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The effect of operations in patients with recurrent diffuse low-grade glioma: A qualitative systematic review

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ABSTRACT

The role of operation for patients with recurrent diffuse low-grade glioma (DLGG) is controversial. A few studies compared the effectiveness between surgery and other treatments for those patients. We did a systematic review for the effects of reoperation for recurrent DLGG. We searched the following databases from 1990 to 2018: Medline, Cochrane Library, Scopus and Opengrey, including researches about reoperation for recurrent DLGG, regardless of comparison and study design. The Newcastle–Ottawa scale (NOS) was used for quality assessment. Ten studies with 358 participants met the criteria. Due to lack of survival data about non-operated group, we failed to analyze the effect of reoperation. The risk bias of included studies was acceptable except the comparability. However, we found 48.4 % (155/320) of patients underwent gross resection and the safety was acceptable. About 1/3 received adjuvant therapy and 41.9 % (125/298) got histologically progressed. In a word, few studies reported the survival data of recurrent DLGG patients received reoperation. Most were young adults and half of them experienced a histological progress. But there are still a lot of shortages of the existing studies and more researches on the reoperation efficacy in recurrent DLGG are needed.

1. Introduction

Glioma is the most common primary malignant brain tumor in adults. Among them diffuse low-grade glioma (DLGG) mainly refers to WHO grade II glioma. DLGG is a rare disease which account for 15 % of central nervous system glioma and it has a high recurrence rate [1]. For recurrent DLGG, there is no standard treatment, although the NCCN guidelines (Version1.2020) suggest that all the recurrent DLGG patients whose lesions are resectable should be undergone surgeries. As the main treatment option for patients, surgery includes gross total resection, subtotal resection and biopsy [2]. But in the real world, whether resections should be done is still remained as an issue to be discussed.

Previous studies have shown that total resection in patients with primary DLGG can significantly improve the survival time [3,4]. For patients with recurrent glioblastomas, some suggest that total resection of lesions is beneficial [5], but it is uncertain whether this conclusion also applies to recurrent DLGG. For patients with glioma, gross total resection of lesions can significantly reduce the tumor load, provide better conditions for subsequent radiotherapy and chemotherapy, and can alleviate the symptoms caused by the mass effect, improving quality of lives of patients [6,7]. These are the benefits of gross total resection. But for patients with recurrent DLGG, there are many potential risks of surgery, and clinicians should weigh these risks against the benefits before making treatment decisions.

Whether patients with recurrent DLGG can be operated should consider the general situation of the patient at first, evaluate whether the patient can be tolerated enough to surgically resection. For those who cannot tolerate surgery, the risk of gross total resection is too high, or even life-threatening. In addition, those patients have experienced surgery and radiotherapy before, the reoperation will be more difficult and risky. The possibility of postoperative complications, including intracranial hemorrhage, intracranial infection, neurological impairment and so on, should also be considered when deciding the treatment regimen [8].

As reoperation in recurrent DLGG patients is still controversial in clinical work, this paper intends to conduct literature research on this

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problem and summarize the previous research results for a systematic review.

2. Methodology

The rules based on PRISMA guidelines were conducted in this systematic review [9]. Literature Database including Medline (PubMed), Scopus, Cochrane Library (Ovid) and Open grey were searched through Oct 2019. The search terms including but not limited to “astrocytoma”, “oligodendroglioma”, “low-grade glioma”, “WHO grades II”, “recurrent”, “surgery” and “operation”. (the details were showed in Appendix). According to the academic vocabulary is not standard, some researchers reported as “surgery for recurrent LGG”, however others reported as “reoperation for LGG”. Therefore, we did an additional search using the terms as “reoperation” and “repeat” published between Jan 2015 to Oct 2019. Furthermore, we manually searched the references of the retrieved articles and relevant bibliographies.

We also reviewed the journals and references. Included studies met the following criteria: 1) patients with recurrent low-grade glioma, 2) patients greater than 18 years of age, and 3) patients treated by operation. Data extraction from eligible trials was performed by Guo R., Guo X.X. and Lu Y. using a predetermined data extraction form. If information on study characteristics was incomplete but important information, the authors were contacted to request additional information.

