



SMARTERFAS



On-the-Horizon Innovations in Cancer Care

Researchers here are developing new methods and technologies to hasten detection, dramatically improve diagnosis and make treatment more targeted, innovations that are close to making—or in some cases already making—patients' lives better By Alisa Kim

STER BETTER

THE ADVANTAGE: CLEARER PICTURES THAT MAY HELP DOCTORS DIAGNOSE BREAST CANCER MORE ACCURATELY AND REDUCE THE INCIDENCE OF MISSED CANCERS AND FALSE ALARMS.

“It was more like a spider web, not a lump.”

That was what Joanne Nevison learned about the mass in her breast when she was diagnosed with breast cancer in March 2007. Within a week of getting the diagnosis from her family doctor, Nevison, aged 50 years, was at Sunnybrook’s Odette Cancer Centre, where she was told that because it was so large, the 7-cm tumour had to be reduced with chemotherapy before surgeons could remove it.

Her oncologist, Dr. Greg Czarnota, who is also a scientist at Sunnybrook Research Institute (SRI), asked whether she would like to be part of a clinical study to evaluate a new imaging system to monitor the effectiveness of chemotherapy.

She was game: “I wanted to help with the research, to help other people,” she says.

Research and education are critical to understanding and preventing disease, and improving patient care. Scientists at SRI are inventing innovative technologies to detect cancer sooner and with greater precision. They are also identifying new ways of evaluating therapies to enable patients to receive more effective, personalized care, and discovering ways to improve existing treatments by reducing harmful side effects.

The technology Czarnota was studying revealed that the drugs Nevison was taking were shrinking the tumour. Surgeons successfully removed it in July of that year. Her treatment concluded with a final round of chemotherapy. The self-employed businesswoman now checks in every six months for follow-up care.

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From his office on the sixth floor of Sunnybrook’s S wing, SRI imaging physicist Dr. Martin Yaffe has his eye on a number of promising directions in cancer research. His focus is on the early detection of cancer, when tumours are one millimetre, the size of a head of a pin. Today, tumours are normally spotted when they are bigger than one centimetre, comprising over 200 million cancer cells.

“Imaging in cancer has been looking for masses, physical changes as the cancer begins to grow. To get to that point, the cancer has to have been there for quite a while, so that approach is never going to be highly sensitive,” says Yaffe, who holds the Tory Family Chair in Oncology Research. “We’re really looking for fingerprints of the cancer, and we’re trying to develop sensitive tools to do that.”

The subtle clues for which Yaffe and his colleagues are sleuthing are functional, or physiological, changes in cellular metabolism and blood flow that betray the presence of otherwise imperceptible malignant cells. As the co-leader of the Ontario Institute for Cancer Research’s (OICR’s) One Millimetre Cancer Challenge, Yaffe oversees projects at SRI and across the province that are using sophisticated technologies to track molecular and functional changes in the body that are associated with cancer—“smarter imaging,” as he puts it.

The research behind the program adapts existing imaging systems such as X-ray, magnetic resonance imaging (MRI), positron emission tomography

and ultrasound, by adding probes to detect early-stage cancers. To this end, Yaffe, who is also a professor in the department of medical biophysics at the University of Toronto, has assembled a team of experts—physicists, chemists, biologists and clinicians—to develop and test advanced imaging and screening techniques.

“Cancer is a complex problem, and the solutions require bringing together talents from different areas,” says Yaffe, of the multidisciplinary approach. “The OICR program has let us ask what we think are the important questions related to imaging and cancer, and find the people we think can contribute to answering them. My job is to pull it together.”

One project harnessing the program’s varied scientific expertise involves the use of microbubbles to track cancer growth. Microbubbles are tiny pockets of gas that are smaller than a red blood cell and can pass harmlessly through the microcirculation. Exploiting these properties, SRI scientist Dr. Peter Burns developed a method that uses bubbles as a contrast agent for ultrasound to visualize blood flow. Injected into blood vessels and excited by high-frequency ultrasound waves, the microbubbles vibrate, displaying areas of angiogenesis (the formation of new blood vessels from pre-existing ones) that may be linked to spreading cancer.

