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Cancer Care Is Getting Better, But Also More Expensive

An effective but costly clinical approach uses faster technology and targeted pharmaceuticals to combine diagnostics with therapeutics.

Hannah McGillivray and Richard Wassersug

Few medical pronouncements carry as much impact as a diagnosis of cancer. When faced with the sudden need to find out a lot about a complicated topic, most of us now look online. Amid the torrent of information available under the heading of "cancer care," it's difficult to discern any general trends in the field. One tendency does stand out, however: Advances in technology are rapidly increasing both the quality and the cost of that care.

As the tools for diagnosis become more sensitive and the modes of treatment more fine-tuned, it's worthwhile to consider the question: Toward what end is the increasing sophistication of cancer care directed? So many different constituencies have a stake in the matter that a consensus seems all but impossible. Patients and healthcare professionals each have their own view of how that care could be improved. Other groups affected by changes in cancer care include health insurance administrators, bioengineers, pharmacists, and public health officials, to name just a few.

Earlier diagnosis of serious conditions and higher survival rates after diagnosis are widely shared goals. In addition, more tolerable treatments with fewer side effects, or even just greater access to palliative care, are shifts that could ease the burden of cancer somewhat. In the United States, however, few aspects of the cancer experience are as onerous, and at the same time as complicated, as the financial burden.

The first step in cancer care, diagnostics, accounts for a significant share of the financial burden. Increasingly, this step entails imaging with computerized tomography (CT), magnetic resonance imaging (MRI), or positron emission tomography (PET). All these scanners depend on fast computers, with each new generation of computers faster than the one before. Diagnostic imaging is not cheap, however, and it's unlikely to get cheaper anytime soon. This cost is a personal concern for both authors of this article. The first author is a medical student in training, who is starting to care for cancer patients. The second author is a psychosocial researcher, who studies ways to improve the quality of life of cancer patients in general. He also happens to be a cancer patient himself, whose future depends on the quality of diagnostic imaging. Together we have teamed up to explore factors that are likely to influence both the quality and the cost of cancer care in the near future.

A major factor in the expense of cancer care is, of course, the cost of diagnostic scanners. One might suppose that the cost of scanners would come down as they have become more widely available, and that has happened to some extent for the most common scanners. But scanners remain expensive and will continue to be so, because they are getting better—which is to say, faster and capable of producing higher-resolution images.

The spiral of increasing quality and higher costs is driven by more than one force. The manufacturers of medical devices have sound business reasons to keep improving their products, and the healthcare industry also has sound clinical reasons to want better hardware. For example, it is now standard practice for a patient who is brought into the emergency room unconscious after a car accident to undergo scanning for signs of internal injury. In such a situation, seconds matter. The goal is to diagnose life-threatening conditions as fast as possible, because getting the right diagnosis quickly is critical to providing proper medical management.

Even in nonemergency situations there is a need for faster, higher-resolution scanners. Here the need arises because our viscera—our lungs, heart, intestines, and other organs—are constantly moving inside us, even while we lie still. Faster scanners can provide crisper images of those moving viscera.

Not only because of its sophistication, but for other logistical reasons as well, diagnostic imaging will continue to be expensive. Today's highest-resolution MRI machines require powerful magnets that depend on liquid helium to keep them supercooled (held at a temperature below 4 degrees Kelvin), and helium is itself an element in lim-

QUICK TAKE

Advances in cancer care are increasingly driven by technology, which provides the tools for more accurate diagnoses as well as more effective treatments—along with soaring costs.

Extremely high-speed computers to run the scanners, the cost of energy to keep the machines running, and the expensive materials all add to the price.

Radioactive drugs that can both locate and destroy cancer cells are a promising development in treatment, but they are unlikely to lower patients' expenses.

Before the establishment of the National Cancer Institute in 1937, biochemical and clinical studies of the disease were sponsored primarily by academia, as at this lab, headed by Shigemitsu Itami at the Graduate School of Medicine, University of Pennsylvania. Cancer research continues to save lives, but the financial burden on patients remains its own form of side effect.

G. Terry Sharrer, Ph.D. National Museum of American History/National Cancer Institute

ited supply. Efforts are underway to develop and market MRI machines that use little or no helium, but these devices produce images of a lower resolution. Thus, although the price of newer, low-resolution scanners may come down and thereby make MRI imaging available to more patients, costs for all the MRI scanners that are currently in use will continue to grow as helium becomes more expensive.

Another factor in the rising cost of digital imaging might best be listed under the heading of "unforeseen consequences." As the resolution of images improves, scanners increasingly find anomalies that the radiologists were not looking for. More often than not, these are benign cysts or other noncancerous, inconsequential lesions. In the 1980s, such findings were nicknamed *incidentaloma*, a term now widely used for any abnormality found on a medical scan that one didn't expect to find.

