The extent of resection and adjuvant treatment are beneficial to the outcome of secondary glioblastoma

Yan Hu (huyan_xian@163.com)
Nanchang University Second Affiliated Hospital

Ze-wei Tu
Nanchang University Second Affiliated Hospital

Pei-gang Ji
Air Force Medical University 2nd Affiliated Hospital: Air Force Medical University Tangdu Hospital

Meng Xu
Air Force Medical University 2nd Affiliated Hospital: Air Force Medical University Tangdu Hospital

Min Chao
Air Force Medical University 2nd Affiliated Hospital: Air Force Medical University Tangdu Hospital

Hai-yan Cao
Air Force Medical University 2nd Affiliated Hospital: Air Force Medical University Tangdu Hospital

Shunnan Ge
Air Force Medical University 2nd Affiliated Hospital: Air Force Medical University Tangdu Hospital

Hua Guo
Nanchang University Second Affiliated Hospital

Guo-dong Gao
Air Force Medical University 2nd Affiliated Hospital: Air Force Medical University Tangdu Hospital

Yan Qu
Air Force Medical University 2nd Affiliated Hospital: Air Force Medical University Tangdu Hospital

Xin-gen Zhu
Nanchang University Second Affiliated Hospital

Liang Wang
Air Force Medical University 2nd Affiliated Hospital: Air Force Medical University Tangdu Hospital

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Research

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Abstract

Backgroud: to investigate secondary glioblastoma (sGBM) patients undergoing resection and evaluate the impact of treatment on survival of malignant progression (PMS) and the prognostic factors of secondary glioblastoma.

Method: the prognostic factors of secondary glioblastoma were analyzed retrospectively including gender, age, the interval between first diagnosis and second, the extent of resection, adjuvant treatment, postoperative Karnofsky score (KPS), 06-methylguanine-DNA methytransferase (MGMT) status, IDH1 mutation status, and PMS in patients with sGBM.

Result: Thirty-four patients with sGBM were included in this study. Sixteen patients were female and eighteen were male. Median PMS in females was longer than male patients with sGBM (17.38 (95%CI 10.63–24.12) vs 10.06(95%CI 5.32–14.79), $p = 0.032$). 22(64.7%) patients achieved gross total resection (GTR),12(35.3%) patients achieved subtotal resection (STR). Kaplan-Meier analysis showed that GTR significantly improved survival after malignant progression (PMS) compared with STR (17.18(95%CI 10.97–23.40) vs 7.17(95%CI 4.97–9.36), $p = 0.004$). Adjuvant treatment after resection was executed in 17 (50.0%) patients, radiotherapy in one (2.9%) patient, chemotherapy in seven (20.6%) patients, and radio-chemotherapy in nine (26.5%) patients. Median preoperative KPS was 80(range 30–100), and 85(range 30–100) after surgery. The difference in PMS probability was significant between patients having a good postoperative clinical status (KPS≥70)versus poor (KPS ≤ 70). Long term survival could be achieved in patients with a good clinical status (16.57(95%CI 10.54–22.60) vs 9.00(95%CI 3.66–14.34), $p = 0.02$). Patients with a greater interval after initial diagnosis had longer survival than those with intervals less than 26.5 months (18.62(95%CI 10.81–26.43) vs 9.22(95%CI 5.61–12.83), $p = 0.025$).

Conclusion: GTR and any adjuvant treatment significantly improved PMS in patients with secondary glioblastoma. Gender, postoperative KPS, time interval since the first diagnosis are associated with prognosis.

1. Background

Glioblastoma is the most common malignant tumor of the nervous system. Some of them have a history of lower-grade glioma, which is called secondary glioblastoma(sGBM), is evolving from previously treated World Health Organization (WHO) II or III grade tumors. Primary and secondary glioblastomas have an identical histopathological feature but distinguishing molecular characteristic and prognosis [1].

Standard treatment for primary glioblastomas (GBM) is maximum safe resection followed by radio-chemotherapy [2]. But for secondary glioblastoma, treatment regimens are not yet uniform, since the previous stage of lower-grade glioma had been treated with surgery, radiation, and chemotherapy. And data about treatment and prognosis of sGBM are very scarce [3–4], prognostic factors are not well understood. This study was dedicated to investigating sGBM patients undergoing resection and sought to evaluate the impact of treatment on survival and the prognostic factors of sGBM.

