WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 12, Issue 13, 359-374. Review Article ISSN 2277– 7105

RADIOLABELED MICROSPHERES OF CANCER

Shiba S. Morris*[1], Anisha Arya[2], Kiran Dangwal[3] and Gulbahar[4]

Gyani Inder Singh Institute of Professional Studies Dehradun.

Article Received on
03 June 2023,

Revised on 24 June 2023,
Accepted on 14 July 2023

DOI: 10.20959/wjpr202313-29094

***Corresponding Author**
Shiba S. Morris
Gyani Inder Singh Institute of Professional Studies Dehradun.

ABSTRACT

Radioactive microspheres can selectively target a variety of tumors without inappropriately irradiating non-tumor tissue. These radioactive microspheres are radioactive atoms that are delivered to tumors. Radioactive microspheres are injected through the blood supply to stop tumor growth and allow surgical abolish once the tumor reduce. This review article gives a perspective on number of feature of radioactive microspheres and their role in the treatment of various melanoma.

KEYWORDS: Cytotoxic, Radio-nuclides, Radiotherapy, Tumors.

INTRODUCTION

Prostate specific membrane antigen [PSMA] is expressed on the neovasculature of tumors, to deliver radio therapeutic nuclides to prostate cancer and other types of carcinomas, small-molecule PSMA inhibitors are changed. Actually, PSMA inhibitors mimic glutamyl folate, neuropeptide N-acetylaspartyl glutamate, and its derivatives. All of these small-molecule RPT medications, including the 177Lu-labeled PSMA-R2 and PSMA-617, are either urea- or phosphoramidate-based inhibitors, or both. The phosphoramidate and urea activities in the main active site of PSMA can interact with zinc. Additionally, these tiny molecules can interact with PSMA's S1 glutamate pocket and entrance funnel. The entry funnel allows for a variety of changes to instantaneous chelators for radiolabeling with therapeutic and imaging radionuclides.

It is just as reliant on comprehending signaling networks and discovering medications that block putative cancer phenotype-causing pathways as natural treatment is. Surprisingly, the failure rate in clinical trials of biological cancer treatments is 96%, this is due to targeting the wrong signaling pathways and the active ingredients selected for clinical trials.[2] Microspheres achieve promise goals in controlled drug delivery and site-specific delivery. In

recently, there have been scientific and technological advances in the research and development of radiolabeled microspheres. They have been successfully used to treat various types of carcinoma and tumors.[3] Chemotherapy and external radiation therapy are ineffective and dangerous, so internal radiation therapy is an alternative treatment for these.

With regards to both primary and metastatic cancers, this radio-labeled microsphere has demonstrated high stability and effectiveness. A variety of tumors can be specifically targeted by radioactive microspheres without overwhelming healthy tissue. To prevent tumor growth from the blood supply, radioactive micro-beads are administered. Once the tumor has decreased, the treatment can be stopped.

This article discusses several facets of radioactive microspheres and how they may be used to treat various cancers and tumors.[4,5] For radioactive transfer, radionuclides with various radiological characteristics—primarily beta particles or extremely potent alpha particles—are utilized. Nuclear medicine imaging tools can almost always observe radio-nuclides to evaluate drug targeting, providing considerable benefits over current therapeutics and enabling precision medicine approaches for RPT administration.[6]

There are several benefits of total-body, high-intensity, short-range radiation therapy over current treatment options for cancer patients. The capacity to map and estimate dosages that directly influence efficacy and possible toxicity is one of these benefits.[7,8]

Types of Radionuclide

The most widely used radiopharmaceutical is a molecule labelled with technetium-99m that has sodium pertechnetate added to it. The physicochemical characteristics of technetium-99m are perfect. It only emits gamma rays that fall inside the gamma camera detector's detection range. The patient's exposure to radiation is kept to a minimum due to its 6-hour half-life. The radioactive isotopes 90Y (Yttrium), 188Re (Rhenium), and 166Ho (Holmium) are also significant.[9,10,11,12]

Yttrium-90Y

Nuclear decay strontium-90 also produces an isotope of yttrium called yttrium-90Y, which has a half-life of 29 days. The high-energy, pure beta-emitting isotope 90Y has a half-life of 64 hours. The maximal radiation dosage received by tissue from beta particles, with an energy of 2.27 MeV, is 11.1 mm. There are two major problems with the 90Y. First, the

neutron activation period needs to be extended (to more than two weeks) for yttrium to be therapeutic. Second, since 90Y is a pure beta-emitter and does not create imaging gamma rays, clinical investigations cannot directly assess the bio-distribution of microspheres loaded with 90Y. Use in the treatment of lymphomas and hepatocellular carcinoma etc.[9,10,11,12]

Rhenium ^{188}Re and ^{186}Re

The use of radioisotopes in radiation treatment is favored due to their distinct physical characteristics. In contrast to 188Re, which has a half-life of 16.9 hours and a maximum beta energy of 2.12 MeV, 186Re has a half-life of 3.8 days and a maximum beta energy of 1.07 MeV. Gamma rays from both isotopes may be captured on camera. Use in the treatment of metastatic prostate, breast, and colon cancers.[9,10,11,12]

Holmium ^{166}Ho

It is created by the neutron capture of the naturally abundant 165 Ho. Maximum beta particle energies for the decay of 166Ho are 1.86 and 1.77 MeV. The half-life of it is 26.8 hours. Its physical properties may be beneficial for a variety of medical ailments, including rheumatoid arthritis, malignant skin disorders, and liver diseases.[9,10,11,12]

Table 1: Type of material used in radio microspheres.