With more scans and better resolution, incidentalomas are among the fastest growing medical conditions. In a recent survey of more than 1,400 medical publications, the continuous rise in reports of incidentalomas over the past 30 years looks almost like an epidemic. These unexpected findings can take a heavy toll on individual patients as well as on the healthcare system as a whole: Investigating suspicious lesions is often costly, and some patients even undergo surgery to remove lesions that are ultimately found to be harmless. Most forms of treatment, especially surgery, carry some risk and a possible need for costly follow-up. In addition, the practice of investigating incidentalomas has contributed to the rise in diagnoses of actual cancers, leading to more treatment. Better scanners thus unavoidably increase the cost of cancer care.

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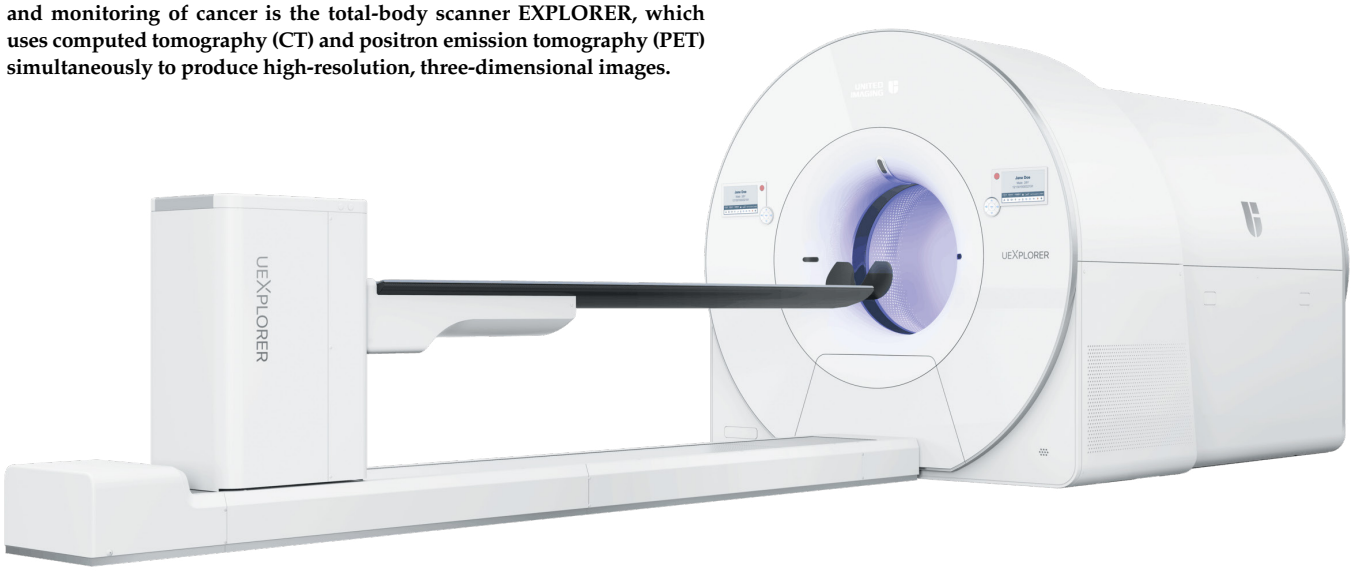
One particularly noteworthy development in the last two decades has been the advent of computers that work so fast that a lesion can be simultaneously tracked and treated with external beam radiation. Patients with lesions in the lungs, for example, can't simply hold their breath for the time it takes to locate and diagnose tumors and then, with a separate piece of equipment, to treat them. These patients in particular stand to benefit from hardware that combines diagnostic imaging and therapeutic radiation. The costs for such a procedure, however, can run into the tens of thousands of dollars, potentially putting it beyond the means of many individuals who may need it while keeping it accessible to relatively few.

Epitomizing this clash between increasing quality and diminishing affordability in the diagnosis of cancer is a scanner known as EXPLORER, a newly developed total-body PET/CT machine from the University of California, Davis. According to its project coleaders, biomedical engineers Simon Cherry and Ramsey Badawi, this device can capture images in 30 seconds that are of comparable quality to those requiring 10 minutes on the best machines available right now. EXPLORER must undergo rigorous human clinical trials to prove its safety and efficacy, but once approved for use it will represent a significant improvement over earlier technology. In addition to great speed, it promises the benefit of much lower exposure to radiation—about one-fortieth the amount emitted by today's state-of-the-art PET scanners. As might be expected, EXPLORER will be an expensive device, with an estimated purchase price in the range of $10 million. It is safe to assume the cost of capturing diagnostic images from individual patients will be accordingly high, perhaps sharply restricting the number of patients who will get access to the hardware.

