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REVIEW ARTICLE

Targeted Alpha Therapy for Glioblastoma: Review on In Vitro, In Vivo and Clinical Trials

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Abstract

Glioblastoma (GB), a prevalent and highly malignant primary brain tumour with a very high mortality rate due to its resistance to conventional therapies and invasive nature, resulting in 5-year survival rates of only 4–17%. Despite recent advancements in cancer management, the survival rates for GB patients have not significantly improved over the last 10–20 years. Consequently, there exists a critical unmet need for innovative therapies. One promising approach for GB is Targeted Alpha Therapy (TAT), which aims to selectively deliver potentially therapeutic radiation doses to malignant cells and the tumour microenvironment while minimising radiation exposure to surrounding normal tissue with or without conventional external beam radiation. This approach has shown promise in both pre-clinical and clinical settings. A review was conducted following PRISMA 2020 guidelines across Medline, SCOPUS, and Embase, identifying 34 relevant studies out of 526 initially found. In pre-clinical studies, TAT demonstrated high binding specificity to targeted GB cells, with affinity rates between 60.0% and 84.2%, and minimal binding to non-targeted cells (4.0–5.6%). This specificity significantly enhanced cytotoxic effects and improved biodistribution when delivered intratumorally. Mice treated with TAT showed markedly higher median survival rates compared to control groups. In clinical trials, TAT applied to recurrent GB (rGB) displayed varying success rates in extending overall survival (OS) and progression-free survival. Particularly effective when integrated into treatment regimens for both newly diagnosed and recurrent cases, TAT increased the median OS by 16.1% in newly diagnosed GB and by 36.4% in rGB, compared to current standard therapies. Furthermore, it was generally well tolerated with minimal adverse effects. These findings underscore the potential of TAT as a viable therapeutic option in the management of GB.

Key Points

Glioblastoma (GB), an aggressive brain cancer, exhibits poor prognosis with a 5-year survival rate of 4-17%

Targeted Alpha Therapy (TAT) emerges as a promising approach, delivering therapeutic radiation doses to malignant cells while minimising exposure to normal tissue.

TAT demonstrated high binding affinity to targeted cells, dose-dependent reduction in cell viability, and cell cycle arrest in G2/M phase.

Intratumoral delivery of targeted agents showed promising biodistribution with significant tumour accumulation.

TAT is generally well-tolerated with minimal side effects, irrespective of the specific alpha-emitting radionuclide used.

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1 Introduction

Glioblastoma (GB) is the most aggressive form of malignant primary brain cancer, carrying an extremely poor prognosis [1]. International studies have shown an annual incidence rate of approximately 0.59–5 per 100,000 persons, with an increasing incidence with age, and have indicated a rise in incidence number [2]. Globally, GB is among the most common primary malignant brain tumour, with a 5-year survival rate ranging from 4 to 17% [3].

GB, previously known as glioblastoma multiforme, is classified as a grade 4 tumour according to the World Health Organization (WHO) grading system for brain tumours [1]. GB is pathologically known to be highly heterogenous, invasive, proliferating and hypoxic [1, 4–7]. These characteristics collectively contribute to the aggressive and therapy resistant nature of GB, making it one of the most difficult types of brain cancers to achieve long-term control. The current standard treatment for GB patients involves maximal safe surgical resection followed by external beam radiotherapy (EBRT) plus concomitant and adjuvant chemotherapy with temozolomide (TMZ) [8]. Due to the diffuse invasiveness of GB, achieving a macroscopic and microscopic complete surgical resection is near impossible [9]. The persistence of subclinical infiltrating tumour cells at the edge of the tumour bed dispersed in the adjacent white matter pathways not eradicated by adjuvant non-surgical oncological treatments ultimately results in disease recurrence and progression [9].

Considering the low survival rate associated with the current standard treatment protocols compared to many other cancers, research has shifted its focus to new therapeutic approaches to address the challenges posed by GB. One promising approach for GB is Targeted Alpha Therapy (TAT), which aims to selectively deliver therapeutic radiation doses using alpha particles to the tissue of remaining malignant tumour cells and the tumour microenvironment, while minimising radiation exposure to surrounding critical normal tissue [10].

1.1 Targeted Alpha Therapy

TAT is a form of Target Radionuclide Therapy (TRT), which involves the administration of alpha-emitting radionuclides into the patient, either intravenously or intratumorally/locally. These radionuclides specifically accumulate at tumour sites due to their inherent chemical properties or active targeting mechanisms, and release ionising alpha particles that can precisely target cancer cells [10]. There are three main methods of delivering TAT:

i. **Passive targeting:** This approach utilises radionuclides that naturally accumulate in certain tissues without a targeting agent. An example is Radium-224 (Ra-224), which has a natural affinity for bone and is under investigation for potential use in glioblastoma (GB) treatment due to its ability to target bone-like or calcified tumour tissues [11, 12].
ii. **Active targeting:** In this more common approach, alpha-emitting radionuclides are conjugated to monoclonal antibodies (mAb), peptides or small molecules that target tumor-associated antigens expressed on cancer cells [13]. This method ensures that the radionuclide is delivered directly to the cancer cells, increasing the treatment's efficacy and reducing uptake by normal tissues.
iii. **Intratumoral implants:** Referred to as diffusing alpha-emitters radiation therapy (DaRT), this method involves implanting sources ('seeds') containing low levels of Ra-224 directly into the tumour [14]. This strategy is akin to brachytherapy, a well-established treatment using radiation sources placed inside or next to the area requiring treatment. Both DaRT and brachytherapy deliver localised radiation; however, DaRT provides a targeted alpha-emission that may offer enhanced tumour control with minimal impact on surrounding healthy tissues [14].

Another form of TRT is Targeted Beta Therapy (TBT), which uses beta-emitting radionuclide instead of alpha. TBT is currently the most common TRT approach; however, TBT has two major drawbacks: beta-particles have a long range in tissue, ranging from 1 to 10 mm, resulting in unwanted exposure to neighbouring healthy tissue [15–17]; and a low linear energy transfer (LET) of around 0.2 keV/µm [16]. LET is a measurement of the mean rate of energy deposited locally along the track of a charged particle. Therefore, with low LET, ionisations within the cell are not as dense, causing a lower probability of irreparable DNA double-strand breaks and base chemical modifications that induce apoptosis (Fig. 1) [10].

Alpha-emitting radionuclides undergo radioactive decay releasing alpha-particles, a helium nucleus consisting of two protons and two neutrons with an electric charge of +2. Unlike beta-particles, alpha-particles have a much shorter range of 50–100 µm and a higher LET, which varies between 50 keV/µm and 230 keV/µm depending on the alpha-emitting isotope used [10]; therefore, they can deliver higher potent short-ranged radiation directly to the tumour cells while sparing more of the neighbouring healthy tissue (Fig. 1). Additionally, cell death due to alpha-particles are near-independent of oxygen level or rate of proliferation,

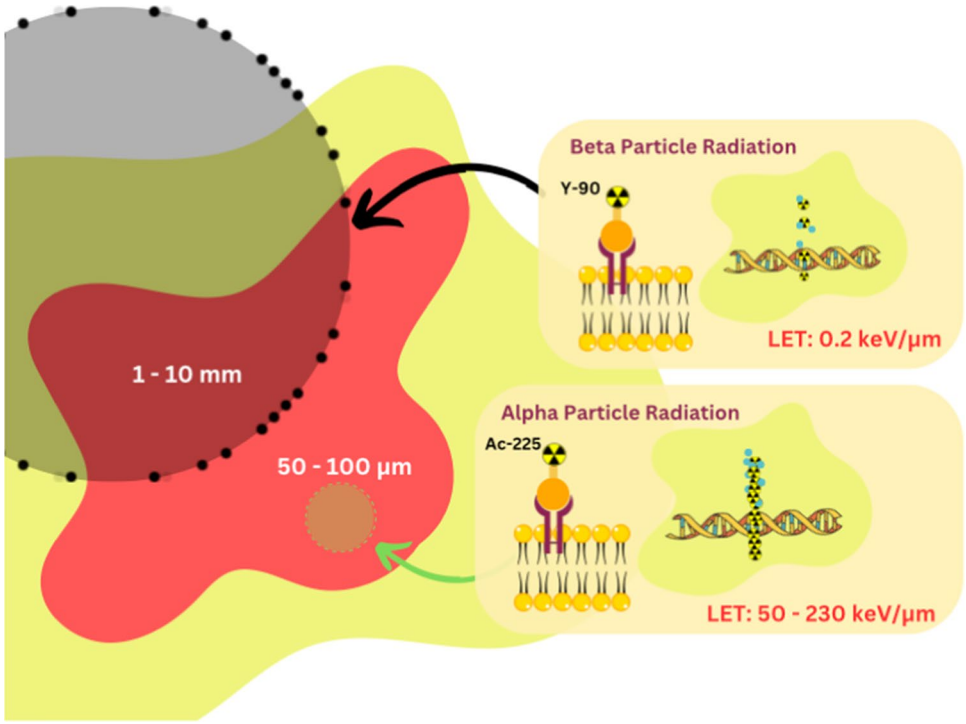

Fig. 1 Comparison of therapeutic particle ranges, LET, and DNA damage potencies (made in Canva)

which makes TAT suitable for treating hypoxic tumours such as GB [18].

