# Treatment Patterns and Outcomes Among Elderly Glioblastoma Patients at KFMC, Riyadh.

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# Abstract

Introduction

Management of elderly patients with cancer is a controversial scenario and needs careful assessment and selection for aggressive radical treatment and chemotherapy protocols versus short-course radiotherapy without chemotherapy. Of note, definitions of the elderly vary in the glioblastoma (GBM) literature, with most of the randomized trials including patients aged 60, 65, or 70 years or older.

Aim of the work

To evaluate treatment patterns and outcome among elderly GBM patients treated in KFMC, Riyadh. The primary endpoint is overall survival (OS) and the Secondary endpoint is progression-free survival (PFS) in relation to different treatment options and prognostic factors.

Methods

This is a retrospective study, included elderly GBM patients treated at KFMC, Riyadh, KSA between 1/2008 till 1/2018. 59 patients diagnosed with GBM ≥ 60 years were reviewed regarding radiotherapy (Rth) fractionation modalities, surgery, and chemotherapy (CTR) given in correlation to PFS, OS.

Results

59 patients were recruited in our study with median age 66 range (60-81) years, 47 (80%) were males. 37 patients (62.7%) had Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≥2, and 22 patients (37.3%) had PS < 2. Gross total resection (GTR) and subtotal resection (STR) was done in 49 (82.9%) patients, and the median follow-up was 12 months.

38 (64%) patients received conventional Rth 60 Gray (Gy)/30 fractions or equal doses and 21 (36%) patients received hypofractionation Rth (40 Gy/15, 25 Gy/5 or 30 Gy/10 fractions).

The median OS was 12 months (95% CI,9.52-14.48). For univariate analysis, receiving a conventional Rth and completion of 6 months adjuvant CTR were significant factors for O.S (P= 0.043 and 0.026) respectively. For multivariate those were also significant (P=0.035 and 0.002) respectively.

The median PFS was 9 months (95% CI, 6.13-11.87). For univariate analysis PS, time to start adjuvant treatment, and completion of 6 months CTR were significant factors for PFS. For multivariate analysis starting adjuvant treatment within 2 months and completed CTR 6 months were significant factors (P=0.032 and 0.04) respectively.

Conclusion

Elderly GBM patients who received conventional Rth and completed adjuvant 6 months CTR achieved a better OS, while starting adjuvant treatment earlier than 2 months and completed adjuvant CTR 6 months

were associated with a better PFS, further prospective studies are needed to confirm our finding.

# Introduction

Glioblastoma (GBM) is the most common malignant primary brain tumor among adults [1]. The reported median age at diagnosis is about 65 years old, with a rapidly increasing incidence among patients aged more than 65 years. Which almost doubled from 5.1 per 100,000 in the year 1970 to 10.6 per 100,000 in the year 1990 [2]. The median survival among all GBM patients ranges between12 to 15 months from diagnosis despite aggressive treatment, while it was markedly shorter (only 4 to 5 months) among elderlies [3,4]. It is evident from existing literature that the elderly GBM patients usually receive less effective therapies including surgery, radiotherapy (Rth), and chemotherapy (CTR) compared to their younger counterparts [5,6]. Even there is a clearly defined survival benefit for elderly GBM patients with favorable performance status receiving longer-course radiotherapy compared to best supportive care [7]. On the other hand, Roa et al explained a non-inferiority of hypo-fractionated Rth course of 40 Gray (Gy) compared to standard Rth of 60 Gy among patients aged 60 years and above with minimum ECOG PS 3 [8].

In this study, we reviewed the different treatment options offered to elderly patients with GBM at a tertiary care center in Riyadh and its impact on overall survival (OS) and progression-free survival PFS.

# Methods

**Study design**: A retrospective cohort study was carried out in the Department of Radiation Oncology, King Fahad Medical City (KFMC), Riyadh, Saudi Arabia. The study was approved by the local Ethics Committee of KFMC. Data were obtained from the electronic medical records of the hospital for elderly GBM cases.

**Eligibility criteria:**

The study included all histologically proven, newly diagnosed elderly (age ≥ 60 years) GBM cases, who were treated at our institute between January 2008 and January 2018. The study excluded patients with recurrent disease at initial presentation.

**Treatment modalities:** All patients underwent surgical intervention either by biopsy only, subtotal resection (STR), or gross total resection (GTR), followed by adjuvant treatment except for one patient who died before starting adjuvant treatment. Adjuvant treatment included either Rth only or Rth concurrent with temozolomide. Radiotherapy included either conventional fractionation (59.4Gy/33 fractions or 60 Gy/30 fractions) or hypofractionation (30 Gy/10 fractions or 40 Gy/15 fractions). A proportion of patients with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤ 2 were offered adjuvant CTR after completion of radiation.

**Definition of survival:** OS was defined as the interval between initial surgery or pathology diagnosis and date of death (where applicable). In patients still alive at the end of the study period, data were censored

on 1st January 2018. PFS was defined as the interval between initial surgery or pathology diagnosis and the date of first progression or recurrence or death (if no progression was reported) or until the last evaluation date.

**Data collection:** The data were collected from electronic medical records through a data collection form which was developed to collect patient characteristics, pathology, external beam radiotherapy (EBRT) and CTR details, and progression and survival times.

**Statistical analysis:** OS and PFS are calculated by using the Kaplan-Meier method, and the difference in survival curves was compared by using the log-rank test. Different categorical variables are compared with the chi-square $\chi^2$ test. The level of significance was set at $P<0.05$ and $P$ values are based on two-sided tests. Multivariate analysis using the Cox proportional hazard model is performed to define various potential prognostic factors. All analyses were performed using the SPSS version (IBM SPSS, Armonk, NY, USA).

# Results

A total of 59 patients met the inclusion criteria out of 158 newly diagnosed GBM cases who were treated in our institution between January 2008 and January 2018. One case died before adjuvant treatment. The median age at diagnosis was 66 years (ranging between 60-81 years); 47 patients were males (79.7%) and 12 were females (20.3 %). 49 patients (83 %) were diagnosed with GBM and 10 patients (16.9 %) with GBM variants. 53 (89.8 %) patients had a unilateral tumor and 6 (10.2 %) patients had bilateral disease. Patients' demographic features and clinical characteristics are included in table1.

| Variables | N(%) |
|---|---|
| Mean age (years) | 66(60-81) |
| K.P.S group | |
| < 2 | 22(37.3%) |
| ≥ 2 | 37(62.7%) |
| Gender | |
| Male | 47(79.7%) |
| Female | 12(20.3%) |
| Surgery type: | |
| Biopsy | 10(16.9%) |
| STR | 42(71.2%) |
| GTR | 7(11.9%) |
| Adjuvant Treatment Types | |
| Radiotherapy | 22(37.3%) |
| CCRT | 13(22%) |
| CCRT + Adj CTR | 23(39%) |
| No treatment | 1(1.7%) |
| Start period of Adjuvant: | |
| < 2 ms | 42 (72.4%) |
| ≥ 2 ms | 16 (27.6 %) |
| Radiotherapy fractionation | |
| Hypofractionation | 20 (33.9%) |
| Conventional | 38 (66.1%) |
| No. of cycles of adjuvant CTR: | |
| ≥ 6 | 12 (52.2%) |
| <6 | 11 (47.8%) |

Patients with ECOG PS ≥ 2 were 37 patients (62.7%) and 22 patients (37.3%) had PS < 2. All patients underwent surgery with 10 (16.9 %) patients had biopsy only, 42 patients had STR (71.2 %) and 7 patients (11.9 %) had GTR. The median time to start adjuvant treatment was 1.58 months (0.43-6.54 months). 58 patients received adjuvant treatment; 22 patients (37.3 %) received Rth only, 13 patients (22 %) received

concurrent chemoradiotherapy and 23 patients (39 %) received concurrent chemoradiotherapy followed by adjuvant CTR. Among patients received adjuvant CTR; 11 patients (47.8 %) received ≥ 6 cycles and 12 patients (52.2 %) received < 6 cycles. Regarding Rth fractionation; 38 patients (64.4 %) received conventional fractionation (59.4Gy/33 fractions or 60 Gy/30 fractions) and 21 patients (35.6 %) received hypofractionation (25 Gy/5, 30 Gy/10 fractions or 40 Gy/15 fractions).

