Current Clinical Applications of 225Ac in Targeted Alpha Therapy

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Abstract

Radioactive targeted drugs have attracted considerable attention as an important therapeutic modality for malignant tumors, owing to their precise tumor-targeting capability and potential efficacy against tumors resistant to conventional treatments. 225Ac has emerged as a highly promising radionuclide for targeted alpha therapy due to its high cytotoxicity, appropriate half-life, and unique decay properties. This review summarizes the clinical research advances of 225Ac in treating prostate cancer, neuroendocrine tumors, and other malignancies, discusses the challenges confronting targeted alpha pharmaceuticals, and outlines future development directions, aiming to provide valuable insights for related research in this field.

Full Text

Current Clinical Application Status of 225Ac in Targeted Alpha Therapy

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Abstract

Radioactive targeted drugs represent an important therapeutic modality for malignant tumors, attracting considerable attention due to their precise tumor-targeting capability and potential efficacy against treatment-resistant cancers. Actinium-225 (225Ac) has emerged as a highly promising radionuclide for targeted alpha therapy, owing to its high cytotoxicity, suitable half-life, and unique decay characteristics. This review summarizes the clinical research progress of 225Ac in treating various malignancies, including prostate cancer and neuroendocrine tumors, and discusses the challenges and future development directions of targeted alpha drugs, aiming to provide valuable insights for related research in this field.

Keywords: targeted alpha therapy; 225Ac; prostate cancer; neuroendocrine tumor

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Malignant tumors constitute a major global health challenge. According to the latest 2024 data from the World Health Organization's International Agency for Research on Cancer, approximately 19.96 million new cancer cases and 9.73 million cancer deaths were recorded worldwide in 2022, accounting for 17.1% of total global mortality. Malignant tumors have become the second leading cause of human death globally after cardiovascular diseases, posing a serious threat to human health. For decades, treatment options for malignant tumors have primarily included surgical resection, radiotherapy, and chemotherapy, either as monotherapy or in combination. However, these conventional therapies have significant limitations: surgery can remove the main tumor mass but often fails to eliminate all microscopic lesions, carrying a risk of recurrence; chemotherapy can widely kill tumor cells but causes severe toxicity to normal cells and has limited efficacy against advanced and metastatic tumors; conventional external beam radiotherapy has a broad radiation field that can damage surrounding normal tissues. Although modern radiotherapy techniques such as intensity-modulated radiotherapy (IMRT) and image-guided radiotherapy (IGRT) can improve targeting accuracy, they still cannot completely and precisely target tumor cells, particularly microscopic metastatic lesions. Therefore, finding more effective treatments is imperative.

With the advancement of modern nuclear medicine, radionuclide-labeled targeted drugs, particularly targeted alpha therapy (TAT), have gained increasing attention due to their potential to precisely kill tumors while maximizing protection of normal tissues. 225Ac, as a highly promising alpha-emitting radionuclide, demonstrates enormous potential in tumor treatment. This article begins with the principles and advantages of targeted alpha therapy, focusing on the characteristics of 225Ac and its applications in tumor treatment, to provide a reference for the development and clinical application of 225Ac radiopharmaceuticals for malignant tumors.

1 Principles and Advantages of Targeted Alpha Therapy

The core mechanism of targeted alpha therapy involves using specific targeting ligands—such as antibodies, peptides, or small molecules—to precisely recognize and bind to specific molecular targets on tumor cell surfaces, thereby delivering alpha-emitting radionuclides to the interior or adjacent regions of tumor tissues. Upon binding to the target, the radionuclide releases alpha particles that cause direct damage to tumor cells through ionizing radiation, particularly by inducing difficult-to-repair DNA double-strand breaks or destroying cell membrane structures. Additionally, this process can trigger radiation-induced bystander effects, leading to death of neighboring tumor cells and potentially activating systemic immune responses that attack distant metastases, achieving broader therapeutic effects.

The unique radiobiological characteristics of alpha particles—extremely high linear energy transfer (LET) and extremely short range (approximately 50-100 micrometers, equivalent to several cell diameters)—form the physical basis for the high efficacy and safety of targeted alpha therapy. Their high LET property enables alpha particles to produce extremely high energy transfer density at the subcellular scale, generating dense ionization clusters that cause irreversible catastrophic damage to critical biomolecules, ensuring efficient cell-killing effects. Simultaneously, the short range of alpha particles results in highly localized energy deposition, strictly confined to target cells and their immediate microenvironment, reducing unnecessary radiation exposure to surrounding normal tissues.

