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CLINICAL STUDY - PATIENT STUDY

# Neoadjuvant targeting of glioblastoma multiforme with radiolabeled DOTAGA–substance P—results from a phase I study

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**Abstract** Complete surgical resection beyond tumor margins cannot be achieved in glioblastoma multiforme (GBM) because of infiltrative nature. In several cancers, neoadjuvant treatment has been implemented to reduce the risk of tumor cell spreading during resection. In GBM, the objective of a neoadjuvant approach is reduction of tumor cells within the main tumor mass and beyond in the infiltration zone. Such an approach can only be performed if elevated intracranial pressure can be medically controlled. In a previous study with recurrent gliomas, we showed that local intratumoral injection of radiolabeled DOTAGA–substance P substantially inhibited further growth and led to radionecrotic transformation of the tumor (CCR 2006). We have now examined this modality as neoadjuvant treatment for GBM, primarily assessing feasibility, toxicity, the extent of resection, and functional outcome. After diagnosis of GBM, 17 patients were included in a prospective phase I study. Repetitive intratumoral injections of radiolabeled DOTAGA–substance P were performed, followed by surgical resection. Chemical synthesis, radiolabeling, and local injection of the peptidic vector [90Yttrium]-DOTAGA–substance P were described previously. Neoadjuvant injection of [90Y]-DOTAGA–substance P was feasible without decompensation of intracranial pressure. Prolonged application of corticosteroids was identified as the main risk factor for side effects. Fifteen patients stabilized or improved their functional status. The mean extent of resection in subsequent surgery was 96%. Neoadjuvant therapy of GBM using locally injected radiolabeled DOTAGA–substance P was feasible and of low toxicity. The high extent of resection and concomitant irradiation of tumor cells in the infiltration zone may be prognostically relevant.

**Keywords** Glioblastoma multiforme · Targeted therapy · Radiopeptides · Neurokinin receptors · Substance P · Yttrium-90

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## Purpose

Malignant gliomas continue to be a therapeutic challenge because the prognosis of gliomas has not significantly improved over recent decades [1]. Median survival in highly proliferative glioblastoma multiforme (GBM) ranges from 10 to 18 months [2–4]. Currently, surgical resection followed by a combination of external beam radiotherapy and chemotherapy [2] is generally accepted as the standard of care for GBM. However, other groups discuss a less aggressive strategy. Ostertag et al. [5] did not find a significant difference in the survival of GBM patients (RTOG classes IV–VI) when treated by surgery and subsequent radiotherapy as compared with biopsy only and subsequent radiotherapy, if there was no significant mass effect.

An essential feature of malignant gliomas is that 95% of these tumors are unifocal lesions that exhibit local recurrence [6]. The extent of resection in malignant gliomas is widely accepted to positively correlate with time to the recurrence of the tumor [7–9], which underscores the

importance of a sufficient local control of the tumor. Currently, several regimens of targeted loco-regional therapy are in development to improve local tumor control. These therapeutic systems are usually locally administered bifunctional molecules that consist of a targeting domain, for example the interleukin-4 or 13 receptors [10, 11] or monoclonal antibodies against tenascin-C [12], and of an effector domain, for example bacterial toxins [13] or radioisotopes [14]. Toxin-delivering conjugates have to target every single tumor cell, whereas radionuclide-based approaches also target receptor-negative tumor cells by the range-dependant crossfire effect [15].

In a previous study we have shown the feasibility and low toxicity of targeting recurrent malignant gliomas with radiolabeled substance P as a second-line treatment [16]. Substance P is the physiological ligand of the transmembraneous neurokinin type 1-receptor (NK1-R) which is consistently overexpressed in malignant gliomas of WHO grade II-IV. NK1-receptors have also been detected on tumor cells infiltrating the intratumoral and peritumoral vasculature [17]. The radiolabeled pharmaceutical 1,4,7,10-tetraazacyclododecane-1-glutaric acid-4,7,10-triacetic acid–substance P (DOTAGA–substance P) has a preserved affinity for the NK-1 receptor in the low nanomolar range. The vector has a low molecular weight of only 1.8 kDa, which is a prerequisite for sufficient and rapid intratumoral distribution following local injection, especially in the critical infiltration zone of the tumor. The targeted second-line treatment as described in our previous study [16] led to a good functional outcome and may also improve survival times. Furthermore, we found tumor resection to be significantly facilitated by better demarcation of the tumor. The fact that tumor vessels also are targeted by this therapy adds another important mode of action, because antiangiogenic therapeutic approaches have repeatedly been shown to exhibit positive therapeutic potential [18–20].

