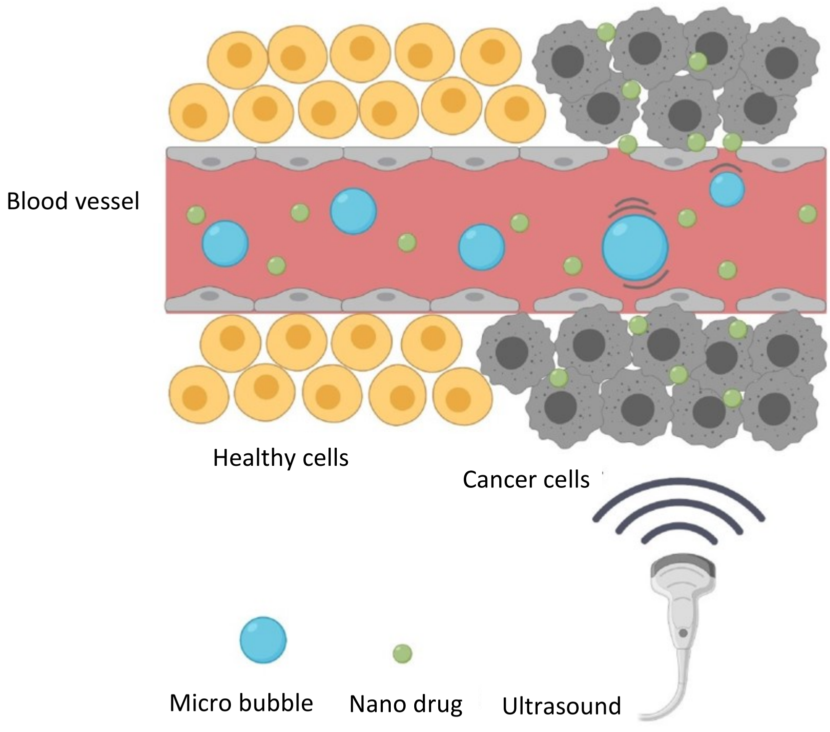
NorMIT
Norwegian Centre for Minimally Invasive Image Guided Therapy and Medical Technologies

Those diseases which medicine do not cure, iron cures; those which iron cannot cure, fire cures; and those which fire cannot cure, are to be reckoned wholly incurable

-Hippocrates-

NEWSLETTER



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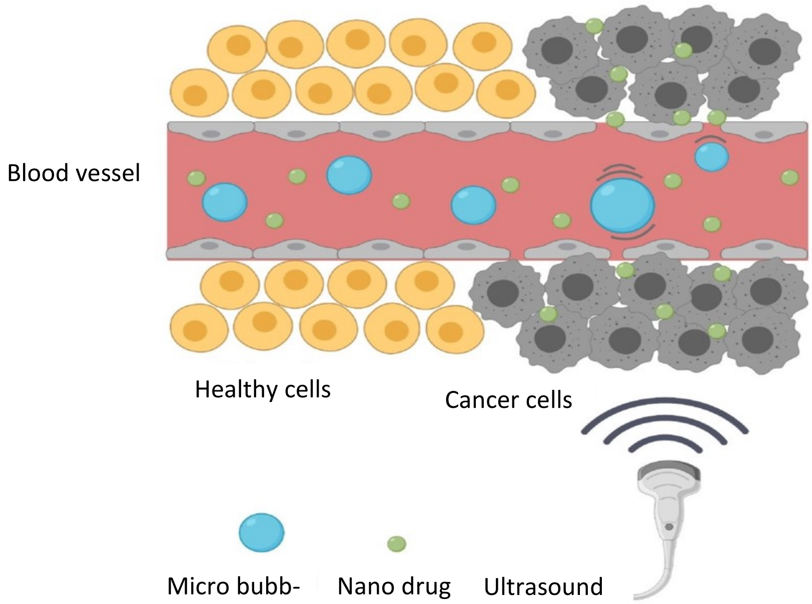
Ultrasound-enhanced uptake of chemotherapy in cancer patients
Clinical studies at St. Olavs hospital