The quality of the included studies was independently assessed by Chang J.B. and Wang Y.N. according to the Newcastle–Ottawa scale (NOS) for case-control study including three dimensions: selection, comparability, and exposure. The maximum score that can be assigned in each study is 9 and 8–9 stars indicate very good studies, 6–7 good studies, 4–5 satisfactory studies, and 0–3 unsatisfactory studies [10].

3. Results

3.1. Search strategy results

Fig. 1 shows the literature search process. 938 studies met our initial search criteria, of which 848 were determined to be irrelevant upon review of titles and abstracts by reviewers (90 duplicate reports, 412 review papers, and 392 studies with no reoperation). Of the remaining 44 studies, fourteen were excluded because they were not about low-grade glioma, twelve were excluded because it did not report surgery, and eight were excluded because it not about recurrent DLGG. Ten studies [2,8,11–18] investigated the role of surgery in patients with recurrent low-grade gliomas.

3.2. Study characteristics

Table 1 shows the characteristics of the 10 eligible studies. All studies were case control or case series studies about the reoperation in low-grade glioma published in peer-reviewed journals. Half of studies were conducted in United States and published before 2010. Most studies were small size with less than 40 participants. There were 358 recurrent DLGG which the mean age was 37.6 years and recurrent time was 44.6 month. Of 358 recurrent DLGG, 320 patients were treated by reoperation and 48.4 % (155/320) got gross total resection, however others failed. There were about 1/3 patients received the chemotherapy or/and radiotherapy besides surgery.

As Table 2 shows, the effect of reoperation was failed to synthesize limited to the survival data. 41.9 % (125/298) tumors got histologically progressed. Most patients were accessed by a lower KPS and no new permanent neurological deficits.

Besides two studies [12,17] was assessed by NOS as 5 stars, other selected studies received over 6, which can be considered at a minimum good quality studies. The comparability was poor quality in most studies (8/10), which failed to report the import factors including the adjuvant therapy and extent of resection. Based on the pathological and surgery records, the quality of selection and exposure in most studies were acceptable (Table 3).

4. Discussion

In present review, ten studies with 358 recurrent DLGG patients were included but the effect of reoperation was failed to be synthesized limited to the survival data. In these ten studies, we summarized the characteristics of patients received reoperation. Most patients were young adults, which half of them received gross resection and about a third treated by chemotherapy or/and radiotherapy besides the operation. In half of the patients, the tumor progressed into higher grade glioma. The probability of the occurrence of permanent neurological deficits after the second surgery was not higher than the first one. This review discusses several potential influencing factors when considering about whether patients should be undergone a reoperation. The factors are: the extent of resection, pathological grade and the complications of reoperation. Except for the comparability part, the quality of other parts of included studies were considered as minimum good quality. The details of adjuvant therapy were not reported separately in experimental group and control group.

Since the extent of resection (EOR) may be related to the survival of patients, the discussion of this problem to a certain extent explains the reasons clinicians choose gross total resection or biopsy. For primary gliomas, previous studies have shown that patients with gross total resection can get a better prognosis, whether it is high-grade gliomas or low-grade gliomas [19]. However, for recurrent gliomas, this conclusion needs to be verified. As patients with GBM have relative short PFS and are easier to recurrent, some studies showed the degree of resection is a very important predictor of the overall survival time of recurrent high-grade glioma [19,20]. When it comes to recurrent DLGG, there are few studies focusing on the EOR. Only the research with 130 cases conducted by Ahmadi Rezvan et al. [15] focused the topic which found reoperation is necessary to prolong OS and PFS in patients with recurrent DLGG, and gross total resection can significantly prolong the survival time of patients. Although most included studies reported the extent of reoperation, the survival outcome is limited and the evaluations of the EOR carried out by the surgeons, it is impossible to conclude that gross total resection can prolong the survival time of the patients and further studies are needed.