2. Materials And Methods

2.1 Study population

All the patients with sGBM between 2014 and 2019 in our institute were reviewed. All patients had undergone surgical resection and biopsy at the time of initial diagnosis, and the pathology showed astrocytoma, oligodendroglioma, anaplastic astrocytoma, anaplastic oligodendroglioma, or anaplastic oligoastrocytoma. All patients underwent surgery again and were pathologically diagnosed as glioblastoma when new lesions were identified by magnetic resonance imaging. We reviewed the clinical data of these patients, including gender, age,interval from initial diagnosis extent of resection, adjuvant treatment, postoperative KPS, the interval between first diagnosis and second, MGMT status, IDH1 mutation status, survival after malignant progression (PMS). This study was approved by the hospital ethical committee.

2.2 Surgical treatment

We made a decision for surgery (resection or biopsy) when the patient's MRI contrast-enhancing mass indicated the malignant transformation. All patients with recurrence were treated with surgery or biopsy, and some patients were assisted with multimodal surgical techniques such as intraoperative arousal anesthesia and neuronavigation. Early postoperative MRI (within 48 hours after surgery) was used to determine the extent of resection (EOR). Gross total resection (GTR) was defined as the absence of residual contrast-enhancing tissue on ceT1-weighted images. Any residual contrast enhancement was assessed as subtotal resection (STR). KPS at postoperative discharge was also recorded.

2.3 Adjuvant treatment

Adjuvant treatment was conducted, included radiotherapy, chemotherapy, radio-chemotherapy, and targeted therapy. Clinical and radiological follow-up was conducted every three months.

2.4 Statistical analysis

Statistical analyses were performed using SPSS Statistics Version 21 (IBM, Chicago IL). Survival rates were estimated using the Kaplan–Meier method. A Chi-square test was used to compare ordinal and categorical variables.

Univariate analysis (Log-rank test) was performed to identify covariables affecting PMS. The following parameters were analyzed: gender, age at primary diagnosis, initial WHO grade, previous treatment, time interview since the first diagnosis, age at diagnosis of sGBM, KPS, the extent of resection, and postoperative adjuvant treatment. The univariate analysis is shown in Table 2.

Table 2
Univariate analysis of the impact of patient, treatment on PMS.

	Median (range)	*p* value
Gender		0.032
Male	10.06(5.32–14.79)	
female	17.38 (10.63–24.12)	
interval since first diagnosis		0.025
≥26.5 months	18.63(10.81–26.44)	
＜26.5 months	9.22(5.61–12.83)	
Primary tumor grade		0.122
WHO Ⅳ	17.81(9.63–25.99)	
WHO Ⅲ	9.94(6.59–13.30)	
Initial adjuvant treatment		0.881
yes	13.75(8.74–18.76)	
no	13.17(4.12–22.21)	
Pre-op KPS		0.578
＞70	13.63(9.16–18.10)	
≤70	13.33(5.54–21.12)	
post-op KPS		0.020
≥70	16.57(10.54–22.60)	
≤ 70	9.00(3.66–14.34)	
IDH mutation status		0.153
mutation	18.89(10.21–27.57)	
wildtype	9.79(6.81–12.76)	
MGMT status		0.272
methylation	19.86(8.51–31.20)	
Not methylation	13.50(5.95–21.05)	
STR	7.17(4.97–9.36)	
Adjuvant treatment		0.050

	Median (range)	*p* value
Yes	17.18(10.94–23.40)	
No	9.44(5.66–13.22)	

P values lower than 0.05 were considered statistically significant.

3. Results

Clinical parameters and baseline epidemiological are shown in Table 1. Thirty-four patients with sGBM were included in this study. Sixteen patients were female and eighteen were male. A gender difference was found in this dataset, the median PMS in female was longer than male patients with sGBM (17.38 (95%CI 10.63–24.12) vs 10.06(95%CI 5.32–14.79), $p = 0.032$, Fig. 1).

