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REVIEW ARTICLE

The prevalence of post-therapy epilepsy in patients treated for high-grade glial tumors: a systematic review and meta-analysis

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Abstract

Gliomas are the most prevalent type of primary brain tumor of the adult central nervous system. High-grade gliomas (HGG) are the most common type of glioma. Epilepsy is often the first clinical manifestation of HGG. Since epilepsy leads to increased morbidity and mortality rates, seizure control is one of the main therapeutic goals for patients with glioma-related epilepsy. Post-therapy epilepsy is observed in a significant percentage of patients, hence, this work aimed to quantify the prevalence of post-therapy epilepsy after HGG treatment. Our search was conducted across PubMed®, EMBASE®, Web of Science™, Cochrane Library, Sicelo and Scopus, adhering to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. This review included articles published in Portuguese or English that evaluate adult patients with newly diagnosed HGG, who were treated with at least surgery or radiation. Thirty-six studies reporting on 4036 HGG patients were included in our meta-analysis. The mean age ranged from 44 to 73 years. Glioblastoma was the most commonly observed HGG, representing 77,8% of all glioma patients. The pre-treatment seizure frequency was observed in 21,2%. All patients underwent surgery as the main therapy, and 1842 patients received standard adjuvant therapy. We also observed a pooled prevalence of post-therapy seizures of 25.5% (95% confidence interval of [19.9%; 31.1%]). Substantial heterogeneity in all assessed variables was observed. Conducting larger prospective studies with suitable epilepsy diagnostic methods would help provide a more precise estimate of the number of HGG patients who develop post-therapy epilepsy.

Keywords High-grade glioma · Post-therapy epilepsy · Glioblastoma · Astrocytoma · Oligodendroglioma · Systematic review

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Introduction

High-grade gliomas (HGG), classified as WHO grade 3 and 4, are the most common type of malignant glioma, accounting for more than half of all malignant primary brain tumors [1].

Patients with gliomas experience a wide range of symptoms, dependent on size and location of the tumor, as well as the degree of peritumoral edema. The most common symptoms at diagnosis are headaches, seizures, progressive focal neurologic deficits, motor weakness, cognitive decline, and blurred vision [2]. Among these, epilepsy is the most common initial clinical manifestation, with over a half of patients experiencing at least one seizure during the disease course [3, 4]. The presence of neurological deficits and seizures can significantly impact quality of life.

Glioma-related epilepsy (GRE), defined as epileptic seizures secondary to the simultaneous existence of a glioma, occurs in approximately half of HGG patients [4]. The pathological mechanisms underlying this condition are thought to be multifactorial. They can be broadly categorized as tumor-centric (resulting from direct tumor effects, such as edema, inflammation, blood hypoperfusion, pH imbalance, electrolyte disturbances or disruption of the BBB) or epileptocentric (involving changes in the homeostasis of neurotransmitters, such as glutamate and GABA) [5, 6].

Epilepsy in HGG causes significant morbidity and disability; thus, controlling epileptic seizures is a primary therapeutic goal for patients with GRE. Standard oncological treatment, with surgery and chemoradiotherapy, remains the therapy of choice in GRE. Extended surgical resection of the tumor results on increased survival and good control of epileptic seizures, with approximately 70% of HGG patients achieving seizure freedom after surgery [5]. Additionally, anti-seizure drugs (ASDs), particularly levetiracetam, are used to manage seizures in GRE patients [4]. However, the prevalence of post-therapy epilepsy is still high. The evaluation of seizure outcomes in patients treated for GRE has gained increasing importance in clinical care, as seizure control is recognized both as critical for quality of life, and as a significant prognostic factor for survival and tumor recurrence [7, 8].

Although the mechanisms of post-therapy epilepsy are not fully understood, it is hypothesized that factors such as complications during surgery, incomplete resection of the epileptogenic area, tumor recurrence and/or the activation of epileptic neuronal networks outside the peritumoral area may be in the origin of epileptic seizures [5, 6].

Through a systematic review with meta-analysis, this work aims to quantify the prevalence of post-therapy epilepsy in patients treated for HGG, as an improvement in therapy as led to an increase in GRE patients' survival and, potentially, to a greater prevalence of post-therapy epilepsy.

Methods

For this systematic review, recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) workgroup were followed. The study protocol was registered on the PROSPERO International Prospective Register of Systematic Reviews database with the registration number CRD42024504910.

Search strategy

The search was conducted in the following databases: PubMed®, EMBASE®, Web of Science™, Cochrane Library, Sicelo and Scopus. For the PubMed® and EMBASE® databases, combinations of controlled terms (MeSH terms—''Glioma'', "Brain Neoplasm", "Astrocytoma", "oligodendroglioma", "glioblastoma", "radiotherapy", "Surgical Procedures, operative", "Epilepsy" and "Seizures", and EMTREE terms – 'glioma', 'brain tumor', 'astrocytoma', 'oligodendroglioma', 'glioblastoma', 'radiotherapy', 'surgery' and 'epilepsy') were used along with non-controlled terms related to gliomas, therapeutic procedures, such as surgery and radiotherapy, and epilepsy. The complete search strategy is outlined in supplementary Table 1.

Selection methods

Using Rayyan [9], a web-based tool for systematic reviews, a first screening of results by title and abstract was independently performed by two investigators, to reduce selection bias. The inclusion criteria included: adult patients with newly diagnosed HGG and of both sexes, who were treated with at least surgery or radiation, and assessed for long-term side-effects, including seizures. Randomized clinical trials, cohort, case–control, and cross-sectional observational studies were included. All publications regarding case reports, comments, reviews, and editorials were excluded. Articles published in languages other than English or Portuguese, and those that only assessed acute/subacute effects were also excluded.

Discrepancies in selection decisions were reconciled by consensus, or by a third investigator. Following this screening, the same authors conducted a full-text evaluation of the selected studies, adhering to pre-established criteria.

Data extraction

Data from the original studies were gathered using a Microsoft® Excel spreadsheet. The collected data included: study details, country, study design, number of participants, demographics (age and sex), tumor features, number of patients with seizures at presentation, therapeutic approach, assessment over time, outcomes of post-therapy epilepsy, seizures characteristics and number of patients medicated with ASD. Tumor features included glioma location and histopathological characteristics, and treatment details included adjuvant therapies, such as RT type, RT dose and CT used. Time assessments encompassed time from the beginning of symptoms until glioma diagnose (GD), time from GD until main therapy, time from main therapy until adjuvant therapy and time from end of therapy until last follow-up.

