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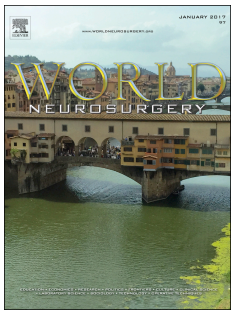


IMPACT OF EARLY RE-OPERATION ON THE PROGNOSIS OF PATIENTS OPERATED ON FOR GLIOBLASTOMA

Marta Troya-Castilla., MD, Ariel Kaen, MD, PhD, Francisco Javier Márquez-Rivas, MD, PhD, Pedro Infante Cossio, MD, PhD, Francisca Rius Díaz, PhD, Professor of Biostatistic, José Luis Narros Gimenez, MD, Marta Gonzalez-Pombo, MD., Palomares Cancela, MD, Miguel Segura Fernández-Nogueras, MD, Miguel Ángel Arráez, MD, PhD

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# IMPACT OF EARLY RE-OPERATION ON THE PROGNOSIS OF PATIENTS OPERATED ON FOR GLIOBLASTOMA

**Marta Troya-Castilla. MD**

martta.troya@gmail.com

Department of Neurosurgery

Hospital Regional Universitario de Málaga

Malaga, Spain

**Ariel Kaen, MD, PhD**

kaenariel@hotmail.com

Department of Neurosurgery

Hospital Universitario Virgen del Rocío

Seville, Spain

**Francisco Javier Márquez-Rivas, MD, PhD**

fjavi.marquez.sspa@juntadeandalucia.es

Department of Neurosurgery

Hospital Universitario Virgen del Rocío

Seville, Spain

**Pedro Infante Cossio, MD, PhD**

pinfante@us.es

Department of Oral and Maxillofacial Surgery

Hospital Universitario Virgen del Rocío

Seville, Spain

**Francisca Rius Díaz, PhD**

Professor of Biostatistic.

Department of Preventive Medicine and Public Health

Faculty of Medicine. Univerity of Malaga.

rius@uma.es

**José Luis Narros Gimenez, MD**

jlnarros@gmail.com

Department of Neurosurgery

Hospital Universitario Virgen del Rocío

Seville, Spain.

**Marta Gonzalez-Pombo, MD.**

Martuchi55@mundo-r.com.

Department of Neurosurgery.

Hospital Universitario Virgen del Rocío

Seville, Spain

**Palomares Cancela,MD**

pacancela@yahoo.es

Department of Neurosurgery

Hospital Universitario Virgen del Rocío

Seville, Spain

**Miguel Segura Fernández-Nogueras, MD**

Msfn27@gmail.com

Department of Neurosurgery

Hospital Regional Universitario de Málaga

Malaga, Spain

**Miguel Ángel Arráez, MD, PhD**

marraezs@commalaga.com

Chief of Department of Neurosurgery

Hospital Regional Universitario de Málaga

Malaga, Spain

**Corresponding author:**

Marta Troya-Castilla

Martta.troya@gmail.com

+34 697316182

Avenida Carlos Haya 86, 29006, Malaga, Spain.

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# IMPACT OF EARLY RE-OPERATION ON THE PROGNOSIS OF PATIENTS OPERATED ON FOR GLIOBLASTOMA


## Abstract

### Introduction

The prognosis for patients with glioblastoma depends particularly on the degree of tumour resection. Patients with tumour remnants in post-surgical MRI (<72 hours) may benefit from early re-operation. We present our results concerning the impact on overall survival (OS) and progression-free survival (PFS) of re-operation in patients who have already undergone surgery for glioblastoma.

### Material and methods

This study included all patients who had undergone surgery for glioblastoma with control MRI, who received adjuvant therapy as per the STUPP protocol, with a minimum follow-up of 24 months. We recorded the number of complete resections, partial resections and early re-operations. We determined the impact on OS and PFS of the early re-operations and the functional status. We considered complete resection when the volume of the residual tumour was 0 cc.

### Results

112 patients were diagnosed with glioblastoma between March 2014 and March 2017. The study included 58 patients who fulfilled all the inclusion criteria. Complete resection was achieved in 24 patients (41.4%) and partial resection in 34 (58.6%). Of these 34 patients, 11 (32.35%) underwent early re-operation. The final result was complete resection in 58.62% of the patients. In the patients who underwent re-operation OS and PFS were 30.3 months and 16.6 months compared to 12.7 months and 6.75 months in those without re-operation (p=0.013 and p=0.012). The functional prognosis was similar between the two groups.

Conclusion

Early re-operation in patients with residual tumour improved OS and PFS without increasing the number of complications as compared with the patients who did not undergo re-operation.