Based on these principles and the physical characteristics of alpha particles, targeted alpha therapy offers significant advantages over conventional external beam radiotherapy. It not only achieves precise intracellular delivery of radionuclides to tumor cells through ligand mediation, effectively overcoming the fundamental limitation of external beam radiation in completely covering diffuse and metastatic lesions, but also provides superior safety. The short range of alpha particles is the key physical attribute protecting normal tissues from unnecessary radiation, thereby reducing treatment-related toxicity. Additionally, it has potential immunomodulatory effects by inducing immunogenic cell death, which may activate the host immune system to recognize and attack tumors, producing synergistic anti-tumor effects. This dual mechanism combining precise, efficient cell killing with potential immune activation offers a highly promising direction for targeted alpha therapy, particularly when combined with potent alpha-emitting radionuclides such as 225Ac.

2 Characteristics and Advantages of 225Ac

In targeted alpha therapy, 225Ac, as an alpha-emitting radionuclide, demonstrates significant application value in tumor treatment due to its unique physical and chemical properties. Compared with many other alpha-emitting radionuclides, 225Ac has a half-life of approximately 9.9 days, providing an adequate

time window for drug distribution in vivo, tumor uptake, and sustained therapeutic effect, thereby ensuring treatment efficiency and stability. In contrast, some short half-life alpha radionuclides (such as 211At with a half-life of only 7.2 hours) have extremely limited time to exert therapeutic effects in vivo, making sustained tumor attack difficult.

Furthermore, 225Ac offers highly controllable therapeutic windows. By optimizing targeting ligand selection, adjusting the radionuclide-to-ligand binding ratio, and refining dosing regimens, the radiation dose and treatment duration of 225Ac can be precisely controlled. This property helps improve therapeutic efficacy while effectively balancing potential toxicities, such as effects on kidneys or bone marrow, thereby enhancing treatment safety and effectiveness.

More critically, the decay chain of 225Ac includes multiple daughter nuclides (such as 221Fr and 213Bi) that can also emit alpha particles, with some even releasing beta particles. Compared with single-nuclide alpha therapy (such as using only 212Pb), the decay chain of 225Ac can provide richer radioactive particles, achieving more efficient tumor killing. However, this complex decay chain may also present challenges. While daughter nuclide production increases radiation dose, it may also increase the risk of off-target effects. Therefore, when leveraging the advantages of the 225Ac decay chain, it is essential to optimize targeting ligand selection, adjust radionuclide-to-ligand binding ratios, and refine dosing regimens to maximize daughter nuclide retention and ensure treatment safety.

3 Clinical Research on 225Ac in Various Tumors

225Ac-labeled targeted alpha drugs have undergone clinical studies in multiple malignant tumor types, including prostate cancer and neuroendocrine tumors. These studies have achieved precise tumor delivery through different targeting ligands (such as peptides and antibodies), demonstrating promising therapeutic efficacy and safety. For example, 225Ac-labeled targeting ligands have shown efficient tumor uptake and significant anti-tumor activity in clinical trials for prostate cancer and neuroendocrine tumors. These clinical trials have provided important data on the pharmacokinetic and dosimetric characteristics of 225Ac targeted alpha drugs and have laid a foundation for their broad application in tumor therapy.

3.1 Prostate Cancer

Prostate cancer is one of the most common malignancies in men globally, particularly among elderly men. With global population aging intensifying, the population aged 65 and above reached approximately 781 million in 2022, accounting for 10% of the total population. This demographic shift has led to continuously increasing risk of prostate cancer. According to the GLOBOCAN 2022 report released by the International Agency for Research on Cancer, there were approximately 1.467 million new prostate cancer cases and 397,000 deaths

globally in 2024, making it one of the leading causes of cancer-related death in men. Prostate-specific membrane antigen (PSMA) has been confirmed to be highly expressed on the surface of metastatic prostate cancer cells, representing an effective therapeutic target.

In a study by Clemens Kratochwil et al., preliminary clinical results of 225Ac-PSMA-617 showed that 63-70% of patients achieved a prostate-specific antigen (PSA) decline of over 50%, with a duration of response of 10-15 months, and approximately 10% of patients achieved complete remission, demonstrating promising anti-tumor activity. Madhav Prasad Yadav et al. treated 28 metastatic castration-resistant prostate cancer (mCRPC) patients with 225Ac-PSMA-617, including 15 who had previously received 177Lu-PSMA-617 therapy. Results showed that 25% and 39% of patients achieved PSA decline of over 50% at week 8 post-treatment and at final follow-up, respectively. The median progression-free survival (PFS) was 12 months, and median overall survival (OS) was 17 months. Disease control rates (based on biochemical and molecular tumor response criteria) were 82% and 63.6%, respectively. No grade 3-4 toxicities were observed, with the most common side effects being transient fatigue (50%) and grade 1-2 xerostomia (29%). These findings indicate that 225Ac-PSMA-617 demonstrates good disease control and low toxicity in mCRPC patients, even after failure of other treatments.

