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THERANOSTICS A PROMISING MODERN MEDICAL TOOL

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ABSTRACT

Among the innovative medical tools emerging in today's world, theragnostics is found to be a remarkable tool that resolves many complicated disease conditions through a single strategy. theragnostic, a term obtained by clipping of two terms, therapeutics and diagnostics is based on the usage of one radioactive element to trace (diagnose) and second radioactive element or drug exhibiting the therapeutic effect at specific site for specific disease. This has been employed as a promising tool itself in the field of cardiology, oncology, osteology and more to discover. By this method, diagnostic biomarkers are combined with therapeutic agents using which both shares a particular target in cell or tissues of the diseased patient. Theranostic works as a magnificent tool in focusing treatment of malignancies, such as neuroendocrine tumors (NETs) and prostate cancer. Radioactive agents such as (90) Y-octreotide, (177) Lu-octreotate and 177Lu-Dotatate works by targeting carcinoid tumors, glucagonomas and gastroenteropancreatic neuroendocrine tumors (GEP-NETs) respectively. Furthermore, as an aid in pain alleviation for patients with osteosarcoma or complicated prostate cancer that develops to bone metastases, through incorporation of [223Ra] Cl2 citrate and Radium-223.Fludeoxyglucose(18F)-NaF and Technetium-99m bisphosphonates are supplementally employed for imaging purpose. In cases with atherosclerosis, 18F-Fluoro-deoxy-glucose (PET) positron emission tomography, (18F-FDG-PET) along with (DCE-MRI) Dynamic contrast-enhanced MRI were engineered for monitoring and evaluating the delivery of L-PLP with its therapeutic efficacy. By this way, theragnostic had lead a pathway to precision medicine to cure diverse diseases in a prominent way. This review article focuses on providing sufficient collective data about theragnostic, a revolutionary medical tool that have led to noticeable approaches with well-designed nanomedicines for diverse disease management.

KEY WORDS: Theranostics, Nanomedicines, Neuroendocrine Tumors, 18f-Fluoro-Deoxy-Glucose, Positron Emission Tomography, Glucagonomas.

INTRODUCTION

In this advancing medical field, there are numerous innovative researches emerging day by day to save and enhance the human life. One among the innovative medical tools is theranostics, which found to be noticeable as this resolves many complicated disease conditions in one single package.

Theranostics have exposed its novelty in 1964, in the management of thyroid cancer using I131 as the radioactive drug and considered as a promising tool. In 1998, The term theranostics was first revealed by John Funkhouser in a public forum. theranostics is a term obtained by clipping of two terms, therapeutics and diagnostics. The word theranostics depicts the usage of one radioactive element to trace (diagnose) and second radioactive element or drug exhibiting the therapeutic effect at specific site for specific disease. This is also termed as theragnostics. This theragnostic has lead a pathway to precision medicine to cure diverse diseases in a prominent way. Theragnostic is a safe and efficacious therapy that improves the hospitality which are provided to the patient.[1].

This revolutionary medical tool has transformed the traditional medicine into precision medicine. [29] Theragnostics rationalizes the pharmacotherapy by

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providing appropriate drug at appropriate time for a specific patient in a unique way [10]. The main principles behind the theragnostics are biomarker profiling, pharmacogenetics and proteomics [2].

The application of this medical tool has proved itself in the field of cardiology, oncology, osteology, etc.

This is achieved by nano medicines via various forms which includes carbon nanotubes, quantum dots, metallic nanoparticles, polymeric nanoparticles, dendrimers and liposomes [1]. The main objective of this review article is to provide a detailed study on this neological medical tool and to ensure that this tool is really a boon to the world.

2. Historical background of Theranostics:

In 1964, the employment of theranostics in the field of oncology was evolved, when thyroid cancer was treated by RAI, at RMC institution with two-three beds indoor facility for the first time. It was now developed to be the country's largest nucleotide facility with isolation ward containing 16 beds and holds the record of providing treatment for countless thyroid cancer cases in world. Noble records of this institution includes treating NET with 177-lutetium (Lu-177) dotatate since2010 and PCa with Lu-177 PSMA since 2017. I-131 MIBG therapy for neuroblastoma and malignant pheochromocytoma are also discovered by the same in situation. Although the molecular imaging facilities have showed an exponential growth in the last five decades [4]. AERBa Government of India regulatory body for looking after the radiation safety aspects pertaining to radionuclide therapies. The most prominent among the logistic issues is the requirement of a large capacity delay and decay tank for the effluents from toilets attached to the isolation wards for radionuclide therapy. This requirement has been an infrastructural compliance challenge especially in an already functioning hospital. At the present moment, there are 92 isolation wards in the country with atotal capacity of about 200+ beds. Our institution has the facility of isolation ward for radionuclide therapy since its inception in 1996 with 3 patient beds [4]