Pathological level is an important evidence for deciding whether patients with recurrent DLGG should receive reoperation and the adjuvant therapy. Eight of ten studies reported the histopathological findings, however, a few showed the OS or PFS in subgroup analysis. Ramakrishna et al. [8] found the pathology at recurrence was associated with PFS based on 52 cases. More aggressive treatment like resection may be a better strategy for the patients with histological progress tumors. Besides the resection, biopsy is an effective way to help clinicians choose a suitable therapy strategy, which provide more information about molecular pathology. The potential benefit of pathology cannot be determined in the review, because of the shortage of survival data.

For reoperation, clinicians have to balance the complications and the benefit. The main complications include perioperative death and postoperative neurological deficit. The perioperative mortality of reoperation shows no statistic difference compared with the first operation [2,8,15]. However, the quality of life, most tested by Karnofsky Performance Scale (KPS) score, declined mildly. Ramakrishna et al. [8] reported that the KPS score was 92.5 ± 1.7 before reoperation while after the surgery, it went down to 88.7 ± 1.7. The similar results showed in other studies, such as 1 of 16 case KPS score lower than 90 after operation in Duffau [16] and 3 of 16 in Kaspera et al. [2] Ahmadi et al. [15] reported 25 of 96 cases KPS score lower than 80. Complications rate was affected by a combination of factors, including differences in intraoperative navigation and monitoring devices, surgeon

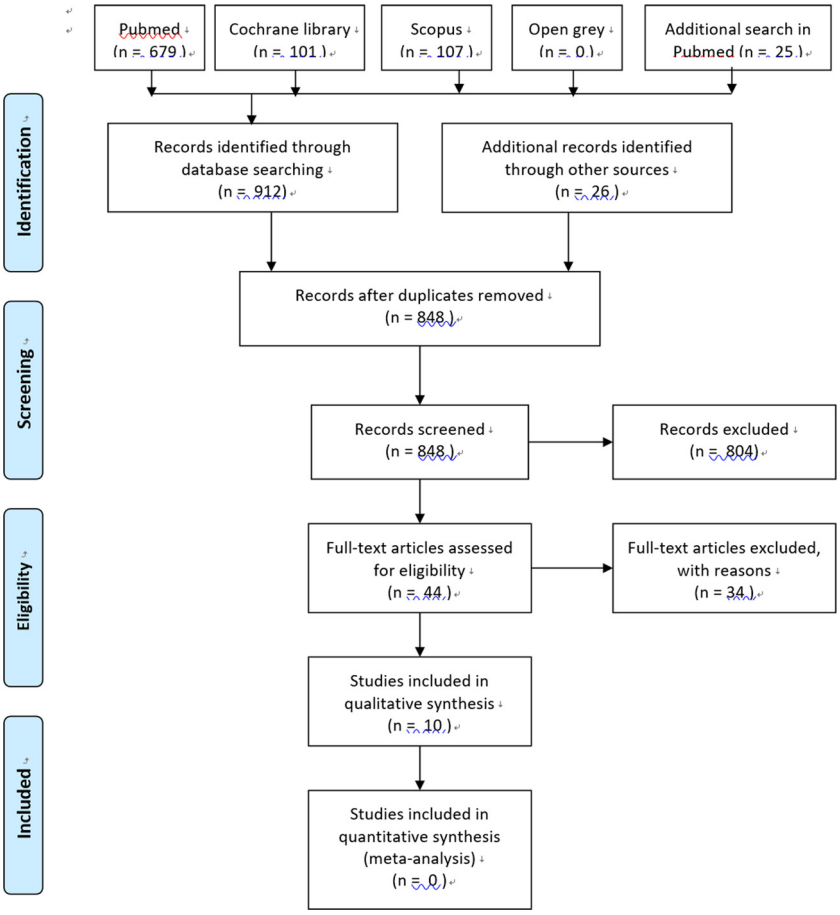

Fig. 1. The result of search flow diagram.

experience and skill. In addition to these factors, other variables can also impact the complication rates for brain tumor operation, such as lesion location, resection range, tumor histology, tumor size, patient's age, and perioperative hyperglycemia. In a word, the complications of reoperation may be acceptable. However, there are many issues that require further study.

