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Expanding Horizons—The Emerging Scope of Proton Therapy in Nuclear Medicine

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The field of Nuclear Medicine (NM) has traditionally been centered on the use of radiotracers for diagnostic imaging and targeted radionuclide therapy, offering a unique combination of molecular specificity and functional assessment. In recent years, however, the boundaries between NM, radiation oncology, and medical physics have increasingly converged, particularly with the advent of advanced particle therapies. Among these, proton therapy has emerged as a transformative modality, offering distinct physical and biological advantages that position it as a valuable complement to the evolving theranostic paradigm (1).

Proton therapy utilizes charged particles i.e. protons, which deposit the majority of their energy at a well-defined depth, known as the Bragg peak (2). This characteristic enables precise dose localization within the tumor while sparing surrounding normal tissues and critical organs. In contrast to conventional photon-based radiotherapy, which delivers dose along the entire beam path, proton therapy significantly reduces integral dose and minimizes off-target radiation exposure (3). Recent research highlights the advantages of proton therapy, such as its higher relative biological effectiveness (RBE) at the end of the proton range, which can enhance the therapeutic dose to tumors compared to normal tissues. Additionally, the compact nature of proton dose distributions minimizes exposure to circulating lymphocytes and immune organs, potentially leading to improved clinical outcomes by sparing the immune system (1).

While proton therapy is traditionally considered a domain of radiation oncology, its conceptual and practical integration with NM is becoming increasingly evident. Nuclear Medicine contributes critically through molecular imaging, which enables accurate tumor characterization, delineation of biological target volumes, and treatment response assessment (4). Childhood cancers, skull based and sinonasal malignancies, brain tumors especially low-grade gliomas, lung cancer, gastrointestinal and esophageal cancers, primary hepatocellular carcinoma, cholangiocarcinoma, prostate cancer and isolated hepatic metastases are effectively treated with proton therapy with the advantage of normal tissue sparing and allowing the escalation of dose. Hybrid imaging modalities such as PET-CT provide both functional and anatomical information, playing a central role in modern oncologic management.

A key area of synergy lies in the concept of biologically guided radiation therapy. Functional imaging with PET enables identification of intratumoral heterogeneity, allowing selective targeting of metabolically active or hypoxic regions (5). Incorporation of PET-derived data into radiotherapy planning has been shown to enhance treatment precision and personalization. This approach aligns closely with the principles of precision oncology and represents a paradigm shift from uniform dose to individualized treatment strategies.

Furthermore, the theranostic approach in modern NM presents exciting possibilities when integrated with proton therapy. Innovations in molecular imaging and targeted radionuclide therapy have revolutionized cancer treatment by allowing personalized treatment selection and monitoring. The integration of systemic radionuclide therapy with localized proton beam therapy may provide

synergistic effects, particularly in complex or oligometastatic disease (6, 7).

Another important dimension is treatment verification and response monitoring. Proton beams induce positron-emitting isotopes through nuclear interactions, enabling in vivo verification of beam range using PET imaging. This technique provides a unique opportunity to assess delivered dose distribution and improve treatment accuracy (8). Additionally, serial PET imaging allows early evaluation of therapeutic response, facilitating adaptive treatment strategies.

Despite its advantages, proton therapy faces several challenges that must be addressed to fully realize its potential within the NM framework. High installation and operational costs, limited accessibility, and technical uncertainties related to range estimation and motion management remain significant barriers (3). These challenges are particularly relevant in low- and middle-income countries like Bangladesh, where resource constraints may limit widespread adoption.

Proton therapy is a costly treatment, ranging from USD 30,000 to 120,000 per course in the U.S., significantly surpassing traditional photon-based radiotherapy. Costs differ by region due to infrastructure and healthcare systems; in Thailand, prices are about USD 15,000 to 40,000, while in lower-cost Asian countries like India, they range from USD 20,000 to 50,000 based on treatment complexity (3).

From a NM perspective, continued development of novel radiotracers targeting specific biological pathways—such as hypoxia, proliferation, and receptor expression—will further enhance the role of molecular imaging in guiding proton therapy (9). Moreover, advances in artificial intelligence and quantitative imaging are expected to improve data integration, enabling more accurate prediction of treatment response and personalization of therapy.

In the context of global oncology, the integration of proton therapy with Nuclear Medicine represents a paradigm shift toward more precise, personalized, and biologically driven cancer care. As the field evolves, interdisciplinary collaboration will be essential to maximize the clinical benefits of these technologies (10).

In conclusion, proton therapy is poised to significantly expand the therapeutic landscape of NM. By leveraging the strengths of molecular imaging and targeted therapy, NM can play a pivotal role in optimizing patient selection, treatment planning, and response assessment in proton therapy. The future lies in a truly integrated theranostic model, where imaging and therapy are seamlessly combined to achieve maximize therapeutic efficacy with minimal toxicity.

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