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LETTERS

Recent advances in Targeted Radionuclide therapy for Cancer treatment

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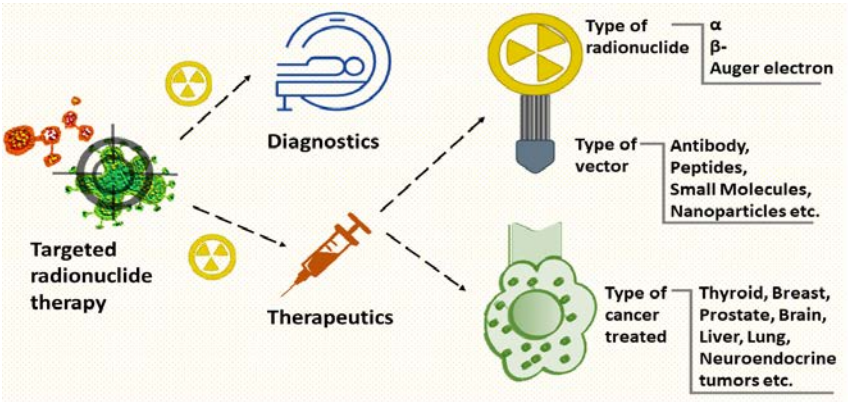
Review

ABSTRACT

In the last two decades, science has largely evolved in methodologies for cancer treatment, yet, the basic backbone of cancer treatment includes surgery, chemotherapy and radiation therapy. In oncology, radiation therapy was first used nearly a century ago but its basic principle is still in application, for example, radionuclide therapy (RNT) or targeted radionuclide therapy (TRT). TRT is effective in micro and macro metastasis and has an advantage due to low dose, high efficacy, easy targeting and treatment. The aim of this article is to review the radionuclides, components of a TRT agent i.e., different types of radionuclides, vectors and chelators and then descriptively highlight the therapeutic potential of TRT agents in the treatment of various types of cancers, namely, breast cancer, metastatic bone pain, thyroid cancer, neuroendocrine neoplasm, prostate tumors, malignant lymphoma, brain tumors, and hepatocellular carcinoma.



Keywords: Radionuclide therapy, targeted radionuclide therapy, radionuclides, oncology, cancer, treatment

INTRODUCTION

Cancer is one of the most challenging diseases, with an increasing prevalence each year, irrespective of the decline in its death rates since 1991 (a drop of 32%).[1] Unfortunately, predictive studies suggest that the graph of cancer prevalence is expected to accelerate further, which is an alarming concern for the future. It can be related to factors like an unhealthy lifestyle, exposure to hazardous carcinogenic materials, genetic changes, evolution, environmental concerns, etc. Effective cancer treatment remains a prominent concern due to cancer heterogeneity, drug resistance, tumor hypoxia, etc. The significant choices for cancer diagnostics are biopsy, computed tomography, and magnetic resonance imaging. They are invasive and do not provide information about tumor target sites. Similarly, the major options for cancer therapy include surgery, chemotherapy, hormone therapy, hyperthermia, immunotherapy, ionizing radiation therapy, photodynamic therapy, combinatorial therapy, etc. Amongst these therapies, surgery and external beam radiation therapy are the predominant treatment choices for primary and large tumors, while chemotherapy is utilized for disseminated tumors. However, these treatment choices fail to eradicate cancer in most cases and usually aim at palliative effects and prolonged life expectancy. Moreover, they have serious side effects related to mental health and quality of life.[2,3]

The goal of nuclear medicine is to first individualize the diagnostics and therapeutics associated to cancer and then employ the diagnostic and therapeutic principles together to overcome the hurdles in cancer treatment. One of these approaches is targeted radionuclide therapy (TRT). The principle of TRT is a modified version of various radiation therapies.[4] For example, external beam therapy uses photons, while TRT uses α or β- particle emissions. Moreover, external beam therapy focuses on brief high-energy radiation exposure, while TRT focuses on prolonged radiation exposures. Similarly, external beam therapy usually employs the same repeatable dose, while TRT uses a declining dose with time.[5] However, TRT is not an isolated treatment method but is used in combination with other therapies or treatments.

Over a hundred years ago, Paul Ehrlich described TRT as a "Magic Bullet" that finds its specific target and delivers the radionuclide to the target site to inhibit its function or destroy its activity. In principle, TRT involves sending a radioactive agent

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to cancerous tissue. The radioactive agent is a radionuclide conjugated with a vector with or without a chelator. The vector can be a bioactive molecule or pharmaceutical that can bind to a receptor present at the tumor site or target the tumor site passively.[6] The dynamic development in TRT-based research is because TRT agents have little to no impact on surrounding non-tumor tissues.[7]

TRT agents can be used for diagnostic and therapeutic purposes. For therapeutic purposes, α, β-, and Auger-electron are employed, while β+, X-rays, and γ-rays are specific to diagnostic purposes. Moreover, the simultaneous use of diagnostic and therapeutic TRT agents has led to the emergence of a new field called Theranostics. This review is focused on TRT agents for therapeutic purposes and schematically reviews the use of different types of radionuclides, vectors, and chelators, and the recent status of the use of TRT in treating various types of cancer.

Components of a Molecule

In the TRT-based therapeutic applications, essential components of a TRT agent are radionuclide, vector, chelator, and target, illustrated in Figure 1.

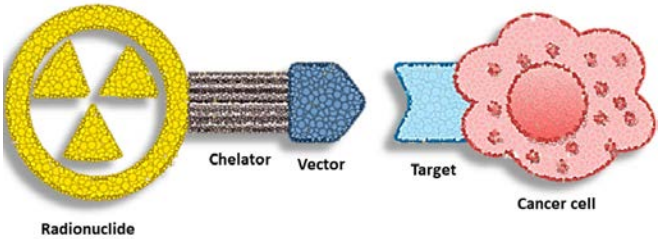

Figure 1. An illustration of TRT agent consisting of a radioactive atom bound to a vector (drug/peptide/antibody etc.) with the help of chelator that acts a tethering molecule.

A radionuclide is an artificially produced radioisotope that emits α, β-, or Auger electron particles. The factors determining the choice of radionuclide are physical half-life, biological half-life, energy, penetration, radiotoxicity, chemical properties, etc.[8] A concise overview of the use of different α, β-, or Auger emitting radionuclides is depicted in Figure 2. Vector is a molecule that binds to the receptors on the target site. It can be an antibody, peptide, peptide analog, nanoparticle, etc. The factors determining the choice of vector are affinity and specificity to the target. The various vectors employed in TRT are reviewed further in following section.

A chelator is a connecting link that acts as a carrier between a vector and a radionuclide. It also stabilizes the vector-radionuclide complex. Chelators are used only when radionuclides cannot bind with high affinity to the amino acids of the vector. The critical factor while employing a vector is that the chelator should not alter the vector's capacity or structure.[9] Chelators can be broadly classified into acyclic and macrocyclic forms.

Target are specific receptors present on the tumor site that have an affinity for the vector of TRT agent. It is a characteristic feature of each cancer type.

Radionuclides for TRT

The central principle of TRT is to deliver potent radiation for tumor cell destruction. Ionizing radiations are of three types: photons, electrons, α- particles.[10] Photons include X-rays and gamma rays, which have a major role in cancer diagnostics.[6] On the other hand, electrons and α- particles play a therapeutic role against cancerous cells via cytotoxic activity. Electrons can be further classified into β+, β- and Auger emitting particles. In TRT, three types of particulate radiation emitters (α, β-, and Auger-particle emitters) are of significant value. These three types of particulate radiation can also be classified into energetic (α, β- particle emitter) and non-energetic particles (Auger-particle emitters). The nuclear decay of these three types of particles is shown in Figure 3. These three types of particulate radiation can be produced by more than 300 types of radionuclides, suggesting relevance in oncology and medicinal biology [11]. Broadly, the efficacy of TRT is dependent on (a) the distance traveled by particles, (b) the energy accumulated by particles in tumor cells, and (c) the direct interaction of particles with DNA.

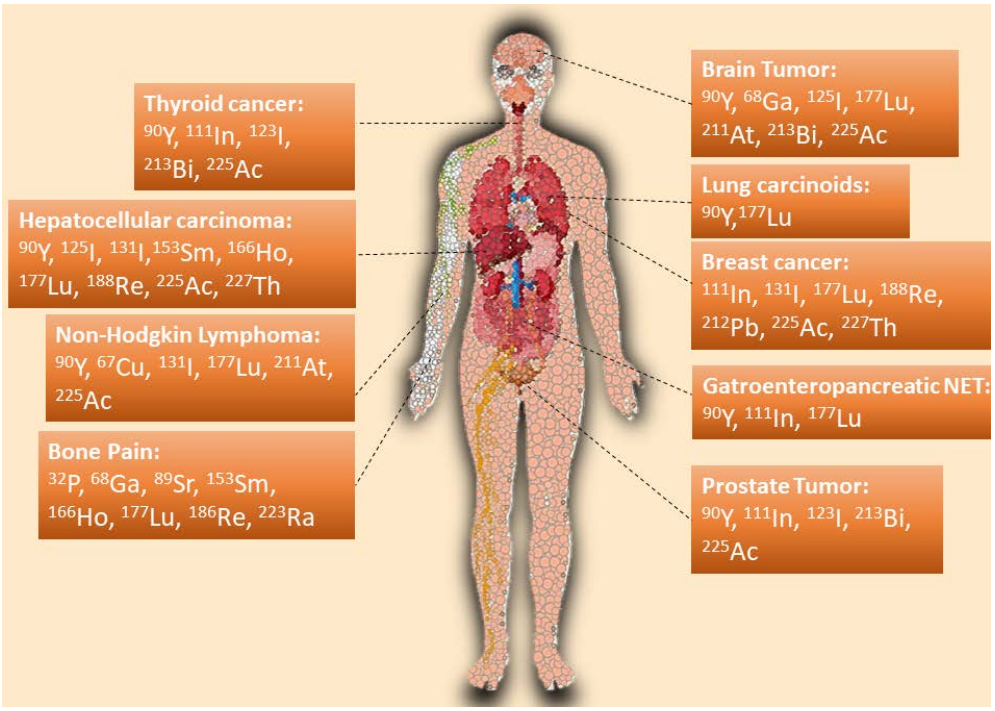

Figure 2. An illustration summarizing the currently investigated radionuclides for cancer treatment.

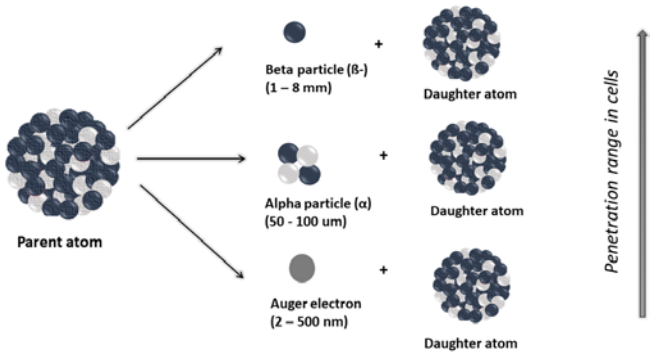

Figure 3. An illustration of nuclear decay of three types of particles, namely, α, ß, and Auger electron, with their penetration range in cells.

