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Radiotheranostics and the Future of Cancer Therapy: Harnessing Combination Strategies and AI

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ABSTRACT

Radiotheranostics, defined as the subset of theranostics wherein both diagnostic imaging and therapeutic functions are specifically enabled by radionuclides, represents a transformative advancement in precision oncology, integrating diagnostic imaging and targeted radionuclide therapy within a single molecular platform. Through coupling radionuclides with highly specific vectors such as antibodies, peptides, or small molecules, this approach enables selective delivery of radiation to tumor sites expressing biomarkers such as prostate-specific membrane antigen (PSMA) and human epidermal growth factor receptor 2 (HER2), thereby maximizing tumor cytotoxicity while sparing healthy tissue. Radiopharmaceuticals are engineered through meticulous radionuclide selection (e.g., Lutetium-177 (^{177}Lu) or Actinium-225 (^{225}Ac)) as well as optimized carrier systems that influence biodistribution, targeting efficiency, and clearance kinetics. Imaging modalities such as positron emission tomography (PET) and single-photon emission computed tomography (SPECT) aid in patient selection, dosimetry, and real-time visualization of therapeutic efficacy. In clinical studies, radiopharmaceuticals have exhibited efficacy across multiple cancers, including prostate, neuroendocrine, breast, and ovarian malignancies. Beyond direct DNA damage, these agents can stimulate immunogenic cell death, boosting anti-tumor immunity. Combining radiopharmaceuticals with immunotherapy, chemotherapy, or PARP inhibitors may offer benefits over standard of care. Further, integration of Artificial Intelligence (AI) into radiotherapy (RT) workflows can potentially revolutionize treatment planning, contouring, adaptive dose management, and predictive modeling. Collectively, radiotheranostics exemplifies evolution of cancer management toward a highly personalized paradigm, combining molecular targeting, multimodal imaging, and AI-driven optimization. As ongoing research refines carrier systems, expands the repertoire of radionuclides, and enhances combinatorial strategies, radiotheranostics remains at the forefront of next-generation cancer therapeutics.

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1. Introduction

Targeted radiopharmaceuticals hold potential to transform the landscape of cancer care through combining the advantages of precise diagnostic and therapeutic capabilities, which forms the basis of radiotheranostics. Radiotheranostics focuses on delivering radionuclides to tumor tissues via molecular vectors such as antibodies, peptides, or small molecules, thereby minimizing radiation exposure to healthy tissues. The targeted mechanism of radiotheranostics is based on clinically relevant biological differences in tumor biomarker expression, enabling selective treatment. Representative examples include Prostate-Specific Membrane Antigen (PSMA) and Human Epidermal Growth Factor Receptor 2 (HER2), for which radioactive payloads such as Lutetium-177 (^{177}Lu) or Actinium-225 (^{225}Ac) can be delivered. Targeted radiopharmaceuticals can offer both diagnostic and therapeutic applications within a single agent, such as ^{177}Lu -PSMA-617 for metastatic castration-resistant prostate cancer and ^{68}Ga-DOTA-TATE for neuroendocrine tumors. Thus, radiopharmaceutical-based cancer treatment has significant potential to further advance the field of precision oncology.[1,2] There are three primary design specifications for radiolabeled agents: (i) high specificity toward the biological target, enabling adequate tumor uptake; (ii) appropriate radionuclide selection, particularly when ^{225}Ac, an alpha-emitting radionuclide, is preferred over ^{177}Lu, a beta-emitting radionuclide, for targeting micrometastatic lesions or larger tumor burdens; and (iii) selection of suitable carrier systems, such as monoclonal antibodies for augmented stability or peptides for rapid clearance.[2] In metastatic cancer, treatment strategies are increasingly shifting from monotherapy toward combination therapeutic approaches. Combinations such as Thorium-227 (^{227}Th) conjugates with Poly (ADP-ribose) Polymerase (PARP) inhibitors, such as Olaparib, may generate synergistic therapeutic effects in Breast Cancer Gene 2 (BRCA2**)**-deficient cancers. This approach may expand treatment opportunities for patients who previously faced limited or no effective therapeutic options for their malignancies**.**[3] Based on these principles, radiopharmaceuticals represent a new class of agents that provide diagnostic imaging and therapeutic utility together. Whereas chemotherapy or external beam radiotherapy (RT) exposes both cancerous and healthy tissue within the irradiated field to treatment, radiopharmaceuticals allow for a systemic administration of the treatment while providing localized radiation at the tumor targeted. The capability of visualizing and treating tumors affords oncologists an important advantage for precision in medicine especially for patient selection, dosimetry, and treatment follow-up in providing appraisal of treatment response.[2] Therapeutic action for cancer consists of multiple types of putative treatments which together all have advantages and disadvantages. Chemotherapy is a systemic approach, applying cytotoxic agents which act upon various normal cells, especially those with rapid division. Even though chemotherapy acts against malignant cells, there are concomitant effects against tissues including bone marrow and hair follicles, which induce the more well-known side effects of chemotherapy. Immunotherapy does not directly act on the tumor; rather, it engages the immune system's ability to recognize and destroy cancer. Although immunotherapy has potential, the effectiveness of this treatment is often based on tumor-specific characteristics as well as patient immune status, translating into often widely variable response rates.[4,5] Radiotherapy lies in an intermediate position between the two above treatment strategies. Unlike chemotherapy, which is delivered systemically, radiotherapy is a localized treatment. This therapy, which utilizes high-energy beams (including X-rays, protons or other charged particles) to induce lethal DNA damage in tumor cells, aims to allow the maximum sparing of surrounding healthy tissues. A major drawback however, is radioresistance: tumors can develop ways to evade radiation through hyperactivation of signaling pathways (e.g., PI3K/AKT), go through epithelial-mesenchymal transition, adapt through developing a higher capacity for DNA

repair and/or proneness towards tumor hypoxia (Fig.1).[6-8] In order to address these barriers, ongoing studies are ascertaining radiosensitizers and combination approaches (including the pairing of radiotherapy with either chemotherapy or immunotherapy), with the aim of maximizing their therapeutic benefit, while also minimizing recurrence. The possibilities offered by a partnering approach to therapy emphasizes radiotherapy, and specifically radiopharmaceuticals, as cornerstones of new precision oncology. This would allow for a more targeted approach to tumor elimination, while also helping to maximize the potential for multimodal treatment and synergy. The advancement of relevant radionuclides with well-defined physical and biological properties has opened new clinical doors; Fluorine-18 (^{18}F) and Gallium-68 (^{68}Ga) remain essential for diagnostic imaging with positron emission tomography (PET), while theranostics with radionuclides such as ^{177}Lu, Yttrium-90 (^{90}Y), and ^{225}Ac have presented potential in the treatment of a number of malignancies. Regarding combination approaches using alpha emitters, these radionuclides have greater linear energy transfer and short penetration distance are particularly attractive to eradicate micrometastatic disease with minor off-target effects.[2,9,10] Over years, monoclonal antibodies have remained in use thanks to their stability and specificity, almost exclusively related to HER2-positive breast cancer at present and PSMA-positive prostate cancer in the past. As a result, limitations pertaining to slow tissue penetration have propelled the interest to apply other various carriers. They include peptides, aptamers, small molecules, and nanoparticles that offer advantages of fast clearance, deeper tumor penetration, and flexible modification for multimodal therapy. Radiopharmaceuticals ^{177}Lu-DOTA-TATE and ^{177}Lu-PSMA-617 are recognized as clinical successes in the development of therapeutic agents, as they exhibit the success of theranostics in cancer treatment. Likewise, ^{68}Ga-DOTA-TATE and ^{68}Ga-PSMA-11 as diagnostic pharmacological products have provided an example of the synergism between imaging and therapy, as they provided a more personalized treatment plan for patients. The advent of the combination of radionuclides with PARP inhibitors and immune checkpoint inhibitors offers room for new modalities to reverse resistance and maximize clinical outcomes.[11-13] Ultimately, radiolabeled targeted drugs are an entirely new direction in cancer treatment, combining targeted imaging, personalized therapy, and possibilities for multimodal treatment opportunities. As they steadily infiltrate clinical applications, they signal a new chapter in healthcare, where oncologists can think of cancer treatment as individualized according to tumor biology and patient-specific molecular characteristics.

