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Molecular Imaging in Medicine: Past, Present, and Future

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Abstract

Recent advances in molecular imaging have facilitated early disease detection, diagnosis, and therapeutic efficacy monitoring. Clinicians aspire to achieve prompt diagnosis, provide personalized treatments, and accurately monitor and quantify therapy effectiveness. This has fueled a growing interest in tracing biomarkers and biochemicals associated with disease progression. Identifying crucial biomarkers and refining accurate, minimally invasive monitoring methods are the pivotal focuses of ongoing molecular imaging research. Consequently, there is a notable surge of interest in developing molecular probes and multi-modal systems to enhance imaging capabilities. This review is intended to provide an overview of the promise and limitations of different modalities employed in molecular imaging for patient care, along with the ongoing research aimed at innovating novel imaging agents and devices. Molecular imaging holds the potential to revolutionize disease diagnosis and treatment.

INTRODUCTION

Molecular imaging represents a rapidly evolving field that is revolutionizing the methodologies employed in disease diagnosis and management. By visualizing molecular and cellular processes *in vivo*, molecular imaging enables earlier detection and characterization of diseases, as well as the monitoring of disease progression and treatment response. Various modalities are used in molecular imaging, each possessing distinct advantages and limitations. This review delves into the diverse modalities used in molecular imaging, including positron emission tomography (PET), single-photon emission computed tomography (SPECT), magnetic resonance imaging (MRI), computed tomography (CT), photo acoustic (PA), optical coherent tomography (OCT) imaging, as well as recent additions like magnetic particle imaging (MPI) and intraoperative fluorescence guided surgery (IFG). The discussion encompasses the underlying principles of each modality, the types of probes employed, and their clinical applications. Furthermore, this paper discusses emerging trends and future directions in molecular imaging, including the development of novel probes and imaging technologies.

Molecular probes are designed with specific properties, such as high affinity for a target molecule or the ability to penetrate cell membranes. For instance, molecular probes can be used to detect cancer cells by targeting specific overexpressed proteins or to identify inflammation or calcification associated with coronary artery disease. These probes can be utilized to target specific molecules or structures in molecular imaging [1].

The purpose of this paper is to provide a structured and comprehensive overview of exiting modalities used in molecular imaging, underscoring the significance of molecular imaging in advancing our understanding and treatment of diseases.

Positron Emission Tomography

Positron Emission Tomography (PET) is a non-invasive imaging technique relying on the detection of two high-energy photons released following the decay of positron-emitting radioisotopes. When a positron collides with an electron, it undergoes annihilation and releases two gamma photons in opposite directions. Specialized gamma cameras detect these emissions and reconstruct a 3D image of radioactivity distribution, where hotspots indicate a higher uptake of a radiotracer. PET resolution and sensitivity have improved dramatically since its inception in the 1970s. Today, many PET scanners are combined with CT or MR scanners, providing additional underlying anatomical information [2].

PET utilizes several radiotracers, including ^{11}C, ^{13}N, ^{15}O,

^{18}F, ^{68}Ga, ^{89}Zr, and ^{64}Cu [3,4]. Fluoride-18 (^{18}F) is a widely used radiotracer with a half-life of approximately 110 minutes. ^{18}F-FDG (fluorodeoxyglucose), a glucose analog, is commonly used to monitor metabolic activity in cancerous tumors or the brain. However, when visualizing vascular inflammation associated with atherosclerosis, ^{18}F-FDG may not be the most suitable contrast agent due to the myocardium's high metabolic activity leading to high glucose uptake. This complicates the ability to distinguish vascular inflammation from the surrounding tissue. To address this limitation, clinicians and researchers follow a protocol involving prolonged fasting for 12 hours, a diet high in fat and low in carbs, and an intravenous injection of heparin to reduce myocardial uptake of FDG and improve the signal-to-noise ratio (SNR) [5-7].

Martineau et al. are evaluating whether ^{18}F-FLT (Deoxy-3'-^{18}F-fluorothymidine) can detect areas undergoing myocardial scarring with high accuracy but without the limitations of ^{18}F-FDG [7]. Thackeray et al., investigated ^{11}C-methionine-based molecular probes post-myocardial infarction and confirmed the location of the hypo perfused myocardial areas by targeting pro-inflammatory macrophages [8]. Heo et al., targeted CCR2+ macrophages with ^{68}Ga-DOTA-ECL1i (gallium-68 dodecane tetraacetic acid extracellular loop 1 inverso) and highlighted its potential to identify inflammatory macrophage accumulation in human hearts [9].

^{18}F-NaF, a popular tracer traditionally used to monitor bone mineralization associated with bone cancer, has gained research interest in identifying vascular calcification related to atherosclerosis. Several studies have shown a positive correlation between ^{18}F-NaF uptake and cardiovascular risk, indicating its potential for clinical use [6,10-12]. However, due to the limited spatial resolution of PET and the complex relationship between calcification and the risk of plaque rupture, some argue that ^{18}F-NaF may not be the most effective tool for distinguishing between micro (<50 μm) and macro-calcification, which can help distinguish stable from vulnerable plaques [6,12-14]. Nonetheless, ^{18}F-NaF remains a promising imaging agent for detecting vascular calcification and could have significant implications for diagnosing and managing atherosclerosis.

