Enhancement results of In-111-DTPA- Octreotide Therapy by Ultrasound microbubbles

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Aim: to estimate the uptake & distribution differentiation of In-111 Octreotide by somatostatin receptor positive tumors, when contrast micro bubbles & ultrasound are applied

in order to : to improve the action of Electron Emission of In-111-octreotide by increasing cell internalization after the sonoporation of the tumor

- Ultrasound interaction with microbubbles provokes them to oscillate, resonate and eventually to be disrupted by the ultrasound energy.
- Liver displays a strong affinity for taking up the microbubbles.

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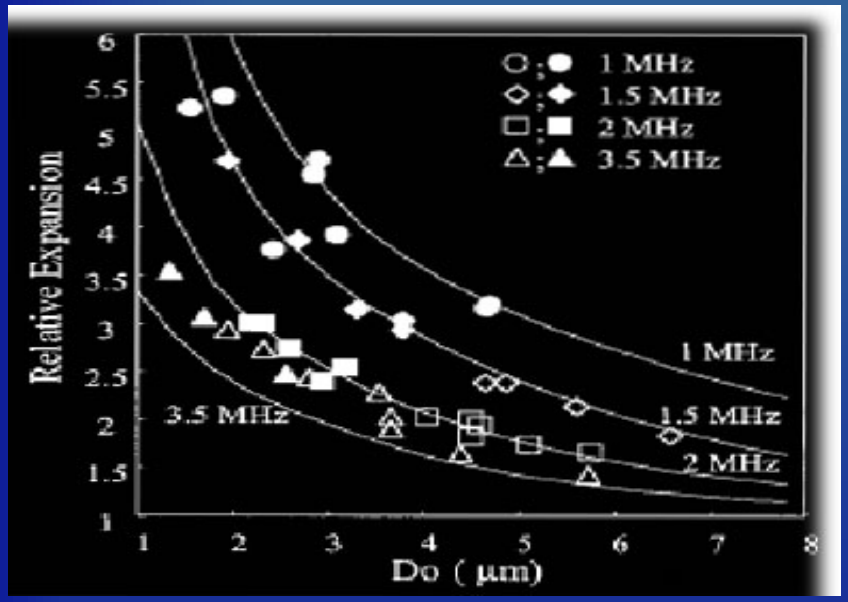
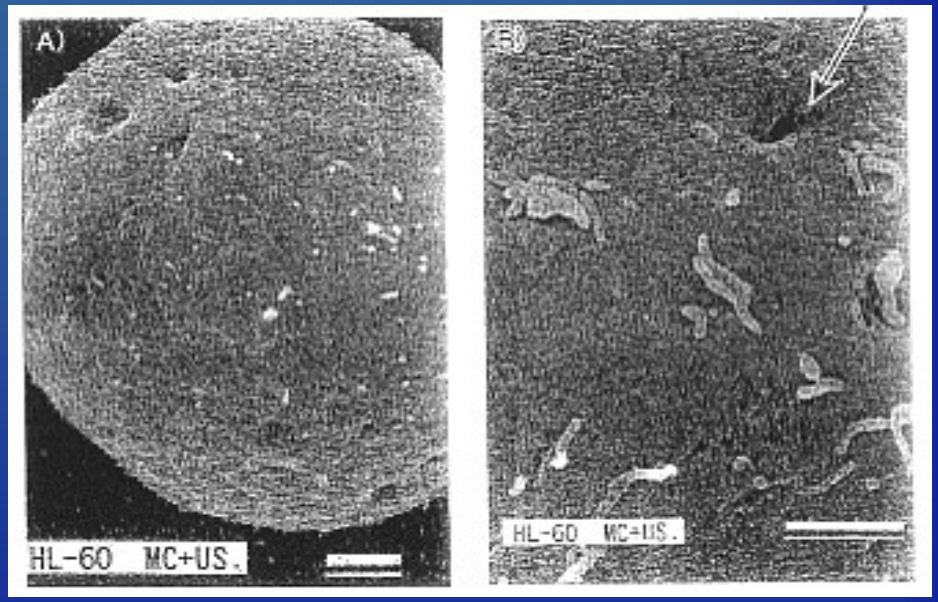
Method

- Patients, suffering of neuroendocrine tumors, were treated by In-111 Octreotide, through hepatic artery catheterization radionuclide infusion.
- Scintigraphic images of the tumor area were taken after the administration of the radiopharmaceutical.
- 18h post infusion 2,4ml contrast agent Sonovue was injected i.v. in a concentration of 45mgr per ml followed by flash of 5ml sodium chloride A 2nd dosage repeated 10 min later. Liver displays a strong affinity for taking up the microbubbles.
- Indium scans were repeated after sonoporation

Sonoporation

- Ultrasound creates transient permeability of cell membranes in the presence of microbubbles.
- This effect allows foreign molecules to enter cell





- Ultrasound results in a great expansion of micro bubbles prior to destruction (depending to frequency).

