The Future of Radiopharmaceuticals in Neuro-Oncology

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NOTHING TO DISCLOSE

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LEARNING OBJECTIVES

(1) Describe radiopharmaceuticals in preclinical and clinical development in neuro-oncology
(2) Outline challenges of radiopharmaceuticals in neuro-oncology
BACKGROUND

- Primary brain tumors (PBTs) are difficult cancers to treat and often carry a **poor prognosis** despite advancements in surgery, chemotherapy, and radiotherapy.

- Radiopharmaceutical therapy may expand treatment options for these patients and improve management of disease.
Background - Common Examples of Adult PBTs

- **Glioblastoma (GBM)**
  - Most common malignant PBT
    - About 10,000 cases per year in the US
  - Standard of care (SOC) since 2005 is relatively unchanged
    - Maximal safe resection followed by 60 Gy of radiation therapy (RT) with concurrent temozolomide (TMZ) followed by adjuvant TMZ +/- Tumor Treating Fields
  - Median overall survival (OS) ranges 12-20 months
Background - Common Examples of Adult PBTs

- High and Low Grade Gliomas (HGG and LGG)
  - Astrocytoma, IDH-mutant
  - Oligodendroglioma, IDH-mutant, and 1p/19q co-deleted
  - SOC is maximal safe resection, RT and chemotherapy (PVC or TMZ)
  - Median OS 1.7 – 14 years, depending on a multitude of factors
Background - Common Examples of Adult PBTs

- **Meningioma**
  - Most common PBT (26,000 cases per year)
  - Treatment and outcome depends on extent of surgical resection and grade of tumor
    - WHO Grade 1
      - SOC is surgical resection, observation if gross total resection (GTR).
      - Five year Progression Free Survival (PFS): ~86%
    - WHO Grade 2
      - SOC is surgical resection +/- RT.
      - 5 year PFS: ~84%
    - WHO Grade 3
      - SOC is surgical resection + RT.
      - 3 year PFS ~59%
Background - Common Examples of Adult PBTs

- Pituitary Adenoma
  - 10,000 cases per year
  - Treatment depends on size, symptoms, and subtype. Local Control ~95% with surgery
    - Asymptomatic adenomas without lab abnormalities can be observed
    - Surgery is first line (except prolactinoma and pituitary carcinoma)
    - RT is second-line for sub-total resection (STR), unresectable, recurrent or refractory disease
Challenges to treatment of Primary Brain Tumors

- Blood Brain Barrier (BBB)
  - Prevents or delays delivery of chemotherapy agents to the tumor
- Removal of tissue must spare normal tissue
- Some lesions may be difficult to reach or in eloquent locations
- Tumor infiltration may be diffuse

Radiopharmaceutical therapy may potentially target cancer cells while sparing normal brain

- Radiopharmaceuticals can selectively bind to specific receptors and emit beta or alpha particles to induce irreparable DNA strand breaks

Potential Target Receptors for PBTs

- Somatostatin receptors (SSTRs)
- Neurokinin type-1 receptors
- Prostate-specific membrane Antigen (PSMA)

The somatostatin analogue (SSA), generally an octreotide derivative, an agonist, is linked to a DOTA chelator, which contains the radionuclide. After binding to the membrane somatostatin receptor (SSR), the radiopeptide is internalized and is transported into the intracellular receptor-recycling compartment.


## Possible Applications of Radiopharmaceuticals for Primary Brain Tumors

<table>
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<tr>
<th>Primary Brain Tumor</th>
<th>Possible Targets</th>
<th>Comment</th>
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| Gliomas             | SSTR2: 25% of Gliomas, variable expression | • Appears safe and feasible  
|                     | Neurokinin type 1: HGG | • Low expression of SSTR2 in GBM per most reports  
|                     | PSMA: HGG          |         |
| Meningiomas         | SSTR2: 90% meningiomas | • Results demonstrated  
|                     |                  | • Included in EANO guidelines |
| Pituitary Tumors    | SSTR1,3,2,5: depends on type | • SS imaging plays crucial role in patient selection  
|                     |                  | • Few reports with SS analogs |
MENINIOMAS
Meningiomas

- **1973** – Somatostatin discovered by Brazeau et al; was found to have potent inhibitor effects on secretion processes in pituitary, pancreatic, and GI tissue

- **1986** – Meningiomas were found to have somatostatin receptors
Meningioma

- Meningiomas grow outside of the BBB
- SSTR2 expression on imaging is significantly lower on WHO III meningiomas when compared to WHO I/II
- Phase 2 prospective trial using Lu in meningioma: 34 patients showed long-term stable disease in 65.6% and a mean overall survival (OS) of 8.6 years
- Salvage study showed similar results with stable disease in 50% and median OS of 20 months
- Europe - EANO guidelines support use of radiopharmaceutical peptide use

Somatostatin Receptor–Targeted Radiolabeled Therapy with $^{90}Y$-DOTATOC and $^{177}$Lu-DOTATOC in Progressive Meningioma: Long-Term Results of a Phase II Clinical Trial

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Meningiomas express members of the somatostatin receptor family. In the present study assessed the long-term benefits and harm of somatostatin-based radiolabeled therapy in meningioma patients. Methods: Patients with progressive unresectable meningiomas were treated with $^{90}$Y-DOTATOC and $^{177}$Lu-DOTATOC until tumor progression or permanent toxicity occurred. Multivariable Cox regression analyses were used to study predictors of survival. Results: Overall, 76 treatment cycles were performed on 34 patients. Stable disease was achieved in 23 patients. Severe hematoxicity occurred in 3 patients, and severe renal toxicity in 1 patient. Mean survival was 8.6 y from the time of enrollment. Stable disease after treatment (hazard ratio, 0.071 vs progressive disease; 95% confidence interval, 0.001–0.34; n = 34; P = 0.010) and high tumor uptake (hazard ratio, 0.046 vs. intermediate or low tumor uptake; 95% confidence interval, 0.004–0.93; n = 34; P = 0.010) were associated with longer survival. Conclusion: $^{90}$Y-DOTATOC and $^{177}$Lu-DOTATOC are promising tools for treating progressive unresectable meningioma, especially in cases of high tracer uptake in the tumor.

