

Review Article

Recurrent glioblastoma in elderly: Options and decision for the treatment

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ABSTRACT

Background: Glioblastoma (GBM) is the most common primary malignant brain tumor in adult. Its incidence increases with age and nearly half of the all newly diagnosed GBM cases are older than 65 years. Management of GBM in elderly is challenging and recurrence poses further challenge. This article aims to review the literature, evaluate the various options, and to decide the treatment plan in elderly cases with GBM recurrence.

Methods: A systemic search was performed with the phrase “recurrent GBM (rGBM) in elderly and management” as a search term in PubMed central, Medline, and Embase databases to identify all the articles published on the subject till February 2022. The review included peer-reviewed original articles, review articles, clinical trials, and keywords in title and abstract.

Results: Out of 473 articles searched, 15 studies followed our inclusion criteria and were included in this review. In 15 studies, ten were original and five were review articles. The minimum age group included in these studies was ≥65 years. Out of 15 studies, eight studies had described the role of resurgery, four chemotherapy, three resurgery and/or chemotherapy, and only one study on role of reradiotherapy in patients with rGBM. Out of eight studies described the role of resurgery, six have mentioned improved survival and two have no survival advantage of resurgery in cases of rGBM.

Conclusion: Resurgery is the main treatment option in selected elderly rGBM cases in good performance status. In patients with poor performance status, chemotherapy has better post progression survival than best supportive care.

Keywords: Elderly, Glioblastoma, Recurrent, Treatment

INTRODUCTION

Glioblastoma (GBM) is the most common primary malignant brain tumor in adult. The current median age is 64 years.^[27] Its incidence increases with age and approximately half of all newly diagnosed GBM patients are older than 65 years.^[11] Despite advanced diagnostic modalities and optimal multidisciplinary treatment, most patients experience tumor progression with nearly universal mortality. Median survival in large retrospective studies is 6 months for newly diagnosed GBM patients older than 65 years.^[3,17]

While the current standard of care for younger patients includes surgical resection followed by concurrent chemoradiation and adjuvant chemotherapy with temozolomide (TMZ),^[21,36] managing elderly cases with GBM can be challenging due to medical comorbidities, lower organ

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function reserve, less aggressive treatment, increase toxicity of therapy, and more aggressive tumor behavior.^[2,8] Many clinical trials in the oncology exclude elderly patients, as such there is less evidence to guide treatment in elderly patients.

Several studies show the benefit from active treatment for newly diagnosed GBM in elderly^[20,22] but still there is no optimal treatment for recurrent GBM (rGBM) in elderly and/or frail patients. The aim of this review is to provide a practical overview of the evidence for treating rGBM in this special subgroup of patients.

MATERIALS AND METHODS

The review was designed in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-analysis.

Search strategy

Articles published in PubMed central, Medline, and Embase data bases till March 2022 were all searched. In relevant literature, references were manually searched for additional articles. We screened the title and abstract by combining the term (“recurrent” [All Fields] AND (“GBM” [MeSH Terms] OR “GBM” [All Fields]) AND (“aged” [MeSH Terms] OR “aged” [All Fields] OR “elderly” [All Fields]) AND (“therapy” [Subheading] OR “therapy” [All Fields] OR “treatment” [All Fields] OR “therapeutics” [MeSH Terms] OR “therapeutics” [All Fields]).

Eligibility criteria

Only nonexperimental and nonanimal clinical studies were included in the study. Articles written only in English language were considered. We have included only those published articles on elderly rGBM, in which patients were managed previously by surgery and postoperative chemoradiotherapy before recurrence, while excluding those articles in which GBM cases were managed either with surgery or radiotherapy.

Outcomes

Median overall survival (OS) (in weeks), progression free survival (PFS) (in weeks), and post progression survival (PPS) (in weeks) were the values collected. These variables were defined as the median time of intervention to death as median OS and to clinical or radiological evidence of tumor recurrence/progression as median PFS. PPS is defined as the time from tumor progression to death after the treatment.

Data management

Results of literature search were imported to EndNote X9 (Clarivate Analytics, Philadelphia, Pennsylvania).

Software utilization sought to reduce data entry errors and bias (i.e., duplicating references). All investigation reports were reviewed to assess for inconsistencies (e.g., design description, outcome presentation, and total patients analyzed).

Statistical analysis

Data work entered in Microsoft Office Excel 2007 and analyzed using SPSS version 24.0 (IBM Corp.; Chicago, United states. Data were analyzed at two levels, descriptive and analytical. Frequency, percentage, range, means, and median were used to describe the characteristics of study participants. $P < 0.05$ was considered statistically significant.