Table 1
Baseline and clinical characteristics of enrolled patients

Parameter	n (%) Median (range)
Gender	
Female	16 (47.1)
Male	18 (52.9)
Age (years)	
First diagnosis glioma	40 (10–61)
Diagnosis sec. GBM	43.5 (15–63)
KPS	80 (30–100)
Initial histology	
Grade II	19 (55.9)
Grade III	15 (44.1)
Therapy prior to sec. GBM	
Resection	34 (100.0)
Radiotherapy	5 (14.7)
Chemotherapy	6 (17.6)
Radio-chemotherapy	17 (50.0)
None	6 (17.6)
Time since first diagnosis (months)	
Grade II	47 (7–102)
Grade III	18 (4–128)
All	26.5 (4-180)
Extent of resection (EOR)	
GTR	22 (64.7)
STR	12 (35.3)
Adjuvant treatment	
Radiotherapy	1 (2.9)
Chemotherapy	7 (20.6)
Radio-chemotherapy	9 (26.5)

Parameter	n (%) Median (range)
None	17 (50.0)
Molecular status	
MGMT promotor methylated (n = 21)	7 (33.3)
IDH1 mutation (n = 28)	17 (60.7)
P53 mutation (n = 23)	15 (65.2)

The median age at primary diagnosis was 40 years (range 10–61), the median age at secondary glioblastoma diagnosis was 43.5 years (range 15–63). The median time interval from the initial diagnosis to sGBM diagnosis was 26.5 months (range 4-128), patients with a greater interval after initial diagnosis had longer survival than those with interval less than 26.5 months (18.62(95%CI 10.81–26.43) vs 9.22(95%CI 5.61–12.83), $p = 0.025$, Fig. 2).

Primary histology tumor grade was WHO II in 19(55.89%) and WHO III in 15 (44.11%) patients. Patients with low-grade tumors at the initial diagnosis tended to have longer survival (17.81 (95%CI 9.63–25.99) vs 9.94(95%CI 6.59–13.30), $p = 0.122$).

Surgical resection was performed on 34 (100%) patients after the initial diagnosis, followed by adjuvant treatment, including radiotherapy (5,14.7%), radio-chemotherapy (17,50%), and chemotherapy (6,17.6%). Median PMS of patients who received adjuvant treatment was 13.75(8.74–18.76) months, which was 13.17(4.12–22.21) in patients not receiving adjuvant treatment ($p = 0.881$).

Median preoperative KPS was 80(range 30–100), and 85(range 30–100) after surgery. Patients with post-op KPS greater than 70 had a longer PMS than those less than 70(16.57(10.54–22.60) vs 9.00(3.66–14.34), $p = 0.02$, Fig. 3), but for pre-op KPS, PMS was 13.63(9.16–18.10) and 13.33(5.54–21.12) when greater than 70 versus less than 70, ($p = 0.578$).

22(64.7%) patients achieved GTR, STR was achieved in 12(35.3%) patients in the operation after malignant progression. Surgical treatment increased median KPS from preoperative 80 to postoperative 85. Median PMS was 10.5 months (range1-55), PMS after GTR and STR was17.18(95%CI 10.97–23.40) and 7.17(95%CI 4.97–9.36), respectively, ($p = 0.004$, Fig. 4).

Adjuvant treatment after resection was executed in 17 (50.0%) patients, radiotherapy in one (2.9%) patient, chemotherapy in seven (20.6%) patients, and radio-chemotherapy in nine (26.5%) patients. Seventeen patients did not receive any adjuvant treatment. Kaplan-Meier analysis showed that any adjuvant therapy prolonged PMS significantly when compared with without adjuvant treatment(17.44(95%CI 10.22–24.67)vs 9.44(95%CI 5.66–13.22), $p = 0.05$, Fig. 5). Interestingly, survival after diagnosis of sGBM for the three kinds of adjuvant treatments was 16.00 months, 14.43 (95%CI 7.08–21.78) months, 15.78 (95%CI 5.31–26.25) months respectively, *P* values of the pairwise comparisons are respectively 0.650,0.686,0.910.

IDH mutation analysis was available in 28 patients, 17(60.7%) patients showed IDH1 mutation. We observed a longer survival tendency in patients with an IDH1 mutation(p = 0.153). O6-methylguanine-DNA-methyltransferase (MGMT) promoter methylation status analysis was available in 21 patients,7(33.3) patients showed MGMT promoter methylation. MGMT promoter methylation had no significant impact on PMS(p = 0.272).

A further recurrence in 4 patients was documented by MRI, 3 of these underwent reoperation and one received adjuvant therapy.

No multivariate analysis was performed since the small cohort size.

4. Discussion

The median survival of secondary glioblastoma is shorter than that of primary glioblastoma. Survival of primary glioblastoma can be prolonged by maximum excision, adjuvant chemoradiotherapy, and tumor-treating fields (TTFields) [5]. But the effect of postoperative treatment on survival is unclear.

