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RESEARCH ARTICLE

The role of nuclear medicine in modern therapy of cancer

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Abstract Nuclear medicine is a multidisciplinary field that develops and uses instrumentation and tracers (radiopharmaceuticals) to study physiological processes and noninvasively diagnose, stage, and treat diseases. Particularly, it offers a unique means to study cancer biology in vivo and to optimize cancer therapy for individual patients. A tracer is either a radionuclide alone, such as iodine-131 or a radiolabel in a carrier molecule such as ^{18}F in fluorodeoxyglucose (^{18}F-FDG), or other feasible radionuclide attached to a drug, a protein, or a peptide, which when introduced into the body, would accumulate in the tissue of interest. Nuclear medicine imaging, including single-photon emission computer tomography and positron emission tomography, can provide important quantitative and functional information about normal tissues or disease conditions, in contrast to conventional, anatomical imaging techniques such as ultrasound, computed tomography, or magnetic resonance imaging. For treatment, tumor-targeting agents, conjugated with therapeutic radionuclides, may be used to deposit lethal radiation at tumor sites. This review outlines the role of nuclear medicine in modern cancer therapy.

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Introduction

The American Medical Association officially recognized nuclear medicine as a medical specialty in 1971, but its origins date back to early twentieth century. Already in 1909, F.H. Williams reported on "early treatment of some epitheliomas by pure radium salts" [1]. In August 1914 issue of Radium, a monthly journal devoted to the chemistry, physics, and therapeutic radium and radioactive substances, Frederick Proescher and B.R. Almquest presented "Contribution on Biological and Pathological Action of Soluble Radium Salts—with Special Reference to its Therapeutic Value in Pernicious Anaemia and Leukemia" and Charles Viol wrote about "Radium Production in America" [2]. The same issue contains several reports on the therapeutic application of radium. Over decades, dramatic changes have occurred, and today, nuclear medicine offers a unique means to study cancer biology, to optimize therapy for individual patients by both imaging of relevant biomarkers (involving the use of γ radiation), and tumor-targeted delivery of therapeuting radionuclides (alpha (α) or beta (β) emitters). Table 1 presents the most significant developments in this field, including the first-ever FDA approval for the use of radioactive material ($Na^{131}I$) for cancer treatment, application of new radionuclides, introduction of new tumor-targeting agents, and development of sophisticated methods for in vivo detection and quantification of radioactivity distribution.

Early diagnosis and individualized therapy have been recognized as crucial for the improvement of the cancer treatment outcome. While proper molecular characterization

Table 1 Examples of significant discoveries in nuclear medicine

1930s
E.O. Lawrence developed the cyclotron at the UC Radiation Laboratory that later on produced the first medically useful radionuclides, including iodine-131, thallium-201, technetium-99 m, carbon-14, and gallium-67
1940s
The first reactor-produced radionuclides for medical research were made at Oak Ridge National Laboratory (ORNL) including phosphorous-32, iron-52, and chromium-51
1950s
Benedict Cassen invented the first automated scanner at the University of California at Los Angeles (UCLA) to image the thyroid gland after administering radioiodine to patients
Hal Anger invented the stationary gamma camera (now known as the Anger camera) at the UC Radiation Laboratory
The molybdenum-99/technetium-99 m generator was developed at Brookhaven National Laboratory (BNL) by Powell Richards
1960s
Scientists at ORNL discovered the affinity of gallium-67 for soft-tissue tumors. This radionuclide had been used to image lymphomas, lung cancer, and brain tumors
1970s
PET scanners were developed by Michael Phelps, Edward Hoffman, and Michel Ter-Pogossian at Washington University based on earlier work by Gordon Brownell at the Massachusetts Institute of Technology (MIT) and James Robertson at BNL
^{18}F-FDG, a positron-emitting compound, was synthesized by chemists at BNL
Scientists at the University of Pennsylvania and at the NIH used ^{18}F-FDG to image glucose metabolism in the human brain
1980s
A new radiopharmaceutical, iodine-131-*m*-iodine-benzyl-guanidine (I-131 MIBG), was developed by Donald Wieland for the diagnosis and treatment of rare childhood cancers
Michael Welch of Washington University and John Katzenellenbogen of the University of Illinois developed the first PET radiotracer used to image tumors expressing the estrogen receptor
1990s
A high-resolution PET scanner designed to image small laboratory animals (i.e., microPET) was developed at UCLA by Simon Cherry
Radiolabeled antibodies were developed for therapy
Advances were made in the application of alpha-particle emitters for therapy

of individual tumor facilitates choice of the right therapeutic strategies, early assessment of tumor response to therapy could allow the physicians to discontinue ineffective treatment and offer the patient more promising alternatives. Nuclear medicine plays crucial role in the modern approach to cancer treatment by providing means to the following:

- Determine the extent or severity of the disease, including metastases
- Select the most effective therapy based on the unique biologic characteristics of the patient and the molecular properties of a tumor
- Accurately assess the effectiveness of a treatment regimen
- Adapt treatment plans quickly in response to changes in molecular and biochemical characteristics of the tumor
- Assess disease progression
- Identify recurrence of disease and help manage ongoing care

It has been known since the beginning of twentieth century [3] that delivery of a sufficient radiation dose at an adequate rate to tumor tissue results in killing of tumor cells. Because cancer is frequently present as a disseminated disease, it is crucial to deliver deadly radiation dose not only to the primary tumor but also to distant metastases while reducing exposure of healthy organs as much as possible. In therapeutic application of nuclear medicine, monoclonal antibodies, their fragments, or other tumor-targeting agents, labeled with therapeutic radionuclides, are used to develop new strategies aiming at concentrating radioactivity at the tumor site and sparing normal tissues.

In this review, we first briefly discuss the basic principles of nuclear medicine imaging and highlight the different classes of the most frequently used radioisotopes, radiotracers, and their targets. Then, we describe the application of molecular imaging, particularly positron emission tomography (PET), for the molecular characterization of the tumor and for the evaluation of tumor response to the treatment. Finally, we describe the therapeutic application of radionuclides.