Among the newest developments in medical imaging for the diagnosis and monitoring of cancer is the total-body scanner EXPLORER, which uses computed tomography (CT) and positron emission tomography (PET) simultaneously to produce high-resolution, three-dimensional images.



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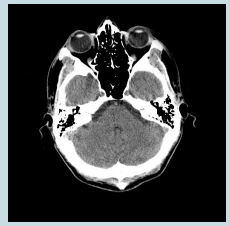
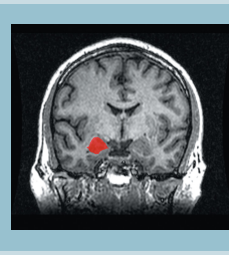
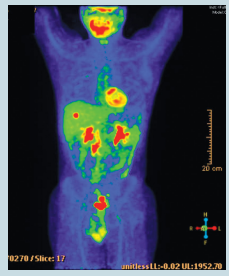
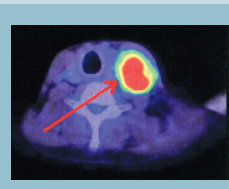
A Brief Look at Some Technologies Widely Used to Diagnose Cancer

technology		basic way it works	examples of use	relative costliness
CT scanning (computed tomography; also, CAT scanning)		series of x-rays taken from various angles, then assembled by computer to produce three-dimensional image of organ or tissues under study	diagnosis; planning or assessment of course of treatment	least costly
MRI scanning (magnetic resonance imaging; formerly, nuclear magnetic resonance imaging)		powerful magnets alter the alignment of molecules in various tissues, which give off radio waves; these waves are then converted into high-resolution images	shows distinction in metabolism between healthy and diseased tissue; well-suited to imaging brain and soft tissue	more costly
PET scanning (positron emission tomography)		radioactive glucose, injected into blood stream, highlights areas of higher metabolic activity—i.e., cancerous cells	detects cancer's higher metabolic activity; useful in monitoring effects of treatment	yet more costly
PET-CT scanning		radiopharmaceutical agent, injected into blood stream, allows simultaneous imaging by both PET and CT	highest-resolution images make it possible to detect otherwise invisible tumors	most expensive

Wikimedia Commons/CC BY SA; chart by Barbara Aulicino

Healthcare professionals today have a wide choice of instruments to deploy against cancer, whether in reaching a diagnosis, monitoring the effects of treatment, or keeping watch against a recurrence. Each specialized device has its own strengths and limitations, but all rely on extremely powerful computers, which accounts at least in part for their high cost.

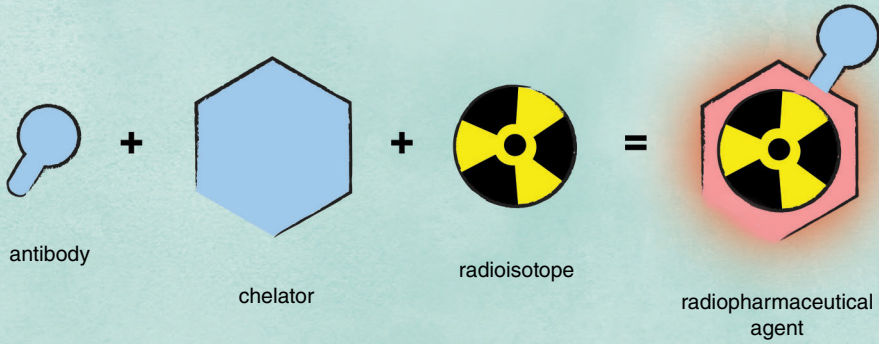
Advancing Technology, Rising Costs

A factor that can be overlooked in the financial picture of cancer care is the cost of the contrast agents that often are administered to patients before diagnostic scans. These are substances that can improve image resolution and clarity. Contrast agents accumulate in some tissues more readily than in others, making it possible to distinguish certain organs or tissues from their neighbors. Similarly, contrast agents can be used to differentiate healthy tissue from tissue that is cancerous or otherwise diseased.

Radionuclides—radioactive atoms that can be bound to pharmaceutical agents—are sometimes injected into patients to improve the diagnostic specificity of PET scans and other medical imaging technologies. During a PET scan, the radiation these compounds emit is detected, creating an image that, when merged with a CT scan, can yield a three-dimensional map of the distribution of certain types of cancer in the body. This technology is changing the approach to both diagnosing and treating prostate cancer, the most common form of cancer in men. According to the National Cancer Institute, an estimated 175,000 new cases are diagnosed each year in the United States (including the second author of this article). The disease is highly amenable to treatment, however, with about 98 percent of patients surviving at least five years beyond their diagnosis.