Gender difference in incidence, prognosis, the outcome of human disease was broadly recognized, however, it was controversial in glioblastoma. Standard therapy is more effective in female compared with male patients with GBM, Yang et al.[6] provides a case in point, in a quantitative imaging-based measure of response. Matteoni S et al. [7] analyzed data in the literature regarding glioblastoma, strongly suggested that clinical approaches should consider patients' sex as a key determinant. Coincidentally, our results are consistent with previous studies, we also found the female has a longer malignant progression survival than male. Other researchers also described the role of sex in glioma at the molecular level, Yuan [8] provided a molecular-level understanding of sex effects and demonstrated that > 50% of the gene (60/114) showed sex-biased signatures, in other words, sex was a key factor affecting cancer prognosis. Sex-specific therapeutic options may be on the horizon in the future.

The interval between first diagnosis and second was significant prognostic factors for survival. A study about recurrent glioblastoma conducted by Minniti Gthe et al, his finding indicated that the interval between primary RT and reirradiation had an effect on survival [9]. This is similar to ours, however, the interval is related to many factors, including the pathology of the initial operation, the EOR of the first operation, and the mode of postoperative treatment. Large cohort studies are needed to study the effect on prognosis.

The extent of resection was an independent prognostic factor of glioblastoma [10]. Tully's study suggests that reoperation in patients with recurrent glioblastoma may also prolong survival [11], and the results of this study were similar. Median survival was significantly longer in patients who underwent total excision of the second operation than in those who did not. The application of multimodal assisted excision can improve the success rate of surgical excision and reduce the dysfunction as much as possible.

Postoperative quality of life score was an independent prognostic factor [12]. Jakola et al suggested in their study that health-related quality of life (HRQoL) was a predictor for survival in GBM [13]. We also discovered in this study that good clinical life status after the second operation influenced PMS remarkably. A prospective study was documented by Jakola suggested that HRQoL was a predictor of newly GBM survival [13]. This is consistent with our findings even though the postoperative clinical status determined the patient compliance with follow-up adjuvant therapy and is to a large extent affect the prognosis of glioblastoma.

Adjuvant treatment was associated with survival after secondary GBM in this study, the therapy model, however, was irrelevant. What a coincidence, the survival of patients who undergo multiple molds of adjuvant therapy is better than without adjuvant treatment for recurrent glioblastoma [14]. Interestingly, no significant differences were found in this study, regardless of the type of treatment received. This finding is contrary to Zhuo's [15], in which he showed a significant improvement in OS of patients treated with RT plus oral chemotherapy compared with that of RT alone by meta-analysis. This difference may be well explained by the small size of the subgroup and need to be verified by a large cohort trial.

IDH1 is an important promoter gene in glioma, and also a prognostic factor [16]. Nobusawa S [3] holds the opinion that IDH1 as a predictive factor of secondary glioblastomas. Similarly, mutations within the IDH protein have been described as diagnostic markers indicative of sGBM [17]. However, the IDH mutation probability of newly diagnosed GBM was low [17]. Interestingly, we revealed that 60% of the patients with sGBM displayed an IDH1 mutation, and we only found a correlation trend between IDH1 mutation and longer survival after diagnosis of sGBM. MGMT promoter methylation is a strong correlation with the survival of patients with glioblastoma [18]. A recent meta-analysis (34 studies, 4097patients) reported that MGMT methylated GBM patients had improved OS compared with unmethylated patients with GBM, whereas, no correlation between MGMT status and PFS [19]. In contrast, Brell et al. [20] indicated that there is no correlation between MGMT methylation and survival in anaplastic glioma, this is similar to our result, we also did not observe a correlation between MGMT status and survival of sGBM. These findings of molecular markers are acceptable as this is a retrospective study with limited molecular information.

The potential limitations of our study include its retrospective nature, limited cohort size, exclusion of other molecular markers, variability in the extent of follow-up, and lack of control groups. It is impossible to say if any slight differences in these factors may have influenced our results. Nevertheless, our findings may encourage prospective, larger cohort size and randomized controlled study.

5. Conclusion

GTR and any adjuvant treatment significantly improved PMS in patients with secondary glioblastoma. Gender, postoperative KPS, time interval since the first diagnosis are associated with prognosis. Further investigation needed to be explored in the future.