Imaging methods

There are three different functional imaging techniques under the general umbrella of nuclear medicine. The most

basic is planar scintigraphy that provides information about the distribution of radioactive material in a single two-dimensional image, analogues to a planar X-ray scan. As computer tomography presents three-dimensional anatomical images, single photon emission computed tomography (SPECT) uses a series of contiguous two-dimensional images of the distribution of the radiotracer using the same agents as planar scintigraphy to provide a three-dimensional distribution of radiotracers. Finally, the most sensitive method, PET, utilizes γ-rays produced in the process of positron–electron annihilation and requires radionuclides emitting positrons. PET and SPECT have very high sensitivity as they allow detection of radiolabeled probe molecules in the ~10^{-11}–10^{-12} and ~10^{-10}–10^{-11} range, respectively. This high sensitivity allows obtaining high-quality three-dimensional images, particularly useful for the detection and characterization of neoplasm. The noninvasive molecular imaging techniques complement well-established ex vivo assays, such as immunohistochemistry, fluorescence in situ hybridization, or enzyme-linked immunosorbent assay, which require invasive sampling procedures and, because of tissue heterogeneity, may not always adequately represent the biochemical or pathological processes [4]. Following is a brief description of each imaging modality.

Planar scintigraphy Figure 1 shows the basic form of the gamma camera, which is used in both planar scintigraphy and SPECT. In planar scintigraphy, a single gamma camera is held stationary above the patient. When a small percentage of γ-rays (the vast majority is absorbed), originating from a radiotracer's decay in the body, passes the collimator, they enter the scintillator and ionize iodine atoms leading to the production of light photons (415 nm). These photons are then converted into an electrical signal by high-gain photomultiplier tubes. The signals from each tube are recorded and used to reconstruct an image showing the two-dimensional distribution and relative concentration of radioactive tracer elements present in the organs and tissues. Planar scintigraphy has rather poor signal-to-noise ratio (SNR) and low special resolution (~5–10 mm) but extremely high sensitivity (being able to detect nanograms of injected radioactive material). These types of scan are mostly used for whole-body bone screening [5]. In addition, the thyroid, liver, and kidney are scanned using specialized agents [6–8]. The most commonly used radiotracers are chemical complexes of technetium (^{99m}Tc), an element that emits monoenergetic γ-rays at 140 keV, $T_{1/2}$=6 h.

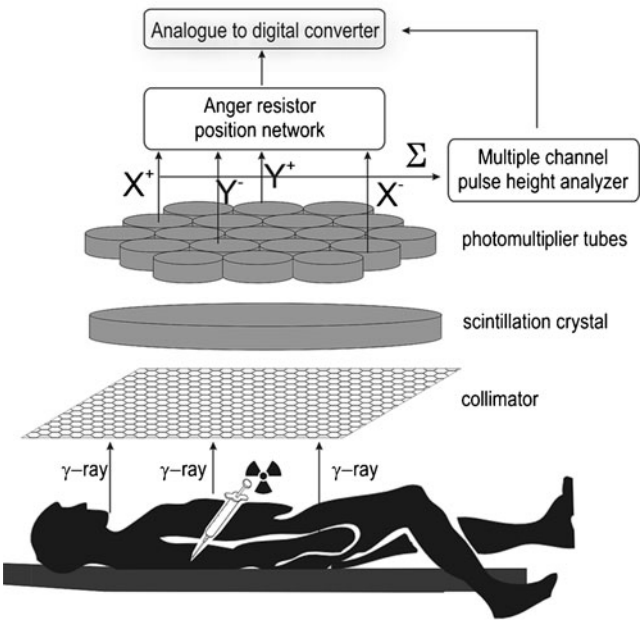

Fig. 1 Gamma camera which is used in both planar scintigraphy (one camera) and SPECT (two or three rotating cameras)

SPECT SPECT forms a three-dimensional image of the distribution of gamma-emitting radiotracer injected into the body. It uses essentially the same radionuclides (Table 2) and instrumentation as planar scintigraphy, but in this case, two or three gamma cameras rotate around the patient, detecting γ-rays at a number of different angels. Subsequently, a combination of reconstructed multiple two-dimensional images leads to the generation of cross-sectional images of the internal distribution of the injected molecules. One advantage of SPECT is that multiple probes labeled with separate isotopes may be studied in parallel since each isotope might be associated with its unique γ-spectrum. However, SPECT compared to PET has a lower sensitivity (one to two orders of magnitude) and a more complex approximate attenuation correction [9]. Presently, the majority of SPECT applications involves studies of cardiovascular diseases, and there is also an increasing interest in using it for brain studies to detect areas of reduced blood flow associated with stroke, epilepsy, or Alzheimer's disease.

PET PET, similar to SPECT, provides information about the biochemical and physiological processes of the human body. In PET imaging (Fig. 2), positron (antimatter electron)-emitting isotopes are used as radiotracers that, attached to biologically relevant molecules, allow to monitor their distribution in the body by detection of the two gamma photons produced in the process of positron–electron annihilation. Briefly, the positron, emitted from the unstable proton-rich nucleus, travels a distance of a few millimeters, depending on the initial positron energy and the density of the surrounding environment. It loses its kinetic energy with neighboring charged particles in the tissue and eventually undergoes annihilation, in a reaction with a nearby electron. This reaction leads to the emission of two annihilation photons that are emitted simultaneously with the energy of 511 keV, in opposite directions (approximately

Table 2 Physical properties of the most commonly used PET and SPACT radionuclides

