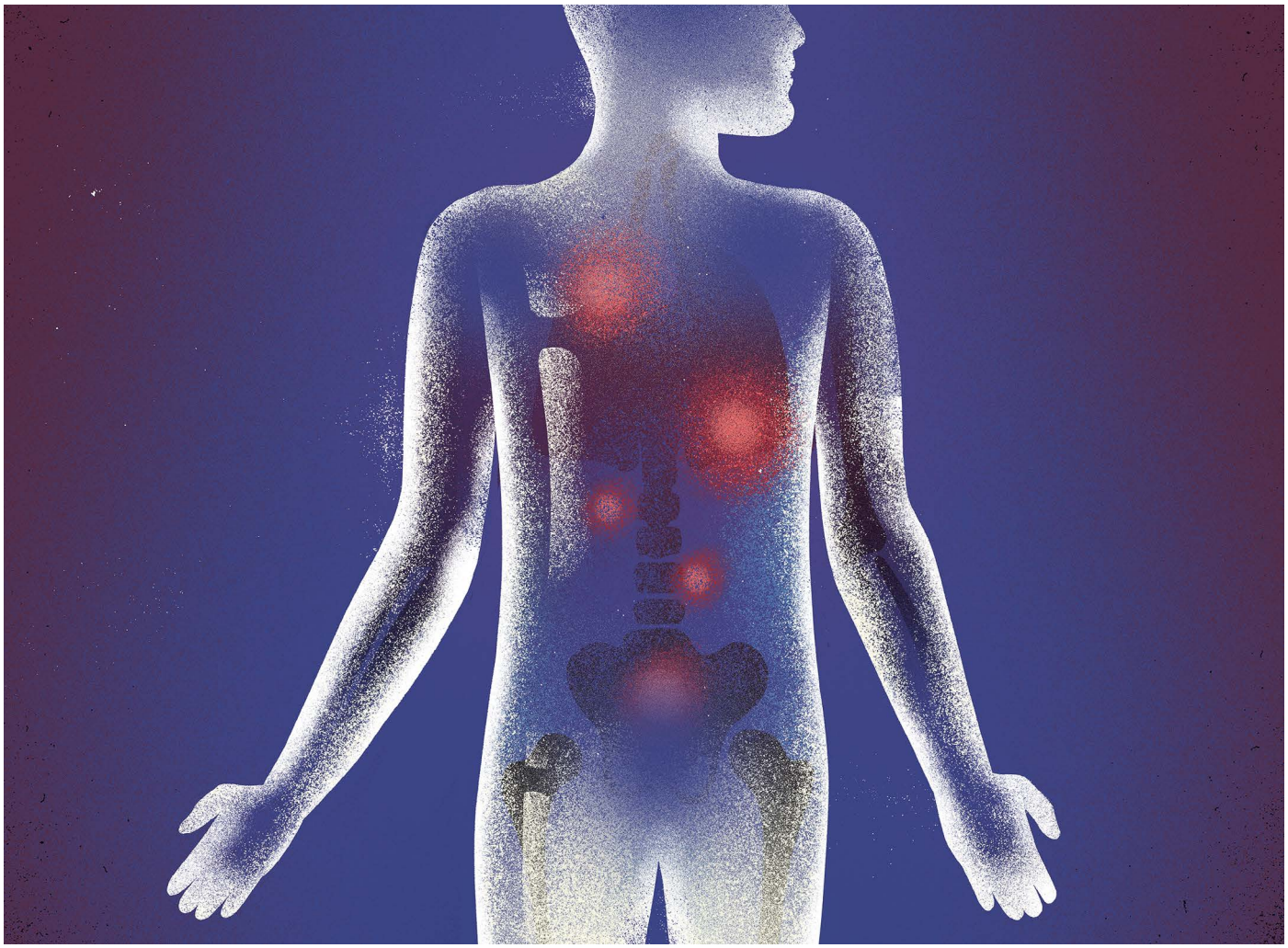


ILLUSTRATION BY SEBASTIAN THIBAULT

A fresh chance of treatment

Advances in the ability to find and treat tumours that have spread around the body are changing the perception of metastatic prostate cancer. **By Charlie Schmidt**

In 2012, a man in his 50s arrived at the Cleveland Clinic in Ohio with high-grade prostate cancer that had spread to a nearby lymph node. The treatment in such cases would ordinarily have been limited to drugs that block testosterone, a hormone that fuels prostate tumour growth. At the time, metastatic prostate cancer was considered uniformly fatal, and physicians were reluctant to subject someone to the side effects of surgery and radiation if these extra measures were unlikely to prolong life.