3. Theranostics and Nanomedicine

The medical application of nanotechnology is referred to as nanomedicine, and this is made possible by a vast range of medical and scientific methodologies. One such approach is the use of nanoparticles in theranostics. The ultimate aim of combining nanomedicine and theranostics is to modify disease and patient-specific outcomes in such a way that they are drastically improved. Owing to their high potential to target specific organs or tissues, as well as their capacity to be manipulated with multifunctionality, nanoparticles possess significant advantages that are brilliantly suitable for employment in theranostic medicine. In line with the preceding statement, nanoparticles are able to target diseased areas within the body, thereby avoiding damage to healthy tissues.[36] Once the area of interest has been pinpointed, nanoparticles may then provide information on the extent of the disease, and even indicate disease response to treatment, if applicable. After acquisition of this information, nanoparticles maythen proceed with the delivery of the therapy as needed. Based on responses to internal or external stimuli, these nanoparticles are capable of administering exact concentrations of the required therapeutic agents. Furthermore, they can play an additional role in the monitoring of the drug delivery, release and efficacy. Nanoparticles are capable of evading premature destruction or degradation by physiological processes, unlike many conventional drug therapies. Moreover, the high surface to volume ratios seen with nanoparticles allows them to transport more diverse substances with the use of less extraneous material. In particular, nanoparticles may be exceptionally used in the diagnosis and treatment of cancers. They are ideal in this regard, because they are capable of rapidly and selectively accumulating at cancer-specific sites, and once there, emitting signals based on their specific biomarkers, subsequently to deliver the necessary therapy according to the data that they acquired.[36]

4.Phases in theranostics:

The proximity between diagnostics and therapy is expressed as "Methodology, which blends a specific drug along with a specific type of diagnostic testing agent that binds to a targeted molecule.[12]. In other words, "It is a technique that combines therapeutics with diagnostics" or is a combination of diagnosis and therapeutics, simultaneously or sequentially to diagnose and treat medical conditions. Theranostics refers to the pairing of diagnostic biomarkers with therapeutic agents that share a specific target in diseased cells or tissues.[11]. This concept plays a remarkable part in describing a fusion of particular radioactive drug, to identify (diagnose) the target receptor on the tumor cell membrane and a supplemental radioactive drug, for the treatment of certain type of tumor.[35]

4.1 Theranostics- Diagnostic phase:

Diagnostic phase of theranostic agent serves as a targeting tool for a therapeutic drug that binds to a membrane protein termed as somatostatin receptor (SSTR2) present in a tumor cell.

In recent study, it is discovered that a radiopharmaceutical tracer named Gallium 68 DOTATOC can target a carcinoid tumor by using a PET (positron emission tomography) scan. This radioactive material traces or localizes carcinoid tumor in an individual by binding to a target receptor containing SSTR2 (Somatostatin receptor type 2) G-protein presenting in the cell membrane of the tumor. This can be made transit to all the tissues and organs and bind to specific G-protein by injecting intravenously to the patient. Finally, the tumor will light up on a PET scan.

4.2 Theragnostic - Therapeutic phase

Let's consider the same study. Once if the carcinoid cancer is spotted out using PET scan with the help of Gallium 68 DOTATOC, it can be restored with another radionuclide that targets and kills a tumor cell. Those radionuclides include yttrium-90 (Y-90) or lutetium-177 (Lu-177).

Same like in Diagnostic phase, the therapeutically radioactive drugs, in particular Y-90-DOTATOC and Lu-177- can be made transit to all the tissues and organs and bind to specific G-protein by injecting intravenously to the patient. This radioactive drug traces or localizes carcinoid tumor in an individual by binding to a target receptor containing SSTR2 (Somatostatin receptor type 2) G-protein presenting in the cell membrane of the tumor where the diagnostic radioactive material is bound. Thereby it targets and kills a tumor cells having SSTR2 G-protein present in it. However, the Healthy cells around the tumor will not get affect by the drug as it does not have SSTR2 proteins on their cell membrane.

