Chapter

Theranostics: New Era in Nuclear Medicine and Radiopharmaceuticals

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Abstract

Malignancy and many inflammatory diseases have become a major concern for mankind over the years. The conventional therapy of these diseases lacks the effectiveness of the better diagnosis and targeted treatment of these diseases, but nuclear medicine can be regarded as a savior in the current scenario. Over the years, radioactivity of radioisotopes has been employed for treatment of many diseases. Nuclear medicines came up with radiopharmaceuticals that impart the ability to destroy specific diseased cells with high-energy-emitting radionuclides. Moreover, the emergence of theranostics, which is a combination of single drug used both for diagnostic as well as therapeutic purpose, has added a new feather in the field of nuclear medicines for providing a specific and personalized treatment to the patient. The current chapter discusses about techniques used for imaging of these radionuclides for better therapy and diagnosis of the root cause of the concerned disease by positron emission tomography (PET)/CT and single photon emission computed tomography (SPECT)/CT as well as the advantages and disadvantages associated with them. It also describes about applications of theranostics and nuclear imaging in cancer treatment and their future perspective.

Keywords: radionuclides, nuclear medicines, nuclear imaging, theranostics, radiopharmaceuticals

1. Introduction to radioisotopes and radiopharmaceuticals

Scientist has discovered that earth contains many elements with varying configuration. These elements with varying configuration are called isotopes. Isotopes are atoms with same atomic number with varying atomic weight. Isotopes can be divided into two parts depending on the ability to emit radiation. One that does not emit radiations is called stable isotopes and other are called unstable isotopes. Unstable isotopes emit radiations to achieve a more stable configuration. These are called as radioisotopes. Instability of radioisotopes is due to presence of unstable combination of neutron and proton in their atoms and nucleus contains excess of energy. This characteristic of radioisotopes can be natural or instability can be created artificially by changing the atoms. Naturally radioisotope is uranium-238 and it accounts to 0.7% of total naturally occurring isotopes. Artificial radioisotopes are fluorine and molybdenum which are produced artificially by using cyclotrons and nuclear reactors respectively. Presently there are

around 3800 radioisotopes out of which 200 radioisotopes are being used. Among the isotopes that are used most of them are of artificial origin. Artificial radioisotopes are primarily made by two methods as mentioned above i.e. through nuclear reactor and by cyclotron. By nuclear reactor neutrons are introduced into the nucleus of atom whereas in case of cyclotron proton are introduced. To become stable radioisotopes emits alpha or beta particle along with electromagnetic radiation of gamma rays. This phenomenon is called as radioactive decay. These radioisotopes have variety of uses, when they are used in the field of pharmaceuticals they are termed as radiopharmaceuticals.

1.1 Radiopharmaceuticals

These are radioactive medicines that can be given by oral, intravenous or interstitial route to treat or diagnose malignancy. Administration of these drugs is done in the presence of specialist called radio pharmacist. These radioactive medicines have the ability to destroy cancerous cell by emitting radiation when it reaches its target cell. Radiopharmaceuticals for treatment and diagnosis of cancers associated with thyroid, brain, bones or lymphoma already been discovered.

In addition to treatment radiopharmaceuticals are also used for the purpose of diagnosis. The drugs used for diagnosis are called as tracers. The radiation of diagnostic radiopharmaceuticals is smaller as compared to radiation emitted by radiopharmaceuticals used for treatment. Radiopharmaceuticals are either single isotopes or sometimes the isotopes are combined with a kit [1]. The kit is prepackaging of ingredients which are sterile and are meant for preparation of radiopharmaceuticals. They are combination of substances such as antioxidant, buffer, reductant and ligands that are when combined with the radioisotopes produces the resultant product. Kits are very beneficial as they are not in contact with the outer environment so there is no chance of any contamination [2].