ALPHA- PARTICLE EMITTERS

α-particle emitters are positively-charged particles that have a mass and charge equal to the helium nuclei. These particles emission produces a daughter nucleus with 2 protons and 2 neutrons less than the parent atom. α-particles are short-range, travel in a straight line, and cause complex and irreparable breaks in the DNA double-strand.[12,13] These agents have an emission range of 50–100 μm, carry a high amount of energy (400 times more than electrons), and have the highest potency amongst all three types of particulate radiation. The therapeutic efficacy of these agents depends on (a) the probability of nuclear travel (i.e., the distance of the targeted tumor cells nucleus to the decaying atom),[14] (b) the daughter atom's potency of heavy ion recoil when α-particles covalently bind to the nuclear DNA,[14] and (c) the extent of the cross-dose from the radioactive source of one tumor cell to a nearby cell.[15] With these agents, cytotoxicity to cancer cells can be achieved with 1 to 20 α-particles crossing the cell's nucleus.[12] Thus, these agents have a high potency, low toxicity (considering α- particles short range), and high cytotoxicity, suggesting their interest in science and technology. A list of α-particle emitting radionuclides with half-lives and energy emitted per nuclear transformation (MeV/nt) is given in Table 1.[16]

Table 1. A schematic representation of a table with a list of α radionuclides used in TRT with their half-life and maximum energy. The data is taken from ICRP 107.[16]

Nuclide	Half-life	Energy emitted (MeV/nt)
Terbium (^{149}Tb)	4.118 h	2.1292
Astatine (^{211}At)	7.214 h	2.5424
Bismuth (^{212}Bi)	60.55 m	2.8247
Bismuth (^{213}Bi)	45.59 m	0.6963
Radium (^{223}Ra)	11.43 d	5.9895
Actinium (^{225}Ac)	10.0 d	5.9338
Thorium (^{227}Th)	18.68 d	6.1955

α-particle nuclear decay reaction: $^{A}_{Z}X \rightarrow {}^{A-4}_{Z-2}Y + {}^{4}_{2}\alpha + +$

The major limitation with α-particles is that their production produces daughter nuclei. These daughter nuclei have a high recoil capacity, which may cause damage to normal cells along with the cancerous cells. Moreover, these emitters have limited penetration into cancer cells.

BETA- PARTICLE EMITTERS

β- particle emitters are negatively charged electrons (-1) produced from a decaying radioactive atom's nucleus (1 electron/decay). The emission from these particles produces a daughter nucleus with 1 extra proton and 1 less electron than the parent atom. These particles have a small mass, low linear energy travel of ~0.2keV/um (up to a centimeter path and a few nanometers at the end of the range), lose kinetic energy quickly, come to a stop in their travel path (because they travel through matter), and have negligible daughter nucleus recoil energy. These agents have long-range emissions of 1-5 mm, based on the emission energy. The β- particles in the tissue break the covalent bond of water molecules and forms free radicles. These free radicles further break DNA double strands and thus cause DNA damage. Out of the various types of β- particle emitters available, only a limited number have been widely studied. The other β-Particle emitters have not been extensively studied due to complex radiochemistry, regulatory and financial hurdles on availability, etc.[17] The therapeutic efficacy of these agents depends on three factors, namely, (a) the probability of nuclear travel (i.e., the distance from the targeted tumor cell nucleus to the decaying atom), (b) the high concentration of the radionuclide in the targeted tissue, and (c) the cross-fire effect produced by each long-range emitting electron (which neutralizes the need to target each tumor cell). A list of β- particle emitting radionuclides with their half-life and energy emitted per nuclear transformation (MeV/nt) is given in Table 2.[16]

β-particle nuclear decay reaction: $^{A}_{Z}X \rightarrow {}^{A}_{Z-1}Y + {}^{0}_{1}\beta -$

Table 2. A schematic representation of a table with a list of β-radionuclides used in TRT with their half-life and maximum energy. The data is taken from ICRP 107.**[16]**

Nuclide	Half-life	Energy emitted (MeV/nt)
Carbon (^{11}C)	20.39 m	1.4043
Nitrogen (^{13}N)	9.965 m	1.5109
Oxygen (^{15}O)	122.24 s	1.7557
Fluorine (^{18}F)	109.77 m	1.2302
Phosphorus (^{32}P)	14.263 d	0.6948
Phosphorus (^{33}P)	25.34 d	0.0764
Manganese (^{52}Mn)	5.591 d	3.5335
Copper (^{62}Cu)	9.673 m	2.2912
Copper (^{64}Cu)	12.700 h	0.3102
Copper (^{67}Cu)	61.83 h	0.2657
Gallium (^{68}Ga)	67.71 m	1.6866

Germanium (^{69}Ge)	39.05 h	1.0708
Arsenic (^{72}As)	26.0 h	2.8240
Bromine (^{76}Br)	16.2 h	3.4430
Rubidium (^{82}Rb)	1.273 m	2.5195
Strontium (^{89}Sr)	50.53 d	0.5846
Yttrium (^{86}Y)	14.74 h	3.7956
Yttrium (^{90}Y)	64.10 h	0.9331
Zirconium (^{89}Zr)	78.41 h	1.2600
Iodine (^{124}I)	4.1760 d	1.3075
Iodine (^{131}I)	8.02070 d	0.5746
Samarium (^{153}Sm)	46.50 h	0.3341
Holmium (^{166}Ho)	26.80 h	0.7264
Lutetium (^{177}Lu)	6.647 d	0.1830
Rhenium (^{186}Re)	3.7183 d	0.3570
Rhenium (^{188}Re)	17.0040 h	0.8406
Lead (^{212}Pb)	10.64 h	0.3217

AUGER-ELECTRON EMITTERS

Auger-electron emitters are generated from suborbital transitions. The decay of certain specific radioactive atoms produces a vacancy in the lower shell (usually in the K shell) due to electron capture (EC) or internal conversion (IC). Electrons from the higher shells fill the electron vacancy in the lower energy shell. It leads to a vacancy in the higher shell, causing atomic electron transitions. Each electronic transition from the outer to the inner energy shell produces emissions of X-ray photons or Auger electrons. Each atom undergoing EC or IC emits 5-30 Auger electrons of a few eV to 1 keV energies. These negatively charged (-1) low-energy Auger electrons have two characteristic features (a) they travel in contorted paths of a few nanometers to 0.5 um range in water, and (b) have multiple ionization when the decay site is a few nanometers away.[18–20] These agents have a short-range emission of 1-1000 nm, based on the emission energy. Therefore, these agents undergo a drop in energy density as they travel their contorted path (usually within a few nanometers).[19,21] There have been a limited number of studies conducted for Auger electrons. It is because these agents need to be integrated with the DNA of tumor cells[22–24] to show cytotoxic activity.[22,24–28] Another believed challenge is that Auger electrons must deposit at a striking distance from the sub-cellular target site to showcase their activity. These factors are believed to be the primary reason for their negative clinical efficacy, even after positive efficacy in preclinical trials.[29–33] However, with the advancements in technological development, there is hope for these agents.[34] A list of Auger electron emitting radionuclides with their half-life and energy emitted per nuclear transformation (MeV/nt) is given in Table 3.[16]

Auger-electron nuclear decay reaction:

$$ {}^{A}_{Z}X \xrightarrow{EC} {}_{Z-1}{}^{A}Y + ({}^{0}_{-1}e -)n $$

Table 3. A schematic representation of a table with a list of Auger electron radionuclides used in TRT with their half-life and maximum energy. The data is taken from ICRP 107.[16]

Nuclide	Half-life	Energy emitted (MeV/nt)
Gallium (^{67}Ga)	3.2612 d	0.1959
Iodine (^{123}I)	13.27 h	0.2012
Iodine (^{125}I)	59.4 d	0.0621

VECTORS FOR TRT

1. ANTIBODIES

The linking of the radionuclides with monoclonal antibodies (mAbs) or their fragments has found therapeutic relevance in TRT and is now studied as a new field known as Radio-Immuno-Therapy (RIT).[35,36] mAbs are the first vectors investigated for the development of radiopharmaceuticals, and RIT is majorly studied for antibodies of the class IgG. Initially, murine origin antibodies were employed but they showed various limitations like immunogenicity, a short serum half-life, etc. The efficacy of RIT-based agents depends on the half-life of the radionuclides and the pharmacokinetic properties of the mAbs. Currently, pure human antibodies and transgenic mice producing human antibodies are employed. Moreover, genetically engineered antibodies are also under development and study.[37]

The application of RIT for solid tumors is a challenging task as antibodies have a poor effect on tumor growth. Various strategies are investigated to employ RIT for solid tumors. One promising technique is combining radio-sensitizing agents (paclitaxel, gemcitabine, topotecan, etc.) with RIT agents.[38] Other RIT e nhancement strategies include multi-step pre-targeting.[39,40] In this, unlabeled bifunctional antibodies are first injected so that they can bind to receptors present on tumor cells. Later, after its clearance, a radionuclide-chelator complex is administered that binds to antibodies on the target site. However, a pre-targeting strategy cannot be employed for antigens that internalize at the tumor site.

2. ANTIBODY FRAGMENTS

Antibody fragments have also been investigated due to the large size and complex structure of monoclonal antibodies. Antigen-binding antibody fragments are usually produced by genetic engineering technology. Different antibody fragments are

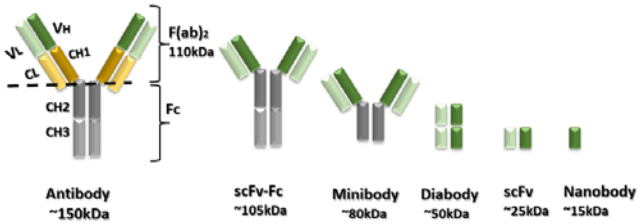

Figure 4. An illustration depicting Antibody and associated fragments with their approximate size in kilo-Dalton, where VH - heavy chain variable region, VL - light chain variable region, CL - light chain constant region, CH1 – constant region of heavy chain, CL - constant region of light chain, CH_2 – Fc constant region 2, CH_3 – Fc constant region 3.

depicted in Figure 4. The VH and VL antibody fragments have poor specificity, low solubility, high aggregation, etc. These limitations can be improved by binding VH and VL together. Flexible polypeptide linkers producing single-chain Fvs (scFv) are also used for VH and VL binding. It is because they provide higher flexibility, quick clearance, etc. Diabodies, Minibodies, and scFv-Fc fragments can also be produced from scFv.[41,42] These fragments have improved tumor targeting, effective tumor accumulation, fast clearance, etc.[42,43] However, mAbs are preferred over their fragments due to easy availability, high tumor uptake, residence time, etc.[44] Moreover, mAbs have lower renal and in-vivo toxicity than mAb fragments.[23]

3. Peptides

The effective binding and interaction properties of proteins (peptides) with receptors have been exploited in various research domains, including cancer. The linking of radionuclides with peptides is highly established in the field of TRT and is studied as a new field known as Peptide Receptor Radionuclide Therapy (PRRT). Peptides, with nearly fifty amino acids, are low molecular weight vectors employed in TRT. The therapeutic advantage of PRRT is its ease of production, efficient conjugation between the vector and the target receptor, quick uptake of agents by tumor cells, greater penetration, and fast renal clearance in comparison to RIT.[45] In the early 1990s, somatostatin (SST) analogue peptides were radiolabeled to revolutionize neuroendocrine tumor (NETs) treatment. The stagnancy in PRRT is due to various factors like stability, toxicity, resistance, etc. Various PRRT-based vectors, namely, somatostatin analogues, gastrin-releasing peptides, bombesin, glucagon-like peptides, cholecystokinin analogues, etc., are discussed in the following section.

