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IN THIS ISSUE

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From diagnostics to theranostics, and why better cancer care will always be costly

A report on this promising technology, and a warning that it will come with a significant price tag.

H.M.K. McGillivray, BSc, C.F. Uribe, PhD, A. Rahmim, PhD, M.M. Muermann, BSc, R.J. Wassersug, PhD

ABSTRACT: The history of radiological scanners and why we can expect diagnosing cancer to continue to get better, but not necessarily cheaper. This is due in part to a continued desire to capture images faster and with higher resolution. Better instruments, at the same time, reveal more incidentalomas, which drive up the cost of medical care.

Theranostics (i.e., *thera*peutics plus dia*gnostics*) using radiopharmaceuticals promises to improve cancer diagnoses and therapeutics. However, some of the most promising theranostic agents depend on rare isotopes that are difficult to acquire and expensive to convert to drugs that can localize and/or kill cancer cells. While better cancer care is likely in the near future, it will come with an unavoidably high price tag.

Ms McGillivray is a medical student at the Edinburgh Medical School, University of Edinburgh in Scotland. Dr Uribe is a medical imaging physicist at the BC Cancer Agency in Vancouver. Dr Rahmim is a senior scientist at the BC Cancer Agency and an associate professor of radiology and physics in the Department of Radiology at the University of British Columbia. Mr Muermann is a medical student at the University of British Columbia. Dr Wassersug is an honorary professor in the Department of Cellular and Physiological Sciences at the University of British Columbia.

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Introduction

The rising cost of cancer care is a major challenge to the medical system worldwide. Media coverage typically focuses on drug costs, hospital stays, and medical procedures, while less scrutiny is given to the cost of diagnostics. Here we focus on diagnostic technologies of computed tomography (CT), positron emission tomography (PET), and single photon emission computed tomography (SPECT), and how they are beginning to blend with therapeutics in a way that foreshadows much better but, unavoidably, more expensive cancer care.

One factor that has contributed to rising health care costs for decades is that diseases, most notably cancers, are being diagnosed more frequently than ever. Cancer risk increases with age, and higher rates of diagnosis can be attributed in part to us simply living longer.[1] However, the increased use of diagnostic technology is also a factor. We now have screening tests for three of the major cancers: prostate, breast, and colorectal.[2] Screening makes it possible to detect and treat cancers early, increasing the chances of a good prognosis.[2] However, screening invariably leads to more cancer diagnoses, as it uncovers tumors that would have never become clinically significant during the patient's lifetime. Health economists have struggled to develop heuristics that best assess the costs versus the benefits. When trying to save lives with finite funds, it is not clear how one should weigh the size of the population at risk and the clinical impact of new technologies, versus the related financial burden.[3-5] This is a moving target as each effort to contain diagnostic costs is met with evidence that diagnostic technology improves patient survival.

Admittedly, there has been progress in cancer care that cannot be accounted for by increased screening and early detection. This shows up in data (e.g., on the 5-year survival rate), which has climbed for nearly all cancers over the last decade. This is true even for cancers that have no dedicated screening tests and disheartening outcomes, such as pancreatic cancer, for which the 5-year survival rate has almost tripled since 1975.[6]

Screening accounts for at most 50% of increased survival of patients with cancer.[7] The decline in deaths from lung cancer can be directly credited to fewer people smoking[8] and advances in treatment.[7] Although we certainly have not won "the war on cancer" that President Nixon declared nearly half a century ago, we are inching in the trenches in the right direction.

But what of the financial burden? Expenditures for cancer diagnoses and treatment in Canada rose from $2.9 billion in 2005 to $7.5 billion in 2012.[9] Additional insights into how much cancer care costs beyond drug costs can be made from a retrospective look at changes in cancer diagnostics and treatment in previous decades as well as projecting cancer incidence.[10]

We argue that among the factors raising the cost of oncological care are diagnostics. Progress in this area depends on early and accurate detection. Our ability to effectively treat cancer often relies on how precisely we can localize tumors. It is only through imaging that surgical intervention and targeted radiotherapies are possible. Even with systemic treatments like

chemotherapy, monitoring tumors can be critical to assessing a patient's response to therapy.

However, precision diagnostics are not cheap, and their cost is likely to rise in the coming decade due to a growing elderly population and technological advancements. One such recent change involves merging therapeutics with diagnostics, potentially improving cancer care dramatically.