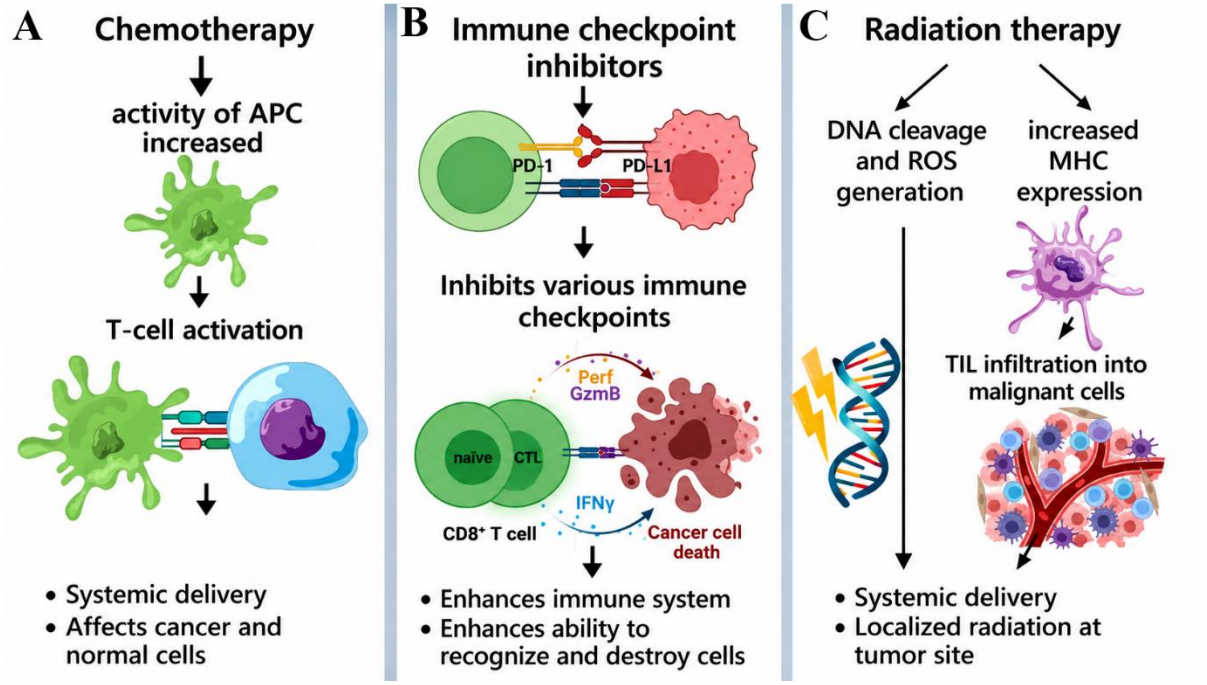

Figure 1. Overview of radiopharmaceutical applications in oncology. (A) Distribution of published studies according to the primary application of radiopharmaceuticals in oncology, including diagnostic and therapeutic approaches. (B) Relative distribution of the major radionuclides used in oncologic applications, including ^{99m}Tc, ^{18}F, ^{68}Ga, ^{131}I, ^{123}I, ^{90}Y, and ^{177}Lu. (C) Schematic illustration of a radiopharmaceutical construct, consisting of a targeting molecule linked to a radioactive moiety through a chemical linker for selective binding to target proteins expressed on cancer cells, enabling both diagnostic imaging and targeted radionuclide therapy.

2. Targeted Radiopharmaceuticals (Structures and Types of Radiopharmaceuticals)

A reproducible approach targeting cancers using radiopharmaceutical therapy has been found to be effective, and is often an attractive option thanks to the merits of radiopharmaceutical therapy over traditional therapies.[14] Targeted radiopharmaceuticals are theragnostic agents that contain a radioactive component and targeting vector, such as an antibody, peptide or small molecule where a specific drug moiety targets specific cells or tissues. The goal of this design is to attach radiopharmaceuticals to specific cell surface molecules, such as receptors or enzymes, particularly on cultured cancer cells.[15,16] Targeted radiopharmaceuticals signify a new class of anticancer agents through combining diagnostic imaging and targeted therapy or "radiotheranostics" by unleashing radionuclides at the site of disease through applying molecular vectors. By utilizing targeting moieties, such as small molecules, peptides, or antibodies, targeted radiopharmaceuticals will selectively home to the tumors while minimizing off-target toxicity, while also enabling both visualization and destruction of malignant cells.[16,17] The clinical development of radiotheranostic agents has grown rapidly in recent years owing to rapid expansion of the classified compounds by FDA approvals. This includes the FDA-approved therapeutic versions of targeted imaging molecules, such as ^{177}Lu-DOTA-TATE and ^{177}Lu-PSMA-617 along with their diagnostic branched analogs for imaging**,** ^{68}Ga-DOTA-TATE and ^{68}Ga-PSMA-11**.** Approved radiopharmaceuticals exhibit dual-purpose diagnostic and therapeutic roles across disease states, while all approved therapeutics are primarily employed in oncology. Diagnostic radiopharmaceuticals can be categorized in seven indication segments and several disease areas may share some radiopharmaceuticals (e.g., Fluorodeoxyglucose **(**^{18}F-FDG**)** in oncology, cardiology, and neurology). Diagnostic radiopharmaceuticals utilized in PET include ^{18}F, ^{68}Ga, Carbon-11 (^{11}C), Nitrogen-13 (^{13}N), Copper-64 (^{64}Cu), and Rubidium-82 (^{82}Rb)**.** Those applied in single-photon emission computed tomography (SPECT) include Technetium-99m (^{99m}Tc), Iodine-123 (^{123}I), Indium-111 (^{111}In), Gallium-

67 (^{67}Ga), Iodine-125 (^{125}I), and Thallium-201 (^{201}Tl)**.** Therapeutic radionuclides used in cancer treatment include Iodine-131 (^{131}I), ^{90}Y, ^{177}Lu, Phosphorus-32 (^{32}P), Strontium-89 (^{89}Sr), Samarium-153 (^{153}Sm), and Radium-223 (^{223}Ra)**.** For PET, ^{99m}Tc is the main imaging agent, while **^{18}F** plays a dominant role in other areas, but especially in oncology and neurodegenerative diseases given its isotopic stability.[2] For cancer therapeutics, it utilizes several biologically-derived targeting agents: small molecules, peptides, antibodies or protein-based carrier. Targeting agents have been the primary focus on radiopharmaceutical development and advancement to date, against which all future development will be determined, where can each serve similar purposes such as achieving the accuracy and precision in targeted imaging and therapy.[16,18] Radiopharmaceutical drug development efforts have redirected and reshifted to address advanced in vivo performance characteristics linked to increased tumor uptake, prolonged retention, and ameliorated pharmacokinetic characteristics. This would enable safer and more effective therapy for patient groups. The approval of radiopharmaceuticals has ushered in a new era of precision cancer management, evidenced by improved patient stratification and the critical role these agents play in developing tumor biology-based individualized treatment regimens (Fig. 2).[17,19,20]

The approvals of radiopharmaceuticals have started a new era of accurate cancer patient management, primarily through improved patient stratification, and have highlighted their critical roles in developing new, individualized treatment regimens based on tumor biology."