Key Words: sstr2; metabolic therapy; targeted therapy; survival

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Meningiomas are the most common intracranial extraneural neoplasms, accounting for approximately 30% of central nervous system tumors in adults. Although usually asymptomatic, meningiomas can be associated with seizures, headaches, vision loss, or focal neurologic deficits depending on their intracranial location. About 80% of meningiomas are benign (World Health Organization [WHO] grade I) and are considered curable with gross total resection. The remaining 20% of meningiomas are atypical (WHO grade II) or anaplastic (WHO grade III) and demonstrate malignant potential, significantly higher recurrence rates, and shorter median survival. The treatment strategy is based on tumor grade, size, and location. Location near vital structures, especially in the skull base, represent a major therapeutic challenge. Overall, less than 50% of newly diagnosed meningiomas are fully resectable. The therapeutic options in those cases are currently limited.

Importantly, meningioma cells express members of the somatostatin receptor family (2), which provided rationale for somatostatin receptor-targeted radiolabeled therapy with radiolabeled DOTATOC in patients with progressive meningioma. Radiolabeled DOTATOC is injected intravenously, binds to the somatostatin receptor on the target cell, and localizes in the tumor via receptor-mediated endocytosis. The present study evaluated the long-term outcome after treatment with the somatostatin-based radiolabeled $^{90}$Y-DOTATOC and $^{177}$Lu-DOTATOC in patients with unresectable progressive meningioma.

MATERIALS AND METHODS

Patients

Eligibility was screened at the University Hospital Basel, Switzerland. Patients were eligible if they met the following criteria: histologically confirmed meningioma, disease progression within 12 mo before study entry; and viable tumor uptake on pretherapeutic extracranial scintigraphy. Patients were excluded if they met one of the following criteria: concurrent antitumor treatment other than somatostatin analogs, pregnancy, breastfeeding, urinary incontinence, preexisting grade 3 or 4 hematologic toxicity, or severe concurrent illness, including severe psychiatric disorder. Initial staging and eligibility were based on CT and MR imaging and clinical results from the referring centers. All patients were prospectively recruited into this study, which was designed and performed in accordance with good clinical practice guidelines, Swiss drug laws, and the Declaration of Helsinki. The study was approved by the local ethics committee for human studies (EKB: reference number MI1907; www.ekb.ch). Written informed consent was obtained from all participants or their legal representa-
tives. The current results represent a post hoc analysis of the long-term data on safety and efficacy.

Trial Drug

$^{90}$Y-DOTATOC was the standard treatment from 1997 to 2001 (3). Combined treatment with $^{90}$Y-DOTATOC plus $^{177}$Lu-DOTATOC be-
European Guidelines for Meningioma (EANO)

**MRI:** meningioma

- No mass effect, no symptoms → Observation
- Mass effect, symptoms, wish of patient → Therapy

**Histology, degree of resection**

- WHO grade I, gross total resection
  - Observation
- WHO grade I, subtotal or partial resection
  - Combined with stereotactic radiosurgery or fractionated radiotherapy
- WHO grade II, gross total resection
  - Observation or fractionated radiotherapy
- WHO grade II, subtotal or partial resection
  - Fractionated radiotherapy
- WHO grade III
  - Fractionated radiotherapy, experimental chemotherapy, or peptide receptor radionuclide therapy

**Good clinical condition** → Surgery → Histology, degree of resection

**Poor clinical condition** → Stereotactic radiosurgery or or fractionated radiotherapy → Observation

*Figure 1: Recommendations for the therapeutic management of meningiomas of WHO grades I-III*
GLIOMAS
4 Steps to Validating a Radiopharmaceutical For Clinical Use

(1) Prove the tumor contains targetable receptors
(2) Prove that the therapeutic has the desired effect in animal models
(3) Use a radioactive tracer to show that tumors have the desired target
(4) Conduct a human clinical trial
Step 1 - What receptors to target?

• 90Y-DOTATOC and 177Lu-DOTATATE are most commonly used in clinical practice

• Main target of these compounds is **SSTR2**

• Gliomas have somatostatin receptors (SSTRs). There are five subtypes (SSTR1 to SSTR5).

• However, there is some controversy regarding tumor grade I-IV and receptor presence
Gliomas

- 1987 – Somatostatin receptors found to exist in the CNS and glial elements

Distribution and Biochemical Characterization of Somatostatin Receptors in Tumors of the Human Central Nervous System

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ABSTRACT

Fifty-two brain tumors, consisting of 17 astrocytomas, 4 oligodendro- gliomas, 23 glioblastomas, 2 neurofibromas, 1 neuroblastoma, 1 gangliocytoma, 1 ganglioglioma, 1 medulloblastoma, 1 pituitary tumor, 1 teratoma, and 1 germinoma, were tested for their content of specific somatostatin receptors using autoradiographic techniques or in vitro binding assays with nanomolar homologous Somatostatin receptors were found in most of the differentiating glioma-derived tumors such as astrocytomas and oligodendrogliomas whereas the poorly differentiated glioblastomas were nearly free of receptors. Tumors originating from neurilemmomas, i.e., gangliogliomas and medulloblastomas, contained a high density of somatostatin receptors, whereas neurofibromas and neuroblastomas as well as the ependymomas, one teratoma, and one pituitary tumor were lacking such receptors. In one germinoma, low amounts of somatostatin receptors were observed over the lymphatic elements.