1.2 Technetium 99m

The isotope that is used for the purpose of labeling of kits used for diagnosis is technetium 99m abbreviated as 99mTc (**Figure 1**). It radiates only gamma radiation that is compatible with gamma camera. 99mTc also has the property of binding with the tracers. Advantage of technetium is that it has smaller biological half-life and better renal clearance for the unabsorbed radiopharmaceuticals that helps in getting a better quality of image from the absorbed ones. The dose of technetium depends on the kit, the organ on which it has to be used for imaging and on the test to be performed [3]. Determination of dose for children is very crucial as the cells

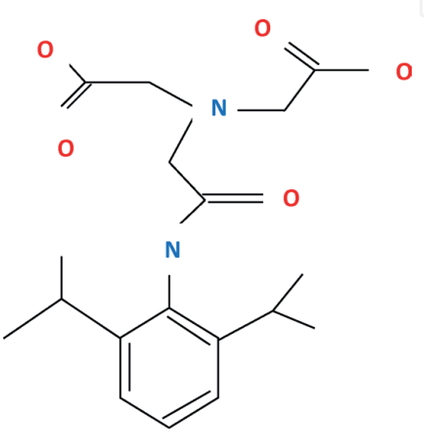

Figure 1.
Chemical structure of technetium 99m.

are in dividing states so sensitivity towards radiation can be higher, organ size body ratio also varies to greater extent in comparison with adult. So in case of children a balanced level of administration is required [4].

Different kit labeled with 99mTc used for imaging of different organs is mentioned below.

1.2.1 Bone

For detection of the areas that are metabolizing the bones kits with bisphosphonates are used. Scan of bone is done by injecting radiopharmaceuticals into the peripheral vein of patient and then after 3 h imaging is done so that within the three hours the bisphosphonates will get incorporated into the osteoblast cells.

1.2.2 Kidney

For the imaging of kidney, there are three radiopharmaceuticals, namely

i. Radiolabelled mercaptoacetyltriglycine (Mag-3; mertiatide)

ii. Radiolabelled diethylenetriaminepentaacetic acid (DTPA; pentetate)

iii. Radiolabelled dimercaptosuccinic acid (DMSA; succimer

Mag-3; mertiatide is used for the purpose of determining the blood flow to the kidney and for graphically presenting the renal function. Mag-3 has a clearance of 94% after 3 h that helps in getting better quality of image and the exposure of patient to the radiation is also lower. DTPA; pentetate is used to determining rate of glomerular filtration during chemotherapy of kidney. Lastly DMSA; succimer is used a tool for studying morphology of renal cortex and ectopic kidney.

1.2.3 Brain

Kit used for the check the blood flow within the brain after conditions like epilepsy, migraine or Alzheimer's disease or stroke of brain contains 99mTc-labeled exametazime. This is product of lipophilic origin without any charge on it and it penetrates better through blood brain barrier. It takes around one minute after injection for it to reach brain and up to 7% reaches the brain.

1.2.4 Heart

For cardiac imaging, two 99mTc-labeled are tetrofosmin and sestamibi which are employed to ascertain the degree to which myocardial infarction is severe and also help to point out the regions of cardiac ischemia. Images are collected at the state of rest and after stressed activity of cardiac cells. This injection are administered when patient must have consumed any kind of fatty meal. This helps in hepatobiliary clearance of administered radiopharmaceuticals thus aid in getting better image. But it should not be administered when patients has consumed some drugs such as nitrates or calcium channel blockers.

1.2.5 Lungs

In case of lungs scan it is used for the purpose of diagnosis of any kind of embolism in pulmonary tract. Lung scan be of two types perfusion scan or

ventilation scan. First, one 99mTc-labeled macroaggregated albumin is injected in the peripheral vein, which is then carried to the pulmonary artery system. It does not get absorbed rather it gets distributed evenly in the capillary bed and helps in diagnosis. Where blood flow is good there will be larger number of particles giving out radiation, whereas where there will less perfusion then less particles will be seen.

In case of ventilation scan, patient is made to inhale radioactive substance such as krypton or 99mTc-labeled DTPA aerosol. Image is obtained where air is seen circulating in lungs [5].