3.1. Somatostatin Analogues

Somatostatin, as depicted in Figure 5, is a cyclic hormone highly expressed in peripheral and central nervous systems. SST binds to the G-protein coupled SST receptor and inhibits the release of growth hormones, namely glucagon and insulin [46]. SST contains various synthetic analogues which are diversely used PRRT vectors. The major SST analogues with or without chelators include octreotide, gastrin, cholecystokinin, prostate specific membrane antigen (PSMA), DTPA-octreotide, [DOTA0,Tyr3]octreotide (DOTATOC), [DOTA0,Tyr3]octreotate (DOTATATE), [DOTA0-1-NaI3]octreotide (DOTANOC), etc.[47]

3.2. Bombesin and Gastrin-Releasing Peptides

Bombesin, isolated from frogs, is a fourteen amino acid neuropeptide as depicted in Figure 6. Gastrin-Releasing Peptides (GRP) are the human-isolated analogs of Bombesin and consist of twenty-seven amino acids. Bombesin and GRP have identical functions in humans and exhibit activity in various tumors, namely breast cancer, lung carcinoid, prostate, and pancreatic cancer.[48] The eight ~~8~~ amino acids on the C-terminal of Bombesin have efficient receptor binding activity and are engineered to develop bombesin analogs. An extensive review of these analogs could be referred elsewhere.[49,50]

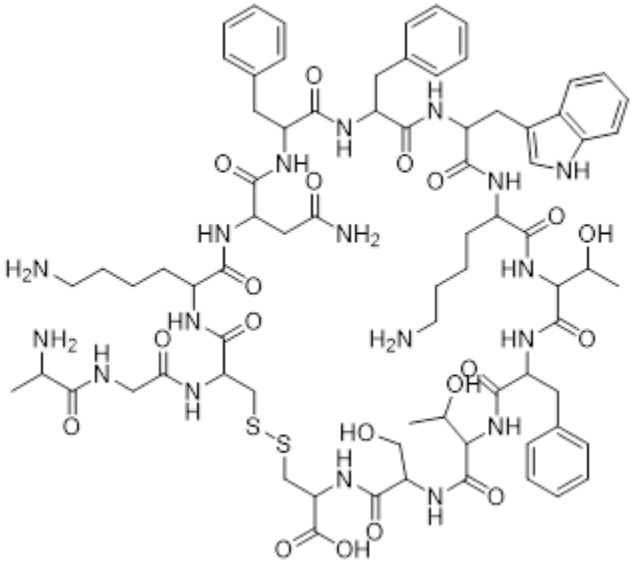

Figure 5. The chemical structure of Somatostatin (DL-alanyl-glycyl-DL-cysteinyl-DL-lysyl-DL-asparagyl-DL-phenylalanyl-DL-phenylalanyl-DL-tryptophyl-DL-lysyl-DL-threonyl-DL-phenylalanyl-DL-threonyl-DL-seryl-DL-cysteine (3->14)-disulfide).

3.3. Cholecystokinin/Gastrin Analogues

Gastrin and Cholecystokinin (CCK) are two hormones that have functional relevance in the central nervous system and gastrointestinal tract. Gastrin has structural and functional similarity with CCK. They bind to the CCK/gastrin G-protein coupled receptors in the central nervous system and gastrointestinal tract.[51] Gastrin and CCK are also overexpressed in various neuroendocrine tumors,[52] and medullary thyroid cancer.[53] The analogues of the CCK/gastrin are structurally similar to the CCK8 and minigastrin. The structures of CCK8 and Minigastrin are depicted in Figure 6. CCK8 is the biologically active CCK's C-terminal octapeptide amide fragment.[54] On the other hand, Minigastrin consists of thirteen amino acids from the C-terminal of truncated gastrin.[55] Various analogues based on CCK8 and minigastrin can be engineered via changes in charge, cyclization, composition, dimerization, sequencing, etc. Analogs produced via these variations affect the affinity, specificity, uptake, internalization, pharmacokinetics, pharmacodynamics, etc.[56]

4. Small Molecules

It includes vector molecules that are smaller than antibodies, peptides, etc., are less than or equal to 500 Da weight, and can quickly move through the plasma membrane. These vectors usually mimic enzyme inhibitors, hormones, steroids, neurotransmitters[57–59] etc. and majorly target overexpressed intra- and extracellular receptors. One prominent example of such molecules is the FDA approved ^{131}ImIBG for the treatment of unresectable metastatic phaeochromocytoma or paraganglioma in patients aged twelve years or more.[60]

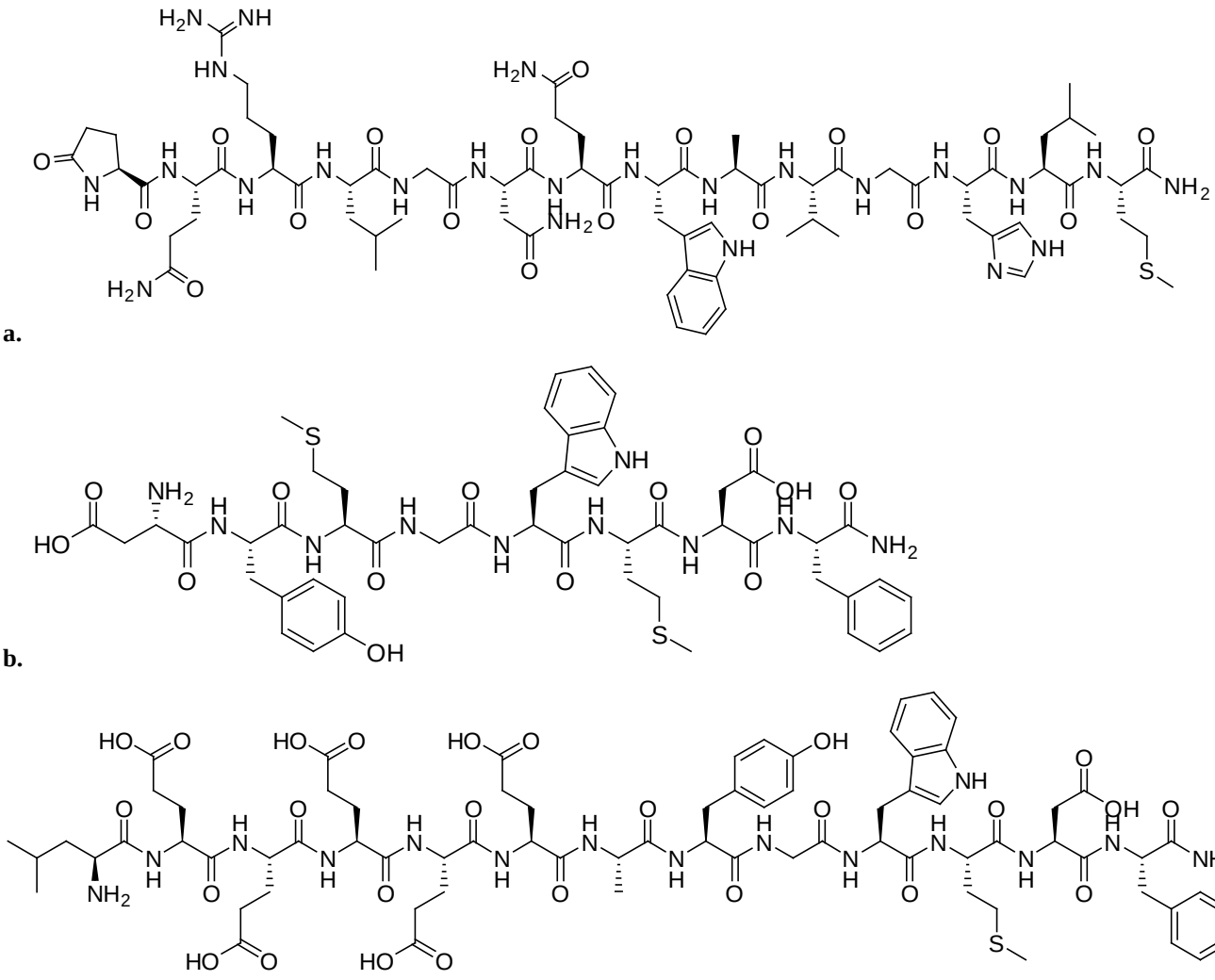

Figure 6. The structure of (a.) Bombesin (with their amino acids in the order; L-pyroglutamyl-L-glutaminyl-L-arginyl-L-leucyl-glycyl-L-asparagyl-L-glutaminyl-L-tryptophyl-L-alanyl-L-valyl-glycyl-L-histidyl-L-leucyl-L-methioninamide) (b.) cholecystokinin octapeptide, CCK8 (with their amino acids in the order L-alpha-aspartyl-L-tyrosyl-L-methionyl-glycyl-L-tryptophyl-L-methionyl-L-alpha-aspartyl-L-phenylalaninamide) and (c.) Minigastrin (with their amino acids in the order L-leucyl-L-alpha-glutamyl-L-alpha-glutamyl-L-alpha-glutamyl-L-alpha-glutamyl-L-alpha-glutamyl-L-alanyl-L-tyrosyl-glycyl-L-tryptophyl-L-methionyl-L-alpha-aspartyl-L-phenylalaninamide

PSMA inhibitors, which are analogues of PSMA substrates, are also extensively studied under the category of small molecules.[61] The significant advantages include bulk and easy production, cost-effectiveness, oral administration, and stability in the gastric environment.[62]

