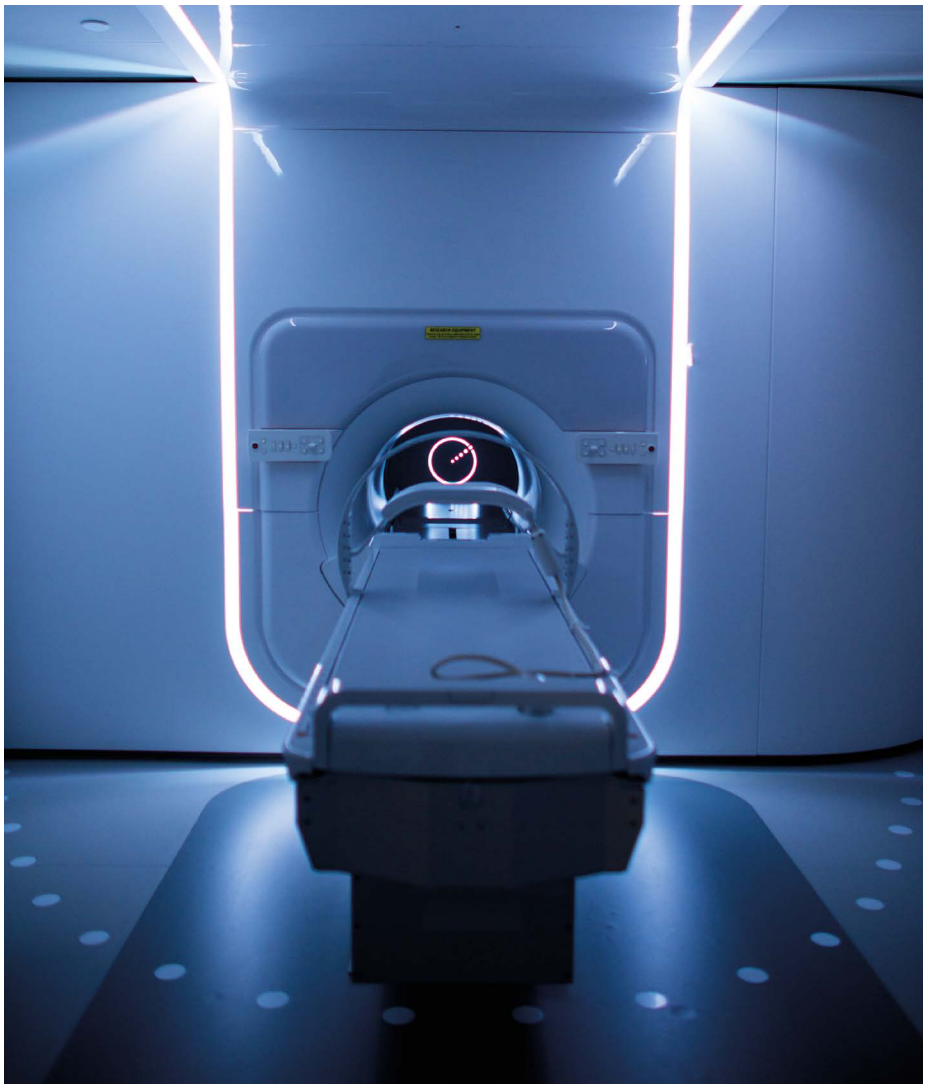


A magnetic resonance linear accelerator generates images and delivers treatment.

NICK DE LA TORRE

Rethink, aim and fire

Technology means radiation oncology is more personalized, but research has not kept pace. **By Amanda Keener**

A man walks into a radiotherapy treatment room. It's his tenth visit. Just as before, he lies on a table attached to a machine that would resemble a futuristic countertop food mixer, were it not three metres tall. A technician places a plastic, cage-like mask over the man's head and form-fitting foam beneath his knees, holding him tightly in place. The machine then delivers beams of high-energy X-rays to his tumour. The whole process takes about half an hour.

From the man's perspective, this treatment session is no different to the first 9, and the next 20 will probably feel exactly the same. But they won't be.

Before the man ever stepped foot in that therapy room, his treatment was planned out using computed tomography (CT) images of his tumour and the surrounding tissues. Based on those images, precise calculations were made so a predetermined radiation dose could be delivered to the tumour, minimizing exposure to normal tissue. That same plan will be fed into the machine every weekday for several weeks. But despite the mask and the mould, the man's anatomy will be different at every visit. Tumours shrink, organs move around and people lose weight — all these changes can alter the dose of radiation that hits the tumour and nearby healthy tissues. Over the course of a treatment, which can be weeks or months, "you may not end up doing anything like what you thought you were doing," says David Sher, a radiation oncologist at the University of Texas Southwestern Medical Center in Dallas. As things shift, more healthy tissue can be damaged by radiation and the risk of short- or long-term side effects increases.

