Timing of Concurrent Temozolomide Chemoradiotherapy in Glioblastoma Patients and Its Impact on Overall Survival: A 14-year Multicentre Retrospective Analysis

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Objectives:

Maximal safe resection followed by concurrent chemoradiation (CCRT) and adjuvant temozolomide is standard-of-care first-line treatment for patients with glioblastoma. However, whether there exists an optimal time interval between surgery and CCRT remains undetermined. This study aims to examine whether the timing of CCRT after surgery improves overall survival (OS).

Materials and Methods:

Records of all histologically-confirmed glioblastoma patients across all seven Hong Kong neurosurgical units from 2006 to 2020 that received CCRT within 90 days after surgery were retrospectively reviewed. Multivariable Cox models with restricted cubic splines (RCS) were used to analyse the association between resection-to-CCRT interval and OS. Conventional prognostic factors were analysed *a priori*, including age, gender, preoperative Karnofsky performance status (KPS), extent of resection (EOR) and *MGMT*-methylation status. Multiple imputation was used to handle missing data.

Results:

Of the 472 patients who satisfied the inclusion criteria, the median resection-to-CCRT interval was 41 days (IQR 33-48). Median OS (mOS) was 17.2 months (IQR 11.4-31.9). Median age at diagnosis was 57 years (range 18-81). Male: female ratio was 1.6:1. 233 patients (49.4%) had a KPS >80. 167 patients (35.4%) underwent GTR, 240 (50.8%) underwent STR, and 63 (13.8%) had a biopsy. Half of the patient cohort (49.9%, 188/377) had *MGMT*-methylated tumours.

RCS analysis revealed an interval with lowest mortality risk between 36-63 days post-resection. Early initiation of CCRT before this interval (<=35 days; n=161; aHR 1.18; 95% CI 0.96-1.46; mOS 16.3 months) and late initiation of CCRT after (>63 days; n=21; aHR 1.32; 95%CI 0.84-2.08; mOS 17.9 months) were not prognostic of OS. Subgroup analysis of conventional prognostic factors also did not reveal an association between OS and the resection-to-CCRT interval. The only independent predictors for better OS were a KPS >80 (aHR 0.74; 95% CI: 0.60-0.90) and *MGMT*-methylated tumours (aHR: 0.50; 95%CI: 0.40-0.61)

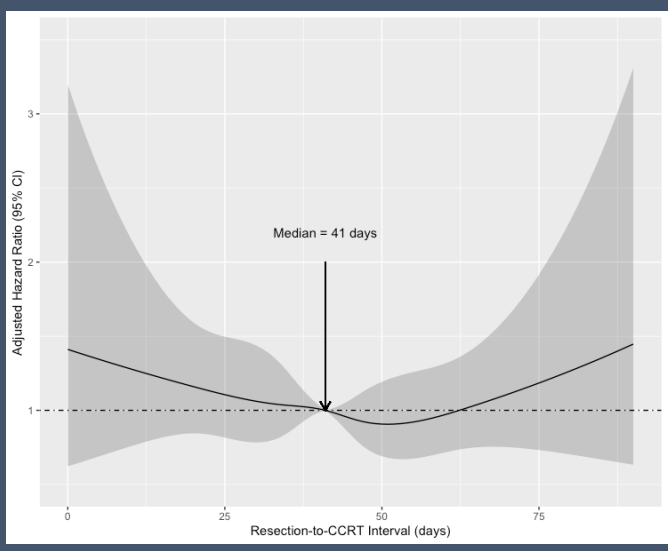

Figure 1: Adjusted HRs with resection-to-CCRT modelled as a continuous variable with RCS

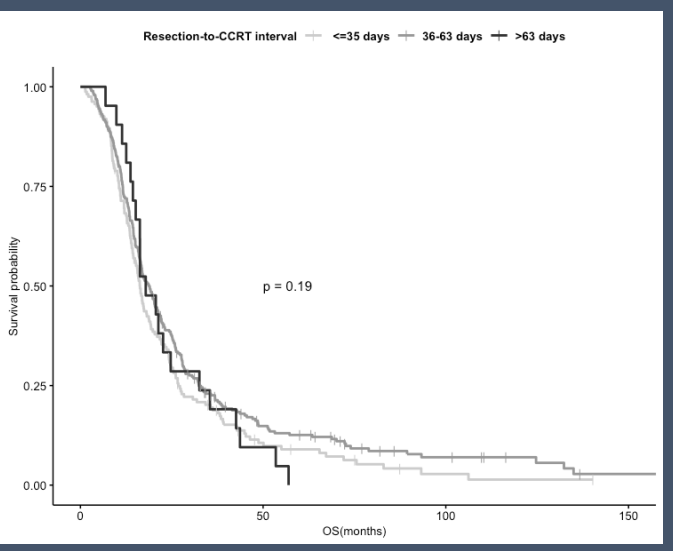

Figure 2: Kaplan-Meier curves for early, reference and late groups of resection-to-CCRT interval

Conclusion:

Neither early nor late initiation of CCRT within 90 days after glioblastoma resection improves OS significantly. Preoperative functional performance and *MGMT* methylation status continued to be significant predictors for OS.