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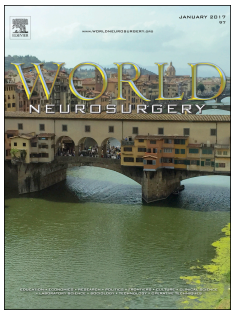

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The Role of Neoadjuvant Therapy to Improve the Extent of Resection in "Unresectable" Gliomas

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The Role of Neoadjuvant Therapy to Improve the Extent of Resection in "Unresectable" Gliomas

Abstract

Introduction: Surgical resection plays a pivotal role in the management of glial tumors and a greater extent of resection should be the goal in most surgeries in order to improve overall survival. Many factors may limit the extent of resection A potential role for preoperative chemotherapy to decrease the volume and/or infiltration of gliomas, thereby facilitating a safe radical resection, has been recently suggested. This review aims to provide an overview of the current state of neoadjuvant therapy in the field of glioma surgery.
Methods: A systematic review was conducted according to PRISMA guidelines to identify articles of low and high-grade gliomas that received neoadjuvant chemotherapy prior to surgery to improve the extent of resection from 2000 to 2020. Full-text papers that addressed this subject were included for evaluation.
Results: Case reports and clinical trials have been published for the use of chemotherapy as a neoadjuvant therapy to improve surgical resection in low-grade gliomas. More scarce information exists regarding this strategy for high-grade glioma surgery.
Conclusion: Neoadjuvant chemotherapy has played a role in overcoming obstacles that limit the extent of resection in patients with complex gliomas, especially low-grade gliomas.

Key Words: Neoadjuvant; Chemotherapy; Temozolomide; Glioma; Resection.

Declarations

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Introduction

Gliomas comprise the most common primary intracranial neoplasms as a whole, and a wide variety of tumors exist in this group, demonstrating various clinical and biological behaviors. Gliomas are the most common primary central nervous system (CNS) tumors, with an estimated annual incidence of 6.6 per 100,000 individuals in the United States [1].
In 2016 the World Health Organization (WHO) established a new classification for glial tumors, that aside from the histological characteristics, included molecular genetics as a form to better understand their behavior [2]. Independent of tumor grade, surgical resection plays a pivotal role in the management of glial tumors and a greater extent of resection (EOR) should be the goal in most surgeries in order to improve overall survival [3, 4].
Many factors, including size, localization and diffusiveness of the tumor may limit the extent of resection [5, 6], a factor that may be obvious to the surgeon in the preoperative period.
A potential role for preoperative chemotherapy to decrease the volume and/or infiltration of gliomas, thereby facilitating a safe radical resection, has been recently suggested [7-9].
This paper aims to review the current strategies utilized as neoadjuvant treatment in patients with glial tumors, in order to improve surgical resection in the follow-up period.

Methods

Literature Review

A systematic review was conducted in accordance with PRISMA guidelines and recommendations to identify all articles on neoadjuvant chemotherapy to improve the EOR on low and high-grade gliomas from 2000 to 2020.
Using the advanced search in PubMed/Medline with terms “glioma” OR “glioblastoma” and “neoadjuvant” OR “upfront”, a total of 340 articles published between January of 2000 and June of 2020 were found in August of 2020.

All 340 articles were browsed in search for information that specifically addressed the use of chemotherapy as a strategy to improve tumor characteristics and therefore improve the EOR. Once the data extraction was completed it was rechecked by the authors independently to rule out any error and duplication.
All articles in which neoadjuvant chemotherapy was not specifically used to improve the EOR in gliomas were excluded from the analysis.
The PRISMA flow chart [Fig. 1] explains the data synthesis from the eligible studies.

Results

A total of 340 articles came up after using the PubMed/Medline search engine. The 340 articles were browsed and all the articles that did not specifically mentioned neoadjuvant chemotherapy as a method to improve the extent of resection in a subsequent surgery were excluded from the final analysis.
At the end 10 articles met the inclusion criteria that included 5 case reports, 3 retrospective studies, one prospective study and one phase II trial.

Seven articles reported the use of chemotherapy to improve the extent of resection in LGG and 5 articles mentioned this strategy in HGG. Two papers reported separate cases of pediatric patients, these were also excluded form the final analysis, although will be mentioned briefly in the discussion [Table 1 and 2].

