ANTICANCER RESEARCH *40*: 3387-3393 (2020)
doi:10.21873/anticanres.14322

Fractionated Stereotactic Sequential Boost in a Selected Cohort of Glioblastoma Patients: A Mono-institutional Analysis

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Abstract. *Aim: To retrospectively assess toxicity and survival in 15 selected Glioblastoma patients treated with a sequential fractionated stereotactic radiotherapy (FSRT) boost after chemo-radiotherapy (CHT-RT) and compare their survival outcomes with a control group. Patients and Methods: Toxicity was assessed with the CTCAE 3.0 scale. The Kaplan-Meier method was used to design survival curves, log-rank test for bivariate analysis and Cox proportional hazard regression model for multivariate analysis. Results: The median follow-up was 16 months (range=5-60). One case of headache and one of radionecrosis (RN) occurred. Median overall survival (OS) was 25 months in the boost group vs. 14 in the no-boost group (p=0.004). Median progression-free survival (PFS) was 15 months in the boost group versus 8 in the no-boost group (p=0.046). At multivariate analysis FSRT boost resulted significantly associated with OS and PFS. Conclusion: In our series a sequential FSRT boost resulted in safe outcomes and significantly associated with survival.*

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Key Words: Glioblastoma, fractionated stereotactic radiotherapy, boost, toxicity, survival.

Current standard of care for patients with glioblastoma (GBM) is maximal surgical resection followed by radiotherapy (RT) plus concomitant and adjuvant chemotherapy (CHT) with temozolomide (TMZ) (1). Despite this multimodal approach, median progression-free survival (PFS) and overall survival (OS) is 6.9 and 14.6 months, respectively (1). Conventional RT treatment consists of 60 Gy in 30 fractions over 6 weeks delivered using three-dimensional-conformal-RT (3DCRT). As the main pattern of GBM failure is local, dose escalation to the tumor bed could be a recommended treatment strategy. A boost dose to the tumor bed was administered in the past using interstitial brachytherapy, stereotactic radiotherapy either fractionated (FSRT), or in single dose (radiosurgery, RSR) and intensity-modulated radiotherapy (IMRT) (2-6). Retrospective and prospective studies evaluating FSRT boost, administered either during (6-8) or after partial brain 3DCRT (3, 9) showed its feasibility and safety. In particular in one small study patients with high-grade glioma were treated with sequential FSRT boost (two patients received 10 Gy in 2 fractions and fifteen patients 20 Gy in 5 fractions) and a survival benefit emerged in comparison with historical mono-institutional data derived from a group of patients matched for age, sex, tumor size and performance status (3). Recently, a phase II study (6) showed a survival benefit in patients treated with conventional 3DCRT and concomitant TMZ associated with a concomitant or sequential FSRT boost.

On the basis of these encouraging results at our Institution in a selected cohort of GBM patients a sequential FSRT boost was prescribed after standard CHT-RT. Herein we report a retrospective analysis investigating feasibility, toxicity and survival outcomes of this treatment schedule.

Table I. *Patients and treatments characteristics*.

	Boost group	No Boost group	*p*-Value
Gender (M/F)*	10/5 (66.7%-33.3%)	11/4 (73.4%-26.6%)	1.000
Age (years)°	58 (36-73)	63 (37-73)	0.205
Surgery (GTR *vs*. SR)*	9/6 (60%-40%)	9/6 (60%-40%)	1.000
Methylation (yes/no)*	6/9 (40%-60%)	6/9 (40%-60%)	1.000
RTOG RPA class*			
3	2 (13.3%)	2 (13.3%)	1.000
4	10 (66.7%)	10 (66.7%)	
5	3 (20%)	3 (20%)	
KPS*			
100	10 (66.7%)	9 (60%)	0.921
90	4 (26.6%)	5 (33.3%)	
80	1 (6.7%)	1 (6.7%)	

°Data are expressed as median (min-max) and *number (percentage). M, Male; F, female; GTR, gross total resection; SR subtotal resection; RPA, recursive partitioning analysis; RTOG, radiation therapy oncology group; KPS, Karnofsky performance status.

Boost group overall survival (OS) and progression-free survival (PFS) were analyzed and compared with OS and PFS of a matched cohort of GBM patients (no-boost group) treated with standard RT dose and fractionation administered with concomitant and sequential TMZ.

