Yves CHAPELON

LAB ((TAU•





Interactions of Ultrasound with biological tissues



In most cases :
Combination of the
different effects



Oncological

Cardiovascular diseases

- Hypertension
- Periphe...
- Arteriosclerotic
- Atherosclerosis
- Atrial fibrillation
- Cardiac arrhythmias
- Congestive heart failure
- Deep vein thrombosis
- Hypoparathyroidism
- Syndromes
- Septal defects

Endocrine diseases

- Thyroid disorders
- Diabetes mellitus
- Obesity

Gastrointestinal diseases

- Liver cancer
- Pancreatic cancer
- Malignant melanoma
- Colorectal cancer
- Esophageal cancer

Miscellaneous diseases

- Soft tissue sarcomas
- Head & neck cancer
- Hypersensitivity
- Melanoma

Musculoskeletal diseases

- Bone marrow
- Back pain
- Osteoporosis
- Back problems
- Bone cancer
- Bone tumors
- Osteosarcoma
- Disc degeneration
- Muscle diseases
- Spinal cord

Bone metastases



genic

Prostate cancer*



itis

Breast cancer



n stump

Kidney cancer



Liver cancer



Pancreatic cancer



Soft tissue cancer



Bone cancer



Brain cancer



Head & neck cancer



Melanoma



Thyroid cancer



Cervical cancer



Lung metastases



Neuroblastoma, pediatric



Bladder cancer



Cancer pain



Colorectal cancer



Esophageal cancer



Lung cancer



Ovarian cancer



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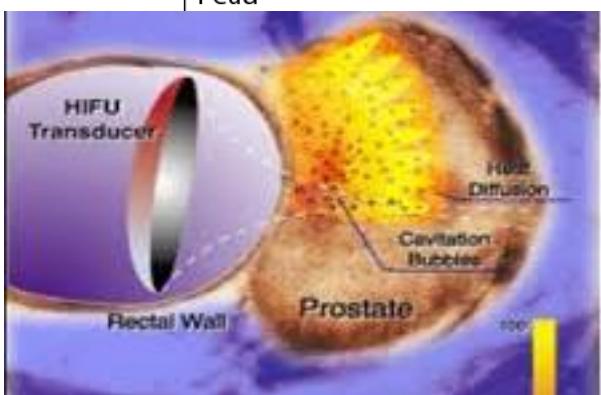
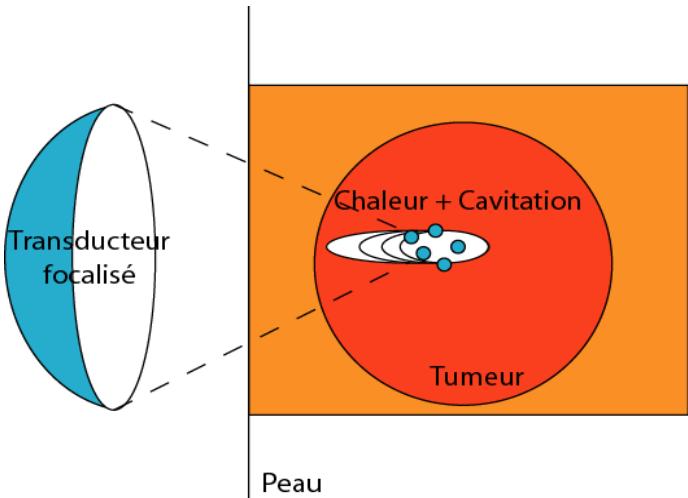
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<https://www.fusfoundation.org>



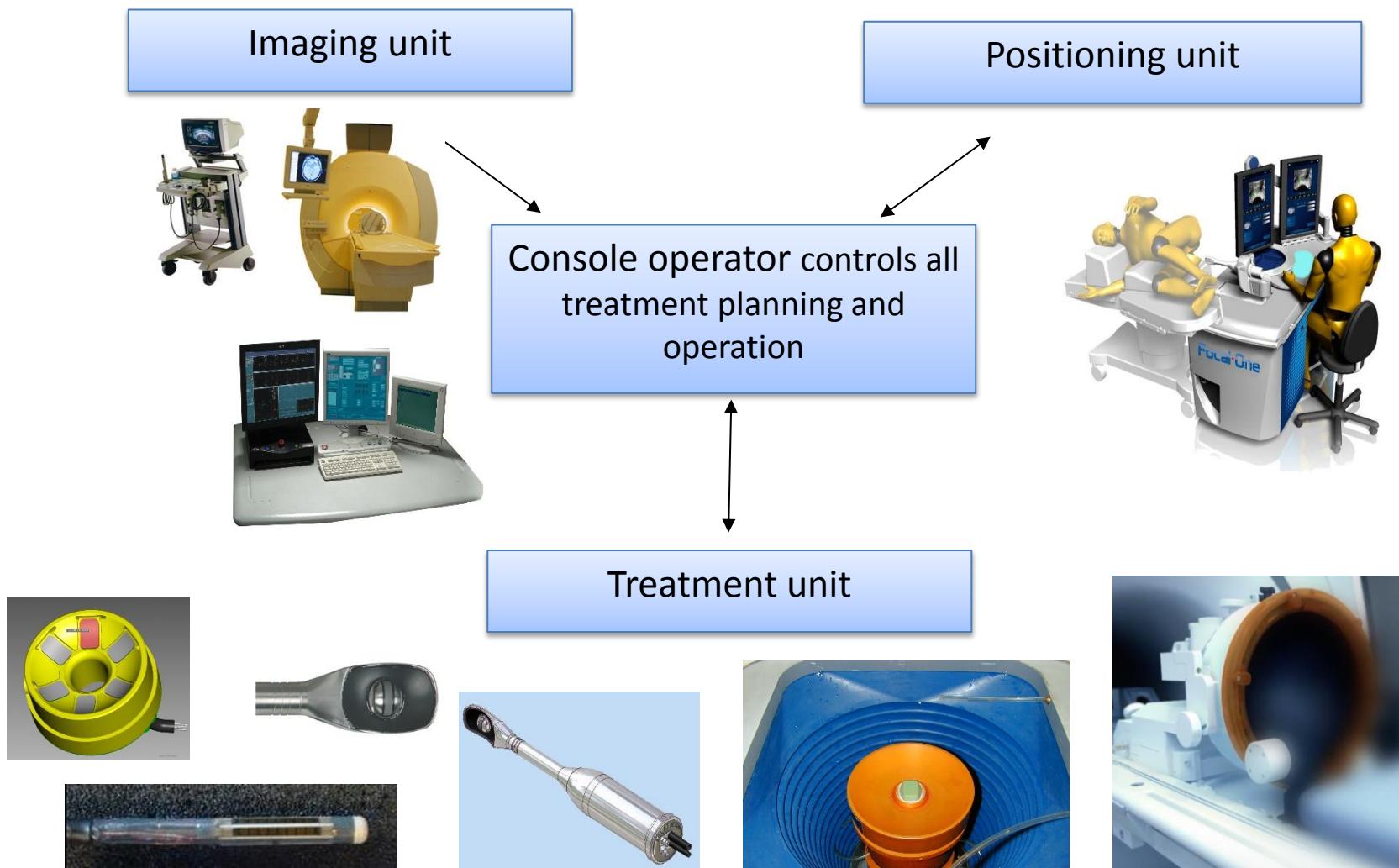
High Intensity Focused Ultrasound (HIFU)