Key Words: Control MRI. Glioblastoma. Prognosis. Re-operation.

## Introduction

Despite advances in genetic understanding, the management of glioblastoma is still surgery followed by oncological treatment[1]. Tumour resection is the modifiable factor most influencing the prognosis of affected patients[2]. In fact, complete resection enables 25% of patients to survive for over 2 years[3].

In centres that have access to intraoperative magnetic resonance imaging (iMRI) it is possible to know the degree of tumour resection during surgery and decide whether to continue resection until complete excision is achieved [4-6]. In centres where iMRI is not available, however, a control magnetic resonance imaging (MRI) study within 72 hours of surgery is an option that provides information about the degree of resection after the surgery [7,8]. If this early study shows tumour remnants, the surgeon may decide to re-operate to try to achieve complete resection [9]. However, few studies exist on this early re-operation based on a control MRI and the association of this practice with survival. The aim, therefore, of this study was to assess the impact of early re-operation based on the results of a control MRI and determine the prognosis and survival of patients with glioblastoma.

## Material and methods

We undertook a retrospective review of all patients who underwent surgery for glioblastoma (WHO 2016) at the Virgen del Rocío University Hospital (Seville, Spain) between March 2014 and March 2017. This study included all patients who also had a control MRI study within 72 hours of surgery, received adjuvant therapy based on the STUPP protocol and had a follow-up of at least 24 months.

Data were collected on epidemiological variables [age, sex, presenting signs, early (<3 months) and/or late (>3 months) complications, pre-operative and post-operative Karnofsky scale, as well as during the follow-up]; radiological variables (tumour site, hemisphere affected,

oedema, mass effect, intensity of the tumour contrast, pre-surgical tumour volume, post-surgical tumour volume, pre-surgical tumour perfusion values, radiological complications, tumour progression); surgical variables (complete resection, partial resection, early re-operations in the patients with tumour remnants); pathological variables (histological classification according to the WHO 2016, IDH determination using immuno-histochemistry [(10)]); oncological variables (adjuvant treatment, complications); functional variables (time to partial dependence (KPS<70) and time to total dependence (KPS<50); and prognostic variables [progression-free survival (PFS) in months and overall survival (OS) in months].

Radiological images

Pre-surgical T1 MRI images (1.5T) were obtained (≥120 slices) with and without contrast, as well as T2, FLAIR and ADC images. We determined the pre-surgical tumour volume (contrast-enhancing lesion) with the software BrainLab iPlan Stereotaxy 3.0.5 (Figure 1). We classified the tumour mass into 4 degrees: no mass effect (I), midline shift <0.5 cm (II), midline shift 0.5-1 cm (III), and midline shift >1 cm (IV) [(11)]. We classified tumour oedema in 4 variants: no oedema, oedema less than the contrast-enhancing tumour volume, oedema equal to the contrast-enhancing tumour volume, and oedema greater than the contrast-enhancing tumour volume [(11)]. Finally, contrast uptake was divided into a scale of 4 points: no uptake (I), low-intermediate uptake (II), intermediate-high uptake (III), and high uptake (IV, similar to fat) [(11)]. We used the criteria of Sawaya et al [(12)] to define brain function: Grade I (noneloquent area), frontal or temporopolar, right parieto-occipital and cerebellar hemisphere areas; Grade II (adjacent to eloquent area), near a motor or sensory area, near Broca's or Wernicke's areas, near the calcarine sulcus or brainstem; Grade III (eloquent area), motor or sensory cortex, language areas, visual areas, brainstem, basal ganglia or internal capsule.

The MRI protocol included perfusion images, obtaining relative cerebral blood volume (rCBV) values comparing the area of contrast uptake with a region of interest in the contralateral white matter [13].

We performed early post-operative MRI ≥1.5T within 72 hours of surgery [7,8,14]. To measure the residual tumour volume (RTV) we used the same method as for the pre-operative volume study (Figure 1). We considered complete tumour resection to be when the early brain MRI demonstrated a resection of 100% of the enhancing portion of tumour, that is with a RTV of 0 cc. Any remnants of enhancing portion of tumour were considered to reflect a partial resection (RTV>0 cc). Ultrasonography and/or neuronavigation were used to facilitate complete resection.

We defined tumour progression according to the RANO criteria [15]: an increase of at least 25% in the volume of the contrast-enhancing lesion compared to the baseline MRI images, increase in T2/FLAIR area with appearance of any new lesion and/or clear clinical worsening not attributable to causes other than tumour progression.