The median OS was 12 months (95% CI ,9.52-14.48) Fig.1. For univariate analysis, receiving a conventional Rth and completion of 6 months adjuvant CTR were significant factors for O.S (P= 0.043 and 0.026) respectively. For multivariate those were also significant (P=0.035 and 0.002) respectively Table (2) and Fig (3,4,5,6).

The median PFS was 9 months (95% CI, 6.13-11.87) Fig 2. For univariate analysis PS, time to start adjuvant treatment, and completion of 6 months CTR were significant factors for PFS. For multivariate analysis starting adjuvant treatment within 2 months and completed chemotherapy 6 months were significant factors (P=0.032 and 0.04) respectively Table 3 and Fig (7,8,9,10).

**Table (2): Analysis of different factors affecting OS for our study group of elderly GBM:**

| | Univariate | | | Multivariate | | |
|---|---|---|---|---|---|---|
| | Crude OR | 95%CI (LL-UL) | P value | Adjusted OR | (LL-UL) | P value |
| Age (≥65 year) | 1.69 | 0.3 – 9.56 | 0.694 | 1.08 | 0.58 - 2.01 | 0.819 |
| ECOG [0 - 1] | 1.30 | 0.26 – 6.45 | 1 | 1.15 | 0.61 - 2.18 | 0.658 |
| Rth Fractionation | 47.42 | 0.09 – 24977.75 | 0.043 | 2.87 | 1.08 - 7.61 | 0.035 |
| Surgery type | 16.67 | 0.03 – 8897.91 | 0.59 | 0.51 | 0.24 - 1.08 | 0.08 |
| Start Adjuvant (<2month) | 1.01 | 0.18 – 5.81 | 1 | 0.90 | 0.42 - 1.9 | 0.775 |
| Concurrent CTR | 4.40 | 0.49 – 39.21 | 0.229 | 0.55 | 0.19 - 1.58 | 0.269 |
| CTR completed | 7.33 | 1.37 – 39.18 | 0.026 | 4.04 | 1.66 - 9.82 | 0.002 |

**Table (3): Analysis of different factors affecting PFS for our study group of elderly GBM:**

| | Univariate | | | Multivariate | | |
|---|---|---|---|---|---|---|
| | Crude OR | 95%CI (LL-UL) | P value | Adjusted OR | (LL-UL) | P value |
| Age (≥65 year) | 1.16 | 0.41 – 3.33 | 0.778 | 1.12 | 0.51 - 2.46 | 0.776 |
| ECOG PS [0 - 1] | 0.20 | 0.06 – 0.66 | 0.006 | 1.90 | 0.85 - 4.27 | 0.117 |
| Rth Fractionation | 0.49 | 0.17 – 1.44 | 0.192 | 1.57 | 0.41 - 6.07 | 0.510 |
| Surgery type | 1.33 | 0.33 – 5.3 | 0.741 | 0.55 | 0.21 - 1.45 | 0.223 |
| Start Adjuvant (<2month) | 0.15 | 0.04 – 0.56 | 0.003 | 3.50 | 1.12 - 10.96 | 0.032 |
| Concurrent CTR | 0.49 | 0.17 – 1.42 | 0.185 | 1.80 | 0.43 - 7.53 | 0.421 |
| CTR completed | 0.18 | 0.03 – 0.89 | 0.048 | 2.77 | 1.05 - 7.36 | 0.040 |

# Discussion

There is no well-established standard of care for the treatment of glioblastoma in the elderly. The goal of the present study is to add to the body of literature about the management of such patients. In the current study we aimed at reviewing the different treatment options offered to elderly patients with GBM at KFMC, and its impact on overall survival (OS) and progression-free survival (PFS). The (OS) of our patients was 12 months which was comparable with 9.2 months for 11,152 1059 patients in Scoccianti S., et al., study [9]. The median PFS was 9 months for our cases, and this was higher than the Ewelt C study which showed 5.9 months PFS for 1201 patients [10]. In a retrospective analysis of American patients more than 65 years of age with a new diagnosis of GBM between 1997 and 2009, median survival ranged between 2 months (for patients who received no postoperative therapy) and 11 months (for those who received standard combined chemoradiation) [11]. In almost all reported series in the literature, we found young age, good performance status, and safe optimal resection to be the well-known good prognostic factors in patients with GBM [12 -14]. In the present study, we found conventional Rth and completion of 6 months' adjuvant CTR were independent prognostic factors for overall survival. In our study extent of surgical resection was found to have no significant impact on either PFS or OS, which is not similar to most published data, may be related to a small proportion of patients that could achieve GTR (7 patients 11.9 % underwent GTR). The results of meta-analysis including 34 studies showed that surgical resection was superior to biopsy regarding OS (mean difference 3.88 months, 95% Ci: 2.14–5.62, P < 0.001) [15]. In a prospective randomized study conducted by Vuorinen et al. discussed the extent of resection in elderly patients with malignant GBM aged >65 years found that surgical removal of the tumor prolonged survival 2.8 times than biopsy (median OS: 171 days after the craniotomy versus 85 days after the biopsy) [16].

| Means and Medians for Survival Time | | |
|---|---|---|
| Modality | Mean[a] | Median |
| | Estimate | Estimate |
| Rt Only | 10.932 | 9.000 |
| Concurrent | 11.077 | 7.000 |
| Concurrent+Chemo | 28.439 | 16.000 |
| No Tx | 15.000 | 15.000 |
| Overall | 18.229 | 12.000 |
| a. Estimation is limited to the largest survival time if it is censored. | | |