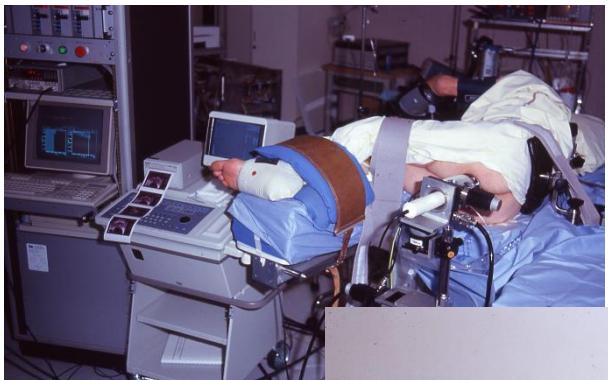
... allow ablating tissues at depth by sparing intervening layers.





Schematic diagram of an ultrasonic device for therapy





ABLATHERM : Devices

← Prototype n° 1 : 1993-1995



Prototype n° 2
1995 - 1999

Ablatherm Maxis
2000 - 2005





ABLATHERM : Devices



Ablatherm II
2006 -2013

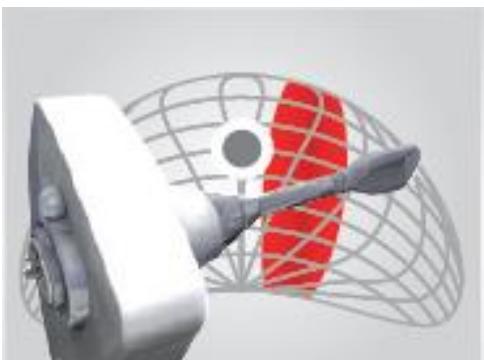


Focal-One
2014 ...

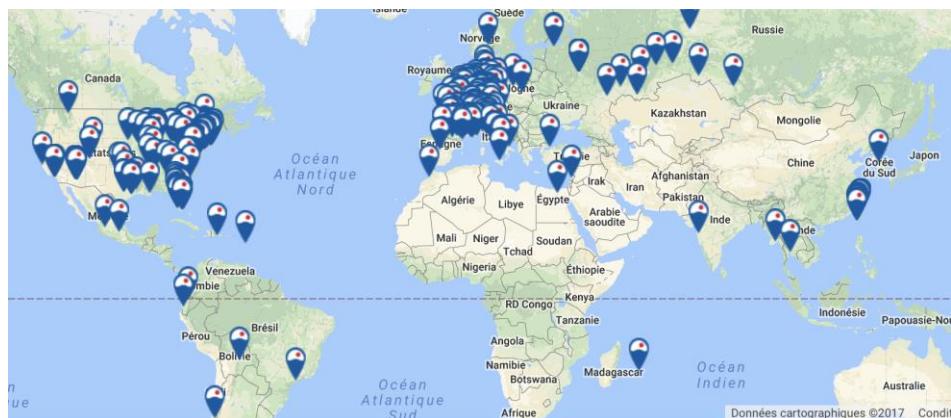
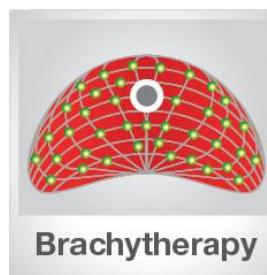
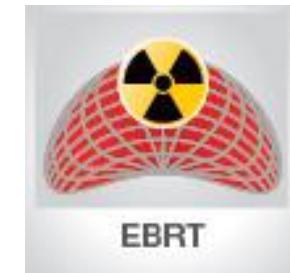


Intended use of Ablatherm®

As a first-line therapy



As a salvage therapy



Worldwide
FDA since Nov 2015





1- HIFU for first line patients



Platinum Priority – Prostate Cancer
Editorial by XXX on pp. x-y of this issue

Whole-gland Ablation of Localized Prostate Cancer with High-intensity Focused Ultrasound: Oncologic Outcomes and Morbidity in 1002 Patients

By: Crouzet, Sébastien; Chapelon, Jean Yves; Rouvière, Olivier; et al.

EUROPEAN UROLOGY Volume: 65 Issue: 5 Pages: 907-914 Published: MAY 2014

Evolution and Outcomes of 3 MHz High Intensity Focused Ultrasound Therapy for Localized Prostate Cancer During 15 Years

Stefan Thüroff*,† and Christian Chaussy†

From Harlachinger Krebs hilfe e.V. (ST, CC) and Department of Urology, Klinikum Harlaching (ST), Munich, and Department of Urology, University of Regensburg, Regensburg (CC), Germany

Fourteen-year oncological and functional outcomes of high-intensity focused ultrasound in localized prostate cancer