Statistical Analysis

The study outcome focused specifically on the decision to re-operate a patient with tumour remnants visible on the post-operative MRI and whether repeat surgery involved an increase in complications and a worse quality of life. In the descriptive analysis, qualitative variables are shown as percentages. Quantitative variables are described by the mean ± SD or by the median. The Kaplan-Meier and Long-Rank curve were used for survival analysis. The association between variables was considered to be significant when the p value was less than 0.05. Statistical analyses were performed using the Statistical Package for the Social Sciences 22.0 (SPSS Inc).

Results

A total of 176 patients were diagnosed with brain glioma between March 2014 and March 2017, of whom 112 underwent surgery due to suspected glioblastoma. This study included 58 patients who fulfilled all the inclusion criteria (diagnosis of glioblastoma according to WHO 2016, control MRI within 72 hours of surgery, adjuvant STUPP therapy and a minimum follow-up of at least 24 months). Tables 1, 2 and 3 summarize the results of the descriptive analysis of our series. The mean age of the patients was 57.53 years (17.3% ≤45 years, 50% between 46 and 64 years, 32.7% ≥65 years); 55.2% were men and 48.8% women. The most common presenting symptom was headache, with the temporal lobe being the most usual site and the left hemisphere most commonly affected. According to the eloquence, 50% of the lesions were Grade II (adjacent to eloquent zone), followed by 43.1% Grade I (non-eloquent lesions); a small percentage were eloquent (6.9%). Most of the lesions had little mass effect (43.1% did not displace the midline and 25.9% displaced it <0.5 cm). However, most lesions presented peri-tumour oedema (only 7% did not have oedema) and important contrast uptake (only 3.4% had intermediate-low uptake). The perfusion values (rCBV) in the pre-operative tumour contrast area were: 2.25-15, with a mean of 6.12 and a mode of rCBV=5. The pre-surgical tumour volume was 39.85 cc (1.2 cc - 182.5 cc). The biopsy findings according to WHO 2016 were 70.7% of patients with glioblastoma IDH-wild type, 1.7% with glioblastoma IDH-mutant and 27.6% with glioblastoma IDH-NOS. Complete resection (RTV=0 cc) was achieved in 58.62% of cases and partial resection (RTV>0 cc) in 41.37%. The VR on discharge was 1.65 cc (0 cc – 16.2 cc). The rate of early complications was 23%, with transient hemiparesis being the most common (9.6%). Late complications appeared in 13.4% of the cases, the most common being infection (5.8%). Most of the patients started complementary therapy at 6 weeks and completed the 6 weeks of adjuvant treatment, in all cases with the STUPP protocol. Of all the patients, 8.8% received no treatment due to death prior to the scheduled date for starting radiotherapy. The mean KPS for the series at diagnosis was 92.12 and on discharge it was 93.4.

Outcome

The mean time to partial dependence (KPS<70) was 12.41 months (0-39 months) and to total dependence (KPS<50) it was 14.5 months (0-4 months). The mean PFS of the series was 13.49 months (0.5-69 months). The main radiological finding of tumour progression was contrast uptake or the appearance of a new lesion. The mean OS was 20.92 months (2-69 months), with 15.5% of the patients alive at the end of follow-up (of whom 89% had complete resection).

Surgical outcome, early re-operations and impact on survival

Tables 3 and 4 summarize the surgical characteristics of the series. The early MRI showed that 24 patients (41.4%) had complete tumour resection and 34 patients (58.6%) partial resection (VR>0 cc). The mean residual volume after this MRI study was 2 cc (0-16.2 cc). Of the 34 patients with partial resections 11 (32.35%) underwent re-operation during the same admission. After the re-operation the control MRI showed complete resection in all cases except one; thus representing complete resection for the series in 34 patients (58.62%) and partial resection in 24 (41.37%).

Mean survival in the group that underwent re-operation (Figure 2) was 30.3 months (SD 7.16) compared to 12.7 months (SD 1.92) in the group that did not (p=0.013). Mean PFS in the re-operated patients (Figure 3) was 16.6 months (SD 5.7) and in the non-re-operated patients it was 6.75 months (SD 1.9) (p=0.012). Table 4 shows all the means and also the medians comparing re-operation VS no re-operation group.

The mean survival among the 34 patients who had complete resection at discharge was 26.4 months compared to 12.64 months in the 24 patients who had partial resection (p=0.002) (Figure 4). The mean PFS in the patients with complete resection was 17.59 months versus 6.078 months in those with partial resection (p=0.001) (Figure 5). Table 5 shows all the means and also the medians comparing complete resection group versus partial resection group at discharge.