The analyzed seizure outcomes were measured through seizure frequency, Engel class, and/or seizure freedom. Data extraction was conducted by one investigator and verified by a second one. Discrepancies were resolved through consensus or by a third investigator.

Statistical analysis

A qualitative synthesis of the major findings of the included studies was performed, namely by assessing the most common clinical and demographic variables among the studies. A quantitative synthesis was obtained through a meta-analysis for a pooled proportion of post-therapy epilepsy rates, using the METAFOR package of the open-source software jamovi, version 2.3.18 [10–12]. The DerSimonian-Laird random-effects model was used, due to high heterogeneity between studies. Heterogeneity was evaluated using Higgins I^2 statistic and Cochrane Q test. Publication bias was evaluated using a funnel plot and an Egger's test for asymmetry, if 10 or more studies were included. A p-value less than 0.05 was considered statistically significant.

Results

Selection and characteristics of the studies

The search strategy implemented retrieved a total of 11,534 articles for this systematic review. Among them, 5072 duplicates were identified through both automatic and manual methods. Following title and abstract evaluation, among the remaining 6462 articles, 6106 were excluded for not meeting the eligibility criteria.

Out of the total, 356 studies were integrally and thoroughly reviewed. The exclusions were determined by the following criteria: 38 studies did not include the desired population, in 3 studies the full text was not available, in 108 studies the long-term post-therapy epilepsy outcome was not evaluated, 1 article had been retracted, and 170 studies didn't have the whole desired information. Of these 170 excluded articles, 17 studies did not specify the follow-up period since the end of therapy, 91 were abstracts from proceedings with insufficient information and 60 studies included types of brain tumors other than high-grade gliomas, and it was not possible to distinguish between them. At the end, 36 studies were ultimately included in this systematic review and meta-analysis [13–48].

Figure 1 represents the article selection flowchart, following PRISMA recommendations.

Included studies were mainly retrospective observational studies (21 studies), 8 were prospective observational studies and 6 clinical trials. Most were conducted in the United States (15 studies), Germany (6 studies), and China (4 studies).

The available data from the included studies were categorized into the following 3 topics: (I) Baseline characteristics (II) Treatment details and (III) Seizure outcomes. All included studies are discussed in the context of these 3 topics in the following sections.

The characteristics of the incorporated studies are outlined in Tables 1, 2, 3.

I. Baseline characteristics

Among the 36 studies included, a combined cohort of 4036 patients with high-grade gliomas took part. From these, in 5 studies it was not possible to distinguish some variables such as age, sex, glioma location and presence of seizures at presentation, from the high-grade glioma patient´s to the other brain tumor patients included in the studies. Hence, only 31 studies referred to high-grade gliomas in baseline characteristics.

In these studies, the mean age ranged from 44 to 73 years. Furthermore, in 31 studies, 1521 (39,9%) patients were female, in a total of 3813 patients documented with high-grade gliomas.

All but 3 studies reported the histopathological glioma type, with glioblastomas being the most common, representing 77,8% of all included high-grade glioma types. Tumor location was reported in 23 studies, and 4 studies reported, also, tumor location based on the involved hemispheric lobes.

The frequency of pre-treatment seizures was reported in 25 studies, and of the analyzed 4036 high-grade gliomas, 855 (21,2%) patients had seizures at presentation.

Only one study assessed the time from the beginning of symptoms until GD and 1 study reported the time since the GD until the beginning of therapy, ranging from 3 to 8 weeks.