- Cell walls show small pores following application of ultrasound in the presence of micro bubbles

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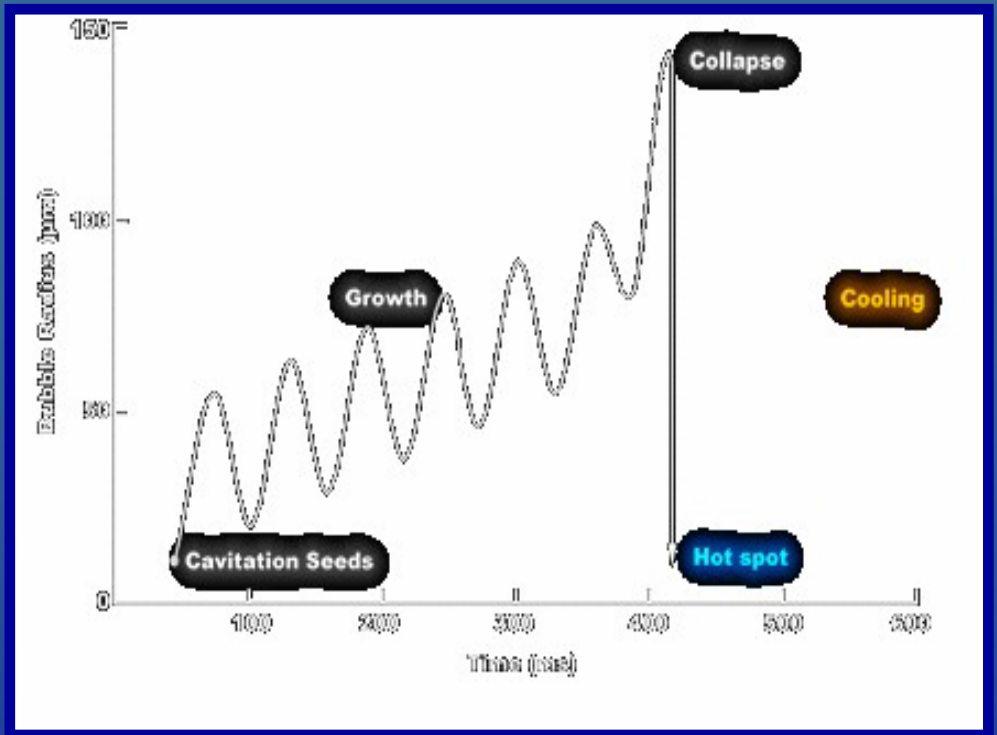
Growth and Collapse of Microbubbles:



- The gas nuclei expand under the influence of the ultrasonic wave and detach to free micro bubbles in the liquid.
- The micro bubbles continue to adsorb energy from the wave and grow isothermally.
- When the micro bubbles reach a critical size (approximately 2 to 3 times the resonance radius) they implode violently.

- *Limiting microbubble concentrations reduces associated cell damage*
- *Membrane recovery time in healthy cells is shown to be as short as 3 to 10 seconds*

