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Radiopharmaceutical Therapy: Current Trends and Clinical Trial Landscape

Senthamizhchelvan Srinivasan
Department of Radiation Oncology, Indiana University, Indianapolis, IN, USA

Abstract:
Radiopharmaceutical therapy (RPT), also referred to as radioligand or targeted radionuclide therapy, has rapidly evolved from a niche salvage option into a central pillar of precision oncology. The field is driven by the success of lutetium-177 based agents in neuroendocrine tumors (NETs) and prostate cancer, the maturation of alpha-emitting therapies, and the emergence of new targets such as fibroblast activation protein (FAP). Recent analyses describe about 30 active phase III trials, with neuroendocrine, prostate, and thyroid cancers representing nearly three-quarters of late-stage development. Concurrently, the global radioligand therapy market is projected to reach roughly USD 13 billion by 2030. This review summarizes key trends in approved and emerging radiopharmaceuticals, highlights pivotal clinical trials across major disease areas, and discusses technical, regulatory, and infrastructure considerations that will shape RPT integration into routine cancer care.

1. Introduction

Radiopharmaceutical therapy combines a radionuclide "warhead" with a tumor-targeting vector commonly a peptide, small molecule, or antibody to deliver ionizing radiation selectively to malignant tissue. Historically, RPT was largely limited to iodine-131 for differentiated thyroid cancer and bone-targeted agents such as strontium-89 or samarium-153. Over the last decade, three landmark phase III trials ALSYMPCA (radium-223), NETTER-1 (^{177}Lu-DOTATATE), and VISION (^{177}Lu-PSMA-617) provided high-level evidence and led to regulatory approvals that transformed the perception of RPT from experimental to mainstream.

A 2025 mini-review of phase III RPT trials identified 34 active phase III studies, with neuroendocrine tumors, prostate cancer, and differentiated thyroid carcinoma accounting for nearly 75% of trials. In parallel, an industry analysis in *Nature Reviews Drug Discovery* reported two currently marketed "new-generation" radioligand therapies and 60-plus additional RPTs in clinical development across a broad range of solid and hematologic malignancies. Economically, recent market reports estimate that the radioligand therapy segment was approximately USD 9.2 billion in 2024 and is expected to grow to about USD 13–13.8 billion by 2030. Growth is fueled by increasing cancer incidence, expanding indications for approved agents, and a robust late-stage pipeline.

2. Approved Radiopharmaceutical Therapies and Core Platforms

2.1 Established Agents

Key approved RPTs include:

1. ^{177}Lu-DOTATATE (Lutathera®) - peptide receptor radionuclide therapy (PRRT) targeting somatostatin receptor 2, approved for SSTR-positive gastroenteropancreatic NETs based on NETTER-1.
2. ^{177}Lu-PSMA-617 (Pluvicto®) - PSMA-targeted small-molecule radioligand therapy for metastatic castration-resistant prostate cancer (mCRPC), initially approved post-taxane based on VISION and subsequently expanded (see below).
3. $^{223}RaCl_2$ (Xofigo®) - alpha-emitting agent targeting bone metastases in mCRPC.
4. ^{131}I (radioiodine) - long-established metabolic therapy for differentiated thyroid cancer, now being refined rather than replaced.

Therapeutic platforms span radiolabeled peptides (PRRT), small-molecule ligands (PSMA, FAP, CXCR4), monoclonal antibodies, and intra-arterial microspheres (e.g., ^{90}Y-labeled glass or resin microspheres) for liver-directed therapy.

2.2 Expansion of Pluvicto into Earlier mCRPC

On March 28, 2025, the U.S. FDA expanded the indication of lutetium Lu-177 vipivotide tetraxetan (Pluvicto) to include adults with PSMA-positive mCRPC previously treated with one androgen receptor pathway inhibitor (ARPI) and deemed appropriate to delay taxane-based chemotherapy.

- The phase III PSMAfore trial randomized 468 patients with PSMA-positive mCRPC progressing on one ARPI to Pluvicto or ARPI switch. Median radiographic PFS was 9.3 vs 5.6 months (HR 0.41), favoring Pluvicto, with a strong trend but non-significant difference in overall survival in the intention-to-treat analysis.
- Novartis reports an updated analysis showing more than a doubling of median rPFS (~11.6 vs 5.6 months) and an OS benefit after adjustment for crossover.
- This label expansion effectively moves radioligand therapy into a pre-chemotherapy setting in mCRPC and is estimated to triple the eligible U.S. patient population.

Guideline-level frameworks for Lu-PSMA use have been published by the Society of Nuclear Medicine and Molecular Imaging (SNMMI) and joint EANM/SNMMI procedure guidelines. These documents define patient selection criteria (PSMA PET positivity, prior therapies), safety monitoring, and scenarios for off-label use.