Receptor-positive tumors had saturable and high affinity receptors with pharmacological specificity for somatostatin and somatostatin analogues resembling that of normal human central nervous system tissues. In most instances, they could be labeled with two different iodinated radioligands, a somatostatin octapeptide derivative (231-I) or a somatostatin-28 analogue.

This is the first time that somatostatin receptors have been shown to exist not only on neural structures of the central nervous system but also on glial elements. The precise function of such somatostatin receptor on glial cells, which might be different from neurotransmitter, remains to be determined.

INTRODUCTION

SS's, a tetradecapeptide discovered by Bruegger et al. (1), has proven inhibitory effects on various secretion processes in pituitary, pancreatic, or gastrointestinal tissue (2). In addition, its localization within CNS neurons and its stimulus-evoked release from nerve terminals suggests that it might be a neurotransmitter in the CNS (3). The various biological actions of SS, including those in the brain, seem to be mediated through specific high affinity receptors (4-7). In the rat and human brain, a specific and dense distribution in cortical and limbic areas of predominantly neurochemically localized SS receptors (8, 9) would support indeed a neurotransmitter role of SS.

Not only normal target tissues for SS but also tumourally transformed tissue of the same origin have SS receptors, as has been shown for pituitary (10, 11) or pancreatic adenomas (12). They are probably the molecular basis for the clinical efficacy of SMS 201-995 therapy in certain tumor patients. SS receptors located on the tumor itself may mediate the inhibition of hormone secretion as well as additional intrinsic anti-proliferative effects (13-19).
Gliomas

Reubi et al. 1987

52 Brain tumors (note pre-molecular era)

- 17 astrocytomas – 14 had SSR
  4 oligodendrogliomas – 2 had high SSR
  20 GBM – none had SSR, except one which was near an area of necrosis

- SSR were present in tumors originating from glial cells, astrocytoma and primitive neuronal neuroblasts. In contrast, de-differentiated glial cells, GBMs did not. **Receptors found mostly in differentiated glia-derived tumors**

- Hypothesized: Perhaps that SSR markers of **differentiation grade** of CNS tumors. In some cells, SS can inhibit the epidermal growth factor induced DNA synthesis and cell replication

- Peripherally applied peptide like SS analogs may be unable to reach brain due to BBB
### Table 1: Individual data of 52 patients with CNS tumors and the result of receptor determinations

| Case | Age (yr) | Sex | Histological diagnosis | WHO grading | Miotosis | Somatostatin receptors
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<td>11</td>
<td>M</td>
<td>Germ cell tumor</td>
<td>IV</td>
<td>++</td>
<td>+</td>
</tr>
</tbody>
</table>

The table includes data on 52 patients with CNS tumors and the result of receptor determinations. The table provides information on age, sex, histological diagnosis, WHO grading, miotosis, and receptor levels. The comments section provides additional details about the tumor type and location.
Gliomas

- 1989 – LGGs have high affinity for SSR2

**Table 2. Distribution of SS-R and EGF-R in Astrocytomas and Glioblastomas**

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Histology</th>
<th>SS-R</th>
<th>EGF-R</th>
</tr>
</thead>
<tbody>
<tr>
<td>29077</td>
<td>Astrocytoma I</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>3134</td>
<td>Astrocytoma I</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>26994</td>
<td>Astrocytoma I</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>9536</td>
<td>Astrocytoma I</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>26221</td>
<td>Astrocytoma II</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>17798</td>
<td>Astrocytoma II</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>5335</td>
<td>Astrocytoma II</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>27049</td>
<td>Astrocytoma II</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>80-2</td>
<td>Astrocytoma II-III</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>E-51-5</td>
<td>Astrocytoma II-III</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>5053</td>
<td>Astrocytoma III</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>2344</td>
<td>Astrocytoma III-IV</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>20195</td>
<td>Glioblastoma</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>19505</td>
<td>Glioblastoma</td>
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<td>-</td>
</tr>
<tr>
<td>19177</td>
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<td>-</td>
<td>-</td>
</tr>
<tr>
<td>19214</td>
<td>Glioblastoma</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
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<td>Glioblastoma</td>
<td>-</td>
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</tr>
<tr>
<td>16212</td>
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<td>-</td>
<td>-</td>
</tr>
<tr>
<td>28504</td>
<td>Glioblastoma</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>21219</td>
<td>Glioblastoma</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>28502</td>
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<td>-</td>
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</tr>
<tr>
<td>26945</td>
<td>Glioblastoma</td>
<td>-</td>
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<tr>
<td>26812</td>
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<td>26090</td>
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<td>-</td>
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</tr>
<tr>
<td>28945</td>
<td>Glioblastoma</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

**Coincidence of EGF Receptors and Somatostatin Receptors in Meningiomas but Inverse, Differentiation-Dependent Relationship in Glial Tumors**

The coincidence of EGF receptors and somatostatin receptors in meningiomas, but an inverse, differentiation-dependent relationship in gliomas, suggests a role for both in the pathogenesis of these tumors. The high affinity of LGGs for SSR2 has been linked to their propensity to form astrocytomas or glioblastomas. A recent study has shown that SSR2 receptors are expressed in astrocytic tumors and may be involved in the growth and invasion of these tumors. The expression of SSR2 receptors in astrocytic tumors suggests a potential role in the differentiation and proliferation of these tumors.
Contrasting results on whether HGGs possess SSTR2 receptors

Some papers report expression

- Dutour et al. 1998 – tested mRNA
- Feindt et al. 1995 – tested glioma tumor cells lines
- Mawrin et al. 2004

Some do not report expression

- (Lamszus et al. 1997; Cervera et al. 2002; Lapa et al. 2015; Kiviniemi et al. 2015, 2017).