Patients and Methods

Inclusion criteria. Inclusion criteria for FSRT boost were as follows: age >18 years, histologically confirmed GBM, Radiation Therapy Oncology Group (RTOG) - Recursive Partitioning Analysis (RPA) prognostic scale III-V(10), residual disease and/or surgical cavity ≤6 cm in the greatest diameter, Planning Target volume (PTV) distance from brain stem, optic chiasm, optic nerves >5 mm. A specific written informed consent was obtained from all patients and treatment decisions were made by an interdisciplinary tumor board. This retrospective study was conducted in accordance with the declaration of Helsinki as revised in 2000.

RT planning and treatment schedule. In order to define the extent of surgery, patients performed a gadolinium magnetic resonance imaging (MRI) within 48-72 h after surgery. Only 1 claustrophobic patient underwent contrast enhanced computed tomography (CT) scan. Before CHT-RT (4-6 weeks after surgery) all patients received a second MRI, (the claustrophobic patient received a second contrast enhanced CT). All patients were immobilized with a personalized thermoplastic mask, a CT scan acquired with slice thickness and step of 2.5 mm was performed. MRI and CT images were co-registered. Gross tumor volume (GTV) was defined as surgical cavity plus every T1 weighted images hyperintensity or contrast CT enhancement. Clinical target volume (CTV) was obtained expanding GTV 1.5 cm in all directions and planning target volume (PTV) expanding 5 mm CTV in all directions. All patients received a partial brain 3DCRT with a conventional fractionation, 30 consecutive fractions of 2 Gy (5 days a week) to a total dose of 60 Gy. Beam energy was 6 MV. Concomitant CHT with TMZ 75 mg/m^2/day was administered during RT. The FSRT boost was delivered 2-4 weeks after the end of CHT-RT. In order to perform boost treatment plan and rule out disease relapse or progression patients underwent a contrast enhanced MRI, (again the claustrophobic patient performed a contrast enhanced CT scan). Patients were immobilized with a personalized thermoplastic mask, a CT scan was performed, as previously described, with a head frame for stereotactic localization (3D Line Medical Systems®, Milan, Italy). MRI and CT images were co-registered, GTV boost was defined as previously described and PTV boost was obtained expanding GTV boost 5 mm in all directions. A total dose of 20 Gy in 4 consecutive fractions of 5 Gy was prescribed at isocenter. FSRT boost was delivered with a 3 mm micro-multileaf collimator (3D Line Medical Systems® Milan, Italy) mounted on a linear accelerator (Linear Accelerator DBX Varian® Medical System Inc, USA), using 4 to 6 noncoplanar arcs. Beam energy was 6 MV. During boost all patients received daily doses of 4-8 mg of dexamethasone for 4-7 days, starting on the first boost fraction. During boost CHT was not administered. Clinical and neurological examinations were performed weekly during partial brain RT and at the first and the last boost fraction. Adjuvant TMZ was administered 4 weeks after CH-RT at 150 mg/m^2/day (first cycle) and 200 at mg/m^2/day starting from the second cycle, for 5 days every 28 days for 6-12 cycles. During the follow-up clinical and neurological evaluations were performed monthly, radiological examinations (gadolinium enhanced MRI and contrast enhanced CT scan for the claustrophobic patient) were performed every 3 months. Relapse was assessed using Response Assessment in Neuro-Oncology (RANO) criteria (11). Toxicity was scored according to the common toxicity criteria for adverse events (CTCAE) 3.0 scale (12). Historical control data derived from a cohort 15 patients (no-boost group) treated at our Institution, during the same time period, matched for gender, age, Karnofsky Performance Status (KPS), extent of surgery (gross total resection, GTR *vs*. subtotal resection, SR), RTOG-RPA prognostic class (10), and O6-methylguanin-DNA-mathyltransferase (MGMT) promoter methylation status (methylated *vs*. non methylated).

Statistical analysis. The Chi-square test with Yates' continuity correction and Fisher's exact test were used for comparisons of categorical variables and the Mann–Whitney *U*-test was used for