1.3 Adverse reactions

The most common adverse reaction associated with radiopharmaceuticals is sweating, nausea, dry mouth and rashes.

2. Recent approaches of injectable radiopharmaceuticals as nuclear medicine for imaging and therapy

The aim of this chapter is to explain about advancements the injectable of biomaterials or radiopharmaceuticals origin used in molecular imaging, therapy and clinical diagnosis. On the basis of intrinsic radiation form, radioisotopes can be divided into following type namely gamma (γ) ray emitters, beta (positron β+ or electron β−) particles emitters and alpha (α) particles emitters or their combinations. In clinical practice and pre-clinical animal studies, mostly used radionuclides are gamma ray emitters like Technetium-99m (99mTc), Iodine-123 (123I) and Galium-67 (67Ga), Positron-emitting radionuclides namely Fluorine-18 (18F), Oxygen-15 (15O), Carbon-11 (11C) and Zirconium 89 (89Zr). Some β-emitters are Rhenium-186/Rhenium-188 (186Re/188Re), Strontium-89 (89Sr), and Yttrium-90 (90Y). Examples of therapeutic α-emitters are Actinium-225 (225Ac), Bismuth-213 (213Bi) and Astatine-211 (211At) [6]. The injected radiopharmaceuticals can be in simple ionic form or in carrier complex form. Carrier complex has better targeting ability for certain tissues and cells and pathways of disease. These are some radioisotopes used for imaging are as follows (**Table 1**):

Organ	Isotope used/activity
Brain	In-113m/7–10 mCi
Kidney	Hg-197/150 mCi
Lungs	Tc-99/1 mCi I-131/0.15–0.3 mCi In-113/1 mCi
Spleen	Cr-51/0.3 mCi
Bone	Sr-85/0.1 mCi Sr-87/1 mCi F-18/1 mCi
Pancreas	Se-75/0.2 mCi
Placenta	Cr-51/0.05 mCi Tc-99/0.5–1 mCi

Table 1.
Radioisotope imaging [7].

In case of imaging, the major focus was development of 11C, 18F or 68Ga radiopharmaceuticals to be used in positron emission tomography (PET) and 99mTc-labeled agents for the used in single-photon emission computed tomography (SPECT) [8]. The merits associated with nuclear medicine are many such as it is noninvasive, it gives better in identifying exact region of tumor and beneficial for diagnosis of challenging diseases [9, 10]. In addition to this there is better quantitative analysis which is achieved with a numerous tools available. For example standard uptake values (SUVs) are taken in PET and in case of SPECT it is compared in vivo distribution of the injected materials [11]. There are some common nuclides mentioned in **Table 2** which are used in radiation therapy are:

Nuclide	Radiation	Half-Life	Treatment
32P	B	14.3 d	Leukemia therapy
60Co	β, γ	5.3 yr	External cancer therapy
123I	Γ	13.3 yr	Thyroid therapy
131Cs	Γ	9.7 days	Prostate cancer therapy
192Ir	β, γ	74 d	Coronary disease

Table 2.
Radiation therapy [12].

This content focuses on the developments in field of imaging technology in relevance to imaging of radionuclide therapy.

2.1 SPECT and scintigraphy

This type of decay of radionuclides determines about the modality for imaging. Planar scintigraphy or SPECT is used for imaging of ^{177}Lu, ^{90}Y, and ^{131}I-which are used for radionuclide therapy. These emit γ-photons (or bremsstrahlung photons), which can be imaged by a γ-camera.

2.1.1 Current status

SPECT/CT systems which are used nowadays are used for both planar and tomographic imaging. Planar imaging is for acquiring whole-body images in when there is limitation of time. SPECT is meant for acquiring 3-dimensional data of structures which would otherwise overlap on each another on planar images.