Radiation oncologists have known about this problem for decades, and in the past ten years companies that make radiation-delivery machines called linear accelerators have worked to address it. Radiation doses can now be adjusted in step with changes in a tumour's size or metabolic activity. The most advanced machines can generate a detailed real-time image of inside a person's body while simultaneously delivering the beam. "Ten years ago, this was science fiction," Sher says.

A handful of linear accelerators with built-in imaging capabilities and software that can make daily adjustments to compensate for anatomical changes are now in use. However, despite their potential to reduce side effects, the research required for this fine-tuning of treatment to become standard practice has not kept pace. As excited as clinicians are to implement the new technology, "up to this point, there has not been really great data to support doing it," Sher says. Trials are now under-way to test the impacts of adapting radiation treatment to changes in a person's anatomy and tumour biology.

In addition to tracking tumours using imaging, some researchers are examining how genetic markers of radiation sensitivity could be used to optimize radiation doses to individuals. Together, the work is making radiation oncology more personalized, but the field is still working out which variables actually matter for factors such as cancer recurrence and secondary growths known as metastases. "We can do all these things we've always wanted to do, but whether it benefits the patient is going to require a lot of careful study," Sher says.

Moving target

Changes to a person's anatomy started to matter to oncologists in the early 2000s

when a form of radiation delivery called intensity-modulated radiation therapy (IMRT) became standard practice. In IMRT, the intensity of a radiation beam is varied to conform to the shape of a tumour; this helps to maximize doses to the tumour and spare non-cancerous tissue. This makes the treatment more precise, but it is less forgiving than older forms of treatment to anatomical changes that might shift parts of the tumour or normal tissue in or out of the radiation beam.

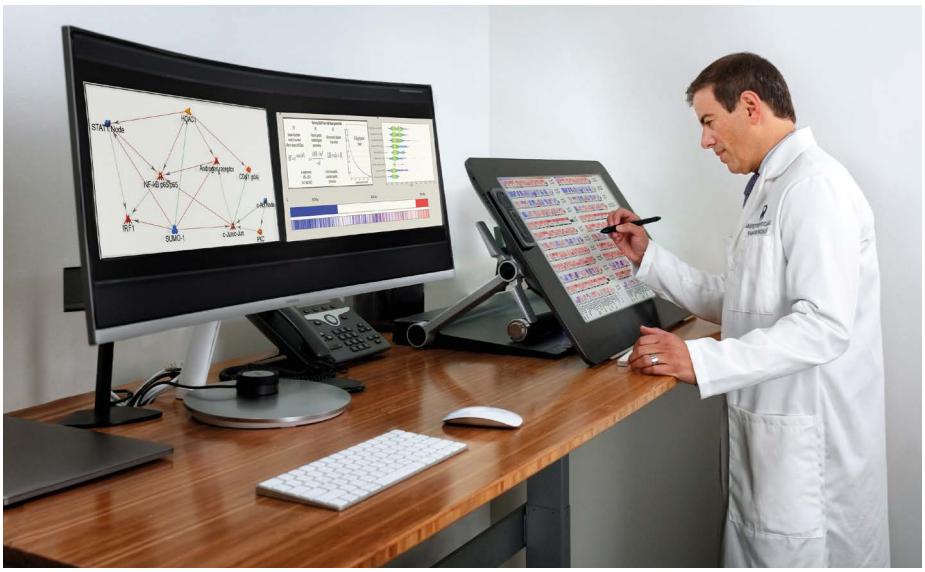
At the time, anatomical changes were rarely considered. If a person lost a lot of weight, Sher says a physician might cancel that day's radiation session and instead send the person for a new CT scan, which could be used to replan the remaining treatment. But this created work for the radiation oncology team, inconvenienced the person being treated and extended the total treatment time, so it was rare that clinicians scheduled regular re-planning to adapt to anatomical changes, Sher says.

Technologies to address this issue are already commonplace, including faster, less-detailed CT scans that can be done while a person is on the treatment table as a final check. These scans might reveal that a person's weight loss was all abdominal fat and doesn't affect the tumour area at all. They might also be used to make slight alterations during a treatment session, or reveal shifts large enough to justify a replan.

In recent years, cancer centres have started using linear accelerators with a built-in magnetic resonance imaging (MRI) scanner, which provides intricate detail of soft tissues. Some companies, including Elekta in Stockholm and ViewRay in Oakwood Village, Ohio, now make hybrid machines that can take MRI scans as the treatment beam is being delivered. "It's amazing to have the ability to see what you're treating as you're treating it," Sher says.