Burns, who is the chair of the department of medical biophysics at U of T, and his SRI colleagues are also using microbubbles to detect cancer by attaching a molecule to the bubbles; the molecule works as a “magnet” to attract other tumour-specific



DR. GEORG BJARNASON

molecules. Finally, they are developing a way to add microbubbles to treat cancer. By loading the bubbles with an anticancer drug and using ultrasound to aim and burst them at the disease site, patients can receive locally targeted therapy.

Burns's work is at the preclinical stage. Yaffe anticipates that research on the use of these methods in humans will begin within one year.

An innovation that is now being studied for clinical use is digital breast tomosynthesis. Like 3-D digital mammography, tomosynthesis uses X-rays to produce an image of the breast, which can be stored or sent electronically. Tomosynthesis takes X-ray photos of the breast snapped at different angles, which are then processed using computer software to construct a 3-D image. The advantage: clearer pictures that may help doctors diagnose breast cancer more accurately and reduce the incidence of missed cancers and false alarms.

The detailed images are also useful in treating breast cancer. "[Digital tomosyn-

thesis] gives the surgeons or whoever performs therapy on the breast cancer a much better idea of what they're dealing with so that they can get a 3-D picture of the disease, and can plan the therapy in a way that's going to be most appropriate," says Yaffe. Sunnybrook Research Institute is part of a multi-institutional study evaluating this technology, the results of which Yaffe expects to have next year.

"We don't have all our eggs in one basket," he says of the various activities comprising the One Millimetre Cancer Challenge. "It's a diversified investment portfolio in research where there's multiple possibilities for solutions to a problem. One of them will likely emerge more quickly or as a better approach, and we'll then follow that more energetically."

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At the bustling Odette Cancer Centre, Yaffe's colleague Czarnota is fighting cancer on two fronts: in the lab and in the clinic. Czarnota is using his passion for medicine

and science to find ways of improving care for Nevison and other women who have breast cancer.

Czarnota, who is also an assistant professor at U of T and was recently named a Cancer Care Ontario Research Chair in Experimental Therapeutics and Imaging, is using ultrasound imaging to study tumour death to develop better cancer treatments. His lab is also designing ways to evaluate treatments more quickly using ultrasound and optical imaging technologies.

He has performed a clinical study monitoring the effectiveness of chemotherapy in women with locally advanced breast cancer—characterized by large, aggressive tumours confined to the breast area—using SoftScan, an optical imaging system created by Advanced Research Technologies Inc. The SoftScan system characterizes delicate but important physiological changes in breast tissue, including blood flow and blood oxygen content, that reveal the status of a tumour. Lasers probe the patient's breasts at four wavelengths of light; a detector then measures how much light the breast absorbs. This information is used to calculate blood proteins, water content and light scattering power, all of which can tell physicians how the tumour is responding to therapy. The process is noninvasive and safe.

Czarnota used the SoftScan system to learn how Nevison and the other women in the study responded to neoadjuvant chemotherapy, drugs used to shrink large tumours before they are surgically removed. Each patient received five scans—one before the therapy began; after they

TIME IS PRECIOUS TO A CANCER PATIENT.

began taking the drugs, at weeks one, four and eight; and prior to surgery.

He began to see results after the patients' third scan.

"What we found is that using this method, we can see changes in breast tumours very early on," says Czarnota, amid an array of computers in his quiet office. "This provides oncologists a measure by which they can objectively change therapies from ones that are ineffective to ones that can be effective. That might mean switching from one [type of] chemotherapy to another; it might mean switching from chemo

to radiation. I think for these women with aggressive breast tumours, it has the potential to improve survival."

The five-year survival rate for women with locally advanced breast cancer ranges from 20% to 40%, versus 87% for women with early-stage breast cancer. Time is precious to a cancer patient; to wait for several months to determine whether chemotherapy is working—especially when drugs are not reducing tumours—can be fatal. "For someone to have six months of a type of chemo or hormone therapy that's not effective is a loss of time for that patient, as well as health care dollars.

Rather than having someone undergo an expensive course of antiangiogenic drugs that can cost tens or hundreds of thousands of dollars, this may allow one to determine quickly whether that drug is useful or not for this type of patient," says Czarnota.