Neoadjuvant therapy is a well-established treatment strategy in different types of cancer, for example neoadjuvant chemoradiation followed by surgery and adjuvant chemotherapy is widely accepted in the treatment of colorectal cancer patients with locally advanced tumors [21, 22]. Different neoadjuvant approaches have also been introduced for the treatment of breast cancer [23, 24]. Improved local control of the tumor and treatment of systemic tumor burden are regarded as the main mechanisms responsible for the positive impact of neoadjuvant therapy.

High-grade gliomas as brain-intrinsic neoplasms differ from other malignancies in several aspects:

1 The location of the tumor in a closed cavity carries the risk of a symptomatic increase of the intracranial pressure because of further tumor growth or peritumoral edema.
2 The surgical principle to perform the resection beyond a safety margin cannot be applied to this highly infiltrative type of tumor which often involves functionally important areas of the brain. In addition, glioma cells infiltrating the surrounding brain tissue cannot be reliably detected by contemporary imaging studies.
3 Systemically administered chemotherapy reaches the cerebral compartment only to a limited extent, because of the blood–brain barrier. Reduced intratumoral drug concentration because of the blood–brain barrier and inherent chemoresistance lead to limited efficacy [25].
4 Hypoxia and an acidotic milieu of the intratumoral and peritumoral microenvironment reduce the efficacy of radiation and chemotherapy. Elevated interstitial fluid pressure induces a heterogeneous blood flow, leading to highly variable distribution of systemically administered drugs and represents an additional barrier against an efficient drug distribution [26].

In this paper we present the results of 17 GBM patients who were treated with radiolabeled substance P as the primary therapeutic modality followed by surgical resection. The main idea behind the local targeted neoadjuvant therapy with radiolabeled substance P is to optimize the achievable extent of resection and reduction of the spreading of tumor cells during resection. An additional factor may be the targeting of tumor cells in the infiltration zone. Primary endpoints of the study are the feasibility and toxicity of this approach. Secondary endpoints are the extent of resection assessed by comparison of preoperative tumor volumes and postoperative residual tumor volumes. The functional outcome of the patients was assessed by use of the Barthel index.

## Patients and methods

### Patients

The clinical data of the study patients are summarized in Table 1. The study protocol as displayed in Fig. 1 was approved by the Ethics Committee of the University Hospitals of Basel. Patients were evaluated weekly for the first two months and thereafter according to the course of the disease. Functional status was assessed by use of the Barthel index [27]. Before inclusion, informed consent was obtained.

### Inclusion criteria

Newly diagnosed and histopathologically confirmed GBM, maximal tumor diameter 7 cm, unifocal lesion, no evidence for obstruction of CSF circulation or decompensating intracranial pressure, Karnofsky performance score of 50 or higher, age 18–75 years, informed consent.