5. NANOPARTICLES

Nanoscience and nanotechnology have revolutionized the diagnosis, detection, and treatments in biomedical sciences. In TRT, nanoparticles are exploited to improve the diagnosis and treatment of cancer. For diagnostics, nanoparticles improve sensitivity, specificity, and precision even at low concentrations of cancer biomarkers.[63,64] On the other hand, nanoparticles improve therapeutic efficacy by encapsulating cytotoxic chemotherapy drugs and lowering drug degradation, interaction, and metabolism. In nanoparticle-based TRT, nanoparticle-encapsulated drugs can be delivered through active and passive targeting approaches.[63] In the active targeting approach, the radionuclide-chelator is functionalized (adsorbed) on the nanoparticle's surface. In this, the kinetically active and stable radionuclide-vector attachment to the nanocarrier is of critical importance.[65] In the passive targeting approach, nanocarriers take advantage of leaky and fenestrated vasculature of tumor tissue (caused by angiogenesis) or poor lymphatic drainage of tumor tissue for indirect infiltration and accumulation.[66,67] This mechanism is called the enhanced permeability and retention (EPR) effect. Based on the active and passive targeting approaches, smart nanocarriers development is also a new advancement that aims for controlled temporal drug delivery to the target site.[68,69] Moreover, extensive reviews on nanoparticle-based TRT could be referred to elsewhere.[70–72]

RADIOLABELING OF RADIOPHARMACEUTICALS

There are various methods of radiolabeling radiopharmaceuticals. Broadly, radiolabeling strategies can be classified into direct method, use of prosthetic group, and indirect method (employing chelators). Direct radiolabeling is a one-step technique. It is robust and useful for short lived radionuclides. However, there is a specific protocol for radiolabeling each radiopharmaceutical via direct radiolabeling. Radioiodination is the most common method of direct radiolabeling.[73] Another method is the use of small molecules that act as prosthetic groups. The small molecules first bind to a specific site of the radionuclide and then simultaneously bind to the vector. This strategy is a two-step flow that involves the incorporation of the prosthetic group in the radionuclide followed by binding to the vector. Each of these two steps can be carried out by various methods.[74] The third strategy is the use of chelators for the conjugation of radionuclides with vectors. The technique is primarily applied to radiometals. Chelators can be classified into cyclic (e.g., DOTA, MACROPA, etc.) and acyclic (e.g., DTPA, OCTAPA, SOCTA, etc.) chelators. There is higher employment of cyclic chelators over acyclic chelators. However, chelators make a TRT agent bulky, affecting its binding and localization at the tumor site. The chemical structures of some chelators employed as TRT agents (discussed in Section 3) are depicted in Figure 7. More extensive review of various chelators, their properties, and their conjugation can be referred to elsewhere.[75–78]

CANCERS

Cancer is a leading public health concern worldwide. There has been a decline in the number of cancer-associated deaths with time, accredited to the continuous efforts of scientists and researchers worldwide. However, there is an increase in the number of cancer cases each year, which requires innovative and personalized treatments. In nuclear medicine and radiation therapy, TRT is an emerging field with therapeutic and diagnostic promises. Advances in TRT could be realized with the steep incline in the number of FDA-approved agents from 2018. A timeline of FDA-approved TRT agents is depicted Figure 8. TRT can be used in the treatment of various types of cancers, namely thyroid cancer, breast cancer, metastatic bone pain, neuroendocrine neoplasm, gastroenteropancreatic NET, lung carcinoids, phaeochromocytoma, paraganglioma, prostate

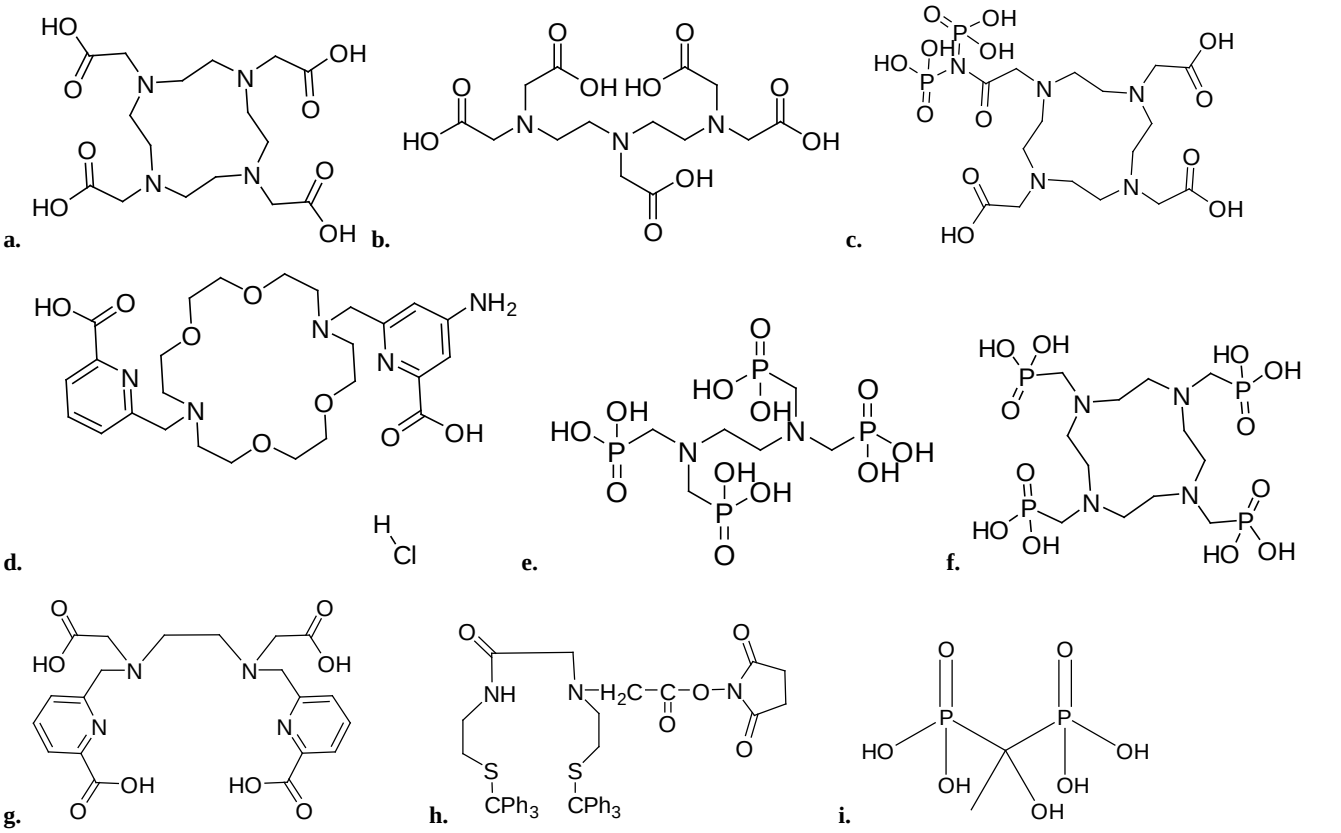

Figure 7. The chemical structure of chelators namely a. DOTA (2-[4,7,10-tris(carboxymethyl)-1,4,7,10-tetrazacyclododec-1-yl]acetic acid) b. DTPA (2-[bis[2-[bis(carboxymethyl)amino]ethyl]amino]acetic acid) c. BPAMD (2-[4,7-bis(carboxymethyl)-10-[2-(diphosphonoamino)-2-oxoethyl]-1,4,7,10-tetrazacyclododec-1-yl]acetic acid) d. MACROPA (4-amino-6-[[16-[(6-carboxypyridin-2-yl)methyl]-1,4,10,13-tetraoxa-7,16-diazacyclooctadec-7-yl]methyl]pyridine-2-carboxylic acid;hydrochloride) e. EDTMP ([2-[bis(phosphonomethyl)amino]ethyl-(phosphonomethyl)amino]methylphosphonic acid) f. DOTMP ([4,7,10-tris(phosphonomethyl)-1,4,7,10-tetrazacyclododec-1-yl]methylphosphonic acid) g. H4OCTAPA (N,N0-bis(6-carboxy-2-pyridylmethyl)-ethylenediamine-N,N0-diacetic acid) h. SOCTA (succinimidyl 3, 6-diaza-5-oxo-3- [2-(triphenylmethyl)thio)ethyl]-8-[(triphenylmethyl)thio]octanoate) i. HEDP ((1-hydroxy-1-phosphonoethyl)phosphonic acid)

tumors, brain tumors, malignant lymphoma, non-Hodgkin's lymphoma, hepatocellular carcinoma etc., as descriptively reviewed in the following section.

Figure 8. A timeline depicting the list of all the FDA-approved TRT agents for therapeutic use against various types of cancers discussed in Section 5.

THYROID CANCER

Thyroid cancer is an endocrine malignancy originating from follicular or parafollicular thyroid cells. It includes differentiated thyroid cancer (DTC),[79] medullary thyroid cancer (MTC), and anaplastic thyroid cancer (ATC).[80,81] Among these, DTC is more prominent than MTC and ATC. DTC derives from epithelial cells and is further classified into the Hürthle cell subtype of thyroid cancer (HTC), follicular thyroid cancer (FTC), and papillary thyroid cancer (PTC).[79] MTC derives from parafollicular cells and is usually considered under neuroendocrine tumors.[81] The effectiveness of TRT in thyroid cancer is due to combined diagnostic and therapeutic approaches of radionuclide therapy (termed theranostics). The majority of research for thyroid cancer treatment includes PRRT targeting the SST receptor (SSTR). SST is a hormone with two active forms, namely SST-14 and SST-28, which bind to SSTR. SSTR is a G-protein-coupled receptor and includes five subtypes, namely SSTR 1, SSTR 2, SSTR 3, SSTR 4, and SSTR 5.[82] SSTR activation causes a decrease in adenylyl cyclase activity and has distinctive effects on the activities of Ca+ and K+ channels, mitogen-activated protein kinase, phosphotyrosine phosphatase, phospholipase C, etc.[83]

In thyroid cancer, SSTR 2 is majorly expressed, SSTR 1, SSTR 3, or SSTR 5 have lower expression, and SSTR 4 has rare expression.[83–86] The synthetic SST analogues, namely octreotide and seglitide, have a high affinity for SSTR 2 and intermediate affinity for SSTR 1 and SSTR 5.[87] The major SST analogues with or without chelators include octreotide, gastrin, cholecystokinin, PSMA, DTPA-octreotide [pentreotide], [DOTA0,Tyr3]octreotide (DOTATOC), [DOTA0,Tyr3]octreotate (DOTATATE), [DOTA0-1-NaI3]octreotide (DOTANOC), etc.[47] Structures of a few SST analogues are represented in Figure 9. Conventionally, octreotide was used for SSTR 2 targeting. Later, DOTATOC exhibited higher affinity than octreotide. It was then replaced by DOTATATE that showcased better efficacy than DOTATOC for SSTR 2.[88] In thyroid cancer, the efficacy of each TRT agent also depends on the radionuclide attached. For example, ^{177}Lu-DTPA-octreotide and ^{90}Y-DTPA-octreotide have higher efficacy