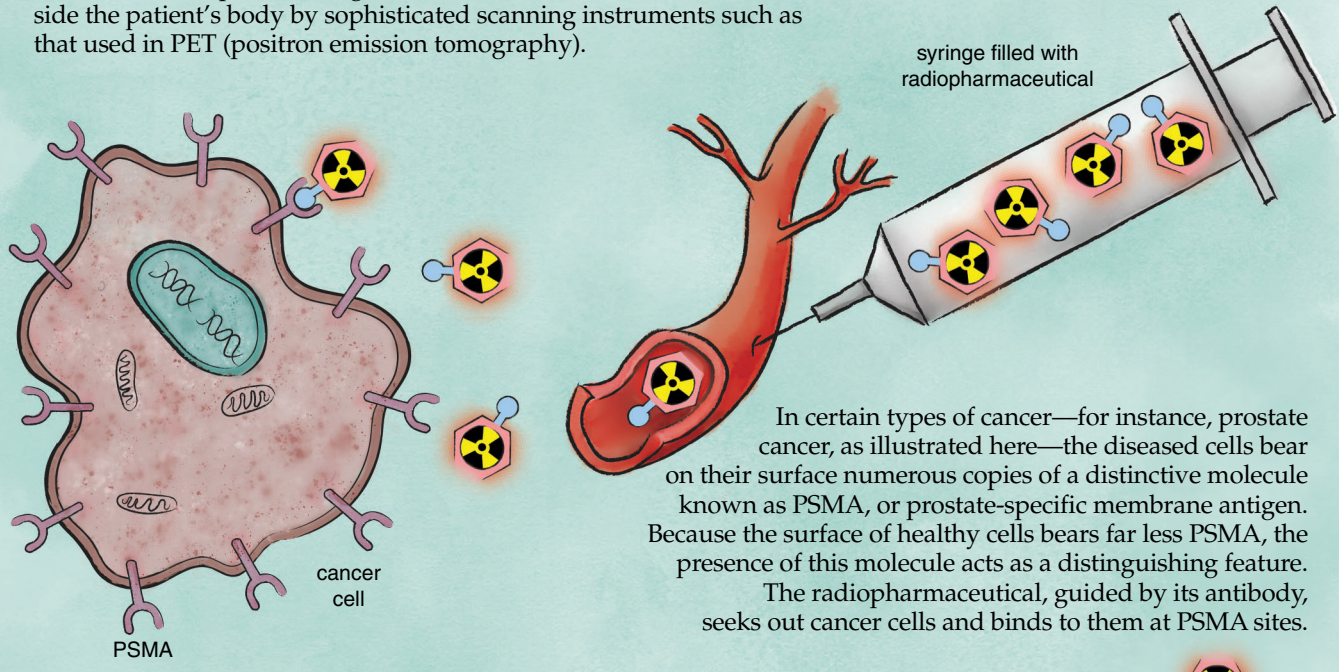
Prostate cancer that has spread through a patient's body is incurable, but in theory it can still be treated by surgery or radiation to slow the progression of the disease and reduce the patient's discomfort. Such tumor-targeted treatment requires that the tumors can be precisely located. Until recently, prostate tumors that had spread beyond the prostate gland were difficult to locate with much accuracy. It is now possible to attach certain radionuclides to an antibody that in turn binds to a molecule called prostate-specific membrane antigen (PSMA) on the surface of prostate cancer cells. The radiation that the radionuclide gives off can then be used with a PET

Molecular Radiotherapy and Medical Imaging



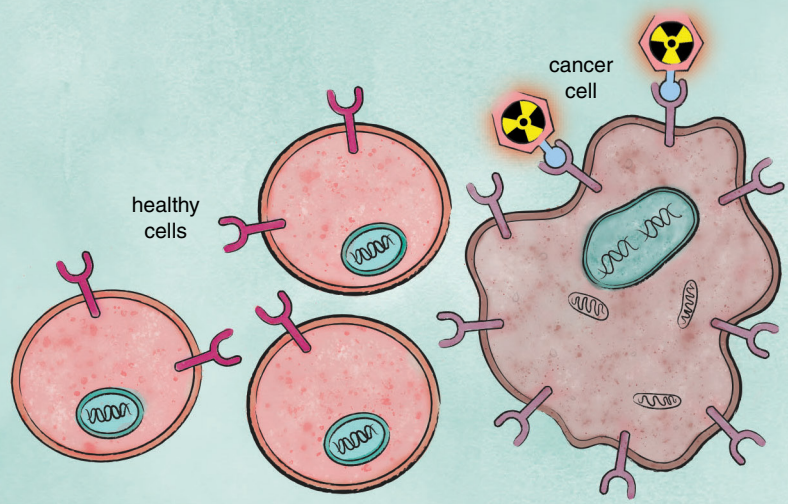
Molecular radiotherapy for cancer uses a drug made up of three elements: an antibody that serves as the targeting mechanism, a radioactive isotope—for example, gallium-68—and a *chelator* that holds the radioisotope. The drug, given by injection, travels through the blood stream to cancerous cells.