### Table 1

<table>
<thead>
<tr>
<th>Receptor Subtype</th>
<th>DA (n = 8)</th>
<th>AA (n = 10)</th>
<th>GBM (n = 32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$sst_1$</td>
<td>0 (0%)</td>
<td>2 (20%)</td>
<td>21 (66%)</td>
</tr>
<tr>
<td>$sst_{2A}$</td>
<td>0 (0%)</td>
<td>1 (10%)</td>
<td>14 (44%)</td>
</tr>
<tr>
<td>$sst_3$</td>
<td>3 (38%)</td>
<td>4 (40%)</td>
<td>27 (84%)</td>
</tr>
<tr>
<td>$sst_4$</td>
<td>7 (88%)</td>
<td>8 (80%)</td>
<td>23 (72%)</td>
</tr>
<tr>
<td>$sst_5$</td>
<td>2 (25%)</td>
<td>3 (30%)</td>
<td>8 (25%)</td>
</tr>
</tbody>
</table>

Percentage of positive cases is indicated in parentheses. Abbreviations: $sst$, somatostatin receptor; DA, diffuse astrocytoma WHO grade II; AA, anaplastic astrocytoma WHO grade III; GBM, glioblastoma multiforme WHO grade IV.
Kiviniemi et al 2017

184 Gliomas retrospectively analyzed for SSTR2A

- 101 GBM (93 IDHwt, 3 IDHmt, 5 NOS)
- 60 astrocytomas (22 IDHwt, 37 IDHmt, 1 NOS)
- 23 oligodendrogliomas (19 IDHmt&1p/19q codel, 4 NOS)

**Oligodendrogliomas**

- 79% SSTR2A positive with homogenous membranous and cytoplasmic staining

**Astrocytomas**

- IDHmut – 27% SSTR2A positive
- IDHwt – 23% SSTR2A positive

**Glioblastoma**

- 13% SSTR2/a positive with a patchy staining pattern

**CONCLUSIONS:**

- Positive SSTR2A correlated with longer OS in GII and GIII gliomas
- SSTRA2 IHC shows that imaging may not be a good surrogate marker
- Conclusion: SSTRA2 significantly associated with oligodendroglioma

Noted: IHC with polyclonal antibodies may display cross-reactivity with other antigens resulting in false positive staining. This study used monoclonal antibody UMB-1, which has more robust staining it provides when compared to polyclonal antisera.
Kiviniemi et al. 2017 Conclusions:

Oligodendrogliomas show intense membranous and cytoplasmic SSTR2A expression, which carries potential diagnostic, prognostic, and therapeutic value.

Table 2: Scoring of SSTR2A immunohistochemistry

<table>
<thead>
<tr>
<th></th>
<th>Most common intensity</th>
<th>Highest intensity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Glioblastoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>IDH</em>-wildtype (n = 93)</td>
<td>90 (97%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td><em>IDH</em>-mutant (n = 3)</td>
<td>3 (100%)</td>
<td>0</td>
</tr>
<tr>
<td>Astrocytoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>IDH</em>-wildtype (n = 22)</td>
<td>19 (86%)</td>
<td>2 (9%)</td>
</tr>
<tr>
<td><em>IDH</em>-mutant (n = 37)</td>
<td>24 (65%)</td>
<td>5 (13.5%)</td>
</tr>
<tr>
<td>Oligodendroglioma</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>IDH</em>-mutant and 1p/19q-codeleted (n = 19)</td>
<td>4 (21%)</td>
<td>1 (5%)</td>
</tr>
</tbody>
</table>

Abbreviations: C cytoplasmic, M membranous.
Receptor expression study in astrocytic brain tumors - Lange et al. 2018

- Reviewed 57 brain tumors in FFPE samples from 54 patients using rabbit monoclonal antibodies
  - Grade I – 1 pt; II – 8 pts; III – 25 pts; IV – 20 patients
  - SST5 present in 84% of tumors; 2.1
  - SST2 in 25 and 21% of cases

- SST2 expression was lower in GBM IV
  - SST5 expression increased with increasing grade
  - SST2 present on tumor micro vessels in 37%; SST3 in 44% and SST5 in 96%
Whereas SST2 and SST3 expression was again lower in grade IV tumors, SST5, CXCR4 and ETA expression further increased with increasing WHO grade.

IDH-1 mutation negatively was associated with higher amount of SST5-positive tumor capillaries (24/24, 100%).

Tumor Microvessels
SST2: 37%
SST3: 44%
SST5: 96%

Panels: Receptor Expression
(A) SST2
(B) SST3
(C) SST5
(D) CXR4
(E) Endothelin receptor A (ETA)
(F) Ki-67

“Indirect targeting of these highly vascularized tumors via SST3, SST5, CXCR4 or ETA on the microvessels, in contrast, may represent a promising additional therapeutic strategy.”
CONCLUSION: Receptor Studies

- Gliomas have SSTRs
- Although controversy exists in the literature, it appears that more modern studies conclude that SST2s are more abundant in lower-grade gliomas, like oligodendrogliomas
- It appears that GBMs have little or no SST2 receptors
- SSTR5 on tumor micro vessels may be a potential target for higher-grade tumors
4 Steps to Validating a Radiopharmaceutical For Clinical Use