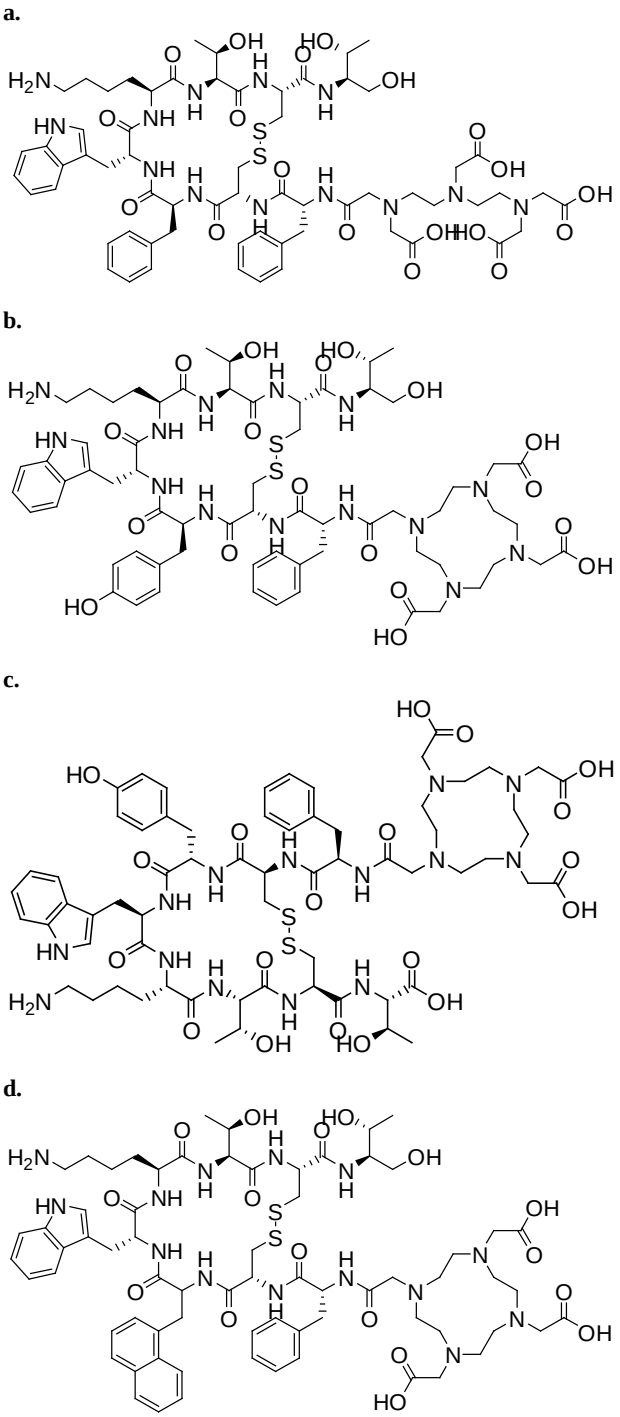

Figure 9. Chemical structures of few of the SST analogues, (a.) DTPA-octreotide (pentreotide), (b.) [DOTA0,Tyr3]octreotide (DOTATOC), (c.) [DOTA0,Tyr3]octreotate (DOTATATE), and (d.) [DOTA0-1-NaI3]octreotide (DOTANOC).

than ^{111}In-DTPA-octreotide due to the different properties of each radionuclide. Apart from this, ^{177}Lu-DOTATATE is most commonly used.

Some of the TRT based agents for thyroid cancer are elaborated in Table 4 and discussed here [89–105]. For MTC treatment, there are a large number of PRRT-based trials. Moreover, pre-targeted RIT is a recent novel technique employed for MTC treatment with a convincingly higher survival rate than conventional treatment [106]. ^{177}Lu-anti-CEA-TF2-HSG and ^{90}Y-anti-CEA-TF2- HSG work on the pre-targeted RIT technique.[95] In MTC, the accumulation of radioactive iodine is very low, suggesting the poor efficacy of ^{131}I-based agents. PRRT-based agents discussed in Table 4 get internalized after binding to the receptor, suggesting their efficacy in MTC. There are very few studies on DTC treatment, as elaborated in Table 4. On the other hand, radionuclides have not shown much progress for ATC due to low tumor prevalence, rapid tumor progression, highly dedifferentiated tumor nature, and associated high morbidity and mortality.

Table 4. The table schematically represents TRT agents, associated vectors, target site, cancer type for thyroid cancer.

Agent	Vector	Chelator	Receptor on cancer cell	Cancer type	Ref.
RIT based agents					
^{131}I-sodium iodide (International Isotopes Inc)			sodium/iodide symporter	FDA approved for thyroid carcinoma	96
^{177}Lu- anti-CEA TF2- HSG	anti-carcinoembryonic antigen (CEA) monoclonal antibodies bound to Histamine-succinyl-glutamine (HSG) peptide	-	carcinoembryonic antigen	MTC	95
^{90}Y-anti-CEA TF2- HSG	anti-carcinoembryonic antigen (CEA) monoclonal antibodies bound to Histamine-succinyl-glutamine (HSG) peptide		carcinoembryonic antigen	MTC	95
PRRT based agents					
^{111}In- Octreotide	Octreotide	-	Somatostatin receptor	MTC	97
^{111}In- Pentreotide	Pentreotide	-	Somatostatin receptor	MTC	98
^{90}Y-DOTATOC	Octreotide	DOTA	Somatostatin receptor	MTC	89–94
^{177}Lu-DOTATATE	Octreotate	DOTA	Somatostatin receptor	MTC	99–101
^{177}Lu-DOTATATE-capecitabine	Octreotate Capecitabine acts as a radio-sensitizing agent	DOTA	Somatostatin receptor	MTC	102
^{177}Lu-DOTA-PP-F11N	PP-F11N is Minigastrin analog	DOTA	Cholecystokinin 2 receptor	MTC	103
^{177}Lu-DOTATATE	Octreotate	DOTA	Somatostatin receptor	DTC	104
^{111}In-DTPA-octreotide	Octreotide	DTPA	Somatostatin receptor	DTC	105

BREAST CANCER

Breast cancer is the most prevalent cancer amongst women worldwide. It is a heterogeneous mixture of four diseases with different subtypes based on hormone receptor (HR) and Human Epidermal Growth Factor-2 (HER2). These four types of diseases are based on: HR (+) and HER2 (+), HR (-) and HER2 (+), HR (+) and HER2 (-), and triple-negative breast cancer (TNBC).[107] In HR (+) cancer, estrogen and progesterone are the major ligands that bind to the HR receptor and cause uncontrolled cell

growth. In HER2 (+) cancer, cancer cells overproduce the HER2/neu protein, which causes uncontrolled cell growth.

Amongst all, HR receptor binding to estrogen is largely studied for breast cancer treatment [108]. Breast cancer is of critical importance in TRT-based treatment. There are extensive studies on breast cancer diagnosis reviewed elsewhere.[109,110]

Some of the TRT based agents for breast cancer are elaborated in Table 5 and discussed here.[108,111–122] TRT based breast cancer treatment includes PRRT, RIT, and endocrine therapy. Inhibiting estrogen activity and estrogen antagonist that bind to the estrogen receptors are the major endocrine-based TRTs for treating breast cancer. Radiolabeling of an estrogen antagonist like fulvestrant is an example of endocrine therapy-based breast cancer treatment.[108] In this, ^{131}I-fulvestrant exhibited good tolerance and therapeutic efficacy against tumor in three MCF-7 cell xenografts models with survival of some normal cells as depicted in Figure 10.[108] Another drug extensively investigated against HER2 (+) cancer cell lines is trastuzumab with comparative studies available for its cytotoxicity as well.[114,115,121–124] Most of the TRT-based treatments for breast cancer are receptor-dependent. However, alkyl phosphocholine follows a receptor-independent mechanism. The glycosphingolipid and cholesterol containing membranes accumulate phospholipid mimics (lipid rafts) in their microdomain.[125,126] Alkyl phosphocholine acts as a lipid raft, accumulates in the phospholipid layer of breast cancer cells, and thereby follows a receptor-independent mechanism for treating breast cancer.[111] Similar to receptor-independent targeting, nanoparticle-based agents follow passive targeting through the EPR effect. Elaborately studied gold nanoparticle-based TRT agents also follow a passive targeting mechanism for treating breast cancer (discussed in Table 5).[112,113]

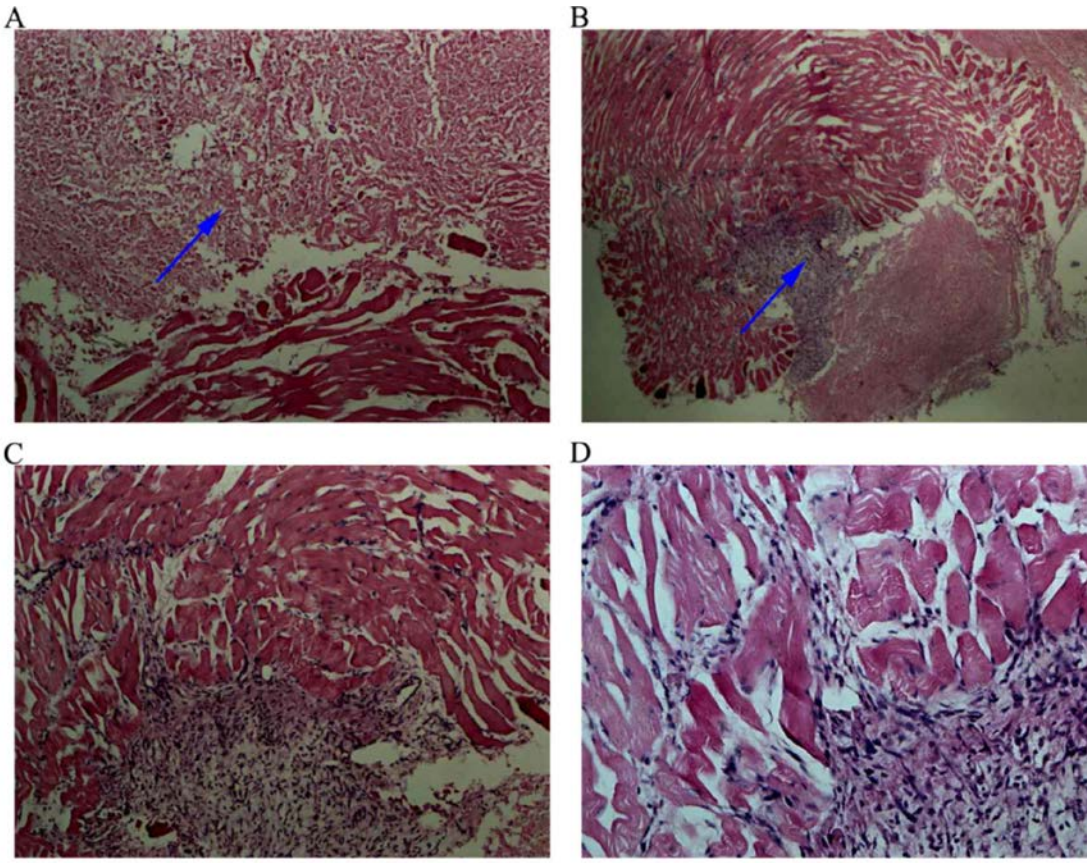

Figure 10. In a study by Yin et al., three nude mice with MCF-7 cells, ^{131}I-fulvestrant was injected. After 72 h, the mice were sacrificed and MCF-7 cell xenografts were observed by H&E staining. Massive necrosis, disappearance of large-area tumor nuclei, alterations in cell morphology, and appearance of amorphous homogeneous red tissues was observed in the xenografts, suggesting 131I-fulvestrant efficacy against the tumor. In Figure 9, (C and D) represents MCF-7 cell xenografts with no interference, and (A and B) represents MCF-7 cell xenografts injected with ^{131}I-fulvestrant. Furthermore, (A) represents massive necrosis (pointed by arrow) with no injury to normal tissues and (B) represents a few remaining tumor cells near muscle tissue (pointed by arrow) but no injury to normal muscle tissues.[108] (Reproduced with permission)