Isotopes such as gallium-68 are suitable for radiotherapy because they emit gamma waves, which can travel a considerable distance but carry little destructive power. The gamma radiation can be detected from outside the patient's body by sophisticated scanning instruments such as that used in PET (positron emission tomography).



In certain types of cancer—for instance, prostate cancer, as illustrated here—the diseased cells bear on their surface numerous copies of a distinctive molecule known as PSMA, or prostate-specific membrane antigen. Because the surface of healthy cells bears far less PSMA, the presence of this molecule acts as a distinguishing feature. The radiopharmaceutical, guided by its antibody, seeks out cancer cells and binds to them at PSMA sites.

The cells thus tagged make up what is essentially a map telling where cancer is located in the patient's body. This ability to search noninvasively for even the smallest clusters of cancerous cells makes molecular radiotherapy useful not only for diagnosis but also for monitoring the effects of treatment and for catching signs of recurrence as early as possible.



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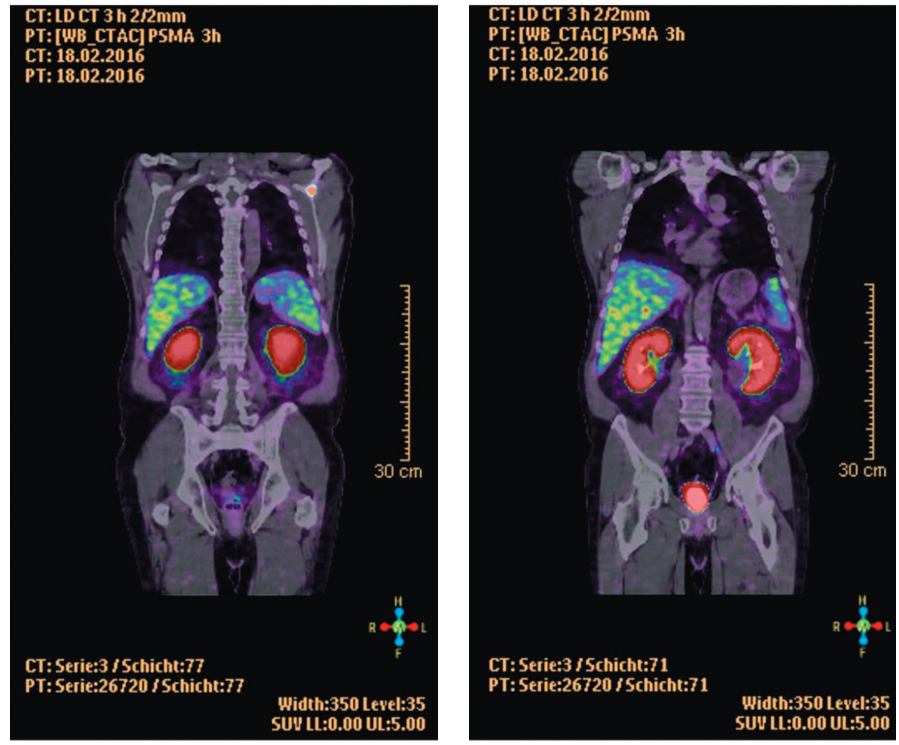
or PET-CT scanner to locate prostate cancer anywhere in the body. This technique makes it possible to detect tumors that were previously invisible to the best diagnostic hardware.

Diagnostics Plus Therapeutics

The most promising aspect of this technology is that for some cancers, such as those of the thyroid and the prostate, it is now possible with radiopharmaceuticals to both image tumors and target them for destruction. For therapeutic purposes, this method requires that the radionuclide give off alpha or beta particles, which don't travel as far as gamma radiation but have high enough energy to destroy cancer cells on-site. The treatment of prostate cancer makes use of the same PSMA-targeting strategy described earlier. Such therapies are "targeted" in the sense that they exploit the exquisite precision of the immune system, setting up biochemical reactions in which the radionuclide binds more strongly to diseased cells than to anything else. This elaborate form of pharmacotherapy is central to the blossoming field of molecular radiotherapy.