3. Market and Industrial Landscape: From Niche to Pillar

Several converging trends underscore that RPT is becoming a durable modality rather than a transient niche:

- Pipeline depth. The 2025 landscape overview counts about 67 radioligand products in clinical development, encompassing a wide variety of targets (PSMA, SSTR, FAP, HER2, TROP2, CD38, CD20, CXCR4, and others).
- Market growth. Independent market analyses project the global radioligand therapy market at USD 13–13.8 billion by 2030, with growth concentrated in prostate cancer and NET indications and rapid uptake in Asia-Pacific.
- Industrial investment. In November 2025, Novartis opened a 10,000-sq-ft radioligand manufacturing facility in Carlsbad, California, as part of a USD 23 billion U.S. expansion plan, specifically to stabilize and accelerate supply of Pluvicto and Lutathera for the western U.S.

Because many therapeutic radionuclides have short half-lives and are often produced in single-patient batches, the field depends on reliable isotope production, regional manufacturing hubs, and robust cold-chain logistics.

4. Disease-Specific Trends and Pivotal Clinical Trials

4.1 Neuroendocrine Tumors (NETs)

4.1.1 PRRT in Earlier-Line GEP-NETs

Following NETTER-1, which established 177Lu-DOTATATE plus octreotide as a standard in progressive midgut NETs, recent trials are pushing PRRT into earlier lines and higher-grade disease.

- NETTER-2 (NCT03972488). In untreated, well-differentiated grade 2–3 GEP-NETs (Ki-67 10–55%), adding ^{177}Lu-DOTATATE to standard-dose octreotide nearly tripled median PFS (22.8 vs 8.5 months) and reduced risk of progression or death by ~72% vs high-dose octreotide alone.
- COMPOSE (NCT04919226) compares ^{177}Lu-DOTATOC with everolimus in progressive GEP-NETs, with recruitment completed and results pending.
- COMPETE (NCT03049189) has completed accrual and will compare PRRT directly with everolimus in GEP-NETs.

These data support a shift toward first-line or early-line PRRT in selected patients with high-burden or higher-grade well-differentiated NETs, although long-term overall survival and health-economic outcomes will be crucial to guideline adoption.

4.1.2 Personalised Dosimetry

Because PRRT produces heterogeneous intra-tumoral dose distributions, fixed activities can yield widely variable absorbed doses between patients.

- The START-NET trial (NCT05387603) randomizes patients to standard 4 × 7.5 GBq ^{177}Lu-DOTATOC vs individualized dosimetry-guided dosing based on dual ^{68}Ga-DOTATOC and ^{18}F-FDG imaging, with outcomes including efficacy, toxicity, and cost.

This aligns with IAEA and JNM initiatives emphasizing patient-specific dosimetry and quantitative SPECT/CT as a route to true theranostic personalization.

4.1.3 Emergence of Alpha PRRT

To improve tumor kill in resistant disease, alpha-emitting isotopes such as actinium-225 are being evaluated:

- ACTION-1 (NCT05477576) is a global phase 1b/3 trial of ^{225}Ac-DOTATATE (RYZ101) vs standard of care in SSTR-positive GEP-NETs progressing after ^{177}Lu-PRRT. Early phase 1b data show encouraging dosimetry and tolerability without dose-limiting toxicities.

If successful, ACTION-1 may establish alpha-PRRT as a salvage or even preferred approach in patients failing lutetium-based therapy.

4.2 Prostate Cancer

Prostate cancer is the most mature non-thyroid indication for RPT, dominated by PSMA-targeted therapies.

4.2.1 Lu-PSMA in mCRPC and Earlier Disease

Beyond VISION and the PSMAfore-driven label expansion discussed above, further trials are exploring:

- ^{177}Lu-PSMA-I&T - two phase III trials in mCRPC (NCT04647526, NCT05204927) have completed recruitment and will determine whether this widely used “compassionate-use” compound achieves registrational status.
- Earlier-stage disease. At least five phase III studies are evaluating ^{177}Lu-PSMA-617 in:

    1. Metastatic hormone-sensitive prostate cancer (mHSPC) e.g. PSMAddition (NCT04720157) and other trials in mHSPC.
    2. Oligometastatic settings (e.g., NCT05939414).

A recent Reuters report on a phase III trial in metastatic hormone-sensitive disease noted that Pluvicto significantly slowed disease progression when combined with hormone therapy, reinforcing prospects for pre-mCRPC indications.

4.2.2 Consensus Guidelines and Real-World Use

The SNMMI consensus statement on patient selection and appropriate use of ^{177}Lu-PSMA-617 and the joint EANM/SNMMI procedure guideline have provided detailed criteria on PSMA PET imaging requirements, prior systemic therapy, performance status, and toxicity management. These guidelines are accelerating standardization of RLT outside clinical trials, particularly in the United States and Europe.

