Theranostics and molecular imaging in Neuro-Oncology: the beginning of a new era

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In recent years, revolutionary advances in diagnostics and therapy of malignant diseases have taken place. The successful translation of biological concepts of precision medicine, targeted therapies and immunotherapies into clinical trials and routine has led to increasing response rates, longer survival times and improved quality of life of cancer patients.

Currently, oncologic nuclear medicine and the application of diagnostic and therapeutic innovations of molecular imaging and radioligand therapy is emerging as development with the potential to further advance research and care in oncology.[1] The utilization of highly specific radioactively labelled ligands allows to not only visualize "druggable targets" but also to directly address them therapeutically in individual patients. The combination of therapy and diagnostics ("theranostics") has already led to approved oncological treatments following positive phase III trial results in extracerebral tumors, and more positive clinical trials are being reported.[2-4] Furthermore, the visualization of metabolic processes, specific cell populations and molecular alterations in tumors of individual patients may allow early assessment of response (or non-response) to oncological interventions such as chemotherapy, radiotherapy, targeted therapies, immunotherapies, or antibody drug conjugates. In addition, heterogeneity in expression of therapy targets between tumor manifestations – even within an individual patient – can be captured by PET, which may facilitate improved prediction of treatment efficacy.

In this special issue of *Neuro-Oncology*, we provide an overview on the emerging and evolving role of nuclear medicine applications in research and clinical practice with a focus on tumors of the central nervous system (CNS). Primary and secondary CNS tumors represent particularly challenging and heterogeneous diseases, and substantial improvements in diagnosis and therapy are urgently needed.[5] Nuclear medicine offers both, diagnostic and therapeutic innovations. Molecular imaging using radiolabeled PET tracers allows in-vivo visualization of tumor characteristics (e.g. metabolism, molecular targets) and extent, which is increasingly used for target delineation (e.g. biopsy planning, surgery planning, radiotherapy planning) and disease monitoring.[6,7] While there is a substantial and growing amount of research and literature on molecular imaging of CNS tumors, the field of theranostics is only starting to evolve in Neuro-Oncology.[7-9] Overall, however, effective translation into clinical practice was hampered by the lack of adequately designed and conducted studies and availability of mainly retrospective case collections and few and small prospective studies. Only recently, prospective clinical trials on therapeutic concepts with radioligand therapies targeting specific molecular alterations are being performed, particularly in gliomas and meningiomas, and may open avenues to novel treatment options.[10]

In this series of dedicated publications, internationally renowned experts provide reviews and critical evaluations of the opportunities and challenges of PET imaging and theranostic approaches in CNS tumors with a focus on dosimetry, design and conduct of clinical trials, and the trial landscape and in gliomas, meningiomas and brain metastases. Galldiks et al. highlight the evolving role of PET imaging in Neuro-Oncology, offering insights into tumor biology and treatment response, thereby informing personalized patient care.[11] Weller et al. focus on the merging clinical trial landscape for radionuclide therapies in gliomas, discuss the various potential target structures and provide an outlook for which glioma entities radionuclide therapy could most likely provide a therapeutic alternative.[12] Mair et al. explore the available evidence for theranostic treatments and ongoing trial initiatives for meningiomas, also highlighting the first randomized clinical trial with [^{177}Lu]Lu-DOTATATE enrolling patients with progressive meningioma (LUMEN-1, NCT06326190).[13] Le Rhun et al. discuss the current state of the art and opportunities of targeted radionuclide therapies for patients with brain and leptomeningeal metastases with a special focus on promising molecular targets such as prostate specific membrane antigen (PSMA) or fibroblast activating protein (FAP).[14] Importantly, the systematic development of theranostic assets for effective translation into the clinical routine requires thorough methodological considerations. To this end, Wen et al. [15] summarize challenges and opportunities of clinical trial design and conduct and Cicone et al. highlight the need to collect dosimetric data to help exploit the full potential of theranostic of CNS tumors.[16] Overall, the six papers of this special issue comprehensively outline the current state of affairs and future avenues for molecular imaging and theranostic treatments for patients affected by tumors of the CNS. We are convinced that research at the intersection of neuro-oncology and nuclear medicine holds transformative potential for improved diagnosis and therapy of CNS tumors and trust that the contributions in this special issue of *Neuro-Oncology* stimulate further investigations that will facilitate translation of nuclear medicine applications towards widespread clinical practice. The current developments of PET imaging and multiple clinical trials investigating radioligand therapies in CNS tumors mark the beginning of a new era and will shape the future of Neuro-Oncology.

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