Radiology

REVIEWS AND COMMENTARY • EDITORIAL

Molecular Imaging, Oncology, and the Arc toward Our Precision Future

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It is an honor to help celebrate the centennial anniversary of *Radiology*, the most important journal in our specialty, by sharing some reflections on the field of molecular imaging and the opportunities to help our oncology patients. Over my quarter century in the field of radiology, I have been fortunate to witness incredible progress in the use of molecular imaging. This progress includes our ability to noninvasively characterize disease, to determine the most effective therapies and treatment doses, and to assess therapeutic response early in the course of treatment. In other words, determining what is wrong, which drugs we should give, and if the drugs are actually helping. We are living in an amazing time for molecular imaging. In the past few decades, we have translated hundreds of imaging molecules and ideas tested in preclinical systems to people, and numerous approaches are already helping our patients daily. While extrapolating the current renaissance in molecular imaging to the next 20–30 years runs many risks, the greatest risk may be from predicting too timidly, as we tend to imagine a linear rather than an exponentially improving future. So, if someone is reading this in 2040 or 2050, please send me a message sharing your thoughts on where I may have missed the mark.

Precision Medicine

Precision medicine highlights that while we all share many traits and experiences, there are important differences that make us individuals. These differences may affect the likelihood of an illness and the types of treatments that may be most effective for each of us. A White House press release in 2015 (1) announcing a large U.S. federal government precision medicine initiative perhaps stated it most succinctly: "Most medical treatments have been designed for the 'average patient.' As a result of this 'one-size-fits-all-approach,' treatments can be very successful for some patients but not for others. This is changing with the emergence of precision medicine, an innovative approach to disease prevention and treatment that takes into account individual differences in people's genes, environments, and lifestyles." The press release further noted that, "Precision medicine gives clinicians tools to better understand the complex mechanisms underlying a patient's health, disease, or condition, and to better predict which treatments will be most effective…enabling physicians to select treatments that improve chances of survival and reduce exposure to adverse effects" (1).

Patient heterogeneity has always existed. Many gains over the past 50 years were achieved by medical insights that were tested and uniformly applied to large patient groups (using a paradigm that we are all the same). In the next few decades, many health outcome improvements will come from understanding our individuality (shifting the paradigm to add in how we are each different). This will continue to accelerate for two reasons: we have increasingly more data, and we have increasingly greater treatment choices. The number of large well-controlled clinical trials continues to rapidly increase. This is coupled with a much greater understanding of the abnormalities that can occur in the signaling pathways in tumor cells and how the composition of the tumor microenvironment can modulate tumor growth. In addition, newer data analysis tools allow us to isolate the impact of specific changes in small groups of patients when analyzing these large trials. In parallel, the number of therapeutics, including small molecules, biologics, cellular therapies, and tumor vaccines, have correspondingly grown along with our deeper mechanistic understanding of cancer (2). A discovered tumor abnormality often quickly becomes a druggable target.

Many current advances in precision medicine have relied on tumor genetic testing and measurements of proteins and other molecules in biopsied tissue. For example, the landmark National Cancer Institute–Molecular Analysis for Therapy Choice (NCI-MATCH) trial (ClinicalTrials.gov identifier: NCT02465060) screened thousands of patients with tumor genomic sequencing and enrolled patients in more than 30 different arms based on the molecular profiles of their tumors. This allowed evaluation of numerous drugs that targeted specific abnormal pathways, grouping treatment arms by molecular abnormality rather than tumor origin. Such trials highlight the continued arc of progress. Early relatively nonspecific cancer treatments targeted all rapidly dividing cells. Today, more precise and pathway-specific targeted therapies increasingly dominate treatment choices. Coupled with this growing ability to intervene at specific nodes is the need to characterize tumors over time. The result is the merging of precision medicine with molecular imaging to yield the concept of precision imaging.

A druggable target often can become an imageable target used for noninvasive assessment. In the coming decades, targeted and individually based cancer treatments will continue to increase. This trend will help drive the growth in molecular imaging to globally quantify

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See also the editorial by Flanders and Geis in this issue.

abnormalities and measure their response to treatment. Unlike blood tests, which do not generally provide information on where these abnormalities are occurring, molecular imaging provides an assessment of the level of a specific target abnormality across all metastatic sites. Moreover, heterogeneity is often seen across tumor foci within individual patients, which is compounded over time by the selection pressure of therapeutics. Cancer cells that accumulate mutations that render an administered drug less effective are more likely to survive. Molecular imaging allows an understanding of how expression varies both at different tumor sites and over time. This enables more effective treatments, combinations, and early changes to regimens when imaging suggests sites of therapy failure are likely to occur. In the coming years, we will see a growing intertwining of advanced genomic analysis of tissue samples before treatment starts, combined with molecular imaging and serum testing performed before and during cancer treatment.