The high LET of alpha particles significantly increases their Radiobiological Effectiveness (RBE) compared to beta particles. RBE is a comparative measure of cellular damage done by different types of radiation, reflecting the efficiency of energy deposition at the molecular level. Remarkably, while the general RBE for alpha particles is typically in the range of 5–10, it can rise dramatically to around 120 in scenarios where alpha particles are targeted internally [15]. This extremely high RBE is due to the fact that targeted alpha particles, due to their short range and concentrated energy deposition, are much more likely to hit and kill cancer cells directly. Most targeted cancer cells receive a large fraction of the alpha radiation's energy directly to the cell nucleus, which induces double-strand DNA breaks. In contrast, beta particles, their longer range and diffuse energy spread result in a significantly smaller fraction of the radiation dose, effectively damaging the targeted cells, and affirming their RBE of about 1 [15]. As such, there has been increased interest in TAT in recent years due to its advantageous characteristics over TBT.

This review aims to provide an overview of the current literature on TAT for GB treatment. Specifically, the focus is on studies investigating TAT efficacy in both pre-clinical models and clinical studies. Additionally, the review aimed to identify and highlight existing gaps in knowledge, and scopes for future research.

2 Search Method

To conduct a review of the existing literature on TAT for GB, a systematic literature search was performed across three databases: MEDLINE, Scopus and Embase. The search strategy (detailed in Appendix A, Online Supplemental Material) was developed in collaboration with a University of South Australia (UniSA) librarian, adhering to PRISMA 2020 guidelines [19]. Additionally, a grey literature search using Google Scholar was conducted, with the first 10 pages of results extracted for screening. The screening process was done through Covidence (Veritas Health Innovation, Melbourne, Australia), a specialised software for literature reviews, and after removing duplicates, exclusion criteria were applied, excluding conference abstracts, posters, review articles, and non-English language publications.

Subsequently, a review of the abstracts and full texts of the remaining papers was conducted independently by two reviewers (MES and EB), and any conflicts were discussed and resolved. Following this evaluation, 34 papers were deemed relevant and selected for inclusion in this review. Figure 2 is the overview of the search and article inclusion process. Although systematic approaches were used in the data extraction and analysis, the large variation in reporting and the small number of studies made meta-analysis of the literature not possible. Therefore, the approach taken involved integrating and synthesising the overall results.

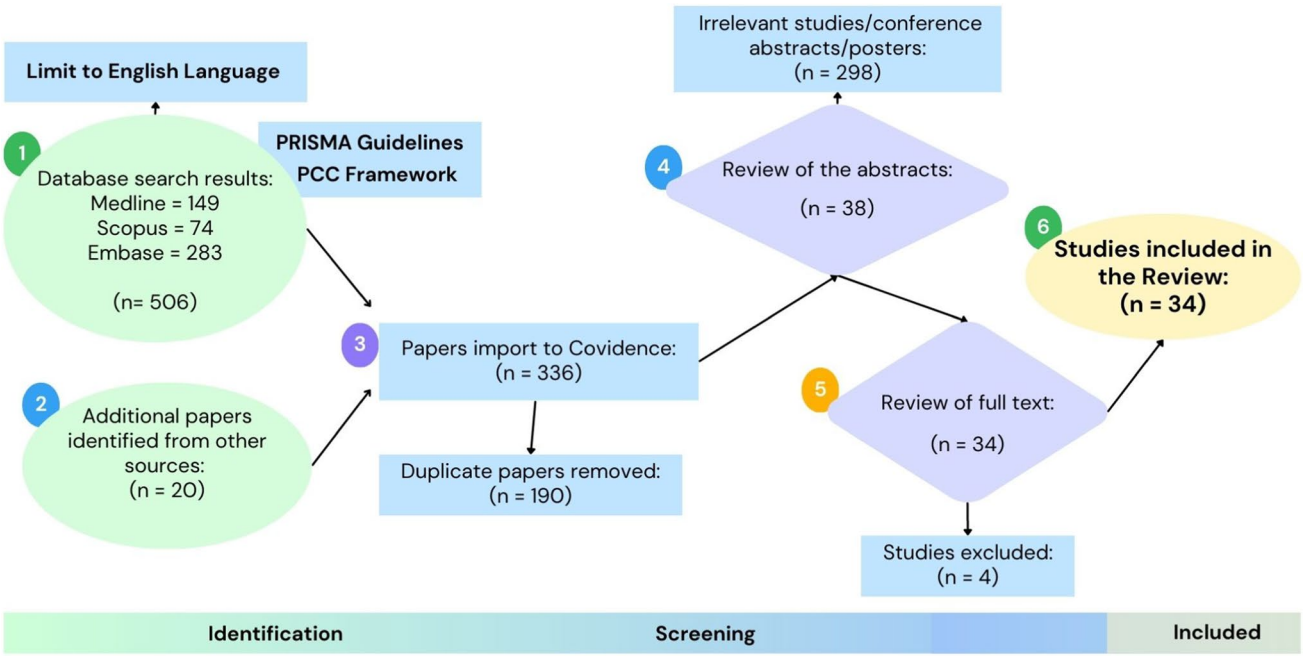

Fig. 2 Overview of the search method

3 Results and Discussion

The results and discussion of this review are organised into sections that detail the use of various radionuclides, as well as summarising findings from in vitro, in vivo and clinical studies relevant to TAT in GB.

3.1 Radionuclides

A wide array of isotopes has been explored for TAT in the context of GB. Among these isotopes, Astatine-211 (At-211) has been used in 14 pre-clinical studies, Bismuth-213 (Bi-213) in five clinical trials, and Actinium-225 (Ac-225) in six pre-clinical studies and one phase I clinical trial. Each isotope exhibits a unique set of characteristics. Ac-225, characterised by its 100% α-emission, a range of 0.04–0.10 mm, and a half-life ($T_{1/2}$) of 238.10 h (~ 10 days), is shown to offer several advantages [20–27]. Notably, it exhibits compatibility with DOTA-complexation, rendering it a versatile choice for a variety of compounds [26]. Furthermore, its relatively extended half-life ($T_{1/2}$) allows for enhanced transport and more efficient distribution before radioactive decay, particularly beneficial when treating larger tumour volumes, as indicated by Cordier et al. [28]. However, the longer $T_{1/2}$ of Ac-225 results in the generation of multiple alpha particles due to its rapid decay chain (as depicted in Fig. 3). Moreover, recoiled daughters might impact its

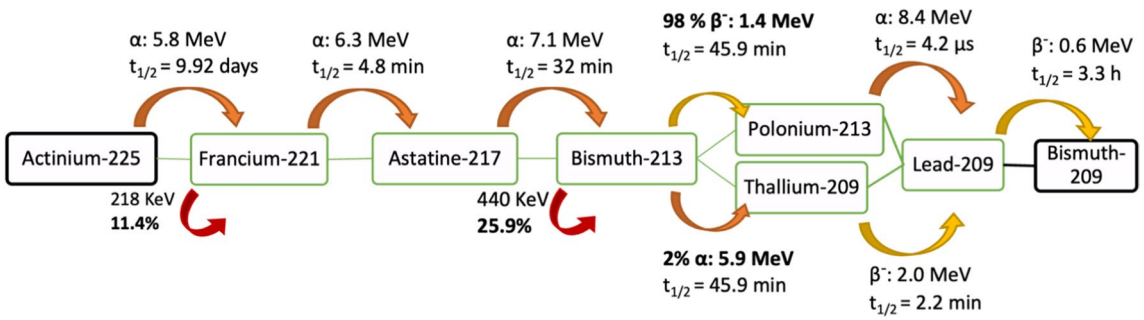

Fig. 3 Ac-225 decay chain; photons with a branching ratio > 3% relative to 225Ac decay are shown

stability. Studies involving Ac-225 can be found in the references [20–26].

