Clinical Neurology and Neurosurgery 151 (2016) 18–23

Contents lists available at ScienceDirect

Clinical Neurology and Neurosurgery

journal homepage: www.elsevier.com/locate/clineuro

Repeat surgery for recurrent low-grade gliomas should be standard of care

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ARTICLE INFO

Article history:
Received 30 June 2016
Received in revised form
20 September 2016
Accepted 21 September 2016
Available online 30 September 2016

Keywords:
Low grade glioma
Radiotherapy
Chemotherapy
Extent of resection
Recurrent low-grade glioma

ABSTRACT

The importance of surgery and maximal extent of resection (EOR) is well established in primary low-grade glioma (LGG) management. However, the role of surgery in the management of recurrent LGG is less clear. A recent review on the management of recurrent LGG concluded there was insufficient evidence to recommend surgery. Here, we summarize the recent advances regarding the role of surgery, radiotherapy (RT) and chemotherapy in the management of recurrent LGG. There is increasing evidence to support maximal EOR for treating recurrent LGG, as it may improve progression free survival (PFS) after recurrence and overall survival (OS). Based on the studies presented in this review, we suggest that repeat surgery with maximal EOR should be standard of care for recurrent LGG treatment.

Contents

1. Introduction

Low-grade gliomas (LGG) are a heterogeneous set of primary brain tumors that are diffuse and slow growing, and are composed of the following broad categories: diffuse astrocytoma, (IDH mutant), diffuse astrocytoma (IDH wild-type), diffuse astrocytoma (NOS), oligodendroglioma (IDH mutant and 1p/19q codeleted), oligodendroglioma (NOS), and oligoastrocytoma (NOS) [1]. Approximately 2000 to 3000 cases of LGG are diagnosed annually in the US, with peak incidence between 35 and 44 years of age. While expectant management was previously the norm, current practice favors active intervention, including clinical consideration of surgery, radiotherapy (RT), chemotherapy, molecular characterization, and advanced imaging for diagnosis, prognosis, treatment and surveillance.

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http://dx.doi.org/10.1016/j.clineuro.2016.09.013
0303-8467/

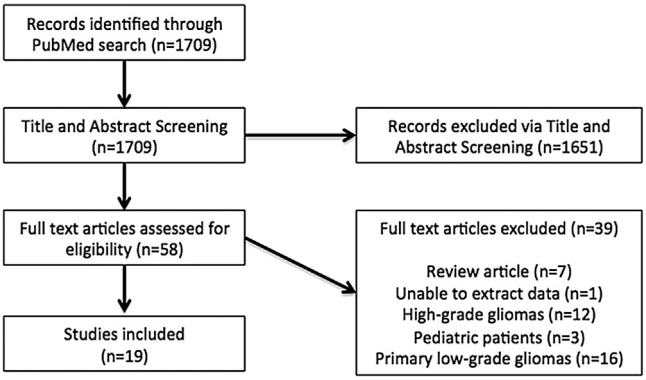

Fig. 1. Criteria for article selection. 1709 articles were identified through our search. Title and abstract screening yielded 58 studies for full text review. Full text review yielded 19 studies for inclusion.

Prognosis and management of LGG depend on several factors, including age, Karnofsky Performance Scale (KPS) score, neurological deficits, tumor diameter, bilaterality, astrocytic histology, and molecular genetic markers [2]. For example, IDH mutation and 1p/19q co-deletion have proven to be powerful prognostic markers [3]. Despite combinatorial approaches, including surgery, adjuvant chemotherapy and RT, 5-year survival ranges from 42 to 92% for primary LGG [4].

Duffau and Talliandier [5] recently proposed individualized, multimodal treatment guidelines for the management of primary LGG. These guidelines stress the importance of regular clinical, radiological and functional re-evaluation of primary LGG. The model also suggests earlier intervention for primary LGG via multiple, staged procedures with regimens of chemotherapy interspersed between surgeries. These guidelines stress the importance of including adjuvant or neoadjuvant therapy and surgery in the treatment algorithm for primary LGG.

Increasing evidence over the last two decades has shown that the extent of resection (EOR) of primary LGG is a major factor influencing patient overall survival (OS) [2,6–14]. However, the role of resection in the management of recurrent LGG has not been well studied. This is noteworthy given that LGG tend to recur, often as higher-grade tumors after initial treatment and lead to significant morbidity and mortality. Furthermore, in a recent comprehensive review on management of recurrent LGG, Nahed and colleagues concluded that there is insufficient evidence to recommend surgery at recurrence [15]. Here, we briefly summarize recent advances in recurrent LGG management and propose that repeat surgery with maximal EOR should be standard of care for recurrent LGG.