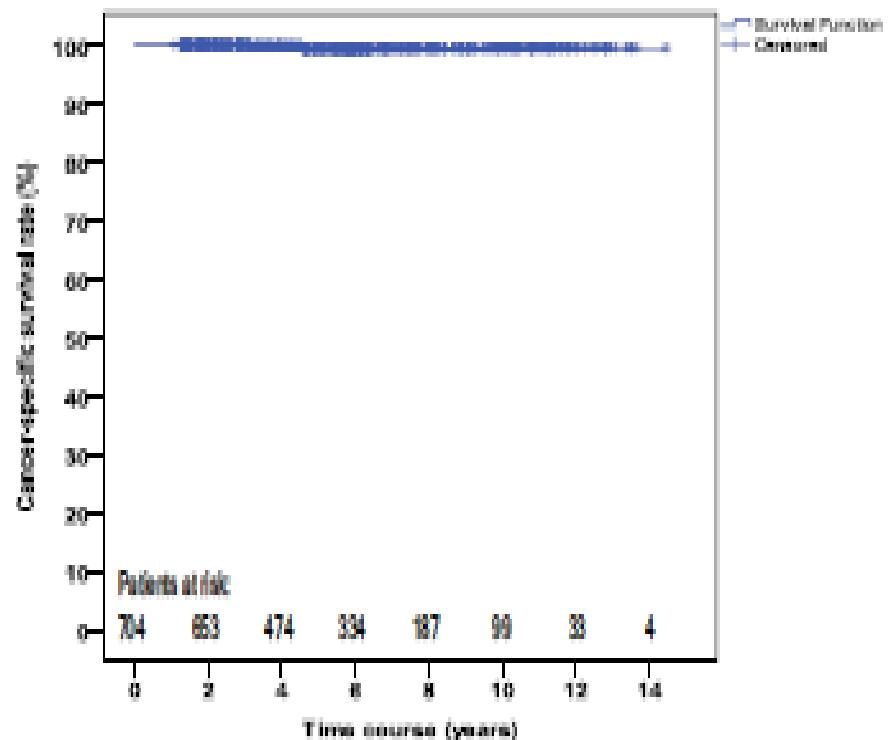
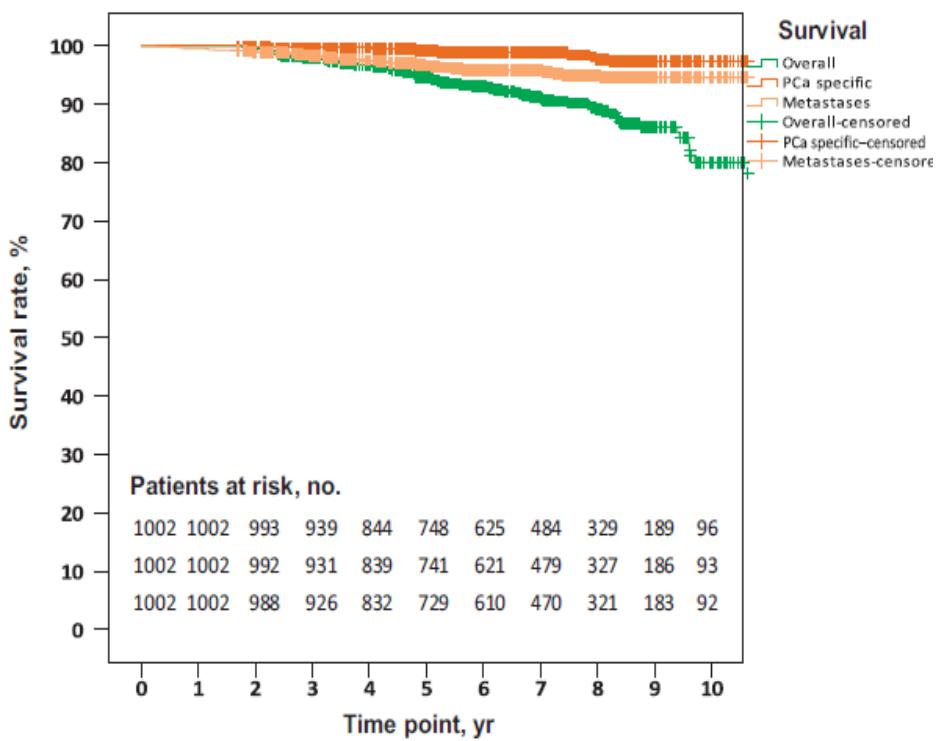
Roman Ganzer, Hans-Martin Fritzsche, Andreas Brandtner, Johannes Bründl, Daniel Koch*, Wolf F. Wieland and Andreas Blana*

Caritas St. Josef Medical Center, University of Regensburg, Regensburg, and *Department of Urology, Fuerth Hospital, Fuerth, Germany



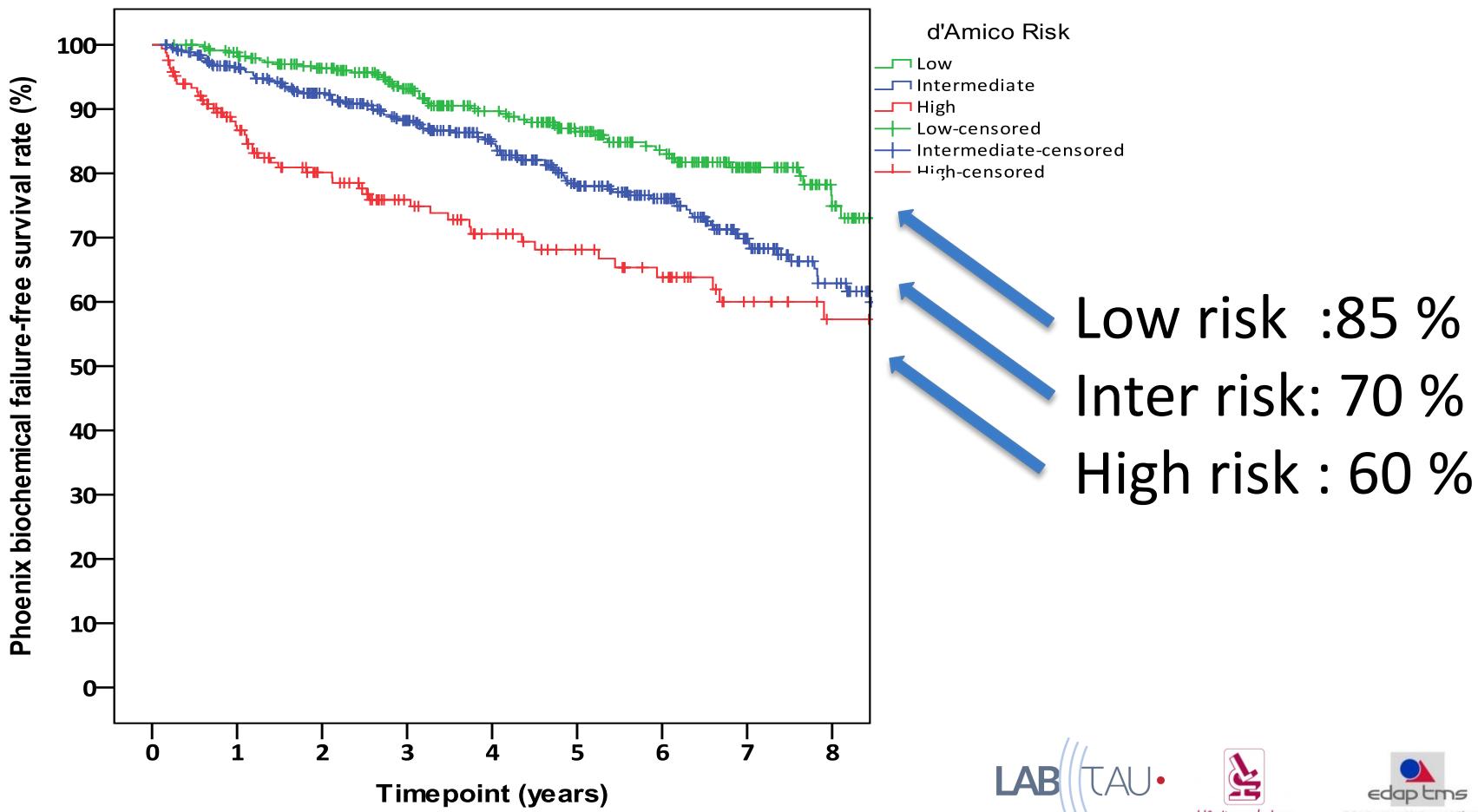
10 years Cancer specific survival rates & Metastasis free survival rates :

