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THERANOSTICS VIEWS ON NEW METHODS AND CLINICAL DEVELOPMENTS

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ABSTRACT

Theranostic nuclear oncology transforms cancer treatment by combining therapeutic radionuclide administration and diagnostic imaging onto a single platform. This method uses radiolabelled biomarkers to target tumour cells accurately, allowing for customised radionuclide therapy and precise molecular imaging. For patient selection, treatment monitoring, and dosimetry calculations, imaging methods like as PET/CT and SPECT/CT are essential for guaranteeing efficient delivery and evaluating therapy response. The radiobiological characteristics of various radiation types, such as alpha and beta particles, vary. Alpha particles are particularly harmful because of their high linear energy transfer and capacity to induce irreversible DNA double-strand breaks. Thyroid cancer, neuroendocrine tumours, and prostate cancer can all be treated clinically using substances like ^131I, ^177Lu-DOTATATE, and ^177Lu-PSMA-617. Despite its effectiveness, side effects such as hematotoxicity and renal damage might happen, hence cautious patient management is required. With new targets and combination medicines, the area is still developing, improving patient outcomes and treatment precision.

INTRODUCTION

Theranostic nuclear oncology combines therapeutic and diagnostic purposes into a single Molecular targeting platform for radiopharmaceuticals, known as A pair of "theranostic." The foundation of this approach is the radiolabelling of biomarkers specific to cancer types, which enables accurate Using molecular imaging, capture the distinct Chemical pathophysiology of cancerous cells (1). It's method finds certain patients that could profit from radionuclide therapy that targets the molecular phenotype of the cancer. To do so administer a radiation dose that is sufficiently absorbed to achieve therapeutic objectives of disease or symptom control, patients are chosen for any radionuclide therapy based on the proof that every active tumor has adequate uptake locations**.**(2) A PET or SPECT scanner can be used to photograph the radiopharmaceutical site, and the standard uptake value is utilised to calculate how much radiopharmaceutical is present in each area of the body. Essentially, the radiopharmaceutical has either left the body, with minute amounts still present within the blood, or is largely attached to the target (low off-target binding). Visualising The diagnosis target and staging, choosing individuals whose tumors express the target, confirming delivery of therapy to every target in a patient, the target's effective radiation exposure (dosimetry), and (i.e., dosimetry), and monitoring subsequent therapies are all made possible by these images.(3)