Mike Sathekge et al. innovatively proposed a combination therapy of 177Lu-PSMA-617 and 225Ac-PSMA-617. In 20 enrolled mCRPC patients, the combination therapy resulted in PSA decline of over 50% in 13 patients (65%), with median PFS of 19 weeks and median OS of 38 weeks. The treatment was well-tolerated, with no grade 3-4 xerostomia observed, and only mild xerostomia in a few patients. These results not only provide a new option for drug-resistant patients but also reveal the biological basis for synergistic enhancement between alpha/beta radionuclides.

The therapeutic advantage is not limited to a single ligand. PSMA-I&T is another small-molecule ligand with high safety and strong binding capacity. Mathias Johannes Zacherl et al. first used 225Ac-PSMA-I&T to treat 14 mCRPC patients, 11 of whom had previously received second-line anti-androgen therapy with abiraterone or enzalutamide, chemotherapy, and 177Lu-PSMA therapy. Clinical data showed that 79% of patients experienced PSA decline, with 50% achieving at least 50% PSA reduction. Among 11 patients previously treated with 177Lu-PSMA, 73% had PSA decline, with 45% achieving at least 50% reduction. Grade 3 anemia occurred in 3 patients, and grade 3 leukopenia in 1 patient. Grade 1-2 oral dryness occurred in 57% of patients, but no worsening of symptoms was reported. These results demonstrate that 225Ac-PSMA-I&T has significant efficacy and acceptable toxicity in treating mCRPC patients, showing good therapeutic effects even in heavily pretreated patients.

Additionally, monoclonal antibodies as PSMA ligands have been extensively studied. However, due to their large size, slower tumor uptake, and longer half-life, monoclonal antibodies result in more systemic radiation exposure and

hematologic toxicity. Nevertheless, compared with small-molecule PSMA ligands, the larger size of monoclonal antibodies means less penetration into other tissues (such as salivary glands and kidneys), which may reduce side effects (such as dry mouth) observed in clinical trials using small-molecule PSMA conjugates. 225Ac-J591 is a targeted alpha drug labeled with 225Ac using a monoclonal antibody. Scott T. Tagawa et al. conducted a phase I dose-escalation study of 225Ac-J591 in mCRPC patients who had received at least one androgen receptor pathway inhibitor and taxane chemotherapy or were deemed unsuitable for taxane chemotherapy. The study started at 13.3 kBq/kg body weight and escalated to 93.3 kBq/kg, with 6 patients in each of 6 dose-escalation cohorts and 10 patients in the highest dose cohort. During follow-up, 46.9% of patients achieved at least 50% PSA decline, with 34.4% having confirmed PSA50 response. At final follow-up, nearly all patients experienced disease progression and/or death. Median PFS was 5.6 months, and median OS was 10.7 months. The results indicate that single-dose 225Ac-J591 demonstrated safety and preliminary efficacy in 32 pretreated progressive mCRPC patients. Therefore, reducing side effects from uptake in kidneys and salivary glands remains an urgent problem to be solved in clinical application of 225Ac-PSMA.

3.2 Neuroendocrine Tumors

Neuroendocrine tumors are a rare and heterogeneous group of neoplasms originating from endocrine cells that secrete biogenic amines and peptide hormones. These cells are distributed throughout the body, including the digestive system, respiratory system, and pancreas. The most common primary sites are the gastrointestinal tract, including the pancreas (62-67%) and lung (22-27%). Treatment options for neuroendocrine tumors are limited, with complete surgical resection being the only curative approach currently. Peptide receptor radionuclide therapy, which combines radioactive substances with octreotide derivatives, has proven to be an effective and well-tolerated treatment. Somatostatin receptors (SSTR), highly expressed in neuroendocrine tumors, enable precise targeted therapy and represent ideal targets for targeted alpha therapy. DOTATATE, as a somatostatin analog, has high affinity and specificity for SSTR, enabling efficient binding and precise targeting. It demonstrates high tumor uptake and has shown good therapeutic efficacy in clinical studies, effectively controlling tumor growth, reducing disease progression risk, and improving patient quality of life.

Emre Demirci et al. focused on patients with grade 1-2 metastatic neuroendocrine tumors, particularly those refractory or intolerant to 177Lu-DOTATATE therapy. Patients received 225Ac-DOTATATE at an average dose of 8.2 $\pm$ 0.6 MBq (range: 7.5-10.0 MBq). Results showed that 225Ac-DOTATATE demonstrated significant efficacy in these refractory patients, with good tumor control and low toxicity during treatment. Although one patient developed grade 2 renal toxicity and grade 2 hematologic toxicity, no more severe grade 3-4 toxic events were observed.