Bi-213, which boasts a 2.2% α-emission and 97.8% β-emission, possesses a range of 0.05–0.10 mm and a $T_{1/2}$ of 0.77 h [27–33]. Like Ac-225, it can be effectively complexed with DOTA, offering a straightforward and universal solution [26, 30–32]. However, its short $T_{1/2}$ and gamma-energy combination make it less efficient in terms of tumour distribution before radioactive decay [28]. The primary drawback of Bi-213 is its brief $T_{1/2}$, which affects its residence time within critical GB cells. In these cases, the ratio between cell membrane coverage (receptor affinity) and time plays a pivotal role. Studies involving Bi-213 are listed in the references [28–33].

Lastly, At-211, featuring 42.0% α-emission and 58.0% electron capture, possesses a range of 0.05 mm and a $T_{1/2}$ of 7.20 h [27, 34–47]. Its longer $T_{1/2}$ gives it the potential to have a more advantageous biodistribution. However, At-211 is limited to applications involving mAb and smaller fragments, which can often exhibit low biological and chemical stability. Relevant studies pertaining to 211At are listed in the references [34–47].

3.2 Pre-Clinical Studies

A total of 26 pre-clinical papers were identified that investigated various aspects of TAT for GB. There were 12 in vitro studies, four in vivo studies, nine combined in vitro/in vivo studies, and one modelling study. A summary of pre-clinical studies is presented in Tables 1 and 2.

3.2.1 In Vitro Studies

In vitro studies primarily focused on several key aspects, including the binding affinity of different targeting agents, clonogenic survival/cell viability, and the potential for cell cycle arrest.

The binding affinity and binding rate of labelled alpha emitters were consistently high compared to non-targeted and unlabelled emitters. Notably, studies conducted by Zalutsky et al. [39, 41] and Larsen et al. [36] demonstrated that At-211 conjugated to mAbs 81C6/Mel-14 and 2'-deoxyuridine (AUdR) exhibited high binding specificity to targeted cells (ranging from 60.0% to 84.2%) and low binding to non-targeted cells (4.0–5.6%). Moreover, Ma et al. [42] and Liu et al. [43] found that the binding rates to targeted cells were 24.9% and 32.0%, respectively, while the binding rate to non-targeted cells was less than 7%. These studies explored At-221 conjugated to either a heterodimeric peptide (targeting vascular endothelial growth factor receptor (VEGFR) and integrins) or a fibroblast activation protein inhibitor (FAPI).

The therapeutic effectiveness of TAT was assessed in various ways in the literature, including cell viability, relative biological effectiveness (RBE), survival fraction of GB cells at specific absorbed dose rates, and activity concentration resulting in a specific survival rate. Larsen et al. [35, 36] and Rosenkranz et al. [37] investigated the activity concentrations resulting in a 37% survival rate (A_{37}) of GB cells using At-211 conjugated to mAbs 81C6/Mel-14, AUdR, and engineered modular recombinant transporters. The A_{37} values for conjugated At-211 were significantly lower (4.4–56.6 kBq/ml) compared to free At-211 (32.6–132 kBq/ml). These findings underscore the heightened effectiveness and precision of At-211 conjugated to a targeting agent in killing clonogenic GB cells.

Majkowska-Pilip et al. [25], Ma et al. [42] and Liu et al. [43] reported on cell viability; a dose-dependent decrease in all studies was observed. Ac-225 conjugated to substance-P reduced cell viability to 50% at 50 kBq/ml; At-211 conjugated to FAPI and control reduced viability to 42.1% and 56.5% at 92 kBq/ml, respectively; and At-211 conjugated to heterodimeric peptide and control reduced viability to 47.5% and 62.0% at 75 kBq/ml, respectively. Furthermore, Majkowska-Pilip et al. [25], Ma et al. [42] and Liu et [43] demonstrated significant cell cycle arrest in the G2/M phase in treated cell lines compared to control, with treated cells in G2/M phase ranging from 62.1% to 80% and control cells at 11.9% to 36.6% (cells are more radiosensitive in these phases).

The therapeutic effectiveness of TAT compared to other treatment modalities was explored in several studies. Carlin et al. [38, 40] and Zalutsky et al. [39] highlighted that the 2 Gy survival fraction (SF2) for At-211 was significantly lower than that of Iodine-131 (I-131) and EBRT, meaning that At-211 is much more effective in killing cancer cells when exposed to a 2 Gy dose compared to I-131 and EBRT (i.e., more cytotoxic at this radiation dose). Additionally, Barazznol et al. [48] reported that the RBE of alpha particles compared to x-rays and protons was higher, with RBE_{10} (calculated at 10% survival) and RBE_{3Gy} (survival level after 3 Gy) being 1.17 and 1.35 for protons and 1.84 and 3.79 for alpha particles, respectively. The RBE is a measure of how effective a particular type of radiation is at causing biological damage, relative to x-rays, although both alpha and protons have a higher RBE than X-rays, alpha particles had the highest RBE, indicating that they are more effective in causing biological damage.

Overall, the pre-clinical in vitro studies on TAT have shown its potential as an effective therapeutic approach for GB treatment. The high binding affinity to targeted cells, dose-dependent reduction in cell viability, and cell cycle arrest and enhanced cytotoxicity compared to other treatments collectively highlight the promising aspects of TAT.

Table 1 Summary of In Vitro Studies Findings.

Study ID	TAT agent/cell line	Cellular response	Binding affinity	Other main findings
Zalutsky 1989 [39]	At-211-(81C6/Mel-14)/ **D54MG**	–	**81C6 Target/Non-target:** 84.2/12.1 % **Mel-14 Target/Non-target:** 62.7/5.6%	–
Larsen 1997 [36]	At-211-(AUdR)/ **D247MG**	**Clonogenic Survival Curve** **At-211-AUdR**: 33 kBq/ml yielding 37% survival **At-211**: 132 kBq/ml yielding 37% survival	**At-211-AUdR**: 60% incorporated into target DNA **At-211**: 4 % incorporated into target DNA	–
Zalutsky 1997 [41]	At-211-(81C6)/ **D54MG**	–	**81C6 Target/Non-target:** 81%/4%	–
Larsen 1998 [35]	At-211-(81C6/Mel-14)/ **D247MG**	**Clonogenic Survival Curve** **At-211-81C6**: 56.6 kBq/ml yielding 37% survival **At-211-Mel-14**: 60.8 kBq/ml yielding 37% survival **At-211**: 116 kBq/ml yielding 37% survival	–	–
Schneeweiss 1999 [47]	At-211/**86HG39**	–	–	Dose ranging from 0.025 to 1.0 Gy led to a significant reduction in PADPR of 85.6 % compared to non-irradiated cells. At lower doses (0.0025 to 0.025 Gy), there was a negative exponential relationship with relative levels of PADPR. Alpha radiation from At-211 is suitable for cancer radiotherapy at dose range of 0.025 to 1.0 Gy
Takahashi 2000 [50]	Am-241/**A-172 (with wild-type p53) and T98G (with mutated p53)**	–	–	**RBE values:** 1.19 for A-172 cells, 1.16 for A-172/neo cells, 1.31 for A-172/mp53 cells, and 1.33 for T98G cells. **Fold inductions of WAF1;** 1.6 to 3.9 for X-rays, 2.3 to 10.0 for C-beams, and 1.5 to 5.1 for alpha particles at different doses. Sensitivity to C-beams and alpha particles was similar between wt/53 and mp53 cells, suggesting that cellular radiosensitivity to heavy ions may be independent of p53 status.

Table 1 (continued)

Study ID	TAT agent/cell line	Cellular response	Binding affinity	Other main findings
Carlin 2002[40] Carlin 2003[38]	At-211-NIS/ **UVW, NIS6**	–	–	Cell-associated At-211 activity was significantly higher (32.5 folds) in NIS-expressing cells compared to control At-211 was ~ 600 and 700 times more cytotoxic than I-131 At-211 had higher absorbed dose (55-65.5 folds) per ID compared I-131 2 Gy survival fraction (SF2) for At-211 was 900 – 1100 times lower than I-131 - beta emitter and EBRT: SF2 At-211 = 7.4×10^{-4}, I-131 = 0.66, and EBRT = 0.61
Rosenkranz 2008 [37]		**Clonogenic Survival Curve** **At-211-EMRT:** 4.4 kBq/ml yielding 37% survival **At-211:** 32.6 kBq/ml yielding 37% survival	–	–
Barazzuol 2012 [48]	Am-241/ **LN18, U87**	–	–	**Chemotherapy (TMZ) response:** MGMT-unmethylated (LN18) cells showed no difference in growth rate with or without TMZ while methylated cells (U87) showed clear decrease in growth rate with TMZ. **DNA repair kinetics:** DSB half-life was 12.56, 10.66 and 12.54 hr for x-rays, protons and alpha particles, respectively. **RBE values:** **3MeV proton – RBE_{10}, REB_{α}, RBE_{3GyE}:** **LN18 -** 1.17, 1.41, 1.35**; U87 -** 1.06, 2.24, 1.37 **6MeV alpha particle – RBE_{10}, REB_{α}, RBE_{3GyE}:** **LN18 -** 1.84, 3.50, 3.79**; U87 -** 1.68, 4.03, 3.38
Sattiraju 2017a [24]	Ac-225-IA-TL/ **U87 MG**	–	–	**γH2A.X Staining**: abundant DNA DSB at site of infusion and no significant observation in surrounding region (0.5mm from GB border)

