Theranostics in Neurooncology: Heading Toward New Horizons

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Therapeutic approaches to brain tumors remain a challenge, with considerable limitations regarding delivery of drugs. There has been renewed and increasing interest in translating the popular theranostic approach well known from prostate and neuroendocrine cancer to neurooncology. Although far from perfect, some of these approaches show encouraging preliminary results, such as for meningioma and leptomeningeal spread of certain pediatric brain tumors. In brain metastases and gliomas, clinical results have failed to impress. Perspectives on these theranostic approaches regarding meningiomas, brain metastases, gliomas, and common pediatric brain tumors will be discussed. For each tumor entity, the general context, an overview of the literature, and future perspectives will be provided. Ongoing studies will be discussed in the supplemental materials. As most theranostic agents are unlikely to cross the blood–brain barrier, the delivery of these agents will be dependent on the successful development and clinical implementation of techniques enhancing permeability and retention. Moreover, the international community should strive toward sufficiently large and randomized studies to generate high-level evidence on theranostic approaches with radioligand therapies for central nervous system tumors.

Key Words: radionuclide therapy; brain tumor; neurooncology; radionuclide therapy; theranostics; blood–tumor barrier

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In the last decade, we have observed a huge step forward in treatment options for a wide range of tumors in terms of both survival and quality of life. However, therapeutic approaches to brain tumors remain a challenge, with considerable limitations regarding delivery of drugs. Because of the recent success of theranostics in oncology with ^{177}Lu-DOTATATE for neuroendocrine tumors and ^{177}Lu-prostate specific antigen (PSMA) for prostate cancer, resulting in Food and Drug Administration and European Medicines Agency approvals, there has been renewed and increasing interest in translating the theranostic approach to neurooncology (*1–3*). Extracranially, such approaches are generally well tolerated, delivering a high absorbed dose with a low dose rate, specifically to the tumor, even on anatomically complex lesions, with a targeting that preserves the surrounding parenchyma. The latter is of course of high critical importance for brain interventions. Theranostics are also particularly adapted to treating multiple tumoral lesions in the whole body at the same time, for example, in metastatic disease. An added benefit is the possibility of identifying patients with high target availability using the corresponding imaging ligand, often the diagnostic twin, such as the positron-emitting version (suitable for PET) of the therapeutic ligand.

In this paper, theranostic approaches to brain tumors will be discussed. For each tumor entity, the general context and future perspectives will be provided. In the supplemental materials (available at http://jnm.snmjournals.org), an overview of the literature and ongoing studies is provided. Table 1 gives an overview of potential molecular targets for theranostic applications in neurooncology. Moreover, strategies to overcome the blood–brain barrier (BBB) and blood–tumor barrier (BTB) will be briefly discussed.

BBB AND BTB

The main obstacle in neurooncology compared with other solid tumors is getting therapeutics through the BBB. Brain tumors are known to alter the physiologic BBB integrity, some producing a highly heterogeneous vasculature—the BTB. This altered physiologic

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TABLE 1
Overview of Molecular Targets for Radionuclide Therapy in Meningioma, Brain Metastases, Glioma, and Pediatric Brain Tumors

Molecular target	Meningioma	Glioma	Brain metastases	Pediatric brain tumors
SSTR	O (phase 1–2) (NCT03971461, NCT04997317, NCT03273712, NCT04082520, NCT05278208)	O (phase 1) (NCT05109728)		O (phase 1–2) (NCT05278208, NCT03273712)
Tenascin		X	O (phase 1–2) (NCT00002752)	
EGFR		X		
NK1R		X		
GRPR		O (phase 1–2) (NCT03872778, NCT05739942)		X
LAT-1		O (phase 1–2) (NCT03849105, NCT05450744)		
Carbonic anhydrase XII		O (phase 1) (NCT05533242)		
Integrins		X		
PARP1		X		
PSMA		X	X	
MMP		X	X	
DNAH1		X		
Chemokine receptor 4		X		
Fibronectin			X	
HER2			O (phase 1–2) (NCT04467515)	
PCSP			X	
Disialoganglioside (GD2)			O (phase 2) (NCT00445965)	X
B7-H3				O (phase 1) (NCT00089245, NCT05063357)
$CuCl_2$				X
FAP		X		