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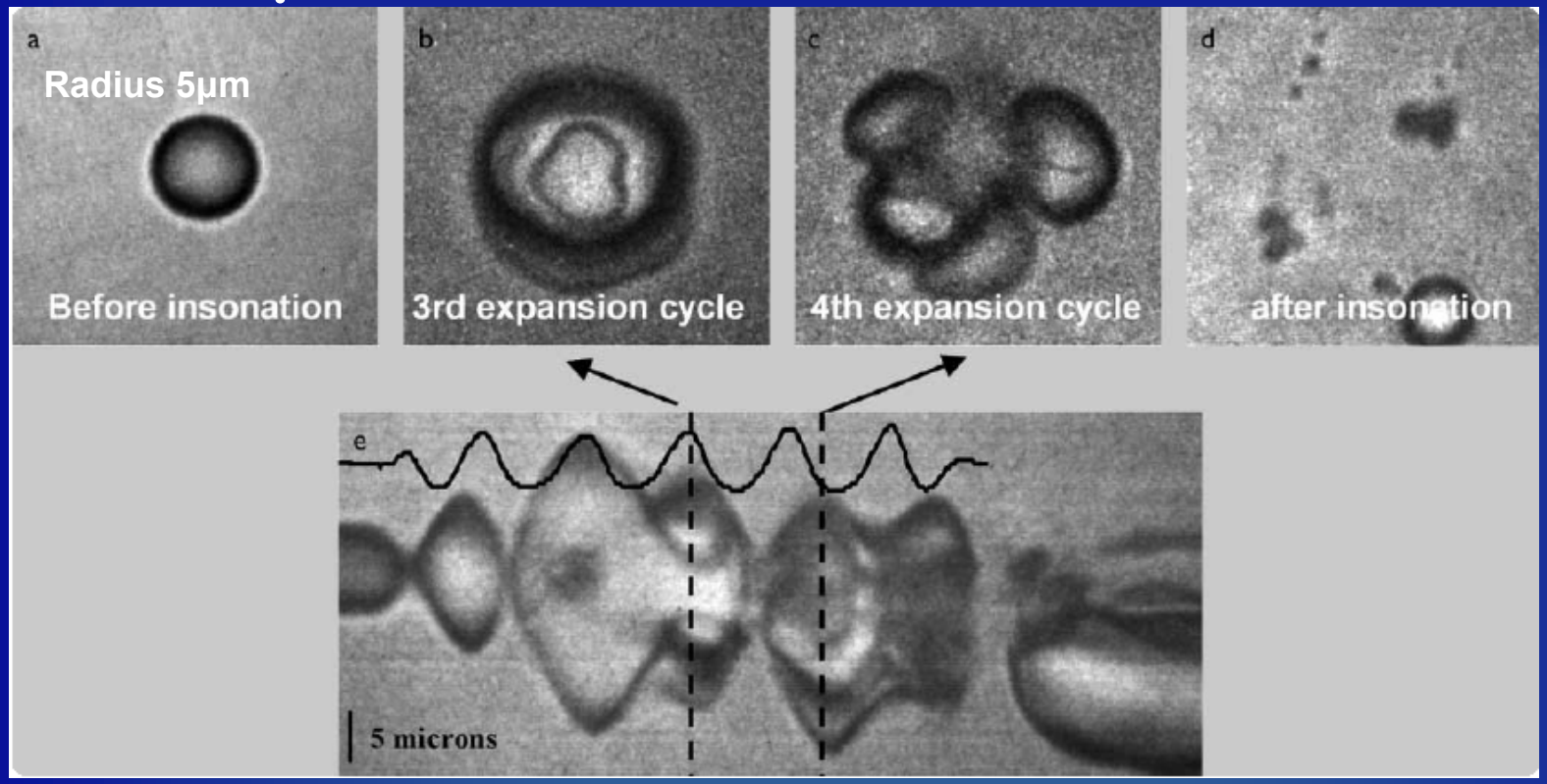
Rupture of microbubbles



Horizontal ⟶ time (5sec) Vertical ⟶ radial distance

- Micrographs show bubble size to oscillate under ultrasound until disintegration occurs.
  - *Recent research suggests a cascade of cavitations initiated by micro bubble collapse.*

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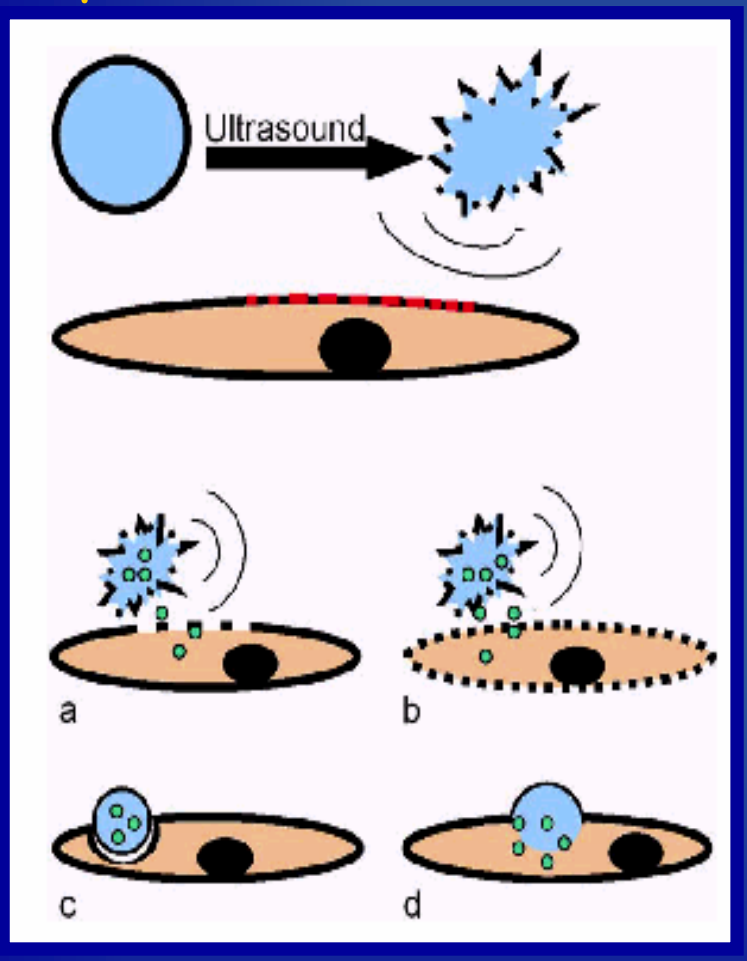
Ultrasound interaction with bubbles

results in increased membrane permeability by shear stress, temperature rise and activation of reactive oxygen species.