**Survival Table**

| Modality | | Time | Status | Cumulative Proportion Surviving at the Time | | N of Cumulative Events | N of Remaining Cases |
|---|---|---|---|---|---|---|---|
| | | | | Estimate | Std. Error | | |
| Rt Only | 1 | 2.000 | Dead | .955 | .044 | 1 | 21 |
| | 2 | 3.000 | Dead | .909 | .061 | 2 | 20 |
| | 3 | 4.000 | Dead | . | . | 3 | 19 |
| | 4 | 4.000 | Dead | .818 | .082 | 4 | 18 |
| | 5 | 5.000 | Dead | . | . | 5 | 17 |
| | 6 | 5.000 | Dead | .727 | .095 | 6 | 16 |
| | 7 | 6.000 | Dead | .682 | .099 | 7 | 15 |
| | 8 | 7.000 | Dead | .636 | .103 | 8 | 14 |
| | 9 | 8.000 | Dead | . | . | 9 | 13 |
| | 10 | 8.000 | Dead | .545 | .106 | 10 | 12 |
| | 11 | 9.000 | Dead | .500 | .107 | 11 | 11 |
| | 12 | 10.000 | Dead | .455 | .106 | 12 | 10 |
| | 13 | 11.000 | Dead | .409 | .105 | 13 | 9 |
| | 14 | 12.000 | Dead | . | . | 14 | 8 |
| | 15 | 12.000 | Dead | .318 | .099 | 15 | 7 |
| | 16 | 13.000 | Dead | .273 | .095 | 16 | 6 |
| | 17 | 14.000 | Dead | .227 | .089 | 17 | 5 |
| | 18 | 15.000 | Dead | .182 | .082 | 18 | 4 |
| | 19 | 19.000 | Dead | .136 | .073 | 19 | 3 |
| | 20 | 20.000 | Alive | . | . | 19 | 2 |
| | 21 | 21.000 | Dead | .068 | .061 | 20 | 1 |
| | 22 | 28.000 | Dead | .000 | .000 | 21 | 0 |
| Concurrent | 1 | 1.000 | Dead | .923 | .074 | 1 | 12 |
| | 2 | 3.000 | Dead | .846 | .100 | 2 | 11 |
| | 3 | 4.000 | Dead | .769 | .117 | 3 | 10 |
| | 4 | 6.000 | Dead | . | . | 4 | 9 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | 5 | 6.000 | Dead | . | . | 5 | 8 |
| | 6 | 6.000 | Dead | .538 | .138 | 6 | 7 |
| | 7 | 7.000 | Dead | .462 | .138 | 7 | 6 |
| | 8 | 9.000 | Dead | .385 | .135 | 8 | 5 |
| | 9 | 10.000 | Dead | .308 | .128 | 9 | 4 |
| | 10 | 12.000 | Alive | . | . | 9 | 3 |
| | 11 | 15.000 | Dead | .205 | .120 | 10 | 2 |
| | 12 | 25.000 | Dead | .103 | .094 | 11 | 1 |
| | 13 | 29.000 | Dead | .000 | .000 | 12 | 0 |
| Concurrent+Chemo | 1 | 7.000 | Dead | .957 | .043 | 1 | 22 |
| | 2 | 8.000 | Dead | .913 | .059 | 2 | 21 |
| | 3 | 9.000 | Dead | . | . | 3 | 20 |
| | 4 | 9.000 | Dead | .826 | .079 | 4 | 19 |
| | 5 | 11.000 | Dead | . | . | 5 | 18 |
| | 6 | 11.000 | Dead | . | . | 6 | 17 |
| | 7 | 11.000 | Dead | .696 | .096 | 7 | 16 |
| | 8 | 12.000 | Dead | .652 | .099 | 8 | 15 |
| | 9 | 13.000 | Dead | .609 | .102 | 9 | 14 |
| | 10 | 14.000 | Dead | . | . | 10 | 13 |
| | 11 | 14.000 | Dead | .522 | .104 | 11 | 12 |
| | 12 | 14.000 | Alive | . | . | 11 | 11 |
| | 13 | 16.000 | Dead | .474 | .105 | 12 | 10 |
| | 14 | 17.000 | Dead | . | . | 13 | 9 |
| | 15 | 17.000 | Dead | .379 | .103 | 14 | 8 |
| | 16 | 19.000 | Dead | .332 | .101 | 15 | 7 |
| | 17 | 21.000 | Dead | .285 | .097 | 16 | 6 |
| | 18 | 34.000 | Alive | . | . | 16 | 5 |
| | 19 | 36.000 | Alive | . | . | 16 | 4 |
| | 20 | 37.000 | Dead | .213 | .095 | 17 | 3 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | 21 | 40.000 | Dead | .142 | .086 | 18 | 2 |
| | 22 | 53.000 | Alive | . | . | 18 | 1 |
| | 23 | 95.000 | Alive | . | . | 18 | 0 |
| No Tx | 1 | 15.000 | Dead | .000 | .000 | 1 | 0 |

Regarding adjuvant treatment modality, there is a significant improvement in mean OS in patients receiving adjuvant chemotherapy after CCRT (RT 10.9 months vs CCRT only 11.1 months vs CCRT + adjuvant chemotherapy 28.4 months (P=0.007). This is in line with recent data that states that the addition of chemotherapy concurrent with radiation and after completion of radiation added many benefits to treatment outcomes of elderly patients. CCTG CE.6, EORTC 26062-22061, the most recently published randomized controlled trial, regarding this issue. The study included 562 patients with GBM aged ≥65 years and compared Hypo-RT (40 Gy/15 Fr) alone versus Hypo-RT with 3 weeks of concomitant TMZ plus monthly adjuvant TMZ until progression or completion of 12 cycles. Combining TMZ with Hypo-RT was tolerable and resulted in prolonged OS and PFS in all GBM patient groups. Hypo-RT plus TMZ was superior in median OS and PFS than radiation alone (9.3 and 5.3 months versus 7.6 and 3.9 months, respectively; HR: 0.67 for OS and 0.50 for PFS). No difference was noted in QOL, but patients in the radiotherapy plus TMZ group demonstrated high levels of nausea, vomiting, and constipation [17].

Studies have shown promising survival with the use of Extended Temozolomide (E-TMZ) as compared to Conventional six cycles of Temozolomide (C-TMZ) in malignant gliomas; however, the reports are mostly limited to retrospective studies with significant bias [18,19].

Our study demonstrated that the number of adjuvant chemotherapy cycles had a significant impact on both median PFS and OS. The median PFS in patients receiving < 6 cycles of chemotherapy was 7 months (95% CI,5.842-8.158) vs 12 months (95% CI, 6.979-17.021) in patients receiving ≥ 6 cycles of chemotherapy (P=0.025). Therefore, even in elderly patients extended regimen of temozolomide inferred a positive impact on survival if tolerated.

In the present study the fractionation of radiotherapy showed OS in the conventional radiotherapy group (14 months (95% CI, 9.787-180213) vs 9 months (95% CI, 6.009-11.991) in hypofractionation group. (P= 0.005)). In further analysis of patients receiving conventional fractionation, the median OS is much improved in the < 70 age group (15 months vs 11 months, P = 0.176) and ≥ 2 PS group (15 months vs 6 months, P= 0.629). Roa et al. conducted a randomized controlled trial comparing standard radiotherapy (60 Gy/30 Fr) with hypofractionated radiotherapy (40 Gy/15 Fr) for 100 postsurgical patients with GBM aged ≥60 years. OS between conventional RT and Hypofractionated RT (5.1 and 5.6 months, respectively) was not significantly different, also no difference was noted in KPS, but steroid use was more frequent in the conventional RT.8 Minniti et al. retrospectively studied patients with GBM aged ≥65 years treated with conventional RT (60 Gy/30 Fr) versus hypofractionated RT (40 Gy/15 Fr) both with concomitant and adjuvant TMZ. Median OS and PFS did not differ between the two treatment arms (12

and 5.6 months for conventional RT, and 12.5 and 6.7 months for hypofractionated RT, respectively). However, conventional RT with TMZ was associated with a significant increase in grade 2 and 3 neurological toxicity, decreased kPS scores, and high steroid requirement [20].

# Conclusion

Interpretation of the present findings is limited by the retrospective nature of the data. Further research is needed to determine the optimal management of older patients with GBM. The study demonstrated the benefit of adding radiation therapy and adjuvant Temozolomide for elderly patients with glioblastoma. The ideal radiotherapy fractionation and the number of chemotherapy cycles given in this population remains an ongoing question. Increased availability and utilization of molecular markers such as MGMT methylation status are now helping to select the patients most likely to benefit from temozolomide.

# Declarations

### Compliance with Ethical standards:

This study was approved by Ethical Committee and get IRB approval No 18-201 April 2018. The study did not interfere with patient management and done retrospectively, collected using medical records without any violation of patients' confidentiality so not needed to have a consent from the patient. Data will be available if needed to be reviewed by authors after approval of research center King Fahad Medical City (KFMC).

