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REVIEW ARTICLE - TUMOR - GLIOMA

Intracavitary radioimmunotherapy of high-grade gliomas: present status and future developments

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Abstract

There is a distinct need for new and second-line therapies to delay or prevent local tumor regrowth after current standard of care therapy. Intracavitary radioimmunotherapy, in combination with radiotherapy, is discussed in the present review as a therapeutic strategy of high potential. We performed a systematic literature search following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA). The available body of literature on intracavitary radioimmunotherapy (iRIT) in glioblastoma and anaplastic astrocytomas is presented. Several past and current phase I and II clinical trials, using mostly an anti-tenascin monoclonal antibody labeled with I-131, have shown median overall survival of 19–25 months in glioblastoma, while adverse events remain low. Tenascin, followed by EGFR and variants, or smaller peptides have been used as targets, and most clinical studies were performed with I-131 or Y-90 as radionuclides while only recently Re-188, I-125, and Bi-213 were applied. The pharmacokinetics of iRIT, as well as the challenges encountered with this therapy, is comprehensively discussed. This promising approach deserves further exploration in future studies by incorporating several innovative modifications.

Keywords Intracavitary radioimmunotherapy · Locoregional therapy · Glioblastomas · High-grade gliomas · Malignant gliomas

Introduction

Owing to its local invasive nature, glioblastoma (GBM) remains an incurable disease and median overall survival (OS) with 14.6 months remains disappointingly low [98, 99]. Novel therapies, ranging from immunotoxins, administered via convection-enhanced delivery [53, 66], anti-angiogenic strategies [20], gene therapy [74, 105] to boron neutron capture therapy [93, 107], have so far failed phase III evaluations. Only a new approach adding tumor-treating fields to maintenance temozolomide chemotherapy significantly prolonged median OS by several months [99]. However, progression is still inevitable and new efficient treatment concepts to further delay local recurrence are desperately needed.

Neurosurgical local therapies as treatment option

Almost all tumor recurrences develop in close adjacency to the resection cavity (RC) [5, 8, 64], indicating that strategies aiming at selectively improving local tumor control may be therapeutically effective. Photodynamic therapy using the endogenous heme precursor 5-aminolevulinic acid (ALA) is one such method [51, 96, 97]. Other approaches were implantation of Gliadel wafers into the RC [16, 104], radiosurgery and brachytherapy to focally escalate the radiation dose

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[19, 21], immunotoxins, administered via convection-enhanced delivery [53, 66], or local gene therapy [74, 105], but results were not or only slightly superior to current standard radiochemotherapy.

Intracavitary radioimmunotherapy (iRIT) is a relatively new local therapeutic approach to delay or even prevent the development of local tumor regrowth. By applying the radioconjugate directly into the postoperative resection cavity (RC) via an Ommaya reservoir, the blood-brain barrier is bypassed, allowing the application of higher local radiation doses than with systemic application, while sparing radiation-sensitive organs in the periphery. Consequently, iRIT is well-tolerated and hematological, renal, and neurological adverse events remain moderate and well controllable [12, 22, 38, 80, 83, 89, 90]. Favorable effects have been observed in clinical iRIT trials suggesting a marked prolongation of median overall survival in patients with GBM and anaplastic astrocytoma [38, 80, 83, 90]. Cell surface receptors/antigens of glioma cells can be used as molecular targets while specifically engineered monoclonal antibodies (mAbs), Fab-fragments, or small peptides can serve as carriers, labeled with a radionuclide, to deliver a therapeutic quantity of radiation to remaining tumor cells.

Here, we performed a systematic review of the available literature to determine the status quo of radioimmunotherapy as a basis for further development of this method.

Literature search with Preferred Reporting Items for Systematic Review and Meta-analysis

We conducted our search according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement [61, 62]. We searched for studies in MEDLINE (Suero Molina E), published until 1 May 2018, where intracavitary radioimmunotherapy in high-grade gliomas was evaluated. The following terms were used to search for title and abstract: "intracavitary" and "radioimmunotherapy", together with "gliomas", "high-grade gliomas", "glioblastoma", and "malignant glioma". We selected studies evaluating intracavitary radioimmunotherapy in high-grade gliomas. Endnote X7 (Thomson Reuters, Carlsbad, CA, USA) was used to assist the search of relevant articles (Fig. 1).

The search resulted in 233 articles. After removing non-relevant articles and duplicates ($n = 119$) and non-English/German articles ($n = 5$), abstracts from 109 articles were screened for relevance. After thorough evaluation and excluding articles that did not evaluate intracavitary radioimmunotherapy ($n = 40$) or were not performed on gliomas ($n = 24$), we identified 46 articles for full-text evaluation and included 40 in our qualitative synthesis. These comprised seven ($n = 7$) preclinical [10, 11, 14, 39, 41, 42, 101] and 25 clinical articles [2, 3, 6, 7, 13, 17, 18, 37, 38, 59, 67, 71, 72, 77, 83–88, 90, 91, 100, 106], as well as eight ($n = 8$) reviews of the literature [25, 26, 40, 75, 79, 81, 103, 108].

Previous experiences with iRIT in high-grade gliomas

In this section, results of clinical studies with I-131-labeled anti-tenascin mAbs as well as with several other antibodies and radionuclides are summarized [18, 23, 25] (see Table 1).

Tenascin as target

Tenascin-C (TN) is an extracellular matrix glycoprotein which is highly expressed by 80–90% of glioblastomas, whereas it is only barely detectable in normal brain tissue [43, 55, 102]. Expression in GBM is confined to the extracellular matrix and proliferating vessels, while tumor cells do not show TN-immunopositivity [55]. In adults, immunopositivity is also found in the liver, kidney, spleen, and papillary dermis [49]. It was shown for tenascin-C that different mAbs (BC1, BC2, BC4, BC24, 81C6, F16, P12) bind to epitopes at different domains of the tenascin-C structure and they may exhibit different immunoreactivities [75, 79].

Two different concepts of application of the radioimmunocomplex (RIC) have been used so far, as a *single dose* or by *fractionated delivery*. Riva et al., one of the promoters of this locoregional concept, used *repeated doses* of 30–55 mCi (1110–2035 MBq) I-131-labeled anti-tenascin murine BC-2 and BC-4 per cycle in primary and recurrent glioblastoma patients and recorded a median survival of 19.0 months [85, 88, 90]. Reardon et al., using a *single dose* of 120 mCi (4400 MBq) I-131-labeled murine 81C6 mAbs in primary GBM, reported a median survival time of 19.9 months [78]. In all cases, the radioconjugate was labeled with I-131 and applied via a subcutaneously implanted Ommaya reservoir. Prolonged median survival of 18 to 25 months was also reported from other studies [2, 4, 38, 76, 79, 80, 85, 89, 90, 108] (Table 1). In a recent pilot study, in which the single dose of I-131-labeled mAb was adapted to the volume of the RC to achieve a 44-Gy boost to the RC margin, median OS in GBM was 22.6 months [80].

