European Journal of Nuclear Medicine and Molecular Imaging (2023) 51:202–205
https://doi.org/10.1007/s00259-023-06425-8

EDITORIAL

EANM position paper: theranostics in brain tumours—the present and the future

Nelleke Tolboom[1] · Antoine Verger[2] · Nathalie L. Albert[3,4,5] · Matthias Brendel[3,4,5] · Diego Cecchin[6] · Pablo Aguiar Fernandez[7] · Francesco Fraioli[8] · Eric Guedj[9] · Ken Herrmann[10] · Tatjana Traub-Weidinger[11] · Silvia Morbelli[12,13] · Igor Yakushev[14] · Pietro Zucchetta[15] · Henryk Barthel[16] · Donatienne Van Weehaeghe[17]

Published online: 12 September 2023

Theranostic pairs have proven value in thyroid diseases, neuroendocrine tumours (NET), and prostate cancer [1, 2]. Recently, the Food and Drug Administration and the European Medicines Agency have approved [^{177}Lu]DOTATATE and [^{177}Lu]prostate-specific membrane antigen (PSMA). Following this recent success in the care of NET and prostate cancer patients, there is increasing interest in theranostics in neuro-oncology.

Patients with brain tumours are often young, working, and socially active with currently limited available therapies and dramatic poor outcomes. With the resulting desperate need for more effective therapy options, there is great hope for theranostics filling this gap for brain tumours. Radiation dose of such treatments is limited to tumoral tissue with preservation of healthy brain parenchyma. Specific molecular targets could realize a personalized treatment with pretherapeutic validation of target presence using the diagnostic ligand of a theranostic pair allowing an upfront prediction of response. Effectiveness could potentially be further increased by combination with current treatments such as external beam therapy or immunotherapy.

This paper states the position of the EANM on theranostics in meningiomas, gliomas, brain metastases, and paediatric brain tumours.

The current state of theranostics in meningioma

Meningiomas, representing 30% of primary intracranial tumours, are the intracranial tumours in which peptide receptor radionuclide therapy (PRRT) has most often been

✉ Donatienne Van Weehaeghe
donatienne.vanweehaeghe@uzgent.be

1 Department of Radiology and Nuclear Medicine, University Medical Centre Utrecht, Utrecht, The Netherlands

2 Department of Nuclear Medicine and Nancyclotep Imaging Platform, IADI, Inserm, UMR 1254, Université de Lorraine, CHRU-Nancy, Nancy, France

3 Department of Nuclear Medicine, LMU University Hospital, LMU Munich, Munich, Germany

4 Munich Cluster for Systems Neurology (SyNergy), Munich, Germany

5 German Center for Neurodegenerative Diseases (DZNE), Munich, Germany

6 Nuclear Medicine Unit, Department of Medicine - DIMED, University Hospital of Padua, Padua, Italy

7 Department of Radiology, Faculty of Medicine and Center for Research in Molecular Medicine and Chronic Diseases (CIMUS), University of Santiago de Compostela (USC), Campus Vida, Santiago de Compostela, Galicia, Spain

8 Institute of Nuclear Medicine, University College London (UCL), London, UK

9 Département de Médecine Nucléaire, Aix Marseille Univ, APHM, CNRS, Centrale Marseille, Institut Fresnel, Hôpital de La Timone Hospital, CERIMED, Marseille, France

10 Department of Nuclear Medicine, University of Duisburg-Essen and German Cancer Consortium (DKTK)- University Hospital Essen, Essen, Germany

11 Department of Biomedical Imaging and Image-Guided Therapy, Medical University of Vienna, Vienna, Austria

12 IRCCS Ospedale Policlinico San Martino, Genoa, Italy

13 Nuclear Medicine Unit, Department of Health Sciences, University of Genoa, Genoa, Italy

14 Department of Nuclear Medicine, School of Medicine, Technical University of Munich and Munich Center for Neurosciences - Brain and Mind, Munich, Germany