Cancer Therapies and Imaging

To identify sites of abnormality, molecular imaging typically uses externally administered molecules that bind or accumulate at sites of target expression. This binding portion of the molecule is coupled or integrated with a detection portion of the molecule. While detection approaches have covered much of the electromagnetic spectrum, due to the extreme sensitivity of nuclear medicine approaches, PET and SPECT molecular imaging currently dominate human translation. For example, given the common downstream changes in tumor glucose metabolism with numerous treatments, fluorine 18 fluorodeoxyglucose is already used for routine oncologic care over 2 million times a year in the United States alone. This dominance, especially for PET, is likely to continue to expand in the coming decades. Molecular imaging approaches such as MRI, optical imaging, US, and other modalities will continue to grow but with typically narrower, more focused applications.

Once pathophysiologic abnormalities are understood, much of the molecular imaging magic is in the molecule. The U.S. Food and Drug Administration (FDA) considers molecular imaging agents to be drugs. But because many radiopharmaceuticals require such a small amount for administration to patients, this reduces the threshold for initial clinical testing, allowing easier translation of PET agents relative to other modalities. Thus, radiopharmaceutical approvals have been rapidly growing in the past few decades (3), and this trend is likely at an inflection point with even much higher rates of FDA approvals in the future. All sizes and types of molecular imaging agents are used to detect target abnormalities in cancers. Agents include small molecules, peptides, nanobodies, antibodies, other biologics, and nanoparticles. In the coming decades, the number of small-molecule, peptide, and nanobody molecular imaging agents will grow relative to their larger counterparts, such as antibody-based agents, given the favorable pharmacokinetics of the smaller constructs.

In all multicellular organisms, cells must communicate and work in concert with one another. That is such a difficult hurdle that it took at least 2 billion years to make the leap from single-cell organisms. Added to this communication complexity is the need to have cells divide at specific times and in specific sequences during development. Cancer reflects the unregulated or uncontrolled growth of cells. While any part of this complex machinery within cells and between cells can go wrong, it is useful to evaluate how cancers become dysregulated by grouping such processes into larger categories. Over the past 2 decades, a series of three highly insightful articles synthesizing abnormalities into "hallmarks of cancer" by Douglas Hanahan and Robert Weinberg have been published in approximately decade intervals (4–6). Each subsequent update distills vast advances in cancer biology understanding into a coherent framework of the mechanisms used to form malignant tumors. This framework also highlights therapeutic targets that can disrupt pathways or tumor microenvironment components and provides a guide to processes we would like to noninvasively assess over time, directly or indirectly, with molecular imaging. Table 1 lists some of these hallmarks of cancer, along with examples of target-specific therapeutics, and example FDA-approved or investigational molecular imaging agents that can help noninvasively assess these targets.

Cancer chemotherapy started in the early 20th century and progressed to combination chemotherapies that resulted in improved outcomes and cures in the 1960s and 1970s (7). The discovery of more specific cancer pathways in the 1980s and 1990s led to the development and testing of drugs targeting the elucidated pathways. The past several decades have seen transformative growth in modulating the immune system to kill tumors (8,9). The next several decades will continue this incredible advancement arc in cancer treatment and early detection. We will witness more personalized therapies based on pretreatment assessments that include molecular imaging, and we will increasingly adjust therapy and dosing iteratively during treatment based on molecular imaging readouts. Novel combinations of treatments will continue to grow as mechanisms of tumor resistance and escape guide synergistic choices. Molecular imaging will be increasingly vital to optimize each therapy component. We will also see a growth in cell-based therapies, biologics (monoclonal antibodies, including bispecific antibodies that bind two different targets simultaneously), personalized tumor vaccines, and newer immunomodulatory approaches. Theranostics will continue its current remarkable upward inflection, with rapid expansion in the next few years in the number and types of tumor and microenvironment targets exploited, the range of ligand constructs used, and the radiotherapeutic isotopes employed (including growth in alpha emitters) for tumor cell killing. Currently, broad subsets of molecular imaging targets are being explored for theranostic potential. A rapid wave of theranostics will likewise follow the growth in the number of molecular imaging agents against newer targets. Theranostics will increasingly be synergistically combined with chemotherapy and immunotherapy approaches to further increase efficacy. Separately, molecular imaging will also be used to identify and localize small and early cancers suggested by cancer screening blood tests. Table 2 highlights broad future trends in molecular imaging as they relate to cancer detection and treatment assessment.