Unfortunately, the radionuclides with the greatest potential use in this form of cancer treatment often derive from rare elements with short half-lives. For example, one promising agent for treating prostate cancer is the alpha-emitting isotope actinium-225 (^{225}Ac), a molecule that can be used in a radiopharmaceutical agent that, in turn, binds specifically to PSMA. There is no natural supply of ^{225}Ac. This isotope can be produced in a laboratory, however, by the neutron irradiation of radium-226 in a cyclotron. At present, few cyclotron facilities are set up to deal with the production and extraction of ^{225}Ac or with the chemistry needed to bind ^{225}Ac to a PSMA-targeted peptide. Because of the short half-life of ^{225}Ac (10 days), the process must be carried out expeditiously to produce quantities of the radiopharmaceutical that will be clinically useful. Both the machinery and the manufacturing of such targeted agents are therefore quite costly.

The most common form of actinium, ^{227}Ac, exists in nature in association with uranium ore. It takes 1,000 kilograms of that ore to get just 0.2 milligrams of actinium, and the 225 isotope is even more rare, earning it the title of "rarest drug on Earth." It is also



In some cases, cancerous cells can infiltrate healthy tissue at some distance from the initial site of the disease. *Metastasis,* as this condition is known, can cause abnormal growth that bears little resemblance to the original cancer, but medical imaging that combines data from PET and CT scans can detect the malignant outposts. These images reveal metastases in a patient's scapula (*image at left, red spot on shoulder blade*) and lymph node of the iliac region (*image at right, red spot above groin*). (Image from Leitsmann, C., et al. 2019. *International Brazilian Journal of Urology* doi: 10.1590/s1677-5538.ibju.2018.0305.)

highly toxic. Safety concerns and the short half-lives of the isotopes drive up the costs, but a team of scientists at the TRIUMF cyclotron facility in Vancouver, British Columbia, are now working on ways to generate more ^{225}Ac.

In the past two years, the U.S. Food and Drug Administration has approved two diagnostic radiotracers to be used with PET scanners. One uses a radioisotope of fluorine, in the drug ^{18}F-fluciclovine (licensed as Axumin), to locate sites of prostate cancer. The other uses the gallium isotope ^{68}Ga, together with the amino acid peptide DOTA-TATE, to locate certain neuroendocrine tumors. These drugs each cost around $3,000 to $4,000 per dose, although the price is starting to come down. ^{68}Ga also has another clinical application: Bonded to a PSMA-targeted molecule, it can be used to image prostate cancer, possibly at higher resolution than ^{18}F-fluciclovine.

Versions of ^{68}Ga PSMA-targeting radiopharmaceuticals are already used clinically for imaging prostate cancer tumors in Australia, Israel, and a number of European countries, and are under development in many others. Meanwhile, as suggested earlier, the improvements in diagnostic imaging made possible by the use of ^{68}Ga PSMA-targeted agents have begun to lead to a rise in incidentalomas. Even though this contrast agent has not yet

