frontiers | Research Topics

Updates on current protocols for the management of brain and spine malignancies

Edited by
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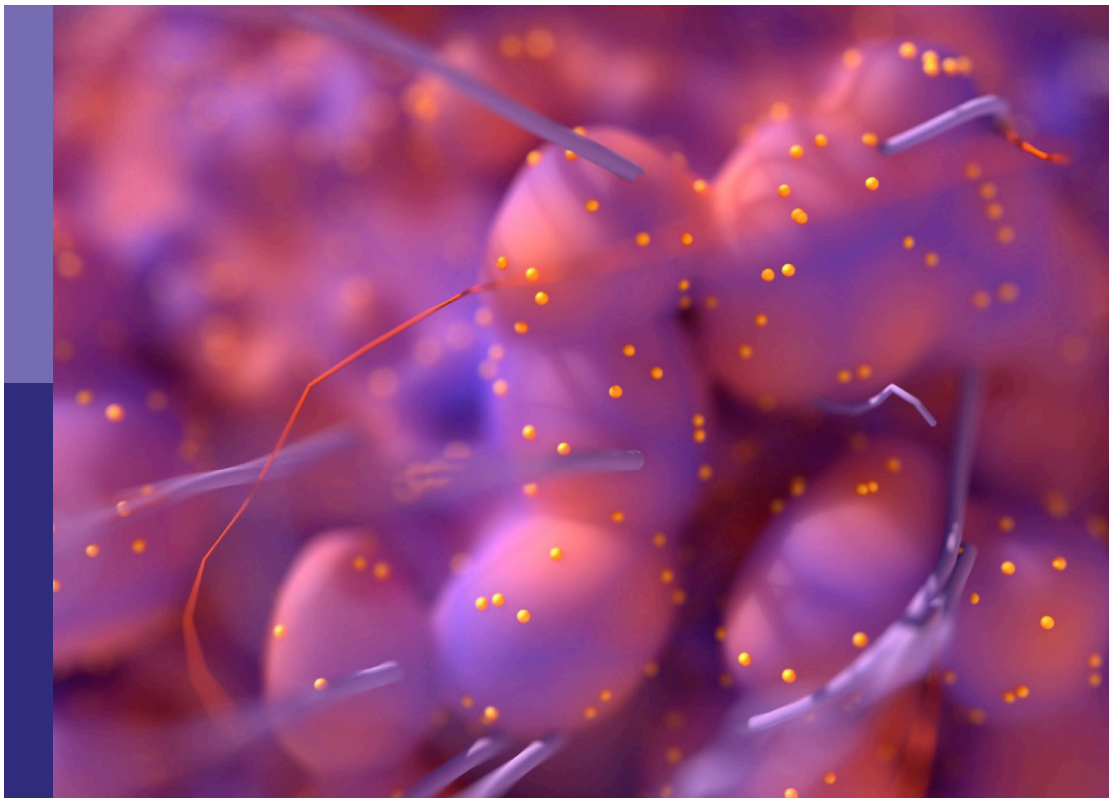
Published in
Frontiers in Oncology
Frontiers in Neurology



ISSN 1664-8714
ISBN 978-2-83251-171-8
DOI 10.3389/978-2-83251-171-8

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Updates on current protocols for the management of brain and spine malignancies

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Citation

Raco, A., Barbagallo, G., Ricciardi, L., Ius, T., Thome, C., eds. (2023). *Updates on current protocols for the management of brain and spine malignancies*. Lausanne: Frontiers Media SA. doi: 10.3389/978-2-83251-171-8

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frontiers | Frontiers in Neurology

TYPE Editorial
PUBLISHED 14 December 2022
DOI 10.3389/fneur.2022.1077973

OPEN ACCESS

EDITED AND REVIEWED BY
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SPECIALTY SECTION
This article was submitted to Neuro-Oncology and Neurosurgical Oncology, a section of the journal Frontiers in Neurology

RECEIVED 23 October 2022
ACCEPTED 28 November 2022
PUBLISHED 14 December 2022

CITATION
Ius T, Ricciardi L, Barbagallo GM, Thomé C and Raco A (2022) Editorial: Updates on current protocols for the management of brain and spine malignancies.
Front. Neurol. 13:1077973.
doi: 10.3389/fneur.2022.1077973

Editorial: Updates on current protocols for the management of brain and spine malignancies

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KEYWORDS

glioma, spinal tumor, brain, neuro-oncology, malignancy

Editorial on the Research Topic
Updates on current protocols for the management of brain and spine malignancies

Cerebral and spinal malignancies involve a highly complex anatomical region, in which a multidisciplinary approach is of utmost importance with regards to clinical management, surgical strategies, and adjuvant therapy. Local therapy with surgery and radiotherapy represents the most effective option both as first-line treatment and treatment at time of tumor recurrence. In recent years, the increasing knowledge in the molecular mechanisms of these tumors and translational research has allowed for new potential systemic treatments, which are constantly evolving. Despite growing knowledge of the molecular changes responsible for tumor development, glioblastoma remains a neoplasm with unmet medical needs, in which prognosis still remains poor. In addition, primary spinal malignancies still represent a challenging scenario for spine surgeons, in which surgical management is associated with high perioperative complication risk.

Our Editorial entitled "*Updates on current protocols for the management of brain and spine malignancies*" provides a general overview in this neuro-oncological setting, in terms of surgical strategy, adjuvant treatments, and molecular discoveries, emphasizing the fundamental role of a multidisciplinary approach tailored for each patient.

In the article entitled "*Pre- and post-surgical poor seizure control as hallmark of malignant progression in patients with glioma?*," the emerging topic regarding the close relationship between epileptogenesis and oncogenesis is presented (Pauletto et al.). Pauletto et al. showed that a poor post-operative seizure outcome in LGG may correlate with a histological progression, highlighting the importance of a closer multidisciplinary follow-up for patients who are not seizure-free after surgery. The detection of early seizure recurrence in an important hallmark of malignant progression, especially in adult LGG patients.

With regards to high-grade gliomas (HGG), two interesting meta-analyses have been reported by Ricciardi, Sturiale et al.. In the study entitled "5-*Aminolevulinic acid false-positive rates in newly diagnosed and recurrent glioblastoma: Do pseudoprogression and radionecrosis play a role? A meta-analysis*," 5-aminolevulinic acid (5-ALA) has been gradually used as a standard tool in neurosurgical procedures for HGG, providing a valuable increase in the extent of resection (EOR) (Ricciardi, Sturiale et al.). Its usefulness in terms of safety and accuracy for HGG recurrence has been reported in recent literature. In this precise systematic review and meta-analysis of comparative studies on the use of 5-ALA in newly diagnosed and recurrent GBM, the authors demonstrated that the 5-ALA plays a possible role in recurrent glioma surgery to appropriately guide surgical strategies. In the study entitled "*Carmustine Wafers implantation in patients with newly diagnosed high grade glioma: Is it still an option*?" the authors investigate the role of Carmustine Wafers in HGG (Ricciardi, Manini et al.). The results suggest that Carmustine Wafers implantation plays a significant role in improving survival when used in patients with newly diagnosed HGG. A careful patient selection is recommended (i.e., younger patients with a high probability of radical resection for small lesions) to minimize the risk of side effects.

Another area of interest which was included in our Research Topic was based on the role of surgery in elderly glioblastoma (GBM) patients. Approximately half of GBM cases occur in geriatric patients, and this trend is destined to increase with the aging of the population. In this clinical setting, Klingenschmid et al. analyzed 121 elderly GMB patients who underwent surgery. The authors reported that elderly patients who underwent a greater extent of resection of HGG lesions showed a significantly longer overall survival rate when compared to those patients that underwent biopsy or subtotal resection. The authors demonstrated that a good preoperative neurological status is a significant factor for overall survival, while the factor of age alone does not seem to influence the prognosis.

In newly diagnosed GBM patients, post-operative radiation with concurrent and adjuvant (six cycles) temozolomide (TMZ) is the standard of care. The potential benefit of extending adjuvant TMZ therapy beyond six cycles, however, remains questionable. To address this issue, Attarian et al.'s study compared the survival outcomes of standard TMZ and extended TMZ as the first-line treatment of patients with GBM. The authors concluded that extended TMZ beyond six cycles did not show an increase in progression-free survival or overall survival rate, thus addressing this important question in current neuro-oncological literature.

Despite the undisputed role of the Stupp protocol, GBM is considered an incurable disease, and the demand for new approaches and specific treatment options remains high. The targeted application of tumor-treating fields (TTFs) is a specific oncological option widely discussed and under investigation. The mechanism of action is based on the interference generated by the electrical fields on the mitotic activity of malignant cells. Krigers et al. evaluated a total of 48 patients harboring a GBM treated with TTF, demonstrating its efficacy in providing additional overall survival.

Novel targeted therapies are gradually changing the management and prognosis of HGG, especially at tumor recurrence. The identification of the oncogenic *FGFR3-TACC3* [*fibroblast growth factor receptor 3* (*FGFR3*)-*transforming acidic coiled-coil 3* (*TACC3*)] fusion highlighted the possibility of identifying a subset of diffuse glioma patients that seem to be potentially responsive to targeted therapy with *FGFR* kinase inhibitors. Broggi et al. describe an original case report and literature review on this emerging topic, emphasizing that an early identification of *FGFR3-TACC3* fusion may help select those patients that could potentially benefit from post-operative treatments with *FGFR* kinase inhibitors.

In the paper entitled "*Current and Future Frontiers of Molecularly Defined Oligodendrogliomas*," Rincon-Torroella et al. summarized the current advancements in the molecular characterization of oligodendrogliomas. The optimal treatment paradigm for molecularly defined oligodendrogliomas is partially understood. The authors provided an extensive review regarding timing of radiation and chemotherapy, efficacy of different chemotherapeutic agents, and genetic factors influencing responsiveness to these agents.

With regards to spinal malignancies, progress has been made in the past years in the field of chemotherapy and radiation treatments. This has provided enhanced survival rates of oncological patients, which has also led to an increase of the number of patients with vertebral metastases. A multidisciplinary approach is of utmost importance, thus allowing for the integration of skills and knowledge of a team of specialists to ensure prompt diagnosis, support, and management of patients with spinal metastases and spinal cord compression. Rispoli et al. analyzed a large homogeneous cohort of 257 patients with vertebral metastasis. The study is based on an interesting multidisciplinary algorithm to optimize the outcomes of these patients. The authors underlined the importance of discussing each individual case during tumor board meetings in order to provide the best individualized, strategic options and management for each oncological patient.

Spinal metastases (SM) are one of the principal causes of morbidity and worsening of the quality of life (QoL) of oncological patients, mainly for neurologic involvement and intractable pain. Traditional open posterior instrumented fusion (OPIF) and percutaneous pedicle screw fixation (PPSF) represent the main surgical treatment alternatives for SM. There is no evidence in the current literature, however, that describes the absolute superiority of one treatment over the other. In recent years, the use of minimally invasive spinal surgery in SM patients has increased. Perna et al. conducted a systematic review and meta-analysis of comparative studies on PPSF vs. OPIF in

patients with SM. The investigation pointed out that the PPSF treatment tends to lead to fewer complications, a lower rate of infections, a reduction in intraoperative blood loss, and a shorter hospital stay when compared to the OPIF treatment.

Unlike other areas of oncology, there are no current standardized markers or clinical indicators that can be used in the diagnosis, prognosis, and risk of recurrence in the field of neuro-oncology. Recent studies have shown the association between sarcopenia and mortality in SM. Tan et al. reported that sarcopenia could be a useful indicator of mortality in spinal metastasis patients. The authors suggested that this parameter could assist in the strategical decision-making process of treatment and management of these patients, even if the data is based on preliminary results and further long-term multicenter trials are needed.

Our Research Topic also touches on a very intriguing topic concerning the management of tumor rarities, such as primary central nervous system lymphomas (PCNSL), metastases of the hypothalamic–pituitary region, and primary sporadic intradural malignant peripheral nerve sheath tumor (MPNST). Scheichel et al. performed an interesting review on this topic, summarizing the diagnostic and surgery workup and carefully discussing the influence of preoperative corticosteroid therapy to reduce diagnostic delay in PCNLS patients. The authors underlined the importance of a multidisciplinary approach in PCNLS management, stressing the importance of timely therapy and providing a detailed systematic workflow for diagnosis.

Baiano et al. described the endoscopic endonasal approach for the management of hypothalamic–pituitary metastases. The authors detected recovery of visual field and improvement of oculomotor nerve palsy in 85.7 and 57.1% of cases, respectively, demonstrating that the endoscopic endonasal approach is a viable approach for the management of hypothalamic–pituitary metastases both in terms of neurovascular decompression and reliability in tissue sampling.

Primary sporadic intradural malignant peripheral nerve sheath tumor (MPNST) represents a rare and challenging disease, with an incidence of one case in 10 million. Spinal MPNSTs account for 2–3% of all MPNSTs, and primary sporadic intradural MPNSTs in the spinal canal are seen even less often. Cao et al. conducted an interesting systematic review, based on pooled data from 55 cases reported in the literature. The article expertly describes pathogenesis, clinical characteristics, imaging manifestations, differential diagnosis, surgical interventions, and pathological features in a systematic manner. The analysis demonstrated that even after surgical treatment and adjuvant treatment, the recurrence rate and mortality rate still tend to be high. Early detection and treatment are fundamental in MPNSTs management. The benefits of radiotherapy and chemotherapy treatments remain controversial, which thus underlies the importance of further multicenter studies.

As guest editors for this Research Topic, we hope you find the manuscripts prepared by our esteemed international colleagues innovative, practical, interesting, and of clinical value.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

frontiers in Oncology

SYSTEMATIC REVIEW
published: 23 November 2021
doi: 10.3389/fonc.2021.779491

OPEN ACCESS

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Specialty section:
This article was submitted to Neuro-Oncology and Neurosurgical Oncology, a section of the journal Frontiers in Oncology

Received: *18 September 2021*
Accepted: *29 October 2021*
Published: *23 November 2021*

Citation:
Attarian F, Taghizadeh-Hesary F, Fanipakdel A, Javadinia SA, Porouhan P, PeyroShabany B and Fazilat-Panah D (2021) A Systematic Review and Meta-Analysis on the Number of Adjuvant Temozolomide Cycles in Newly Diagnosed Glioblastoma. Front. Oncol. 11:779491. doi: 10.3389/fonc.2021.779491

A Systematic Review and Meta-Analysis on the Number of Adjuvant Temozolomide Cycles in Newly Diagnosed Glioblastoma

Fahimeh Attarian[1†‡], Farzad Taghizadeh-Hesary[2‡], Azar Fanipakdel[3†], Seyed Alireza Javadinia[4†], Pejman Porouhan[5], Babak PeyroShabany[6†] and Danial Fazilat-Panah[7†]*

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Background: In newly diagnosed glioblastoma, radiation with concurrent and adjuvant (six cycles) temozolomide (TMZ) is the established standard of postsurgical care. However, the benefit of extending adjuvant TMZ therapy beyond six cycles has remained unknown.

Methods: We searched PubMed, Web of Science, Scopus, and Embase up to October 1, 2021. The search keywords were "glioblastoma," "adjuvant chemotherapy," and their synonyms. The data of randomized clinical trials were extracted and included in this meta-analysis if they had reported patients' median overall survival (OS) or median progression-free survival (PFS). The standard and extended chemotherapy regimens were considered as adjuvant TMZ up to six cycles and beyond six cycles (up to a total of 12 cycles), respectively. The median OS and median PFS were pooled and compared.

Results: Four studies consisting of 882 patients (461 patients for the standard chemotherapy group and 421 patients for the extended chemotherapy group) were included in this meta-analysis. The extended TMZ regimen was associated with a nonsignificant improvement in PFS [12.0 months (95% CI 9.0 to 15.0) *vs*. 10.0 months (95% CI 7.0 to 12.0), $P = 0.27$] without corresponding improvement in OS [23.0 months (95% CI 19.0 to 27.0) and 24.0 months (95% CI 20.0 to 28.0), $P = 0.73$].

Conclusions: In newly diagnosed glioblastoma, continuing adjuvant TMZ beyond six cycles did not shown an increase neither in PFS nor OS.

Keywords: adjuvant, extended chemotherapy, glioblastoma, temozolomide, treatment duration, The Stupp protocol, high-grade gliomas

1 INTRODUCTION

Glioblastoma is the most common primary brain tumor of glial origin in adults. It is characterized by rapid progression, a high recurrence rate, and a dismal prognosis (1–3). Historically, the management of glioblastoma was maximal safe surgical resection (MSR) followed by radiotherapy. In the early 21st century, a large randomized clinical trial (RCT) converted the standard of care to MSR, adjuvant chemoradiotherapy (CRT) [with concurrent temozolomide (TMZ), an oral alkylating agent], followed by TMZ for six cycles (4). Dismal prognosis of glioblastoma brought up the extended adjuvant TMZ (ext-TMZ) and changed the clinical practice to continue adjuvant TMZ up to 12 cycles or until tumor progression. Since then, numerous studies have attempted to compare the ext-TMZ and the standard Stupp protocol (std-TMZ). However, there is still no consensus on the duration of adjuvant TMZ (5).

In the English literature, there are several studies as case report (6), cohort study (7–18), clinical trial (19–24), and review article (5, 25, 26) assessing the potential benefits of ext-TMZ in patients with glioblastoma. In a pooled analysis of four RCTs (4, 21, 27, 28), the authors concluded that ext-TMZ did not improve the overall survival (OS) of patients with glioblastoma (26). This study did not include three recent RCTs (19, 20, 23). On the other hand, two other meta-analyses noted the improved OS and progression-free survival (PFS) with ext-TMZ (5, 25). These findings might be biased by their search strategy, as well as not including the recent RCTs. The present meta-analysis was therefore designed to compare the survival outcomes of std-TMZ and ext-TMZ in the first-line treatment of patients with glioblastoma.

2 METHODS

2.1 Study Design and Types of Included Studies

This meta-analysis was conducted per the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guideline (29). It included RCTs comparing std-TMZ and ext-TMZ—as the first-line treatment in glioblastoma—in terms of median OS and median PFS.

2.2 Search Strategy

Two authors (S.A.J and F.A) independently searched the English literature for free-text and standard MeSH (Medical Subject Headings) terms in PubMed, Web of Science, Scopus, and Embase up to October 1, 2021. The search keywords were: high-grade glioma OR malignant glioma OR glioblastoma OR glioblastoma multiforme OR grade IV glioma OR grade IV astrocytoma OR GBM, adjuvant chemotherapy OR temozolomide OR temodar, AND extended OR long-term OR prolonged OR maintenance OR cycles OR months. Also, the two review authors handsearched the reference lists of the relevant articles to identify the possible missed RCTs. Thereafter, they downloaded all titles and abstracts retrieved by electronic searching to EndNote™ V.20.0, removed duplicates, and excluded the studies that did not meet the eligibility criteria, clearly (mentioned below). Eventually, they debated on the disagreements to improve the search results.

2.3 Study Screening

2.3.1 Participants

Adult patients with glioblastoma who underwent surgery, radiotherapy (concurrent with TMZ), and adjuvant TMZ as the primary treatment.

2.3.2 Inclusion Criteria

RCTs comparing std-TMZ and ext-TMZ, in which the median OS and/or median PFS were reported.

2.3.3 Exclusion Criteria

Studies if (i) not following the standard treatment sequence of MSR, CRT (with TMZ), and adjuvant TMZ, (ii) submitted only as abstracts or proceedings from scientific meetings, (iii) lacking English full text or summaries, or (iv) including patients with recurrent glioblastoma were excluded. Eligible studies were assessed finally for quality of methodology (30, 31).

2.4 Data Extraction

The following data were extracted from the studies: (i) study information (the first author, year of publication, study country, sample size), (ii) patient baseline characteristics (age, sex ratio), (iii) intervention duration (std-TMZ, ext-TMZ), and (iv) treatment outcomes (median OS, median PFS). Only data from the first-line therapy of both groups were extracted.

The standard chemotherapy regimen (std-TMZ) was defined as ≤ 6 cycles of TMZ following MSR and adjuvant CRT. The extended chemotherapy regimen (ext-TMZ) was defined as > 6 cycles of TMZ (up to 12 cycles) following MSR and adjuvant CRT. The median OS and PFS were extracted directly from the text or the Kaplan-Meier survival curves.

2.5 Quality Assessment

Two investigators (S.A.J. and F.A) assessed the methodological quality and risk of bias of the included studies. All four included studies were assessed using Cochrane's Risk of bias tool (31). They resolved differences by discussion or appeal to a third review author (F.T) and presented results in a "Risk of bias" table. The risk of bias summary consists of 5 questions (also known as the Oxford quality scoring system), ranging from 0 to 5. Studies with a quality score less than 3 were regarded as poor quality and excluded from the study (**Table 1**).

2.6 Statistical Analysis

The main objective of this meta-analysis was to compare the median PFS and OS for std-TMZ versus ext-TMZ as the first-line treatment of patients with glioblastoma. The individual patient data (IPD) is essential in the standard approach to pooled survival estimates (26). However, IPD was unavailable in this meta-analysis, and we used the median PFS and OS (weighted by the inverse of variance) to estimate the pooled median and 95% confidence interval (95% CI) of PFS and OS in each group of RCTs. The statistical heterogeneity

TABLE 1 | Methodological quality summary for the included studies.

Risk of bias	Balana, 2020	Bhandari, 2017	Blumenthal, 2017	Refae, 2015
Random sequence generation (selection bias)	+	+	+	+
Allocation concealment (selection bias)	+	+	+	+
Blinding (performance bias and detection bias)	-	-	-	-
Incomplete outcome data (attribution bias)	+	+	+	+
Selective reporting (Reporting bias)	+	+	+	+

+ means that the corresponding article (in column) consider the criteria (the row) or not (-).

between studies was evaluated using Cochran's Q test and quantified by I^2 statistics (high heterogeneity was defined as I^2 > 20% or P-value < 0.1). We applied Stata V.14.0 (Stata Corp, College Station, TX, USA) for the quantitative synthesis. The statistical significance level was set to 0.05.

3 RESULTS

Our databases searching identified 45,060 potentially relevant studies. After deleting duplicates (10,351 records), 22 articles were included in the evaluation through screening titles, abstracts, and full texts. Then, we excluded eighteen studies (4–10, 12–17, 21, 22, 24, 32) on eligibility criteria. **Figure 1** details the PRISMA flow diagram.

A total of 882 glioblastoma patients were included in the four studies. Of these, 461 patients were treated by std-TMZ regimen, and 421 patients received ext-TMZ regimen. The median PFS of patients with glioblastoma who were treated by the standard or extended chemotherapy regimens is shown in **Figure 2**. The overall median PFS was 10.0 months (95% CI 7.0 to 12.0) in the std-TMZ group (TMZ ≤ 6 cycles). The studies had homogeneity in median PFS in this group (P = 0.82). Likewise, in the ext-TMZ group, all studies had homogeneity in the median PFS 12.0 months (95% CI 9.0 to15.0 months) (P = 0.91). The least record of median PFS (10.0 months 95% CI 5.0 to 19.0) in arms with ext-TMZ (TMZ > 6 cycles) was equal to the upper record of median PFS in the std-TMZ group (10.0 months 95% CI 4.0 to 26.0). Comparison between the two groups showed that ext-TMZ was associated with an improved PFS (12.0 months, 95% CI 9.0 to 15.0 *vs.* 10.0 months, 95% CI 7.0 to 12.0), although this improvement was not statistically significant (P = 0.27) (**Figure 2**).

The median OS of the analyzed studies ranged from 14.0 to 25.0 months for the std-TMZ group (n = 461) versus 19.0 to 27.0 months for the ext-TMZ group (n = 421) (**Figure 3**). Three out of four studies reported superior median OS in the ext-TMZ group; however, Balana et al. found the contrast results (median OS: 19.0 months in ext-TMZ *vs.* 23.0 months in std-TMZ). The pooled estimated median OS of patients in the std-TMZ and ext-TMZ were statistically consistent [23.0 months (95% CI 19.0 to 27.0) and 24.0 months (95% CI 20.0 to 28.0), respectively, P = 0.73].

4 DISCUSSION

This meta-analysis assessed the survival benefit of adjuvant ext-TMZ (7-12 cycles) against the standard 6-cycle regimen for patients with newly diagnosed glioblastoma. The literature search yielded four studies (three RCTs and one pooled analysis) that met our eligibility criteria, including 461 patients in the std-TMZ group and 421 patients in the ext-TMZ group. The quantitative analysis showed trend, although nonsignificant, towards improved PFS with the ext-TMZ regimen [12.0 months (95% CI 9.0 to 15.0) *vs.* 10.0 months (95% CI 7.0 to 12.0), P > 0.05]. However, the OS of patients who were treated by the ext-TMZ and the std-TMZ remained almost identical [23.0 months (95% CI 19.0 to 27.0) *vs.* 24.0 months (95% CI 20.0 to 28.0), P > 0.05, respectively]. These findings are inconsistent with the previous meta-analyses by Alimohammadi et al. and Xu et al.,

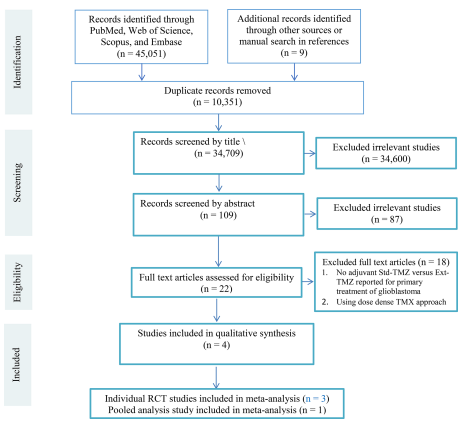

FIGURE 1 | The PRISMA flow diagram. Three out of four eligible studies were randomized comparisons of adjuvant std-TMZ versus ext-TMZ for primary treatment of glioblastoma (19, 20, 23).The remaining study was a pooled analysis of four RCTs (26). The main characteristics of the eligible studies are shown in **Table 2**.

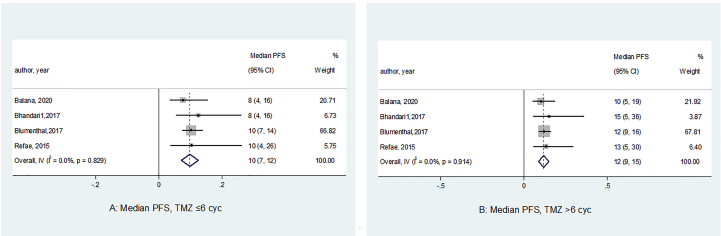

FIGURE 2 | Forest plots of the median progression-free survival (PFS) according to the number of adjuvant temozolomide cycles. The horizontal line of the diamond summary represents the average 95% CI. The statistical heterogeneity between studies was assessed using the I^2 test, which revealed a homogeneity in the results (PFS in the std-TMZ, I^2 = 0.0%, P = 0.82; and PFS in the exd-TMZ, I^2 = 0.0%, P = 0.91).

stating that extended adjuvant TMZ improves both PFS and OS in patients with newly diagnosed GBM (5, 25). However, these findings might be affected by the included retrospective records, which constituted 28.9% and all of the analyzed cases in the Alimohammadi et al.'s and Xu et al.'s studies, respectively. In our analysis, we excluded all retrospective studies to enhance the power of the results.

In summary, the current meta-analysis did not demonstrate the survival benefit of prolonged adjuvant TMZ in newly diagnosed glioblastoma. This might be explained by adaptive resistance. To better understand this issue, we need to recognize the mechanism of action of TMZ. As an alkylating agent, TMZ acts as a prodrug and induces cell cycle arrest at G_2/M through methylation of DNA or RNA. The methylated sites can remain mutated by DNA mismatch repair (MMR) proteins, dealkylated by the action of O^6-methylguanine methyltransferase (MGMT), or be removed by the base excision repair (BER) enzymes [such as alkylpurine-DNA-N-glycosylase (APNG)]. Cells are TMZ sensitive when MMR is overexpressed and active. On the other hand, MGMT or BER proteins overexpression increases the resistance of glioblastoma cells to TMZ. *In vitro* studies have delineated several mechanisms of adaptive resistance to TMZ in glioblastoma cell lines. For example, increased MGMT protein expression (33), decreased Tumor Necrosis Factor-Alpha-Induced Protein 3 (TNFAIP3) expression (34), upregulation of Signal Transducer and Activator of Transcription 3 (STAT3) (35), loss of MSH6 MMR gene (36), or upregulation of NTL1 (a BER enzyme) (37). Therefore, prolonged adjuvant TMZ can promote the development of tumor-resistant clones with more aggressive features. This issue can contribute to a dismal prognosis in salvage therapy of tumor recurrence. A multicenter, phase II trial—evaluating the efficacy of continuous dose-intense TMZ for recurrent glioblastoma—concluded that patients who had received adjuvant std-TMZ got more benefit from therapy in comparison with ext-TMZ group (38).

In addition to the idiosyncratic adverse effects of TMZ (such as aplastic anemia, cholestatic hepatitis, and myelosuppression), clinicians must consider the numerous intrinsic adverse effects of TMZ that might affect the quality and quantity of life of the patients with glioblastoma. In this regard, different retrospective studies have reported different rates of toxicities, as follows: lymphopenia (30-50%), nausea (28-44.3%), vomiting (20-37%), fatigue (10-33%), anorexia (14%), thrombocytopenia (12-13.7%), anemia (1-11%), neutropenia (6.3-7%), leukopenia (1.3-7%), myelodysplasia, or leukemia. The diverse rates of TMZ adverse effects might be due to different distribution of basic characteristics (vomiting and thrombocytopenia are more common in females), stage of treatment (hematological toxicities are more common in the concurrent chemoradiation phase), and the numbers of adjuvant TMZ cycles. In the context of lymphopenia, TMZ can increase the risk of opportunistic infections (such as pneumocystis jiroveci pneumonia, herpes zoster, candida) through selective $CD4^+$ T-cell depletion (39, 40). The intrinsic adverse effect of TMZ is another evidences to avoid prolonged adjuvant TMZ. In an RCT, patients in the ext-TMZ

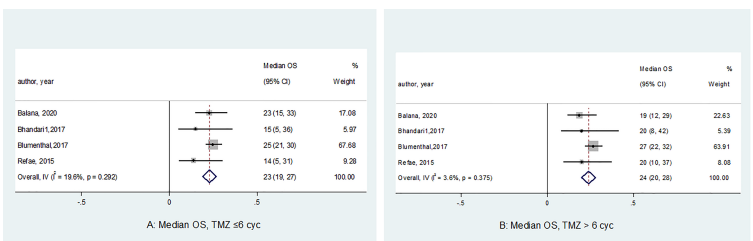

FIGURE 3 | Forest plots of the median overall survival (OS) according to the number of cycles of adjuvant temozolomide (P = 0.99). The horizontal line of the diamond summary represents the average 95% CI. The statistical heterogeneity between studies was assessed using the I^2 test, which revealed homogeneity in the results (OS in the std-TMZ, I^2 = 19.6%, P = 0.29;and OS in the ext-TMZ, I^2 = 3.6%, P = 0.37).

TABLE 2 | Main characteristics of four studies included in the current meta-analysis.

ID	First Author, year	Country	Study design	Study population	Age distribution (years old)	Sex ratio (M/F)	No. of TMZ cycles (n)	
							≤6	>6
1	Balana, 2020	Spain	RCT	159	≥ 18	83/76	79	80
2	Bhandari, 2017	India	RCT	40	18-65	24/16	20	20
3	Blumenthal, 2017	International	RCT	624	N/A	354/270	333	291
4	Refae, 2015	Egypt	RCT	59	19 – 72	47/12	29	30
Total				882	≥ 18	508/374	461	421

RCT, randomized clinical trial; TMZ, temozolomide; NA, not available.

arm experienced more grade ≥ 3 hematological toxicities (5% *vs*. none), vomiting (15% *vs*. 10%), and insomnia (10% *vs*. 5%) in comparison to the std-TMZ regimen. However, the rates of fatigue and headache were more prevalent in the std-TMZ arm (50% *vs*. 45% and 15% *vs*. 10%, respectively) (20).

Our study harbors several limitations. Lack of access to IPD and not reporting the hazard ratio in most of the studies are among the main ones. Besides, the current evidence on the role of MGMT methylation in the value of prolonged TMZ therapy beyond six months is either not addressed properly in the clinical trials (20, 23), or is assessed retrospectively (26). Therefore, prospective data on the predictive value of MGMT methylation is lacking, and our analysis cannot provide any comment in this regard. Among the included studies, only Balana et al. evaluated the role of MGMT on the survival of patients with glioblastoma receiving first-line adjuvant TMZ. By multivariate analysis, they showed that MGMT methylation was an independent factor for longer PFS and OS. However, this finding was not translated into the survival benefit of extended TMZ in patients with MGMT methylation (19).

In conclusion, prolonged adjuvant TMZ (beyond six cycles) did not provide OS and PFS benefits in patients with newly diagnosed glioblastoma. Considering this finding, along with the adverse effects of TMZ, the economic burden and psychosocial impacts of prolonged treatment can underscore the rationality of the current practice, which is 6 cycles of adjuvant TMZ. Further studies are needed to determine the predictive value of MGMT status on the long-term TMZ maintenance therapy. Moreover, the role of surgically validated results of dynamic imaging such as O-(2-[^{18}F] fluoroethyl-)-L-tyrosine positron emission tomography (^{18}F-FET PET) on the extending of TMZ should be assessed in future studies.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

SJ, FT-H, and FA designed the meta-analysis, screened the studies and wrote the manuscript. FA analyzed data. AF, PP, and BP helped designed the study. All authors reviewed the manuscript finally. DF-P and AF wrote the initial draft. SJ, FA, PP, and BP approved the final submission of the manuscript.

ACKNOWLEDGMENTS

We would like to express our gratitude to Vasei Clinical Research Development Unit in Sabzevar University of Medical Sciences for their sincere cooperation.

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frontiers in Neurology

MINI REVIEW
published: 09 February 2022
doi: 10.3389/fneur.2022.823015

Glioblastoma, *IDH*-Wild Type With *FGFR3-TACC3* Fusion: When Morphology May Reliably Predict the Molecular Profile of a Tumor. A Case Report and Literature Review

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Specialty section:
This article was submitted to Neuro-Oncology and Neurosurgical Oncology, a section of the journal Frontiers in Neurology

Received: *26 November 2021*
Accepted: *11 January 2022*
Published: *09 February 2022*

Citation:
Broggi G, Piombino E, Altieri R, Romano C, Certo F, Barbagallo GMV, Vigneri P, Condorelli D, Colarossi L, Colarossi C, Magro G and Tirrò E (2022) Glioblastoma, IDH-Wild Type With FGFR3-TACC3 Fusion: When Morphology May Reliably Predict the Molecular Profile of a Tumor. A Case Report and Literature Review. Front. Neurol. 13:823015. doi: 10.3389/fneur.2022.823015

It has been reported that in-frame *FGFR3-TACC3* fusions confer to glioblastomas, *IDH*-wild type (GBMs, *IDH*wt) some unusual morphologic features, including monomorphous rounded cells with ovoid nuclei, nuclear palisading, endocrinoid network of "chicken-wire" vessels, microcalcifications and desmoplastic stroma, whose observation may predict the molecular profile of the tumor. We herein present a case of recurrent GBMs, *IDH*wt, exhibiting some of the above-mentioned morphological features and a molecularly-proven *FGFR3-TACC3* fusion. A 56-year-old man presented to our hospital for a recurrent GBM, *IDH*wt, surgically treated at another center. Histologically, the tumor, in addition to the conventional GBM morphology, exhibited the following peculiar morphologic features: (1) monomorphous neoplastic cells with rounded nuclei and scant pale cytoplasm; (2) thin capillary-like vessels with "chicken-wire" pattern; (3) nuclear palisading; (4) formation of vague perivascular pseudorosettes; (5) spindled tumor cells embedded in a loose, myxoid background. Based on this unusual morphology, molecular analyses were performed and an *FGFR3* exon17-*TACC3* exon 10 fusion was found. The present case contributes to widening the morphologic spectrum of *FGFR3-TACC3*-fused GBM, IDHwt and emphasizes that pathologists, in the presence of a GBM, *IDH*wt with unconventional morphology, should promptly search for this fusion gene.

Keywords: FGFR3-TACC3 fusion, glioblastoma, unusual morphological features, molecular biology, diagnosis, IDH-wildtype, high-grade glioma

INTRODUCTION

Adult glioblastomas, *IDH*-wild type comprise a molecularly and histopathologically heterogeneous spectrum of neoplasms, characterized by poor prognosis and frequent resistance to the conventional radio-chemotherapy treatments (1–3). According to the cIMPACT-NOW criteria (4), the molecular diagnosis of glioblastomas, *IDH*-wild type (GBMs, *IDH*wt) is essentially based on the presence of at least one of the following alterations in the context of an adult diffuse astrocytic neoplasm, *IDH*-wt: i) combined *7p* gain and *10q* loss, ii) *epidermal growth factor receptor* (*EGFR*) amplification, and iii) *telomerase reverse transcriptase* (*TERT*) promoter mutation (5, 6). GBM, *IDH*wt also shows a wide morphological spectrum, and some histopathologic variants exhibit additional molecular alterations with potential therapeutic implications (7). Genomic profiling studies revealed that GBMs show an extensive molecular heterogeneity and about 30–50% of malignant gliomas harbor targetable gene fusion mainly involving *EGFR*, neurotrophic tyrosine receptor kinase (*NTRK*), and fibroblast growth factor receptor (*FGFR*) genes (8). In the past, *fibroblast growth factor receptor 3* (*FGFR3*)-*transforming acidic coiled-coil 3* (*TACC3*) gene fusion was identified as a rare molecular feature in grade 1 to 4 adult diffuse gliomas lacking *IDH1/2* mutations but always carrying *TERT* promoter mutations or *CDKN2A* loss in about 75% of cases (9, 10). The *FGFR3-TACC3* gene fusion acts as an oncogene, encoding a protein, located on mitotic spindle poles, with constitutive kinase function, that causes a loss of the normal chromosomal segregation and stimulates aneuploidy (11). The identification of the oncogenic *FGFR3-TACC3* fusion highlighted the possibility of identifying a subset of diffuse glioma patients potentially responsive to targeted therapy with *FGFR* kinase inhibitors (12, 13). In the last few years, Bielle et al. have described a series of 30 adult high-grade diffuse gliomas, harboring an in-frame *FGFR3-TACC3* fusion and exhibiting the conventional molecular alterations of GBMs, *IDH*wt, but peculiar histopathologic features; interestingly, the following unusual morphological features were found: *"monomorphous ovoid nuclei, nuclear palisading, and thin parallel cytoplasmic processes, an endocrinoid network of thin capillaries) associated with frequent microcalcifications and desmoplasia"* (14). Since then, additional cases with the co-occurrence of *FGFR3-TACC3* fusion and the above-mentioned histopathologic features have been reported in the literature (15), raising the question of whether this unusual morphology may predict the presence of this equally rare molecular finding.

We herein report a case of a 56-year-old male patient affected by a recurrent GBM, *IDH*wt, showing both an unconventional morphology and a molecularly-proven *FGFR3-TACC3* gene fusion. A critical review of the literature that emphasizes the potential association between morphology and molecular status of this GBM subtype is also included.

CASE PRESENTATION

A 56-year-old man was admitted to our hospital on March 2021 for the recurrence of a GBM, *IDH*wt, which had been surgically treated with a subtotal resection at another center in October 2017. After Stupp regimen and some months of wellness, he developed aphasia and confusion. Brain MRI showed a left parieto-occipital mass with infiltration of the splenium of the corpus callosum (**Figure 1A**) and a gross total resection with a good clinical result was surgically achieved (**Figure 1B**).

Histologically, the tumor was composed of spindled to rounded astrocytic cells that showed an infiltrating growth pattern and high-grade features, such as hypercellularity, high mitotic index (nine mitoses per 10 high-power fields), foci of microvascular proliferation, and pseudopalisading necrosis (**Figure 2A**). Interestingly, the tumor also exhibited some unusual morphological features (**Figures 2B–D**): i) presence of monomorphous ovoid cells with rounded nuclei and sometimes scant pale cytoplasm; ii) numerous thin capillary-like vessels with "chicken-wire" pattern, arranged in an endocrinoid pattern; iii) nuclear palisading; iv) focal perivascular arrangement of neoplastic cells, resulting in the formation of vague perivascular pseudorosettes; v) spindled neoplastic cells embedded in a loose, myxoid background, producing a "tissue culture-like" appearance. Neither microcalcifications, desmoplastic stroma, nor histologic signs of previous treatments were seen. The above-mentioned unusual morphological features were found both distant and in close proximity to tumor areas containing foci of necrosis and microvascular proliferation (**Figure 2B**). Neoplastic cells were diffusely stained with GFAP and OLIG-2. No immunoexpression of IDH1 R132H, H3K27M, H3G34M, and CD34 was found. Nuclear expressions of ATRX and H3K27me3 were retained; <10% of the neoplastic cells were stained with p53 and the Ki-67 proliferation rate was about 10%. Based on both morphological and immunohistochemical features, a diagnosis of recurrent *"WHO grade 4 glioblastomas, IDH-wild type"* was rendered.

Subsequently, because of the unusual morphology encountered, next-generation sequencing (NGS) was chosen to identify further molecular alterations. NGS was performed using a custom panel for the identification of point mutations, INDEL and copy number variations (Glio-panel DNA), and a custom panel for the detection of gene fusions (Glio-panel RNA). The RNA sequencing of recurrent GBM revealed the presence of *FGFR3* exon17-*TACC3* exon 10 (Catalog of Somatic Mutations in Cancer mutation identifier COSF1434) fusion (**Figure 3**). Moreover, NGS sequencing identified the presence of the most common mutations associated with *FGFR3-TACC3* fusion in GBM, *IDH*wt: the pathogenic deletion on the *PTEN* gene (p.Trp111Ter) and *TERT* c.C228T promoter mutation (16). Furthermore, chromosome 10q loss without chromosome seven gain was detected, while no *EGFR*, *MDM2,* and *CDK4* amplification nor *CDKN2A* homozygous deletion were found in the analyzed sample.

DISCUSSION

FGFR3-TACC3 fusions are oncogenic drivers that were first reported in GBMs and bladder urothelial carcinomas (17); in more detail, this unusual fusion was first detected on a series of

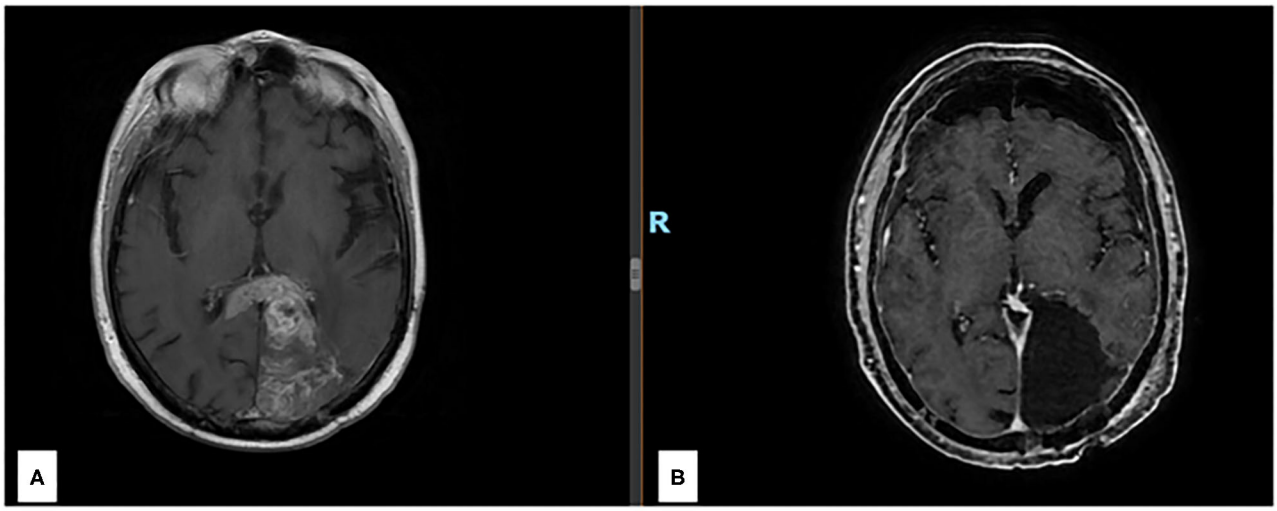

FIGURE 1 | (A) Preoperative axial section of a T1 w MRI after gadolinium injection revealing a left parieto-occipital recurrent lesion with infiltration of the splenium of the corpus callosum. **(B)** Postoperative axial section of a T1 w MRI after gadolinium injection revealing the complete resection of the enhancing nodule.

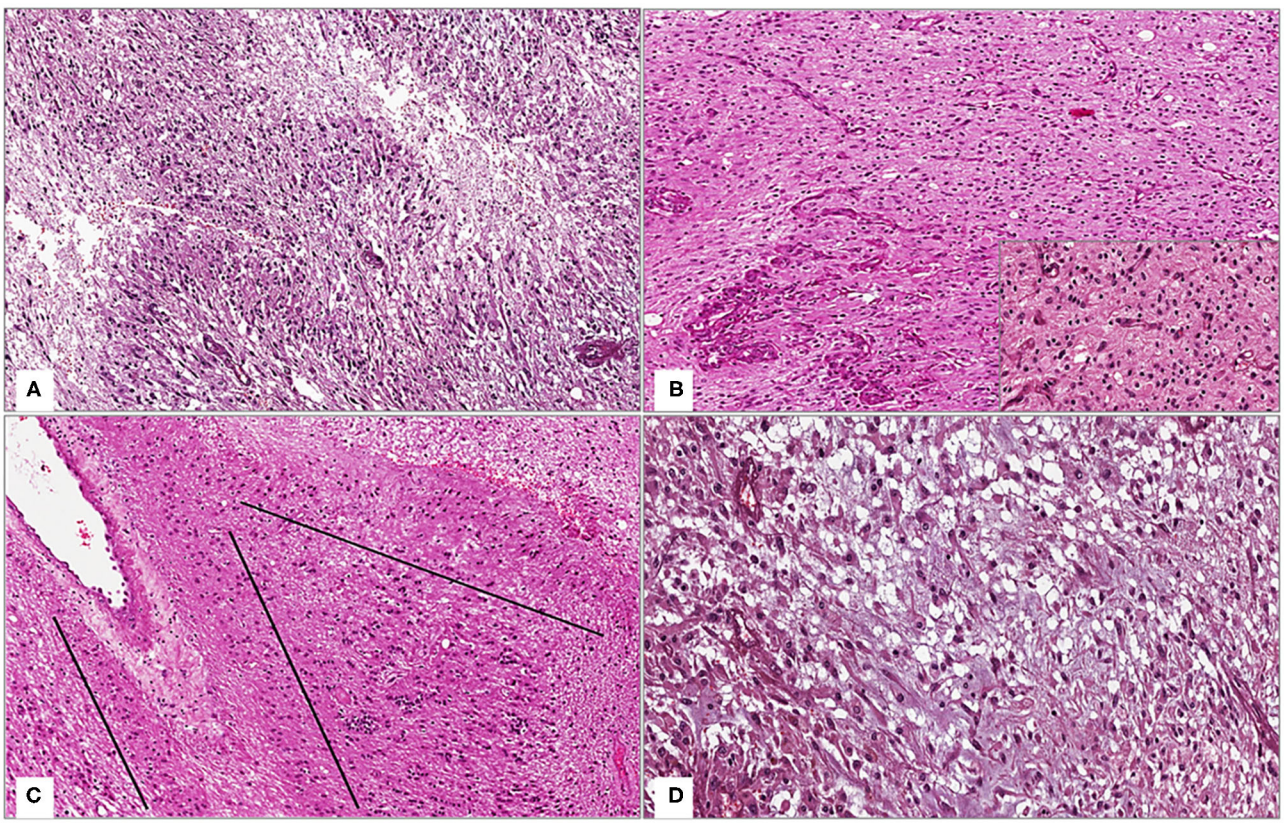

FIGURE 2 | (A) Low magnification showing the conventional morphology of WHO grade IV glioblastoma, IDH-wild type: a moderately cellular astrocytic tumor with foci of pseudopalisading necrosis (hematoxylin and eosin; original magnification 150x); **(B)** Tumor exhibits, as an unusual morphologic feature, more bland-looking areas composed of monomorphous round-shaped cells and thin capillary-like vessels with "chicken-wire" pattern, arranged in an endocrinoid pattern (insert); these features are also found close to foci of microvascular proliferation [hematoxylin and eosin; original magnifications 150x and 300x (insert)]; **(C)** Tumor areas with nuclear palisading (lines) are seen (hematoxylin and eosin; original magnification 150x); **(D)** Spindled neoplastic cells set in a loose, myxoid background, imparting to the tumor a focal "tissue culture-like" morphology (hematoxylin and eosin; original magnification 300x).