Sanjana Ballal et al. conducted a prospective study to evaluate 225Ac-DOTATATE targeted alpha therapy in patients with stable or refractory gastroenteropancreatic neuroendocrine tumors after 177Lu-DOTATATE treatment. All enrolled patients had previously received 177Lu-DOTATATE with poor response or disease progression. Patients received 225Ac-DOTATATE at 100 kBq/kg body weight every 8 weeks. Among 24 treated patients, 15 achieved partial response and 9 had stable disease, with no disease progression or treatment-related deaths observed. Post-treatment plasma chromogranin A levels decreased significantly, and no grade 3-4 toxicities were reported. These preliminary results indicate that 225Ac-DOTATATE is a stable, safe, and effective treatment option for patients with advanced neuroendocrine tumors, particularly those refractory to 177Lu-DOTATATE, offering new therapeutic hope. However, long-term drug safety remains a major challenge for clinical application.

3.3.1 Metastatic Paraganglioma

Metastatic paragangliomas originate from the adrenal gland, with the abdomen being the most common site, followed by the chest, pelvis, and neck. Recent studies indicate that metastatic paragangliomas are abnormal tissues composed of tumor vessels and nerve cells derived from pluripotent mesenchymal stem cells or progenitor cells. Generally, metastatic paragangliomas are curable; however, once metastasis occurs, treatment options become limited and cure is rare. Similarly, in treating metastatic paragangliomas with 225Ac-labeled targeted alpha drugs, SSTR remains the chosen target because metastatic paragangliomas, as a type of neuroendocrine tumor, also overexpress SSTR receptors, particularly SSTR2. Therefore, 225Ac-DOTATATE is used for treatment.

Madhav Prasad Yadav et al. conducted a pilot study of 225Ac-DOTATATE targeted alpha therapy for metastatic paragangliomas. The study included 9 patients (6 male, 3 female) with histologically confirmed metastatic paraganglioma who received 225Ac-DOTATATE targeted alpha therapy with concurrent radiosensitizer capecitabine every 8 weeks until cumulative activity reached approximately 74 MBq. Results showed that 50% of patients achieved partial response, 37.5% had stable disease, and 12.5% had progressive disease, with an overall disease control rate of 87.5%. Among patients previously treated with 177Lu-PRRT, 66.6% responded to 225Ac-DOTATATE. No severe hematologic, renal, or hepatic toxicities were observed, indicating that 225Ac-DOTATATE is safe and effective in patients with advanced paragangliomas, even in those refractory to 177Lu-PRRT. Thus, 225Ac-DOTATATE demonstrates potential therapeutic efficacy in various diseases including neuroendocrine tumors and metastatic paragangliomas.

3.3.2 Acute Myeloid Leukemia

Acute myeloid leukemia (AML) is a rapidly progressing myeloid neoplasm characterized by clonal expansion of immature myeloid-derived cells (blasts) in

peripheral blood and bone marrow, leading to ineffective erythropoiesis and megakaryopoiesis. Clinically, this manifests as relatively rapid bone marrow failure, resulting in insufficient production of red blood cells and platelets. Despite therapeutic advances, prognosis remains unsatisfactory in middle-aged and elderly populations. CD33 is a cell surface antigen present on mature normal hematopoietic cells and AML cells but absent on normal hematopoietic stem cells. This expression pattern makes CD33 an ideal target for selective ablation of malignant cells and immature normal cells while preserving normal hematopoietic stem cells. Both leukemic cells and AML stem cells express CD33 in approximately 90% of AML cases, making CD33 a viable target for immunotherapy. Lintuzumab (HuM195) is a humanized anti-CD33 monoclonal antibody targeting myeloid leukemia cells with modest activity in AML. It can specifically bind to CD33, enabling targeted tumor therapy. Meanwhile, the use of 225Ac-Lintuzumab can avoid non-specific cytotoxicity that may occur with beta-emitting radionuclides, improving treatment safety and efficacy.

Todd L. Rosenblat et al. conducted a study to evaluate the safety and efficacy of 225Ac-Lintuzumab in AML treatment. The study enrolled 18 patients with relapsed or refractory AML who received single intravenous injections of 225Ac-Lintuzumab at different doses (18.5-148 kBq/kg body weight). The maximum tolerated dose (MTD) was determined to be 111 kBq/kg. Among 16 evaluable patients, 10 (63%) had elimination of leukemic cells from peripheral blood, but this effect only occurred at doses of at least 37 kBq/kg. Among 15 evaluable patients, 10 (67%) had reduced leukemic cells in bone marrow, including 3 patients with less than 5% leukemic cells and 1 patient achieving morphologic leukemia-free state. However, myelosuppression was the most common toxicity and was dose-related. The results indicate that 225Ac-Lintuzumab is feasible for AML treatment with acceptable safety and anti-leukemic effects observed at all dose levels. Although 225Ac-Lintuzumab demonstrates anti-leukemic effects and acceptable safety in AML treatment, its clinical application still faces challenges, such as common dose-related myelosuppression, which limits its potential for improved efficacy at higher doses.