**Author Contribution:** All authors shared in collection of data of patients equally, first two authors wrote the manuscript and reviewed by other authors, statistics done by help of unit of medical statistics, KFMC Research center.

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### Competing interests

None.

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# Figures

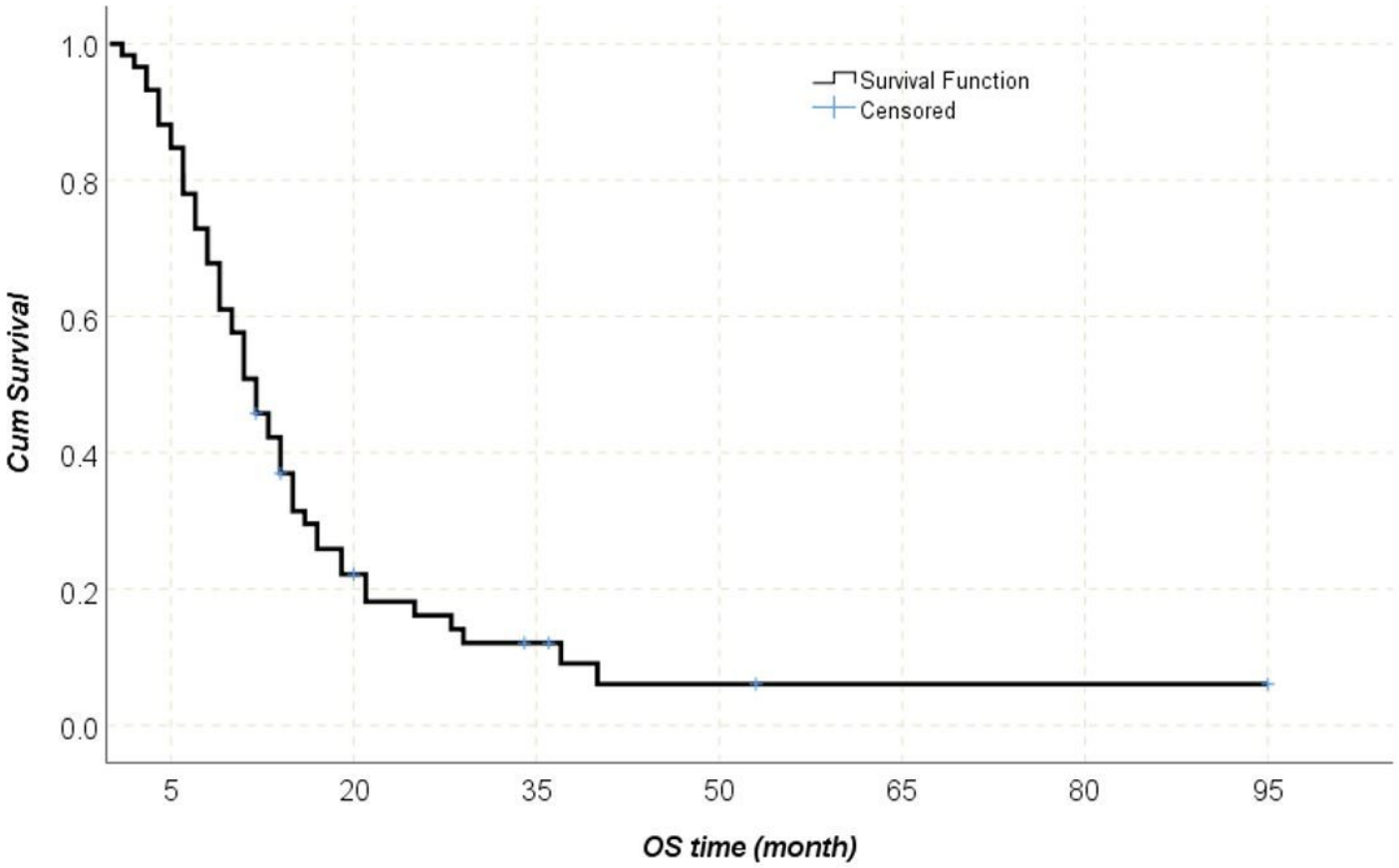
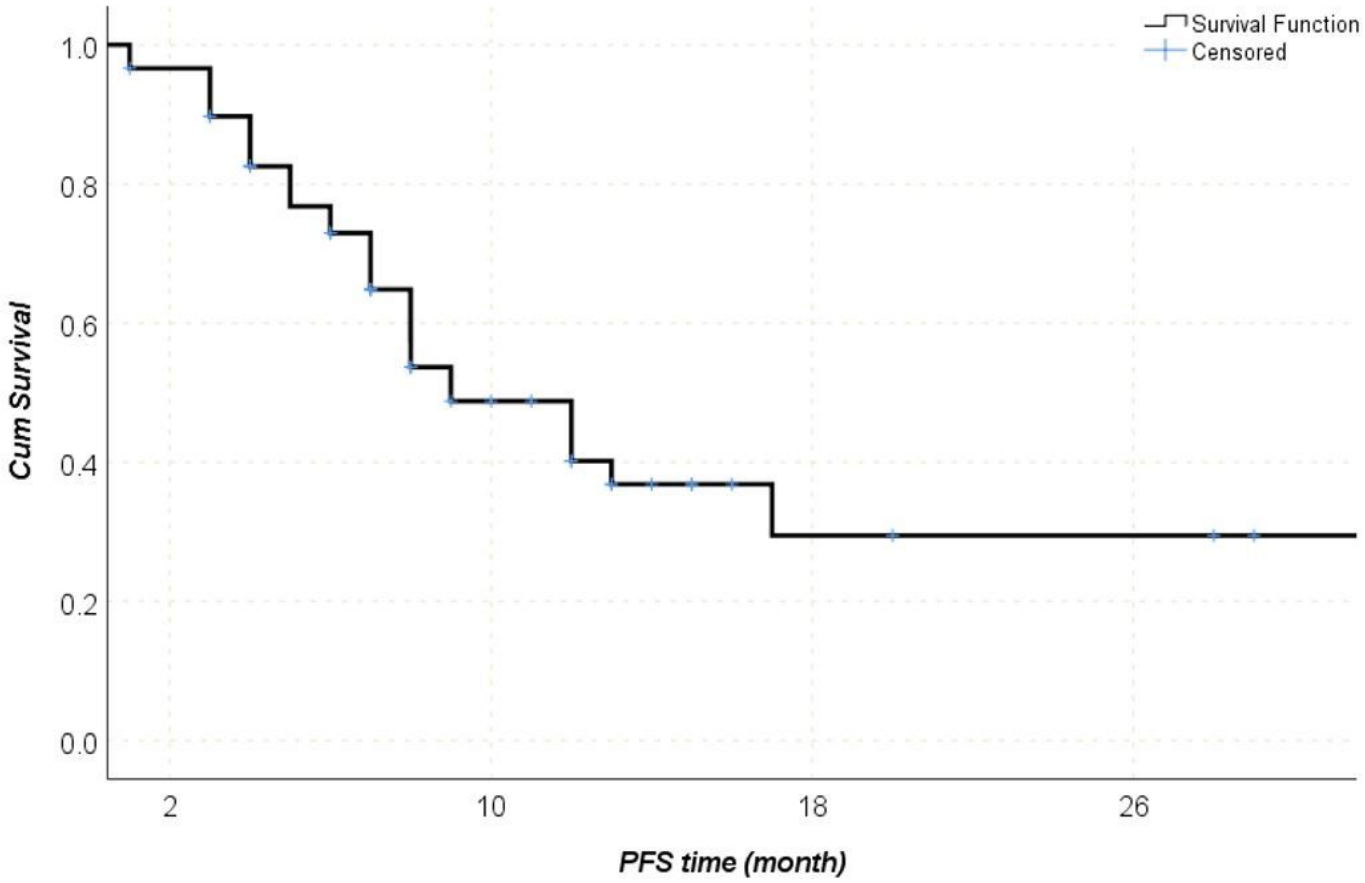



**Figure 1**

OS of all study groups of elderly GBM.




