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Glioblastoma

Delaying standard combined chemoradiotherapy after surgical resection does not impact survival in newly diagnosed glioblastoma patients

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ABSTRACT

Background: To assess the influence of the time interval between surgical resection and standard combined chemoradiotherapy on survival in newly diagnosed and homogeneously treated (surgical resection plus standard combined chemoradiotherapy) glioblastoma patients; while controlling confounding factors (extent of resection, carmustine wafer implantation, functional status, neurological deficit, and postoperative complications).

Methods: From 2005 to 2011, 692 adult patients (434 men; mean of 57.5 ± 10.8 years) with a newly diagnosed glioblastoma were enrolled in this retrospective multicentric study. All patients were treated by surgical resection (65.5% total/subtotal resection, 34.5% partial resection; 36.7% carmustine wafer implantation) followed by standard combined chemoradiotherapy (radiotherapy at a median dose of 60 Gy, with daily concomitant and adjuvant temozolomide). Time interval to standard combined chemoradiotherapy was analyzed as a continuous variable and as a dichotomized variable using median and quartiles thresholds. Multivariate analyses using Cox modeling were conducted.

Results: The median progression-free survival was 10.3 months (95% CI, 10.0–11.0). The median overall survival was 19.7 months (95% CI, 18.5–21.0). The median time to initiation of combined chemoradiotherapy was 1.5 months (25% quartile, 1.0; 75% quartile, 2.2; range, 0.1–9.0). On univariate and multivariate analyses, OS and PFS were not significantly influenced by time intervals to adjuvant treatments. On multivariate analysis, female gender, total/subtotal resection and RTOG-RPA classes 3 and 4 were significant independent predictors of improved OS.

Conclusions: Delaying standard combined chemoradiotherapy following surgical resection of newly diagnosed glioblastoma in adult patients does not impact survival.

Glioblastoma (World Health Organization grade IV astrocytoma) is the most common malignant primary brain tumor in adults [1]. Maximal safe resection is recommended as the first treatment to reduce symptoms and improve survival [2]. Following surgery, the current standard of care for newly diagnosed

Abbreviations: HR, hazard ratio; CI, confidence interval; MRI, Magnetic Resonance Imaging; OS, overall survival; PFS, progression-free survival; RPA, recursive partitioning analysis; RTOG, Radiation Therapy Oncology Group; WHO, World Health Organization.

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glioblastoma consists of radiotherapy and concomitant and adjuvant temozolomide, the so-called standard combined chemoradiotherapy. This treatment regimen increases median overall survival (OS) compared with radiotherapy alone [3,4]. Delay in the initiation of radiotherapy after surgery has been evaluated for several types of cancers and recognized as a detrimental factor for radiotherapy outcomes [5–8]. Glioblastoma is among the most aggressive malignant brain tumors and a rapidly growing tumor with a short doubling time [9,10]. For adjuvant treatment of glioblastoma, delaying the initiation of combined chemoradiotherapy has been theoretically questioned as a detrimental parameter on patient's survival [11]. Previous retrospective analyses in the pre-temozolomide era have shown that delaying radiotherapy, due to postoperative complications, longer patient recovery, or organizational difficulties, could negatively impact patients' survival [12,13]. New data have been published on this specific issue with patients mostly treated by standard combined chemoradiotherapy, with and without prior surgical resection, but these studies presented contradictory results [14–26]. A recent meta-analysis based on published data (12 publications, 5212 patients) did not find any influence of the time interval to radiotherapy on OS [27]. However, confounding factors, including extent of surgical resection, carmustine wafer implantation, postoperative complications, pre-treatment neurological impairment, and patients' performance status, that may account for a delayed adjuvant oncological treatment, were not sufficiently explored to draw any reliable conclusions [28]. It remains inconclusive whether time interval between surgery and standard combined chemoradiotherapy onset may influence survival in adult patients harboring a newly diagnosed glioblastoma and treated with first-line large surgical resection, with or without carmustine wafer implantation. Here we report a large and multicenter study aiming to assess the prognostic weight of time interval to standard combined chemoradiotherapy after surgery in a homogeneous series of adult patients with a supratentorial glioblastoma all receiving surgical resection, with or without carmustine wafer implantation, plus standard combined chemoradiotherapy as first-line oncological treatment. For the first time, the potential pre-treatment and therapeutic confounding factors (functional status, neurological deficit, extent of surgical resection, intraoperative carmustine wafer implantation, and postoperative complications) were specifically controlled to shed new light on the issue of "time to adjuvant treatment post surgical intervention".