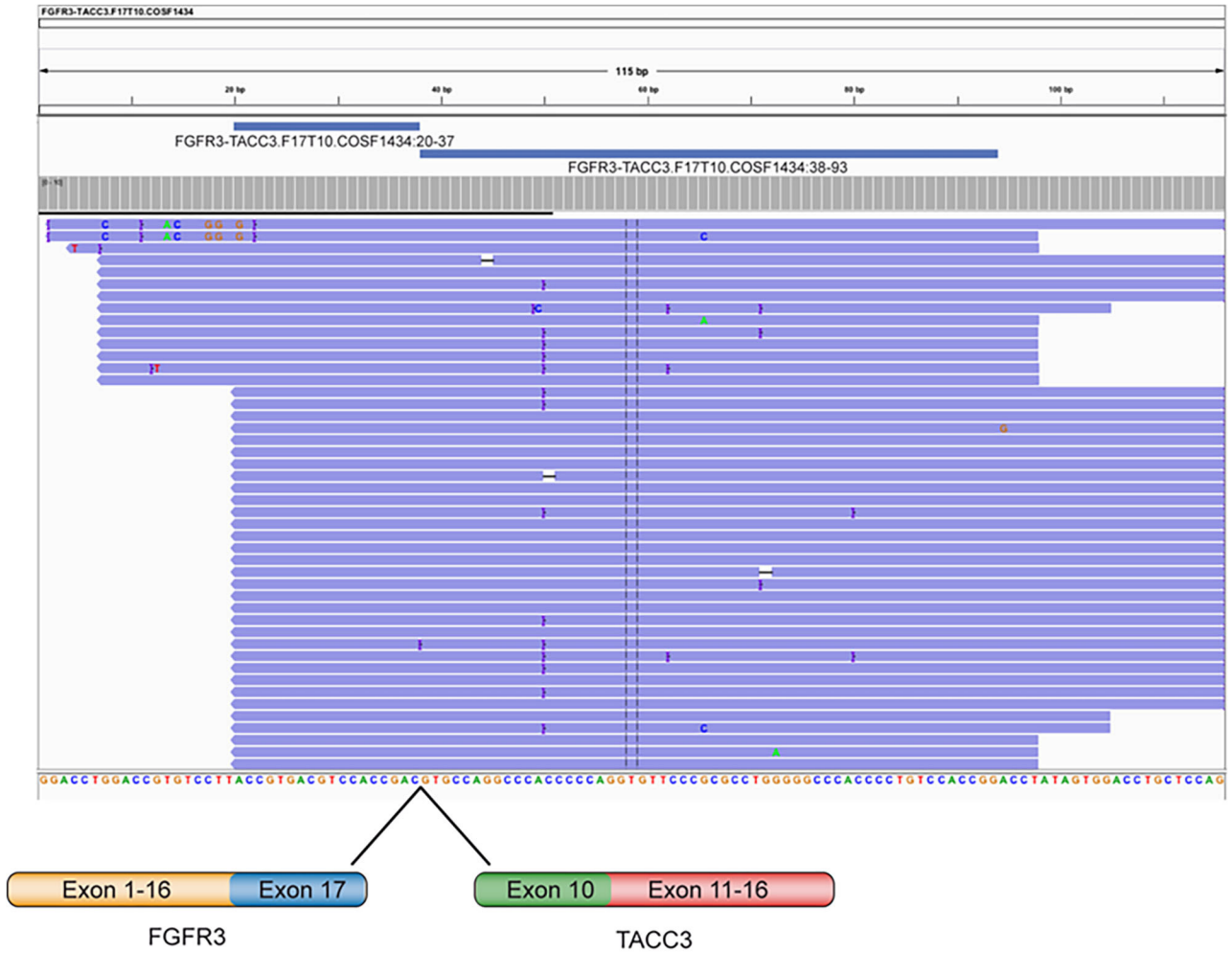

FIGURE 3 | Representation of the *FGFR3-TACC3* fusion gene identified by Next Generation Sequencing in a GBM *IDH*wt patient. Visualization of RNA sequencing reads supports the fusion junction between *FGFR3* exon 17 and *TACC3* exon 10.

97 GBM cases, two of which harbored the *FGFR3-TACC3* fusion (18). Subsequently, larger molecular studies on 584 GBMs and 211 lower-grade diffuse gliomas reported 17 GBMs and three lower-grade gliomas with FGFR3-TACC3 fusions (11). Based on other studies reported in the literature, it is estimated that only a small percentage of GBMs (1–8%) harbor this gene fusion and the incidence decreases further if grade 2 and 3 diffuse gliomas are also considered (17). *FGFR3-TACC3* fusions, although less frequently reported than *FGFR2* and *BRAF* alterations, have also been identified in cases of "polymorphous low-grade neuroepithelial tumor of the young" (PLNTY) (19).

In 2017 Bielle et al. reported a series of 30 patients affected by *FGFR3-TACC3*-fused adult gliomas (age range: 42–87 years), which exhibited some unusual morphological features, combined with microcalcifications and desmoplasia; their cohort included 25 cases of GBMs, *IDH*wt, one case of gliosarcoma, *IDH*wt, one case of GBM, not otherwise specified, two cases of diffuse astrocytomas "with molecular features of GBM" (7p gain, 10q loss, and *TERT* promoter mutation) and one case of histological grade 2 diffuse astrocytoma, *IDH*wt with no additional molecular analyses available (14). Furthermore, 73% of these cases showed some recurrent unusual morphological features, including monomorphous ovoid nuclei, endocrinoid network of capillary vessels, vague formation of perivascular pseudorosettes, nuclear palisading, microcalcifications, and desmoplastic stroma. The presence of this unusual morphology in GBM cases was restricted to areas that lacked necrosis and/or microvascular proliferation and extravascular immunohistochemical staining for CD34 was found in about 50% of cases. These tumors molecularly showed, in addition to the *FGFR3-TACC3* fusion, the conventional GBM, *IDH*wt features (absence of *IDH1/2*, *ATRX* and *TP53* mutations, 7p gain, 10q loss, and *TERT* promoter mutations), except for *EGFR* amplification (0/29), combined with a higher incidence of *CDKN2A* homozygous deletions.

The study of Gilani et al. recently described the histopathologic features of six adult GBMs, *IDH*wt with *FGFR3-TACC3* fusion and lack of *EGFR* amplification, confirming the

presence of the above-mentioned unusual morphologic features, variably combined, in five out of six cases. The remaining case, despite harboring the *FGFR3-TACC3* fusion, exhibited a different morphology from that previously published, characterized by less "bland-looking" cellularity and more striking nuclear atypia (15). Despite being aware that the detection of monomorphous ovoid cells with endocrinoid network of vessels, microcalcifications, and desmoplasia on a high-grade glioma, *IDH*wt might justify the search for *FGFR3-TACC3* fusions, the authors concluded that morphology alone could not predict the molecular status of these rare subsets of GBMs, as some *FGFR3-TACC3*-fused cases, that lacked these peculiar features, occurred, and, conversely, GBM cases, exhibiting this unusual morphology, lacked the *FGFR3-TACC3* fusion.

The present paper reports an additional case of a recurrent GBM, *IDH*wt, and *FGFR3-TACC3* fused with emphasis on the potential correlation between histopathology and molecular status. Histologically, our case showed tumor areas with conventional morphology of GBM, alternating with areas with some of the above-mentioned unusual morphological features. Compared to those cases reported in the literature, the present case showed, as an additional and previously unreported morphologic feature, a spindled neoplastic component, embedded in a loose, myxoid background, producing a "tissue culture-like" appearance. These particular histopathologic features were also found close to tumor areas with necrosis and foci of microvascular proliferation and led us to request a further molecular test for diagnostic confirmation and for the search of *FGFR3-TACC3* fusion, whose presence has not only a speculative but also a practical function as it identifies a subset of patients with a slightly better prognosis than those affected by conventional GBM, *IDH*wt and who could benefit from a targeted therapy with *FGFR* kinase inhibitors. As some of these uncommon morphologic features are shared with other brain tumors, they often represent diagnostic challenges: i) oligodendrogliomas, *IDH*-mutant, and 1p/19q codeleted often exhibit monomorphic rounded cells with pale cytoplasm and a "chicken-wire" vascular network; ii) ependymomas and angiocentric glioma characteristically show perivascular pseudorosettes; iii) glioneuronal tumors, in general, may exhibit extravascular positivity for CD34 and desmoplastic stroma (14). These histological findings in a diffuse glioma *IDH*-wildtype should prompt pathologists to consider *FGFR3-TACC3* fusion and look for additional genetic alterations that are required for the diagnosis of GBM, *IDH*wt. The treatment for patients with GBM includes combined radio and chemotherapy (20). Temozolomide (TMZ) is the standard chemotherapeutic used alone or in association with a DNA alkylating agent: however, chemoresistance and not well-characterized mechanisms involved in the development of tumors are the most common cause of therapy failure (21–25). Furthermore, for recurrent gliomas, standard-of-care treatments are not well defined; treatment is usually selected based on prior therapy, age, Karnofsky Performance Scale (KPS), MGMT promoter methylation status, and patterns of disease progression (26). Bevacizumab, an anti-vascular endothelial growth factor (VEGF) monoclonal antibody that has been introduced in the USA in 2009 as a treatment for recurrent high-grade gliomas, has become one of the first-choice therapies for recurrent GBMs, according to National Comprehensive Cancer Network (NCCN) guidelines. The combination of bevacizumab and chemotherapy represents an additional treatment option for these patients. However, when the standard therapeutic regimens lack efficacy, targeted therapies for patients with primary and recurrent GBMs are currently limited, and novel molecular biomarkers are needed to improve the development of personalized treatments.

Xu et al. reported that potentially targetable molecular alterations, mainly involving *NTRK*, *EGFR,* and *FGFR* genes, occurred in about 30 to 50% of GBMs (8). In more detail, while *NTRK* rearrangements are very rare, being found in <2% of GBM cases and consisting of fusions between *NTRK1* and other genes, such as *NFASC*, *BCAN, CHTOP,* and *ARHGEF2, EGFR* in-frame fusions are much more frequent (*EGFR-SEPT14* and *EGFR-PSPH* fusion genes were observed approximately in 4 and 2% of cases) and frequently lead to EGFR overexpression in GBM (8); however, all clinical trials with EGFR inhibitors did not demonstrate longer survival times in GBM patients so far, probably due to the inclusion of poorly homogeneous patient populations. Finally, these authors reported that about 1 to 8% of GBMs harbored potentially druggable *FGFR-TACC* rearrangements, being *FGFR3-TACC3* the gene fusion most frequently encountered in 5% of cases, followed by *FGFR1-TACC1* (8). Nowadays, tyrosine kinase fusion genes are an important class of oncogenes associated with different hematological and solid tumors (27), thus targeting gene fusion has been a promising therapeutic option in several types of cancer models (28–30). The growing therapeutic relevance of FGFR alterations, including fusions, in different cancer types, has greatly supported the development of a variety of tyrosine kinase inhibitors (TKIs) (31–33). Although these drugs exhibit good anticancer effects in many, their use in the treatment of brain malignancies is limited. Among the reasons for this is the presence of the blood-brain barrier that influences the delivery of drugs to the central nervous system as well as patient-to-patient variability.

The presence of the *FGFR3-TACC3* fusion gene certainly represents a further targetable mutation within the molecular heterogeneity typical of the majority of GBMs (34). The reassuring outcome of anti-FGFR inhibitors in different preclinical studies strengthened the rationale to employ FGFR tyrosine kinase inhibitors in GBM patients harboring the *FGFR3-TACC3* fusion gene (11, 18). Different clinical trials studies have been completed (NCT02824133 and NCT01975701) or are still recruiting GBM patients (NCT04424966 or NCT04547855) to test the efficacy of multi-targeted receptor tyrosine kinase inhibitors, such as Anlotinib, or selective FGFR1-3 inhibitors, such as Infigratinib, in relapsed or progressed GBM patients. In this regard, Wang et al. described a partial response (>17 months of follow-up) in a 44-year-old woman affected by recurrent GBM, *IDH*wt, that harbored simultaneously an *FGFR3-TACC3* fusion and *FGFR3* amplification, treated with Anlotinib 12 mg p.o. once every day plus oral TMZ chemotherapy (35). Interestingly, the authors speculated that the coexistence of two different *FGFR3* alterations *(FGFR3-TACC3* fusion and *FGFR3* amplification)

in the same tumor could be the main reason for the significant efficacy of Anlotinib therapy and emphasized that tumors harboring *FGFR3-TACC3* rearrangements and/or *FGFR3* amplification should be selected for clinical trials featuring *FGFR* inhibitors (35).

CONCLUSIONS

The present case highlights that neuropathologists should be aware that the presence of an unusual morphology may reliably predict a distinct molecular profile of GBM, *IDH*wt, and that, in the presence of the above-mentioned features, they must promptly consider a *FGFR3-TACC3* fusion. The spindle cell component embedded in a myxoid stroma, found in our case, contributes to expanding the spectrum of morphologic features that may predict the presence of *FGFR3-TACC3* fusions. To this end, the detection of a fusion gene using transcriptome sequencing may represent a novel approach (36). In conclusion, we strongly emphasize that the prompt identification of the combination between unusual morphology and presence of *FGFR3-TACC3* fusion has mainly the practical purpose of identifying a subset of patients with a slightly better outcome than those affected by conventional GBM, *IDH*wt, and for whom the use of personalized treatment with *FGFR* kinase inhibitors may be considered.

AUTHOR CONTRIBUTIONS

GB, EP, and ET: conceptualization. DC and ET: methodology. CR, PV, and ET: validation. GB and ET: formal analysis, writing–original draft preparation, writing–review, and editing. GB: investigation. EP, LC, and CC: resources. RA, FC, and GM: supervision. All authors have read and agreed to the published version of the manuscript.

FUNDING

This study was partially funded by the Research plan of the University of Catania-Linea di intervento 2-entitled MultiDisciplinary RESEarch and Targeted Therapy for malignant GLIOmas (MD-RESETT-GLIO).

ACKNOWLEDGMENTS

The authors wish to thank the Scientific Bureau of the University of Catania for language support.

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frontiers in Oncology

SYSTEMATIC REVIEW
published: 17 February 2022
doi: 10.3389/fonc.2022.848036

5-Aminolevulinic Acid False-Positive Rates in Newly Diagnosed and Recurrent Glioblastoma: Do Pseudoprogression and Radionecrosis Play a Role? A Meta-Analysis

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OPEN ACCESS

Edited by:
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Reviewed by:
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Federico Giuseppe Legnani, Carlo Besta Neurological Institute Foundation (IRCCS), Italy

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Specialty section:
This article was submitted to Neuro-Oncology and Neurosurgical Oncology, a section of the journal Frontiers in Oncology

Received: *03 January 2022*
Accepted: *24 January 2022*
Published: *17 February 2022*

Citation:
Ricciardi L, Sturiale CL, Scerrati A, Stifano V, Somma T, Ius T, Trungu S, Acqui M, Raco A, Miscusi M and Della Pepa GM (2022) 5-Aminolevulinic Acid False-Positive Rates in Newly Diagnosed and Recurrent Glioblastoma: Do Pseudoprogression and Radionecrosis Play a Role? A Meta-Analysis. Front. Oncol. 12:848036. doi: 10.3389/fonc.2022.848036

Background: Several studies have confirmed the impact of 5-aminolevulinic acid (5-ALA) on the extent of resection in newly diagnosed glioblastoma (GBM). However, there are controversies on the 5-ALA fluorescence status in recurrent GBM surgery, with specific reference to pseudoprogression or radionecrosis; therefore, the safety and accuracy of surgical planning in 5-ALA-assisted procedures in the recurrent context are still unclear.

Materials and Methods: This is a systematic review and meta-analysis of comparative studies on the use of 5-ALA in newly diagnosed and recurrent GBM, consistently conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. Data on fluorescence status and correlation between fluorescence and histological findings were collected. We performed a meta-analysis of proportions to estimate the pooled rates of each outcome.

Results: Three online medical databases (PubMed, Scopus, Cochrane Library) were screened, 448 articles were evaluated, and 3 papers were finally included for data analysis. Fluorescence rate was not different between newly diagnosed and recurrent GBM [p = 0.45; odds ratio (OR): 1.23; 95% CI: 0.72–2.09; I^2 = 0%], while the rate of 5-ALA fluorescence-positive areas not associated with histological findings of GBM cells was higher in recurrent GBM (p = 0.04; OR: 0.24; 95% CI: 0.06–0.91; I^2 = 19%). Furthermore, there were no cases of radionecrosis in false-positive samples, while inflammation and signs of pseudoprogression were found in 81.4% of the cases.

Discussion and Conclusions: Therefore, a robust awareness of 5-ALA potentialities and pitfalls in recurrent GBM surgery should be considered for a cognizant surgical strategy. Further clinical trials could confirm the results of the present meta-analysis.

Keywords: glioblastoma, high-grade glioma (HGG), recurrent glioblastoma, 5-ALA fluorescence, pseudoprogression, radionecrosis

INTRODUCTION

An extended microsurgical resection over the anatomical limits of the solid lesion on contrast-enhanced T1-weighted MRI images is currently established as a paramount determinant in terms of both overall survival (OS) and progression-free survival (PFS) similarly in newly diagnosed and recurrent glioblastoma (GBM) (1, 2). Since the approval of 5-aminolevulinic acid (5-ALA) for medical use in 2007 in Europe and in 2017 in the United States, several studies have confirmed its impact on the extent of resection rate in GBM surgeries. Therefore, 5-ALA has been progressively adopted as a standard tool in neurosurgical procedures for GBM, providing valuable clinicoradiological outcomes (1, 3–5).

After its administration, 5-ALA mainly accumulates in malignant glial cells, where it is converted to fluorescent protoporphyrin IX (PpIX). However, it should be carefully considered that PpIX can also be found in non-tumoral structures, such as ependymal cells (6, 7). Furthermore, the presence of inflammatory tissue, such as in the case of peritumoral reactive inflammation, pseudoprogression (PP), or radiation-induced necrosis [radionecrosis (RN)] may influence the intraoperative fluorescence detection (8, 9). Therefore, surgeons must be aware that *not everything that glitters is gold*. Hence, a critical analysis of the clinicoradiological outcomes of 5-ALA-guided surgery in recurrent gliomas may help shed light on this (8).

The aim of the present systematic review and meta-analysis of comparative studies, reporting the 5-ALA fluorescence status in newly diagnosed and recurrent GBM, is to investigate true-positive and false-positive fluorescence rates, histological findings in 5-ALA-positive samples with no evidence of GBM cells, and the fluorescence status of RN and PP areas.

MATERIALS AND METHODS

Study Design

The present investigation is a systematic review and meta-analysis conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

Search Strategy

The review question was formulated according to the PICO (P: patients; I: intervention; C: comparison; O: outcomes) scheme, as follows: in case of newly diagnosed or recurrent glioblastoma multiforme (P), is 5-ALA (I) a useful tool for increasing the extent of resection (O), considering the tumor fluorescence positivity and the false-positive rates (C)?

Three different medical databases (PubMed, Scopus, and Cochrane Library) were screened using the following search terms: "5-ALA", "aminolevulinic", "recurrent glioma", "recurrent glioblastoma", "radionecrosis", "pseudoprogression", "glioma recurrence", "glioblastoma recurrence", "radiation necrosis" [MeSH], combined using Boolean operators "AND" and "OR".

Titles and abstracts were screened in the first search round. In the second round, full text of eligible papers and their reference lists (forward search) were evaluated. Then, papers were considered for data reporting and availability in the third round of search. Studies matching our inclusion criteria were finally included in the present systematic review and meta-analysis. Two authors (GDP and AS) independently conducted the first two search rounds, and any discordance was solved by consensus with a third senior author (LR).

Inclusion and Exclusion Criteria

Comparative studies in English language on newly diagnosed and recurrent GBM, reporting data on the intraoperative 5-ALA fluorescence status (positive/negative), and histological findings of 5-ALA-positive regions were considered for eligibility. True positive was considered as 5-ALA-positive fluorescence and histological confirmation of GBM; false positive, instead, as 5-ALA-positive fluorescence and no histological diagnosis of GBM. Reviews, case reports, letters, technical notes, video articles, and studies on pediatric population (<18 years old) were not considered. The inclusion and exclusion critera are summarized in **Table 1**.

Data Extraction

Included studies were screened for the number of newly diagnosed and recurrent GBM patients, their demographics, type of operative microscope, and percentage of true and false positives in each group. Furthermore, histological findings in case of false-positive samples were also collected.

TABLE 1 | Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
• English language • Comparative studies on 5-ALA fluorescence rate in newly diagnosed and recurrent glioblastoma • Histological findings in case of false positivity • Adult population	• Reviews, clinical case, editorial, technical notes studies • Pediatric population (<18 years) • Published prior to 2007

Statistical Analysis

We performed a meta-analysis of proportions to estimate the pooled rates of each outcome. Proportion meta-analyses were not used when the frequency of an outcome was reported in <1% of the sample [raw proportions and 95% confidence interval (95% CI) were reported in such cases], and a random-effects model was adopted to account for the inter-study heterogeneity.

RESULTS

Study Selection

A total of 448 titles and abstracts were firstly screened. Eighteen papers were considered as eligible, and their full text was evaluated. After the full-text analysis and the forward search, 3 papers were finally included for meta-analysis. The search strategy is summarized in **Figure 1**. Papers excluded with reason after their full-text examination are summarized in **Supplementary Table S1**.

Included Studies

We included 331 patients from 3 studies, 1 retrospective (10) and 2 prospective (11, 12).

A newly diagnosed GBM was reported in 212 patients while a recurrent GBM in 119. Patient's gender and age were reported in 1 out of the 3 (33%) included studies.

All patients received histological diagnosis according to the WHO 2016 guidelines. All patients who underwent second surgeries for GBM recurrence received the Stupp protocol between the two procedures.

The use of 5-ALA fluorescence was used to perform multiple biopsies in each included study, and the definition of *"false positive"* was homogeneously considered as the absence of GBM cells at least in one of the analyzed samples.

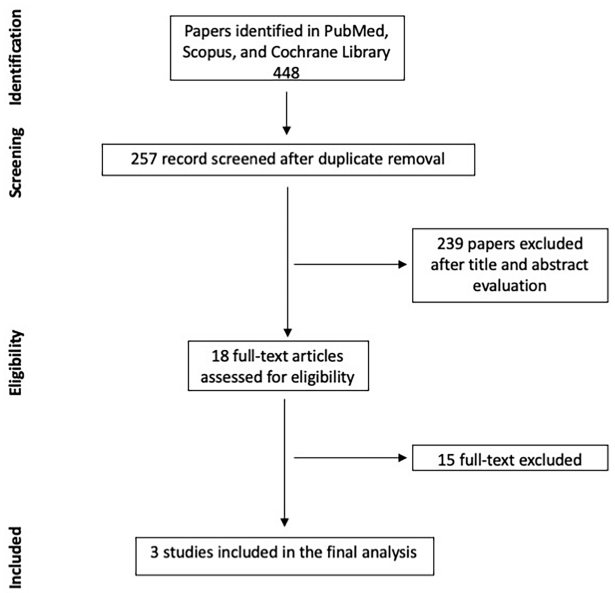

FIGURE 1 | Search strategy.

Positive 5-Aminolevulinic Acid Fluorescence Rate

The type of operative microscope used for conducting the surgical procedures was reported in 1 out of the 3 included studies, and it was Pentero (Carl Zeiss, Oberkochen, Germany).

A positive 5-ALA fluorescence was reported in 169 (79.7%) out of the 212 newly diagnosed GBM and in 89 (74.8%) out of the 119 recurrent GBM.

The rate of positive 5-ALA fluorescence was not significantly different between newly diagnosed and recurrent GBM [p = 0.45; odds ratio (OR): 1.23; 95% CI: 0.72–2.09; I^2 = 0%]. The heterogeneity was very low, confirming the reliability of data (**Figure 2**).

False-Positive 5-Aminolevulinic Acid Fluorescence Rate and Histological Findings

The histopathology did not confirm the presence of GBM cells in 7 (4.1%) out of the 169 5-ALA fluorescence-positive newly diagnosed cases and in 9 (10.1%) out of the 89 5-ALA fluorescence-positive recurrent GBM.

The incidence of false positives was significantly higher in recurrent GBM cases (p = 0.04; OR: 0.24; 95% CI: 0.06–0.91; I^2 = 19%) with a relatively low heterogeneity rate.

Histological report was available in 13 (81.3%) out of the 16 false-positive cases. It reported "abnormal brain tissue characterized by reactive astrocytes and scattered inflammatory cells" in 11 (68.8%), "normal brain tissue" in 1 (6.3%), "infiltrating neutrophils" in 1 (6.3%), and not reported in 3 (18.8%). No cases of RN were reported in false-positive cases among the recurrent GBMs (**Figure 3**).

DISCUSSION

The present systematic review and meta-analysis demonstrates no significant differences in terms of positive 5-ALA fluorescence rates between newly diagnosed and recurrent GBM, while the rate of 5-ALA-positive areas not associated with histological finding of GBM cells is significantly higher in recurrent GBM surgeries (**Figures 2**, **3**).

Our data analysis also confirmed that 5-ALA accumulates in malignant glial cells in both newly diagnosed and recurrent GBM, showing that there are no differences between newly diagnosed and recurrent GBM in terms of intraoperative 5-ALA-positive fluorescence rates. This implies that 5-ALA can be considered a useful and reliable tool for identifying GBM cells during microsurgical procedures. Furthermore, the accumulation of 5-ALA in peritumoral inflammatory areas also leads surgeons to conduct a supramarginal resection, which is a pursuable outcome in GBM surgeries.

Conversely, in literature and in general practice, its indisputable role has been well underlined for newly diagnosed

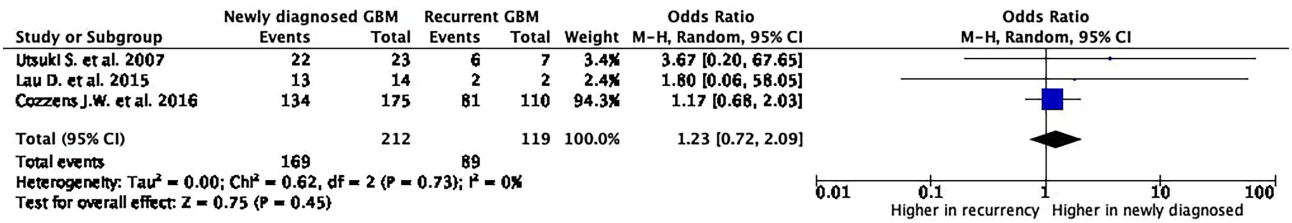

FIGURE 2 | 5-Aminolevulinic acid (5-ALA) fluorescence rate in newly diagnosed and recurrent glioblastoma. The Foster Plot, from the meta-analyses of proportions to estimate the pooled rates of 5-ALA-positive fluorescence rate in newly diagnosed and recurrent glioblastoma. According to the Plot, there are no significative differences comparing the pooled rates from the two meta-analytic groups (p = 0.45).

high-grade glioma (HGG) cases (13, 14). On the other hand, its significance and possible pitfalls in recurrent HGGs are less delineated; potentialities and drawbacks in the recurrent setting are instead less clear (15).

Recent literature, indeed, focused on false-negative conditions specifically addressing the issues of PP and RN in HGGs (16, 17). Recurrent GBMs represent different entities from newly diagnosed ones in terms of peritumoral peculiar findings, such as RN and PP. Therefore, 5-ALA fluorescence status in recurrent GBMs and their peritumoral area may be influenced by the aforementioned modifying factors. This should be carefully considered when planning 5-ALA-assisted procedures in recurrent GBM to avoid resections improperly exceeding planned limits.

Our results showed that the rate of 5-ALA-positive areas with no GBM cells in their context, classified as false-positive regions, is significantly higher in recurrent GBMs than in newly diagnosed ones (p = 0.04). A critical analysis of this finding could aim to better understand mechanisms underlying the higher false-positive rate in recurrent glioma.

Pseudoprogression

PP is defined as peritumoral inflammatory tissue that may be erroneously reported as tumor progression or recurrence on MRI images (18). The PP phenomenon is well documented, and its MRI aspect is justified by its histological findings, consisting of inflammation, neutrophil and macrophage infiltration, reactive astrocytes, high mitotic rate, and neoangiogenesis (19). This may justify the 5-ALA fluorescence in these peritumoral areas, as confirmed in our results. In fact, "*abnormal brain tissue characterized by reactive astrocytes and scattered inflammatory cells*" was found in 68.8% of false-positive specimens and "*infiltrating neutrophils*" in 6.3%. The histological report was "*normal brain*" in 6.3%, while it was not available in 18.8% of the included cases. Accordingly, inflammatory findings were found in 82.1% of false-positive samples, confirming that PP could represent the underlying mechanism of 5-ALA accumulation in non-malignant GBM peritumoral areas.

Post-surgical or post-radiation infiltration of reactive astrocytes (responsive astrocytosis), immune cell presence, and 5-ALA extracellular accumulation can be responsible for false-positive cases. Indeed, histiocytes/macrophages (which have function of phagocytosis) and lymphocytes can internalize 5-ALA: this may lead to a significant buildup of porphyrin precursors, making the tissue fluorescent (8). Regarding 5-ALA leakage and extracellular fluorescence accumulation, the latter is true mostly for lesions with pronounced perifocal edema.

Radiation Necrosis

RN is a relatively frequent finding in postoperative follow-up imaging from GBM patients. It consists of local necrosis and fibrous tissue spreading, usually contiguously to the surgical cavity. Although RN consists of a relatively low-activity metabolic tissue, its enlargement may determine some grade of compression on the surrounding brain tissue, resulting in inflammatory phenomena (20). Conversely, RN is not

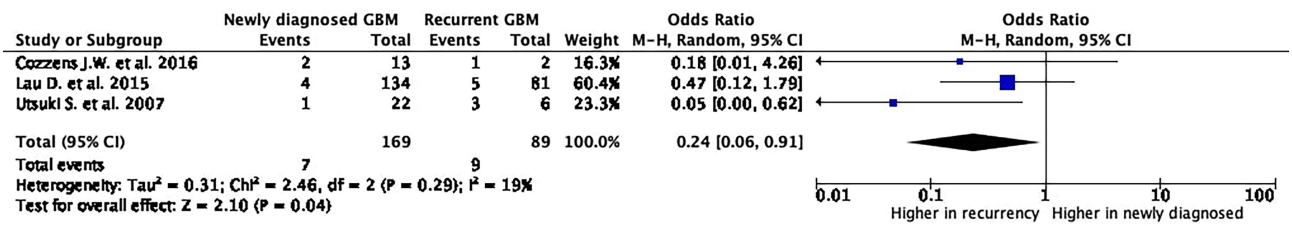

FIGURE 3 | 5-Aminolevulinic acid (5-ALA) fluorescence-positive areas non-associated with histological finding of glioblastoma cells. The Foster Plot, from the meta-analyses of proportions to estimate the pooled rates of 5-ALA-positive fluorescence areas non-associated with histological finding of glioblastoma cells, defined in the paper as false-positive areas. According to the Plot, a significantly higher false-positive rate occurs in recurrent glioblastoma.

supposed to be 5-ALA positive due to its metabolic status and histological characteristics (8).

This meta-analysis confirms this evidence, as no cases of RN were reported among false-positive samples.

These data are of importance, as there is not a clear picture about its behavior in literature with 5-ALA. Indeed, an aspect to be critically appraised concerning this issue, especially in oldest reports, is the fact that neuropathological examination in many reports could underestimate the presence of tumor cells. As a matter of fact, in many cases, hematoxylin–eosin staining depicting reactive changes only can be actually converted to the diagnosis of infiltrating tissue after additional immunohistochemistry investigations. Furthermore, while RN can occur in a relatively small area, the surrounding tissue has been radiated itself, then some grade of radiation-induced inflammation has to be considered. Therefore, while proper RN tissue should not display fluorescence, the surrounding brain may be characterized by inflammatory phenomena and histologically related findings and hence might display some degree of 5-ALA fluorescence.

Surgical Considerations

The present analysis demonstrated that the incidence of false positives in recurrent glioma surgery is not negligible. This is especially true when PP is considered for differential diagnosis. PP has been reported to occur predominantly (almost 60% of cases) within the first 3 months after completing adjuvant treatments, although it may occur later, as reported after medical administration of lomustine and temozolomide. In addition, methylguanine-DNA methyltransferase (MGMT) methylation tumor's status has been associated with PP occurrence (21). Hence, if timing and molecular status are consistent, it is important for the neurosurgeon performing 5-ALA-guided resections to be aware of concerns regarding the accurate diagnosis of this phenomenon and that fluorescence status might hinder non-neoplastic tissue. On the other hand, in this setting, non-tumor-related 5-ALA positivity can be used as a guide to target surgical excision to areas of inflammatory infiltrations or reactive gliosis when surgery is indicated for edema relief.

Nevertheless, 5-ALA in the recurrent setting is valuable to the surgeon when RN is suspected: as demonstrated in the present analysis, 5-ALA-related fluorescence is rather more specific. Hence, this can provide surgeon guidance for proper histopathological sampling to increase diagnostic yield and tailor resection.

Indeed, 5-ALA can provide a feasible guidance especially in the recurrent setting, where MRI-based information often fails to preoperatively identify proper oncological tissue.

The "real-life" intraoperative picture corresponds to a substantial lack of textural feedback (tumor is often friable) and presence of scar, inflammation, neo-angiogenesis, and gliosis that further compromise a surgeon's ability to distinguish tumor from non-tumoral tissue. This corresponds to a mixture of reactive/regressive tissue that shows areas with different degrees or absence of fluorescence along with proper neoplastic tissue that display fluorescence (17).

Therefore, a robust awareness of 5-ALA potentialities and pitfalls in recurrent glioma surgery is therefore paramount for a cognizant surgical strategy, especially when in proximity to eloquent brain areas where oncological benefit and functional cost associated with an aggressive resection should be considered.

CONCLUSIONS

5-ALA is considered as one of the most valuable and widespread innovations in the field of HGG surgery. Its indisputable role has been well underlined for newly diagnosed HGG cases, whereas its significance, potentialities, and drawbacks in the recurrent setting are less clear.

The present study sheds light on 5-ALA's possible role in recurrent glioma surgery, to appropriately guide surgical strategy, especially when PP or RN is suspected. Further clinical trials could confirm the results of the present meta-analysis.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**. Further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

LR, CS, GDP, and AS contributed to conception and design of the study. VS, MA, and TS organized the database. TI and ST performed the statistical analysis. LR and CS wrote the first draft of the article. AR, MM, and GDP supervised the article. All authors contributed to article revision and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2022.848036/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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SYSTEMATIC REVIEW
published: 04 April 2022
doi: 10.3389/fonc.2022.884928

Posterior Percutaneous Pedicle Screws Fixation Versus Open Surgical Instrumented Fusion for Thoraco-Lumbar Spinal Metastases Palliative Management: A Systematic Review and Meta-analysis

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OPEN ACCESS

Edited by:
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Sapienza University of Rome, Italy

Reviewed by:
Giovanni Noia,
Azienda Ospedaliero-Universitaria Ospedali Riuniti di Foggia, Italy
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Specialty section:
This article was submitted to Neuro-Oncology and Neurosurgical Oncology, a section of the journal Frontiers in Oncology

Received: 27 February 2022
Accepted: 14 March 2022
Published: 04 April 2022

Citation:
Perna A, Smakaj A, Vitiello R, Velluto C, Proietti L, Tamburrelli FC and Maccauro G (2022) Posterior Percutaneous Pedicle Screws Fixation Versus Open Surgical Instrumented Fusion for Thoraco-Lumbar Spinal Metastases Palliative Management: A Systematic Review and Meta-analysis. Front. Oncol. 12:884928. doi: 10.3389/fonc.2022.884928

Background: Surgical palliative treatment of spinal metastases (SM) could influence the quality of life (QoL) in cancer patients, since the spine represents the most common site of secondary bony localization. Traditional open posterior instrumented fusion (OPIF) and Percutaneous pedicle screw fixation (PPSF) became the main surgical treatment alternatives for SM, but in Literature there is no evidence that describes the absolute superiority of one treatment over the other.

Materials and Methods: This is a systematic review and meta-analysis of comparative studies on PPSF versus OPIF in patients with SM, conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. The outcomes of interest were: complications, blood loss, infections, mortality, pain and also the Quality of Life (QoL).

Results: There were a total of 8 studies with 448 patients included in the meta-analyses. Postoperative complications were more frequent in OPIF (odds ratio of 0.48. 95% CI, 0.27 to 0.83; p= 0.01), PPFS was associated with blood loss (odds ratio -585.70. 95% IC, -848.28 to -323.13.69; p< 0.0001) and a mean hospital stay (odds ratio -3.77. 95% IC, -5.92 to -1.61; p= 0.0006) decrease. The rate of infections was minor in PPFS (odds ratio of 0.31. 95% CI, 0.12 to 0.81; p= 0.02) whereas the occurrence of reinterventions (0.76. 95% CI, 0.25 to 2.27; p= 0.62) and the mortality rate was similar in both groups (odds ratio of 0.79. 95% CI, 0.40 to 1.58; p= 0.51). Finally, we also evaluated pre and post-operative VAS and the meta-analysis suggested that both techniques have a similar effect on pain.

Discussion and Conclusion: The PPSF treatment is related with less complications, a lower rate of infections, a reduction in intraoperative blood loss and a shorter hospital stay compared to the OPIF treatment. However, further randomized clinical trials could confirm the results of this meta-analysis and provide a superior quality of scientific evidence.

Keywords: spinal metastasis, cancer surgery, minimally invasive spine surgery, MIS, percutaneous pedicle screws

INTRODUCTION

The bone represent the third most frequent secondary cancer location, after lung and liver, especially for solid tumour such as lung, prostate and breast (1). Spinal metastases (SM) is the most frequent metastatic bone lesion (MBL) and one of the principal causes of morbidity and worsening of the quality of life (QoL) in cancer patients due to neurologic involvement and intractable pain (2). It is estimated that about 10% of cancer patients have symptomatic SM, and the thoraco-lumbar region seems to be the most involved (3). Furthermore the life expectancy of cancer patients increased, and consequently both the incidence and prevalence of symptomatic SM represents growing condition (4). Often the correct management of SM is challenging for doctors. The SM patient treatment must be individualized for each patient, requiring a multidisciplinary approach among the various medical specialists (5).

Several therapeutic alternatives were described such as chemotherapy or radiotherapy, however surgery seems to be the best choice for spinal instability related pain and neurological impairment (6). The presence of SM often reflects an advanced disease where is not possible for a spinal surgeon to be radical. Therefore palliative surgery, with the aim of improving the patient's QoL for the remaining life, represents an increasingly occurrence in spinal oncology (7).

Traditional open posterior instrumented fusion (OPIF) with or without decompression was described as effective in the neurological status improvement. However, the high rate of peri and post-operative complications could affect the final outcome and consequently the patients' QoL (8). Percutaneous pedicle screw fixation (PPSF) advantages (reduced blood loss, less soft tissue trauma, less perioperative pain, shorter hospitalization and earlier return to normal activities) were widely reported in polytrauma patients and degenerative spinal diseases (9). Nevertheless, only in recent years, the use of minimally invasive spinal surgery (MISS) in SM patients has increased. Currently in Literature there is no evidence that indicates the absolute superiority of one treatment over the other (10). Therefore, the aim of the present systematic review and meta-analysis was to evaluate PPSF versus OPIF approaches in treatment of SM patients.

MATERIALS AND METHODS

Study Setting and Search Strategy

A systematic literature review according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines was conducted (**Figure 1**) in this study (11). An electronic search on Scopus, Cochrane Library and MEDLINE *via* PubMed database was performed using the following keywords: "minimal invasive surgery", "minimally invasive surgery", "MISS", "MIS", "conventional open surgery", "traditional open surgery", "open surgery", "spinal metastasis", "spine metastasis", "vertebral metastasis", "spinal metastatic disease" and their MeSH terms in any possible combinations using the logical operators "AND" and "OR". The reference lists of relevant studies were forward screened to identify other studies of interest. The search was reiterated until October 3, 2021. The review protocol started on September 10, 2021 was registered on the International Prospective Register of Systematic Reviews (PROSPERO), ID: CRD42021283003.

Inclusion and Exclusion Criteria

In the present review, the full-text English written articles reporting comparisons of PPSF versus OPIF in patients with SM were considered eligible. No date of publication limits were set. Study with follow up shorter than 60 days were excluded from analysis. Expert opinions, studies on animals, unpublished reports, *in vitro* investigations, case reports, case series, letters to the editor, abstracts from scientific meetings and book chapters were excluded from review. The inclusion and exclusion criteria were summarized in **Table 1**.

Review Question

The review questions were formulated following the PICO scheme (12) (population (P), intervention (I), comparison (C), and outcome (O)) as follows:

Do the patients affected by spinal metastases (P) treated with PPSF surgery (I) have better clinical and functional outcomes (minor blood loss, surgical pain and complication) (O) compared to those treated with OPIF (C)?

Data Extraction

Two independent authors (A.P. and R.V.) performed the title and abstract screening and collected data from the included studies. Any discordances were solved by consensus with a third author (A.S). The following data were extracted: demographic features, primitive cancer, level involved, Tokuhashi score, Frenkel or American Spinal Injury Association (ASIA) score, intraoperative blood loss, operative time, length of stay, clinical and functional outcomes, possible complications, and follow-up.

Statistical Analysis

Numbers software (Apple Inc., Cupertino, CA) was used to tabulate the obtained data. Categorical variables are presented as frequency and percentages. Continuous variables are presented as means and standard deviation. Only one decimal digit was reported and was rounded up.

The mean difference (MD) and odds ratio (OR) with 95% confidence interval (CI) were used for each relevant outcome measure. The measured outcomes were presented as a Forest plot. The $\chi 2$ test was used to evaluate the heterogeneity between included studies. The I^2 statistic was performed to estimate the proportion of total variation among analyzed studies; a value higher than 50% was interpreted as substantial heterogeneity. When a large value of I^2 was obtained a random-effect model was tested, else a fixed-effect model was used. The publication bias was analyzed, according to the MOOSE criteria (**Table 2**) by creating a funnel plot for each outcome analyzed, analyzing its asymmetry. Review Manager Version 5.4.1 (Cochrane Collaboration, Software Update, Oxford, United Kingdom) was used for statistical analysis and generation of Forest plots.

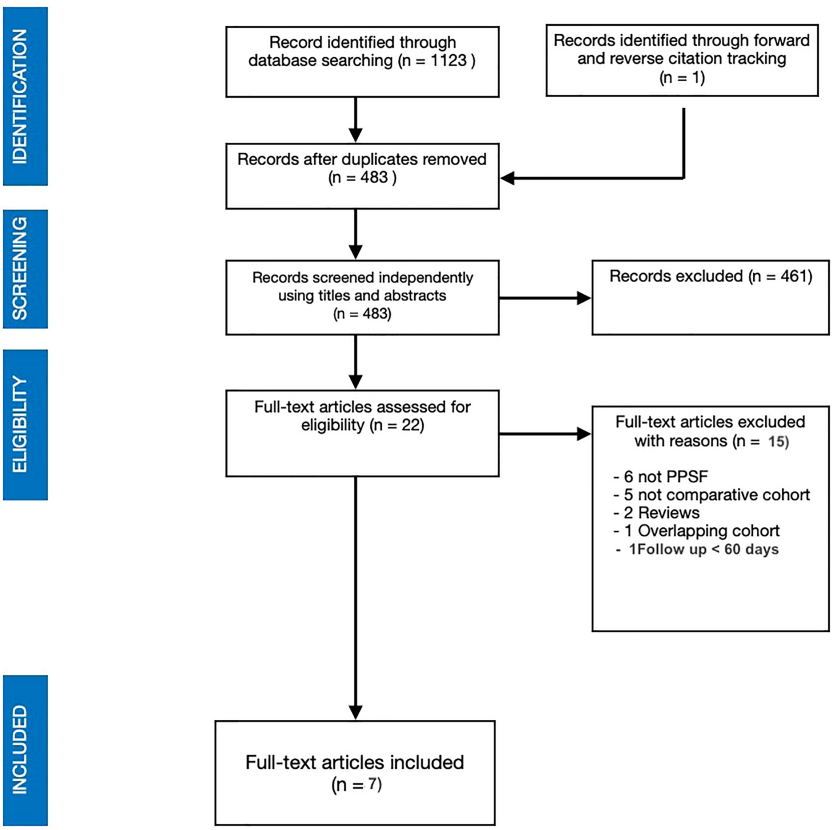

FIGURE 1 | PRISMA search strategy flow chart.

TABLE 1 | Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
English languages	Expert opinions or letters to the editor
Comparative studies between PPSF versus OPIF in patients with spinal metastasis	studies on animals or *in vitro* investigations
Full text article available	unpublished reports or abstracts from scientific meetings
	case reports, case series
	book chapter
	Follow up shorter than 60 days

PPSF, Percutaneous pedicle screw fixation; OPIF,open posterior instrumented fusion.

RESULTS

Study Selection

The electronic research of the literature consisted of 1123 studies. Duplicates and non-English articles were removed. Screening by titles and abstracts was performed with subsequent full text reading of the remaining articles. A total of 7 studies met our inclusion criteria and fulfil the purpose of the review (13–19). One of the eligible study was excluded for a short follow up (30 days) (20). The patients included in the meta-analysis were 448, 253 were in the OPIF group whereas 195 were treated with PPSF. **Table 3** summarizes the main characteristics of the included studies such as year of publication, study design and Level of Evidence (LoE), population and recorded variables, type of procedure and instrumented levels. **Table 4** reports primary lesions and the SM locations as well as some demographic data. The mean age of the included patients was 60.7 and the M/F ratio was 1.09 with no differences between the two groups. The most frequent primary lesion was breast, followed by lung and liver.

The number of instrumented levels was not always specified. In five of the included studies, patients had posterior pedicle screw instrumentation of two levels above and two levels below the metastatic lesion at least. Data about that were inhomogeneous as two articles even reported the number of instrumented levels.

TABLE 2 | Results of MOOSE assessment for quality of evidence and risk of bias assessment for the included studies Y, yes; N, no.

	Chi et al., 2021 (13)	Zhu et al., 2021 (14)	Morgen et al., 2020 (15)	Saadeh et al., 2019 (16)	Hikata et al., 2017 (17)	Hansen-Algenstaedt et al., 2017 (18)	Kumar et al., 2017 (19)
Clear definition of study population?	Y	Y	Y	Y	Y	Y	Y
Clear definition of outcomes and outcome assessment?	Y	Y	Y	Y	Y	Y	Y
Independent assessment of outcome parameters?	N	N	N	N	N	N	N
Sufficient duration of follow-up?	Y	Y	Y	Y	Y	Y	Y
No selective loss during follow-up?	Y	Y	Y	Y	Y	Y	Y
Important confounders and prognostic factors identified?	Y	N	Y	Y	Y	N	Y

TABLE 3 | Baseline characteristics of the included studies; open posterior instrumented fusion (OPIF) and percutaneous pedicle screw fixation (PPSF).