These new machines deliver the same radiation at the same doses as conventional linear accelerators, so they are already available at dozens of cancer centres around the world; their use is paid for by health insurers. But they cost millions of dollars more than standard machines, require more staff to operate them and take longer to deliver treatment. It's therefore essential to test their clinical value. An adapted plan might look great on a computer screen, Sher says, "but does it really matter to the patient? We have yet to find out".

A handful of trials are now recruiting people to find out whether closely monitoring their anatomy and adapting the treatment plan can reduce the risk of radiation side effects. Head and neck cancers are popular candidates for testing adaptive therapy because the size of the tumour can dramatically change in as little as two weeks, increasing the risk of overdosing the surrounding anatomy. This can include major salivary glands called the parotids. Radiation damage to the parotid glands can lead to long-term dryness of the mouth, and treatment plans designed to avoid the glands reduce the risk of damage.



NICHOLAS J. GOULD

Javier Torres-Roca developed a panel of genes that predicts response to radiation.

In a trial taking place at the University of Zurich in Switzerland, a team led by Panagiotis Balermpas is using ViewRay's machine to carry out daily MRI scans and adapt treatments for 44 people with head and neck cancer. Six months after treatment, and again after two years, the team will assess whether the rate of dry mouth is lower than the current average rate for standard therapy. A similar study, at the University of Texas MD Anderson Cancer Center in Houston, is testing whether adapting treatment based on weekly MRI scans can reduce the number of people with head and neck cancer who have difficulty swallowing after radiation therapy.

If you build it

Adapting therapy might also mean rethinking treatment plans to match the tumours' changing biology. "We are gradually moving from just thinking about the anatomy to thinking about the biology," says Ricky Sharma, a clinical oncologist at University College London and vice-president of clinical affairs at the radiation-oncology company Varian in Palo Alto, California.

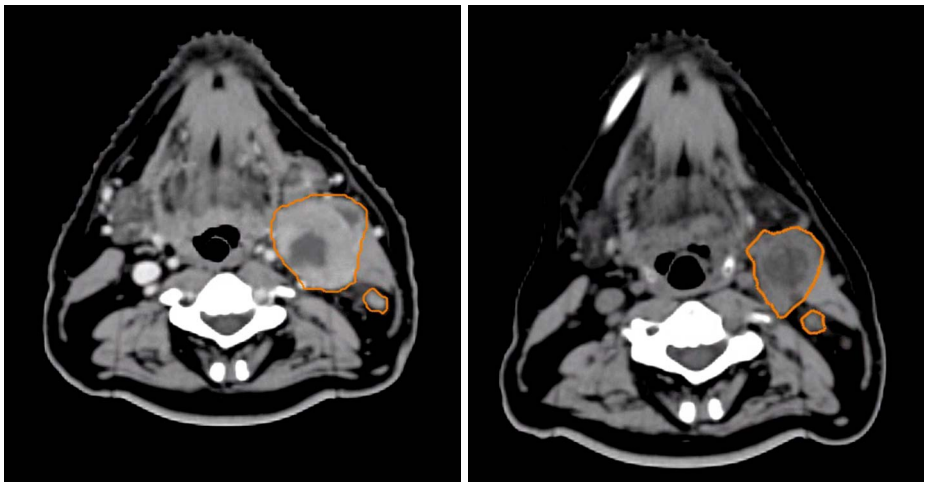
The biology of the tumour environment affects how susceptible different parts of a tissue are to radiation damage. In poorly oxygenated areas, for example, cells are sometimes more resistant to radiation-induced DNA damage. Some imaging techniques can capture this sort of biological information. The most widely used are positron emission tomography (PET) scans that trace the metabolism of a radioactively labelled sugar called fluorodeoxyglucose (FDG) that is injected into a person's bloodstream. Clinicians use FDG–PET to identify areas of active tumour growth. Other types of tracer reveal different kinds of information, such as the hypoxic regions of a tumour.

Some groups are testing whether these tracers can be used to improve radiotherapy outcomes by allowing clinicians to direct the strongest doses of radiation to particular parts of a tumour. For example, in 95 people with head and neck cancer, researchers at Ghent University in Belgium are monitoring whether increasing radiation doses at more-metabolically active tumour areas improves people's chances of being cancer-free a year later. In another trial, the same group is using FDG–PET and MRI data to reduce doses to areas of the neck that are less likely to host metastases. The researchers think that this will reduce treatment side effects such as difficulty swallowing.

Sher is working towards a similar goal. His team at the University of Texas is teaching machine-learning algorithms to use PET data to identify lymph nodes that are most likely to harbour metastases. He hopes that, rather than treating the entire neck, such algorithms could guide radiation to just those sites. "If we know where the cancer is and where the cancer is not, we can start really shrinking our treatment volumes, which could mean a lot less normal tissue toxicity," Sher says.