S.No	Type of material used in radio microspheres	Microsphere diameter (µm)	Radioisotope use	Purpose of application
1	Glass Aluminosilicate Lithium silicate Magnesium alumino silicate Potassium silicate	20-30	^{32}P ^{186}Re/^{188}Re ^{90}Y ^{166}Ho	For imaging of primary and metastatic tumors
2	Albumin Human bovine serum albumin	25	^{90}Y ^{186}Re/^{188}Re ^{99m}Tc,	Lung-tumours, Radiosynovectomy, Lung scanning
	Resins Aminex A-27 Aminex A-5 BioRex-70	29-35	^{166}Ho ^{90}Y ^{186}Re/^{188}Re	For liver cancer
	Polymers a) Polylactic acid b) Polyglycolic acid	25-50	^{186}Re/^{188}Re ^{90Y}	For head and neck cancer

The mechanism of action for Radio - Microsphere

Radiation-induced cell death serves as the radio microspheres' primary mode of action. The radio-microsphere has the advantage of providing access to an extensive knowledge base on

radiation therapy. However, unlike radiotherapy, it is important to understand how these factors contained in the radioactive microspheres affect the treatment.[13]

RPT works by destroying cells through radiation-induced cell death. Soon after radiation and radioactivity were discovered, research into their impact on tissues and malignancies began. RPT offers the advantage of utilizing the extensive radiation body of knowledge. It is crucial to comprehend how RPT varies from radiation and how these features are exclusive to RPT-related therapy. Where the agent localizes and how long it functions are two questions regarding RPT. Responses to these queries, the dosage absorbed by malignant tissue in comparison to healthy tissue, and any potential therapies are all assessed. A specific absorbed dose may have varied biological effects on a malignancy depending on how quickly it is supplied.[8-10] The effects of giving a tumor a dose of 30 Gy As is customary with RPT, over a period of weeks at an exponentially falling dosage rate, will differ greatly from those of giving the same dose at the much higher dose rates used in radiotherapy (for instance, daily, 2-Gy fractions over 15 days). The biological healing and radio sensitivity characteristics of the malignancy determine how differently things manifest physically. Problems with dose-rate may potentially have an impact on healthy organs.[14]

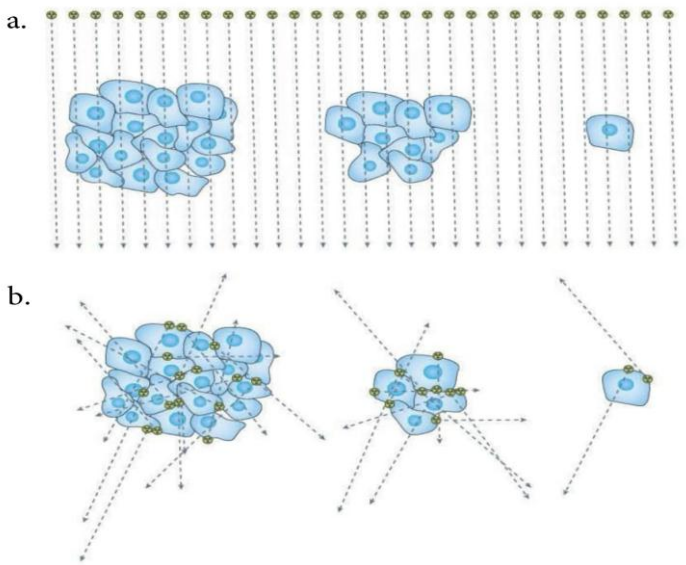

Fig1 a. Radiation given by external beam delivers to the whole body.

b. Radiation is directly administered to cancerous cells or their surroundings during radiopharmaceutical treatment

Another key differentiator that is important in understanding this therapy is its reduced ability to heal due to reduced numbers of target cells shown in figure 1. As the number of target cells

decreases during radiation therapy, the likelihood that a fixed absorbed dosage will kill every cell increases. The likelihood that all cells will die increases with the number of cells destroyed by an absorbed dose of radiation.[15] On the other hand, with RPT, fewer cells do not raise the possibility of tumor control. This is due to the fact that different cells are exposed to radiation in different ways. Less cancer cells are present when more of the radiation's energy is deposited in the target cells when it is released by radionuclides on the surface of tumor cells.[14]

Radionuclides used for RPT

The capacity to deliver a very powerful kind of radiation directly to tumor cells is one of the characteristics of RPT. An understanding of RPT includes three types of radiation: photons, electrons and alpha particles.[16] Gamma and X-ray photons are the two different kinds of photons. X-rays have a lower energy than gamma rays and are produced via orbital electronic transitions. The distribution of RPT can be mapped using photon emissions from radionuclides, but localized cytotoxic radiation cannot be. Images may be created using photon energy ranging from 75 to 400 keV. All nuclear medicine imaging cameras, including -cameras and single-photon emission computed tomography cameras, function well at photon emission energies between 100 and 200 keV. Due to their 511 keV photon emission, many radionuclides also produce positrons or antielectrons, which PET cameras can detect. Energy levels and the kind of decay have an impact on electron emission.