Quantitative analysis of SPECT images is determined by converting the acquired counts in terms of distribution of absorbed dose (in Gy), which is beneficial for planning and dosimetry of therapy involving radionuclide. In clinical practice scatter correction is also implemented and is generally performed employing the triple-energy window method [13]. Quality of image can be enhanced by using resolution recovery. It is performed by characterizing the shape of the point-spread function accurately, that depends its distance from the camera and there is rotational variation due to the hexagonal pattern of the collimator septa. Reconstruction algorithm can be incorporated with point-spread function model subsequently [14].

Effects like scatter, blurring and attenuation which degrades image can be corrected to some extent, Although SPECT images can be degraded by partial-volume effects and quantification errors.

2.2 PET

^{18}F-FDG PET is used for many PET studies that are in the field of clinical practice and is employed for staging and follow-up post radionuclide therapy.

However, PET has application in planning of treatment, dosimetry, and assessment of treatment after radionuclide therapies.

2.2.1 Current status

Similar to SPECT quantitative PET is also used for correction techniques. Correction of attenuation for PET can be done through determination of the sonogram associated with attenuation correction, which works on the basis of co-registered CT data. Scatter correction is often done with single-scatter simulation method in clinical practice [15]. Correction for random counts is often done using delayed-event subtraction [16].

The difference in time between annihilation photons gives information regarding location of the annihilation and also about the line of response. Now time-of-flight information in the reconstruction at the time of back projection step enhances image quality. The availability of time-of-flight estimation has opened the opportunities for low positron abundance imaging isotopes like ^{90}Y.

As intrinsic resolution of PET detectors are not freely available, so shape of the point-spread function is used to improve the quality of images by incorporating it during reconstruction method. This is called as resolution recovery.

When there are high count rate radiation detection systems does not work properly due to dead-time effect caused by pulse pile-up. Because of these Dead-time losses are corrected regularly.

2.2.2 Advances

There are better quality of PET images with enhanced resolutions and sensitivity due to regular improvement in the instrument which provides precise determination of the SUV [17].

2.3 PET/MRI

The advantages of PET/MRI over PET/CT are higher soft-tissue contrast that is essential for planning of treatment, dosimetry, and assessment post radionuclide therapies. Additionally, for accurate dosimetry it is beneficial as it provides the simultaneous coregisteration of MR images. Also, MRI can be employed for determining the tolerable dose with least organ damaging activity of radionuclide. Along with it anatomic and molecular images acquisition provides better motion correction.

Integrating of PET and MRI modalities is challenging as there will be interference between both the modalities. For instance, photomultiplier tubes that are present in PET detectors malfunction in magnetic fields exerted by MRI. In addition to this, PET module affects the radiofrequency signal associated with MRI [18]. Due to this, the first generation of PET/MRI systems modalities were separated. Integration of PET detectors and MR scanner has been done to obtain PET and MR images simultaneously. Detector systems is avalanche photodiodes types or SiPMs types which are not sensitive to magnetic field. The simultaneous measurement provides better 4-dimensional acquisitions because of spatial agreement of PET and MRI data.

Disadvantages associated with PET/MRI are high costs and the ferromagnetic metallic implants which are used is contradictory to MRI. In addition to this it's challenging to correct attenuation of PET/MRI. For dosimetry it is essential to have accurate attenuation correction. As CT images are electron-density images and MR images are proton density image, CT image are better suited for attenuation

correction. But MR images can be used for attenuation correction by using techniques such as segmentation-based or template- or atlas-based which derives electron density information from MR images [19]. Alternatively, estimation of the attenuation maps can be done by employing algorithms which uses the time-of-flight emission or transmission data [20].

2.4 Future perspectives

2.4.1 Simultaneous X-ray and nuclear imaging

Till today there are no real-time hybrid imaging modalities that can merge nuclear and anatomic for interventional purposes. Fluoroscopic imaging in combination with real-time nuclear imaging gives physicians with valuable information during procedures like as ^{90}Y liver radio embolization by image distribution of the radionuclide in association with the anatomy and the interventional instruments that enhances therapeutic efficiency. Image of same field can be seen by arranging X-ray tube, an X-ray detector, and a γ-camera in a single line [21].