## Figure 2

PFS of all study groups of elderly GBM.

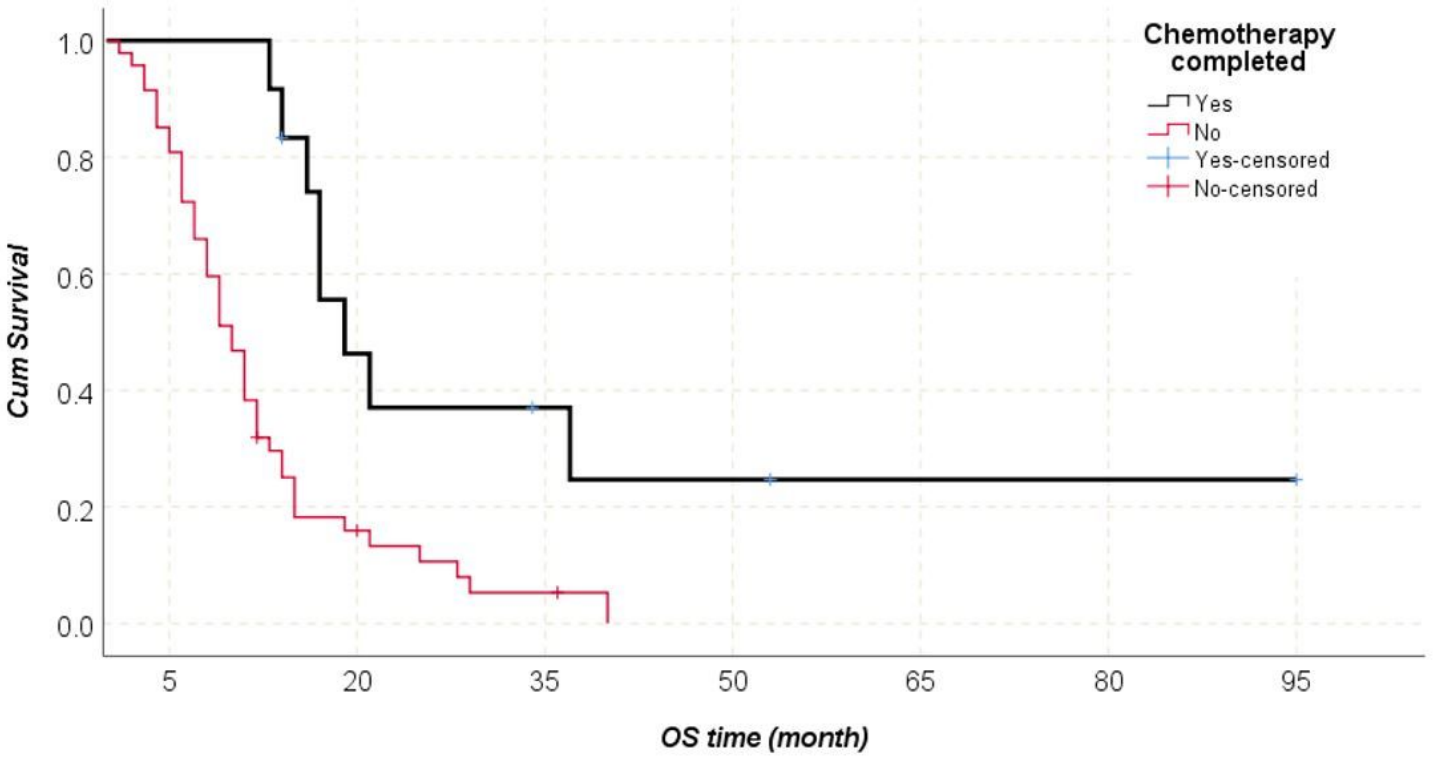



**Figure 3**

Effect of completed CTR on OS of elderly GBM patients.