Auger electrons, beta particles, and monochromatic electrons are associated with the RPTWhen an electron beam strikes a surface, it produces auger electrons. These electrons leave holes in the bottom shell (K, L, or M), which are then filled by electrons from the top shell. These emissions have a relatively small range, ranging from 1 to 1000 nm depending on the emission energy. These excretions can turn very cytotoxic when RPT agents build up in the nucleus.[16-20] rarely are RPTs with auger electron emitters used. Although a few human studies have not produced clinical efficacy, preclinical studies have demonstrated significant therapeutic efficacy.[21-24]

Electrons released from the nucleus are known as beta particles. They are the most prevalent kind of RPT agents and have a wider tissue range (between 1 and 5 mm). There are various radionuclides that release beta particles, and many of them also emit photons with energies that are suitable for imaging.

Samarium-153, lutetium-177, yttrium-90, and I-131 have been produced and are now being used extensively as beta-particle emitters. The most common and well-known of these is iodine-131, which is used to treat thyroid cancer.

A radioactive atom's nucleus releases the alpha particle, which is a helium nucleus with two protons and two neutrons. It may pierce tissue 50 to 100 meters deep, depending on the energy emitted. They are significantly bigger than electrons and positively charged. In comparison to an alpha particle, an electron has about 400 times more energy per route length. Compared to electrons, this results in far more damage along the route. The quantity of -particles that pass the cell nucleus affects the absorbed dosage necessary to produce cytotoxicity.

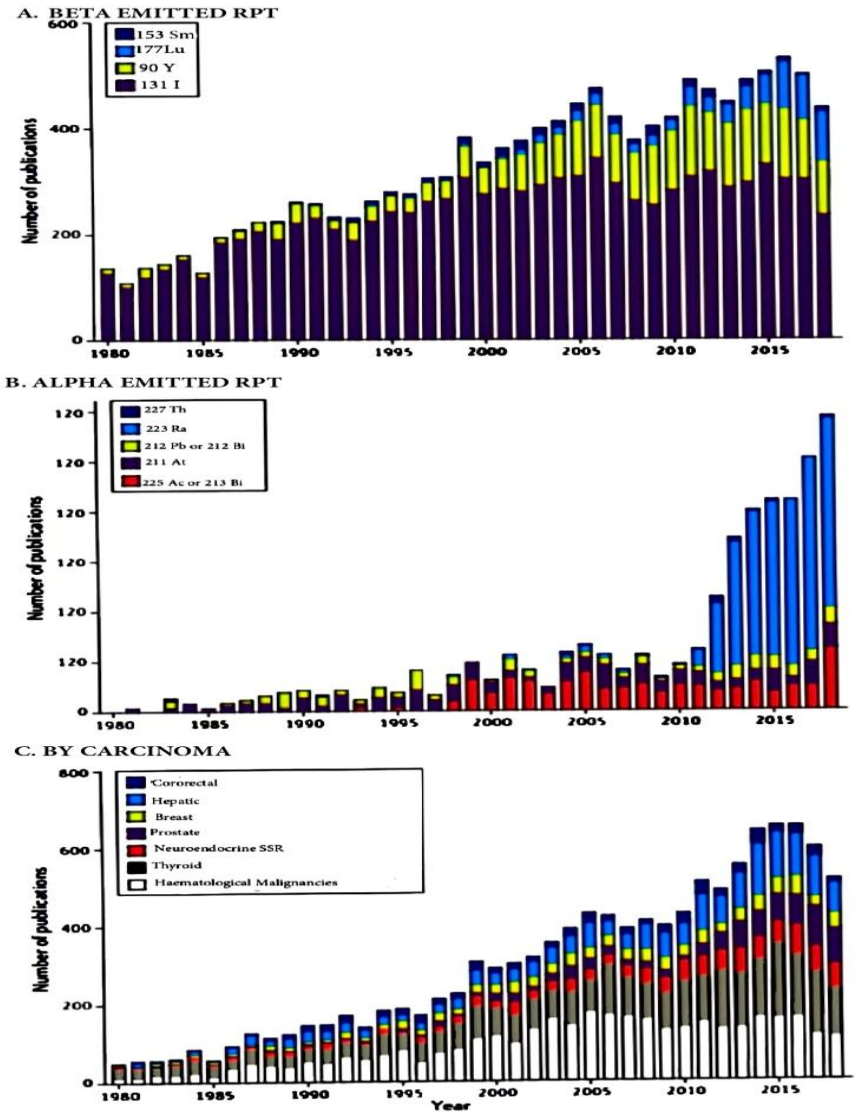

Fig. 2: A Several databases provide information on the number of publications on radiopharmaceutical treatment (RPT) for each radionuclide that produces beta

particles during a specific year. For instance, the description of lutetium-177 for usage in his RPT dates back to 1991.