**Table 1** Patients included in the study

| Patient no. | Age at diagnosis (years), sex | GBM location | Cycles/ cumulative dose (mCi) | Extent of resection (%) | Barthel index [d] (pre/post) | Post-op. adjuvant therapy | Progression free survival (months) | Overall survival (months) |
|---|---|---|---|---|---|---|---|---|
| *GBM study patients* | | | | | | | | |
| 1 | 43, m | t, L | 4/120 | 90 | 100/100 | SP, RT, CH | 9 | 18 |
| 2 | 69, m | f, L | 4/120 | 90[b] | 80/70 | SP | 7 | 10 |
| 3 | 61, f | p, L | 4/120 | [c] | 50/60 | r/s | [c] | 15 |
| 4 | 66, f | f, L | 2[a]/100 | 95 | 90/100 | RT, CH | 5 | 16 |
| 5 | 59, f | po, L | 3/170 | 97 | 100/100 | SP, CH | 7 | 10 |
| 6 | 74, f | f, L | 3/180 | 99 | 80/80 | s | 6 | 8 |
| 7 | 64, m | po, L | 4/210 | 98 | 100/100 | SP | 8 | 10[e] |
| 8 | 63, m | t, R | 4/240 | 100 | 85/100 | SP | 21 | 23 |
| 9 | 50, f | po, R | 4/240 | 98 | 100/100 | SP | 12 | 19 |
| 10 | 54, f | f, L | 4/345 | 100 | 75/90 | SP, CH | 8 | 13 |
| 11 | 55, m | po, R | 4/120 | [c] | 90/90 | r/s | [c] | 6 |
| 12 | 60, m | po, L | 0[a]/– | 100 | 100/100 | RT, CH | 23+ | 23+ |
| 13 | 34, f | ft, R | 2/140 | 98 | 100/100 | RT, CH | 5 | 18+ |
| 14 | 32, f | p, R | 1/100 | 97 | 100/100 | RT, CH | 17+ | 17+ |
| 15 | 67, m | t, L | 1/100 | 95 | 100/100 | RT, CH | 11+ | 11+ |
| 16 | 60, m | t, L | 2/240 | 100 | 80/80 | RT, CH | 9+ | 9+ |
| 17 | 54, m | t, L | 2/240 | 89 | 80/90 | RT, CH | 7+ | 7+ |

f, frontal; t, temporal; po, parieto-occipital; L, left; R, right; SP, intracavitary radiolabeled substance P; RT, external beam radiotherapy; CH, temozolomide chemotherapy; r, refusal; s, supportive care

[a] Obstruction of catheter system

[b] No complete resection intended

[c] Refusal of follow-up and imaging studies

[d] Examination at diagnosis and after neoadjuvant radiopeptide therapy

[e] Death due to intracerebral hemorrhage

## Exclusion criteria

Previous treatment of the glioma, low-grade glioma or anaplastic glioma, concurrent malignant neoplastic disease, inability to give informed consent.

## Study protocol

### *Week 1*

Stereotactic biopsy, intratumoral implantation of 1–3 catheter systems in case of confirmation of GBM in a fresh frozen section. Catheter systems (Fig. 2) were stereotactically placed within the tumor margins, usually at the site of assumed prognostically relevant further tumor spread. The number of implanted catheter systems depended on the size and configuration of the tumor. Local test injection for confirmation of positive expression of binding sites and evaluation of intratumoral dose distribution was performed with [111Indium]-DOTAGA–substance P.

### *Weeks 2–5*

Intratumoral injection of [90Y]-DOTAGA–substance P at weekly intervals. Cumulative injected activities were in the range between 120 mCi and 345 mCi with an increase of the dose in the course of the study (dose escalation). Corticosteroid medication was administered throughout the pre-OP treatment protocol.

### *Week 7*

Surgical resection of the tumor. MRI scan within 72 h for assessment of the extent of resection.

### *Follow up*

MRI scan every six weeks; clinical evaluation every 4–6 weeks after resection of the tumor; clinical evaluation weekly during application of radiopeptides.