There are some other factors that clinical workers should consider about before reoperation, such as the molecular pathology and the imaging characteristics of tumor. DLGG is a chronic invasive disease of the central nervous system. And the therapeutic effect of the operation on recurrent DLGG is controversial. There are many studies focusing on the association between molecular pathology and surgery benefit in primary DLGG. The gross total resection prolonged the OS significantly in tumors with IDH 1/2 mutation without the 1p/19q co-deletion, and no significant difference in IDH 1/2 mutation and 1p/19q [21]. Similar results also showed in other studies [22]. There was also no statistic difference between GTR and non-GTR in tumors with IDH wild-type [23]. Few studies reported the molecular pathology of recurrent DLGG in the past.

Regarding whether recurrent DLGG should be surgically removed, the imaging characteristic of tumors plays an important role. Ferracci et al. concluded that patients with different recurrence patterns should adopt different surgical strategies [24]. Surgery is not a good choice for patients with very diffuse progression pattern, because lesions has invaded the subcortical cerebral white matter, and neuroplastic potential of this part of the brain is very limited and surgery may cause an irreversible impact on neural function [25]. However, the patterns of multifocal progression, leptomeningeal dissemination or bulky relapse into the surgical cavity, surgery may be the preferred treatment. The patients with malignant transformation recurrence pattern often occurs long after the first operation, so frequent follow-up is the most meaningful approach for this group of patients. In recent years, the research on the recurrence pattern of recurrent DLGG has gradually increased [26], which further indicates that whether recurrent DLGG should be operated again need to be considered comprehensively.

As a whole, there were a few studies focused on the role of reoperation in recurrent DLGG. And most included articles did not provide enough necessary data about the topic. The limitation follows: 1) The main topic of the included original studies were different. there are only 4 articles focused on the effect of reoperation [2,8,14,18]. Another five studies [11,12,15–17] focused the long-term outcomes of DLGG and one study [13] about biopsy approach, which showed the reoperation effects in subgroup analysis. 2) Most studies did not compare survival data for patients who had reoperation with those who did not. The quantitative analysis was failed limited to the data. 3) The data-integrity of the included studies was not enough. Much essential information was not reported. Of 10 studies, the situation of histological progress, types of reoperation and complications were reported in 8, 7 and 6 articles, respectively. 4) The molecular biomarkers and imaging characteristics were not reported in the existing studies. 5) Lack of survival data, the comparability was evaluated as the main deficiency in quality assessment.

In view of the deficiencies in the above researches, this review proposes the following suggestions:

1) Since there is no standard treatment plan for recurrent DLGG at present, it is recommended to divide the patients into different subgroups when doing researches, such as surgical group and non-surgical group, so researchers can conduct studies more targeted on different patients.

Table 1
Characteristics of the included studies.

No	Author	Country	Published year	Total Patients	Recurrent patients	Gender (M:F)	Recurrent Age	Recurrent Time	Surgery patients (number)				Radiotherapy Patients (number)	Chemotherapy patients (number)
									Gross resection	Subtotal resection	Partial resection.	Biopsy		
1	Steiger	Switzerland	1990	50	10			36mo	4					
2	McCormack et al.	United States	1992	41	24		35y	54 ± 11.0mo		7				12/24
3	Forsyth et al.	United States	1995	40	30	24:27	38y		20	7		3	30/30	11/30
4	Schmidt et al.	United States	2003	40	40		Grade II : 32y(24−45); Grade III-IV: 42y(28−51)	Grade II: 22.5mo(3−45) Grade III-IV:42mo(6−86)	10	17	13			
5	Ahmadi et al.	Germany	2009	130	96	78:52	36y		51		45(partial or biopsy)		20/96(no operation)	12/96(no operation)
6	Kaspera et al.	Porland	2013	68	22		34y(IQR = 29−42)	19mo(IQR = 15−33)	1	4	10	3	11/16	
7	Ramakrishna et al.	United States	2015	52	52	32:20	38.9y	74.76 ± 6.12mo		38	16		29/52	37/52
8	Hugues Duffau	France	2016	16	8	7:9	41.3y (26−63)	70.3mo(32–105)		2			2/8	3/8
9	Spitaels et al.	Belgium	2017	35	32	20:15	39y(18−78)	26mo(2−104)	25				2/32(no operation)	5/32(no operation)
10	Morshed et al.	United States	2018	44	44		44y ± 9.4	54 ± 36mo	44				17/44	37/44
Summury				516	358	161:123	37.6y	44.6mo	155	75	84	6	111/278	117/286