2. Literature review

We conducted a PubMed search from January 1, 2001 to December 31, 2015 using the following search terms: ("glioma" OR "astrocytoma" OR "oligodendroglioma") AND ("low-grade" OR "low grade") AND ("chemotherapy" OR "resection" OR "radiotherapy"). Included studies met the following criteria: 1) peer-reviewed publication, 2) patients with low-grade oligodendrogliomas, astrocytomas or oligoastrocytomas, 3) patients greater than 17 years of age, and 4) publications in English.

A total of 1709 studies met our initial search criteria. Title and abstract screening produced 58 studies for possible inclusion. Full text screening eliminated 39 additional studies (see Fig. 1). Seven studies investigated the role of surgery (Table 1), five studies investigated the role of chemotherapy (Table 2), and seven studies investigated the role of radiotherapy (Table 3). Considering the recently published extensive review of recurrent LGG management by Nahed et al. [15], studies published since December 2012 were a large focus of our discussion.

3. Management of recurrent low-grade gliomas

3.1. Maximal surgical resection

Maximal EOR of primary LGG is crucial in improving progression-free survival (PFS) and OS after initial resection [2]. Similarly, maximal EOR of recurrent LGG has also been shown to improve PFS (after recurrence) and OS. Repeat surgery for recurrent LGG should be standard of care when gross or near total resection is possible.

As LGG do not typically enhance, the goal of surgery both at presentation and recurrence should be to resect all T2- Fluid-attenuated inversion recovery (FLAIR) hyperintense disease, if possible. Recent evidence has shown that removal of all T2-FLAIR demarcated disease at initial and repeat resection of LGG was associated with improved long-term survival compared to simply removing >90% observable tumor [8,16]. In a study with a mean follow-up of 15.9 years, it was reported that the absence of residual tumor after the initial operation and repeat operation for recurrence was associated with significantly increased OS (16.7 years ± 1.8 for no residual tumor vs. 10.5 years ± 1.0 for presence of residual tumor [$P = 0.004$] after initial operation for primary LGG; 17.2 years ± 1.7 vs. 9.8 years ± 0.9 [$P < 0.001$] after repeat operation for recurrent LGG) [4]. This is consistent with a previous study that assessed the impact of EOR in recurrent LGG [8]. In a focused multivariate analysis, maximal EOR in both primary and recurrent LGG conferred a positive prognosis, regardless of patient age, pathology, chemotherapy or radiation therapy (RT) [4].

The available evidence demonstrates that the percentage of tumor removal is less important than whether or not there is *any* residual tumor after recurrent LGG resection. As such, patients with totally resectable recurrent LGG should be offered repeat surgery in advance of any further treatments.

While reoperation is desired when LGG recur, the risks of another surgery must be carefully weighed against the benefits. There appears to be no decrement in OS or postoperative KPS in carefully selected patients undergoing 2 or more operations for recurrent LGG [4]. Nearly 20% of the recurrent LGG patients underwent >2 surgeries with no associated decrease in performance status [4]. Furthermore, reoperation for recurrent LGG in or near eloquent areas does not pose a higher risk of neurological sequelae when compared to initial surgery [16,17]. As with initial surgery, it is important, however, that reoperation be supplemented with measures to ensure surgical safety, including functional mapping, intraoperative MRI and/or intraoperative molecular imaging.

3.2. Chemotherapy for recurrent LGG prior to repeat surgery

The first case of resection of recurrent LGG following preoperative chemotherapy was described by Duffau et al. [18]. A 40 year-old man presented with a grade II left frontal lobe oligodendroglioma with invasion of the corpus callosum. A partial resection was performed. Subsequent imaging demonstrated progression of the LGG to the right hemisphere, at which time the patient was treated with eight cycles of oral TMZ over the course of 13 months. Through the first six TMZ treatments, serial MRIs demonstrated tumor regression, with absence of right hemisphere infiltration and decreased callosal invasion, which subsequently allowed for gross total resection (GTR). There was no MRI evidence of recurrence at 2-year follow up.

A subsequent case report by Spena et al. [19] corroborated these results. A 38 year-old woman presented with a grade II left frontal