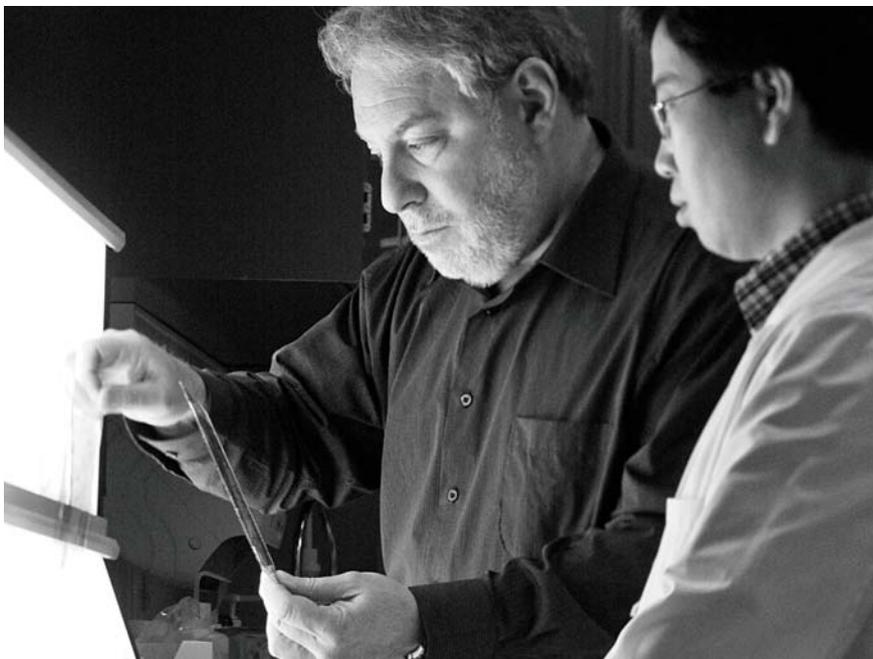
His findings have important implications for changing clinical practice. Typically, breast cancer patients receive an MRI scan before therapy and just prior to surgery, with no imaging test ordered in-between. This research suggests that optical imaging may be a viable means of filling the gap. "Oncologists will see patients on a week-to-week basis and feel patients' tumours. That's a very subjective measure of response. This [technology] could be developed as a standard method to assess tumour response."

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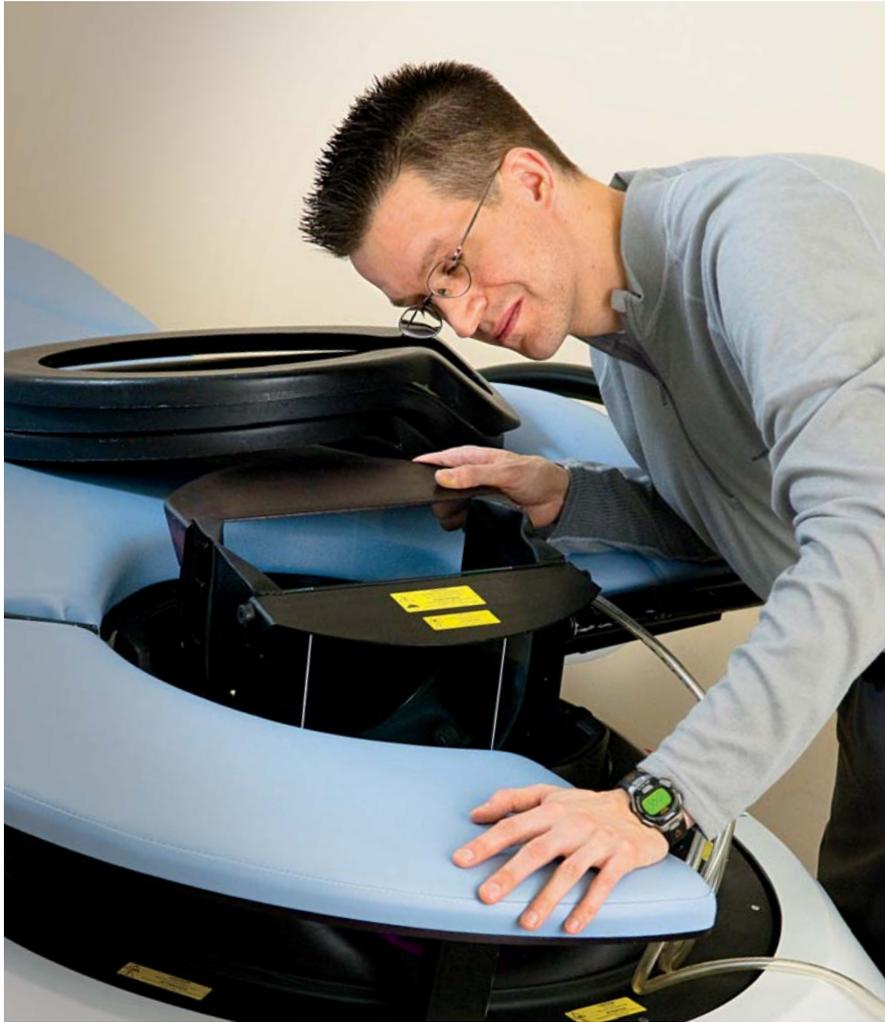
Down the hall, on the second floor of the Odette Cancer Centre, Dr. Georg Bjarnason is watching the clock.