A long-term follow-up after *fractionated* iRIT study with I-131 mAbs denoted a median OS for GBM and AA patients of 25.3 and 77.2 months, respectively, thus markedly exceeding survival of historical control patients, as defined by the Radiation Therapy Oncology Group recursive partitioning analysis (RTOG-RPA) classes. The greatest treatment effect in GBM was observed in RPA classes III and IV with a gain in survival of 13 and 7.5 months, respectively, as compared to RTOG data. The Cox multivariate analysis showed RPA-status—including age—to be the strongest significant prognostic

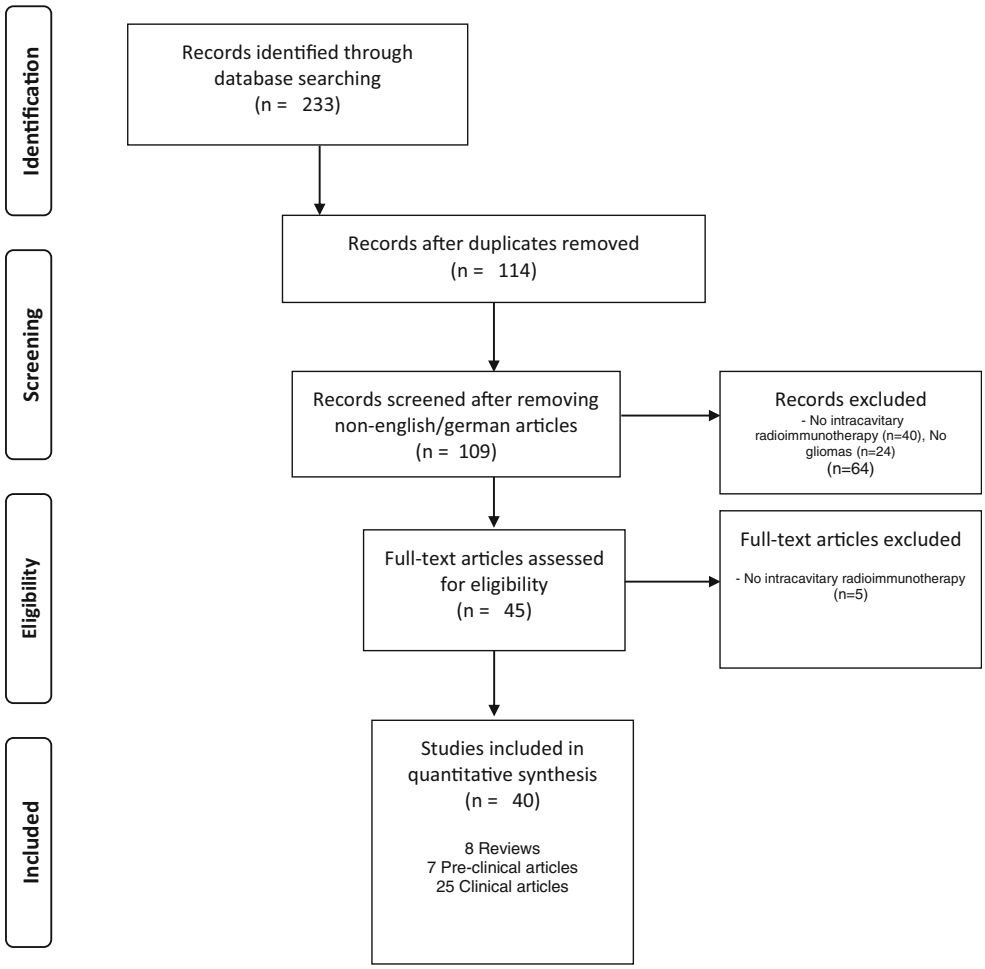

Fig. 1 PRISMA flow diagram. Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) diagram outlining specifics of our systematic literature review

factor for survival. Importantly, IDH1 mutations and the MGMT methylation status were balanced and did not skew results. Five of 15 patients (33%) with anaplastic astrocytoma were alive after a median observation time of 162.2 months [83]. In the above-mentioned studies, iRIT was applied after external radiotherapy (RT) and chemotherapy.

Other targets

Two phase I trials with the EGFR-specific mAb nimotuzumab labeled with 188-Re have been published [18, 101] and a median overall survival of 18.7 months was reported. The use of EGFR (and variants) as a target is restricted by the fact that only 60–80% of high-grade gliomas [56], according to other studies only 50–60% [34, 65] of gliomas, overexpress the molecule.

In several phase I and I/II trials, small regulatory receptor peptides were employed as carrier. Cordier et al. [23] and Kneifel et al. [50] selected neurokinin type 1 receptor (NK1 receptor) as target, substance P (~ 1.8 kDa) as ligand, and Bi-213 as radionuclide. A median OS of more than 20 months was reported after receiving one to seven intracavitary cycles of 1.85 GBq Bi-213 substance P.

In yet another phase I trial, Mamelak et al. [59] investigated I-131-labeled TM-601 (4 kDa), a synthetic version of a scorpion-derived 36-amino acid peptide that binds with high affinity to malignant brain tumor cells and not to normal brain tissue. Immunohistochemistry of the tumor tissues showed intense positive staining for TM-601 in all patients. Coregistration of MRI and SPECT images suggests that by using I-131-TM-601, the extent of tumor infiltration outside of the contrast-enhancing tumor can be reliably estimated [46]. In three reviews, a compilation of various tumor targets and clinically useful monoclonal antibodies and antibody fragments has been listed [29, 34, 54].

Most of the above studies mentioned that patients after radiotherapy and iRIT received chemotherapy, but it was not reported whether this had some influence on survival. However, two trials compared RIT alone with RIT plus adjuvant temozolomide (TMZ): Bartolomei et al. [7] in a prospective study applied intracavitary pre-targeted Y-90 biotin RIT in 38 patients and compared this with a group of 35 patients with additional application of adjuvant TMZ.