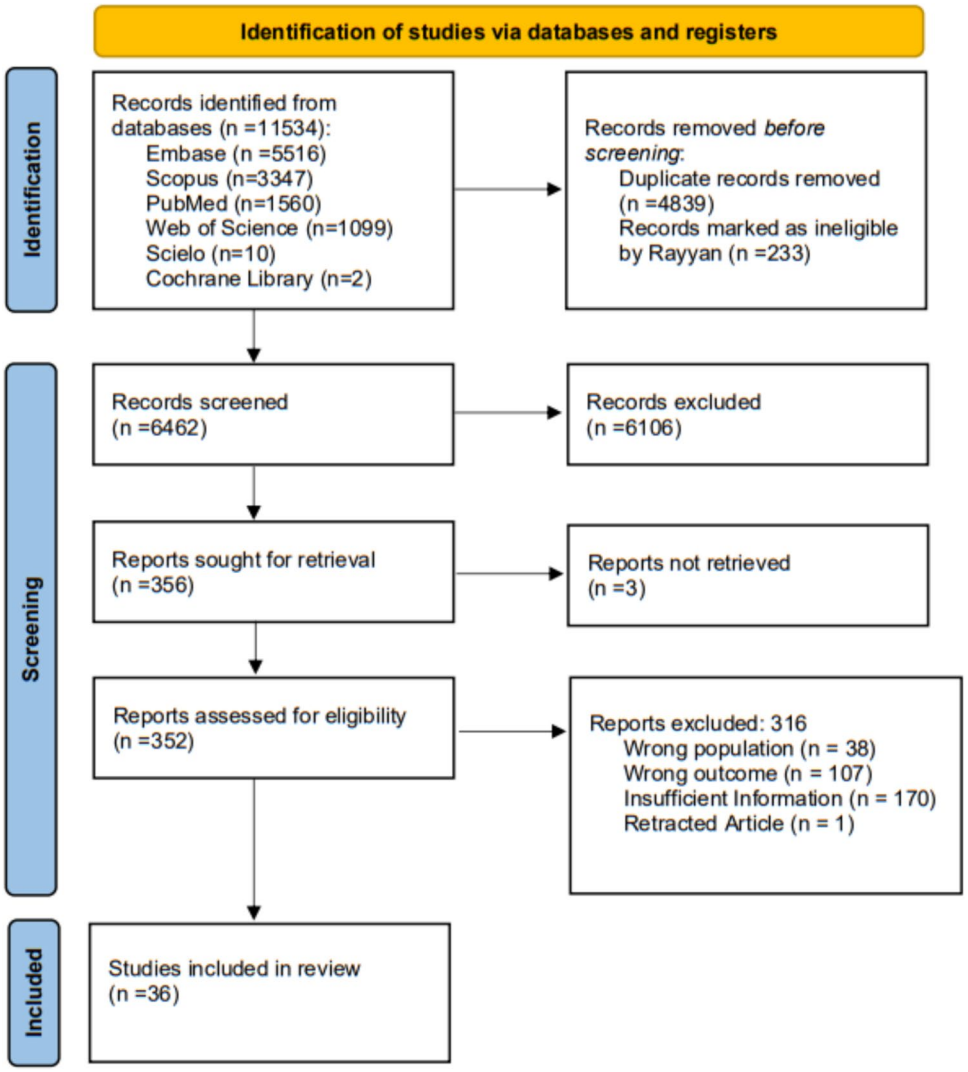

Fig. 1 Flowchart of research and study selection for the systematic review according to the PRISMA guidelines

II. Treatment details

All patients underwent surgical procedures as the main therapy. Extension of the high-grade glioma's removal was reported in 28 studies, with gross total resection/maximal safe resection being the most common technique in 16 of the evaluated articles.

The use of adjuvant chemotherapy or radiation therapy was reported in a total of 28 articles, with 1842 patients receiving the standard therapy for high-grade gliomas. The number of patients with high-grade gliomas that received adjuvant RT was 2228, with a mean total dose of 54,6 Gy, and with the external beam therapy being the most commonly used technique. The number of patients who have also received concomitant CT was 2146, with 1559 patients receiving the standard chemo agent Temozolomide (TMZ). Other therapies were reported in 7 studies.

Only 6 studies assessed the time since the main therapy until adjuvant therapies, with time ranging from 2 to 8 weeks.

III. Seizure outcomes

Evaluation of follow-up since the last performed therapy until seizures assessment was inconsistently evaluated among the total 36 studies. In 20 studies, the pooled mean duration of follow-up was 17 months, whereas in 18 studies the follow-up duration ranged from 1 month to 13,6 years.

Only 5 studies addressed the type of post-therapy seizures presented.

In 16 studies, 1061 patients were under ASDs before treatment and in 1602 patients after treatment. The most common ASD used was levetiracetam, as 5 studies reported.

Table 1 Baseline characteristics of the studies included in the systematic review

Author, year	Country	Study type	High-Grade Glioma Patients (n)	Age (years), mean±SD	Females n (%)	Glioma type	Glioma Location	Epilepsy at Presentation	Time since the beginning of symptoms until Glioma diagnose (GD)	Time since GD until therapy
Cifarelli CP, et al. (2023) [39]	USA	Retrospective	6	62	1 (17%)	GBM: 6	Frontal: 3 Parietal: 2 Temporal: 1	NA	NA	NA
Hansen AL, et al. (2023) [35]	USA	Retrospective	19	67.2 ± 9.08	7 (36.8%)	GBM: 19	**Temporal** - Right hemisphere: 4 - Left hemisphere: 5 **Parietal** - Right hemisphere: 3 **Frontal** - Right hemisphere: 7	2	NA	NA
Harwick E, et al. (2023) [15]	USA	Prospective	7	65	2 (28.6%)	GBM: 6 AA: 1	Left frontal: 3 Left parietal:2 Left frontoinsular: 1 Left temporal: 1	2	NA	NA
Li L, et al. (2023) [13]	China	Retrospective	42	44 (19–68)	23 (54.8%)	AA: 15 AO: 12 GBM: 15	Frontal: 27 Temporal: 13 Left: 21 Right: 17 Bilateral: 4	15	NA	NA
Ollila L & Roivainen R (2023) [30]	Finland	Retrospective	74	48.0 ± 16.8*	43 (35%) *	WHO grade III: 19 WHO grade IV: 55	Frontal: 53 Temporal: 18 Parietal: 11 Occipital: 3 Several lobes/large: 38*	87*	NA	NA
Sim HW,et al. (2023) [24]	15 hospital sites in Australia and 1hospital site in the United States	Randomized phase II trial	103 Experimental arm: 69 Control arm: 34	73 (65–88)	37 (36%)	GBM: 103	NA	NA	NA	NA

Table 1 (continued)

Author, year	Country	Study type	High-Grade Glioma Patients (n)	Age (years), mean±SD	Females n (%)	Glioma type	Glioma Location	Epilepsy at Presentation	Time since the beginning of symptoms until Glioma diagnose (GD)	Time since GD until therapy
Stritzelberger J, et al. (2023) [22]	Germany	Retrospective	421	61.7±12.2	186 (44.2%)	GBM: 421	Frontal: 185 Parietal: 127 Temporal: 213 Occipital: 79 Insular: 8	154	NA	NA
Liu S, et al. (2022) [27]	China	Retrospective	4	48.7	1 (25%)	GBM: 4	NA	NA	NA	NA
Ricklefs FL, et al. (2022) [14]	Germany	Retrospective	111	61.9 ± 11.7	46 (41.4%)	GBM: 111	Frontal: 36 Parietal: 55 Temporal: 44 Occipital: 22	36	NA	NA
Weber L, et al. (2022) [21]	Switzerland	Prospective	283	63 (52-72)	95 (34%)	GBM Grade IV: 245 AA Grade III: 38	NA	NA	NA	NA
Borger V, et al. (2021) [40]	Germany	Prospective	33	59 ± 14	14 (42%)	GBM: 33	Temporal: 33	33	NA	NA
Li L, et al. (2021) [46]	China	Retrospective	449	47 (18–74)	183 (40.8%)	AA: 138 AO: 79 GBM: 232	Temporal: 194 Other: 255	153	NA	NA
Pepper J, et al. (2021) [28]	UK	Retrospective	38	45.7 ± 2.48	14 (36.8%)	WHO grade III: 26 WHO grade IV: 12	NA	36	NA	NA
Climans SA, et al. (2020) [37]	Canada	Phase 3 trial	562	65-70 years: 165 71-75 years: 231 ≥76 years: 166	219 (39%)	GBM: 562	NA	8	NA	NA
Eichberg DG, et al. (2020) [32]	USA	Retrospective	26	51.6*	58 (51.3%) *	GBM: 26	NA	10/113*	NA	NA
Maialetti A, et al. (2020) [31]	Italy	Prospective	14	46.6	3 (21.4%)	NA	Multilobar: 5 Frontal: 4 Occipital: 2 Temporal: 3	14	NA	NA
Masuda Y, et al. (2019) [48]	Japan	Prospective	2	52	1(50%)	1 GBM 1 AA	NA	2	NA	NA