Abbreviations

sGBM
secondary glioblastoma
PMS
survival of malignant progression
KPS
Karnofsky
MGMT
O6-methylguanine-DNA-methyltransferase
IDH
Isocitrate dehydrogenase
GTR
gross total resection
STR
subtotal resection
EOR
the extent of resection

Declarations

Ethics approval and consent to participate

The study was approved by the ethics committee of The Second Affiliated Hospital (TDLL-2017-172).

Consent for publication

All authors agree with the publication.

Availability of data and material

All the data are true and reliable, for original data, please email the corresponding author.

Competing interests

We declare no competing interests.

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Author's contributions

YH collected the data, participated in the statistical analysis, and drafted the manuscript. ZT participated in the writing of the manuscript. MX participated in collecting the data. PJ, MC, and HC carried out the statistical analysis. HG, SG, GG, and YQ participated in its design and coordination. LW and XZ had the idea for and designed the study and had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors reviewed and approved the final version.

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Figures

Fig. 1

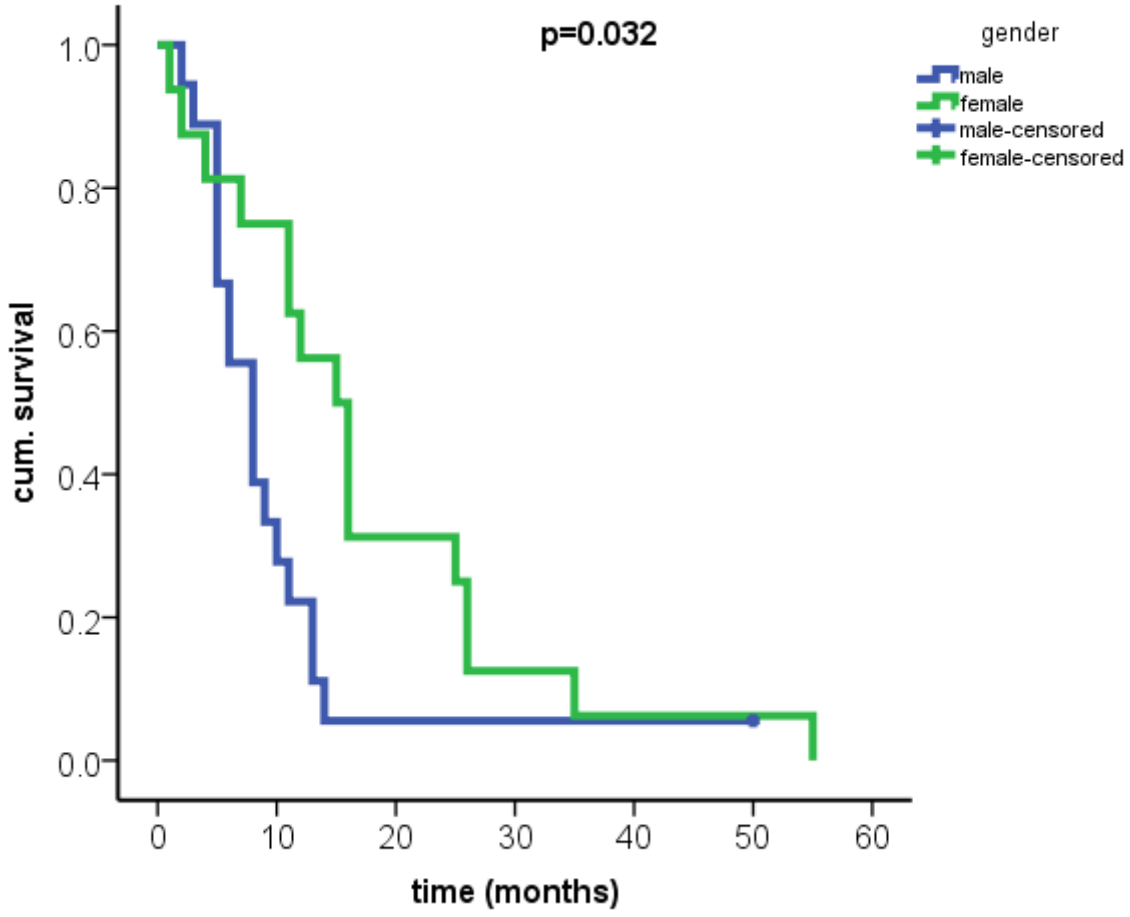

Figure 1

Survival after malignant progression (PMS) and gender.