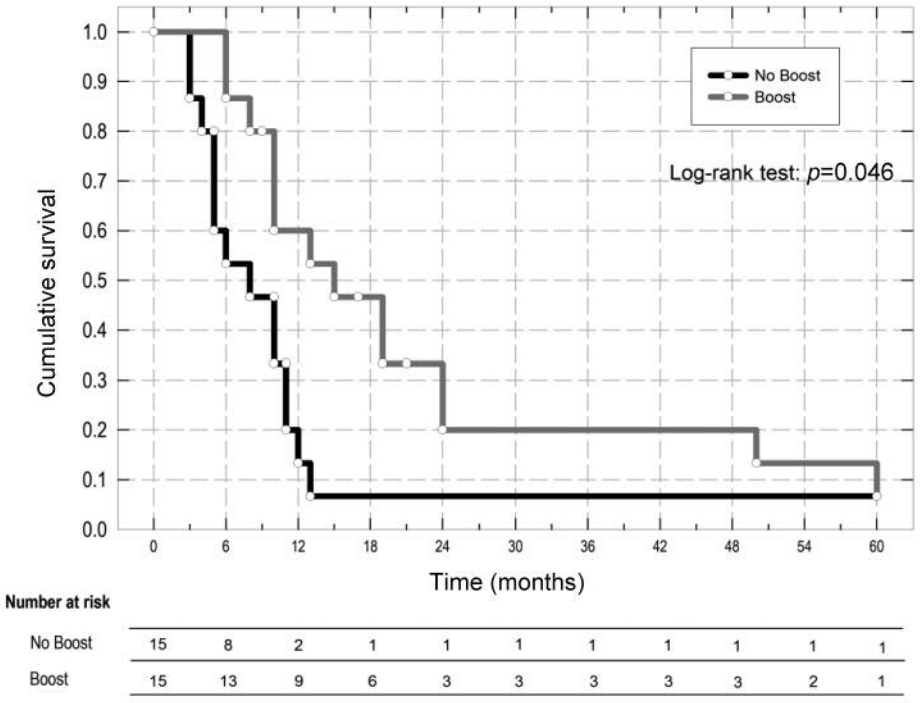

Figure 1. *Kaplan-Meier curves for progression free survival (PFS).*

comparisons of continuous variables. Survival curves were calculated using the Kaplan-Meier product-limit method followed by log-rank test to evaluate differences in expected event probability between two groups (bivariate analysis). Cox proportional hazard regression model was used for multivariate analysis. In the bivariate analysis risk factors for local relapse and survival included, boost, RTOG-RPA class, surgery and MGMT methylation status. Variables with significance according to bivariate analysis ($p<0.05$) were included in multivariate analyses. Statistical significance was set at $p\leq0.05$. All *p*-values were two-sided. Statistical analyses were performed using IBM-SPSS (Statistical Package for the Social Sciences) release 25.0 (IBM Corp., Armonk, NY, USA).

Results

From January 2007 to June 2013 fifteen GBM patients met the boost inclusion criteria. Boost and no-boost patient characteristics are shown in Table I. The two groups were well matched for patients, tumor and treatment characteristics. Median follow-up for both groups, calculated from surgery to the last follow-up or death, was 16 months (range 5-60 months). PTV-boost median volume was 69.6 cm3 (range 22.3-122 cm^3). FSRT boost was well tolerated, since acute toxicity occurred in only one case of G1 headache successfully treated with corticosteroids. One patient developed symptomatic radionecrosis (RN) 6 months after the end of boost. The patient was referred to a second surgical treatment and the histological examination confirmed RN, excluding disease relapse. None of fifteen boost patients developed steroid dependence after FSRT boost completion. Median PFS was 15 months in the boost group (95% CI=6.2-23.8) *vs*. 8 months in the no-boost group (95% CI=3.3-12.7), $p=0.046$ (Figure 1). In particular, in the boost group the estimated PFS at 1, 2, 5 years of follow up was respectively 60.0%, 20.0% and 7.0%, while in the no boost group was 13.0%, 7.0% and 7%. Median PFS was 8 months in patients treated with SR (95% CI=4.7-11.3) *vs*. 12 months in patients treated with GTR (95% CI=7.8-16.2), $p=0.014$. Median OS was 25 months in the boost group (95% CI=16.2-33.8) *vs*. 14 months in the no-boost group (95% CI=11.5-16.5), $p=0.004$ (Figure 2). In particular, in the boost group the estimated OS at 1, 2, 5 years of follow up was respectively 80%, 53.3% and 13.3%, while in the no boost group was 66.7%, 6.7% and 0%. Median OS was 13 months in patients treated with SR (95% CI=7.9-18.1) *vs*. 18 months in patients treated with GTR (95% CI=12.5-23.5), $p=0.017$. Multivariate analysis showed that boost administration and GTR were the only variables significantly related to PFS ($p=0.020$ and $p=0.007$ respectively) and OS ($p=0.003$ and $p=0.008$, respectively) (Table II).