3.3.3 Glioblastoma

Glioblastoma is the most common primary malignant brain tumor in adults. Current treatment primarily relies on surgical resection with adjuvant radiotherapy and chemotherapy. Despite some understanding of glioblastoma pathogenesis, challenges persist, including increasing incidence, altered quality of life, poor prognosis, disease recurrence, and median overall survival of 15 months. Substance P (SP) is a neuropeptide that serves as the natural ligand for the neurokinin-1 receptor (NK-1R) and is highly and specifically expressed in glioblastoma. Its high expression in tumor cells makes it an ideal target for precise targeted therapy. Additionally, the pleiotropic effects of SP in the tumor microenvironment, including promoting cell proliferation, invasion, and regulating inflammatory responses, further enhance its potential as a

therapeutic target. Preclinical studies have confirmed that targeting SP or its receptor NK-1R can effectively inhibit glioma growth and prolong survival, showing good therapeutic prospects.

Leszek Królicki et al. conducted a dose-escalation study using 225Ac-DOTA-SP (225Ac-labeled DOTA-SP) for targeted alpha therapy in recurrent glioblastoma patients, primarily evaluating safety and tolerability. The study enrolled 21 patients (mean age 43.0 ± 9.5 years) with recurrent or transformed grade 4 glioblastoma after standard treatment. Treatment used an escalating dose regimen (10, 20, and 30 MBq per cycle), with patients receiving 1 to 6 treatments of 225Ac-DOTA-SP at 2-month intervals. Results showed the treatment was generally well-tolerated, with mild, transient adverse reactions observed mainly in patients receiving 30 MBq doses, including edema, seizures, aphasia, and hemiparesis. Only one patient receiving 30 MBq developed grade 3 thrombocytopenia. No other grade 3 or 4 toxicities related to 225Ac-DOTA-SP treatment were observed across all dose groups. Median OS from initial diagnosis was 35.0 months; from recurrence/transformation diagnosis, median OS was 13.2 months. From 225Ac-DOTA-SP treatment initiation, median PFS was 2.4 months and median OS was 9.0 months. The study demonstrated that 225Ac-DOTA-SP is safe and well-tolerated for recurrent glioblastoma at 30 MBq per cycle. The escalating dose regimen showed good tolerability with only mild, transient adverse reactions and no significant hematologic, renal, or hepatic toxicity. Although this study confirmed the safety and short-term efficacy of 225Ac-DOTA-SP in recurrent glioblastoma, the results are based on small sample sizes and short follow-up periods. Data on long-term efficacy and potential delayed toxicity are insufficient, limiting its widespread clinical application.

Conclusion and Future Perspectives

In summary, various 225Ac-labeled targeted radiotherapies have demonstrated significant potential in treating multiple malignant tumors, including prostate cancer and neuroendocrine tumors, with preliminary studies showing positive effects on tumor control and patient survival. However, current studies are limited by small sample sizes and short follow-up periods, lacking comprehensive evaluation of long-term survival and quality of life. Additionally, toxicities observed in some studies (such as myelosuppression and renal toxicity) and standardization of treatment protocols require further optimization through larger-scale clinical trials and long-term follow-up studies to enhance clinical application value.

Despite demonstrating significant anti-tumor activity in refractory malignancies, 225Ac-targeted alpha therapy faces multiple critical constraints in clinical application. Toxicity control is the primary obstacle. The high energy of alpha particles, while killing tumor cells, can cause daughter nuclides (such as 213Bi) to detach from targets and migrate to healthy tissues, causing unpredictable dose-limiting toxicities including renal damage and myelosuppression. Current chelator systems cannot achieve stable retention of daughter nuclides. Weak clinical evidence is another major issue, as existing studies are mostly small-scale

with short follow-up, lacking systematic evaluation of long-term cumulative toxicity, overall survival, and quality of life, resulting in a lack of standardized basis for individualized dosing regimens (dose, cycle, treatment course). More critically, supply bottlenecks severely limit progress. 225Ac production relies on high-energy accelerators with complex processes and extremely scarce global capacity, severely hindering large-scale clinical trials and clinical promotion.