(1) Prove the tumor contains targetable receptors ✓
(2) Prove that the therapeutic has the desired effect in animal models
(3) Use a radioactive tracer to show that tumors have the desired target
(4) Conduct a human clinical trial
Step 2

- Radiation is the “therapeutic” in the radiopharmaceutical.
  - Radiation is effective at killing glioma cells in both animal models and clinical trials
  - Radiotherapy remains standard care for all gliomas after surgery
4 Steps to Validating a Radiopharmaceutical For Clinical Use

1. Prove the tumor contains targetable receptors
2. Prove that the therapeutic has the desired effect in animal models
3. Use a radioactive tracer to show that tumors have the desired target
4. Conduct a human clinical trial
Step 3

• Radioactive tracer imaging is possible with PET/ CT with Ga-DOTA peptides
• However, there are some challenges with this approach
Kivniemi et al 2015 set to prospectively study potential of 68Ga-DOTANOC and 68Ga-DOTATOC to target SSTR2 in HGGs and to detect HGGs suitable for PRRT in vivo

- 27 patients with HGG were prospectively enrolled
- PET/ CT with Ga-DOTA peptides was performed prior to surgical resection
- SSTR2 IHC scored
  - Positive in 38% - 8 anaplastic gliomas, 1 glioblastoma with oligodendroglioma component
  - Negative in 68% - 6 anaplastic gliomas, 13 GBM

No Correlation with SUVmax or BP was found

- 7/8 HGGs with no 68Ga-DOTA-peptide uptake were classified as SSTR2 positive; 17/19 HGGs with tracer uptake were classified as SSTR2 negative.
- SSTR5 not detected
- All HGG with uptake demonstrated disrupted BBB. No uptake seen in intact BBB
Challenges with Imaging, Kivniemi et al 2015

- 68Ga-DOTA-peptide uptake in high-grade gliomas does not correspond to SSTR2 immunohistochemistry

- Additionally, STTR2 IHC corresponded with IDH1 mutation, lower tumor grade, and oligodendroglioma component.

- Median PFS for SSTR2-positive and SSTR2-negative HGGs was 60.9 versus 10.9 months, respectively.
Conclusions Kivniemi et al 2015:

- SST-based imaging is feasible
- However, no correlation between SST2 expression on tumor cells and SST-based imaging could be demonstrated
- Thus, PET/CT shows limited value to detect HGGs suitable for PRRT.
- These findings correspond to previous studies
  - Note: There is correlation in meningiomas
Why is this the case?

- It is possible that DOTA- peptides may cross-interact with SST5.
- DOTA- peptides may bind to SSTs expressed on tumor capillaries.
- In HGG, 68Ga-DOTA-peptides is associated with disrupted BBB.
Challenges with Imaging and Drug Delivery

- Gadolinium 68, Yttrium 90 and Lutetium 177 are chelated to Octreotide, Octreotate, NaI3-Octreotide
  - (synthetic somatostatin analogs)
  - DOTATOC is very affine for SSTR2 and more moderate for SSTR5
  - **DOTATATE is specific to SSTR2**
  - DOTANOC binds with great affinity to SSTR2, SSTR3, and SSTR5
Challenges with Permeability of the BBB

- Y, Ga, or Lu - DOTATOC, DOTATATE, and DOTANOC are molecules that use octreotide to bind to SSRs
- Octreotide is a polar, water soluble peptide.
- For this reason, it must be presumed they may only penetrate tumors with a disrupted BBB for tumors within the brain parenchyma, such as GBM
- Note: this is not the case for meningioma, which is located outside the BBB
4 Steps to Validating a Radiopharmaceutical For Clinical Use

(1) Prove the tumor contains targetable receptors

(2) Prove that the therapeutic has the desired effect in animal models

(3) Use a radioactive tracer to show that tumors have the desired target

(4) Conduct a human clinical trial
Gliomas

- Step 4
  - With regard to gliomas, encouraging results have been reported in three pilot studies investigating treatment with $^{90}$Y-DOTATOC in progressive grade II–IV gliomas.
  - Locoregional delivery to circumvent BBB; no planer diffusion detected.
  - Procedure was clinically demanding.
Challenges with Drug Delivery
Challenges with Drug Delivery

Strategies to enhance general pharmacokinetics and BBB penetration

A successful strategy to bypass the BBB is loco-regional compound injection or convection enhanced delivery (CED). This is possible because 95% of GBs manifest as a unifocal lesion that recurs within a 2 cm margin at the primary site.

Most clinical RIT studies for malignant gliomas were performed via local administration
1999 - Merlo et al.

Locoregional Regulatory Peptide Receptor Targeting with the Diffusible Somatostatin Analogue 90Y-Labeled DOTA0 -D-Phe1-Tyr3-octreotide (DOTATOC): A Pilot Study in Human Gliomas