- a: transient holes induced by shear stress;
- b: increase in membrane fluidity
- c: endocytosis of micro bubbles
- d: fusion of the micro bubble membrane with the cell membrane

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SonoVue® microbubbles

Commonly used to improve contrast in diagnostic ultrasound

- SonoVue, is an aqueous suspension of stabilized microbubbles.
- Size of microbubbles is between 1 and 10 μm
- No is between 200 and 500 / mL.
- Gas used is Sulphur HexaFluoride in a phospholipids surface layer encapsulated in sphere
- Bubbles behave isothermally, but their radius violently changes
- Their coating controls the way in which respond to ultrasound

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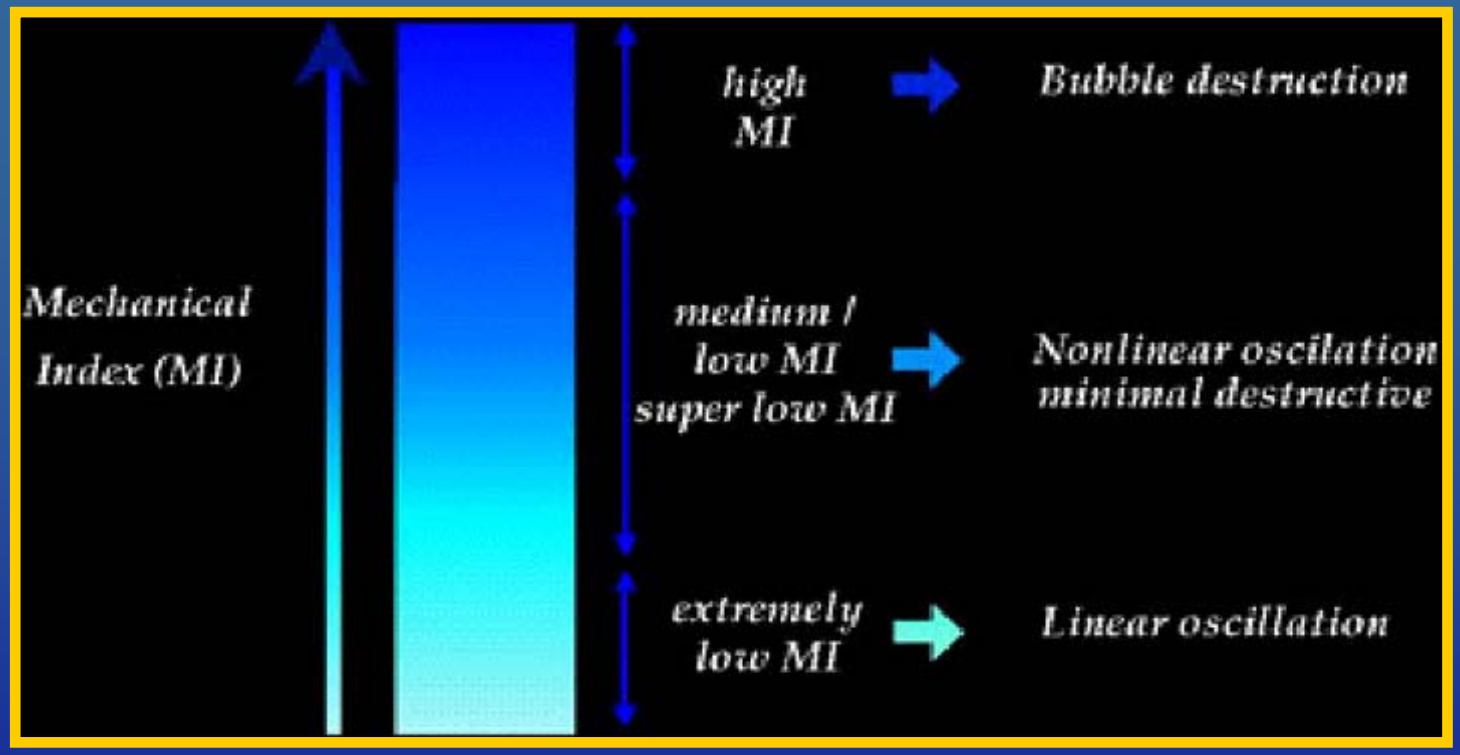
Response of bubbles to ultrasound as function of Mechanical Index