Table 1 Clinical phase I and II studies using iRIT for malignant glioma. Application of different antibodies in combination with different nuclides

Authors	No. of pat.	Type of study	Histology	Tumor-assoc. antigen	Antibody	Nuclide	MTD	Median survival or other aim
Papanastassiou et al. 1993 [68]	7	Phase I dos.esc.st.	5 GBM 1 AA 2 OA	NCAM	ERIC-1	131-I	1350–2193 MBq	Not reported dosimetry toxicity
Hopkins et al. 1995 [47, 48]	15	Phase I	Glioma rec.	NCAM	ERIC-1	90-Y	20 mCi	No reported dosimetry
Bigner et al. 1998 [12]	34	Phase I dos.esc.st.	26 GBM rec 3 AA rec	Tenascin (TN)	Anti-tenascin 81C6	131-I	100 mCi	All pat 60 weeks GBM 56 weeks
Riva et al. 1999 [89]	20	Phase I dos esc.st.	18 GBM rec. 2 AA rec.	TN	Anti-tenascin BC2 and BC4	90-Y	25 mCi	Not reported
Riva et al. 1999 [90]	111	20 Phase I 91 Phase II	91 GBM n.d./rec. 10 AA 7 AO 2 grade II	TN	Anti-tenascin BC4	131-I	70–80 mCi	19 months GBM 46 months AA 23 months AO
Akabani et al. 1999 [2]	9	Phase I	9 GBM rec.	TN	Anti-tenascin 81C6	131-I	100 mCi	Not reported, dosimetry
Cokgor et al. 2000 [22]	42	Phase I dos esc.st.	32 GBM, 3 AA, 5 AO, n.d.	TN	Anti-tenascin 81C6	131-I	120 mCi	79 weeks all pt. 69 weeks GBM
Akabani et al. 2000 [3]	42	Phase I dos esc st	32 GBM; n.d. 3 AA, n.d. 7 AO, n.d.	TN	Anti-tenascin 81C6	131-I	120 mCi	69 weeks GBM
Paganelli et al. 2001 [67]	24	Phase I dos escal.	16 GBM 8 AA	TN	Anti-tenascin BC4, avidin/biotin, 3-step pretargeting	^{90}Y-biotinT	25–30 mCi	52 months AA ($n = 8$), 20 months GBM ($n = 16$)
Pöpperl et al. 2002 [72]	12	Phase I/II	8 GBM rec 4 AA rec	TN	Anti-tenascin BC4	131-I	Var. dose	18.5 months all pat.
Goetz et al. 2003 [38]	37	Phase I/II	24 GBM, 13 AA, n.d.	TN	Anti-tenascin BC4	131-I or 90-Y	Var. dose	GBM 17 months
Bartolomei et al. 2004 [7]	73	Phase II	73 GBM rec. 38 pat. RIT 35 pat. RIT + TMZ	TN	BC4, avidin/biotin, 3-step pretargeting	90-Y	Var. dose	17.5 months RIT 25 months RIT + TMZ
Akabani et al. 2005 [4]	33	Phase II n.d.	27 GBM, n.d. 4 AA, n.d. 2 AO, n.d.	TN	Anti-tenascin 81C4	131-I	120 mCi	86 weeks all pat. 79 GBM w
Hockaday et al. 2005 [46]	18	Phase I/II	High-grade glioma rec.	MMP2-receptor	TM-601	131-I	Tumor extension, biodistribution	8.1 months
Kneifel et al. 2006 [50]	20	Phase I/II	14 GBM, 2 AA 4 grade II	NK-1 receptor	Substance P	90-Y or 213 Bi	Var. dose	7–26 months
Reardon et al. 2006 [77]	43	Phase II	33 GBM, 6 AA, 2 AO	TN	Anti-tenascin 81C6	131-I	100 mCi	GBM 64 weeks 99 weeks all pat
Reardon et al. 2006 [78]	47	Phase 3 strata	38 GBM rec. + n.d. 7 AA 2AO	TN	Anti-tenascin ch81C6	131-I	80 mCi	n.d. 88.6 weeks rec. 65 weeks

Table 1 (continued)

Authors	No. of pat.	Type of study	Histology	Tumor-assoc. antigen	Antibody	Nuclide	MTD	Median survival or other aim
Mamelak et al. 2006 [59]	18	Phase I	17 GBM rec 1 AA rec.	MMP2-receptor	TM-601	131-I	Not reported	Not reported
Reardon et al. 2008 [80]	21	Phase II	16 GBM, n.d. 5 AA	TN	Anti-tenascin 81C6	131-I	44 Gy boost to 2cm-rim	90.6 weeks GBM 96.6 weeks
Torres et al. 2008 [100]	9	Phase I	Rec. glioma grade III + IV	EGFr	Anti-EGFR nimotuzumab	188-Re	370 MBq	MS not rep, biodistr., dosim., tox.
Casaco et al. 2008 [18]	11	Phase I	9 GBM, 3AA, recurrent	EGFr	Anti-EGFR nimotuzumab	188-Re	370 MBq	18.7 months all pat
Cordier et al. 2010 [23]	?	Phase I	WHO II–IV	NK-1 receptor	Substance P	213 Bi/ 90-Y	Not reported	Ca. 20 months in GBM
Reulen et al. 2015 [83]	55	Phase II	40 GBM, (n.d.) 15 AA	TN	Anti-tenascin BC4 and BC24	131-I + 90-Y	Var. dose	25.3 GBM 77.2 months AA

GBM glioblastoma, *AA* anaplastic astrocytoma, *AO* anaplastic oligodendroglioma, *TN* tenascin, *NCAM* human neural cell adhesion molecule, *EGFR* epidermal growth factor receptor, *mOS* median overall survival, *n.r.* not reported, *dos esc st* dose escalating study, *n.d.* newly diagnosed, *rec.* recurrent

The median overall survival in the first group was 17.5 months and was significantly prolonged to 25 months in the iRIT + TMZ group.

Li et al. [56], in a long-term phase II observational study, used *systemically* applied I-125-labeled anti-EGFR mAb 425 (3 cycles of 50 mCi, totaling 150 mCi), starting 4–6 weeks after completion of surgery and radiotherapy. Among the 192 patients, 132 were treated with I-125-mAb 425 alone and 60 at a later time were treated with I-125-mAb 425 plus temozolomide. The median survival was 14.5 months (12.1–16.7) in the RIT group and 20.4 months (14.9–25.8) in the RIT plus TMZ group. The authors themselves comment that the study spans over 20 years with several treatment changes and patients were not systematically allocated to the two treatment groups.