Discussion

Low-Grade Gliomas

Low-grade gliomas (LGG) are slow growing primary brain tumors classified as mainly astrocytomas or oligodendrogliomas grade II by the WHO classification of brain tumors [2]. The natural history of these tumors is to slowly grow overtime and eventually transform into high-grade gliomas (HGG) and ultimately lead to death [10, 11]. Currently, guidelines recommend maximal surgical resection as the first therapeutic option for LGG [12], as it has a great impact on the natural history of the disease and improves the overall survival (OS) and progression free survival (PFS) in these patients. Regarding LGG, the EOR is evaluated based on magnetic resonance imaging (MRI), and a complete resection of the hyperintense region on the FLAIR sequences is considered a GTR for these tumors.
Having this principle in mind, many strategies have been proposed to improve the EOR in those cases where the extension of the lesion or location, make a gross total resection (GTR) unfeasible.

Temozolomide (TMZ) is an oral alkylating agent introduced in the early 1990s with great enthusiasm given its penetration of the blood-brain barrier and excellent overall tolerability [13], and is now recommended for adjuvant treatment after surgical resection in patients with LGG [14]. It has been used as an up-front treatment in a series of studies, and despite the quality of the studies, it has shown promising results.

According to the literature search, in 2005 Voloschin published the first reported case of TMZ used as neoadjuvant treatment in LGG [7]. In this paper a 38 year-old woman was diagnosed with a grade II oligodendroglioma in the right frontal lobe that was initially considered unresectable due to its size and location. The patient

received TMZ for 24 months, and presented a partial response on the MRI, reason why the authors decided to perform a new surgery to achieve GTR. The patient remained alive and well without evidence of recurrence 7 months after resection and 48 months after initial diagnosis.
In 2006 Duffau and colleagues described the case of a 40 year-old man with a progressive grade II oligodendroglioma that showed invasion to the contralateral frontal lobe via the corpus callosum, at the time of initial evaluation the tumor was considered unresectable [8]. The patient received 8 cycles of TMZ and the tumor showed regression of the contralateral invasion as well as the corpus callosum compromise. Due to the new imaging characteristics, the patient was taken into surgery to achieve GTR of the visible tumor. After a 2-year follow-up the patient had no recurrence.

Even though case reports lack strong clinical evidence, these two case reports are of great importance because they opened the door for other investigations regarding this issue and provided a new strategy for the management of patients with LGG in whom initial resection seems unfeasible.

Following these reports, a retrospective study with 17 patients was published in 2013 that analyzed several characteristics of patients that received neoadjuvant therapy with TMZ prior to surgical resection [15]. They achieved a tumor volume reduction of 35.6% in average, and that correlated with a posterior greater extent of resection. This is an interesting study because it defines a tangible goal of volume reduction that may be used in order to plan the treatment with upfront chemotherapy and a subsequent surgery.
Despite its limitations, it was concluded that chemotherapy with Temozolomide could optimize the surgical resection of LGG and could impact prognosis in these patients. It is interesting that tumor molecular profile was included as a variable in this study and suggested that isocitrate dehydrogenase 1 (IDH1) mutation and MGMT promoter methylation could be a factor on tumor response to TMZ as a neoadjuvant agent, just as it has been established in the adjuvant setting.

It is not surprising that glial tumors with a favorable molecular profile would respond well to chemotherapy, and so it makes you wonder if the order of the treatment modalities would affect the final result. It would be reasonable to think that maybe adjuvant chemotherapy could show the same complete response in these patients after an initial STR, and the benefit of the treatment could only be attributed to the TMZ alone, and not to the moment it was administered.

In contrast to these prior findings, another retrospective study published in 2014 showed that volumetric reduction of the tumor after neoadjuvant chemotherapy was significant; although it did not improve the EOR after neoadjuvant treatment [16]. It is worth noticing that similar tumor volume reduction was achieved in this study, at an average reduction of 32%, which is similar to what Blonski and colleagues reported in their study [15], this means that other factors aside from tumor volume reduction may be involved in the resectability of these tumors after neoadjuvant therapy.

Finally, a prospective study published in 2015 aimed to assess the effectiveness of the neoadjuvant strategy in a prospective series of gliomas with favorable molecular status [17]. The authors treated 26 patients after incomplete resection with TMZ in 20 of the cases, and PCV (procarbazine, lomustine, vincristine) in the other 6 patients. All patients had LGG with IDH1 mutation, and seventeen of these were MGMT promoter methylated and 1p/19q co-deleted. This study showed that neoadjuvant chemotherapy based on molecular guidance often produces significant volume decrease of incompletely resected gliomas and radical second-look resection could be an optional advantage of upfront chemotherapy for chemosensitive gliomas compared with initial radiotherapy. This study is also valuable because it includes patients treated with PCV rather than TMZ, that is the primary treatment in all other trials.