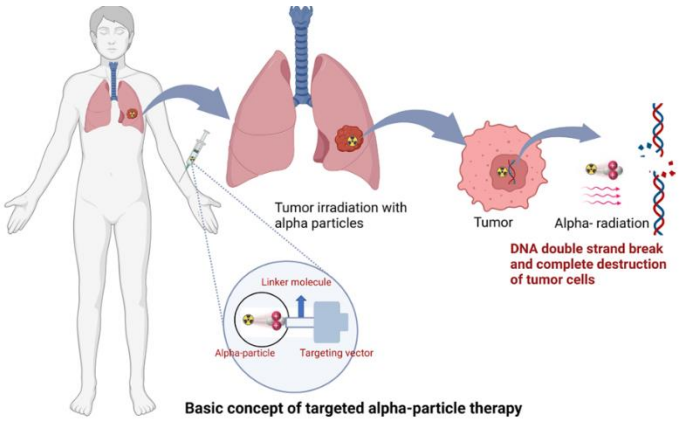


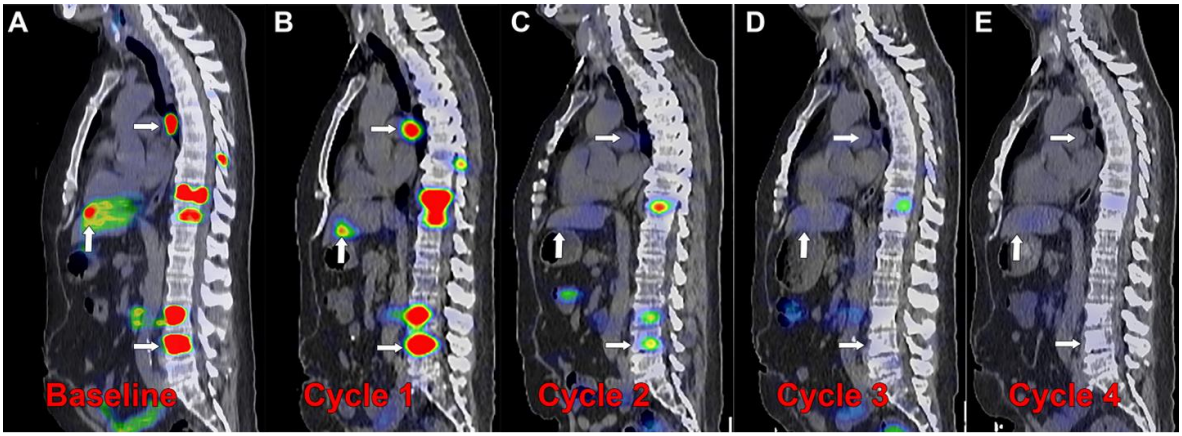
Figure:1 Schematic for targeted α-particle treatment. Via a vector connected to the radionuclide, the intravenous radionuclide therapy attaches itself to the tumour. Emission from α-particles when bound to the tumour delivers radiation to the tumour specifically. Because they result in irreversible double-strand DNA breaks that kill cells, More harmful than β particles are α particles, produced with BioRender.com. (3)

HISTORICAL DEVELOPMENT

Nuclear theranostics was born in 1946 when Sam Seidlin employed radioactive iodine (I-131) for thyroid cancer imaging and treatment. Its uses were increased over the years by developments in targeted radionuclide therapy and molecular imaging (4). Peptide receptor radionuclide treatment (PRRT) for neuroendocrine tumours was a significant advancement that led to the 2017 NETTER-1 trial. Theranostics made significant strides with PSMA-targeted prostate cancer treatment. Today, it offers individualised, targeted treatment and is revolutionising cancer management worldwide by combining diagnosis and therapy with radiolabelled chemicals that are matched to tumor-specific biomarkers. (2)

IMAGING IN THERANOSTICS

The visualisation, measurement, and tracking of radiopharmaceuticals used for diagnosis and treatment are made possible by imaging, which is essential to theranostics. Personalised identification of candidates for radionuclide therapy is made possible by theranostic applications, which first employ imaging to identify individuals whose tumours express certain molecular targets. To identify neuroendocrine tumours that express the somatostatin receptor (SSR), for example, 68Ga-DOTATATE PET/CT is utilised, whereas Prostate cancer is detected by 68Ga-PSMA-11 PET/CT that is PSMA-positive. Imaging helps with therapeutic monitoring after treatment by verifying that radiopharmaceuticals are delivered to tumour sites and assessing how well a treatment is working. Radiotracer uptake can be visualised using techniques like SPECT/CT or PET/CT with therapeutic isotopes like 177Lu, which aid in response evaluation and dosimetry calculations. In order to guide decisions about repeated or modified therapy, imaging also helps detect remaining or recurrent disease. Imaging can also provide early indications of the efficacy of treatment, such as variations in tumour sizes or standardised uptake values. Regular follow-up anatomic and molecular imaging is now part of the guidelines, guaranteeing thorough management of disease progression or remission. From target identification and treatment planning to post-therapy evaluation, imaging is therefore essential to theranostic management at every stage, thereby solidifying its position as the foundation of precision radiopharmaceutical therapy. (3)



A) Carboxyl Carbonyl amino-pentyl-ureido-pentanedioic acid (DCFPyL) and fluoropyridine , or baseline fluorine 18 (18F) Intense PSMA uptake is seen in the hepatic, osseous, and nodal metastases (arrows) of the PET/CT scan. **(B-E**) The radiopharmaceutical treatment was localised to the spreads, as evidenced by a post therapy CT/SPECT imaging 177Lu-PSMA-617 with taken about 24 hours subsequent to the therapeutic radiotracer was infused following each of four cycles given six weeks apart. Index lesions in the liver, bone, and lymph nodes (arrows) show a decline in uptake intensity with each treatment cycle**. (C)** The nodal and hepatic metastases were no longer noticeable following cycle 2, and **(E)** The spine metastases was no longer noticeable after cycle 4. By tracking imaging of the therapeutic radionuclide and variations in the imaged index lesions over time allows for both verification of successful delivery to the cancer webs and the identification out of treatment response during therapy. (3)

PROPERTIES OF RADIOBIOLOGICAL

The use of particles in systemic radiation therapy: When released close to DNA, auger electrons (AEs), which possess an elevated linear energy transfer (LET) and deposit energy over nanometre to micrometre ranges, can kill cancer cells. Reactive oxygen species or direct DNA double-strand breaks are caused by AEs. Their limited range minimises off-target effects by ensuring localised cytotoxicity. When localised in the nucleus, AEs have a higher relative biological efficiency (RBE), frequently outperforming β- or γ-radiation. Adjacent cells are harmed by AEs' bystander effects and cross-dose events. Because of these characteristics, AEs are effective agents in targeted radionuclide therapy with low toxicity to normal tissue.