But the man insisted on doing more. In addition to undergoing six months of hormonal therapy, he had his prostate and cancerous lymph node surgically removed. A tumour that was detected in his pelvic bones one year later was treated with radiation. The extra effort paid off. "He's eight years out now with no sign of cancer in his body," says Eric Klein, a urologist at the Cleveland Clinic who consulted on the case. "Ever since, I've been asking if there is a subset of patients like him who would also benefit from more aggressive treatment."

Mounting evidence suggests that there is. People with fewer than five metastases have what is known as oligometastatic prostate cancer — a transitional stage in progression that offers an increasingly promising window of therapeutic opportunity. With targeted treatments, researchers say it might be possible to change the course of the disease, if not cure it. "The conversation around oligometastatic prostate cancer has changed," says William Oh, an oncologist at the Icahn School of Medicine at Mount Sinai in New York City. "More and more data show we can delay progression, and often significantly."

Finding tumours

Sometimes, as evidenced in the case of the man who arrived at the Cleveland Clinic in 2012, people who are diagnosed with prostate cancer are found to already have progressed to the oligometastatic stage. In other cases,

metastatic tumours might be detected in people who have already been diagnosed and treated for cancer when it was still contained in the prostate. What gives these 'oligorecurring' cancers away is a rising level of a protein called prostate-specific antigen (PSA) in the blood. Prostate cancer cells release much more PSA than healthy prostate cells do, so levels should plummet after initial treatment with surgery or radiation. An increase in PSA suggests that metastatic tumours might be lurking somewhere in the body.

For decades, physicians used computed tomography (CT) and bone scans to hunt for metastatic disease. These imaging methods are still widely used today, but newly formed tumours are often too small for them to pick up. Advances in molecular imaging are now bringing these tiny cancerous deposits to light so physicians can treat them before they grow and spread further.

The crucial technology is positron emission tomography (PET). A PET scan shows the locations and activities of injectable tracers that bind with cancer cells in the body. The first PET tracers used for detecting oligometastatic prostate cancer marked a significant advance compared with CT scans. Choline C-11, approved in 2012, tracks cells undergoing rapid proliferation. Fluciclovine F-18, a synthetic amino acid that was approved four years later, flags cells with high rates of metabolism. But these initial tracers left room for improvement: neither of them is selective for prostate cancer cells, and they have only limited capacity to detect metastases early, before PSA levels have risen substantially.

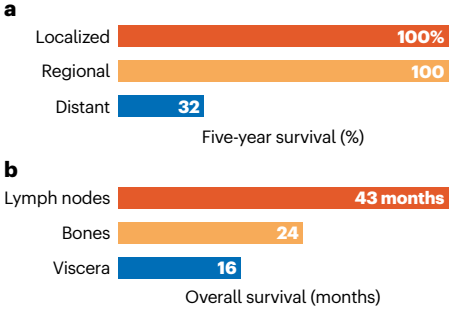
That is where a much more sensitive category of tracer enters the picture. These compounds bind to a cell-surface protein called prostate-specific membrane antigen (PSMA). Normal prostate cells contain small amounts of PSMA, but prostate cancer cells express the protein at high levels. That makes PSMA-directed tracers highly selective for prostate tumours, which show up on a PET scan like lit matches in a dark room.

In the past few years, two PSMA-PET tracers have become available for diagnosis of prostate cancer. The first to reach the market, called Gallium 68 PSMA-11, has been available in Europe since 2019. It was subsequently approved by the US Food and Drug Administration in 2020, but only for use at two hospitals that manufacture it: one at the University of California, Los Angeles (UCLA), and another at the University of California, San Francisco (UCSF). A second PSMA-directed radiotracer, piflufolastat F-18, was approved for broad distribution across the United States in 2021.

PSMA-PET has been a game changer. "It is at least 20 times better at finding oligometastatic prostate cancer than conventional imaging," says Oliver Sartor, an oncologist and research scientist at the Tulane University School of Medicine in New Orleans, Louisiana. "Because of PSMA, we are now able to offer patients therapeutic options that were not previously feasible because we didn't have the tools to detect the disease."

SURVIVING METASTASES

Rates of survival fall precipitously once tumours spread beyond the prostate and regional lymph nodes (**a**). Metastases to the internal organs (viscera) are especially dangerous (**b**), although these are rare for oligometastatic prostate cancer.



SOURCES: A. NATIONAL CANCER INSTITUTE SURVEILLANCE, EPIDEMIOLOGY, AND END RESULTS PROGRAM; B. G. GANDAGLIA *ET AL. EUR. UROL.* **68**, 325–334 (2015).

