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Review

Management of glioblastoma after recurrence: A changing paradigm

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Abstract Glioblastoma remains the most common primary brain tumor after the age of 40 years. Maximal safe surgery followed by adjuvant chemoradiotherapy has remained the standard treatment for glioblastoma (GBM). But recurrence is an inevitable event in the natural history of GBM with most patients experiencing it after 6–9 months of primary treatment. Recurrent GBM poses great challenge to manage with no well-defined management protocols. The challenge starts from differentiating radiation necrosis from true local progression. A fine balance needs to be maintained on improving survival and assuring a better quality of life. Treatment options are limited and ranges from re-excision, re-irradiation, systemic chemotherapy or a combination of these. Re-excision and re-irradiation must be attempted in selected patients and has been shown to improve survival outcomes. To facilitate the management of GBM recurrences, a treatment algorithm is proposed.

Contents

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Introduction

Glioblastoma (GBM) is the most common primary brain cancer in the age group after 40 years and the prognosis gets worse as the age increases. The land mark trial by Stupp et al. led to acceptance that maximal safe surgery followed by adjuvant chemoradiotherapy and adjuvant chemotherapy to be the standard of care [1]. But local infield recurrence is an inevitable event, with most patients experiencing it after 6–9 months of primary treatment because of resistant GBM stem cell and neuronal stem cells, suboptimal mean dose to the ipsilateral subventricular zone (SVZ) or involvement of corpus callosum [2,3]. Different molecular factors like P53 mutation, MIB-1 labeling index, and O-6-methylguanine-DNA methyltransferase (MGMT) methylation have been correlated with recurrence in GBM [4,5]. The various radiation treatment protocols with dose escalation beyond 60 Gy have been unsuccessful and have led to increased toxicity. There has been much controversy in the diagnosis of recurrence with the definitive diagnosis only via histopathological examination. But most of the patients with imaging finding suggestive of progression may not be fit for a surgical procedure, making the diagnosis of recurrent GBM difficult. The main differential diagnosis includes radiation necrosis which also occurs at the same time period and may be symptomatic thus mimicking progression. But the recent advances in imaging have helped us in a great way in differentiation between the two. The treatment of recurrent glial tumors has always been challenging and is associated with significant toxicities and always a balance has to be achieved between local control and treatment related morbidities and mortalities [6,7].

Surgery remains an important therapeutic strategy. However, only a small proportion of patients are found eligible for a total surgical resection. Re-irradiation (ReRT) has evolved as a salvage option in the last decade [8]. Evolution of new radiotherapy techniques and better image guidance may help in giving highly conformal doses and thus limiting toxicity. Chemotherapy has also been used by various groups with an aim to improve survival outcomes. But despite these various treatment options, outcome of these patients has remained dismal [9–11]. There has been some recent interest with some new modalities showing promising results available for some of these. But the presence of the blood–brain barrier (BBB) limits the delivery of most chemotherapeutic agents [12,13]. However, most of the treatment regimens have surfaced with single institute retrospective analysis or few phase II clinical studies. So, there hardly exists any standard treatment. In this review we intend to review available investigations for the diagnosis and treatment modalities with meaningful impact on survival and derive a possible therapeutic algorithm for patients with recurrent GBM.

Search methodology

We searched the PubMed for literature of recurrent glioblastoma. We used the following MeSH terminology: recurrent glioblastoma retrieved 2023 entries; recurrent glioblastoma AND treatment retrieved 1775 entries (4 phase III, 230 Phase II, 104 phase I study, 2-metaanalysis). We retrieved a total of 57 articles pertaining to recurrent glioblastoma AND reirradiation but none of these were a phase I/II study. Only 16 found to describe retrospective result of treating recurrent GBM with reirradiation. We also searched for recurrent glioblastoma AND surgery we retrieved 31 entries with one phase II study. There were 56 entries for the MeSH term of recurrent glioblastoma AND vaccine out of which only fourteen described a phase I/II study. 187 phase I/II and 2 phase III trials described chemotherapy/targeted therapy for rGBM.

Diagnosis of a recurrence

Diagnosing a recurrence in GBM patients remains a challenge with radio necrosis closely resembling changes of recurrence on imaging. Examination of the surgically resected specimen remains the gold standard for the diagnosis of radiation necrosis. The picture is in fact further complicated by coexistence of both in many cases. The new advances in radiology and nuclear medicine may help in some cases to differentiate these entities. A good clinical judgment along information from these various imaging modalities may help us in majority of the cases.

Combination of contrast enhanced (CE) T1-weighted imaging, diffusion-weighted (DW) imaging, and perfusion MR imaging resulted in significantly better diagnostic accuracy without much impact from selection of perfusion MR method (dynamic CE [DCE]) vs dynamic susceptibility CE) [14]. In magnetic resonance spectroscopy (MRS) tumor recurrence is characterized by a higher Choline (Ch)/N-acetylaspartate (NAA) and Ch/(creatine) Cr ratio but a low NAA/Cr ratio. Lower lipid signals in MRS are also characteristic of tumor recurrence. Hence, the presence of elevated lipid signals along with low choline/NAA ratios may help to differentiate radiation changes from tumor recurrence [15]. Relative cerebral

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