Discussion

In our small series of selected GBM patients treated with sequential boost very low toxicity rates occurred. In our opinion our favourable acute and late toxicity results might

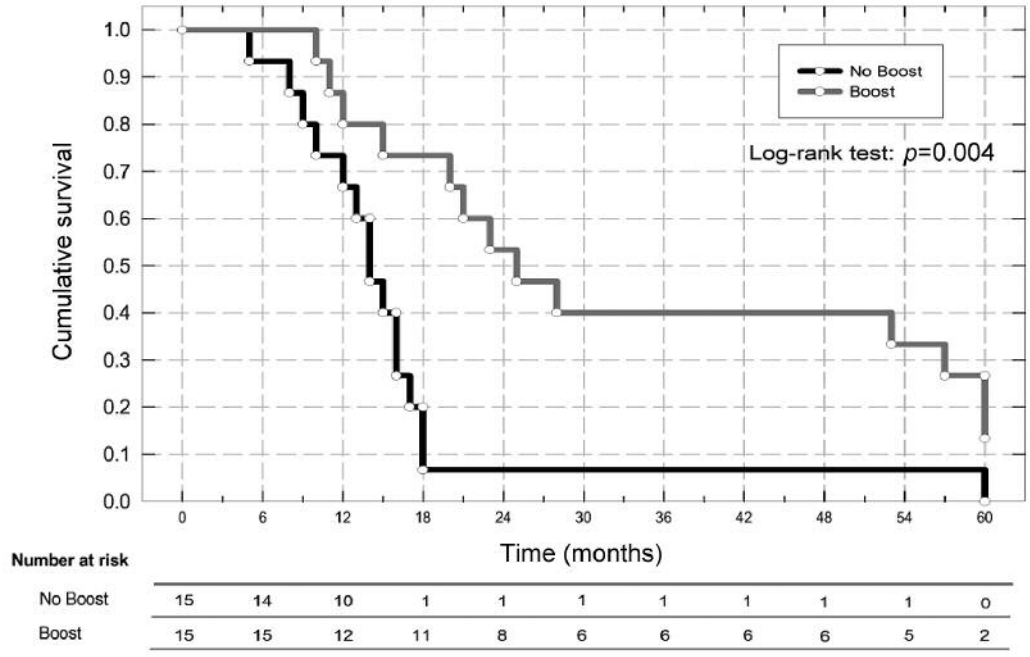

Figure 2. *Kaplan-Meier curves for overall survival (OS).*

Table II. *Multivariate Cox regression analyses of overall survival (OS) and progression-free survival (PFS).*

Predictors	OS			PFS		
	HR	95%CI	*p*-Value	HR	95%CI	*p*-Value
Boost						
No	1	-	-	1	-	-
Yes	0.286	0.125-0.654	0.003	0.388	0.175-0.863	0.020
Surgery						
GTR	1	-	-	1	-	-
SR	3.089	1.335-7.147	0.008	3.058	1.352-6.915	0.007

GTR, Gross total resection; SR: subtotal resection.

be related to strict patient selection criteria (age, KPS, type of surgery and absence of concomitant disease) and to the treatment schedule (*i.e.* RT dose and fractionation used and TMZ not administered during boost). Regarding OS and PFS, in our opinion, our positive results could be related again to strict patient selection criteria that identified patients with good prognostic factors. Moreover, the planned interval of 2-4 weeks from the end of CHT-RT to the start of boost, detecting early recurrent disease, allowed a further selection of patients with a favourable prognosis. Furthermore, analyzing boost group survival outcomes it should be considered the type of treatment performed at disease relapse or progression. In fact, given that there is not a standard treatment for recurrent GBM (13), in our series boost patients compared to no-boost group were more frequently referred to a second surgery treatment (4/15 *vs.* 0/15 respectively) and were more likely treated with combined treatment modalities including CHT (3/15 *vs.* 0/15 respectively). From our point of view, the advantages of this mono-institutionl study are the positive survival outcomes and the low toxicity rates, while the main disvantage is the need for strict patient selection criteria.

In the past, given the extremely poor prognosis of GBM patients, trials evaluated dose intensification regimens investigating RT dose up to 90 Gy (14) or dose-dense and extended sequential TMZ schedules (15, 16). Unfortunately,

both strategies failed to demonstrate a survival benefit in GBM patients. Since the main pattern of failure in gliomas is local relapse and modern techniques can allow dose escalation limiting normal brain and organs at risk (OARs) toxicity studies reporting the use of a boost dose were performed showing favorable outcomes. In particular, as previously reported, FSRT used as a boost in newly-diagnosed glioma patients was considered safe and feasible. In the past, two prospective trials, RTOG 93-05 (17) and RTOG 0023 (8), investigating respectively the use of stereotactic RSR boost before and FSRT boost during 3DCRT, did not show any survival benefit. However, it has to be noticed that in both trials concomitant TMZ was not included in the treatment schedule.

