Glioblastoma

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

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A B S T R A C T

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 post-operative 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 operative 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, 18.3–21.0). 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.

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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 (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...
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 pretemozolomide 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. All patients underwent a surgical resection (65.5% total/subtotal resection, 34.5% partial resection), with carmustine wafer implantation, extent of surgical resection based histopathologically, when available, after a second surgical procedure. The actual tumor progression was confirmed histopathologically, when available, after a second surgical procedure. 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.

Patients' main characteristics are detailed in Table 1. A total of 692 patients (434 men, 258 women) were included, with a mean age of 58.75 ± 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 implantation of 75 mg/m²/day, then adjuvant temozolomide at 75 mg/m²/day, then adjuvant temozolomide at 75 mg/m²/day, then adjuvant temozolomide at 75 mg/m²/day.
implantation in 36.7% of cases. A mean dose of radiotherapy of 59.3 ± 4.7 Gy was administered and systematically associated with concomitant daily oral temozolomide, then followed by a mean of 5.9 ± 3.8 cycles of adjuvant temozolomide (60.7% of patients performed at least 6 cycles, 7.9% of patients continued temozolomide to one year or more).

The time to initiation of standard combined chemoradiotherapy according to patients’ characteristics is detailed in Table 1, with a median time of 1.5 months (25th percentile, 1.0; 75th percentile, 2.2; range, 0.1–90). The waiting time to standard combined chemoradiotherapy was significantly longer for patients with carmustine wafer implantation (p < 0.001); however, it was significantly shorter for patients with RTOG-RPA classes 5–6 (p < 0.001), with neurological deficit (p < 0.001), and with postoperative epileptic seizures (p = 0.049). Of note, the presence of postoperative complications, including postoperative infections, did not significantly impact the time to standard combined chemoradiotherapy.

The median follow-up period was 18.0 months (range, 2.4–95.0). Five hundred twenty-three patients (75.6%) died over the follow-up period, of whom six (1.1%) died from an unrelated cause. Six hundred thirty-five patients (91.7%) experienced disease progression, which was subsequently proven histopathologically in 122 cases (19.2%) following a second surgical resection.

The median PFS was 10.3 months (95% CI, 10.0–11.0). The median OS was 19.7 months (95% CI, 18.5–21.0). Survival rates as a function of the time to initiation of standard combined chemoradiotherapy are presented in Fig. 1.

Unadjusted and adjusted predictors of PFS are detailed in Table 2. Since Carmustine wafer implantation impacted both survival and time to initiation of standard combined chemoradiotherapy (Table 1), we performed complimentary subgroup analyses. In the subgroup of 438 patients without carmustine wafer implantation, the time to initiation of combined chemoradiotherapy was not an independent predictor of PFS, regardless of the threshold used (continuous variable, p = 0.757; median, p = 0.165; second quartile as compared to first quartile, p = 0.662; third quartile as compared to first quartile, p = 0.075; fourth quartile as compared to first quartile, p = 0.865). Similarly, in the subgroup of 254 patients with carmustine wafer implantation, the time to initiation of combined chemoradiotherapy was not an independent predictor of PFS, regardless of the threshold used (continuous variable, p = 0.433; median, p = 0.789; second quartile as compared to first quartile, p = 0.660; third quartile as compared to first quartile, p = 0.985; fourth quartile as compared to first quartile, p = 0.881).

Unadjusted and adjusted predictors of OS are detailed in Table 3. In the subgroup of 438 patients without carmustine wafer implantation, the time to initiation of combined chemoradiotherapy was not an independent predictor of OS, regardless of the threshold used (continuous variable, p = 0.505; median, p = 0.678; second quartile as compared to first quartile, p = 0.980; third quartile as compared to first quartile, p = 0.812; fourth quartile as compared to first quartile, p = 0.723). Similarly, in the subgroup of 254 patients with carmustine wafer implantation, the time to initiation of combined chemoradiotherapy was not an independent predictor of OS, regardless of the threshold used in Cox models (continuous variable, adjusted HR 0.99 (95% CI, 0.95–1.04), p = 0.918; median, adjusted HR 1.15 (95% CI, 0.96–1.37), p = 0.120; second quartile as compared to first quartile, adjusted HR 1.21 (95% CI, 0.86–1.67), p = 0.259; third quartile as compared to first quartile, adjusted HR 1.14 (95% CI, 0.93–1.40), p = 0.206; fourth quartile as compared to first quartile, adjusted HR 1.02 (95% CI, 0.81–1.27), p = 0.886).

Discussion

Concern about glioblastoma regrowth [33], with the related risk of clinical degradation, has frequently led to consider a time interval of less than four to six weeks post surgical intervention

Table 1
Patient characteristics and time to adjuvant treatment (n = 692).