Table 1 (continued)

Author, year	Country	Study type	High-Grade Glioma Patients (n)	Age (years), mean±SD	Females n (%)	Glioma type	Glioma Location	Epilepsy at Presentation	Time since the beginning of symptoms until Glioma diagnose (GD)	Time since GD until therapy
Alimohamadi M, et al. (2016) [42]	Iran	Prospective	3	63.6	2 (66.7%)	NA	Insula	2	NA	NA
Liang S, et al. (2016) [47]	China	Retrospective	184	49.08 ± 10.59	84 (45.7%)	GBM: 184	Thalamus: 20 Frontal: 61 Temporal: 38 Parietal: 26 Occipital: 13 Midline or bilateral: 26	43	NA	3-8 weeks
Woo PY, et al. (2015) [20]	Hong Kong	Retrospective	198	55 (18–88)	76 (38.4%)	WHO grade IV: - GBM: 125 WHO grade III: - AA: 49 - AOA: 8 - AO: 6 - GS: 5 - AE: 5	Frontal: 79 Temporal: 53 Parietal: 39 Occipital: 10 Basal ganglia and thalamus: 17	47	NA	NA
Ansari SF, et al. (2014) [44]	USA	Retrospective	74	55.5 (20–83) *	102 (50.5%) *	GBM: 74	NA	NA	NA	NA
Sommer B, et al. (2014) [23]	Germany	Prospective	8	44.75	3 (37.5%)	WHO grade III - AA: 3 - AOA: 4 - AO: 1	NA	8	NA	NA
Garbossa D, et al. (2013) [29]	Italy	Retrospective	91	61.8 ± 12.03	39 (42.9%)	AA: 33 GBM: 58	Frontal:41 Occipital: 5 Parietal: 9 Temporal: 36	0	NA	NA
Kim YH, et al. (2013) [34]	South Korea	Retrospective	406	51 (18–86)	162 (39.9%)	AO: 43 AOA: 14 AA: 67 GBM: 282	Frontal: 116 Temporal: 78 Parieto-occipital: 34 Axial: 53	104	NA	NA
Rudá R, et al. (2013) [26]	Italy	Retrospective	10	40.6*	15 (34.9) *	NA	NA	10	NA	NA

Table 1 (continued)

Author, year	Country	Study type	High-Grade Glioma Patients (n)	Age (years), mean±SD	Females n (%)	Glioma type	Glioma Location	Epilepsy at Presentation	Time since the beginning of symptoms until Glioma diagnose (GD)	Time since GD until therapy
Waters JD, et al. (2013) [18]	USA	NA	11	62.1 (53-78)	4 (36.4%)	GBM: 11	Frontal: - Right side: 1/11 Temporal: - Right side: 6/11 - Left side: 3/11 Parietal: - Right side: 1/11	0	NA	NA
Chen C, et al. (2011) [41]	USA	Prospective Phase I trial	16	69 (34–84)	4 (25%)	GBM:16	Frontal: 6 Temporal: 4 Parietal: 5 Occipital: 1	NA	NA	NA
Della Puppa A, et al. (2011) [36]	Italy	Retrospective	55	55 ± 12	17 (30.9%)	WHO grade IV gliomas: 52 WHO grade III gliomas: 3	NA	14	NA	NA
Bock HC, et al. (2010) [45]	Germany	Retrospective	44	57 ± 10.9	NA	WHO grade IV - GBM: 44	NA	NA	NA	NA
Chaichana KL, et al. (2009) [38]	USA	Retrospective	648	55 ± 17	274 (42.3%)	GBM: 505 AA: 143	Frontal: 279 Parietal: 121 Temporal: 176 Occipital: 34	153	NA	NA
Baumert BG, et al. (2008) [43]	European Multi-centric	Phase III trial	14	49.4 (30-65)	7 (50%)	WHO grade III: 1 WHO grade IV: 13	Supratentorial	NA	NA	NA
Lai A, et al. (2008) [33]	USA	Phase II pilot study	10	54.3 (42–67)	6 (60%)	GBM: 10	NA	NA	NA	NA
Yang SH, et al. (2007) [17]	South Korea	Retrospective	39	51.9*	58 (58%) *	GBM: 22 AA: 8 AO: 7 Gliomatosis cerebri: 2	Frontal: 29 Temporal:12 Frontotemporal: 4 Other: 55*	10	NA	NA
Schwartz TH, et al. (2000) [25]	USA	Prospective	2	62.5	0 (0%)	GBM: 2	Insula: 1 Frontal:1	0	NA	NA

Table 1 (continued)

Author, year	Country	Study type	High-Grade Glioma Patients (n)	Age (years), mean±SD	Females n (%)	Glioma type	Glioma Location	Epilepsy at Presentation	Time since the beginning of symptoms until Glioma diagnose (GD)	Time since GD until therapy
Brem H, et al. (1995) [16]	USA	Phase I clinical Trial	22	60 (42-86)	7 (31.8%)	GBM: 21 AA: 1	Frontal: 6 Temporal: 11 Parietal:8 Occipital: 1	5	NA	NA
Whittle IR & Beaumont A (1995) [19]	Scotland	Retrospective	7	47.1	4 (57.1%)	AO: 7	Frontal: 10 Temporal: 7 Callosal-cingulate: 8 Other: 5 Perirolandic: 3 Occipital pole: 1 *	4	median: 15 months (range 1-168 days) *	NA

NA—Not Available; GBM–Glioblastoma; AA–Anaplastic Astrocytoma; AO–Anaplastic Oligodendroglioma; AOA–Anaplastic Oligoastrocytoma; GS–Gliosarcoma; AE – Anaplastic Ependymoma