In another study, the quality of life and cognitive status was evaluated in 10 patients who had LGG that were initially classified as inoperable, who then received TMZ as initial treatment in order to shrink the tumor and later on, being taken into surgery for GTR. The authors concluded that the combined treatment is feasible, efficient (surgery made possible by neoadjuvant chemotherapy) and well tolerated [18].
Regarding this topic is valuable to mention that although TMZ is usually well tolerated it is not without complications, especially when combined with other agents such as Bevacizumab, so complications should be discussed with the patient and family before recommending this approach.

Table 1 summarizes the available studies that involve neoadjuvant treatment for LGG.

It should be noted that since the publication of the first case report in 2005 there have been advances in technology and surgical techniques and the EOR of these lesions has improved over the years and so has the survival for these patients, making the term “unresectable” a matter of interpretation [20].
Also the diagnostic criteria used in these articles differ from the current criteria established since 2016 by the WHO [2].
These factors should be taken into account as a limitation of the study and be kept in mind when making a surgical decision based on these studies.

Even though it is considered a different tumoral entity, it is worth mentioning that neoadjuvant chemotherapy has been also implemented in pediatric patients with LGG.
We found two separate articles that treated LGG in pediatric patients with chemotherapy in order to shrink the tumor and attempt a radical surgery afterwards.
Cartmill and colleagues treated a pleomorphic xanthoastrocytoma in a 6-year old patient with two cycles of vincristine and carboplatin, and complete resection was achieved 9 weeks later [21].
Also Valera in 2003 reported two cases of patients with pilocytic astrocytomas in which upfront treatment with vincristine and cyclophosphamide improved tumor

characteristics so that complete resection was attempted after the initial treatment with good results [22].

Again, these pediatric cases are to be considered separately from the adult cases, given the different natural history and behavior of the tumors. But it is important to keep this in mind for future studies and analysis.

High-grade Gliomas

As previously mentioned, gliomas are subject to the WHO classification, and gliomas grade III and IV are considered high-grade gliomas. The most common and biologically aggressive subtype of HGG is the glioblastoma (GB) World Health Organization grade IV. GB and anaplastic astrocytomas (grade III) account for about 76% of all gliomas [2, 23].
The initial therapeutic approach for HGG is surgery, where maximal resection is associated with longer PFS and OS [3, 4, 24]. In the case of HGG, it is accepted that GTR is the total resection of the enhancing lesion on T1 weighted images in the preoperative MRI.
It is important to note that resection is not a curative approach; and so, patients need to undergo radiotherapy and chemotherapy as adjuvant therapy [25].

Due to the aggressiveness of the tumor, current trends favor performing surgery as soon as possible, leaving little room for “experimental therapies” that may delay the resection of the tumor.
Nevertheless there have been cases where upfront chemotherapy has been used to improve tumor characteristics in the pursuit of achieving a more radical resection.

In a letter to the editor, Kaloshi and colleagues published a report of a 66 year-old patient with a left insular GB [26]. Because of location and extension of the lesion the authors opted to try neoadjuvant therapy with TMZ and bevacizumab. Eight weeks later, after 2 monthly cycles of TMZ and 2 biweekly cycles of bevacizumab the tumor showed improvement in imaging characteristics, and the patient was taken into surgery where a GTR was achieved without further neurological decline. This is an interesting report because it illustrates a case that many surgeons would consider to be not a good candidate for further measures, given that the patient is older and harbors a high-grade tumor. So in this case the authors show that even under not ideal circumstances neoadjuvant chemotherapy may be feasible and give a fighting chance for these patients.

In 2015 a phase II trial was performed to determine the safety of the combination of bevacizumab (BV) plus chemoradiation with TMZ in patients who had already received primary surgery for GB [27]. The authors hypothesized that a neoadjuvant treatment for patients with newly diagnosed GB using chemoradiotherapy plus BV would improve resectability and thus survival. Unfortunally, the authors concluded that although the combination of bevacizumab with radiotherapy and TMZ is safe

and feasible in patients with newly diagnosed GB, because of the low response rates, this treatment strategy does not favor a neoadjuvant approach.
Just as previously mentioned, other combination therapies have been tested as neoadjuvant treatment for patients with GB. A randomized phase II trial failed to show any benefit from the combination of bevacizumab and irinotecan in first-line therapy in comparison to bevacizumab and TMZ regarding the response and PFS [28].
These studies suggest that in the current setting there is not enough evidence to support rutine use of neoadjuvant treatment in the setting of newly diagnosed GB, although we believe that could be useful in individualized cases.