PET imaging has several limitations: *(1)* low spatial resolution, *(2)* the radiotracers required for PET imaging have short shelf lives, increasing the cost, and *(3)* patient exposure to radiation. In recent years, PET scanners have been paired with CT or MR imaging devices to allow multimodal imaging of functional information along with the underlying anatomical information to help clinicians make more informed decisions regarding patient care and overcome PET's limitation of low spatial resolution. It should be noted that PET/CT systems do not image both modalities simultaneously, requiring software co-registration that may still result in misalignment between the PET and CT data [15].

Single Photon Emission Computed Tomography

Single Photon Emission Computed Tomography (SPECT) operates similarly to PET, but the radiotracers used in SPECT imaging emit a gamma ray directly when decaying, following intravenous injection [16]. The most commonly used radiotracer in today's SPECT imaging is Technetium-99m (^{99m}Tc), which has gained widespread popularity due to its reliable generation from ^{99}Mo, lower cost compared to PET tracers, and the development of cold kits for the preparation of radiotracers [17].

For decades, SPECT has been used to conduct stress perfusion imaging to assess the risk in patients with suspected coronary artery disease. During the 1980s, the tracer of choice for myocardial perfusion imaging was ^{201}Tl. Today, both Tl-201 and Tc-99m sestamibi SPECT perfusion studies demonstrate similar sensitivity for diagnosing CAD [18].

Beyond traditional myocardial perfusion imaging, a multitude of probes has been developed to identify various features associated with CAD. One such method involves the use of ^{99m}TcAnnexin, which can detect apoptosis in the coronary vessels [19]. ^{99m}Tc-IL2 has been shown to accumulate in vulnerable carotid plaques [20], while ^{99m}Tc-duramycin shows promise in localizing advanced atherosclerotic plaques . Additionally, ^{99m}Tc-MAG3-anti-CD11b has proven effective in detecting inflamed atherosclerotic plaques [21]. Stress adenosine ^{99m}Tc-MIBI G-myocardial perfusion imaging has been demonstrated to be a sensitive, specific, and accurate method for detecting coronary artery stenosis, with improved performance compared to exercise myocardial perfusion imaging in some patients [22].

Cadmium Zinc Telluride (CZT) detectors are a type of solid-state radiation detector poised to replace the traditionally used photomultiplier tubes in SPECT systems. CZT detectors offer several advantages over conventional SPECT detectors, including high sensitivity, improved spatial resolution, faster imaging, reduced radiation dose, and a compact design [23]. Similar to PET, SPECT has limitations in patients' exposure to ionizing radiation and in resolving spatial details, with its accuracy limited by the attenuation of low-energy photons. However, with advancements in nuclear imaging technologies and the ongoing development of new probes targeting almost every conceivable pathology involved in the progression of a disease, SPECT imaging will remain a clinically relevant tool [24].

Magnetic Resonance

Magnetic Resonance Imaging (MRI) utilizes strong magnetic fields, radio waves, and their gradients to non-invasively image tissue. However, the low sensitivity in the tissue of interest necessitates the use of contrast agents to increase the signal-to-noise ratio. Advances in the development of contrast agents for magnetic resonance imaging enable non-invasive detection and monitoring of specific biomarkers.

Moreover, real-time MRI, characterized by its groundbreaking millisecond-scale image acquisition time, amalgamates the fast low-angle shot (FLASH) gradient-echo MRI technique with radial encoding and iterative reconstruction. The extension of regularization and filtering into the temporal domain markedly

enhances radial under sampling, thereby ensuring a sustained high image quality [25]. Nevertheless, the method involves trade-offs in spatial resolution to facilitate expedited acquisition, poses potential challenges related to motion artifacts, soft tissue contrast, and relies on specific hardware and sequences. Noteworthy implementation costs may arise due to the utilization of advanced technology. A recent study shows that the use of significantly under sampled gradient-echo sequences with radial encoding schemes demonstrates the capability to deliver exceptionally high image quality with unparalleled temporal resolution [26]. Ongoing advancements are directed towards mitigating these challenges, thereby augmenting the applicability of real-time MRI in specialized clinical and research domains.

Gadolinium-based contrast agents (GBCAs) are popular choices for MRI and real-time MRI. They work by shortening the relaxation time of nearby water molecules and can be used to target inflammation in atherosclerotic plaques [27]. Engel et al., demonstrated good sensitivity and specificity in the non-invasive detection of thin-cap fibroatheroma, a plaque morphology vulnerable to rupture in coronary arteries leading to acute coronary syndromes, with the albumin-binding probe gadofosveset (a GBCA) in a small sample of 25 individuals [28]. However, its withdrawal from commercial production [29] will require the investigation for alternatives. Iron oxide nanoparticles (IONP) and ultrasmall superparamagnetic iron oxide (USPIO) contrast agents can alter the magnetic properties of nearby tissues, highlighting areas of inflammation or infection. IONPs are highly configurable, and by choosing the surface molecules, they can both target specific biomarkers and increase the imaging contrast [30-32]. For example, during the progression of atherosclerosis, macrophages accumulate in the arterial wall and can be targeted by IONPs doped with dextran [33].