Margrete Haram, consultant radiologist,
St. Olavs hospital Trondheim

Cytotoxic drugs given intravenously show very limited uptake into malignant tumors. High systemic doses cause side effects that limit treatment outcome and prognosis. Adenocarcinoma of the pancreas (PDAC) is a cancer in which cytotoxic drugs have a limited effect. This is thought to be due to conditions in the tumor that make it difficult for the substances to reach the cancer cells. Ultrasound in combination with gas bubbles increases the uptake of cytotoxic drugs in tumors and has given promising results both preclinically in mice and in clinical studies. This gives hope that especially chemo-resistant tumors such as PDAC can be treated more effectively. Collaboration between the research communities for medical technology at St. Olav's hospital, NTNU and SINTEF has made it possible to start two clinical studies on this field. Both studies are aiming to achieve an increased effect of cytotoxic drugs in tissues by means of gas bubbles that oscillate under the influence of ultrasound. The gas bubbles exert a mechanical effect on the vessel walls and temporary pores are formed where cytotoxic drugs can pass. Increased local uptake into the tumor could lead to increased local effect and improved survival.

The first study includes patients with colorectal cancer and with liver metastases (NTC03477019). Two metastases in the liver are selected on CT and these are randomized to either treatment or control. The ultrasound probe is fixed over the metastasis randomized for experimental treatment. Volume change of treated metastasis compared to control metastasis is the primary endpoint. To ensure that the correct metastasis is treated and that the control metastasis is not in the treated area, fusion of CT and ultrasound is used at the Custus X platform, developed by SINTEF Digital, as part of (and funded by) The Norwegian National Competence Centre for Ultrasound and Image-Guided Therapy. An E9 ultrasound scanner and 4V matrix probe are used in Doppler mode for optimal ultrasonic pulses. The ultrasonic pulses are given at a frequency of 1.67 MHz, with a pulse length of 33 cycles and a 3 s scan interval with a mechanical index (MI) of 0.5. The study has so far completed 15 patients. Results from the study are planned to be published in the spring of 2023.



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The second study includes patients with inoperable PDAC (NCT04146441), eligible for life-prolonging treatment with chemotherapy according to national guidelines. Participants are randomized 50/50 to control arm or experimental arm. A two-frequency ultrasonic transducer developed by Professor B. Angelsen, SURF technology, is used. The transducer is designed to provide therapeutically optimal pulses during real-time imaging and delivers high-frequency pulses for imaging and low-frequency for therapy. Here, therapy pulses with 0.35 MHz with pulse length 1000 cycles and pulse length 2.9 ms are used, with scan period 20s and MI 0.5. Volume change measured on CT of treated primary tumor in pancreas compared to control group is primary endpoint. So far, 18 patients have been included. The results will be published in the spring of 2023.

Experimental treatment in both studies consists of focused ultrasound (FUS) and microbubbles (MB) in the form of SonoVue® given intravenously. The treatment is given as soon as practicable after the patient has received chemotherapy intravenously. The studies are single-center studies that recruit patients from the cancer outpatient clinic at St. Olav's hospital, but there is great interest in the PDAC study in particular from all over the country. The studies are good examples of collaboration between the technological and the clinical environment in Trondheim. We hope that the results will make a useful contribution to the work of improving the prognosis in patients with inoperable cancerous tumors.

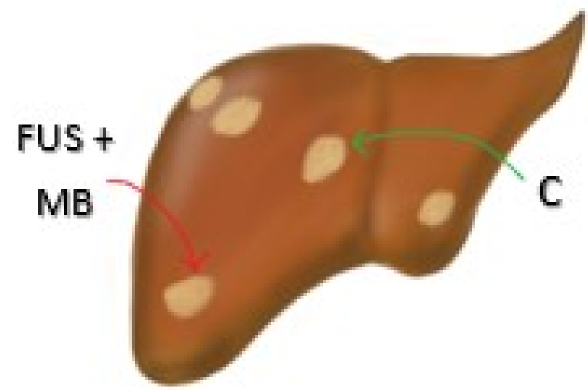

Figure 1: Study design with internal randomization of liver metastases.
C: control. Experimental treatment with FUS + MB