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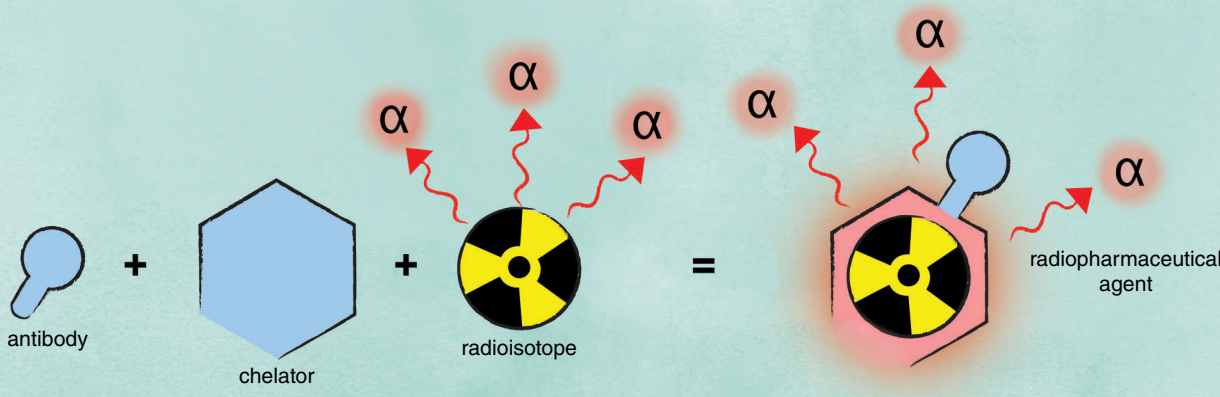
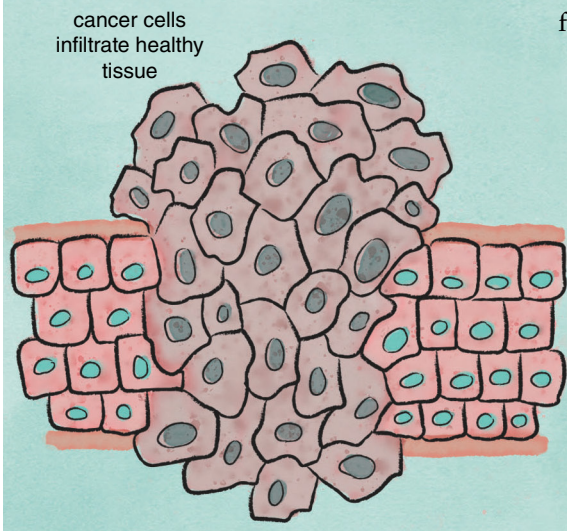
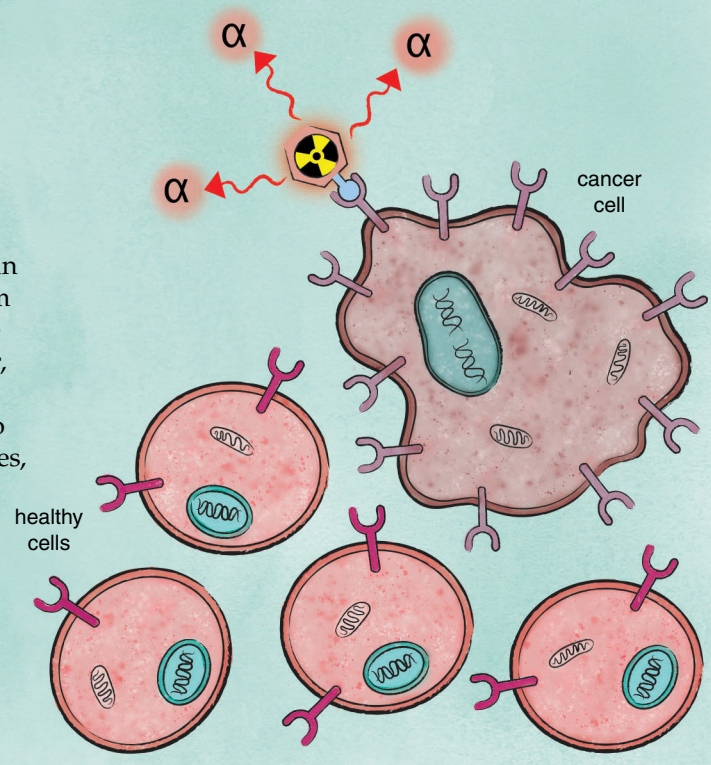
Dual-Use Radiopharmaceuticals: Imaging Plus Therapy



Depending on the type of radiation it emits, a radioisotope may be able to carry out more than one function in molecular radiotherapy. The isotope actinium-225, for example, emits alpha waves, which can travel only short distances but are toxic to living tissues—a combination of traits that makes it ideal for attacking precisely focused areas. (The decay chain of other radioisotopes may vary somewhat, giving off different numbers of alpha particles.)



When cancer cells infiltrate previously healthy tissue, the goal must be to destroy diseased cells while leaving healthy ones unharmed. By means of an antibody that binds to a specific molecule on the surface of cancer cells, a radiopharmaceutical containing actinium-225 can confine its destructive power to the cancer cells; alpha rays emitted by the radioisotope do not reach the nearby healthy cells.



Actinium is a rare element, found in nature in association with uranium and extracted from it only by painstaking effort. The radioactive isotope ^{225}Ac is still more rare and, moreover, has a short half-life. Radiopharmaceuticals based on ^{225}Ac thus are unlikely to come into clinical use any time soon; several alternatives, however, are available but costly.

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been officially licensed in the United States to diagnose prostate cancer, 34 reports of incidentalomas found with ^{68}Ga have already been published.

The apparent epidemic of incidentalomas, which has its source in the growing use of ever-more-sensitive imaging techniques, is a relatively new phenomenon. By contrast, *theranostics* ("therapeutics" plus "diagnostics"), the name now given to the medical field built on concurrently diagnosing and treating diseases, goes back decades. Radioisotopes of iodine were first used to both diagnose and treat thyroid diseases in the early 1940s. Today, with the development of extremely high resolution imaging machines, fast computers, and the ability to target certain radiopharmaceuticals to specific cancers, the field of theranostics is showing explosive growth. The number of research articles on the topic affirms this: The term "theranostics" has been referenced in more than 4,500 published papers since it first appeared in the medical literature in 2000.

