YOUR IMPACT

Sunnybrook FOUNDATION

Dear Ms. Carson:

The Breast Cancer Society of Canada is an important catalyst in our work to predict, influence and monitor the outcomes of breast cancer treatment. I am very grateful for your longstanding support.

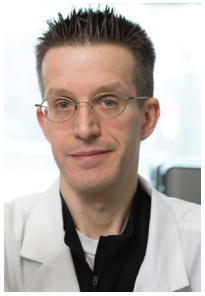
In this report, I'm proud to share the details of our efforts to gauge tumour response using blood flow. We are using diffuse optical spectroscopy methods and ultrasound to study blood vessel response in patients receiving chemotherapy.

Thanks to your investment, my team and I also completed an important study using a newly customized ultrasound machine, microbubbles and radiation. The findings of this trial were exceptional and set the stage for a world first clinical breast therapy trial, which we plan to launch later this year.

Finally, the Breast Cancer Society of Canada's support also helped advance the next, important phase of our first clinical trial testing the ability of quantitative ultrasound (we call it WaveCheck) to measure tumour change. The results of that study led to new discoveries about the use of upfront ultrasound to predict chemotherapy effects in advance of the treatment. In more than 90 per cent of the cases, WaveCheck accurately predicted the impact of the chemotherapy on the tumour. These findings show real promise for the use of the technology as a diagnostic tool to help women and their doctors plan the best possible treatment for their cancer.

Underlying each of these accomplishments is your generous support. Without the Breast Cancer Society of Canada, none of this would be possible.

Gratefully yours,



Dr. Gregory Jan Czarnota
Chief, Department of Radiation Oncology
James & Mary Davie Chair in Breast Cancer Imaging and Ablation Research

Cover image is from a unique photo series by Sunnybrook staff photographer Kevin Van Passen. It portrays Dolores, a Sunnybrook breast cancer patient who graciously shared her story.

Thanks to your support of Dr. Gregory Czarnota, chief of Radiation Oncology, and his world-leading ultrasound-enhanced therapies, Sunnybrook is inventing the future of breast cancer care. Dr. Czarnota and his team have continued their breakthrough research involving ultrasound-activated microbubbles and radiation, and advanced their use of a second homegrown ultrasound technology to both change the way we treat breast cancer and help newly diagnosed women and their doctors make effective treatment decisions.

Gauging tumour response using blood flow

New photoacoustic imaging machine may be paired with quantitative ultrasound

After seeing the role quantitative ultrasound can play in characterizing breast tumours and predicting treatment outcomes, Dr. Czarnota embarked on a new study to determine the role tumour biology might play in treatment response.

"We wanted to know if there are biological changes happening inside the tumour that set it up to respond or not respond to treatment," he explains.

He recruited 46 patients with locally-advanced breast cancer and used a specialized 3D imaging machine called diffuse optical spectroscopy to measure the blood flow in the tumours.

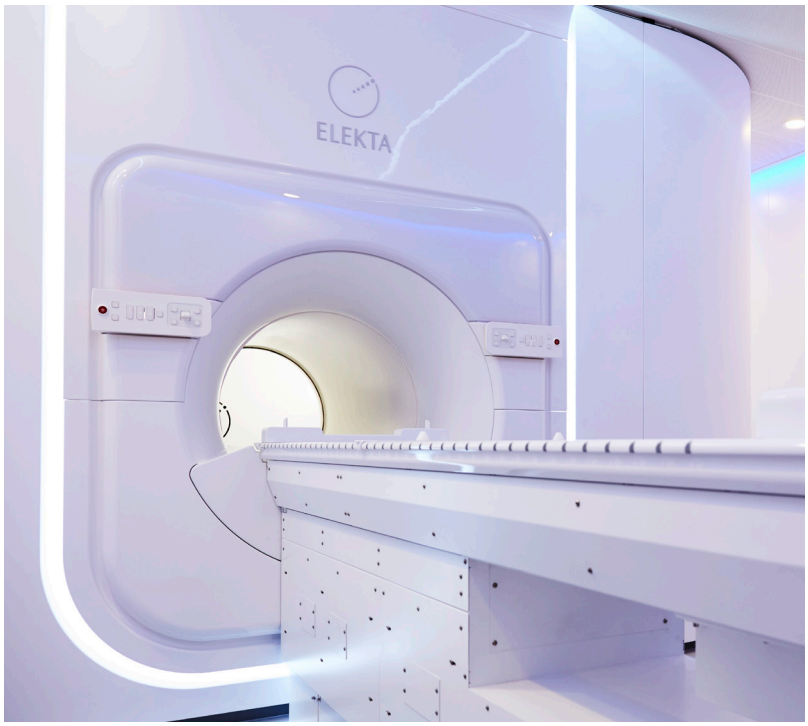
The early proof-of-concept study confirmed that high vascularity resulting from a significant number of blood vessels is an important measure of a tumour's aggressiveness and how it responds to treatment.