Treatment opportunity

One such option is to treat metastatic tumours directly with surgery or high-precision forms of radiation. The use of metastasis-directed therapy (MDT) marks a drastic departure from the days when people were treated with hormonal therapy indefinitely. Kenneth Pienta, a urologist and oncologist at the Johns Hopkins University School of Medicine in Baltimore, Maryland, says that at a minimum MDT can prevent symptoms, such as the pain that accompanies tumours growing in bones. "But MDT also has the potential to interrupt the further spread of cancer cells from a treated site," he says. "And that can prevent further metastases."

"More and more data show we can delay progression, and often significantly."

PSMA-enabled MDT is still in its infancy. Clinical data supporting its use are accumulating, but because prostate cancer is often a slow-growing disease, evidence associating MDT with longer survival is in short supply. Instead, clinicians have to rely instead on surrogate end points, such as tumour progression or PSA levels. "We're building on a base of early- to mid-phase clinical trials," says Brendan Connell, an oncologist at the Lahey Hospital and Medical Center in Burlington, Massachusetts.

One study, led by researchers at UCLA and UCSF, set out with the main aim of assessing the accuracy with which Gallium 68 PSMA-11 detects oligorecurring tumours in people with rising PSA levels[1]. The results, published in 2019 and which clinicians now rely on, showed that the tracer was highly sensitive for prostate cancer: PSMA-PET correctly identified up to 92% of cases. However, the study did not stop there. Some men were also treated with MDT, and roughly six months later, most of them were still benefiting from it: PSA levels had declined in 36 of the 39 treated individuals. In 31 of them, the levels were down by more than 50%, and in 10, PSA was still undetectable.

Another frequently cited study[2] that supports MDT is a phase II clinical trial called ORIOLE, which was published in 2020. The investigators in this trial randomized 54 men with PSMA-confirmed oligometastatic disease to treatment or merely observation. Six months later, only 7 of the 36 men who received treatment (19%) experienced disease progression, compared with 11 of the 18 (61%) men who did not.

Changing tack

All the participants in the ORIOLE trial (and some of those in the 2019 UCLA- and UCSF-led study[1]) were treated using a technique called stereotactic ablative radiotherapy (SABR) that focuses intense beams of radiation on tumours from multiple directions. SABR offers the advantage of treating tumours while sparing surrounding tissues. And like PSMA-PET, it has become a transformative technology.

Connell and other physicians who spoke to *Nature* say they tend to offer SABR as a lone treatment to people with favourable disease characteristics, such as slow-rising PSA levels, low-grade cancer and short intervals between recurrence and initial treatment. This strategy, Connell says, could allow some people to delay or even completely avoid the need for hormonal therapy and its challenging metabolic side effects, which include hot flushes, fatigue, loss of libido and heightened risk of cardiovascular disease (see page S46).

Further evidence in favour of this approach comes from a phase II clinical trial by researchers in Belgium[3]. They enrolled 62 participants with oligorecurring cancer, randomized them to either MDT or observation, and initiated hormonal therapy only if their disease progressed. In 2017, after a median follow-up of 3 years, the investigators reported that the men who received MDT had avoided hormonal therapy for an average of 21 months, which was 8 months longer than individuals in the control group.

Using SABR to stave off hormonal therapy "is a huge win", Connell says. "The aim isn't just to live longer, but also to live better." Sartor agrees: "For some men, the goal is not to eradicate all the disease but to live life as normally as possible while they are still asymptomatic."

Other physicians, however, opt for the more conservative strategy of giving SABR together with hormonal therapy, on the basis that this will enhance radiation's beneficial effects in people with high-risk tumours localized to the prostate. "I always include a certain amount of hormonal therapy," Oh says. "It might be for as little as six months, or it might be longer."

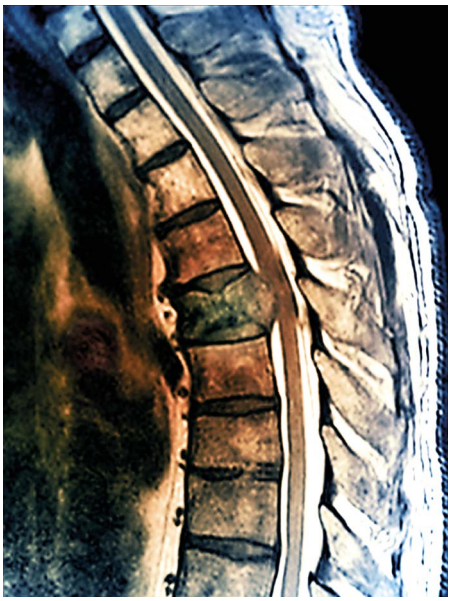
But more research is needed on how to optimize hormonal therapy for oligometastatic disease. Questions remain about the length of treatment, Oh says, as well as the types of drug to use. Physicians can treat people with first-generation drugs such as leuprolide, which reduce levels of testosterone by targeting signalling systems in the brain. They can also opt for newer, more-powerful therapies such as anti-androgens, which prevent testosterone from binding to its cell receptor, as well as a drug called abiraterone that blocks synthesis of the hormone throughout the body. Oh typically sticks to first-generation therapies for men with a better prognosis, and uses combinations of first- and later-generation drugs for men in riskier categories. "But without the clinical trials there's a lot we don't know," Sartor says.