15 Department of Nuclear Medicine, University Hospital Of Padova, Padova, Italy

16 Department of Nuclear Medicine, Leipzig University Medical Centre, Leipzig, Germany

17 Department of Radiology and Nuclear Medicine, Ghent University Hospital, C. Heymanslaan 10, 9000 Ghent, Belgium

performed. Standard treatment options mainly encompass neurosurgical resection and external beam irradiation. PRRT is currently considered when these therapeutic options are exhausted [3, 4]. PRRT targets the somatostatin receptor (SSTR) type 2, which is invariably expressed in a very high concentration in meningiomas, and as well in well-differentiated NET [5, 6]. Expression can be monitored with SSTR-targeting PET. Most of the data on PRRT in meningiomas consist of retrospective studies of patients in the late course of the disease [3, 7]. Evidence gathered in prospective randomized controlled trials or in early disease stages is still lacking and urgently needed. However, the available data [8] seems promising—with disease control in 63% of patients, especially with grade I and II tumours, which is impressive taking into consideration that the patients are often heavily pretreated. Potentially, the application of PRRT in earlier disease stages may result in even higher stabilization rates. Moreover, identification of meningiomas with poorer prognosis (lesions with high glucose consumption and low SSTR expression) using dual-tracer imaging with pretherapeutic SSTR-PET and ^{18}F-FDG PET imaging [9] may help to stratify patients with regard to the predicted PRRT success. In addition, synchronous application of sequential external beam radiotherapy could boost efficiency [10].

The current state of theranostics in other intracranial malignancies

Gliomas

Gliomas are the most common malignant brain tumours and are characterized by a high level of treatment resistance and immune escape as well as temporospatial heterogeneity. Their limited overall survival, in particular for patients with glioblastoma, underlines the need for new therapeutic concepts in the treatment of patients [11]. A wide range of potential theranostic targets have been investigated in gliomas (tenascin, epidermal growth factor receptor, neurokinin type 1 receptor, SSTR, gastrin-releasing peptide receptor, L-type amino transporter 1 (LAT-1), carbonic anhydrase XII, PSMA, matrix metalloproteinase, DNA histone H1 complex, poly(ADP-ribose) polymerase 1, integrins, chemokine receptor 4, disialoganglioside, and fibroblast activation protein), in varying settings and with variable, but mostly no encouraging, results [10, 11]. However, out of all these targets, amino acids addressing LAT-1 are particularly interesting as they are transported across the blood–brain barrier (BBB) and are therefore also taken up in tumour with intact BBB [12]. Both existing theranostic strategies and novel targets are currently under exploration [8, 9]. The success of most theranostic agents will greatly depend on the success of strategies increasing BBB permeability. Innovative administration methods, such as radioembolization (combining radionuclide therapy and embolization), are also investigated [13].

Future studies should focus on identifying favourable theranostic target(s). As gliomas are characterized by large molecular heterogeneity, this could be achieved by transcriptome or multiplex immunohistochemistry. Regardless, the success of the so far tested theranostic approaches seems to also be partially nfluenced by glioma size, type, grade, anatomical location, and its extent of tumour cell invasion in the brain as well as time point of treatment during the course of the disease [14].

Brain metastases

As oncology care, in particular primary cancer control is advancing dramatically, brain metastases occur more frequently in many types of cancer. This leads to an increasing need for more effective therapies. Current therapeutic options consist of a combination of surgery, external radiotherapy, and targeted and immune-modulating therapies [15].

A potential advantage of radionuclide therapy over immune therapy is that targeting can be directly reviewed using post-therapy PET/SPECT scanning [1, 2], possibly leading to prediction of response and assessing heterogeneity within the patient.