Readionuclide	Imaging modality	Half-life	Energy	Examples of radiotracers
^{15}O	PET	2.05 min	1.7 MeV	^{15}O-water
^{13}N	PET	9.96 min	1.20 MeV	$^{13}NH_3$
^{11}C	PET	20.4 min	0.96 MeV	^{11}C-methionine
^{18}F	PET	109.7 min	0.69 MeV	^{18}F-FDG, ^{18}F-FLT
^{68}Ga	PET	67.6 min	1.89 MeV	^{68}Ga-DOTA-TATE
^{64}Cu	PET	12.7 h	0.65 MeV	^{64}Cu-ATSM
^{89}Zr	PET	78.4 h	0.90 MeV	^{89}Zr-trastuzumab
^{86}Y	PET	14.7 h	3.14 MeV	^{86}Y-citrate
^{76}Br	PET	16.1 h	3.94 MeV	^{76}Br-A33 mAb
^{124}I	PET	4.18 days	2.14 MeV	^{124}I-annexin
^{99m}Tc	SPECT	6.02 h	140 keV	^{99m}Tc-RGD
^{111}In	SPECT	2.8 d	171, 245 keV	^{111}In-octreotide
^{131}I	SPECT	8.02 days	364, 637 keV	^{131}I-rituximab
^{123}I	SPECT	13.2 h	159 keV	^{123}I-MIBG
^{67}Ga	SPECT	3.3 days	93, 185, 300 keV	^{67}Ga-citrate

Energy of the PET nuclides affects the range of positrons before the annihilation event, not the energy of the resulting γ-rays detected by the PET scanner

180 ° apart) due to conservation of energy and momentum. Some of these photons are coincidently detected by the PET/computed tomography (CT) camera, which consists of the ring of detectors placed around the body of the patient. These photons are registered within a very short time interval, and it is assumed that somewhere along the line between two of the detectors, an annihilation event takes place. Crossing of all those lines of response approximately determines the location of the radiation source. Once all the events are collected, mathematical tomographic image reconstruction algorithms transform them into a cross-sectional image. When appropriate corrections for γ-ray attenuation and scatter events are performed, quantification by PET can provide a reliable information about the concentration of the positron-emitting radionuclide inside the body.

Radionuclides

The choice of a radionuclide depends on particular application. While radionuclides used for nuclear medicine imaging emit γ-rays, which can penetrate deeply into the body, the radionuclides used for therapy must emit radiation with relatively short path length in order to deposit their energy locally and minimize the whole-body irradiation. There are three types of particulate radiation of consequence for radionuclide therapy—beta particles, alpha particles, and Auger electrons.

The physical half-life of the radionuclide should match the biological half-life of the labeled monoclonal antibody (mAb), mAb fragments, small peptides, or small organic molecules to achieve the optimal SNR. In practice, the half-life of the selected isotope should be, at a minimum,

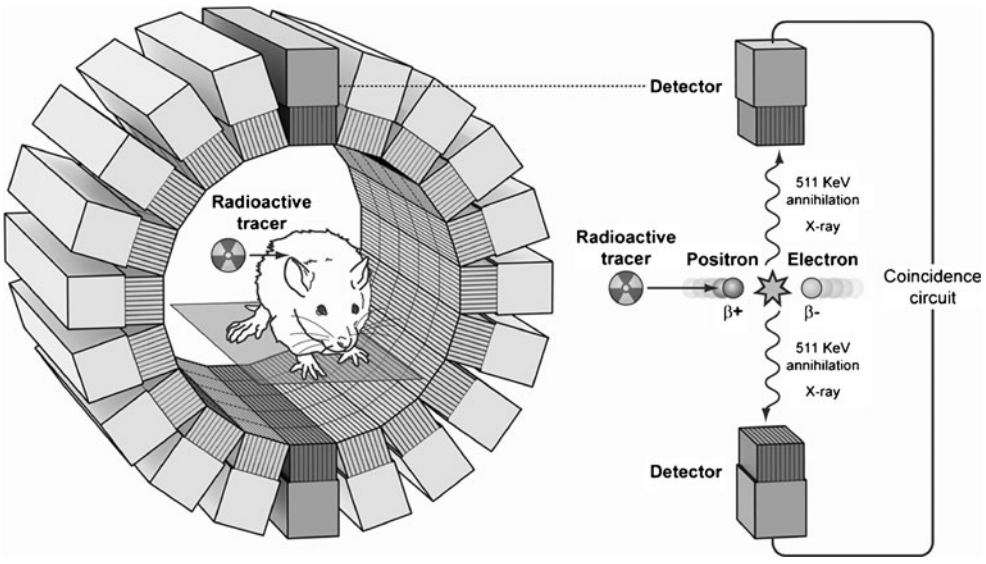

Fig. 2 A schematic diagram showing positron emission during the decay process of a radionuclide

twofold longer than the biological half-life of the event kinetics to be imaged [10]. Its production should be rather easy and cheap. In addition, chemical properties of radionuclide should facilitate labeling and prevent accumulation of radioactivity in nontargeted organs. Following are the main categories of radionuclide utilized in nuclear medicine.

Photon emitters The radionuclides used in SPECT imaging emit γ-rays with energies in the range of 30 to 300 keV and have longer half-lives (from hours to several days) as compared to the typical rapidly decaying positron-emitting isotopes used in PET (Table 2). They are commercially available, which makes them relatively cheap and easy to handle. The radiometal technetium-99 m (^{99m}Tc) is so far the most commonly used radionuclide in nuclear medicine due to its favorable physical properties ($T_{1/2}$=6 h, Eγ=140 keV) for diagnostic imaging and its widespread availability as a column elute from commercially ^{99}Mo/^{99m}Tc generators. Apart from ^{99m}Tc, the other commonly used γ-emitting radionuclides are gallium-67 (^{67}Ga), indium-111 (^{111}In), and iodine-123 (^{123}I). Since γ-radionuclides have their own spectra, SPECT imaging has the unique capability of imaging multiple probes labeled with different isotopes allowing the simultaneous study of multiple cellular or molecular events.

Positron emitters The most common cyclotron-produced, positron-emitting radionuclides are common elements found in biologically active molecules and pharmaceuticals. Carbon-11 (^{11}C, $T_{1/2}$=20.4 min), nitrogen-13 (^{13}N, $T_{1/2}$=9.96 min), oxygen-15 (^{15}O, $T_{1/2}$=2.05 min), and fluorine-18 (^{18}F, $T_{1/2}$= 109.7 min). They all have short a half-life, which often complicates the radiolabeling process but also has a few advantages. The absorbed radiation dose to the patient being studied is generally less than with a longer-lived tracer, allowing more amount of the tracer to be injected that in turn increases the SNR. Furthermore, more than one study may be performed on the same patient, even on the same day since the tracer radioactivity decays quickly. On the other hand, their short half-lives limit their use to institutions that have cyclotron, a radiochemical laboratory, and PET scanner located near each other so that imaging studies can be completed before the radioactivity decays.