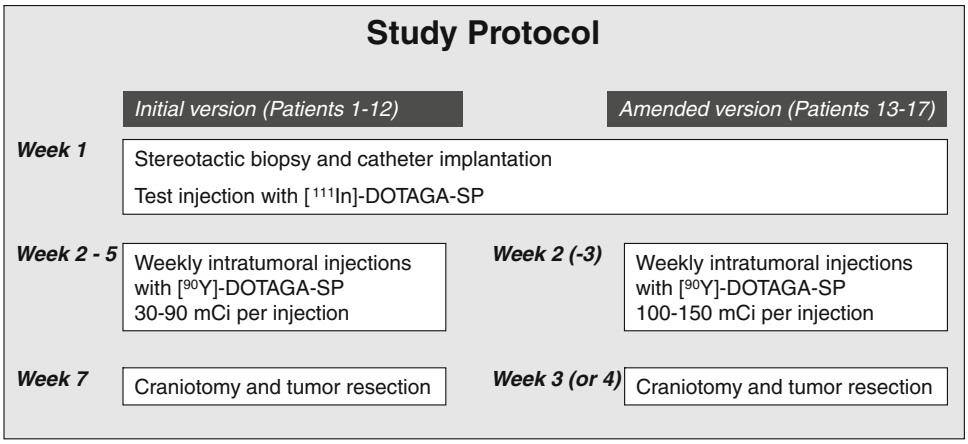


**Fig. 1** Study protocol for neoadjuvant application of [90Y]-DOTAGA–substance P

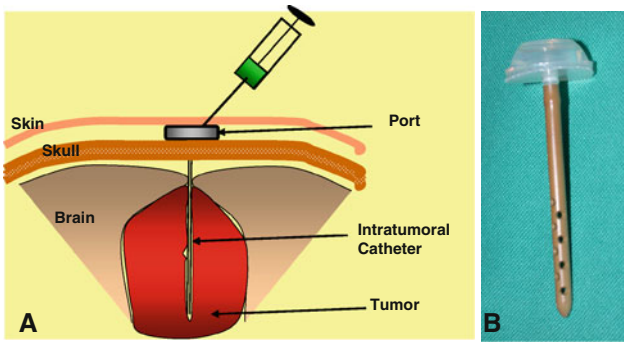


**Fig. 2** Intratumoral catheter system. **a** Schematic drawing of implanted catheter system. **b** Catheter system, consisting of a bottom outlet port capsule and a connected standard intraventricular catheter

*Postoperative treatment*

According to the patient's wish, continuation of radiopeptide therapy after the resection or standard treatment with external beam radiotherapy and/or chemotherapy.

Approved amendment of the treatment protocol after 12 patients: Shortening of the protocol from four preoperative injections to only one or two injections with a minimum injected dose of 100 mCi preoperatively.

Radioconjugates

For the synthesis, radiolabeling, and preparation of the peptidic vector 1,4,7,10-tetraazacyclododecane-1-glutaric acid-4,7,10-triacetic acid-substance P see Kneifel et al. [16].

Injection of the radiopharmaceutical [28–30]

Preparation of the patient with 12 mg dexamethasone and, immediately before injection, 60 g of the osmodiuretic drug mannitol for transient reduction of the intratumoral pressure. Before injection of the active compound, the system is flushed with 1.5 ml 5% human albumin to coat the plastic surface. Thereafter the active drug is injected in a volume of 0.5–1.5 ml. Finally, the system is flushed again with 1.5 ml 5% human albumin. Usually patients stayed in the hospital for the day of injection and the subsequent day.

Evaluation of binding sites and dose distribution [31]

Each patient was injected with 1 MBq [111Indium]-DOTAGA–substance P as a test injection before the first therapeutic cycle. The biodistribution was followed by SPECT/CT performed 0, 6, 24, and 30 h after injection. Therapeutic activity was administered only if a localized orthotopic dose distribution within the tumor could be observed, i.e. no dose deposition outside the tumor margins visible on CT scan. Images were acquired on a dedicated SPECT/CT system (SYMBIA T2; Siemens, Malvern, PA, USA). Four time points were chosen to prove the stable binding of the radiopharmaceutical within the tumor.

Estimation of the extent of resection

The chosen modality for imaging was magnetic resonance imaging (MRI); calculation of tumor volumes was performed by using the contrast enhanced T1-sequence. The tumor area was defined as the area of significant contrast media enhancement, the perifocal edema was not included in the calculation. Tumor volumes were calculated by using the workstation of a commercially available neuronavigation system (BrainLab, Germany).