Paediatric brain tumours

Paediatric central nervous system tumours remain the leading cause of cancer-related death in childhood and are, thus, in high need for improved treatment options. They differ in many aspects when compared to the disease in the adults, both in site and histology [16]. Only few studies have been published, mostly case series or safety studies combining innovative routes of administration with theranostics [17, 18]. More systematic research is, thus, clearly needed to investigate the potential role of theranostic concepts in paediatric brain tumours.

Challenges in neuro-oncologic treatment

The main obstacle in treating brain compared to extracerebral tumours is getting therapeutics over the BBB. This is despite some brain tumours and metastases disturbing the BBB integrity, and some producing a highly heterogeneous vasculature known as the blood tumour barrier (BTB) [19]. The frequency and extent of BBB and BTB integrity alteration are heterogeneous between various brain tumour types, as shown by contrast enhancement on MRI [20]. Several strategies are being developed to bypass the BBB/BTB [20–22]: local administration (including intraventricular administration), convection-enhanced delivery (CED) for

which a microcatheter is implanted into the tumour and hydraulic pressure is used to deliver the drugs into the tissue of interest, focused ultrasound (FUS) reshaping the BBB/BTB using a targeted ultrasonic wave resulting in enhanced vessel permeability, and innovatively designed monoclonal antibodies and neural stem cells enabling passage through the BBB/BTB. These techniques are still under investigation without proven efficacy and are complex and, as such, can only be performed in expert centres. Regardless, these innovative techniques should be further evaluated in clinical trials to determine the clinical effectiveness in the different brain tumour types and theranostic targets.

Perspective of the EANM

As the need to improve brain tumour patient care is high, the potential for theranostics needs to be evaluated urgently. The EANM would like to initiate a discussion and start considering to facilitate prospective trials together with other societies and stakeholders. Related regulatory aspects are rather heterogeneous across European countries, complicating large multicentre trials. Here, the member states of the EANM should support the harmonization of the different regulations across the countries, which will facilitate collaborations. The policy and regulatory affairs committee is currently beside several other aspects also working on a central proposal; however, the harmonization will have to be done actively by all members for each country.

Unmet needs and factors for success

With regard to the exciting potential of theranostics in brain malignancies, the EANM should help to define unmet needs in the operational, physics, and clinical fields. By working together, urgent issues along with those that are most likely to be factors for success can be identified.

So far, PRRT is based on the standard approach for NET, i.e. a sequential treatment by multiple doses. This paradigm requires re-evaluation for intracranial malignancies, ideally including personal tumoral dosimetry as well as alternative administration routes potentially boosting targeting [23]. Moreover, as currently most PRRT studies in meningiomas used beta-emitters (^{177}Lu, ^{90}Y, and ^{131}I), the efficiency of labelling with shorter range alpha-emitters should be investigated.

In general, synergistic approaches with external beam radiation or immunotherapy could potentially even be more effective than standalone therapy. Additionally, as with all theranostic approaches, the most optimal positioning in time (e.g. phase of treatment) and optimal target should be explored.

A major obstacle in moving this field forward so far has been the use of underpowered and uncontrolled clinical trial designs. The international community should, thus, strive towards sufficiently large and prospective randomized studies in order to generate high-level evidence on the efficacy of theranostic approaches in central nervous system tumours. Also, more basic and clinical research is necessary to define the added value of theranostics in brain tumours by defining novel targets, discovering mechanisms of action, and guide dosing of theranostics in brain tumours.

Finally, efforts could also include the development of criteria for an appropriate use of radioligand therapy in neuro-oncology and recommendations to harmonize procedures which are highly variable across centres. A joint international procedure guideline is currently in preparation for PRRT in meningiomas and could serve as an example for other potential nuclear neuro-oncological therapy options.

In conclusion, expanding the theranostic approach to intracranial malignancies is an exciting field of nuclear medicine. Precision medicine using a diagnostic-theranostic radionuclide pair could be the therapy approach of the (near) future: individual patients would receive a diagnostic PET/SPECT scan, preferably based on personalized targets through tissue characterization. If adequate targeting is visualized, this could be followed by specific radionuclide therapy. Several clinical studies are on their way, but only if the international community works together towards large and prospective randomized studies, the future will show whether theranostic approaches will be able to serve as the desperately needed tools to improve patient care in neuro-oncology.