In this study a maximal Mechanical Index 0.9-1 was used

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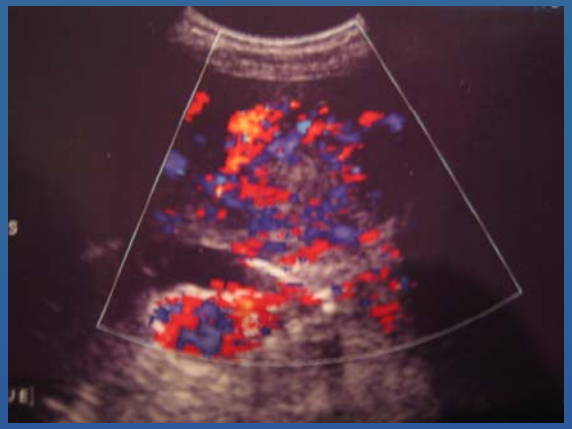
Ultrasound Parameters

- Ultrasound beam of an HDI-ATL 3000 system
- a broadband convex transducer 2- 4 MHz frequency
- a max pulse repetition frequency 0.05%,
- a maximal Mechanical Index 0.9-1,
- was applied externally to the treatment area for a total time of 12 to 20 minutes.

Restriction in the duration of ultrasound examination was necessary due to the In-111 radiation burden of the examiner.

Micro bubbles sonoporation of Liver metastatic lesions

Ultrasound Blood perfusion study without contrast media



Ultrasound/sonovue application for 12 *minutes-increased perfusion*

After 80% of bubbles rupture *Perfusion back to normal*

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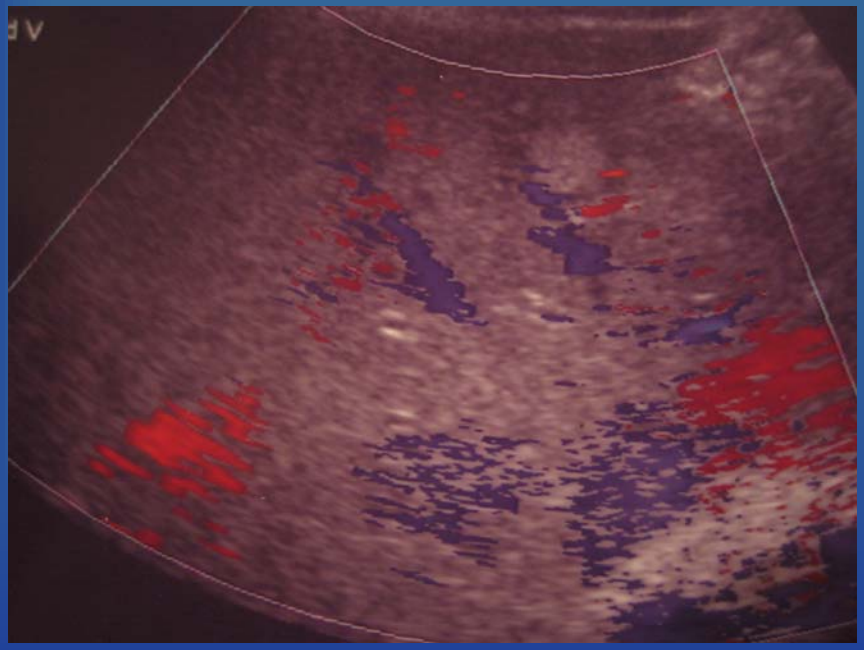
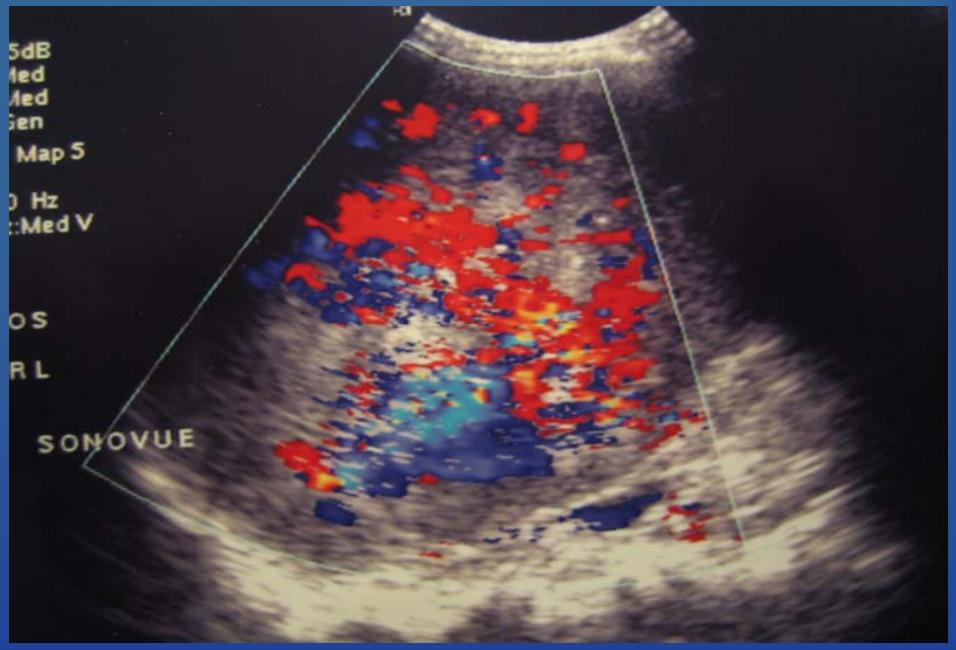
microbubbles sonoporation of Liver metastatic lesions