There is also a lot of interest in gallium-68 (^{68}Ga, $T_{1/2}$= 68 min), a metallic positron emitter, produced from a generator with a rather long-lived mother nuclide, ^{68}Ge ($T_{1/2}$= 270.8 days). It provides a convenient alternative, especially to ^{18}F-labeled compounds, in the places where access to a cyclotron is limited. The short half-life of radionuclides allows mainly for labeling of small molecules and peptides with very rapid kinetics.

Other, less commonly used cyclotron-produced isotopes, having much longer half-life include copper-64 (^{64}Cu, $T_{1/2}$= 12.7 h), yttrium-86 (^{86}Y, $T_{1/2}$=14.7 h), bromine-76 (^{76}Br, $T_{1/2}$= 16.1 h), zirconium-89 (^{89}Zr, $T_{1/2}$=78.4 h), and iodine-124 (^{124}I, $T_{1/2}$=4.18 days). They are particularly suitable in combination with intact mAbs because they match well to their biological half-lives, giving optimal contrast for imaging purposes. The characteristics of the most commonly used positron-emitting radionuclides are listed in Table 2.

Beta emitters Beta emitters (Table 3) are commonly used radiotherapeutics, since they have relatively long path length (0.8–5 mm) and low linear energy transfer (LET) of approximately 0.2 keV/μm [11]. The long range results in a pronounced cross-firing effect which may affect antigen-negative, tumor cells but also contributes to nonspecific toxicity of nontargeted tissues. These properties make beta emitters such as ^{90}Y or ^{188}Re more suitable for treating poorly perfused, bulky tumors but less suited for targeting small metastases as their energy would be deposited outside of the target volume. In this case, low-energy β-rays as those emitted by ^{177}Lu would be more efficient. Of course, for conjugation purposes, the half-life of these particles need to match the pharmacokinetic properties of particular targeting agents, even though there are some indications that longer half-life of therapeutic radionuclides might be advantageous [12]. The broad scope of preclinical and clinical research in the therapy field also involves holmium-166, rhenium-186, copper-67, promethium-149, gold-199, and rhodium-105 [13].

Also, low-energy Auger electrons, resulting from electron capture or isomeric transition decay, are investigated. Most commonly used Auger electron emitters are bromine-77, indium-111, iodine-123, and iodine-125. When used in concert with targeting vehicles that can localize these subcellular-range radiations in close proximity to cellular DNA, studies in cell culture have shown highly effective and specific tumor cell killing [14, 15].

Table 3 Therapeutic radionuclides used for nuclear medicine

Radionuclide	Description	Production
Lutetium-177	Beta emitter, 6.7-day half-life	Reactor
Astatine-211	Alpha emitter, 7.2-h half-life	Accelerator
Yttrium-90	Beta emitter, 64-h half-life	Reactor
Rhenium-186	Beta emitter, 3.7-day half-life	Reactor
Rhenium-188	Beta emitter, 17-h half-life	Reactor
Holmium-166	Beta emitter, 27-h half-life	Reactor
Iodine-131	Beta emitter, 8-day half-life	Reactor
Samarium-153	Beta emitter, 46-h half-life	Reactor
Bromine-77	Beta emitter, 57-h half-life	Accelerator
Copper-67	Beta emitter, 62-h half-life	Accelerator
Actinium-225	Alpha emitter, 10-day half-life	Accelerator
Strontium-89	Beta emitter, 50.5-day half-life	Reactor

Alpha emitters Alpha particles have much higher energy (4–9 MeV) but travel in tissue over only a few cell diameters (i.e., 40–100 μm), offering the exciting prospect of matching the cell-specific nature of molecular targeting with radiation of a similar range of action [16]. Another attractive feature of alpha particles for targeted radionuclide therapy is that, due to their size and charge, the energy is deposited at relatively short distances resulting in high LET (~100 keV/μm). In fact, alpha particles loose 100 to 1,000 times more energy, via relatively dense ionization events, while traversing DNA than either conventional external beam X-ray radiation or beta particles do. Since the average distance between ionization events matches the distance between the two strands of DNA, the high LET of alpha particles is effective in creating double-strand breaks in DNA, and therefore, quiescent cells are also affected by this process [17]. Over the last decade, application of alpha emitters for targeted radionuclide therapy has been actively investigated. Studies have been done with bismuth-213- and astatine-211-labeled monoclonal antibodies in patients with leukemia and brain tumors [18], respectively, and radium-223 chloride was evaluated in breast and prostate cancer patients with bone metastases [19, 20]. Recently, there is a growing interest in using actinium-255, a radionuclide that generates four net alpha particle isotopes in a short decay chain to stable bismuth-209, as a source of therapeutic alpha particles [21]. Actinium-255-labeled antibodies are being tested in patients with advanced myeloid malignances. The results of clinical trials using alpha emitter-containing radiopharmaceuticals indicate that this therapeutic strategy presents a promising alternative for the treatment of cancer.

Radiotracers

Small molecules

Fluorine-18-2-fluoro-2-deoxy-D-glucose (^{18}F-FDG) is a radiolabeled glucose analogue. This nontumor-specific molecule that visualizes the glucose metabolism, often increased in tumor cells as compared to normal cells, is by far the most widely used (>90 % of all PET imaging procedures) nontumor-specific tracer for PET imaging [22]. Since glucose metabolism is not specific for malignant processes, physiologic ^{18}F-FDG uptake occurs in normal tissues (brain, muscles, salivary gland, myocardium, urinary tract). It is also taken up by different inflammatory as well as benign lesions, which potentially could lead to false-positive or false-negative findings. A large number of studies clearly demonstrate that ^{18}F-FDG imaging had improved staging and detection of recurrence in oncology, and several excellent papers reviewing such data have already been published [23, 24].