O = ongoing studies; X = target that has been investigated in previous studies; EGFR = epidermal growth factor receptor; NK1R = neurokinin type 1 receptor; GRPR = gastrin-releasing peptide receptor; PARP1 = poly(adenosine diphosphate ribose) polymerase 1; PSMA = prostate-specific antigen; MMP = matrix metalloproteinase; DNAH1 = DNA histone ^{1}H complex; HER2 = human epidermal growth factor receptor 2; PCSP = proteoglycan chondroitin sulfate-associated protein; FAP = fibroblast activation protein.

NOTEWORTHY

- In this paper, we describe the general context of, an overview of the literature for, and future perspectives on radionuclide therapy for meningiomas, gliomas, brain metastases, and pediatric brain tumors.
- Preliminary research on theranostics in meningiomas and leptomeningeal spread of certain pediatric brain tumors is encouraging. To date, other entities fail to impress.
- Successful development of other principles enabling BBB passage is crucial for the future success of radionuclide therapy for brain tumors.

BBB and BTB integrity is heterogeneous between metastatic lesions and various primary tumor types and shown by contrast enhancement on MRI (*4*). Several strategies have been developed to bypass the BBB and BTB (*4–6*): local administration (including intraventricular administration), convection-enhanced delivery (CED), focused ultrasound (FUS), and innovatively designed monoclonal antibodies and neural stem cells. We will describe some of these mechanisms in more detail (Fig. 1). Most of these techniques are complex and, as such, can be performed only in expert centers.

Therapeutics can be directly administered into the tumor or into surgical or anatomic cavities (such as intraventricular administration using a catheter). Compared with systemic therapy, the toxicity to the body is thereby reduced. Nevertheless, a certain grade of

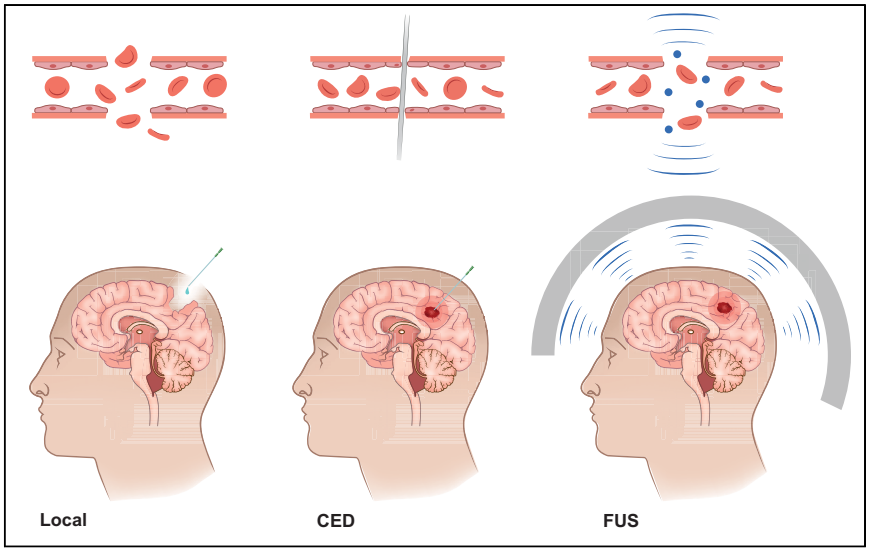

FIGURE 1. Example of interventional approaches to bypass physiologic BBB and BTB. Normal transport in BBB is not included. (Left) Local delivery with administration of radioactivity directly into resection cavity. (Middle) CED: microcatheter is implanted into tumor, and hydraulic pressure is used to distribute drugs in brain parenchyma. (Right) FUS reshapes BBB using targeted ultrasonic wave. This in turn causes interaction between administered microbubbles and capillary bed, resulting in enhanced vessel permeability.

hematologic and neurologic toxicity can still be present through dissemination of the compound into the blood, catheter dislocation and leakage in other vital areas (*7*).