More recently, a single-arm phase II trial (6) investigated in 41 malignant gliomas patients (36 affected by GBM) the use of FSRT boost administered using two different schedules tailored on CTV boost diameter. Briefly, patients with CTV boost ≤6 cm received concomitant (9 Gy in 10 fractions on alternating days, staring the third week of 3DCRT) and sequential boost (10 Gy in 4 fractions), while patients with CTV boost >6 cm received only sequential boost (10 Gy in 4 fractions). TMZ was not administered during boost. Therefore, patients with smaller CTV boost received concomitant CHT only during the first 2 weeks of 3DCRT, while the others received concomitant CHT during the first 4 weeks of 3DCRT. Median OS for GBM patients was 28 months and toxicity was acceptable.

In our series, toxicity rates were similar to those reported in the literature, confirming that a sequential FSRT boost is feasible and well tolerated. In particular, in our series toxicity rates were quite low although TMZ, unlike in the aforementioned studies, was administered during all courses of 3DCRT (every day for 6 weeks). Regarding survival outcomes, OS and PFS were significantly higher in the boost group and FSRT boost resulted significantly associated to OS and PFS. Our boost dose was safe and effective and our RT treatment schedule corresponded to quite high total biological effective doses ($BED_{cumulative}$). In fact, assuming alpha/beta ratio for GBM equal to 10, the RT schedules employed in the boost group reaches a $BED_{cumulative}$ dose of 102 Gy, while assuming a lower alpha/beta ratio for GBM, *i.e.* equal to 5 as suggest by a recent review (18), a $BED_{cumulative}$ dose of 124 Gy. Furthermore, since a preclinical study (19) reported that the use of large RT fractions over standard fractionation confer better glioma stem cells (GSCs) treatment response, the use of stereotactic RT either fractionated (FSRT), or in single dose (RSR) is highly recommended to administer a boost dose. These findings are particularly relevant since GSCs are the most radioresistant (20) subpopulation of GBM tumor cells and are responsible for disease recurrence (21).

In our opinion the major limitations of our series are: the retrospective nature of the study and the small number of treated patients, while major strengths are strict patient selection criteria, and extended long follow-up period. Moreover, the planned comparison with a historical group, matched for treatment and patients' characteristics, allowing to overcame a selection bias, strengthens our results.

At present RT dose escalation is still a pivotal research issue in the treatment of GBM patients and literature data reported favourable results derived from phase II prospective studies evaluating a concomitant or sequential boost (22-27). Only two phase III randomized trials evaluating the administration of an additional boost in GBM patients are ongoing (28, 29). Briefly, in the first (28), study patients will be randomized to receive 3DCRT or IMRT delivering 60 Gy with concomitant and sequential TMZ or IMRT delivering 60 Gy with concomitant and sequential TMZ with an additional IMRT-simultaneous integrated boost (SIB) of 72 Gy/2.4 Gy, in the second (29) study patients will be randomized to receive either 60 GyE (2 GyE per fraction) of proton RT with concurrent TMZ or a carbon ion radiotherapy boost (dose determined in the Phase I of this trial) followed by 60 GyE of proton RT with concurrent TMZ.

In conclusion, in our analysis, a sequential boost administered in 4 daily fractions of 5 Gy after standard CHT-RT was well tolerated and significantly associated whit higher survival rates. However, our findings need to be confirmed given the small number of evaluated patients and the retrospective nature of the analysis. Results of phase III randomized ongoing trials will clarify the role of an additional boost in the treatment of GBM patients.

Conflict of Interest

The Authors declare that they have no conflicts of interest in regard to this study.

Authors' Contributions

AM collected data, analyzed data and wrote the manuscript. IP collected data, analyzed data and wrote the manuscript. GM collected data and contributed in manuscript writing. VB analyzed data and contributed in manuscript writing. NC PC and SS collected data. CZ performed treatments plans and collected data. CA conceived and designed the study and revised the manuscript. ML selected patients, approved treatment plans, conceived and designed the study and revised the manuscript. All Authors read and approved the final manuscript.

Funding

This work was partially supported by the Italian Ministry of Education, University and Research (MIUR) within the Individual Annual Funding for Fundamental Research "FFABR" 2018 (I.Palumbo).

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Received March 3, 2020
Revised April 21, 2020
Accepted April 28, 2020