97% and 94% (Lyon)
99% and 95% (Munich)





Influence of pre-HIFU risk on the survival rate with no post-HIFU biochemical progression





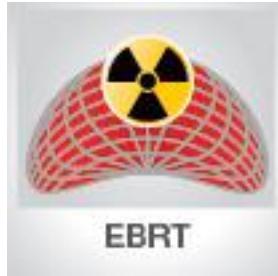
Conclusion

First-line treatment – whole gland ablation

- Median PSA-nadir : 0.14 ng
 - PSA-nadir < 0.3 ng : 786 / 1002 patients
- **Excellent cancer free survival rate at 10 years**
 - for low- and intermediate-risk patients (99 - 98%).
 - This result can be explained by the efficacy of the post-HIFU EBRT.
 - HIFU is not a therapeutic impasse.
- Quite acceptable morbidity



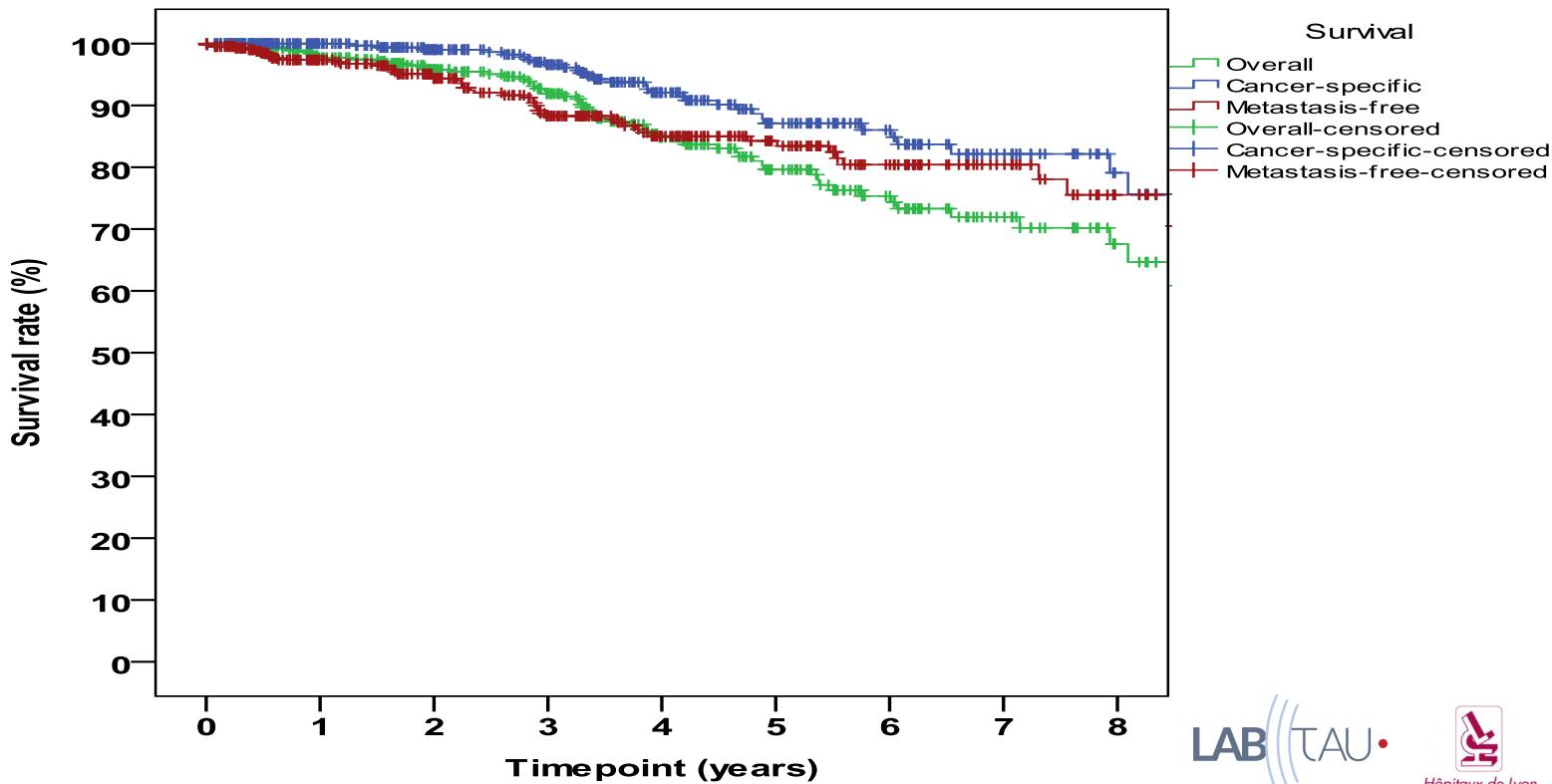
2- HIFU as salvage therapy after radiation therapy



Salvage surgery for locally recurrent prostate cancer after Radiation Therapy is a challenging procedure with severe side effects.



Metastasis free survival rate S-HIFU : 83% & Cancer specific survival rate : 82% after 8 years post S-HIFU





S-HIFU versus S- Surgery

Salvage HIFU

- Short procedure
- Spinal anesthesia
- No bleeding
- PFSR at 5 years: 67%, low risk, PSA < 4 ng : 47%
- Fistula: 0.4%
- Severe Incontinence : 20%
- Short hospital stay

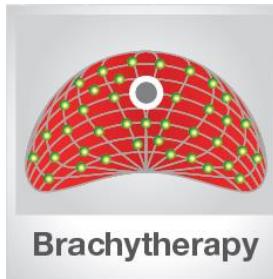
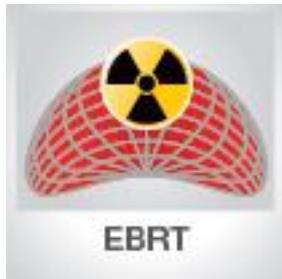
Salvage surgery

- Challenging procedure
- General anesthesia
- Blood transfusions
- PFSR at 5 years : 40-58%
- Fistula:
 - Old series*: 2-7%
 - Recent study**: 1%
- Severe incontinence
 - Old series* : 45-51%
 - Recent study** : 20%



Conclusion Salvage therapy after EBRT

Salvage HIFU challenges salvage
surgery for locally recurrent prostate
cancer after Radiation Therapy.