<table>
<thead>
<tr>
<th>Parameters</th>
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<td>0.200</td>
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<td>1.4</td>
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<td>97.4</td>
<td>1.0</td>
<td>0.049</td>
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<td>No</td>
<td>610</td>
<td>94.7</td>
<td>1.2</td>
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</table>

RTOG-RPA: RTOG-Recursive Partitioning Analysis.
as optimal in daily practice [28]. This question was initially raised in the era preceding the standard combined chemoradiotherapy. Do et al., showed on a retrospective study based on 182 patients with grade III/IV gliomas that the risk of death increased by 2% per day of waiting for radiotherapy [13]. On a retrospective study based on 172 patients with grade III/IV gliomas, Irwin et al. found that the risk of death increased by 8.9% per additional week of delay between surgery and radiotherapy [12]. These retrospective findings suffered from selection biases, as poor clinical condition and postoperative complications could lead to longer delay and interfere with survival [34]. They were contradicted by studies demonstrating that longer delay to radiotherapy had no detrimental impact on survival [14,15]. Indeed, the largest study based on the prospective trials of the RTOG analyzed the impact of time to initiation of adjuvant oncological treatment on a pooled cohort of 2855 patients with glioblastomas, with the delay limited to six weeks as an eligibility criterion [14]. Blumenthal et al., demonstrated that delaying radiotherapy within six weeks after histological confirmation did not reduce survival [14]. On the other hand, the shortest delay (less than 2 weeks) as compared to the longest delay (more than 4 weeks) was considered as significantly detrimental. Initiating radiation therapy too early after surgery could be detrimental by three intertwined mechanisms: (1) hypoxia and edema surrounding the surgical bed may decrease the radiosensitivity; (2) the need for a larger volume planned radiation target due to a poorly shrinkable surgical cavity and; (3) increased risks of brain injury when radiotherapy is initiated within the first three weeks post surgery, as suggested in a preclinical model [35].

These results are supported by recent studies, suggesting a significant association between a longer delay to therapy with adjuvant treatment and OS [19,23,25]. These results should be interpreted with caution as physicians may attempt to treat patients in poor condition or with a biopsy only earlier. The previously published retrospective series did not correct the results for these confounding factors. After adjusting for confounders, a SEER Medicare database study included 1375 elderly patients with glioblastomas and failed to demonstrate an impact of time to initiation of oncological treatment on overall survival [15].

More recent publications addressed this question in the era of standard combined chemoradiotherapy with equivocal results [16–24]. The interpretation of the results is made difficult due to heterogeneous treatments: glioblastoma patients were not systematically treated with concomitant temozolomide (47–100%) and the proportion of patients who underwent a biopsy only was also heterogeneous (0–39%). Most of the studies [16,20–22] did not find any significant impact of the waiting time to radiotherapy on OS, three studies found a significant detrimental effect of shorter delays on OS [19,23,25], and three studies reported a significant detrimental effect of longer delays on OS [17,18,24]. Sun et al., reported a series of 218 glioblastoma patients all treated with combined chemoradiotherapy from The Cancer Genome Atlas database [17]. The time to initiation of combined chemoradiotherapy stratified by median (27 days) and by quartiles (<20 days, 20–27 days, 27–36 days, >36 days) did not significantly impact PFS or OS, but the patients with a time to adjuvant radiotherapy superior of 42 days demonstrated a significant detrimental impact on OS.

**Fig. 1.** Kaplan–Meier curves showing overall survival (On the left) and progression free survival (on the right), in the whole cohort (A) and depending on median time to initiation of standard combined chemoradiotherapy (1.5 month) (B).
Two main concerns can be raised: the threshold of 42 days determined only a very small subset of patients and many confounding factors were not analyzed in the multivariable model, including extent of surgical resection and postoperative complications. Another study, based on a retrospective study on 107 glioblastoma patients suggested that the time to initiation of combined chemoradiotherapy inferior to 42 days improved OS, but it included few patients and the subgroups were unevenly balanced in terms of concomitant temozolomide or not (72% in the longest delay subgroup versus 93% in the shortest delay subgroup) [18]. Integrating molecular biomarkers of glioblastoma, including O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation, is of paramount interest in the present issue as these prognostic factors [36] could interfere with the delay to adjuvant treatment [19]. One study found, in a multivariate model integrating the MGMT promoter methylation, a significant detriment delaying treatment over 6 weeks. In this study, the MGMT status was determined only in 45.8% of the entire cohort of 345 patients [24]. These results are contradicted by a German cohort with determination of the MGMT status, showing that initiating chemoradiotherapy sooner than 24 days after radiotherapy has a detrimental effect on OS [19]. Seidlitz et al. limited statistical analysis of the MGMT status to univariate analysis due to lack of data concerning the MGMT methylation status [22]. This is the same reason we did not investigate the impact of the MGMT methylation status. A recent meta-analysis by Loureiro et al., based on published data of 12 studies and including 5212 patients, analyzed the effect of delaying radiotherapy for glioblastoma patients [27]. This meta-analysis supports the present results and does not find any evidence of effect of the delay to radiotherapy on OS. This study suffers from inherent limitations of meta-analyses: individual patients data not available, pooled biopsy and large surgical resections, and pooled exclusive radiotherapy and concomitant chemoradiotherapy. In addition, reasons for delaying treatments were not discussed.

