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Hypofractionated re-irradiation with bevacizumab for relapsed chemorefractory glioblastoma after prior high dose radiotherapy: a feasible option for patients with large-volume relapse

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Abstract

Purpose: There remains no standard of care for patients with recurrent and chemorefractory glioblastoma. Re-irradiation (reRT) provides an additional management option. However, published series predominantly focus on small reRT volumes utilizing stereotactic hypofractionated regimens. Concerns regarding toxicity have limited utilisation of reRT for larger recurrences, however this may be mitigated with use of bevacizumab (BEV).

Methods and materials: A prospective database of patients managed with the EORTC-NCIC (Stupp) protocol 60 Gy chemoradiotherapy protocol for glioblastoma between 2007 and 2021 was reviewed for those patients receiving reRT for chemorefractory relapse. Serial MRI and PET were used to establish true progression and exclude patients with pseudoprogression or radionecrosis from reRT. The primary endpoint was overall survival (OS) from date of reRT. Prognostic factors were also assessed.

Results: 447 patients managed for glioblastoma under the Stupp protocol were identified, of which 372 had relapsed and were thus eligible for reRT. 71 patients underwent reRT. Median relapse-free survival from diagnosis for the reRT and overall cohorts were similar at 11.6 months (95%CI:9.4-14.2) and 11.8 months (95%CI:9.4-14.2) respectively. 60/71 (85%) reRT patients had received BEV prior to reRT and continued concurrent BEV during reRT. Of the 11 patients not managed with BEV during reRT, 10 required subsequent salvage BEV. ReRT patients were younger (median 53 vs. 59 years, $p < 0.001$), had better performance status (86% vs. 69% ECOG 0-1, $p = 0.002$) and more commonly had MGMT promoter-methylated tumours (54% vs. 40%, $p = 0.083$) compared to non-reRT patients. Median reRT PTV volume was 135cm^3 (IQR: 69-207cm^3). Median OS from reRT to death was 7.1 months (95%CI:6.3-7.9). Patients aged < 50, 50-70 and > 70 years had post-reRT median OS of 7.7, 6.4 and 6.0 months respectively ($p = 0.021$). Median post-reRT survival was longer for patients with ECOG performance status 0-1 compared to 2-3 (8.1 vs. 6.3 months, $p = 0.039$). PTV volume, site of relapse, MGMT promoter-methylation status and extent of initial surgical resection were not associated with post-reRT survival. ReRT was well-tolerated. Out of the 6 patients (8%) admitted to hospital after reRT, only one was for reRT toxicity. This was a CTCAE grade 3 radiation necrosis event in a patient managed without prior BEV.

Conclusion: Patients with recurrent glioblastoma who have been previously treated with 60 Gy radiotherapy have a meaningful survival benefit from large volume re-irradiation which is well tolerated. ReRT should not be ignored as a salvage treatment option in patients with chemorefractory progressive disease.

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