METASTATIC BONE PAIN

Metastasis is the spread of cancer cells from the original site to other sites. Bones are the principal target of metastasis, after the lungs and liver.[127] Bone metastasis (osteoblastic and osteolytic) commonly arises from breast, kidneys, lungs, ovaries, prostate, and thyroid cancer.[127] Osteoblastic metastasis occurs due to prostate cancer, while osteolytic metastasis occurs due to renal cancer, thyroid cancer, and multiple myeloma. Osteoblastic and osteolytic metastasis occur in breast, lungs, colorectal, and pancreatic cancers. The bloodstream is the primary route by which cancer cells spread.[128] Bone metastasis occurs more frequently in the vertebrae (69%), pelvic bones (41%), long bones (25%), and skull (14%), and less frequently in the ribs and sternum.[129] Bone pain is the most common exhibited amongst patients, experienced at varying degrees in bone metastasis and other types of cancer.[130] Apart from bone pain; hypercalcemia,

Table 5: The table schematically represents TRT agents, associated vectors, target site, cancer type for breast cancer.

Agent	Vector	Chelator	Receptor on cancer cell	Cancer type	References
RIT-based agents					
^{188}Re-SOCTA-trastuzumab	drug trastuzumab (Herceptin) is a humanized anti-HER-2/neu monoclonal antibody	SOCTA	HER-2/neu	Human breast cancer cells BT-474	[114]
^{225}Ac-CEPA-trastuzumab (RIT)	drug trastuzumab (Herceptin) conjugated with CEPA (3-phosphonopropionic acid) nanoparticles	-	HER-2	SKOV-3 ovarian cancer cells	[115]
^{225}Ac - anti-hK2	hu11B6 antibody (anti-hK2)	-	Androgen receptor	Breast cancer cells	[116]
^{177}Lu-PSMA-617	CD31-specific antibody	-	PSMA on endothelial HUVEC cells	TNBC MCF-7 (ER+), MDA-MB231 (TNBC)	[117]
^{227}Th - BAY2287411	BAY2287411 (anti-mesothelin mAb anetumab) is an overexpressed membrane glycoprotein	3,2-HOPO chelator	Mesothelin (GPI-anchored membrane glycoprotein)	ST2185B cancer cell line	[118]
^{212}Pb -225.28	225.28 (CSPG4-specific monoclonal antibody)	-	chondroitin-sulfate-proteoglycan-4	TNBC (SUM159 and 2LMP) cells	[119]
PRRT-based agents					
^{177}Lu-BN-PLGA-PTX	Bombesin (BN) hormone conjugated with drug paclitaxel (PTX) PLGA nanoparticles help in controlled drug release	-	Gastrin-secreting peptide receptor	MDA-MB-231	[120]
Other agents					
^{177}Lu-T-AuNP	Gold nanoparticles (AuNP) binds to chelator and PEG chains then complexes with 177Lu bound panitumumab	DOTA	Epidermal growth factor receptor	TNBC MDA-MB-468	[112,113]
Trastuzumab-AuNP-^{177}Lu	Gold nanoparticles (AuNP) binds to chelator and PEG chains then complexes with 177Lu bound panitumumab	DOTA	HER2	SK-BR-3 and MDA-MB-361 cells	[121]
^{111}In-AuNP-trastuzumab	Gold nanoparticles (AuNP) binds to chelator and PEG chains then complexes with 177Lu bound panitumumab	DOTA	HER2	SK-BR-3 and MDA-MB-361	[122]
^{131}I - fulvestrant	Fulvestrant is an endocrine therapy drug for breast cancer	-	Estrogen receptors	MCF-7 and MDA-MB-231 cells	[108]
^{177}Lu-NM600	alkylphosphocholine (NM600)	-	glycosphingolipid- and cholesterol-rich cellular membrane microdomain	TNBC, 4T07 and 4T1 murine models	[111]

Table 6. The table schematically represents TRT agents, associated vectors, target site, cancer type for metastatic bone pain.

Agent	Vector	Chelator	Receptor	Cancer type/cell line	Ref.
^{89}SrCl	89Sr is a calcium mimic	-	89Sr is absorbed by the inorganic bone matrix	FDA-approved for metastatic bone pain to prostate and breast carcinoma. (182)	147
^{186}Re–HEDP	HEDP (hydroxy-ethylidene Diphosphonate) is a phosphonate complex	HEDP	binds to hydroxyapatite crystals		134
^{188}Re-HEDP	HEDP (hydroxy-ethylidene Diphosphonate) is a phosphonate complex	HEDP	binds to hydroxyapatite crystals		135
^{153}Sm-EDTMP	lexidronam or EDTMP (ethylene diamine tetramethylene phosphonate) is a phosphonate complex	EDTMP	binds to hydroxyapatite crystals	FDA approved for prostate and breast metastatic bone pain lesions	136–138
^{177}Lu-EDTMP	lexidronam or EDTMP (ethylene diamine tetramethylene phosphonate) is a phosphonate complex	EDTMP	binds to hydroxyapatite crystals	metastatic bone pain	139–142
^{166}Ho-BPAMD	4-{[(bis(-phosphonomethyl))-carbamoyl]-methyl}-7,10-bis(carboxymethyl)-1,4,7,10-tetraazacyclododec-1-yl) acetic acid	BPAMD	binds to hydroxyapatite crystals	metastatic bone pain	143
^{177}Lu-DOTA-ZOL	zoledronic acid (ZOL) is a biphosphate	DOTA	hydroxyapatite binding and internalization by osteoclasts	metastatic bone pain	144
^{177}Lu-DOTMP	DOTMP is a bone-seeking chelating agent	DOTMP	binds to hydroxyapatite crystals	skeletal metastases	146
Xofigo (^{223}RaCl) (Bayer HealthCare Pharmaceuticals Inc.)	223Ra is a calcium mimetic that deposits on hydroxyapatite		binds to hydroxyapatite crystals	FDA approved for metastatic bone pain due to castrate-resistant prostate cancer	145

pathological fractures, spinal cord compression, etc. are other bone metastasis-associated complications [131]. TRT is extensively applied for pain palliation in osteoblastic metastasis associated with prostate and breast cancer.[132] TRT for metastatic bone pain not only acts as a bone-palliative but also targets metastatic foci.[133]

Some of the TRT based agents for metastatic bone pain are elaborated in Table 6.[134–147] The two classes of TRT agents used in metastatic bone pain are based on calcium analogs and phosphonates. ^{89}SrCl is among the first FDA-approved TRT agents followed by ^{153}Sm-EDTMP and ^{223}RaCl. ^{89}SrCl efficacy has also been compared to ^{153}Sm-ethylenediamine tetramethylene phosphonate (^{153}Sm-EDTMP) and ^{186}Re/^{188}Re-hydroxyethylidene diphosphonate (186Re–HEDP/^{188}Re-HEDP) with no significant variability.[148–151] Different TRT based agents

are developed and are in design with the aim to decrease toxicity apart from increasing efficacy in metastatic bone pain.

Neuroendocrine Neoplasm

Neuroendocrine neoplasms (NENs) include various tumors migrating from endoderm to tissues.[152] The occurrence of NEN could theoretically be destined to any organ of the body. The gastrointestinal tract is the most commonly affected, followed by the lungs. Earlier, NEN was classified based on the tumor in the foregut (developed from the thymus, respiratory system, and upper gastrointestinal tract), midgut (developed from the appendix, ascending colon, and small bowel), or hindgut (developed from the distal colon and rectum).[153] According to the recent World Health Organization (WHO) classification, NEN is the umbrella term and is distinguished into NET and neuroendocrine carcinoma (NEC). Furthermore, WHO proposed NET for GI and pancreatic-originating tumors and NEC for lung tumors.[154] NET includes well-differentiated neoplasms, while NEC has poorly differentiated neoplasms.

3.4.1. Gastroenteropancreatic NET (GEPNET)

NET includes carcinoids, GEPNETs, MTC, meningioma, Merkel cell carcinoma, neuroblastoma, pancreatic NETs (PNETs), paraganglioma (PPGL), and pheochromocytoma [155]. GEPNET can be further classified into rectal (39.2%), small intestine (27.8%), gastric (10.5%), appendiceal (8.8%), colonic (7.8%), and cecel (5.8%) [156]. They are extensively investigated through SSTR-based PRRT. TRT majorly focuses on studying ~~studies~~ GEPNET. The ongoing TRT-based therapeutic approaches are undergoing enhancement to improve efficacy. For example, SSTR-targeting is currently studied with antagonists along with agonists, PRRT-based investigation focuses on ~~of~~ α-particles along with β-particles, intra-arterial applications along with the intravenous applications are also employed.[157] There are extensive studies on GEPNET diagnosis that are out of the scope of this article and reviewed elsewhere.[157,158]

Some of the TRT based agents for GEPNET are elaborated in the Table 7.[159–165] In 1994, ^{111}In-DTPA-octeoride, was used for NEN.[161] Later, ^{111}In-pentetreotide was studied for GEPNET [162] suggesting easy tolerance but limiting efficacy in NET.[105] Clinical trials were also carried out using ^{90}Y-DOTATOC, suggesting a good response and survival rate.[163] Among them, O'Donoghue et al. suggested the efficacy of ^{90}Y-DOTATOC for large lesions and ^{111}In-pentetreotide for small lesions.[164] Moreover, ^{111}In-pentetreotide suggested better efficacy and less damage than ^{90}Y-DOTATOC.[165]

With the discovery of DOTATATE, it was found that DOTATATE has a higher affinity for SSTR than DOTATOC (discussed earlier).[165] Thus, ^{111}In-DOTATATE was found to be a safer drug. Due to the potential of ^{177}Lu, FDA in 2018 approved ^{177}Lu-DOTATATE for the treatment of SSTR+ GEPNETs.[159,160]