Computed Tomography

Computed Tomography (CT) is a non-invasive imaging technique that utilizes X-rays to produce detailed, cross-sectional images of the body. Initially, CT was used to provide anatomical details of organs and tissues. However, researchers have explored the use of contrast agents to improve the signal-to-noise ratio in soft tissues and enable the targeting of specific tissues, expanding the utility of CT imaging. Currently, iodine-based contrast agents, such as Iopromide, Iohexol, or Iodixanol, are the gold standard for X-ray imaging [34]. These agents have higher X-ray absorption, making them useful for CT angiography to identify narrowing in the heart's blood vessels. However, high volumes of these contrast agents quickly injected intravenously can lead to adverse reactions in some patients [35].

On the other hand, dark-field and phase-contrast radiography, advanced techniques in CT imaging, enhance contrast and visualization beyond conventional methods. These methods provide crucial insights into tissue microstructure and density variations. Dark-field radiography, sensitive to small-angle X-ray scattering, detects subtle tissue changes like collagen fibers and microcalcifications [36]. It complements conventional CT by offering a more comprehensive view of tissue composition. In contrast, phase-contrast radiography emphasizes the phase shift of X-rays through tissues, revealing details often obscured in conventional CT. This heightened sensitivity enables clearer visualization of soft tissues, improving contrast for low-density structures such as muscles and ligaments [37,38].

The emergence of dual-energy and spectral photon counting CT scanners (SPCCT) has resulted in technological improvements in CT imaging. Dual-energy CT imaging uses two different X-ray energies, usually a high and low energy, to create two sets of images of the same body part. The images are then combined, allowing for better tissue characterization and improved differentiation between different types of tissue [39]. Spectral photon counting CT removes scintillation crystals in traditional CT detectors, converting X-rays directly into an electronic signal, bypassing the conversion of X-rays to visible light [40]. The new CT systems not only have increased sensitivity to traditional iodine-based agents but also can differentiate between iodine-based agents and other radiopaque agents. This technological improvement has created the opportunity for the development of new CT contrast agents to provide clinicians with greater diagnostic information, such as identifying calcification in blood vessel walls. Sartoretti et al. found that tungsten, bismuth, and hafnium contrast agents were able to identify stenoses in tissue phantoms with high confidence, where hafnium exhibited the highest confidence level at75%, compared to iodine and holmium at 50% [41]. However, the pace of approvals for CT contrast materials now lags far behind that of radiolabeled agents used for PET/SPECT imaging [42].

Contrast-Enhanced Ultrasound

Ultrasound is a commonly used medical imaging modality that utilizes high-frequency sound waves and their reflections off tissues to non-invasively image the body. Unlike other imaging modalities, such as X-ray or CT, ultrasound does not involve the use of ionizing radiation [43]. Ultrasound imaging can provide real-time visualization of organs and blood vessels.

However, conventional ultrasound imaging has limitations, particularly in the visualization of small blood vessels and tissue perfusion. Contrast-enhanced ultrasound (CEUS) addresses these limitations by using microbubble contrast agents that enhance the contrast between blood vessels and surrounding tissue, allowing for improved visualization of tissue perfusion and blood flow dynamics. While this phenomenon was discovered in the mid-1960s by creating microbubbles through passing almost any liquid through a small-bore needle [43], the regulatory approval and commercial sale of stable microbubbles enclosed in a shell of albumin or phospholipids took several decades [44].

Microbubbles are excellent contrast agents for ultrasound imaging due to their ability to reflect ultrasound waves and enhance the acoustic signal, providing better imaging contrast and resolution. Additionally, encapsulated microbubbles can be doped with ligands or antibodies [45] to target specific cells or tissues, making them valuable tools for targeted imaging. The ability to manipulate microbubble properties, such as size,

shell composition, and functionalization, has opened exciting opportunities for research and development in the field of contrast-enhanced ultrasound.

CEUS offers several advantages over other imaging modalities. Unlike CT or MRI, CEUS does not involve the use of ionizing radiation. Furthermore, CEUS is a relatively inexpensive and widely available imaging modality, with the potential for real-time imaging. However, regulatory approval and commercial sale of novel microbubble probes remain obstacles [44].

Photoacoustic

The phenomenon of photoacoustic has been known for a long time, with the first studies dating back to the 19th century [46]. In recent decades, research into using photoacoustic imaging for medical applications has gained momentum. Unlike ultrasound imaging, which uses high-frequency sound waves and their reflections from tissues to reconstruct and image, photoacoustic imaging generates acoustic waves with laser pulses. The energy from these laser pulses is absorbed by the tissue and converted to heat, leading to thermal expansion, and creating an acoustic response. These waves are recorded by an ultrasonic transducer and reconstructed into a 3D image of the tissue.

One of the unique features of photoacoustic imaging is that tissue composition can be identified by its unique absorption characteristics, based on the molecular makeup of the tissue. For example, different types of molecules absorb light at different wavelengths, and this can be used to differentiate tissues based on their molecular composition. By tuning the wavelength of light, one can infer the tissue makeup from the acoustical response received [47]. Additionally, contrast agents can be used to increase the sensitivity and specificity of photoacoustic imaging [48]. This technique has advantages over other modalities such as PET ^{18}F-FDG, which suffers from reduced signal-to-noise ratio due to myocardial glucose uptake.

Despite the potential benefits of photoacoustic imaging, its clinical implementation is still in the early stages. Several recent studies have investigated the use of photoacoustic imaging for various clinical applications; however, more research is needed to fully evaluate its clinical potential. Compared to other imaging modalities, photoacoustic imaging has advantages such as high spatial resolution and the ability to differentiate tissues based on their molecular composition, but with limited penetration depth.

