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Molecular Imaging for Early Cancer Diagnosis

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Molecular imaging is quickly gaining acceptance as a technique that has the potential to enhance every aspect of cancer treatment. Oncologists use molecular imaging to characterize and measure important biomolecules and molecularly based events that are essential to the malignant state in living organisms. New molecular imaging methods have the potential to greatly improve cancer treatment's diagnostic and therapeutic modalities. Novel molecular enhancers for imaging modalities including US, CT, MRI, and PET, in especially for solid tumors, may enable earlier and more precise diagnosis and staging, which are necessary for effective surgical therapy. Over the past few decades, medical imaging has grown significantly and is now a key component of clinical oncology. Molecularly tailored imaging agents are the imaging technology of the future for the treatment of cancer patients. Molecular imaging is distinct from traditional anatomical imaging in that it makes use of imaging probes to see the target molecules. By enabling earlier diagnoses, gauging early treatment response, and predicting treatment response, molecular imaging is expected to have a significant impact on oncology and personalized medicine. This review article describes the characteristics of molecular imaging methods and their capabilities of early cancer diagnosis. This review study was performed on the literature sourced from the World Health Organization (WHO) and scientific citation websites such as Google Scholar, PubMed, Researchgate and Web of Science until December 2022.

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1. INTRODUCTION

For better cancer management, it is fundamental to predict and track the effects of cancer therapy. Cancer lesion characterization and cancer response monitoring can help the doctor choose an appropriate therapy and minimize side effects, delaying the progression of the disease or perhaps curing it. Because it can see molecular aberrations in real time, molecular imaging is frequently used to characterize cancer [1]. In the field of medical imaging known as "molecular imaging," advanced diagnostic imaging techniques are used to produce precise images and information as well as to see molecular and cellular events occurring within the bodies of living creatures. It is able to identify tumors/cancer at their early stage and give its specific location, information that is impossible to obtain with other imaging technologies or that would require more intrusive treatments like biopsy or surgery. By creating whole new opportunities for the early identification and successful treatment of cancer, molecular imaging may very well have the capacity to transform every element of cancer care [2,3].

1.1 Mechanism of Molecular Imaging

Cells within and around tumors start to change their biochemical activity when they grow in the body. As the disease worsens, this abnormal cellular activity starts to harm body structures and tissue, leading to structural alterations that may be noticed as having a different density from the surrounding normal parts. Throughout most molecular imaging methods, a contrast agent, such as a microbubble, metal ion, or radioactive isotope, is injected into the patient's circulation, and an imaging modality—such as ultrasound, MRI, CT, or PET—is used to follow its movement in the body. The imaging agent builds up in a target organ or binds to specific cells after being introduced into the body. A radiotracer, which is a chemical that includes a radioactive atom or isotope, is one of the imaging agents that can be used to see cellular activity. The imaging tool picks up the imaging substance and generates images that depict the distribution of the substance throughout the body. The ultimate objective of molecular imaging is to offer non-invasive, real-time monitoring of all interior metabolic processes. Some examples of modalities being used for noninvasive molecular imaging, (i) ultrasound (US), (ii) optical imaging (OI), (iii) molecular magnetic resonance imaging (mMRI), (iv) Nuclear Imaging [3,4].

2. TYPES OF MOLECULAR IMAGING TECHNIQUES

“Molecular imaging offers an excellent visualization, characterization and quantification of biologic process taking place at the cellular and sub-cellular levels. There are four main categories of molecular imaging modalities; ultrasound, optical imaging, magnetic resonance imaging (MRI), and nuclear imaging techniques” [5,3]. Bonekamp [6] in his paper reported that “the selection of the imaging modality often is determined based on the temporal and spatial resolution, field of view, sensitivity of the imaging system, depth of the biological process, the molecular or cellular process to image, and the availability of suitable probes and labels than can be delivered to the imaging target” [5].

2.1 Ultrasound

“An ultrasound (also known as ultrasonography, sonography, or sonogram) is a non-surgical procedure that helps doctors look for tumors in certain areas of the body that don’t show well on x-rays. An ultrasound machine creates images called sonograms by giving off high-frequency sound waves that go through the body” [3]. It examines interior organs and soft tissues inside the body using high-frequency sound waves. The real-time ultrasound image allows the doctor to observe both the blood flowing through the veins and the movement of the body's internal organs. A handheld transducer is pressed against the skin during an ultrasonic examination. High frequency sound waves from the transducer bounce off the body's structures. Echoes, which are monitored with the aid of a computer and translated into real-time images of organs and tissues, are created as sound waves transmitted through the body bounce back as they hit various tissues. The frequency, intensity, and duration of the sound signal, as well as how long it takes the patient's sound to return to the transducer, all affect the image that is taken [7]. In order to identify minor lesions in biological tissue, ultrasound may generate meaningful signals with a dynamic range of more than 120 dB and has good resolution to human soft tissue. When living tissues are visible in ultrasound images, the necessary images can be obtained without staining [8]. “Breast ultrasound presents a potentially viable alternative for early breast cancer detection in some resource-limited areas because it is portable, less expensive than

mammography, and versatile across a wider range of clinical applications. Breast ultrasound is used in high-resource settings to supplement mammography in certain clinical scenarios. Additionally, ultrasonography is the best imaging tool for guiding future operations if a biopsy is necessary, significantly boosting its usefulness in the diagnosis of breast cancer" [9].

