Long-Term Survival Outcomes of Hypofractionated Stereotactic Radiotherapy Combined with Anlotinib for Recurrent Glioblastoma: An Extended Follow-up Report

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Abstract: Background: The clinical management of recurrent glioblastoma (rGBM) is highly challenging. We previously reported the preliminary safety and efficacy of hypofractionated stereotactic radiotherapy (HSRT) combined with anlotinib for rGBM. This brief report provides an extended long-term follow-up of this cohort to evaluate survival outcomes and late toxicities. Methods: The original cohort of five patients treated with HSRT (25.0 Gy in 5 fractions) and concurrent/adjuvant anlotinib (12 mg daily, days 1–14 every 3 weeks) was retrospectively analyzed for long-term progression-free survival (PFS), overall survival (OS), and late adverse events. Results: Over a significantly extended observation period, the updated median PFS was 9.9 months, and the median OS reached an encouraging 29.1 months. At the latest follow-up, two patients had experienced in-field disease progression and died, while one patient died from a cerebral infarction. Two patients were alive at their last clinical contact, and their robust survival times were appropriately right-censored at 42.1+ and 46.8+ months post-treatment, respectively. No severe late radiation necrosis (grade ≥ 3) or uncontrollable targeted-therapy toxicities were observed. Conclusion: The extended follow-up confirms that HSRT combined with anlotinib provides a durable clinical response and a highly meaningful long-term survival benefit for select patients with rGBM, maintaining a favorable long-term safety profile.

***Keywords*:** glioblastoma, CyberKnife, anlotinib, bevacizumab, anti-VEGF

1. Introduction

Glioblastoma is the most aggressive primary brain tumor in adults. Despite standard initial therapy comprising maximum safe resection and chemoradiotherapy [1], recurrence is nearly inevitable [2]. The prognosis for recurrent glioblastoma (rGBM) remains dismal, and effective salvage treatments are urgently needed. While anti-angiogenic agents such as bevacizumab can prolong progression-free survival (PFS) [3], they often fail to significantly improve overall survival (OS) in randomized clinical trials [4]. Furthermore, single-agent options often yield transient effects with rapid progression shortly after salvage intervention.

To maximize local control and target tumor angiogenesis, our center previously initiated a salvage regimen combining hypofractionated stereotactic radiotherapy (HSRT) with anlotinib, an oral multi-target tyrosine kinase inhibitor targeting VEGFR, PDGFR, and FGFR [5]. Anlotinib has previously demonstrated promising early tumor control and case-specific clinical responses in malignant gliomas [6, 7]. In our 2022 preliminary report [8], this combination yielded a remarkable 100% objective response rate (ORR) with an acceptable acute toxicity profile in five rGBM patients. However, whether this robust initial tumor shrinkage translates into a durable long-term OS benefit, and whether the regimen induces delayed neurotoxicity, required extended investigation. Herein, we report the extended long-term clinical and survival outcomes of this original cohort.

2. Methods

This extended retrospective analysis includes the five rGBM patients (median age at treatment: 51 years; range: 43–60) treated at our institution. All patients had radiographically confirmed recurrence and a Karnofsky Performance Status (KPS) ≥ 70. The treatment protocol was maintained as previously described: patients received HSRT delivered by a CyberKnife system to a total dose of 25.0 Gy in 5 consecutive fractions. Anlotinib was administered at a dose of 12 mg daily for 14 consecutive days every 3 weeks, starting concurrently with HSRT. Clinical and radiological follow-ups were conducted to assess long-term OS, PFS, and late toxicities. Toxicity was graded using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. For patients who were alive at the time of data cutoff, survival data were right-censored at the date of their last successful clinical contact.

3. Results

3.1 Long-Term Survival Outcomes

At the time of the initial report, the follow-up duration ranged from 20 to 26 months. As of the current data cutoff in May 2026, the follow-up period has been substantially extended. The updated median PFS for the cohort was 9.9 months (range: 4.0–24.7+ months). The updated median OS, calculated from the completion of salvage HSRT, reached an encouraging 29.1 months (range: 15.6–46.8+ months). During the extended follow-up, three patients died. Specifically, two patients succumbed to in-field tumor progression, while one patient died of a cerebral infarction, representing a non-tumor-specific mortality. Notably, two patients demonstrated exceptional durable responses; they were alive at their last clinical evaluation at 42.1 and 46.8 months post-salvage treatment, respectively, and their survival data were appropriately right-censored at these time points.

3.2 Failure Patterns and Late Toxicity

Among the patients who experienced disease progression, the exclusive pattern of failure was in-field local recurrence (observed in 2 patients), indicating that while long-term disease control remains a spatial challenge, distant dissemination was successfully prevented in this cohort. Critically, the extended follow-up confirmed the long-term safety of the 25.0 Gy/5 fx HSRT regimen. No instances of grade 3 or higher delayed radiation necrosis were observed. Long-term adherence to anlotinib was well-tolerated; chronic toxicities were primarily limited to grade 1 or 2 hand-foot syndrome and hypertension, which were effectively managed with dermatologic treatments and standard antihypertensive medications without requiring permanent discontinuation of the targeted therapy.

4. Discussion

This extended update addresses the critical gap regarding the durability and late safety of HSRT combined with anlotinib for rGBM. While our preliminary data [8] showed excellent initial tumor volume reduction, this analysis confirms that the initial ORR successfully translated into a meaningful long-term survival benefit, with an updated median OS of 29.1 months and a median PFS of 9.9 months. The observed survival outcomes compare highly favorably to historical data for single-agent anti-angiogenic therapies or re-irradiation alone, where historical post-recurrence OS typically hovers around 6–9 months [9, 10].

The synergistic effect is likely twofold: HSRT provides high-intensity local tumor ablation, while anlotinib's multi-target inhibition suppresses tumor angiogenesis and potentially induces vascular normalization. A vascular normalization index has been noted to correlate with prolonged survival by alleviating tumor hypoxia and optimizing local control [11]. The fact that the only tumor-related mortalities were due to in-field recurrence highlights the robust prevention of distant spread.

Regarding the non-tumor-specific mortality (cerebral infarction), although it was not definitively linked to tumor progression, the potential risk of arterial thromboembolic events associated with continuous multi-target anti-angiogenic TKIs and high-dose brain re-irradiation cannot be entirely ruled out, warranting rigorous cardiovascular monitoring in future applications. Furthermore, the absence of severe late radiation necrosis over this extended observation period is highly encouraging. High-dose re-irradiation in the brain carries a notorious risk of late neurotoxicity, yet our intensive 25.0 Gy in 5 fractions regimen, even when combined with continuous multi-target anti-angiogenic blockade, proved exceptionally safe in the long term, aligning with the safety signals observed in controlled trials of re-irradiation with anti-VEGF combinations [12, 13].

The primary limitation of this report is the small cohort size and the retrospective nature of the extended follow-up. Additionally, exploring how specific molecular subgroups correlate with these exceptional long-term responses remains a critical avenue for future research. Nonetheless, these long-term results provide strong preliminary evidence supporting this combination strategy.

5. Conclusion

HSRT combined with anlotinib offers a durable clinical response and a tangible long-term overall survival benefit for patients with recurrent glioblastoma. The late toxicity profile, particularly regarding radiation necrosis, is highly manageable. Further validation in larger prospective cohorts is warranted.

Acknowledgments

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