B. Annual number of RPT releases using various data base alpha radionuclides.

C. Number of RPT articles per particular cancer per particular year recorded in various data bases.[21]

Cancer types targeted by RPT

RPT has had a significant historical influence on thyroid cancers and continues to do so now. Since his early 90s, hematologic malignancies have been researched and are still a hot issue. Since the 1980s RPT has significantly increased for both malignant liver disease and prostate cancer. This rise is related to the introduction of novel RPT agents, micro beads loaded with 90Y, and tiny emitter- and tag-tagged PSMA targeting structures (see below). Interest in RPT treating prostate cancer has considerably expanded after the Food and Drug Administration approved the alpha emitter 223Ra. The groundbreaking structures that started interest in RPT in liver and prostate cancer have not been able to be replicated in other solid tumors, including as colon and breast cancer**.** RPT drugs that target somatostatin receptor and neuroendocrine tumors may become accessible once 177Lu-labeled compounds are developed.[22] All cancers that meet the targeting requirements for radionuclide delivery are treatable with RPT. RPT, however, has only been investigated for a few different cancer types. The cancers under study are a reflection of the targets that are available, the accessibility of his RPT drugs to targets, institutional knowledge, and the advancement of clinical investigators.[21]

RPT medications in use and in clinical trials

RPT agents are freely accessible, and a large number are now being created. There are a total of four emitters of beta particles and five emitters of alpha particles. In order to give the -emitter 212Bi without being constrained by a half-life of one hour, lead-212 decomposes to bismuth-212. Alpha-emitters represent a possible area of RPT expansion.[24]

RPT may involve straight transporting of the radioactive component itself. RPT also uses a variety of 'delivery vehicles', including small molecules, radionuclides, radiolabeled peptides antibodies etc. make up the bulk of clinically studied RPT agents. Approaches to deliver liposomes or nanostructures have been investigated preclinical but have yet to be try out in human studies. Microspheres which are made up of resins and glass are proportionate well

entrenched. They are used to treat liver metastases from hepatocellular carcinoma or colon cancer and they are well provided through the hepatic artery.

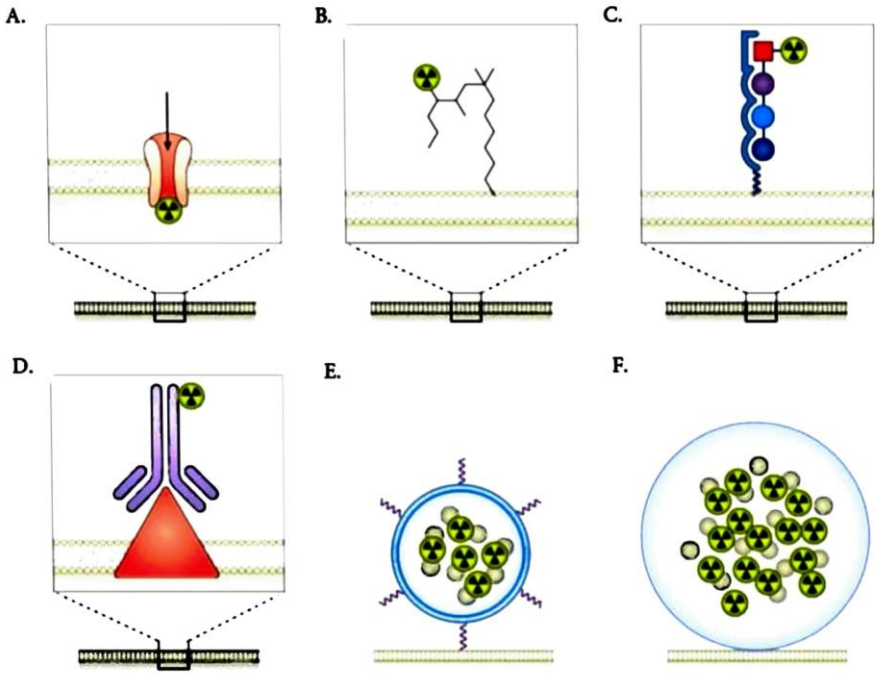

Fig 3. A] illustrated: radioactive element, B] small molecules, C] peptides, D] antibodies, E] Nano-constructs, and F] micro-beads are only a few examples of the several radiopharmaceutical therapeutic agent architectures utilized to deliver radiation.[26]

It is quite difficult to generalize. The prolonged circulation half-life of antibodies causes higher organ damage, particularly hepatotoxicity, despite the fact that antibody-mediated conveyance is bivalent and generally results in longer retentively. Small molecules and peptides, on the other hand, often have a limited tumor residence period but have the advantages of quick targeting and clearance. In any event, the goal retention period is greater than the medication's clearance rate when the drug is absorbed into the body and the radionuclide is held intracellular. Additionally, synthetic medicines that maximize tumor retention while enhancing clearance kinetics can be created.[27]

Chelated Radionuclide RPT

Radioiodine 131 I A well-known example of RPT is radioactive iodine treatment for thyroid conditions. The beta particle iodide 131, which emerges from the synchrotron irradiation of tellurium and emits a radioactive halogen with an 8.01-day half-life, was found by J. Livingwood and Glenn Seaborg. In nuclear reactors, tellurium-130 is radioactively

transformed into iodine-131 for industrial usage. Initially, thyroid cancer and hyperthyroidism were treated with radioactive iodine. With the aid of sodium iodide co-transporter, thyroid follicular cells and differentiated follicular thyroid cancer cells concentrate iodine. Thyroglobulin molecules, which have a high iodine content and are broken down to produce thyroid hormones, are where iodide is concentrated. The standard prescription for treatment for patients with metastatic differentiated thyroid cancer is radioactive iodine therapy. For individuals with thyroid cancer that arises from undifferentiated cells that have lost the molecular mechanisms of iodine concentration or from cells that do not engage in iodine concentration, radioiodine therapy is ineffective. Radioactive iodine, however, can be used to treat the latter group of patients.[28]