Nuclides used in iRIT and their characteristics

A number of radionuclides have been used in iRIT, which differ in physical half-life as well as the maximum energy, range, and type of decay particles (Table 2). For delivery of a sufficiently high absorbed dose, a prolonged effective half-life might be favorable, which is given by a long physical half-life and a slow biological washout, while a nuclide with a very short physical half-life may decay too fast. The optimal maximum range of the therapeutically relevant decay particles (α, β^-) is driven by the disease-specific lesion size. For example, radionuclides characterized by a larger maximum range may be favorable for larger lesions [44]. An additional photon component offers the possibility for in vivo quantification of the whole-body activity or the activity in tumors or risk organs via probe measurements or 2D and 3D quantitative imaging. For example, a γ-component can be used for 2D planar scintigraphy or 3D SPECT imaging. The imaging of Bremsstrahlung is also possible via planar scintigraphy or SPECT; however, the activity quantification is challenging due to the lack of a defined photo-peak [28]. Thus, for Y-90 the imaging of the β^+-component and the subsequent emission of 511-keV-coincidences via PET might be favorable [30].

In summary, the median OS achieved with iRIT is encouraging but has to be interpreted with caution. All studies cited comprised only a limited number of cases and were performed at a single institution, and none of the trials was randomized. A detailed discussion on the issue of selection and small case numbers in phase I and II studies is presented in the "The issue of selection and small patient numbers in phase I and II trials" section.

New experimental developments in iRIT

With the availability of new mAbs [14, 18, 26, 56, 101] or smaller compounds such as peptides and engineered antibody fragments [26, 40] on the one side, and improved radiochemistry on the other, there is revived interest in this promising

Table 2 Nuclides used in iRIT and their characteristics

Nuclide	Half-life (days)	Primary decay (probability)	Maximum energy of primary therapeutic component (keV)	Maximum range of primary therapeutic component in soft tissue (mm)	Possible component for localization/ quantification
Y-90	2.7	β^- (100%)	2280	11.4	Bremsstrahlung, β^+ for PET
I-125	59.4	EC (100%)	32 (via Auger electrons)	< 0.0005	γ (35 keV 7%)
I-131	8.0	β^- (100%)	971	4.2	γ (364 keV 81%)
Lu-177	6.6	β^- (100%)	498	1.7	γ (208 keV 10% and/or 113 keV 6%)
Re-188	0.7	β^- (100%)	2120	10.6	γ (155 keV 28%)
Bi-213	0.03	β^- (98%); α (2%)	1423; 5869 (1.9%)/5549 (0.1%)	7.1; < 0.1	γ (440 keV 26%)
Ac-225*	9.9	α (100%)	5800	< 0.1	γ (218 keV 12% and/or 440 keV 26%)

EC electron capture

*Decays to Bi-213

http://www.nucleide.org/DDEP_WG/DDEPdata.htm

approach. Consequently, Lu-177 and Ac-225 served as radionuclides in a number of recent experimental studies, which are summarized in Table 3 [10, 41, 42].

Other delivery modalities of RIT in high-grade gliomas

Systemic delivery

In a few trials, radioimmunoconjugates (RICs) were delivered by intravenous injection. Li et al. [56], in the above-mentioned study (see "Other targets" section), compared 132 patients treated with I-125-mAb 425 alone with 60 patients treated with I-125-I-mAb plus temozolomide. The median survival was 14.5 months (12.1–16.7) in the RIT group and 20.4 months (14.9–25.8) in the RIT plus TMZ group. The authors themselves mention that during the long span, over 20 years, many treatment changes and advancements have taken place [15, 56].

Wygoda et al. [106] compared radiotherapy alone (10 patients) versus radiotherapy plus intravenous (eight patients) administration of anti-EGFR-I-125-mAb 425) in patients with grades III and IV glioma. RIT was given parallel with RT and started not later than 8 weeks after surgery, repeated three times with 1-week interval and a total dose of 5026 ± 739 MBq/patient. The median OS was ca. 14 months (range 3.5–28 months) in both groups and there was no improvement in disease-free or OS in the group of patients treated by RT + systemic RIT. The immunohistological analysis of tumor tissues indicated the presence of EGFR in only ca. 70% of both GM and AA. The authors, therefore, recommended for future anti-EGFR RIT trials to confirm individually the presence of EGFR expression prior to treatment.

Reasons for the limited effect of *systemically* applied RIT may be that only a small fraction of the given activity dose was able to cross the blood-brain barrier and to reach tumor cells.

Convection-enhanced delivery

Convection-enhanced delivery (CED) is yet another method to bypass the BBB for locoregional delivery of RICs. After

Table 3 Preclinical experimental models

Authors	Type of study	Tumor	Aim	Tumor-associated antigen	Antibody	Radionuclide
de Santis et al. 2006 [27]	Exper	Glioma xenograft	Biodistribution affinity of carrier to tumor	Tenascin	Anti-tenascin ST2146biot	I-125
Veeravagu et al. 2008 [101]	Exper	Glioma xenograft	Biodistribution	Abegrin	Integrin alpha V beta 3	Y-90
Hens et al. 2009 [41]	Exper	Glioma xenograft	Labeling of chelator	L8A4	Anti-EGFvIII	Lu-177
Hens et al. 2010 [42]	Exper	Glioma xenograft	Labeling of chelator	L8A4	Anti-EGFvIII	Lu-177
Beckford et al. 2013 [9]	Exper	Tumor xenograft	Bifunctional chelating	EGFR- and HER2/c-neu	Trastuzumab	Lu-177/Y-90
Behling et al. 2016 [10]	Exper	Glioma model	Biodistribution	E4G10	Anti-VEC	Ac-225
Fiedler et al. 2018 [33]	Exper	Glioma xenograft	Biodistribution	CA 12	6A10-fabs	Lu-177

stereotactic placement of one to three catheters at the target site, intraparenchymal infusion is generated by means of a syringe pump at a low positive pressure of 10–18 mmHg. Pressure-dependent convection may account for 6–9 mm propagation per hour in linear distance and distributes a drug in a larger tissue volume.

Safety and feasibility of CED of an I-131-labeled chTNT-1/B mAb were examined in 51 patients with histologically confirmed malignant glioma (45 GBM, 6 AA). I-131-chTNT-1/B mAb (Cotara®) is a genetically engineered chimeric monoclonal antibody that binds specifically to an intracellular antigen (i.e., DNA/histone H1 complex) and delivers a cytotoxic dose of radiation to the core lesion and the invasive portion of the tumor. The RIC was infused over either 1 or 2 days and the total activity administered was 1.25–2.5 mCi/cm^3, depending on the tumor volume. Single-photon emission computed tomographic imaging was used to determine the spatial distribution of the RIC. Drug-related neurologic adverse events included brain edema (16%), hemiparesis (14%), and headache (14%). Systemic adverse events were mild and most of the symptoms improved with adequate treatment. Several patients had objective MRT responses and the median OS was 37.9 weeks [40, 69, 95]. In 2012, a proposed phase III study design was agreed on with the FDA, but this trial does not seem to have progressed [34].