5. THERANOST ICS IN ONCOLOGY:

As Exciting tool in cancer Treatment:

Over the last few years, the application of theranostics have become more diverse with its benefits in carcinoid cancers and prostate cancers in particular. There are a various kind of tumors which are commonly found in the gastrointestinal and bronchopulmonary tracts which usually express somatostatin receptors. These somatostatin receptors provide symptomatic relief and treatment. Discovering new molecular targets that mainly focus on immunology are the recent advancement in the field of preclinical oncology which shows a budding future application in theranostics. There are so many recent studies that employ radioactive elements such as CD45-targeted therapy of acute leukemias and CD37-targeted therapy of B-cell lymphomas as an immunotherapy.[35] Commonly used radiopeptides for peptide receptor radionuclide therapy (PRRT); (90)Y-octreotide and (177) Lu-octreotate focuses on targeting carcinoid tumors, glucagonomas and various pituitary adenomas. Furthermore, using ^{223}Ra in a radioactive therapy of osseous metastases of prostate cancer proves that the application of radioactive materials is not limited only to thyroid cancer. Among such progressive therapiesavailable, PRRT is found to be very promising. In January 2018, the Food Drug and Authority (FDA) approved ^{177}Lu-Dotatate for use in gastroenteropancreatic neuroendocrine tumors (GEP-NETs).[15].

In peptide receptor radionuclide therapy, a specific radiopeptide is created that consist of a small radionuclide or radioactive material combined with a somatostatin like peptide or proteins that targets the cell containing somatostatin hormone in it. This radiopeptide can target the tumor cell by an overexpression mechanism. Theradiopeptide can be made transit to the tissues and organs containing carcinoid tumor cells and delivers a high dose of radiation by binding to specific somatostatin G-protein by injecting intravenously to the patient. Lutetium is a lower energy beta-emitting radionuclide. The therapeutic use of lutetium-^{177} (^{177}Lu) has shown better results in advanced gastroenteropancreatic and bronchial neuroendocrine tumors when compared with other therapies available.[37]

Myelotoxicity and nephrotoxicity are the adverse effects asscociated with this therapy since the radiopeptides are reabsorbed and accumulate in the renal interstitium. potent option in patients pretreated with ^{177}Lu-Dotatate is everolimus. Lutetium, combined with somatostatin analogs, has proven efficacy to treat gastroenteropancreatic NET in candidates with somatostatin receptor-positive advanced tumors and normal renal function. [40] This therapy has great potential as it decreases tumor size, improves symptoms, and improves quality of life. Additionally, we can conclude that the PRRT can prolong the survival of patient by low downing or inhibiting the cancer progression. Recent studies of theranostics in earlier tumor stages had optimized the dose and dosage schedule of radionuclide and discovered new targets by combining the diagnosis and therapy.[13]

6. THERANOSTICS IN OSTEOLOGY:

As a primer for molecular imaging & Aid in pain palliation.

Prostate cancer that occurs in the prostate gland, is the most common cancer affecting men. Estimated that, nearly 1.3 million new cases were recorded in 2019, worldwide. Development of bone metastases is seen in advanced prostate cancer patients which may lead to increased mortality, skeletal fracture and arthralgia. The occurrence of bone metastasis is round to be due to the interaction of osteoclasts (Bone resorbing cells) and osteoblasts (bone forming cells) with invading cancer cells. Recent surveys had reported that the advanced prostate cancer patients with bone metastases development shown a mortality rate of 90.1% (male).[38] The cancer cell growth gets enhanced when various growth factors enter the bone environment by activating receptor activator of nuclear factor-kappa B ligand (RANKL) by osteoclast-activating factor (parathyroid hormone-related peptide, PTHrP). According to Paget, "the growth of tumor foci tends to be the direct result of a specific organ's microenvironment" and this is called as seed and soil theory. Where the prostate cells are considered as seeds and bone (as a host land) is considered as soil. These cells slowly invade and proliferates in the axial bones where the red marrow will be in abundant like spine, pelvis and ribs.[22]

Additionally, leading to formation of lesions. These lesions are often painful, and may also further degrade quality of life through fracture, spinal cord compression, hypercalcemia, and impaired mobility. Resistance to the treatment occurs due to the disseminate nature of tumor cells that occupy the nutrient rich niche in

the bone.[24] Hence in development of bone metastasis in prostate cancer, the earlier diagnosis and therapy will be recommended.[43]