CED represents a well-studied way to bypass the BBB in which one or more microcatheters are implanted into and around the tumor. CED, mostly of chemo- and immunotherapeutic drugs, has a long history and has been repeatedly used safely in clinical trials in both adult and pediatric patients (*8*,*9*). However, no durable clinical impact has been seen, despite multiple clinical trials (*10*). Because of the complex nature of CED, studies vary with respect to agent, infusion volume, and rate and cannula design, for example. CED has specific issues due to slow and continuous delivery with varying clearance via the interstitial fluid and back into the bloodstream over the BBB. Personalized image-guided drug delivery using PET before, during, and after CED could increase the potential of this technique. Upfront pharmacokinetic imaging, especially for large drugs such as monoclonal antibodies, using imaging ligands with a long half-life could be applied for patient selection, treatment planning, and dose scheduling. A recent study in murine models of diffuse intrinsic pontine glioma revealed significant variability in post-CED clearance within and across injection cohorts with post-CED PET. This was probably due to the heterogeneity of the tumors and from inherent technical variance. The use of PET-guided CED dosing schedules did, however, prolong survival (*11*). Clinical studies combining CED with labeled drugs have recently been performed. Safety and feasibility were shown in a study evaluating CED of ^{124}I-8H9, a monoclonal antibody targeting the glioma-associated B7-H3 antigen in children with diffuse midline glioma (*5*). Safety and feasibility were also confirmed in glioblastoma (*6*). For ligands with simultaneous diagnostic–theranostic characteristics such as ^{124}1-8H9 (*12*), posttherapy dosimetry can be used not only to validate the principles of CED but also to verify and adjust the dosing schedule and treatment plan.

An alternative method to enhance radioisotope-labeled drug delivery to the brain is FUS-mediated BBB opening, which uses low-frequency ultrasound waves inducing stable cavitation of intravenously injected microbubbles (*13*) Mechanical interaction of microbubbles with the BBB temporarily dislocates tight junctions between endothelial cells and increases transcytosis, thereby enhancing permeability into the brain parenchyma (*13*,*14*).

This technique has been explored only in limited clinical trials (*15*,*16*), and different technical implementations of this technology exist. Technical implementations are diverse, ranging from implanted ultrasound transducer designs (*17*) appearing favorable for cost-effective repetitive openings of the supratentorial brain to fully MRI-guided transcranial (and thus noninvasive) devices (*18*), which appear favorable for deep-seated lesions in the brain stem or thalamus. Although this technology has not yet been used clinically in combination with a theranostic approach, preclinical studies demonstrating enhanced delivery of monoclonal antibodies to the parenchyma have shown considerable promise (*19*–*21*).

Innovatively designed monoclonal antibodies also show promise to pass the physiologic BBB, such as single-domain antibodies and antibodies modified into a bispecific format (*22*,*23*). Additionally, various transporters such as the L-type amino acid transporter 1 (LAT-1) are present on the physiologic BBB. These transporters deliver essential nutrients and energy and can be used in a carrier-mediated manner to cross the BBB. LAT-1 is promising for carrier-mediated brain drug delivery: it has a rapid BBB exchange and accepts various amino acids and analogs, and a transient disruption in essential amino acid transport will not cause irreversible brain damage (*24*). The use of LAT-1 targets is further discussed in the glioma section.

MENINGIOMAS

Context

Meningiomas are the brain tumors for which peptide receptor radionuclide therapy (PRRT) has been most performed. They represent 30% of primary intracranial tumors. Although approximately 80% of these tumors are benign (central nervous system [CNS] World Health Organization [WHO] grade 1), the remaining cases are classified as high-grade meningiomas (related to CNS WHO grades 2 and 3) (*25*,*26*). Treatment options encompass mainly neurosurgical resection and external-beam irradiation. PRRT is currently considered in meningiomas that cannot be treated by surgery or conventional radiation therapy regardless of their grade (*27*,*28*). PRRT targets somatostatin receptor (SSTR) type 2, since meningiomas almost invariably express SSTR type 2 (*29*) which can be monitored with SSTR-targeted PET imaging. Patients with grade 1 well-differentiated and thus generally less aggressive meningiomas exhibit higher levels of SSTR and may have the best responses to PRRT (*30*). ^{90}Y-SSTR–targeted PRRT and ^{177}Lu-SSTR–targeted PRRT similarly combine a molecular vector targeting the SSTR receptor with a β-emitting radioactive label and are used in PRRT of meningiomas.