2.2 Optical Imaging

In optical imaging, proteins that produce light are made to bind to particular molecules, such as those found in the brain or on the surface of cancer cells. Low quantities of light released by particular molecules from inside the body are picked up by highly sensitive detectors. Fluorescence imaging and bioluminescence imaging are the two main categories of optical imaging. A protein that naturally emits light is used in bioluminescent imaging to track the movement of particular cells or pinpoint the location of particular chemical processes within the body. Contrarily, fluorescence imaging makes use of proteins that are activated by an external light source, such as a laser, to produce light [5]. For the non-invasive detection of human tumors in areas that are accessible by an optical imaging instrument, optical imaging is quick, affordable, and sensitive [10]. Fluorescence and bioluminescence are frequently used in optical imaging techniques as sources of contrast. One drawback limits its application for whole-body imaging: the lack of penetration depth brought on by tissue dispersion and light absorption, this is a relatively small drawback for intraoperative guiding, as tumors are frequently directly visible [11].

2.3 Magnetic Resonance Imaging

"Magnetic resonance imaging, more commonly referred to as MRI, is an imaging method used mostly in medical contexts that employs magnetism and radio waves to produce high quality images of within the human body. Magnetic resonance imaging. The spatial mapping of endogenous metabolites provided by MRI can reveal the heterogeneous distribution of these metabolites in cancer tissue" [12]. "Nuclear magnetic resonance (NMR), a spectroscopic method used by scientists to gather microscopic chemical and physical information about molecules, provides the theoretical foundation of the mechanism behind MRI. A huge, round magnet surrounds a tube in an MRI scanner. The patient is positioned on a mobile bed that is introduced into the magnet for normal MRI testing. A powerful magnetic field produced by the magnet aligns the protons of hydrogen atoms so that they can be struck by a radio wave beam. This causes the body's protons to spin, producing a weak signal that the MRI scanner's receiver section may pick up. A computer processes the receiver information to create an image" [5]. Although MRI offers better soft tissue contrast than computed tomography (CT), a benefit in many organs, the physical characteristics of the lungs and mediastinum provide special difficulties for lung MRI [13], Additionally, standard MRI lacks breast cancer specificity despite having the highest sensitivity (80–100%) of these methods [14].

2.4 Nuclear Imaging

"Radiologists can use nuclear imaging, also known as radionuclide scanning, as a useful diagnostic tool since it demonstrates both the anatomy and the function of an organ. Small amounts of radioactive material, or a tracer, are frequently used in nuclear imaging for diagnostic purposes. In nuclear imaging, a radioactive tracer is often a targeted probe. To precisely interact with protein targets in particular cells or subcellular compartments, it could be antibodies, ligands, or substrates. These interactions are either based on the binding of a radioligand to a receptor or the trapping of a radiolabeled substrate by an enzyme. The majority of radioactive tracers used in nuclear imaging are injected into a vein, while some are also given orally. After receiving radioactive tracers, the patient must rest for a predetermined amount of time to allow the tracers to be distributed throughout the body. In the end, a specialized gamma camera is employed for imaging purposes to detect radiation throughout the body. Positron emission tomography (PET) and single photon emission computed tomography are the most frequently utilized nuclear imaging modalities (SPECT)" [5]. Despite the significance of nuclear imaging in vitro, a number of drawbacks must be taken into account. First, like X-rays and CT, gamma waves—which are ionizing—are what PET and SPECT rely on for wave detection. Additionally, the pricey and inadequate spatial and temporal resolution of such modalities prevents the viewing of tissue structures at the sub-millimeter scale [15].