Lung Carcinoids

According to WHO classification, lung tumors can be differentiated into typical carcinoid (TC), atypical carcinoid (AC), large cell neuroendocrine lung carcinoma (LCNELC), and small cell lung carcinoma (SCLC).[166] TC and AC are well differentiated, while LCNELC and SCLC are poorly differentiated. Moreover, TC is low grade, AC is intermediate grade, while LCNELC and SCLC are high-grade tumors.[166] Similar to GEPNET, the majority of the studies for TC and AC have been highly explored via PRRT targeting SSTR. It includes the agonists ^{177}Lu-DOTATATE, ^{90}Y-DOTATATE, ^{177}Lu-DOTATOC and ^{90}Y-DOTATOC. The~~ir~~ efficacies of these agents are under evaluation in various clinical trials reviewed elsewhere.[167] The recent advancement is the study of ^{177}Lu-OPS201 (also known as ^{177}Lu-DOTAJR11) which acts as an antagonist and has a strong affinity for SSTR.[168] This is a breakthrough as antagonists, unlike agonists, do not generally get internalized in tumor cells. However, antagonists have better efficacy due to the higher availability of binding sites in comparison to agonists.[169]

Phaeochromocytoma and Paraganglioma

Phaeochromocytoma and paraganglioma are two rare NETs arising in the chromatin tissue of the adrenal medulla. According to the WHO, they are classified as paragangliomas.[170] They majorly arise from the sympathetic tissue and, to some extent, from parasympathetic tissues. Common sites of metastatic phaeochromocytoma and paraganglioma arising from sympathetic tissues are lymph nodes, bone, liver, and lung.[171] Phaeochromocytoma and paraganglioma arising from parasympathetic tissues often occur in the head and neck. In tumors arising from sympathetic tissue, there are elevated levels of epinephrine, norepinephrine, or their metabolites (metanephrine and normetanephrine, respectively). In tumors arising from parasympathetic tissue, there are high levels of dopamine or its metabolite, 3-methoxytyramine. The current

Table 7. The table schematically represents TRT agents, associated vectors, target site, cancer type for GEPNET.

Agent	Vector	Chelator	Receptor	Cancer	Ref.
PRRT-based agents					
^{111}In-DTPA-Octeoride	Octeoride	DTPA	Somatostatin receptor	NEN	161
^{111}In-pentetreotide	Pentetreotide		Somatostatin receptor	Small lesions of GEPNET	162,164
^{90}Y-DOTATOC	Octreotide	DOTA	Somatostatin receptor	Large lesions of GEPNET	163
^{177}Lu-DOTATATE	Octreotate	DOTA	Somatostatin receptor	FDA for the treatment of SSTR+ NETs	159,160

Table 8. The table schematically represents TRT agents, associated vectors, target site, cancer type for prostate cancer.

Agent	Vector	Chelator	Receptor	Ref.
RIT based agents				
^{90}Y-huJ591	Humanized form of murine antibody huJ591	-	PSMA	181,182
^{177}Lu-huJ591	Humanized form of murine antibody huJ591	-	PSMA	182–184
^{131}I-MIP-1095	MIP-1095 is a small molecule	-	PSMA	185
Other Agents				
^{177}Lu-PSMA I&T	DOTAGA-(I-y)fk(Sub-KuE)	DOTAGA	PSMA	186,187
^{177}Lu-PSMA-617	urea-based small molecule PSMA-617	DOTA	PSMA	188–191,194,195
^{225}Ac-PSMA-617	urea-based small molecule PSMA-617	DOTA	PSMA	192,193

treatments for metastatic phaeochromocytoma and paraganglioma are rarely curative. The treatments include external-beam radiation therapy and TRT, which only aims at palliative results. The majority of TRT agents are ~~is~~ based on radiolabeling small molecules, or PRRT. For the radiolabeled small molecules based TRT, ^{131}I-mIBG is FDA-approved for the treatment of unresectable metastatic phaeochromocytoma or paraganglioma in patients aged twelve years or older.[60] It is because mIBG is a guanethidine derivative with an affinity for norepinephrine (noradrenaline) transporter.[172] As somatostatin receptors are highly expressed in NET; ^{177}Lu-DOTATATE, ^{177}Lu-DOTATOC, ^{90}Y-DOTATATE, and ^{90}Y-DOTATOC are also under research study for evaluation of their efficacy.[173,174] A recent investigation carried out comparative studies between small molecule (mIBG) and PRRT (DOTATE) based agents for imaging and therapeutic efficacy.[175] The study obtained differential results for imaging and therapeutic efficacy suggesting that clinical decision depends on individual conditions.[175]

Prostate Tumors

Prostate cancer is the most commonly diagnosed cancer in men. The primary therapies include radical prostatectomy, external beam radiotherapy, and brachytherapy. However, prostate cancer is an excellent target site for TRT study.[176] It is because the prostate is a small organ with many lymph nodes (allowing for easy antibody infiltration), numerous tissue-specific antigens, and many prostate-specific antigen serum markers.[177–179] The primary target for prostate cancer is PSMA, while other targets are Prostate Stem Cell Antigen (PSCA), Six-Transmembrane Epithelial Antigen of Prostate (STEAP), and a G-protein coupled receptor named OXER1.[180]

For prostate cancer, numerous preclinical, ongoing clinical, and completed clinical studies have been carried out and reviewed elsewhere.[180] However, this article only reviews the completed clinical studies. Some of the TRT based agents for prostate cancer are elaborated in Table 8.[181–195]

PSMA targeting has emerged as a promising agent as it is highly overexpressed in prostate cancer cells. A recent study on twenty-one patients expressing prostate specific antigen in prostate cancer exhibited therapeutic efficacy with agent ^{177}Lu-PSMA-617.[195] There are significant challenges in RIT-based prostate cancer treatment, but advancements have been made with the development of radiolabeled antibodies. For example, FDA approved ProstaScint™ (^{111}In conjugated with 7E11/CYT-356 to target PSMA) for diagnostics of metastatic prostate cancer led to the development and trials of various antibodies as vectors for RIT-based therapeutics of prostate cancer.[196] It includes murine antibodies (muJ415, muJ533, muJ591, and muE99) and a humanized form of muJ591 (huJ591) to target the PSMA-external domain.[197–201] PSMA-targeting vectors also include urea, phosphorus, and thiol-based ones. Amongst them, urea-based compounds have a very high PSMA binding affinity.[202] However, PSMA targeting has some expected toxicity due to PSMA expression in the renal tubules, duodenum, salivary and lacrimal glands, and non-myelinated ganglia.[203]

Brain Tumors

Brain tumors are the most lethal cancers to date. They are classified into primary and secondary (also called metastatic) tumors. Primary brain tumors originate from the brain tissues or their surrounding region and are further classified as glial (originating from glial cells) or non-glial (nerves, blood vessels, and glands in the brain) and malignant or benign. Metastatic brain tumors migrate to the brain from the breast (5.1%), colorectal (1.8%), lungs (19.9%), melanoma (6.9%), and renal (6.5%) organs via the bloodstream [204]. Benign brain tumors include ganglioma, ganglioglioma, meningioma, etc., while malignant brain tumors include glioblastoma multiforme (GBM), astrocytoma, etc.[205]

Some of the TRT based agents for brain tumors are elaborated in Table 9.[206–226] SSTR2 is highly expressed in low-grade and anaplastic gliomas, leading to the development of ^{90}Y-DOTATOC with effective results.[206,207] It has also proven efficacious for recurring or progressing glioblastoma.[208]

Trans-membranous neurokinin type-1 receptors are highly expressed in brain tumors and act as a physiological receptor for the ligand neuropeptide Substance P (SP). Various radionuclides bound to DOTA-SP are discussed in Table 9. Moreover, it has led to the development of two new bioconjugates, namely, ^{68}Ga-DOTA-SP and ^{213}Bi -DOTA-SP.[227]

Epidermal Growth Factor Receptor (EGFR), a tyrosine kinase receptor, is overexpressed in glioblastoma multiforme. EGFR activates MAPK and PI3K–Akt pathways, causing excessive proliferation. Interestingly, EGFR is an internalizing receptor and thus acts as an attractive site for Auger electron-based radionuclide agents.[209–211] It is also targeted for imaging.[228] Similar to EGFR, EGFRvIII is also a tumor-specific site.[229,230] Antibodies like Cetuximab and mAb 425 are specific to EGFRvIII for diagnostic purposes, but therapeutic agents are yet to be developed.[231–234] ^{131}I-chTNT-1/B Mab are specific to histone H1 complexed to DNA. Interestingly, they do not target the cell membrane of healthy cells and are specific to the non-

Table 9. The table schematically represents TRT agents, associated vectors, target site, cancer type for brain tumors.

Agent	Vector	Chelator	Target	Cancer type	Ref.
PRRT-based agents					
^{90}Y-DOTATOC	Octreotide	DOTA	SSTR2	Low-grade and anaplastic glioma, recurring or progressing glioblastoma.	206–208
^{225}Ac-DOTA-SP	neuropeptide Substance P	DOTA	Neurokinin type I receptor	Human glioblastoma cell lines (T98G, U87MG, U138MG)	215
				Recurrent glioblastoma	216
^{90}Y-DOTAGA-SP	neuropeptide Substance P	DOTA	Neurokinin type I receptor	Grade II and III glioma	217
^{177}Lu-DOTAGA-SP	neuropeptide Substance P	DOTA	Neurokinin type I receptor	Grade II glioma	217
^{213}Bi-DOTA-SP	neuropeptide Substance P	DOTA	Neurokinin type I receptor	Grade II- IV gliomas	218
RIT-based agents					
^{125}I-mAb 425	Monoclonal antibody 425	-	Epidermal growth factor receptors	Glioblastoma multiforme	209–211
^{131}I-labeled 3F8	murine monoclonal antibody 3F8	-	cell-surface disialoganglioside GD2	Recurrent medulloblastoma	219
^{188}Re-Nimotuzumab	Nimotuzumab is a humanized monoclonal antibody	-	epidermal growth factor receptors	Recurrent high-grade glioma	220,221
^{125}I-mAb 425-TMZ	mAb 425 is murine monoclonal antibody Temozolomide (TMZ) acts as an adjuvant	-	epidermal growth factor receptor	Astrocytoma and Glioblastoma multiforme	210,222
Cotara® (^{131}I -chTNT-1/B Mab)	chimeric monoclonal antibody (chTNT-1/B MAb)	-	H1 histone complexed with DNA	Gliomas and anaplastic astrocytoma	212–214
^{131}I-BC2	murine monoclonal antibodies BC-2	-	Tenascin (glycoprotein)	Malignant glioma	223
^{131}I-BC4	murine monoclonal antibodies BC-4	-			
^{131}I-8IC6	monoclonal antibody 81C6	-	Tenascin (glycoprotein)	Malignant glioma	224,225
^{90}Y-biotin	3 step strategy, first biotinylated anti-tenascin MoAb is administered followed by avidin followed by 90Y-biotin	-	Tenascin (glycoprotein)	Glioma	235
^{131}I-L19SIP	human antibody L19SIP (Radretumab)	-	antigen extra-domain B fibronectin (EDBF)	brain metastatic lesions	226

diffusible protein of malignant brain tumors.[212–214] Another specific target, tenascin, is expressed in high grade gliomas but absent in normal tissues. It has led to the development of specific antibodies discussed in Table 9. Due to the efficiency of tenascin-based agents, a three-step pre-targeting strategy with ^{90}Y-biotin has also been investigated. This technique offers maximum potential with minimum toxicity.[235]

Therefore, PRRT and RIT are primarily employed for the treatment of different types of brain tumors. Overall, PRRT-based treatment usually targets SSTR, neurokinin Type 1 receptors, and prostate membrane antigen, while RIT majorly targets EGFR, the DNA-Histone H1 complex, Tenascin, and Fibronectin.