DOSIMETRIC CHARACTERISTICS

Cellular and organ dosimetry of adverse events: Due to their very small radiation range, Auger electron (AE) emitters require both organ-level and cellular-level dose estimates for dosimetric evaluation. Because AEs deposit significant linear energy transfer (LET) energy within nanometres to micrometres, subcellular localization—particularly in the nucleus—is essential for efficient cytotoxicity. The energy contributions from AEs, internal conversion electrons, and associated gamma/X-rays are taken into consideration by dosimetry. Absorption doses are frequently estimated using the Medical Internal Radiation Dose (MIRD) methodology. In order to provide insight into biological impacts and direct safe, efficient therapeutic techniques, cellular dosimetry measures energy deposition in compartments such as the cytoplasm and nucleus.(5)

DETECTING DNA DAMAGE

Ionising radiation, notably Auger electron (AE) emitters, is one of the agents that can cause DNA damage, especially double-strand breaks (DSBs). It is essential to detect such damage in order to evaluate cytotoxicity. Pulsed-field gel electrophoresis (PFGE), comet assay, and γH2AX immunofluorescence are the most commonly utilised assays. Confocal microscopy is used to see γH2AX foci, which are a sensitive and measurable marker that appear quickly at DSB sites. The comet assay uses electrophoresis in an alkaline environment to assess DNA strand breakage at the single-cell level, creating a fragmented DNA "tail." PFGE is appropriate for high-throughput analysis of DSBs and enables the resolution of huge DNA fragments. These methods correspond with chromosomal abnormalities and reduced clonogenic survival, and they are crucial in research on AE-induced DNA damage. These assays are essential for assessing radiopharmaceuticals' efficacy and comprehending how cells react to specific DNA damage**.** (5)

IMPACTS OF DIFFERENT TYPES OF RADIATION ON BIOLOGY

Tumour cells respond differently to the various forms of radiation utilised in radionuclide therapy, including Auger electrons, β particles, and α particles. Due to their negative charge and wide tissue range (2–12 mm), β particles provide a crossfire effect that is advantageous for treating large or diverse tumours. Single-strand DNA breaks are the main result of their low linear energy transfer (LET), which the cell may frequently fix. However, the effectiveness of β particles in hypoxic tumours is limited since they require oxygen to produce reactive oxygen species (ROS). α particles, on the other hand, have a high LET (50–

230 keV/μm) and short range (50–100 μm), making them extremely pathogenic. Dense ionisation is induced, leading to greater immunogenic responses, including T-cell activation, and irreversible double-strand DNA breaks. In hypoxic tumour microenvironments, they are more effective because to their oxygen-independent action. Auger electrons are deadly only when they are located close to DNA, like in the nucleus, and have extremely short path lengths, while being comparable to β emissions. Their potential resides in minimising off-target damage while treating tiny tumours in delicate areas. But because of the difficulties in targeted nuclear delivery, their clinical usage is restricted. In general, the radiation type selection affects therapy effectiveness, off-target toxicity, and appropriateness for various tumour forms and microenvironments. (3)

a) The First Adverse Effects: Amino acid infusions utilised for renal protection are mostly responsible for the early negative effects of PRRT, especially with ~177Lu-DOTATATE. Up to 71% of patients using commercial solutions experience nausea and vomiting after these infusions, which are frequently caused by high osmolality amino acids such as Tryptophan, alanine, threonine, isoleucine, and leucine. Only lysine and Arginine-derived Combined infusions considerably lessen these symptoms (down to 5%). Pre-infusion antiemetics aid in the management of these side effects.