RESULTS

Out of 473 articles searched, 15 studies followed our inclusion criteria and were included in this study [Figure 1].

In 15 studies, ten were original and five were review articles. The minimum age group included in these studies was ≥ 65 years. Out of 15 studies, eight studies had described the role of re-surgery, four chemotherapy, three resurgery and/or chemotherapy, and only one study on role of reradiotherapy in patients with rGBM. Out of eight studies described the role of resurgery, six had mentioned improved survival and two had no benefit of resurgery in cases of rGBM. Three studies had mentioned the role of TMZ rechallenged, three fotemustine (FTM), one lomustine, and one on the role of bevacizumab (BEV) [Table 1].

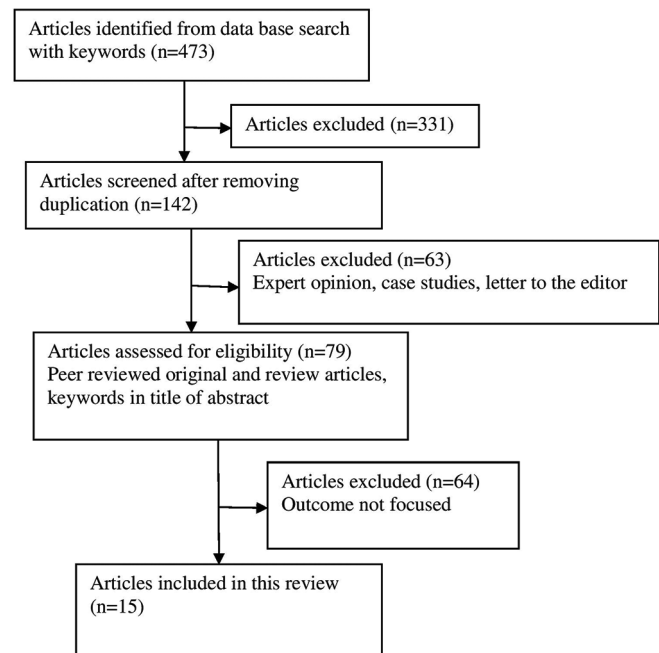


Figure 1: Flow chart (Preferred reporting items for systematic review and meta-analysis) for articles selection.

Table 1: The previous studies on elderly recurrent glioblastoma.

S. No	Authors	Articles type	Publication year	No of cases	Age of cases (years)	Remark
1.	Ironside <i>et al.</i> ^[14]	Review	2021	NA	>65	Chemotherapy (CCNU/Lomustine) or BEV can be considered at the time of recurrence
2.	Nibali <i>et al.</i> ^[25]	Review	2021	NA	>65	Re-surgery has better overall survival
3.	Nuñez <i>et al.</i> ^[26]	Original	2020	39	>65	Significant survival benefit in resected group as compare to nonresected group
4.	Carola <i>et al.</i> ^[4]	Review	2020	NA	≥70	Elderly cases who received any therapy on relapse responded with the same rate and for the same time period as adult cases
5.	Goldman <i>et al.</i> ^[13]	Original	2020	343	≥66	Resurgery has no survival advantage
6.	Addeo <i>et al.</i> ^[11]	Original	2019	58	>65	Chemotherapy with fotemustine is effective and safe treatment
7.	Chen <i>et al.</i> ^[6]	Original	2018	496	≥66	Resurgery increased survival as compare to who did not have resurgery
8.	Jasmin <i>et al.</i> ^[15]	Original	2018	59	≥71	Resurgery does not show any survival benefit
9.	Young <i>et al.</i> ^[39]	Review	2017	NA	>65	Reoperation seemed to be more effective in selected elderly patients with a KPS ≥60
10.	Zanello <i>et al.</i> ^[40]	Original	2017	777	≥70	KPS is an important prognostic factor. Oncological treatment (resurgery, chemotherapy, or BEV) had longer OS. In patients with poor KPS, chemotherapy is better option.
11.	Mallick <i>et al.</i> ^[23]	Review	2016	NA	>65	Resurgery has better survival as compare to no surgery
12.	Lombardi <i>et al.</i> ^[19]	Original	2016	44	≥65	Alternative schedule of FTM may be an active and safe treatment for elderly patients with rGBM
13.	Socha <i>et al.</i> ^[34]	Original	2015	84	>65	Local treatment (re-surgery and/or re-RT) has better survival in good KPS patients. Chemotherapy is better option in patients with poor KPS.
14.	D Amico <i>et al.</i> ^[9]	Original	2015	28	>65	Resurgery has better survival and has comparable complication between first and resurgery group
15.	Santoni <i>et al.</i> ^[33]	Original	2013	65	>65	FTM is a valuable treatment option in elderly rGBM cases