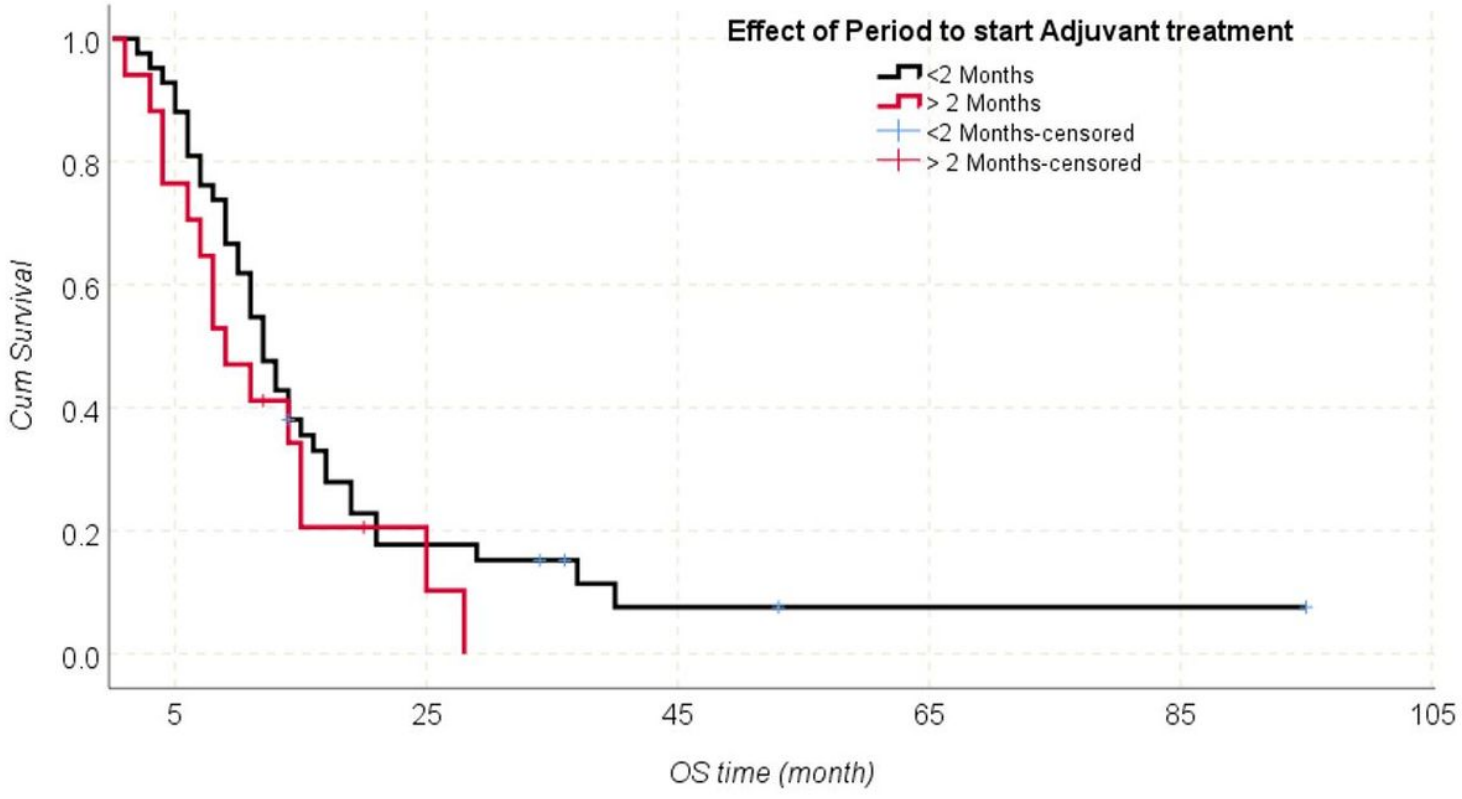



**Figure 4**

Effect of Period to start Adjuvant treatment on OS of elderly GBM patients

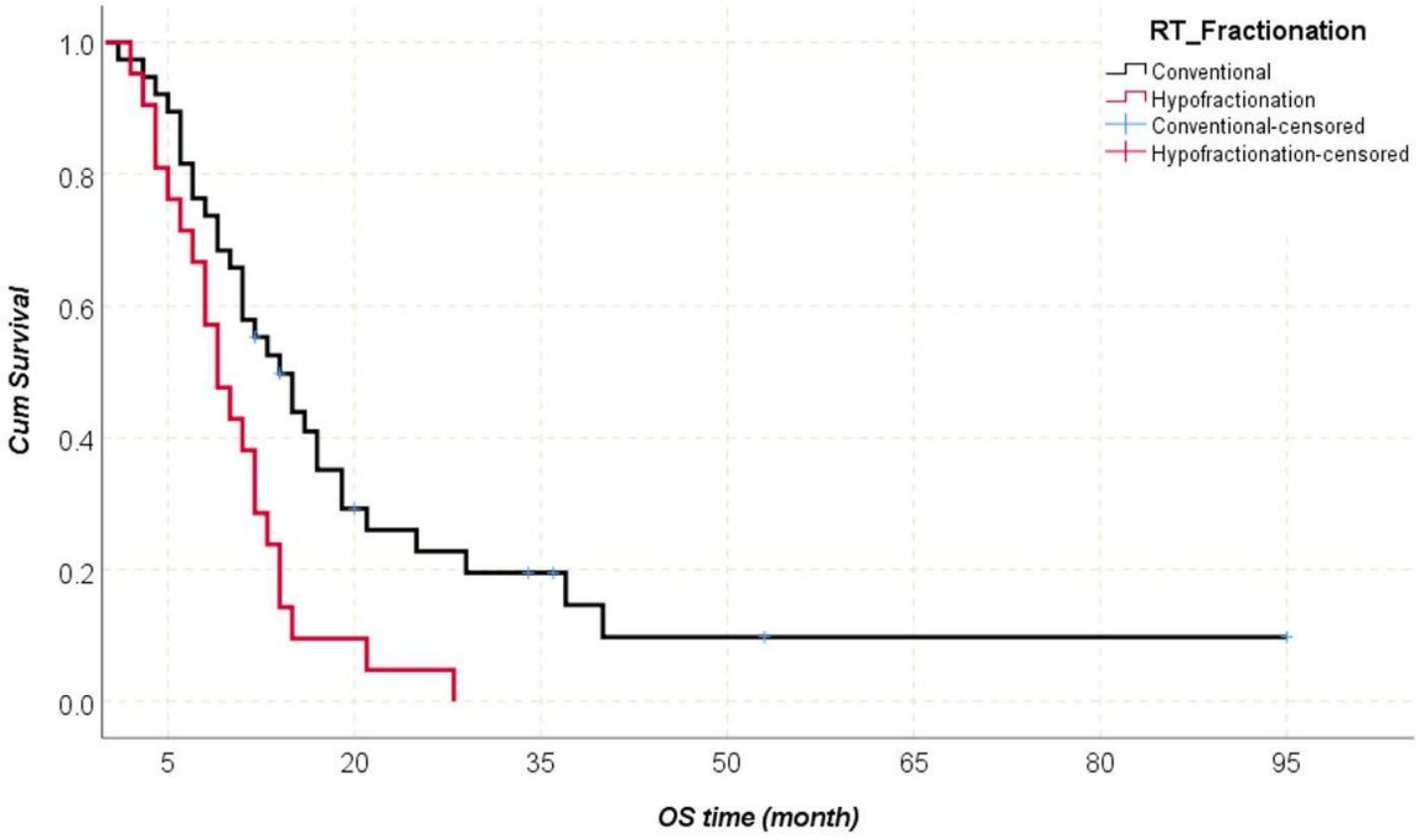



**Figure 5**

Effect of Rth fractionation on OS of elderly GBM patients.

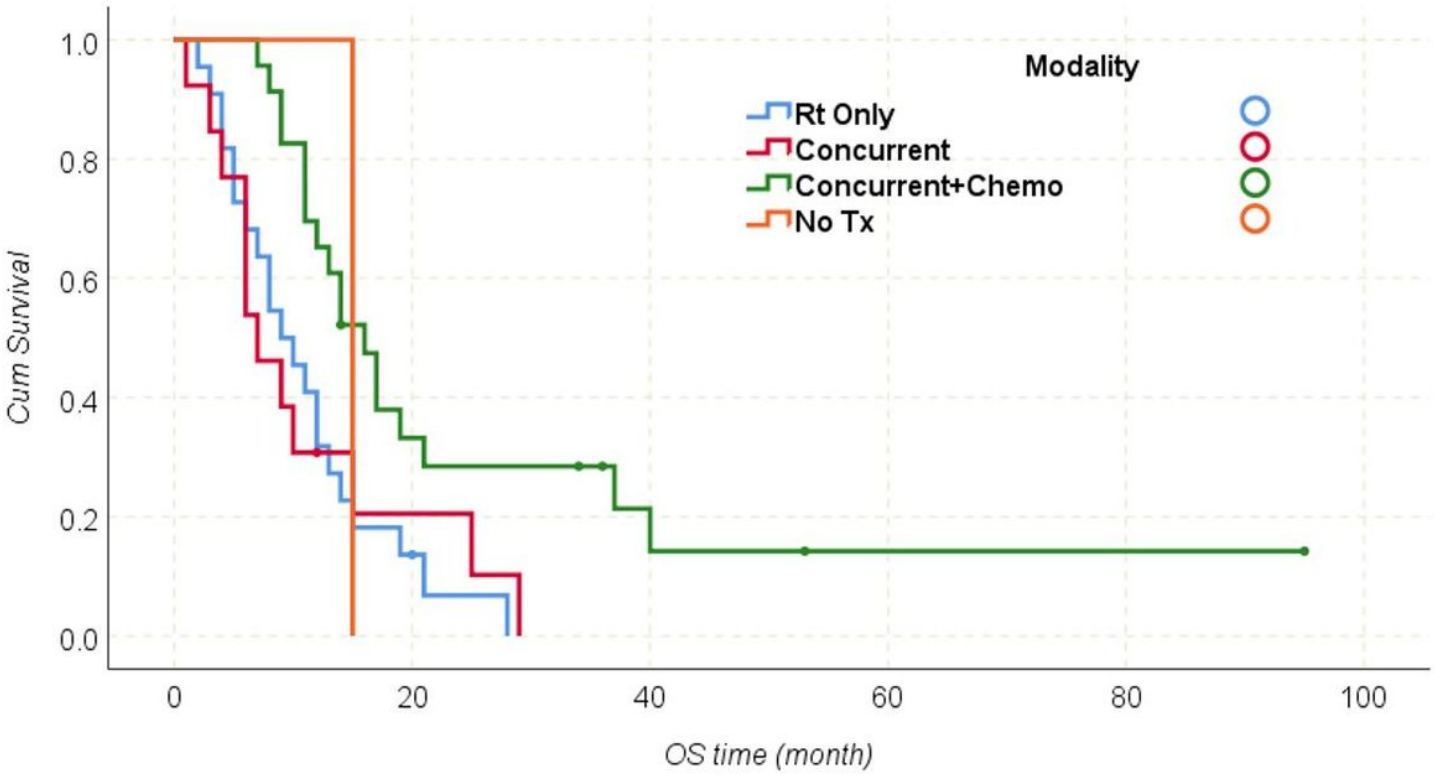



**Figure 6**

Effect of treatment modality on OS of elderly GBM patients.