Perspectives

Most of the available data on PRRT in meningiomas are from patients at a late stage of the disease (*27*,*30*), when the efficacy of the treatment is potentially limited. Achieving a partial response after PRRT (*31*) or other systemic therapies (*32*) in meningiomas is rare. It might therefore be advantageous to start PRRT earlier in the disease course (after surgery)—that is, before patients develop treatment-refractory, progressive, and extensive disease. Moreover, identification of potentially dedifferentiated meningiomas with a poorer prognosis (lesions with high ^{18}F-FDG uptake and low SSTR uptake) with multitracer pretherapeutic SSTR PET and ^{18}F-FDG PET (*33*) could help to select patients for whom PRRT could provide more benefit. Meningiomas are considered a heterogeneous group, and even the pathologically benign subtypes (grade 1) can have a high recurrence risk depending on their molecular alterations (*34*,*35*). PRRT should be investigated not only in refractory (end-stage) meningioma but also in surgically inoperable, high-grade, and high–recurrence-risk meningioma. In high-grade meningioma, because additional value for dedifferentiated meningioma can be expected, pretherapeutic ^{18}F-FDG PET will be critical (*36*). Future efforts should include the development of criteria for appropriate use of PRRT in the specific subtypes (with the current insight on molecular alterations and the risk of recurrence) and the determination of efficacy in randomized prospective trials.

Moreover, SSTR-targeted PRRT in meningiomas has been based on the standard approach in neuroendocrine tumors, that is, sequential treatment by multiple doses. This paradigm requires reevaluation in meningiomas, ideally including personal tumor dosimetry and alternative administration modes. For the latter, promising preliminary results were reported for intraarterial administration boosts of ^{177}Lu-SSTR–targeted PRRT in salvage meningioma patients (*37*). Moreover, as β-emitters (^{177}Lu and ^{90}Y) have been used in all studies, the efficiency of labeling STTRs with α-emitters should be investigated.

Lastly, future studies should also focus on treatment combinations. The combination of external-beam radiation therapy and PRRT, for instance, could improve the absorbed dose while limiting the organ-at-risk irradiation. This improvement would be due to the difference in radiation fields between the 2 modalities, thereby potentially providing better local disease control than PRRT alone (*38*,*39*). In a study of Kreissl et al. (*38*), one cycle of PRRT was administered in combination with external radiation therapy, bringing us to the point mentioned above. A randomized controlled trial comparing the effect of 1 cycle versus 4 cycles of PRRT with or without external-beam radiation therapy should be investigated in terms of safety and efficacy. Also, because radiation exposure increases SSTR type 2 expression, pre-PRRT external radiation therapy might be able to boost the antitumor effects of PRRT (*40*). As another example, PRRT and targeted therapies such as everolimus, an inhibitor of mammalian target of rapamycin, may potentially act synergistically without potentiating adverse effects (*41*). Phase II trial results with a combination of everolimus and nonradiolabeled octreotide have been encouraging in terms of progression-free survival (55% after 6 mo) in a study population of whom 90% had WHO grade 2 and 3 meningiomas (*42*).

GLIOMAS

Context

Gliomas are the most common malignant brain tumors. They include diffuse gliomas such as astrocytomas, oligodendrogliomas, and glioblastomas, as well as ependymomas. Around 80% are high-grade gliomas. They are classified according to the WHO as CNS WHO grade 2, 3, or 4 (*43*). Currently, a combined approach of maximal safe surgical resection, external-beam radiation therapy, and chemotherapy represents the standard of care for diffuse gliomas, but new therapeutic approaches are needed (*44*).