To evaluate the potential of CED in diffuse intrinsic pontine glioma, an experimental study in rats and two primates examined safety and feasibility of CED with an anti-glioma monoclonal antibody 8H9, labeled with the positron emitter I-124, following slow infusion into the pons. PET analysis in rats and primates yielded a pontine-absorbed dose of 3.7 Gy/mCi and 3.8 Gy/mCi, respectively. The mean volume of distribution (Vd) was 0.14 cc in the rat and 6.2 cc in primate. No toxicity was observed in primates [58]. No corresponding clinical study has been published so far.

Despite its potential efficacy, it appears that technical challenges such as catheter placement, volume of distribution, shielding, as well as catheter-related complications, will limit the widespread use of intraparenchymal radioimmunotherapy, delivered by CED, in glioma therapy.

Pharmacokinetics of intracavitary RIT in humans

The pharmacokinetics of intracavitary administered I-131- or Y-90-labeled anti-tenascin mAb, Re-188-labeled-nimotuzumab, and I-131-labeled TM-601 have been extensively studied and will be reviewed in the following sections.

Residence time in the resection cavity

After a single intracavitary administration of 100 mCi (3700 MBq), the estimated total absorbed dose to the cavity interface was between 290 and 3200 Gy and the estimated total absorbed dose to the adjacent 2-cm rim was 16–65 Gy. The wide range may be explained by the variance in cavity volume [2, 3]. The time-activity curve for the resection cavity and the whole body, generated from the serial gamma camera images, was published by Akabani et al. [2] and by Torres et al. [100]. The median residence time (biological half-life) of the I-131 radioconjugate in the RC averages between 79 and 111 h [2, 3, 59, 71, 79, 80], as compared to the physical half-life of I-131 of 8.04 days. When using Re-188-anti-EGFR mAb, a shorter biological half-life of 22.7 ± 8.9 h was reported [18, 100]. It seems that in the latter study, no leakage test and exclusion of patients with a significant leakage has been performed and this would explain the short biological half-life. When using a carrier with smaller size (TM-601, MW = 4 kDa), the median residence time for I-131-TM-601 was 70–80 h (32–193 h) [59]. Cavity retention times were not reported for substance P, a very small carrier (~ 1.8 kDa) labeled with Bi-213 [23, 50]. Altogether, this indicates a median retention time within the cavity of at least 3–5 days. Samples taken from the RC showed a stable radioimmunoconjugate—I-131-labeled anti-tenascin mAb—at least for 5 days [71]. In vitro testing of the radiochemical stability of another conjugate - 177Lu- CHX-A″-DTPA-6A10 Fab showed stability greater than 90% over a period of 72 h and 86% after 96 h in CSF and in plasma [32].

Accumulation of activity in the cavity margin

Conceptually, due to the slow migration of the RIC through brain tissue surrounding the RC, long-lasting stability of the radioimmunocomplex and a high binding affinity to the tumor target are required.

After injection of I-131-labeled anti-tenascin mAb, a significant accumulation of activity in the 2-cm tissue margin of the RC and even beyond was observed, in particular when edema was present [4, 18, 59, 80]. In patients with and without edema, the activity concentration in the 2-cm margin was about 26% and 5% ($p < 0.05$), respectively, of the activity in the RC [2, 89]. Akabani et al. calculated the dose absorbed by the 2-cm RC margin as 46–51 Gy (range 25–116 Gy) after a single intracavitary injection of 120 mCi [2, 4]. With intracavitary application of 10 mCi I-131 and TM-601 as carrier, the median biologic half-life in the RC margin was nearly the same as that within the RC and was longer than that in other organs [59]. Similar retention in the RC margin was described for Re-188 nimotuzumab [18, 100]. Thus, the majority of the administered radioactivity stayed tightly localized to the RC

and surrounding tissue, for several days which is important for the therapeutic effect [59].

Considering the prior external beam therapy with 60 Gy, Akabani et al. emphasized that patients who received an absorbed dose to the 2-cm margin of more than 44 Gy were more likely to develop radionecrosis, whereas patients who received less than 44 Gy were more likely to develop recurrent tumor [2].

Mechanism of migration of the RIC

For optimal therapeutic efficacy, the RIC should target tumor cells which have migrated away from the RC margin into the brain tissue. For this reason, calculation of the absorbed dose in the 2-cm margin is of relevance. Akabani et al. have estimated the absorbed dose in the RC-adjacent brain based on the concept that the activity remains predominantly within the RC [2, 3]. Hopkins et al. expanded this concept by considering migration of the RIC from the RC into the surrounding tissue by diffusion along the concentration gradient between the tumor cavity and the surrounding tissue [47, 48]. Diffusion depends on the size of the compound, the concentration gradient, the diffusion coefficient, and the width and tortuosity of the extracellular space [1, 39, 81, 82]. Diffusion may account for migration of 0.15–0.5 mm/h linear distance in normal and edematous tissue for whole antibody molecules [1, 39, 47, 82] and is faster for fragments [36, 37].

In principle, by increasing the concentration gradient, the diffusion depth of the RIC may be extended. However, this is limited by the activity doses absorbed in the most adjacent ring of the tumor cell-bearing cuff of tissue, probably surpassing the critical threshold of brain tissue tolerance and resulting in neurological deficits. Thus, to reach a tumor cell-destroying dose at a distance of 2 cm from the RC, a compromise has to be found between a high-concentration gradient and a tolerable dose in the inner ring. Using smaller compounds with a higher diffusion coefficient is another way to improve the distance of diffusion. This can be accomplished by using smaller Fab fragments (MW approx. 55 kD) instead of the complete antibody (MW approx. 150 kD). The use of very small conjugates with extremely rapid diffusion may result in a too rapid transit into CSF and loss via capillaries. So far, the optimal tumor target and respective carrier have not yet been defined.