Data availability Not applicable.

Declarations

Ethical approval Not applicable to this editorial.

Informed consent Not applicable.

Conflict of interest NLA has received honoraria for consultation or advisory board participation from Novartis and Telix and research funding from Novocure. AV has received honoraria for lectures from General Electrics, Curium, and Eisai. HB received reader honoraria from Life Molecular Imaging, and dosing committee honoraria from Pharmtrace. IY receives speaker honoraria from Piramal and consultant fees from ABX-CRO and Blue Earth Diagnostics. IY receives research funding from the Federal Ministry of Education And Research Germany (grant number 031L0200B, PI, 2020–2022), German Research Foundation (grant number 491096247, PI, 2021–2024), international Brain Research Organization (meeting support award 2022), and International Society for Cerebral Blood Flow and Metabolism (Satellite Symposia Sponsorship 2022).
SM was involved in advisory boards for Ely-Lilly and received speaker honoraria from GE Healthcare, Life Molecular Imaging, Novartis.
MB is supported by grants from the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) under Germany's Excellence Strategy within the framework of the Munich Cluster for Systems Neurology (EXC 2145 SyNergy – ID 390857198). MB received speaker honoraria from GE healthcare, Roche, and LMI and is an advisor of LMI.

References

1. Kratochwil C, Fendler WP, Eiber M, Hofman MS, Emmett L, Calais J, et al. Joint EANM/SNMMI procedure guideline for the use of 177Lu-labeled PSMA-targeted radioligand-therapy (177Lu-PSMA-RLT). Eur J Nucl Med Mol Imaging. 2023;50(9):2830–45.
2. Zaknun JJ, Bodei L, Mueller-Brand J, Pavel ME, Baum RP, Hörsch D, et al. The joint IAEA, EANM, and SNMMI practical guidance on peptide receptor radionuclide therapy (PRRNT) in neuroendocrine tumours. Eur J Nucl Med Mol Imaging. 2013;40(5):800–16.
3. Salgues B, Graillon T, Horowitz T, Chinot O, Padovani L, Taïeb D, et al. Somatostatin receptor theranostics for refractory meningiomas. Curr Oncol. 2022;29(8):5550–65.
4. Minczeles NS, Bos EM, de Leeuw RC, Kros JM, Konijnenberg MW, Bromberg JEC, et al. Efficacy and safety of peptide receptor radionuclide therapy with [177Lu]Lu-DOTA-TATE in 15 patients with progressive treatment-refractory meningioma. Eur J Nucl Med Mol Imaging. 2022. https://doi.org/10.1007/s00259-022-06044-9.
5. Dutour A, Kumar U, Panetta R, Ouafik L, Fina F, Sasi R, et al. Expression of somatostatin receptor subtypes in human brain tumors. Int J Cancer. 1998;76(5):620–7.
6. Graillon T, Defilles C, Mohamed A, Lisbonis C, Germanetti AL, Chinot O, et al. Combined treatment by octreotide and everolimus: octreotide enhances inhibitory effect of everolimus in aggressive meningiomas. J Neurooncol. 2015;124(1):33–43.
7. Seystahl K, Stoecklein V, Schüller U, Rushing E, Nicolas G, Schäfer N, et al. Somatostatin-receptor-targeted radionuclide therapy for progressive meningioma: benefit linked to ^{68}Ga-DOTATATE/-TOC uptake. Neuro Oncol. 2016;now060. https://doi.org/10.1093/neuonc/now060.