Table 1 (continued)

Study ID	TAT agent/cell line	Cellular response	Binding affinity	Other main findings
Sattiraju 2017b [23]	Ac-225-Pep-1/ **U251**	–	–	**Histological analysis:** Increased γH2A.X subnuclear accumulation, lower Ki67 expression and greater propidium iodide internalisation (indicates apoptosis/necrosis)
Wank 2018 [51]	Am-241/ **LN229, LN18, U87**			**Tumour invasion**: Alpha particles (1.3 Gy) had no effect on the invasion of primary GB cells, whereas x-rays (4 Gy) significantly increased GB cell invasion by 1.4 - 1.7 folds.
Majkowska-Pilip 2018 [25]	Ac-225-DOTA-SP/ **T98G, U87MG, U138MG**	**Cell viability:** At 50 kBq/ml cell viability dropped to 50 % **Cell cycle arrest:** Treated cells (10 kBq/ml) in G2/M phase ranged from 62.1-80% and control was 21.8 - 36.6%	Max no. binding site of 0.27 ng/ml corresponding to 4.6 x 10^4 receptors per cell	–
De Kruijff 2018 [22]	Ac-225-polymersomes/ **U87, U251**	–	–	**IC50:** 0.16 μM for U87; 0.11 μM for U251 (concentration that cause 50% reduction in cell viability)
Watabe 2020 [45]	At-211-PA/ **C6, U87MG, GL261**	–	–	**Addition BCH:** Significantly inhibits uptake by C6 (12.2 %), U-87MG (27.6 %) and GL-261 (12.6 %). Suggesting that At-211uptake is predominantly mediated by system L amino acid transporters
Feuerecker 2021 [33]	Bi-213-anti-EGFR-immunoconjugate/ **LN8**	**Clonogenic cell kill**: 1480 kBq/ml of 213Bi lethal to approximately 99% of LN8 glioma cells.	–	–
Dabagian 2021 [46]	At-211-MM4/ **U87MG**	**Dose response curve**: 50% reduction in cell survival for LN18 cell lines were ten times more sensitive than U87MG even though targeted expression was equal.	–	**Combination therapy:** At-211-MM4 plus anti-PD-1 (PARP inhibitor) had longest progression free of 65 days and best tumour response ($p<0.05$) compared to either alone.

Table 1 (continued)

Study ID	TAT agent/cell line	Cellular response	Binding affinity	Other main findings
Ma 2022 [42]	At-211-FAPI-04/	**Cell viability:** At-211-FAPI-04: 61.9 % at 12 kBq; 42.1 % at 92 kBq At-211: 84.2 % at 12 kBq; 56.5 % at 92 kBq **Cell cycle arrest:** Treated cells (23 kBq/ml) in G2/M and G0/G1 phase was 62.7% and 21.9% and pre-treatment was 15.7% and 69.9% **Clonogenic assay:** Relative survival 28.1, 8.1 and 1.97 % for 4.6, 9.2 and 18.5 kBq	Target 24.9%; non-target 6.87%; At-211 alone <1%	–
Liu 2022 [43]	iRGD-C6-lys(211At-ATE)-C6-DA7R	**Cell viability (at 75 kBq/ml):** Reduced to 47.5 % and 62% with labelled- At-211 and At-211 **Cell cycle arrest:** Treated cells in G2/M and G0/G1 phase were 62.1% and 32.2% and untreated cells were 11.9 % and 68.7%	Target 32%; At-211 alone ~1%	–
Nishri 2022 [52]	Am-241/**U87MG**	**Viability assay:** Combined TMZ + alpha particles nearly doubled the cytotoxicity relative to each treatment alone.	–	$\mathbf{RBE_{10}}$ = 1.5 Survival fraction decreased by 40-50% with TMZ

GB glioblastoma, *TMZ* temozolomide, *EBRT* External Beam Radiation Therapy, *%ID/g* percent of the injected dose per gram, *EMRT* engineered modular recombinant transporters, *IC50* half maximal inhibitory concentration, *DSB* double strand break, *γH2A.X* phosphorylated that forms when DSB appear, *Ki67* proliferation marker, RBE_{10} values calculated at 10 % survival, REB_{α} initial slope of the survival curve (α test radiation/ α reference radiation), RBE Relative Biological Effectiveness, RBE_{3GyE} Survival level after 3 Gy, BCH 2-Aminobicyclo-(2,2,1)-heptane-2-carboxylic acid, *LAT1-IN-1* an inhibitor of system L amino acid transporter, *PADPR* poly-ADP-ribosylation (plays a role in detecting and repairing DNA damage in cells), *WAF1* gene that is localised to chromosome 6p21.2, and its sequence, structure, and activation by p53 (a lower fold induction of WAF1 indicates that the cells are more sensitive to that particular type of irradiation)

Table 2 Summary of in vivo study findings

Study ID	TAT agent/cell line	Biodistribution	Median survival	Tumour response	Toxicities
Zalutsky 1989 [39]	At-211-(81C6/Mel-14)/ **D54MG**	Tumour uptake at 3, 16, 24 h: Intravenously: 11.0, 15.0, 8.7 %ID/g	–	Dose to tumour was two- to 15-fold higher for At-211 compared to I-131	Higher doses were calculated for liver, lungs, and spleen for At-211-labeled mAb compared to I-131-labeled mAb, likely due to higher retention of Astatine in these tissues.
Zalutsky 1997 [41]	At-211-(81C6)/ **D54MG**	Tumour uptake at 4, 16, 24 h: Intravenously: 11.3, 20.0, 16.9 %ID/g	–	–	The radiation dosimetry estimates for human administration – absorbed doses to most organs ranged from 2 to 3 mSv/MBq. The bone surfaces received the highest dose, followed by red marrow. The absorbed doses were significantly lower when the antibodies were administered directly into the cerebrospinal fluid compared to intravenous injection
Rosenkranz 2008 [37]	At-211-EMRT/ **D247MG, U87MG**	–	Treated – 70 days Control – 26 days Significant reduction in tumour size compared to control	–	–
Cooks 2012 [12]	Ra-224	–	–	**Activity range:** Wire carried activity range of 21.3–24.3 kBq **Tumour suppression effect:** Significant inhibition of tumour growth. Treatment yielded a reduction of over 90% in tumour volume compared to the control	The study evaluated the toxicity of the treatment by measuring changes in body weight and blood cell counts. They found that there were no significant differences in these measures between the Ra-224 treated group and the control group, suggesting that the treatment was not associated with significant toxicity
Borrman 2013 [44]	At-211-Phe	–	**Median survival and Necrotic area:** 1xAt-Phe – 14.6 days & 17.1 mm^2 2xAt-Phe – 15.4 days & 22.9 mm^2Control – 13.0 days & 9.03 mm^2	**Intravenous administration:** 1xAt-Phe = 2000 kBq in 300 ml; 2xAt-Phe = 3000 kBq in 500 ml	No clinical adverse effects were observed during the study
Behling 2016a [20]	Ac-225-E4G10	–	**Median survival:** Ac-225 – 30 days Control – 17 days	**Intravenous administration:** 7.4 kBq **Histological analysis**: 68 % drop in overall vascularity	–
Behling 2016b [21]	Ac-225-E4G10	**Biodistribution:** 7.7-fold higher absorbed dose to tumour compared to healthy tissue	**Median survival:** Ac-225 – 21 days Ac-225 + TMZ – 30 days Control – 9 days	**Intravenous administration:** 11.1 kBq (300 nCi) **Histological analysis**: 64 % drop in overall vascularity	Liver had highest estimated dose among non-target tissue 20% ID/g after 10 days, and the estimated dose to the liver was the highest among nontargeted tissues (1,577 Gy/MBq in GB animals)

Table 2 (continued)