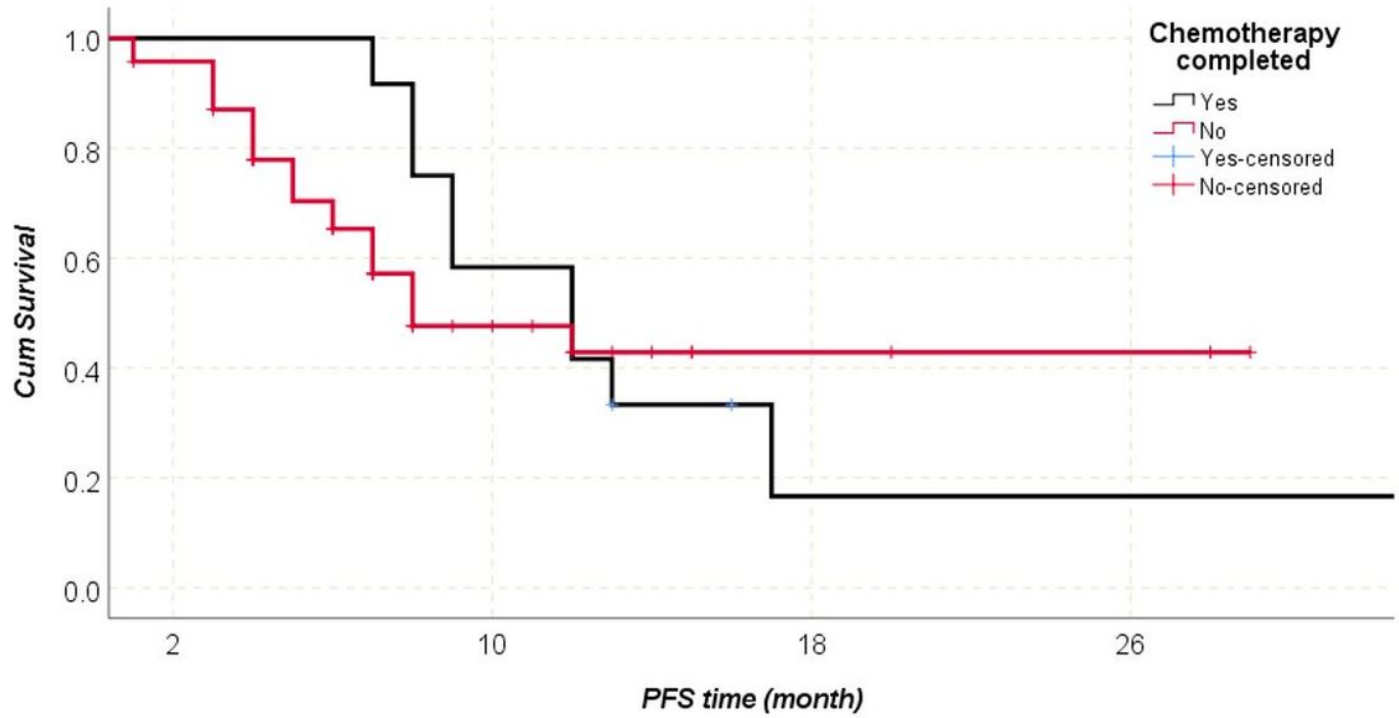



**Figure 7**

Effect of completed CTR on PFS of elderly GBM patients.