3. Different types and applications of radioisotopes for imaging and therapy

S. no	Radioisotopes	Uses
1.	Calcium-47	Important aid to biomedical researchers studying cellular functions and bone formation in mammals
2.	Caesuim-137	Used to treat cancerous tumors and to measure correct dosages of radioactive pharmaceuticals
3.	Chromium-51	Used in research in red blood cells survival studies
4.	Cobalt-57	Used as a tracer to diagnose pernicious anemia
5.	Cobalt-60	Used to sterilize surgical instruments and used in cancer treatment, food irradiation and radiography
6.	Copper-67	When injected to monoclonal antibodies into a cancer patient, helps the antibodies bind to and destroy the tumor
7.	Gallium-67	Used in medical diagnosis
8.	Iodine-123	Widely used to diagnose thyroid disorders and other metabolic disorders including brain functions
9.	Iodine-125	Major diagnostic tool used in clinical test and to diagnose thyroid disorders. Also used in biomedical research
10.	Iodine-129	Used to check some radioactivity counters in in-vitro diagnostic testing laboratories
11.	Iodine-131	Used to treat thyroid disorders (Graves' disease)
12.	Iridium-192	In brachytherapy/tumor irradiation
13.	Phosphorous-32 and Phosphorous-33	Used in molecular biology and genetics research
14.	Technetium-99m	Most widely used radioactive pharmaceutical for diagnostic studies in nuclear medicine. Different chemical forms are used for brain, bone, liver, spleen and kidney imaging
15.	Uranium-234	Used in dental fixtures like crowns and dentures to provide a natural color and brightness
16.	Xenon-133	Used in nuclear medicine for lung ventilation and blood flow studies

3.1 Applications

Applications of different radioactive isotopes in nuclear medicine are [22]:

- Cobalt-60 is used in radiation therapy for prevention of cancer.
- Iodine-131 has been used for locating brain tumors, monitor activity of cardiac, liver and thyroid cells.
- Carbon-14 used for determining metabolic changes happening in patients of diabetes, gout and anemia.
- Carbon-11 is used to monitor organs during PET scan by tagging it into glucose.
- Thallium-201 has been in use for determining damage in heart tissue, detection of tumors.
- Technetium-99m act as radiotracer in medical diagnostics for obtaining the image of organs and study of blood flow. It also crucial for locating brain tumors and damaged heart cells [23].

4. Advantages and disadvantages of injectable radiopharmaceuticals

4.1 Properties of all radiopharmaceutical injectable

1. It should be sterile and free from Pyrogens. Sterility means absence of any living things even the spores or any related substances that can develop into something living. Culturing samples with special growth media is most common way to perform the assessment of sterility. Pyrogens are endotoxins that have the ability to cause pyrexia. They cannot be destroyed by autoclave and cannot be filtered. Testing for Pyrogens can be tested by using the rabbit test or the Limulus amebocyte lysate (LAL) test.

2. The isotonicity of injectable drug should be equal to 0.9% NaCl solution, and the pH should be 7.5.

3. In case of radioactive substance dose calibration should be done and it should be within ±10% of the prescribed dose. This calibration provides assurance that dose is as low as possible and it gives high quality image.

4.1.1 Advantages

- It is used for diagnosis and treatment of patients.
- It is commonly used to cure to cancers and can treat many other sites of disease.
- Treats tumor such as bone metastasis.
- Provide faster onset of relief from pain.
- Single dose is effective for some patients.
- Tests of nuclear medicine can be done on children.

- Nuclear medicine procedure less costly and painless.
- Nuclear medicine procedures are safe with no side effects [24].

4.1.2 Disadvantages

- Some allergic reactions can be seen.
- Risk of radiation is associated.
- Myelosuppression may occur before chemotherapy.
- Prolonged in convenience and discomfort can be experienced by patients due to administration of multiple fraction.
- Nuclear medicine tests cannot use for pregnant women because of potential risk to unborn babies.