Dr. Czarnota is now preparing to embark on the next phase of his study. Sunnybrook recently purchased a photoacoustic imaging machine, which uses a simple handheld probe and laser pulses to generate detailed images of body tissues, including blood vessels. More precise and less invasive than diffuse optical spectroscopy, photoacoustic imaging can even show the levels of hemoglobin and oxygen saturation within tumour cells.

Dr. Czarnota plans to pair this technology with quantitative ultrasound to create the first complete characterization of breast tumours, including data on size, shape, texture and vascularity.

"Using these two imaging modalities, we hope to offer a detailed assessment of how each patient will respond to treatment and monitor their progress during treatment."

Recruitment for Dr. Czarnota's 50-patient pilot study of qualitative ultrasound and photoacoustic imaging began in February 2018.



Left: Delivery of the MR-Linac's large gauntry (ring) in July 2017. Right: The MR-Linac suite in completion

Ten-fold increase in tumour response using combination therapy

Planning underway for world first clinical breast therapy trial

A breakthrough treatment technology supported by the Breast Cancer Society of Canada has resulted in a 10-fold increase in breast cancer tumour response in rabbits. Dr. Czarnota used focused ultrasound to agitate microbubbles in the blood vessels of the tumours, making them more susceptible to low-dose radiation. "We found high areas of cell death in the rabbit tumours," he explains.

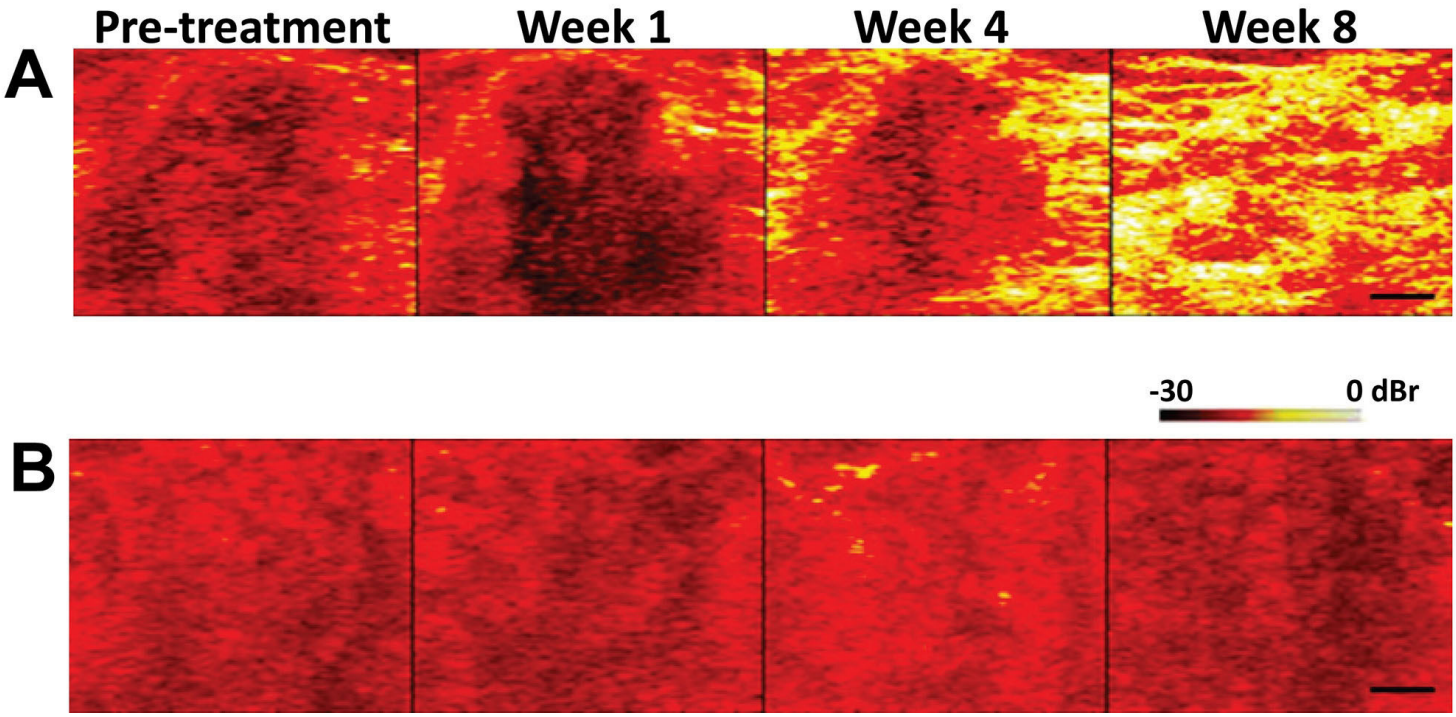
The study, which was completed last April, was recently submitted for publication in *Oncotarget*, a peer-reviewed biomedical journal of oncology.