^{18}F-labeled thymidine analogue 3-deoxy-3-[^{18}F]-fluorothymidine (^{18}F-FLT) is transported across cell membranes by nucleoside transporter proteins and retained in the cell after phosphorylation by thymidine kinase 1 (TK1), whose levels correlate with cell proliferation [25]. Similarly, to ^{18}F-FDG, the phosphorylated ^{18}F-FLT is trapped intracellularly but is not further incorporated into the DNA. It has been demonstrated in many types of cancer that ^{18}F-FLT uptake in vivo is a measure of tumor proliferation. Beyond this, ^{18}F-FLT uptake is dependent on TK1 activity through the activation of a salvage pathway that does not correlate with cell proliferation in all tumor types [26]. This lack of correlation could explain the variances in response between different cancer types, since in some the de novo pathway seems to be dominant.

Targeting agents

Antibodies mAbs form a basis of a rapidly growing class of targeted therapeutics, particularly in oncology. In addition, radiolabeled mAbs have been used extensively since the 1970s as molecular imaging probes (immunoscintigraphy) as well as radiotherapy agents. Presently, imaging of radiolabeled mAbs provides specific information regarding the expression, location, and modulation of targets in a noninvasive manner in vivo. mAbs typically have affinities in the nanomolar range, well matched to the ability of radioactive scanners to detect tracers at nanomolar concentrations. Their rather large molecular size (~150 kDa) allows the introduction of a labeling group without significant interference in their behavior in vivo. On the other hand, their size leads to a rather long half-life which, in turn, contributes to very slow clearance from the bloodstream and leads to slow and restricted delivery to the intended target. In human, the residence time of intact mAb ranges from a few days to weeks, which results in optimal tumor-to-background ratios 2–4 days postinjection. To date, a number of antibody-based radioconjuates were developed for imaging and therapy in oncology. For example, anti-vascular endothelial growth factor (VEGF) antibodies, including bevacizumab and ranibizumab [27], have been used for imaging of VEGF, a potent mitogen that is considered to be the most important and best explored factor in angiogenesis of tumor. More recently, radiolabeled mAbs that bind to the extracellular domain of PSMA have been developed. Among these, the humanized version of J591 has had promising results in imaging and targeted radiation therapy (TRT) of prostate cancers [28–30]. Much research has been also carried out on labeling anti-epidermal growth factor receptor (EGFR) antibody (cetuximab) with a wide variety of positron emitters. However, all the reported PET imaging studies of EGFR expression were performed only in preclinical animal models. mAbs such as trastuzumab and pertuzumab are used as human epidermal growth factor receptor 2 (HER2)-targeting agents.

Antibody fragments The advantages of smaller molecules include rapid accumulation in tumor and clearance from most normal tissues, which make them well-suited to use in tandem with short-lived positron emitters (e.g., carbon-11, fluorine-18, gallium-68) as well as the most promising radionuclides for TRT such as astatine-211 and rhenium-188, which have half-lives of less than 24 h. Therefore, besides intact mAb molecules, mAb fragments and engineered variants, such as domain antibodies: nanobodies (~15 kDa), F(ab′)$_2$ (~105 kDa), F(ab′) (~52 kDa), single-chain Fv (scFv, ~25), diabodies (~50 kDa), and minibodies (~80 kDa), are also used [22]. They have shown improved pharmacokinetics for tissue penetration and better contrast in molecular imaging because of their smaller size.

Protein scaffolds Protein scaffolds such as monobodies and affibodies are constrained polypeptides that consist of either α-helix or β-sheet, with a size of 3–20 kDa [31]. Their clearance route can be optimized by modification of the protein sequence and labeling strategies. They possess high tumor penetration abilities, low toxicity, and low immunogenicity because of their relatively small size. They can be chemically or biologically synthesized and modified with different reporting moieties. Affibody molecules, for example, were derived from the B-domain of staphylococcal protein A. The B-domain is a relatively short cysteine-free peptide of 58 amino acids that is folded into a three-helical bundle structure [32]. It was mutated in one position in helix 2 to obtain increased chemical stability, and the resulting engineered variant was denoted to the Z-domain. The new molecules retained the capability to bind Ig Fc-regions, while Fab-binding activity was almost completely lost [33]. Affibody molecule libraries have been constructed through the genetic randomization of 13 amino acid positions in helices 1 and 2 that comprise the original Fc-binding surface of the Z-domain. They show selective binding to a range of different proteins (e.g., insulin, transferin, tumor necrosis factor-α, CD28, human serum albumin, HER2, and EGFR), demonstrating affinities in the picomolar to millimolar range [34, 35].

Aptamers Nucleic acid aptamers are single-stranded oligonucleotides that could also be attractive candidates for targeted molecular imaging. Aptamers are highly specific for their targets and possess binding affinities rivaling antibodies, largely due to the ability of the molecules to fold into complex three-dimensional structures [36]. They are generated in in vitro settings and can be screened against molecules that have weak immunogenicity or high toxicity [37, 38]. The polyanionic properties of aptamers, along with their small size (15 kDa), favor short circulating plasma half-lives and high permeability in solid tumors, thereby facilitating the delivery of radionuclides for imaging. However, a few issues have yet to be addressed for their practical applications as diagnostic and drug delivery agents. One difficulty is that nucleic acid aptamers could be vulnerable to nuclease degradation in cells or in blood [38]. This problem can be more significant for RNA aptamers because RNA molecules are much more vulnerable to hydrolysis in biological fluid. Another challenge is the development of general methods to convert the highly specific molecular recognition between aptamers and their targets into detectable signals. Nevertheless, more recently, a lot of interest has been evinced in radiolabeling of aptamers with a positron-emitting radionuclide such as ^{64}Cu [39].

Applications of molecular imaging in oncology

Tumor detection, characterization, and staging

Until recently, patients had to undergo several different examinations for whole-body cancer detections and staging. Right now, the advent of nuclear imaging techniques over anatomical imaging has introduced systemic approach that allows detecting functional alternations long before any morphological changes are identified with established sequential, diagnostic algorithms. Importantly, the combination of PET and SPECT with the detailed anatomical information of CT as dual-modality scanners has also dramatically increased lesion localization and diagnostic accuracy compared with both modalities as separate applications.