Addressing these challenges requires breakthroughs from both technical innovation and clinical practice perspectives. At the drug design level, developing novel chelators with ultra-high daughter retention (such as topologically constrained macrocyclic ligands) and modular drug platforms is key to addressing off-target toxicity. At the clinical translation level, integrating real-time dosimetry models with imaging biodistribution data to establish precise individualized dosing systems, and validating long-term benefits through multi-center prospective trials (evaluating progression-free survival and quality of life) are essential. Supply chain optimization depends on the gradual implementation of novel preparation technologies: the proton irradiation of thorium targets pathway is expected to significantly increase 225Ac production, though technical challenges remain. Meanwhile, development of 225Ac/225Ra generator technology may reduce usage costs. These technological advances will drive 225Ac therapy from a "last-line rescue approach" to a treatment strategy covering broader disease stages, though comprehensive application still requires further research and validation.

References

1. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, Jemal A. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2024;74(3):229-263. DOI: 10.3322/caac.21834.

2. Liu B, Zhou H, Tan L, et al. Exploring treatment options in cancer: tumor treatment strategies. *Signal Transduction and Targeted Therapy*. 2024;9(1):175. DOI: 10.1038/s41392-024-01856-7.

3. Anand U, Dey A, Singh Chandel AK, et al. Cancer chemotherapy and beyond: Current status, drug candidates, associated risks and progress in targeted therapeutics. *Genes & Diseases*. 2023;10(4):1367-1401. DOI: 10.1016/j.gendis.2023.06.001.

4. Rehman JU, Zahra N, Ahmad N, et al. Intensity modulated radiation therapy: A review of current practice and future outlooks. *Journal of Radiation Research and Applied Sciences*. 2018;11(4):361-367. DOI: 10.1016/j.jrras.2018.07.006.

5. Kong FS. Precision radiation therapy in the modern era of multidisciplinary care in oncology: What matters to our patients and beyond? *J*

Natl Cancer Cent. 2024;4(3):260-262. DOI: 10.1016/j.jncc.2024.05.004.

6. Song Z, Zhang J, Qin S, Luan X, Zhang H, Yang M, Jin Y, Yang G, Yu F. Targeted alpha therapy: a comprehensive analysis of the biological effects from "local-regional-systemic" dimensions. *J Nucl Med Mol Imaging*. 2025. DOI: 10.1007/s00259-025-07390-0.

7. Kim YS, Brechbiel MW. An overview of targeted alpha therapy. *Tumour Biol*. 2012;33(3):573-590. DOI: 10.1007/s13277-011-0286-y.

8. Huang RX, Zhou PK. DNA damage response signaling pathways and targets for radiotherapy sensitization in cancer. *Signal Transduction and Targeted Therapy*. 2020;5:60. DOI: 10.1038/s41392-020-0150-x.

9. Cannan WJ, Pederson DS. Mechanisms and Consequences of Double-Strand DNA Break Formation in Chromatin. *J Nucl Med Mol Imaging*. 2016;231(1):3-14. DOI: 10.5045/br.2016.51.3.157.

10. Jeong H, Bok S, Hong BJ, Choi HS, Ahn GO. Radiation-induced immune responses: mechanisms and therapeutic perspectives. *Blood Research*. 2016;51(3):157-163. DOI: 10.5045/br.2016.51.3.157.

11. Pedro Cruz-Nova, Maydelid Trujillo-Nolasco, Liliana Aranda-Lara, Guillermina Ferro-Flores, Blanca Ocampo-García. Radiobiological effect of alpha particles. The scientific basis of targeted alpha-particle therapy. *Nuclear Medicine and Biology*. 2025;146-147:109044. DOI: 10.1016/j.nucmedbio.2025.109044.

12. Carter RJ, Nickson CM, Thompson JM, Kacperek A, Hill MA, Parsons JL. Complex DNA Damage Induced by High Linear Energy Transfer Alpha-Particles and Protons Triggers a Specific Cellular DNA Damage Response. *Int J Radiat Oncol Biol Phys*. 2018;100(3):776-784. DOI: 10.1016/j.ijrobp.2017.11.012.

13. Zhang S, Wang X, Gao X, et al. Radiopharmaceuticals and their applications in medicine. *Signal Transduction and Targeted Therapy*. 2025;10:1. DOI: 10.1038/s41392-024-02041-6.

14. Wang X, Wang Y, Zhang Y, et al. Immune modulatory roles of radioimmunotherapy: biological principles and clinical prospects. *Frontiers in Immunology*. 2024;15:1357101. DOI: 10.3389/fimmu.2024.1357101.

15. Dhiman D, Vatsa R, Sood A. Challenges and opportunities in developing Actinium-225 radiopharmaceuticals. *Nuclear Medicine and Biology*. 2022;43(9):970-977. DOI: 10.1097/MNM.0000000000001594.