*Data regarding the not high-grade glioma brain tumor cohort

Table 2 Treatment details of the studies included in the systematic review

Author, year	Main therapy (MT)	Extent of Tumor Removal	Time from MT until Adjuvant Therapy	Radiotherapy (RT)	RT Technique	RT Total Dose (Gy)	Chemotherapy (CT)	Other Therapies
Cifarelli CP, et al. (2023) [39]	Surgery	NA	NA	Yes	IORT	NA	NA	NA
Hansen AL, et al. (2023) [35]	Surgery	GTR: 16 STR: 3	NA	Yes (14)	NA	NA	TMZ	RT + Chemo + Bevacizumab: 3
Harwick E, et al. (2023) [15]	Surgery	GTR: 2 STR: 2 NTR: 3	NA	No	NA	NA	NA	NA
Li L, et al. (2023) [13]	Surgery	GTR: 26	NA	Yes	NA	NA	Yes	NA
Ollila L & Roivainen R (2023) [30]	Surgery	Resection: 108 Biopsy: 19*	NA	Yes	NA	NA	Yes	NA
Sim HW,et al. (2023) [24]	Surgery	GTR: 53 STR: 18 Biopsy: 32	Maximum 7 weeks + 3 days	Yes	EBRT	40	TMZ	**Experimental arm**: Standard therapy then adjuvant nivolumab and temozolomide
Stritzelberger J, et al. (2023) [22]	Surgery	Biopsy: 152 Partial: 140 Gross: 226 Missing: 2	NA	Yes (41)	NA	NA	TMZ (427)	TTF: 32 Immunotherapy (Avastin): 69
Liu S, et al. (2022) [27]	Surgery	NTR: 3 STR: 1	NA	Yes	NA	NA	TMZ	NA
Ricklefs FL, et al. (2022) [14]	Surgery	GTR: 42 NTR: 23 Partial resection: 21 Biopsy: 25	NA	No	NA	NA	NA	NA
Weber L, et al. (2022) [21]	Surgery	Biopsy: 89 STR (EOR <98%): 114 GTR (EOR ≥98%): 69 Unclear extent of resection: 11	NA	Yes	NA	60	TMZ	NA
Borger V, et al. (2021) [40]	Surgery	GTR: 20 Anterior temporal lobectomy: 13	NA	Yes	NA	NA	Yes	NA
Li L, et al. (2021) [46]	Surgery	GTR: 186 Non-GTR: 263	NA	Yes (369)	NA	NA	Yes (335)	NA

Table 2 (continued)

Author, year	Main therapy (MT)	Extent of Tumor Removal	Time from MT until Adjuvant Therapy	Radiotherapy (RT)	RT Technique	RT Total Dose (Gy)	Chemotherapy (CT)	Other Therapies
Pepper J, et al. (2021) [28]	Surgery	GTR: 6 Non-GTR: 32	NA	Yes	NA	NA	Yes	NA
Climans SA, et al. (2020) [37]	Surgery	Biopsy: 178 Partial or complete resection: 384	NA	Yes (281)	NA	40,5	TMZ (281)	NA
Eichberg DG, et al. (2020) [32]	Surgery	GTR: 81 MSR: 20 STR: 10 (8.8) *	NA	No	NA	NA	NA	NA
Maialetti A, et al. (2020) [31]	Surgery	GRT: 7 Partial resection: 5 Biopsy: 2	NA	Yes (11)	NA	NA	- TMZ: 12 - CCNU: 2	NA
Masuda Y, et al. (2019) [48]	Surgery	GRT: 1 STR: 1	NA	No	NA	NA	No	NA
Alimohamadi M, et al. (2016) [42]	Surgery	92%: 1 70%: 1 90%: 1	NA	No	NA	NA	NA	NA
Liang S, et al. (2016) [47]	Surgery	NA	2 weeks	Yes	^{131}I brachytherapy: 86 EBRT: 98	NA	TMZ (85)	Nimustine (99)
Woo PY, et al. (2015) [20]	Surgery	Biopsy: 28 MSR: 170	NA	Yes (88)	NA	NA	TMZ (36)	PCV/CCNU (3)
Ansari SF, et al. (2014) [44]	Surgery	NA	NA	No	NA	NA	Carmustine: 9	NA
Sommer B, et al. (2014) [23]	Surgery	Complete resection: 3 Subtotal resection: 5	NA	No	NA	NA	NA	NA
Garbossa D, et al. (2013) [29]	Surgery	NA	NA	No	NA	NA	NA	NA
Kim YH, et al. (2013) [34]	Surgery	GRT: 406 ≥95%: 219 <95%: 187	NA	Yes (58)	NA	NA	Yes (16)	CCRT (193)
Rudá R, et al. (2013) [26]	Surgery	NA	Early (within 8 weeks of surgery) Late (at tumor progression)	Yes	EBRT	50-60	No	NA
Waters JD, et al. (2013) [18]	Surgery + brachytherapy	GTR: 8 STR: 3	4 weeks	Yes	EBRT	46	TMZ	NA

Table 2 (continued)

Author, year	Main therapy (MT)	Extent of Tumor Removal	Time from MT until Adjuvant Therapy	Radiotherapy (RT)	RT Technique	RT Total Dose (Gy)	Chemotherapy (CT)	Other Therapies
Chen C, et al. (2011) [41]	Surgery	GTR: 8 STR: 5 Biopsy: 3	8 weeks	Yes	EBRT - IMRT	60	TMZ	NA
Della Puppa A, et al. (2011) [36]	Surgery + BCNU wafers implantation	GTR: 42 STR: 11	NA	Yes	EBRT	59.4-60.0	TMZ BCNU	NA
Bock HC, et al. (2010) [45]	Surgery + BCNU wafers implantation	NA	RT + Chemo: 4 weeks Chemo alone: 6-8 weeks	Yes	NA	59-60	TMZ BCNU	NA
Chaichana KL, et al. (2009) [38]	Surgery	GTR: 217*	NA	Yes (371)	NA	NA	TMZ (173)	NA
Baumert BG, et al. (2008) [43]	Surgery	Radical: 11 Subtotal: 2 Biopsy: 1	NA	Yes	EBRT	i) 60 ii) 80	NA	NA
Lai A, et al. (2008) [33]	Surgery	GTR: 5 STR: 3 Biopsy: 2	3-5 weeks	Yes	EBRT	60	TMZ	NA
Yang SH, et al. (2007) [17]	Surgery	NA	NA	Yes	NA	NA	Yes (9)	NA
Schwartz TH, et al. (2000) [25]	Surgery	NA	NA	No	NA	NA	NA	NA
Brem H, et al. (1995) [16]	Surgery	Total: 3 STR: 14 Lobectomy: 5	NA	Yes	EBRT	55.8	Interstitial chemotherapy with the BCNU-loaded polymer	NA
Whittle IR & Beaumont A (1995) [19]	Surgery	biopsy:6 stereotactic CT-guided resection: 5 Conventional resection: n= 21*	NA	Yes*	NA	48-54*	TCNU or PCV (7) *	NA