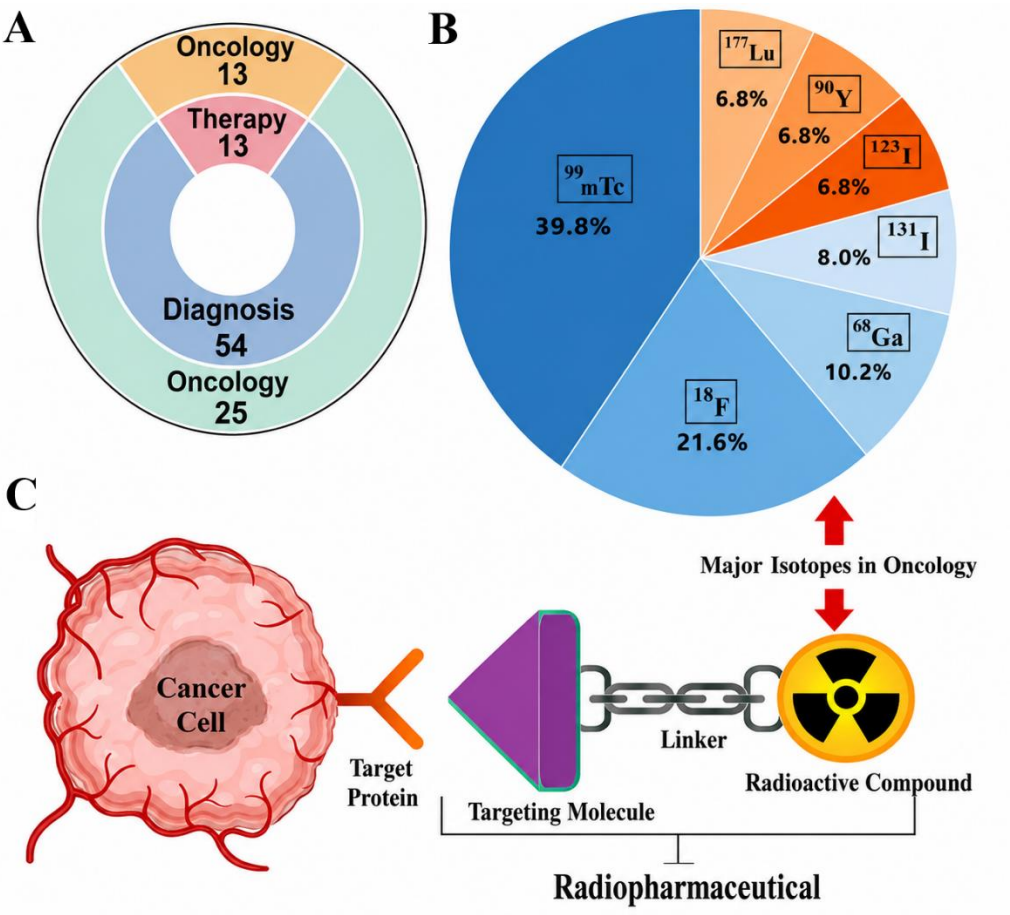

Figure 2. Overview of FDA-approved radiopharmaceuticals. (A) In total, there are 67 radiopharmaceuticals on the FDA-approved list in the world: 54 for diagnosing disease and 13 for therapeutic purposes. All therapeutic radiopharmaceuticals are used in the diagnosis and treatment of cancer, 25 of these radiopharmaceuticals are approved for the diagnosis of cancer. (B) The distribution of the major radionuclides used in diagnostic and therapeutic radiopharmaceuticals. (C) Graphic

representation of a radiopharmaceutical with a targeting molecule that binds to a surface protein on a cancer cell and is bound through a linker to a radioactive molecule used for imaging or treatment

3. Carrier systems of radiopharmaceuticals

The development of radiopharmaceuticals is a very dynamic period of sciences all striving to bring equal parts speed towards developing cancer therapies as well as safe and effective patient therapy. The multidisciplinary approach will assist in the discovery of agents that can target and deliver reactive radioactive isotopes into malignant tissues while also minimizing damage to healthy tissues and addressing overall patient safety with the minimum degree of side effects. An exciting aspect of radiopharmaceutical therapeutics where they will be able to refine their agents is having the ability to design carriers that can target radionuclides for dispersion to tumor locations. The carriers that are available for testing and will undergo preclinical development need to have high specificity, stability, and optimized pharmacokinetics for targeted dispersion as well as retention of the desired tumor. There are many different variations of carriers that can be examined and developed with different mechanisms of action and with their own advantages (Fig. 3).[15,17,21] Monoclonal antibodies (mAbs) are a widely accepted choice for radiolabeled antibody treatments. This is because mAbs have very high specificity, and have virtually no affinity for any nontumor-associated antigens. Thus, it would be easy to engineer a mAb that only binds to cancer cells, delivers radiation dose to the tumors, and spares non-cancerous cells. However, a drawback to using mAbs is that they are very large, meaning that they cannot penetrate tissues well, and are slow to clear from organs that are not targeted for treatment, signifying that there is added off-target toxicity from the treatment.[22,23] Peptides, on the other hand, are small carriers, have good receptor affinity, offer a rapid tissue penetration, and are thus excellent carriers of receptors that have been over-expressed in all types of tumor. Since they have high clearance rates from the systemic circulation, the background beta or gamma radiation will diminish. This means an improvement in the imaging contrast, as well as amelioration in the safety in the therapeutic window.[24,25] Nucleic acid-based carriers, such as aptamers, provide opportunities in the development of radiopharmaceuticals thanks to their ability to bind to a specific molecular target with high specificity. The nuclear target could be tumor-specific mRNA, protein and thus allow for highly personalized and gene-directed radiotherapy, improving selectivity and therapeutic effects.[26,27] Small molecules have fast tumor uptake, followed by rapid clearance from normal tissues which enhances the therapeutic window and lowers the radiation dose associated with the treatment to normal organs. The versatility as well as the fact that many small molecules can be modified without too much effort and expense allows for developing radiopharmaceuticals for a large number of tumor types.[28,29] Nanoparticles provide an extremely novel platform, which also have a very high surface area and could be modified further in regards to the number of radionuclides and/or multiple targeting ligands carried in one agent. This multivalency boosts the therapeutic payload and the possibility of enabling combination therapy, such as chemotherapy, chemotherapy and a radionuclide, with one molecule. Nanoparticles would also enable these capabilities to be engineered to potentially enhance pharmacokinetics, biodistribution, and tumor penetration.[30-32]

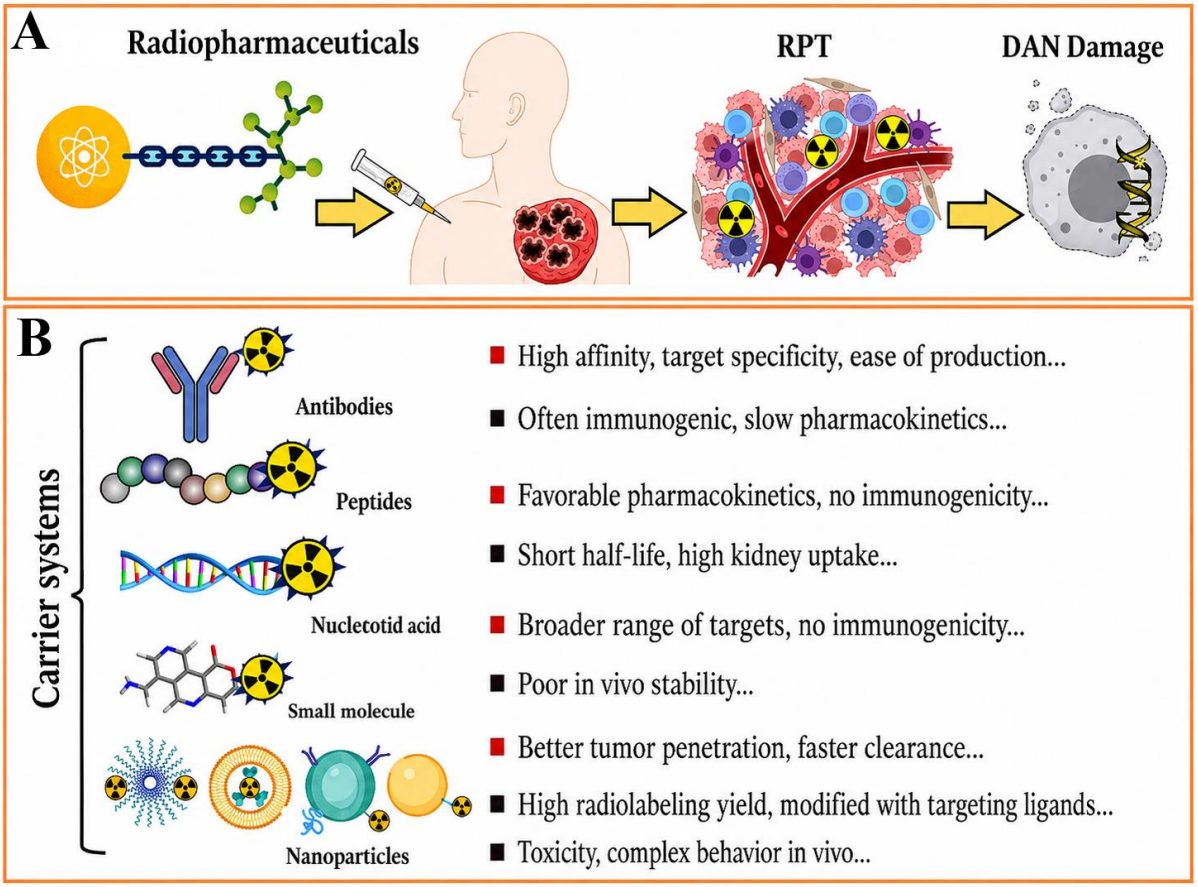

Figure 3. A. Carriers with high affinity and specificity for tumor targets can precisely deliver therapeutic radionuclides to cancer cells, enabling targeted treatment. B. The primary categories of carrier systems used in radiopharmaceutical development include their respective advantages and disadvantages