Gliomas are characterized by a high level of treatment resistance, immune escape, and temporospatial heterogeneity. It is not surprising that although considerable effort has been put into the development of new treatment options, the last few decades have revealed only a few significant changes in the outcome of glioma patients. The limited overall survival, especially for patients with glioblastoma, underlines the need for new therapeutic concepts in the management of glioma patients (*45*). Many potential theranostic targets for gliomas have been investigated, with variable but mostly discouraging results: tenascin, epidermal growth factor receptor, neurokinin type 1 receptor, SSTR, gastrin-releasing peptide receptor, LAT-1, carbonic anhydrase XII, PSMA, matrix metalloproteinase, DNA histone ^{1}H complex, poly(adenosine diphosphate ribose) polymerase 1, integrins, chemokine receptor 4, disialoganglioside, and fibroblast activation protein.

Perspectives

Similar to the situation in meningiomas, most theranostic studies on gliomas have been performed either after incomplete surgery or as a second line in recurrent disease, the latter most often being in combination with chemotherapy or radiation therapy (*46*). The main weaknesses of the current studies are selection bias in patient inclusion, small patient numbers, or lack of efficacy data. All planned and performed glioma studies based on systemic administration of a non–BBB-penetrant compound have failed or are likely to fail, and all performed studies that include direct tumor administration have been discouraging. Therefore, currently, the most promising studies are trials targeting LAT-1, although the low residence time and radiation burden to normal brain parenchyma should be closely investigated. Moreover, future studies should focus on using multimodal approaches combining theranostic agents with techniques enhancing BBB or BTB permeability.

BRAIN METASTASES

Context

Brain metastases are diagnosed in 50% of patients with advanced primary lung cancer and melanoma and 20% of patients with breast cancer (*47*). The presence of brain metastases is associated with a poor prognosis. The current therapeutic options consist of a combination of surgery, external radiation therapy, and targeted and immune-modulating therapies (*48*). As primary cancer control is advancing dramatically, brain metastases across many cancer types occur more frequently, illustrating the need for more effective therapies.

Perspectives

Radionuclide therapy for brain metastases has scarcely been investigated. As in primary brain tumors, in brain metastases the physiologic BBB is usually altered with formation of a BTB (*49*). An advantage of radionuclide therapy over immune therapy is that the effective targeting of all lesions can be visualized using intratherapy scanning (*1*,*2*). Although studies of radionuclide therapy in brain metastases are scarce and efficacy needs to be proven, there are very preliminary data on example cases in breast cancer, prostate cancer, and melanoma.

The added value of radionuclide therapy for metastasis is the simultaneous treatment of most tumor localizations in the body when using intravenous or intraarterial administration. Moreover, the effective targeting of brain metastases can be noninvasively—that is, repeatedly—monitored by PET imaging. These features might translate into an advantage over the current standard of care in terms of clinical benefit. With regard to the development of theranostic radiopharmaceutical pairs to treat brain metastases, these must focus on specific targets for specific cancer types.

PEDIATRIC BRAIN TUMORS

Context

Brain tumors are the most frequent solid malignancy in childhood and account for around 20% of all pediatric tumors (the second most frequent after leukemias). They differ in many aspects from the disease in adults, both in site (pediatric brain tumors are more often infratentorial [≤60% of cases]) and in histology (*50*), as has been recognized in the most recent WHO classification of CNS tumors (fifth edition, 2021), in which specific pediatric variants have been added (e.g., pediatric-type low-grade and high-grade diffuse gliomas) (*51*–*53*). Recent advances in molecular and genetic characterization have detected many peculiarities of pediatric CNS tumors, significantly impacting spreading, response to treatment, and survival (*54*,*55*).

Surgery is the mainstay in many pediatric brain tumors. It offers a prospective cure in the noninfiltrating forms but is often performed also to treat diffuse infiltrating disease, because debulking can improve survival and quality of life. Surgery can be combined with adjuvant therapy (external radiation therapy or chemotherapy) when complete resection is not achievable or when microscopic persistence of disease is probable (*56*).