5. Theranostics

Theranostics is a combination of two words **Thera**peutics and diag**nostics**. This is an emerging field of medicine where drugs and/or techniques are used in combination for treatment as well as treatment. It's a game changer as it provides diagnosis as well as therapy in single combination. It is economical as well as less time consuming. It uses PET scan to target tumor receptors which are present in tumor cell. If it is found in the cells radioactive drug is used to treat it. There are not much clinical trials found related to use of application of theranostics in prostate cancer by Australian Medicines Regulator—The Therapeutic Goods Administration (TGA) [25] (**Figure 2**).

5.1 Theranostics: Nuclear Medicine Imaging

The Nuclear Medicine Imaging approach is revolutionized by use theranostics [targeted therapeutic (Rx) + companion diagnostic (DX)] to establish tools for specific molecular targeting. It provides personalized treatment plan for the patient by targeting specific targets. Various department of nuclear science can utilize theranostic agents [26].

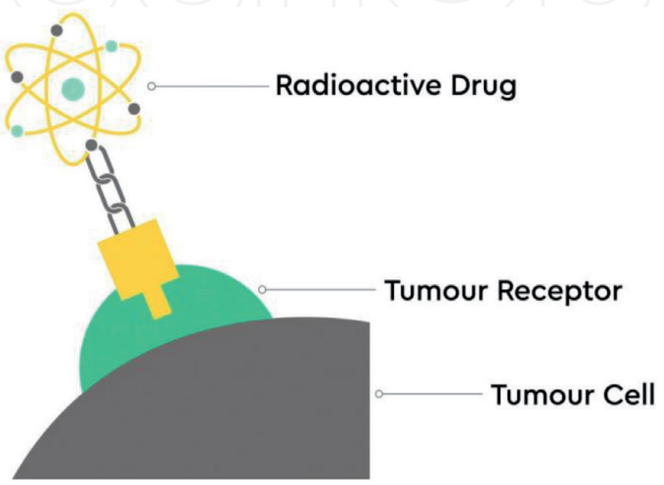

Figure 2.
Theranostics working on tumor cell.

5.2 Therapeutic bullets

Theranostics takes advantage of biological pathways specific to any system of human body to acquire diagnostic images. These images enhances the probability that the targeted therapeutic dosing of radiation that will only target disease part sparing the healthy one.

5.3 Nuclear Medicine Imaging

In past 100 years a similar kind of model for neuroendocrine tumors has been developed that has used radionuclide gallium-68. This PET radiotracer has been chelated to DOTA-octreotate and used for diagnosis of tumor with higher sensitivity compared to Indium-111 octreotide imaging.

The disease of patients can be determined by using the gallium-68 DOTA-TATE for targeting the somatostatin receptor volume and having image using hybrid scanner like PET-CT (Positron Emission Tomography-Computer Tomography). Lutetium Octreotate Therapy is a radiopharmaceuticals which emits beta radiation is available in 5 medical centers in north America and European medical centers [27].

Some of the milestones in the field of theranostics becoming personalized medicine are as follows:

- Lutetium PSMA therapy for metastatic or treatment-resistant prostate cancer
- Yttrium-90 SIRT therapy for liver cancer
- Iodine-131 therapy for thyrotoxicosis and thyroid cancer
- Radium-223 therapy for metastatic prostate cancer in bones
- Yttrium-90 radiosynovectomy therapy for inflammatory synovitis of joints

Theranostics targeted therapy is difficult in case of cancer treatment due to heterogeneity of cancer cells. Ibritumomab a monoclonal antibody detects B-cells and produces the beta/alpha-emitting radiometal for destroying the lymphoma. SPECT imaging confirms distribution of antibody in the body. The indium-111 combined with radionuclide yttrium-90 transports beta particles for killing the B-cells [28] (**Figure 3**).