NA–Not available; IORT–Intraoperative radiotherapy; TMZ–Temozolomide; GTR–Gross Total Resection; STR–Subtotal Resection; NTR–Near Total resection; EBRT–External Beam Radiotherapy; TTF–Tumor Treating Fields; EOR–Extent of Resection; Gy–Gray; CCNU–Lomustine; MSR–Maximal Safe Resection; PCV–Procarbazine, Lomustine and Vincristine; CCRT—Concurrent Chemoradiotherapy; BCNU–Carmustine; IMRT–Intensity – Modulated Radiation Therapy; TCNU–Tauromustine

*Data including the non-high-grade glioma brain tumor cohort

Table 3 Seizure outcomes of the studies included in the systematic review

Author, year	Follow-up	Patients with Post-Therapy Epilepsy (n)	Type of Seizures	Pre-therapy ASDs	Post-Therapy ASDs
Cifarelli CP, et al. (2023) [39]	14 months	1	NA	NA	NA
Hansen AL, et al. (2023) [35]	Mean: 15,2 ± 9,74 months	12	NA	NA	NA
Harwick E, et al. (2023) [15]	3 months	0	NA	NA	NA
Li L, et al. (2023) [13]	12 months	7	NA	NA	42
Ollila L & Roivainen R (2023) [30]	> 12 months	56	NA	74	NA
Sim HW,et al. (2023) [24]	> 24 months	Experimental arm: 7 Standard arm: 5	NA	NA	NA
Stritzelberger J, et al. (2023) [22]	≥30 days	152	NA	213	330
Liu S, et al. (2022) [27]	2-16 months	0	NA	NA	NA
Ricklefs FL, et al. (2022) [14]	Mean: 12.7 months (range: 3–64 months)	53 (21 with preoperative seizures and 32 with new seizures)	NA	NA	NA
Weber L, et al. (2022) [21]	until 3 months post-op	19	NA	NA	NA
Borger V, et al. (2021) [40]	12 months	>= ILAE II: 10	Focal aware: 4 (40%) Focal to bilateral tonic-clonic: 6 (60%)	33	NA
Li L, et al. (2021) [46]	12 months	87 (23 new)	NA	NA	NA
Pepper J, et al. (2021) [28]	Mean: 2 years.	Engel class II: 2 Engel class III: 5 Engel class IV: 3	NA	36	36
Climans SA, et al. (2020) [37]	Up to 40 months	151	NA	NA	NA
Eichberg DG, et al. (2020) [32]	Months ± SD 4.64 ± 8.55	0	NA	NA	NA
Maialetti A, et al. (2020) [31]	6 months	4	NA	14	14
Masuda Y, et al. (2019) [48]	>= 6 months	0	NA	NA	NA
Alimohamadi M, et al. (2016) [42]	3 months	1	NA	NA	NA
Liang S, et al. (2016) [47]	> 1 month	83	Simple partial: 23 Complex partial: 26 Partial and secondary generalized: 77	43	73
Woo PY, et al. (2015) [20]	Mean: 8.2 months	93	NA	165	126
Ansari SF, et al. (2014) [44]	Mean:(days) 321 (6–4,882)	21	NA	47	NA
Sommer B, et al. (2014) [23]	mean of 53, 8 months	Engel IIa: 2 Engel IIb: 1	NA	NA	NA
Garbossa D, et al. (2013) [29]	3 months 6 months	17	NA	43	43
Kim YH, et al. (2013) [34]	Until 60 months	127	Generalized tonic–clonic: 57 Complex partial: 19 Simple partial: 32 Others: 19	263	NA
Rudá R, et al. (2013) [26]	3 months12 months	5 4	NA	NA	NA
Waters JD, et al. (2013) [18]	Up to 46,4 months	0	NA	NA	NA
Chen C, et al. (2011) [41]	≥ 30 days after IMRT	1	Partial seizure	NA	NA
Della Puppa A, et al. (2011) [36]	60th postoperative day 90th postoperative day	0 0	NA	55	NA

Table 3 (continued)

Author, year	Follow-up	Patients with Post-Therapy Epilepsy (n)	Type of Seizures	Pre-therapy ASDs	Post-Therapy ASDs
Bock HC, et al. (2010) [45]	median follow-up 15.6	7	NA	NA	NA
Chaichana KL, et al. (2009) [38]	Mean: 13,7 months (range: 8,9-20,3 months)	66	NA	185	422
Baumert BG, et al. (2008) [43]	Mean: 39,2 (range: 9.8 - 65,8) months	3	NA	NA	NA
Lai A, et al. (2008) [33]	up to 40 weeks	2	1 focal 1 generalized	NA	NA
Yang SH, et al. (2007) [17]	mean follow-up: 16.6 months	9	NA	39	39
Schwartz TH, et al. (2000) [25]	5-6 months (until death)	0	NA	NA	NA
Brem H, et al. (1995) [16]	mean survival follow-up: 42 weeks	12	NA	NA	NA
Whittle IR & Beaumont A (1995) [19]	median follow up: 30 months	3	NA	29	28

NA–Not available; ILAE–International league against epilepsy; IMRT–Intensity-modulated radiation therapy

With the inclusion of 36 studies in our meta-analysis, we observed a pooled prevalence of post-therapy seizures of 25.5%, with a 95% confidence interval of [19.9%;31.1%] ($Z = 8.90$, $p < 0.001$). Figure 2A shows the forest plot, with the weighted contribution for each included study. There was a significant heterogeneity between studies ($I^2 = 96\%$, Q (35) = 784, $p < 0.001$). However, funnel plot analysis (Fig. 2B) showed no significant asymmetry ($Z = 1.27$, $p = 0.20$), representing a potential lack of publication bias.