Companies such as Elekta and Varian have developed software that make it possible to overlay many different types of PET and MRI

outlook



A tumour shrinks significantly after 5 weeks of treatment (right). To minimize the dose to healthy tissue the radiotherapy plan would need to be adjusted.

data. In 2017, a group at the University of Tübingen in Germany showed that it could use Elekta's technology to overlay PET–CT imaging with two biological markers for prostate cancer, a low oxygen tracer and MRI data, to increase the likelihood that treatment covers the whole area containing tumour cells[1].

The biological meaning of all these changes, however, is still murky. "We do the best we can with what we know, but there is a gap between the clinical evidence base and where we want to be with biologically targeted therapy," Sharma says. Researchers can identify low-oxygen regions in a tumour and target them with higher radiation doses, but no one knows whether doing so can improve a person's outcome. Those trials have just not been done yet. "I think that will come," Sharma says.

More than meets the eye

Most of the biology that affects a person's response to radiation doesn't show up on an MRI or CT scan. So although biomarkers and genetic tests that give an idea of how well a person might respond to a particular treatment are already the mainstays of chemotherapy and immunotherapy, for radiotherapy, these are still blind spots. "We have had now 20 years of data about the heterogeneity of cancer, and we are still treating everybody with uniform doses of radiotherapy," says Javier Torres-Roca, a radiation oncologist at the Moffitt Cancer Center in Tampa, Florida. Torres-Roca thinks precision medicine won't really reach his field until it can adapt treatments to aspects of a person's molecular biology.

For example, some people are more likely to experience long-term side effects of treatment, such as skin damage. In an effort to identify those at highest risk and look for ways to reduce that risk, the international group the Radiogenomics Consortium has created a standardized biobank of tissue samples paired with donor radiotherapy history and treatment outcomes. One of the consortium's projects, called REQUITE, found an association between radiation side effects and variants of two genes linked with circadian rhythm found in some people with breast cancer[2]. This correlation applied only to people who received treatments in the morning, suggesting that genotype might matter for apparently mundane treatment details such as scheduling. The team is now repeating this analysis prospectively in another cohort.

There is, however, more to personalizing radiotherapy than mitigating side effects. Currently, radiation doses are based on largely empirical data for individual cancer types – people with stage three lung cancer receive one dose, and people with stage two breast cancer get another, for example. But sensitivity to radiation varies between people and tumour types, so the same dose of radiation does not always translate to the same biological effect on tumour cells in every individual. "We're darn good at putting radiation where it needs to go, but we're not giving the same biological effect of radiation," says Torres-Roca.

One way to optimize the biological radiation dose is to look for genetic signatures of radiation sensitivity. A handful of genetic tests in radiation responsiveness for individual cancer types are already available, but they are qualitative and hard to incorporate into treatment decisions. Torres-Roca wants to change that. He has developed a panel of ten genes that predicts responses across several different types of cancer. His team came up with a calculation called GARD (genomic-adjusted radiation dose) that uses the ten-gene panel to work out the biological dose on the basis of an individual's radiation sensitivity.

In a 2017 study, the team calculated adjusted doses using data and tissue samples from people in five different cancer-study cohorts[3]. People with breast cancer who had the highest GARD scores, and therefore the greatest biological effect of radiation, had the highest rates of survival without cancer spread at five years. Higher GARD scores also correlated with better survival or cancer control among people with three other types of tumour.

Torres-Roca has faced criticism for GARD, partly because the gene panel that it uses doesn't include many of the standard DNA-repair genes known to be involved in radiation responses. This seems at odds with the basic concept that radiation kills cancer by damaging DNA. But Torres-Roca defends his technique, saying that, rather than a few pre-selected genes, his unbiased approach to building the gene panel means that it represents major hubs in a larger network of radiation-responsive genes – something he argues makes GARD useful across cancer types. Since he developed the panel, some of those pathways have proved their worth, including those involved in anti-tumour immunity, which is now recognized to have a major role in radiotherapy. In a study on the preprint server bioRxiv, Torres-Roca and his team have linked their radiosensitivity panel to increased immune-cell activity in tumours[4]. He expects to treat the first person using GARD at Moffitt sometime this year, and says he will let the results speak for themselves.

Whether through genetics or advanced imaging, the field of radiation oncology is slowly but steadily adopting principles of personalized medicine. There is a long way to go before it catches up with other areas of cancer therapy. But Sher is encouraged by the progress; 20 years ago, he still used wax pencils on printed radiographs to plan out some treatments. Now, clinicians have the technology to adapt plans not just daily, but even mid-treatment – they just need to work out how best to use it. "I think the landscape in the next decade is going to hopefully change remarkably, as we have both the technology and the understanding of what all of these imaging changes mean," Sher says.

Amanda Keener is a freelance science writer in Littleton, Colorado.

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