Some history

Seven decades after W.C. Röntgen discovered X-rays, Sir Godfrey Hounsfield built a system that could irradiate the body with them at different angles. Applying similar mathematics as originally developed by Johann Radon in 1917 and later by Allen Cormack in the 1960s, Hounsfield was able to generate 3D images of internal structures. This led to the first computed tomography (CT) machine, the EMI Scanner.[11]

Pixels on the original CT images measured 3 x 3 mm.[12] Newer scanners have reduced this to the submillimetre range.[13] Improved spatial resolution has provided radiologists with enhanced clarity that allows them to locate tumors that are barely different from normal tissue. Some of these tumors are even difficult to identify with the naked eye when surgically removed.[14]

Scanning speed has also dramatically improved. In the 1970s when the first CT scanner was used to image the head, a single scan could take up to 20 minutes.[12] A single comparable CT scan now takes less than one-third of 1 second, meaning images can be produced 3000 times faster.[12]

PET scanners have also become increasingly popular due to their higher sensitivity compared to other imaging modalities. PET involves injecting radioactive tracers that emit pairs of photons that interact with a ring of detectors to generate images. PET images combined with the anatomical information obtained with CT or MRI can localize tumors as well as reveal other possible lesions.

As impressive as scanners are today, there is good reason to want them to be better. Making scanners faster can improve spatial resolution and increase their sensitivity. Faster scanners reduce wait times and increase diagnostic efficiency. Improved resolution allows for detection of smaller lesions that may have previously gone unnoticed. Better sensitivity increases the chance of early detection leading to a better prognosis.

The costs

The BC Ministry of Health will spend approximately $21 billion in the 2019/20 fiscal year, not counting additional costs due to the COVID-19 pandemic.[15] According to the *American Journal of Medicine*, diagnostic imaging is a major contributor to rising health care expenditures across North America.[16]

Improved imaging modalities are uncovering additional incidentalomas, which lead to often-unnecessary investigations and invasive treatments.

In 2004 American citizens were already spending US$100 billion per year on diagnostic imaging,[17] either out of pocket or through insurance programs, and that amount has increased annually.[18]

Admittedly, defensive medical decision making by physicians has contributed to some overuse of diagnostic imaging. Recognizing this problem, the American College of Radiology (ACR) developed clinical guidelines for physicians to help them decide when scans are warranted. The Choosing Wisely campaign, founded by the ACR in 2012 and adopted by the Canadian Medical Association in 2014, offers clinical recommendations for scanner use.[19,20] The consortium's goal is to reduce unnecessary imaging and save costs across the board.[16] The concern is justified as the demand for diagnostic imaging is increasing. In BC alone, funding for MRI scans was recently increased by 20% in 2018–2019 in order to conduct 37 000 additional tests per year.[21] However, only a fraction of that growth can be accounted for by clinical scanner overuse.

The growth in clinical scanner overuse can also be partially attributed to the medical devices market, which exploded in the 1970s but has since shrunk to a limited monopoly. EMI was the first company in this space and started marketing its CT scanner in 1972. Within 2 years, 10 companies were selling CT hardware.

Modern scanners are produced by a few large companies. While many smaller companies have contributed to advances in CT, MRI, PET, and SPECT technology, these start-ups have been continually acquired and absorbed by the bigger players. There is now a limited monopoly of international companies controlling the scanner markets; five companies account for approximately three-quarters of the global market in medical imaging.[22] Some critics believe the lack of competition contributes to the high cost of modern scanners, but modern medical imaging machinery is complex and unavoidably expensive to manufacture and maintain.

Scanner technology has improved in recent years and there is a desire for this to continue, and the drive for quality (i.e., fast machines, higher resolution, higher sensitivities) largely exceeds the concern for cost.

An epidemic of incidentalomas

With improved resolution, scanners increasingly find incidentalomas—incidental findings of benign tumors, cancerous lesions, or other abnormalities.[23] With improved scanning, more scans, and better technology, incidentalomas are among the fastest-rising medical findings.