Author	Year	Study design	Level of evidence (1 – 5)	Period of study	Treatment (Open/MIS)	Number of patient	Male	Female	Age
Chi EJ (13)	2021	Retrospective choort study	3	2014-2019	OPIF	29	20	9	61.74 ± 14.72
					PPSF	21	15	6	66.94 ± 10.92
Zhu X (14)	2021	Retrospective choort study	3	2017-2019	OPIF	105	65	40	54,1 (26–75)
					PPSF	49	21	28	53.85 (12–82)
Morgen SS (15)	2020	Prospective Trial	2	2014-2017	OPIF	26	43%	57%	67.6 (range=42-88)
					PPSF	23	38%	62%	65.9 (range=49-85)
Saadeh YS (16)	2019	Retrospective choort study	3	2003-2017	OPIF	20	12	8	60.3 ± 10.9
					PPSF	20	9	11	56.4 ± 9.9
Hikata T (17)	2017	Retrospective choort study	3	2009-2015	OPIF	25	12	13	62.8 ± 13.2
					PPSF	25	15	10	63.6 ± 16.0
Hansen-Algenstaedt N (18)	2017	Prospective propensity score-matched study	2	2008-2010	OPIF	30	18	12	60.2 ± 15.1
					PPSF	30	13	17	61.8 ± 11.5
Kumar N (19)	2017	Prospective cohort study	2	2011-2015	OPIF	18	8	10	65 (49–84)
					PPSF	27	15	12	62 (50–78)

Among the included articles, the mean reported follow-up period was 16.2 months. The longest one was that by Kumar N et al. which last up to five years (19).

Complications

All the included studies reported postoperative complications, with 195 patients in the PPSF group and 249 in the OPIF group (13–19). The meta-analysis of these data showed an odds ratio of 0.48 (95% CI, 0.27 to 0.83; p= 0.009), showing a decreasing odd of complications in the PPSF group compared to OPIF (**Figure 2A**).

Blood Loss

All the included studies reported intraoperative blood loss, with 195 patients in the PPSF group and 253 in the OPIF group (13–19). The meta-analysis of the data revealed a mean difference of -585.70 (95% IC, -848.28 to -323.13; p< 0.0001), thus suggesting a decreasing odd of complications in the PPSF group compared to OPIF (**Figure 2B**). Transfusions were reported in two studies only (16, 18)

Hospitalization

The length of hospitalization was reported in 5 of the included papers, with 147 patients in the PPSF group and 202 in the OPIF group (13, 14, 16, 18, 19). The meta-analysis of the data revealed a mean difference of -3.77 (95% IC, -5.92 to -1.61; p= 0.0006), thus suggesting a decreasing mean hospital stay in the PPSF group compared to OPIF group (**Figure 2C**).

Infections

Six of the included studies reported the occurrence of postoperative infections, with 170 patients in the PPSF group and 228 in the OPIF group (13–16, 18, 19). The meta-analysis of these data showed an odds ratio of 0.31 (95% CI, 0.12 to 0.81; p= 0.02), showing a reduced infection rate in the PPSF group compared to the OPIF group (**Figure 2D**).

Reinterventions

A total of three studies described the occurrence of reinterventions, with 64 patients in the PPSF group and 75 in the OPIF group (13, 15, 16). The meta-analysis of these data

TABLE 4 | Patients features and peri-operative data (complications, surgery, blood loss).

Author	Treatment (Open/ MIS)	N° of patient	Primary lesion	Level of lesion	Operative time (min)	Blood loss (ml)	Instrumented levels	Decompression	Transfusions (n° of patients)	Length of stay (days)	Complications	Reinterventions
Chi EJ (13)	OPIF	29	Liver (6) Lung (9) Prostate (2) Thyroid (1) Kidney (1) Breast (3) Gastrintestinal (2) Others (5)	T3 (1), T4 (2), T5 (4), T6 (3), T7 (2), T8 (2), T9 (4), T10 (4), T11 (5), T12 (5), L1 (7), L2 (6), L3 (4), L4 (3), L5 (2)	181.47 ± 40.77	696.55 ± 519.43	not specified ("one or two levels")	yes	–	25.35 ± 20.65	17.2%: 4 surgical site infection 1 vertebral body oozing	5
	PPSF	21	Liver (4) Lung (7) Prostate (2) Thyroid (2) Kidney (0) Breast (0) Gastrintestinal (5) Others (1)	T3 (1), T4 (2), T5 (1), T6 (2), T7 (1), T8 (1), T9 (3), T10 (2), T11 (4), T12 (3), L1 (2), L2 (5), L3 (8), L4 (4), L5 (2)	143.56 ± 49.44	116.67 ± 109.92	not specified ("one ore two levels")	no decompression	–	11.90 ± 9.69	4%, 1 diplegia after surgery	1
Zhu X (14)	OPIF	105	Breast (18), Lung (19), Kidney (8), Liver (12), Thyroid (4), Myeloma (4), Colorectal (4), Unknown (9), Prostate (4), Nasopharynx (5), Uterus (2), Other (16)	Thoracic (82), Lumbosacral (23)	221.03	950.48	minimum two levels above and below the lesion	yes	–	9.94	10 Total, 2 Dural tears, 1 brain metastases, 0 Wound hematoma, 6 Wound infection, 1 Early death	–
	PPSF	49	Breast (12), Lung (9), Kidney (7), Liver (2), Thyroid (3), Myeloma (3), Colorectal (1), Unknown (3), Prostate (2), Nasopharynx (3), Uterus (1), Other (3)	Thoracic (36), Lumbosacral (13)	213.45	748.57	minimum two levels above and below the lesion	yes	–	7.35	3 Total, 1 Dural tears, 0 brain metastases, 1 Wound hematoma, 1 Wound infection, 0 Early death	–
Morgen SS (15)	OPIF	26	Lung (6), Breast (7), Prostate (1), Unidentified (1), Renal (3), Pancreatic (0), Melanoma (1), Thyroid (1), Lymphoma (0), Other (3)	Thoracic (20), Lumbar (6)	103	500	Two levels above and two below	yes	–	–	2	2
	PPSF	23	Lung (3), Breast (9), Prostate (4), Unidentified (4), Renal (2), Pancreatic (1), Lymphoma (3),	Thoracic (17, Lumbar (6)	142	175	Two levels above and two below	yes	–	–	2	2
Saadeh YS (16)	OPIF	20	Breast (20), Colon (10), Lung (20), Melanoma (4) Renal (10), Squamous cell (10), Other (25)	Cervicothoracic (10), Thoracic (40), Thoracolumbar (20), Lumbar (30);	266	1732 ± 359	5.7 ± 1.8	yes	50	8.3 ± 1.4	8 total (2 DVT, 1 PE, 2 Thrombocytopenia, 1 Wound complication, 1	2

(Continued)

TABLE 4 | Continued

Author	Treatment (Open/ MIS)	N° of patient	Primary lesion	Level of lesion	Operative time (min)	Blood loss (ml)	Instrumented levels	Decompression	Transfusions (n° of patients)	Length of stay (days)	Complications	Reinterventions
											Durotomy, 1 Mortality (30 day))	
	PPSF	20	Breast (20), Colon (10), Lung (20), Melanoma (5), Renal (10), Squamous cell (10), Other (25)	Thoracic (40), Thoracolumbar (55), Lumbar (5)	296	805 ± 138	6.2 ± 2.2	yes	30	8.3 ± 1.7	8 total (1 DVT, 0 PE, 2 Respiratory complication, 1 Wound complication, 1 Heart failure, 1 Acute kidney injury, 1 Durotomy,	3
Hikata T (17)	OPIF	25	Lung (2), Thyroid (6), Breast (4), Kidney (3), Liver (3), Lymphoma (1), Rectus (1), Uterus (1), Larynx (1), Myeloma (1), Unknown (2)	Thoracic (18), Lumbosacral (7)	188.9 ± 43.6	714.3 ± 545.9	8.1 +- 2.9	yes	–	–	7 Massive bleeding (>1000 mL), 2 Wound hematoma, 2 Neurological deficit	–
	PPSF	25	Lung (7), Thyroid (2), Breast (3), Kidney (2), Liver (1), Prostate (4), Lymphoma (2), Rectus (1), Gastric (1), Rhabdomyosarcoma (1), Melanoma (1)	Thoracic (17), Lumbosacral (8)	204.6 ± 55.4	340.1 ± 302.5	8.3 ± 2.4	yes	–	–	1 Massive bleeding (>1000 mL), 1 Wound hematoma, 1 Neurological deficit,	–
Hansen-Algenstaedt N (18)	OPIF	30	Breast (4), Prostate (8), Lung (3), Thyroid (4), Renal (1), Gastrointestinal (1), Others (5)	–	220.4 ± 57.9	2062.1 ± 1148.0	3.8 ± 1.7	yes	23	21.1 ± 10.8	3 Wound infection, 2 Dural tear, 3 Neurological, 2 Lung infection, 2 Urinary tract infection	–
	PPSF	30	Breast (14), Prostate (3), Lung (5), Thyroid (1), Gastrointestinal (4), Others (3)	–	190.9 ± 78.4	1156 ± 572.3	5.5 ± 3.1	yes	12	11.0 ± 5.0	2 Dural tear, 2 Neurological, 1 Lung infection, 2 Urinary tract infection	–
Kumar N (19)	OPIF	18	Lung (5), Breast (5), Gastrointestinal (1), Prostate (5), HCC (1), Other (1)	–	269	961	–	yes	–	13	16%	–
	PPSF	27	Lung (7), Breast (3), Gastrointestinal (2), Renal (2), Prostate (1), Lymphoma (3), HCC (2), Others (3)	–	253	184	–	yes	–	9	3%	–

Open posterior instrumented fusion (OPIF) and Percutaneous pedicle screw fixation (PPSF), Deep Vein Thrombosis (DVT), Pulmonary Embolism (PE).

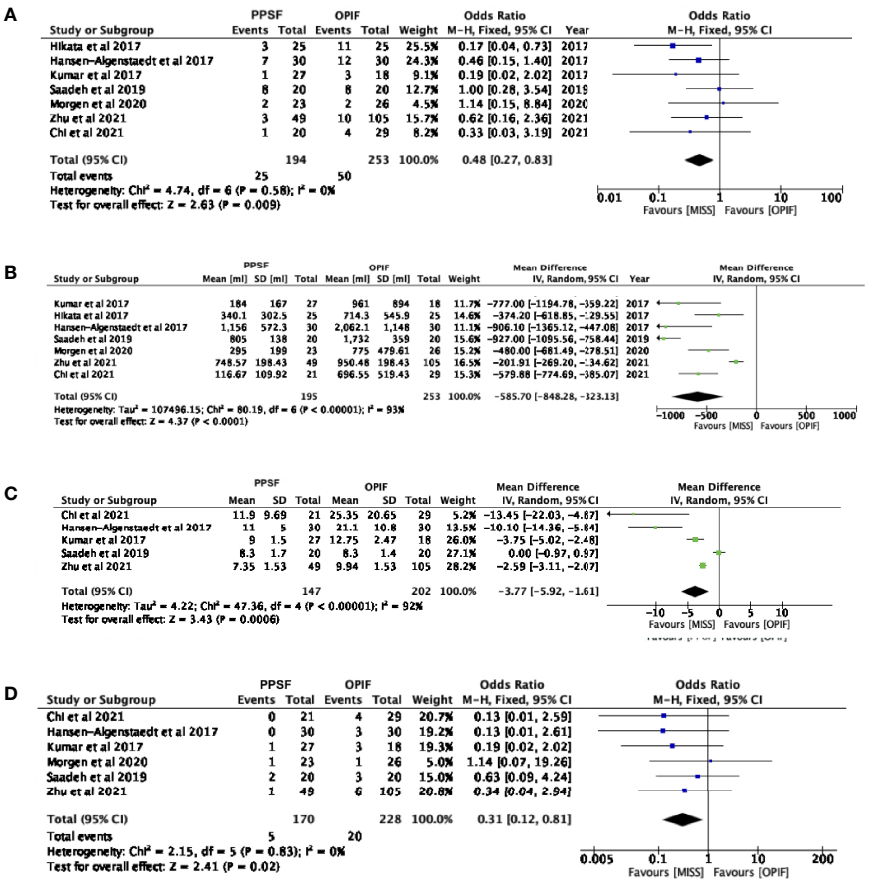

FIGURE 2 | Forest plots comparing surgical outcomes between Open posterior instrumented fusion (OPIF) and Percutaneous pedicle screw fixation (PPSF). **(A)** Complications, **(B)** blood loss **(C)** hospital stay, **(D)** infection rate. SD, standard deviation; IV, inverse variance; CI, confidence interval.

showed an odds ratio of 0.76 (95% CI, 0.25 to 2.27; p= 0.62), suggesting that both techniques demand a similar reintervention rate (**Figure 3A**).

Mortality

A total of six studies described mortality, with 142 patients in the PPSF group and 197 in the OPIF group (13, 14, 16, 17, 19). The meta-analysis of these data showed an odds ratio of 0.79 (95% CI, 0.40 to 1.58; p= 0.51), demonstrating that both techniques have a similar mortality rate (**Figure 3B**).

Pain

Among the included studies, four articles described pre and post-operative VAS, with 103 patients in the PPSF group and 102 in the OPIF group (13, 17–19). The meta-analysis of the preoperative VAS data revealed a mean difference of -0.03 (95% CI, -0.30 to 0.25; p= 0.84), whereas the mean postoperative VAS difference was -0.55 (95% CI, -1.41 to 0.32; p= 0.22). The meta-analysis suggested that both techniques have a similar postoperative VAS (**Figure 3C**).

Clinical Outcomes and Survival

An heterogeneous set of scores was applied to assess preoperative health status and clinical outcomes but none of them was used in each of the included studies. Therefore, a statistical analysis was not possible. Preoperative evaluation of metastatic spine tumor prognosis was measured by using the Tokuhashi scoring system in half of the selected papers (15, 17–19). The Frankel Scale for spinal cord injuries was employed in four of the included studies to classify the pre- and postoperative extent of the neurological and functional deficit (14, 17–19). Many other scores were employed in search strategies, such as Oswestry Disability Index (ODI), American Spinal Injury Association (ASIA) Impairment Scale and Spinal instability neoplastic score (SINS), Tomita score, the Karnofsky performance scale index, etc. Also survival was not always specified. In fact, a total of four studies described the mean survival time but as data were presented in heterogeneous forms, it was not possible to perform a statistical analysis.

Surgical Decompression

Both techniques, PPSF and OPIF, allow for a decompression of neurological structures. In fact conventional open or mini-open

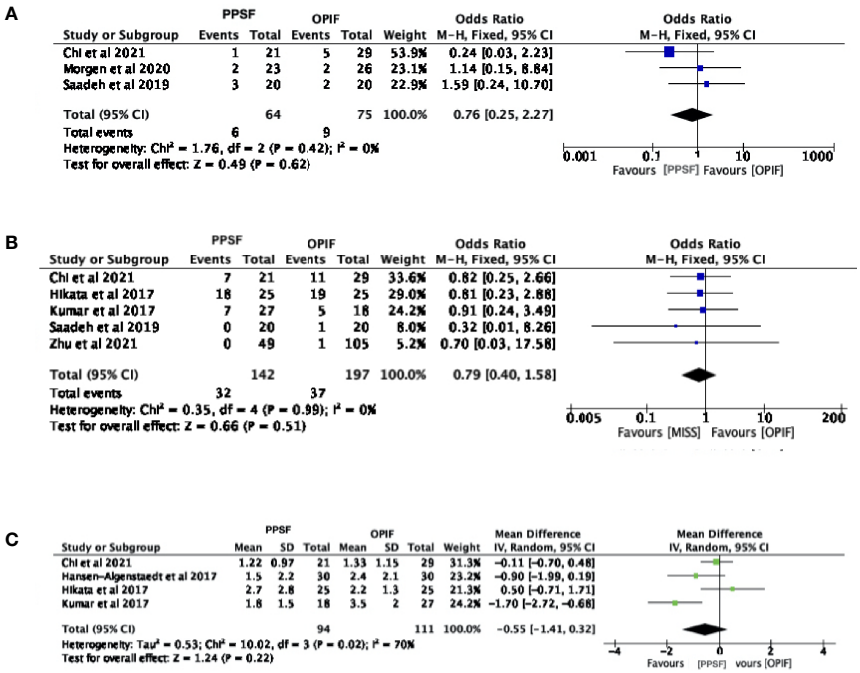

FIGURE 3 | Forest plots comparing clinical outcomes between Open posterior instrumented fusion (OPIF) and Percutaneous pedicle screw fixation (PPSF). **(A)** Reintervention, **(B)** mortality, **(C)** postoperative pain. VAS, Visual Analogue Scale; SD, standard deviation; IV, inverse variance; CI, confidence interval.

decompression was performed in all the included cases except for the PPSF group by Chi E J et al. (13). The OPIF procedure, with a midline incision and a large dissection of paraspinal muscle, allows wider neurological decompression, and major possibility of tumour lesion debulking (14, 15). On the other hand to obtain a satisfying decompression with PPSF approach, various techniques were described. In the case of a unilateral tumour spinal cord compression, the same paramedian access for screw placement could be used, through the use of dedicated retractors, for decompressive manoeuvres (18).

While in case of a 180 degree compression a midline mini-open could be performed with the possibility to obtain a sufficient posterior decompression (14–18). An hybrid approach could be the choice in cases that requires long fixation and wide neurological decompression (9).

Response to Review Question

SM patients treated with PPSF compared to those treated with OPIF have a lower rate of complications and infections, less intraoperative blood loss and a shorter hospital stay. A doubt still remains about mechanical complications, short and medium-term survival and post-operative pain.

Bias Assessment

A risk of bias assessment was performed by the MOOSE criteria of included study as reported in **Table 2**. No obvious bias risk was found for the included study. A funnel plot for all analyzed outcomes was obtained. Nevertheless, no significant asymmetry was found.

DISCUSSION

There is a growing interest in managing SMs because of their crucial clinical implications in oncological patients and their consequent increasing social and economic burden (21). The spine represent the most common localization of bone metastasis, accounting for about 50% of all the secondary malignant growths (22, 23). Moreover, up to 20% of these patients will experience metastatic spinal cord compression (MSCC). This is an oncological emergency characterized by severe spinal pain increased by load and impaired neurological function (limb weakness, difficulty walking, sensory loss, bladder or bowel dysfunctions) (24).

In recent years, cancer survival improved for all of the most common malignant tumours just as the mortality rate has decreased, indicating a progression in fight against cancer due to prevention, early detection and new treatment innovations (25).

The prognosis and the mean survival in SMs patients essentially depends on the primary tumour biology. A longest survival was reported in patients with haematological malignancies and prostate cancer compared to those with lung cancer (26, 27). Notwithstanding only 10% to 20% of patients with SMs are still alive two years after the diagnosis of metastatic disease (5).

Besides, the QoL of these patients is often not impaired by cancer. Hence, when a surgical treatment is indicated, an interdisciplinary evaluation of the patient's overall disease situation should be performed and the target of the treatment

planning should be the preservation of the QoL, shifting the treatment goals from cure to palliation (28). The aim of surgery is: (I) neurological impairment prevention by posterior or anterior decompression (laminectomy and hemi-facetectomy), (II) reduction of tumour volume or tumour debulking and (III) stabilize the affected spinal segment to allow the patient mobilization safely without bracing (5).

Up to 25% of patients who undergo conventional open surgery for SMs present perioperative complications (29, 30). During the last decade, PPSF appeared to be an appealing alternative for the management of spinal fractures (31–33) and its advantages became early attractive for the stabilization in spinal metastatic disease (9). Minimally invasive approaches for posterior spinal fixation allows minor intraoperative blood loss, an earlier adjuvant therapy, and a shorter overall hospital stay (32). On the other hand, by using OPIF techniques, posterior elements from the vertebra above to the vertebra below the involved segments are exposed, resulting in extensive damage to back muscles and soft tissues with delay of mobilization and prolonged hospital stay (32)

An earlier mobilization avoids the complications linked to bed rest such as muscular mass loss and sarcopenia, constipation, altered ventilation/perfusion, deep vein thrombosis and pulmonary embolism (32). Furthermore, a shorter hospitalization reduces the exposure of the patients to infectious disease, especially during the present SARS-cov2 pandemic (34). A faster postoperative recovery and a poor need for care reduces economic burden and present and a significant psychological and social impact.

Moreover, PPSF permit to avoid the back muscle detachment and retraction, which causes postoperative pain and profuse bleeding, thus reducing intraoperative blood loss and consequent demand for transfusions (28). Furthermore, smaller incisions reduce the wound complications and offer a better aesthetic outcomes (35).

The abovementioned advantages are crucial in preserving and improving the QoL of oncological patients with poor midterm life expectancy.

In patients with metastatic spinal disease, meta-analysis of the available data revealed that PPSF is associated with a statistically significant reduction of blood loss, postoperative complications, infection, and hospitalization when compared with OPIF. Above all, the reduction of infections plays an important role in the management of these patients who present themselves at an increased risk of infection due to tumour-induced immune suppression and radio-chemotherapy which could reduce the wound healing ability.

Furthermore, even if it was not statistically significant, PPSF revealed lower post-op VAS rates compared to OPIF group, suggesting that percutaneous procedures may have better results in terms of pain. Moreover, PPSF was not inferior to OPIF with respect to mortality and reintervention.

Our results suggest comparable rates of perioperative surgery-related complications between the study groups, confirming the safety of the PPSF technique.

No implant failures or other mechanical complications such as septic or aseptic loosening were reported in both study groups. However, the mean follow-up of the included studies was short, which does not permit further consideration on implant loosening.

Few studies considered the QoL of surgically treated oncological patients with SMs. Therefore, we believe that clinical outcomes measurement will be a major topic of interest for future studies in order to determine which of the above-mentioned surgical treatments achieve the best QoL preservation and improvement with the lowest number of complications.

Clinical Implication

Patients treated with PPSF, due to fast clinical recovery and surgical wound healing, could resume or start faster chemo- and radiotherapy than those treated with OPIF. This could play a crucial role in determining patient survival and local disease control (17).

The results of this meta-analysis suggest a minimal superiority of the PPSF treatment compared to OPIF in SMs patients who require spinal stabilization with or without neurological decompression. Therefore, PPSF should be considered the first-line choice in these patients if there are no contraindications.

Relative contraindications could be: (I) more than 6 levels of spinal fusion, (II) need for extensive neurological decompression, (III) correction of important post traumatic deformities.

Limitation

This meta-analysis is not without limitations. First of all, all included studies are observational studies except one which is a randomized clinical trial. Secondly, the number of included studies is not large enough to perform a meta-regression analysis. Finally, the data of some studies on certain outcomes are too inhomogeneous to be able to perform an accurate analysis of the data.

CONCLUSION

The PPSF treatment is associated with fewer intra and peri-operative complications, a lower rate of infections, a reduction in intraoperative blood loss and a shorter hospital stay compared to the OPIF treatment. PPSF treatment should be used whenever possible for palliative surgery in SM patients. Studies focused on the patient's quality of life and randomized clinical trials are however necessary to provide superior quality scientific evidence.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

AUTHOR CONTRIBUTIONS

AP, AS, FT and GM contributed to conception and design of the study. AS and CV organized the database. performed the

statistical analysis. AP, AS, RV wrote the first draft of the manuscript. CV, LP and FT wrote sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

FUNDING

Publication costs are founded by the Catholic University of Sacred Heart, department of Orthopedics and Traumatology.

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SYSTEMATIC REVIEW
published: 05 April 2022
doi: 10.3389/fonc.2022.864501

Sarcopenia in Patients With Spinal Metastasis: A Systematic Review and Meta-Analysis of Retrospective Cohort Studies

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OPEN ACCESS

Edited by:
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Specialty section:
This article was submitted to Neuro-Oncology and Neurosurgical Oncology, a section of the journal Frontiers in Oncology

Received: *28 January 2022*
Accepted: *28 February 2022*
Published: *05 April 2022*

Citation:
Tan H, Gao X, Li X, Huang Y, Cao Q and Wan T (2022) Sarcopenia in Patients With Spinal Metastasis: A Systematic Review and Meta-Analysis of Retrospective Cohort Studies. Front. Oncol. 12:864501. doi: 10.3389/fonc.2022.864501

Background: As a metastasis cancer that happens up to 70% of the cancer patients, spinal metastasis is drawing attention for its significant impairment to health. There exist several predictive models designed to estimate mortality in spinal metastasis patients but they are reported with limited accuracy. In recent years, some retrospective cohort studies have been carried out to associate sarcopenia with mortality in spinal metastasis.

Introduction: As a risk factor leading to adverse events in many diseases, sarcopenia was considered to significantly impact on patients with spinal metastasis in mortality by some scientists. We aimed to look through the current evidence and use statistic measures to value the role of sarcopenia in spinal metastasis. In this study, we are going to perform a systematic review and meta-analysis of available retrospective cohort studies where sarcopenia is assessed for outcomes in spinal metastasis patients.

Methods: On October 7, 2021, we performed a search in PubMed, Embase, and the Cochrane Library. We set no restrictions on language, date or areas. Results were expressed as hazard ratio (HR) or odds ratio (OR) with 95% CI by random effects model. Sensitivity analyses were performed to explore sources of heterogeneity and stability of results.

Results: Of the 4,196 papers screened, 10 retrospective cohort studies were included, with a total of 1,674 patients. Results showed that sarcopenia was associated with higher overall mortality (OR, 1.60; 95% CI 1.35–1.90) and lower overall survival (HR, 2.08; 95% CI 1.55–2.80). The sensitivity analysis proved the stability of results in terms of publication years, region, time of diagnosis, sample size, female rate, measurement and follow up period.

Conclusions: Sarcopenia is a robust indicator of mortality in spinal metastasis patients and it might be applied to decision-making tools to assess survival probability and adjust the extent of treatment, while a lack of higher level of evidence is existing.

Systematic Review Registration: PROSPERO CRD42021283348.

Keywords: sarcopenia, spine, metastasis, meta, retrospective study

INTRODUCTION

Up to 70% of cancer patients develop secondary spinal metastasis, suffering from structural changes of the bone. With a progress in original cancer treatment, the metastasis is becoming more relevant (1). The surgery or immunotherapy effects of spinal metastasis are uncertain and patients may be selected for treatment without clear estimate of possible outcomes, such as survival rate and therapeutic options. Current predictive models designed to estimate mortality in patients with spinal metastasis are described with limited accuracy, though an improvement has been made in patients due to advances in multimodal therapy (2–5). Surgical decision-making tools like Tomita, Tokuhashi, Bauer, Van der Linden, Bollen, and Rades help doctors assess survival probability and adjust the extent of treatment, but ignore the significance of variables such as sarcopenia (2, 6).

As a skeletal muscle disorder affects muscle mass and function, sarcopenia is regarded as a risk factor that leads to adverse events in diseases (7–10). Sarcopenia has been shown by systematic reviews to negatively influence outcomes in digestive, cardiovascular, orthopedic diseases and tumor treatment in terms of survival rates, physical activity, length of hospital stay and other complications (11–17). Shachar et al. performed a meta-analysis confirming sarcopenia was risky on overall survival in patients with solid tumors (18). In recent years, many studies have been conducted to evaluate the prediction ability of sarcopenia on spinal metastasis, especially focused on mortality or survival (19).

The common measurement of sarcopenia is by computed tomography (CT) scans, but the selection of muscle varies in different studies. Psoas muscle size has been shown to predict perioperative outcomes and mortality after abdominal surgery (20). Total psoas muscle surface area (TPA) divided by vertebral body area (VBA) has been depicted to predict the likelihood of survival in metastatic spinal cord compression patients (21). We cannot find a clear definition of measurement for sarcopenia.

To clarify whether sarcopenia is predictive of survival in patients with spinal metastasis, we performed a systematic review of studies focusing on relationships between sarcopenia and outcomes in patients with cancer metastasis to the spine.

METHODS

The results were reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) for systematic reviews and meta-analyses (22) and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) recommendations (23).

Data Sources and Searches

We searched the PubMed, Embase, and the Cochrane Library using the terms Sarcopenia/Muscle Strength/Physical Fitness/Geriatric Assessment, Neoplasm Metastasis up to October 7, 2021. In addition, articles listed in the reference lists and related reviews were carefully selected identified. Only literature published in English were included (**Supplementary Material 1**).

Study Selection

Two authors independently reviewed the title and abstract of each identified article and selected articles that might meet the criteria, and then read the full text of each selected literature to finish selection. Inclusion criteria were established *a priori*.

Population: Patients with spinal metastasis.

Comparator: sarcopenia patients versus non-sarcopenia patients

Outcome: mortality and survival

Study design: retrospective cohort study

Only original studies and conference abstract with available data were included.

Data Extraction and Quality Assessment

Two authors independently extracted participant characteristics, namely, study design, region, diagnosed period, sample size, female%, original cancer type, measurements of sarcopenia, sarcopenia definition, outcomes, and follow-up period. Disagreement was resolved by discussion and consulting with the senior author (In some articles, there was no definition of sarcopenia but a divide of muscle mass into 3 tertile. Finally, we defined the 1st tertile as sarcopenia.) The quality score was derived by the Cochrane Collaboration's tool and the Newcastle Ottawa Scale (24) (**Supplementary Material 2**), where selected items regarding the representativeness of the patients, ascertainment of exposure and outcomes, and adequacy of follow-up (25). We scored the quality ranging from 0 to 9 points for each study and defined a score of 8 or 9 as high-quality.

Statistical Analysis

The primary outcomes analyzed were overall survival and overall mortality. Overall survival, defined as the time from surgery to death or the last follow-up, was calculated by HR. Pielkenrood's study depicted 365-day mortality as HR, we took its reciprocal and defined it as overall survival. Overall mortality is defined as the time from surgery to death or the last follow-up or 1-year mortality.

We used Stata software (version 12.0) for data analysis. To meta-analyze the effect estimates (HRs) of overall survival, we applied random-effects models (the DerSimonianeLaird method), accounting for heterogeneity among studies (26). The risk estimates (HRs) were transformed into log HRs, along with their corresponding 95% CIs (27). To meta-analyze the effect estimates (ORs) of overall mortality, we converted reported ORs to log ORs and used a generalized inverse variance method with a random effects model combining data. Results are reported with both effect estimates and 95% confidence intervals (CIs). We used the I^2 statistic to assess heterogeneity between studies, with I^2 values >50% indicating significant heterogeneity (28). Begg's funnel plot was used to detect publication bias in studies reporting overall survival, with a P-value <0.1 indicating a significant difference (29).

RESULTS

Search Results

We identified a total of 4,196 documents from the systematic literature search, of which 8 were evaluated for eligibility. In addition, a scan in the reference lists and related reviews was conducted to obtain 2 eligible studies. Finally, 10 eligible studies containing 1,674 patients were included. We excluded 2 comments, meta or review-type articles and 1 duplicate cohort study and 6 studies for which no relevant data were available. These studies were conducted in 3 countries on 3 continents: the USA, Netherlands, and Japan. The search and screening process is detailed in the PRISMA flowchart (**Figure 1**). Details of the included studies are shown in **Tables 1**, **2**.

Study Characteristics

Design of included studies: Retrospective cohort studies.

Original cancer type: Lung, prostate, kidney, breast, hematopoietic, gastrointestinal, nasopharynx, thyroid, liver, skin, myeloma, lymphoma.

Measurements of sarcopenia: One study used L3 skeletal muscle index (L3-SMI), two studies used psoas size (PS), four studies used average psoas/vertebral body area (VBA), one study used total muscle area, one study used paravertebral muscles, and one study used TPA/VBA. L3-SMI meant measuring the cross-section area of skeletal muscles (cm^2) at L3 disc space divided by the square of the height of the patient (m^2). The muscles included psoas, erector spinae, quadratus lumborum, transversus abdominis, external and internal oblique, and rectus abdominis muscles; PS meant measuring the size of psoas muscle at the L3/4-disc space or the L4 pedicle; Average psoas/VBA meant average psoas muscle size at the L4 vertebral level divided by the size of L4 vertebral body; Total muscle area meant total muscle size at L3 vertebral level which was the same to L3-SMI; Paravertebral muscles were measured by aggregating the cross-sectional area (mm^2) at the L3 level; TPA/VBA meant total psoas muscle size at the L4 vertebral level divided by the size of L4 vertebral body.

Sarcopenia definition: For study used L3-SMI, sarcopenia was defined as L3-SMI <41 cm^2/m^2 in women, <43 cm^2/m^2 in men with BMI <25 kg/m^2, and <53 cm^2/m^2 in men with BMI >25 kg/m^2.Studies used PS defined sarcopenia as Men: <10.5 cm^2, Women: <7.2 cm^2 or 1st tertile. For the study that used paravertebral muscles sarcopenia was defined as the size less than median. Studies that used TPA/VBA defined sarcopenia as the lowest quartile. Other studies defined sarcopenia as the 1st tertile.

Analysis of Outcome Measures

Overall Survival

Eight studies reported overall survival (6, 30–36). Seven of these showed a significantly increased overall mortality related to sarcopenia. The random-effects meta-analysis showed that sarcopenia was associated with overall survival (HR = 1.60; 95% CI = 1.35–1.90; P-value <0.001) (**Figure 2** and **Table 3**).

Overall Mortality

Three studies reported overall mortality (21, 31, 37). The random-effects meta-analysis showed that sarcopenia was associated with overall mortality (OR = 2.08; 95% CI = 1.55–2.80; P–value <0.001) (**Figure 2** and **Table 3**).

Risk of Bias and Quality Assessment

Both visual inspection funnel plots and Begg's test suggested that no publication bias was found for overall survival, and Begg's test was significant (Pr >|z| = 0.108) (**Figure 3**) (38). To assess the stability of the results, we performed sensitivity analyses. Criteria included: (1) publication in recent five years; (2) region in occident; (3) studies include diagnosis before 2010; (4) studies include diagnosis after 2015; (5) sample size >100; (6) female <50%; (7) exclude PS and L3-SMI; and (8) follow up longer than 2 years (**Supplementary Material 2**).

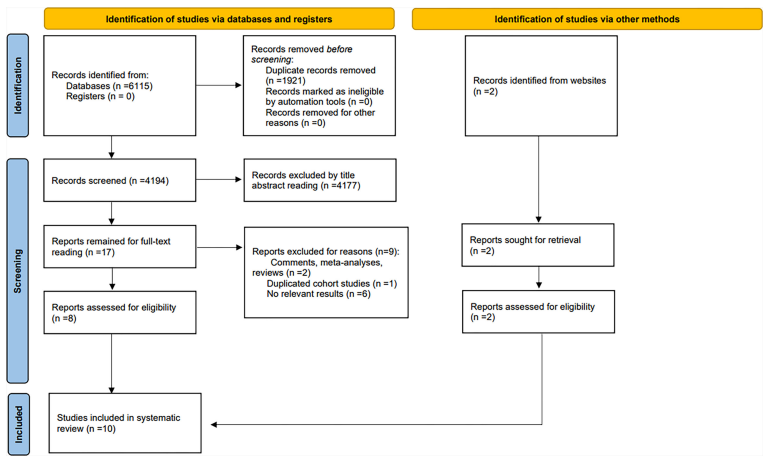

FIGURE 1 | Flow diagram for the selection of studies.

TABLE 1 | Characteristics of studies included in meta-analysis of sarcopenia for spinal metastasis.

First author	Year	Study design	Region	Diagnosedperiod	Sample size	Female %	Median age	Original cancer type
Massaad	2021	Retrospective cohort study	USA	2010 to 2019	88	26.1	62	Renal cell carcinoma
Zakaria1	2020	Retrospective cohort study	USA	1999 to 2017	271	42.1	57.4–61.3	Lung, prostate, kidney, liver, breast, hematopoietic, nasopharynx, skin, thyroid gastrointestinal
Zakaria2	2020	Retrospective cohort study	USA	2002 to 2012	417	51	65.3	Lung, breast, prostate, myeloma
Pielkenrood	2020	Retrospective cohort study	Netherlands	2013 to 2016	310	37	67	Lung, prostate, breast and other
Dohzono	2019	Retrospective cohort study	Japan	2009 to 2016	78	44	68.3	Gastrointestinal cancer
Zakaria3	2018	Retrospective cohort study	USA	2002 to 2012	92	NR	72.8	Prostate cancer
Zakaria4	2018	Retrospective cohort study	USA	2002 to 2012	118	100	63.8	Breast cancer
Zakaria5	2018	Retrospective cohort study	USA	2002 to 2012	46	43.7	63.2	Multiple myeloma
Zakaria6	2016	Retrospective cohort study	USA	2002 to 2012	168	46	64	Lung cancer
Gakhar	2015	Retrospective cohort study	USA	2009 to 2013	86	48.9	62–68	Breast, lymphoma, gastrointestinal, prostate, renal, lung and other

All results remained stable in the sensitivity analysis (**Supplementary Material 3**).

DISCUSSION

In this systematic review and meta-analysis, the results suggest that sarcopenia is likely to have an increased risk of mortality in patients with spinal metastasis. Our findings show that the pooled HR for survival among spinal metastasis patients with sarcopenia was 1.6 times higher than non-sarcopenia spinal metastasis patients. The ability to predict mortality was independent of publication years, region, diagnosed years, sample size, female rate, measurements, and follow up period. Since surgery for spinal metastasis may lead to higher mortality, neurological outcome, and pain, we came to a conclusion that sarcopenia may help in guiding treatment decision-making (39, 40).

In oncology surgery, sarcopenia has been applied to evaluate the risk of postoperative morbidity and survival of the patients. In the study by Sheetz, overall survival after esophagectomy for cancer was associated with core muscle size (P = 0.017) adjusted for age, gender, and stage (41). In hepatocellular carcinoma sarcopenia patients had lower survival (P = 0.012) and higher risk of low visceral fat area (p <0.001) (42). Otherwise, the similar association was proved in colorectal cancer and endometrial cancer (43, 44).

Sarcopenia and malnutrition often occur in the context of cancer and are also usually predictive of a poor prognosis (45). Therefore, detailed evaluation and regular monitoring of sarcopenia in the context of cancer is necessary. Nutritional care of cancer patients requires caution when treating sarcopenia, and the limited effectiveness of drugs and pharmacologic nutrients makes it necessary for cancer survivors to also exercise regularly to reduce the occurrence of sarcopenia (46). When sarcopenia occurs

TABLE 2 | Characteristics of studies included in meta-analysis of sarcopenia for spinal metastasis.

First author	Year	Measurements of sarcopenia	Sarcopenia definition	Treatment	Outcomes	Follow-up period
Massaad	2021	L3-SMI	Males: <43 cm^2/m^2 with BMI <25, <53 cm^2/m^2 with BMI >25 Females: <41 cm^2/m^2	Surgery	Overall mortality	1 to 104 months
Zakaria1	2020	PS	Male: <10.5 cm^2 Female: <7.2 cm^2	Surgery	Overall survival	NR
Zakaria2	2020	Average psoas/VBA	1st tertile	Radiation therapy, or with surgery	Overall survival	NR
Pielkenrood	2020	TPA/height^2	Male:<52.4 cm^2/m^2 Female:<38.5 cm^2/m^2	Radiation therapy	Overall survival Overall mortality	2 to 5 years
Dohzono	2019	Paravertebral muscles	Less than median	Chemotherapy or surgery	Overall survival	1 to 8 years
Zakaria3	2018	Average psoas/VBA	1st tertile	Radiation therapy	Overall survival	NR
Zakaria4	2018	PS	1st tertile	Radiation therapy	Overall survival	600 days
Zakaria5	2018	Average psoas/VBA	1st tertile	Radiation therapy	Overall survival	5 years
Zakaria6	2016	Average psoas/VBA	1st tertile	Radiation therapy	Overall survival	5 years
Gakhar	2015	TPA/VBA	Lowest quartile	Surgery	Overall mortality	1 year

L3-SMI, L3 skeletal muscle index; PS, Psoas size; TPA, total psoas area; VBA, vertebral body area. BMI, body mass index; NR; not reported.

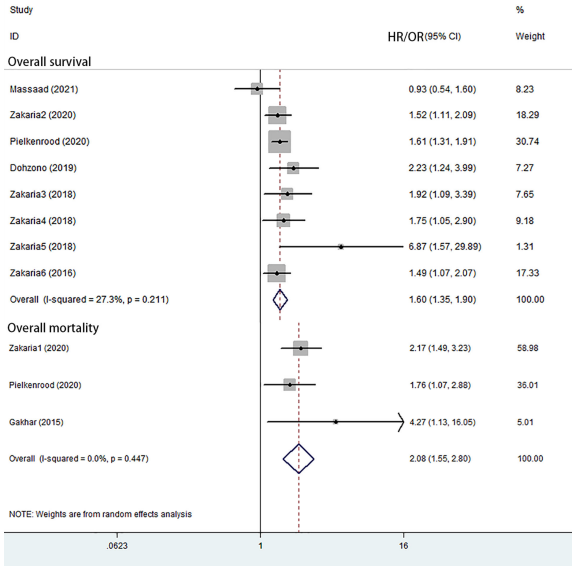

FIGURE 2 | Forest plot of overall survival and overall mortality.

in the heart, heart failure and sarcopenia may reinforce each other. Heart failure may trigger sarcopenia due to hormonal changes, malnutrition and lack of physical activity, while sarcopenia may also promote the development of heart failure through pathological ergoreflex (47). Sarcopenia in heart failure is very common and is also associated with a poor prognosis, for which both nutritional and exercise therapies are important. Exercise, in particular, is the only treatment option for which there is sufficient clinical evidence (48). In addition, the use of drugs, ACE inhibitors and ARBs are both considered to have some muscoprotective effect, but the current clinical meta-analysis and basic studies on the role of this drug are still contradictory and further laboratory designs are needed to prove their effect (49). Sarcopenia occurs in the kidney when a negative nitrogen balance usually develops as chronic kidney disease progresses to its end stage (50). Therefore, sarcopenia due to uremia has more severe protein degradation on top of the primary sarcopenia and must restore appropriate exercise activity and adequate quality of life (51). Dietary interventions are considered to be a better way to ensure protein and energy intake in uremia to improve muscle mass reserve. However, it is important to note that according to epidemiological data, most of the good outcomes of reduced mortality associated with an oral nutritional high protein diet occur in individuals over 66 years of age (52). Current nutritional modalities for uremic sarcopenia generally include oral nutritional supplements, amino acids supplementation, intra-dialytic parenteral nutrition and enteral and total supplementation. Various nutritional modalities can help combat uremic rhabdomyosarcoma (53).

Due to the lack of an appropriate method and the limitation of content of included articles, we cannot carry on sensitivity analysis in terms of age, eventual hospitalization and oncological treatments. But we would like to discuss their impact on possible bias. The age of patients may correlate to mortality as sarcopenia happens more likely to old people and old patients are in commonly worse health condition (54). All the 10 articles are reported with a mean age over 60-y, and did not discuss young patients separately, so we have to be prudent when further studying this subject. All the 4,196 patients were in hospital, treated for spinal metastasis. We could not define who were considered as eventual hospitalization cases. The treatments for spinal metastasis in the 10 articles include surgery, radiotherapy and chemotherapy, which may differ from original cancer or life expectancy. When life expectancy is less than 3 months, a patient is not considered for surgery, as surgery takes time to recovery and is hard for him to justify (31). Sarcopenia seems to be predictive of mortality in 9 articles no matter which treatment is taken and the association between muscle mass and overall survival had been revealed independent of surgical procedure (30). Original cancer type, which was evaluated for sensitivity and proved the results stable, should be regarded attention to. The studies reported different original cancer types and some mixed several together. To clarify whether all original cancer types are sensitive to sarcopenia requires more specific studies.

Among the 10 included studies, only 1 study concluded that sarcopenia was not a risk factor to spinal metastasis which might be the result of strict inclusion criteria (6).This indicates that a unified criteria for selecting patients and operating method may reduce study bias (55, 56).

Though sarcopenia is widely studied by scientists, there is still a lack of consensus criteria and methods to investigate sarcopenia (57). The European Working Group on Sarcopenia in Older People advocates that the psoas is to be representative of sarcopenia (10). While other studies indicated that skeletal muscle in the level of L3 is associated well with whole body tissue mass in non-malignant populations (58, 59). In addition to muscle size, muscle strength and function might be factors to measure sarcopenia. These studies suggest that the use of different measurements for sarcopenia has a substantial conclusion on its effect.

Given the retrospective nature of these studies, we were unable to account for unintended bias and the heterogeneity of complications. The region was a limitation of our studies as most of the studies were carried in occident, a more convincing conclusion could be reached with more statistic from Asia, Africa, Latin America, and Oceania.

Given its consequences, sarcopenia might be applied to decision-making tools to assess survival probability and adjust

TABLE 3 | Meta analysis of outcomes.

Variables	HR/OR	95% CI	p-Value for Association	I^2 Value, %	p-Value for heterogeneity	Studies, n
Overall survival	1.60	1.35–1.90	<0.001	27.3	0.211	8
Overall mortality	2.08	1.55–2.80	<0.001	0	0.447	3

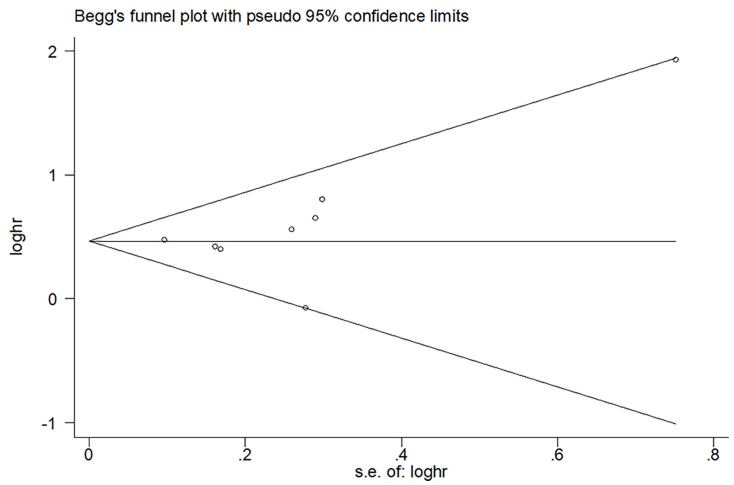

FIGURE 3 | Publication bias of overall survival.

extent of treatment, but there is not enough evidence to deem it as an independent predictor. Thus, sarcopenia should be considered in a multidisciplinary way and evaluated in complexity. Additionally, sarcopenia can be regarded as a vital health problem, and an effort to prevent and treat sarcopenia is requisite.

CONCLUSIONS

In this article, we performed a systematic evaluation and meta-analysis of sarcopenia in spinal metastasis patients. The results suggest that sarcopenia might be an indicator of mortality in spinal metastasis patients. Sensitivity analysis on some baseline factors suggests that this relation is stable. However, there is still a need to conduct larger prospective cohort studies to confirm the conclusion.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**. Further inquiries can be directed to the corresponding authors.

AUTHOR CONTRIBUTIONS

HT and TW conceived and designed the experiments. HT and TW performed the experiments. HT and TW contributed material/analysis tools. HT, XG, and XL wrote the manuscript. TW, and YH performed reference collection and data management. HT performed statistical analyses. QC and TW critically revised and edited successive drafts of the manuscript. All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

ACKNOWLEDGMENTS

We would like to thank Weiming Guo and Gang Fan for their advice on some issues in the designing and writing process of this article.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2022.864501/full#supplementary-material

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MINI REVIEW
published: 20 April 2022
doi: 10.3389/fonc.2022.884724

An Update on Neurosurgical Management of Primary CNS Lymphoma in Immunocompetent Patients

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Primary central nervous system lymphomas (PCNSL) are rare CNS tumors that harbor a conspicuously longer diagnostic delay compared to other malignant brain tumors. The gold standard for diagnosis is stereotactic biopsy to acquire tissue for histopathological analysis and therefore neurosurgery plays a central role when reducing the diagnostic period is mandated. However, histopathological diagnosis could be complicated if the patient was preoperatively exposed to corticosteroids. Besides the histopathological result, diagnosis of a PCNSL also requires full diagnostic workup to exclude cerebral metastatic disease of a systemic lymphoma. Most reviews of PCNSL discuss recent advancements in systemic treatment options from an (neuro-)oncologic viewpoint, whereas our intention was to discuss the optimization of the diagnostic period and therefore describe current standards of imaging, summarizing the diagnostic workup, discussing the surgical workup and future diagnostic prospects as well as the influence of preoperative corticosteroid therapy to reduce the diagnostic delay of PCNSL patients.