Since prospective data is more likely to have higher quality, a subgroup analysis of the 14 prospective studies was conducted. A pooled prevalence of post-therapy seizures of 20.4%, with a 95% confidence interval of [12.3%;28.5%] was observed ($Z = 4.92$, $p < 0.001$), while maintaining significantly heterogeneity between studies ($I^2 = 87\%$, Q (13) = 97.0, $p < 0.001$) and no funnel plot asymmetry ($Z = 1.17$, $p = 0.24$).

In 3 studies, authors reported 60 new post-therapy seizures in patients without seizures at presentation. In most studies, seizure outcomes were assessed through seizure frequency, with only 3 studies using scales: 2 studies used Engel classification and 1 study used the ILAE outcome scale.

Discussion

Epilepsy is one of the main clinical characteristics observed in patients with HGG. Acknowledging the considerable impact of epilepsy on a patient´s life, achieving better seizure control is a crucial treatment goal for patients treated for GRE. Seizure remission significantly enhances patient´s quality of life, potentially alleviating burdens on families and society. As far as we know, the mechanism underlying postoperative seizure control remains poorly understood, with results showing inconsistency. Furthermore, few are the studies that reported the prevalence of seizures after therapy in patients treated for high-grade gliomas.

Therefore, in our systematic review of the published literature, we analyzed the prevalence of post-therapy epilepsy in patients treated for high-grade gliomas in a cohort of 4036 high-grade glioma patients.

Our results showed that, despite most patients being submitted to the current standard glioma therapy, 25,5% of patients treated for high-grades gliomas still presented seizures after treatment. This number reflects a significant percentage of patients with unwanted seizures outcomes.

Various factors such as glioma type, use of pre- or post-therapy ASMs, extent of tumor resection, the prevalence of seizures at presentation, the type of therapy used and the time of follow-up may influence patient´s seizure outcome, and it´s crucial to comprehend these factors to be able to interpret our results and achieve better seizure control. Since our study revealed a great heterogeneity across the different studies, our seizures prevalence outcomes need to be interpreted with caution.

Demographic characteristics such as glioma type and glioma location have been associated with the prevalence of post-therapy epilepsy. In fact, two studies included in our analysis reported a higher incidence of epilepsy among patients with tumors situated in the temporal (86.8%) and frontal (82.0%) lobes, aligning with the hypothesis that the epileptogenic zone in secondary neocortical epilepsy is typically found within the frontal and/or temporal regions [38, 47]. Moreover, Pepper, J et al. reported a higher trend for epileptogenicity in WHO grade III gliomas compared with