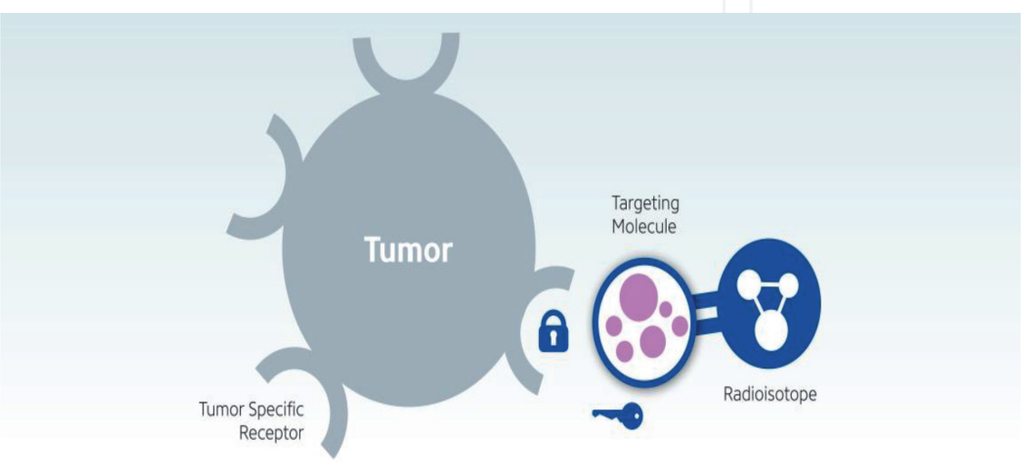

Figure 3.
Theranostics in cancer targeting and treatment.

5.4 Theranostics: Zevalin therapy

Zevalin therapy is used for determining the indications for relapsed or refractory, low-grade or follicular, B-cell non-Hodgkin's lymphoma. Zevalin is FDA approved for the treatment of relapsed or refractory low-grade follicular. In the year 2008 Zevalin was approved as the first-line drug for follicular lymphoma in the European Union.

5.4.1 Characteristics

5.4.1.1 Diagnostic component

The diagnostic component contains radiotracer, a contrast agent molecule, and a particulate system with either inherent physical property like optical, magnetic property or an acquired physical property such as, contrast enhanced ultrasound property or combinations of both. Combination systems exhibits dual functions like oximetry and detection in cellular and molecular imaging [29].

5.4.1.2 Therapeutic component

The therapeutic component includes drug molecule that is associated with diagnostic component or carrier system. Examples of the former are radiotracer-labeled non-peptide like gallium-68-labeled bisphosphonates for osteoblastic bone metastases and peptide-based molecules such as gallium-68-labeled somatostatin analogs for somatostatin receptor which targets neuroendocrine tumors. Examples of therapeutic components associated with a carrier system are where integrated entities are attaches to macromolecular carrier covalently. In addition to this, drug molecules co-encapsulation is done with diagnostic components such as chelated radiotracers and gadolinium (III), quantum dots, gold nanoparticle into particulate carrier systems namely polymeric nanospheres, liposomes, polymersomes, and mesoporous silica nanoparticles.

5.5 The application of theranostics in cancer

Cancer is a serious condition of heterogeneous group of diseases where there is uncontrolled and rapid cell growth. This is because of changes at genetic and/or epigenetic level in patient's body. Current treatment for cancer is chemotherapy, radiotherapy, immunotherapy and surgery.

Chemotherapy is not that much useful as a very low level of concentration of drug reaches the tumor. Moreover there is chances development of resistance during treatment and associated side effects. For example, chemotherapeutic agents known as taxanes have emerged as one of the most powerful classes of compounds to combat cancer, exhibiting a wide range of activity. The tubulin/microtubule complex has been proven to be a clinically useful antitumor target. The examples of chemotherapeutics that act *via* perturbation of tubulin polymerization include paclitaxel (Taxol®), docetaxel (Taxotere®), vinblastine, and discodermolide. First, docetaxel is a semi-synthetic derivative of paclitaxel. Next, vinblastine, unlike the other three compounds that all stabilize microtubules, aggregates tubulin and leads to microtubule depolymerisation. Randomized clinical trials evaluating docetaxel and paclitaxel in a first-line treatment setting for metastatic breast, lung, ovarian, and digestive cancers, as well as in the adjuvant setting for breast cancer, have confirmed that taxanes are leading contributors to the armamentarium of cancer treatments. Paclitaxel is used as a first-line chemotherapy treatment for NSCLC, but patients' acquired resistance becomes a critical problem.