Metabolic ^{18}F-FDG-PET imaging is the most widely used for initial tumor staging of newly diagnosed malignancies and the detection of clinically or radiologically suspected recurrences. Because most malignancies exhibit increased glucose uptake and glycolytic metabolism, whole-body ^{18}F-FDG-PET can also provide information on tumor aggressiveness and is recognized as a procedure of choice for the evaluation of tumor response during the course of treatment [10, 40]. Beyond the imaging of glucose metabolism using ^{18}F-FDG, many other biomarkers have been labeled with positron and photon emitters for imaging specific mechanisms and targets. Here, we provide a few examples. It has been demonstrated in many types of cancer that ^{18}F-FLT uptake in vivo is a measure of tumor proliferation. The uptake of ^{11}C-methionine was found to be proportional to the amino acid transport and, to some extent, to protein synthesis, so it correlates with the amount of viable tumor tissue [41]. ^{18}F-Fluoromisonidazole (^{18}F-FMISO) was the first nitroimidazole compound developed for hypoxia in tumors, but its slow cellular washout rate leads to the development of several alternatives, including ^{123}I-iodoazomycin arabinoside (^{123}I-IAZA) and ^{18}F-azomycin arabinoside (^{18}F-FAZA) [42]. Imaging of ^{11}C-choline that enters the phospholipid synthesis pathways allows for visualization of

malignant tumors through its increased uptake into cell membranes during duplication. The most promising for SPECT imaging is the artificial amino acid L-3-ido-α-methyl-L-tyrosine (IMT) labeled with iodine-123. In two clinical studies, uptake of this tracer corresponded to Ki-67 proliferation marker and mitotic index in patients with gliomas [43].

Selection of optimal therapy

Currently, image-guided therapies attract a lot of attention, due to advances in both minimally invasive surgical procedures and to developments in imaging modalities. The integration of metabolic and anatomical information obtained with PET/CT allows identification of the hypermetabolic subregions of CT tumor volume and allows to determine the optimal biopsy trajectory [44]. Radiation therapy has relied heavily on imaging technologies to identify both malignancies to be irradiated, as well as the critical normal tissues to be avoided. However, several issues still need to be resolved. For instance, segmentation of the PET signal is highly operator dependent, which affects interpretation of the PET images. Studies presented by Schinagl et al. clearly indicated that the interpretation of ^{18}F-FDG uptake strongly depends on the PET segmentation tool. Thus, PET should not be used yet for defining the tumor volume in routine clinical practice [45]. In a personalized therapeutic approach, PET can provide information about the target presence by using mAbs as tracers. In this case, patients who could benefit most from expensive mAb-based therapies might be selected, and treatment schedules, adopted to improve the efficacy of therapy and to predict potential toxicity. mAb imaging might provide this information in an efficient and safe way. Thereby, molecular imaging can provide a real-time information about target status.

In current practice, the target presence is confirmed on biopsy of the tumor by ex vivo methods. However, it is questionable whether a representative overview of the level of receptor expression can be obtained by analysis of just one single biopsy, especially considering the heterogeneity of tumor tissues. This is a case particularly in patients with metastatic disease, where receptor status can also be different in primary tumors and in metastatic lesions, and dramatically changes during the course of the treatment [46, 47]. Therefore, it seems worthwhile to evaluate the receptor expression by noninvasive and quantitative imaging methods.

Treatment planning

Many centers investigate the application of multimodality molecular imaging for optimization of radiation therapy and for developing an individualized approach to the treatment that would take into account the radiosensitivity of individual tumors and would monitor their response to radiation. During radiotherapy planning, ^{18}F-FDG-PET/CT has been shown to be useful to better delineate the biologically active tumor volume and to distinguish between viable tumor tissue and nonspecific changes due to surgical and/or radiotherapeutic treatments. There are also several potential molecular markers that can predict tumor radiosensitivity. For instance, it is known that hypoxia creates resistance to radiation and induces an aggressive cancer phenotype [48]. Therefore, the hypoxic parts of the tumor need to be exposed to a higher radiation dose. In the future, the presence of tumor hypoxia may be an indicator for the concomitant use of agents that target hypoxic pathways; a number of these agents are under development. ^{18}F-fluoromisonidazole (FMISO) is the most extensively studied hypoxic PET radiopharmaceutical that has been used to quantitatively assess tumor hypoxia in lung, brain, and head-and-neck cancer patients and in the hearts of patients with myocardial ischemia [49]. Because of high lipophilicity, slow clearance kinetics, reaction mechanisms, low uptake in hypoxic cells, and the absence of active transport of this radiotracer, the identification and quantification of hypoxic tumor areas necessitate imaging for longer periods of time postinjection. Therefore, several other analogs, such as ^{18}F-fluoroerythronitroimidazole (FETNIM), ^{18}F-fluoroetanidazole (FETA), and 1-(5-[^{18}F]Fluoro-5-deoxy-D-arabinofuranosyl)-2-nitroimidazole (FAZA), have been developed with more favorable pharmacokinetics [50]. FETNIM is more hydrophilic than FMISO and shows promise for hypoxia imaging in humans. It has been also reported that FAZA displayed a hypoxia-specific uptake mechanism and provided tumor-to-background ratios superior to that of the standard hypoxia tracer FMISO [26, 51].

A variety of radiolabeled RGD peptides for PET and SPECT have been developed for planning treatments targeting αvβ3 integrin [52]. Even though the most studied is the ^{18}F-galacto-RGD for PET, the ^{99m}Tc-RGD derivatives are also considered to be good candidates. ^{9m}Tc-NC100692, a cyclic peptide containing the RGD motif showed efficient αvβ3-integrin targeting and can be safely administrated into patients for detection of αvβ3-positive tumors [53].