KPS: Kernofsky performance status, NA: Not available, FTM: Fotemustine, BEV: Bevacizumab

DISCUSSION

Management of elderly patients with GBM is difficult due to the poor prognosis, multiple comorbidities, and an increased risk of adverse effects from radiotherapy.^[30] Most clinical trials have excluded patients older than 65 years, which has resulted in no uniform optimal chemotherapy regimen and treatment protocol for elderly patients with GBM.^[29,36] Recurrence of GBM in elderly poses further challenge for the treatment as the patients have limited life expectancy. The management of rGBM generally depends on the extent of disease and patient condition and is particularly difficult in the elderly subgroup, as they are very heterogeneous population.^[24] In elderly patients, it remains unclear to what extent additional treatment including resurgery, reirradiation, and chemotherapy would be appropriate. There is only a little evidence regarding the best course of treatment when facing a GBM recurrence in elderly.^[10,31,32]

Decision-making

Age, although associated with comorbidities and overall frailty, does not necessarily reflect the patients physiologic reserve or functional capacity^[11] and thus should not preclude active

management of recurrence. Performance status, being the next most important prognostic factor for survival,^[30] must be factored heavily into the decision-making process, as it generally reflects the patient ability to receive any form of active treatment. Other factors such as site and size of tumor help to decide the appropriate form of treatment. O⁶ methylguanine DNA methyl transferase (MGMT) methylation helps to decide the form of chemotherapy and is associated with better prognosis. Status of isocitrate dehydrogenase (IDH) mutation helps in prognostication of patients. Salvage treatment should be decided on the basis of performance status of the patients.

(A) Elderly rGBM patients in good performance status (KPS ≥70%).

In these cases, local treatment (surgery and/or radiotherapy) results in better survival.

Resurgery versus conservative

The decision for resurgery after recurrence should be individualized as it is associated with greater morbidity and mortality.^[35] The goal of resurgery should be to relieve the mass effect and to achieve safe maximal extent of resection

which improves survival and also the overall effect of adjuvant therapy. Resurgery should be considered when (1) patient is in good functional status, (2) the procedure can reduce the raised intracranial pressure, (3) it can reasonably improve the quality of life of the patients, (4) it did not cause significant new neurological deficit or morbidity, (5) when it is possible to resect the contrast enhancing tumor tissue, and (6) the disease is focal and not involving eloquent brain regions, deep structures, or both hemispheres.^[32] Several previous studies had reported improved post recurrence survival of at least 7 months for patients who underwent resurgery at GBM recurrence in elderly.^[5,7]

Núñez *et al.*^[26] done a prospective study on 39 elderly rGBM patients which were reoperated on recurrence and showed significant survival benefit (HR: 0.6, 95% CI 0.36–0.9, $P = 0.0427$) for the reoperated group (18 months, 95% CI 13.97–23.2 months) compared to the group without resurgery (10.1 months, 95% CI 8.09–20.9 months). Young *et al.*^[39] reported that reoperation seemed to be the most effective salvage strategies in selected elderly patients with a KPS $\geq 60\%$. Most of the other studies like Chen *et al.*^[6] (12.0 months versus 5.0 months, HR = 0.666, $P < 0.0001$) and Zanello *et al.*^[40] (aHR, 0.67 [95% CI: 0.56–0.81], $P < 0.001$) had also reported increased survival with resurgery. Only two studies had no survival benefit with resurgery.^[13,15] It may be due to poor selection of elderly rGBM cases for resurgery.

Chen *et al.*^[6] studied 496 cases of elderly rGBM cases of age ≥ 66 years and reported that only 12% of cases underwent at least 1 reoperation at an average of 7.2 months after the initial diagnosis. There were no significant differences in the complication of initial and resurgery. The overall complication rate was 21.7% in the initial resection versus 20.4% in the first reoperation group and 25.3% in the second reoperation group. Núñez *et al.*^[26] also have similar complication rates.

Resurgery versus chemotherapy

Resurgery had more survival benefits as compare to systemic therapy (chemotherapy) in rGBM in elderly patients with good KPS. A Korean study had evaluated the outcome of various salvage strategies in rGBM patients after upfront maximum debulking surgery followed by chemoradiotherapy and adjuvant TMZ, median PPS was 13.2 months after resurgery versus 5.6 months after TMZ chemotherapy.^[16] Socha *et al.*^[34] in his study of 98 elderly rGBM patients reported that patients receiving resurgery (51 weeks, 95% CI 6.3–95.7 weeks) had better median PPS as compare to CHT (21 weeks, 95% CI 11.4–34.6), $P = 0.36$.