Transition of the RIC into the blood

It became apparent that a limited transition of activity into the bloodstream is inevitable. Papanastassiou et al. noticed a maximum blood activity of 15% of the injected dose 48 h post-injection [68], and this was confirmed by Torres et al. [100]. After intracavitary administration of 100 mCi of I-131-labeled 81C mAb, the radioactivity concentration of I-131 in blood is characterized by an exponential uptake phase followed by an exponential clearance phase (Fig. 2b). The time-activity clearance for the whole body follows the functional form of a serial two-compartment model (Fig. 3).

When applying Re-188 nimotuzumab, blood activity showed a peak already at 5–8 h after RIT administration. It seems that in this study, no leakage test and exclusion of patients with a significant leakage has been performed, thus explaining the early blood activity peak. Unfortunately, blood activity time curves were not reported for studies with small peptides as carriers [23, 50, 59].

Activity concentrations in organs

Following intracavitary administration of I-131-labeled anti-tenascin mAb, the activity values in critical organs like the kidneys and liver reached maximum levels of 4–6% of the injected dose 6–48 h post-injection [2, 18, 59, 68, 100]. I-131 activity concentrations as a function of time after intracavitary injection have been published for the thyroid, liver, and spleen [2] (Fig. 2). In a study using TM-601 as carrier [46, 59], it was stated that organ doses for the kidneys, the liver, and the bone marrow remained safely below the critical thresholds [31, 92], which is in line with previous reports [2, 4].

Excretion

According to Casaco et al., about 6.2 ± 0.8% ID was excreted during the first 48 h post-administration via the urinary pathway. It seems that urine is the main clearance pathway of the radiolabeled compound [18, 100].

Challenges encountered so far with iRIT and future developments

The issue of selection and small patient numbers in phase I and II trials

Most of phase I and phase II studies are nonrandomized and consist of a limited case number and often a selected patient group. This may render validation of results difficult with regard to OS. The RTOG-RPA classification is a method developed to overcome this problem by obtaining homogenous subsets of patients and compare survival in these subsets with data from the large RTOG-RPA database. Only one group in their RIT phase II study used RTOG-RPA classification of GBM patients by RPA classes III, IV, and V and described

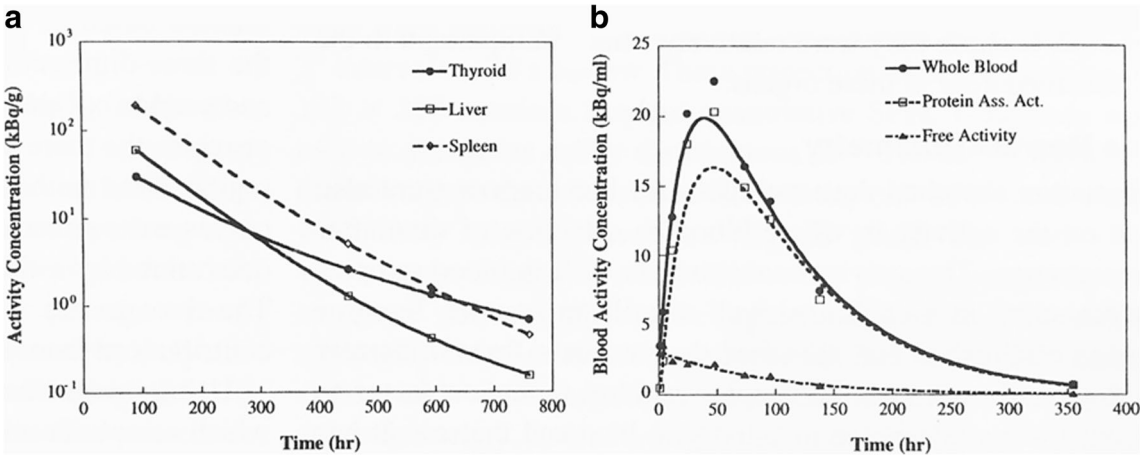

Fig. 2 **a** I-131 activity concentration in the thyroid, liver, and spleen as function of time post-injection. Data points denote whole-body imaging performed immediately after patient's discharge from isolation and 1, 2, and 3 weeks afterward. Quantitative SPECT imaging was used to assess activity concentrations in organs in which imaging was quantifiable. Data were extrapolated to $t = 0$ to assess total absorbed dose. **b** Measured activity concentration in blood for I-131 as function of time after administration of 3700 MBq (100 mCi) I-131-labeled 81C6 (From Akabani et al. [2])

median OS of 31.1, 18.9, and 14.5 months, respectively ($p = 0.004$) [83], which compared favorably with the RTOG database results [24, 57] as well as with the control and even the treatment arms of the Stupp trial [60] and the ALA study [70] (Table 4).

Two phase II studies on iRIT [4, 80] have published individual data of all patients on age and KPS, which allows a retrospective stratification on the basis of these two prognostic factors. Unfortunately, neurologic function and mental status were not reported in these studies. The Reardon study [80] compares best with RPA class III. In the Akabani study [4] with newly diagnosed GBM, the recalculated results fit approximately to RPA classes III and IV. Although such recalculation must be interpreted with caution, both studies compare favorably with regard to median OS and the 1- or 2-year survival with the RPA database [24, 57] and the control group in the study of Mirimanoff [60] and Pichlmeier [70].

The encouraging but still preliminary results represent an incentive to undertake a larger randomized trial. We recommend that future phase I and II studies should include RPA classification to enable statistical adjustment for imbalances in prognostic factors and selection bias. Also, molecular marker analysis (MGMT promoter methylation and IDH1 mutation status) was not performed in the initial studies, as these methods were not yet available. In a more recent study, MGMT and IDH1 were analyzed retrospectively. Both markers were balanced equally between the treatment groups and did not skew results [83]. Future studies should include analysis of such markers as they may significantly influence prognosis.