- Electrolyte abnormalities (such as hyperkalaemia) brought on by concentrated amino acid solutions, particularly in people who are at risk for heart attacks.
- local infusion site responses, like phlebitis or erythema.
- volume overload, which may cause congestive heart failure in those who are vulnerable.
- patients with paraganglioma or pheochromocytoma experiencing hypertensive crises.

b) Delays in Adverse Effects: Haematologic and renal damage are the main delayed side effects of peptide receptor radionuclide treatment (PRRT), especially when using ~177Lu-DOTATATE. The most frequent hazard is hematotoxicity, which can show up as anaemia, thrombocytopenia, or leukopenia. About 11% of patients experience Grade 3–4 toxicity, which is usually curable in two years. Nevertheless, 2–4% of individuals may develop acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS), which may start years after therapy, particularly those who have received alkylating agent treatment in the past. Radiation exposure to the renal tubules can also cause nephrotoxicity, a delayed risk that results in Grade 3 renal failure in 1% to 2% of cases. Diabetes, advanced age, and preexisting hypertension are risk factors. Neoprotective amino acids are co-infused to reduce renal injury.

Although rare, liver damage can occur in patients who have a significant burden of hepatic tumours. Effective management of delayed toxicity requires careful patient selection, dose modification, and ongoing monitoring.(6)

ONCOLOGISTS' INVOLVEMENT IN THERANOSTICS

Theranostics is being more and more integrated by oncologists into individualised cancer treatment. The novel approach improves treatment precision by combining targeted radiopharmaceutical therapy with diagnostic imaging. It gives medical professionals the ability to choose appropriate treatment candidates and view tumour biology in real time. More efficient, customised patient care is made possible by the capacity to simultaneously diagnose and cure cancers. In addition to minimising toxicity and streamlining treatment response monitoring, this dual strategy maximises therapeutic outcomes. Theranostics's significance as a revolutionary, multidisciplinary pillar in contemporary cancer practice is being strengthened as research and clinical trials increase doctor involvement in the field. Globally improving patient quality and results**.** (2)

CURRENT CLINICAL PRACTICE OF RADIONUCLIDE THERAPY AND ITS FUTURE

Radiopharmaceuticals made of radioactive isotopes connected to vectors (ligands) that attach to tumor-specific molecular targets are used in radionuclide therapy, a targeted cancer treatment. Clinically approved treatments include ~131I for thyroid cancer, ~177Lu-DOTATATE for neuroendocrine tumours, and ~177Lu-PSMA-617 for prostate cancer that has spread. For theranostic applications, these treatments reduce collateral damage to healthy tissues and are frequently used in conjunction with diagnostic agents (e.g., ^68Ga-DOTATATE, ^68Ga-PSMA) to provide PET/SPECT imaging for patient selection, dosimetry, and therapy monitoring. Recent advancements include α-emitting treatments, such as ^225Ac-PSMA and ^223$RaCl_2$, which provide greater linear energy transfer and cause double-stranded DNA breaks for stronger cytotoxicity, which is particularly advantageous in tumours that are hypoxic or resistant (7). Somatostatin receptor antagonists, bombesin receptors, and fibroblast activation proteins are examples of emerging targets. Combination treatments involving radiosensitizers, chemotherapy, and immunotherapy are being researched. Additionally, sophisticated radiomics and dosimetry techniques are being developed to customise treatment.

a) Therapy with 223RaCl2: Alpha-emitting radionuclide therapy, known as $223RaCl_2$ therapy, is used to treat castration-resistant prostate cancer that has spread to the bone and is exhibiting symptoms. By providing high-energy, short-range radiation that breaks double-strand DNA in places with accelerated bone turnover, it increases longevity while reducing systemic toxicity. For metastases to soft tissues, it is ineffective**.**

b) Targeting Somatostatin Sensors with Radionuclide Therapy: Somatostatin receptor-targeted radionuclide therapy treats neuroendocrine tumours that express somatostatin receptors, particularly SSR2, by using radiolabeled peptides such as ^177Lu-DOTATATE. By delivering targeted radiation under the guidance of ~68Ga-DOTATATE imaging, it enhances progression-free survival. For advanced, incurable, or metastatic neuroendocrine tumours, this FDA-approved medicine provides efficient treatment with controllable toxicity.

C)Targeting Prostate-specific Membrane Antigens with Radionuclides: Castration-resistant metastatic prostate cancer can be preferentially treated using PSMA-targeted radionuclide treatment, which employs drugs such as ^177Lu-PSMA-617. It provides targeted beta radiation, enhancing survival and illness control, under the guidance of ~68Ga-PSMA PET imaging. □225Ac-PSMA-617 is one of the emerging alpha emitters that exhibits improved efficacy in instances that are resistant or advanced.(3)

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