16. Lyczko M, Pruszynski M, Majkowska-Pilip A, et al. 211At labeled substance P (5-11) as potential radiopharmaceutical for glioma treatment. *Nuclear Medicine and Biology*. 2017;53:1-8. DOI: 10.1016/j.nucmedbio.2017.05.008.

17. Bidkar AP, Zerefa L, Yadav S, et al. Actinium-225 targeted alpha particle therapy for prostate cancer. *Theranostics*. 2024;14(7):2969-2992. DOI: 10.7150/thno.96403.

18. Ackerman NL, de la Fuente Rosales L, Falzone N, et al. Targeted alpha therapy with 212Pb or 225Ac: Change in RBE from daughter migration. *Physica Medica*. 2018;51:91-98. DOI: 10.1016/j.ejmp.2018.05.020.

19. Hooijman EL, Radchenko V, Ling SW, et al. Implementing Ac-225 labelled radiopharmaceuticals: practical considerations and (pre-)clinical perspectives. *EJNMMI Radiopharmacy and Chemistry*. 2024;9:9. DOI: 10.1186/s41181-024-00239-1.

20. OpenMedScience. Actinium-225: The emerging star in targeted alpha therapy. https://openmedscience.com/actinium-225-the-emerging-star-in-targeted-alpha-therapy/. Accessed 2025-07-09.

21. Padeiro M, Santana P, Grant M. Global aging and health determinants in a changing world. In: Oliveira PJ, Malva JO, eds. *Aging*. Academic Press; 2023:3-30. DOI: 10.1016/B978-0-12-823761-8.00021-5.

22. Cancer Today. Another option for metastatic prostate cancer. https://www.cancertodaymag.org/summer-2025/another-option-for-metastatic-prostate-cancer. Accessed 2025-07-09.

23. Kratochwil C, Haberkorn U, Giesel FL. Ac-PSMA-617 for therapy of prostate cancer. *Seminars in Nuclear Medicine*. 2020;50(2):133-140. DOI: 10.1053/j.semnuclmed.2020.02.004.

24. Yadav MP, Ballal S, Sahoo RK, et al. Efficacy and safety of 225Ac-PSMA-617 targeted alpha therapy in metastatic castration-resistant prostate cancer patients. *Theranostics*. 2020;10(20):9364-9377. DOI: 10.7150/thno.48107.

25. Sathekge M, Bruchertseifer F, Vorster M, et al. mCRPC patients receiving 225Ac-PSMA-617 therapy in the post-androgen deprivation therapy setting: Response to treatment and survival analysis. *Journal of Nuclear Medicine*. 2022;63(10):1496-1502. DOI: 10.2967/jnumed.121.263618.

26. Jones TN, Nauseef JT, Bander NH, et al. Emerging prostate-specific membrane antigen-based therapeutics: Small molecules, antibodies, and beyond. *European Urology Focus*. 2021;7(2):254-257. DOI: 10.1016/j.euf.2021.02.006.

27. Zacherl MJ, Gildehaus FJ, Mittlmeier L, et al. First clinical results for PSMA-targeted α-therapy using 225Ac-PSMA-I&T in advanced-mCRPC patients. *Journal of Nuclear Medicine*. 2021;62(5):669-674. DOI: 10.2967/jnumed.120.251017.

28. Abusalem M, Martiniova L, Soebianto S, et al. Current status of radiolabeled monoclonal antibodies targeting PSMA for imaging and therapy.

Cancers. 2023;15(18):4537. DOI: 10.3390/cancers15184537.

29. Tagawa ST, Thomas C, Sartor AO, et al. Prostate-specific membrane antigen-targeting alpha emitter via antibody delivery for metastatic castration-resistant prostate cancer: A phase I dose-escalation study of 225Ac-J591. *Journal of Clinical Oncology*. 2024;42(7):842-851. DOI: 10.1200/JCO.23.00573.

30. Sultana Q, Kar J, Verma A, et al. A comprehensive review on neuroendocrine neoplasms: Presentation, pathophysiology and management. *Journal of Clinical Medicine*. 2023;12(15):5138. DOI: 10.3390/jcm12155138.

31. Cleveland Clinic. Peptide receptor radionuclide therapy (PRRT). https://my.clevelandclinic.org/health/treatments/24073-peptide-receptor-radionuclide-therapy-prrt. Accessed 2025-07-09.

32. Rogoza O, Megnis K, Kudrjavceva M, et al. Role of somatostatin signalling in neuroendocrine tumours. *International Journal of Molecular Sciences*. 2022;23(3):1447. DOI: 10.3390/ijms23031447.