Keywords: Primary central nervous system lymphoma (PCNSL), corticosteroid therapy, diagnostic workup, diagnostic delay, diagnostic yield

OPEN ACCESS

Edited by:
Luca Ricciardi,
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Reviewed by:
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Specialty section:
This article was submitted to Neuro-Oncology and Neurosurgical Oncology, a section of the journal Frontiers in Oncology

Received: *26 February 2022*
Accepted: *18 March 2022*
Published: *20 April 2022*

Citation:
Scheichel F, Pinggera D, Popadic B, Sherif C, Marhold F and Freyschlag CF (2022) An Update on Neurosurgical Management of Primary CNS Lymphoma in Immunocompetent Patients. Front. Oncol. 12:884724. doi: 10.3389/fonc.2022.884724

INTRODUCTION

Primary central nervous system lymphoma (PCNSL) is defined as extranodal malignant non-hodgkin lymphoma of the brain, spinal cord or the leptomeninges in absence of systemic involvement. Histologically, most PCNSL are diffuse large B-cell lymphomas, followed by Burkitt, lymphoblastic, marginal zone and T-cell lymphomas (1). It therefore constitutes a fairly rare CNS neoplasm with an incidence of 0.26 to 0.48 per 100.000 person-years, which accounts for approximately 3% of all primary brain tumors (2–4). Immunocompromised patients after transplantation or being affected by AIDS have a higher relative risk of development of PCNSL (5). Recently, most PCNSL patients are immunocompetent patients and the incidence within an elderly cohort is still increasing (4, 6, 7). Clinical symptoms can be concealed with cognitive impairment being the most frequent, followed by gait disturbances, focal neurologic deficits, symptoms of increased intracranial pressure and seizures (8). Treatment for PCNSL differs from systemic lymphomas and consists of different chemotherapy regimens, all containing systemic high-

dose methotrexate (9, 10). Additionally, autologous stem cell transplantation is becoming more important, whereas radiotherapy is only rarely applied, e.g. in selected cases not suitable for aggressive systemic therapy (11, 12). The median community based overall survival has increased from 8.9 to 10 months to 25.3 months in recent studies, with a 5-year survival rate of 38% (7, 8, 13). Known favorable prognostic factors are high Karnofsky performance status and younger age at the time of diagnosis and treatment initiation (8). The primary role of neurosurgery is focused on safe and efficient planning and procedure of surgical biopsy to acquire tissue for histopathological diagnosis. Diagnostic biopsy represents the most time-critical step in the further course of the disease, resulting in a timespan between onset of symptoms to histopathological diagnosis described to range between 35 and 75 days, whereas more recent studies showed a decrease in this period (8, 13, 14). As a result, the diagnostic delay from the first imaging to definitive histopathological diagnosis is found to be significantly longer in PCNSL compared to, e.g., glioblastoma (15).

Most reviews of PCNSL encompass recent advances of systemic treatment from a neuro-oncological viewpoint. The aim of this particular review was to focus on the period between imaging and diagnosis, surgical planning and potential pitfalls in diagnosis, especially after corticosteroid therapy. Furthermore, we want to provide an overview of the diagnostic workup, which should be performed until histopathological confirmation.

IMAGING

If PCNSL is suspected, early competent imaging analysis is crucial as it strongly influences further decision making and helps avoid hasty corticosteroid treatment (CST) before surgery. In clinical practice, unenhanced computed tomography (CT) is mostly used as first imaging resource after emergence of symptoms. Sometimes the classical location and appearance in CT imaging can already be indicative of PCNSL, radiographically, as CT shows an iso- to hyperdense lesion due to the hypercellularity and the relatively high ratio of the nucleus to the cytoplasm in PCNSL (**Figure 1A**) (16, 17). Though magnetic resonance imaging (MRI) is warranted for the imaging modality of choice for diagnosis and surgical planning, its accessibility during nights and weekends could be reduced. Upon imaging, typical regions where PCNSL can be found are periventricular, in the corpus callosum and deep gray matter (9, 18). In 30–48% of all cases PCNSL show multiple lesions (13, 17, 19). Classic findings in MRI are iso- to hypointense lesions on unenhanced T1-weighted MRI and iso- to hyperintense on T2-weighted MRI sequences (**Figure 1C**) (17, 20). In immunocompetent patients usually there is a strong to moderate homogenous contrast enhancement (**Figure 1B**), but rarely atypical enhancement patterns and cases with no enhancement have been described (17–19). Advanced imaging like diffusion-weighted imaging (DWI) and spectroscopy can help distinguish the lesion from other entities in atypical cases (21). DWI is usually restricted due to high cellularity, resulting in a hyperintense signal b-1000 and hypointense signal on ADC maps (**Figures 1D, E**) (17, 21, 22). Furthermore, low ADC values where shown to be a surrogate parameter for cellular density and potentially predict outcome (23). Spectroscopy usually shows a large choline peak, decreased N-acetylaspartate (NAA), a decrease of creatine and an increase in lactate and lipids (**Figure 1F**) (17, 19). Additional information can be obtained by performing cerebral ^{18}F-Fluorodeoxyglucose-positrone-emission tomography (FDG-PET). FDG-PET analysis hereby focuses mainly on standardized uptake values (SUV), which are higher in PCNSL compared to glioblastomas (24).

Recent studies on the use of radiomics, based on either MRI or FDG-PET, to differentiate PCNSL from other entities, particularly glioblastoma, have shown promising results (25–29) and wider use in practice is desirable, as quantitative imaging or the combined analysis of a radiologist and radiomics provide better diagnostic results than radiologists alone (26, 29). However, diagnostic models for PCNSL have been defined in retrospective studies with small patient cohorts and need to be validated in large data sets and in prospective multicenter studies. Solving other challenges of quantitative imaging techniques such as reproducibility, standardization, and different imaging protocols between different centers should only be a matter of time (30).

DIAGNOSTIC WORKUP

The diagnostic workup of PCNSL has the aim to rule out a systemic involvement and should either be performed while waiting for surgery or for the histopathological result. The preclusion of systemic disease is important as it influences the treatment regime and therefore time to initiate chemotherapy can be shortened. An interdisciplinary effort of neurology, radiology, neurosurgery, neuropathology and medical oncology is necessary to complete the accurate diagnosis of a PCNSL and to determine the extent and degree of the disease.

If spinal symptoms are suspected, MRI of the complete neuroaxis should be performed to rule out spinal or meningeal involvement (31).

Independent of visual symptoms, ocular examination including fundoscopy should be performed to determine potential ocular involvement (9), which can be found in 15 to 25% of all patients and needs further ophthalmological therapy (32).

Furthermore, staging should contain at least a contrast-enhanced CT scan of the chest, abdomen and pelvis, testicular ultrasound in older men and bone marrow biopsy (9, 31).

In patients without systemic involvement in contrast-enhanced CT, ^{18}F-Fluorodeoxyglucose-PET revealed systemic PCNSL in 8% (33, 34) but it is not as easily available as contrast-enhanced CT and therefore not performed on a regular base.

Lumbar puncture should be performed after the preclusion of contraindication in imaging as CSF cytomorphology and flow cytometric analysis potentially allow a definitive diagnosis and can in some cases obviate the need for surgery (9). However, the

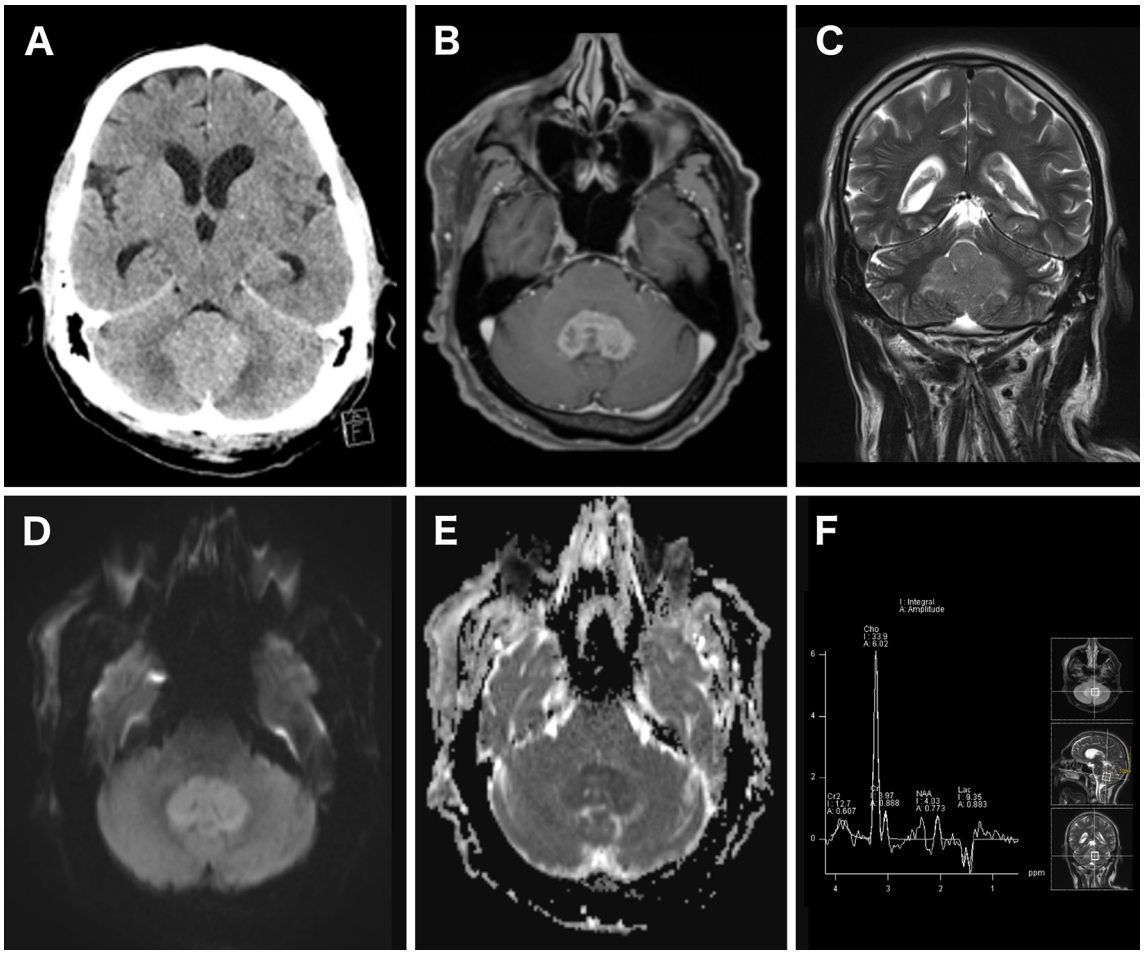

FIGURE 1 | Imaging of a patient with a histopathological proven PCNSL. Unenhanced CT scan showed a hyperdense cerebellar lesion **(A)**. Contrast-enhanced T1-weighted axial MRI showed a strong and homogenous contrast enhancement of the lesion **(B)**. The lesion homogeneously appeared hyperintense in T2-weighted MRI **(C)**. Diffusion restriction was detected as well, resulting in a bright DWI (b = 1,000) **(D)** and dark ADC map signal **(E)**. 1H-MR spectroscopy showed an increased choline peak and decreased creatinine and N-acetylaspartat **(F)**.

diagnostic yield of cytomorphologic lumbar puncture is only 6–13.3%, which inevitably requires biopsy in most cases (35–38). Only if lumbar puncture successfully acquires the diagnosis, the inherent risk of brain biopsy can be avoided. However, prolonged time to therapy could decrease the outcome in PCNSL (15), and thus lumbar puncture should not delay surgery in clinical practice. As the period from imaging to histopathological diagnosis has been described to be as long as 28 days (14) and the time from imaging to biopsy 19 days (15), LP and CSF analysis could be performed without delay of surgery in many cases if performed early in the clinical course. Notably, recent research on additional analyses in liquid biopsy of CSF and serum showed promising results harboring great potential to possibly replace diagnostic brain biopsy in PCNSL. CSF analysis for CD79B and MYD88 or diagnostic markers like CXCL-13, B2M, and neopterin are promising prospects, yet there is currently not enough evidence for standardized clinical use (39–41) and therefore brain biopsy remains the current gold standard for diagnosis. However, digital PCR of cell-free DNA for mutations in the MYD88 gene showed a sensitivity and specificity of up to 100% in a small series by Yamagishi et al. (42). Moreover, the detection of mutations in genes such as MYD88 or CD79B in liquid biopsy could have additional clinical implications, as these mutations could enable targeted therapies (43). Because liquid biopsy has the advantage of being minimally invasive and does not require scheduling, it could also help reduce diagnostic delays once the findings allow for broad clinical application. The impact of CST on the diagnostic accuracy of liquid biopsy has not yet been studied.

SURGICAL WORKUP

Stereotactic or frameless biopsy is the standard neurosurgical procedure for acquiring tissue in PCNSL and achieves a diagnostic yield of more than 91% (13, 44). Overall,

stereotactic biopsy is accompanied a periprocedural morbidity of 8.5% and mortality of 0.9% (45). Additional periprocedural techniques like frozen section (46) and 5-ALA fluorescence (47, 48) might help determine whether diagnostic tissue has been acquired (**Figure 2**). 5-ALA-Fluorescence in PCNSL is described in 79–83% with a high positive predictive value for diagnostic tissue (47, 49). Furthermore, positive 5-ALA fluorescence can help shorten surgical duration (50). Open

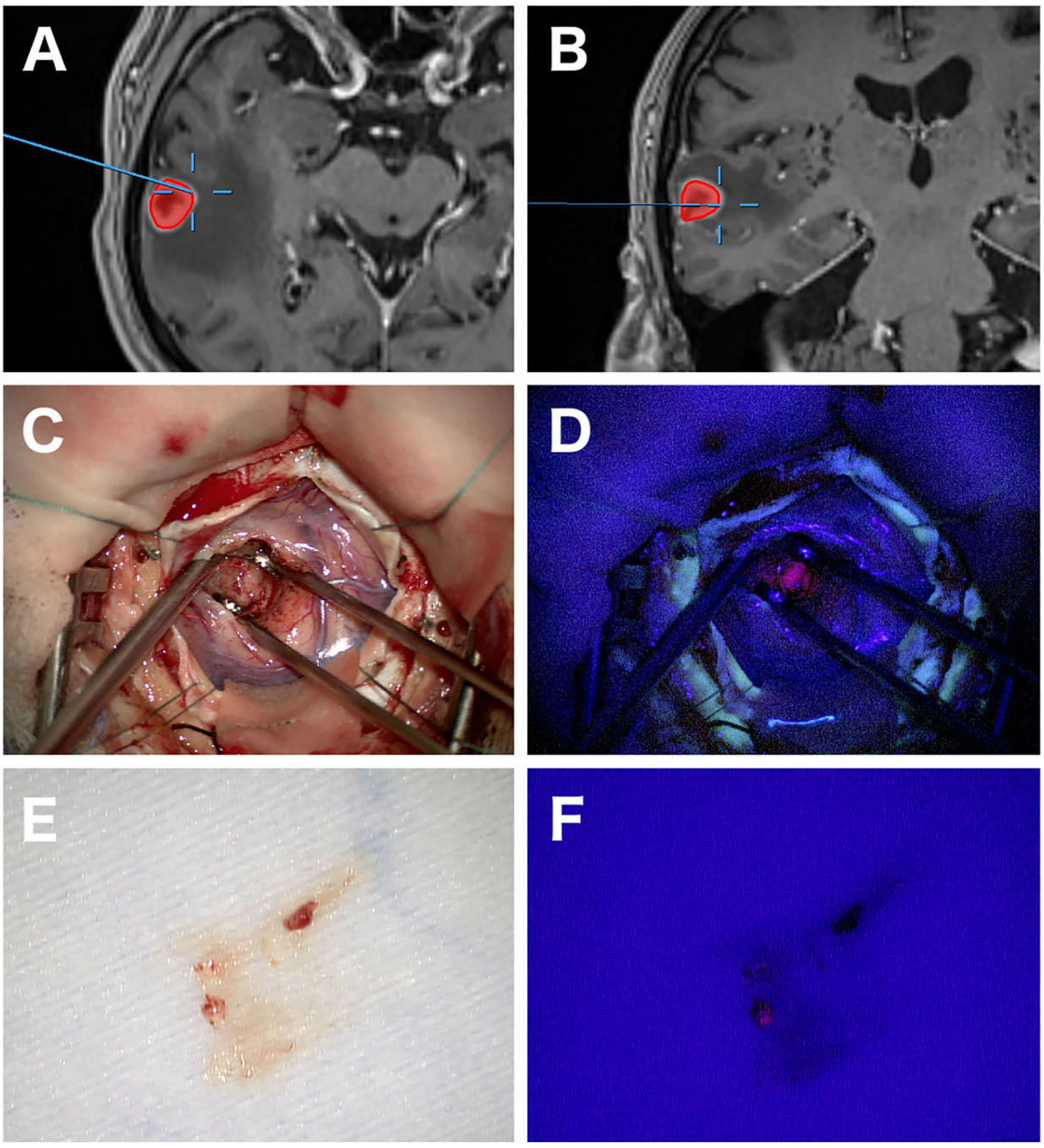

FIGURE 2 | Images of open biopsy of a PCNSL with the aid of 5-ALA fluorescence. Axial and coronal navigational MRI showing a heterogeneous contrast enhancing lesion in the right temporal lobe and the exact location of the biopsy **(A, B)**. Intraoperative images at the biopsy location with strong 5-ALA fluorescence **(C, D)**. A tissue specimen later diagnosed as PCNSL showing positive fluorescence under 405 nm wavelength blue light in another patient **(E, F)**.

surgery was historically without significance in PCNSL patients due to worse outcomes in older studies (51–53). However, this tenet has been challenged in a recent study by Weller et al. (54). The authors described an improvement of progression-free survival (PFS) and overall survival (OS) after resection compared to biopsy in their *post hoc* analysis. Yet, patients with single lesions more often underwent resection, and after further statistical adjustment for the number of lesions, only advantage for PFS remained. Other studies came to a similar conclusion reflecting that this might be due to a selection bias for patients with single lesions and patients without the involvement of deep structures (55–57). In contrast, a large retrospective study by Houillier et al. including 1002 patients did not find a difference in outcome regarding the type of surgery (8). As surgical procedures evolved, surgical resection appears to be safe nowadays in selected cases, but its clinical significance still must be determined in further studies (58).

PREOPERATIVE CORTICOSTEROID THERAPY

Preoperative corticosteroid therapy in PCSNL has been a point of debate for many years. As PCNSL cells may react with cell arrest and apoptosis to corticosteroid therapy (59–61), transient tumor shrinkage and morphological changes can be seen in up to 50%, potentially hindering histopathological diagnosis (62, 63). This phenomenon also gave PCNSL the name "ghost" or "vanishing" tumor (64). This was formerly described as diagnostic for PCNSL, but is obsolete nowadays, as also other tumor entities were identified to show transient regression after CST (65–68). Retrospective studies showed an increased rate of inconclusive biopsies after CST of 11–22% (13, 14, 69), while recent retrospective studies showed that there is not necessarily a decrease in the diagnostic yield after preoperative CST (44, 70–72). However, besides a potential selection bias, these studies lacked the statistical power to identify small differences in diagnostic rates. A recent combined analysis of the available studies showed an odds ratio of 3.3 for inconclusive biopsy after CST (44). Although absolute numbers of inconclusive biopsies decreased, the odds ratio for inconclusive biopsy after preoperative CST remained the same. Thus, CST should not be administered before surgery if PCNSL is suspected and tissue must be acquired (9). Yet, the clinical condition of patients sometimes require preoperative CST treatment, resulting in most PCNSL patients receiving CST preoperatively (13). A single dose of CST can already pose a challenge for histopathological diagnosis in some cases but prolonged CST led to a higher incidence of inconclusive biopsies in one study (69), therefore accurate evaluation of duration and dosage of CST is mandatory for further workup. The optimal management of PCNSL patients with preoperative CST remains controversial. The exact time of CST tapering that is necessary to overcome the influence of CST on diagnostic yield is not defined (13, 44). In practice, if a contrast-enhanced lesion shows distinct regression, surgery is usually delayed until new progression is evident in serial MRI (9, 73). In case of a PCNSL that only reacts with little or no regression, the risk of inconclusive biopsy must be weighed up against the significant delay to definitive therapy when biopsy is delayed.

DISCUSSION

Diagnosis and therapy of PCNSL is a multidisciplinary task, with brain biopsy as performed by neurosurgery being at the center of it. These multiple intersections between different disciplines like neurology, radiology, neurosurgery, pathology and oncology harbor a risk of unnecessary delays and might account for the prolonged diagnostic period of PCNSL compared to other brain malignancies (15). At present, no clear evidence has been found that resection offers an outcome advantage for the patient. Therefore, and contrary to many other brain malignancies, neurosurgery cannot influence the outcome of the patient with resection itself. This highlights the potential benefit of non- or minimally-invasive diagnostic tools that have lower morbidity than surgery. Liquid biopsy, alone or along with quantitative imaging techniques, has great potential to replace stereotactic biopsy in diagnosis of PCNSL especially in radiologically typical cases. Although the available data do not allow a standard application, Yamagishi et al. described a case of pontine PCNSL that was successfully treated on the basis of diagnosis by imaging and MYD88 mutation analysis in CSF (42). In such cases where brain biopsy is expected to cause high morbidity and when PCSNL is highly suspected, diagnosis by liquid biopsy should be considered. However, based on the available evidence, brain biopsy remains the current gold standard and the goal for neurosurgery must be a most efficient management and safe diagnostic brain biopsy to facilitate adjuvant treatment. Even if biopsy is performed early in the clinical course, there is still a median period of 14 days to definitive adjuvant treatment (7). This time needs to be used efficiently to avoid further delay of definitive treatment and its potential negative influence on the outcome. A major clinical issue that may be responsible for distinct diagnostic delay is preoperative CST, especially if CST must be stopped before surgery due to regression (13). If clinically possible, CST should therefore strictly be avoided in potential PCNSL patients as it increases the rate of inconclusive biopsies (44). In patients with no history of malignancy or immunosuppression and periventricular tumors upon initial CT, we recommend withholding the patient from CST treatment until MRI provides further diagnostic information and subsequent steps of diagnosis should be executed shortly after. It remains unclear how long the pause of CST treatment should be carried out. Currently, many centers wait for another progression of PCNSL upon MRI, which leads to a significant delay. The ongoing debate on the clinical impact of preoperative CST must be clarified through future prospective studies. However, current evidence shows that the risk of inconclusive biopsies is significantly higher with preoperative CST treatment (44, 62). Even though absolute rates of inconclusive biopsies after

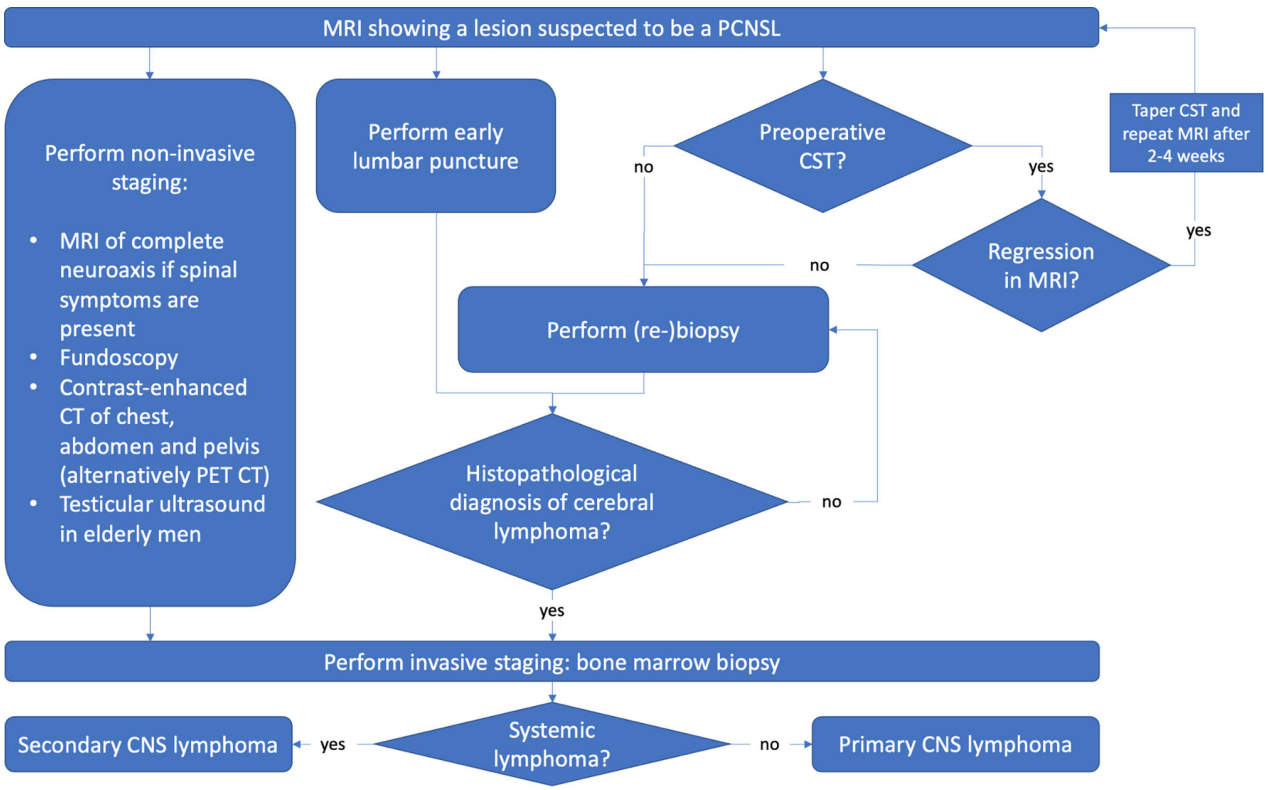

FIGURE 3 | A systematic workflow for diagnosis of PCNSL. Ideally, lumbar puncture and CSF analysis should be performed early without delaying biopsy. Non-invasive staging should be performed while waiting for biopsy or histopathological results to reduce diagnostic delay.

CST are quite low in recent studies, it is recommendable to avoid this issue in the first place if possible.

To sum up, a potential PCNSL must be recognized as early as possible to avoid preoperative CST and schedule early surgery. Next, full diagnostic workup of PCNSL should be initiated while waiting on surgery or histopathological results to reduce delay in therapy (**Figure 3**).

AUTHOR CONTRIBUTIONS

FS, DP, BP, FM, and CF contributed to conception and design of the study. FS wrote the first draft of the manuscript. All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

FUNDING

The article processing charge was covered by the Open Access Publishing Fund of Karl Landsteiner University of Health Sciences, Krems, Austria.

ACKNOWLEDGMENTS

The authors want to appreciate the contribution of NÖ Landesgesundheitsagentur, legal entity of University Hospitals in Lower Austria, for providing the organizational framework to conduct this research. The authors also acknowledge support by Open Access Publishing Fund of Karl Landsteiner University of Health Sciences, Krems, Austria.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers | Frontiers in Neurology

ORIGINAL RESEARCH
published: 16 May 2022
doi: 10.3389/fneur.2022.890857

Pre- and Post-surgical Poor Seizure Control as Hallmark of Malignant Progression in Patients With Glioma?

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Background: Regarding brain tumor-related epilepsy (BTRE), there is an increasing number of evidence about a relationship between epileptogenesis and oncogenesis. A recent study suggests a role of post-surgery seizure outcome on the survival of patients with low-grade glioma (LGG), underlying the need for a targeted and aggressive epilepsy treatment.

Objective: This study aims at investigating the possible correlation between pre- and post-surgical seizure control and tumor progression in patients who underwent surgery for LGG.

Methods: We performed a retrospective analysis of patients affected by LGGs and BTRE, in a single high-volume neurosurgical center. Seizure control was assessed before surgery and at 3 years of follow-up. Patients with histological progression in high-grade glioma (HGG) have been evaluated. Clinical features, pre-surgical electroencephalograms (EEGs), and electrocorticography (ECoG) have been analyzed.

Results: Among 154 subjects, we collected 32 patients who presented a tumor progression in HGG during the follow-up period. The majority had poor seizure control both pre- and post-surgery, never being in Engel class Ia throughout the whole history of their disease. Almost all patients with poor seizure control had pathological ECoG recording. Clinical features of seizures did not correlate with seizure outcome. On the univariate analysis, the age, the post-operative Engel class, and the extent of resection (EOR) were the prognostic factors significantly associated with oncological outcome; nevertheless, on multivariate analysis, Engel class significance was not confirmed, and the only predicting factor were age and EOR.

Conclusions: Although not confirmed on multivariate analysis, post-surgical seizure control could be a relevant factor to consider during follow-up of BRTE, in particular, when gross total resection is not achieved. Pathological findings on the ECoG may suggest a "hidden" propensity to malignant progression, strictly related to the persistent neuronal hyper-excitability. Further studies with longer follow-up period are needed to confirm our observations.

Keywords: brain-tumor epilepsy, low-grade glioma, malignant progression, electrocorticography, seizure outcome

OPEN ACCESS

Edited by:
Alireza Mansouri, The Pennsylvania State University (PSU), United States

Reviewed by:
Ignazio Gaspare Vetrano, IRCCS Carlo Besta Neurological Institute Foundation, Italy
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Specialty section:
This article was submitted to Neuro-Oncology and Neurosurgical Oncology, a section of the journal Frontiers in Neurology

Received: *06 March 2022*
Accepted: *14 April 2022*
Published: *16 May 2022*

Citation:
Pauletto G, Nilo A, Lettieri C, Verriello L, Tomasino B, Gigli GL, Skrap M and Ius T (2022) Pre- and Post-surgical Poor Seizure Control as Hallmark of Malignant Progression in Patients With Glioma? Front. Neurol. 13:890857. doi: 10.3389/fneur.2022.890857

INTRODUCTION

Brain tumors (BTs) are considered rare tumors accounting for 1–2% of all tumors in adult people. Seizures represent one of the most frequent presenting signs of gliomas, so that epileptic seizures contribute to glioma diagnosis and impair its evolution (1).

Patients affected by supratentorial gliomas develop brain tumor-related epilepsy (BTRE) with an incidence varying from 60 to 100%, according to tumor type, grade, and location (1–3).

Seizure outcome has become more and more relevant in the clinical management of patients with glioma, and nowadays, it has been recognized not only as a negative factor for quality of life of these patients (3–5), but also as a significant prognostic factor for survival (6).

There is an increasing number of evidence about a close relationship between epileptogenesis and oncogenesis. Not only gliomas induce the onset of seizures, but also the epileptic activity influences tumor growth and progression (7). Anatomically, low-grade gliomas (LGGs) infiltrate the cortex and subcortical white matter and slowly disrupt functional networks. Glioma-related glutamatergic activity has been demonstrated to promote epileptic discharges in tumor-surrounding tissue and simultaneously stimulate tumoral cell proliferation, migration, and invasion of health brain parenchyma, inducing neuronal death *via* calcium excitotoxicity (8, 9).

Although there are several mechanisms to explain seizures development in the setting of BT (10, 11), predicting whether a patient will develop refractory epilepsy or experience a more malignant disease course remains a challenge in the clinical setting (12). A recent study suggests a role of post-surgery seizure outcome on the survival of patients with LGG, underlying the need for a targeted and aggressive epilepsy treatment (6).

In this study, we investigated the possible correlation between pre- and post-surgical seizure control and tumor progression in patients who underwent surgery for LGGs.

MATERIALS AND METHODS

Study Population

We performed a retrospective analysis of 154 consecutive patients who presented a newly diagnosed supratentorial LGG with seizures as clinical presentation, in a single high-volume neurosurgical center (University Hospital of Udine, Italy). These patients underwent surgery between January 2007 and May 2018. Follow-up was extended until November 2021.

Abbreviations: ASMs, anti-seizure medications; BT, brain tumor; BTRE, brain tumor-related epilepsy; DICOM, Digital Imaging and Communications in Medicine; EAAT2, excitatory aminoacidic transporter 2; ECoG, electrocorticography; EEG, electroencephalogram; EOR, extent of resection; EZ, epileptogenic zone; GRS, glioma-related seizures; HFF, high-frequency filter; HGG, high-grade glioma; IDH1/2, isocitrate dehydrogenase 1 and 2; ILAE, International League Against Epilepsy; IOS, intraoperative seizures; iTLE, idiopathic temporal lobe epilepsy; LFF, low-frequency filter; LGG, low-grade glioma; LOCF, last observation carried forward; MGMT, O(6)-methylguanine-DNA methyltransferase; MPFS, malignant progression-free survival; MRI, magnetic resonance imaging; SD, standard deviation; WHO, World Health Organization.

Patients were enrolled according to the following criteria:

- Age $\geq$ 18 years
- Pre-operative magnetic resonance imaging (MRI) suggestive of supratentorial LGG, confirmed by histology [according to the WHO 2016 classification (13)]
- One or more epileptic seizures as the clinical presentation of the glioma with a consequent diagnosis of BTRE
- No previous surgery
- No pre-operative chemo- or radiotherapy
- Objective evaluation of the extent of resection (EOR) on MRI in Digital Imaging and Communications in Medicine (DICOM) format based on T2-weighted MRI sequences
- Histological progression in high-grade glioma (HGG) within the observational period.

Needle biopsies were excluded from the study.

The local ethics committee (Comitato Etico Unico Regionale del Friuli Venezia Giulia) approved this investigation (protocol N.0036567/P/GEN/EGAS, ID study 2540). Considering that the study was retrospective, written consent to participate in the study was not applicable. Written informed consent was obtained for surgery from all patients.

Clinical Data

Clinical information was retrieved from medical records.

We collected the following data: sex, age, time at first and second surgery, tumor localization and side, seizure type and frequency, type and number of anti-seizure medications (ASMs), pre-operative electroencephalogram (EEG), EOR, first and second histological molecular class, intraoperative electrocorticography (ECoG), the presence of intraoperative seizures (IOSs), and post-surgery seizure outcome.

Histological progression on the specimen from the subsequent surgeries was recorded and it was defined as increased glioma grade. Malignant progression-free survival (MPFS), defined as the time between initial surgery and demonstration of higher-grade tumor on subsequent biopsies, was calculated during the follow-up period for each patient. In those patients who died before the second surgery, MPFS was calculated as the time between initial surgery and demonstration of gadolinium enhancement on follow-up imaging.

The 2017 ILAE classification was applied to classify seizures (14). For statistical analysis, seizures were dichotomized, according to ictal semeiology, in motor (tonic, atonic, clonic, myoclonic, and hypermotor) and non-motor (sensory, autonomic, emotional, and cognitive) seizures.

Seizure frequency was assessed before surgery and after surgery for every 3 months for the first year and every 6 months thereafter for 2 years.

Post-operative seizure outcome was defined following the Engel Classification of Seizures (15) and dichotomized into 2 classes: Engel class Ia (completely seizure-free) vs. Engel class > Ia.

Engel class categories were assigned on the bases of self-completed seizure diaries. Engel class at 1-, 2-, and 3-years follow-up was used for the analysis.

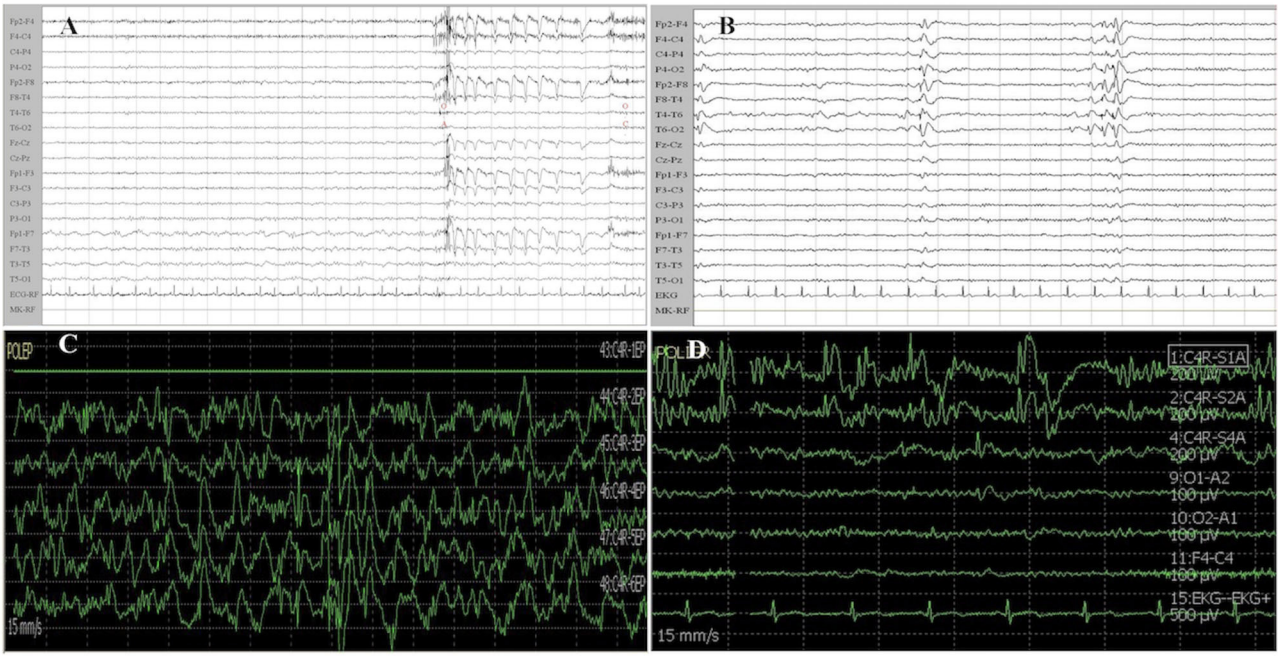

FIGURE 1 | Examples of EEG and ECoG recordings from patients of the study cohort. **(A)** Patient 1 was affected by a left insular LGG. EEG recording shows a slow activity in delta band (1–2 Hz) mixed with an alpha background rhythm on the left frontotemporal regions. **(B)** Patient 2 suffered from a right temporal LGG. EEG shows interictal epileptiform activity characterized by spike-and-wave complexes on right temporal region (T4–T6 electrodes) which rapidly spread to the homolateral supra-sylvian region. **(C)** Patient 3 was affected by a right frontal LGG. ECoG traces recorded from a contact subdural strip located near the Rolandic region show a high amplitude diffuse and continuous slow activity (delta band). **(D)** Patient 1 was affected by left insular glioma (the same patient of **A**). ECoG traces (1, 2) recorded near the insular region show epileptic activity characterized by high amplitude spike-and-wave complexes. Other ECoG traces present low amplitude theta–alpha activity. ECoG gain 400 μV/div, time base 15 mm/s, bandpass 1–80 Hz. EEG gain 100 μV/cm, time base 15 mm/s, and bandpass 1–70 Hz.
ECoG, electrocorticography; EEG, electroencephalography.

Pre-operative EEG Recordings

Patients underwent a pre-operative EEG recording (32-channel EB Neuro Mizar Sirius system with Galileo NT software, EB Neuro) according to the 10–20 International System, within 7 days before surgery.

EEGs were scored as follows:

- Normal (N): background activity with alpha or faster rhythms, no focal or diffuse slowing, no epileptic discharges;
- Slow (S): alpha or faster rhythms as background with focal or multifocal slow activity, or alpha rhythm mingled with diffuse theta–delta activity (**Figure 1A**). Epileptic activity was absent;
- Epileptic (E): alpha activity in the background with faster rhythms or mixed with slower activity. Localized or diffused interictal epileptiform abnormalities (spikes, polyspikes, spike-and-wave, polyspike-and-wave complexes) were present (**Figure 1B**).

Surgical Procedure

All patients underwent awake surgery following the standard protocol previously described (16). When necessary, general anesthesia was performed. The surgical procedures were conducted under cortical and subcortical white matter brain mapping, according to the previously reported intraoperative technique (17).

Anesthetic Protocol

Total intravenous anesthesia with Propofol and Remifentanil infusions was used for patients operated under general anesthesia.

In the case of awake surgery, Remifentanil was used at a median dose of 0.02 μg/kg/min. The scalp was injected with local anesthetic (20 ml 2% lidocaine). Low doses of Propofol were allowed only at the end of surgery. Mannitol 18% 0.25–0.5 g/kg was administered in the case that the neurosurgeon complained of severely impaired brain relaxation.

Intraoperative Electrocorticography

Electrocorticography was recorded using a 32-channels device (Axon System Eclipse®) and carried out by the experienced neurophysiologists. Recordings were analyzed separately offline by two neurophysiologists (G.P. and C.L.). In the case of discordance, a final review of ECoG traces was performed by a third neurophysiologist (A. N.). Recordings started before resection by placing 2–3 subdural strip electrodes over and around the lesion. During surgery, the strips were placed on the margin of the

exposed area. The reference electrode was located on the forehead (Fpz).

The low-frequency filter (LFF) was set at 1 Hz, the high-frequency filter (HFF) at 80 Hz, and sensitivity was set between 300 and 500 μV/mm, according to the amplitude of background and epileptiform activity. A simultaneous EEG was acquired, with the following reduced montage: O1-Pz, O2-Pz plus F3-C3 or F4-C4 plus P4-O2 or P3-O1 depending on the tumor side. LFF was set at 1 Hz, and HFF was set at 70 Hz.

ECoG recordings were scored as follows:

- Normal (N): background activity with alpha or faster rhythms, with no epileptic discharges and slow activity;
- Slow (S): background alpha or beta rhythms with focal or multifocal slow activity, but no epileptic discharges (**Figure 1C**);
- Epileptic (E): alpha or slow activity in the background with focal or diffuse interictal epileptiform activity (**Figure 1D**), which is described according to the classification of Palmini et al. (18).

Intraoperative seizures were defined as any seizure observed during surgery. If no detectable clinical sign was witnessed, the seizure was described as electrographic; otherwise, the seizure was scored as electro-clinical. Spontaneous ECoG/EEG ictal activity was defined as evolving discharges characterized by one of the following patterns: rhythmic waves (in theta, delta, or alpha bands), rhythmic spiking, repetitive spike/polyspikes-waves or electro-decremental pattern, represented by a general attenuation of background rhythms which are substituted by low-voltage, high-frequency activity (19). These patterns were characterized by an abrupt onset, a clear evolution in amplitude, frequency, and/or topography over time and must last at least 10 s (20). Similarly, stimulation-induced seizures were defined as trains of after-discharges that evolved in terms of distribution, morphology, and/or frequency (21).

Statistical Analysis

Descriptive analysis of the main features of the study population was performed using mean ± SD or median and range for continuous variables, and percentages for categorical variables. For the statistical analysis, we considered the oncological progression (i.e., the malignant transformation) as the function of the MPFS. The *t*-test or Mann–Whitney U-test, as appropriate, was used to compare continuous variables between groups. For categorical variables, cross-tabulations were generated, and a chi-square or Fisher's exact test was used to compare distributions, as appropriate. Survival was analyzed by means of Cox regression method.

In univariate analysis, the variables considered as possible prognostic factors were as follows: age, sex, post-operative Engel class, pre-operative EEG (epileptiform vs. not epileptiform), pre-operative seizures frequency, pre-operative seizure semiology and duration, ASMs, intraoperative ECoG data (epileptiform vs. not epileptiform), and the presence of IOS and EOR.

To assess the potential impact of missing data on the long-term results, the last observation carried forward (LOCF) analysis was performed. The seizure frequency at the last observation was carried forward for dropouts and used to impute the missing values. The combination of the observed and imputed data was then analyzed as though there were no missing data. After 3 years of follow-up, Engel class data were too numerically limited to perform a reliable LOCF analysis, so they were not considered in the study.

The results are presented as hazard ratios and 95% confidence intervals. All analyses were conducted using STATA/SE (version 14.0 Stata Corp.) for Windows. All two-tailed statistical significance levels were set at $p < 0.05$. Covariates with $p < 0.05$ at univariate analysis were selected for multivariate stepwise analysis.

RESULTS

A total of 154 patients affected by LGGs with seizures as clinical manifestations have been evaluated. In **Table 1**, demographic, clinical, and neurophysiological data are reported.

Regarding epilepsy characteristics, the majority of patients experienced focal to bilateral tonic–clonic seizures (57.14%), while the remaining 66 patients (42.86%) suffered from focal seizures. Pre-surgery, seizures recurred daily in 11 patients (7.14%), weekly in 51 (33.12%), and monthly in 92 patients (59.74%). The most used ASM regimen was monotherapy (126 patients, 81.82%).

Pre-operative EEG showed no abnormalities or only slow activity (focal or bilateral) in the majority of patients (114, 74.02%). Intraoperatively, epileptic and not epileptic abnormalities were almost equally represented as shown by ECoG (72 patients vs. 82 patients, respectively). The majority of patients did not show any IOS (116, 75.32%).

Then, 1 year post-surgery, all patients completed seizure diaries: the majority of them (108, 70.13%) were in Engel class Ia. At 2 and 3 years post-surgery follow-up, the cohort that completed diaries included 110 and 87 patients, respectively. Missing data were due to the loss of follow-up and/or patients' death.

During the 3 years of follow-up (from 2018 to 2021), 32 patients presented a histological or radiological progression into HGG. Median MPFS was 70.5 months with a range of 6–239 months. The majority of them (67.8%) had poor seizure control both pre- and post-surgery, never being in Engel class Ia throughout the whole history of their disease. Considering pre-surgery seizure frequency, they presented daily or weekly attacks. All patients with poor seizure control had pathological ECoG recording, particularly about 60% showed an epileptic ECoG.

Seizure characteristics did not differ significantly between patients with HGG who were seizure-free and patients with HGG who were not.

The univariate analysis by means of Cox regression (**Table 2**) showed that the covariates associated with oncological outcome were as follows: age, post-operative Engel class, and EOR. Indeed, at 1-year post-surgery, we observed that the majority of patients with no evidence of histological progression (90, 73.78%) were in Engel class Ia with a statistically significant correlation (*p*

TABLE 1 | Baseline characteristics of the study population.

Variables	
No. of patients	154
Sex, *n* (%)	
Male	95 (61.68)
Female	59 (38.32)
Age, (years)	
Median (IQR)	37.00 (58)
Range	15–73
Seizure onset	
Focal seizures	66 (42.86)
Focal to bilateral tonic–clonic seizures	88 (57.14)
Seizure types	
Motor	105 (68.18)
Non-motor	49 (31.82)
autonomic	9 (5.80)
cognitive	13 (8.40)
sensory	18 (11.70)
emotional	9 (5.80)
Pre-operative seizures frequency	
Monthly	92 (59.74)
Weekly	51 (33.12)
Daily	11 (7.14)
ASMs regimen	
Monotherapy	126 (81.82)
Levetiracetam	91 (72.22)
Sodium channel blockers	24 (19.05)
Valproic acid	7 (5.50)
Phenobarbital	3 (2.38)
Zonisamide	1 (0.85)
Polytherapy	28 (18.18)
Pre-operative EEG features	
Normal	71 (46.10)
Slow	43 (27.92)
Epileptic	40 (25.98)
Tumor side	
Left	89 (57.10)
Right	66 (42.90)
Tumor site	
Frontal	52 (33.80)
Parietal	14 (9.10)
Temporal	24 (15.60)
Insular	64 (41.60)
Pre-operative tumor volume (T2-weighted MRI images – cm^3)	
Median	48
Range	(6–144)
EOR % (range)	88 (38–100)
Molecular Class	
Oligodendroglioma IDH1/2 mutated 1p-19q codeleted	44 (28.60)
Diffuse astrocytoma IDH1/2 mutated 1p-19q non codeleted	92 (59.70)
Diffuse astrocytoma IDH1/2 wild-type	18 (11.70)
MGMT promoter methylation	
Yes	135 (87.70)
No	19 (12.30)
Time between seizure onset and first surgery (months)	6 (4–20)
Intraoperative seizures	
Yes	38 (24.68)
No	116 (75.32)
Intraoperative ECoG features	
Normal	48 (31.15)
Slow	24 (15.65)
Epileptic	82 (53.20)
Post-operative Engel class at 1 year	
Ia	108 (70.13)
>Ia	46 (29.87)
Post-operative Engel class at 2 years	
Ia	104 (67.53)
>Ia	50 (32.47)
Post-operative Engel class at 3 years	
Ia	99 (64.28)
>Ia	55 (35.72)

ASMs, anti-seize medications; ECoG, electrocorticography; EEG, electroencephalogram; EOR, extent of resection; IDH, isocitrate dehydrogenase; IQR, interquartile range; MGMT, O(6)-methylguanine-DNA methyltransferase.
Patients' characteristics are described using median and range for continuous variables, the number of cases with relative percentages (in parentheses) for categorical variables.