Dr. Czarnota pioneered the ultrasound-activated microbubble technology two years ago. An initial study involving mice with human breast cancer tumours showed the combination treatment could destroy as much as 50 per cent of a tumour and its blood vessels within 24 hours of treatment. To help ready the technology for human trials, Sunnybrook partnered with Philips Healthcare in 2016 to customize an MRI-guided focused ultrasound machine to emit the required low-intensity ultrasound.

The modified technology was used to successfully treat the rabbit models. Two scientific manuscripts from that work are currently in preparation for submission for publication.

Dr. Czarnota is now using the rabbit data as the foundation of a Sunnybrook Research Ethics Board proposal to launch a world first trial of the treatment in women with breast cancer. Initially planned for last year, the trial was delayed to allow for delivery of a revolutionary technology combining external-beam radiation and real-time imaging. Known as an MR-Linac, the machine will allow Dr. Czarnota to precisely target breast tumours with powerful radiation doses and immediately see how the tumours respond.

Sunnybrook accepted delivery of the MR-Linac last summer with a goal of readying the technology and receiving Health Canada approval to proceed with patient trials by the summer of 2018. Dr. Czarnota hopes to launch his trial later this year.



WaveCheck in action: the yellow colouring in the top row shows tumour cells are responding to chemo; red indicates no response. The technology is being tested in a clinical trial in Canada and the U.S.

Breast cancer technology may aid treatment decisions

WaveCheck accurately predicted chemotherapy outcomes in 90% of patients

A second treatment technology supported by the Breast Cancer Society of Canada and co-invented by Dr. Czarnota to gauge the effectiveness of chemotherapy on breast cancer has been shown to accurately predict the effectiveness of the treatment before it has even started.

Known commercially as WaveCheck, the technology uses quantitative ultrasound and custom-designed software to measure the impact of chemotherapy weeks instead of months into treatment. WaveCheck was first used successfully in 2014 as part of an early clinical study involving more than 100 Sunnybrook patients with locally-advanced breast cancer. In 2015, with support from the Breast Cancer Society of Canada and the Ontario Institute for Cancer Research, Dr. Czarnota expanded the proof of effectiveness study to include a total of 300 patients at Sunnybrook. St. Michael's Hospital and Princess Margaret Hospital in Toronto each recruited an additional 15 patients, and 20 women were invited to join the study at MD Anderson Cancer Center in Houston, Texas.

After seeing early, positive results involving the ability of WaveCheck to detect tumour changes in these patients, Dr. Czarnota asked how the technology might also benefit women newly diagnosed with breast cancer. "I wondered if we could use what we learned from women who have had treatment to help those early on in their cancer journey make important treatment decisions," he explained.

He selected 56 of the 300 study participants who had yet to receive treatment and used WaveCheck's high-tech imaging capabilities to deliver a detailed characterization of the tumour's size, shape and texture. The WaveCheck technology includes the ability to recognize even subtle changes in the cellular structure of specific parts of the tumour. These findings were then compared to data recorded after each patient's chemotherapy treatment.

In more than 90 per cent of the cases, WaveCheck accurately predicted the impact of the chemotherapy on the tumour in advance of the treatment delivery.