The Ulrasound, CT scan and MRI are the Conventional imaging modalities for Prostate cancer bone metastasis, that are employed in the bone lesion diagnosis.[18]. The agents that are administered at the metastasis site for imaging includes Fludeoxyglucose (18F)-NaF and Technetium-99m bisphosphonates. Samarium (153Sm) lexidronam EDTMP and Strontium-89 chloride were the phosphoric acid and ion that are approved for the palliative therapy of bone pain.[23] These are the beta particle-emitting agents that emits images for diagnosis.[14] However, there are some draw backs with these agents like; as per clinical trial it will not produce proper survival improvements, some organs cannot be imaged and irradiation of bone marrow.[41][223Ra] Cl2 citrate,[39] (Xofigo), was the first radiopharmaceutical agent that targets bone and used as a palliative treatment agent for pain. 223 Ra mimics the calcium and localize the site of prostate tumor cells that subsequently decays the bone.[3]. However, the drawback of 223 Ra is some organs cannot be imaged. The short path lengths of the alpha particles do not result in anemic responses and the drug is well-tolerated.[42] While difficult to image, efforts are underway to provide quantitative assessment of 223RaCl2 distribution to inform absorbed dose measures at sites of disease and background organs.[25]

7. THERANOSTICS IN CARDIOLOGY

Emergence of theranostics, a multifaceted agent have been promoted by the recent approaches in therapeutics coupled with nanoparticles, for providing synchronized diagnosis and treatment for Cardiovascular diseases.[6] The distribution time of therapeutic or diagnostic agent is elevated and target toxicity of the drugs is reduced by nano particle delivery system.[9].

MRI magnetic resonance imaging is a higly conceptual resolution with various outputs of vessels and plaque morphology. [17] Extensively studied novel magnetic resonance imaging (MRI) contrast agents includes Iron oxide nanoparticles (SPIONs) which encloses a combination of biodegradability , surface properties and favourable superparamagnetic properties of multifunctionality and easy modification for improved in vivo kinetics.[8].With the development of (HDL) high-density lipoprotein -like nanoparticles which exhibit an intrinsic affinity for atherosclerotic plaque macrophages due to the monolayer of apolipoproteins (ApoA-I or ApoA-II) have been a reason of continuous evolution in MRI technique and its contrast agents.[16] These HDL-like particles imposes several benefits, for-instance: (1) (7-12 nm diameter) small size, (2) protein constituents that are biodegradable , endogenous and withhold provoke immunoreactions, (3) mononuclear phagocyte system (MPS) does not recognize those particles. Furthermore, a significant network of contrast agents like (Gd-DTPA-DMPE) phospholipid-based gadolinium are carried and reconstitutes HDL-like particles. Doxorubicin filled hyaluronicacid-polypyrrole nanoparticles (DOX@HA–PPyNPs) is a higly encouraging theranostic agent for proliferating macrophages present in atherosclerosis lesions and is pH-responsive. Recent studies, reports continuous use of metal nanoparticles for effective imaging and targeted treatment of atherosclerosis with targeted gold-coated iron oxide (Fe2O3) nanoparticles in order to detect CD163 in atherosclerosis by MRI. Depending on the improved aspects of CD163 membrane receptor in macrophages, found in hemorrhagic sites of intraplaque or asymptomatic plaques, lies this targeting approach. Certain imaging modalities, such as 18F-Fluoro-deoxy-glucose (PET) positron emission tomography, (18F-FDG-PET) along with (DCE-MRI) Dynamic contrast-enhanced MRI were engineered for monitoring and evaluating the delivery of L-PLP and its therapeutic efficacy [7].

CT (Computed tomography),a potent and accurate technique for determining plaque calcification along with assessing coronary artery stenosis . The exactitude with contrast have been promoted using nanoparticles with distinctive properties like growth of CT imaging of macrophages in case of coronary atherosclerotic plaques through iodinated polymer nanoparticles [9].

An additional imaging technique, so- called photoacoustic imaging, through which the actual distribution of light absorbance within the organs is detected. According to this, for investigation of early inflammation that rises in endothelial cells, feasibility of gold nanorods (GNR) that are fused with anti-intercellular adhesion molecule-1 (ICAM-1) have been employed. This could be relatable to the growth of the atherosclerotic plaques. [19] For improved detection, multimodal nanosystems , aims to collaborate with the characteristics of various nanoparticles by genesis of hybrid nano systems incorporated with imaging techniques. namely, PET-CT and PET-MRI are techniques which combines the anatomical distinctness in CT and the superlative structural and functional properties of the cell receptors in tissues or sensitivity of this technique for imaging and tracing the metabolism of labeled cells by MRI [21].

