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Original Article

Promising outcome of patients with recurrent glioblastoma after Gamma Knife-based hypofractionated radiotherapy

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Abstract

Background

The role of Gamma Knife radiosurgery (GKRS) in recurrent glioblastoma remains unclear. The purpose of this study is to evaluate the effects of GKRS in a group of patients with recurrent glioblastoma, focusing on survival and safety.

Methods

Patients undergoing GKRS for recurrent glioblastoma between September 2014 and April 2019 were included in this study. Relevant clinical and radiosurgical data, including GKRS-related complications, were recorded and analyzed. Overall survival (OS), local progression free survival (LPFS) and prognostic factors for outcome were thoroughly evaluated.

Results

Fifty-three patients were analyzed (24 female, 29 male). The median age was 50 years (range, 19–78 years). The median GKRS treatment volume was 35.01 cm^3 (range, 2.38-115.57 cm^3). Twenty patients (38%) were treated with single fraction GKRS, while 33 (62%) were treated with GKRS-based hypofractionated stereotactic radiotherapy (HSRT). The median prescription dose for single fraction GKRS, 3-fractions HSRT and 5-fractions HSRT were 16 Gy (range, 10–20 Gy), 27 Gy (range, 18–33 Gy) and 25 Gy (range, 25–30 Gy), respectively. The median LPFS and OS times were 8.1 months and 11.4 months after GKRS, respectively. HSRT and Bevacizumab were associated with improved LPFS, while HSRT alone was associated with longer OS.

Conclusion

Our findings suggested that HRST would likely improve LPFS and OS in definite settings; the addition of Bevacizumab to GKRS was associated with increased rates of local control. No major complications were reported. Further prospective studies are warranted to confirm our findings.

Introduction

Glioblastoma represents the most common malignant primary brain tumor with poor survival rates despite of standard radical treatment, which includes maximal surgical resection and chemo-radiation therapy. Recurrence is widely considered inevitable with almost 100% of patients developing signs of progressive disease 6–10 months following diagnosis [1]. Moreover, the management of recurrent glioblastomas remains tortuous and complex with a median survival time precluded to 6 months [2]. Although microsurgery is often considered in these cases, feasibility remains surrogate to key factors such as the degree of regional infiltration, patients' performance status, neurological function, and underlying co-morbidity [3]. Systemic treatment is seldom effective at long-term and often associated to toxicity [4], [3]; indeed, only the anti-VEGF monoclonal antibody Bevaczumab has been approved by Food and Drug Administration (FDA) for recurrent disease [5], [6], [7]. Re-irradiation schedules utilizing single fraction stereotactic radiosurgery (SRS), repeat conventional fractionated radiotherapy and hypofractionated stereotactic radiotherapy (HSRT), have also been proposed; yet to this day, there is no clear consensus on the subject [2], [8], [9], [10], [11], [12], [13], [14], [15]. Toxicity to normal brain tissue, which is dose-volume dependent, appears to be the main limiting factor for repeat radiation treatments [16], [17], [18], [19]. In this context, SRS facilitates a more accurate high dose to the target with a rapid dose fall-off at the normal brain tissue as compared to conventional radiation therapy. Nonetheless, SRS also implies collateral cytotoxic effects to peri-lesional healthy tissue; as such, its use is mainly limited to small-sized lesions [20], [21], [22]. Alternatively, HSRT has been shown to overcome this problem, as confirmed by multiple studies; this is possibly due to a set of radiobiological events carefully interacting with the immune system, not necessarily seen on SRS [11], [23], [24], [25], [26]. Extensive evidence highlighting the benefits of Gamma Knife radiosurgery (GKRS) in distinct fractionation setups (SRS or HSRT) can be found in the literature; however, studies on GKRS and recurrent glioblastoma remain scarce [27]. So far, there is no consensus on the use of SRS or other radiation treatment schedules for recurrent glioblastoma. To contribute with the existing data, we investigated the effects of GKRS-based SRS and HSRT on a patient population with recurrent glioblastoma; overall survival (OS), local progression free survival (LPFS), and safety were thoroughly analyzed.

Section snippets

Patients

We retrospectively reviewed patients with recurrent glioblastoma treated with GKRS between September 2014 and April 2019 (Bezmialem Vakif University Hospital, Istanbul, Turkey). All patients were initially treated with microsurgical resection followed by conventional fractionated radiation therapy (60 Gy in 30 fractions) with concomitant and adjuvant cyclic Temozolomide chemotherapy. Patients who presented with recurrence after standard treatment were considered for GKRS by multi-disciplinary…

Patients' characteristics

We analyzed 53 patients who were treated with GKRS for recurrent glioblastoma during the study period. All patients had the histological diagnosis of glioblastoma from their initial surgery, and received conventional

radiation therapy with a dose of 60 Gy and concurrent and adjuvant Temozolomide chemotherapy. Patients underwent only stereotactic biopsy and those who did not receive conformal radiation therapy were excluded from the study. 24 patients were female (45%) and 29 (55%) were male.…

Discussion

We investigated the effects of GKRS in terms of local tumor control and OS in a group of patients with recurrent glioblastoma; as such, we tried to identify factors associated with LPFS and OS time. We found that hypofractionation and the addition of Bevacizmab to HSRT were significantly associated with significant improvement in LPFS time. Also, a strong association between hypofractionation and overall survival was also noticed.

The management of patients with recurrent glioblastoma is…

Conclusion

Patients with recurrent glioblastoma have a poor prognosis and there is no standard established treatment. In this study, GKRS re-irradiation proved to be a plausible, non-invasive treatment option with favorable outcome in terms of OS, LPFS, and ARE. We suggest that GKRS-based extreme HSRT (3–5 fractions) is equally effective as longer HSRT schedules described in the literature in terms of safety, patient outcome, and logistics. Most importantly, our HSRT protocol may be considered as a…

Author contribution

Conception or design of the work: Mustafa Aziz Hatiboglu, Mustafa Namik Oztanir, Georges Sinclair.

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Critical revision of the article: Mustafa Aziz…

Ethics approval

Approved by Bezmialem Vakif University No. 24/452.…

Conflict of interest

No conflict of interest.…

Consent for publication

MA Hatiboglu, certify on behalf of all authors that this manuscript is a unique submission and is not being considered for publication, in part or in full, with any other source in any medium.

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