Assessment of tumor response

Currently, the better understanding of tumor biology allows us to identify targets involved in tumor proliferation, invasion, and metastases that are addressed by newly developed therapies, which in most cases are very expensive and have substantial toxic effects. Therefore, it is very important to have tools that help to identify these patients who might benefit from particular treatment at an early stage of disease. Evaluating tumor response based on the measurements of tumor volume using conventional tools like CT sometimes may provide inaccurate results, since changes in tumor volume do not occur

early enough, and there are some instances tumors that even grow initially in spite of responding to the treatment. Nuclear medicine methods allow imaging and provide quantified information about tumor function and therefore offer excellent surrogate markers of early response assessment. Again, the most frequently used tracer is ^{18}F-FDG.

Targeted radionuclide therapy

Radioimmunotherapy (RIT) or TRT combines the advantages of radiation therapy and specific immunotherapy using mAbs. The antibody serves primarily as a delivery vehicle of radiation and has no significant effect on function. The therapeutic effect is achieved by tissue absorption of the energies from continuous, low-dose radiation emitted from the radionuclides tagged to mAbs. The exact choice of radionuclide used for RIT depends on the radiation characteristics of the nuclide, the radiolabeling chemistry, and the type of malignancy or cells targeted. Beta emitters, because of their lower energy and longer path length, are more suitable for targeting bulky, solid tumors, whereas alpha emitters and Auger emitters, with their high LET and short-distance energy deposition, are better suited for targeting single cells, as in micrometastatic disease, blood borne malignancies, and locoregional application [54]. RIT has been evaluated in clinical trials across the full spectrum of malignancies [55].

There are two different approaches that have been introduced into clinical practice including the use of direct conjugation of radioisotope tagged to mAb or pretargeting of the tumor. In the first case, the patient receives a diagnostic dose of an antibody labeled with a radionuclide compatible with an appropriate imaging modality (SPECT or PET). If the conjugate is stable and sufficient localization of an antibody at the site of disease is observed, the patient may be injected with a therapeutic dose, capable of inducing cytotoxic and potentially curative effects. This approach, however, has some limitations. First, radiation dose delivered to solid tumors might be insufficient due to poor penetration of the large-size radioimmunoconjugate. Moreover, rather long serum half-life of mAbs together with long decay time of the radioisotope increases the radiation exposure to normal organs and can contribute to bone marrow toxicity.

In a pretargeting approach, the radionuclide is administrated separately from the antibody vehicle. There are two strategies; one involves the administration of radioactive biotin for selective localization on antibody–streptavidin conjugates. This approach takes advantage of the rapid pharmacokinetics of the small biotin molecule and the high affinity of avidin–biotin binding. Alternatively, chelators of radioactive metals and multispecific antibodies that are capable to simultaneously bind to a tumor-associated antigen and to a metal chelator are used.

A number of antigens and receptors present on the tumor cell surface including CD20, PSMA, mucin 1 (MUC1), HER2, EGFR, tumor necrosis factor, as well as VEGF and $\alpha v\beta 3$ abundant on the vascular endothelial cells within newly developed blood vessels have advocated as potential targets for RIT in patients. However, currently, only two radioimmunoconjugates targeting CD20 have been approved for the treatment of non-Hodkin's lymphoma, i.e., ^{90}Y-ibritumomab tiuxetan (Zevalin®) and ^{131}I-tositumomab (Bexxar®). It has been shown that both radiolabeled mAbs are more efficacious at inducing remissions compared with the respective unlabeled molecules, including rituximab [56], and are also more effective than earlier courses of chemotherapy in these patients [57]. One hundred different clinical trials involving radioimmunotherapy are listed on the NIH website clinicaltrials.com. Table 4 presents summary of currently active phase II trials.

So far, the application of TRT for the treatment of solid tumors has been less successful than in patients with malignant lymphoma. There are several problems that have to be addressed in order to improve its efficacy [58]. First, the bulky tumors indicate usually lower radiosensitivity. Secondly, the delivery of therapeutic radionuclide to solid tumors might be less effective due to limited vascularization, elevated intratumoral hydrostatic pressure, and heterogeneous uptake of the radionuclide. Nevertheless, a recently completed global phase III clinical trial (ALSYMPCA) with radium-223 chloride (Alpharadin®) in patients with castration-resistant prostate cancer and bone metastases showed that these limitations can be successfully circumvented and nuclear medicine may became an effective treatment modality for disseminated solid tumors as well [59].

Future perspective

Modern oncology follows the general path towards individualized medicine. New molecular targets for therapeutic intervention are being discovered and validated. Development of reliable prognostic and predictive biomarkers associated with new targeted therapies is becoming a common practice encouraged by the regulatory agencies. Considering the unique noninvasive means for in vivo characterization of tumor tissue provided by nuclear medicine imaging, it is clear that it will play a crucial role in the future of oncology. The sensitivity and resolution of obtained images will be enhanced by the application of new targeting molecules, optimization of radiolabeling methodology, and technological advances of the scanners. The clinical utility of nuclear medicine will be further improved by introduction of standard quality assurance procedures facilitating reliable quantification of the observed phenomena.

Following successful application of therapeutic radiopharmaceuticals for the treatment of malignant lymphoma, nuclear