Lipid nanoparticles, including liposomes and HDL-like nanoparticles have been categorized with contrast agents and flourishingly incorporated in techniques of multimodal molecular imaging. [30] Some researchers laid the development of dextran-coated magneto fluorescent Fe2O3 iron oxide nanoparticles, that are labeled along with near-infrared fluorochrome to interpret a PET and PET tracer 64Cu and accurately detectable imaging agent.[28] For early and effective detection of atherosclerosis, inflammatory biomarkers have been formulated in recent years.[31].

Nanoparticles plays a role as vehicles in drug delivery systems to correlate sustained release of the targeted drug

with targeting systems for delivery in specific tissues that are labelled. For instance, polymer nanoparticles have been incorporated for drug delivery in treating restenosis, that occurs after intervention in percutaneous coronary artery .[32] These nanosystems composed of polyethyleneglcol-based block copolymers containing core-shell nano particles incorporated with doxorubicin, an antiproliferative drug which is continuously released to the balloon-injured artery during procedure.[34] The stainless-steel balloon-expandable stents are coated using drug delivery nanosystem. This showed unique aspects of unusual vascular compatibility, electrodeposition coating technology with sustained delivery of the FITC marker into the porcine coronary artery which is stented, when corelated with the polymer-eluting stent that is dip-coated. [5].Improving the blood half-life along with vascular margination, and active targeting of drugs, lies the treatment goal of atherosclerosis.[26] Studies shows, comparing spherical and rigid discoidal structure, with that of platelet-like nanoparticles (PLN) having discoidal structure with mechanical flexibility, expressed enhanced surface-binding.[33] In vivo studies reported that these particles bombarded at the site of wound, was effectively mimicking and bleeding time was reduced by 65%, thus the natural platelets and its hemostatic function have been improved greatly.[20].

Figure-1.

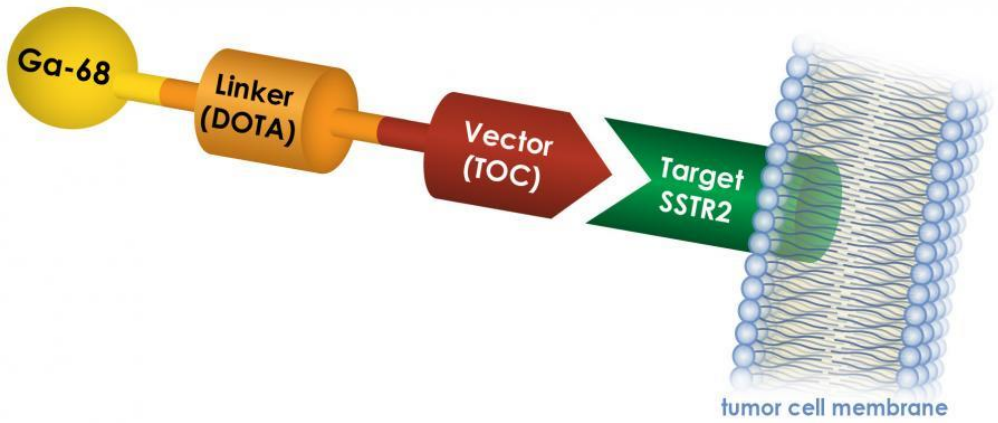


Figure-2.