11 patients on pilot study that had progression despite other therapies

7 LGG

4 anaplastic glioma

The radiopharmakon was injected into a stereotactically inserted Port-A-Cath

• 370-3300 MBq, equivalent to 60 +/-15 and 550 +/-110 Gy

• Activity injected in 1-4 fraction

Abstract:
Human gliomas, especially of low-grade type, have been shown to express high-affinity somatostatin receptor type 2 (L-C. Bentel et al., Am. J. Radiol. 185: 537-544, 1995). We studied seven low-grade and four anaplastic gliomas patients in a pilot study using the diffusible peptide vector 90Y-labeled DOTATOC (D-Phe1-Tyr3-octreotide) for receptor targeting. The pharmacokinetics was measured in a stereotactically inserted Port-A-Cath. DOTATOC complexed specifically with somatostatin binding to somatostatin receptor type 2 in the low nanomolar range as shown by a displacement curve of 90Y(Tyr3)octreotate in human serum. Diagnostics led to the labeled DOTATOC scintigraphy following local injection depicting homogeneity to similar intratumoral uptake distribution. The cumulative activity of locally injected peptide-bound 90Y accounted for 770-3300 MBq, which is equivalent to an effective dose range between 0.15 and 550 +/-110 Gy. Activity was injected in one to four fractions according to tumor volumes. 1110 MBq 90Y-labeled DOTATOC was the maximum activity per single injection. We obtained no side effects, no stimulation and shrinking of a cyclic low grade astrocytoma component. The only toxicity observed was secondary intellectual decline. The activity dose ratio (MBq/Gy) represents a measure for the (86Rb) uptake in the regions of interest. The a 90Y-labeled peptide D-Phe1-Tyr3-octreocodep (DOTATOC) can be evaluated in phase I clinical trials. The radiopharmakon was injected into a stereotactically inserted Port-A-Cath.
Gliomas

- Merlo et al. RESULTS
- 6 disease stabilizations and shrinking of low grade astro component
- Only toxicity was perifocal edema
- Study says that DOTATOC has high affinity binding to SR-2 in low nanomolar range
- In 1 patient, vector diffused across corpus callosum
Gliomas

- Merlo et al. RESULTS
- Responses appear to directly correlate with a given tumor’s SR status as calculated by the activity: dose ratio – can be regarded as quantitative in vivo measure for peptide binding.
- Patients with a ratio of >>5 MBq/Gy are not likely to benefit from this approach

Fig. 4  Tumor uptake of $^{111}$In-labeled DOTATOC (images 1–6) and marked reduction of perifocal enhancement after $^{90}$Y-labeled DOTATOC treatment (images 7–12) in oligoedendroglialoma patient CM (Table 1). The cranial scintigram after i.v. injection is shown as compared with direct intratumoral (images 5–6) stereotactically guided administration at denoted time points. Coronal gadolinium-enhanced, T1-weighted MRI prior to (images 7–9) and after (images 10–12) local injection of 2405 MBq of $^{90}$Y-labeled DOTATOC shows complete vanishing of perifocal edema. The effective dose was 550 ± 110 Gy, and the activity-dose ratio was 4.4 MBq/Gy. Steroid medication had been stopped 4 months before the control MRI.
Merlo et al. Conclusions

Targeting SRs with locoregionally administered 90Y-labeled DOTATOC has the potential to become a therapeutic option for SR-positive solid and cystic gliomas, especially of low-grade type.

In a future controlled trial, it will be mandatory to monitor residual tumor during therapy, for instance by positron emission tomography using the positron emission tomography-tracer 86Y.

For most glioblastomas displaying reduced expression of SR, more specific receptor-ligand systems need to be developed.
Local injection of the 90Y-labelled peptidic vector DOTATOC to control gliomas of WHO grades II and III: an extended pilot study


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Abstract. We have previously presented preliminary observations on targeting somatostatin receptor-positive malignant gliomas of all grades by local injection of the radiolabelled peptidic vector \(^{90}\text{Y}\)DOTATOC. We now report on our more thorough clinical experience with this novel compound, focusing on low-grade and anaplastic gliomas. Small peptidic vectors have the potential to target invisible infiltrative disease within normal surrounding brain tissue, thereby opening a window of opportunity for early intervention. Five progressive gliomas of WHO grades II and III and five extensively debulked low-grade gliomas were treated with varying fractions of \(^{90}\text{Y}\)DOTATOC. The vectors were locally injected into the resection cavity or into solid tumour. The activity per single injection ranged from 555 to 1,375 MBq, and the cumulative activity from 555 to 7,030 MBq, according to tumour volumes and eloquence of the affected brain area, yielding dose estimates from 76±15 to 312±62 Gy.

Response was assessed by the clinical status, by serial brain conventional and diffusion-weighted magnetic resonance imaging, and by fluorine-18 fluoro-deoxyglucose positron emission tomography. In the five progressive gliomas, lasting responses were obtained for at least 13–45 months without the need for steroids. Radiopeptide brachytherapy had been the only modality applied to counter tumour progression. Interestingly, we observed the slow transformation of a solid, primarily inoperable anaplastic astrocytoma into a resectable miliary lesion 2 years after radiopeptide brachytherapy. Based on these observations, we also assessed the feasibility of local radiotherapy following extensive debulking, which was well tolerated. Targeted beta-particle irradiation based on diffusable small peptidic vectors appears to be a promising modality for the treatment of malignant gliomas.

Keywords: Gliomas – Peptidic receptor targeting – Ytrium-90 labelled octreotide – Local injections

Introduction

Survival in glioma patients correlates well with tumour grade on the WHO grading system and the cell lineage-specific differentiation pathway [1]. Only the rare pilocytic astrocytomas of WHO grade I are curable by surgery alone. Gliomas of grades II–IV displaying astrocytic, oligodendrocytic or mixed phenotypes are characterised by relentless tumour cell infiltration and variable growth rates, yielding, in the most favourable case with oligodendrocytic differentiation, a mean survival of 4–8 years [2]. Survival differences and response to therapy are genetically regulated, for instance by distinct expression of genes like the DNA-repair gene MGMT [3], which may be silenced during cellular differentiation in some precursor cells [4]. Nowadays, the prevalent glioblastomas are managed aggressively in most centres even though long-term survival is rarely achieved [5]. There is, however, no consensus on how best to treat low-grade gliomas which manifest at a younger age, and clinical decisions are made case by case on an individual basis [6, 7].
Local Injection of the 90Y-labeled peptidic vector DOTATOC to control gliomas of WHO grades II and III