## Results

Seventeen patients with GBM were included in this study as presented above (Table 1). The treatment was well

tolerated by all patients without acute toxicity or side effects. The preliminary GBM diagnosis from the fresh frozen sections was confirmed by definite histology in all cases. Positive NK-1 receptor expression was demonstrated by the test injection with [111In]-DOTAGA–substance P (Fig. 3a) in all patients included in the study. The dose distribution of the test injection was congruent with the tumor morphology in all cases, with an expected dose decline towards the tumor periphery. This effect is because of the three-dimensional spatial distribution of the substance with a decrease in tissue concentration with increased distance from the site of injection.

In eight patients four injections were performed in accordance with the initial study protocol. Patient 4 had craniotomy and tumor resection after only two injections because of obstruction of the catheter system, because implantation of a new catheter system with consecutive test injection would have added at least one more additional week to the treatment protocol. In patient 5 and 6 the protocol was shortened to three preoperative injections only because of increasing signs of corticosteroid administration (weight gain). After successful test injection in patient 12, an obstruction of the catheter system was noted. According to the patient's wish in a difficult familial situation, tumor resection was performed without implantation of a new catheter and without neoadjuvant pretreatment. In the remaining five patients, the neoadjuvant treatment protocol was shortened to only one or two injections with an increase of the injected dose per treatment cycle for avoidance of long-term corticosteroid medication.

During the high-dose beta-irradiation performed in this study, we did not see signs of increasing or decompensating intracranial pressure in our patients. Another observation during surgery of these pretreated tumors was that resectability was found to be markedly facilitated by pseudoencapsulation of the tumor accompanied by reduced intraoperative bleeding. Pseudoencapsulation as observed in this study simply describes the intraoperative finding that the tumor is surrounded by a capsule-like structure that can be better dissected from the surrounding cerebral tissue than in conventional glioma surgery. A non-pretreated malignant glioma intraoperatively appears as an ill-defined mass. The peripheral zone of tumor infiltration can often not be distinguished from surrounding brain parenchyma. Increasing the administered activity revealed that higher doses lead to a better and more circumferential demarcation of the tumors. Patient 10 received the highest dose in this series and exhibited complete encapsulation of the tumor (Fig. 3c). Increasing the doses remained without relevant side effects possibly attributable to high dose irradiation, as, for example, a critical increase in perifocal edema.

At craniotomy, the extent of tumor resection achieved was in the range between 90 and 100% (statistical mean 96.6%, SD 3.4) in the 13 patients relevant for evaluation. In 11 out of these 13 patients the extent of resection was at least 95%. Patient 4 may serve as an illustrative case for the radiological findings before and after the operation, including a CT-SPECT-fusion image displaying the dose distribution at the second therapeutic intratumoral injection (Fig. 3d–g). Four patients were not included in evaluation of the extent of resection: patient 2 was not intended for a