In recent years, there has been growing interest in developing photoacoustic nanoprobes and acoustogenic probes for various applications. These probes can be designed to respond to specific stimuli such as enzyme activities, pH, ROS, RNS, reactive sulfur species, metals, temperature, voltage, and polarity, enhancing the sensitivity and specificity of photoacoustic imaging [49]. These developments hold promise for advancing the field of photoacoustic imaging and expanding its applications.

Optical Coherent Tomography

Optical Coherence Tomography (OCT), first proposed by Huang et al., in 1991 at the Massachusetts Institute of Technology (MIT) [50], has garnered widespread attention. OCT imaging systems utilize low-coherence interferometry with a broadband light source to achieve high-resolution real-time three-dimensional tomographic imaging. The first generation of OCT is known as Time-Domain Optical Coherence Tomography (TDOCT) [51]. Subsequently, the application of array detectors in OCT led to the development of the second generation, known as Spectral-Domain Optical Coherence Tomography (SDOCT) [52], significantly improving imaging speed. With the introduction of swept-source lasers, Swept-Source Optical Coherence Tomography (SSOCT) emerged [53]. SDOCT and SSOCT are collectively referred to as Frequency-Domain Optical Coherence Tomography (FDOCT) [54].

Despite its relatively limited penetration depth of 2-3 mm compared to other imaging techniques, OCT achieves micron-level high resolution without tissue contact, akin to optical microscopy. Therefore, it serves as the preferred tool for early in situ biopsy of tumors, particularly in fields such as retinal imaging, dermatology, dentistry, and neurology [55]. OCT has made significant strides in sensitivity.

However, traditional OCT struggles to distinguish signals from different molecules and backgrounds and is less effective in detecting incoherent processes like Raman scattering or fluorescence emission. To selectively image molecular information in vitro, ex vivo, and in vivo, Molecular contrast OCT technologies are combined with contrast agents to enhance diagnostic capabilities [56]. Molecular contrast agents can be endogenous or exogenous, relying on observing absorption effects associated with excitation or producing photons through coherent processes detected via interferometric measurements. Nanoparticles, especially, are well-suited for reflection or scattering-based imaging methods. With advancements in nanomaterial's, numerous engineered nanoparticles have been reported as non-specific or targeted contrast agents in OCT. In Molecular Imaging OCT, these nanoparticles can generate clear molecular contrast, extending OCT's capabilities in in vivo cancer molecular imaging and opening new avenues in fundamental cancer research and clinical oncology studies [57].

Magnetic Particle Imaging

As a relatively new quantitative functional imaging technology, Magnetic Particle Imaging (MPI) harnesses the magnetic properties of injected nanoparticle tracers within the bloodstream to generate real-time three-dimensional vascular images. The concept of MPI was first proposed by scientist B. Gleich from the Philips Laboratory in Hamburg, Germany, in 2001. In 2005, B. Gleich and another scientist, J. Weizenecker, successfully developed the first MPI device, and its feasibility was first published in the journal "Nature" the same year [58].

It uses two core technologies, a specialized imaging hardware and an imaging tracer to produce a 3D imaging [59,60]. The MPI imaging system employs a composite combination of a rotating variable gradient magnetic field and directly detects a tracer

known as Super-Paramagnetic Iron Oxide (SPIO) particles or ultra-small SPIO (USPIO) [61]. Iron oxide nanoparticles are favored for MPI due to their superparamagnetism, generating a strong and specific signal. They are biocompatible, tunable for specific imaging characteristics, and generally exhibit low toxicity. Due to their nanoparticle size, SPIO particles remain confined within blood vessels unless they are compromised [62]. These properties, along with a prolonged blood circulation time, make them an ideal choice for MPI applications. This technology only detects the USPIOs rather than tissue. However, these tracers can be exclusively modified for targeting specific treatments. The properties of the tracer significantly determine the image quality of MPI. Since tracers are typically absent in the body under normal conditions, MPI images exhibit exceptional contrast and high sensitivity [63].

MPI boasts high spatial and temporal resolution, linear quantification, absence of ionizing radiation, no need for toxic tracers, no imaging depth limitations, and no interference from biological background signals. It can perform continuous tracking imaging for several months [64]. Therefore, it meets clinical demands for a safe, rapid three-dimensional vascular imaging technique, aiding researchers in gaining in-depth insights into the pathology at the organ, cellular, and molecular levels. Currently, MPI has made significant progress in various fields such as multimodal *in vivo* imaging, cell tracking, inflammation tracking, drug delivery and detection, blood pool imaging, tumor detection, and precise magnetic hyperthermia therapy [65].

Invasive Imaging

While many molecular imaging modalities are non-invasive, there are probes under development that compete against traditional invasive diagnosis methods. For instance, in angiography, a catheter is guided near the heart to inject a dye (varies based on the imaging modality used, whether MR or CT) to enhance the imaging contrast of the blood. This enables doctors to evaluate the blood perfusion through the heart and diagnose arterial narrowing.

Hybrid Imaging

Hybrid molecular imaging technologies represent a burgeoning area of research because they enable the integration of two or more imaging modalities, such as PET/CT, PET/MRI, or SPECT/CT, in a single examination. This approach offers numerous advantages over traditional imaging techniques, including improved sensitivity, specificity, and spatial resolution, as well as the ability to correlate functional and anatomical information [66]. By leveraging the strengths of different imaging modalities, hybrid molecular imaging technologies can provide more comprehensive and accurate insights into the location and nature of diseases, facilitating earlier and more precise diagnoses, better treatment planning, and improved patient outcomes.