In recurrent GB, the prognosis is even worse with a median overall survival of 24 to 44 weeks after diagnosis [29], and many patients with recurrent GB have little options for treatment, this is why we need to come up with different strategies that may overcome these limitations.
In more recent years there has been increased interest about immunotherapeutic agents in GB patients, in particular, programmed cell death 1 (PD-1) monoclonal antibody inhibitors. Most of the literature is focused on PD-1 inhibitors in the adjuvant setting, but there have been also some studies that suggest that neoadjuvant use of this therapy may enhance antitumor immune responses; these responses may give a survival benefit over adjuvant therapy alone [30].

Although not aimed to address the issue of improving EOR, it is worth mentioning that in 2019 the Ivy Foundation Early Phase Clinical Trials Consortium performed a randomized, multi-institution clinical trial to evaluate immune responses and survival following neoadjuvant and/or adjuvant therapy with pembrolizumab in 35 patients with recurrent, surgically resectable glioblastoma [31]. Patients were randomized to receive either neoadjuvant pembrolizumab with subsequent surgical resection or surgical resection followed by adjuvant pembrolizumab. An intention-to-treat analysis was performed and demonstrated a statistically significant increase in OS in the group of patients treated with neoadjuvant therapy, with a hazard ratio of 0.39, compared to the adjuvant-only group; OS was also improved in the neoadjuvant group with an estimated OS of 13.7 months versus 7.5 months in the adjuvant group.
We believe that these results may encourage developing trials in patients with unresectable HGG and testing the benefit of neoadjuvant treatment using immunotherapy on the EOR.

Additional to the benefit that neoadjuvant chemotherapy can provide to the EOR by means of tumor volume reduction, another strategy that has been explore is to use this volume reduction to improve radiation parameters in the adjuvant setting.
In a recent multicenter study the authors showed that upfront combined chemotherapy with TMZ and BV could reduce tumor volume at around 25% of its initial value, and by doing this they could perform the standardized Stupp protocol in patients who otherwise because of the tumor extension or clinical status were no able to do so before [32], similar results have been achieved in other studies [33, 34].

Even though the clinical and pathological behavior is very different, we believe is worth mentioning pediatric cases that have used this strategy.
A case of a HGG treated presurgically with chemotherapy was reported, but this time in a pediatric patient.
In a series of pediatric cases, Iwama and colleagues reported the case of a 16 month-old female patient with a right parietal GB. After recurrence of the tumor, the patient received 2 cycles of vincristine, cyclophosphamide, etoposide, and cisplatin. Although the tumor increased in size after neoadjuvant treatment, the authors described that intraoperative characteristics were more favorable and so GTR was achieved [35].

Table 2 summarizes the available studies that involve neoadjuvant treatment to improve EOR in HGG.

We believe it is worth mentioning that the studies included in this article are heterogeneous in terms of age group, histological diagnosis, type of chemotherapeutic agents used, indications off their use, and also they lack a statistical significance due to the very limited number. This is an important limitation of this review and should be taken into account when analyzing this study.

Conclusions

Glial tumors as a whole are still a complex pathology with evolving therapeutic strategies. Extent of resection has a great impact in the prognosis and quality of patients with LGG and HGG. Still many challenges inhibit our ability to achieve GTR in all of the cases. At the time very little evidence exists to recommend routinary use of neoadjuvant therapy to treat gliomas, and even though the articles included in this review lack statistical power, it is all the current evidence that is available to date.
According to the findings in the literature search, neoadjuvant chemotherapy has played a role in overcoming obstacles in achieving an adequate EOR and as investigations progress; we will see more of this strategy in the managing of patients with complex gliomas.

Conflicts of Interest

The authors declare that they have no conflict of interest.

Ethical Statement

• Funding: No funding was received in the making of this article
• Conflict of Interest: The authors declare that they have no conflict of interest.

• Ethical approval: This paper received ethical approval from the institution
• Informed consent: There is no patient information that requires consent