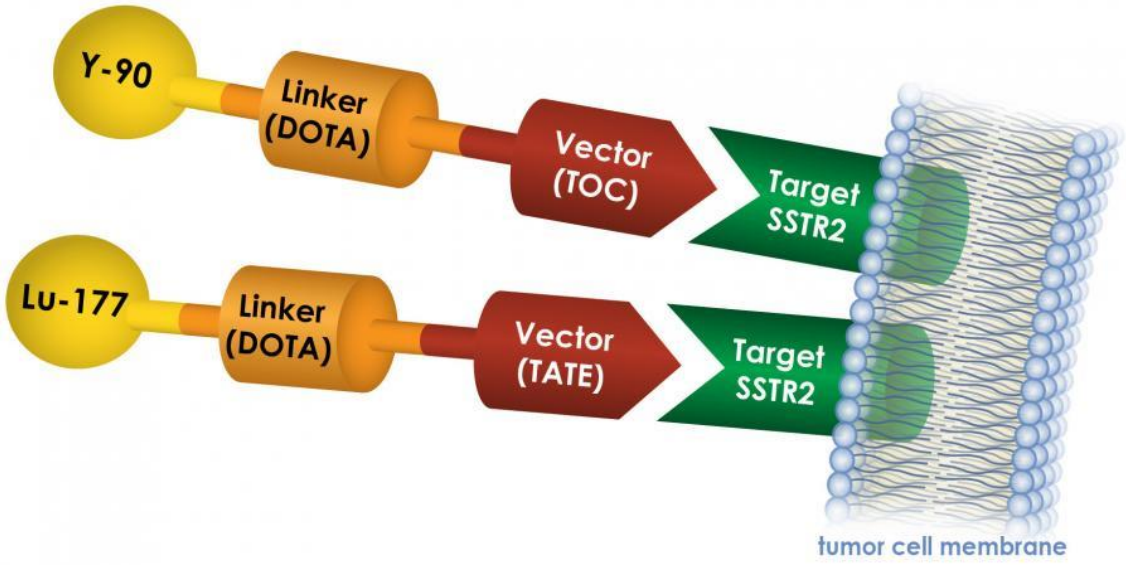


Figure-3.