^{32}P, ^{90}Y

Some of the unconjecturable RPT drugs were originally evolved for radio synovectomy (there are no specifically approved radiopharmaceuticals) low cost compared to surgical synovectomy.[29] In addition to radio synovectomy, colloidal chromium phosphate and glathrin-32-containing microglobules have been found useful to treat refractory solid tumors. Malignant tumors can be stopped from growing by using these radiopharmaceuticals to shrink and destroy tumor cells. The main drawback of the aforementioned applications is that particle deposition depends on beam guidance (e.g., CT, X-ray, ultrasound, or direct inspection of the surgical region).[30]

^{223}Ra

The Food and Drug Administration recognized Radium-223 as the first alpha emitter, which was a crucial step in the development of subsequent alpha emitters that are now being produced. Radium-223 emits high-energy alpha particles that are known to damage nearby osteoblasts and osteoclasts' DNA double strands permanently. When it embodied into the freshly created bone matrix of osteoblastic metastases. This affects not only the cellular level, but also the signaling level of adjacent cancer arising in a depletion of effectors for abnormal bone formation and ultimately tumor growth, growth is impaired. The details mechanism of this complex interaction are still under investigation.[31,32]

^{153}Sm

Samarium-153 is 46.3 hours for half-life. It is a beta-emitting radionuclide that has been used to treat individuals who have osteoblast and mixed bone metastases, as well as prostate, breast, and other primary malignancies, to reduce their symptoms. By neutron bombarding

concentrated 152Sm2O3, which is melted in hydrochloric acid, into 153Sm2O3 yields 153Sm2O3, which is then converted into 153SmCl3. When combined with a number of phosphate ligands, 153SmCl3, which has poor bone absorption on its own, forms a complex that enriches in hydroxyapatite. The affinity of phosphonates for calcium in rapidly developing bone allowed for the accumulation and chemosorption of 153Sm in metastatic lesions next to healthy bone.[33,34]

Small-molecule RPT

[^{131}I]mIBG

Iodide-131 is currently utilized to treat a larger variety of cancers as a result of its inclusion in the targeting aim and effectiveness in treating thyroid conditions and carcinoma. For instance, patients with neuroblastoma get treatment with iobenguan I-131, a radio iodinated low molecular weight meta-iodobenzylguanidine ([131I]mIBG). It is the adrenergic neurotransmitter norepinephrine's counterpart. Selected vectors have been injected with the extremely sensitive electrophilic iodine compound iodide-131. It allows for quick iodination of the molecule by nucleophilic attack or substitution with an active aromaticity group.[34-35]

PSMA and folate receptor ligands

To target receptors, very small-molecule radiotherapeutic medicines have been used in the past. Think about the PSMA receptor and the folate receptor. Since PSMA is expressed on the neovasculature of tumours, small-molecule PSMA inhibitors are modified to deliver radiotherapeutic nuclides to prostate cancer and other types of carcinomas. In actuality, neuropeptide N-acetylaspartyl glutamate and its derivatives, as well as glutamyl folate, are mimicked in PSMA inhibitors. Like the 177Lu-labeled PSMA-R2 and PSMA-617, all of these minute molecule RPT drugs are either urea- or phosphoramidate-based inhibitors, or both. Zinc can interact with urea and the phosphoramidate activities in PSMA's major active site. Additionally, the S1 glutamate pocket and the entrance funnel of PSMA are designed to interact with these tiny molecules. For radiolabeling with medicinal and imaging radionuclides, the entrance funnel enables a choice of modifications to immediate chelators.[36]