Theranostics does not reduce the cost of the diagnostic hardware, nor that of the radiopharmaceuticals used to diagnose and treat the disease. But, where a theranostic approach is possible, it may reduce the patient's time in the clinic and thereby lessen the financial and psychological toll somewhat.

Killing Cancer at Close Range

One more advance in cancer care is highly promising, although it will certainly not be cheap. This is the category of targeted alpha therapies (TAT), a specialized form of molecular radiotherapy. Alpha-emitting isotopes are extremely destructive at short range. TATs currently in clinical trials for the treatment of prostate cancer, such as ^{225}Ac and bismuth-213 (^{213}Bi), thus have the potential to destroy tumors with little collateral damage to neighboring tissue. Their safety will depend on how specifically they can bind to cancer cells alone.

Yet again, though, the cost for TAT agents is likely to be prohibitive for the vast majority of patients who depend on publicly funded health systems, such as Medicare and Medicaid. Although it's not possible to patent radionuclides, which are natural elements, drug companies have already begun to patent the specialized peptide portions that link radionuclides to the molecule that in turn binds to PSMA. For this reason, alpha-emitting radionuclides with half-lives in the appropriate range for clinical use will likely remain expensive for the foreseeable future.

Alpha-emitting radionuclides with half-lives in the appropriate range for clinical use will likely remain expensive for the foreseeable future.

Radiopharmaceuticals using the isotope ^{225}Ac exemplify the current dilemma. These compounds may prove to be more effective in treating advanced prostate cancer than any therapy previously developed, but there is simply not enough of the isotope currently available to support broad clinical use. First produced synthetically in 2000, ^{225}Ac is now in production in at least four labs in North America: Oak Ridge, Los Alamos, and Brookhaven national laboratories in the United States, and the TRIUMF cyclotron facility in Canada. A number of labs elsewhere in the world have also successfully produced ^{225}Ac. Nevertheless, current production levels are not yet high enough to meet the demand for purposes of research, let alone the anticipated surge in demand once the radioisotope is approved for clinical use. According to a publication by NorthStar Medical Technologies, the current cost of ^{225}Ac is "much too high to be sustainable long term in the market." How high is too high? One estimate is that it may cost $30,000 for a single dose, and it is not yet known what the optimal dose or number of doses is for each patient.

Altogether, cancer care has the prospect of becoming much better soon, but also much more expensive. Increasingly, oncologists refer to the cost of cancer care as a toxic side effect. Theranostics may be the best thing on the horizon for cancer patients such as the second author. It remains an open question, though, as to whether he and other patients like him can overcome the financial toxicity.

Hannah McGillivray is a medical student in her third year at the University of St. Andrews in Scotland, with an interest in oncology and therapeutic radiology. She will continue her medical training at the University of Edinburgh. Richard Wassersug is honorary professor of cellular and physiological sciences at the University of British Columbia. His previous article, "Estrogen in Men," with co-author Erik Wibowo, was published in the November–December 2014 issue of American Scientist. *Email: richard.wassersug@ubc.ca*

Bibliography

Badawi, R. D., et al. 2019. First human imaging studies with the EXPLORER total-body PET scanner. *Journal of Nuclear Medicine* 60:299–303.

Beyder, D. 2017. Axumin and NETSPOT are approved—Now what? *Uptake* 3: January–February 2017.

Cherry, S. R., T. Jones, J. S. Karp, J. Qi, W. W. Moses, and R. D. Badawi. 2018. Total-body PET: Maximizing sensitivity to create new opportunities for clinical research and patient care. *Journal of Nuclear Medicine* 59:3–12.

Harvey, J. T. 2018. NorthStar perspectives for actinium-225 production at commercial scale. *Current Radiopharmaceuticals* 11:180–191.

Melville, G., and B. J. Allen. 2009. Cyclotron and linac production of Ac-225. *Applied Radiation and Isotopes* 67:549–55.

O'Sullivan, J. W., T. Muntinga, S. Grigg, and J. P. A. Ioannidis. 2018. Prevalence and outcomes of incidental imaging findings: Umbrella review. *British Medical Journal* 361:k2387.

Silberstein, E. B. 2012. Radioiodine: The classic theranostic agent. *Seminars in Nuclear Medicine* 42:164–170.

STORYHIVE. 2018. The rarest drug on Earth. Accessed January 17, 2020. https://www.youtube.com/watch?v=8DkhSFS0FY4.

Wibmer, A. G., H. Hricak, G. A. Ulaner, and W. Weber. 2018. Trends in oncologic hybrid imaging. *European Journal of Hybrid Imaging* doi: 10.1186/s41824-017-0019-6.

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