4. Applications of Radiopharmaceuticals in Cancer Diagnosis

Radiopharmaceuticals are integral to contemporary nuclear medicine as they enable visualizing organ functional and pathological involvement with sufficient specificity. Radiopharmaceuticals are designed to optimize pharmacokinetic behavior (i.e, adsorption, distribution, metabolism, and excretion (ADME)), and typically consist of a radioactive portion leading to either the emission of gamma photons or positrons. These agents have different half-lives and emissions that are practical in many nuclear medicine applications, including those of Oxygen-15 (^{15}O), ^{11}C, ^{68}Ga, ^{18}F, ^{99m}Tc, ^{111}In, and ^{123}I [33] (Table 1). Planar imaging is the simplest form of nuclear medicine and generates two-dimensional scintigrams of a target organ or part of an organ using gamma cameras. Even though planar imaging is cost-effective and provides sufficient image quality for many applications, anatomical planar images have limitations. One major constraint is that image analysis, quantification, and resolution can be compromised by the superimposition of non-target organ activity, which can lower diagnostic accuracy.[34] [34]Computerized imaging can help alleviate some of these issues through expanding the region of interest and providing a better visualization of functional information. SPECT improves on planar imaging through capturing multiple angular images and reconstructing those into cross-sectional (3D) images, establishing lesion localization, organ function assessment, and metastasis imaging. Commonly used radionuclides such as ^{201}Tl, ^{99m}Tc, and ^{123}I have spatial resolutions within the 10–14 mm range. PET detects coincident 511 keV gamma rays produced along positron–electron annihilation events. PET radionuclides, such as ^{18}F, ^{68}Ga, ^{11}C, and ^{15}O, enable highly sensitive, quantitative, and tomographic imaging of human metabolic and functional processes, making

PET the imaging modality of choice in many applications, even at the molecular level (Fig. 4).[33,35,36] These imaging techniques are fundamental for theranostics in oncology, which is a strategy that combines diagnostic imaging with a targeted therapy. Theranostics is a process that unites 'therapeutics' and 'diagnosis' and is involved in specifically identifying cancers, developing an individualized treatment plan, as well as monitoring and evaluating therapy response in vivo.[37,38] When diagnostic radiopharmaceuticals provide pharmacokinetic information, it would be possible to predict tissue specificity in absorbed radiation dose for the therapeutic. The idea is to minimize absorbed dose to non-target organs, while maximizing efficacy; this is the whole point of radiotheranostics.

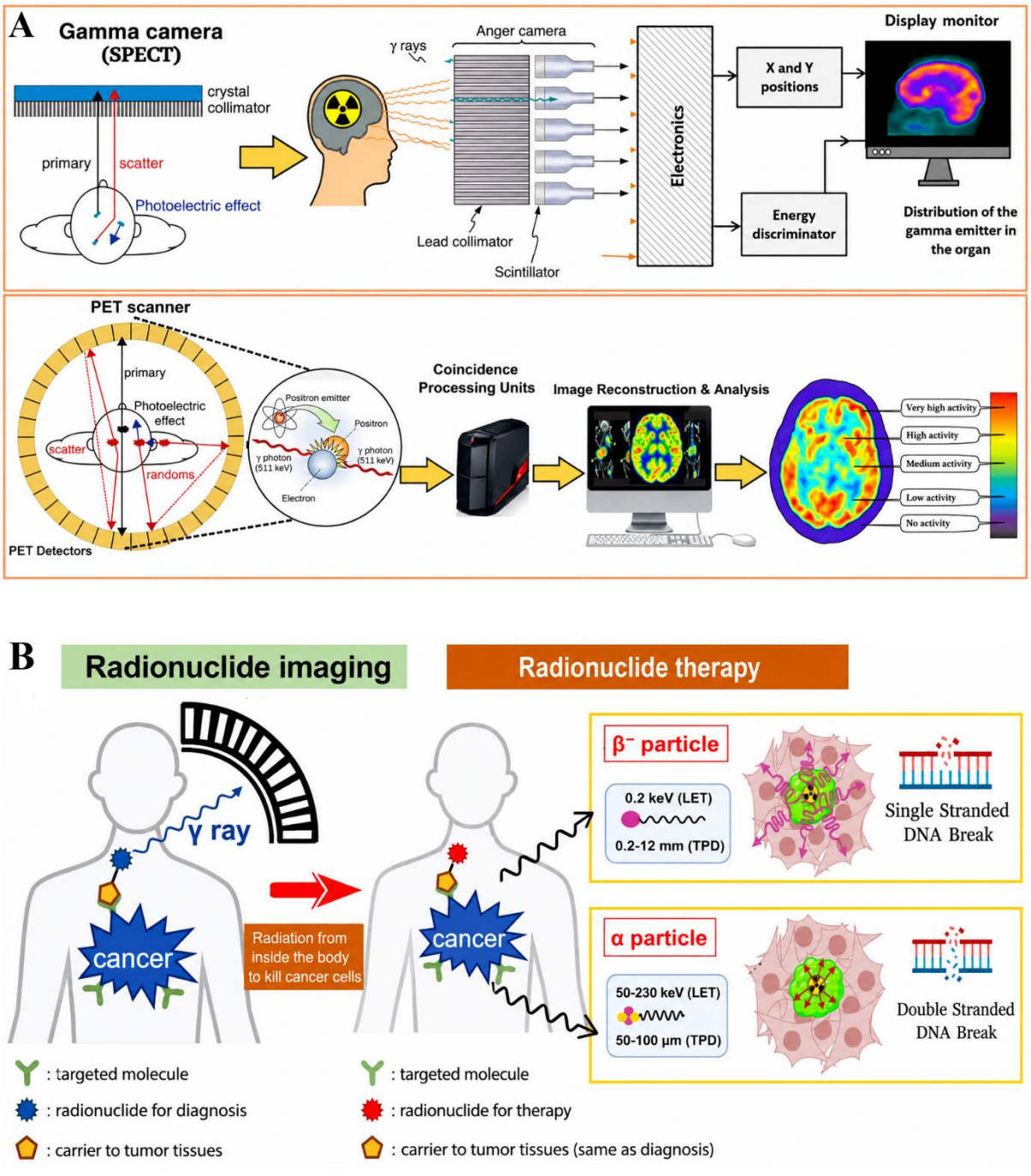

Figure 4. Mechanisms of radionuclide imaging and therapy. **(A)** Schematic illustration of single-photon emission computed tomography (SPECT) gamma camera imaging. Gamma photons emitted from the radiotracer within the patient pass through a lead collimator, where scattered photons are rejected. The transmitted photons interact with the scintillation crystal via the

photoelectric effect, generating light signals that are detected by the Anger camera. These signals are electronically processed to determine X–Y coordinates and energy discrimination, enabling reconstruction and visualization of radiotracer distribution in the target organ. **(B)** Schematic illustration of radionuclide imaging and radionuclide therapy. In diagnostic imaging, a targeting molecule linked to a carrier and a diagnostic radionuclide selectively accumulates in tumor tissue and emits gamma (γ) rays for tumor visualization. In radionuclide therapy, the same targeting platform delivers therapeutic radionuclides directly to cancer cells. Beta (β^-)-emitting radionuclides exhibit longer tissue penetration and primarily induce single-strand DNA breaks, whereas alpha (α)-emitting radionuclides have high linear energy transfer (LET), short tissue penetration, and mainly induce double-strand DNA breaks, resulting in effective tumor cell destruction.