Here nanomedicine is better as it allows molecular targeting to get higher concentrations of drug molecules at targeted site. Studies have been to make sure that required amount of drug reaches the site actively or passively which ensures better therapeutic index.

Few examples of nanomedicine in this context are polymeric micelles, polymer-drug conjugates and liposomes. Whereas traditional small molecular drugs n get eliminated from bloodstream quickly but nanomedicine possess longer half-lives.

Furthermore there is enhanced bioavailability and augmented tumor delivery. In addition to it integration of imaging and nanomedicine helps as diagnostic arm of theranostics. The advantages of using such strategy are immense, that will assist in management of oncogenic conditions with the help of theranostics [30].

Applications of theranostics in medicine include:

- It is a noninvasive molecular imaging method to evaluate of disease heterogeneity.
- Gives better idea about biodistribution and about accumulation of drug at target-site.
- Better understanding of process of local drug release.
- Facilitation of drug release (through application of stimuli-responsive theranostics).
- Prediction of drug responses and associated adverse effects with personalized therapies [31].

6. Health and safety

Radiopharmaceuticals are as safe as other medicine and before use they are tested carefully.

- The quantity of the pharmaceutical part of the radiopharmaceutical is very small, generally 1/10th of a millionth of an ounce. The risk of a reaction is 2–3 incidents per 100,000 injections, over 50% of which are rashes as compared to 2000–3000 per 100,000 injections of X-ray contrast media.
- For childrens most radiopharmaceuticals, the amount of radiation used for a diagnostic test is very low and considered safe [32].
- Radiopharmaceuticals usually are not recommended for use during pregnancy. This is to avoid exposing the fetus to radiation. His is specially important with radiopharmaceuticals that contain radioactive iodine, which can go to the baby's thyroid gland and in high enough amounts may cause thyroid damage.
- Although exposure to the radioactivity in very large doses can be harmful the radioactivity in radiopharmaceuticals is carefully selected by the nuclear medicine physician to be safe.
- If anybody will be receiving albumin in the form of radioiodinated albumin, technetium Tc 99m albumin aggregated, technetium Tc 99m albumin colloid,

or technetium Tc 99m albumin for test, Consult doctor if have ever had any unusual or allergic reaction to products containing human serum albumin [33].

- Side effects: when radiopharmaceuticals are used in very small doses to study an organ of the body, side effects are rare and usually involve an allergic reaction. These effects may occur almost immediately or a few minutes after the radiopharmaceutical is given.

7. Conclusion

In recent past radiopharmaceuticals made steady progress towards nuclear imaging and therapy. The benefit of molecular imaging and therapy can obtain when required amount of diagnostic probes reaches the targeted site. Effort have been taken in enhancing specificity of targeted radiotracers in both pre-clinical research and clinical trials. In recent discussions the advancement in the said field has been discussed taking into account multi-modal molecular imaging probes for sentinel lymph node mapping and image-guided surgery, radiotracers for targeted imaging of cancer and neurodegenerative diseases, along with probes for monitoring therapy responses. For better diagnosis and therapy design of radiopharmaceuticals as well as route of administration plays a major role. At last dose of radioactive medicine should be set with caution to prevent over exposure of patient, the principle of 'As Low as Reasonably Achievable' (ALARA) used for protection of employee as well as general public. The knowledge about medical physics is essential because of interactions between ionizing radiation and biological tissues. According to author we can be optimistic for the future growth of radiopharmaceuticals. This trend can be seen in recent future with the help of thriving research and fast translations into clinic. The high cost, demanding hardware requirements and specialized personnel training are major factors that may confine the development of radiopharmaceuticals. However, the huge needs for nuclear medicine from the public and the benefits to patient care far outweigh the risks.

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