2.4.1 Positron Emission Tomography (PET)

"Positron emission tomography (PET) is a nuclear medicine imaging procedure that uses a

Table 1. Key strength and weakness of the main available imaging modalities used in molecular imaging [5]

Imaging modality	Electro magnetic radiation spectrum	Advantages	Disadvantages
Ultrasound	High-frequency sound	Real time and low cast	Limited spatial resolution, mostly morphologic although targeted micro bubbles under development
Optical bioluminescence imaging	Visible light	Highest sensitivity, quick, easy, low cost and relatively high throughput	Low spatial resolution, current 2-D imaging only, relatively surface weighted, limited translational research
Optical fluorescence imaaing	Visible liaht or near-infrared	High sensitivity, detects fluorochrome in live and dead cells	Relatively low spatial resolution, relatively surface weighted
Magnetic resonance imaging (MRI)	Radio waves	Highest spatial resolution, combines morphologic and functional imaging	Relatively low sensitivity, long scan and post processing time, mass quantity of probe may be needed
Positron Emission Tomography (PET)	High eneray gamma rays	High sensitivity, shorter time scan, enable quantitative analysis	PET cyclotron or generator needed, relatively low spatial resolution
Single photon emission computed tomography (SPECT)	Lower energy gamma rays	Many molecular probes available, can image multiple probes simultaneously, may be adapted to clinical imaging system	Relatively low spatial resolution, high radiation to subjects due to —_longer tracer half-life's, non-quantitative tool, Longer scanning time

radiotracer that is injected into the patient's circulation along with an imaging device (PET scanner) to create a three-dimensional image or picture of the body's functioning processes" [3]. It is a quantitative tomographic imaging method that generates composite cross-sectional pictures from volume elements. The activity of radionuclides tagged with radioactive tracer that were intravenously supplied at an earlier stage before the scanning took place determines the signal strength for PET pictures in each voxel. In a scanner known as a PET scanner, oppositely directed annihilation photons that are indirectly released by the positron disintegration of PET radionucleotide are detected using a gamma photon coincidence detection system. Due to the use of this logic, quantitative three-dimensional (3-D) maps of radiolabeled tracers in tissue can be acquired [5]. "FDG is used today in almost all clinical cancer imaging procedures. FDG typically has increased tumor absorption compared to background in most normal tissues (including the normal breast), making it an appealing agent for cancer diagnosis. Accelerated glycolysis is a fundamental component of many malignancies, including breast cancer" [16].

2.4.2 Single Photon Emission Computed Tomography (SPECT)

"Similar to PET, single photon emission computed tomography (SPECT) records data that a computer generates into two or three-dimensional images using a radioactive tracer that is delivered to the patient and a scanner. To detect a radioactive tracer in the body, the SPECT approach, on the other hand, uses a gamma camera that spins around the patient. Unlike SPECT tracers, which have a longer half-life, PET tracers have a shorter half-life. The antibodies will adhere to the tumor if one is present, making it possible to identify tumorous cells" [16]. The primary downside of SPECT imaging with tumor-seeking agents is the lack of anatomical demarcation of the diseased process they detect; this shortcoming occasionally makes SPECT interpretation challenging and can reduce its diagnostic adequacy [17]. Table 1 provides a summary of the imaging techniques with its respective strength and weakness.

3. INTEGRATED MOLECULAR IMAGING TECHNIQUES (FDG PET-CT)

Radionuclides or chemically altered molecules are used in molecular imaging to view specific targets or pathways that are significant in the pathophysiology of a given disease. Many transporter-based probes, such as [18F] fluoro-D-glucose ([18F]FDG), are utilized to diagnose cancer and determine the subsequent prognosis [18]. The astounding success of the molecular imaging technology depends on its capacity to detect changed metabolism in a specific diseased cell when two imaging modalities, such as PET-CT, SPECT-CT, and PET-MRI, are combined in a single environment. It incorporates quantification across time and two- or three-dimensional imaging (Fig. 1). Integrated molecular imaging techniques increasingly offer great spatial resolution, but more importantly, high contrast, mostly independent of structural disruptions. Due to their propensity to participate in biological processes of interest, tiny amounts of radioactive elements can offer extremely sensitive indicators of how the body functions in both health and sickness. As a result, faulty physiology or metabolism can be identified with high specificity, and the anatomical distribution of the anomaly can be pinpointed with better accuracy than with the traditional method. Given their limitations to only evaluating structural changes or functional changes disjointedly, traditional imaging techniques such as computed tomography (CT) and single positron emission tomography (SPECT) are now not very used [5]. "It was shown that PET/CT offers a high diagnostic accuracy, both in the evaluation of suspected tumor recurrence and in persistent disease" [19].

3.1 FDG PET-CT and Standard Uptake Value (SUV)

In contrast to the response assessment offered by traditional morphologic imaging, imaging of the altered glucose metabolism, as indicated by cellular uptake and trapping of the glucose analog 18F-fluorodeoxyglucose (FDG), can be sufficient. The standardized uptake value, obtained through quantitative evaluation of FDG PET scans, is a form of quantitative data (SUV). This measure of uptake gives a median for comparing FDG uptake between various lesions. To prevent FDG uptake fluctuation caused by variations in tumor habitus inside the body, attenuation correction is necessary when measuring SUV. This number normalizes the body weight, FDG injection activity, and tumor FDG uptake. "The cut-off value of 2.5 in differentiating malignant and benign is at large limited due to varied tumor histological characteristic in malignant tumor" [5,16].