4.2.3 Alpha PSMA Therapy

The next wave in prostate RPT involves alpha-emitting PSMA ligands:

- FPI-2265 (^{225}Ac-PSMA-I&T, AlphaBreak; NCT06402331) is a phase II, randomized, open-label trial optimizing dose and schedule in PSMA-positive mCRPC. The study aims to define a recommended regimen based on safety, tolerability, and anti-tumor activity, and the first patient has already been dosed.
- Alpha-PSMA agents may offer higher linear energy transfer and shorter path length, potentially overcoming resistance to beta-PSMA therapies while raising new questions about marrow and kidney toxicity.

4.3 Differentiated Thyroid Cancer: Refining Radioiodine Use

Radioiodine has been used for more than 70 years in differentiated thyroid cancer (DTC), but optimal indications and doses remain under evaluation.

4.3.1 ESTIMABL2: De-escalating RAI in Low-Risk DTC

The ESTIMABL2 phase III trial (NCT01837745) randomized low-risk DTC patients to postoperative ^{131}I ablation vs surveillance after total thyroidectomy.

- Five-year results showed non-inferior event-free survival with surgery alone (94% in both arms), indicating no loss of oncologic opportunity when omitting RAI in carefully selected low-risk patients.

These data support restricting radioiodine in low-risk DTC and concentrating its use in higher-risk or metastatic disease.

4.4 Liver Tumors and Pediatric Malignancies

4.4.1 Hepatocellular Carcinoma (HCC): ^{90}Y Microspheres

While radioembolization with ^{90}Y microspheres has been used for years, high-level randomized evidence has been relatively sparse.

- MANDARIN (NCT05016245) is a multicenter, prospective phase III trial in China comparing TheraSphere™ ^{90}Y glass microspheres to conventional TACE in inoperable HCC (China liver cancer stages Ib–IIb). The study is active, with an estimated completion around 2026.

MANDARIN will help clarify whether ^{90}Y radioembolization should be preferred to TACE in intermediate-stage HCC, at least in selected populations.

4.4.2 High-Risk Neuroblastoma: ^{131}I-MIBG and ALK Inhibition

In pediatric oncology, ^{131}I-metaiodobenzylguanidine (MIBG) is an established targeted agent for neuroblastoma. Current studies are incorporating it earlier:

- NCT03126916 is a phase III trial testing ^{131}I-MIBG or lorlatinib plus intensive multimodal therapy in newly diagnosed high-risk neuroblastoma/ganglioneuroblastoma. The trial compares standard therapy and these additions, aiming to improve survival while carefully monitoring late effect.

This study exemplifies broader efforts to integrate RPT into front-line pediatric regimens where biologically targeted radiation may complement chemotherapy, surgery, and external beam radiotherapy.

4.5 Fibroblast Activation Protein (FAP)–Targeted Radioligand Therapy

FAP is a type II transmembrane serine protease highly expressed on cancer-associated fibroblasts in the stroma of more than 90% of epithelial cancers, including pancreatic, colorectal, breast, and lung tumors. The success of FAPI-based PET imaging has established FAP as a “pan-tumor” theranostic target.

Recent reviews provide an overview of clinical advances in FAP-targeted radioligand therapy (FAP-RLT):

- Early quinoline-based agents (e.g., FAPI-04, FAPI-46) demonstrated high tumor uptake but short tumor retention, limiting therapeutic efficacy when labeled with beta-emitters.
- Next-generation ligands incorporate albumin-binding moieties, cyclic peptides, or dimeric designs to prolong tumor retention and improve tumor-to-organ dose ratios (e.g., FAP-2286, EB-FAPI, $(SA.FAPi)_2$, 3BP-3940).
- Early phase clinical data with ^{90}Y-FAPI-46 report manageable hematologic toxicity and disease control (PR+SD) in roughly half of heavily pretreated patients, with strongest signals seen in sarcoma and solitary fibrous tumor.
- Currently, FAP-RLT remains early-phase, with multiple trials in pancreatic ductal adenocarcinoma, colorectal cancer, sarcoma, and other stromal-rich tumors. Well-designed randomized trials will be needed to clarify its comparative value versus chemotherapy, external beam radiotherapy, and immunotherapy.

4.6 Emerging Targets Beyond SSTR, PSMA, and FAP

The RLT pipeline is expanding across a range of targets already familiar from monoclonal antibody and ADC development:

- HER2, HER3, and EGFR – radiolabeled antibodies and small molecules are being tested in breast, gastric, and other HER-driven cancers.
- CXCR4: a 2025 preclinical/early translational report on ^{177}Lu-DOTA-CXCR4 highlights favorable biodistribution with reduced liver and kidney uptake compared with some prior CXCR4 agents, supporting its potential as a theragnostic agent for hematologic and solid tumors.
- Other immune and stromal targets (e.g., CD38, CD20, TROP2) are being radiolabeled in exploratory programs, often aiming for synergistic combinations with checkpoint inhibitors or established systemic therapies.