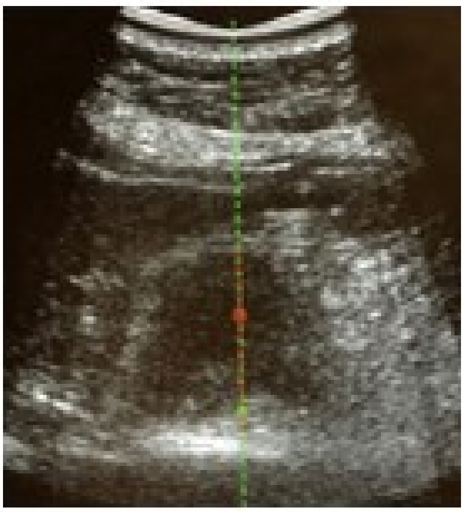

Figure 2: Inoperable PDAC fabricated with bifrequency transducer, under treatment

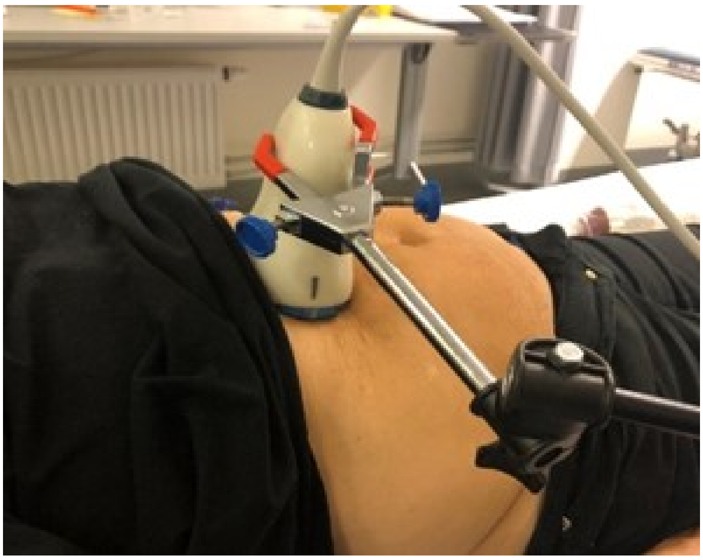

Figure 3: Fixed bifrequent transducer during treatment

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Development of quantitative ultrasound techniques using the Verasonics Vantage research scanner

Sigrid Berg, senior research scientist, SINTEF

Diagnostic ultrasound is today mainly a **qualitative** imaging modality. This can in some situations make it difficult for the physician to set an accurate diagnosis. SINTEF and NTNU are collaborating with engineers at SURF Technology AS and medical doctors at St. Olavs Hospital and Levanger Hospital to develop novel methods where the goal is to use ultrasound imaging to extract **quantitative** information about the tissue in question, and the research ultrasound system Verasonics Vantage provided by NorMIT is essential in this work.

Ultrasound has proved to be an invaluable modality for visualization of lesions in several organs because the lesions often have a different echogenicity compared to the surrounding normal organ tissue. However, for some lesions, e.g in the prostate, breast or liver, or in lymph nodes, ultrasound does not always provide adequate differentiation and there is need for a new approach. In cases where major parts of the organ tissue itself has changed from its normal healthy state to a diseased state, such as in patients with liver steatosis (fatty liver), there is no reference tissue which can be used for qualitative comparison, hence a quantitative method is needed.

The researchers are developing and testing two different quantitative ultrasound imaging methods. By using the Verasonics vantage research ultrasound scanner they have full control of the transmit and receive sequences, signal processing and visualization. This enables development, testing and optimalization of new method which are not available on ultrasound scanners in clinical use.

Quantification of shear stiffness

Shear stiffness is related to shape deformation, without any volume deformation. Water does not have any preferred shape and its shear stiffness is zero. Soft tissues typically consist of approximately 65% water and therefor have low shear stiffnesses compared to solids. An increase in shear stiffness due to pathology such as cancer, for example a lesion in the breast, can sometimes be detected by palpation. Quantifying the increased stiffness, either in palpable lesions close to the skin surface or lesions deeper in the body, can be done by ultrasound shear wave imaging.

In shear wave imaging, shear waves are induced by special ultrasound push-pulses and the propagation velocities of these waves are measured. With the processing power of the Verasonics system, the shear wave velocity can be tracked in real-time, and a resulting shear wave map can be superimposed on conventional anatomical ultrasound images. The obtained shear wave velocity is a direct and quantitative measure of the tissue shear stiffness parameter.