Fig. 2

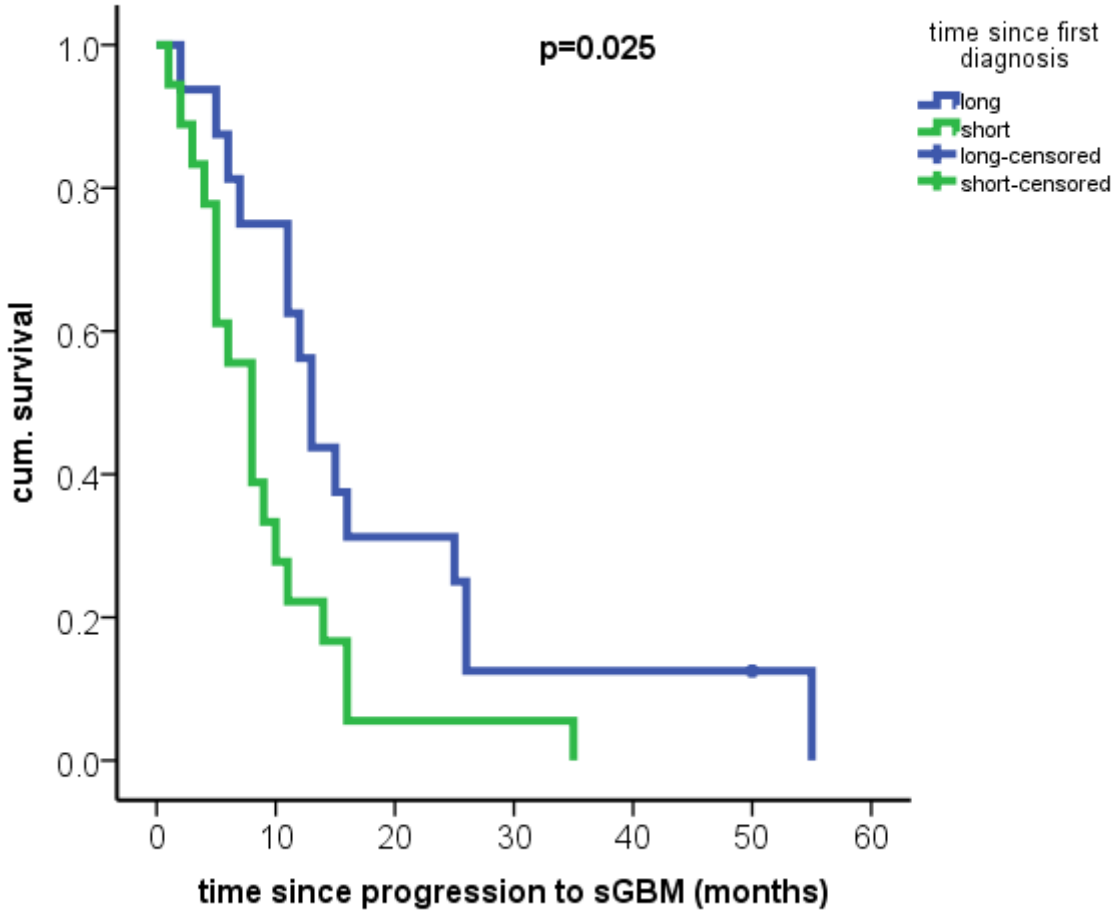

Figure 2

PMS and time interval since the first diagnosis.