< 0.01). Then, 2 and 3 years post-surgery, we observed a stronger association between Engel class Ia and the absence of progression with high levels of statistical significance ($p < 0.001$), regardless of the type of analysis performed (observed data plus LOCF vs. observed data only). Nevertheless, on multivariate analysis, the only independent predictor factors associated with the oncological outcome were age and EOR, as observed by the previous studies (22), whereas Engel class significance was not confirmed.

Demographic features, as well as pre-operative seizures characteristics and intraoperative data, were not statistically associated with oncological outcomes.

DISCUSSION

In this study, we investigated the potential role of post-surgical seizure outcome on tumor progression in a cohort of patients affected by LGGs and BTRE. We observed that poor post-surgery seizure control was potentially associated with tumor progression into HGG within 3-year follow-up, although not confirmed on multivariate analysis.

The extent of surgical resection is an established prognostic factor for seizure and oncological outcomes (22, 23). Thus, post-surgical persistence of seizures is often the consequence of an

TABLE 2 | Predictors of the oncological outcome on univariate and multivariate analysis by means of Cox regression.

		MPFS			MPFS		
		Univariate analysis			Multivariate analysis		
		HR	95% CI	*p*	HR	95% CI	*p*
Clinical feature	**Reference variable**						
Sex	Male	0.9492	0.6292–1.4319	0.8038			
Age§		1.0303	1.0121–1.0489	**<0.01**	1.0238	1.0050–1.0430	**0.0129**
Pre-operative epilepsy features							
Seizure type	Motor	0.9072	0.5919–1.3903	0.6548			
Seizure onset	Focal (incl. FTBTC)	0.7101	0.4762–1.0593	0.0934			
Seizure frequency	Monthly	1.1487	0.7689–1.7159	0.4985			
Duration	<1 year	1.0590	0.6102–1.8380	0.8385			
Pre-operative EEG	Not epileptiform	1.1122	0.7089–1.7449	0.6436			
ASMs	Monotherapy	1.6210	0.9887–2.6577	0.0555			
Intraoperative features							
ECoG	Not epileptiform	1.3127	0.8789–1.9607	0.1837			
Intraoperative seizures	None	1.0463	0.6670–1.6413	0.8438			
Postoperative features							
Engel class (1 year post-surgery)	Engel I	2.2633	1.4921–3.4332	**<0.01**	1.0911	0.5548–2.1457	0.8005
Engel class (2 years post-surgery)*	Engel I	2.2144	1.4737–3.3274	**<0.001**	1.0936	0.3424–3.4931	0.8800
Engel class (3 years post-surgery)*	Engel I	2.1617	1.4493–3.2421	**<0.001**	1.6769	0.5968–4.7172	0.3267
EOR (%)§		0.9598	0.9458–0.9741	**<0.0001**	0.9680	0.9519–0.9845	**<0.001**

§*Modeled as continuous variable.*

**Observed data plus LOCF (Last Observation Carried Forward).*

EEG, electroencephalogram; ASMs, anti-seizure medications; ECoG, electrocorticogram; MPFS, malignant progression-free survival.

Significant p-values are reported in bold.

uncomplete resection of epileptogenic zone (EZ), even in the case of glioma surgery.

In fact, two scenarios may be observed: the EZ may lie away from the tumoral area or may be nestled within the residual tumor. In this context, an extended pre-surgical neurophysiological evaluation may be useful to better define the EZ and so to guide intraoperative monitoring, to maximize the EOR.

In our experience, the presence of interictal ECoG activity on surgical margins suggests a post-surgical seizure recurrence.

Moreover, the persistence of seizures after surgery could facilitate tumor progression not only because it is an indirect clue of an uncomplete resection, but also for the possible enhancement of oncogenetic process driven by seizures themselves.

In fact, the importance of seizure control in patients with gliomas is increasingly emerging. Our results are in line with this evidence.

Santos-Pinheiro et al. showed that a high post-surgical seizure frequency and an increase in seizure frequency from pre- to post-operative period were associated with a greater rate of early tumor recurrence in a LGG population (12). Furthermore, in another recent Italian work, seizure outcome after surgery emerged as an independent strong predictive factor of overall survival in patients with glioma (6).

In our study, we focused mainly on clinical and epileptological features for two reasons. First of all, neurosurgical and molecular characteristics associated with tumor progression or recurrence have already been extensively evaluated (23–28). In the last decades, this growing body of literature remarks as an extensive early surgery leads to obtain a good oncological and epileptological outcomes (23–26). Second, recent studies have pointed out that epileptogenesis and tumor growth in LGGs may share common pathogenetic mechanisms that can influence each other (28, 29).

In this context, an early, careful, and constant evaluation and management of seizures, both pre- and post-surgery, in patients with glioma, finds its rational.

In fact, after glioma resection, Neal et al. found a prevalence of fluctuating seizure control pattern in patients affected by grade II and III gliomas and BTRE (30). They interpreted this result as the consequence of the natural history of delayed but expected progression. Therefore, the first period of seizure freedom might be the result of removing the epileptogenic zone with a gross total resection, whereas seizure relapse might reflect tumor progression (3, 30, 31). Moreover, Mittal et al. performed intracranial EEG analyses on patients affected by glioma-related drug-resistant epilepsy and showed that seizure onset zone included tissue located beyond 1.5 cm from the tumor margin (32).

Taken together, all this evidence suggests that glioma surgery, at least in patients already affected by BTRE, should include, when possible, the resection of epileptogenic zone, removing peritumoral tissue where epileptic foci are more

likely to be nested. In fact, seizures arise electrographically from the peritumoral cortex in most of the patients, due to induced changes rather than from the tumor proper (33).

The mechanisms of epileptogenesis in gliomas are multifactorial and some are also involved in neuronal death, changes in cellular mobility, and oncogene expression *via* second messengers. Among the epileptogenic pathways, it is of main importance the so-called glutamatergic one.

In peritumoral cortex, an increase in glutamatergic activity has been demonstrated (33, 34). In their experimental work, Buckingham et al. implanted human-derived glioma cells into combined immunodeficient mice. These glioma-bearing mice developed spontaneous and recurring epileptic activity, as a consequence of marked glutamate release from the tumor, mediated by the system xc– cystine–glutamate transporter (34).

Moreover, the high glutamate levels in tumor tissue are also a consequence of both increased release of a glutamate agonist in the synaptic cleft, induced by mutation of IDH 1/2 (isocitrate dehydrogenase 1 and 2) (9), and a reduced glutamate removal from extracellular space, caused by the downregulation of excitatory aminoacidic transporter EAAT2 (35).

Peritumoral astrocytes that would normally be able to remove and catabolize extracellular glutamate are overwhelmed by glutamate release from the tumor, and peritumoral neurons exhibit a lower epileptic threshold. Furthermore, glutamate release from glioma leads to tumor growth, tumor-associated excitotoxicity, tumor invasion of health parenchyma and edema (34).

Finally, Feyissa et al. performed a transcriptome-wide comparison between patients with glioma-related seizures (GRS), subjects with glioma but no seizures (non-GRS), and patients with idiopathic temporal lobe epilepsy (iTLE) (36). They found differential expressed genes associated with patients with GRS vs. non-GRS. Particularly, in the former group, there were a significant overexpression of genes involved in cell-to-cell and glutamatergic signaling (CELF4, SLC17A7, and CAMK2A) and a down-regulation of genes involved immune-trafficking (CXCL8, H19, and VEGFA). Comparing GRS with patients with iTLE, an overexpression of genes considered markers of oncogenesis was observed in the first group (36).

Thus, the post-surgical persistence of seizures may depend on the impossibility of removing the epileptogenic zone, the multiple pathogenetic mechanisms that are involved in seizure generations, and the activation of different epileptic networks. Epileptic firing might enhance oncogenesis by the amplification of common pathogenetic pathways.

We acknowledge that our study is retrospective and it carries all the intrinsic limitations of this study design. Furthermore, histological reports were classified according to the previous 2016 WHO classification of brain tumors (13). Thus, the prognostic role of CDKN2A/2B, ATRX, TERT, EGFR, and TP53 mutations emerged by the 2021 WHO Classification (37) was not assessed, explaining an overestimation of the real number of LGGs included in our study population. However, this study analyzes a homogeneous population (all patients with a first diagnosis of LGG and affected by BTRE from the beginning), with a long follow-up and it focuses on epileptological and electroencephalographic features, since patients have been evaluated by a multidisciplinary team including neurologists expert in epilepsy and clinical neurophysiology.

CONCLUSIONS

Seizure control has major implications for the quality of life in patients with BRTE, as intractable seizures are associated with significant morbidity. In LGG population, the possibility that a poor seizure outcome may correlate with a histological progression corroborates the importance of an early, constant, and careful evaluation and management of seizures, considering also target therapy for BTRE, such as ASMs that could impair common pathogenic pathways. A closer follow-up for patients who are not seizure-free after surgery should include also prolonged EEG recordings, to evaluate subtle seizures.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Comitato Etico Unico Regionale del Friuli Venezia Giulia. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

GP and AN: conception and design. AN, GP, CL, and LV: acquisition of data. CL: formal analysis. TI, GP, GLG, and MS: supervision. GP and TI: validation. GP, AN, and CL: writing–original draft. GP, TI, AN, BT, and LV: writing, reviewing and editing. All authors have read and agreed to the published version of the manuscript.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers | Frontiers in Oncology

ORIGINAL RESEARCH
published: 26 May 2022
doi: 10.3389/fonc.2022.900382

Surgical Management of Malignant Glioma in the Elderly

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Background: The median age for diagnosis of glioblastoma is 64 years and the incidence rises with increasing age to a peak at 75-84 years. As the total number of high-grade glioma patients is expected to increase with an aging population, neuro-oncological surgery faces new treatment challenges, especially regarding aggressiveness of the surgical approach and extent of resection. In the elderly, aspects like frailty and functional recovery time have to be taken into account before performing surgery.

Material & Methods: Patients undergoing surgery for malignant glioma (WHO grade III and IV) at our institution between 2015 and 2020 were compiled in a centralized tumor database and analyzed retrospectively. Karnofsky Performance Scale (KPS) and Clinical Frailty Scale (CFS) were used to determine functional performance pre- and postoperatively. Overall survival (OS) was compared between age groups of 65-69 years, 70-74 years, 75-79 years, 80-84 years and >85 years in view of extent of resection (EOR). Furthermore, we performed a literature evaluation focusing on surgical treatment of newly diagnosed malignant glioma in the elderly.

Results: We analyzed 121 patients aged 65 years and above (range 65 to 88, mean 74 years). Mean overall survival (OS) was 10.35 months (SD = 11.38). Of all patients, only a minority (22.3%) received tumor biopsy instead of gross total resection (GTR, 61.2%) or subtotal resection (STR, 16.5%). Postoperatively, 52.9% of patients were treated according to the Stupp protocol. OS differed significantly between extent of resection (EOR) groups (4.0 months after biopsy vs. 8.3 after STR vs. 13.8 after GTR, $p < 0.05$ and $p < 0.001$ correspondingly). No significant difference was observed regarding EOR across different age groups.

Conclusion: GTR should be the treatment of choice also in elderly patients with malignant glioma as functional outcome and survival after surgery are remarkably better compared to less aggressive treatment. Elderly patients who received GTR of high-grade gliomas survived significantly longer compared to patients who underwent biopsy and STR. Age seems to have little influence on overall survival in selected surgically extensive treated patients, but high preoperative functional performance is mandatory.

Keywords: malignant glioma, glioblastoma, elderly, surgery, survival

OPEN ACCESS

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Specialty section:
This article was submitted to Neuro-Oncology and Neurosurgical Oncology, a section of the journal Frontiers in Oncology

Received: *20 March 2022*
Accepted: *13 April 2022*
Published: *26 May 2022*

Citation:
Klingenschmid J, Krigers A, Kerschbaumer J, Thomé C, Pinggera D and Freyschlag CF (2022) Surgical Management of Malignant Glioma in the Elderly. Front. Oncol. 12:900382. doi: 10.3389/fonc.2022.900382

INTRODUCTION

Glioblastoma has an incidence of 3.2 cases per 100.000 adults and therefore constitutes the most common malignant primary brain tumor. Median age at diagnosis is 64 years with an increasing incidence with rising age, peaking at 75-84 years (1). Median survival lies between 12-15 months in all patients despite aggressive treatment, being markedly decreased in elderly patients with only 4-5 months from diagnosis (2, 3). As the average age of the population rises, elderly patients represent already up to 25% of all WHO° IV brain tumor patients (4, 5). Thus, treatment options and prognostic factors must be re-evaluated in the face of an aging patient group.

Age per se is known to be a negative prognostic factor in patients with malignant glioma with a statistically significant decrease of survival per each additional year of age (6–9). Further, molecular diagnosis in the older population prominently reveals primary glioblastoma, lacking IDH mutation (10). MGMT promoter methylation can be found in approximately 40-60% of elderly glioblastoma patients, being a favorable prognostic factor in all age groups (11–14).

Performance status has gained more and more impact in the individual assessment of elderly patients regarding their prognosis and eligibility for treatment. Physical wellbeing including organ function and associated comorbidities play a more important role than chronological age alone (15). KPS and more modern score systems assessing frailty help to depict a holistic image of elderly patients including strength, endurance and physiologic function resulting from diseases or diverse medical conditions (16).

Surgery in malignant gliomas aims to prolong overall survival (OS) and progression free survival (PFS), helps to gain histopathological and molecular information as well as, due to the reduction of mass effect, decreases the use of steroids . Yet, for a long time, extensive resection was withheld in the elderly fearing a worse outcome. Recent data, however, underlines the importance and safety of aggressive surgical treatment even in the elderly (17–21).

Following surgery, further oncological treatment in the elderly depends mainly on the overall functional status as benefits of any therapy become more closely balanced with risks of toxicity. Elderly patients with poor performance status often better tolerate single-modality therapy that is radiotherapy or temozolomide alone. Both sole hypofractionated radiotherapy and temozolomide chemotherapy are administered provides good results in elderly patients with poor performance status (11, 22). Recent data, however, favors a combined radiotherapy as well, especially in MGMT-methylated patients, the method of radiation still matter of debate (23).

The WHO defines 'elderly' above 65 years of age, therefore data on surgical treatment of malignant glioma in the large cohort of the elderly is started at this age, mostly without further subdivision. Thus, we aimed to analyze the influence of extent of surgical resection on survival in different age groups above 65 years. Furthermore, a literature review was performed with focus on the surgical treatment modalities and compared to our data.

MATERIAL AND METHODS

A total of 121 patients aged 65 years and above with histologically confirmed WHO grade III and IV tumors who underwent surgical treatment at our institution between 2015 and 2020 were analyzed. Surgical therapy included biopsy (either stereotactic or frameless), subtotal resection (STR) or gross total resection (GTR, defined as EOR > 98% of all contrast-enhancing tumor, as gauged by MRI). STR was defined as partial tumor removal with an EOR >80% in the light of preserving neurological status but with residual nodular enhancement in MRI (24).

Clinical performance was assessed using the Rockwood Clinical Frailty Scale (CFS) and Karnofsky Performance Scale (KPS). Examinations were performed preoperatively, postoperatively and three to six months after surgery. CFS was assessed retrospectively blinded to the outcome data using the functional description and standardized neurological status of the patients, which were documented in patients' charts. Karnofsky Performance Status Scale (KPS) was prospectively assessed in all patients preoperatively and 3 to 6 months after surgery as an institutional clinical routine.

Neuropathological grading was based on the revised 4th WHO classification of CNS tumors. Presence of IDH1 mutation, as well as nuclear ATRX expression was proven by immunohistochemistry. DNA sequencing was applied to evaluate MGMT promotor methylation, using a cut-off at 8%.

Statistical analysis was performed using IBM SPSS Statistics (IBM SPSS Statistics for Windows, Version 27.0. Armonk, NY. IBM Corp.). Normal distribution of scale data was checked using Kolmogorov-Smirnov test and if normal distribution was not confirmed, Mann-Whitney-U test for unpaired or Wilcoxon and Friedmann test for paired ranked or scale parameters were applied. Spearman's test was used to assess correlations of non-parametric data. Overall survival was estimated using Kaplan-Meier processing and log-rank tests. Results with $p < 0.05$ were considered as statistically significant.

RESULTS

We included 121 patients with an age of 65 years and older in this investigation – 46 females and 75 males. To be precise, 27 patients (22.3%) had an age of 65 – 69 years at time of surgery, 35 patients (28.9%) were 70 – 74 years old, 41 (33.9%) were 75 – 79, 12 (9.9%) were 80 – 84 and 6 (5.0%) were 85 years old or older. Mean age at surgery was 74 years (SD = 5). Mean estimated overall survival (OS) was 10.35 months (CI 95%: 8.26-12.45).

All except to four patients (WHO grade III) showed WHO grade IV tumors. Of all patients, only three (2.5%) showed IDH1 mutation, whereas 111 patients (91.7%) had an IDH1 wildtype tumor. In seven patients (5.8%) IDH1 mutation status was not available due to missing histopathological data.

MGMT promotor methylation was present in 58 patients (47.9%) in contrast to 52 patients (43.0%) where no methylation was found. In ten patients, methylation status was not available.

Nuclear ATRX was found to be expressed in specimens of 105 patients (86.8%), not expressed in two (1.7%) and not tested for in 14 (11.6%) patients.

As far as the extent of resection (EOR) is concerned, 27 patients (22.3%) received a biopsy only while 74 patients (61.2%) were treated with gross total resection (GTR). Twenty patients (16.5%) had a subtotal resection (STR). **Table 1** shows the distribution of age groups amongst the different extents of resection.

A total of 65 patients (53.7%) were treated with a 6-week period of radiotherapy with a radiation dose of 60 Gy and concomitant temozolomide (18). Additionally, fifty patients (41.3%) received adjuvant temozolomide with a mean of 2.2 cycles (SD = 3.72). By default, radiotherapy was performed using a regime of 60 Gy over 6 weeks and temozolomide was administered according to the Stupp protocol in a weight-based manner. Only both in five patients the radiation was adapted to a dose between 30 and 50 Gy, and temozolomide was administered in a low-dose scheme. Sole radiation monotherapy was applied to 14 patients (11.6%). In 42 patients (34.7%) no further treatment was carried out.

Results regarding patient assessment for functional status using KPS and CFS are shown in **Table 2**. KPS stayed stable with a light increase at follow up, whereas CFS remained stable. Changes were not statistically significant (p – ns.)

Preoperative KPS and CFS were significant better in the GTR group compared to biopsy and STR (KPS: $p < 0.01$ and CFS: $p < 0.05$, respectively). At the follow-up visit after 3 to 6 months, no significant difference in KPS could be shown (p – n.s.), see **Figure 1**.

Patients receiving biopsy had a mean OS of 3.96 months (CI95% = 2.23 – 5.67). After STR, patients lived for a mean of 8.30 months (CI95% = 4.05 – 12.55), while mean OS following GTR was 13.80 months (CI95% = 10.46 – 17.15). **Figure 2** shows the corresponding Kaplan-Meier curves. When examining the significance more closely, looking at EOR in pairs, biopsy versus STR showed no significant difference in OS, while biopsy versus GTR demonstrated a significant difference ($p < 0.05$), as well as STR versus GTR ($p < 0.001$).

Patients who received GTR showed no significant differences in OS with regard to their age (p – n.s.). Furthermore, OS following STR did not differ significantly either (p – n.s.) (**Figures 3**, **4** and **Table 3**).

TABLE 1 | EOR according to different age groups.

			65-69	70-74	75-79	80-84	≥ 85
EOR	Biopsy	quantity	9	3	10	2	3
		% of age groups	33.3%	8.6%	24.4%	16.7%	50.0%
		% of total	7.4%	2.5%	8.3%	1.7%	2.5%
	GTR	quantity	18	27	19	7	3
		% of age groups	66.7%	77.1%	46.3%	58.3%	50.0%
		% of total	14.9%	22.3%	15.7%	5.8%	2.5%
	STR	quantity	0	5	12	3	0
		% of age groups	0.0%	14.3%	29.3%	25.0%	0.0%
		% of total	0.0%	4.1%	9.9%	2.5%	0.0%
total		quantity	27	35	41	12	6
		% of total	22.3%	28.9%	33.9%	9.9%	5.0%

TABLE 2 | Median pre- and postoperative as well as follow-up values for KPS and CFS, including IqR, are depicted.

	preoperatively	postoperatively	3-6 months follow-up
KPS (median (SD))	80 (20)	80 (20)	90 (20)
CFS (median (SD))	3 (1)	–	3 (2)

DISCUSSION

Extensive resection benefits overall survival within all elderly age groups, even in the very old. OS after sole biopsy was shorter (approximately 4 months) than after STR (8 months) and GTR (14 months) for elderly patients. Additionally, our findings suggest that patients with good preoperative functional status, as assessed in KPS, are more likely to be treated by extensive surgery.

Extent of Resection

With most of the elderly patients (61.2%) treated with GTR and more than 50% receiving postoperative therapy according to the Stupp protocol, we aim for an extensive tumor therapy also in this age group. Nearly all our patients` histopathological and molecular testing showed WHO grade IV tumors without IDH1 mutation which matches literature data (19, 25, 26).

Our results are congruent to previous findings, indicating that a more aggressive surgical approach leads to longer survival (18–20). A retrospective case-control analysis conducted by Chaichana et al. found overall survival (OS) time to be increased by 40% (which equaled 2 months in their cohort) in elderly patients who underwent surgical resection compared to those undergoing needle biopsy. At the same time, surgery-related morbidity was demonstrated to be similar in case of aggressive resection and biopsy (18). This was confirmed in another retrospective study which assessed 178 patients with a median age of 71 years, showing a 2-year-OS three times higher, when the contrast-enhancing tumor was resected completely compared to patients with biopsy alone (19). A systematic review and meta-analysis including more than 12.000 elderly patients confirmed that maximal resections are safe and are associated with longer survival (increased by an average of 7 months in gross total resection compared to biopsy), improved functional recovery and delayed tumor progression while showing no higher rates of mortality or morbidity according to the extent of resection (20). Data of the SEER (Surveillance, Epidemiology, and End Results) cancer registry also found GTR to be associated with improved overall survival (27). Analysis of 20.705 patients harboring glioblastoma found a strong association between EOR and OS, regardless of age. Yet, their OS is lower than our findings, possibly due to historic data. Contrary to our findings, Babu et al. demonstrated a decreased survival in patients aged above 75 years in their series, yet, the other results are in line with our data (EOR, KPS) (28). Niare et al. presented a series of selected patients 80 years or older, which revealed that radical resection of GBM was associated with acceptable survival in contrast to sole biopsy. Moreover, their

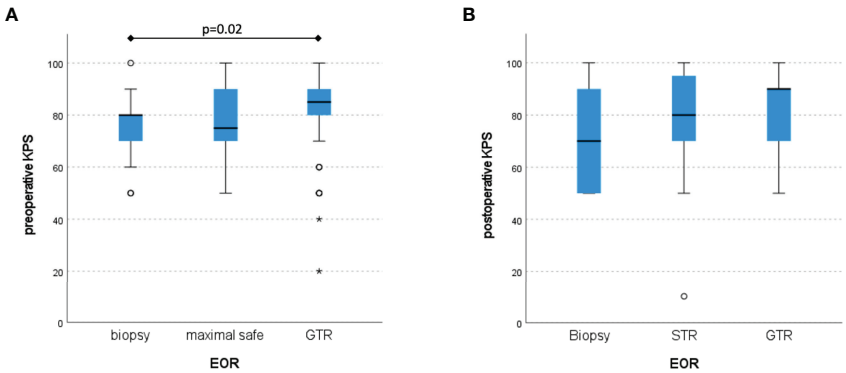

FIGURE 1 | Distribution of KPS according to the different EOR with a significant preoperative difference **(A)**, but non-significant values postoperatively **(B)** (Box plot diagram).

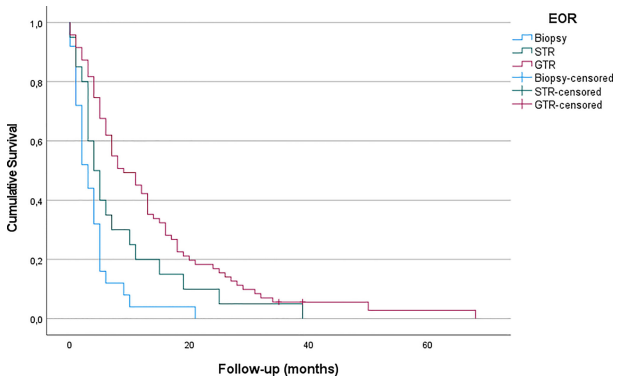

FIGURE 2 | Differences of OS in the treatment groups (biopsy, GTR, STR) are shown in Kaplan-Meier processing. LogRank test Biopsy-GTR: p<0.001.

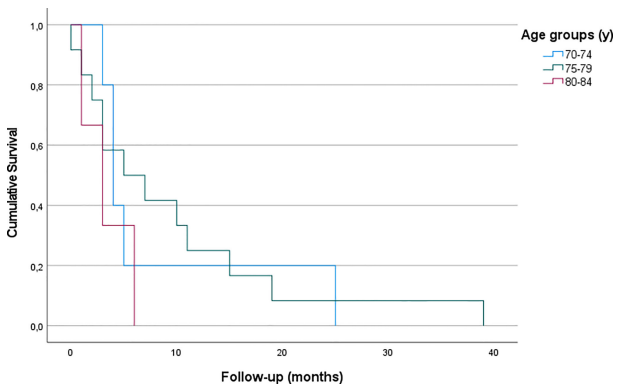

FIGURE 3 | Kaplan-Meier curves for patients of all age groups who received GTR (p - ns).

data underlined the need for adjuvant treatment with the complete Stupp protocol (29, 30). Nevertheless, direct comparison is cumbersome, as the distribution of EOR in their age comparison is not mentioned. A recent review reports data showing GTR to be more effective than STR in achieving longer survival in elderly patients with high-grade glioma as it can significantly improve OS and 3-, 6-, 9-month, and 1-year mortality (21).

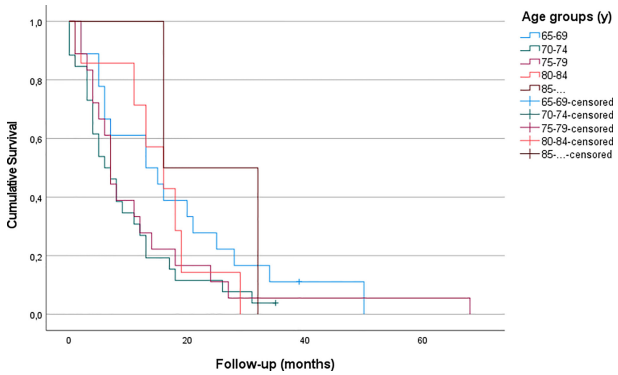

FIGURE 4 | Kaplan-Meier curves for patients of all age groups who were treated with STR (no patients under 70 and over 84 years received STR in our cohort) (p - ns).

Overall, recent literature favors extensive surgical resection also in the elderly, even though uncertainties due to comorbidities and tumor localization remain (19, 20, 25, 26, 28)

Performance

Geriatric glioblastoma patients with increased frailty have shown to have a higher probability for poor survival with increasing patient age (26). Thus, preoperative functional status should be considered in individual treatment decision making as a more relevant factor than chronologic age. Both KPS and CFS show congruent results at the post-operative follow up in our series and similar to preoperative assessment supporting the importance of proper patient selection. Recent data analyzing 110 elderly patients described an association between preoperatively increased frailty and decreased survival following surgical treatment of geriatric glioblastoma patients. Moreover, an increased comorbidity burden and subtotal resection was associated with poor survival (26). Although our series did not include comorbidities, latter results are in line with our surgical series. Zorman et al. recently proposed both the Elderly Glioblastoma Surgical Score (EGSS) and the Elderly Glioblastoma Oncological Score (EGOS). Both were proven to be capable to estimate the survival of elderly glioblastoma patients, considering age, WHO performance status, surgical intervention and chemoradiotherapy (23).

Limitations of this study are its retrospective character and the potential interrater variability in assessment of the functional scores. Like with most comparable studies, there is a risk of selection bias. Patients with initially higher KPS tend to be treated more aggressively, reflected by the lower KPS in the biopsy cohort also in our study. Additionally, in more eloquent lesions only STR may be possible and outcome with earlier neurologic decline with tumor progression may be inferior. Nevertheless, our data demonstrate a clear survival benefit with aggressive surgery.

TABLE 3 | Mean and median OS in different age groups receiving GTR and STR.

Age groups	GTR			STR		
	median OS (months)	mean OS (months)	CI 95%	median OS (months)	mean OS (months)	CI 95%
65-69	14.00	17.67	10.76 – 24.57			
70-74	5.00	9.46	5.95 – 12.97	4.00	8.20	.00 – 16.46
75-79	7.00	12.61	5.39 – 19.84	6.00	9.58	3.38 – 15.79
80-84	12.00	15.43	9.31 – 21.55	3.00	3.33	.49 – 6.18
≥ 85.	24.00	24.00	8.32 – 39.68		-	.
Total	7.00	13.80	10.46 – 17.15	9.00	8.30	4.05 – 12.55

No significant differences were present.

CONCLUSION

Elderly patients who received GTR of high-grade gliomas live significantly longer compared to patients who underwent biopsy or STR. Age per se seems to have no influence on overall survival in selected extensive operated patients, but good preoperative performance status is mandatory. Thus, we should strive for maximal tumor resection in patients of all ages with malignant glioma. Nonetheless, the process of decision making in patients with high grade brain tumors remains a complex, interdisciplinary process and must imply the individual patient`s expectations and needs.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the local ethics committee of the Medical University

Innsbruck (Protocol number: AN 1333/2021). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JuK: acquisition, analysis of data, interpretation of data and drafting the article. JuK: acquisition and interpretation of data. AK and DP: acquisition, analysis of data and drafting the article. CF and CT: design of the study and revisions. CF: conception/design of the study and interpretation of data. All authors have approved the submitted version and have agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, have been appropriately investigated, resolved, and the resolution documented in the literature.

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frontiers | Frontiers in Oncology

ORIGINAL RESEARCH
published: 07 June 2022
doi: 10.3389/fonc.2022.902928

Multidisciplinary Approach to Patients With Metastatic Spinal Cord Compression: A Diagnostic Therapeutic Algorithm to Improve the Neurological Outcome

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Reviewed by:
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Specialty section:
This article was submitted to Neuro-Oncology and Neurosurgical Oncology, a section of the journal Frontiers in Oncology

Received: *23 March 2022*
Accepted: *16 May 2022*
Published: *07 June 2022*

Citation:
Rispoli R, Reverberi C, Targato G, D'Agostini S, Fasola G, Trovò M, Calci M, Fanin R and Cappelletto B (2022) Multidisciplinary Approach to Patients With Metastatic Spinal Cord Compression: A Diagnostic Therapeutic Algorithm to Improve the Neurological Outcome. Front. Oncol. 12:902928. doi: 10.3389/fonc.2022.902928

Introduction: The morbidity associated with metastatic spinal disease is significant because of spinal cord and/or nerve root compression. The purpose of this paper is to define a diagnostic-therapeutic path for patients with vertebral metastases and from this path to build an algorithm to reduce the devastating consequences of spinal cord compression.

Materials and Methods: The algorithm is born from the experience of a primary care center. A spine surgeon, an emergency room (ER) physician, a neuroradiologist, a radiation oncologist, and an oncologist form the multidisciplinary team. The ER physician or the oncologist intercept the patient with symptoms and signs of a metastatic spinal cord compression. Once the suspicion is confirmed, the following steps of the flow-chart must be triggered. The spine surgeon takes charge of the patient and, on the base of the anamnestic data and neurological examination, defines the appropriate timing for magnetic resonance imaging (MRI) in collaboration with the neuroradiologist. From the MRI outcome, the spine surgeon and the radiation oncologist consult each other to define further therapeutic alternatives. If indicated, surgical treatment should precede radiation therapy. The oncologist gets involved after surgery for systemic therapy.

Results: In 2021, the Spine and Spinal Cord Surgery department evaluated 257 patients with vertebral metastasis. Fifty-three patients presented with actual or incipient spinal cord compression. Among these, 27 were admitted due to rapid progression of symptoms, neurological deficits and/or spine instability signs. The level was thoracic in 21 cases, lumbar in 4 cases, cervical in 1 case, sacral in 1 case. Fifteen were operated on, 10 of these programmed and 5 in emergency.

Discussion: Patients with a history of malignancy can present to the ER or to the oncology department with symptoms that must be correctly framed in the context of a

metastatic involvement. Even when there is no previous cancer history, the patient's pain characteristics and clinical signs must be interpreted to yield the correct diagnosis of vertebral metastasis with incipient or current spinal cord compression. The awareness of the alert symptoms and the application of an integrated paradigm consent to frame the patients with spinal cord compression, obtaining the benefits of a homogeneous step-by-step diagnostic and therapeutic path. Early surgical or radiation therapy treatment gives the best hope for preventing the worsening, or even improving, the deficits.

Conclusions: Metastatic spinal cord compression can cause neurological deficits compromising quality of life. Treatment strategies should be planned comprehensively. A multidisciplinary approach and the application of the proposed algorithm is of paramount importance to optimize the outcomes of these patients.

Keywords: spinal metastasis, spinal cord compression, pathological spine fractures, diagnostic-therapeutic algorithm, neurological deficits

INTRODUCTION

About 60% of secondary tumor localizations involves the spinal column (1). This is commonly believed to result from the large vascular supply and lymphatic drainage of vertebral bones (2). The progresses of chemo and radiation therapy treatments improved the survival of oncological patients and led to an increase of the number of patients with vertebral metastases (3, 4). Currently, spinal metastases are identified in approximately 20% of all oncological patients (5) and, among them, symptomatic spinal cord compression occurs in 25-50% (6–9). Cancers of the lung, breast, and prostate metastasize more frequently to the spine with a percentage that exceeds 60%; in about 7% of cases the primary tumor remains unknown (10).

Spinal cord compression occurs in 80% of patients with a known history of cancer and in the remaining 20% of cases, is the first manifestation of the tumor. These synchronous presentations are seen most frequently in lung cancer, but also in hematological malignances, like multiple myeloma and non-Hodgkin lymphomas, and require histological confirmation to plan the best therapeutic strategy (2, 9). Spine metastases with related neurological impairment are more often localized in the thoracic tract (11). The morbidity associated with metastatic spinal disease is significant. Subsequent mechanical instability and/or spinal cord or roots compression lead to paralysis, sensorial deficits and sphincter dysfunctions that impact on the quality of life and increase mortality.

Treatment of spinal metastases requires a multidisciplinary approach that integrates the knowledge of a team of specialists for prompt diagnosis of patients with spinal metastases and cord compression and optimal support after diagnosis. The purpose of this paper is to build an algorithm with the aim of reducing and preventing the irreversible neurological deficits and the devastating consequences of spinal cord compression.

MATERIALS AND METHODS

The institution where the algorithm was built is a primary care center. A team of specialists, emergency room (ER) physician, spine surgeon, neuroradiologist, radiation oncologist, and oncologist, got together and agreed on the crucial points and steps to follow.

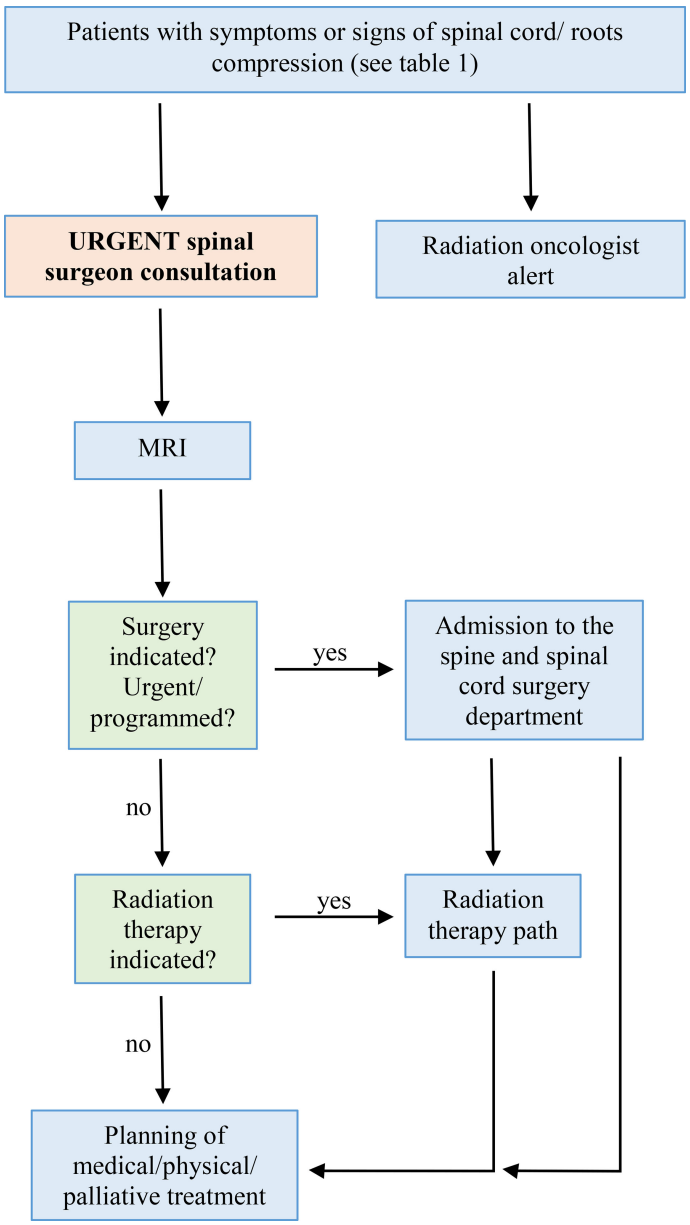
The ER physician or the oncologist has the assignment to recognize the symptoms and signs of a metastatic spinal cord compression and has to trigger the next steps of the flow-chart. The alert symptoms are neck or back nocturnal pain, axial mechanical pain (induced or worsened by movements and under pressure relieved by lying down), sudden onset of axial pain, radicular pain radiating to arms or legs associated or not with numbness, tingling, dysesthesia, walking or balance difficulties or arms/hands weakness for impairment of one or more muscles, bladder or bowel control disorders, urinary retention (**Table 1**). These clinical manifestations induce the team's physicians to follow the next step of the algorithm. If the symptoms are consistent with spinal cord compression, The spine surgeon takes charge of the patient, defines the neurological deficits and the appropriate timing for magnetic resonance imaging (MRI) in collaboration with the neuroradiologist. From the MRI outcome, the spine surgeon and the radiation oncologist consult each other to define further therapeutic alternatives. If indicated, surgical treatment should precede radiation therapy. The oncologist gets involved after surgery for systemic therapy. The proposed algorithm is illustrated in **Table 2**.

The muscular strength is graded with the manual muscle testing (MMT) scale from 5 (normal) to 0 (no visible movement

TABLE 1 | Summary of the alert symptoms for metastatic roots or spinal cord compression (MSCC) and progression of metastatic spine disease.

- neck or back nocturnal pain
- axial mechanical pain (induced or worsened by movements and under pressure relieved by lying down)
- sudden onset of axial pain
- radicular pain radiating to arms or legs associated or not with numbness, tingling, dysesthesia
- walking or balance difficulties or arms/hands weakness for impairment of one or more muscles
- bladder or bowel control disorders, urinary retention

TABLE 2 | Diagnostic-therapeutic algorithm for patients with metastatic roots or spinal cord compression (MSCC).



MRI, magnetic resonance imaging.

or palpable muscle contraction) (12). The Frankel grading system is used to summarize the functional grade of the patients (13). The neurological exam is completed with the sensory function and sphincter function evaluation.

RESULTS

In 2021, the Spine and Spinal Cord Surgery department evaluated 257 patients with vertebral metastasis. Fifty-three patients presented with actual or incipient spinal cord compression. Among these, 27 were admitted due to rapid progression of the symptoms, neurological deficits and/or spine instability signs; 14 were male and 13 female, mean age was 68.2 years. Breast (5 cases) and lung (4 cases) were the most frequent primitive cancer, followed by mesenchymal (3 cases), prostate (2 cases), kidney (2 cases), urothelial (2 cases), gastrointestinal (2 cases), hematologic (2 cases), neuroendocrine (1 case); in 4 cases the primitive was unknown. The level was thoracic in 21 cases, lumbar in 4 cases, cervical in 1 case, sacral in 1 case. Frankel grade at admission was A in 3 patients, B in 6 patients, C in 7 patients, D in 8 patients, and E in 3 patients.

Fifteen were operated on, 10 of these programmed and 5 in emergency.

The stratification and the characteristics of the patients are summarized in **Table 3** and in **Table 4**.

TABLE 3 | Stratification of patients with vertebral metastases who were evaluated at the Spine and Spinal Cord Surgery department in the year 2021.

Number of patients evaluated with vertebral metastasis	Patients with actual or incipient spinal cord compression	Patients admitted with spine metastasis and neurological compression	Patients operated on for spine metastasis (total)	Patients operated on in emergency (<72h)
257	53	27	15	5

TABLE 4 | Characteristics of the patients with spine metastasis and neurological compression admitted (n = 27) to the Spine and Spinal Cord Surgery department in the year 2021.

Gender distribution	Mean age	Primitive cancer of the patients admitted to the hospital	Level of the compression	Frankel grade at admission
14 males 13 females	68.2 years	5 breast, 4 lung, 3 mesenchymal, 2 prostate, 2 kidney, 2 urothelial, 2 gastrointestinal, 2 hematologic, 1 neuroendocrine 4 unknown	21 thoracic 4 lumbar 1 cervical 1 sacral	3 A 6 B 7 C 8 D 3 E

DISCUSSION

Metastases to the spine may be asymptomatic. Alternatively, patients with unknown metastatic disease could have nonspecific symptoms, including back pain. Due to the extraordinarily high frequency of back pain in middle age from a variety of root causes (14), the metastatic origin of the pain may be underestimated.

In the literature there are numerous algorithms on the treatment of spinal metastases but there are no formal protocols on how to prevent spinal cord compression. Communication and sharing information, as a means to establishing a multidisciplinary approach for the management of spine metastases in hospitals, is crucial.

Alert Symptoms: Pain

The definition of alert symptoms is fundamental and is the first tool to identify patients at risk or with spinal cord compression. From 80 to 95% of patients with spinal metastases report spine pain as their first symptom (15). Pain can occur in different forms: localized, mechanical and radicular. Localized pain is related to periosteal inflammation, mechanical pain is suggestive of impending or established spinal instability, radicular pain may develop from nerve root compression by the tumoral tissue or secondary to vertebral collapse (16, 17). Localized spine pain is usually constant throughout the day, exacerbating at night or early morning, typically with posture changes, coughing or sneezing and lying flat (18). Sudden axial pain evokes a pathological fracture. Furthermore, the cancer pain could radiate through radicular districts. Patients with spine metastases can refer midscapular pain, band-like pain across the chest or hip pain, depending on the cervical, thoracic or lumbar localization of the metastases (18). Patients with a known diagnosis of neoplasm must be studied as soon as possible with whole spine MRI, with the hope of uncovering the metastases before compression occurs. Likewise, patients in apparent good health who show recent back pain must be examined as soon as possible (19). The first four parameters of the alert symptoms deal with pain that must be promptly recognized and framed (**Table 1**).

Alert Symptoms: Neurological Deficits

Cord and root compression is characterized by motor, sensory and sphincter disorders (17, 18). Weakness and awkwardness in the movement of the limbs are the first signs of motor disturbance; dysesthesia and paresthesia indicate an initial sensory disturbance. Neurological symptoms and signs sometimes develop late, and they commonly call for urgent surgical treatment in order to preserve or improve the residual neurological functions (20–22). The last two parameters of the alert symptoms deal with the neurological deficits that must be properly evaluated (**Table 1**).

Diagnosis: MRI

Once framed correctly, on the base of the alert symptoms, the patient is evaluated by the spinal surgeon who decides the timing of performing the MRI which is superior to all other imaging modalities in its uncovering of spinal metastases. MRI provides essential information about spinal cord and nerve root compression.

The study protocol requires the MRI exam of the whole spine. The MRI determines the extent of the disease both in terms of a single vertebra and in terms of the number of vertebrae involved. The exam is able to show the compression or infiltration of the spinal cord and nerve roots. It is essential to carry out sagittal T1 and T2 weighted MRI sequences of the whole spine and axial T2-weighted sequences of the affected spinal levels. Spinal metastases are usually hypointense on T1 sequences; they can be hypo- or hyper-intense on T2 MRI sequences depending on their blastic or lytic characteristics, respectively. A fat suppression sequences such as T2-weighted short-tau inversion recovery (STIR) is useful to better define the metastatic lesions (23). Diffusion-weighted sequences can also be used to enhance the diagnostic accuracy in particular for the differential diagnosis with other alterations of the vertebral signal, often present and concomitant in the cancer patient (osteoporosis, bone marrow reconversion) (24). Contrast enhancement is not required to demonstrate spinal bone metastasis, but it can be useful if spinal cord localization or leptomeningeal metastatic infiltration is suspected (24, 25).

Algorithms for Patient Management

Several guidelines for spine metastases recommend that clinicians pay great attention to the early signs of metastatic spinal cord compression and advise an early diagnosis through the execution of the MRI examination of the whole spine (26). Some studies have demonstrated that specific systems developed for earlier diagnosis and treatment can decrease treatment delays, which is in turn associated with improved neurological outcomes of patients. Some authors report that delayed treatment leads to a worse surgical and post-operative outcome (surgical timing, blood loss, length of stay and postoperative adverse events) with a negative influence on the patient's quality of life (27, 28). Allan et al. proposed a system to detect early symptoms of spine metastases through a telephone interview with cancer patients performed in order to define the most appropriate timing for an MRI examination. This process reduced the timing of the diagnosis, improved outcomes and the appropriateness of the MRIs (29). Savage et al. reported that the formalization of a system for providing fast access to MRI derived from the collaboration between specialists can improve outcomes, agreeing with the National Institute for Health and Care Excellence (NICE) guidance (30). Nakata et al. established a multidisciplinary approach with the aim of providing an urgent MRI and referral to the spine surgeon in order to reduce or avoid neurological deficits caused by metastatic spinal cord compression (31). In our algorithm, if the symptoms are consistent with spine metastases, the spine surgeon defines the appropriate timing for MRI in collaboration with the neuroradiologist. The awareness of the alert symptoms and the application of an integrated paradigm create a rapid, essential portrait of patients with spinal cord compression. Compared to other systems, ours benefits from both a homogeneous step-by-step diagnostic (early whole spine MRI) and therapeutic (early surgery or radiation therapy) path.

Guidelines Treatment

The spine is a complex system from an anatomical, biomechanical, neurological point of view; for this reason, the treatment of spinal metastases is more challenging than that of other bones. There are no homogeneously applied guidelines for spinal metastases but there is the unanimous opinion that this disease must be treated simultaneously by several specialists (32).

Before planning a treatment, the patient's performance status, the cancer type, the systemic burden of disease and availability of effective systemic treatment options must be considered. The possible benefits to be accrued from any treatment should be carefully weighed against the morbidity and risks involved. The Spine Oncology Consortium (SOC) has divided the treatment options for spinal metastasis into three categories – radiotherapy, surgery and neurointerventional procedures – that can be applied simultaneously, consequentially and/or individually (22). Frameworks for decision making in regard to spine metastases management such as the neurological, oncological, mechanical and systemic (NOMS) and the location, mechanical instability, neurology, oncology and patient's factors (LMNOP) have been developed (18, 33). LMNOP is the most used algorithm to determine a therapeutic strategy (34). The Spine Oncology Study Group developed the Spinal Instability Neoplastic Score (SINS) to determine the degree of instability associated with a spinal metastasis. With this system, specialists and non-specialists can directly judge the spine instability (35, 36). In general, invasive locoregional treatments may be preferentially considered in patients with better prognosis. In patients with poor performance status (≤40%) and with less than two months of life expectancy, the multidisciplinary team should preferentially consider best supportive care (22). Since there is no consensus to specify what life expectancy justifies a surgical intervention, the NOMS working group reported that the surgical option should not be excluded *a priori* in patients with low life expectancy but should be the object of a multidisciplinary discussion. This discussion should address the likelihood of the patient recovering from surgery and thereby continuing systemic anticancer treatment (21).