Stage migration of Prostate cancer

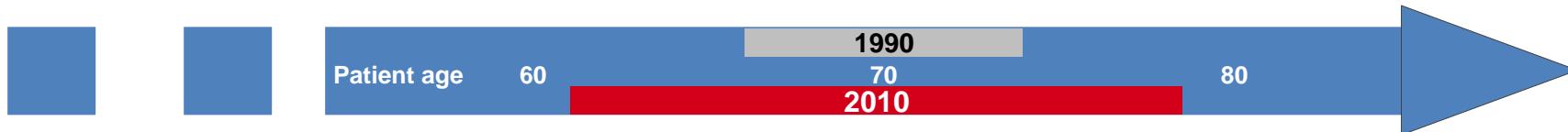
1990

Patient lived 7 years with Prostate Cancer

Treatment strategy:

Efficacy at all price

- Single treatment approach
- Aggressive Radical Surgery
- Radical Radiotherapy



2010

Patient lives 15 years with Prostate Cancer

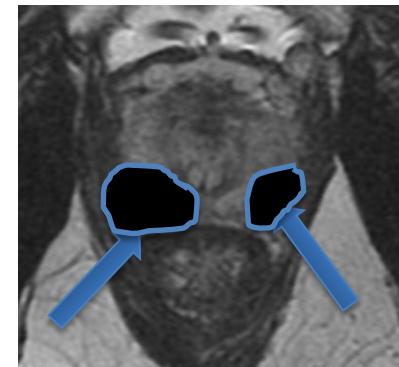
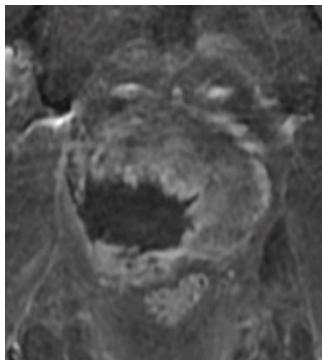
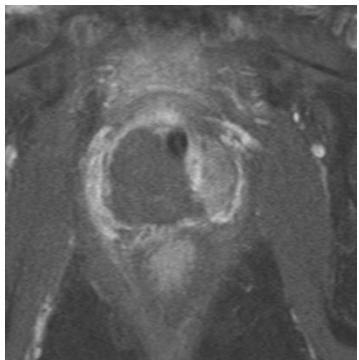
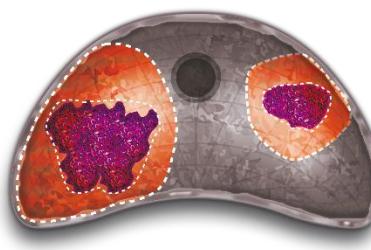
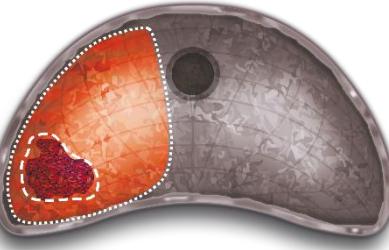
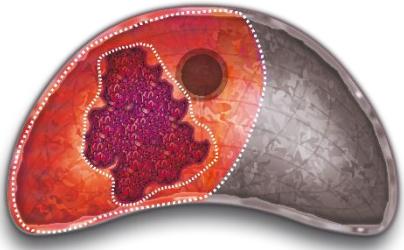
Treatment strategy:

disease control with QoL preservation

- Multi-treatment approach
- Non invasive techniques
- **Focal therapy**



HIFU is a promising option for focal treatment of prostate cancer



Baco et al. BJU Int. 2014

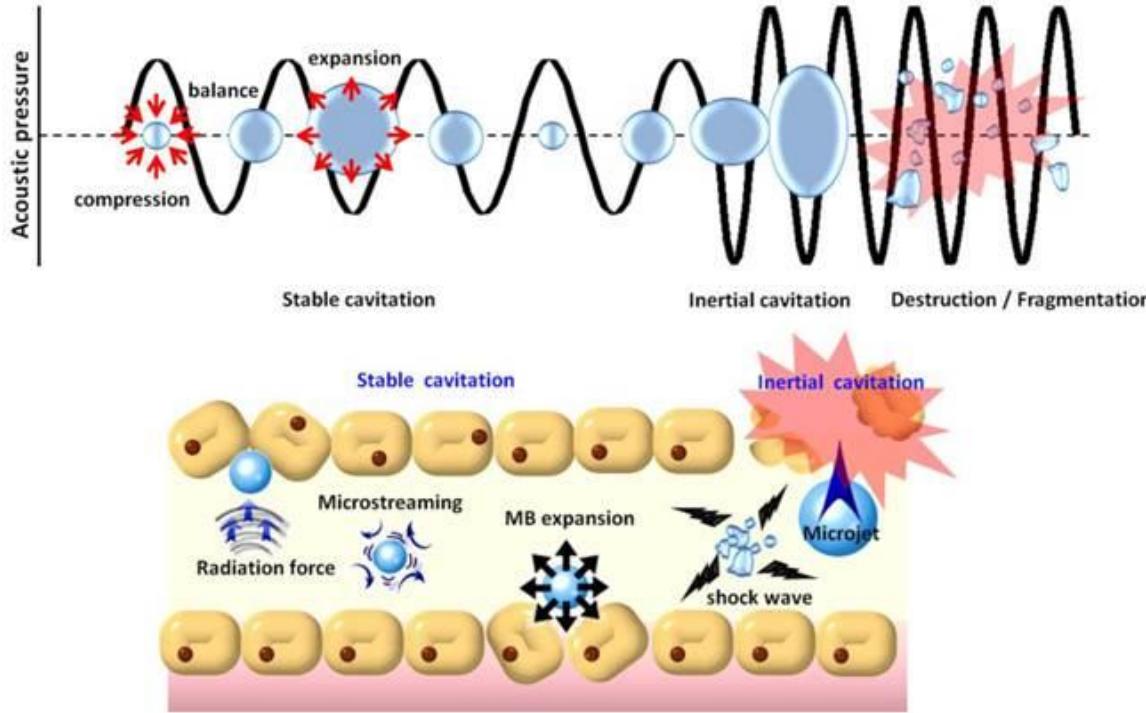


Projet PERFUSE lauréat du 3e appel à projets « Recherche Hospitalo-Universitaire en santé » (RHU-2017).