Table 1: Example Hallmarks of Cancer, Therapeutics, and Current Molecular Imaging Approaches

Hallmark of Cancer	Example Therapeutics	Example Molecular Imaging Approaches
Sustaining proliferative signaling	Hormone receptor antagonists, receptor tyrosine kinase inhibitors	Estrogen receptor (^{18}F FES) imaging, androgen receptor (^{18}F FDHT) imaging, EGFR imaging, HER2 imaging
Deregulating cellular metabolism	Aerobic glycolysis inhibitors, nucleic acid synthesis and/or nucleotide incorporation inhibitors, protein synthesis inhibitors, lipid synthesis inhibitors	Glucose (^{18}F FDG) imaging (both as a direct target and common downstream effect of numerous therapies); lipid and/or precursor imaging; amino acid (^{18}F–fluciclovine, ^{11}C methionine) imaging; nucleic acid (^{18}F FLT) imaging
Avoiding immune destruction	PD-1 inhibitors, CTLA4 inhibitors, PD-L1 inhibitors	CD8 imaging, granzyme B imaging, PD-L1 imaging
Genomic instability and mutation	PARP inhibitors	PARP imaging
Evading growth suppressors	Octreotide LAR	Somatostatin receptor (^{68}Ga DOTATATE) imaging
Inducing or accessing vasculature	VEGF signaling inhibitors	VEGF receptor imaging, hypoxia imaging, integrin imaging
Nonmutational epigenetic reprogramming	HDAC inhibitors, HMT inhibitors	HDAC imaging
Resisting cell death	Numerous classes of therapeutics	Annexin imaging, caspase imaging

Note.—^{11}C = carbon 11, CTLA4 = cytotoxic T lymphocyte-associated protein 4, DOTATATE = DOTA-0-Tyr3-Octreotate, EGFR = epidermal growth factor receptor, ^{18}F = fluorine 18, FDG = fluorodeoxyglucose, FDHT = 16β-[18F]-fluoro-5α dihydrotestosterone, FES = fluorestradiol, FLT = fluoro-3′-deoxy-3′-L:-fluorothymidine, ^{68}Ga = gallium 68, HDAC = histone deacetylase, HER2 = human epidermal growth factor receptor 2, HMT = histone methyltransferase, LAR = long acting release, PARP = poly-ADP ribose polymerase, PD-1 = programmed death-1, PD-L1 = programmed death ligand 1, VEGF = vascular endothelial growth factor.

Table 2: Broad Future Trends in Molecular Imaging

Trend
The growth in oncologic molecular imaging will parallel the growth in precision oncology
There will be a vast increase in the number of specific cancer abnormalities that can be imaged, allowing markedly improved noninvasive tumor characterization
Multiplexing of target imaging, allowing simultaneous measurement of distinct abnormalities, will increasingly lead to cancer-specific imaging mini-arrays for treatment planning and selection of antineoplastic drug combinations
A marked reduction in injected radioactive dose and in PET scan times is on the horizon, allowing greater integration of PET imaging and its expanded use in treatment planning and response assessment; submillicurie doses and PET scan times of less than 2 minutes will be routine
Theranostic expansion will parallel the growth of molecular imaging
Theranostics will increasingly be combined with chemotherapy and immunotherapy
Much greater integration of molecular imaging with in vitro diagnostics and serum markers will improve diagnostic and treatment workflows
Greatly improved quantitation and increasingly automated analysis of target distribution will advance treatment and drug dosing decisions
The high sensitivity of molecular imaging, for example for prostate cancer detection, will enable more localized and focal treatment of oligometastatic disease
Molecular imaging will be increasingly combined with cancer screening tests to localize very early disease and assess for false-positive screens, enabling better outcomes from earlier intervention

Conclusion

The remarkable growth in knowledge of the drivers of cancer, development of cancer therapeutics, innovation in molecular imaging agents, and advancement of molecular imaging systems over the past several decades will continue to greatly accelerate over the next few decades. The improvement in all these areas will directly synergize with each other in a virtuous cycle. Our ability to noninvasively characterize disease using a broadening array of molecular imaging agents will allow us to increasingly optimize treatment for each individual oncology patient. A foundational strength of radiology over the last century is that we have readily embraced new approaches and technologies, improving diagnostic certainty and patient outcomes. Our embrace of precision medicine will enable us, in partnership with our oncology colleagues, to substantially reduce the scourge of cancer in the coming decades.

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of directors, RSNA; board of trustees, RSNA R&E Foundation; board of directors, SNMMI; board of directors, ISR executive committee; board of directors, AIBIR; shareholder and cofounder of Cytosite; stock options in Ziteo.

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