Malignant Lymphoma

Malignant lymphoma is an umbrella term for several types of haematological cancers originating from lymphocytes (white blood cells). Lymphomas can be classified into Hodgkin's lymphoma, non-Hodgkin lymphoma, multiple myeloma, and immunoproliferative diseases. According to the 2016 classification by the WHO, lymphomas can be subdivided into dendritic cell neoplasms, histiocytic neoplasms, Hodgkin lymphoma, mature B-cell neoplasms, mature NK neoplasms, mature T neoplasms, and post-transplant lymphoproliferative disorder (PTLD).[236] These lymphomas can be subclassified based on histological subtypes, immature or mature forms. Amongst all the lymphoma subdivisions, B-cell lymphomas have the highest prevalence. RIT is the most commonly exploited therapy for lymphoma treatment due to the radiosensitivity of lymphoma cells.[237,238] The significant antigens overexpressed in various lymphomas are anti-CD20, anti-CD22, and anti-CD37.

CD19 is transmembrane protein overexpressed in B-cells. Anti-CD19 mAb bound to radionuclides has shown efficacy in Burkitt's lymphoma xenograft murine model.[239] CD20, an activated glycosylated phosphoprotein, is normally expressed in B-cells but overexpressed in many B-cell lymphomas. CD22 is a transmembrane protein expressed only on mature B cells. CD30 or tumor necrosis factor receptor superfamily 8 (TNFRSF8) are overexpressed in many B-cell lymphomas. ^{90}Y conjugated with HeFi-1 (anti-CD30 mAb) is under investigation for Hodgkin lymphoma.[240] CD37 is an internalizing transmembrane antigen overexpressed in many B-cell lymphomas. CD38 is a transmembrane glycoprotein overexpressed in multiple myeloma and other B-cell lymphomas. CD74 is the gamma chain invariant of MHC class II overexpressed in many B-cell lymphomas. Anti-CD74 mAb bound to β- or Auger-particle emitting radionuclides have shown efficacy in Burkitt's lymphoma in-vitro cells.[241] These are the various vectors that bind to radionuclides for RIT in various lymphomas.

Table 10. The table schematically represents TRT agents, associated vectors, target site, cancer type for non-Hodgkin's Lymphoma.

Agent	Vector	Chelator	Target	Cancer type	Ref.
RIT-based agents					
Bexxar® (^{131}I-tositumomab)	Tositumomab is an immunoglobulin G murine monoclonal antibody	-	CD20	FDA approved for non-Hodgkin's Lymphoma	252
Zevalin® (^{90}Y-Ibritumomab tiuxetan)	murine antiCD20 monoclonal antibody	-	CD20	FDA approved for non-Hodgkin's Lymphoma	252
^{131}I-labeled Rituximab	Rituximab is chimeric IgG1 monoclonal antibody	-	CD20	Relapsed or refractory non-Hodgkins lymphoma.	248
177Lu-c-DTPA-Rituximab	Rituximab is chimeric IgG1 monoclonal antibody	CHX-A"-DTPA	CD20	non-Hodgkins lymphoma.	253
^{177}Lu-lilotomab-satetraxetan (Betalutin)	murine antibody lilotomab	Satetraxetan is DOTA Chelator	CD20	rituximab-resistant Raji2R and the parental Raji cell lines	249
^{90}Y- epratuzumab	Epratuzumab is humanized monoclonal antibody	DOTA	CD22	non-Hodgkin's lymphoma	250,251

Non-Hodgkin's Lymphoma

Non-Hodgkin lymphoma is a highly prevalent cancer (nearly 85%) that arises from B cells and has numerous immunological tumors associated with it.[242] Various factors leading to non-Hodgkin lymphoma include age, sex, ethnicity, genetics, Epstein-Barr virus infection, human immunodeficiency virus-induced immunosuppression, etc.[243] The major TRT agents for non-Hodgkin lymphoma are ~~is~~ based on RIT. Certain studies suggest that RIT, if used as the first line of defense, has higher efficacy than other treatments. A descriptive comparative analysis of RIT with other treatments and the use of RIT as the first or second line of defense is reviewed elsewhere.[244]

The significant radionuclides investigated for non-Hodgkin lymphoma are ^{90}Y and ^{131}I. The potential of other possible radionuclides is under investigation, with major hopes for ^{177}Lu, ^{67}Cu, ^{225}Ac, and

^{211}At.[245–247] Some of the TRT based agents for non-Hodgkin's lymphoma are elaborated in Table 10 .[248–253] Due to the success of Bexxar and Zevalin, CD20 is a major target for non-Hodgkin lymphoma. Rituximab is a chimeric IgG(1) anti-CD20 monoclonal antibody employed as a targeting agent for CD20 and has recently found efficacy in B-cell lymphoma apart from non-Hodgkin lymphoma.[248,254] However, it causes myelosuppression, grade IV hematological toxicity, and patients may develop resistance to Rituximab.[248] ^{177}Lu-lilotomab-satetraxetan (Betalutin) is studied for rituximab-sensitive non-Hodgkin lymphoma. It is believed reverse rituximab resistance, promote rituximab binding, and act synergistically with rituximab.[249] Apart from CD20, CD22 has also been targeted for non-Hodgkin's lymphoma.[250,251] Moreover, the combination of epratuzumab with rituximab,[255] anti-CD22 ^{90}Y-epratuzumab tetraxetan with the anti-CD20 veltuzumab, has also been investigated for possible therapeutic efficacy.[256]

Table 11. The table schematically represents TRT agents, associated vectors, target site, cancer type for Hepatocellular Carcinoma.

Agent	Vector	Chelator	Target	Cancer cells/Clinical trials	Ref.
RIT-based Agents					
^{131}I-labeled Metuximab or ^{131}I-labeled HAb18 F(ab′)2 (LICARTIN)	LICARTIN is an FDA approved drug. HAb18 F(ab′)2 (Metuximab) is bivalent fragment of HAb18G/CD147		HAb18G/CD147	FHCC-98 and MHCC97-H cells	265,266
^{131}I-CD147-Ab	CD147 is a monoclonal antibody		CD147	Rabbit VX2 animal model	269
^{225}Ac-MACROPA-GC33	GC33 (codrituzumab) is a humanized monoclonal IgG1	MACROPA	Glypican-3 (GPC3)	Human liver cancer cell line HepG2 xenografted in Female mice strain Crl:NU(NCr)-Foxn1nu	267
^{227}Th-OCTAPA-antiGPC3 or nanobody VHHGPC3	GC33 (codrituzumab) is a humanized monoclonal IgG1	OCTAPA	Glypican-3		268

HEPATOCELLULAR CARCINOMA

In the liver, cancer can be both primary and malignant. Hepatocellular carcinoma is the primary malignant liver tumor associated with cirrhosis, hepatitis B, hepatitis C, non-alcoholic fatty liver, etc.[257] In hepatocellular carcinoma, the arterial system supplies blood to malignant hepatocellular tissues, while the portal system supplies blood to normal hepatocellular tissues. There are limited nuclear medicine-based study for liver cancer due to the high risks of radiation-induced liver disease or radiation hepatitis.[258–260]

TRT (as internal radiation therapy) and RIT have shown some efficacy in hepatocellular carcinoma.[261] In treating malignant hepatocellular carcinoma, various locoregional therapies like endo-radiotherapy and trans-arterial radiation embolization are also used.[262] Furthermore, various studies based on trans-arterial radioembolization principle have also been conducted.[263,264] These therapies are usually used in combination for improved effectiveness.

Some of the TRT based agents for hepatocellular carcinoma are elaborated in Table 11.[265–269] CD147, a glycosylated transmembrane cell surface protein, is found in various tumors.[270] Certain studies suggest the role of CD147 in hepatocellular carcinoma;[271,272] however, its specific activity remains to be elucidated. HAb18 mAb, and its bivalent fragment, HAb18 F(ab′)2 (Metuximab), are specific to CD147, and bind to the cells with high affinity. Studies like the development of HAb18G/CD147 and ^{131}I-labeled Metuximab are focused on investigating the role of CD147 in Hepatocellular Carcinoma and have shown positive results.[265] Moreover, phase I and II clinical trials suggest in favor of its efficacy.[266] Glypican-3 (GPC3) is highly expressed in hepatocellular carcinoma. It could be targeted with humanized monoclonal antibody GC33. However, GC33 is found effective only in combination with a radioactive compound like ^{225}Ac.[267] Nanobody VHHGPC3 has also been developed to target GPC3.[268]

OUTLOOK

The preliminary principle of TRT is to target receptors or sites highly expressed in tumor tissues but absent in healthy tissues. This principle is aimed at minimizing the side effects of currently available cancer treatment methodologies on health issues. Isotopes of various elements are now available to produce α, β-, and Auger electron-based radionuclides. A radionuclide may bind to one or more vectors specific to the tumor site. These vectors, primarily produced biologically, are based on proteins, antibodies, their fragments, etc. Direct or indirect methods can help achieve radionuclide-vector association. The direct methods are usually one-step reactions but with various limitations. On the other hand, indirect methods are more precise but complicated. The binding efficacy of the radionuclide-vector can be improved by the employment of acyclic or macrocyclic chelators.

However, these chelators may affect the binding affinity of a TRT agent due to their large size.

TRT has been the subject of research and study for over forty years, with considerable recognition given to it. Researchers and medical practitioners have some earnest hope for this therapy in improved cancer treatment. It could be realized with an uptrend in FDA-approved therapeutic drugs starting from 2018. The treatment has proven more effective in curing untreatable cancer and has numerous advantages over conventional oncology strategies. TRT is a boon in cancer therapeutics when the standard oncological therapies fail. However, it is usually incorporated as an alternative rather than a priority treatment strategy. It is because of the numerous associated challenges, such as pre-set perceptions amongst the public, a lack of medical specialties in nuclear medicine, technical issues with radionuclide supply, etc., that need to be addressed for future advances in this field of study. Moreover, it is a broad field of study that has yet to strike the right balance between diagnostics and therapeutics. TRT and its associated fields require further investigation to incorporate this field of radiation therapy as a primary, alternative, or combinatorial treatment method.

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Conflict of Interest

The authors declare no competing interests.

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