Table 2
Main results of the included studies.

No	PFS(Mean ± SD)			OS(Mean ± SD) Recurrent	Histologically Progressed (number)	Surgical complications	Remark
	Recurrent	Reoperation	Adjuvant therapy				
1					4/4	Perioperative death 1/4	
2				12 months	3/7		Neither chemotherapy (P > 0.1) nor another operation (P > 0.25) prolonged survival after recurrence
3					17/51		Median survival times after biopsy were 0.83 year for patients with tumor recurrence.
4					20/40		EOR was NOT the risk factor for recurrent
5	156mo(CI = 114−264)	78 % in 5y	40 % in 5y	193 m(CI = 137−264)	43/96	KPS < 80 25	Re-operation for recurrent LGG significantly increased overall survival. No significant differences for RT and chemotherapy.
6	Survival 35 % in 5y	19mo(IQR = 15−33)			10/16	neurological deficits before 2/16; after 5/16; KPS > 90 before 13/16; after 8/16	
7	6.23 ± 0.51y; Survival 60 % in 5y			12.95 6 ± 0.96 y	22/52	KPS before 92.5 ± 1.7; after 88.7 ± 1.7;	Language mapping At First 4/52 (8%) At second Recurrence 12/52 (23 %)
8						KPS > 90 before 16/16; after 15/16	All patients continue to enjoy a normal life
9	23mo(2–104)	10mo	24mo		6/32		
10						neurological deficits 4/40	EOR was the risk factor for recurrent

Table 3
Risk of bias assessment of case-controlled studies.

No	Author	Published year	Selection				Comparability		Exposure			Total stars
			Case definition	Representativeness	Control selection	Control definition	Important factor	Second important factor	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-response rate	
1	Steiger	1990	*	*	*	*			*	*		6
2	McCormack	1992	*		*	*			*	*		5
3	Forsyth	1995	*	*	*	*			*	*	*	7
4	Schmidt	2003	*	*	*	*			*	*		6
5	Ahmadi	2009	*	*	*	*			*	*		6
6	Kaspera	2013	*	*	*	*			*	*		6
7	Ramakrishna	2015	*	*	*	*	*	*	*	*	*	9
8	Duffau	2016	*	*	*	*	*	*	*	*		8
9	Spitaels	2017	*	*	*	*			*	*		5
10	Morshed	2018	*	*	*	*			*	*		6

2) Surgery, as a relatively invasive treatment of recurrent glioma, should be paid enough attention by researchers. Therefore, it is necessary to collect more comprehensive information about the operation of patients, including secondary postoperative complications, secondary postoperative survival, imaging characteristics and the molecular biomarkers such as IDH mutation status of recurrent tumors.
3) For researches that include only a small number of patients who underwent reoperation after recurrence, the information of each patient should be introduced in detail, so that it can tell the readers the effects of reoperation more clearly.

5. Conclusions

Most recurrent DLGG patients were young adults and half with gross total resection and histological progress. There were few studies to analyze the effect of reoperation for recurrent patients and more researches are needed.

Disclosure

All the date and material in this study were available.

The authors declare that they have no competing interests.

The authors have no personal financial or institutional interest in any of the drugs, materials, or devices described in this article. All authors declare no competing interests.

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Chang JB and Wang YN contributed equally to the manuscript which did the main study analysis and co-wrote the manuscript. Wang R.Z. and Ma W.B. were co-corresponding author.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.clineuro.2020.105973.

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