Study ID	TAT agent/cell line	Biodistribution	Median survival	Tumour response	Toxicities
Sattiraju 2017a [24]	Ac-225-IA-TL/ **U87 MG**	–	–	Ac-225-IA-TLs enhanced the permeability of the BBB and BTB	–
Sattiraju 2017b [23]	Ac-225-Pep-1/ **U251**	–	**Median survival:** Treated – 55 days; Control = 29 days	Significant reduction in tumour size compared to control	
Watabe 2020 [45]	At-211-PA/ **C6, U87MG, GL261**	–	–	**Tumour size ratios at 3wks post injection:** 0.6, 0.4 and 0.25 with 100, 500 and 1000 kBq	–
Dabagian 2021 [46]	At-211-MM4/ **U87MG**	–	–	**Combination therapy:** At-211-MM4 plus anti-PD-1 (PARP inhibitor) had longest progression free of 65 days and best tumour response ($p<0.05$) compared to either alone	–
Ma 2022 [42]	At-211-FAPI-04/	**Biodistribution:** Tumour uptake at 0.5, 2.0, 6.0 h: Intravenously: 4.04, 3.12, 1.86 %ID/g Intratumorally: 132.5, 19.24, 11.47 ID/g	**Median survival:** 24, 30 and 33 days at 180, 370 and 550 kBq	**Tumour volume reduction:** 55, 70 and 76% at 180, 370 and 550 kBq **Biological effect:** Immunohistochemical analysis of tumour sections showed remarkably inhibited cell proliferation in At-211-FAP treated group (17.9%) compared to saline group (49.8%) at 2 days	Histopathological analysis (H&E staining) of normal organs, including the kidney, liver, stomach, and thyroid, revealed no significant evidence of toxicity following intratumoral injection of At-211-FAPI-04. Furthermore, functional assessments of liver and kidney, measured by alanine aminotransferase (ALT) and blood urea nitrogen (BUN) respectively, showed no significant differences between the At-211-FAPI-04 treated group and the saline control group at both 2 and 12 days post-treatment. These results suggest that intratumoral administration of At-211-FAPI-04 does not induce significant toxicity in normal organs. Notably, the study did not report on the toxicities for the intravenous group, leaving an assessment gap in this administration method

Table 2 (continued)

Study ID	TAT agent/cell line	Biodistribution	Median survival	Tumour response	Toxicities
Liu 2022 [43]	iRGD-C6-lys(211At-ATE)-C6-DA7R	**Biodistribution:** Tumour uptake at 1.0, 3.0, 6.0 h: Intravenously: 4.0, 3.48, 1.14 %ID/g Kidney uptake: 9.67, 8.81, 4.75 %ID/g	**Median survival:** Treated: 30 days; Control: 15 days	**Tumour suppression effect:** Dose-dependent tumour effect 180, 370 and 740 kBq reduced volume by 48, 61 and 77%	iRGD-C6-lys(211At-ATE)-C6-DA7R exhibited high kidney uptake and no detachment in thyroid and stomach during circulation. Histological analysis showed a larger necrotic area in treated groups, but iRGD-C6-lys(211At-ATE)-C6-DA7R demonstrated minimal radiation damage in hepatic, gastric, and renal tissues compared to free At-211, which caused gastric mucosal necrosis
Nishi 2022 [52]	Ra-224+TMZ	**RBE_{10}** = 1.5 Survival fraction decreased by 40-50% with TMZ	**Viability assay:** Combined TMZ + alpha particles nearly doubled the cytotoxicity relative to each treatment alone	**Mean lethal dose without TMZ** = 1.2 Gy	

GB glioblastoma, *TMZ* temozolomide, *EBRT* External Beam Radiation Therapy, *%ID/g* percent of the injected dose per gram, *EMRT* engineered modular recombinant transporters, *IC50* half maximal inhibitory concentration, *DSB* double strand break, *γH2A.X* phosphorylated that forms when DSB appear, *Ki67* proliferation marker, RBE_{10} values calculated at 10 % survival, REB_{α} initial slope of the survival curve (α test radiation/ α reference radiation), *RBE* Relative Biological Effectiveness, RBE_{3GyE} survival level after 3 Gy, *BCH* 2-aminobicyclo-(2,2,1)-heptane-2-carboxylic acid, LAT1-IN-1 is an inhibitor of system L amino acid transporter, *PADPR* poly-ADP-ribosylation (plays a role in detecting and repairing DNA damage in cells), *WAF1* gene that is localised to chromosome 6p21.2, and its sequence, structure, and activation by p53 (a lower fold induction of WAF1 indicates that the cells are more sensitive to that particular type of irradiation)

Building on the existing in vitro studies that detail the binding affinity of TAT, cell viability, cell cycle arrest, and other cellular responses in GB treatment, further research is suggested in the following areas to address existing knowledge gaps. This recommendation aligns with the International Atomic Energy Agency (IAEA) [49] guidance for pre-clinical studies with radiopharmaceuticals. Below is an outline of studies that are covered by the included literature and those requiring further investigation:

IAEA Recommended Studies—Covered in Included Literature:

i. **Binding affinity and specificity:** Several studies have examined the binding affinity and specificity of radiopharmaceuticals like At-211 conjugated with monoclonal antibodies and peptides. For example, Zalutskys and Larsen's [35, 39] studies show significant differences in binding to target versus non-target cells, which aligns with the IAEA's emphasis on understanding binding characteristics.
ii. **Cell viability and clonogenic survival:** Studies (Table 1) have provided detailed clonogenic survival curves, showing how different doses affect survival rates of GB cells, addressing the IAEA's recommendation for cell viability studies.
iii. **Cellular response to radiation:** The cellular response to radiation was also explored, including dose-dependent effects and RBE, contributing to understanding the efficacy of different types of radiation as recommended by IAEA.
iv. **Therapeutic efficacy:** Carlin's [38, 40] studies demonstrated higher cytotoxicity and absorbed dose effectiveness of At-211 compared to I-131 and external beam radiation, providing crucial data on the therapeutic potential of radiopharmaceuticals.

IAEA Recommended Studies—Require Further Investigation:

i. **Internalisation and intracellular/subcellular distribution:** Despite detailed binding and viability studies, the internalisation dynamics and subcellular localisation of tracers post-binding are not clearly addressed in the summarised studies. These are crucial for understanding how tracers behave inside cells after binding to their targets.
ii. **Blocking studies:** Although high binding specificity is demonstrated, there is no clear mention of blocking studies to assess the saturability and specificity of binding beyond competitive interactions. Such studies would help confirm the selectivity and potential off-target effects.

iii. **Efflux pump assays and blood-brain barrier permeability:** There is a lack of explicit studies on how these radiopharmaceuticals interact with the blood-brain barrier or efflux pumps, which is critical for CNS-targeted therapies like those for GB.
iv. **Metabolite analysis:** It is important to understand the metabolic pathways and by-products after tracer uptake, which has not been detailed in the summary. This could affect both efficacy and toxicity profiles of the radiopharmaceuticals.
v. **Functional/efficacy assays beyond viability:** Additional functional assays to evaluate the biochemical pathways affected post-binding could provide deeper insights into the mechanistic effects of TAT agents on GB cells.

By addressing these gaps, further research can enhance the understanding of the comprehensive therapeutic profile of TAT, particularly focusing on areas like tracer internalisation and metabolic processing, which are pivotal for ensuring the safety and effectiveness of treatment strategies for GB.

3.2.2 In Vivo Studies

In vivo studies primarily focused on three aspects: biodistribution of targeted agents, median survival in treated animals versus control groups, and tumour growth/size reduction. Figure 4 provides a summary of the biodistribution of various targeting agents. It reveals that intravenous delivery of targeted agents resulted in tumour uptake ranging from 0.13% to 20.0% of the total injected dose per gram (%ID/g), while intratumoral delivery demonstrated a significantly higher tumour accumulation of 132.5%ID/g [20, 21, 39, 41–43]. Furthermore, intravenous injection groups displayed higher tumour-to-organ ratios, with the most significant uptake observed in the liver, spleen and kidneys (Fig. 4B) [20, 41–43]. Ma et al. [42] reported more favourable results concerning the tumour-to-organ ratio with intratumoral injection, including tumour-to-liver, tumour-to-kidney, and tumour-to-blood ratios of 11.13, 6.39, and 14.17, respectively, post-injection.

The studies revealed promising results in terms of the median overall survival (OS) of mice treated with TAT. Treated groups demonstrated OS ranging from 14.6 to 41 days, while untreated/control groups ranged from 9 to 23 days [20, 21, 24, 42–44]. TAT also exhibited a dose-dependent tumour suppression effect, with doses between 180 and 740 kBq resulting in reduced tumour volume ranging from 48% to 77% [12, 37, 42, 43, 45]. Additionally, Watabe et al. [45] reported that TAT effectively suppressed tumour growth, with tumour size ratios of 0.6, 0.4 and 0.25 post-injection at 100, 500 and 1,000 kBq, respectively.