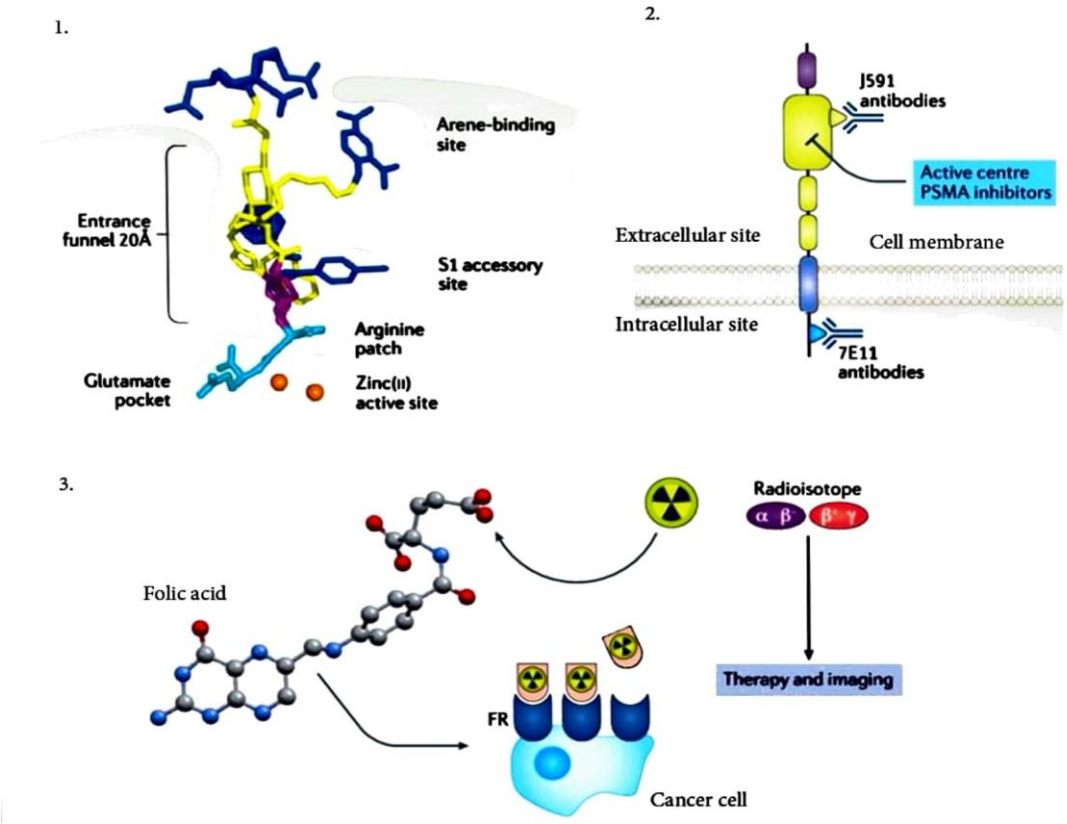

Fig. 4 1: PSMA and RPT for folate receptor binding of the PSMA inhibitor; prostate-specific membrane antigen. 2. The PSMA receptor reveals the locations where small molecules and anti-PSMA bind. 3; radiopharmaceutical therapy for the folate receptor. alpha emitter or beta emitter conjugation for therapeutic purposes.

RPT for peptide and antibody

The development of peptide receptor radionuclide therapy employing radiolabelled somatostatin analogue peptides was prompted by somatostatin receptor-mediated radionuclide localisation of neuroendocrine tumours in the 1990s. The more powerful semitter's yttrium-90 and, subsequently, lutetium-177, with their longer range emissions, have been utilised in the last 20 years following early success with the diagnostic radionuclide indium-111. This kind of therapy has received commendation for its success in treating bronchiogenic tumors, gastro-entero-pancreatic tumors, and metastatic paragangliomas. Disease-control rates for the two most often utilized radio peptides for PRRT, 90Y-octreotide and 177Lu-octreotate, range from 68 to 98%. A common finding is an increase in life quality together with cancer-related symptoms. The likelihood of identifying and defining the target cells, the somatostatin receptor, before to the initiation of therapy is one of the key advantages of PRRT over conventional therapies.[37]

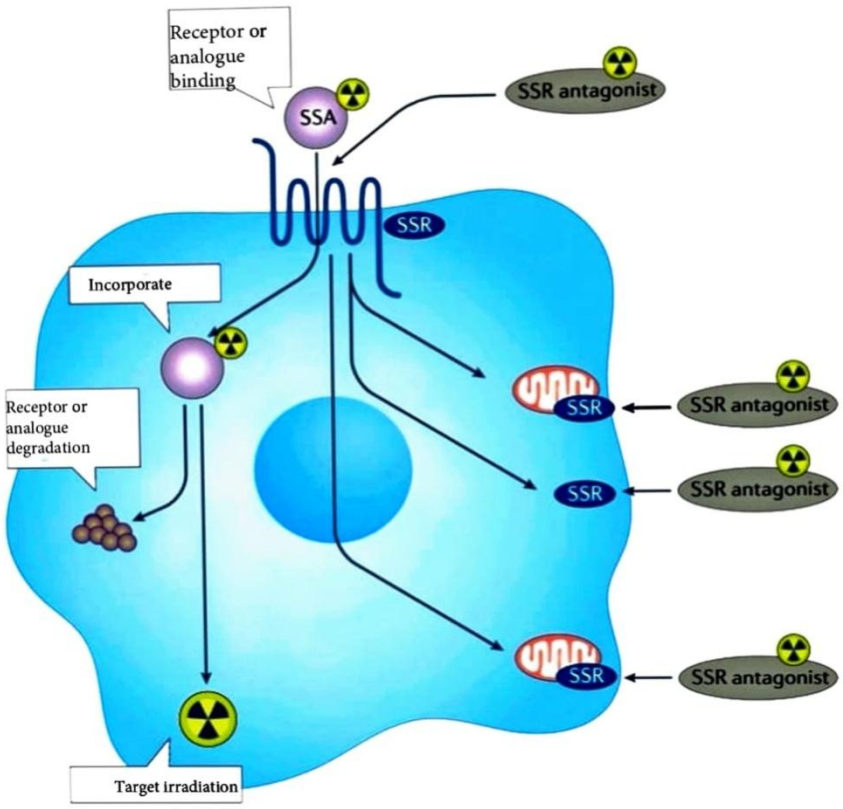

Fig. 4: Mechanism of activity of the peptide receptor & radionuclide therapy.

Antibody-based RPT

For RPT, almost exclusively IgG class antibodies have been employed. The IgG antibodies are proteinous, with a molecular weight of 150,000, a long circulation half-life of 2 to 5 days, and are finally broken down by the reticuloendothelial system and liver components.[38] A need for employing antibodies as workable radionuclide delivery systems was the capacity to produce antibodies (i.e., monoclonal antibodies) with exact reactivity and properties for the selected antigens. RPT research is dominated by hematological and lymphatic cancers.