Lab experiments with various tissue samples from animals have shown promising results, and further work on optimalization of the method is ongoing. Clinical studies are being planned.

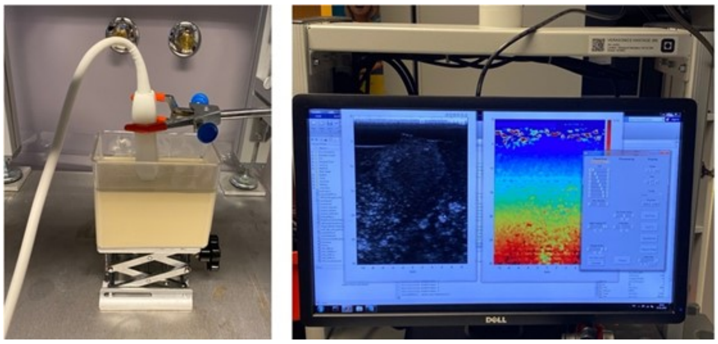

Figure 1: In laboratory experiments various types of tissue from animals have been assessed with the tissue characterization methods.

Quantification of nonlinear compressibility

Nonlinear compressibility, on the other hand, is related to volume deformation without any shape deformation. Water has high resistance to volume deformation and most soft tissues have a nonlinear compressibility similar to water. Fat is, however, more compressible than other typical soft tissues, hence quantifying the nonlinear compressibility can be particularly helpful in the evaluation of fat fraction in the liver of patients with suspected liver steatosis. The nonlinear compressibility cannot currently be measured in vivo with any commercially available methods, but by combining the use of specially designed ultrasound transducers that can transmit ultrasound waves at two very distinct frequencies simultaneously, with novel algorithms implemented on the Verasonics system, the researchers can now extract this parameter. Lab experiments on agar-based materials with a varying fraction of added fat show very promising results, and preliminary results are shown in Figure 2. Pre-clinical and clinical studies are being planned.

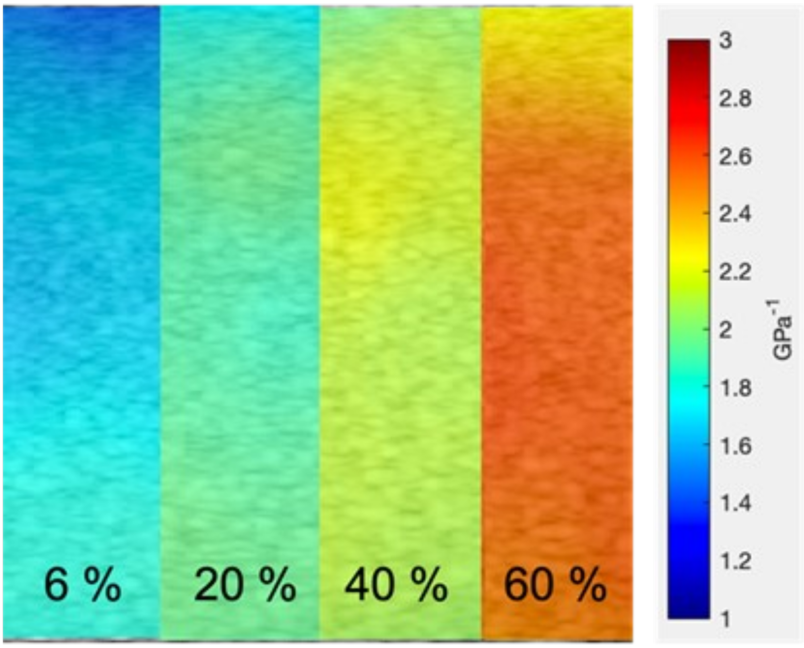

Figure 2: Quantification of the nonlinear compressibility in agar-based ultrasound phantoms with addition of a varying amount of soybean oil. Higher concentrations of fat in the sample causes higher compressibility.

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Otto Schnell Husby

After 41 years in the patients' service as one of the country's leading prosthetic surgeons, professor and chief physician dr. Otto Schnell

Photo: St. Olavs hospital

Husby ends his work at the hospital.

Otto has assisted NorMIT/FOR in the establishment of the NorMIT/FOR surgery room in the orthopedic surgery department. He was one of the driving forces to investigate whether the design of and heat development from the operating lamps could have an impact on changed airflow in the operating field and cause potentially increased risk of infection. Under the auspices of NorMIT/FOR, a number of studies have been carried out that have provided important knowledge on this topic with publication in several internationally renowned journals.