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Cavitation



Liu H-L, Fan C-H, Ting C-Y, Yeh C-K. Combining Microbubbles and Ultrasound for Drug Delivery to Brain Tumors: Current Progress and Overview. *Theranostics*. 2014;4:432–44.

Physical effects

- Linear oscillation of microbubbles
- Stable cavitation
- Non-linear oscillation of microbubbles
- Inertial cavitation

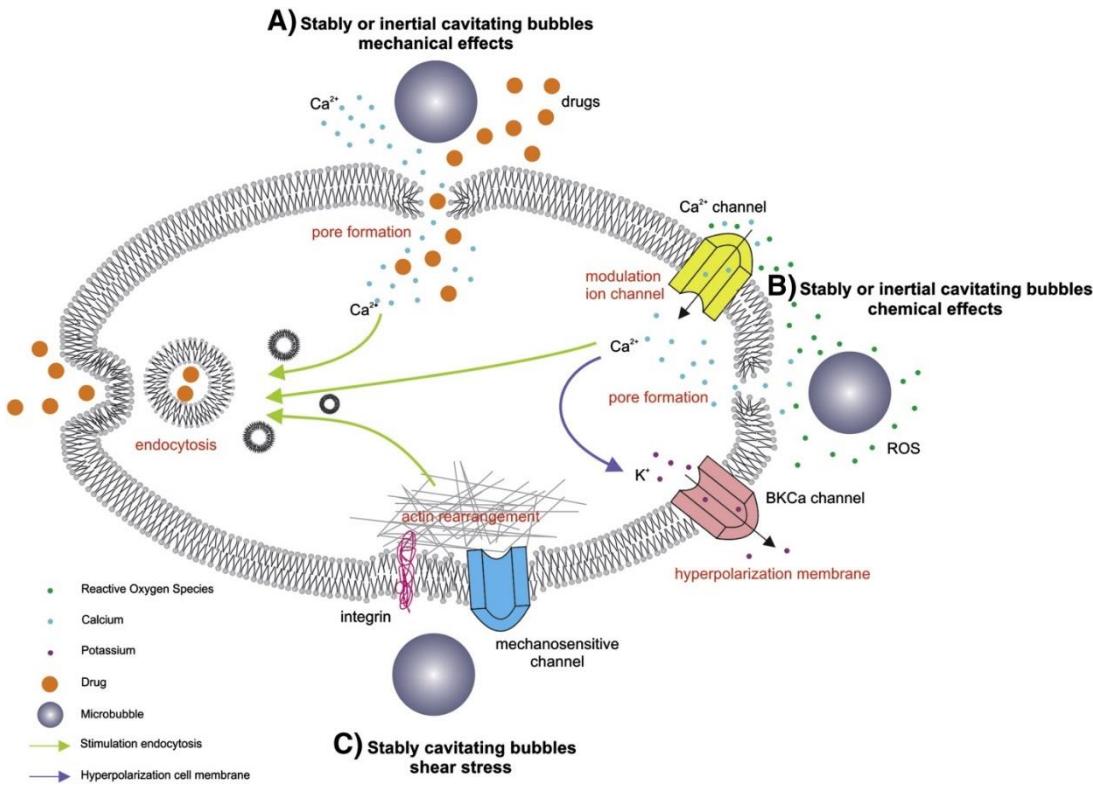
Biophysical effects

- Pushing-Pulling
- Microstreaming
- Shear stress
- Shock waves
- Microjets



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Cavitation



Biological effects

- Mechanical effects
 - Pore formation
 - Drug diffusion
- Reactive oxygen species
 - Activation of ion channels
 - Membrane opening
- Microstreaming & shear stress
 - Membrane deformation
 - Activation of mechano-sensors
- Endocytosis of drug carriers

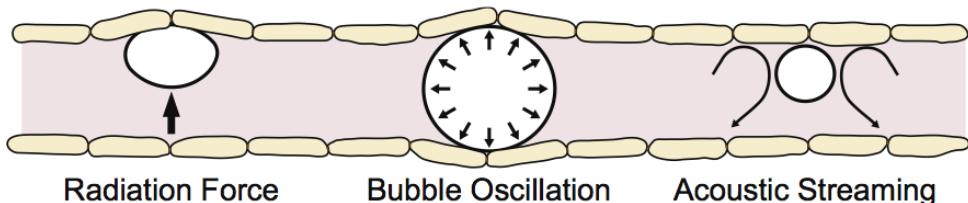
Lentacker I, De Cock I, Deckers R, De Smedt SC, Moonen CTW. Understanding ultrasound induced sonoporation: definitions and underlying mechanisms. *Adv Drug Deliv Rev.* 2014;72:49–64.



US-induced BBB opening

US-induced temporary BBB opening using pulsed ultrasound + US contrast agents has been shown in pre-clinical studies

Vykhodtseva et al. (2008)



[McDannold et al. 2012, *Cancer Research*]

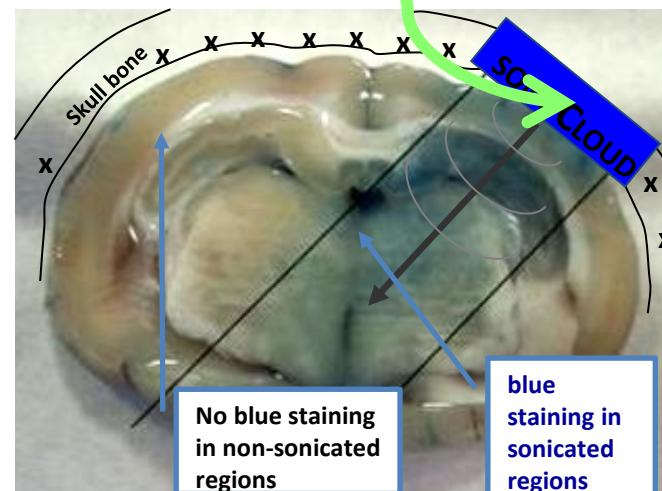
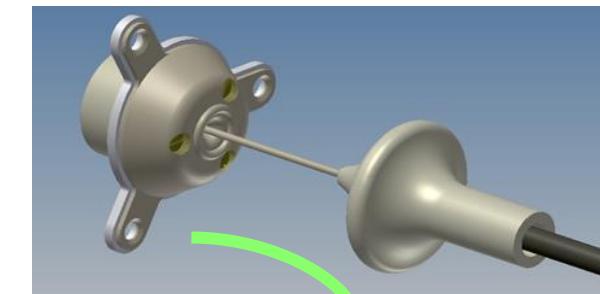
Skull is main problem for clinical application

Clinical trial of blood-brain barrier disruption by pulsed ultrasound

Alexandre Carpentier^{1,2,*}, Michael Canney³, Alexandre Vignot³, Vincent Reina^{1,2}, Kevin Beccaria¹, Catherine Horodyckid¹, ...