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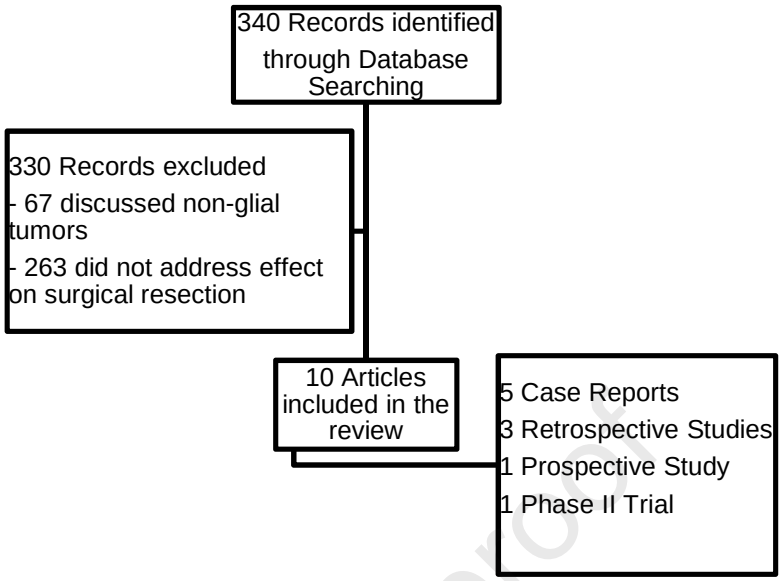
Author	Year	No. of Patients	Diagnosis/ Molecular Profile	Chemotherapy	Rationale for Chemotherapy use	Conclusion
Voloschin et al. (7)	2005	1	Oligoastrocytoma* 1p/19q Loss	TMZ	Chemotherapy considered because extend of the lesion after biopsy only	GTR achieved, no recurrence for 48 months.
Duffau et al. (8)	2006	1	Oligodendroglioma No molecular profile	TMZ	Due to contralateral extension chemotherapy was given after a subtotal resection	GTR achieved, no recurrence for 2 years.
Spena et al (19)	2010	1	Oligoastrocytoma* No 1p/19q Loss MGMT unmethylated	TMZ	Chemotherapy was initiated due to large tumor extension and contralateral compromise after biopsy.	STR achieved, improvement of seizures. Stable disease for 18 months.
Blonski et al. (18)	2012	10	WHO grade II oligodendroglioma ir six cases, WHO grade II astrocytoma in two cases, and WHO grade II oligoastrocytoma in two cases No molecular profile	TMZ	Chemotherapy was given for an inoperable diffuse cortico-subcortical supra-tentorial glioma due to involvement of eloquent regions or due to bilateral diffusion.	Neoadjuvant treatment with TMZ is well tolerated and improves cognitive function and quality of life.
Blonski et al. (15)	2013	17	Six patients had 1p19q codeletion, 12 patients had IDH mutation and MGMT promoter methylation, and eight patients had p53 overexpression.	TMZ	Chemotherapy was given to patients with tumor infiltration of functional areas and/or large contralateral extension	Upfront chemotherapy with TMZ could optimize the surgical resection of LGG and could impact prognosis in these patients.
Jo et al. (16)	2014	20	1p/19q co-deletion in 8 patients IDH1 mutation in 17 patients	TMZ	Chemotherapy was given to patients with previous diagnosis via biopsy and had a diffuse glioma deemed unresectable	Volumetric reduction of the tumor was significant; although it did not improve the EOR.

					upon neurosurgical evaluation	
Sasaki et al. (17)	2015	26	All patients had LGG with IDH1 mutation, and seventeen of these were MGMT promoter methylated and 1p/19q co-deleted.	TMZ PCV	After incomplete resection, patients with potentially chemosensitive gliomas based on molecular status were treated with upfront chemotherapy.	Neoadjuvant chemotherapy based on molecular guidance often produces significant volume decrease of incompletely resected gliomas

* According to WHO 2007 guidelines

Author	Year	No. of Patients	Diagnosis/ Molecular Profile	Chemotherapy	Rationale for Chemotherapy use	Conclusion
Kaloshi et al. (26)	2015	1	Glioblastoma No molecular profile	TMZ and BV	Extensive involvement of eloquent area.	GTR was achieved without further neurological decline.
Iwama el al. (35)	2015	1	Glioblastoma No molecular profile	Vincristine, cyclophosphamide, etoposide	Chemotherapy was initiated as adjuvant treatment after subtotal resection	Increased tumor volume, improved tumor characteristics and GTR achieved
van Linde et al. (27)	2015	19	Glioblastoma No molecular profile	RT, TMZ and BV	Strategy to improve extend of resection as part of a trial	This treatment strategy does not favor a neoadjuvant approach.



Abbreviations

CNS: Central Nervous System
WHO: World Health Organization
EOR: Extent of Resection
LGG: Low-Grade Glioma
HGG: High-Grade Glioma
OS: Overall Survival
PFS: Progression Free Survival
GTR: Gross Total Resection
TMZ: Temozolomide
BV: Bevacizumab
MRI: Magnetic Resonance Imaging
IDH1: Isocitrate Dehydrogenase 1
GB: Glioblastoma
PD-1: Programmed Cell Death 1