[39]For radiolabeling and clinical research, the antibody against cell surface differentiation antigens is available. Prior research employed the widely accessible radioisotope ^{131}I. This enables the bio distribution of the radio iodinated antibodies that SPECT imaging might detect. These radiolabeled antibodies have been utilized as molecularly targeted alternatives to total body radiation in order to prepare for bone marrow transplantation or to directly target lineages with unchecked proliferation. In recent studies, astatine 211, an emitter that also contains anti-CD45, has been investigated as a less dangerous alternative to radiation or iodine-131 for myeloablation in preparation for transplantation.[40]

B-particle-emitting additionally, type 1 insulin-like growth factor receptor-expressing solid tumours can be treated with yttrium-90 radionuclides, and -emitter is currently being studied for this purpose. Thorium-227 is one of the antibodies being studied for the delivery of a low-dose-rate particle emitter. Coupled antibodies that target mesothelin are now undergoing phase-I clinical trials.[41,42]

Micro globules made of resin and glass that are 90Y-loaded have been colliding, and more research is being done. One study discovered extremely comparable findings for progression-free survival and overall survival, for example, hepatocellular carcinoma demonstrated considerably longer overall survival when treated with 90 Y-loaded glass micro globules as compared to 90 Y-loaded resin micro globules. Patients who are treated with 90 Y-loaded resin-based micro globules and 90 Y-loaded glass-based microspheres are compared.[41-42]

Challenges and considerations in RPT

Where other conventional therapeutic treatment techniques have fallen short, RPT has really demonstrated to be a very successful cancer treatment. RPT has not been incorporated into the cancer treatment after over 40 years of clinical trials. Because the drugs targeted a pathway that was not involved in the phenotypic development of the cancer, "targeted" cancer therapies have clinical trial failure rates of 96%. RPT has failed as a result of a failure to embrace and reevaluate this treatment, which may be partially accounted for by the treatment's interdisciplinary structure.

CONCLUSION

With improvements in clinical results of cancer treatment and a focus on reducing radiation therapy-related side effects, radio microspheres can be employed repeatedly as an ant cytotoxic drug. Additionally, radiation treatment is seeing technological and procedural advancements. In the end, it will lead to a continuous improvement in cancer therapy.

REFERENCES

1. Wong, C. H. et.al Estimation of clinical trial success rates and related parameters. Biostatistics, 2018; 20: 273–286.
2. Lin, A. et al. Off-target toxicity is a common mechanism of action of cancer drugs undergoing clinical trials. Sci. Transl Med., 2019; 11: 84-92.
3. Gill, M. R. et.al Targeted radionuclide therapy in combined-modality regimens. Lancet Oncol, 2017; 18: 414–423.

4. Dolgin, E.et.al Radioactive drugs emerge from the shadows to storm the market. Nat. Biotechnol, 2018; 36: 1125–1127.
5. Bentzen, S. M. et al. Quantitative analyses of normal tissue effects in the clinic (QUANTEC): an introduction to the scientific issues. Int. J. Radiat. Oncol. Biol. Phys., 2010; 76: 3–19.
6. Dale, R. & Carabe-Fernandez, A. The radiobiology of conventional radiotherapy and its application to radionuclide therapy. Cancer Biother. Radiopharm, 2005; 20: 47–51.
7. Amro, H., et.al Methodology to incorporate biologically effective dose and equivalent uniform dose in patient-specific 3-dimensional dosimetry for non-Hodgkin lymphoma patients targeted with 131I-tositumomab therapy. J. Nucl. Med., 2010; 51: 654–659.
8. Fowler, J. F. Radiobiological aspects of low-dose rates in radio immunotherapy. Int. J. Radiat. Oncol. Biol. Phys., 1990; 18: 1261–1269.
9. McDevitt, M. R. et al. Radio immunotherapy with alpha-emitting nuclides. Eur. J. Nucl. Med., 1998; 25: 1341–1351.
10. Wessels, B. W. & Rogus, R. D. Radionuclide selection and model absorbed dose calculations for radiolabeled tumor associated antibodies. Med. Phys., 1984; 11: 638–645.
11. Bloomer, W. D., McLaughlin, W. H., Adelstein, S. J. & Wolf, A. P. Therapeutic applications of Auger and alpha emitting radionuclides. Strahlentherapie, 1984; 160: 755–757.
12. O'Donoghue, J. et.al Relationships between tumor size and curability for uniformly targeted therapy with beta-emitting radionuclides. J. Nucl. Med., 1995; 36: 1902–1909.
13. Cherry, S. R., Sorenson, J. A., & Phelps, M. E. Physics in Nuclear Medicine e-Book (Elsevier Health Sciences, 2012).
14. Behr, T. M. et al. Therapeutic advantages of Auger electron- over beta-emitting radio metals or radioiodine when conjugated to internalizing antibodies. Eur. J. Nucl. Med., 2000; 27: 753–765.
15. Bodei, L., et.al Radionuclide therapy with iodine-125 and other Auger-electron-emitting radionuclides: experimental models and clinical applications. Cancer Biother. Radio pharm., 2003; 18: 861–877.
16. Howell, R. W. et al. in Biophysical Aspects of Auger Processes (Howell, R. W., Narra, V. R., Sastry, K. S. R. & Rao, D. V. Eds)., 1991; 290–318.
17. Kassis, A. I. et.al Radiolabeled nucleoside analogs in cancer diagnosis and therapy. Q. J. Nucl. Med., 1996; 40: 301–319.