He led the work of introducing the Fasttrack model for prosthetic surgery at St. Olav's hospital, and has also with his expertise and long experience handled the most demanding prosthetic revisions both in the region and on a national basis. In spinal surgery, Husby has performed more than 2,000 microsurgical procedures, and he has operated on several of our cross-country stars.

Together with Professor Pål Benum and chief physician Arild Aamodt, they developed an individualized hip prosthesis, Unique, in the 90s. The individualized design made it possible to correct a number of anatomical defects in the hip joint. The project received start-up funds for commercialization, and several investors supported the company, Scandinavian Customized Prosthesis (SCP). The prosthesis was somewhat widespread in the Nordic countries, Germany, the Netherlands and the United Kingdom and was mainly offered to patients suffering from hip dysplasia. The prosthesis did very well in the Norwegian hip joint register, but became too expensive for a small Norwegian player to make an impact in a larger market.

Although Otto is leaving St. Olav's hospital, he has no plans to put orthopedics on the shelf. Otto was born and raised in Kristiansund, and will continue to operate and help to further develop the hip replacement surgery at the hospital in the city, where he, for a number of years, has both performed operations and supervised PhD candidates. The plan is to start prosthetic surgery as day surgery, and to establish the orthopedic department in Kristiansund as a learning center for the English prosthetic company JRI.

Otto has been an important contributor to the specialization of new orthopedists through the Røros course as a co-funder, and which he has led for many years. We at FOR want to thank Otto for the help, and wish him luck with the projects in his hometown.

-Gunnar Gjeldnes-

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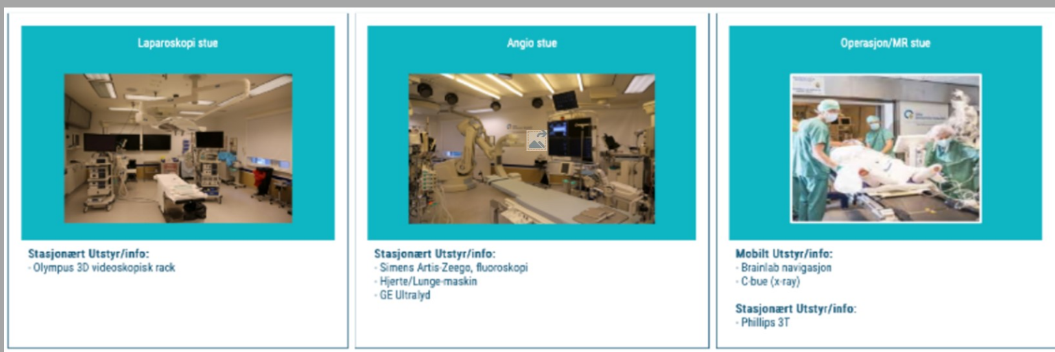

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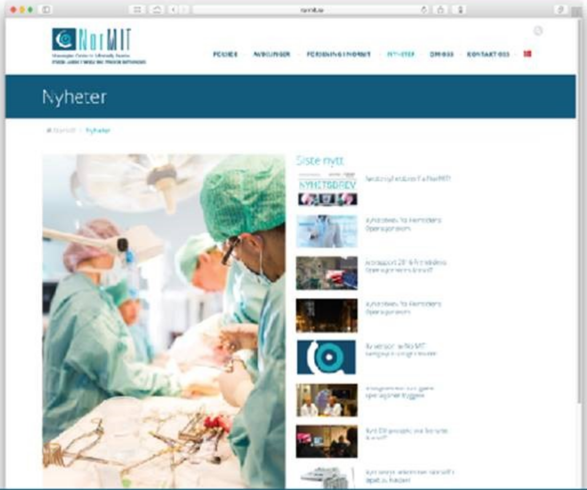

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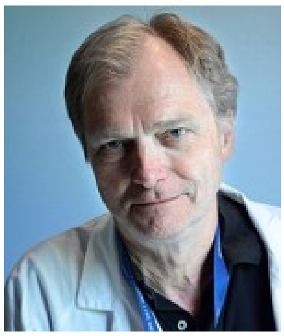

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