- 5 progressive WHO II and III Gliomas and 5 extensively debulked (10 total) LGG were treated with varying fractions of Y DOTATOC
- Vectors locally injected into resection cavity or into solid tumor

**Abstract.** We have previously presented preliminary observations on targeting somatostatin receptor-positive malignant gliomas of all grades by local injection of the radiolabeled peptidic vector 90Y-DOTATOC. We now report on our more thorough clinical experience with this novel compound, focusing on low-grade and anaplastic gliomas. Small peptidic vectors have the potential to target invisible infiltrative disease within normal surrounding brain tissue, thereby opening a window of opportunity for early intervention. Five progressive gliomas of WHO grade II and III and five extensively debulked low-grade gliomas were treated with varying fractions of 90Y-DOTATOC. The vectors were locally injected into the resection cavity or into solid tumor. The activity per single injection ranged from 555 to 1,475 MBq, and the cumulative activity from 555 to 7,039 MBq, according to tumor volumes and eloquence of the affected brain area, yielding dose estimates from 76±15 to 312±62 Gy.

**Keywords.** Gliomas – Peptidic receptor targeting – Yttrium-90 labeled octreotide – Local injection

**Introduction.** Survival in glioma patients correlates well with tumour grade on the WHO grading system and the cell lineage-specific differentiation pathway [1]. Only the rare pilocytic astrocytomas of WHO grade I is curable by surgery alone. Gliomas of grades II-IV displaying astrocytic, oligodendroglial or mixed phenotypes are characterised by relentless tumour cell infiltration and variable growth rates, yielding, in the most favourable case with oligodendrocytic differentiation, a mean survival of 8.8 years [2]. Survival differences and response to therapy are genetically regulated, for instance by distinct expression of genes like the DNA-repair gene MGMT [3], which may be silenced during cellular differentiation in some precursor cells [4]. Nowadays, the prevalent glioblastomas are managed aggressively in most centres even though long-term survival is rarely achieved [5]. There is, however, no consensus on how best to treat low-grade gliomas which manifest at a younger age, and clinical decisions are made case by case on an individual basis [6, 7].
The activity per single injection ranged from 555 to 1,875 MBq, and the cumulative activity from 555 to 7,030 MBq, dose estimates from 76±15 to 312±62 Gy.

**RESULTS**

- In 5 progressive gliomas, lasting responses were obtained for 13-45 months without need for steroids.
- Slow transformation of solid primarily inoperable anaplastic astrocytoma into resettable multicystic lesion 2 years after therapy.

### Table 1. Clinical data and response rates in glioma patients treated with $^{90}$Y-DOTATOC brachytherapy

<table>
<thead>
<tr>
<th>Patient location</th>
<th>Age</th>
<th>Histology</th>
<th>Previous therapy</th>
<th>KPS (pre-/post-brachytherapy)</th>
<th>Autoradiography</th>
<th>Toxicity (WHO grades I-IV)</th>
<th>Response</th>
<th>Progression-free survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Progressive disease</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. f.R</td>
<td>31, M</td>
<td>AII</td>
<td>Seed, S</td>
<td>80/80</td>
<td>NA</td>
<td>None</td>
<td>R</td>
<td>+45</td>
</tr>
<tr>
<td>2. f.L</td>
<td>42, F</td>
<td>OAII</td>
<td>RT, S</td>
<td>70/60</td>
<td>ND</td>
<td>pN(II)*</td>
<td>R</td>
<td>+33/+38</td>
</tr>
<tr>
<td>3. f.L</td>
<td>35, M</td>
<td>AIII</td>
<td>B</td>
<td>90/90</td>
<td>(+)</td>
<td>pN(II)*</td>
<td>R</td>
<td>+28</td>
</tr>
<tr>
<td>4. f.R</td>
<td>36, F</td>
<td>AIII</td>
<td>S, RT, Ch</td>
<td>100/100</td>
<td>ND</td>
<td>None</td>
<td>R</td>
<td>+13/25</td>
</tr>
<tr>
<td>5. f.R</td>
<td>65, F</td>
<td>aOIII</td>
<td>S</td>
<td>100/100</td>
<td>(+)</td>
<td>None</td>
<td>R</td>
<td>24**</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Radical resection</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>6. p.L</td>
</tr>
<tr>
<td>7. f.R</td>
</tr>
<tr>
<td>8. f.R</td>
</tr>
<tr>
<td>9. f.L</td>
</tr>
<tr>
<td>10. f.L</td>
</tr>
</tbody>
</table>

---

*ND, Not done; NA, not assessable; (+), low to moderate somatostatin receptor density; (+), weak staining
*N, Neurological; p, permanent; t, transient; *p-pre-existing neurological deficit
*SD, Stable disease; R, response defined as halting of tumour progression, see Materials and methods
*+, Alive; ** non-tumour-related death (heart attack)
RESULTS

- 7 of 10 were evaluated with in vitro receptor autoradiography; all seven had tumor tissue
- Tumor progression stopped for 13-45 months for all 5 patients with symptomatically expanding LGG and anaplastic types
- Conclusion: Targeted beta-particle irradiation based on diffusible small peptidic vectors appears to be a promising modality for the treatment of malignant gliomas.
  - SSRS are prerequisite; in brain tumors a clear distinction between receptors in normal brain and tumor cannot be made
  - Controlled trial is needed
• 3 patients with recurrent GBM (after initial standard of care) were treated with Y labeled DOTATOC
  - Starting 1-2 months after tumor recurrence, Injection done via subcutaneous reservoir
  - 1,660–2,220 MBq of 90Y-DOTATOC were given in 3 or 4 fractions at an interval of 3–4 months