Patients and methods

Patient population

Patients entered into the CASTE1 database, run by the Club de Neuro-Oncologie of the Société Française de Neurochirurgie between 2005 and 2011, constituted the study group for this article [29]. Inclusion criteria were: (1) patients older than 18 at diagnosis; (2) histologically confirmed supratentorial glioblastoma; (3) surgical resection followed by the standard combined chemoradiotherapy (radiotherapy, 60 Gy, and daily concomitant temozolomide at 75 mg/m^2/day, then adjuvant temozolomide at 150–200 mg/m^2/day five days every 28 days for theoretically 6 cycles) as first-line treatment [3,4]. Exclusion criteria included: (1) bevacizumab administration during the first-line treatment; (2) unknown date of initiation of adjuvant chemoradiotherapy; (3) incomplete outcome data. A total of 820 patients were screened. We excluded 128 patients (15.6%) from the cohort: 95 did not have an available time interval between surgery and radiotherapy, six did not have the full radiotherapy dose, three did not receive concomitant chemoradiotherapy, and 24 were not available for follow-up. In the end, a total of 692 cases were available for survival analysis. The institutional review board of the Sainte-Anne Hospital Center University Paris Descartes approved the study protocol (No. AC036).

Data collection

The patient- and tumor-related characteristics collected at the time of histopathological diagnosis included: gender, age, the revised Radiation Therapy Oncology Group recursive partitioning analysis (RTOG-RPA) classification system for glioblastoma [30], Karnofsky performance status, presence of a neurological deficit, and tumor location. Treatment-related characteristics included: carmustine wafer implantation, extent of surgical resection based on early postoperative MRI (within 48 h) on contrast-enhanced T1-weighted sequence (subtotal and total resections defined by removal of $\geqslant$90% of enhancing tumor) [31,32], postoperative complications (neurological deficit, epileptic seizures, infections), first-line oncological treatment modalities (time to initiation of standard combined chemoradiotherapy, radiotherapy dose, number of adjuvant temozolomide therapy cycles).

Statistical analyses

The end goal was to assess the impact of the time to initiation of standard combined chemoradiotherapy on OS as primary endpoint and on progression-free survival (PFS) as secondary endpoint. Overall survival was measured from the date of histopathological diagnosis to the date of death from any cause. Progression-free survival was measured from the date of histopathological diagnosis to the date of evidence of progression or to the date of death. Tumor progression was defined according to the Macdonald criteria as being any of the following: (1) 25% increase in the total perpendicular diameters of an enhancing lesion; (2) any new lesion; or (3) clinical deterioration. The actual tumor progression was confirmed histopathologically, when available, after a second surgical progression. Time to initiation of standard combined chemoradiotherapy was measured as the interval between the surgical resection and the beginning of radiotherapy. The time to initiation of standard combined chemoradiotherapy was treated as a continuous variable as well as a dichotomous variable stratified as time intervals relative to the median time and to the quartile time to therapy.

Univariate analyses were carried out using chi-square or Fisher's exact test for comparing categorical variables, and the unpaired *t*-test or Mann–Whitney rank sum test for continuous variables, as appropriate. The Kaplan–Meier method, using log rank tests to assess significance for group comparisons, plotted unadjusted survival curves for OS and PFS. A Cox proportional hazards model was performed in a multivariate analysis. We created Cox proportional hazards regression models on the whole series using a backward stepwise approach. We entered the predictors previously associated with mortality and progression in a univariate analysis at the significance level, and used the time to initiation of chemoradiotherapy variable in the model as the main variable of interest. A probability value <0.05 was considered statistically significant. Statistical analyses were performed using the JMP software (version 11.0.0, SAS Institute Inc).

Results

Patients' main characteristics are detailed in Table 1. A total of 692 patients (434 men, 258 women) were included, with a mean age of 57.5 ± 10.8 years. At diagnosis, 65.9% of patients presented with a neurological deficit, 34.2% with a Karnofsky performance status of 70 or less, and 55.1% with a RTOG-RPA class at 5 or 6. All patients underwent a surgical resection (65.5% total/subtotal resection, 34.5% partial resection), with carmustine wafer