5. Radionuclide Science: Lutetium Dominance and Alpha Expansion

5.1 Lutetium-177 as the Workhorse

The Frontiers overview notes that ^{177}Lu is used in 17 of 34 active phase III RPT trials and in more than 200 ongoing studies overall, reflecting its favorable half-life (~6.7 days), beta energy, and co-emitted gammas enabling post-therapy imaging.

Recent work on ^{177}Lu-based therapy emphasizes:

- Optimization of patient-specific dosimetry, moving beyond fixed activities to individualized treatment courses.
- Development of new carrier molecules and bifunctional chelators under IAEA-sponsored coordinated research projects.

5.2 Targeted Alpha Therapy (TAT)

Alpha-emitters such as ^{225}Ac, ^{211}At, ^{212}Pb/^{212}Bi, ^{223}Ra, ^{149}Tb, and ^{227}Th deliver high-LET radiation over a very short path length, potentially enhancing tumor cell kill while sparing surrounding healthy tissue.

Key trends in TAT include:

- Clinical maturation in NETs and prostate cancer, exemplified by ACTION-1 (^{225}Ac-DOTATATE) and AlphaBreak (^{225}Ac-PSMA-I&T).
- Renewed efforts to solve production and supply challenges for alpha emitters, particularly ^{225}Ac, which historically has been limited by generator capacity and cost.

A 2024 review in *European Journal of Nuclear Medicine and Molecular Imaging* underscores broad interest in TAT across brain tumors, bladder cancer, leukemia, NETs, and prostate cancer, while cautioning that toxicity profiles, dosimetry, and long-term safety remain incompletely defined.

6. Dosimetry, Quality Assurance, and Regulatory Initiatives

6.1 Toward Routine Patient-Specific Dosimetry

Modern RPT is moving from empiric dosing towards quantitative, individualized planning:

- The IAEA monograph “Dosimetry for Radiopharmaceutical Therapy” and related coordinated research projects promote standardized methods for SPECT/CT-based activity quantification, time–activity curve fitting, and absorbed dose estimation.
- JNM reviews emphasize that dosimetry can optimize tumor control while respecting organ-at-risk constraints, but implementation varies widely between centers and software platforms.

Trials such as START-NET will provide critical prospective evidence for whether dosimetry-guided PRRT improves outcomes compared with simple fixed-activity regimens.

6.2 Operational Readiness and Quality Assurance

Implementing RPT requires:

- Reliable radionuclide supply, hot-lab infrastructure, and radiation safety protocols.
- Multidisciplinary teams (nuclear medicine, medical physics, nursing, pharmacy, oncologists) trained in handling unsealed sources and managing therapy-specific toxicities.
- Center-level quality assurance programs to ensure accurate activity calibration, imaging quantification, and record-keeping for regulatory compliance.

- Regulatory and professional bodies (e.g., SNMMI, EANM, IAEA) increasingly provide guidance on appropriate use criteria, dosimetry standards, and clinical trial design, helping to harmonize practice across regions.

7. Future Directions and Conclusions

Radiopharmaceutical therapy is entering what many have called its "third wave":

1. Expansion of approved indications: earlier-line use of ^{177}Lu-PSMA-617 in mCRPC and likely in mHSPC, and first-line PRRT for selected higher-grade GEP-NETs (NETTER-2).
2. New targets and tumor types: FAP-RLT, CXCR4, HER2/HER3, and others broaden RPT beyond NETs and prostate cancer, with pan-tumor theranostic strategies under active investigation.
3. Technical differentiation: alpha-emitters, innovative chelators, and sophisticated dosimetry may allow therapies to be tailored according to tumor biology, spatial disease distribution, and patient-specific radiobiology.
4. System-level integration: large-scale investments in manufacturing (e.g., Novartis's Carlsbad facility and U.S. expansion) and maturing regulatory frameworks indicate that RPT is being treated as a strategic long-term modality rather than a niche.

For clinicians and trialists, the implications are clear:

- Oncology teams should anticipate earlier referral points for PRRT and Lu-PSMA therapies and consider clinical trial enrollment as part of first- or second-line treatment pathways.
- Nuclear medicine and medical physics units need to invest in dosimetry capabilities, QA, and multidisciplinary training to meet increasing demand.
- Health systems and payers must plan for the cost and logistical complexity of RPT while recognizing its potential to improve progression-free survival, quality of life, and, in some settings, overall survival.

As of late 2025, radiopharmaceutical therapy is firmly established as a critical component of precision oncology, with the next decade likely to bring more indications, more isotopes, and more personalized treatment paradigms.

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