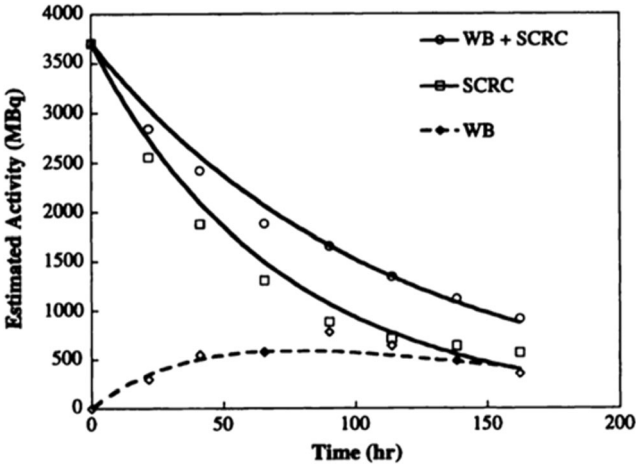

Fig. 3 Estimated time-activity clearance for the whole body (WB) and surgically created resection cavities SCRC. Difference between WB + SCRC and SCRC activities represents net activity in whole body. As expected, time-activity clearance for WB follows functional form of serial two-compartment model. This is corroborated from blood sample data obtained after I-131-81C6 administration (from Akabani et al. [2])

Amount of activity administered into the RC

In most previous studies [2–4, 7, 21, 33, 34, 41, 45, 52, 58, 66, 67, 73, 74, 76, 91], the administered radioactivity into the RC was the same among all patients. Thus, the administered activities were not adjusted for RC volumes or residence times, resulting in a wide range of doses absorbed to the 2-cm margin of the RC. In future studies, the amount of activity administered into the resection cavity has to be adjusted to compensate for the varying volumes of the RC and for the RC residence time to obtain the same radiation absorbed dose to the 2-cm margin of the RC in all patients. A 44-Gy boost to the 2-cm RC margin seems to be an optimal dose, considering that patients had received prior standard radiotherapy with 60 Gy [80]. Patient-specific dosimetry offers the possibility for improved therapy response and the protection of risk organs (e.g., healthy brain structures, kidneys, liver, and bone

Table 4 Results of various GBM studies stratified by RTOG-RPA classes

Author	*n*	M/F	Median OS (months)			1-year survival (%)			2-year survival (%)		
			RPA III	RPA IV	RPA V	RPA III	RPA IV	RPA V	RPA III	RPA IV	RPA V
Li et al. [57]	1669	n.a.	17.1′	11.2′	7.5′	70%	46%	28%	n.a.	n.a.	n.a.
Curran et al. [24]	1672	1053/619	17.9′	11.1′	6.5′	n.a.	n.a.	n.a.	35%	15%	5%
Mirimanoff et al. [60]											
RT alone	286	175/111	15.0′	13.0′	9.0 ′	n.a.	n.a.	n.a.	20%	11%	6%
RT + TMZ	287	185/102	21.4′	16.3′	10.3′	n.a.	n.a.	n.a.	43%	28%	17%
Pichlmeier et al. [70]											
incompl.res.	122	79/42	16.3′	11.8′	10.4%′	n.a.	n.a.	n.a.	21.45′	4.4%′	2.6%′
complete res.	121	74/48	19.9′%	17.7′%	13.7%′	n.a.	n.a.	n.a.	29.1%′	21.0%′	11.1%
Reulen et al. [83]	40	22/18	31.1	18.9	14.5	98.8%′	76.5%′	71.4%′	68.8%′	35.3%′	0%
Reardon et al. [80]	15	12/3′	22.7′	n.a.	n.a	72%	n.a.	n.a.	n.a.	n.a.	n.a.
Akabani et al. [4]	27	18/9′	28.0′	18.7′	n.a.	91%	63%	n.a.	n.a.	n.a.	n.a.

marrow). By using an appropriate radionuclide with a small gamma component, i.e., Lu^{177}, SPECT imaging can be applied for dosimetry estimations.

Figure 4 illustrates an example of estimated dose profiles for Lu^{177}-Fab in proximity to the RC border by applying different parameters R0 to the diffusion model described in Hopkins et al. [47, 48]. R0 characterizes the magnitude of diffusion, i.e., a low R0 indicates slow diffusion and vice versa. Without or with only minimal diffusion, the dose profile in the tissue falls steeply as a function of the distance from the cavity border, while with increasing diffusion values, the dose profile becomes shallower and the cuff of tissue exposed to a certain dose threshold is much greater. In addition, with high diffusion values, the absorbed dose close to the cavity border is much lower, resulting in a reduced risk of neurological deficits.

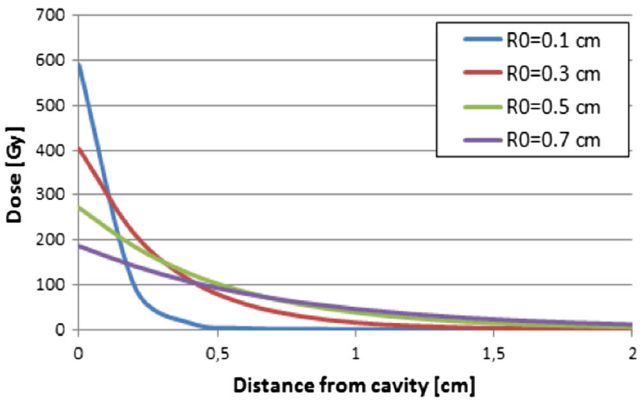

Fig. 4 Example of estimated dose profiles over the 2-cm shell for various diffusion values (R0) as defined in a method proposed by Hopkins et al. [48]. The calculation is based on an injected activity of 65 MBq/ml of Lu-177 6A10 Fabs and a cavity radius of 1.6 cm (Gosewich A. and Böning A.)

Leakage

Most authors report the placement of a subgaleal Ommaya or Rickham reservoir with a catheter into the resection cavity following tumor removal. Four to 6 weeks later, prior to iRIT, catheter patency and leakage of the RIC into the subgaleal space, the subarachnoid space, or the ventricles are examined by slowly injecting a tracer dose of ca. 2 mCi (74–111 mBq) Tc-99m human serum albumin (HSA) into the RC via the reservoir. Prior to the injection, 1–2 ml fluid is removed from the cavity to compensate for the injection volume. Gamma camera images are obtained immediately thereafter and 4–24 h later. In about 5–10% of the patients, leakage into CSF spaces or ventricles becomes obvious. For safety reasons, these patients are not eligible for treatment [80, 83]. Guidelines on how to measure precisely the amount of leakage have not been reported.

Selection of an appropriate target or carrier

Crucial to the success of this therapy is the selection of a cell surface antigen present on nearly 100% of tumor cells, as well as a specific targeting antibody. Tenascin is expressed in 80–90 of high-grade gliomas [43, 46, 102], EGFR (and variants) in 60–80% [56], according to other studies in only 50–60% [34, 36]. TM 601 as carrier for the MMP2 receptor, neurokinin type 1 receptor as target with substance P as carrier, and carbonic anhydrase 12 (CA12) as target for 6A10 Fab-fragments as carrier are interesting new candidates for RIT, since all seem to bind to nearly 100% of malignant glioma cells with no or only minimal binding to normal brain tissue [46, 50, 59, 94]. TM 601 and substance P are small proteins with a molecular weight of ca. 4 kDa and 2 kDa, respectively [46, 50,

59], while 6A10 is a recombinantly produced Fab fragment with a MW of ca. 60 kDa [10].