5. Applications in Cancer Therapy

Patients with advanced-stage prostate cancer who have not responded to other established therapies can consider targeted radiopharmaceutical therapy against PSMA as an intermediate alternative. Banerjee et al. tested a new generation of PSMA-based radiopharmaceuticals, including **^{213}Bi-L1** and **^{225}Ac-L1**, as observed in Figure 1, for their safety and efficacy in prostate cancer models. Both agents were efficacious in killing cancer cells and getting concentrated in PSMA-positive lesions. Both agents brought clear uptake in PSMA1-expressing cells and were then captured as PSMA1 lesions were injected. Administration of ^{225}Ac-L1 also mitigated tumor growth and ameliorated survival in a cancer-bearing mouse model. Nevertheless, we also noted some off-target toxicity in rats, including high doses of ^{225}Ac-L1 causing some degree of liver and kidney dysfunction. Through imaging performed by a camera, ^{225}Ac-L1 clearly accumulated in the kidneys initially, and then cleared readily within 24 hours. The authors concluded that ^{225}Ac-L1 represents a promising therapeutic approach which warrants continued future clinical assessment.[39] Elsewhere, researchers described a targeted radiotherapy treatment for metastatic castration resistant prostate cancer (mCRPC). ^{177}Lu was the radioactive agent used for therapy; it is used to target PSMA which has a far higher expression on prostate cancer cells. The researchers identified 14 different formulations of the therapy by applying different changing components and tested the formulations for efficacy against human prostate cancer cells in vitro or in vivo. The researchers found one formulation, ^{177}Lu-L1, which appeared significantly more effective at targeting and killing cancer cells while minimally impacting the normal healthy tissue. The authors concluded that ^{177}Lu-L1 could potentially proceed to clinical evaluation in patients with PSMA expressing cancers.[40] In contrast, the next study ascertained the combination therapy of Terbium-161 (^{161}Tb) with PSMA-617. This combination has been heralded as a possible better combination to the ^{177}Lu-PSMA-617 ^{161}Tb-PSMA-617**.** The isotope ^{161}Tb emits both conversion and Auger electrons, which is a process that can accept/affect the distribution of absorbed dose deposition for radioimmunotherapy. The authors subsequently noted that when looking at PC-3 PIP tumor cells that were dosed with ^{161}Tb-PSMA-617, the cells had diminished viability and/or ability to survive compared to the same equivalent dose of ^{177}Lu-PSMA-617. The authors concluded that ^{161}Tb-PSMA-617 led to a superior outcome compared to ^{177}Lu-PSMA-617 in both pre-clinical in vitro and in vivo studies. The authors proposed that ^{161}Tb-PSMA-617 created a novel pathway for further pre-clinical investigations into the assumed compound, which would result in another possible clinical application for ^{161}Tb-PSMA-617 in treating mCRPC.[41,42] As a cancer treatment strategy, targeted alpha therapy (TAT) has garnered significant interest thanks to the high cytotoxicity and short tissue range of alpha particles. This would enable lethal radiation doses to be delivered to cancer cells while sparing surrounding healthy tissues. ^{223}Ra-dichloride is the first Food and Drug Administration (FDA)-approved alpha-emitting therapeutic radiopharmaceutical and has been found to prolong overall survival in patients with castration-resistant prostate cancer with bone metastases, while also enabling diagnostic correlation with ^{99m}Tc-MDP. ^{225}Ac-PSMA-617 is an alpha-emitting radiopharmaceutical agent that targets PSMA and has demonstrated antitumor effects in phase II clinical trials. Although promising in terms of efficacy, its widespread clinical use has been constrained by challenges related to isotope supply and chelation chemistry. Astatine-211 (^{211}At) has also emerged as a promising

alpha-emitting radionuclide, with ^{211}At –sodium astatide (^{211}At-NaAt) and ^{211}At-MABG analogues currently undergoing phase I clinical studies for the treatment of solid tumors.[43-45] Of all gynaecologic cancers, ovarian cancer is currently the most lethal. Most patients are diagnosed with stage III/IV disease, with microscopic peritoneal metastases, which cannot be removed or treated effectively through chemotherapy.[46] Targeted radiopharmaceuticals as theranostics offer the unique ability to link a radionuclide to a tumor-specific molecule (i.e., small molecule, antibody, antibody pulls, peptide) that has the capability of specifically imaging the tumor and directly treating that tumor with radiation therapy.[47] Factors that can be employed as targeting agents are cancer-associated markers. Through binding the cancer-associated markers, it enables directing radioactive pharmaceuticals towards a tuft with maximal uptake and minimal impact on surrounding tissues. For instance, at highly ionizing doses, alpha-emitting radionuclides such as Lead-212 (^{212}Pb) and Astatine-211 (^{211}At) can induce irreversible tumor cell death when the tumor-associated marker is present, allowing radionuclide uptake or close tumor proximity. The resulting DNA damage is significant, while the short range of alpha particles minimizes toxicity to healthy cells at the periphery of the treatment field.[48] Beta particles have clinically more significance as they have fair penetrating abilities and, in turn, enjoy wider fields of potential uptake, e.g., ^{177}Lu and ^{90}Y beta-particle generations. Nevertheless, there also exist pure Auger electron emitters (i.e., ^{125}I) with the decay route of the radioactive decay of radioactive particles requiring a nuclear conversion before induction of damage to DNA, as it is a threshold.[21] There were multiple types of targets depicted and included: secreted glycoproteins (CA-125, TAG-72, YKL-40), tumor cell membrane antigens (HER2, mesothelin, folate receptor α, NaPi2b, CD276), cytoplasmic proteins (PARP-1), and tumor microenvironment proteins fibroblast activation protein. Different cancer-associated molecular targets have been identified for radiotheranostic applications. Preclinical studies and early-clinical studies (ongoing) with various agents, including NaPi2b-targeting, ^{211}At conjugates, HER2-targeting ^{212}Pb therapies, radiolabelled PARP inhibitors, and ^{177}Lu- Fibroblast Activation Protein Inhibitor (**FAPI)**, have all provided significant and powerful evidence for tumor occupancy and a reasonable degree of efficacy, promising avenues for precision treatment of ovarian cancer.[49] Anti-MUC1 antibodies are ideal subjects as they are validated antibodies for both therapy and to identify cancer cells, especially breast cancer cells where MUC1 is a very large glycoprotein that is very abundant on the cell surface.[50] For instance, Alirezapour et al. applied a monoclonal antibody called PR81 that has a strong affinity to MUC1 which was labelled with a radioactive isotope **^{64}Cu** employed for positron imaging through modifying the antibody with putting on a DOTA moiety, and then purifying it. The purified molecule, (^{64}Cu-DOTA-PR81) was tested for purity, ability to bind to its target, toxicity to cells, and molecular integrity. It was also tested in rats to determine biodistribution. The study results indicated that the labelled molecule was pure, retained molecular structure as well as function, and provided the same biodistribution as other labelled antibodies. This suggests that it can identify tumors and monitor the expression of MUC1 in breast-cancer patients.[51,52] A study parallel to our work found that the labeled antibody PR81, conjugated with the radioisotope ^{131}I, was able to identify and target MUC1-expressing breast tumors. The authors designed assays to evaluate stability, toxicity, and cellular internalization. They also appraised the biodistribution profile of radioiodinated PR81 in normal mice at 4, 24, and 48 hours and summarized its ability to visualize breast tumors. The study demonstrated that PR81 when radioiodinated was able to exhibit high immunoreactivity to MUC1, and revealed strong in vitro proliferation suppression of breast cancer cells. Ultimately, the ability of the antibody to visualize breast tumors suggests that PR81 is becoming more sensitive and appears to be the most promising therapeutical option for MUC1 breast cancer targeted therapy.[53,54] Radiopharmaceuticals induce DNA damage via α-, β-, and Auger electron emissions, resulting in tumor cell death and immune modulation through pathways such as cGAS–STING and ROS generation.[46,55,56] The combination of radiopharmaceuticals with other