In addition to the tumor burden, the histology and biology of a tumor is a strong prognostic element and is also important in guiding the choice of treatment to be pursued. According to literature, some tumors (Hodgkin and non-Hodgkin lymphomas, germ-cell neoplasm, myelomas, neuroblastoma, prostate and breast cancer) present high chemo and/or radiosensitivity. For these cancer types, a medical and/or a radiation treatment might be preferred over surgery (21, 22). On the contrary, other tumors (non-small cell lung cancer, colon carcinoma and carcinoma of unknown primary origin) showed radio-resistance and, in some series, short survival outcomes after spine surgery and thus the benefit from extensive intervention is less marked (37).

Radiation Therapy

Symptomatic patients with documented metastatic spinal cord compression not suitable for surgery, must be urgently referred to the radiation oncologist in order to be treated with radiotherapy (38). The optimal timing of treatment delivery from the onset of symptoms is within 24-72 hours. According to the speed of onset, duration, severity of neurological symptoms, patient's performance status and prognosis, radiotherapy can be offered as definitive treatment. It could be fractionated, generally 20 Gray (Gy) in 5 fractions and 30 Gy in 10 fractions, or a single fraction of 8 Gy. No differences in clinical outcome, defined as motor function improvement, were described. Nevertheless, the long-term outcomes showed better local controlled disease in patients who received a longer radiotherapy course (39). A preliminary report from the single-fraction radiotherapy compared to multifraction radiotherapy (SCORAD) randomized phase III trial recommend the use of single fraction over 5 fractions in patients with short-term prognosis (median survival 3 months) (40). Several studies demonstrated that urgent radiotherapy delivered as 8 Gy single fraction is generally the best therapeutic regimen for symptoms palliation, even when the patient is completely paralyzed. Moreover, further radiotherapy can be considered for patients who reacted well to previous treatment. The NICE guidelines suggest fractionated radiotherapy should be considered for patients having good

prognosis (38). Patients with complete neurologic deficit for more than 72 hours or poor prognosis are not candidates for urgent radiotherapy. Pre-operative radiotherapy is not a standard of care, whereas post-operative radiotherapy can be offered to patients having a good surgical outcome. Fractionated radiotherapy can be offered in the adjuvant setting, once the surgical scar is completely recovered. The most common radiotherapy schedule is 30 Gy in 10 fractions.

Surgery and radiotherapy are the cornerstones of metastatic spinal cord compression treatment. Whether to prefer one to the other approach is a complex decision, requiring a multidisciplinary approach. The decision-making process takes into account patients' prognosis, performance status and comorbidity, grade of neurological functions and spine instability. Patchell et al. (41) reported that a larger percentage of patients treated with surgery and adjuvant radiotherapy had better outcome and remained ambulatory (84% vs 57%, p = 0.001) compared to the patients treated with radiotherapy alone.

Surgery

Surgery aims to decompress of the neural structures, to locally remove the tumor (separation surgery), and to afford the stability of the spine (42). Some authors recommend surgery only if the patient has a life expectancy longer than 3 months. Although some minimally invasive procedures to decompress and stabilize the spine can be offered to the patients with severe root pain or axial pain due to instability, independently from other variables (34, 42). According to many authors, minimally invasive surgery should be considered the first-choice treatment in patients with metastatic spinal compression. It has many advantages, such as shortening the surgical time, reducing the trauma of soft tissues and blood losses, consenting early mobilization, shortening the length of stay in hospital and good pain control. All these factors favor a greater speed in starting the adjuvant treatment, providing the patient with a greater therapeutic possibility (43–45). Laminectomy without stabilization is no longer used because it can create iatrogenic instability (46). However, in selected cases of tumor involving only the posterior elements or epidural tumor without bone involvement, laminectomy is a reasonable surgical option. Separation surgery is a technique that has the objective to create a safe distance between the spinal cord/roots and the tumor that will be then treated with radiation therapy (47, 48). Spine stereotactic radiosurgery (SRS) is increasingly considered as a first-choice treatment when possible so that *en bloc* removal is less used in recent years. More innovative materials, like poly-ether-ether-ketone (PEEK) and carbon-fiber, are used in order to reconstruct the vertebral body and create fewer artifacts in radiological images to favor radiotherapy techniques (49, 50). Even more recently, CT guided three-dimensional printing of plastic polymers or titanium constructs, is being developed to create customized supports for patients (51).. Robot-assisted guidance and spine navigation provide greater precision and definition in tumor removal and placement of pedicle screws (52).

Medical, Physical, Palliative Treatment

The oncologist cares for the patient after the surgical or/and radiation therapy treatment and defines the subsequent follow-up and the appropriate systemic anticancer treatment, tailored on patient and cancer characteristics.

Lastly, rehabilitation, bracing and muscular strengthening can improve the patient's quality of life. Analgesia steroids, drugs for neuropathic pain and bisphosphonates can be used if necessary (52, 53).

CONCLUSIONS

Spine metastases cause serious morbidities, such as pathological fractures, spinal cord/root compression, and neurological deficits. Our hospital, a primary care center, has developed an algorithm that defines the parameters useful for avoiding metastatic spinal cord compression and improving the patients' outcome.

The expectation for 2022 is to verify the effectiveness of the methodology introduced in the integrated care pathway. We plan to identify and check the following key performance indicators (KPI):

1) Time elapsed between first consultation (emergency room) and the MRI
2) Time from MRI to start of treatment (surgery or radiation therapy)
3) Grade of neurological deficits (Frankel scale) at the time of their recognition and at follow-up.

The future objective is to statistically analyze and compare the parameters listed above among the two groups, i.e. patients of the year 2021, without the application of the algorithm, and patients of the year 2022, after application of the algorithm.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

Authors are responsible for the entire content of each article. Co-authorship should be based on the following four criteria: (1) substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; (2) drafting of the work or revising it critically for important intellectual content; (3) final approval of the version to be published; and (4) agreement to be accountable for all aspects of the work and ensuring

that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Each author must affirm that they participated in and contributed sufficiently to the work to take public responsibility for the following: (1) conception and design, (2) data acquisition, (3) analysis of data, (4) drafting of the manuscript, (5) critical revision, (6) obtaining funding, (7) administrative support, or (8) supervision.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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ORIGINAL RESEARCH
published: 16 June 2022
doi: 10.3389/fneur.2022.900377

The Routine Application of Tumor-Treating Fields in the Treatment of Glioblastoma WHO° IV

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Introduction: Tumor-treating fields (TTFs) are a specific local oncological treatment modality in glioblastoma multiforme WHO° IV (GBM). Their mechanism of action is based on the effect of electrical fields interfering with the mitotic activity of malignant cells. Prospective studies have demonstrated efficacy, but TTF benefits are still controversially discussed. This treatment was implemented in our center as the standard of care in January 2016. We thus discuss the current state of the art and our long-term experience in the routine application of TTF.

Methods: The data of 48 patients suffering from GBM and treated with TTF were assessed and compared with previously published studies. Up-to-date information from open sources was evaluated.

Results: A total of 31 males and 17 females harboring a GBM were treated with TTF, between January 2016 and August 2021, in our center. In 98% of cases, TTFs were started within 6 weeks after concomitant radiochemotherapy (Stupp protocol). Mean overall survival was 22.6 months (95% CI: 17.3–27.9). Current indications, benefits, and restrictions were evaluated. Future TTF opportunities and ongoing studies were reviewed.

Conclusion: TTFs are a feasible and routinely applicable specific oncological treatment option for glioblastoma multiforme WHO° IV. Further research is ongoing to extend the indications and the efficacy of TTF.

Keywords: glioblastoma, TTF = tumor-treating field, neurosurgery, neurooncology, combined treatment approach

OPEN ACCESS

Edited by:
Sara Grazia Maria Piccirillo, University of New Mexico Health Sciences Center, United States

Reviewed by:
Antonio Silvani, IRCCS Carlo Besta Neurological Institute Foundation, Italy
Ashley Ghiaseddin, University of Florida, United States

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Specialty section:
This article was submitted to Neuro-Oncology and Neurosurgical Oncology, a section of the journal Frontiers in Neurology

Received: *20 March 2022*
Accepted: *25 April 2022*
Published: *16 June 2022*

Citation:
Krigers A, Pinggera D, Demetz M, Kornberger L-M, Kerschbaumer J, Thomé C and Freyschlag CF (2022) The Routine Application of Tumor-Treating Fields in the Treatment of Glioblastoma WHO° IV. Front. Neurol. 13:900377. doi: 10.3389/fneur.2022.900377

INTRODUCTION

Glioma is the most frequent primary malignant tumor of the central nervous system (CNS) (1). High-grade glioma, especially glioblastoma multiforme WHO° IV (GBM), behaves aggressively with the corresponding unfavorable outcome and thus limited life expectancy (2). The established standardized treatment consists of a neurologically safe tumor resection (3–5), followed by adjuvant concomitant radiochemotherapy and six cycles of temozolomide (TMZ) monotherapy thereafter. This strategy is known as the Stupp protocol (6, 7). The disease, however, is considered incurable and there is a lack of efficient treatment options in the case of recurrent or progressive disease (8, 9).

Therefore, the demand for new approaches and targeted treatment options remains high. Although there is extensive research in this field, very few promising treatment options succeeded in the translation to clinical routine. One of them is the targeted application of tumor-treating fields (TTFs) (10). This method is based on the local effect of electric fields to interfere with the mitotic activity of the tumor. Proliferating cells are blocked in metaphase and anaphase as the formation of the mitotic spindle is disturbed, which results in slower cell replication or apoptosis (11–14).

TTFs are FDA- and EMA-approved for the treatment of adults with newly diagnosed GBM. In this case, TTFs are started within 6 weeks after the end of concomitant radiochemotherapy, ideally simultaneously with TMZ monotherapy (15, 16). Alternatively, TTF therapy can be an optional treatment in the case of recurrent GBM, overcoming the side effects of systemic second-line chemotherapeutics (17). Nevertheless, controversies considering TTF benefits are still conveyed (18).

Practically, four soft non-invasive adhesive electrode arrays are placed on the shaved head of the patient. The electric field is generated between the poles of the electrode arrays, which are supplied through a wire. The control device with pacemaker and the changeable accumulator is placed in a carry-on bag or backpack. Therapeutic success was seen when the device was worn for at least 18 h per day, with increasing benefits for every additional hour (15–17, 19). TTF therapy normally does not require an in-patient stay or additional oncological follow-ups. Technical assistance is provided by the service team of the manufacturer. Still, daily support by a person from the patient's household remains mandatory.

This kind of treatment in the case of GBM is incorporated in the international clinical guidelines (4, 20) and is implemented as a standard of care in our center since January 2016. During the following years, we gained practical know-how in TTF initiating, namely, informed consent, compliance, and follow-up. Thus, we aimed to discuss the current state of the art together with our long-term experience with the routine application of TTF. Moreover, we evaluated current indications, benefits, restrictions and also future TTF opportunities and ongoing studies.

MATERIALS AND METHODS

According to international guidelines (4, 20) and consequently internal standard operating procedures, all patients harboring a histologically proven new or recurrent glioblastoma WHO° IV since January 2016 were considered for TTF therapy. Neuropathological tumor assessment was performed in all cases according to the revised 4th WHO classification of CNS tumors (21). The TTF indication was individually confirmed by the multidisciplinary neuro-oncological tumor board. Regardless of TTF, elective clinical and MRI follow-ups were performed every 3 months, in which the general and neurological condition, compliance, potential side effects, and oncological status were checked. In the case of recurrent or progressive disease, the eligibility for TTF was discussed in the multidisciplinary neuro-oncological tumor board. If there were no beneficial options for oncological resection, targeted systemic, or radiotherapy, TTF could be offered in case of expected compliance. TTF therapy is accepted by the Austrian healthcare insurance and, after formal approval of the indication, treatment costs are covered.

We assessed all patients who received the entire neuro-oncological treatment (surgery, radiation therapy, and chemotherapy) from the TTF starting in January 2016 till August 2021 from the institutional database. Patients who received either one of recommended treatments in external institutions were excluded. Each case data, namely, epidemiological, clinical, neuropathological, and follow-up records, was collected in the institutional database. The evaluation of this information for the scientific purpose was approved by the ethics committee of the Medical University of Innsbruck (No.: 1402/2020). It was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

All available publications and open-source data considering TTF application in high-grade gliomas were gathered and evaluated.

RESULTS

A total of 48 patients harboring a GBM treated with TTF were evaluated. Surgical intervention was performed in all cases, whereas gross neurologically safe resection was performed in 44 (92%) and biopsy in 4 (8%) patients. Among the patients, which were treated with TTF in our center, 31 (65%) were men and 17 (35%) were women with a median age of 57 years (interquartile range (IqR): 44–62), whereas 18 (38%) patients were older than 60 years and one was 16. The isocitrate dehydrogenase (IDH) status was routinely evaluated in 38 cases: IDH was mutated in 9 (23%) and remained wild-type in 30 (67%) tumors. In 22 (60%) patients, O(6)-methylguanine-DNA methyltransferase (MGMT) promoter was methylated and in 15 (40%) it stayed unmethylated. The Karnofsky performance index before surgery amounted to 80–100. Epileptic seizures before the surgery were reported in 13 patients. During TTF treatment, epileptic seizures were found in 6 patients, whereas in 2 cases a patient had them before the surgery and in 4 cases epilepsy developed *de novo* after it. TTFs were administered for the recurrent GBM in a single case only.

If the eligible patient agreed with the initiation of TTF, the service team arranged an appointment, which was usually held in our outpatient department. During this meeting, the technical and everyday aspects were discussed, and the patient and the assistant were trained to operate the device. The service team is available for technical questions around the clock. It was essential, that a person from the patient's household was ready to help in daily activities considering device management. As it is crucial, that the system is active for at least 75% of the time, the automatically generated compliance reports were sent to our center monthly. At the same time, no report concerning the interaction between a patient and the service team was usually available. Of course, any unplanned or urgent visit to our center remained possible.

The daily support was mostly provided by a partner (15/25, 60%), children (5/25, 20%), parents (3/25, 12%), siblings (1/25, 4%), or friends (1/25, 4%). No defined assistant was specified by 23 patients.

No TTF-associated serious adverse effects were reported during the median follow-up of 17 months (IqR: 11–23). No interruption of follow-ups or technical service, hence, TTF application, was noticed due to the COVID-19 pandemic, the associated lock-down, or due to limited access to healthcare facilities.

Mean overall survival inside our cohort according to Kaplan–Meier assessment was 22.6 months (95% CI: 17.3–27.9). IDH-status did not predict OS among patients with TTF therapy, which remained 25.7 months (95% CI: 14.0–37.4) in case of IDH mutation or 20.8 months (95% CI: 15.6–26.1) in case of IDH wild-type tumor, LogRank $p = 0.549$. At the same time, OS was significantly more favorable in the case of methylated MGMT promoter: 29.7 months (95% CI: 22.4–37.0) vs. 16.7 months (95% CI: 11.4–22.0), LogRank $p = 0.002$.

DISCUSSION

Current Status

Tumor-treating fields are an established option in case of recurrent or newly diagnosed GBM. Their practical and routine application is feasible, nevertheless, some points require attention.

In the PubMed database, 274 results were associated with the term "Tumor-Treating Fields," showing a strong rise in recent years: 15 papers were published in 2015, 39 papers in 2019, and already 57 in 2021. Nevertheless, more than 80% of them are reviews, preclinical studies or are attributed to non-CNS tumors. Thus, even if TTF as a specific oncological option is widely discussed, the translational and applied experience remains limited.

Tumor-treating fields are the first treatment option in many years, that has shown successful results in GBM therapy (10). It is labeled as the fourth modality in cancer therapy among surgery, systemic pharmacological, and radiation therapy (22).

The EF-11 study from 2012 was performed on 237 patients (1:1 randomization). Even if it did not demonstrate the superiority of TTF compared to the local standard of care in the case of recurrent GBM, the safety and routine feasibility of TTF were proven (17). The pivotal EF-14 trial on 695 patients (2:1 randomization), which was published in 2015 and consistently actualized in 2017, showed a statistically significant overall survival benefit of 4.9 months for patients harboring newly diagnosed GBM. Moreover, 2- and 5-year survival was significantly more favorable in the TTF group compared to the control arm as well – 43 vs. 31% ($p < 0.001$) and 13 vs. 5% ($p = 0.004$), respectively (15, 16, 23). According to both studies, the TTF was approved for newly diagnosed and recurrent GBM by FDA and EMA and consequently included in the guidelines (4, 20). Our survival data are concordant to EF-14 published material with comparable overall survival of 22.6 vs. 20.9 months, whereas selection bias in the case of clinical routine could play a role. According to our data, MGMT promoter methylation provides significant additional survival benefits even within the TTF cohort.

In our center, TTF was only applied to a single patient with recurrent GBM. It is known that a prolonged period of time is necessary until TTF effects can be observed (24). In the case of recurrent GBM, the length of therapy remains short and usually consists only of several months, as was shown in the EF-11 and PriDE studies (17, 25).

There are practical advantages of TTF compared to other specific oncological treatment modalities with the noninvasiveness being a key point. Moreover, during hygienic procedures, sports, and MRI the device can be put off. More than one-third of the patient in our cohort were older than 60 years. The feasibility and safety of an elderly population were also shown in the subgroup analysis of the EF-14 study (26). Hence, TTFs are also feasible in the case of an aged population, even when the full dose of radiochemotherapy is not suggested. Another point is that TTF localized treatment allows it to be considered in settings where conventional cytotoxic chemotherapy may be contraindicated due to systemic complications and/or adverse events.

No clinically relevant TTF interaction with the radiotherapy field was found (27). Moreover, TTFs delay DNA damage repair following conventional photon-beam radiotherapy (28) and work as a sensitizer for proton-beam therapy (29). According to the literature, dexamethasone administration does also not interfere with TTF (30).

There were concerns that the COVID-19 pandemic could interfere with the TTF support (31). In our center, however, no interruption of the TTF service and follow-ups were observed.

Even if TTFs are permitted by FDA and EMA, their limitations and potential drawbacks remain intensely discussed. The approval EF-11 and EF-14 studies were open-labeled, thus, providing potential bias. On the other hand, there was no technical possibility to randomize by imitation of the working device, as the arrays cause a superficial warmth sensation. Another potential drawback is the lack of industry-independent validation trials, which, however, is the case for most (pharmaceutical) oncological treatment studies as well. In addition, EF-11 was criticized due to the heterogeneous previous treatment and control population.

We did not observe any severe adverse effects in the routine application of the TTF system. Only skin irritation was reported as a device-related side effect in the EF-11 and EF-14 studies. In 2% of cases, severe local skin damage was described. In the EF-14 trial for newly diagnosed GBM patients, where the treatment exposure was longer than that for recurrent disease, grades 1 and 2 skin reactions were reported in 43% of patients. Similar data were shown during a phase 4 study with 11.000 patients (32). Therefore, sensitivity to the conductive hydrogel, which is used as an adhesive agent for the electrodes, is mentioned as a limitation for starting the therapy. Recently, the prediction algorithm for skin irritation probability was presented. According to it, the variation of array positioning reduced the risk of skin irritation by about one-third (33). Moreover, practical suggestions for dermatological symptomatic treatment have been distributed (34).

TABLE 1 | Applied advances and limitations of TTF therapy nowadays.

Advances	Limitations
A novel effective therapy option for GBM	Translational experience is limited
Approval in guidelines	Criticism of pivotal trials
Non-invasiveness	Requires skin preparation and shaving
Possible in aged / frailty patients	Several implants remain contraindication
TTF acceptance is good	Device requires extra bag
High quality of life	Active use at least 18 h a day
MGMT promoter status remains relevant	Support from family remains important
Skin irritation is rarely severe	Skin irritation comes in 2% of cases
Costs are covered in some	High device expenses
EU countries	
Possible sensitizer for radiotherapy	
Does not interfere with dexamethasone	

We have mentioned that the daily help in routine maintenance of the device from the side of relatives or another assisting person is needed. Every 3-day shaving, application of adhesive electrodes, technical device management, and even contact with the service team is time-consuming. The favorable effect of TTF is magnified if the device is active for more than 18 h per day based on the *post-hoc* subgroup analysis of the EF-14 trial. Moreover, the survival benefit rises with each added hour (19). Thus, even if a patient showed a high-performance index like KPI 80–100 as in our series, external support remains essential. On the other hand, even if the daily life of patients might be affected by the TTF, two-thirds of them would decide in favor of the treatment (35). The quality of life and TTF acceptance remained high (36, 37). Moreover, the technical upgrade of the device like reduced weight and higher accumulator capacity solved some problems (38).

Another point is the limited data in the case of an implanted CSF shunt or pacemaker that can potentially interfere with TTF. Nevertheless, case reports and a retrospective study demonstrated a high likelihood of to use of TTF devices even in these patients (39, 40), but larger trials would be necessary.

The cost-effectiveness was discussed, as monthly costs of about 20.000*e* are to be considered (35, 41, 42) and the high price was thought to limit the access to this treatment option (41). Nevertheless, the insurances in the United States and several European countries do cover the routine application of TTF, preventing costs for patients.

Thus, the TTF therapy is nowadays advisable for all patients harboring GBM, including frailty ones, when demanding high-dose radiochemotherapy could not be applied. The efficacy of dexamethasone or radiotherapy is not negatively interfered with. Nevertheless, the external support from relatives and compliance stays crucial. There are also other restrictions like cranial or active implants. Skin irritation does not look to be an inevitable restriction. The summary of positive and negative points considering the TTF application is provided in **Table 1**.

Future Clinical Opportunities

Research regarding further applications of TTF is ongoing. The TRIDENT (EF-32, NCT04471844) study was recently initiated to demonstrate the potential benefits of TTF starting parallel to concomitant radiochemotherapy in the case of newly diagnosed GBM. The feasibility and safety were checked on 10 patients during a phase 1 study (43). The results of an analogous 1:1 randomized phase 2 study (NCT03869242) on 60 patients with an estimated completion date is December 2021 have not been published yet.

The combined treatment option of TTF and bevacizumab (BEV) in the case of recurrent GBM was suggested already in 2014 (44). Nevertheless, the study evaluating concomitant TTF with BEV and hypofractionated stereotactic radiotherapy was abandoned due to poor recruiting in 2019 (NCT01925573). On the other hand, there are reports that BEV with concomitant TTF is applied in an off-label fashion. In one retrospective study, all 48 patients received BEV as monotherapy or in combination with other systemic chemotherapeutics concomitant to TTF. However, due to the lack of a control arm, which would include BEV cases without TTF therapy, no conclusion regarding a potential co-influence of TTF and BEV is possible (45).

According to the guidelines, the treatment strategy in the case of anaplastic glioma is often similar to glioblastoma (4, 20). Nevertheless, the data considering TTF application for anaplastic glioma are limited. Due to the high clinical demand, a respective study is currently ongoing (46).

No sufficient data are available for pediatric cases. According to a case series of 4 patients under 16 (2 of them with GBM) 53–92% compliance without severe adverse effects was described (47). In another publication, the partial response was shown in 5 pediatric high-grade glioma cases (48). Large trials on a pediatric population are ongoing (49).

There is a single spinal glioma case, in which TTF was applied for primary thoracolumbar anaplastic astrocytoma. After decompression surgery and adjuvant chemoradiotherapy, one adhesive array was placed above the tumor projection on the back and another below it. According to the virtual modeling, this way of application provided sufficient TTF power density at the target site (50).

An enhancing effect of TTF after skull remodeling surgery was described. For superficial tumors, removal of a standard craniotomy bone flap increased the electrical field strength by up to 70% (51). A phase 1 safety study on 15 patients with recurrent GBM confirmed the safety of this approach (52) and a phase 2 study was announced (53).

The exact molecular pathways of the TTF effect remain unclear (54). Multiple studies here are ongoing. On the other hand, there is encouraging preclinical data considering increased synergistic efficacy of checkpoint inhibitor anti-PD-1 therapy when combined with TTF. It was demonstrated that the volume of two tumor models declined and the number of cancer-infiltration immune cells raised when TTF was added to the anti-PD-1 therapy (55). Similar results were shown in another study of non-small cell lung cancer (NSCLC), where the concomitant TTF and checkpoint inhibitor treatment led to a decrease in the tumor volume (56).

Tumor-treating field (TTF) application is being investigated also for other solid cancers: the LUNAR trial for lung cancer, HEPANOVA for hepatocellular cancer, INNOVATE-3 for ovarian cancer, PANOVA-3 for pancreatic cancer, and METIS for brain metastasis (57). According to the results of

the STELLAR study, a specific device modification is approved by FDA for adult patients harboring unresectable, advanced, and malignant pleural mesothelioma together with standard chemotherapy (58).

CONCLUSION

Tumor-treating fields are a feasible and routinely applicable specific oncological treatment option in the case of glioblastoma multiforme WHO° IV. As TTF provides additional overall survival, this option should be presented and advised to all GBM patients. Nevertheless, practical restrictions stay relevant, which limit the usage of this modality like insufficient external assistance. Additional work is necessary and is intensely ongoing to extend the indications and the efficacy of TTF and to reduce restrictions.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of the Medical University of Innsbruck. Written informed consent from the patients/participants or patients/participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

AK: acquisition, analysis of data, interpretation of data, and drafting the article. JK, DP, MD, and L-MK: acquisition and interpretation of data. CFF and CT: design of the study and revisions. CFF: conception/design of the study and interpretation of data. All authors have approved the submitted version and have agreed with both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, have been appropriately investigated, resolved, and the resolution documented in the literature.

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Conflict of Interest: CFF declares he is participating in a speaker bureau and an advisory board of Novocure.

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frontiers | Frontiers in Neurology

SYSTEMATIC REVIEW
published: 23 June 2022
doi: 10.3389/fneur.2022.884158

Carmustine Wafers Implantation in Patients With Newly Diagnosed High Grade Glioma: Is It Still an Option?

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Background: The implantation protocol for Carmustine Wafers (CWs) in high grade glioma (HGG) was developed to offer a bridge between surgical resection and adjuvant treatments, such as radio- and chemotherapy. In the last years, however, a widespread use of CWs has been limited due to uncertainties regarding efficacy, in addition to increased risk of infection and elevated costs of treatment.

Objective: The aims of our study were to investigate the epidemiology of patients that underwent surgery for HGG with CW implantation, in addition to the assessment of related complications, long-term overall survival (*OS*), and associated prognostic factors.

Methods: Three different medical databases were screened for conducting a systematic review of the literature, according to the PRISMA statement guidelines, evaluating the role of BCNU wafer implantation in patients with newly diagnosed HGG. The search query was based on a combination of medical subject headings (MeSH): "high grade glioma" [MeSH] AND "Carmustine" [MeSH] and free text terms: "surgery" OR "BCNU wafer" OR "Gliadel" OR "systemic treatment options" OR "overall survival."

Results: The analysis of the meta-data demonstrated that there was a significant advantage in using CWs in newly diagnosed GBM in terms of *OS*, and a very low heterogeneity among the included studies [mean difference 2.64 (95% *CI* 0.85, 4.44); $p = 0.004$; I2149 = 0%]. Conversely, no significant difference between the two treatment groups in terms of PFS wad detected ($p = 0.55$). The analysis of complications showed a relatively higher rate in Carmustine implanted patients, although this difference was not significant ($p = 0.53$).

Conclusions: This meta-analysis seems to suggest that CWs implantation plays a significant role in improving the *OS*, when used in patients with newly diagnosed HGG. To minimize the risk of side effects, however, a carful patient selection based mainly on patient age and tumor volume should be desirable.

Keywords: glioma surgery, Carmustine, extent of resection, overall survival, complications

OPEN ACCESS

Edited by:
Alireza Mansouri, The Pennsylvania State University (PSU), United States

Reviewed by:
Francesco DiMeco, IRCCS Carlo Besta Neurological Institute Foundation, Italy
Francesco Acerbi, IRCCS Carlo Besta Neurological Institute Foundation, Italy

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Specialty section:
This article was submitted to Neuro-Oncology and Neurosurgical Oncology, a section of the journal Frontiers in Neurology

Received: *25 February 2022*
Accepted: *17 May 2022*
Published: *23 June 2022*

Citation:
Ricciardi L, Manini I, Cesselli D, Trungu S, Piazza A, Mangraviti A, Miscusi M, Raco A and Ius T (2022) Carmustine Wafers Implantation in Patients With Newly Diagnosed High Grade Glioma: Is It Still an Option? Front. Neurol. 13:884158. doi: 10.3389/fneur.2022.884158

INTRODUCTION

Therapeutic, surgical, and genetic refinements have evolved in these past decades, however, High Grade Glioma (HGG) still remains to be the highest-grade malignant primary tumor of the central nervous system with an extremely poor prognosis, especially in patients with grade WHO IV (1–3).

Despite extensive resection, HGG remains almost incurable because of its deep tumoral infiltration, which tends to promote HGG recurrence that generally occurs in the proximity of the original tumor site (4, 5). By virtue of the growing pattern, tumoral HGG cells can be found beyond the infiltrative tumor area intraoperatively detected by 5-ALA fluorescence, thus supporting the role of supramaximal resection, when functionally possible (6–8).

Carmustine wafers (CWs) marketed as Gliadel®, biodegradable copolymers discs impregnated with the alkylating agent (Bis-ChloroethylNitrosoUrea: BCNU), have been developed as a therapeutic bridge during the period between tumoral surgical resection and standard chemo-radiotherapy onset (Stupp regimen) (9–14). The use of CWs, however, represents a controversial topic among neurosurgeons mainly due to the lack of phase III studies in this field (5, 10, 15, 16). In addition, CWs use has been greatly limited for several reasons, including elevated costs, and the precluded enrolment of patients in subsequent clinical trials because the use of CW could give rise to confounding results (5, 11, 15–20).

Although this treatment option seems to have lost clinical importance in the recent few years, current long-term follow-up investigations have demonstrated a survival benefit in newly HGG treated with CWs implantation, shedding thus the light on the effectiveness of this option (21, 22).

The aim of this meta-analysis, which reports the intraoperative implantation of CWs in newly HGG patients, is to investigate its impact in terms of overall survival (*OS*) and progression-free survival (*PFS*) in comparison with standard surgical treatment without CWs. Side effect and complication data were also evaluated and discussed.

MATERIALS AND METHODS

Study Design

The present study is a systematic review of the literature, consistently conducted according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement guidelines.

Review Question

The review questions, according to the PRISMA statement, were formulated following the PICO (P: patients; I: intervention; C: comparison; O: outcomes) scheme, as it follows:

In newly diagnosed HGG (P), has the intraoperative implantation of CWs (I) revealed as effective when compared to the standard treatment (Stupp Regimen) (C), in terms of *OS* and *PFS* (O)?

Inclusion and Exclusion Criteria

The investigations were selected according to the following criteria: 96 English language, comparative study on CWs implantation in newly HGG patients, and adult study populations. Exclusion criteria included language other than English, non-comparative studies, and non-reported quantitative data for analysis.

Search Strategy

Four different medical databases (PubMed, Scopus, Cochrane Library, and Mendeley) were screened for conducting a systematic review of the literature, according to the PRISMA statement, evaluating the role CWs implantation in patients with newly diagnosed HGG.

The search query was based on a combination of medical subject headings (MeSH): "high grade glioma" [MeSH] AND "Carmustine wafer" [MeSH] and free text terms: "surgery" OR "Gliadel" OR "Gliadel" OR "glioblastoma" OR "systemic treatment options" OR "overall survival" OR "side effects."

Papers reporting incomplete or non-poolable data, such as means missing standard deviations or medians missing interquartile ranges, were excluded or included only for the follow-up periods during which the data were complete. The "Title" and "Abstract" of the papers were independently screened by two authors (A.P. and A.M.).

Duplicated papers were excluded from the screening. In the second review round, papers included for the Full text analysis were screened, and considered for inclusion according to the inclusion criteria. The references of papers considered were then screened for papers erroneously missed in the first round of review round (forward search). Papers not considered as eligible were excluded with reason. Any discordance in the screening process was solved by consensus with a third senior author (T.I.). Included papers were considered for data analysis and evidence synthesis.

Outcome Measurements

Title, list of authors, year and journal of publication were collected for every included paper. The following outcomes were extracted from the included papers:

- Overall survival: The OS time was defined as extending from surgery until patient death.
- Progression-free survival: The PFS time was defined as extending from surgery until the demonstration of gadolinium enhancement on follow-up imaging.
- Complications.

Statistical Analysis

Data of the study populations were summarized using proportion and weighed means. The means and standard deviations in individual studies were estimated from the median and interquartile ranges, when needed, according to the method described by Wan et al. (23). Pooled mean differences (PMD) for

Abbreviations: BCNU, Bis-ChloroethylNitrosoUrea; CWs, Carmustine Wafers; EOR, extent of resection; HGG, high grade glioma; HR, hazard ratio; GBM, glioblastoma; OS, overall survival; PFS, progression-free survival.

TABLE 1 | Studies excluded from the analysis.

First author, year of publication, journal	Reason for exclusion
Westphal et al., 2003, Neuro Oncol (9)	Recurrent glioblastoma multiforme
Attenello et al., 2008, Ann Surg Oncol (25)	Glioma grade III and IV were included
Salmaggi et al., 2013, Journal of Neurosurgery (12)	Not including standard treatment (surgery + chemo-/radio-therapy) group for comparison
Jungk et al., 2016, BMC Cancer (13)	Included recurrent glioblastoma cases only, Not including Carmustine Wafer treatment group for comparison
Della Puppa et al., 2017, J Neurooncol (14)	Not including NON-Carmustine Wafer treatment group for comparison
Champeaux et al., 2019, Journal of Neuro-Oncology (22)	Not including standard treatment (surgery + chemo-/radio-therapy) group for comparison
Ius et al., 2020, Cancer (2)	Not including Carmustine Wafer treatment group for comparison
Iuchi et al., 2022, *Neurooncol Adv* (21)	Not including NON-Carmustine Wafer treatment group for comparison

continuous variables were computed between outcome groups with a random effects model (24). Comprehensive meta-analysis software (Review Manager – RevMan 5.4.1 The Cochrane Collaboration, 2020) was used for pooling data. The *p*-value was considered significant at $\alpha < 0.05$.

RESULTS

Included Studies and Patients

A total of 130 Abstract were screened in the first review round, after duplicates removal, and 12 papers were considered for full-text analysis. After excluding with reason eight manuscripts (**Table 1**), four paper were included in the present meta-analysis (10, 11, 19, 20) (**Figure 1**, **Table 2**). From the included studies, 525 patients were included in the Carmustine wafer group (Experimental Group), and 753 in the standard protocol group (Control Group).

Overall Survival

Quantitative data on *OS* were reported for all of the included patients (10, 11, 19, 20). The analysis of the meta-data demonstrated that there was a significant advantage in using CWs in newly diagnosed GBM in terms of *OS*, and a very low heterogeneity among the included studies (mean difference 1,492.64 (95% *CI*: 0.85, 4.44); $p = 0.004$; $I^2 = 0\%$; **Figure 2**).

Progression Free Survival

The quantitative data on PFS were reported in three (10, 19, 20) out of the four included studies, which was based on a total of 171 patients in the Experimental group and 300 in the Control Group. The analysis of meta-data demonstrated that there were no significant differences between the two treatment groups in terms of PFS, even though a high heterogeneity must be considered mean difference [1.18 (95% *CI* −2.69, 5.04); $p = 0.55$; $I^2 = 87\%$; **Figure 3**].

Complications' Rate

The complication rate was reported in three (11, 15, 16) out of the four included studies. This rate was 25.73% in the CWs group and 18.33% in the non-CWs group. The analysis of complications showed a relatively higher rate in carmustine-implanted patients, although this difference was not significant ($p = 0.53$).

DISCUSSION

Despite extensive resection, HGG remains virtually an uncurable disease because of the tendency of diffuse infiltrative growth beyond the radiological tumor borders (2, 4, 6–8). The current standard of care is based on combined maximal safe-resection and concomitant radiation and alkylating chemotherapy (1, 26).

After decades of research in therapeutic and molecular refinements, the traditional multimodal approach still leads to a mean survival rate of 14–16 months, with a 2-year survival rate of 26.5%; and <10% of patients alive 5 years after diagnosis (27).

In 2003, the intraoperative treatment with CWs implantation in newly HGG was introduce as a therapeutic bridge during the period between tumoral surgical resection and chemoradiotherapy onset, with the aim of interfering with the potential tumor growth at resection margins (5, 9–14). Different studies demonstrated a promising result in terms of PFS without a marked increase in toxicities as compared with the Stupp regimen. However, the gain in median survival using this schedule was less clear (10–12, 14, 19).

After an initial promising success, CWs implantation in HGGs have been gradually abandoned in day-to-day clinical practice since 2017 for several reasons. A specific position that is totally against the use of CWs is not reported in current literature. In a recent intersociety SNO-EANO (Society for Neuro-Oncology-European Society of Neuro-Oncology) consensus review, Wen et al. (17) summarized the current status of the treatment of newly diagnosed glioblastoma. With regards to the CWs, the authors stated that this treatment option provides a modest survival advantage of approximately 2 months It tends to be considered only in sporadic cases, mainly because issues related to risks involving safety and tolerability, in addition to the precluded enrollment of in other clinical trials in subsequent trials for the possible confounding effects generated by CWs. These points do not prevent or forbit the use of this treatment, however, provides indirect discouragement.

Recent long-term follow-up investigations, however, have shown survival benefits in newly HGG treated with CWs implantation, shedding light, for a second time, on the effectiveness of treatment with CWs.

Overall Survival and Progression-Free Survival

The presents systematic review and meta-analysis, based on the comparative studies on CW effectiveness, demonstrates a significant advantage in using CWs in newly diagnosed GBM in terms of *OS*, but not in terms of PFS.

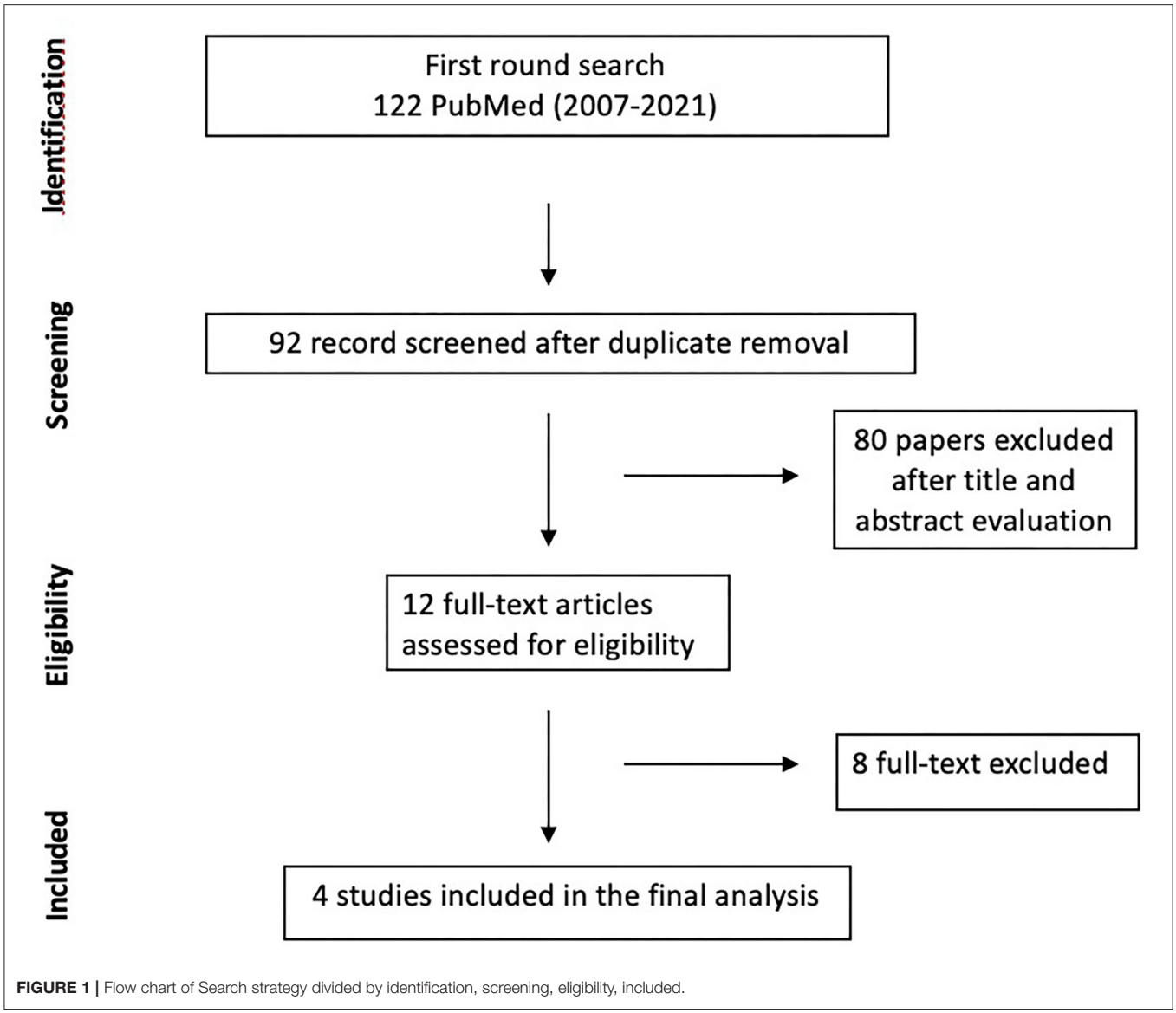

FIGURE 1 | Flow chart of Search strategy divided by identification, screening, eligibility, included.

Conversely the propensity-matched French multicenter cohort study stated opposite conclusions, reporting that CWs implantation was independently associated with longer *PFS* in patients with subtotal/total surgical resection in the entire series ($p = 0.005$) and after propensity matching ($p = 0.008$) (10). In addition, the authors evidenced that there was no benefit for CWs implantation unless maximal resection was achieved. The role of extent of resection (*EOR*) in improving *OS* in patients with GBM has widely been demonstrated, with more extensive resections providing added survival benefits (1, 2, 5, 10, 11). To optimize the *EOR*, especially in deep fields or in conditions of non-orthogonal working corridors, the effectiveness of 5-ALA-guided surgery has been proven in volumetric investigations (28). In a level 2B evidence investigation, 5-ALA-assisted surgery intraoperative fluorescence was shown to be more effective than conventional surgery in increasing EOR and prolonging, thus *OS* in GBM patients (29). Della Puppa et al., further demonstrated that on GBM patients, 5-ALA technology and CW implantation provided a synergic action on patient outcomes without increasing adverse events occurrence, highlighting the importance of adequate patient selection.

Subsequently, Roux et al. concluded that wafer implantation in combination with maximal resection, followed by standard combined chemoradiotherapy is safe, efficient, and well-tolerated in newly diagnosed supratentorial glioblastomas in adults. Moreover, unlike the French study, in which the volume analysis was categorical, Roux includes a quantitative analysis emphasizing the maximum efficacy of CWs for lesions with *EOR* $>$ 90% [adjusted hazard ratio (*HR*), 0.52 (95% *CI* 0.38–0.70), $p <$ 0.001] (11).

Despite the lack of comparative analysis, Ius et al. found a longer survival in a CW subgroup of patients with *EOR* $\leq$100%.

TABLE 2 | Characteristics of included studies.

Authors, year, journal	Type of study	Patients with/without CWs	Adjuvant therapy	Grade of Glioma	Molecular markers	EOR	OS results	PFS results	Side effects
De Bonis et al.,2012, *Acta Neurochir (Wien)* (19)	Randomized controlled trial	10/67	Adjuvant therapy with TMZ	IV	NA	Non volumetric study	Adding CWs to standard treatment did not significantly improve the outcome Multivariate analysis showed the only was resection extent ($p = 0.048$)	NA	The toxicity after CW use was significantly higher, both for patients with newly diagnosed and patients with recurrent glioblastoma
Pallud et al., 2015, *Neuro Oncol* (10)	Randomized controlled trial	354/433	Chemoradiation standard protocol	IV	NA	Surgical resection at progression whether alone or combined with CW implantation was independently associated with longer overall survival in the whole series ($p = 0.0001$)	The median overall survival was 20.4 months and 18.0 months in the CWs group and non CWs group respectively	The median PFS was 12.0 months and 10.0 months in the CWs group and non CWs group respectively	The higher postoperative infection rate in the implantation group did not affect survival
Roux et al., 2017, *J Neurooncol* (11)	Randomized controlled trial	123/217	Standard combined chemoradiotherapy	IV	NA	Volumetric estimation In CWs group and non-CWs group the Subtotal (90% and >) and total (100%) removal were achieved in 55.6 and 55.1% of cases, respectively ($p = 0.887$)	CWs implantation was were independently associated with longer OS ($p = 0.029$)	CWs implantation was were independently associated with longer PFS ($p = 0.045$)	CWs did not significantly increase postoperative complications, including postoperative infections ($p = 0.269$, and $p = 0.446$, respectively)
Akiyama et al., 2018, *World Neurosurg* (20)	Randomized controlled trial	25/29	Standard combined chemoradiotherapy	IV	Evaluation of the IDH-1/2 mutation, which has been reported as a predictive factor, was performed in only a small percentage of patients	Volumetric estimation The median EOR was 93% in CWs group vs. 96% in non CWs gruop ($p = 0.129$)	The median OS in the CWs group and non CWs group was 24.2 months and 15.30 respectively ($p = 0.027$)	The median PFS in the CWs group and non CWs group was 16.8 months and 7.30 months, respectively ($p = 0.009$)	The incidence of adverse events were similar between the treatment groups, except for infection that was more common in the CWs patients (3.5% vs. 0%)

CWs, Carmustine Wafers, EOR, extent of resection, NA, not applicable, PFS, Progression-free survival, OS, overall survival.

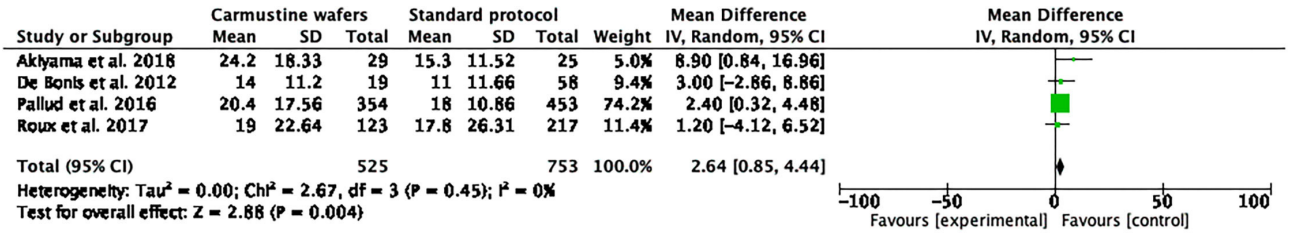

FIGURE 2 | Foster plot—overall survival (*OS*). The *OS* of all included patients demonstrating that there was a significant advantage in using Carmustine Wafers (CWs) in newly diagnosed glioblastoma (GBM) in terms of *OS* and low heterogeneity in all included studies.

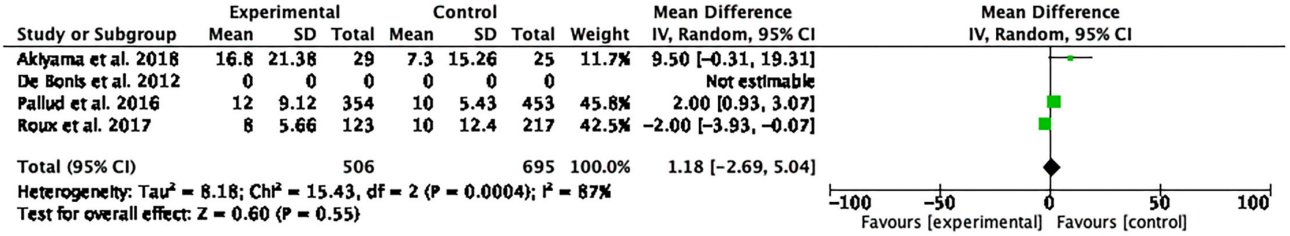

FIGURE 3 | Foster plot—progression-free survival (*PFS*). The analysis of meta-data demonstrated that there were no significant differences between the two treatment groups in terms of *PFS*, even though a high heterogeneity should be considered.