Ultrasound Blood perfusion study
before contrast media application



Increased perfusion after 1 min of contrast media sonovue use.
Application of ultrasound bubbles for 15 minutes

A series of corresponding scintigraphic images was obtained →

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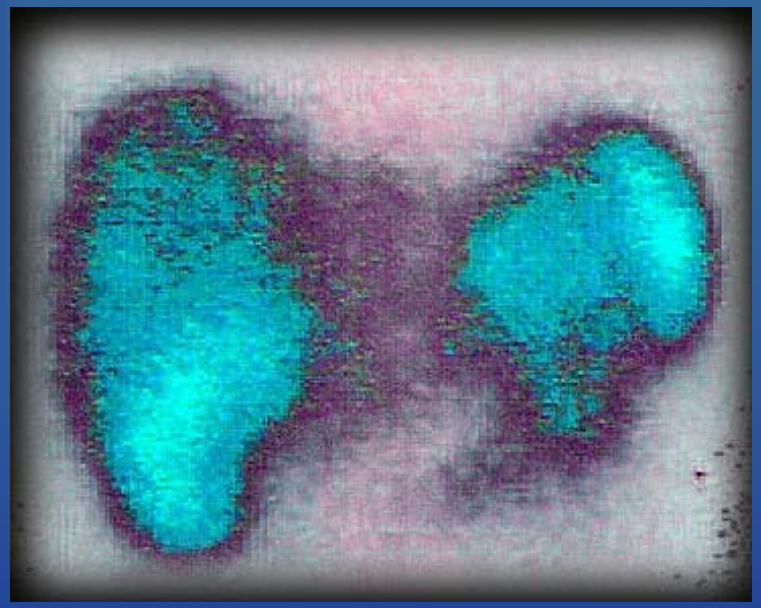
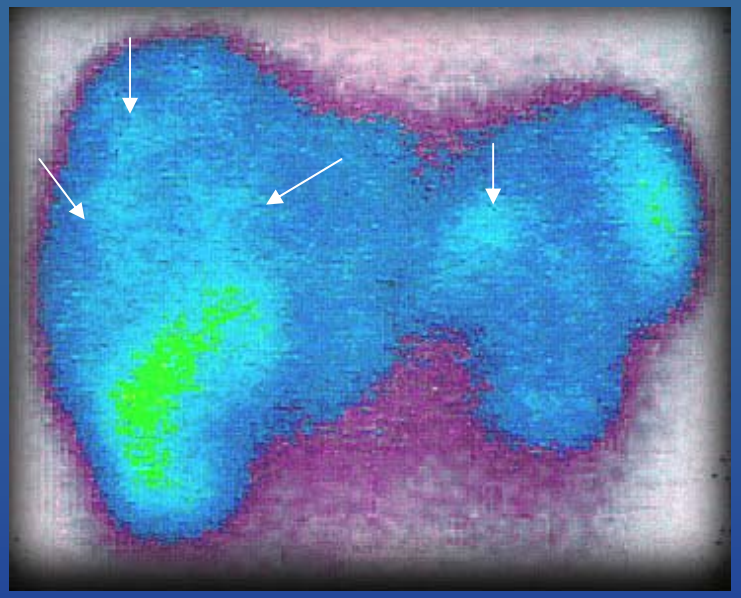
Neuroendocrine tumors treated by In-111 Octreotide catheterization.



In111 Octreotide scan pre bubbles/ ultrasound treatment



Post sonoporation In111 Octreotide scan

Uptake measurements were performed to the In111 scans taken before and after the ultrasound application and differences, on the relative activity and in the target area In-111 redistribution, were indicated