therapeutics may be beneficial as a treatment modality versus standard of care therapies. For example, Wickstroem et al. tested the combination of Targeted ^{227}Th Conjugates (TTCs) with a drug known as olaparib, which inhibits a protein employed in DNA damage repair, in a BRCA2 Deficient Xenograft Model. A TTC consists of the radioactive ^{227}Th and a molecule which targets cancer cells. When the ^{227}Th emits alpha particles, the alpha particles damage the cancer cell's DNA and kills them. According to that study, the combination was effective for killing cancer cells in vitro as well as in vivo, specifically in cell lines with an underlying mutation, and found a strong synergistic effect. The accepted conclusion presented by the study indicates that the combination of the theranostic agent with the therapeutic agent holds potentials be a new treatment strategy for cancers with specific mutations.[3] D'Huyvetter et al. ascertained a new targeted radionuclide theranostic agent, designated as ^{131}I- GMIB-anti- HER2-VHH1, which was developed to differentiate and treat HER2 expressing cancers, a single domain antibody conjugated with therapeutic ^{131}I using the SGMIB linker.[57] The phase I study inspected the biodistribution, safety, radiation dosimetry, and tumor-imaging potential of this agent in healthy volunteers and breast cancer patients. There were no adverse events linked to the drug and it was observed to be cleared mainly by the kidneys. SPECT and Computed Tomography (CT) imaging in patients with late-stage breast cancer revealed focal uptake of the agent in the metastatic lesions. Thus, this radiopharmaceutical offers a new treatment option to patients who have failed trastuzumab, pertuzumab, or trastuzumab emtansine, given its low toxicity and uptake in HER2-positive lesions.[58] Pankratov et. al. have made two radiopharmaceuticals with HER2/neu tumor marker as a target based on a specific polypeptide called ZHER2 with labeled ^{177}Lu or ^{212}Pb radionuclides. The aim of the two radiopharmaceuticals was to document their cytotoxicity in vitro, using two human breast cancer cell lines (SK-BR3 with high HER2/neu marker expression and MCF-7 with low HER2/neu marker expression). The results indicated that both preparations exhibited statistically greater cytotoxicity to the SK-BR3 cells. The cytotoxicity grew with a longer incubation period (72 h where the cytotoxicity was greater than at 24 h) and was substantially greater than the radionuclide salts using the neutralization ligand (ZHER2) without specificity to HER2. The authors concluded that further preclinical studies in animal models with xenografts that have robust expression of the HER2/neu marker would generate promising results.[59] Programmed death receptor 1 (PD-1) is a protein expressed on T cells which can suppress or stop the response of the immune system. Cancer cells overexpress a PD-1 inhibitor protein (PD-L1) to evade the immune system. In a study by Gutiérrez et al., PD-L1 inhibitory peptides labeled with ^{177}Lu (^{177}Lu-DOTA-PD-L1-i) and ^{225}Ac (^{225}Ac-HEHA-PD-L1-i) were synthesized and appraised for targeted radiotherapy at the tumor microenvironment level. The conjugates were analyzed using UV-vis spectroscopy, FT-IR, and HPLC techniques. Subsequent assessments included cellular uptake, conjugate specificity, impact of radiotracer on cell viability, biokinetics, biodistribution, as well as determination of radiation absorbed dose in mice with induced lung micrometastases. The findings revealed that the radiotherapeutic PD-L1-i ligands utilizing ^{225}Ac and ^{177}Lu, as established in this study, could potentially be combined with immunotherapy to boost the therapeutic efficacy across different cancer types.[60]

Table 1. Summary of Targeted Radiopharmaceutical Studies and Their Applications

Targeting Category	Molecular Target	Radionuclide(s) Used	Study Example	Cancer Type	Therapeutic Goal	Research Stage	Ref.
Cell Surface Glycoprotein	MUC1	^{64}Cu, ^{131}I	PR81-DOTA / PR81-^{131}I	Breast Cancer	Imaging and Therapy	Preclinical (mice)	51,53
Prostate-Specific Antigen	PSMA	^{225}Ac, ^{213}Bi, ^{177}Lu, ^{161}Tb	^{225}Ac-L1 / ^{177}Lu-L1 / ^{161}Tb-PSMA	mCRPC (Prostate)	Tumor growth inhibition, survival enhancement	Preclinical	39,40
HER2 Receptor	HER2/neu	^{131}I, ^{177}Lu, ^{212}Pb	^{131}I-GMIB-VHH1 / ZHER2	HER2+ Breast Cancer	Metastasis tracking, targeted cytotoxicity	Phase I / In vitro	58,59
DNA Repair Mutations	BRCA2	^{227}Th	TTC + Olaparib	BRCA2-deficient Cancers	Combination therapy with DNA repair inhibitors	Xenograft Model	3
Immune Checkpoint Pathway	PD-L1	^{225}Ac, ^{177}Lu	PD-L1-i-Radio	Lung and other cancers	Micrometastasis targeting, immune enhancement	Preclinical	60

6. The AI Revolution in Radiotherapy (RT)

Early and accurate cancer diagnosis is critical for successful treatment outcomes. Artificial intelligence (AI), particularly through machine learning (ML) and deep learning (DL), has revolutionized medical imaging through enabling automated disease detection with high precision. For instance, integration of AI with optical coherence tomography (OCT) has enabled high-resolution, non-invasive cancer detection as well as real-time tumor margin assessment, particularly for epithelial cancers such as skin, oral, and gastrointestinal malignancies [65]. Following RT is one of the pillars of modern oncology, anti-cancer treatment; approximately 50% of all cancer patients will receive RT at some stage along their treatment (A:1). Nevertheless, the path from diagnosis to initiation of treatment is complicated, labor intensive, and resource consuming. The growing global incidence of cancer will influence the number of patients requiring RT and heighten the demand for RT services, resulting in an urgent need for innovative solutions to boost efficiency whilst maintaining or improving quality. Artificial Intelligence (AI) including machine learning (ML) and deep learning (DL) has presented itself as potentially disruptive in this space, to automate complex tasks, standardize workflows of treatment, and provide a means of personalizing treatment. AI has the ability to help re-engineer radiotherapy from an already time-efficient approach to RT as a safe, quicker, and more accurate treatment approach.[61,62]

7.1. Harnessing AI for Radiotherapy Planning and Delivery

One of the most revolutionary uses of AI has been in the area of image segmentation, a fundamental aspect of creating an RT plan. Outlining tumors and organs-at-risk (OARs) is very important but often tedious and takes away from patient encounters, and there is often considerable inter-observer variability. For instance, data from Microsoft's InnerEye, trialed at Addenbrooke's Hospital in Cambridge, have indicated that AI-assisted human contouring is 13 times faster than an unaided contour, with a reduction of clinician time preparing images by 93% without a decline in image quality.[63] Trials looking at abdominal OARs have noted segmentation times dropping from 22.6 minutes to 7.1 minutes, with no clinically unacceptable contours.[64,65] Such decrements in time for image preparation provide clinicians with more time for direct patient care and informed decision-making. In addition to the contouring process, AI-implemented treatment planning can widen the entire radiotherapy workflow. Automatic Treatment Planning (ATP), which often implements knowledge-based planning (KBP), can leverage previous plans of similar quality to generate optimal dose distributions for new patients. This creates less variability among planners, provides more reliability with the clinical protocol, and offers improved planning standardization among institutions.[66,67] Adaptive radiotherapy (ART), which modifies a radiotherapy plan according to patient anatomy, is similarly accepting greater input from AI for plan adaption. In specific cases, such as lung and prostate cancers, AI can utilize neural networks to monitor movement of the tumor by utilizing surrogate signals such as movement of the chest wall while breathing, which aligns with expected tumor motion.[68-70] Note that an integral advancement of AI in the process is its facilitation of the entire continuum of planning, daily delivery, adaptive process, and outcome assessment. The process usually starts with CT or MRI imaging, where AI-enhanced auto-segmentation identifies both the tumor and organs-at-risk with high accuracy.[71,72] The resulting contours serve as inputs into auto-planning workflows, which employ knowledge-based models to create treatment plans that are compliant with treatment protocols in a matter of minutes. Once the initial plan is generated, patients proceed to receive their first fraction of Image-Guided Radiotherapy (IGRT). At this stage, AI-enhanced cone-beam CT (CBCT) or MR images allow enhanced patient positioning accuracy and real-time verification of tumor targeting.[65,73] Critically, AI is not static but adaptive. For example, when patients treated with radiation experience significant anatomical changes (e.g., tumor shrinkage or weight loss) requiring repeat CT simulation (Re-CT), AI enables rapid re-contouring and replanning[74,75] This adaptive loop IGRT, reimaging, re-contouring and replanning can repeat multiple times along a treatment course, with AI enabling efficiency and feasibility. In addition to these technical aspects, AI systems are increasingly being created to pull together multimodal data, imaging, pathology and genomics, to forecast treatment outcomes. For instance, DL radiomics can identify which patients can benefit from frequent adaptive replanning, or who are at higher risk of radiation toxicity.[72] Even though outcome prediction models exist mostly in the research sphere, they represent an important leap toward precision oncology: a framework whereby every course of radiotherapy consideration is individualized concerning a patient's anatomy as well as their predicted biological response.[76] Taken together, this provides a glimpse of how AI will enable radiotherapy to be converted into a dynamic learning system, in real-time, based on individual, patient-specific needs.[73] AI is also aiding Image-Guided Radiotherapy (IGRT). Support vector machine-based DL models enhance the quality of cone-beam CT (CBCT) to levels comparable to planning CT scans, which can translate into dose delivery more accurately. While currently it may not be common practice, AI is also working to forecast treatment outcomes by ascertaining a multimodal set of data to inform on tumor control and the risk of toxicity.[77,78] Even though these predictive systems of treatment outcomes are yet to have standard practice, they provide a basis towards precision oncology, where treatments are suited to the