For example, when identifying vulnerable, high-risk plaques, CT calcification imaging can only accurately identify macro-calcification. Utilizing a hybrid method to identify both calcification and inflammation can facilitate diagnoses [67].

However, these hybrid techniques are not without limitations. Misregistration of the imaging modalities may occur due to cardiac or respiratory motion, which can be minimized with cardiac and respiratory acquisition gating. Even movement of the legs and feet can impact fusion accuracy, highlighting the need for careful review of the fused images [68].

Challenges and Future Directions

Over the past two decades, molecular imaging has experienced unprecedented expansion, marking a transformative era in biomedical research and clinical applications. This period has been characterized by remarkable progress, with Molecular Imaging emerging as a cornerstone in advancing our understanding of complex biological processes, as shown in [Table 1]. The field has not only witnessed a surge in technological advancements but has also made seminal contributions to both basic science and clinical practice, reshaping the landscape of medical imaging.

However, amidst the commendable achievements, molecular imaging grapples with persistent challenges that necessitate strategic exploration. Heightened spatial resolution stands as a critical frontier, requiring innovations to discern minute details within cellular and molecular structures accurately. Augmented sensitivity remains a paramount objective, enabling the detection of subtle biological changes crucial for early disease diagnosis. Furthermore, the development of novel imaging agents tailored to diverse biological targets is imperative, as it holds the key to enhancing specificity and versatility in investigative approaches.

The future trajectory of molecular imaging holds exciting promises and potentials. The integration of artificial intelligence (AI) into image analysis is poised to revolutionize the field, ushering in an era of advanced data interpretation and pattern recognition. Concurrently, the optimization of multimodal imaging methodologies, leveraging the synergies between different imaging modalities, promises comprehensive insights into biological processes. Additionally, the exploration of nascent technologies, notably theragnostic, represents an uncharted frontier with immense potential. Theragnostic approaches, intertwining diagnostic and therapeutic capabilities, herald a new era of personalized medicine and targeted interventions.

CONCLUSION

The numerous techniques being investigated hold promise, but the cost of conducting large-scale, multicenter clinical trials to establish the efficacy of a single tracer poses a significant hurdle in finding the golden goose for any ailment. The clinical transition of novel imaging probes is also hindered by the requirement for FDA approval, the need for reliable manufacturing processes, and challenges related to clinical adoption.

Nevertheless, the potential benefits of molecular imaging are profound. Ongoing research and development in this field are likely to lead to novel and improved techniques, thereby augmenting clinicians' ability in diagnosing and treating diseases. The endeavors to advance molecular imaging technologies

Table 1: Comparison of Molecular Imaging Modalities

Imaging Modality	Modality Type	Spatial Resolution	Depth	Acquisition Time	Agents	Sensitivity	Ionizing Radiation	Typical Applications
PET	Nuclear Medicine	1–7 mm	++	min–hour	Shorter lived positron emitting radionucleotides: ^{11}C, ^{13}N, ^{15}O, ^{18}F, ^{68}Ga, ^{89}Zr, and ^{64}Cu	High (Tracer Dependent)	Yes	Oncology, Neurology, Cardiology
SPECT	Nuclear Medicine	1–15 mm	++	min–hour	Longer lived gamma emitting radionucleotides: ^{99m}Tc,	Moderate	Yes	Bone Scans, Cardiac Imaging, Neurology
MRI	Magnetic Resonance	1-2 mm	+++	min–hour	Superparamagnetic nanoparticles, Gadolinium-chelates	Moderate to High	No	Neuroimaging, Musculoskeletal, Cardiac Imaging
Real-time MRI	Magnetic Resonance	1-3 mm	+++	ms-sec	Gadolinium-based	Moderate	No	Dynamic imaging (e.g., cardiac)
CT	X-ray	0.5–1 mm	++	sec–min	Iodinated molecules, heavy metals (hafnium, tungsten)	Moderate to High	Yes	Trauma, Cancer Imaging, Angiography
CEUS	Ultrasound	0.5-2 mm	+	min	Targeted Microbubbles	Moderate	No	Liver, Kidney, Cardiac Imaging
PA	Hybrid (Laser & Ultrasound)	100-300 µm	++	sec–min	Targeted Microbubbles, ICG doped, NETs, Gold NP	Moderate to High	No	Cancer Imaging, Functional Imaging
Optical Imaging	Optical	1100 µm	+	sec–min	NIR dyes	Moderate	No	Cancer Research
OCT	Optical	1-15 µm	+++	sec–min	N/A	Moderate to High	No	Ophthalmology, Cardiology, Dermatology
MPI	Magnetic Resonance	1-3 mm	++	sec–min	superparamagnetic iron oxide nanoparticles	High (Magnetic Tracers)	No	Cardiovascular Imaging, Tracer Development

and establish their roles in clinical practice are warranted and portend great promise for the future of medicine.

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Key Points

QUESTION: How has molecular imaging evolved over the last several decades?

PERTINENT FINDINGS: Numerous researchers are pioneering investigations into novel contrast agents that improve imaging clarity, refining conventional imaging technologies, and developing hybrid multi-modal imaging devices to demonstrate the potential benefits of new tracers, contrast agents, and imaging hardware. The sustained interest in identifying the optimal imaging modality and contrast agent for any specific aliment will continue to enhance our understanding of the relationship between tissue morphology and disease.