Finding ways to accurately predict tumour response and the impact of various treatment options has long been a significant hurdle for doctors and their patients. "This [discovery] puts us in an entirely new category of what we can do for our patients," says Dr. Czarnota. Armed with potential success rates, women and their doctors will be better able to make effective treatment decisions from the outset, without the potential consequences associated with changing treatment mid-course.

Dr. Czarnota published the results of his study in the April 2017 issue of *Nature Scientific Reports*, one of the world's most cited scientific journals. His paper also included data pointing to the potential benefits of WaveCheck on patients' outcomes with real-life impact on emotional health. "They told us overwhelmingly that this was something they needed to feel less anxious and more positive about their treatment."

Data analysis on the initial 300-patient cohort will continue this summer as the final patients undergo surgery to complete the pathology on their tumours. Dr. Czarnota hopes to publish the complete WaveCheck study results later this year.

First full WaveCheck trial to launch this April

A clinical pilot study involving WaveCheck and personalized chemotherapy has received Sunnybrook Research Ethics Board approval and will launch in April 2018. Unlike previous studies, the "Chemo Switch" trial will allow doctors to monitor and recommend treatment changes based on the image findings. A total of 12 women will be recruited for the first three-month cohort. Initially planned to start in 2016, the trial was deferred to allow Dr. Czarnota and his team the time to refine their use of the technology and analyse earlier data.

On behalf of Dr. Czarnota and the countless women and their families who have and will continue to benefit from the Sunnybrook's world-class breast cancer imaging research, we thank you for your support. With your help, we are inventing the future of cancer care.

APPENDICES

PUBLICATIONS

- Breast-Lesion Characterization using Textural Features of Quantitative Ultrasound Parametric Maps.
  Sadeghi-Naini A, Suraweera H, Tran WT, Hadizad F, Bruni G, Rastegar RF, Curpen B, Czarnota GJ.
  Sci Rep. 2017 Oct 20;7(1):13638. doi: 10.1038/s41598-017-13977-x.

- Chemotherapy-Response Monitoring of Breast Cancer Patients Using Quantitative Ultrasound-Based Intra-Tumour Heterogeneities.
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- Microbubble-based enhancement of radiation effect: Role of cell membrane ceramide metabolism.
  Al-Mahrouki A, Giles A, Hashim A, Kim HC, El-Falou A, Rowe-Magnus D, Farhat G, Czarnota GJ.
  PLoS One. 2017 Jul 26;12(7):e0181951. doi: 10.1371/journal.pone.0181951. eCollection 2017.

- Ultrasound Imaging of Apoptosis: Spectroscopic Detection of DNA-Damage Effects In Vivo.
  Tadayyon H, Gangeh MJ, Vlad R, Kolios MC, Czarnota GJ.
  Methods Mol Biol. 2017;1644:41-60. doi: 10.1007/978-1-4939-7187-9_4.

- Ultrasound Imaging of DNA-Damage Effects in Live Cultured Cells and in Brain Tissue.
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  Methods Mol Biol. 2017;1644:23-40. doi: 10.1007/978-1-4939-7187-9_3.

- Predicting breast cancer response to neoadjuvant chemotherapy using pretreatment diffuse optical spectroscopic texture analysis.
  Tran WT, Gangeh MJ, Sannachi L, Chin L, Watkins E, Bruni SG, Rastegar RF, Curpen B, Trudeau M, Gandhi S, Yaffe M, Slodkowska E, Childs C, Sadeghi-Naini A, Czarnota GJ.
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- A priori Prediction of Neoadjuvant Chemotherapy Response and Survival in Breast Cancer Patients using Quantitative Ultrasound.
  Tadayyon H, Sannachi L, Gangeh MJ, Kim C, Ghandi S, Trudeau M, Pritchard K, Tran WT, Slodkowska E, Sadeghi-Naini A, Czarnota GJ.
  Sci Rep. 2017 Apr 12;7:45733. doi: 10.1038/srep45733.

- Effect of chromatin structure on quantitative ultrasound parameters.
  Pasternak M, Doss L, Farhat G, Al-Mahrouki A, Kim CH, Kolios M, Tran WT, Czarnota GJ.
  Oncotarget. 2017 Mar 21;8(12):19631-19644. doi: 10.18632/oncotarget.14816.

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