18. Kiess, A. P. et al. Auger radiopharmaceutical therapy targeting prostate-specific membrane antigen. J. Nucl. Med., 2015; 56: 1401–1407.
19. Macapinlac, H. A. et al. Pilot clinical trial of 5-[125I] iodo-2'-deoxyuridine in the treatment of colorectal cancer metastatic to the liver. J. Nucl. Med., 1996; 37(4): 25–29.
20. Daghighian, F. et al. Pharmacokinetics and dosimetry of iodine-125-IUdR in the treatment of colorectal cancer metastatic to liver. J. Nucl. Med., 1996; 37(4): 29–32.
21. Sgouros, G. et al. Mathematical model of 5-[125I] iodo-2'-deoxyuridine treatment: continuous infusion regimens for hepatic metastases. Int. J. Radiat. Oncol. Biol. Phys., 1998; 41: 1177–1183.
22. Rebischung, C. et al. First human treatment of resistant neoplastic meningitis by intrathecal administration of MTX plus 125IUdR. Int. J. Radiat. Biol., 2008; 84: 1123–1129.
23. Behr, T. M. et al. Therapeutic efficacy and dose-limiting toxicity of Auger-electron vs. beta emitters in radio immunotherapy with internalizing antibodies: evaluation of 125I- vs. 131I-labeled CO17-1A in a human colorectal cancer model. Int. J. Cancer., 1998; 76: 738–748.
24. Ku, A., Facca, V. J., Cai, Z. & Reilly, R. M. Auger electrons for cancer therapy - a review. EJNMMI Radio pharm. Chem., 2019; 4: 27.
25. Brooks, R. C. et al. Metal complexes of bleomycin: evaluation of [Rh-105]-bleomycin for use in targeted radiotherapy. Nucl. Med. Biol., 1999; 26: 421–430.
26. Miao, Y. et.al Therapeutic efficacy of an 188Re-labeled alpha-melanocyte-stimulating hormone peptide analog in murine and human melanoma-bearing mouse models. J. Nucl. Med., 2005; 46: 121–129.
27. Champion, C. et.al Comparison between three promising ß-emitting radionuclides, 67Cu, 47Sc and 161Tb, with emphasis on doses delivered to minimal residual disease. Theranostics, 2016; 6: 1611–1618.
28. Howell, R. W. et.al Application of the linear-quadratic model to radio immunotherapy: further support for the advantage of longer-lived radionuclides. J. Nucl. Med., 1994; 35: 1861–1869.
29. Watson, E. E. et.al a model of the peritoneal cavity for use in internal dosimetry. J. Nucl. Med., 1989; 30: 2002–2011.
30. Zimmermann, R. G. Why are investors not interested in my radiotracer? The industrial and regulatory constraints in the development of radiopharmaceuticals. Nucl. Med. Biol., 2013; 40: 155–166.

31. Mikheev, N. B. Radioactive colloidal solutions and suspensions for medical use. At. Energy Rev., 1976; 14: 3–36.
32. Bayly, R. J., et.al 90Y ferric hydroxide colloid. Ann. Rheum. Dis., 1973; 32: 10.
33. Washburn, L. C. et al. 90Y-labeled monoclonal antibodies for cancer therapy. Int. J. Radiat. Appl. Instrum. Part B Nucl. Med. Biol., 1986; 13: 453–456.
34. Kozak, R. W. et al. Nature of the bifunctional chelating agent used for radio immunotherapy with yttrium-90 monoclonal antibodies: critical factors in determining in vivo survival and organ toxicity. Cancer Res., 1989; 49: 2639–2644.
35. Brechbiel, M. et.al Backbone-substituted DTPA ligands for 90Y radio immunotherapy. Bioconjug. Chem., 1991; 2: 187–194.
36. Stewart, J. S. et al. Intraperitoneal radio immunotherapy for ovarian cancer: pharmacokinetics, toxicity, and efficacy of I-131 labeled monoclonal antibodies. Int. J. Radiat. Oncol. Biol. Phys., 1989; 16: 405–413.
37. Oei, A. L. et al. Decreased intraperitoneal disease recurrence in epithelial ovarian cancer patients receiving intraperitoneal consolidation treatment with yttrium-90-labeled murine HMFG1 without improvement in overall survival. Int. J. Cancer, 2007; 120: 2710–2714.
38. Waldmann, T. A. et al. Radio immunotherapy of interleukin-2R alpha-expressing adult T-cell leukemia with yttrium-90-labeled anti-Tac. Blood, 1995; 86: 4063–4075.
39. Foss, F. M. et al. Phase I study of the pharmacokinetics of a radioimmunoconjugate, 90Y-T101, in patients with CD5-expressing leukemia and lymphoma. Clin. Cancer Res., 1998; 4: 2691–2700.
40. Witzig, T. E. et al. Phase I/II trial of IDEC-Y2B8 radio immunotherapy for treatment of relapsed or refractory CD20+ B-cell non-Hodgkin's lymphoma. J. Clin. Oncol, 1999; 17: 3793–3803.
41. Nisa, L., Savelli, G. & Giubbini, R. Yttrium-90 DOTATOC therapy in GEP-NET and other SST2 expressing tumors: a selected review. Ann. Nucl. Med., 2011; 25: 75–85.
42. Salem, R. & Thurston, K. G. Radio embolization with 90yttrium microspheres: a state-of-the-art brachytherapy treatment for primary and secondary liver malignancies. Part 1: technical and methodologic considerations. J. Vasc. Interv. Radiol., 2006; 17: 1251–1278.