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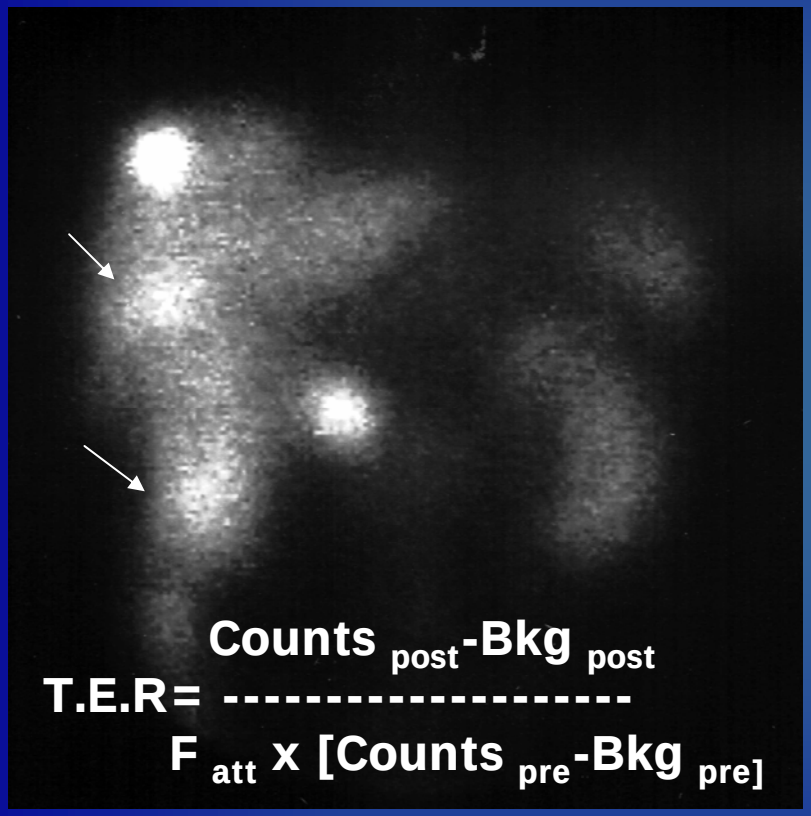
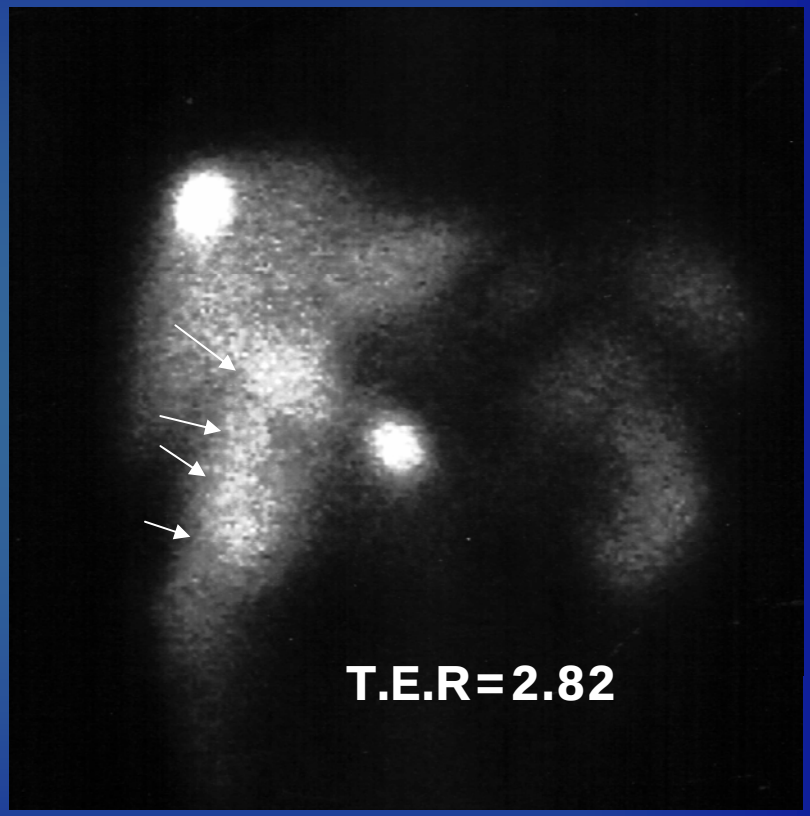
In111 Octreotide therapy

Enhancement and pattern differentiation of the mean counts on tumor regions after sonoporation.

Pre-ultrasound



Post-ultrasound treatment



Induced acceleration of intracellular motion of the receptors in the tumor after the micro bubbles – ultrasound application is estimated by index TER.