IMPLICATIONS FOR PATIENT CARE: The next generation of imaging tracers faces significant hurdles before achieving widespread clinical adoption. As established tracers and technologies transition into clinical settings, patients can expect more accurate diagnoses through non- to minimally invasive imaging procedures.

REFERENCES

1. Zeng Y, Zhu J,Wang J, Parasuraman P, Busi S, Nauli SM, et al. Functional probes for cardiovascular molecular imaging. Quant Imaging Med Surg. 2018; 8: 838-852.
2. Jones T, Townsend D. History and future technical innovation in positron emission tomography. J Med Imaging (Bellingham). 2017; 4: 011013.
3. Pichler V, Infante NB, Philippe C, Vraka C, Klebermass EM, Balber T, et al. An Overview of PET Radiochemistry, Part 1: The Covalent Labels (18)F, (11)C, and (13)N. J Nucl Med. 2018; 59: 1350-1354.
4. Brandt M, Cardinale J, Aulsebrook ML, Gasser G, Mindt TL. An Overview of PET Radiochemistry, Part 2: Radiometals. J Nucl Med. 2018; 59: 1500-1506.
5. Pelletier-Galarneau M, Ruddy TD. Molecular imaging of coronary inflammation. Trends Cardiovasc Med. 2019; 29: 191-197.
6. McKenney-Drake ML, Moghbel MC, Paydary K, Alloosh M, Houshmand S, Moe S, et al. (18)F-NaF and (18)F-FDG as molecular probes in the evaluation of atherosclerosis. Eur J Nucl Med Mol Imaging. 2018; 45: 2190-2200.
7. Martineau P, Galarneau MP, Juneau D, Leung E, Nery PB, Kemp RD, et al. Imaging Cardiac Sarcoidosis With FLT-PET Compared With FDG/Perfusion-PET: A Prospective Pilot Study. JACC Cardiovasc Imaging. 2019; 12: 2280-2281.
8. Thackeray JT, Bankstahl JP, Wang Y, Wollert KC, Bengel FM. Targeting Amino Acid Metabolism for Molecular Imaging of Inflammation Early After Myocardial Infarction. Theranostics. 2016; 6: 1768-1779.
9. Heo GS, Kopecky B, Sultan D, Ou M, Feng G, Bajpai G, et al. Molecular Imaging Visualizes Recruitment of Inflammatory Monocytes and Macrophages to the Injured Heart. Circ Res. 2019; 6: 881-890.
10. Kitagawa T,Yamamoto H,Toshimitsu S, Sasaki Ko, Senoo A, Kubo Y, et al. (18)F-sodium fluoride positron emission tomography for molecular imaging of coronary atherosclerosis based on computed tomography analysis. Atherosclerosis. 2017; 263: 385-392.
11. Krishnan S, Otaki Y, Doris M, Slipczuk L, Arnson Y, Rubeaux, et al. Molecular Imaging of Vulnerable Coronary Plaque: A Pathophysiologic Perspective. J Nucl Med. 2017; 58: 359-364.
12. Bailey G, Meadows J, Morrison AR. Imaging Atherosclerotic Plaque Calcification: Translating Biology. Curr Atheroscler Rep. 2018; 18: 51.
13. Salarian M, Sadeghi MM. Hype or Hope((18)F-NaF Positron Emission Tomography for Vulnerable Coronary Plaque Imaging. Circ Cardiovasc Imaging. 2019; 12: e009591.
14. Guaraldi G, Milic J, Prandini N, Ligabue G, Esposito F, Ciusa G, et al.

(18)Fluoride-based molecular imaging of coronary atherosclerosis in HIV infected patients. Atherosclerosis. 2020; 297: 127-135.

15. Slomka PJ, Pan T, Germano G. Recent Advances and Future Progress in PET Instrumentation. Semin Nucl Med. 2016; 46: 5-19.

16. Hutton BF. The origins of SPECT and SPECT/CT. Eur J Nucl Med Mol Imaging. 2014; 41: S3-16.

17. Papagiannopoulou D. Technetium-99m radiochemistry for pharmaceutical applications. J Labelled Comp Radiopharm. 2017; 60: 502-520.

18. Patel KK, Badarin FA, Chan PS, Spertus JA, Courter S,Kennedy KF, et al. Randomized Comparison of Clinical Effectiveness of Pharmacologic SPECT and PET MPI in Symptomatic CAD Patients. JACC Cardiovasc Imaging. 2019; 12: 1821-1831.

19. Johnson LL, Schofield L, Donahay T, Narula N, Narula J. 99mTc-annexin V imaging for in vivo detection of atherosclerotic lesions in porcine coronary arteries. J Nucl Med. 2005; 46: 1186-1193.

20. Annovazzi A, Bonanno E, Arca M, Alessandria CD, Marcoccia A, Spagnol LG, et al. 99mTc-interleukin-2 scintigraphy for the in vivo imaging of vulnerable atherosclerotic plaques. Eur J Nucl Med Mol Imaging. 2006; 33: 117-126.

21. Liu G, Hu Y, Xiao J, Li X, Li Y, Tan H, et al. 99mTc-labelled anti-CD11b SPECT/CT imaging allows detection of plaque destabilization tightly linked to inflammation. Sci Rep. 2016; 6: 20900.