Enhanced survival benefits among CWs patients were observed in those patients with a higher percentage of methylated MGMT promoter, lower age, and total resection, thus highlighting several prognostic factors that could be evaluated in the selection process of patients with potentially better chances of postoperative success (5). On the bases of these results, an appropriate pre-operative patient screening based on the development of cell-free plasma DNA techniques to detect the methylation status of the MGMT promoter could prove to be important to preoperatively select young patients with small lesions that could potentially benefit from CWs implantation (30, 31).

Iuchi et al. (21) recently detected that CWs implantation in younger patients with an *EOR* >95% significantly prolongs the *OS* (median = S 27.4 months, 2-year *OS* = 46%). This latter investigation supports the criticism related to the effectiveness of CWs underlined by Champeux et al. (22) in a 9-year nationwide retrospective study in which the author found that the increase in *OS* after CW implantation was affected by age, gender, extent of surgery, and postoperative complications.

It is important to assess all potential treatment benefits of this treatment in selected HGG patients, even if literature in this field centers on the limits of this option when considered in HGG patients in general. Perhaps the comprehensive efficacy of this treatment should be reassessed in subpopulations of newly HGG patients.

Side Effects and Surgical Considerations

The high number of adverse events reported in the literature has certainly limited the use of CWs in newly HGG patients (5, 10–17). The various complications, however, vary considerably among different investigations. These reported complications include malignant cerebral edema, resection cavity cyst formation, cerebrospinal fluid leak, wound healing abnormalities, and increased perioperative seizure activity. In this study, the overall complication rate was 25.73% in the CWs group (44 of 171 patients), while 18.33% in the standard treatment (55 of 300 patients; $p = 0.53$).

In a large meta-analysis, Bregy et al. (15) reviewed 19 studies based on a total of 795 patients, and reported a complication rate of 42%. Contrary results, however, were reported in 2008 by Attenello et al. (25) that retrospectively analyzed a cohort of more than 1,000 patients (including 288 patients implanted with CWs) and found that the morbidity rate between the CWs and non-CWs groups was similar, despite patients being slightly older in the CWs group. The efficiency and safety of CWs in newly diagnosed supratentorial glioblastomas in adults were also demonstrated by Roux et al. (11). Interestingly, De Bonis et al. (19) listed a statistically significant higher risk of side-related toxicity in patients treated for tumor recurrence, emphasizing the importance of patient selection.

Major studies agree on the importance of an adequate surgical technique to reduce the risk of common side effects (10, 11).

The most commonly observed postoperative complications are due to infection and development of hydrocephalus. Hydrocephalus tends to be caused by migration of wafers or inflammatory response to CWs diffusion through the defect. Implantation of CWs is not recommended in patients that involve the surgical opening of the ventricular system, considering that acute occlusive hydrocephalus can be brought on by the dislocation of the wafers into the ventricular system and ventriculitis in association with transient hydrocephalus (32, 33).

Limitations

The interpretation of this present investigation should be considered in light of several limitations. The principle drawback concerns the information on the type of treatment carried out at tumor recurrence. It was difficult to assess whether the best *OS* in CWs patients was determined solely by CWs or by alternative treatments at the time of progression. It would be thus useful in future studies to evaluate the opportunity of exploring the survival benefits of salvage treatments, considering these covariates both time-dependent and fixed. Longer PFS, however, resulted in late tumor recurrence and consequently in better *OS* (34).

Another important issue contributing to reluctance to use CWs involves the lack of reliable survival data for patients treated with CWs, which might lead to confusion during the statistical analysis of the survival data of patients in a given trial. Moreover, it is well-known that to strengthen the survival benefit, salvage treatment information should ideally be included in the analysis at the time of tumor progression. The lack of standardized protocols for treatments at tumor progression represents thus an additional drawback. Overall, in future studies it would be useful to include the type of treatment at recurrence, considering this covariate both time-dependent and fixed to further render the survival data as a combination of all selected treatments used during the disease history.

With regards to the four investigations selected for the meta-analysis, raw data regarding the EOR in different subgroups were unfortunately not retrievable and thus was a limit of this study.

In addition, the majority of studies enrolled patients with Grade III and IV Gliomas, without stratifying the survival results according to the molecular profile or histological class, generating potentially confusing results.

In closing, in light to the novel 2021 WHO classification (35), it is important to integrate the volumetric data and the CDKN2A/2B, ATRX, TERT, EGFR, and TP53 status in future survival analysis to detect different categories of responders to a specific treatment protocol.

CONCLUSIONS

The results of this meta-analysis seem to suggest that CWs implantation plays a significant role in improving survival when used in patients with newly diagnosed HGG. To minimize the risk of side effects, however, a careful patient selection should be considered, i.e., younger patients with a high probability of radical resection for small lesions (5). The predictive molecular biomarkers for Carmustine efficacy need to be investigated in future studies to better identify those patients that could benefit from this treatment option. Considering the crucial role of tumor microenvironment (TME) on the GBM progression (6, 7), the transcriptomic profile of cells representing the TME of patients responsive and not responsive to CW implantation could provide new insights in an appropriate patient selection.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

AUTHOR CONTRIBUTIONS

Data curation and writing—original draft: AM, AP, DC, IM, and ST. Methodology and writing–review and editing: LR and TI. Formal analysis: LR and ST. Supervision: TI, AR, and MM. Validation: TI, AR, ST, and MM. All authors have read and agreed to the published version of the manuscript.

FUNDING

This work has been supported by Progetto Ministero 291 della Salute, Giovani Ricercatori 2016 GR-2016-02364678. Application of GLIADEL wafers (BCNU, Carmustine) followed by temozolomide and radiotherapy in patients with high-grade glioma: a precision medicine based on molecular landscape. CUP: J26C16000000005.

ACKNOWLEDGMENTS

We are grateful to Mark Zeppieri for the scientific English revision of the manuscript.

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SYSTEMATIC REVIEW
published: 08 July 2022
doi: 10.3389/fonc.2022.911043

Epidemiology, Characteristic, and Prognostic Factors of Primary Sporadic Intradural Malignant Peripheral Nerve Sheath Tumor in the Spinal Canal: A Systematic Literature Review

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Purpose: Primary sporadic intradural malignant peripheral nerve sheath tumor (MPNST) in the spinal canal is a type of rare neoplasm with challenging diagnosis and therapy. The overall prognosis of this tumor is markedly different from that of the usual spinal intradural tumors. The purpose of this systematic review is to reduce the misdiagnosis and enhance the prognosis of the disease by reviewing the literature.

Methods: PubMed, Medline, and Embase databases were searched for articles in English language published from 1980 to May 2021, yielding 500 potentially relevant articles. The keywords were as follows: “spinal”, “malignant peripheral nerve sheath tumor”, “neurosarcoma”, “malignant schwannoma”, and “malignant neurofibroma”. Thirteen papers met the eligibility criteria, including 55 cases with spinal intradural primary sporadic MPNSTs, which were confirmed by post-operation pathology. We further analyzed the clinical manifestations, radiological manifestations, pathological features, comprehensive treatment strategies, and prognosis.

Results: Fifty-five spinal intradural primary sporadic MPNSTs from 30 (54.5%) male and 25 (45.5%) female patients with an average age at diagnosis of 40 years (range, 3–70 years) were included in the study. The most common clinical manifestations were local or radicular pain and motor disturbance. All tumors had significant enhancement and heterogeneous enhancement was more common. Out of 18 lesions, 14 were diagnosed as high grade and the remaining 4 were diagnosed as low grade. The ki-67 labeling index ranged from 5% to 60%. The median recurrence and survival time were 36 and 72 months, respectively. The log-rank tests indicated that significant predictors of OS were patient age (≤30 vs. >30 years) at the time of diagnosis and the presence of metastatic disease, and similar analyses for RFS demonstrated that the presence of metastatic disease was the only significant predictor (60 vs. 10 months). The multivariate

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Edited by:
Luca Ricciardi, Sapienza University of Rome, Italy

Reviewed by:
Mirza Pojskic, University Hospital of Giessen and Marburg, Germany
Vadim Byvaltsev, Irkutsk State Medical University, Russia

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This article was submitted to Neuro-Oncology and Neurosurgical Oncology, a section of the journal Frontiers in Oncology

Specialty section:
Received: *01 April 2022*
Accepted: *13 June 2022*
Published: *08 July 2022*

Citation:
Cao Y, Wang Y-B, Bai Y, Tan X-y, Ma C-y, Chen Y, Yu H-q, Xu H-Y and Zhao G (2022) Epidemiology, Characteristic, and Prognostic Factors of Primary Sporadic Intradural Malignant Peripheral Nerve Sheath Tumor in the Spinal Canal: A Systematic Literature Review. Front. Oncol. 12:911043. doi: 10.3389/fonc.2022.911043

Cox proportional hazards regression analysis revealed that absence of metastasis was an independent factor for predicting a favorable prognosis.

Conclusions: Spinal intradural primary sporadic MPNSTs are challenging malignant tumors without a systematic treatment plan. The factors affecting its prognosis are not clear. Even after surgical treatment and adjuvant treatment, the recurrence rate and mortality rate are still high. Clinicians should be alert to the possibility of this disease and achieve early detection and treatment.

Keywords: malignant peripheral nerve sheath tumor, intradural, spinal, diagnosis, treatment, prognosis

INTRODUCTION

Malignant peripheral nerve sheath tumor (MPNST) is a highly malignant soft tissue tumor originated from mesenchymal cells and mainly distributed in the trunk, limbs, head and neck, and other areas of peripheral nerve distribution. MPNST (1 case in ten million) is an unusual disease and represents 2% to 4% of all soft tissue sarcomas and 23% to 51% of these tumors were associated with neurofibromatosis type 1 (NF1) (1). Spinal MPNSTs accounted for 2%–3% of all MPNSTs (2). Primary sporadic intradural MPNST in the spinal canal is even more exceptional, and it is easy to be misdiagnosed as central nervous system tumors or other types of soft tissue sarcomas. En bloc resection with a wide margin with adjuvant radiotherapy is considered as the first line for the therapy of non-spinal MPNSTs, and the implementation of this strategy is significant but not easy in the management of intradural MPNSTs. Research on the benefit of adjuvant chemotherapy is limited. In addition, compared to the usual spinal intradural tumors, overall prognosis of this tumor is distinctly different. We summarized 55 cases in the previous literature and analyzed their pathogenesis, clinical characteristics, imaging manifestations, differential diagnosis, surgical interventions, and pathological features to reduce the misdiagnosis and enhance the prognosis.

MATERIALS AND METHODS

Literature Search

We searched the PubMed, Medline, and Embase databases for spinal MPNST-related articles. We have reviewed English literature in English language published from 1980 to May 2021. Search strategy was based on the following medical subject headings (MeSH) and keywords: "spinal", "malignant peripheral nerve sheath tumor", "neurosarcoma", "malignant schwannoma", and "malignant neurofibroma". Inclusion criteria were as follows: (i) published in English, (ii) MPNST identified by pathological examination, (iii) some or all of the intradural tumors, and (iv) management options including subtotal resection, gross total resection, radiotherapy, chemotherapy, or combined treatments. We excluded the following three situations from our study: (i) malignant transformation in NF1, (ii) malignant transformation of other tumors like schwannoma or gangliocytoma, and (iii) radiotherapy-induced neoplastic lesions.

Article Selection

The search yielded 500 unique articles. Two authors reviewed each article title and abstract, and reached consensus regarding article eligibility based on the inclusion/exclusion criteria. A total of 13 papers including 55 cases with spinal intradural primary sporadic MPNSTs, which were confirmed by post-operation pathology, met all criteria and were included in the final review (**Figure 1**).

Data Extraction and Analysis

We further analyzed the clinical manifestations, radiological manifestations, pathological features, comprehensive treatment strategies, and prognosis. Moreover, relapse-free survival (RFS) period was defined as the time from tumor resection to tumor relapse on imaging, and total survival period (OS) was defined as the time from tumor resection to death. RFS and OS curves were calculated by the Kaplan–Meier method. Log-rank test was adopted in the single-factor analysis to assess the intergroup differences. All variables with a significant result in the univariate Cox proportional hazard regression analysis were included in the following multivariate analysis. The hazard ratios (HR) and 95% confidence intervals (CIs) were estimated to identify the independent prognostic factors associated with RFS and OS in patients with primary sporadic intradural MPNST. A p-value of ≤ 0.05 was considered statistically significant.

RESULTS

Clinical Data

Fifty-five spinal intradural primary sporadic MPNSTs [6 cervical (10.9%), 12 thoracic (21.8%), 6 lumbar (10.9%), 2 sacral (3.6%), and 29 unknown (52.7%)] from 30 (54.5%) male and 25 (45.5%) female patients with an average age at diagnosis of 40 years (range, 3–70 years) were included in the study. The maximum diameter of the tumors ranged from 1 cm to 9 cm. The most common clinical manifestations were local or radicular pain and motor disturbance. The mean duration of pre-operative clinical history was 12.6 months (range, 0.5–108 months) in 24 patients with relevant information. On T1-weighted imaging, 9 lesions appeared as isointense (9/16, 56.3%), and 7 lesions appeared as

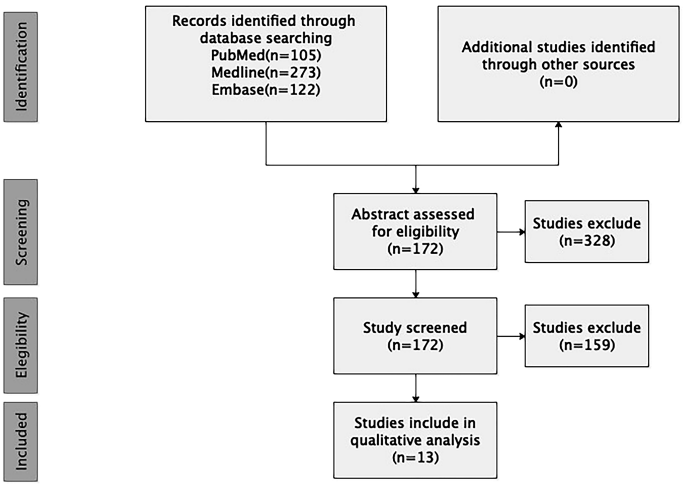

FIGURE 1 | PRISMA flow diagram.

hypointense (7/16, 43.8%) signals. On T2-weighted imaging, 7 lesions were isointense (7/20, 35.0%), and 13 lesions were hypointense (13/20, 65.0%). Twenty-two cases recorded enhanced MRI information following gadolinium administration: The most common shape of tumors was oval (14/22, 63.6%), followed by irregular (4/22, 18.2%) and dumbbell (4/22, 18.2%); 15 tumors exhibited relatively clear boundaries (15/22, 68.2%), while 7 tumors exhibited obscure boundaries (7/22, 31.8%). All tumors had significant enhancement and heterogeneous enhancement was more common (11 vs. 3). Only 3/26 cases showed bone destruction on imaging. The demographic and clinical characteristics of these patients are summarized in **Table 1**.

Pathological Features and Therapy

Immunohistochemical examinations revealed that S-100 protein was positive in 15/17 cases, vimentin in 10/14 cases, glial fibrillary acidic protein (GFAP) in 5/14 cases, desmin in 5/9 cases, epithelial membrane antigen (EMA) in 2/10 cases, cytokeratin in 1/8 cases, CD34 in 5/9 cases, and anti-smooth muscle antibody (SMA) in 5/9 cases. Based on the WHO classification, 14/18 lesions were diagnosed as high grade and the remaining 4 were diagnosed as low grade. The ki-67 labeling index ranged from 5% to 60%. All patients underwent microsurgical treatment. Eight patients received subtotal resection (8/27, 29.6%), and 19 patients received gross total resection (19/27, 70.4%). Thirty-three patients underwent postoperative radiotherapy and 14 patients underwent postoperative chemotherapy. The pathological features and therapy of these patients are summarized in **Table 2**.

Follow-Up and Prognosis

The average follow-up period was 31.4 months, with a range of 0.3–120 months. During the follow-up period, 29 patients suffered from a local recurrence (29/55, 52.7%), and 11 patients experienced metastasis (11/26, 42.3%). The mean RFS was 30.8 months. Twenty-six patients died during the study period (26/55, 47.3%). Except for two relapse-free survivors with a follow-up of less than 2 years, 2-year recurrence rate and 2-year mortality rate were 43.4% (23/53) and 41.8% (22/53), respectively. The follow-up and prognosis of these patients are summarized in **Table 3**.

Statistical Analysis

The summary of patient data is shown in **Table 4**. The Kaplan–Meier curves of OS and RFS are shown in **Figure 2A**. The median recurrence and survival time were 36 and 72 months, respectively. The log-rank tests indicated that age at diagnosis (**Figure 2B**) and presence or absence of metastasis (**Figure 2C**) were the potential risk factors for OS, and presence or absence of metastasis (**Figure 2D**) was also the potential risk factor for RFS. The patients who were older than 30 years showed better OS, whose mean OS was 82 months, while the other patients had a mean OS of 17.5 months. The patients without metastasis had better OS and RFS, whose mean values were 82 months and 60 months, respectively. The mean OS and RFS of patients with metastasis were 14 months and 10 months. The patients without metastasis who were older than 30 years old have a better prognosis. The age at diagnosis and presence or absence of metastasis were included in the multivariate analysis. The multivariate Cox proportional hazards regression analysis revealed that absence of metastasis was an independent factor for predicting a favorable prognosis. The statistical results are summarized in **Table 5**.

DISCUSSION

MPNSTs are highly aggressive and locally invasive rare malignancies with an incidence of 0.0001% in the general

TABLE 1 | The demographic and clinical characteristics of these patients.

Study	Year	Nb		Location	Age (years)	Gender	Clinical symptoms	History (months)	Maximum diameter (cm)	Shape	Boundary of tumor	T1W1	T2W2	Enhancement	Bone destruction
Honda et al. (2)	2020	1	1	C5–C6	56	F	lt UE numbness and weakness	NA	NA	Dumbbell	Obscure	NA	Hyperintense	Yes	No
Chen et al. (3)	2019	8	1	T11/12	21	M	LE pain, low back pain	12	3	Oval (4/8), irregular (3/8), dumbbell (1/8)	Clear (5/8), obscure (3/8)	Isointense (4/8), hyperintense (4/8)	Isointense (3/8), hyperintense (5/8)	Heterogeneous enhancement (5/8), homogeneous enhancement (3/8)	Yes (1/8), no (7/8)
			2	L3–S1 (cauda equina)	29	F	rt LE numbness and weakness	6	4						
			3	L3–L4 (cauda equina)	52	M	low back pain	8	7.2						
			4	T2–L1	47	M	lt LE pain and weakness	1	4.6						
			5	C1–C3	39	F	lt UE and LE numbness and weakness	3	6.5						
			6	T6–T8	68	M	LE weakness	3	4.7						
			7	C5–C6	53	F	UE pain	6	3.2						
			8	T11	46	M	LE weakness	1	3						
Bettaswamy et al. (4)	2017	1	1	T8–T9	7	M	Low back pain	2	9	Dumbbell	Clear	Isointense	Isointense	Yes	Yes
Ghailane et al. (5)	2017	1	1	T12–L1	70	M	lt LE pain, low back pain	24	3.2	Dumbbell	Clear	Isointense	Isointense	Heterogeneous enhancement	No
Chou et al. (6) (multicenter study without individual information)	2017	29	29	NA	5–47 (mean 40)	M (17/29) F(12/29)	Pain (27/29), pathological fracture (2/29)	NA					NA		
Baharvahdat et al. (7)	2015	1	1	C1–T1	3	F	Back pain, UE and LE weakness	1	NA	Oval	Obscure	Isointense	Hyperintense	Heterogeneous enhancement	Yes
Thomas et al. (8)	2014	1	1*	Cauda equina	49	M	Low back pain, constipation, LE pain and weakness	0.5	NA	Oval	Obscure	Hyperintense	Isointense	Heterogeneous enhancement	No
Li et al. (9)	2014	1	1	T12–L1	33	F	Low back pain, rt LE pain	1	3.4	Oval	Clear	Isointense	Hyperintense	Heterogeneous enhancement	No
Yone et al. (10)	2004	1	1	L3–L5 (cauda equina)	4	M	lt LE pain, low back pain	NA	6	Oval	Clear	Isointense	Isointense	Heterogeneous enhancement	No
Celli et al. (11)	1995	5	1	T2	52	F	Pain, motor disturbance	8	1	Oval	Clear	NA		Yes	No
			2	L4 (cauda equina)	68	F	Pain, motor disturbance	9	2	Oval	Clear	NA		Yes	No
			3	L3 (cauda equina)	43	M	Pain	3	1	Oval	Clear	NA		Yes	No
			4	T11	36	F	Pain	5	3	Oval	Clear	NA		Yes	No
			5	T7	30	M	Pain, motor disturbance	72	3	Oval	Clear	NA		Yes	No
Seppälä et al. (12)	1993	3	1	Lumbar	13	M	Low back pain	6				NA			No
			2	Upper thoracic	23	F	Back pain	4				NA			No
			3	Lower cervical	37	F	Neck pain	12				NA			No
Valdueza et al. (13)	1991	2	1	T10–T12	43	F	Low back pain, LE weakness	1	NA	Irregular	Obscure	Hyperintense	Hyperintense	Yes	No
			2*	C4–C6	70	F	Neck pain, rt UE pain	6	NA	Oval	Clear	Hyperintense	Hyperintense	Heterogeneous enhancement	No
Thomeer et al. (14)	1981	1	1	Cauda equina	42	M	Low back pain, lt LE pain	108				NA			No

*NA: not available; lt: left; rt: right; UE: upper extremity; LE: lower extremity; * two relapse-free survivors with a follow-up of less than 2 years.*

TABLE 2 | The pathological features and therapy of these patients.

Study	Year	Nb		Grade	Pathology									Surgery		Postoperative radio-therapy	Postoperative che-motherapy
					S-100	Vimentin	Desmin	GFAP	EMA	Cytokeratin	CD34	SMA	Ki-67				
Honda et al. (2)	2020	1	1	IV	NA									Dorsal standard midline approach	STR	Yes	No
Chen et al. (3)	2019	8	1	Low grade	+ (6/8)	+ (5/8)	+ (4/8)	+ (3/8)	+ (2/8)	+ (1/8)	+ (6/8)	+ (4/8)	5%–60% (low 5-10%, mean 6.8%)	Dorsal standard midline approach	GTR	No	Yes
			2	(3/8)											GTR	Yes	No
			3	high grade									(high 20%–60%, mean 40%)		GTR	Yes	No
			4	(5/8)											STR	Yes	Yes
			5												STR	Yes	No
			6												GTR	NA	NA
			7												STR	Yes	No
			8												GTR	NA	NA
Bettaswamy et al. (4)	2017	1	1	NA										Posterolateral thoracotomy approach	GTR	Yes	No
Ghailane et al. (5)	2017	1	1	IV	+	NA	+	NA						Dorsal standard midline approach	GTR	No	No
Chou et al. (6) (multicenter study without individual information)	2017	29	29	NA												Yes (19/29)	Yes (10/29)
Baharvahdat et al. (7)	2015	1	1	NA	+	+	NA	_	_	NA				Dorsal standard midline approach	STR	No	No
Thomas et al. (8)	2014	1	1*	NA	+	+	NA						7-10%	Dorsal standard midline approach	STR	No	No
Li et al. (9)	2014	1	1	NA	+	+	NA	_	_	NA	+	_	NA	Dorsal standard midline approach	STR	Yes	No
Yone et al. (10)	2004	1	1	NA	+	+	NA					+	NA	Dorsal standard midline approach	GTR	Yes	Yes
Celli et al. (11)	1995	5	1	IV	NA									NA	GTR	No	No
			2	IV	NA									NA	GTR	No	No
			3	IV	NA									NA	GTR	No	No
			4	IV	NA									NA	GTR	No	No
			5	IV	NA									NA	GTR	No	No
Seppälä et al. (12)	1993	3	1	NA	_	+	NA	_	NA					Dorsal standard midline approach	GTR	Yes	No
			2	NA	_	_	NA	+	NA					Dorsal standard midline approach	GTR	Yes	No
			3	NA										Dorsal standard midline approach	GTR	Yes	No
Valdueza et al. (13)	1991	2	1	III	+	NA		_	NA					Dorsal standard midline approach	STR	Yes	No
			2*	III	+	NA		+	NA					Dorsal standard midline approach	GTR	No	No
Thomeer et al. (14)	1981	1	1	II	NA									Dorsal standard midline approach	GTR	Yes	Yes

GTR, gross total resection; STR, subtotal resection.

TABLE 3 | The follow-up and prognosis of these patients.

Study	Year	Nb		Follow-up time (months)	Recurrence	Metastasis	Outcome
Honda et al. (2)	2020	1	1	36	Yes	No	Alive
Chen et al. (3)	2019	8	1	56	Yes	No	Died
			2	21	No	Lung	Died
			3	82	Yes	No	Died
			4	19	Yes	No	Died
			5	160	Yes (at 120 months)	No	Died
			6	15	Yes	No	Died
			7	10	Yes	Lung	Died
			8	28	No	No	Alive
Bettaswamy et al. (4)	2017	1	1	60	Yes	No	Alive
Ghailane et al. (5)	2017	1	1	10	Yes (at 3 months)	Yes	Died
Chou et al. (6) (multicenter study without individual information)	2017	29	29	24	Yes (11/29)	NA	Died (12/29)
Baharvahdat et al. (7)	2015	1	1	0.3	Yes	Brain, spinal	Died
Thomas et al. (8)	2014	1	1*	1.5	No	Brain, spinal	Alive
Li et al. (9)	2014	1	1	29	Yes (at 4 months)	Brain, spinal	Alive
Yone et al. (10)	2004	1	1	21	Yes (at 6 months)	Brain, spinal	Died
Celli et al. (11)	1995	5	1	72	No	No	Alive
			2	24	No	No	Alive
			3	72	No	No	Alive
			4	48	Yes	No	Alive
			5	14	No	Lung	Died
Seppälä et al. (12)	1993	3	1	7	Yes	Yes	Died
			2	8	Yes	Yes	Died
			3	72	Yes (at 24 months)	Yes	Died
Valdueza et al. (13)	1991	2	1	120	Yes (at 96 months)	No	Alive
			2*	7	No	No	Alive
Thomeer et al. (14)	1981	1	1	36	Yes	No	Alive

population and 3%–5% in patients with neurofibromatosis type 1 (NF1) (2). Lesions are most frequently found on the trunk, extremities, and head and neck. There are three main forms of histogenesis of MPNSTs (15): half of the cases are sporadic and derive from peripheral nerves that originate from Schwann cells or pluripotent cells of neural crest origin (sporadic type) (16); about 50%–60% MPNSTs occur in the malignant transformation of NF1 (NF1 type); and a few cases are radiotherapy-induced or malignant change of schwannoma and ganglioma. Thus, primary sporadic MPNST with an intradural occurrence of the spine outside the setting of neurofibromatosis was extremely rare and associated with an extremely rare diagnosis and an extremely poor prognosis in comparison to non-spinal MPNST. In our present research, we conducted a retrospective study to thoroughly analyze the pathogenesis, clinical characteristics, imaging manifestations, differential diagnosis, surgical interventions, pathological features, and prognosis of primary sporadic intradural MPNSTs.

We found only 55 cases of primary sporadic intradural MPNSTs without neurofibromatosis in our search to this date —more men than women (54.5% > 45.5%). The median age at diagnosis was 40 years, with a range of 3–70 years. As reported in the previous study, this kind of tumor occurred primarily in adults, which was largely consistent with those of our research. The disease history in our study had a median of 12.6 months, which was much longer than that found in previous reports (3). The thoracic spine was the most frequently affected area. Local or radicular pain and motor disturbance were the most common clinical symptoms, which were nonspecific and made a challenging diagnosis. Furthermore, MPNST can masquerade as common benign nerve sheath tumors on imaging (16, 17), which generally exhibit an isointense signal in T1-weighted imaging and a hyperintense signal in T2-weighted imaging. In the present investigation, there were still 43.8% of the tumors that showed hyperintensity in T1-weighted imaging. All tumors showed varying degrees of enhancement. Furthermore, MPNST did not show typical invasive growth (irregularly or obscure bordered) and destruction of surrounding osseous structures on the radiograph. Since MPNSTs show higher metabolic activity, 18F-FDG PET/CT may be helpful for the diagnosis (18). A tumor SUV is higher than that of normal liver tissue, which is considered to be a sensitive and specific index of MPNST (19). According to the authors' experience, when the imaging findings are benign intraspinal tumors, but the adhesion between the tumor and the nerve is serious intraoperatively, the possibility of MPNST should be considered. Thus, we advocate that regardless of the clinical manifestation or imaging characteristics, surgeons should retain a high index of suspicion for an MPSNT, especially when excision is laborious during surgery. Spine MRI is essential in postoperative follow-up because of the high incidence of drop metastasis (20).

Surgical biopsy result is the gold standard and past medical history is an important diagnostic evidence. Pathological characteristics of spinal MPNST are high cellularity with spindle-shaped cells, nuclear atypia, necrosis, endothelial proliferation, and so on (7). HE staining was characterized by "marble-like" spindle-shaped tumor cells, alternating between dense and loose areas, and arranged in bundles or swirls (21). There were no ganglion cells in the tumor. S-100 is a characteristic protein of primary MPNST, but when the tumor

TABLE 4 | The summary of patient data.

Variables	Number		%
Gender (*n* = 55)			
Male	30		54.5%
Female	25		45.5%
Age at diagnosis (years, *n* = 55)			
Mean		40	
Range		3–70	
≤30	8		14.5
>30	18		32.7
Unknown	29		52.7%
Location (*n* = 55)			
Cervical	6		10.9
Thoracic	12		21.8
Lumber	6		10.9
Sacral	2		3.6
Unknown	29		52.7
History (months, *n* = 24)			
Mean		12.6	
Range		0.5–108	
≤6	16		66.7
>6	8		33.3
Size (cm, *n* = 17)			
Range		1–9	
≤3	10		58.8
>3	7		41.2
Shape (*n* = 22)			
Oval	14		63.6
Irregular	4		18.2
Dumbbell	4		18.2
T1-weighted (*n* = 16)			
Isointense	9		56.3
Hypointense	7		43.8
T2-weighted (*n* = 20)			
Isointense	7		35.0
Hypointense	13		65
Boundary (*n* = 22)			
Clear	15		68.2
Obscure	7		31.8
Bone destruction (*n* = 26)			
Yes	3		11.4
No	23		88.6
Grade (*n* = 18)			
Low grade	4		28.6
High grade	14		71.4
S-100 (*n* = 17)			
+	15		88.2
–	2		11.8
Vimentin (*n* = 14)			
+	10		71.4
–	4		28.6
EMA (*n* = 10)			
+	2		20.0
–	8		80.0
CD34 (*n* = 9)			
+	5		55.6
–	4		44.4
SMA (*n* = 9)			
+	5		55.6
–	4		44.4
Desmin (*n* = 9)			
+	5		55.6
–	4		44.4
Cytokeratin (*n* = 8)			
+	1		12,5
–	7		87.5
Surgery (*n* = 27)			
Subtotal resection	8		29.6
Gross total resection	19		70.4
Postoperative adjuvant treatment (*n* = 53)			
Radiotherapy	33		62.3
Chemotherapy	14		26.4
Recurrence (*n* = 55)			
Yes	29		52.7
No	26		47.3
Metastasis (*n* = 26)			
Yes	11		42.3
No	15		57.7
Vital status (*n* = 55)			
Alive	29		52.7
Died	26		47.3

(Continued)

is recurrent or highly malignant, the positive rate of S-100 is significantly decreased (10, 22). S-100 was negative only in 2 patients in our study; hence, the clinical significance of it needs to be further investigated. Positive CD34 indicates the presence of heterogeneous cellular components in the tumor. In addition, high-grade MPNST often expresses p53. Loss of SMARCB1 expression plays an important role in the occurrence and development of MPNST (21). Due to incomplete sample information, we only made a summary of the pathological results. Except for the surgical biopsy result, an accurate diagnosis of primary spinal intradural MPNSTs depends on the exclusion of metastasis, malignant transformation, radiotherapy-induced tumor, and NF1. Further study of molecular pathology is an effective way for diagnosis and treatment. In addition, the analysis of cancer stem cells and genetics in MPNSTs is helpful to design new treatment schemes (23). Spyra et al. suggested the increased expression of CD133, Oct4, and Nestin, and decreased markers of NCAM and CD90 (24). Genetic mutations such as SUZ12, EED, $BRAF^{V600E}$, and TP53 have been reported in sporadic MPNSTs (25–28).

Due to the lack of a large amount of clinical data about primary sporadic intradural MPNSTs, there is no mature and effective treatment plan at present. A reasonable stage and risk grouping of MPNSTs is beneficial to the subsequent management (18). Surgical resection is the mainstay of treatment currently, while the outcomes of surgical management are widely disparate (8). Generally speaking, there are two types of resections: one is piecemeal resection, which means that an intralesional resection involved violation of the tumor capsule, and the other is en bloc resection, which refers to the circumferential separation of the tumor without violation of its border or capsule, and can be categorized into wide margin and marginal margin according to the different surgical margin (29). Radical en bloc resection with wide margins is a difficult but significant factor in tumor control and future prognosis (30). The surrounding vital structures, including critical nerves and blood vessels, restrict the extent of the resection range. Chou et al. classified the surgical technique for spinal MPNSTs as Enneking appropriate (EA) or Enneking inappropriate (EI) to investigate the effects of two types on

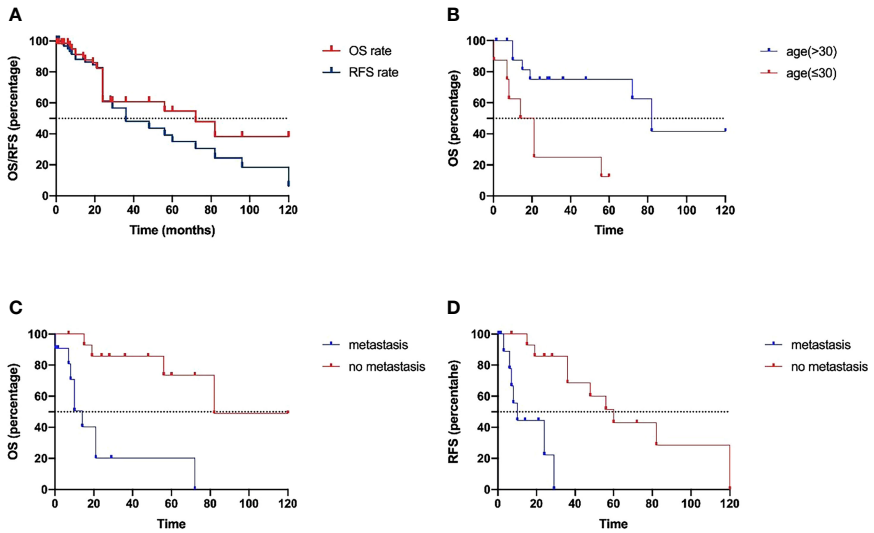

FIGURE 2 | **(A)** The Kaplan–Meier curves of OS and RFS. The log-rank tests indicated that age at diagnosis **(B)** and presence or absence of metastasis **(C)** were the potential risk factors for OS, and presence or absence of metastasis **(D)** was also the potential risk factor for RFS.

TABLE 5 | The results of the log-rank test, and univariate and multivariate Cox regression analysis.

Variable	Log-Rank Test		Univariate Analysis				Multivariate Analysis	
	OS	RFS	OS		RFS		OS	
	p-value	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Gender (*n* = 26)	0.279	0.356	Reference		Reference			
Male								
Female			0.545 (0.176–1.681)	0.291	0.588 (0.208–1.662)	0.317		
Age (>30) (*n* = 26)	0.004	0.221	Reference		Reference		Reference	
>30								
≤30			0.196 (0.057–0.670)	0.009	0.501 (0.169–1.539)	0.232	0.345 (0.095–1.256)	0.107
Location (cervical or not) (*n* = 26)	0.888	1	Reference		Reference			
Cervical								
Not cervical			1.097 (0.298–4.038)	0.889	1.003 (0.315–3.190)	0.996		
Boundary (*n* = 14)	0.894	0.685	Reference		Reference			
Obscure								
Clear			1.167 (0.120–11.341)	0.894	0.642 (0.074–5.583)	0.688		
Shape (oval or not) (*n* = 14)	0.762	0.633	Reference		Reference			
Oval								
Not oval			1.167 (0.120–11.341)	0.894	0.738 (0.155–3.508)	0.702		
Maximum diameter (>3 cm) (*n* = 17)	0.223	0.131	Reference		Reference			
>3 cm								
≤3 cm			2.567 (0.517–12.760)	0.249	3.162 (0.653–15.310)	0.152		
GTR vs. STR (*n* = 26)	0.538	0.652	Reference		Reference			
GTR								
STR			1.508 (0.400–5.692)	0.544	1.306 (0.405–4.213)	0.655		
Postoperative radiotherapy (*n* = 24)	0.953	0.276	Reference		Reference			
Yes								
No			0.964 (0.282–3.300)	0.954	2.013 (0.551–7.351)	0.29		
Postoperative chemotherapy (*n* = 24)	0.41	0.135	Reference		Reference			
Yes								
No			1.744 (0.448–6.788)	0.422	2.411 (0.723–8.038)	0.152		
Presence or absence of metastasis (*n* = 26)	<0.05	<0.05	Reference		Reference		Reference	
Metastasis								
Not metastasis			8.554 (2.254–32.464)	0.002	12.782 (2.529–64.605)	0.002	6.504 (1.579–26.796)	0.010

recurrence and survival (6). EA surgery is en bloc resection with wide or marginal margins and EI surgery is a piecemeal or an intralesional resection. In their study, there was no difference in recurrence or survival rate based on the two resection techniques. They also suggested that EA resection was not necessary to improve the overall survival because of the spread along nerves and multiple skip metastases, but better progression-free period may be obtained. However, the benefit of EA resection may be undermined by operation-related structure damage compared to EI resection (especially intralesional piecemeal resections). Another study suggested that the reason of relapse and metastasis in piecemeal total resection probably originated from tumor cell contamination in the surgical field (3). In our research, the present results suggest that the extent of surgical resection may not affect overall or local relapse-free survival. Although piecemeal total resection may not yield a conclusive tumor-free margin, it may alleviate symptoms, achieve sufficient volume reduction and bring greater benefit to patients. A reasonable surgical design is an effective and primary way to gain time for subsequent treatment. The best adjuvant treatment remains poorly defined due to the lack of prospective trials. Previous literature suggests that adjuvant radiotherapy after surgery could be an effective treatment for patients, especially in lesions larger than 5 cm in size or with residual tumor, which is critical in the prognosis of primary spinal intradural MPNSTs (2, 7, 8, 31). However, our study revealed that radiotherapy is ineffective in controlling recurrence and does not appear to affect overall survival, which may be due to the bias caused by the fact that more aggressive tumors are more likely to undergo radiotherapy. Additionally, radiotherapy had the risk of increasing the mutational burden of the tumor (23). Further exploration is required to elucidate the effect of surgical type and adjuvant radiotherapy. At present, there is no consensus on chemotherapy and it requires personalized design for MPNSTs. Chemotherapy did not show benefit in our present study. In view of the resistance of MPNSTs to traditional chemotherapy (32), targeted therapy is a new therapeutic strategy and direction (33). Some other new treatments, like carbon ion radiotherapy (CIRT), are currently under study and being explored (2).

The clinical outcome of primary sporadic intradural MPNSTs is poor (34). The rate of metastasis at the time of initial diagnosis is 10.4% (35), and 5-year survival rate is 42%–50% in sporadic cases (36). In our research, the rate of tumor recurrence was 52.7%, and the rate of tumor metastasis was 42.3%. The 2-year recurrence rate and the 2-year mortality rate were 43.4% and 41.8%, respectively. The median recurrence and survival time were 36 and 72 months, respectively. In this retrospective study, we found age and presence of metastasis as two prognostic factors, which could influence the OS and RFS. The patients who were older than 30 years showed better OS than the other patients. The patients without metastasis had better OS and RFS. Furthermore, the multivariate Cox proportional hazards regression analysis revealed that absence of metastasis was an independent factor for predicting a favorable prognosis. However, the patients' gender, the position of the tumor, surgery, adjuvant therapy, and many other factors did not appear to affect the prognosis.

LIMITATION

The study is limited by its small sample size, and some data are not detailed and complete. The criterion of "exclusion of tumors that had undergone secondary transformation" is perhaps misleading. It is possible that some patients may have had undiagnosed schwannomas/other tumors that underwent secondary transformation and were only diagnosed at that point. More relevant clinical data need to be screened, collected, and studied.

CONCLUSION

Primary sporadic intradural MPNSTs are aggressive malignant tumors with high mortality and morbidity rates, even after formal treatment. It is difficult to make a diagnosis based on clinical and imaging findings alone. Surgical resection and pathological examination are necessary. The benefit of radiotherapy and chemotherapy treatments remains controversial. In our present study, early detection of diseases in adults may predict better clinical outcomes. However, we should be aware that further studies with larger cohorts are needed to explore the prognostic factors and reasonable treatment plans.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding authors.

AUTHOR CONTRIBUTIONS

YC and Y-BW conducted the data analysis, interpreted the data, and wrote the main manuscript. YB, C-YM, and H-QY supervised the data analysis and interpreted the data. H-YX and GZ designed the research and critically revised the article. All other co-authors helped to interpret the data and critically reviewed the article. All authors approved the final article for submission.

FUNDING

This work was supported by National Nature and Science Foundation of China (81772684), the S&T Development Planning Program of Jilin Province (20200201469JC, 20200201613JC, and 20200201388JC), Foundation from the Development and Reform Commission of Jilin Province (Grant No. 2017C059-2), and Chinese People's Brain Neural Network Research and Innovation Cooperation Platform Construction Project.

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frontiers | Frontiers in Oncology

OPINION
published: 25 July 2022
doi: 10.3389/fonc.2022.934426

Current and Future Frontiers of Molecularly Defined Oligodendrogliomas

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OPEN ACCESS

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Specialty section:
This article was submitted to Neuro-Oncology and Neurosurgical Oncology, a section of the journal Frontiers in Oncology

Received: 02 May 2022
Accepted: 13 June 2022
Published: 25 July 2022

Citation:
Rincon-Torroella J, Rakovec M, Materi J, Raj D, Vivas-Buitrago T, Ferres A, Reyes Serpa W, Redmond KJ, Holdhoff M, Bettegowda C and González Sánchez JJ (2022) Current and Future Frontiers of Molecularly Defined Oligodendrogliomas. Front. Oncol. 12:934426. doi: 10.3389/fonc.2022.934426

Oligodendrogliomas are a subtype of adult diffuse glioma characterized by their better responsiveness to systemic chemotherapy than other high-grade glial tumors. The World Health Organization (WHO) 2021 brain tumor classification highlighted defining molecular markers, including 1p19q codeletion and IDH mutations which have become key in diagnosing and treating oligodendrogliomas. The management for patients with oligodendrogliomas includes observation or surgical resection potentially followed by radiation and chemotherapy with PCV (Procarbazine, Lomustine, and Vincristine) or Temozolomide. However, most of the available research about oligodendrogliomas includes a mix of histologically and molecularly diagnosed tumors. Even data driving our current management guidelines are based on *post-hoc* subgroup analyses of the 1p19q codeleted population in landmark prospective trials. Therefore, the optimal treatment paradigm for molecularly defined oligodendrogliomas is incompletely understood. Many questions remain open, such as the optimal timing of radiation and chemotherapy, the response to different chemotherapeutic agents, or what genetic factors influence responsiveness to these agents. Ultimately, oligodendrogliomas are still incurable and new therapies, such as targeting IDH mutations, are necessary. In this opinion piece, we present relevant literature in the field, discuss current challenges, and propose some studies that we think are necessary to answer these critical questions.

Keywords: oligodendroglioma, diffuse glioma, 1p19q codeletion, EORTC, RTOG, POLCA, CODEL, NCCN

INTRODUCTION

Oligodendrogliomas are a subtype of adult diffuse glioma characterized by isocitrate dehydrogenase (IDH) mutation and the codeletion of the short arm of chromosome 1 (1p) and the long arm of chromosome 19 (19q) (1). They are rare primary brain tumors that present with variable outcomes and for which curative therapy does not exist. Oligodendrogliomas have evoked much interest given their favorable prognosis and better response to treatment compared to astrocytomas and

glioblastomas, their more malignant counterparts. Historically, the diagnosis of oligodendrogliomas was purely histological, based on the characteristic "fried-egg" appearance of oligodendroglial cells, which was subject to considerable interobserver variation (2, 3). Exhaustive research led to discovering the 1p/19q codeletion, a molecular marker that has come to define oligodendroglioma (4–6). Hence, the diagnosis of oligodendroglioma became molecular instead of histological.

The WHO 2021 brain tumor classification reinforced this requirement and included 1p/19q codeletion and IDH mutation as defining traits of oligodendroglioma (1). Given that this change became official in relatively recent times, it is not surprising that pivotal prospective trials that guide current clinical decisions were based on the histological diagnosis of oligodendroglioma (7, 8). Retrospective research conducted before or even after that critical change studied a mix of histological and molecularly diagnosed oligodendrogliomas with the risk of including tumors that may not be classified as oligodendrogliomas now (9–15). There is a paucity of studies on purely molecularly defined oligodendrogliomas and those usually have a small number of patients or limited follow-up time (16–22).

Technological developments over the past decade allowed the implementation of genomic studies to our current standard of care for brain tumors, including complex next-generation sequencing (NGS) to decipher their genomic features. Consequently, patients may receive detailed results of NGS panels that describe several tumor-associated mutations. Although many advances have been made, we do not fully understand the clinical implications of those mutations and how a specific genomic signature affects an individual patient's outcome. This is especially true for oligodendrogliomas, where follow-up lasting 10-20 years may be required to understand the impact on prognosis.

Here, we summarize the scientific basis of current management decisions, pose critical questions that remain unanswered, and highlight ongoing or future studies that can improve the management of patients with oligodendrogliomas.

OLIGODENDROGLIOMA: A MOLECULAR DIAGNOSIS

Oligodendrogliomas represent only 5%-10% of all glial tumors in population-based studies (23, 24). Although they typically occur in younger adults, they can appear at any age, have a higher incidence in men, and are rare in children (24, 25). More than 70% of oligodendrogliomas are WHO grade 2, and approximately 20% are WHO grade 3 (1, 24).

The diagnosis of oligodendrogliomas requires the presence of both 1p/19q codeletion and IDH mutation (1). Two landmark papers in 2015 were pivotal to adopting this change. The first was a population-based study of 1087 diffuse gliomas that analyzed the mutation status of 1p/19q, IDH1 and 2, and TERT promoter. Classifying grade 2 and 3 gliomas based upon those mutations stratified the tumors into five molecular subgroups that were independently associated with clinical outcomes. This included the "triple positive" group, which harbored 1p/19q codeletion, IDH, and TERT promoter mutations. Triple-positive gliomas were most strongly associated with the oligodendroglial histologic type and better overall survival (4). This strengthened the importance of harboring an IDH mutation in addition to a 1p19q codeletion to confer a better prognosis, which was already described by Cairncross et al. and Jiao et al. in prior studies (26, 27). The second landmark paper was a genome-wide study of 293 low-grade gliomas by the TCGA Research Network. The group identified three molecular subtypes of lower-grade gliomas using a wide array of genomic, methylation, and protein expression analyses. The IDH-methylated, the IDH-wildtype, and the 1p/19q codeleted subgroups were found to be three prognostically significant and non-overlapping subtypes. Those two molecular markers (IDH mutation and 1p/19q codeletion) became critical in the current diagnosis of gliomas (5). This study also confirmed previous reports by our team and others identifying CIC and FUBP1 as potential oligodendroglioma tumor suppressor genes lost on chromosomes 1p and 19q, respectively (27, 28). Other molecular mutations frequently reported in gliomas, including chromosome 9p deletion and subsequent CDKN2A gene loss, have also been postulated to be involved in oligodendroglioma pathogenesis and malignant progression (29). Markers that drive an aggressive phenotype specifically in anaplastic oligodendroglioma have also been reported, including the transcription factor TCF12 (29). The specific role of these and other molecular markers and their effect on survival remain unclear.