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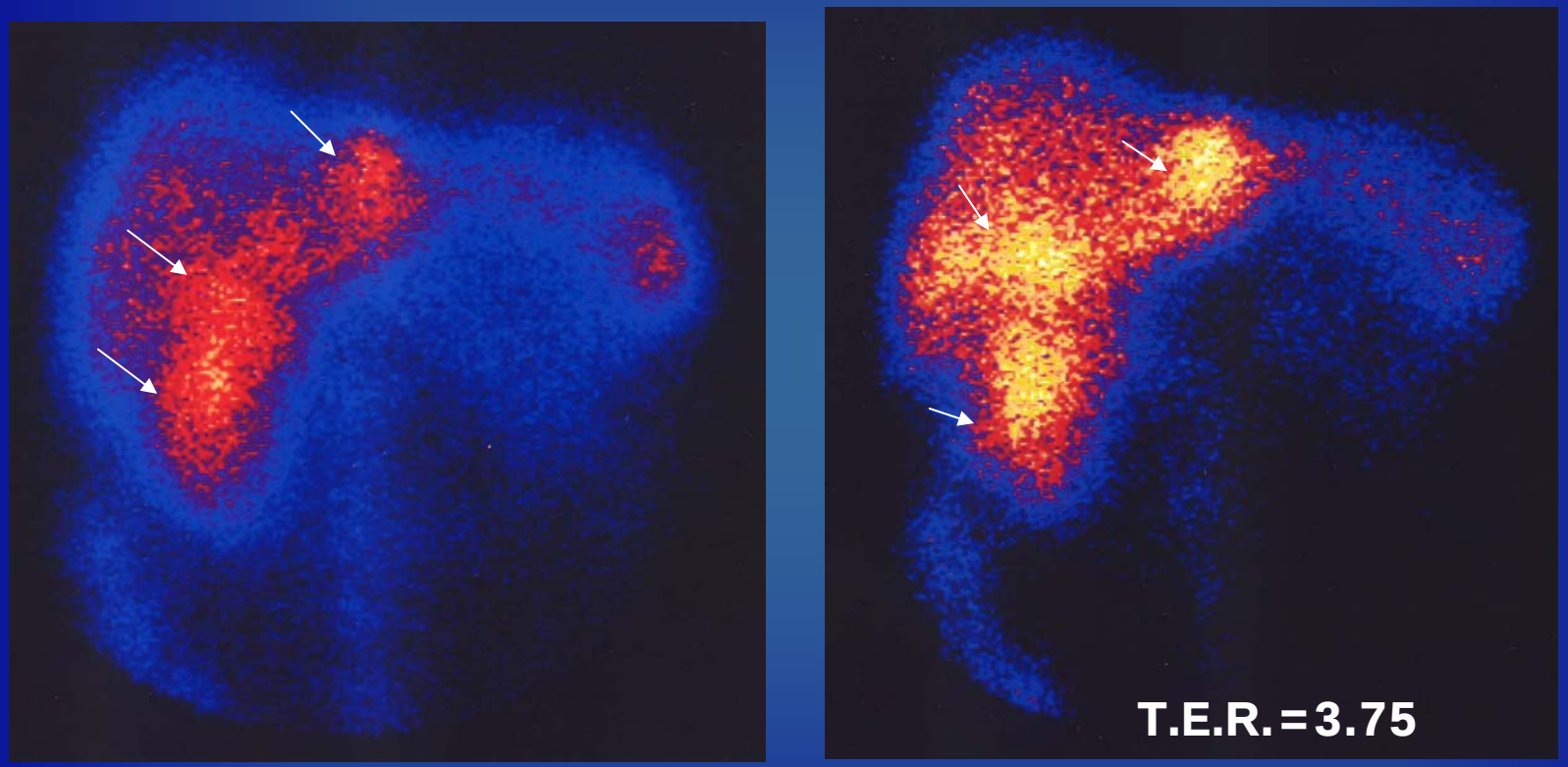
In111 Octreotide therapy

Enhancement and pattern differentiation of the mean counts on tumor regions after sonoporation.

Pre-ultrasound

Post-ultrasound treatment



Induced acceleration of intracellular motion of the receptors in the tumor after the micro bubbles – ultrasound application is estimated by index TER

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Results

- Uptake measurements were performed to the images taken before and after the Ultrasound-microbubbles application and the differences on the relative activity (tissue/background) on the target area, pre- and post- sonoporation, gave a Treatment Enhancement Ratio (TER) in a range 2.5-4 that shows a statistical significant peptide internalization increase in the combined treatment of In-111-Octreotide and Ultrasound micro-bubble contrast application.

Conclusion 1:

- Ultrasound- micro bubbles application increases and differentiates the uptake and distribution of In-Octreotide in somatostatin receptor positive tumours

- After sonoporation, scintigraphic images analysis gives semi quantitative data and a Treatment Enhancement Ratio (TER) specific for tumour region

- Radiopharmaceutical distribution pre and after micro bubbles application shows pattern differentiation of the mean counts on tumour selective regions

Conclusion 2:

- The internalization increment seems to be directly analogue to the duration of the bubble treatment up to 20 minutes

- Cell permeabilization enhancement by the ultrasound bubble contrast application leads to peptide internalization increase,
in In-111 Octreotide infusion
which becomes more effective
for the benefit of the treated patient.