22. Alenezi MM, Majrashi NA, Sharif H, Alyami AS, Ageeli WA, Salawi MH, et al. A systemic review of rubidium-82 PET contrasted with 99mTc-MIBI SPECT for imaging coronary artery disease. Medicine (Baltimore). 2023; 102: e33068.

23. Hutton BF, Occhipinti M, Kuehne A, Mathe D, Kovacs N, Waiczies H, et al. Development of clinical simultaneous SPECT/MRI. Br J Radiol. 2018; 91: 20160690.

24. Lee SJ, Paeng JC. Nuclear Molecular Imaging for Vulnerable Atherosclerotic Plaques. Korean J Radiol. 2015; 16: 955-966.

25. Uecker M, Zhang S, Voit D, Karaus A, Merboldt KD, Frahm J. Real-time MRI at a resolution of 20 ms. NMR Biomed. 2010; 23: 986-994.

26. Frahm J, Voit D, Uecker M. Real-Time Magnetic Resonance Imaging: Radial Gradient-Echo Sequences With Nonlinear Inverse Reconstruction. Invest Radiol. 2019; 54: 757-766.

27. Karagkiozaki V, Logothetidis S, Pappa AM. Nanomedicine for Atherosclerosis: Molecular Imaging and Treatment. J Biomed Nanotechnol. 2015; 11: 191-210.

28. Engel LC, Landmesser U, Gigengack K, Wurster T, Manes C, Girke G, et al. Novel Approach for In Vivo Detection of Vulnerable Coronary Plaques Using Molecular 3-T CMR Imaging With an Albumin-Binding Probe. JACC Cardiovasc Imaging. 2019; 12: 297-306.

29. Shahrouki P, Khan SN, Yoshida T, Iskander PJ, Ghahremani S, Finn JP. High-resolution three-dimensional contrast-enhanced magnetic resonance venography in children: comparison of gadofosveset trisodium with ferumoxytol. Pediatr Radiol. 2022; 52: 501-512.

30. Vazquez-Prada KX, Lam J, Kamato D, Xu ZP, Little PJ, Ta HT. Targeted Molecular Imaging of Cardiovascular Diseases by Iron Oxide Nanoparticles. Arterioscler Thromb Vasc Biol. 2020; 41: 601-613.

31. Botnar RM, Ebersberger H, Noerenberg D, Jansen CH, Wiethoff AJ, Schuster A, et al. Molecular imaging in cardiovascular diseases. Rofo. 2015; 36; 92-101.

32. Anwaier G, Chen C, Cao Y, Qi R. A review of molecular imaging of atherosclerosis and the potential application of dendrimer in imaging of plaque. Int J Nanomedicine. 2017; 12: 7681-7693.

33. Mahler SA, Register TC, Riley RF, D'Agostino RB, Jr, Stopyra JP, Miller CD. Monocyte Chemoattractant Protein-1 as a Predictor of Coronary Atherosclerosis in Patients Receiving Coronary Angiography. Crit Pathw Cardiol. 2018; 17: 105-110.

34. Schockel L, Jost G, Seidensticker P, Lengsfeld P, Palkowitsch P, Pietsch H. Developments in X-Ray Contrast Media and the Potential Impact on Computed Tomography. Invest Radiol. 2020; 55: 592-597.

35. Christiansen C. X-ray contrast media--an overview. Toxicology. 2005; 209: 185-187.

36. Viermetz M, Gustschin N, Schmid C, Haeusele J, Teuffenbach MV, Meyer P, et al. Dark-field computed tomography reaches the human scale. Proc Natl Acad Sci U S A. 2022; 119: e2118799119.

37. Croton LCP, Morgan KS, Paganin DV, Kerr LT, Wallace MJ, Crossley KJ, et al. In situ phase contrast X-ray brain CT. Sci Rep. 2018; 8: 11412.

38. Zhang J, Tian D, Lin R, Zhou G, Peng G, Su M. Phase-contrast X-ray CT imaging of esophagus and esophageal carcinoma. Sci Rep. 2014; 4: 5332.

39. Karcaaltincaba M, Aktas A. Dual-energy CT revisited with multidetector CT: review of principles and clinical applications. Diagn Interv Radiol. 2011; 17: 181-194.

40. Tortora M, Gemini L, D'Iglio I, Ugga L, Spadarella G, Cuocolo R. Spectral Photon-Counting Computed Tomography: A Review on Technical Principles and Clinical Applications. J Imaging. 2022; 8: 112.

41. Sartoretti T, Eberhard M, Nowak T, Gutjahr R, Jost G, Pietsch H, et al. Photon-Counting Multienergy Computed Tomography With Spectrally Optimized Contrast Media for Plaque Removal and Stenosis Assessment. Invest Radiol. 2021; 56: 563-570.

42. Yeh BM, FitzGerald PF, Edic PM, Lambert JW, Colborn RE, Marino ME, et al. Opportunities for new CT contrast agents to maximize the diagnostic potential of emerging spectral CT technologies. Adv Drug Deliv Rev. 2017; 113: 201-222.

43. Frinking P, Segers T, Luan Y, Tranquart F. Three Decades of Ultrasound Contrast Agents: A Review of the Past, Present and Future Improvements. Ultrasound Med Biol. 2020; 46: 892-908.