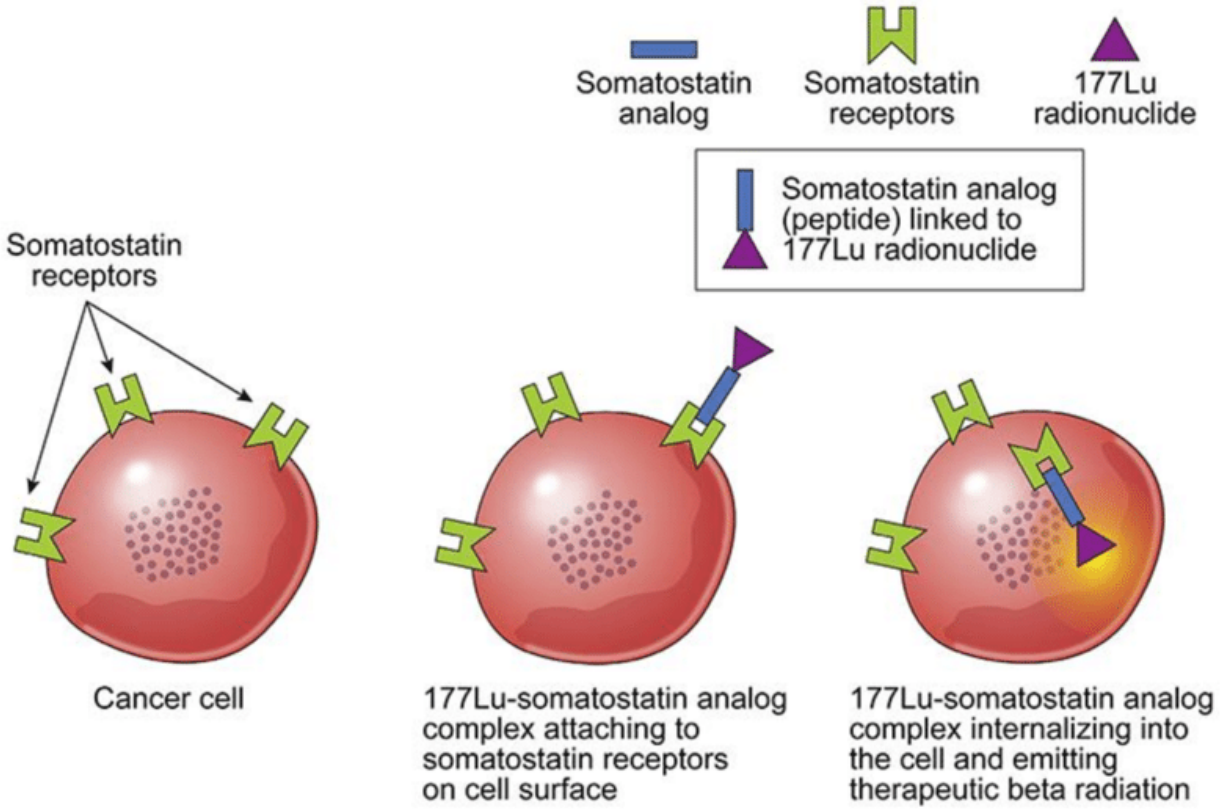
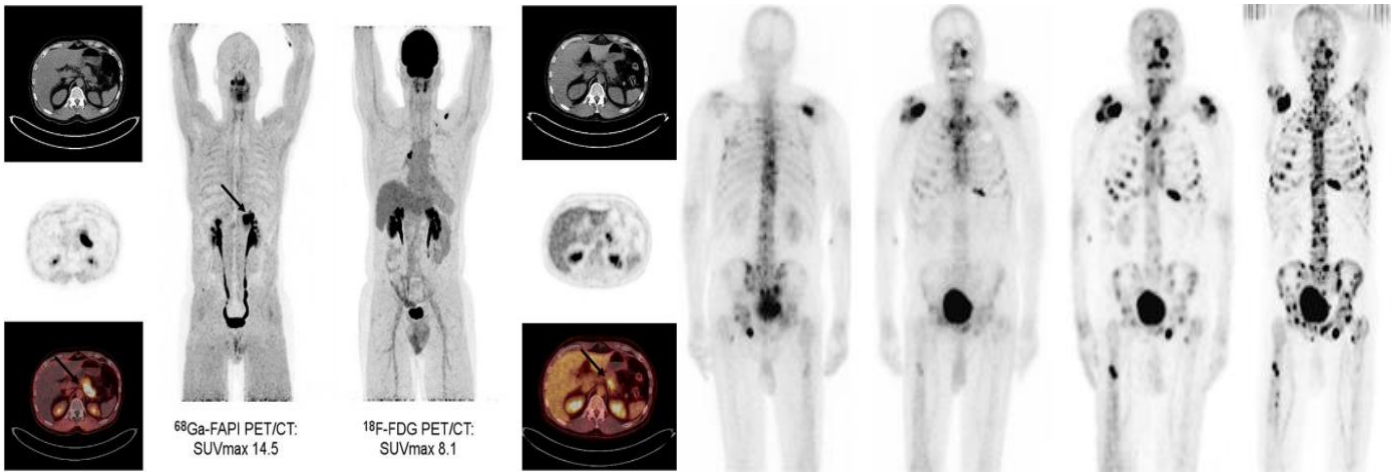
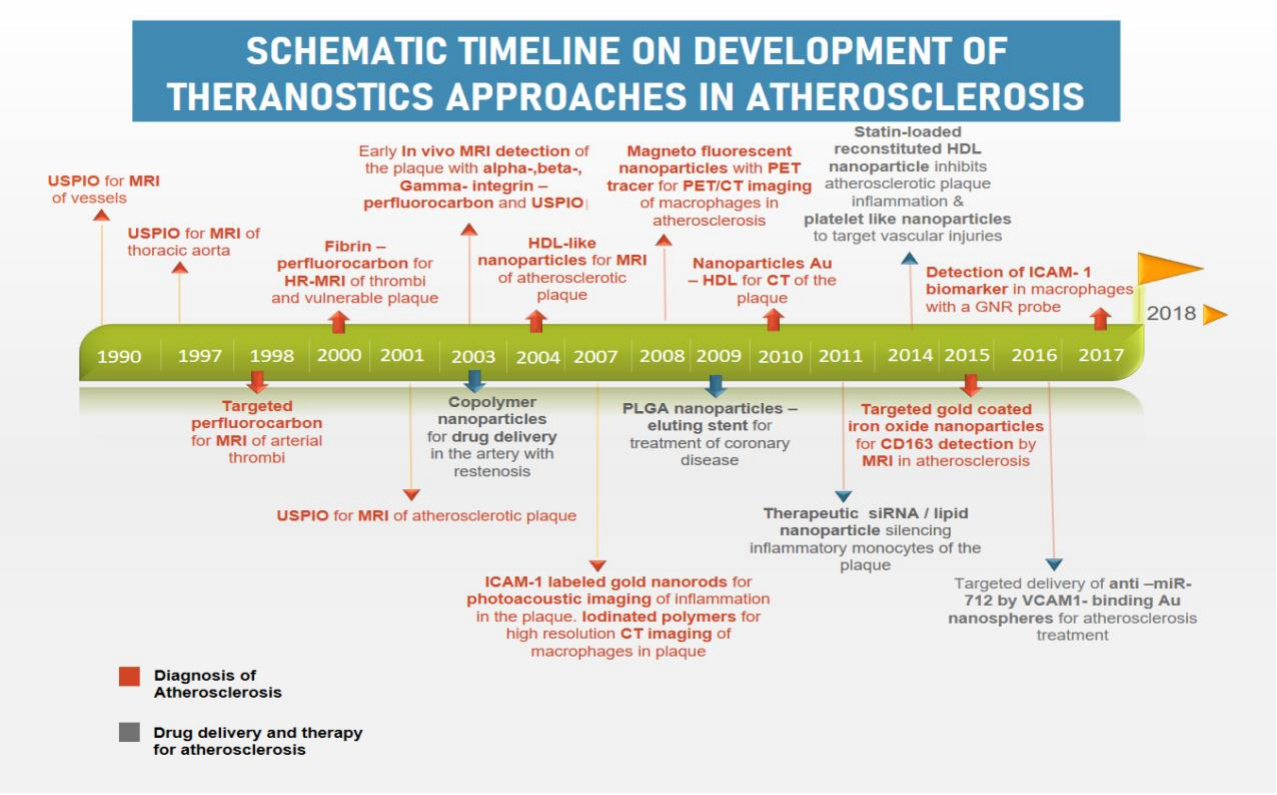


Figure-4.