individual biology. Collectively, advances in AI/ML will accelerate workflows, improve precision and accuracy, and aim to improve survival outcomes while minimizing side effects or toxicity (Fig. 5).

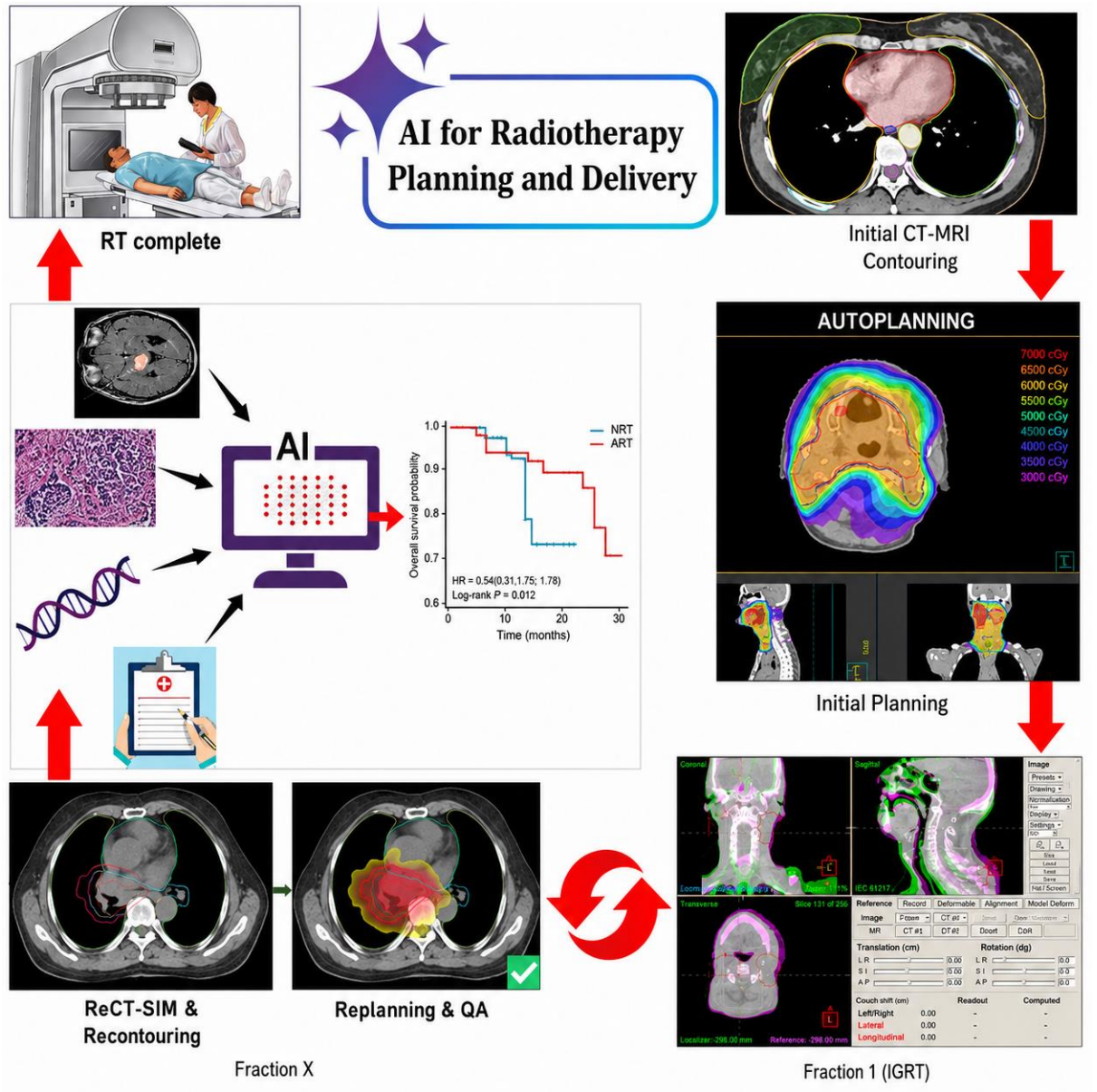

Figure 5. Workflow for the AI-Aided Planning and Delivery of Radiotherapy. Radiotherapy treatment begins with CT or MRI simulating, followed by the manual or AI-assisted delineation of tumors and organs-at-risk. Afterward, treatment plans are generated by AI-aided autoplanning to create optimized treatment plans to improve efficiency and consistency of treatment. Then, during each fraction of treatment, the patient is accurately positioned through daily image-gated radiotherapy (IGRT), and the process of checking and refining image quality and registration is AI-aided. Over the course of therapy stretching over several weeks, the process of imaging and recontouring and replanning (taking into account changes in anatomy) continues, aided by AI. This adaptive loop at the fraction level and simultaneously using data to analyze and potentially predict response and toxicity continues through all fractions until the treatment process is complete and the patient has been delivered personalized, precision and effective radiotherapy.

7.2. **The DL Revolution in Imaging and Outcome Prediction**

The vast majority of transformative advances in medical physics have emerged from DL, mainly convolutional neural networks (CNNs), U-Nets, and generative adversarial networks (GANs).[79,80] Such architectures have led to innovations in medical imaging, treatment planning, and predictive oncology. They have paved the way for

completely integrated AI workflows, with the potential for improved values of clinical radiotherapy in terms of consistency, speed, and personalization, ranging from image acquisition, reconstruction, and finally to outcome prediction.[81] DL approaches have outperformed traditional analytic algorithms for image reconstruction specifically in reducing noise and time of acquisition for CT as well as MRI images. Using residual encoder-decoder CNN (RED-CNN) architectures and the U-Net architecture, DL approaches have demonstrated utility in low-dose CT denoising and MRI acceleration with sustained diagnostic usability.[82] More generally, GAN-based methods can generate realistic synthetic images for data augmentation, bridging low-dose/accelerated scans and high-quality clinical images. Aside from low-dose CT denoising and MRI acceleration, VA-GAN models generate images that are perceptively realistic and clinically usable, akin to conventional CT and MRI acquisitions.[83,84] U-Nets have become the top standard in segmentation, achieving performance on par with human ratings in the assessment of brain, thoracic, as well as head and neck anatomy along with lower inter-reader variability. Further, state-of-the-art segmentation frameworks now include uncertainty estimation as a way of helping to direct clinician review and enhance safe practice in adaptive workflows. Likewise, DL has transformed image registration, automatically learning complex non-linear deformations to align scans across different modalities or scans from the same modality that have been obtained at different time points, which is critical for adaptive radiotherapy.[85,86] In addition, deep learning models are fundamental to radiomics, moving from engineered features to automatic learning of multi-scale features that capture hidden biological structures. Models such as ResNet and DenseNet pre-trained on natural images have been fine-tuned to predict tumor phenotype, response to treatment, and outcome. These works are exemplary of a transitional shift in science mediated by computational power and access to large datasets.[87,88] Deep Learning-based Knowledge Based Planning (DL-KBP) enables predicting complete three-dimensional dose maps for treatment planning as opposed to only dose-volume histograms, which gives planners a patient-specific reference or benchmark for plan optimizing purposes. Through providing voxel-level dose predictions, DL-KBP shortens planning time, improves consistency, and adapts to complex anatomical variations. αDiar and similar systems indicate that automated KBP can improve plan quality even for less-experienced dosimetrists.[89,90] Likewise, in quality assurance, virtual QA powered by DL will predict gamma passing rates based upon treatment planning data, thus ameliorating disposition. Further, for treatment delivery, attempts are being made to use DL to help track tumors in real time, predict respiratory motion, and may someday be employed to guide adaptive patient beam positioning.[91] Perhaps the most futuristic application is in predicting outcomes. DL models that include pre-treatment imaging, DOS distributions, and clinical information will predict both disease control and toxicity risk. Predictive modeling allows early intervention, patient-specific adaptive therapy, and integration of longitudinal data for refined accuracy. This ability to predict will also allow moving towards fully personalized adaptive radiotherapy.[92,93] The greatest frontier is in integrating knowledge, in particular combining DL with natural language processing (NL) as well as graph neural networks (GNNs) to develop patient-specific knowledge graphs. Such approaches combine radiomics, clinical text, genomics, and treatment history into interpretable frameworks, supporting explainable AI in oncology and bridging human expertise with data-driven insights. This may pool together radiomic data with clinical text, integrating data-driven insight with human-readable reasoning a major step towards explainable AI in oncology (Fig. 6).[94,95]