Elimination strategy

Specialists are also exploring strategies for treating people who have already developed oligometastatic disease by the time they are diagnosed with cancer. This '*de novo* oligometastatic cancer' poses different challenges from recurring disease. The metastases develop earlier on in the disease, suggesting that it is aggressive, and the risk of further micrometastases that even PSMA-PET might not pick up is higher, Connell explains.

The options for treating recurring cancer are limited to MDT or systemic hormonal or chemotherapy, either alone or in combination. With *de novo* metastatic cancer, however, physicians also have the option of targeting the prostate gland itself. Not long ago, few would have done that. Physicians conventionally avoided treating the prostate in people with metastatic disease, thinking that radiation or surgery to remove the gland — known as a radical prostatectomy — would be too burdensome for those who were more likely to die from complications caused by tumours elsewhere in the body.

But newer evidence is turning that assumption on its head. Researchers working on a clinical trial called STAMPEDE, for instance, reported earlier this year that people with *de novo* oligometastatic cancer live longer when they receive prostate-targeted radiotherapy than when they received hormonal therapy alone[4]. Conducted in the United Kingdom and Switzerland, STAMPEDE launched in 2005 with an aim of evaluating treatment methods in up to 10,000 men with high-risk prostate cancer. In one part of the study, more than 2,000 individuals with newly diagnosed oligometastatic cancer were randomized to receive either hormonal therapy plus radiation or hormonal therapy by itself. After a median duration of 61 months, 156 of the radiation-treated men had died, compared with 202 of the men treated with hormonal therapy only.



Prostate cancers often spreads to the spine and other bones.

"The aim isn't just to live longer, but also to live better."

Promising start

Whether removing the prostate gland might bring similar benefits is unknown. According to Connell, smaller clinical studies evaluating surgery in people with *de novo* oligometastatic prostate cancer are in progress, and they should provide more evidence in the next couple of years. But early data suggest that radical prostatectomy can be a promising option, especially when combined with other treatments.

Pienta and his colleagues have developed an approach they call total eradication therapy (TET) for *de novo* oligometastatic malignancies. The aim of TET is to eradicate all traces of cancer in the body, and in 2020, the team published findings that move the ball a bit closer to that goal[5]. The researchers enrolled 12 people with newly diagnosed oligometastatic cancer, all of whom were given a radical prostatectomy along with other treatments such as chemotherapy, hormonal therapy (including abiraterone in some cases), radiation to the pelvis and SABR to other metastatic sites in the body.

The results were impressive. The five-year survival rate for newly diagnosed metastatic prostate cancer is only around 30% (see 'Surviving metastases'). But after more than four years, all the men in the study were still alive. At the three-year mark, eight of the men still had undetectable levels of PSA. Pienta says that the results provide further evidence that oligometastatic prostate cancer is a distinct entity that responds to different treatment strategies. The evidence available so far suggests that it might be possible to cure some men with oligometastatic disease, Pienta says — something that would have been unthinkable just a decade ago — although larger studies are needed to further explore this, he adds.

Connell, too, thinks that the progress being made at the moment means that cures might be possible for some people. "This is the golden goose we're all chasing," he says. The ORIOLE investigators proposed that repeat rounds of MDT might whittle away at a patient's overall tumour burden, until too little cancer is left to support future spread.

People who seem to be cancer-free on the basis of PSA monitoring and imaging might still have residual tumours below the limits of detection. But even so, their quality of life can be drastically improved by allowing them to enjoy longer periods free of treatment than was achievable previously. This is arguably the greatest gift from research in this area. "We certainly seem to be slowing down the disease trajectory," Klein says. The individual he saw at the Cleveland Clinic ten years ago, he says, is currently enjoying life with a PSA of zero. "Early in my career, these patients had a poor prognosis. They are doing a lot better now."

Charlie Schmidt is a science writer based in Portland, Maine.

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