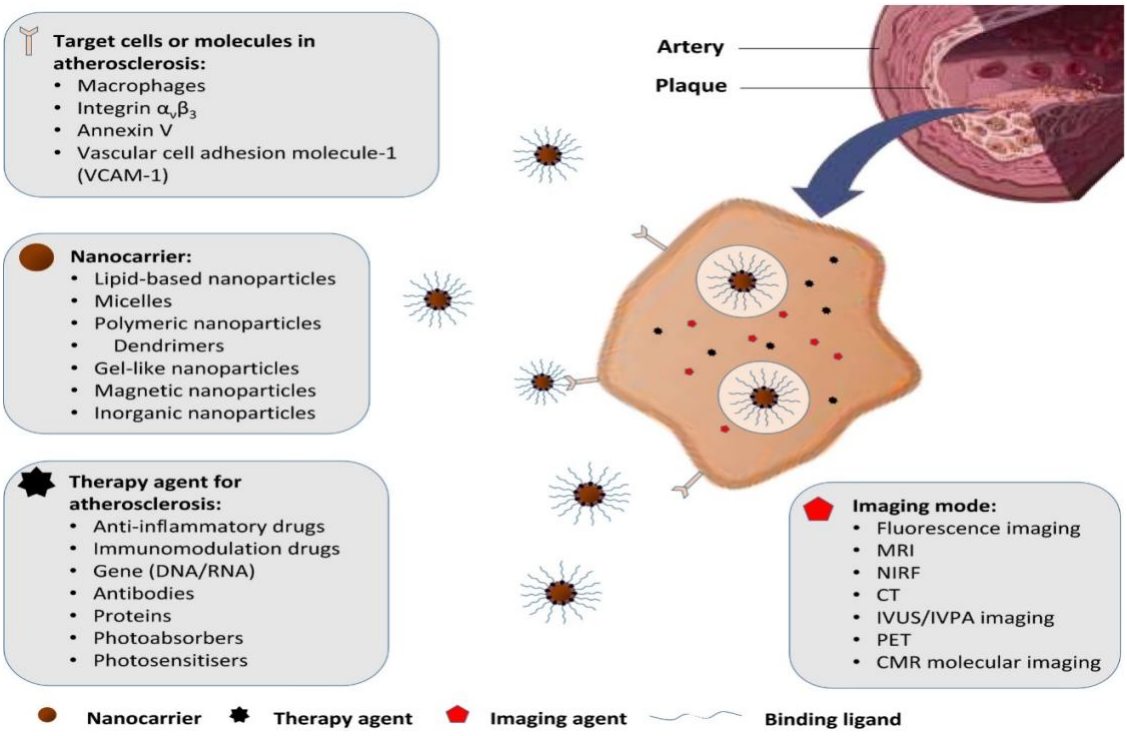
An 82-y-old patient with numerous bone metastases. From lef t to right: posterior and anterior planar BS, multi-FOV SPECT, and 18F-Fluoride PET images. More lesions are detected on SPECT compared with planar images and on 18F-Fluoride PET compared with SPECT images.

Figure-5.



A schematic timeline portrays the development of nanoparticle and radioactive elements came out for diagnosing and treating atherosclerosis safe and effectively, due to its diverse properties along with its material and biomolecules.[27].

Figure-6.



Conclusion:

This review summarizes about Theranostic strategies, a notable phenomenon that correlates imaging and therapeutic part by working as an imaging based- therapeutic (drug) delivery system. A new targeting approach in diagnosing and treating tumors and plaques in case of atherosclerosis, with other cardiovascular diseases such as myocardial infarction. The development of new generation radioactive agents brings out personalized and customized treatment for each patient, in respect with their specific type of tumor cells and proteins it possesses. Theranostics lead the way for new trend in medical field, ensuring promising approaches in future with well-designed nanomedicine for diverse disease management.

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