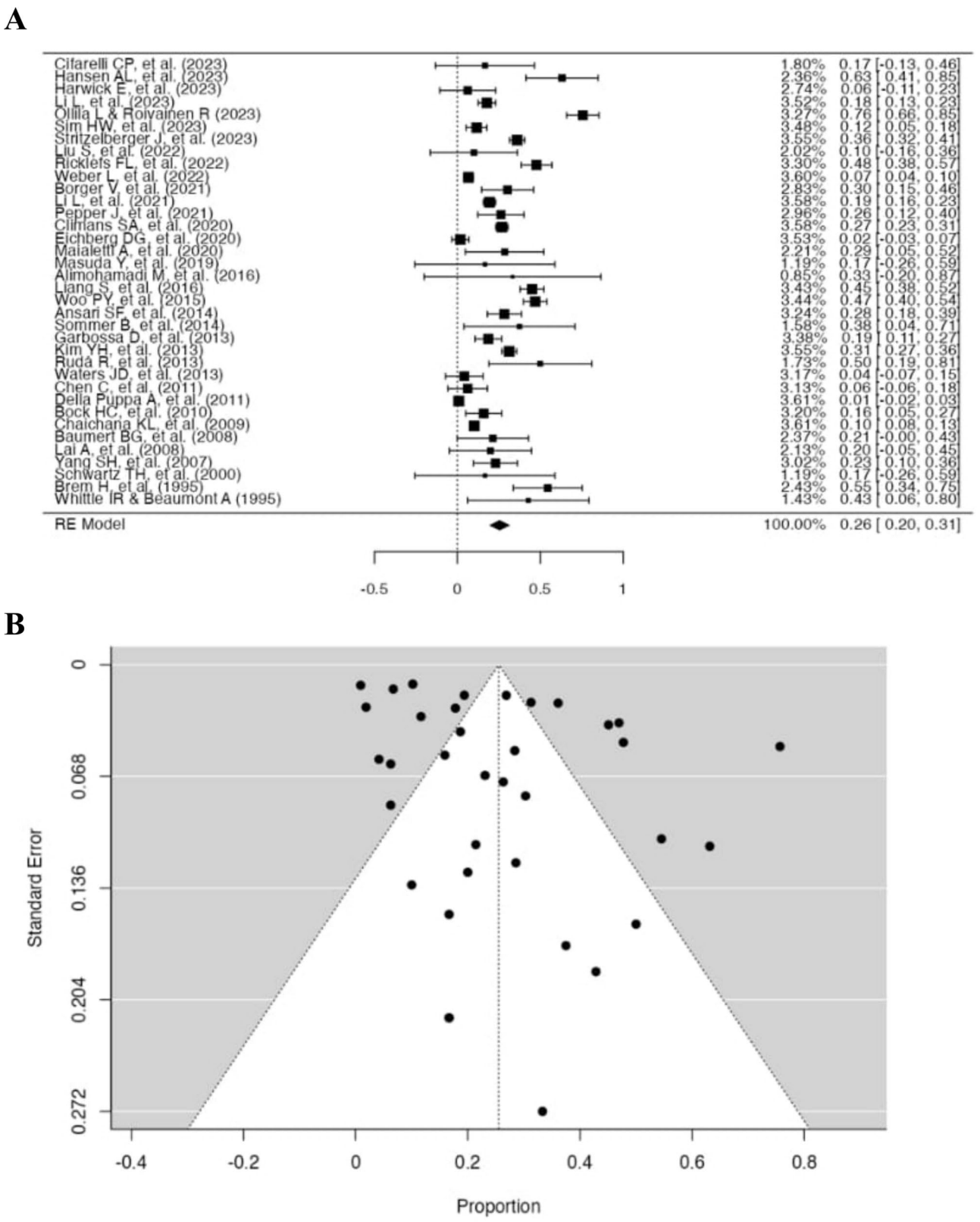

Fig. 2 Statistical analysis. **A**—Forest plot on the proportion of post-therapy epilepsy in high-grade glioma patients. An estimated pooled proportion of 25.5% was obtained (95% confidence interval: [19.9%;31.1%], Z = 8.90, p < .001), with significant heterogeneity (I2 = 96%, 22 Q(35) = 784, p < .001); **B**—Funnel plot for the pooled proportion of post-therapy epilepsy for high-grade glioma patients. No funnel plot asymmetry was observed (Z = 1.27, p = 20)

WHO grade IV gliomas [28]. However, our several included studies regarding the analysis of post-therapy seizures, comprised studies with different types of brain tumors, and not only high-grade gliomas. Therefore, obtaining demographical and clinical variables of high-grade glioma patients was not always possible, limiting the characterization of this population for correlation with our desired outcome.

ASDs in high-grade glioma patients are used for seizure prevention, both in a pre- and post-treatment setting. In fact, combining the antineoplastic standard treatment with personalized and appropriately dosed anti-seizure medications has the potential to improve seizure management [4]. However, one of the included studies concluded that ASD prophylaxis does not provide a substantial benefit in seizure outcomes to surgically treated high-grade glioma patients, with cumulative rates of seizures at 6 months postoperative of 18,5% in the patients group that received ASD prophylaxis with levetiracetam, and 18,75% in the patients group without seizures prophylaxis [29]. Furthermore, Kim YH et al. also reported that 32% of patients who received ASD prophylaxis experienced a seizure, whereas 29% of patients without ASD prophylactic administration experienced an epileptic event [34]. This difference was deemed statistically insignificant.

As we previously mentioned, epilepsy is the most common initial clinical manifestation of high-grade glioma patients, with over a half of patients having at least a seizure during the disease course [4]. The presence of preoperative epilepsy entails the development of matured epileptic networks, and complete tumor resection doesn't always guarantee removal of epileptogenic foci [46]. Therefore, the prevalence of epilepsy at presentation may influence the results of seizures outcomes. In fact, one study identified preoperative seizure incidence as an independent factor for poor seizure control after surgery, showing the greatest impact on seizure outcome among other variables [49].

As we know, surgery plays a crucial role in treating patients with glioma-related epilepsy, functioning both as a neoplastic treatment and as an antiepileptic therapy for these patients. In fact, some studies indicated that approximately two thirds of the epileptogenic focus in GRE patients is situated within or near the tumor [50]. Moreover, it has been reported that patients who undergo gross total resection of the tumor exhibit higher rates of seizure freedom [51]. One of our included studies reported that patients who underwent initial surgical techniques resulting in gross total resections were significantly more likely to achieve seizure freedom compared to those who underwent major or partial resections, with 80% of patients who underwent gross total resections being seizure-free, whereas only 30.4% of partial resection patients achieved seizure freedom. [47] On the other hand, Liang S, et al. also showed that different adjuvant treatments employed in each patient´s management showed no apparent influence on the occurrence of new-onset epilepsy following the initial surgical resection [47]. Consequently, no significant disparity in post-resection epilepsy prevalence was observed between patients who underwent various types of radiotherapy techniques: 53% in patients who underwent 3D- conformal radiotherapy and 47% in those treated with ^{131}I intra-tumor radiotherapy, nor between patients receiving temozolomide (48.2%) and nimustine (51.8%) as adjuvant chemotherapy [47].

As we assessed before, the most common way of documenting seizures outcomes often involves the utilization of the Engel classification system for patients who have undergone surgical resection [52]. Other alternative approaches for reporting seizure outcomes in non-surgical procedures comprehend the evaluation of seizure frequency, seizure reduction and seizure freedom. The several included studies in this analysis utilized diverse post-therapy epilepsy assessments, resulting in considerable heterogeneity in seizure evaluation. Furthermore, most of the articles incorporated in this study didn´t use appropriate and necessary techniques for post-therapy epilepsy diagnoses, such as electroencephalography (EEG). In futures studies, this aspect should be addressed since many epileptic patients experience seizures without motor involvement or clinically observable crises.

Time of seizure assessment is also a likely crucial factor in determining seizure occurrences. In fact, it must be taken into a count that, in some studies, seizure outcomes were assessed in close temporal proximity to the therapeutic intervention [21, 22, 41]. Considering that the effects of radiation may extend beyond 30 days, it cannot be excluded that some of the seizures observed were, in fact, adverse events related to the therapy. Furthermore, the timing of seizure evaluation is also a likely critical factor in establishing the association between seizure incidence and GRE patients' survival. While certain studies have identified a correlation between seizures and enhanced survival [53, 54], seizures occurring later in the disease's progression may signify tumor progression and are linked to poorer outcomes. Other included study stated that among patients initially achieving a 12-month seizure-free period, the recurrence of seizure after therapy aligned with glioma progression in the majority (60.7%) [30]. This evidence suggests that patients who live longer and experience a less malignant disease course are more likely to develop seizures after treatment, which can be of great impact on daily life activities, such as driving. An individualized assessment of this impact should be undertaken after treatment completion.

In conclusion, the high heterogeneity present in all the evaluated variables are a result of an extremely high diversity of study designs, patient's characteristics, and patients' evaluation methodology.

Conclusion

Our systematic review analysis aimed to quantify the prevalence of epilepsy in patients treated for high grade glial tumors. In our study, we observed a high heterogeneity in all the evaluated variables, resulting of an extremely high diversity of results. Larger prospective studies using appropriate epilepsy diagnostic techniques would be beneficial to have a more exact number of the high-grade glial patients that develop post-therapy epilepsy.

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Declarations

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Ethical approval Regarding ethical considerations, the systematic review will rely on previously published data, therefore ensuring compliance with ethical and integrity standards in the conduct of the review.

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