Table 2. Data shows the accuracy of the PET-Ct and the CT in the evaluation of various tumors [5]

Published data	Sensitivity versus specificity (%)	
	PET-CT	CT
Niikura N et al. Metastatic breast cancer [2]	97.4 versus 91.2	85.9 versus 67.3
Kim SK et al. (solitary pulmonary lesion) [3]	97.0 versus 85	93.0 versus 31.0
Pim A. et al (malignant lymphoma) [4]	100.0versus 95.0	91.0 versus 96.0
Ozkan et al. (colorectal cancer recurrence) [5]	98.0 versus 85.0	73.0 versus 86.0

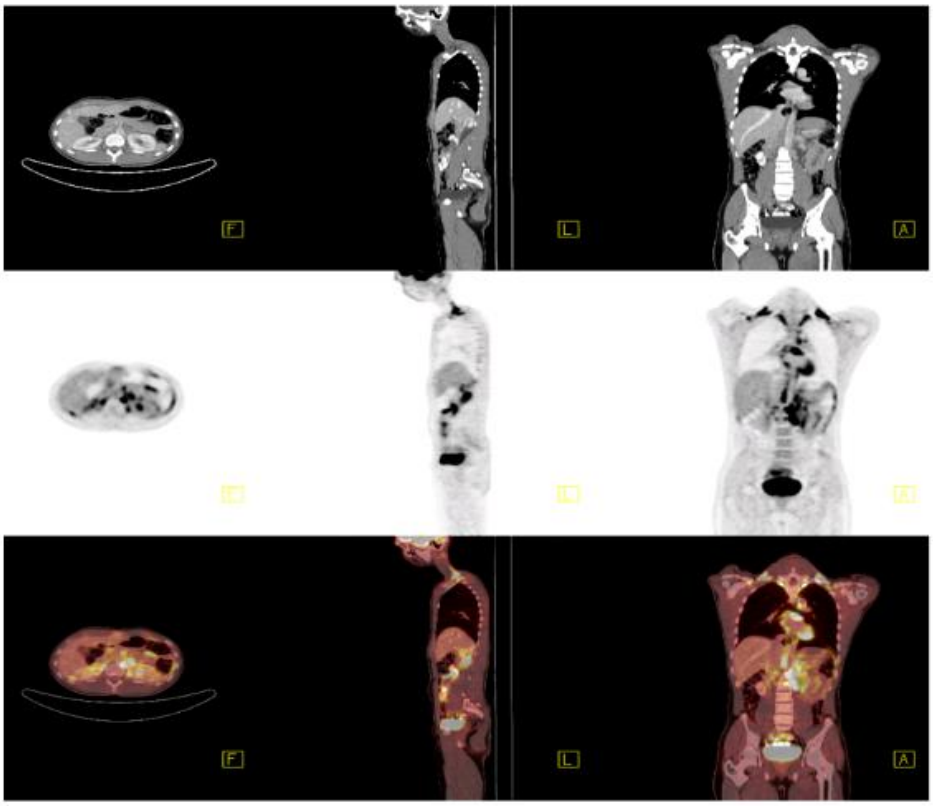

Fig. 1. PET-CT image display on the Syngo console panel showing series of CT, PET and fused images [5]

3.2 FDG PET-CT and Radiation Issues

The most often utilized positron emitting radiopharmaceutical in PET exams is 18F-fluorodeoxyglucose (FDG), sometimes known as 18F-FDG, because it is a glucose analogue. The creation of the radioisotope fluorine-18 to tag with a glucose derivative is necessary for the manufacture of 18F-FDG. Fluorine-18 is a positron emitter with gamma energy of 511 keV and total energy of 1022 keV as a result of positron annihilation. This is nearly ten times more intense than typical X-ray radiation. It exposes radiation workers and patients to high levels of activity and dose.

4. FUTURE PERSPECTIVE

Many (physicians) now recognize the value of molecular imaging as a platform for translating genetic flaw via aberrant protein function and cellular transformation and development. However, depending on the kind of radiopharmaceutical marker employed to indicate

the biological processes, different molecular imaging approaches have different degrees of sensitivity. Numerous restrictions apply to the use of FDG as a ligand in PET-CT.

5. CONCLUSION

In conclusion, molecular imaging will be crucial in three key areas of oncology: 1) as the foundation for determining the best course of treatment for a given patient (personalized medicine); 2) as a tool for guiding targeted therapies, such as those that call for real-time interventions; and 3) as a component of the "toolkit" that will be used to develop and optimize new therapeutics and to document the efficacy of new classes of drugs in particular patient populations. In the advancement of both hardware and probes, multimodality approaches to molecular imaging will become more and more important. Molecular imaging tools have the exciting potential to advance the development of new breast cancer therapeutics and bring tissue-based, genomic findings into the clinic

CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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