44. Abou-Elkacem L, Bachawal SV, Willmann JK. Ultrasound molecular imaging: Moving toward clinical translation. Eur J Radiol. 2015; 84: 685-693.

45. Alonso A, Artemis D, Hennerici MG. Molecular imaging of carotid plaque vulnerability. Cerebrovasc Dis. 2014; 39: 5-12.

46. Han SH. Review of Photoacoustic Imaging for Imaging-Guided Spinal Surgery. Neurospine. 2018; 15: 306-322.

47. Wang LV, Yao J. A practical guide to photoacoustic tomography in the life sciences. Nat Methods. 2016; 13: 627-638.

48. Mantri Y, Jokerst JV. Engineering Plasmonic Nanoparticles for Enhanced Photoacoustic Imaging. ACS Nano. 2020; 14: 9408-9422.

49. Reinhardt CJ, Chan J. Development of Photoacoustic Probes for in Vivo Molecular Imaging. Biochemistry. 2018; 57: 194-199.

50. Huang D, Eric A. Swanson, Charles P. Lin, Joel S. Schuman, William G. Stinson, Warren Chang et al. Optical coherence tomography. Science. 1991; 254: 1178-1181.

51. Leitgeb R, Hitzenberger CK, Fercher AF. Performance of fourier domain vs. time domain optical coherence tomography. Optics Express. 2003; 11: 889-894.

52. De Boer JF, Cense B, Park BH, Pierce MC, Trarney GJ, Bouma BE, et al. Improved signal-to-noise ratio in spectral-domain compared with time-domain optical coherence tomography. Opt Lett. 2003; 28: 2067-2069.

53. Lains I, Jay C. Wang, Ying Cui, Raviv Katz, Filippos Vingopoulos, Giovanni Staurenghi et al. Retinal applications of swept source optical coherence tomography (OCT) and optical coherence tomography angiography (OCTA). Progr Retin Eye Res. 2021; 84: 100951.

54. Leitgeb RA, Christoph K. Hitzenberger, Adolf F. Fercher, Tomasz Bajraszewski. Phase-shifting algorithm to achieve high-speed long-depth-range probing by frequency-domain optical coherence tomography. Opt Lett. 2023; 28: 2201-2203.

55. Kim J, William Brown, Jason R. Maher, Howard Levinson, Adam Wax. Functional optical coherence Tomography: principles and progress. Phys Med Biol. 2015; 60: R211-R237.

56. Wang A, Wenliu Qi, Tianxin Gao, Xiaoying Tang. Molecular contrast optical coherence tomography and its applications in medicine. Int J Mol Sci. 2022; 23: 3038.

57. Mattison S P, Kim W, Park J, Applegate B E. Molecular imaging in optical coherence tomography. Curr Mol Imaging. 2014; 3: 88-105.

58. Gleich B, Jürgen Weizenecker. Tomographic imaging using the nonlinear response of magnetic particles. Nature. 2005; 435: 1214-1217.

59. Panagiotopoulos N, Robert L. Duschka, Mandy Ahlborg, Gael Bringout, Christina Debbeler, Matthias Graeser et al. Magnetic particle imaging: current developments and future directions. Int J Nanomedicine. 2015; 10: 3097-3114.

60. Weizenecker J, Gleich B, Rahmer J, Dahnke H, Borgert J. Three-dimensional real-time in vivo magnetic particle imaging. Phys Med Biol. 2009; 54: L10.

61. Buzug TM, Gael Bringout, Marlitt Erbe, Ksenija Gräfe, Matthias Graeser, Mandy Grüttner et al. Magnetic Particle Imaging: introduction to imaging and hardware Realization. Z Med Phys. 2012; 22: 323-334.

62. Bulte JWM. Superparamagnetic iron oxides as MPI tracers: A primer and review of early applications. Adv Drug Deliv Rev. 2018; 138: 293-301.

63. Lu C, Linbo Han, Joanna Wang, Jiacheng Wan, Guosheng Song, Jianghong Rao. Engineering of magnetic nanoparticles as magnetic particle imaging tracers. Chem Soc Rev. 2021; 50: 8102-8146.

64. Zheng B, Marc P. von See, Elaine Yu, Beliz Gunel, Kuan Lu, Tandis Vazin, et al. Quantitative magnetic particle imaging monitors the transplantation, biodistribution, and clearance of stem cells in vivo. Theranostics. 2016; 3: 291-301.

65. Talebloo N, Mithil Gudi, Neil Robertson, Ping Wang. Magnetic particle imaging: current applications in biomedical research. J Magn Reson Imaging. 2020; 51: 1659-1668.

66. Baker S, Chambers C, Mc Quillan P, Janicki P, Kadry Z, Bowen Daniel, et al. Myocardial perfusion imaging is an effective screening test for coronary artery disease in liver transplant candidates. Clin Transplant. 2015; 29: 319-326.

67. Van der Heiden K, Barrett HE, Meester EJ, Gaalen KV, Krenning BJ, Beekman FJ, et al. SPECT/CT imaging of inflammation and calcification in human carotid atherosclerosis to identify the plaque at risk of rupture. J Nucl Cardiol. 2022; 29: 2487-2496.

68. Glaudemans AW, Israel O, Slart RH. Pitfalls and Limitations of Radionuclide and Hybrid Imaging in Infection and Inflammation. Semin Nucl Med. 2015; 45: 500-512.