According to a recent systematic review, incidentalomas appear in over a third of cardiac MRI, chest CT, and CT colonoscopy scans.[23] While incidentalomas are almost always benign, certain cancers prove exceptions to this trend (e.g., less than 5% of lung and brain incidentalomas are malignant; 25% of ovarian incidentalomas are malignant). The highest incidence of malignant incidentalomas is for the breast, at 42%.[23] In a review of CT lung cancer screening, incidental lung nodules were found in 51% of study participants; however, 95% of those incidental findings were benign.[24]

There are benefits and disadvantages to the incidentaloma epidemic. When an

incidentaloma is identified, patients can expect additional investigations.[23,25] While the majority of incidentalomas are benign, many patients experience great distress at the prospect that it may be malignant between the time of discovery and definitive diagnosis. Patients have undergone unnecessary procedures, even surgery, to eliminate suspicious lesions that were found postoperatively to be benign and harmless.[25] Benign incidentalomas are responsible for much patient anxiety and exposure to unnecessary surgeries with significant downstream costs. If a benign incidentaloma had not been picked up on diagnostic scanning, it would have made no difference to a patient's life.[23,25]

Incidentalomas have also contributed to the rise in diagnoses of true cancers. Prior to the 1980s, pancreatic cancer was almost always diagnosed too late. Imaging technology was not advanced enough to identify it in time for successful treatment. Although pancreatic cancer is still highly lethal, incidental findings on modern scans are resulting in a growing portion of patients being diagnosed earlier, treated earlier, and living longer.[26]

Advances in technology

Newer radiopharmaceuticals have also helped make the images captured by diagnostic hardware more specific. Most PET imaging relies on the fact that glucose metabolism is accelerated in cancer cells relative to healthy cells, which also consume glucose. The most commonly used PET radiopharmaceutical is a molecule similar to glucose (labelled with ^{18}F radioisotope of fluorine) to create fluorodeoxyglucose (FDG). Because of their higher metabolic rate, most cancer cells take up this radiopharmaceutical faster than normal cells, meaning they appear brighter on PET images.

A major recent advance in prostate cancer imaging makes uses of prostate-specific membrane antigen (PSMA). There are now pharmaceuticals that, when injected into patients, specifically bind to PSMA.[27] Radioisotopes (e.g., ^{18}F, ^{68}Ga) attached to those molecules allow us to detect prostate cancer cells wherever they may be in the body. A PET scan using the radiopharmaceuticals that target PSMA in combination with a CT scan can locate prostate cancer tumors that would be invisible with other imaging modalities.

Targeting PSMA isn't useful only for locating prostate cancer—it can also be used to treat the disease. This can be done by linking a PSMA-binding pharmaceutical with a radioisotope such as Lutetium-177 (^{177}Lu) or Actinium-225 (^{225}Ac), which are beta and alpha radiation emitters, respectively. The goal is no longer to simply locate the cancer cells; it is to use the radiation to kill them. Alpha and beta particles can irreparably cleave cellular DNA and kill the cells in situ.

Upgrading radioisotope functionality from purely diagnostic to therapeutic by binding PSMA is an example of the blossoming field of theranostics. Theranostics begins with diagnostic imaging assessing disease location and tumor burden. Based on the tumor load, several therapy cycles with alpha or beta emitters can treat the disease first identified and monitor it via diagnostic images.

In some cases, the same isotope can be used to both image and treat. This is the case with ^{177}Lu bound to PSMA, which has a radio-decay pattern that can be imaged using SPECT while its beta emissions simultaneously kill the cancer cells. This makes it possible to assess and optimize how much radiation is being delivered to tumors while minimizing toxicity to normal tissues.

What's the catch?

Whether for diagnostics or therapeutics, no pharmaceutical company can patent a radionuclide or the PSMA molecule itself, as both exist in nature. That said, there is great competition to develop molecules that bind to PSMA and can be labeled (i.e., chelated) with a radioisotope of interest either for diagnostics or therapy. The best molecule will bind to cancer cells while sparing healthy tissue. As one indication of the amount of industrial interest here, in 2018 Novartis (Novartis International AG, Switzerland) purchased biopharmaceutical manufacturer Endocyte Inc. for US$2.1 billion in order to acquire the rights to market PSMA-617, a PSMA ligand that can be labeled with ^{177}Lu, a beta-emitting radioisotope.[28] This isotope has been of special interest because it also emits gamma particles when it decays. These photons allow for the generation of diagnostic images using SPECT, at the same time as beta particles are used to treat the cancer.

A large multicentre phase III clinical trial of a ^{177}Lu-radionuclide PSMA target therapy recently closed to accrual.[29] It is anticipated to lead to FDA approval of this radionuclide therapy within a year.