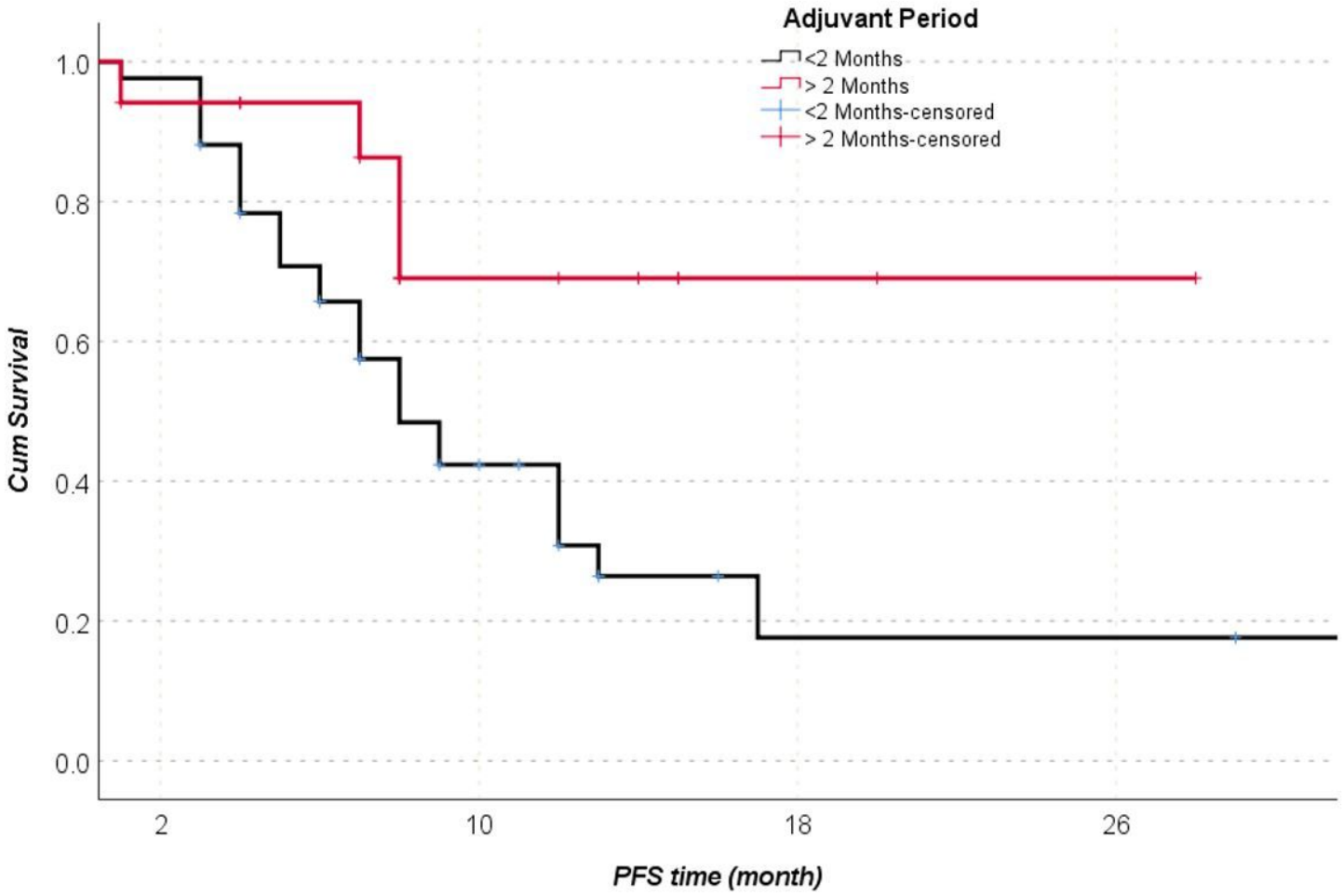



**Figure 8**

Effect of Period to start Adjuvant treatment on PFS of elderly GBM patients

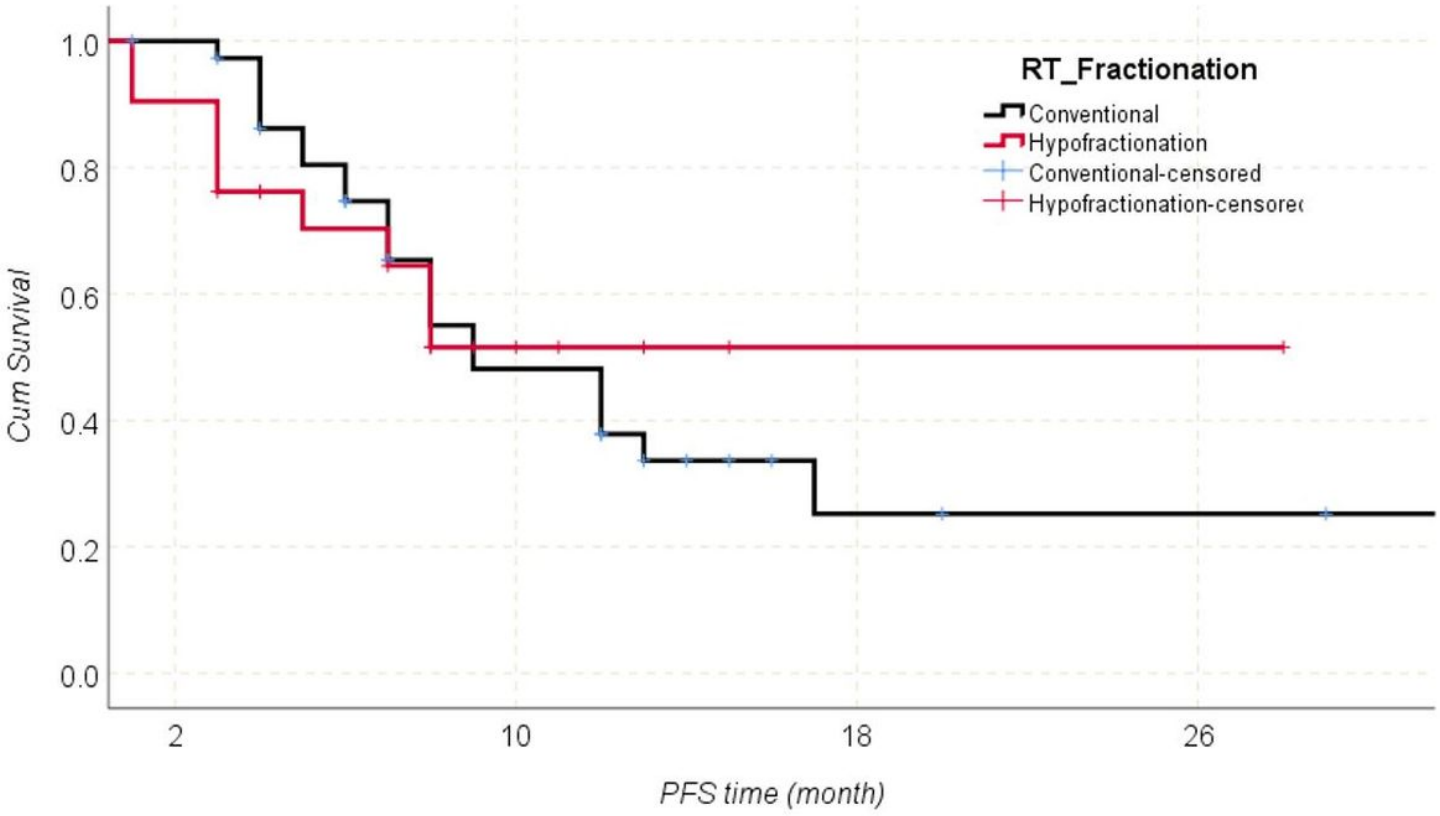
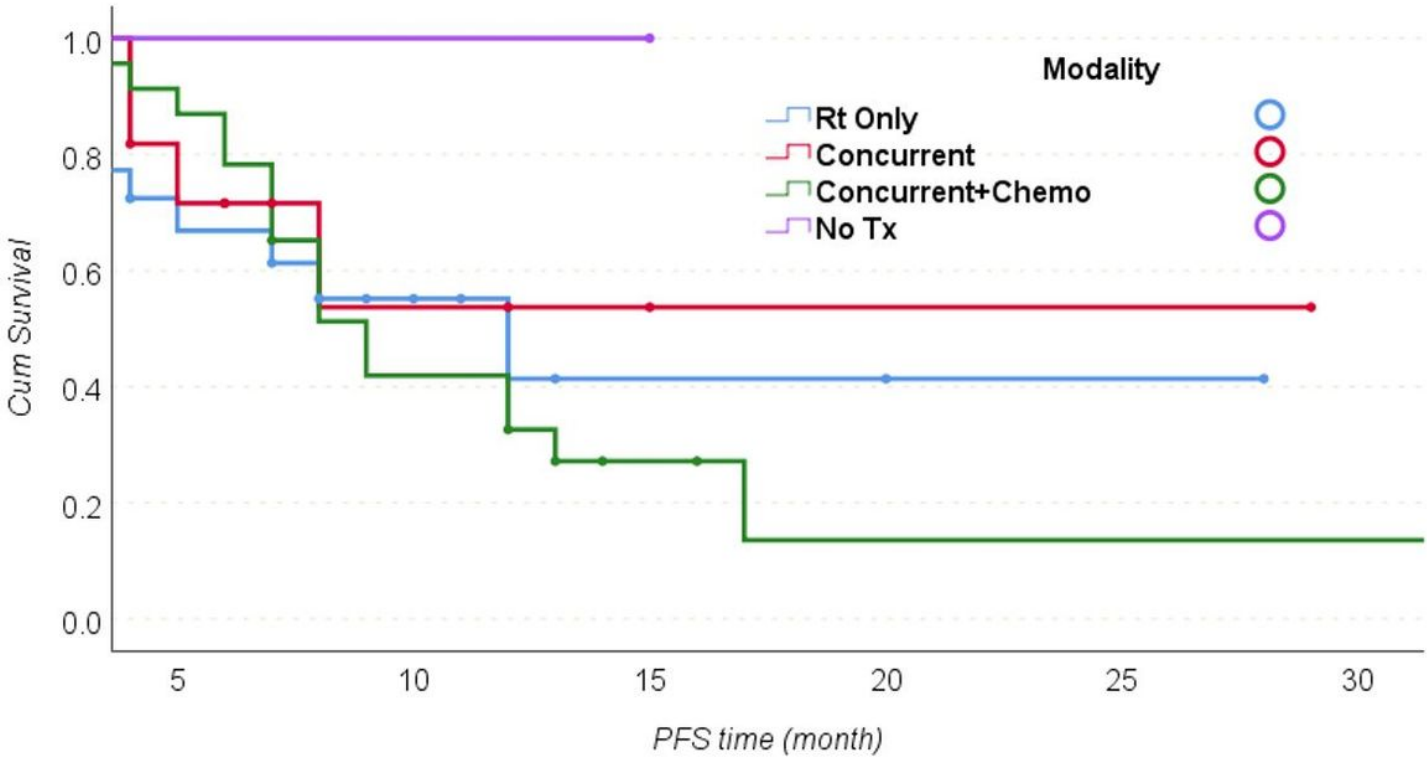



**Figure 9**

Effect of Rth fractionation on PFS of elderly GBM patients.



## Figure 10

Effect of treatment modality on PFS of elderly GBM patients.