* See all authors and affiliations

Science Translational Medicine 15 Jun 2016:
Vol. 8, Issue 343, pp. 343re2
DOI: 10.1126/scitranslmed.aaf6086



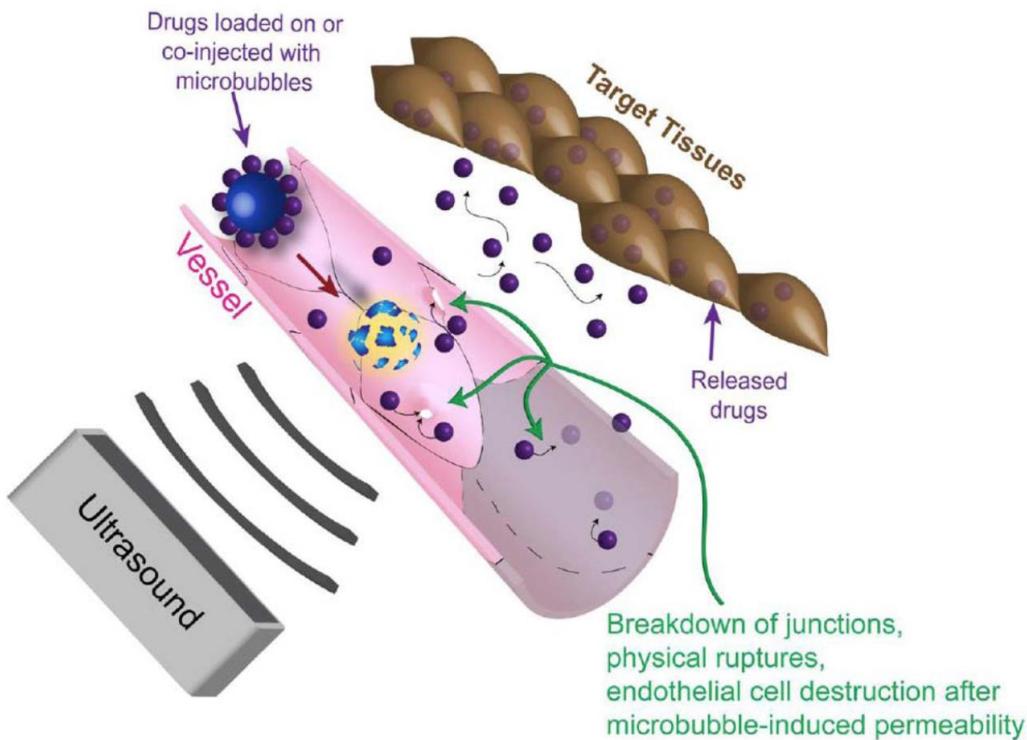
K. Beccaria et al, J Neurosurg, 2013





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Ultrasound drug delivery

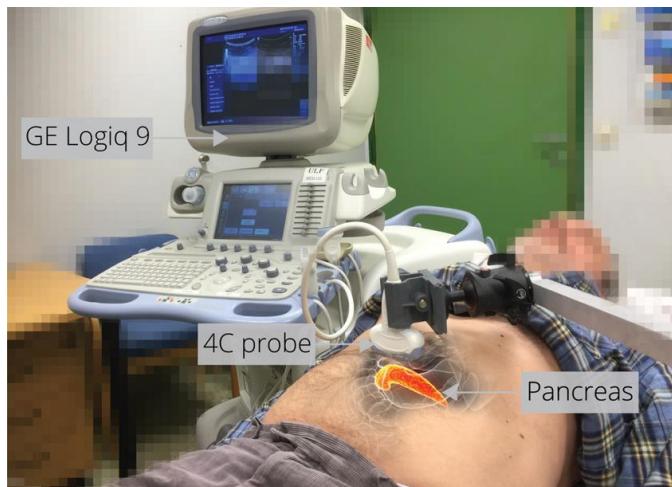
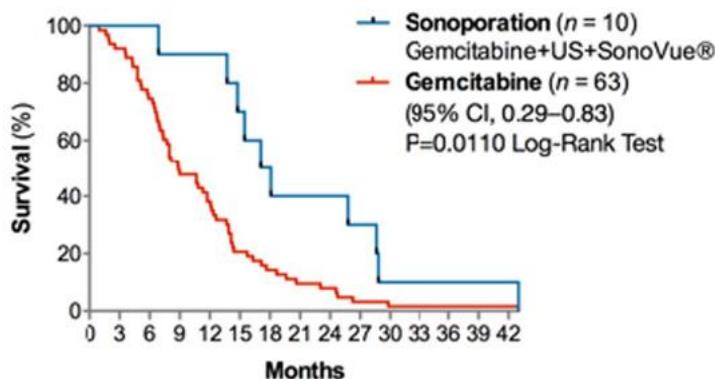


- Systemic intravenous injection of drug-loaded microbubbles
- or
- Co-injection of microbubbles and drug carriers (e.g. polymer nanoparticles)
- Local application of focused ultrasound to trigger cavitation
 - Vessel wall and membrane permeabilization
 - Intra-tumoral drug release

Wang T-Y, Wilson KE, Machtaler S, Willmann JK. Ultrasound and Microbubble Guided Drug Delivery: Mechanistic Understanding and Clinical Implications. *Curr Pharm Biotechnol.* 2014;14:743–52.