Results
• After treatment MRI and PET showed CR in 1 and PR in 2
• Improvement of QOL
• KPS improved 10-40% of cases
TABLE 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age (y)</th>
<th>Sex</th>
<th>Histopathology</th>
<th>Distribution of recurrent tumor</th>
<th>Cumulative dose</th>
<th>Mean dose to tumor tissue*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>24</td>
<td>F</td>
<td>Glioblastoma, grade IV</td>
<td>Circular, around cavity</td>
<td>2,220 MBq (4 cycles)</td>
<td>38 Gy/GBq</td>
</tr>
<tr>
<td>2</td>
<td>61</td>
<td>M</td>
<td>Glioblastoma, grade IV</td>
<td>Irregular, with occipital focus</td>
<td>1,950 MBq (3 cycles)</td>
<td>105 Gy/GBq</td>
</tr>
<tr>
<td>3</td>
<td>62</td>
<td>M</td>
<td>Glioblastoma, grade IV</td>
<td>Irregular, regional, and invasive</td>
<td>1,660 MBq (3 cycles)</td>
<td>150 Gy/GBq</td>
</tr>
</tbody>
</table>

*Calculated by individual dosimetry with $^{111}$In-DOTATOC.

TABLE 2. Results

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>MRI evaluation</th>
<th>Improvement in Karnofsky performance score</th>
<th>Change in $^{18}$F-FDG PET SUVmax during therapy</th>
<th>Change in maximum $^{18}$F-FET uptake relative to contralateral background</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No recurrent tumor tissue</td>
<td>60% – 100%</td>
<td>13.5–2.6 g/mL</td>
<td>1.07–1.3</td>
</tr>
<tr>
<td>2</td>
<td>Necrosis in target volume</td>
<td>70% – 80%</td>
<td>6.8–5.3 g/mL</td>
<td>3.2*</td>
</tr>
<tr>
<td>3</td>
<td>Necrosis in target volume</td>
<td>60% – 80%</td>
<td>7.3 g/mL*</td>
<td>2.0–2.9</td>
</tr>
</tbody>
</table>

*Follow-up data not available.

SUV$_{max}$ = maximum standardized uptake value; FET = fluoroethyltyrosine.
• A – T1 MRI showing diminishing contrast
• B – Ga-DOTATOC PET
• C – F-FDG EPT
• D – MRI and F fluoethyltyrosine PET

**FIGURE 1.** Response of high-grade glioma to local therapy with cumulated 2.2-GBq dose of $^{90}$Y-DOTATOC, given in 3 cycles (from left to right: study before therapy, control study 3 mo after second dose, control study 3 mo after third dose, and control study 23 mo after third dose). (A) T1-weighted enhanced MR images show diminishing contrast agent in tissue surrounding resection cavity throughout therapy. (B) $^{68}$Ga-DOTATOC PET images representing somatostatin receptor status show increased tracer uptake around resection cavity before therapy and normalization in control studies. (C) $^{18}$F-FDG PET images show highly increased glucose metabolism at rim of tumor cavity before therapy and diminishing uptake after therapy. (D) T1-weighted unenhanced MR image before therapy shows previously implanted reservoir system well positioned in resection cavity in left parietal lobe. Follow-up images ($^{18}$F-fluoroethyltyrosine PET) show that ratio of uptake per pixel was lower in region adjacent to tumor cavity than in contralateral region, giving no evidence of residual or relapsing tumor.
Results and Conclusions

- All 3 pts with improved QOL,
  - 2 returned to work
  - 1 with 4 year OS, other 2 died of progression 10-12 months later
- First application in recurrent high grade glioma
- Receptor- mediated radionuclide therapy by locally injected 90Y-DOTATOC is feasible and well tolerated. This approach represents an attractive strategy for the treatment of locally recurring or progressing glioblastoma.
- “Major disadvantage of local chemotherapy is limited penetration into the tumor. This limitation does not apply to local injection of 90Y-DOTATOC, because after diffusion into the tissue and binding of the compound to the receptor, the b-particles reach even 5–10 mm beyond the point of decay.”
4 Steps to Validating a Radiopharmaceutical For Clinical Use

(1) Prove the tumor contains targetable receptors ✓
(2) Prove that the therapeutic has the desired effect in animal models ✓
(3) Use a radioactive tracer to show that tumors have the desired target ~ ✓
(4) Conduct a human clinical trial ✓
2022 – where are we today?

- Several Radiopharmaceuticals have been studied in human trials for Gliomas:
  - **Iodine-131**
    - Several studies showing tolerability, including a Phase I/II trial of 111 patients with diverse malignant gliomas
  - **Yttrium-90**
    - Several studies beyond those mentioned, including safety and efficacy shown in 73 recurrent GBM patients
  - **Rhenium-188**
    - Single Phase I dose escalation study with maximum tolerated dose of 370 MBq
  - **Lutetium-177**
    - Single GBM case
  - **Astatine-211**
    - Single study involving 18 patients
  - **Bismuth-213**
    - Several small studies (up to 20 patients)
  - **Actinium-225**
    - Several small studies
  - **Iodine-125**
    - Phase II Clinical Trials
2022 – Future Perspectives

• Radiopharmaceutical therapy can be considered as treatment for recurrent gliomas or in addition to standard therapy

• Radiopharmaceuticals offer new possibilities for personalized treatment for patients with gliomas

• Molecules are needed that overcome physiologic barriers, such as BBB penetration, tumor diffusion, and intracellular accumulation

• Well-designed, randomized, and multi-centered clinical trials are needed to establish ideal management
SUMMARY - Learning Objectives

(1) Describe radiopharmaceuticals in preclinical and clinical development in neuro-oncology
(2) Outline challenges of radiopharmaceuticals in neuro-oncology