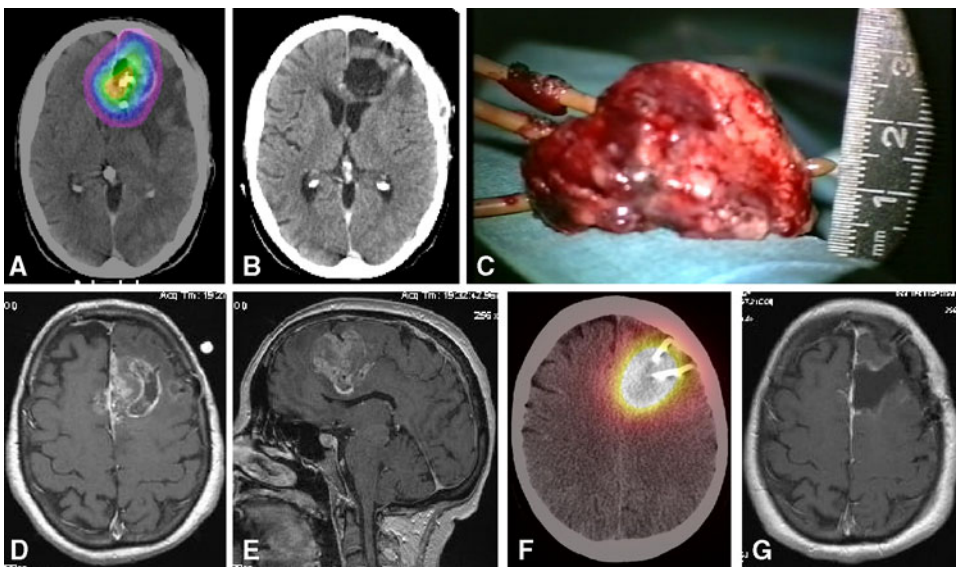


**Fig. 3** **a–c**: Patient 10: **a** Dose distribution as assessed by CT-SPECT at the pretherapeutic intratumoral test injection. **b** Contrast-enhanced postoperative CT-scan. **c** En bloc removal of the GBM after internal decompression. Note the capsule-like surface of the resected tumor. The three catheter systems have been left in situ as anatomical landmarks. **d–g** Patient 4: (**d**, **e**) Large left frontal GBM in preoperative T1-weighted and contrast-enhanced MR imaging. (**f**) Dose distribution by CT-SPECT at the second therapeutic intratumoral injection. (**g**) T1-weighted and contrast-enhanced MR imaging after resection of the tumor

full resection because of his precentral, functionally critically located tumor; patients 3 and 11 refused any further diagnostic workup after uneventful surgery because of severe depression (patient 3) and anosognosia (patient 11). Patient 12 did not receive the neoadjuvant treatment because of an obstructed catheter system (see above).

Functional status was evaluated using the Barthel score [27]. Initial scores were >80 in 10 out of the 16 patients relevant for evaluation (excluding patient 12), being consistent with no or minor restrictions in everyday-life activities. After neoadjuvant treatment, nine out of these 10 patients reached a score of 100. The remaining six patients exhibited scores between 50 and 80. Two of these improved by 10 points and one by 15; one worsened by 10 points during neoadjuvant treatment; two remained stable (Table 1).

The postoperative adjuvant treatment of the patients was adapted to the patients' wishes and was planned interdisciplinarily (Table 1).

Side effects and adverse events: In the early postoperative phase, patient 16 developed a small dehiscence of the cranial wound. Local purulent outflow prompted MR imaging, which was suggestive of an epidural and subdural abscess. The operative revision confirmed this diagnosis, the infection was treated with antibiotics according to the bacterial resistance. In the follow-up six months after resection of the tumor, patient 8 exhibited a local CSF-fistula in this late postoperative phase because of a wound-healing problem. Ten months after diagnosis, patient 7 developed an acute intracerebral hemorrhage adjacent to the resection cavity within a zone of local tumor recurrence. The patient refused further treatment and rapidly deteriorated. The cause of this hemorrhage could not be clarified by autopsy which was declined. Most likely, the hemorrhage originated from local tumor regrowth.

Administration of corticosteroids over the preoperative neoadjuvant phase led to weight gain in patients 5 and 6. This prompted patients 5 and 6 to stop further local injections after three therapeutic cycles and move on to surgery.

No other substantial acute local or systemic toxicity could be attributed to radiopeptide therapy according to the NCI CTC toxicity scale (Version 2.0). In the long-term follow-up, no further relevant local or systemic toxicity could be found.

## Discussion

Although the treatment of malignant gliomas is still controversial, local tumor control is considered to be an important aspect of treatment. The loco-regional therapeutic system developed by our group consists of radiolabeled substance P, which is a low-molecular-weight compound of only 1.8 kD. According to our experience, these small drug-like peptidic vectors rapidly distribute within the target site and can cross midline structures to bind to contralateral tumor cells within less than 1 h, as shown previously [28]. This may be an advantage of small peptidic vectors in comparison with pharmaceuticals with a higher molecular weight, e.g. monoclonal antibodies or immunotoxine conjugates.