In table 6 we have the differences between re-operation and non-re-operation group. The only variable we found statistically significant was Karnofsky scale after first surgery (p=0.004). Age, site, eloquence grade, initial VR and molecular biomarker were not statistically associated with the patients who underwent re-operation versus those who did not (p>0.05).

## Discussion

Surgical excision of glioblastoma is the modifiable factor that can most influence the prognosis [(2)]. A meta-analysis in 2016 confirmed that survival of patients who had a biopsy was lower than that of patients who had surgical resection: one year after diagnosis 75% of the patients with a biopsy had died compared to 44% of the patients who underwent surgical resection [(3)]. Despite the many past and present studies on the genetic behaviour of these tumours, we are still far from being able to offer affected patients individualized treatment and surgery remains the fundamental pillar of treatment [(10,16-18,20-24)].

Many studies have concluded that the degree of resection influences survival, with the first article showing an impact published in 2001. Between 2001 and 2014, all authors mentioned the extend of resection (EOR) as the percentage of resection. More recent studies mention the influence on survival of surgery measuring the RTV rather than the percentage resection. In 2014 Chaichana et al. showed that resections with RTV<5 cc were associated with increased survival (16.3 months mean) compared to resections with RTV≥5 cc (12.1 months mean) [(27)]. Grabouwski et al. studied survival according to a RTV cut point of 2 cc; 16.75 months for the group with RTV<2 cc and 14.6 months for the group RTV≥2cc [(17)]. Awad et al. again highlighted that the lower the RTV the better the prognosis, though they failed to set a cut point [(28)]. However, only a few studies have actually differentiated between resections of 100% and resections of <100%, with the result that the heterogeneity in the literature about what is considered complete resection is almost as great as the number of articles themselves

[2,3,16,17,26-32]. Nevertheless, all the studies defend a common hypothesis: the greater the resection the better the prognosis, with complete resection being the goal [3]. In our COX regression analysis (figure 6) we show the same result: the lower RTV the greater OS.

Pesudo Martinez et at. achieved 52% complete resection [36], Orringer et al. 17.4% [2], Grabowski et al. 28% [17], and Li YM et al. 71% [32]. A meta-analysis by Li XZ et al found a percentage of complete resection of 32% [29]. Our percentage of complete resection (RTV=0 cc) was almost 59%. This figure is similar, or even better than the mean in the literature. In addition, the literature shows that complete resection significantly improves the prognosis. In our study, 26.4 months for complete resections versus 12.64 months for partial resections, p=0.002 (Table 5). The study most influencing the management of glioblastoma was that of Stupp et al. These authors demonstrated that radiotherapy plus temozolomide increased survival by 2.5 months compared to patients just treated with radiotherapy [37]. Furthermore, complete resection also significantly prolonged PFS. In our study, 17.59 months after complete resection versus 6.02 months after partial resection, p=0.001 (Table 5). Thus, neurosurgeons must use all available measures to achieve complete resection. While some centres have all the technology to achieve this aim (navigator, 5-ALA, iMRI), this is not so in others. The use of early post-operative MRI within 72 hours of surgery is a useful tool to determine the degree of resection achieved [7,8,14] and establish a treatment plan. We might suppose that if iMRI can be used to assess surgical remnants and decide whether to continue surgery, post-operative MRI could have the same function. However, very few studies have addressed this issue. In order to justify the expense of iMRI some have mentioned that those patients with remnants on the post-operative control MRI have to undergo another operation during the same hospital admission [4,6,33-35]. However, none of these articles mentions the protocol used based on control MRI, the results obtained after these re-operations, or a comparison with iMRI-guided resections. Schucht et al published a study based on the fact that as they did not have iMRI they performed control MRI within 72 hours of surgery. If resectable tumour remnants were

visible the patient underwent early surgery. They included 208 patients, of whom just 9 (4.3%) were candidates for early re-operation. A very important limitation of this study was that no association was studied between early re-operation and patient survival [9]. The lack of this information in the literature led us to undertake this study to be able to ascertain whether it is an advisable practice, whether re-operated patients have a better prognosis and whether exposing the patient to another operation may increase the number of complications.

Our results show that early re-operations improve both OS and PFS with no increase in the number of complications compared with the group of patients who did not undergo repeat surgery (Table 4 and 6). The initial rate of complete resection (RTV=0 cc) was 41.4% (24 patients) with partial resections (RTV>0 cc) in 58.6% (34 patients). Of these 34 patients, 11 underwent re-operation, and the other 23 were discharged with the tumour remnants. As seen in Figure 2, Figure 3 and Table 4, the group of patients that underwent early re-operation experienced greater OS and PFS than the group that did not (p=0.013 and p=0.012, respectively). All those who underwent re-operation had a complete resection except for one patient who had RTV <2 cc. Thus, of the 58 patients in the study, complete resection was achieved in 58.62% (34 patients) of the cases and partial resection in 41.37% (24 patients).