Fig. 3

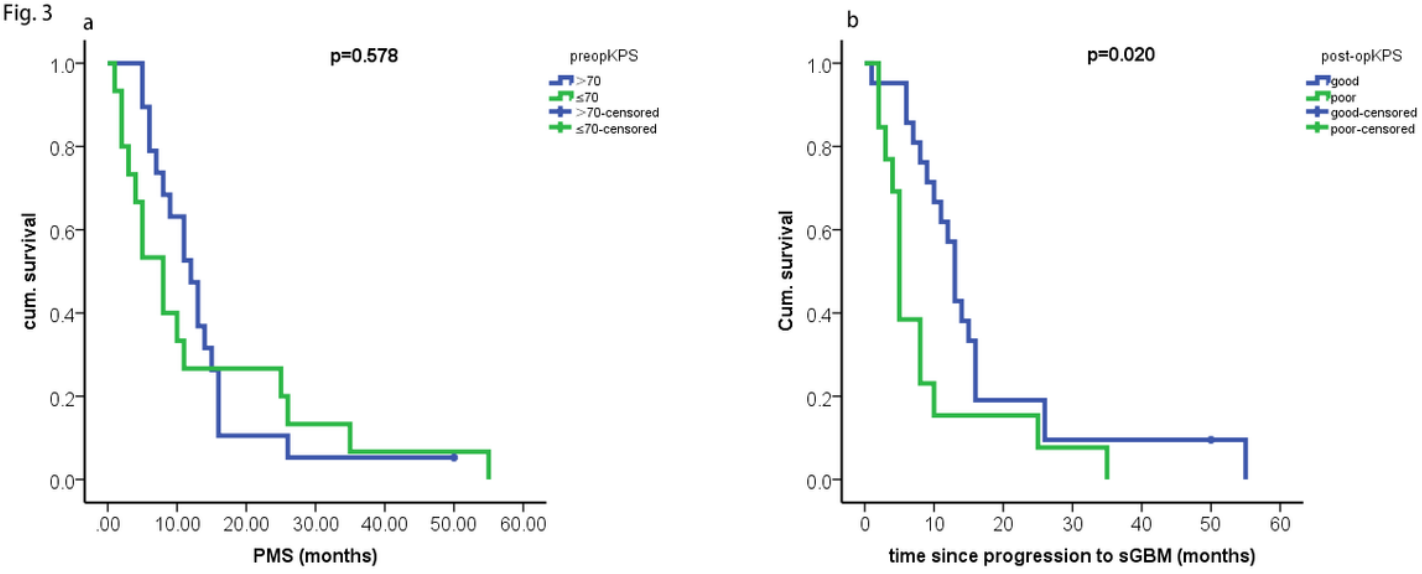

Figure 3

PMS and post-op KPS.