OLIGODENDROGLIOMA MANAGEMENT: EVIDENCE AND CONTROVERSIES

Despite prior research, the optimal treatment paradigm for oligodendrogliomas is still in question (25). Management may start with surgery or observation. Many glioma studies have indicated that more extensive tumor resection with functional preservation is associated with prolonged survival (10–12, 30–33). Thus, although there is limited specific data on molecularly defined oligodendrogliomas, surgery for pathological diagnosis and maximal safe resection remains the favored initial therapeutic approach (31–34).

After surgical removal, upfront treatments for grade 2 oligodendrogliomas include observation (specifically in younger patients who underwent gross total resection [GTR]) or radiation with adjuvant chemotherapy. Grade 3 oligodendrogliomas are typically treated by surgical resection followed by radiation and chemotherapy, although observation may be an option in low-risk cases (35, 36). High-risk has been traditionally considered as being over 40 years of age or receiving less than GTR; however, this is controversial given the indolent biology of these tumors.

Current adjuvant treatment guidelines for oligodendrogliomas are based on two landmark clinical trials in anaplastic oligodendrogliomas and anaplastic oligoastrocytomas. These were the EORTC 26951 by the European Organization for

Research and Treatment of Cancer and RTOG 9402 by the Radiation Therapy Oncology Group (7, 8). Both studies compared the role of Procarbazine, Lomustine - also known as CCNU, and Vincristine (PCV) in combination with radiotherapy with that of radiation therapy alone. However, the timing of radiotherapy was not evaluated. In addition, these trials were designed before discovering the prognostic implications of 1p/19q codeletion and IDH mutations. The 1p/19q codeletion was detected in 48% (126 of 263) of the cases in the RTOG and only 25% (80 of 316) in the EORTC trial (7, 8). In *post-hoc* analyses, both trials demonstrated that tumors with a 1p/19q codeletion benefitted from adding PCV to radiation therapy, markedly increasing the overall survival (OS) of patients with anaplastic oligodendroglioma. Specifically in RTOG 9402 the addition of PCV to RT improved OS from 7.3 to 14.7 years, and OS was not reached at the time of the EORTC 26951 data publication (7, 8). Studies attempting to identify the molecular determinants of survival from the RTOG 9402 were unsuccessful, largely due to a lack of sufficient samples (37).

The PCV regimen entails considerable side effects, including myelosuppression, hepatotoxicity, and neurotoxicity. Grade 3 or 4 hematologic toxicity was reported in more than 45% of the patients assigned to the experimental arm in the EORTC 26951 and RTOG 9402 trials (8, 38). Both studies were launched before the introduction of the oral alkylating agent temozolomide (TMZ) into neuro-oncology practice. TMZ has a more favorable toxicity profile than PCV and neuro-oncologists had become familiar with it in treating high-grade astrocytomas. With the RTOG 9402 and EORTC 26951 data pending, many neuro-oncologists started treating patients with the same regimen used for glioblastoma. TMZ resulted in considerable response rates and promising survival when used as "salvage" chemotherapy in oligodendroglioma relapse after the failure of PCV (39). However, retrospective studies of newly diagnosed oligodendrogliomas treated with TMZ alone revealed very variable outcomes with controversial conclusions (40, 41). The striking results of RTOG 9402 and EORTC 26951, two independently conducted, randomized studies with PCV, challenged the use of radiation and TMZ for oligodendrogliomas, as a comparable level of evidence did not exist for this regimen (25, 42, 43).

An ongoing international phase III clinical trial (CODEL, NCT00887146) was designed to resolve this mystery (44). The CODEL trial compares the efficacy of concomitant radiotherapy with TMZ followed by adjuvant TMZ versus radiotherapy with adjuvant PCV. It is well known that radiotherapy provides an improved progression-free survival for oligodendroglioma patients. In fact, the CODEL trial was initially designed to compare TMZ alone, radiotherapy alone, and radiotherapy with concomitant and adjuvant TMZ. Because the TMZ-alone patients experienced significantly shorter progression-free survival when compared to the patients in the radiotherapy arms, CODEL was redesigned to its current paradigm (44). Radiotherapy has shown promising efficacy with oligodendrogliomas, but there is significant concern for its long-term neurocognitive effects, and the timing of radiotherapy is questioned (16, 25). An ongoing clinical trial (POLCA, NCT02444000) investigates the difference between upfront radiotherapy with PCV versus upfront PCV with deferred radiotherapy. Another active phase III clinical trial (NCT00978458) conducted by the Eastern Cooperative Oncology Group and the National Cancer Institute (NCI) is evaluating whether the addition of TMZ to adjuvant radiation therapy improves survival in patients with low grade glioma, including oligodendroglioma (45). These studies may provide some answers to those critical questions, but the final results will not be available for years. In fact, the expected completion time for primary outcome data collection since the initiation of the CODEL and POLCA trials is 16 and 9 years, respectively (46, 47).

In light of those challenges, both the European Association of Neuro-Oncology (EANO) and the joint American Society of Clinical Oncology (ASCO) and Society for Neuro-Oncology (SNO) recognized the need for clarification by publishing recent evidence-based guidelines on the management of diffuse gliomas, including oligodendrogliomas (35, 36). There have also been changes in the National Comprehensive Cancer Network (NCCN) guidelines for oligodendrogliomas (48). A comparison of those guidelines is presented in **Table 1**.

In summary, the current management for suspected oligodendroglioma consists of observation, surgery, radiation treatment, and chemotherapy. Observation is questionable given the strong evidence in favor of adjuvant therapy. Radiation treatment can be given after surgery and before chemotherapy, or chemotherapy can be given first, with radiation deferred to tumor progression. PCV is the chemotherapy of choice in the official guidelines, with TMZ reserved in those cases with PCV toxicity. In the past, both radiation and chemotherapy were usually delayed in the treatment of oligodendrogliomas. However, given the striking response to chemotherapy, the early use of adjuvant therapies has been favored in the past few years, especially in grade 3 oligodendrogliomas. For example, a 2019 study of the National Cancer Database showed that radiation followed by chemotherapy is the favored sequence of adjuvant therapy for grade 3 oligodendrogliomas in the US (13). Beyond current treatment, new therapeutic avenues are necessary and underway. Exciting work has been done targeting mutant IDH or related pathways. An important example is INDIGO (NCT04164901), an ongoing randomized phase III study of vorasidenib, a promising oral inhibitor of IDH1/2 mutations that has shown a 30.8% objective response rate in non-enhancing glioma patients (49). Other drugs that target molecular markers including abemaciclib, a CDK inhibitor selective for CDK4 and CDK6, are also being investigated for use in oligodendroglioma patients in ongoing clinical trials (NCT03969706) (50).

DISCUSSION

As described, many questions remain unanswered regarding the management of oligodendrogliomas, and a comprehensive understanding of current practices is not known. This was stressed in the oligodendroglioma workshop organized by the National Cancer Institute's NCI-CONNECT in 2018 (25).

TABLE 1 | Societal guidelines for oligodendroglioma management.

Guidelines	American Society of Clinical Oncology and Society for Neuro-Oncology		European Association of Neuro-Oncology		NCCN Guidelines® for Central Nervous System Cancers	
WHO Grade	2	3	2	3	2	3
Molecular diagnosis	IDH1 or IDH2 mutation, 1p19q codeletion					
Surgical therapy	Maximal safe resection					
When to "wait and see"	Defer RT-CT *if*: Absent symptomatic or radiological progression Positive prognostic factors (e.g., complete resection younger age) or concerns about toxicity	NA	Defer RT-CT *if*: GTR, incomplete, resection, <40 y.o., and absent neuro deficits beyond symptomatic epilepsy	Defer RT-CT *if*: GTR, <40 y.o., no neurological deficits, and without homozygous *CDKN2A/B* deletion	Defer RT-CT *if*: Low-risk patients (e.g., GTR and ≤40 y.o) High-risk patients (e.g., >40 y.o. or STR or open/stereotactic biopsy) that are neurologically asymptomatic or stable	NA
Adjuvant Therapy	RT followed by CT					
Radiation therapy	54 Gy in 30 fractions over 6 wk	59.4 Gy in 33 fractions at 5 fractions per wk	50–54 Gy in 1.8–2 Gy fractions	54–60 Gy in 1.8–2 Gy fractions	45-54 Gy	59.4 Gy in 1.8 Gy fractions for 28 fractions followed by a 5-fraction boost of 1.8 Gy/fraction
Chemotherapy	RT followed by PCV: procarbazine 60 mg/m^2 PO QD d 8 – 21, lomustine 110mg/m^2 PO QD on d 1, vincristine 1.4 mg/m^2 IV QD d 8 and 29 in 8 wk cycle for a total of six cycles C/f PCV toxicity, adjuvant TMZ 150-200 mg/m^2 PO QD d 1-5, every 4 wk for a maximum of 12 mo		RT followed by PCV (PCV alone remains investigational, may reduce the risk of late cognitive deficits)	RT followed by PCV (PCV alone remains investigational, may reduce the risk of late cognitive deficits)	Consider clinical trial for those eligible RT followed by PCV RT with or without concurrent TMZ followed by adjuvant TMZ PCV or TMZ alone in rare circumstances	Consider clinical trial for those eligible RT with neoadjuvant or adjuvant PCV RT with or without concurrent TMZ followed by adjuvant TMZ
Surveillance	No recommendation		Neurological exam and imaging every 3-6 mo		MRI every 3-6 mo for 5 y then every 6-12 mo or as clinically indicated	MRI 2-8 wk after RT, then every 2-4 mo for 3 y, then every 3-6 mo indefinitely
Treatment at progression/ recurrence	No recommendation		Based on response to first-line therapy, consider: - Repeat surgery - Re-irradiation - PCV - TMZ - Experimental therapy for WHO grade 3: bevacizumab[a]		Surgery if resectable Biopsy if unresectable Consider clinical trial for those eligible No prior RT, consider: - RT + adjuvant PCV - RT + adjuvant TMZ - RT + concurrent and adjuvant TMZ - CT alone - RT alone[b] Prior RT, consider: - PCV - TMZ	Surgery if resectable Consider clinical trial for those eligible Systemic CT ± RT - RT + adjuvant PCV - RT + adjuvant TMZ - RT + concurrent and adjuvant TMZ - Re-irradiation[d] - TMZ - Lomustine or carmustine - PCV - Platinum-based regimens Palliative/supportive care

(Continued)

TABLE 1 | Continued

Guidelines	American Society of Clinical Oncology and Society for Neuro-Oncology	European Association of Neuro-Oncology	NCCN Guidelines® for Central Nervous System Cancers
			- Lomustine or carmustine - Platinum-based regimens - Reirradiation[c] ± CT - Palliative/supportive care - Observation if low-risk MRI every 2–3 mo

C/f, concern for; CT, chemotherapy; GTR, gross total resection; d, days; Gy, gray; IDH, isocitrate dehydrogenase; mg/m^2, milligram per square-meter; PCV, procarbazine/ lomustine/ vincristine; QD, once a day; mo, months; RT, radiation therapy; TMZ, temozolomide; WHO, World Health Organization; y, years; y.o., years old.

[a] *Used for symptom control.*

[b] *RT alone is generally not the preferred treatment option except in select cases (e.g., poor performance status).*

[c] *Consider if a new lesion outside the target of prior RT or recurrence is small and geometrically favorable.*

[d] *Consider re-irradiation if long interval since prior RT and/or if there was a good response to prior RT.*

Adapted from Weller M et al. EANO guidelines on the diagnosis and treatment of diffuse gliomas of adulthood. Nat Rev Clin Oncol. 2021;18(3):170–86., Mohile NA et al. Therapy for Diffuse Astrocytic and Oligodendroglial Tumors in Adults: ASCO-SNO Guideline. J Clin Oncol. 2022;40(4):403–26.

NA, not applicable.

However, in part due to the low incidence and high complexity of oligodendroglioma management, few of those questions have been clarified. In addition, available prospective data on the management of molecularly defined oligodendrogliomas are either indirect or from *post-hoc* subgroup analysis with potential risk of bias. More definitive answers may be provided by ongoing long-lasting multi-institutional clinical trials based on molecular criteria. In our opinion, intermediate answers are required to shed light on the current management of this type of tumor and standardize practices. First, it is paramount that any future oligodendroglioma study is based on the current molecular definition of oligodendroglioma, confirming 1p19q codeletion and IDH mutation. Second, we believe that surveying the oncological and neurosurgical societies would clarify if current treatment trends, especially adjuvant therapy utilization and chemotherapy regimen selection, differ between geographical regions given the current lack of universal and standardized worldwide guidelines. Although not definitive, an exhaustive study of the clinical features, management, genetic profile, and outcomes of purely molecularly defined oligodendrogliomas in a large retrospective cohort would potentially unveil characteristic features and provide updated management guidance based on current diagnostic standards. This can also help improve risk stratification to extend beyond age and extent of resection. Changes in medical practice are complex and require widespread dissemination of information. In the long run, a worldwide task force in charge of revising and implementing the CODEL and POLCA trial results will be essential to translate high-quality data into daily practices. Finally, oligodendrogliomas are still not curable, and new therapeutic avenues are imperative. Whether IDH inhibitors become integral to treating this disease remains to be evaluated. These and other important clinical trials are desperately needed to improve outcomes for patients with oligodendroglioma.

CONCLUSION

Here, we have summarized the current advancements in the molecular characterization of oligodendrogliomas and reviewed adjuvant treatment modalities currently used in its treatment. The future directions in research we have outlined, including retrospective and clinical trials, have significant potential to further advance the management and prognosis of oligodendroglioma patients when effectively translated into clinical practice.

AUTHOR CONTRIBUTIONS

JR-T, CB, and JJGS devised the project, the main conceptual ideas, and the proof outline. JR-T, MR, JM, DR, TV-B, AF, WRS, KR, MH, CB, and JJGS contributed to the design and implementation of the research, the analysis of the results, and the writing of the manuscript. In addition, WRS, CB, and JJGS provided institutional support. All the authors approved and reviewed the submitted version of the manuscript.

FUNDING

JR-T is an NINDS R25 training grant awardee (5R25NS065729).

ACKNOWLEDGMENTS

We thank Universidad de Santander and Universitat de Barcelona for their administrative support.

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Conflict of Interest: CB is a consultant for Depuy-Synthes, Bionaut Labs and Galectin Therapeutics and a co-founder of OrisDx. KR: Research support from Elekta AB, Accuray, Canon; Data Safety Monitoring Board for BioMimetix; Travel expenses from Brainlab, Elekta AB, Accuray, Icotec, RSS; Honorarium for speaking engagement NCCN, Accuray.

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frontiers | Frontiers in Oncology

TYPE Original Research
PUBLISHED 28 July 2022
DOI 10.3389/fonc.2022.975738

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Neuro-Oncology and Neurosurgical Oncology, a section of the journal Frontiers in Oncology

RECEIVED 22 June 2022
ACCEPTED 30 June 2022
PUBLISHED 28 July 2022

CITATION
Baiano C, Somma T, Franca RA, Di Costanzo M, Scala MR, Cretella P, Esposito F, Cavallo LM, Cappabianca P and Solari D (2022) Evolution in endoscopic endonasal approach for the management of hypothalamic–pituitary region metastasis: A single-institution experience.
Front. Oncol. 12:975738.
doi: 10.3389/fonc.2022.975738

Evolution in endoscopic endonasal approach for the management of hypothalamic–pituitary region metastasis: A single-institution experience

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Introduction: Endonasal endoscopic surgery has changed the treatment perspectives for different lesions of the hypothalamic–pituitary region. The metastases of the hypothalamic–pituitary region represent 0.4% of all intracranial metastatic tumors and account for only 1.8% of surgically managed pituitary lesions. The aim of tshis study is to describe a single-center institutional experience with 13 cases of hypothalamic–pituitary metastasis focused on presurgical workup, the evolution of the surgical technique, and postsurgical management according to our protocols, showing effects on progression-free and overall survival rates for this relatively uncommon location.

Material and Methods: We retrospectively reviewed the whole series of patients that received the endoscopic endonasal approach at the Division of Neurosurgery at the University of Naples "Federico II" undergoing surgery from January 1997 to December 2021. We identified 13 cases whose pathology reports revealed a metastatic lesion. Statistical analysis was performed to determine the Kaplan–Meier survival function and assess for log-rank differences in survival based on gender, surgical treatment, and postoperative therapy (p-value < 0.02*).

Results: The pathology report disclosed lung adenocarcinoma (six cases, 46%), breast adenocarcinoma (two cases, 15.4%), clear cell renal carcinoma (one case, 7%), melanoma (one case, 7%), colorectal adenocarcinoma (one case, 7%), uterine cervix carcinoma (one case, 7%), and follicular thyroid carcinoma (one case, 7%). A standard endoscopic endonasal approach was performed in 10 patients (76.9%), while an extended endonasal procedure was performed in only three cases (23%). Biopsy was the surgical choice in five patients with infiltrative and invasive lesions and a poor performance status (38%), while in the cases where neurovascular

10.3389/fonc.2022.975738

decompression was necessary, a subtotal resection was achieved in five patients (38%) and partial resection in three patients (23%). Recovery of visual field defect was observed in six of seven patients with visual loss (85.7%), improvement of oculomotor nerve palsy occurred in four of seven patients with this defect (57.1%), while the impairment of oculomotor palsy was observed in three patients (42.9%). Visual function was stable in the other patients. The median progression-free survival and overall survival were 14 and 18 months, respectively. There were statistically significant differences in PFS and OS in patients who underwent adjuvant radiotherapy (p=0.019 is referred to OS and p=0.017 to PFS, respectively; *p*-value = 0.02).

Conclusions: The endoscopic endonasal approach is a viable approach for the management of hypothalamic–pituitary metastases as this surgery provides an adequate opportunity to obtain tissue sample and neurovascular decompression, both being crucial for continuing the integrated adjuvant therapy protocols.

KEYWORDS

hypothalamic–pituitary pathology, endoscopic endonasal surgery, brain metastasis, neuro-oncology-surgical, surgical procedures

Introduction

The inherent characteristics of endonasal endoscopic surgery have changed the treatment perspectives and operative nuances for different lesions of the hypothalamic–pituitary region (1).

This surgical route, in the standard version, has provided a more accurate distinction between healthy and pathological tissues in pituitary micro- and macroadenoma removal, thus ensuring pituitary gland preservation, an increase in the extent of resection, and an accurate histopathological characterization. Then, the extended approach, through access to the suprasellar, parasellar, retrosellar, clival, and retroclival spaces by shorter surgical corridors than the transcranial route, has revolutionized the management of complex and non-adenomatous midline lesions such as craniopharyngiomas, meningiomas, and clival chordomas (2–5). For the less common and more infiltrating lesions such as sarcomas, gliomas, metastases, and granulomatosis (sarcoidosis), it has enabled a minimally invasive biopsy and/or the identification of surgical removal limits, taking into consideration the principles of maximal safe resection (6).

The metastases of the hypothalamic–pituitary region represent 0.4% of all intracranial metastatic tumors and account for only 1.8% of surgically managed pituitary lesions (7). Metastatic tumor cells may involve the pituitary gland *via* different patterns of spread, including direct hematogenous, from the hypothalamus or stalk through the portal hypophyseal vessels or from the juxtasellar or skull base metastasis through the arachnoid of the suprasellar cistern (8, 9).

At our institution, in a dedicated tertiary center for hypothalamic–pituitary disorders, the possibility of observing more than one hundred endoscopic endonasal procedures per year has granted the wide series and also the variety with the inclusion of metastatic pathology of the aforementioned region (10–12).

In the circular process of update application in clinical complementary fields adjacent to the midline skull base surgery (endocrinology, neuroradiology, pathology, radiotherapy, and oncology), the new strategies of approach to hypothalamic–pituitary lesions are dependent on a multidisciplinary approach (13–18). Furthermore, advancements in target systemic radiosurgery and whole-brain radiotherapy and therapy for brain metastasis management have changed prognostic models (19–22). In this setting, the endoscopic endonasal approach is proposed as a valid tool for obtaining tissue for histological examination and determining consequently therapeutical steps in the treatment of metastatic patients (23–25).

The aim of this study is to describe a single-center institutional experience with 13 cases of sellar metastasis focused on presurgical workup, evolution of surgical technique, and postsurgical management according to our protocols, showing effects on progression-free and overall survival rates for this relatively uncommon location.

Methods

This study was approved by the Institutional Review Board of the School of Medicine of the University of Naples "Federico II," which waived the need for informed consent due to the retrospective nature of the study. Written informed consent was obtained from the patients prior to any invasive clinicodiagnostic and surgical procedure; indeed, it was obtained for the eventual publication—for scientific purposes—of any patient records/information anonymously.

We retrospectively reviewed the whole series of patients that received the endoscopic endonasal approach at the Division of Neurosurgery at the University of Naples "Federico II" undergoing surgery from January 1997 to December 2021. We identified 13 cases whose pathology report revealed a metastatic lesion.

Case history, histological diagnosis, endocrinological assessment, preoperative and postoperative radiological records, preoperative treatment, intraoperative surgical videos, and instrumental eye examinations were revised. All patients underwent a pituitary pre- and postsurgical function assessment, pre- and postoperative post-gadolinium magnetic resonance (MRI), and complete visual assessment (computerized visual field, Lancaster red-green test, visual acuity).

Statistical analysis was performed to determine the Kaplan–Meier survival function and assess for log-rank differences in survival based on gender, surgical treatment, and postoperative therapy (p-value < 0.02). All analyses were performed using the R environment software for statistical computing (Figure 1) (R Development Core Team, Vienna, Austria, 2013).

Surgical Technique

All the patients underwent an endoscopic endonasal approach. For intrasellar lesion, a standard operative nuance was performed, while in the case of supradiaphragmatic lesion, the most suitable extended approach was chosen according to the techniques already described (2). In all cases, extemporaneous histological examination was decisive for subsequential surgical steps.

Pathology

Unusual morphological patterns can cause diagnostic concern for other lesions (sinusoidal pattern and macronodular or festoon-like features, as well as lesions with diffuse epithelioid features). In these

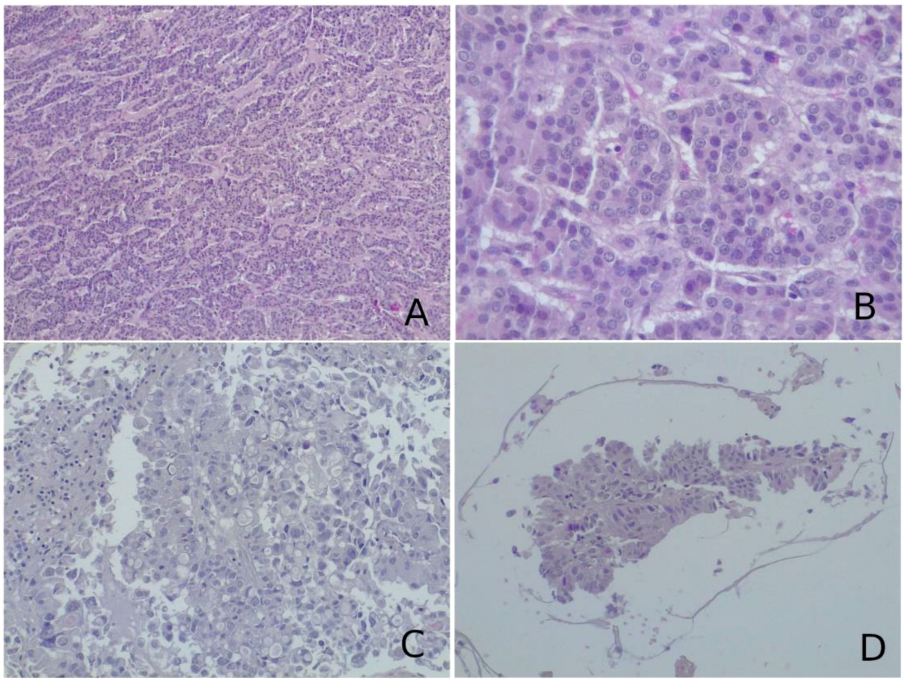

FIGURE 1
(A, B) Histological examination of the lesion biopsied revealed a neoplasm composed of cells arranged in follicular, cord-like, and nodular structures. On immunohistochemistry, neoplastic cells were positive for thyroglobulin, PAX8, TTF1, and cytokeratin 19 and negative for CD56 and CDX2. This morphological picture was suggestive of metastatic follicular thyroid carcinoma. **(C, D)** On histological slides, a glandular neoplasm, composed of pleomorphic, vacuolated cells with high-grade characteristics and papillary arrangement [most clear in **(D)**], was seen. Neoplastic cells were immunoreactive for cytokeratin 7 and TTF1 and negative for cytokeratin 20. These characteristics were more suggestive of adenocarcinoma metastasis from a lung primary tumor. **(A–D)** Hematoxylin–eosin, original magnification ×40.

cases, a routine immunohistochemical panel was performed (ACTH, PRL, GH, TSH, FSH, LH, GH, Ki67), including reticulin staining, neuroendocrine differentiation using immunohistochemical markers (chromogranin, synaptophysin), and immunoreactivity for transcription factors (T-Pit, Pit1, SF1), which were directed toward a correct diagnosis.

The differential diagnosis between a pituitary adenoma and metastatic cancer is rarely a problem: mitotic activity and cellular pleomorphism are nearly always the hallmarks of a metastatic neoplasm, while these are rare in pituitary adenomas.

When a lesion is thought to be a metastasis with no primary tumor clearly diagnosed, additional markers should be performed to define the tumor lineage: LCA (CD45) positivity is seen in lymphoproliferative lesions; carcinomas are nearly always pan-cytokeratin-positive; TTF1 positivity suggests a pulmonary or thyroid origin (the latter being positive also for thyroglobulin and PAX8); CDX2 positivity suggests cancer originating in the gastroenteric tract; HMB45 along with MART1, SOX10, and S100 immunoreactivity is a feature of melanoma; GCDFP-15 and mammaglobin are markers of breast cancer; PSA positivity suggests a prostate primitivity; and PAX8 immunoreactivity supports a diagnosis of metastatic renal cell carcinoma.

A challenging differential diagnosis concerns distinguishing null cell adenoma from metastatic neuroendocrine carcinoma: indeed, both are tumors immunonegative for all the hypophysial markers (hormones and transcription factors) but positive for neuroendocrine markers. Morphology, mitotic activity, and lineage differentiation markers (TTF1, CDX2, CK, calcitonin, etc.) are useful to make a correct diagnosis. However, it must be kept in mind the possibility of the debated entity of primary intracranial neuroendocrine carcinoma arising in the sellar region (TTF1−) and small cell carcinoma of unknown primary (SCUP) (TTF1+) (Figure 2).

Results

Between around 1997 and December 2021, 2,303 patients underwent endonasal endoscopic surgery for the removal of different skull base lesions—mostly pituitary adenomas—at the Division of Neurosurgery at the University of Naples "Federico II." Of these patients, 13 (0.6%) had a metastatic lesion (Table 1). Nine patients were women and four were men; the mean age was 58 years. Three patients presented a pure infradiaphragmatic intrasellar lesion (23%); four patients presented intra-, supra-, and parasellar lesions (30%); and six patients had intra-, supra-, and retrosellar lesions (46%). The most common presentation was headache in 10 patients (76.9%), followed by visual loss in 7 patients (53.8%), adenohypophysis dysfunction in 6 patients (46%), diabetes insipidus in 6 patients (46%), visual field defect in 3 patients (23%), and oculomotor nerve palsy in 3 patients (23%) (Table 2). In the five cases of lung adenocarcinoma, pituitary metastasis was the first presentation of neoplastic disease.

The surgical strategy was tailored based on the lesion extension and the performance status of the patients: in three

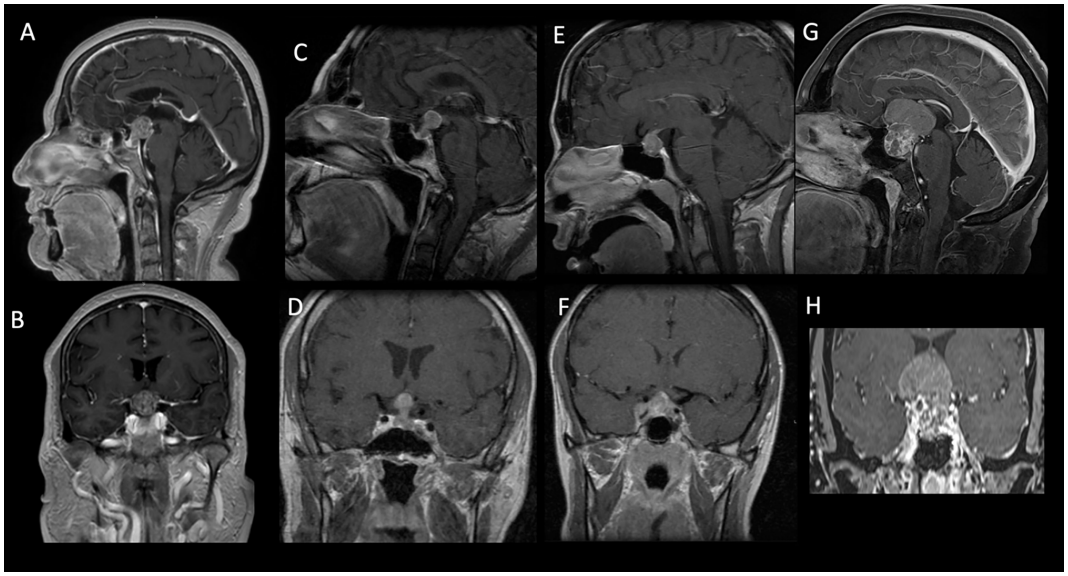

FIGURE 2
Sagittal and coronal preoperative MRI T1-weighted contrast-enhanced images of patients from our cohort showing intra- and suprasellar lesions with inhomogeneous enhancement. The pathology report disclosed breast adenocarcinoma **(A**, **B)**, lung adenocarcinoma **(C**, **D)**, clear cell renal carcinoma **(E**, **F)**, and uterine cervix carcinoma (**G, H**).

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TABLE 1 Patient demographics and primary neoplasm.

Patient	Age (years)	Sex	Cancer type	Known metastatic disease
1	45	M	Lung adenocarcinoma	–[a]
2	48	F	Lung adenocarcinoma	–[a]
3	68	F	Melanoma	+
4	53	F	Breast carcinoma	+
5	59	F	Lung adenocarcinoma	–[a]
6	68	M	Squamous cell carcinoma (lung)	+
7	65	F	Lung adenocarcinoma	–[a]
8	50	F	Cervical carcinoma	+
9	62	F	Follicular thyroid carcinoma	+
10	67	F	Colorectal adenocarcinoma	+
11	80	M	Clear cell renal carcinoma	+
12	65	F	Breast carcinoma	+
13	51	M	Lung adenocarcinoma	–[a]

[a]Pituitary metastasis was the first presentation of neoplastic disease.

cases, an extended endonasal approach was required; in five cases, only a biopsy was performed. The endoscopic endonasal standard approach was used in 10 patients; for the other three patients, an extended trans-planum approach was performed. Osteodural defect reconstruction was necessary in two cases (Table 3).

The pathology report disclosed lung adenocarcinoma (six cases, 46%), breast adenocarcinoma (two cases, 15.4%), clear cell renal carcinoma (one case, 7%), melanoma (one case, 7%) colorectal adenocarcinoma (one case, 7%), uterine cervix carcinoma (one case, 7%), and follicular thyroid carcinoma (one case, 7%) (Table 1 and Figure 1).

The standard endoscopic endonasal approach was performed in 10 patients (76.9%), while the extended endonasal procedure was used in only three cases (23%). Biopsy was the surgical choice in five patients with infiltrative and invasive lesions and a poor performance status (38%). On the other hand, in the cases where neurovascular decompression was necessary, a subtotal resection was achieved in five patients (38%) and a partial resection in three patients (23%).

Recovery of visual field defect was observed in six of seven patients with visual loss (85.7%), improvement of oculomotor nerve palsy occurred in four of seven patients with this defect (57.1%), while impairment of oculomotor palsy was observed in three patients (42.9%). Visual function was stable in the other patients.

Concerning complications, no infection and CSF leak were seen; we observed one patient developing transient diabetes insipidus.

Adjuvant therapy was used in all cases. Ten patients were treated with systemic chemotherapy (59%), two patients (20%) had stereotactic radiotherapy, and one patient with a clear cell renal carcinoma had a combination of radio- and chemotherapy.

TABLE 2 Symptoms at presentation.

Patient	Cranial nerve palsy (3, 4, 6)	Visual field defect	Adenohypophyseal dysfunction	Diabetes insipidus	Headache
1	–	BT	Hypothyroidism, hypercortisolism	–	+
2	+ (3, 6, 4)	–	Hypocortisolemia, hypogonadism	+	–
3	+ (3)	–	–	–	–
4	–	BT	–	+	+
5	+ (3, 6)	–	–	–	+
6	–	–	–	–	+
7	–	–	Hypergonadism, hypocortisolism	+	–
8	–	+	Hypercortisolemia	+	+
9	+	+	Hypothyroidism		+
10	–	–	/	–	+
11	+	+	–	+	+
12	+	+	–	–	+
13	+ (3)	+	Hypocortisolemia, hypogonadism	+	+

(3), 3rd cranial (oculomotor) nerve; (4), 4th cranial (trochlear) nerve; (6), 6th cranial (abducens) nerve; BT, bitemporal hemifield defect.

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TABLE 3 Surgical approach and reconstruction data.

Patient	Extended procedure	Reconstruction
1	–	NA
2	–	–
3	–	–
4	+	+
5	–	–
6	–	–
7	–	–
8	+	+
9	–	–
10	+	–
11	–	–
12	–	–
13	–	–

+ extended procedure, - not extended procedure; + osteo-dural reconstruction, - not osteo-dural reconstruction; NA information not available.

After adjuvant treatment, three patients (23%) developed pan-hypopituitarism.

The median progression-free survival and overall survival were 14 and 18 months, respectively (Table 4). There were statistically significant differences in PFS and OS in patients who underwent adjuvant radiotherapy (p=0.019 is referred to OS and p=0.017 to PFS, respectively; *p*-value = 0.02) (Figure 3).

Discussion

Hypothalamic–pituitary metastatic lesions represent a very challenging diagnosis: clinical signs are not different from the other lesions affecting this area, and there are no pathognomonic signs at MRI or CT scan (6, 26). Moreover, the lack of a certain presence of tumor history jeopardizes the likelihood of a lesion of the hypothalamic–pituitary region being a metastasis (9). In the present series, we found five cases of hypothalamic–pituitary metastasis figured out as the first lesion of neoplastic disease.

A positive oncological anamnesis for the most common primary tumors associated with hypothalamic–pituitary metastasis (breast cancer in women, 40% of the cases; lung cancer in men, 24% of the cases) could verify the suspicion. Other primary tumors that are less common include gastrointestinal tract (6.3%), prostate (5%), melanoma (2.4%), and thyroid (2.2%) malignancies (8, 23, 27). Primitive tumors observed in this series were lung adenocarcinoma (six cases, 46%), breast adenocarcinoma (two cases, 15.4%), clear cell renal carcinoma (one case, 7%), melanoma (one case, 7%), colorectal adenocarcinoma (one case, 7%), cervical carcinoma (one case, 7%), and follicular thyroid carcinoma (one case, 7%) (Table 1).

In agreement with the current literature (8, 27–30), the main clinical manifestation was headache (76.9%), followed by visual loss (53.8%), adenohypophysis dysfunction (46%), diabetes insipidus (46%), visual field defect (23%), and oculomotor nerves palsy (23%). In this scenario, we have to consider diabetes insipidus as a typical feature of infiltrative non-adenomatous sellar lesions (sarcoidosis, hypophysitis, histiocytosis, craniopharyngiomas, ATRT) and, above all, when it is associated with visual loss and/or nerve palsy (6, 31).

Microsurgical trans-sphenoidal, open transcranial, and trans-facial surgery were the last common surgical routes to be reported in the management of pituitary metastasis, and the mortality and morbidity related to these procedures were not insignificant (28, 32).

Initially, the endoscopic endonasal technique was considered a two-handed technique, and similar to the microsurgical technique, the basic principles used are not far from those when operating using a microscope. The evolution of the four-

TABLE 4 Surgical and adjuvant management.

Patient	Surgery (EEA)	Adjuvant therapy	Progression-free survival	Overall survival
1	Debulking	Chemotherapy	8 months	10 months
2	Biopsy	Chemotherapy	6 months	7 months
3	Debulking (partial)	Chemotherapy	8 months	9 months
4	Debulking	Chemotherapy	34 months	36 months
5	Debulking (partial)	Chemotherapy	1 month	2 months
6	Biopsy	Chemotherapy	3 months	4 months
7	Biopsy	Chemotherapy	1 month	2 months
8	Debulking (partial)	Radiotherapy	48 months	Alive
9	Biopsy	Radiotherapy	48 months	Alive
10	Debulking	Chemotherapy	8 months	NA
11	Biopsy	Radiotherapy + chemotherapy	2 months	3 months
12	Debulking	Chemotherapy	20 months	2 years
13	Debulking	Chemotherapy	4 months	6 months

EEA, endoscopic endonasal approach; NA, not available.

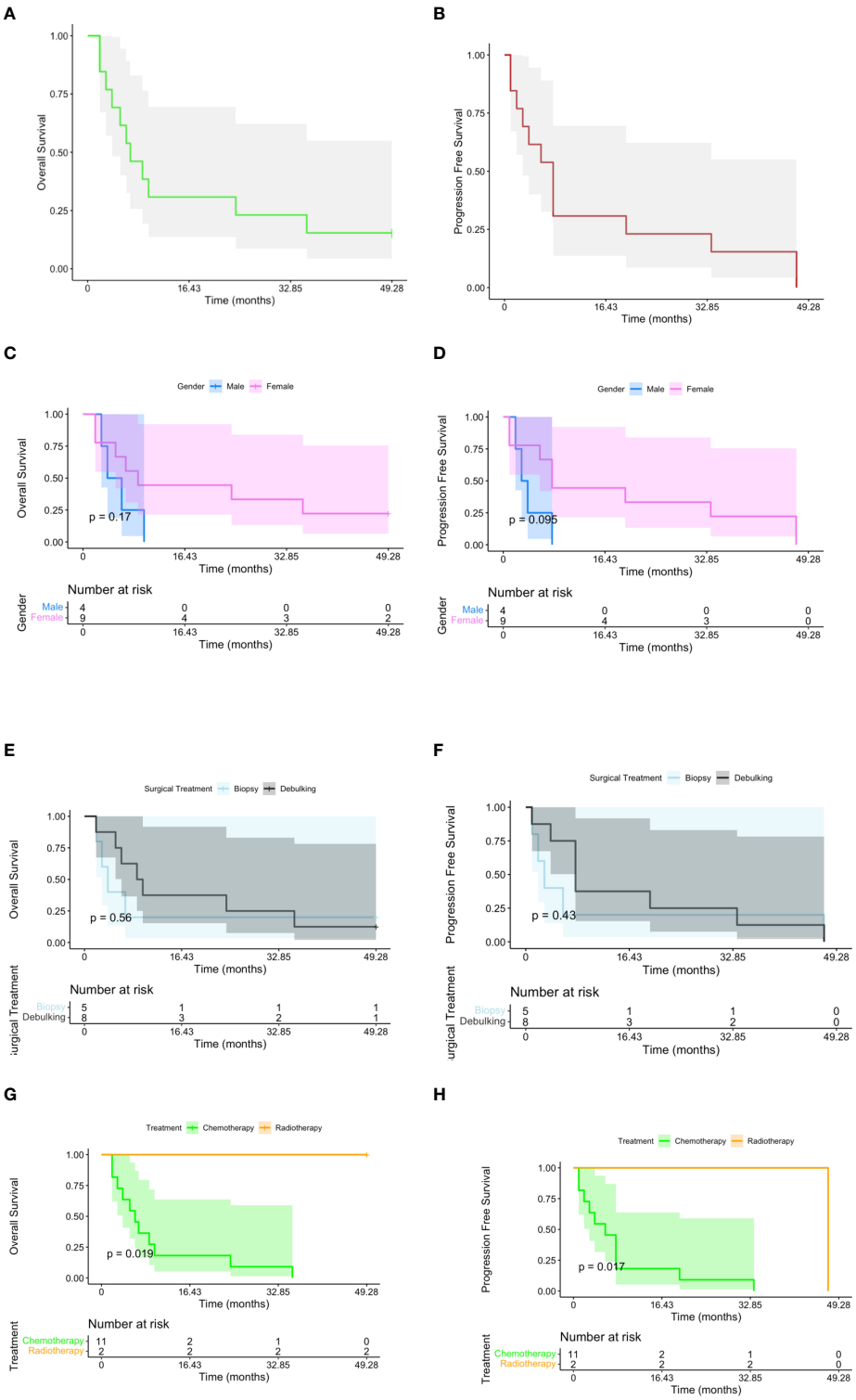

FIGURE 3
Kaplan–Meier plots reporting overall survival (OS) and progression-free survival (PFS) for all the subjects included in the study **(A, B)**. OS and PFS have been stratified, respectively, by gender **(C, D)**, surgical treatment **(E, F)**, and postoperative therapy [**G** (p-value < 0.02), **H** (p-value < 0.02)].

handed technique, in a setting of close and dynamic cooperation between two operators, has granted a useful amplification of the surgical corridor and the augmentation of the angle of exposure by a continuous change of framing, focus, and distance view. The increase in surgical agility, allowing improvement in the dissection method, has made the endoscopic endonasal technique a valid tool for managing the entire ventral skull base, according to the same surgical principles of the open approaches, offering a possibility of treating a wide variety of median and paramedian lesions with satisfactory outcomes (2, 5, 33, 34).

The possibility to access the supra-, para-, and retrosellar spaces by extended procedures has changed the way of exploring and removing even more complex lesions. Extended approaches may be considered in selected cases, and it allows the removal of a vascularized tumor or suprasellar residual tumor in order to avoid postoperative hematoma. The benefit offered by the extended endonasal route is to allow an extracapsular dissection of the tumor beside the standard endosellar corridor (3, 5, 35). Advancements in surgical route reconstruction techniques have contributed to ameliorate postsurgical outcome and performance status (36, 37).

Analyzing our metastasis series, three patients presented a pure intrasellar lesion (23%); four patients had intra-, supra-, and parasellar lesions (30%); and six patients had intra-, supra-, and retrosellar lesions (46%). Surgical strategy was tailored based on lesion extension, intraoperative histological examination, and performance status of the patients: in three cases, an extended endonasal approach was required; in five cases, only a biopsy was performed. The endoscopic endonasal standard approach was used in 10 patients; for the other three patients, an extended trans-planum approach was performed with good control of piecemeal resection.

Based on intraoperative histological examination, in the cases of intrasellar tumors, debulking could be smoother than supra- and retrosellar lesions, even if a poor performance status and a fibrous consistency with infiltrative pattern make biopsy a more reasonable choice. This principle is applied also in lesions extended to the supra-, para-, and retrosellar spaces in the cases which only a neurovascular decompression is possible (14) (15, 27, 30, 38).,

The proper management of a hypothalamic–pituitary metastasis requires a cogent balance between medical treatment, watchful waiting, surgery, and radiation therapy (1, 15, 23–25). Surgical resection can be complicated by fibrous consistency, irregular shape, and invasiveness of the tumor, which often lead to incomplete resections, increasing the risks of morbidity (27). Current literature shows one case report about a case of non-small cell lung cancer (NSCLC) with EGFR exon 19 deletion mutation, in which osimertinib eradicated the metastasis and prevented the need for radiation therapy (39).

In other studies, the main treatment for single brain metastasis is maximal safe surgical resection in combination with radio- and chemotherapy (16, 27, 30, 38, 40–42). In our series, this approach together with the combination of surgery and adjuvant therapy showed improvement in PFS and OS. Indeed, after multidisciplinary concertation, adjuvant therapy was used in all cases according to cogent protocols (24, 25). Ten patients were treated with systemic chemotherapy (59%), two patients (20%) had stereotactic radiotherapy on residual disease, and one patient with a clear cell renal carcinoma had a combination of radio- and chemotherapy. After adjuvant treatment, three patients (23%) developed pan-hypopituitarism.

In this study, the median progression-free survival and overall survival were 14 and 18 months, respectively (Table 3). Two patients are still alive 1 year after surgery. There were statistically significant differences in survival based on the type of adjuvant therapy on Kaplan–Meier analysis (i.e., radiotherapy was associated with a survival increase than chemotherapy). A limitation of this study is the reduced sample size. Before endonasal endoscopy introduction, the microsurgical transsphenoidal approach with partial resection and adjuvant treatment (local radiation) was associated with better symptom relief without effects on survival rates, which is less than 12 months in several studies; furthermore, the mean survival length in the clinical series was 6–7 months (28, 43–45). Zoli et al. reported a median survival of 11.8 months after transsphenoidal surgery followed by radiation therapy (46). In the series of anterior skull base metastases managed by the endoscopic endonasal approach reported by Zacharia et al., PFS and OS were 18 and 16 months and any correlation between survival and other variables was detected (41). In a similar multicentric study involving 12 patients, the mean OS was reported to be 17 months (30). The increase in survival is due to advancements in the surgical and oncological fields, and we do not speculate that only the endonasal approach has impacted survival.

Concerning outcomes, recovery of the visual field defect and impairment of oculomotor nerve palsy were both observed in three of four patients (75%). Recovery of visual field defect was observed in six of seven patients with visual loss (85.7%), improvement of oculomotor nerve palsy occurred in four of seven patients with this defect (57.1%), while impairment of oculomotor nerve palsy was observed in three patients (42.9%). These results validate the role of endoscopic surgery as a tool for a satisfying decompression of the optic pathways. Regarding postsurgical complications, no postoperative cerebrospinal fluid leak occurred in any of the patients; one patient developed transient diabetes insipidus. According to current literature about the cases of pituitary metastasis managed with endoscopic endonasal surgery, this strategy is associated with a few complications and does not have an impact on the performance status of patients (1, 30, 34, 40, 41, 46).

A correct balance between surgical indications and evaluation of functional recovery impact on quality of life is mandatory. Indeed, not being able to know *a priori* if a lesion is

metastatic or not, presurgical workup combined with surgical endoscopic experience has allowed a better interpretation of intraoperative features guiding the diagnosis and the subsequent management of the lesions. Furthermore, an extemporaneous histological examination is crucial to determine the surgical procedure and level of resection for improving PFS and OS (24, 25, 41).

Conclusions

Pituitary metastasis surgery requires a cogent balance between medical treatment, watchful waiting, surgery, and radiation therapy; it requires cleverness, great versatility, and the collaboration of different specialists.

The endoscopic endonasal approach is a viable approach for the management of hypothalamic–pituitary metastases as this surgery provides adequate opportunity to obtain tissue sample and neurovascular decompression, both being crucial for continuing the integrated adjuvant therapy protocols.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/supplementary material.

Ethics statement

This study was approved by the institutional review board of the School of Medicine of University of Naples "Federico II", which waived the need for informed consent due to the retrospective nature of the study. Written informed consent was obtained from the patients prior than any invasive clinico-diagnostic and surgical procedure; indeed, it was obtained for the eventual publication – for scientific purpose - of any patient records/information anonymously. The patients/participants provided their written informed consent to participate in this study.

Author contributions

CB: writing of the original draft, review, and editing. TS, DS, and LC: revisions. RF and PCr: responsible for the pathology methods section; MDC, RF, and PC: acquisition of data. MS: statistic analysis. DS, FE, LC, and PCa: supervision and validation. All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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