Adverse events and toxicity

There appears an association between cumulative administered radioactivity and hematologic and neurologic adverse events (AEs). No grade 3 or 4 hematologic or neurologic toxicity was observed with a *single* or *repeated* intracavitary doses up to 80 mCi/2960 MBq of I-131-conjugated anti-tenascin mAb [2, 11, 20, 34, 68, 73, 78]. However, the intracavitary administration of a *single dose* of 100 mCi/3700 MBq resulted in hematologic grades 3 or 4 toxicity in 23%, and grade 3 neurotoxicity in 12% of the patients. Fortunately, all adverse events were responsive to steroids and did not require reoperation for radionecrosis [4, 66, 67, 71, 73]. MTD after iRIT in newly diagnosed gliomas was observed at 120 mCi [4, 22] and in recurrent gliomas at 100 mCi [2, 12]. Conversely, with the *fractionated application* and 6-week intervals between the cycles no grade 3 or 4 hematologic, nephrologic, or hepatic toxicity, a low number of grade 3 neurological toxicity (9%) and no grade 4 neurologic toxicity were observed [34, 73].

The hematologic and neurologic grade 3 toxicities following administration of 100 and particular 120-mCi 131-I mAb into the resection cavity are likely to be explained by the fact that the varying sizes of the RC volume were not taken into consideration and the average absorbed dose to the 2-cm margin of the cavity in some patients may have exceeded the dose tolerance of brain tissue. In a pilot study with a precisely volume-adapted dose of I-131 mAb to achieve a 44-Gy boost to the 2-cm RC margin, no neurologic and only mild hematologic toxic effects (neutropenia, thrombocytopenia) were observed, while median OS in GBM remained at 22.6 months [80]. Thus, using precise dosimetry, the toxicity profile will be manageable. It must be considered further that many of the patients in the cited studies simultaneously received adjuvant chemotherapy which per se has some type of grade 3 and 4 hematologic toxic effects [18, 86].

Other studies using Re-188 nimotuzumab or I-131-labeled TM-601 reported mild headache and nausea in some patients but no grades 3 or 4 neurologic toxicity with doses below the predetermined MTD [18, 100]. In the study with Bi-213-labeled substance P, only "minimal toxicity" was reported [23]. Human anti-mouse antibodies (HAMA) were detected in 40–80% of patients when treated with murine anti-tenascin mAbs. However, HAMA reactivity was not associated with any symptomatic sequelae and was not reported to affect mAb pharmacokinetics [11, 20, 66, 67, 69, 74, 78]. When using a humanized monoclonal antibody or small peptides, no treatment-induced human antibodies were reported [18, 23, 50, 59, 100].

Depth of tumor cell migration—a potential limitation of iRIT?

The question has been raised whether tumor cells that have migrated beyond the 2-cm margin of the RC may escape treatment. It is known that migration of tumor cells often follows edematous white matter tracts and expanded perivascular spaces along the subependyma [35]. Since the activity concentration in the 2-cm margin was found to be significantly higher in areas with edema than in areas without edema (ca. 26% vs 5% of the activity in the RC [4]), it is likely that edematous enlargement of the extracellular and perivascular spaces facilitates diffusion and delivery of the RIC to deeply invaded tumor cells. However, there certainly exist spatial limits of this method, particularly with regard to recent findings allowing to detect a "cloudy-enhancing compartment" outside the solid contrast-enhancing area of GBM that is invisible in standard MRI and may represent tumor infiltration [63]. This is a new aspect and should be considered in any future evaluation of treatment response in malignant gliomas.

Time point of administration of iRIT

In the above-cited clinical trials, iRIT has been used as second-line therapy after standard therapy. In only one study, iRIT was applied prior to conventional RT (approximately 2–4 weeks after surgery), and RT was given approximately 4 weeks after iRIT, followed by chemotherapy. The median overall survival was 22.6 months [80]. So far, no prospective study was performed dedicated in comparing both application modalities. The advantage of iRIT as a first-line therapy would probably be facilitated diffusion of the RIC into edematous tissue unimpeded by prior radiotherapy and chemotherapy.

Anaplastic Astrocytomas (WHO grade III)

Some of the cited clinical studies contain small subgroups of patients with anaplastic astrocytomas. There is strong evidence that this group has a particular benefit from the therapy [80, 83, 90]. Out of a group of 15 anaplastic astrocytomas (AAs), five patients had survived more than 11 years, most in good condition and without recurrence [83]. In the series of Reardon et al. [80], five of six patients with AA remained alive after a median follow-up of 151 weeks. Since the incidence of AA is considerably smaller than that of GBM, a separate study with AA has not been reported so far. Even with the small number of reported results, it would seem appropriate to consider iRIT for the treatment of AA.

Conclusions

Intracavitary radioimmunotherapy is discussed in the present review as a therapeutic strategy of high potential to delay or prevent local tumor regrowth. Application of the RIC into the postoperative resection cavity via an Ommaya reservoir has the advantage to bypass the blood-brain barrier and to deliver higher local radiation doses than with systemic application. Cell surface receptors/antigens of glioma cells can be used as molecular targets for specifically engineered mAbs, Fab-fragments, or small peptides, labeled with a radionuclide, to deliver a therapeutic quantity of radiation to the remaining tumor cells.

Several phase I and II clinical studies have proven this concept and have shown prolongation of median overall survival to 19–25 months while adverse events (hematological, renal, and neurological) remain moderate and well manageable. In these trials, the pharmacokinetics of the treatment has extensively been studied and relevant results are reported. However, all the cited studies comprised a limited case number and were performed at a single institution, and none of the trials was randomized, therefore, the results need to be corroborated.

There is ample potential to refine this technology. New strategies could, for example, use novel target molecules expressed ubiquitously in all glioma cells, in addition to using smaller Fab fragments instead of the whole antibody or small receptor peptides as carrier. Furthermore, selecting a radionuclide to ensure adequate tissue penetration and allowing advanced patient-specific dosimetry might offer further advantage. A clinical trial will soon be started comprising these innovations.

To further improve the therapeutic potential of iRIT, techniques have to be developed to measure the extension and the density of invading tumor cells, which would allow optimizing the provision of RICs. Rational combination strategies, such as dual targeting or use of two carriers with different diffusion properties, have to be considered. Last but not least, optimal timing of RIT application, prior or post radiotherapy, still remains an unsolved question.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of expert review, formal consent is not required.

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