Surgical options are often heavily limited by the anatomic relationships between lesions and critical structures, as is often the case for H3-K27–altered diffuse midline gliomas (formerly known as diffuse intrinsic pontine gliomas), for which external radiation therapy offers the best chance for palliation. External radiation therapy increases survival in many high-grade tumors, as in medulloblastoma, one of the most frequent CNS neoplasms in childhood, typically located in the posterior fossa. However, radiation therapy can have devastating long-term effects (neurocognitive, endocrine, etc.), particularly in younger patients (0–3 y) (*57*). Therefore, external radiation therapy is often avoided when prolonged survival is expected in younger patients, despite its efficacy.

Chemotherapy is used in combination with surgery or external radiation therapy, considering the interactions of the drug with the BBB. Intraventricular administration is often used in young children with embryonal tumors (atypical teratoid rhabdoid tumor, medulloblastoma), who cannot receive external radiation, to treat or prevent meningeal spread or dissemination through the cerebrospinal fluid circulation. Pediatric CNS tumors remain the leading cause of cancer-related death in childhood, despite much progress in comprehension of their molecular bases, and greatly need alternative treatment options, as in the case of the theranostic approach.

Perspectives

Considering the field, a relatively large amount of literature is available on theranostic approaches toward radioligands in pediatric neurooncology. One of the best-documented and promising approaches is the use of intracranioventricular [^{131}I]omburtamab via an intrathecal Ommaya reservoir in metastatic neuroblastoma, recurrent medulloblastoma, and ependymoma for treatment of leptomeningeal disease (*58*).

In leptomeningeal disease, cancer cells are located in the cerebrospinal fluid space. Intracranioventricular administration enables targeted treatment with high regional tracer concentrations and a low systemic distribution, confirmed by pretherapeutic [^{131}I]omburtamab scans (*58*).

It is too early to know which radionuclide therapy shows the greatest potential, and as in adults, more research must be done with innovative techniques to resolve the issue of penetrability of the physiologic BBB and BTB. Several preclinical and clinical studies are in progress and will soon show whether theranostic approaches will be able to serve as the desperately needed tools to improve patient care in neurooncology.

CONCLUSION

Theranostics is an exciting field of nuclear medicine with proven efficacy in, up to now, mainly thyroid cancer, prostate cancer, and neuroendocrine tumors. The theranostic concept is increasingly also being tested in brain tumors, with preliminary encouraging results for meningiomas and leptomeningeal spread of pediatric brain tumors but discouraging results for gliomas. To date, no studies have proven clinical efficacy. Existing concepts from extracranial malignancies—such as ^{177}Lu-DOTATATE for neuroendocrine tumors—are being translated to the brain tumor setting. In parallel, new theranostic targets are being explored. However, unlike extracranial malignancies, the BBB and BTB form a significant hurdle in the development of effective therapies for primary and secondary brain tumors. Respective therapeutics that can cross the intact or partially intact BBB and BTB are desired. Although some therapeutics do, in fact, actively cross these barriers, the success of most agents will depend on the successful development and clinical implementation of other principles that increase the permeability of the BBB in combination with agents that decrease efflux. These techniques are still under development, without proven efficacy, and are found in multiple versions. Here, nuclear medicine techniques can aid and potentially speed development by enabling visualization and verification of the principle, such as imaging after FUS with radiolabeled monoclonal antibodies, which are large by nature and normally would not cross the BBB (*59*,*60*). Besides standalone therapy, synergistic approaches with external-beam radiation or immunotherapy could potentially be even more effective and are being evaluated. Additionally, as with all theranostic approaches, the optimal timing (e.g., phase of treatment) should be explored. Another major limitation of substantial progress is the use of underpowered and uncontrolled clinical trial designs. The international community should strive toward sufficiently large and randomized studies to generate high-level evidence on radioligand therapies for CNS tumors. More basic and clinical research is certainly necessary.

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