By analogy with successful neoadjuvant therapy against other types of cancer, our objectives are to reduce and demarcate the main tumor mass and to target tumor cells in the adjacent area of tumor cell infiltration before surgery. As a hypothesis, better demarcation should lead to less tumor cell spread during surgery and a higher extent of resection. Furthermore, targeting cells in the infiltration zone of the tumor could carry the potential to prolong the time to tumor recurrence. Based on our previous experience with adjuvant radiopeptide therapy, we have set up a neoadjuvant treatment protocol. This regimen includes repetitive intratumoral injections with radiolabeled substance P followed by subsequent resection of the tumor. Neoadjuvant therapy has so far not been implicated in the therapeutic algorithm for malignant gliomas, because such a preoperative procedure always requires a period of time before definite tumor removal. According to a widely accepted view among neurosurgeons, a large space-occupying mass ought to be rapidly debulked to reduce increased intracranial pressure. The need for immediate aggressive therapy is, however, not generally accepted. Ostertag et al. [5] did not find a significant difference in the survival of GBM patients (RTOG classes IV–VI) when treated by surgery and subsequent radiotherapy compared with biopsy only and subsequent radiotherapy, if there was no significant mass effect. For this reason, we did not include patients with signs and symptoms of decompensating intracranial pressure. Concerning this specific aspect, in this study we showed that neoadjuvant therapy is feasible. In the patients treated so far, we did not observe signs of decompensating intracranial pressure either caused by further tumor growth or increased perifocal edema following local high-dose beta-irradiation. To the contrary, patients often improved after intratumoral radiopeptide injections. One problem, however, is prolonged dependence on corticosteroids with the risk of secondary Cushing's syndrome. This risk can potentially be minimized by reducing the number of treatment cycles and by increasing the target dose per treatment cycle, as was done in the course this study. Such intensified treatment algorithms have been successfully applied in stereotactic radiosurgery. A rare treatment-related problem in stereotactic radiosurgery is late manifestation of cerebral edema, usually after a few months [32–34]. This delayed phenomenon should not be relevant in our treatment strategy, because patients are operated on before reaching the critical time point.

At the time of resection after neoadjuvant pretreatment, these diffusely growing tumors were found to be demarcated by a pseudocapsular structure. The resection of the tumors was markedly facilitated, more resembling an "enucleation" after circumferential microsurgical dissection (Fig. 3c) than conventional glioma surgery. Intraoperative bleeding was also found to be markedly reduced, most probably resulting from the fact that tumor cells attach to and grow along vascular structures which are effectively irradiated by the so called crossfire effect of the beta-particle emitting radionuclides. We expect that these improvements will lead to a spatially more exact and more complete removal of the tumor. This is an important aspect, because a higher extent of resection has been shown to positively correlate with a prolonged time to recurrence [8] and possibly overall survival [9]. In this study we observed a mean extent of resection of 96%, which compares well with other contemporary techniques with the objective of optimization of the extent of resection, for example by using 5-aminolevulinic acid [8] or intraoperative MRI [35, 36]. A substantial advantage of radiopeptide therapy using small-drug like diffusible vectors may be the additional targeting of the tumor-infiltrated marginal zone.

Because survival times are very limited in patients with malignant gliomas, quality of life becomes a fundamental issue. In the patients treated so far we saw stabilization or even improvement of neurological status in 15 out of 16 patients. The hospital stay for every neoadjuvant therapeutic cycle is currently two days and has the potential to become an ambulatory procedure. Concerning toxicity, we mainly have to face the side effects of steroid medication during neoadjuvant treatment. In the patients treated by the abbreviated amended protocol, we did not observe significant weight gain or the development of Cushing's stigmata.

## Conclusion

Neoadjuvant therapy is a well established oncological strategy in several types of cancer. As an innovative therapeutic strategy in neuro-oncology, neoadjuvant local treatment of malignant gliomas using the peptidic vector [90Y]-DOTAGA–substance P could be shown to be feasible. By achieving a high extent of resection and additional targeting of tumor cells in the infiltration zone, this method carries the potential to prolong the time to recurrence and to improve the overall outcome in respect of survival times and quality of life.

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