Fig. 4

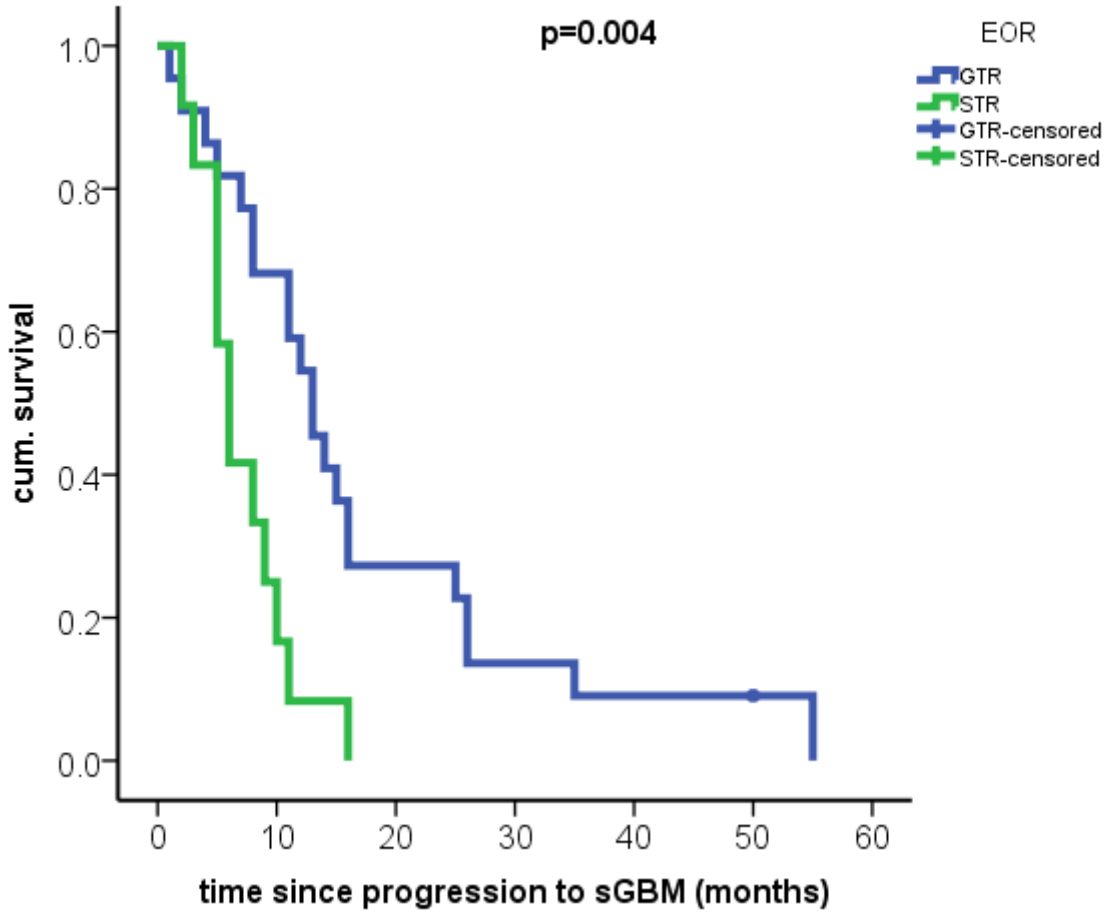

Figure 4

PMS and extent of resection.

Fig. 5

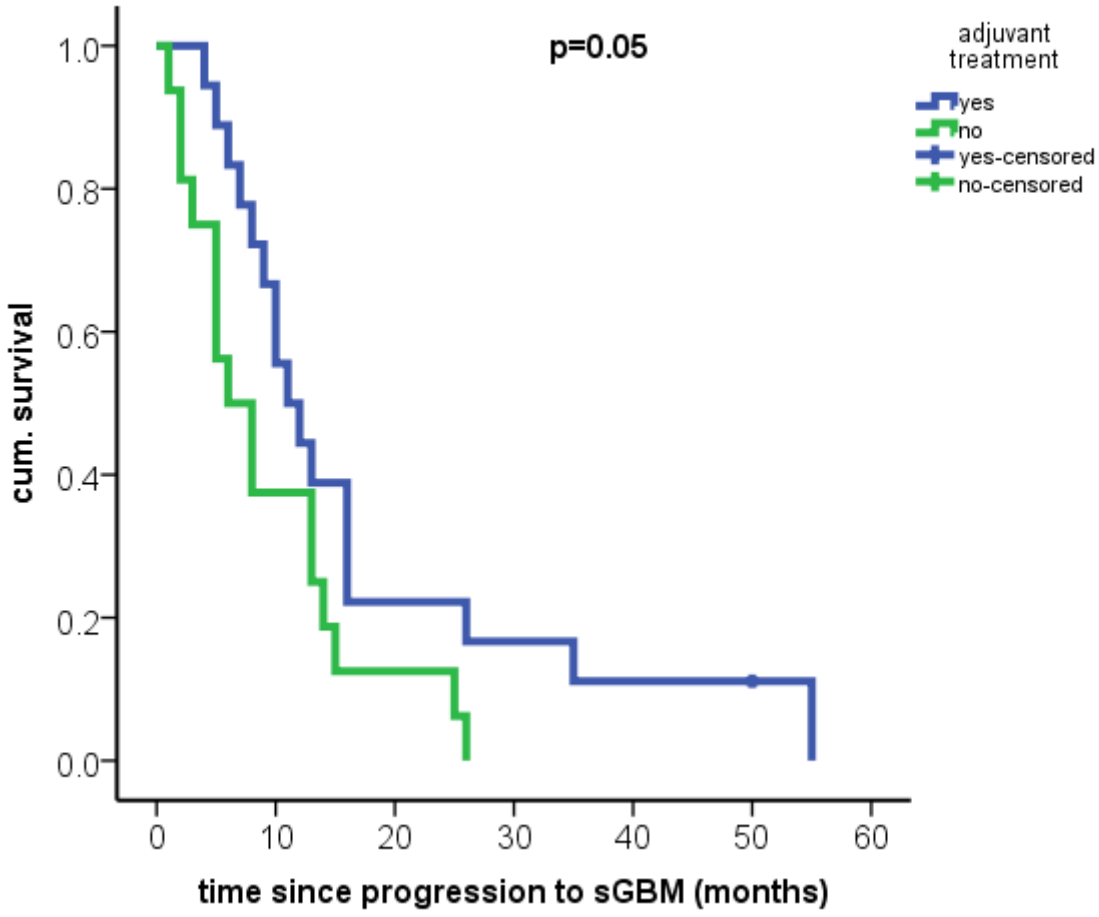

Figure 5

PMS and adjuvant treatment.