Human clinical trial Sonochemotherapy



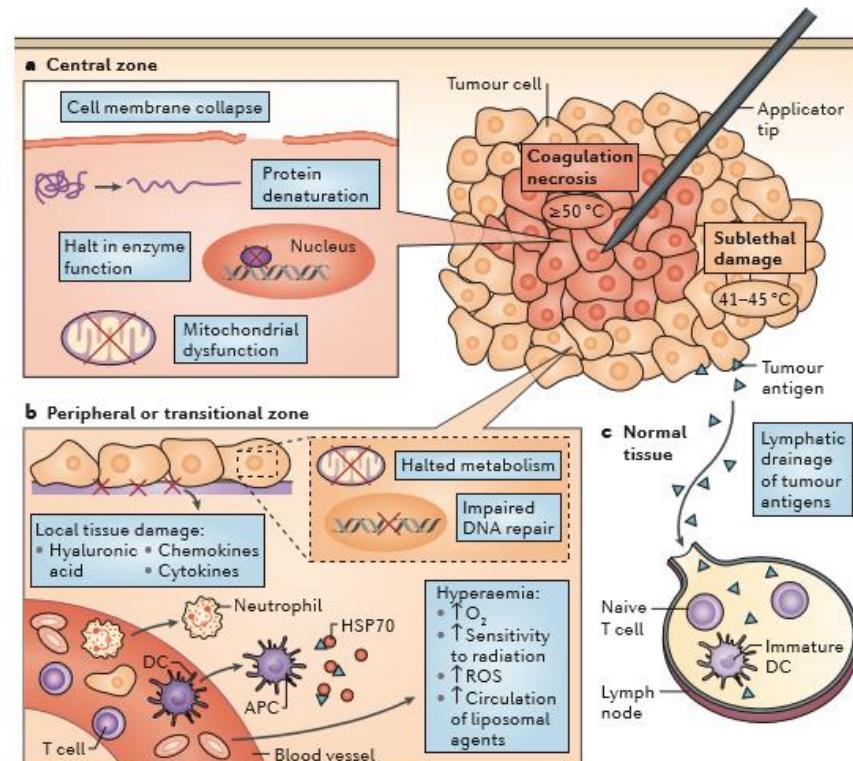
Dimcevski G, Kotopoulos S, Bjånes T, Hoem D, Schjøtt J, Gjertsen BT, et al. A human clinical trial using ultrasound and microbubbles to enhance gemcitabine treatment of inoperable pancreatic cancer. *J Control Release*. 2016;243:172–81.

- Treatment of inoperable human pancreatic cancer
- Combination of microbubbles, gemcitabine, and ultrasound
- Sonochemotherapy is safe
- Improved physical state
- More treatment cycles were tolerated
- In 50% of patients, the tumor size decreased
- Prolonged survival – median survival time was doubled
- Etude chinoise (Pekin) avec Sonovue et Gemcitabine Safety Study of Combining Ultrasound Microbubbles and Chemotherapy to Treat Malignant Neoplasms of Digestive System
- Etude à Tours appelée SONCHIMIO et financée par l'Inca-DGOS : combinaison de Sonovue et FOLFIRI (chimio+anticorps thérapeutique) pour le traitement des métastases hépatiques du CCR.
- Autre étude en Chine à Hangzhou du Pr Pintong Huang , Zhejiang University , Hangzhou · School of Medicine sur le pancréas et gemcitabine



Ultrasound induced immune response

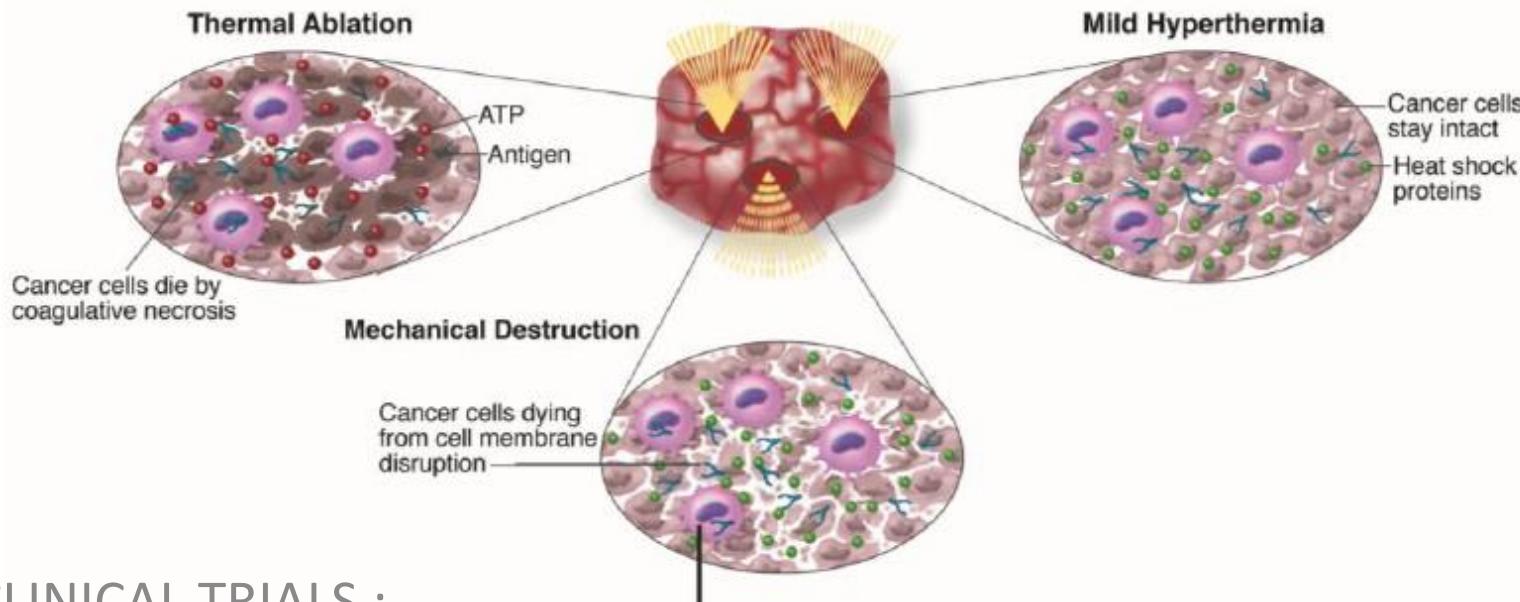
- Immune cells exposed to tumor debris and immune stimulatory substances
- Increase of blood inflow with hyperthermia
- Mechanical destruction increases cell trafficking
- Possible combination with immunotherapies, US acts as a enhancer of the immune response



Chu and Dupuy, *Nature Reviews*, 2014



Ultrasound induced immune response



FIRST CLINICAL TRIALS :

- Ongoing clinical trial at the University of Virginia investigating using focused ultrasound in combination with the immunotherapy drug Keytruda® in patients with metastatic breast cancer
- Clinical trial scheduled at Lyon in 2018 investigating induced immune response after treatment of PCa with HIFU.



Merci pour votre
attention !





Acknowledgements

**Urologists from
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Albert Gelet

Sébastien Crouzet



**Radiologists from
Edouard Herriot Hospital**

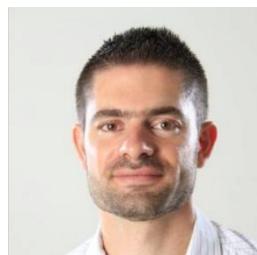
- Olivier Rouvière



Hospices Civils de Lyon

Engineers from Edap

- Emmanuel Blanc
- Nicolas Guillen



Bringing New Horizons to Therapy