Overall, the in vivo studies underscore the potential of TAT in improving overall survival and reducing tumour growth in animal models. The findings suggest that intratumoral delivery may offer more favourable outcomes in terms of biodistribution and tumour-to-organ ratio. Further research is needed to optimise dosing and administration methods to maximise the therapeutic benefits of these targeted agents.

3.3 Clinical Studies

Despite many recent advances in anti-cancer treatment modalities, (surgery, external beam radiotherapy and chemotherapy) over the last decade, the overall median survival (OS) for newly diagnosed primary GB remains extremely low, ranging from 12 to 18 months [53–58]. There are currently limited clinical data, with only six phase I clinical studies identified, four of which were conducted by the same research group. A summary of these phase I studies is presented in Table 3, where different alpha-emitting radionuclides, such as At-211, Bi-213 and Ac-225, conjugated to various targeting agents, were investigated. The primary aim of these clinical studies is to assess the viability of TAT as a treatment option for recurrent glioblastoma (rGB).

In a clinical trial by Zalutsky et al. [34], At-211 was employed alongside Ch81C6, targeting Tenascin C, in 14 rGB patients. The treatment plan involved doses ranging from 71 MBq to 347 MBq, all conjugated to 10 mg of Ch81C6 within the surgical cavity. The study reported a median OS of 12 months, with observed variations in surgical cavity resection site volumes, highlighting the need for further evaluation of multiple dose administration schedules to optimise treatment efficacy.

Cordier et al. [28] delved into the use of Bi-213 in combination with Substance P/NK-1, focusing on two critically located GB patients. Patient 1 (P1) received one cycle of 1.07 GBq, and Patient 2 (P2) received one cycle of 1.92 GBq, involving intratumoral injection via two to three catheters with three to five injections per cycle. The findings from this investigation revealed a median OS-t (overall survival from the start of treatment (first cycle of TAT) to death from any cause) of 16 months for P1 and 19 months for P2, and no acute local or systemic toxicity were reported. However, both patients eventually experienced tumour recurrence, with the recurrence period spanning from 2 to 11 months post-treatment. Notably, the study showed that smaller tumours displayed a comprehensive radionecrotic transformation, while larger tumours primarily exhibited necrosis in the proximity of the catheters used for injection. This discrepancy in response is likely attributable to the relatively short $T_{1/2}$ of Bi-213 ($T_{1/2}$ of 0.77 h), potentially resulting in inadequate intratumoral distribution before radioactive decay occurs. These results have raised valid concerns

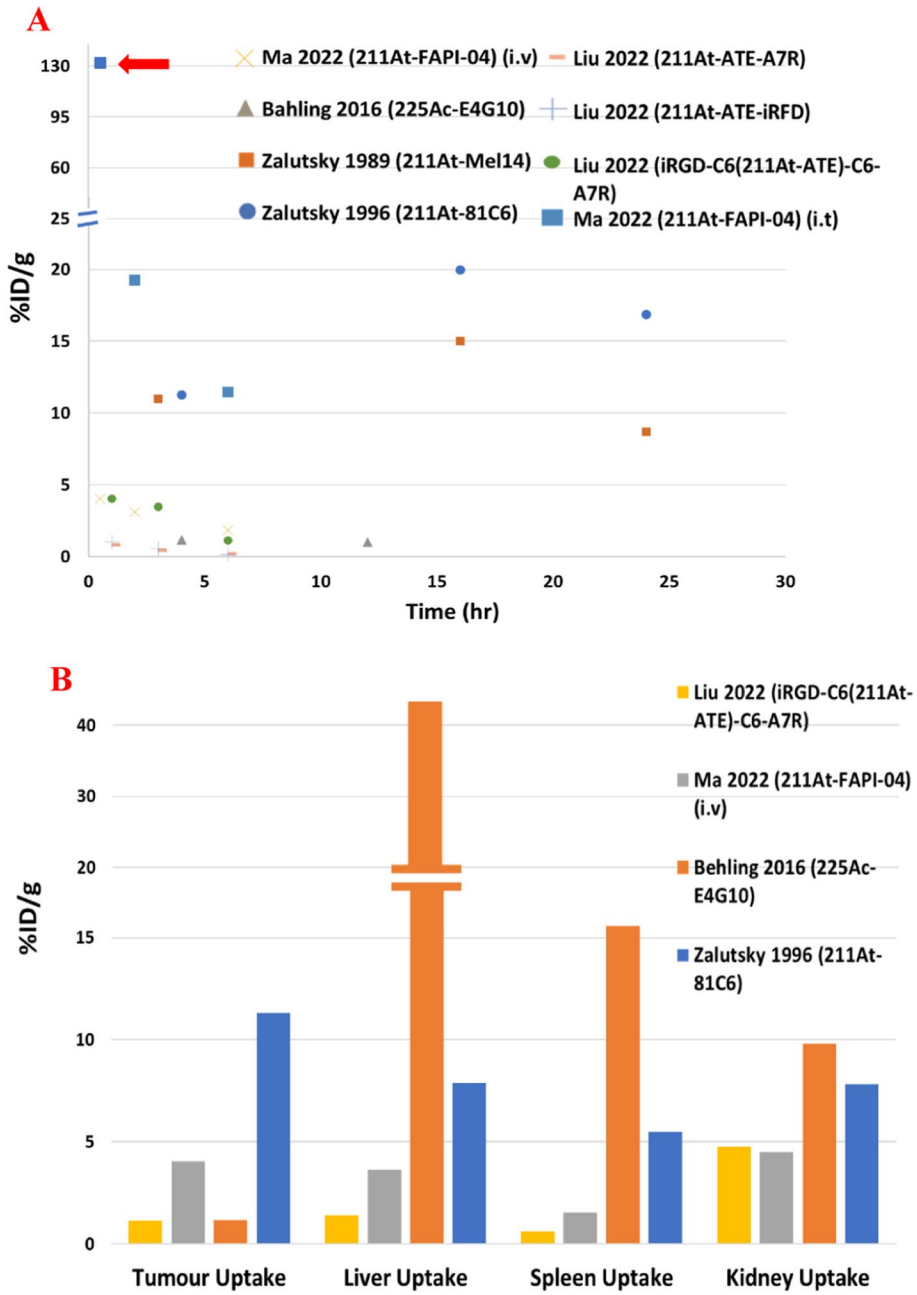

Fig. 4 Biodistribution of the targeting agent. (**A**) The tumour accumulation (red arrow indicates the intratumoral injection result). (**B**) The intravenous injection distribution in tumour and healthy organs

regarding the suitability of Bi-213 for the treatment of larger tumour volumes. It suggests that Ac-225 ($T_{1/2}$ of 238.10 h) may be a more appropriate choice for addressing such cases, potentially offering improved outcomes.

The studies conducted by Krolicki et al. [26, 30–32] have contributed to advancing our understanding of TAT for GB. Their clinical trials began in 2018 when they investigated the use of Bi-213 conjugated with Substance P/NK-1 in nine patients with secondary GB. This results showed a diverse spectrum of outcomes, with a median OS of 16.4 months. In 2019, Krolicki et al. [32] expanded their scope to include 20 rGB patients, categorised into NIH0, NIH1 and NIH2 groups based on the National Institutes of Health (NIH) clinical grading scale for GB. This scale ranges from 0 to 5, reflecting various levels of neurological function, with higher grades indicating worse neurological function. Notably, the study observed longer OS and PFS in patients with lower-grade NIH scores, highlighting the significance of patient stratification.

Their exploration of TAT continued with studies involving 21 and 29 patients with primary and secondary rGB, employing Ac-225 and Bi-213 conjugated with Substance P/NK-1, respectively. Surprisingly, the treatment effect appeared independent of the radioisotope injected activity

Table 3 Summary of clinical trials performed investigating targeted alpha therapy (TAT) in glioblastoma