8. Mirian C, Duun-Henriksen AK, Maier A, Pedersen MM, Jensen LR, Bashir A, et al. Somatostatin receptor–targeted radiopeptide therapy in treatment-refractory meningioma: individual patient data meta-analysis. J Nucl Med. 2021;62(4):507–13.
9. Mairal E, Chevalier E, Imbert L, Boursier-Joppin C, Verger A. Multiparametric 18F-FDG and 68GA-DOTATOC PET imaging in bone metastatic meningioma before radionuclide therapy. Clin Nucl Med. 2022;47(3):e321–2.
10. Kreissl MC, Hänscheid H, Löhr M, Verburg FA, Schiller M, Lassmann M, et al. Combination of peptide receptor radionuclide therapy with fractionated external beam radiotherapy for treatment of advanced symptomatic meningioma. Radiat Oncol. 2012;7(1):99.
11. Weller M, Wick W, Aldape K, Brada M, Berger M, Pfister SM, et al. Glioma Nat Rev Dis Primers. 2015;1:15017.
12. Pichler J, Hayward C, Jessel M. 823 IPAX-1 Phase ½ Study of 4-L-[131I] IODO-Phenylalanine (131I-IPA) Combined with external radiation therapy (XRT) as treatment for patients with glioblastoma multiforme. Neurosurgery. 2022;68(Supplement_1):138–9.
13. Pasciak AS, Manupipatpong S, Hui FK, Gainsburg L, Krimins R, Zink MC, et al. Yttrium-90 radioembolization as a possible new treatment for brain cancer: proof of concept and safety analysis in a canine model. EJNMMI Res. 2020;10(1):96.
14. Li Y, Marcu LG, Hull A, Bezak E. Radioimmunotherapy of glioblastoma multiforme - current status and future prospects. Crit Rev Oncol Hematol. 2021;163:103395.
15. Le Rhun E, Guckenberger M, Smits M, Dummer R, Bachelot T, Sahm F, et al. EANO-ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up of patients with brain metastasis from solid tumours. Ann Oncol. 2021;32(11):1332–47.
16. Sturm D, Pfister SM, Jones DTW. Pediatric gliomas: current concepts on diagnosis, biology, and clinical management. J Clin Oncol. 2017;35(21):2370–7.
17. Souweidane MM, Kramer K, Pandit-Taskar N, Zhou Z, Haque S, Zanzonico P, et al. Convection-enhanced delivery for diffuse intrinsic pontine glioma: a single-centre, dose-escalation, phase 1 trial. Lancet Oncol. 2018;19(8):1040–50.
18. Kramer K, Pandit-Taskar N, Kushner BH, Zanzonico P, Humm JL, Tomlinson U, et al. Phase 1 study of intraventricular 131I-omburtamab targeting B7H3 (CD276)-expressing CNS malignancies. J Hematol Oncol. 2022;15(1):165.
19. Upton DH, Ung C, George SM, Tsoli M, Kavallaris M, Ziegler DS. Challenges and opportunities to penetrate the blood-brain barrier for brain cancer therapy. Theranostics. 2022;12(10):4734–52.
20. Arvanitis CD, Ferraro GB, Jain RK. The blood-brain barrier and blood-tumour barrier in brain tumours and metastases. Nat Rev Cancer. 2020;20(1):26–41.
21. Benmelouka AY, Munir M, Sayed A, Attia MS, Ali MM, Negida A, et al. Neural Stem cell-based therapies and glioblastoma management: current evidence and clinical challenges. Int J Mol Sci. 2021;22(5):2258.
22. Aboody KS, Brown A, Rainov NG, Bower KA, Liu S, Yang W, et al. Neural stem cells display extensive tropism for pathology in adult brain: evidence from intracranial gliomas. Proc Natl Acad Sci U S A. 2000;97(23):12846–51.
23. Vonken EJPA, Bruijnen RCG, Snijders TJ, Seute T, Lam MGEH, de Keizer B, et al. Intraarterial administration boosts ^{177}Lu-HA-DOTATATE accumulation in salvage meningioma patients. J Nucl Med. 2022;63(3):406–9.