Resurgery versus reradiotherapy

Elderly rGBM cases managed with resurgery had better survival benefit as compare to reradiotherapy. On analyzing

the previous literature, it is found that patients managed with resurgery (51 weeks, 95% CI 28.9–73.1 weeks) have better median PPS as compare to patients given only re-RT (17 weeks, 95% CI 12.2–21.8 weeks), $P = 0.62$.^[34] Further studies are required to validate these results.

(B) Elderly rGBM patients in poor performance status (KPS < 70%)

Chemotherapy versus local treatment

Local treatment (resurgery) results in improved survival benefit in rGBM in elderly patients with good KPS score, but it is associated with poor outcome in patients with poor KPS score (KPS < 70%) probably due to postoperative complications. In this special subgroup, chemotherapy seems to be optimal therapeutic approach.

Zanello *et al.*^[40] reported that age of ≥ 70 year was not a significant independent predictor of OS (median 19.6 versus 17.0 months, aHR, 1.17 [95%CI: 0.93–1.46], $P = 0.190$). The performance status of the patients at recurrence is the most important factor deciding the OS of the patients. Elderly patients with a KPS at recurrence of 60 or less did not benefit from surgery or radiotherapy at that time compared with chemotherapy instead.

After multiple adjustment using cox models, poor KPS from recurrence was independently associated with shorter OS from recurrence (aHR, 1.52 [95% CI: 1.27–1.82], $P < 0.001$). On reviewing the literature, patients treated with chemotherapy had better median PPS (21 weeks, 95% CI 8.8–33.2) as compare to patients treated with local treatment (14 weeks, 95% CI 0.9–46.7) $P = 0.88$.^[34]

Several studies^[1,19,33] have reported that FTM is a valuable therapeutic option for elderly patients with rGBM. Paccapelo *et al.*^[28] and Perry *et al.*^[31] had compared the FTM with TMZ rechallenged in elderly rGBM cases and reported that TMZ seemed to be active in early and late progression while FTM was always active in recurrent cases. The major difference was registered in GBM patients who failed after more than 6 months of TMZ.^[28] Young *et al.*^[39] had reported that oral nitrosourea (lomustine) has emerged as an option for rGBM in elderly patients. This chemotherapeutic drug is easily dosed, typically 110 mg/m² once every 6 weeks for a total of six cycles if efficacious and tolerated.^[37,38] Prolonged cytopenia caused by this drug should be kept in mind during treatment in elderly and frail patients.

Best supportive care (BSC) versus any treatment

Elderly rGBM patients with poor KPS need not be automatically precluded from salvage treatment. Instead, the treatment should be individually tailored based on the presenting symptoms and the patient specific needs and

goals. Some previous study^[34] had reported that rGBM patients with poor KPS may also benefit from active treatment, as the active treatment approach more than doubled median PPS in these patients (21 weeks vs. 9 weeks with BSC, $P = 0.014$). Socha *et al.*^[34] had compared outcomes in elderly rGBM with poor KPS treated with BSC and with any treatment and reported that median PPS with BSC was 9 weeks (95% CI 2.9–15 weeks) and 21 weeks (95% CI 8.9–33.1 weeks) with any treatment, $P = 0.014$. Nibali *et al.*^[25] have similar results.

BEV may be most beneficial for patients with more robustly enhancing tumors that are associated with substantial cerebral edema. This therapeutic agent is associated with improved PPS and radiographic response rate, which are secondary in part to its mechanism of action of decreasing cerebral edema and normalizing the tumor vasculature.^[12,18]

The newer treatment modalities such as molecular targeted therapy, immunotherapy, tumor treating fields, photodynamic therapy, intraoperative radiotherapy, laser interstitial thermal therapy, nuclear medicine thermal therapy, chimeric antigen receptor T-cell therapy, and various combination therapy have been investigated in elderly patients with newly diagnosed GBM cases but not in recurrent cases. At present, there is no evidence to support the role of these newer treatments outside the clinical trials, particularly for elderly cases. Further randomized control trials are required to validate efficacy and safety of these newer treatments and to analyze the role of molecular markers such as IDH mutant status, EGFR amplification, and MGMT methylation status to prognosticate these patients.

CONCLUSION

Management of elderly rGBM depends on the extent of the disease and performance status of the patients. Resurgery has better OS than other modalities of treatment and should be considered in selected elderly rGBM patients with good performance status. It has comparable complication rates as in nonelderly rGBM cases. Chemotherapy has better survival than BSC in elderly rGBM cases with poor performance status. Role of reradiotherapy and other newer treatments require further evaluation in well-designed, randomized, and control trials.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

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