Study ID	Isotope	Target agent/ target	Patient population	Treatment plan/ route	Main finding	Limits/further work	Toxicities
Zalutsky et al. 2008 [34]	At-211	Ch81C6/ Tenascin C	14 Recurrent GB	71–347 MBq, all conjugated to 10 mg of ch81C6/ surgical cavity	OS-t: 12 mos (3.22–34.8 mos); RT: 10.05 ± 0.37 h; % 211At decays in SCRC: 96.7% ± 3.6%; %ID in blood pool (6–12 h): 0.044 to 0.067; 8 biopsies confirmed recurrence	Variations in the volumes of the surgical cavity resection sites. Further evaluation of multiple dose administration schedule.	No patient in the study experienced dose-limiting toxicity. No episodes of grade 2 or higher hematologic toxicity.
Cordier et al. 2010 [28]	Bi-213	Substance P/ NK-1	2 critically located GB	P1: 1 cycle of 1.07 GBq; P2: 1 cycle of 1.92 GBq ; 1 cycle (Intratumoural injection via 2–3 catheters, 3–5 injections/ cycle)	OS-t: 16 mos (P1), 19 mos (P2); PFS: 2 mos (P1), 11 mos (P2); %ID in blood pool: max < 0.04; Recurrence occurred in both patients (2–11 mos after treatment)	Short half-life of 213Bi which may result in insufficient intratumoral distribution before decay. Ac-225 suggested to be more suitable for larger volumes.	Intratumoural injection was well tolerated by all patients; no relevant acute local or systemic toxicity were found according to the National Cancer Institute (NCI) Common Toxicity Criteria (CTC) scale (version 2.0). In the long-term follow-up, no further substantial local or systemic toxicity was found.
Krolicki et al. 2018 [31]	Bi-213	Substance P/ NK-1	9 Secondary GB	1–6 cycles in 2-month intervals. 1–3 injections of up to 1.8 GBq per injection/ cycle. Median total injected activity was 5.8 GBq (range, 1.4–9.7 GBq)	OS-t: 16.4 mos OS-d: 52.3 mos PFS: 0.3–51.5 mos (median 5.8 mos)	More extensive studies to evaluate PFS and OS in a larger number of patients, and the optimisation of patient inclusion criteria should be taken into consideration. NIH scale seems to be good stratification factor for qualification to TAT. Lack of dosimetry data in studies protocol. Local radioisotope treatment of brain tumours requires further dosimetry studies. Frequent administration of low doses and convection-enhanced diffusion of radiopharmaceuticals by a modified application procedure should be considered.	Local treatment was well tolerated. In only two patients, mild flush of the face was observed as a systemic SP effect when a small amount of the tracer was absorbed in the blood. In one patient, transient worsening of paresis and aphasia were observed for five days. No other severe adverse events occurred.

Table 3 (continued)

Study ID	Isotope	Target agent/ target	Patient population	Treatment plan/ route	Main finding	Limits/further work	Toxicities
Krolicki et al. 2019 [32]	Bi-213	Substance P/ NK-1	20 Recurrent GB NIH0n = 6 NIH1n = 7 NIH2n = 7	Up to 2.1 GBq (median 1.7 GBq) *	OS-d: 23.6 mos OS-r: 10.9 mos OS-t: 7.5 mos PFS: 2.7 mos **NIH0 vs NIH1 vs NIH2:** PFS: 5.4 vs. 1.6 vs. 0.9 mos; OS: 17.1 vs. 4.2 vs. 3.3 mos		The treatment was well-tolerated by the patients, with only minor side effects observed. Two patients experienced facial flushing. One patient had a transient worsening of paresis for five days.
Krolicki et al. 2021 [26]	Ac-225	Substance P/ NK-1	21 Recurrent GB (primary and secondary)	10 MBq (n=4), 20 MBq (n=10), 30 MBq (n=7) *	**10MBq:** PFS: 4.5 mon. OS-d:18 mos OS-r/c: 13.0 mos OS-t: 7.0 mos **20MBq:** PFS: 2.6 mos OS-d: 33.0 mos OS-r/c:12.5 mos OS-t: 5.0 mos **30MBq:** PFS: 2.3 mos **Primary GBM** (n=15): PFS: 2.4 mos OS-d: 21.0 mos OS-r/c: 12.0 mos OS-t: 5.0 mos **Secondary GBM** (n=6): PFS: 2.9 mos OS-d: 65.0 mos OS-r/c: 36.0 mos OS-t: 16.0 mos		Toxicity grades were classified using the Common Terminology Criteria for Adverse Events. **In the group treated with Bi-213:** No signs of haematological, liver, and kidney toxicity were observed; four out of 29 patients had flush of face - due to systemic SP effects (some traces found in bloodstream); tow patients transient worsening of paresis and aphasia were observed for five days; No other severe adverse events in Bi-213 group. **In the group treated with Ac-225:** six patients had worsening of hemiparesis or aphasia; Only adverse effects were seen in the group treated with 20 MBq and 30 MBq - In two patients, 2 & 3 weeks after treatment with 30 MBq, severe perifocal brain edema was observed, requiring hospitalisation, without intubation; Observed haematological toxicity: thrombocytopenia grade 2 in one patient in the 20 MBq group and thrombocytopenia grade 3 in one patient in the 30 MBq group, and hepatic toxicity grade 1 was seen in one patient of the 30 MBq dose escalation group.
Krolicki et al. 2023 [30]	Bi-213	Substance P/ NK-1	29 Recurrent GB (primary and secondary)	1.85 GBq per cycle *	**Primary GBM:** PFS: 2.7 mos OS-d: 23.6 mos OS-r: 10.9 mos OS-t: 7.5 mos **Secondary GBM:** PFS: 5.8 mos OS-d: 52.3 mos OS-c: 18.4 mos OS-t: 16.4 mos		

* Same method of delivery as described in Krolicki et al.[31]

SCRC surgically created resection cavity, *RT* residence time for At-211 in the SCRC, *%ID* percent of injected dose, *PFS* progression-free survival time is the time from the start of radioisotope treatment to clinical or imaging signs and symptoms of progression, relapse, or death, *OS-d* overall survival from time of initial diagnosis to death from any cause, *OS-r/OS-c* overall survival from recurrence or conversion in primary tumours or conversion into secondary GBM to death from any cause, *OS-t* overall survival from the start of treatment (first cycle of TAT) to death from any cause

within the range of 10–30 MBq. This could be attributed to the limited diffusion of the treatment into the tumour, predominantly influencing the peripheral regions near the cavity. Furthermore, the study noted the potential influence of tumour heterogeneity, exemplified by a diverse range of apparent diffusion coefficient (ADC) values observed in MRI scans, partly explaining the varied responses to treatment. The data from these trials showed that the OS time in primary GB increased to 23.6 months with Bi-213 and 21 months with Ac-225, and OS in rGB increased to 10.9 months with Bi-213 and 12 months with Ac-225 when compared to the OS with standard treatment [53–58]. Notably, the analysis showed a statistically significant longer OS-d and OS-r/c time for patients with secondary glioblastoma compared to those with primary glioblastoma. However, when comparing PFS and OS-t (the two most treatment-related parameters), both groups of patients demonstrated similar outcomes. This implies that local treatment administration of radionuclides effectively targets tumours in both patient groups, regardless of the genetic attributes of their tumours.

3.3.1 Delivered Dose

The published clinical studies touch upon factors influencing the radiation dose delivered by TAT, such as the total injected activity and the diffusion rate of the radiopharmaceutical into the tumour. However, specific numerical values for the actual radiation doses delivered to the tumour/target volume are not provided. The biodistributions of the radiopharmaceutical were assessed using PET/CT post-injection, and similar to the in vivo studies, the clinical studies reported on the %ID retaining in the blood pool. All clinical studies consistently reported a high retention of the radiopharmaceutical at the target site, a finding further confirmed by the low percentage values of the injected dose in the blood pool (maximum values in all studies were < 4–6 %ID) [26, 28, 30–32, 34]. The absence of detailed information on the translated dose to the target volume complicates the ability to establish definitive correlations between administered activities; a dose-response relationship and therapeutic outcomes becomes challenging.

Understanding the actual radiation dose delivered to the tumour is essential for optimising treatment protocols, ensuring adequate tumour coverage, and minimising treatment associated side effects. This highlights the critical need for further dosimetry studies that take into account the unique characteristics of the radiopharmaceutical, diffusion rates, and potential variations in individual tumour structures.

Additionally, while reports consistently detail the amount of activity administered, they lack quantification of how effectively this activity translates into energy deposition at the targeted volume. To bridge this gap, multiple imaging sessions are needed to estimate the activity within normal tissues and tumours. These imaging data allow for the reconstruction of a detailed spatial dosimetry based on time-activity curves. It is essential to ascertain whether the radiopharmaceutical accumulates uniformly, achieves sufficient intensity, and reaches the peripheries of the tumour where residual cells may exist. This dual challenge of delivery and dosimetry underscores the need for advanced imaging techniques and precise dosimetric calculations to ensure that the radiation dose is accurately distributed throughout the tumour volume.

3.3.2 Toxicities

Toxicity assessments across the studies by Zalutsky et al. [34], Cordier et al. [28] and Krolicki et al. [26, 30–32] revealed that TAT is a generally well tolerated treatment with minimal side effects (Table 3). Notably, toxicity profiles were similar between Ac-225 and Bi-213 when doses were equivalent, suggesting that adverse effects may be more related to dosing than the specific radionuclide used [30]. These findings underscore the importance of precise dosing considerations and careful dose-escalation protocols to minimise potential risks associated with targeted radionuclide therapies, particularly for Ac-225. Continued research and clinical monitoring are essential to refine treatment protocols and ensure patient safety.