One of the most promising radioisotopes for treating prostate cancer, also mentioned above, is ^{225}Ac coupled to a PSMA-targeting molecule. The alpha particles emitted in the decay of ^{225}Ac are more lethal to cancer cells because they deposit all the energy locally (generating DNA breaks that are harder to repair), compared to beta particles, which travel further in tissue. This reduces injury to normal tissue surrounding prostate cancer cells. Because ^{225}Ac is difficult to produce and concentrate in the lab, it is rare and costly to use in clinical practice. To safely produce and purify such radionuclides as well as label molecules for targeted molecular radiotherapy requires infrastructure such as cyclotrons and multidisciplinary staff such as physicists, radio chemists, and biologists. Right now, ^{225}Ac is so challenging to produce that it has been labeled "the rarest drug on earth."[30] The TRIUMF facility based in Vancouver is working diligently to become one of the few suppliers of ^{225}Ac.[31] Ironically, while the only two places in the world where ^{225}Ac can be produced are both in British Columbia, it is clear that our health care system cannot afford to use it at present.

Although targeted radionuclide therapies are likely to significantly extend the lives of patients with advanced cancer, additional variables can further affect the cost. The radionuclides with the greatest therapeutic potential are generally too rare to be acquired through mining. Instead, they need to be manufactured in nuclear reactors or cyclotrons. However, the main purpose of a nuclear reactor is to generate electricity, not radioisotopes. Extracting radioisotopes for medical use is an expensive secondary use and may require reactor retrofitting. On the other hand, cyclotrons dedicated to the commercial production of radiopharmaceutical agents exist but are expensive, with prices in the range of US$2 to $3 million. This is the basic hardware cost and does not account for specialized staff needed to run such facilities.

Newer radiopharmaceuticals continue to drive costs up beyond the cost of the drugs themselves. The more sensitive they are as diagnostic agents the more cancer they are likely to detect. But if their specificity is not exceptionally high, the more incidentalomas will be found.

Additional costs

An additional factor adding to the climbing cost of cancer diagnostics is multimodal imaging, which involves merging images from different scanners.[32] Hybrid imaging is not cheap; a PET/CT scanner costs approximately $2.7 to $4 million, while a PET/MRI costs upwards of $7 million.

The newest state-of-the-art PET/CT scanner is a total-body machine developed by the multi-institutional EXPLORER consortium. Its system has a sensitivity 40 times greater than what is presently available and can collect images in seconds as opposed to the current standard of 10 to 20 minutes.[33] Furthermore, total-body PET/CT scans expose the patient to 1/40th of the radiation of current state-of-the-art PET scanners.[33,34] Estimated costs for these machines are in the range of approximately US$10 million. However, such models can enable significantly higher throughput in the clinical setting, which may offset some costs over time.

Currently there are five PET/CT scanners in BC: four are at BC Cancer's sites (Vancouver, Victoria, and Kelowna), and one is in a private practice. It was recently announced that a new regional cancer treatment centre in Surrey will have two PET/CT scanners, including a cyclotron as well as a radiopharmacy facility, and it is expected to become an important centre for future radiopharmaceutical therapies.[35]

Theranostics and the future

Theranostics is more than just a clever moniker.[36] Theranostics lends itself to precision medicine and is built on the principle that visualization is key to treatment and monitoring. New targeted therapies within a theranostic framework allow oncologists to treat what they see and see what they treat.

Enthusiasm for this approach is evident in the increase of medical literature using the term *theranostics*. According to PubMed, the term did not appear in medical literature before 2000 yet has since been referenced in 4500 articles.

Given the sophistication of the hardware and rarity of the compounds used in treatment, the economic barriers to accessing the cutting edge in theranostic care are likely to be too high for most provincial health budgets. Greater government investment is needed to make the latest forms of oncological care accessible to the Canadian public.

Summary

We have witnessed momentous advances in diagnostic imaging over the years, which are increasingly being integrated with cancer treatments. Merging diagnostics with therapeutics will likely improve future cancer care. However, the rare isotopes yielding great promise in theranostics will not be cheap. Nor will the molecules that bind them to specific cancer cells. Improved imaging modalities are uncovering additional incidentalomas, which lead to often-unnecessary investigations and invasive treatments. The continued push for enhanced diagnostic imaging is justifiable, but it also implies that the cost is not likely to decrease in the near future.

All factors indicate that cancer care will continue to improve but will be pricey. State-of-the-art cancer care is already financially beyond the reach of many. If we are to have widespread access to the best treatments in the future, both the public and those in health policy should count on spending much more on oncological diagnostics and treatment. ■

Competing interests

None declared.

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Continued on page 379

areas to access buprenorphine/naloxone and methadone may be a reasonable interim strategy to combat the opioid overdose crisis. ■

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Continued from page 376

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