33. Demirci E, Alan Selçuk N, Beydağı G, et al. Initial findings on the use of [225Ac]Ac-DOTATATE therapy as a theranostic application in patients with neuroendocrine tumors. *Molecular Imaging and Radionuclide Therapy*. 2023;32(3):226-232. DOI: 10.4274/mirt.galenos.2023.38258.

34. Ballal S, Yadav MP, Bal C, et al. Broadening horizons with 225Ac-DOTATATE targeted alpha therapy for gastroenteropancreatic neuroendocrine tumour patients stable or refractory to 177Lu-DOTATATE PRRT: First clinical experience on the efficacy and safety. *European Journal of Nuclear Medicine and Molecular Imaging*. 2020;47(4):934-946. DOI: 10.1007/s00259-019-04567-2.

35. Ikram A, Rehman A. Paraganglioma. StatPearls Publishing; 2025. https://www.ncbi.nlm.nih.gov/books/NBK549834/. Accessed 2025-07-09.

36. Corssmit EP, Romijn JA. Clinical management of paragangliomas. *European Journal of Endocrinology*. 2014;171(6):R231-R243. DOI: 10.1530/EJE-14-0396.

37. Garcia-Carbonero R, Matute Teresa F, Mercader-Cidoncha E, et al. Multidisciplinary practice guidelines for the diagnosis, genetic counseling and treatment of pheochromocytomas and paragangliomas. *Clinical and Translational Oncology*. 2021;23(10):1995-2019. DOI: 10.1007/s12094-021-02622-9.

38. Yadav MP, Ballal S, Sahoo RK, et al. Efficacy and safety of 225Ac-DOTATATE targeted alpha therapy in metastatic paragangliomas: A pilot study. *European Journal of Nuclear Medicine and Molecular Imaging*. 2022;49(5):1600-1610. DOI: 10.1007/s00259-021-05632-5.

39. Cleveland Clinic. Acute myeloid leukemia (AML). https://my.clevelandclinic.org/health/diseases/6212-acute-myeloid-leukemia-aml. Accessed 2025-07-09.

40. Vakiti A, Reynolds SB, Mewawalla P. Acute myeloid leukemia. StatPearls Publishing; 2025. https://www.ncbi.nlm.nih.gov/books/NBK507875/. Accessed 2025-07-09.

41. Kim MY, Yu KR, Kenderian SS, et al. Genetic inactivation of CD33 in hematopoietic stem cells to enable CAR T cell immunotherapy for acute myeloid leukemia. *Cell*. 2018;173(6):1439-1453.e19. DOI: 10.1016/j.cell.2018.05.013.

42. De Propris MS, Raponi S, Diverio D, et al. High CD33 expression levels in acute myeloid leukemia cells carrying the nucleophosmin (NPM1) mutation. *Haematologica*. 2011;96(10):1548-1551. DOI: 10.3324/haematol.2011.043786.

43. Hatcher-Lamarre JL, Sanders VA, Rahman M, et al. Alpha emitting nuclides for targeted therapy. *Nuclear Medicine and Biology*. 2021. DOI: 10.1016/j.nucmedbio.2020.08.004.

44. Rosenblat TL, McDevitt MR, Carrasquillo JA, et al. Treatment of patients with acute myeloid leukemia with the targeted alpha-particle nanogenerator actinium-225-lintuzumab. *Clinical Cancer Research*. 2022;28(10):2030-2037. DOI: 10.1158/1078-0432.CCR-21-3712.

45. Schaff LR, Mellinghoff IK. Glioblastoma and other primary brain malignancies in adults: A review. *JAMA*. 2023;329(7):574-587. DOI: 10.1001/jama.2023.0023.

46. Rajaratnam V, Islam MM, Yang M, Slaby R, Ramirez HM, Mirza SP. Glioblastoma: Pathogenesis and Current Status of Chemotherapy and Other Novel Treatments. *Cancers (Basel)*. 2020;12(4):937. DOI: 10.3390/cancers12040937.

47. Schank JR, Heilig M. Substance P and the neurokinin-1 receptor: The new CRF. *International Review of Neurobiology*. 2017. DOI: 10.1016/bs.irn.2017.06.008.

48. Hong X, Ma J, Zheng S, Zhao G, Fu C. Advances in the research and application of neurokinin-1 receptor antagonists. *Journal of Zhejiang University Science B*. 2024;25(2):91-105. DOI: 10.1631/jzus.B2300455.

49. Królicki L, Bruchertseifer F, Kunikowska J, et al. Dose escalation study of targeted alpha therapy with [225Ac]Ac-DOTA-substance P in recurrence glioblastoma — safety and efficacy. *European Journal of Nuclear Medicine and Molecular Imaging*. 2021;48(11):3595-3605. DOI: 10.1007/s00259-021-05350-y.

Note: Figure translations are in progress. See original paper for figures.