Overall, these studies contribute to understanding TAT for GB, emphasising patient stratification and dosimetry considerations. Despite variations in outcomes, local administration of radionuclides demonstrated effective tumour targeting, impacting both primary and secondary GB. Further exploration is crucial for optimising treatment schedules and improving overall survival and progression-free survival for GB patients.

4 Delivery Methods

The blood-brain barrier (BBB) is a semi-permeable membrane, comprised of specialised endothelial cells supported by pericytes and astrocytes, that tightly regulates the passage of molecules into the brain [59]. The BBB's selective physical barrier, which restricts the entry of molecules larger than 400 Daltons, poses a challenge for delivering therapeutic agents to treat brain tumours [59]. Furthermore, brain tumours compromise the BBB, resulting in the formation of the blood-tumour barrier (BTB), characterised by heterogeneous permeability and active efflux mechanisms [60]. This creates a challenging scenario for drug delivery, as the efficacy of therapies is impeded by the expression of transport proteins and efflux transporters in both the BBB and the BTB [60].

To overcome these barriers, various strategies have been explored. One avenue is the use of peptide-drug conjugates, where peptides facilitate targeted drug delivery [61]. Peptide-drug conjugates exploit specific receptors on target tissues for selective drug transport; this is used for intravenous delivery. However, challenges persist, requiring stable conjugates with strong binding affinity, and the need to avoid modifying the drug's stability or binding affinity during delivery [61]. In vivo studies [21, 42, 43] demonstrate that only a few targeting agents can effectively cross the BBB to reach brain tissue, and systemic delivery often results in undesirable side effects in non-targeted tissues.

Particularly in GB treatment, the localised nature of the disease and the absence of distal metastases underscore the inherent risks of systemic radionuclide administration, such as off-target radiation exposure. Clinical evidence increasingly supports localised delivery methods like intratumoral or post-surgical cavity administration. These methods not only bypass the BBB but also target microscopic disease directly, overcoming the dilution effect typical of systemic administration. This approach aligns with the fact that GB does not typically metastasise, making localised delivery especially suitable. Clinical trials consistently utilise intratumoral and intracavitary delivery to maximise the efficacy of TAT agents and minimise systemic exposure.

Intratumoral and intracavitary methods involve direct injection, which provides localised TAT agent release, minimising systemic exposure. In the clinical studies, intratumoral and intracavitary delivery was implemented, and the biodistribution of the radiopharmaceutical was assessed using PET/CT [26, 30–32]. The local delivery of the TAT agents for the treatment of GB faces intricate challenges associated with the increased tissue pressure within tumours and adjacent tissues [26, 28, 30–32]. This elevated pressure diminishes the gradient that drives the diffusion process, resulting in a notable reduction in the absorbed dose by the peripheral areas of the treatment volume [30]. Tumour structural differences further complicate matters, highlighting the need for an understanding of tissue heterogeneity and variations in radiopharmaceutical diffusion. Apparent diffusion coefficient measurements derived from MRI examinations offer insights into diffusion variations within tumours, potentially influencing treatment responses [30]. Factors affecting successful locoregional therapy include molecular weight, physicochemical properties, extracellular space density, and the impact of repetitive injections on glial scarring [30]. The slow diffusion rate into swollen brain tissue poses a significant challenge, prompting exploration into convection-enhanced diffusion (CED) techniques [30, 62]. CED utilises a small hydraulic pressure that results in bulk/convection flow, enabling a homogeneous drug distribution directly into the adjacent brain [62].

Despite the progress, challenges persist in achieving effective drug delivery to the brain and overcoming the barriers imposed by the BBB and BTB. The complex interplay of biological processes necessitates further exploration and understanding for the successful implementation of local TAT in the treatment of GB, emphasising the importance of ongoing dosimetry studies and a nuanced approach to treatment protocols.

5 Limitations and Gaps in Literature

While the current literature on TAT for GB shows promise, several gaps and limitations necessitate further investigation and the optimisation of future clinical trials . Here are the limitations and gaps we identified:

i. **Radiation dose to susceptible organs:** Systemically administered radionuclides pose a limitation due to the radiation dose reaching susceptible organs, including the liver, spleen, stomach and kidneys as seen in [20, 41–43]. Pre-clinical in vivo studies have indicated that intratumoral or local injection of the radionuclide is likely more effective and less toxic to healthy tissues [21, 42, 43].
ii. **Limited number of patients sampled:** The clinical studies have been conducted on a very limited number of patients and have not been randomised to alternative available conventional therapies. Expanding the scope of studies to include a larger and more diverse patient population will provide a more comprehensive understanding of the therapy's efficacy and safety. These studies should also consider optimising patient inclusion criteria for further research and thus enable randomised studies.
iii. **Dosimetry studies:** Additional dosimetry/radiobiological modelling studies are needed to better comprehend the complex biological processes involved in local radioisotope treatment of GB. These studies can give quantifiable evidence of TAT's effectiveness in tumour cell kill, help refine treatment protocols, and optimise radiation dosages. Further dosimetry studies that quantify the radiation doses at the target site are crucial, considering factors such as the unique characteristics of the radiopharmaceutical, diffusion rates, and potential variations in individual tumour structures. Moreover, there is a significant need for cellular dosimetry studies to understand and predict the biological effects of alpha-particle radiopharmaceuticals. Dosimetry at the micro- or multi-cellular scale level can inform treatment optimisation and efficacy assessment by elucidating the radiation effects at the cellular

level, which are critical for tailoring therapy to achieve maximum therapeutic benefit while minimising harm.

iv. **Microdosimetry models:** The limited application of microdosimetric models highlights the importance of future studies in this area. Understanding radiation effects at the cellular level is critical for optimising treatment strategies.

v. **Intratumoral distribution:** The challenge of achieving effective intratumoral distribution of alpha emitters, especially in larger tumours/volumes, needs further exploration. Using radioisotopes with longer half-lives such as Ac-225 may have an impact on this distribution issue and should be investigated in greater detail.

vi. **Mechanisms of action for TAT:** Further research could delve into the mechanistic differences between TAT and other treatment modalities in terms of GB treatment. This would provide insights into the unique benefits and challenges associated with alpha-particle irradiation. Also, exploring its synergy with other treatment modalities such as external beam radiotherapy and chemotherapy could hold promise.

vii. **Delivery methods/diffusion of alpha-emitting agents:** Innovative delivery methods for alpha-particle-emitting agents, especially considering their limited range, need to be explored. Additionally, looking at how to quantify the distribution of the agents after injection and predicate its path within treatment volume are important. Finding ways to ensure effective distribution within tumours is crucial.

viii. **Recoil effect of radionuclides:** None of the reviewed studies have addressed the recoil effect, which is challenging to measure as it requires tracking daughter nuclides independently. This gap is critical as it could impact the stability and efficacy of radionuclide therapies. Recent simulation studies, such as those by Tronchin et al. [63], begin to address this by examining dosimetry from recoil daughter nuclides.

ix. **Factors affecting cytotoxicity:** It is essential to explore the factors affecting the cytotoxicity of available alpha-emitting agents, comparing different radioisotopes and their potential clinical applications. This could lead to a more nuanced understanding of their therapeutic potential.

Overall, while TAT shows promise as a treatment for GB, addressing these identified gaps and optimising treatment protocols underpinned by further well designed preclinical and clinical studies are imperative for its successful application. TAT has significant potential to improve outcomes in a patient group with no material survival improvement over the last two decades and persistently remaining extremely low survival rates.

6 Review Limitations

It is important to recognise the limitations of this review. The search strategy was executed across diverse databases (MEDLINE, Embase and Scopus, supplemented by Google Scholar for grey literature), with papers published in non-English language and conference abstracts, posters and review articles excluded during the full-text review. Although the search strategy (Appendix A, Online Supplemental Material) was developed with aid of a UniSA librarian, it is acknowledged that these exclusions and limitations may have led to the oversight of some relevant articles.

7 Conclusion

TAT offers a promising avenue for treating GB, but its full potential hinges on overcoming significant challenges. Systemic administration of radionuclides raises concerns about radiation exposure to vulnerable adjacent normal tissues, advocating for localised delivery methods. Small patient samples in current studies necessitate larger and more diverse clinical trials to establish real-world effectiveness. Dosimetry studies and the investigation of local distribution methods are vital for refining dosing and enhancing treatment outcomes. Additionally, exploring the synergy of TAT with other novel therapies could hold promise.

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Ethics Approval This review did not require ethics approval as it is a literature review and does not involve any new studies of human or animal subjects.

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Consent for Publication All authors consent to the publication of this article.

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