An oncologist and senior scientist in clinical integrative biology at SRI, Bjarnason is studying chronobiology—how biological processes are linked to the body's circadian rhythm. The only researcher in Canada studying the effects of chemotherapy and radiation on people at different times of the day, Bjarnason aims to determine the optimal time for treatment, to maximize efficacy and minimize side effects.

In a paper published last year in the *International Journal of Radiation Oncology, Biology and Physics*, Bjarnason,



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DR. GREG CZARNOTA

who is also an associate professor in the department of medicine at U of T, showed the results of a proof-of-principle study comparing the effects of radiation given in the morning versus the afternoon. In it, Bjarnason and colleagues across Canada studied the incidence and severity of oral mucositis (inflammation of the mouth lining) in over 200 patients with head and neck cancer receiving radiotherapy either between 8 and 10 a.m., or between 4 and 6 p.m.

Oral mucositis is a side effect of radiation that plagues head and neck cancer patients, often forcing doctors to stop treatment prematurely. Its symptoms include pain, dryness of the mouth, changes in saliva and taste, and difficulty swallowing. Severity of mucositis ranges from mild discomfort to extensive damage such that patients cannot eat on their own and require feeding through a tube connected to their stomachs. In the study, researchers scored the patients' mucositis based on visible damage to the mouth.

Having determined from his prior research that the cells lining the mouth go

through the phases of the cell division cycle over 24 hours, and that healthy cells are in a phase that is less sensitive to radiation early in the day, Bjarnason surmised that giving radiation in the morning could reduce oral mucositis. "If we wanted to get a theoretical answer, we would have treated people at 3 a.m. but that wouldn't have any impact, because you're not going to do that in clinical practice," he says, wearing his physician's hat. "So we said, realistically, people can have treatment early in the day or at the end of the day. Are these times going to have a clinically significant impact?"

It appears they do.

Bjarnason found that, compared with the afternoon group, there were fewer patients in the morning group who had severe oral mucositis. What he found most compelling was that weight loss—caused by difficulty eating due to mucositis—among patients in the morning group stabilized five months after treatment, whereas patients in the afternoon group continued to lose weight for much longer. "I think that is the strongest evidence, because when looking

at the mucositis grade, there's inter-observer variability. But when the patient steps on the scale, that's pretty objective," says Bjarnason.

The benefits of morning radiotherapy were even more striking in a subset of 100 patients who, due to their inoperable tumours, required higher doses of radiation. Within this subset, 44% of patients in the morning group developed severe mucositis, compared to 67% in the afternoon group. Moreover, it took longer to reach this level of damage in the morning group. "The clinical scales to measure mucositis are imperfect because they're so subjective. When we took the people who got the highest dose, this reduction [of mucositis] became statistically significant, and the time until they developed this was prolonged," he says.

Determining whether this innovation can improve the survival rate of head and neck cancer patients will require a larger clinical trial, says Bjarnason. But, he notes, "I've received calls from people who do this kind of therapy in the States and elsewhere saying 'I've seen your paper. We now try to do the treatment early in the day.'" As to when this research will more widely change the way in which therapy is delivered to these patients, it may be just a matter of time.

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