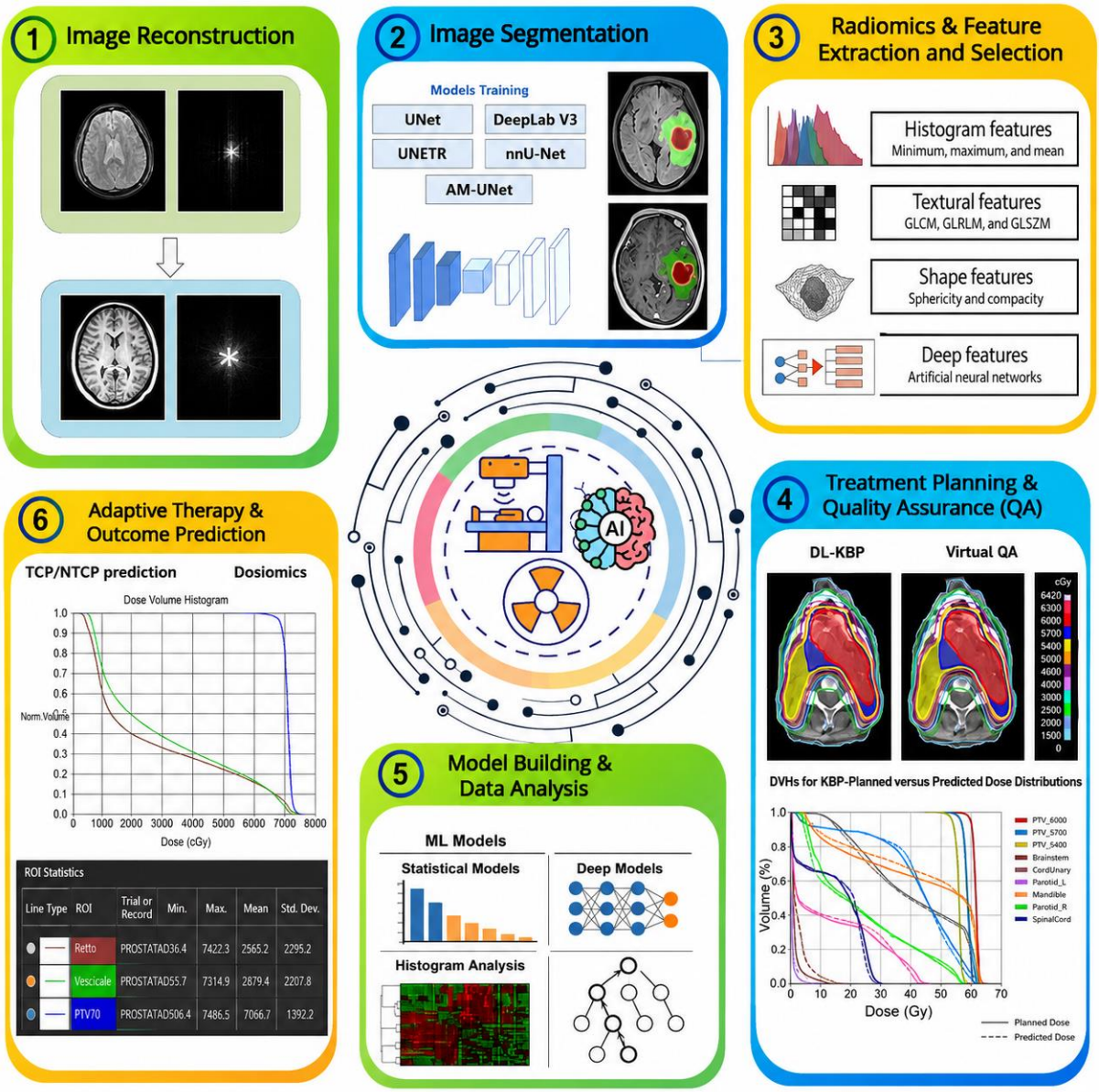

Figure 6. An AI-based imaging and treatment plan workflow in radiotherapy. (1) The workflow begins at image reconstruction from raw data from the scanner. (2) The next step is image segmentation to produce targets and organs at risk. (3) The radiomics and feature extraction step utilizes the reconstructed images to produce quantitative features to utilize in (4) treatment planning and quality assurance. (5) Model building and data analysis takes place from several different methodologies such as statistical, machine learning, or deep learning (DL) and can help provide predictive output. (6) Adaptive therapy, and predicting outcomes combines TCP/NTCP modeling and dosiomics to inform treatment adaptation and forecast personalized outcomes.

Nevertheless, it is crucial to appreciate the fact that there are significant challenges in the area of AI integration into the workflow of radiotherapy, especially in the realms of "interpretability" and "generalizability" of AI models for clinical adoption. DL models have proved to be very accurate for segmentation, dose prediction, and outcome prediction; however, the "black-box" nature of some model types may limit clinician's integration trust.[96] Explainable artificial intelligence (XAI) methods, e.g., attention maps, surrogate models, and feature attribution, provide some visualization of model reasoning and identifies interpretable model outputs.[97] Generalizability of the AI model to real world clinical care practice is often the most challenging to achieve, requiring a multi-institutional validation and standardized/reporting of AI model performance, as encouraged by ESTRO–AAPM

guidelines. It is almost certain that the ultimate success of adopting AI should rest on a multidisciplinary effort, including prospective clinical validating studies as well as sensible regulatory implications and responsibilities. The ultimate aim is to collaborate safely, allowing AI to provide personalized, precise, and ideally adaptive radiotherapy.[98]

8. Conclusion

In conclusion, targeted radiopharmaceuticals represent a paradigm shift in oncology, moving beyond conventional one-size-fits-all treatments. The radiotheranostics model successfully integrates precision diagnosis and therapy, enabling selective delivery of cytotoxic radiation to tumor cells while largely sparing healthy tissue. The continued development of novel carrier molecules and optimized radionuclides, including powerful alpha-emitters, is expanding the therapeutic arsenal against a growing range of cancers. Further, the synergistic potential of combining these agents with immunotherapy or targeted drugs promises to overcome resistance and unlock more durable responses. Indeed, the future of oncology is being redefined as these scientific advances converge with the operational precision offered by AI in treatment planning and adaptation. In spite of these advances, several challenges need to be overcome before radiotheranostics can achieve widespread clinical adoption. These include complex and costly regulatory approval pathways, limited production capacity and supply chain constraints for critical radionuclides (particularly alpha-emitters such as ^{225}Ac), specialized infrastructure requirements for manufacturing and handling, as well as high treatment costs that restrict limit patient access. These important barriers should be addressed through coordinated efforts from academia, industry, and regulatory bodies. Radiotheranostics is therefore poised to remain a central pillar of precision medicine, offering an increasingly personalized and robust path for patient care.

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Competing Interests

The authors declare that they have no conflicts of interest.

Ethical Approval

Not applicable. This study is a review of publicly available data and did not involve new experiments with human participants or animals.

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