In the present study, we attempted to reduce biases inherent to a retrospective design by: (1) assessing a homogeneous population in terms of the oncological treatment, validated as the current standard of care (surgical resection systematically followed by standard combined chemoradiotherapy); (2) analyzing the effects of pretreatment clinical conditions; (3) incorporating surgical treatment modalities (surgical resection in all cases, extent of surgical resection, Carmustine wafer implantation), and postoperative complications. In addition, as there is no particular and planned reason to delay oncological treatment of a glioblastoma, we shed light of the possible confounders that can explain delayed adjuvant oncological treatment following surgery in clinical practice. The postoperative complications, except postoperative epileptic seizures, were not associated with a longer time to initiation of combined chemoradiotherapy. This would suggest that glioblastoma patient outcomes are not hampered by postoperative complications, including infections. The time to initiation of combined chemoradiotherapy was significantly shorter for patients with RTOG-RPA classes 5–6 and for patients with a neurological deficit. Thus this would suggest that patients with a poor clinical condition at diagnosis seem to be submitted faster to the adjuvant treatment, which can negatively impact the prognosis of the subgroup of patients with a short delay to treatment. On the contrary, carmustine wafer implantation was significantly associated with a longer time to initiation of combined chemoradiotherapy. Carmustine wafer implantation was not correlated with higher postoperative complications but was interpreted as a physician’s preference.

### Table 2

Univariate and multivariate predictors of progression-free survival. Unadjusted hazard ratios by log rank tests and adjusted hazard ratios by Cox proportional hazards model (n = 692).

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<td>Partial</td>
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<tr>
<td>Total/SubTotal</td>
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<td>Total/SubTotal</td>
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<tr>
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<td>0.93</td>
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<tr>
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<td>≥1.5 months</td>
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<tr>
<td>&lt;1.0 month</td>
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<td>0.79–1.09</td>
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<tr>
<td>&gt;2.2 months</td>
<td>0.95</td>
<td>0.78–1.17</td>
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</tbody>
</table>

CI: confidence interval; HR: hazard ratio; RTOG-RPA: RTOG-Recursive Partitioning Analysis.

* Results of Cox proportional hazard models are presented with the parameter threshold as quartiles. Thresholds based on time to initiation of chemoradiotherapy as a continuous variable and as median were also tested in Cox proportional hazard models but were not significant.
deliberative choice to postpone treatment due to theoretical toxicities induced by adjunction of carmustine wafers and concomitant chemoradiotherapy. We have ruled out the possibility of an interaction between carmustine wafer implantation and time to initiation of chemoradiotherapy impacting survival. We found that the time to initiation of standard combined chemoradiotherapy, treated as a continuous as well as a dichotomous variable did not significantly impact PFS or OS. These results are in agreement with recent retrospective published series, [16,20–22] and a meta-analysis [27] considering patients treated with combined chemoradiotherapy, showing that time to adjuvant treatments does not impact survival. However, despite our rigorous analysis, the retrospective methodology did not allow corrections for all underlying confounding factors dealing with delay to adjuvant treatment (physician subjective decision, treatment availability, socio-economic status, technical difficulties). In conclusion, in this cohort of 692 adult patients with newly diagnosed glioblastomas, all homogeneously treated by surgical resection followed by standard combined chemoradiotherapy, there is no evidence that delaying adjuvant standard combined chemoradiotherapy for clinical purposes (management of postoperative complications, patient’s recovery) negatively impacts survival. These results are found equally in the patients with or without carmustine wafer implantation and equally in the patients with or without complete resection. It is highly unlikely, for obvious ethical reasons, that a prospective randomized trial could ever be designed to address this question. We believe that, following extensive surgical resection, patients’ recovery after surgery within the first postoperative 6 weeks should not be jeopardized and hastened due to fear of postponing adjuvant treatments based on the idea that it might worsen OS.

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### Conflict of interest

None.

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### Table 3

Univariate and multivariate predictors of overall survival. Unadjusted hazard ratios by log rank tests and adjusted hazard ratios by Cox proportional hazards model (n = 692).

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Unadjusted hazard ratio</th>
<th>Adjusted hazard ratio</th>
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<td></td>
<td>HR</td>
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<tr>
<td>Gender</td>
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<td>Female</td>
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<td>Male</td>
<td>1.33</td>
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<td>5–6</td>
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<td>Karnofsky performance status</td>
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<td>Per one unit increase</td>
<td>0.96</td>
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<td>&lt;1.5 months</td>
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<tr>
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<td>0.85–1.22</td>
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<td>1.0–1.5 months</td>
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<tr>
<td>&gt;2.2 months</td>
<td>0.89</td>
<td>0.63–1.29</td>
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CI: confidence interval; HR: hazard ratio; RTOG-RPA: RTOG-Recursive Partitioning Analysis.
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Appendix A. Supplementary data

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References