Table 4 Current phase II (efficacy testing) clinical trials

Official title	Number of patients	Latest update
Prospective multicentric optimization and phase I/II study of pretargeted radioimmunotherapy (PRAIT) using anti-CEA×anti-HSG TF2 bispecific antibody (bsmab) and 177Lu-IMP-288 peptide in patients with CEA-expressing small cell lung carcinoma (SCLC)	33	November 2011
A prospective non-randomized study of 131I-L19SIP radioimmunotherapy (RIT) in combination with whole brain radiation therapy (WBRT) in patients with multiple brain metastases from solid tumors	40	October 2011
Hematopoietic cell transplantation for patients with high-risk acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), or myelodysplastic syndrome (MDS) using radiolabeled DOTA-biotin pretargeted by BC8 antibody-streptavidin conjugate	30	September 2011
A phase I/II dose finding and efficacy study of the tumour targeting human 131I-F16SIP monoclonal antibody in patients with cancer	68	November 2011
Induction chemotherapy with TPF followed by radioimmunotherapy with cetuximab and intensity modulated radiotherapy (IMRT) plus carbon ion boost for locally advanced tumors of the oro-, hypopharynx and larynx: TPF-C-HIT	50	November 2011
A phase II trial of radioimmunotherapy (Y-90 M5A) following hepatic resection and FOLFOX chemotherapy for metastatic colorectal carcinoma to the liver	25	October 2011
Safety and efficacy of 90Y Zevalin in nonmyeloablative transplantation for lymphoid malignancies	70	May 2011
A phase I/II trial of radioimmunotherapy (Y-90 cT84.66), gemcitabine and hepatic arterial infusion of Fudr for metastatic colorectal carcinoma to the liver	30	January 2011
A pilot phase II study of sequential treatment with chemotherapy, radioimmunotherapy (Zevalin) a nd autologous hematopoietic stem cell transplantation in patients with follicular lymphoma	50	July 2011
A phase I/II trial of CpG 7909, rituximab immunotherapy, and Y-90 Zevalin radioimmunotherapy for patients with previously treated CD20+ non-Hodgkin lymphoma	63	August 2010
Phase I/II trial of yttrium-90-labeled daclizumab (anti-CD25) radioimmunotherapy with high-dose BEAM chemotherapy and autologous hematopoietic stem cell rescue in recurrent and refractory Hodgkin's lymphoma	95	October 2011
Phase II trial of yttrium-90-ibritumomab tiuxetan (Zevalin) radioimmunotherapy after cytoreduction with ESHAP chemotherapy in patients with relapsed follicular non-Hodgkin's lymphoma	52	June 2011
A phase II study of yttrium-90-labeled ibritumomab tiuxetan (Zevalin) radioimmunotherapy as first line treatment in indolent non-Hodgkin's lymphoma	28	July 2009
A study of I-131-tositumomab (Bexxar) consolidation in patients with B-cell chronic lymphocytic leukemia or small lymphocytic lymphoma in first remission	30	June 2011
A phase II study of R-FND, followed by Zevalin radioimmunotherapy, and subsequent maintenance rituximab for advanced stage follicular lymphoma with high-risk features	50	August 2011
A phase I/II study of I-131 tositumomab in patients with relapsed/refractory Hodgkin's lymphoma	30	April 2011
A multicenter, open Label, phase II study of bendamustine and rituximab followed by 90-yttrium (Y) ibritumomab tiuxetan for untreated follicular lymphoma	39	October 2011
A phase II, safety and efficacy study of fixed dose radioimmunotherapy (Zevalin, yttrium-90 ibritumomab tiuxetan) for patients with incomplete response to chemotherapy prior to autologous stem cell transplant for multiple myeloma	14	September 2011
A phase II study of allogeneic hematopoietic stem cell transplant for b-cell non-Hodgkin lymphoma using Zevalin, fludarabine and melphalan	46	September 2011
A prospective study with individually adjusted high dose 90Y-ibritumomab tiuxetan treatment with peripheral blood stem cells support to improve outcome for patients with refractory/recurrent b-cell lymphoma, stage II-IV	24	October 2011
A phase II trial evaluating the efficacy of radioiodinated tositumomab (anti-cd20) antibody, etoposide and cyclophosphamide followed by autologous transplantation, for relapsed or refractory non-Hodgkin's lymphoma	140	October 2011
Hematopoietic bone marrow transplantation for patients with high-risk acute myeloid leukemia (aml), acute lymphoblastic leukemia (all), or myelodysplastic syndrome (mds) using related hla-mismatched donors: a trial using adiolabeled anti-cd45 antibody combined with immunosuppression before and after transplantation	50	November 2011
Dose-intensive chemotherapy combined with monoclonal antibody therapy and targeted radioimmunotherapy for untreated patients with high-risk b-cell non-Hodgkin's lymphoma	35	June 2011
Phase II trial of low-dose methotrexate and iodine i 131 tositumomab for previously untreated, advanced-stage, follicular lymphoma	61	August 2011
Phase I/II study of combination veltuzumab (anti-cd20) and fractionated 90Y- epratuzumab (anti-cd22) radioimmunotherapy in patients with follicular lymphoma	20	October 2010
A phase 2 study of inotuzumab ozogamicin (cmc-544) in subjects with indolent non-Hodgkin's lymphoma (NHL) that is refractory to or has relapsed after rituximab and chemotherapy or radioimmunotherapy	80	November 2011

medicine is on the way to become a part of mainstream oncology. As indicated by the success of the recent clinical trial in patients with castration-resistant prostate cancer and bone metastases and the ongoing preclinical efforts, it is also a promising therapeutic modality for treatment of disseminated solid tumors. Particularly promising in this regard might be utilization of the antibodies that are being developed for interfering with cell signaling pathways such as trastuzumeb, pertuzumab, or cetuximab. These biological therapeutics, although initially effective in a selected patient populations, become useless after the targeted tumors develop resistance. Assuming that the target molecules are still expressed in the tumor, the same antibodies might be used for targeted delivery of therapeutic radionuclide extending their application. However, more efforts are needed in order to fully utilize the potential of targeted radiation therapy, including improvement of labeling methods, identification of an optimal choice of a radionuclide or mixture of radionuclides to treat individual tumor types, combination of TRT with more conventional treatment modalities, and application of new treatment planning strategies to properly adjust the administered dose of radiotherapeutics and the treatment schedule, which will improve its safety and efficacy.

Conclusion

Nuclear medicine offers a unique capacity to improve the outcome of cancer treatment by providing means to optimize the treatment of individual patients by characterization of tumor physiology and its early repose to therapy as well as complementing the standard therapeutic approaches with targeted, systemic radiotherapy capable of delivering cytotoxic radiation dose not only to the tumor bulk but also to spread metastatic disease including undetectable micrometastases. Although the routine application of nuclear medicine in oncology is currently mainly limited to ^{18}F-FDG scans, an increasing amount of data indicate that, in the near future, it will be used widely to facilitate cancer diagnosis, augment the treatment, and improve the outcome of therapeutic interventions.

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