Undertaking a second operation during the same admission could imply an increase in the number of complications, as well as a worse functional status of the patient on discharge. However, as we see in Table 6, there were no significant differences between the two groups. We might think that those patients who experienced early complications after the first operation or who had tumours at eloquent sites or adjacent to these sites did not undergo re-operation in order not to worsen their quality of life. However, comparison between the group of patients who underwent re-operation and those who did not only showed significant relationship between the Karnofsky scale after first surgery (p=0.004). Patients with KPS=80 did not receive new re-operation. For the rest of variables both groups were homogeneous:

age, site, eloquence, histology and post-surgical tumour volume did not show statistically significant differences. In addition, the patients who underwent re-operation had no increase in complications or worse functional prognosis. Similar results have been noted by others. In 2016, Sawaya et al. published a study involving some 400 patients and found no significant association between the number of craniotomies performed on the same patient and the presence of complications [12]. Nor did Schucht et al. find a significant increase in complications in the patients who underwent re-operation [9].

Study limitations and strengths

One of the limitations of this study concerns the sample size. Most published reports include a greater number of patients. However, our sample was very homogenous and the inclusion criteria were very strict. Although the number of patients who underwent re-operation was also small (N=11), there were statistically significant important differences between these 11 patients in comparison to the group that did not undergo re-operation in both OS and PFS. Another limitation of our study is the lack of any biomarker such as MGMT. However, the adjuvant treatment is the same for all patients (STUPP protocol), regardless of genetic biomarkers.



Conclusion

Early re-operation in patients with residual tumour detected on the early post-operative MRI improved OS and PFS without increasing the number of complications as compared with the patients who did not undergo re-operation. This protocol, based on early post-surgical control MRI, could substitute the use of iMRI in those centres where this is not available.

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Captions

Figure 1. Pre and postsurgical measurement (A, C), pre and postsurgical volume (B, D) obtained with Brainlab iPlan Stereotaxy 3.0.5. This patient underwent re-operation a few days later.

Figure 2. Survival Funtions shows higher total survival at the end of follow up in the re-operation group (blue) compared to the no re-operation group (green).

Figure 3. Survival funtions shows higher progression free survival in the re-operation group (blue) compared to the no re-operation group (green).

Figure 4. Survival funtions shows higher survival in patients with complete resection (blue) compared to patients with partial resection (green).

Figure 5. Survival functions shows higher progression free survival in patients with complete ressection compared to patients with partial resection. PEndofFollowup: Progression end of follow up.



References

1. Moton S, Elbanan M, Zinn PO, Colen RR. Imaging Genomics of Glioblastoma: Biology, Biomarkers, and Breakthroughs. Top Magn Reson Imaging TMRI. junio de 2015;24(3):155-63.

2. Orringer D, Lau D, Khatri S, Zamora-Berridi GJ, Zhang K, Wu C, et al. Extent of resection in patients with glioblastoma: limiting factors, perception of resectability, and effect on survival: Clinical article. J Neurosurg. noviembre de 2012;117(5):851-9.

3. Brown TJ, Brennan MC, Li M, Church EW, Brandmeir NJ, Rakszawski KL, et al. Association of the Extent of Resection With Survival in Glioblastoma: A Systematic Review and Meta-analysis. JAMA Oncol. 1 de noviembre de 2016;2(11):1460.

4. Díez Valle R, Tejada Solis S. To what extent will 5-aminolevulinic acid change the face of malignant glioma surgery? CNS Oncol. julio de 2015;4(4):265-72.

5. Senft C, Bink A, Franz K, Vatter H, Gasser T, Seifert V. Intraoperative MRI guidance and extent of resection in glioma surgery: a randomised, controlled trial. Lancet Oncol. octubre de 2011;12(11):997-1003.

6. Kubben PL, ter Meulen KJ, Schijns OE, ter Laak-Poort MP, van Overbeeke JJ, Santbrink H van. Intraoperative MRI-guided resection of glioblastoma multiforme: a systematic review. Lancet Oncol. octubre de 2011;12(11):1062-70.

7. Smets T, Lawson TM, Grandin C, Jankovski A, Raftopoulos C. Immediate post-operative MRI suggestive of the site and timing of glioblastoma recurrence after gross total resection: a retrospective longitudinal preliminary study. Eur Radiol. junio de 2013;23(6):1467-77.

8. Ekinci G, Akpınar İN, Baltacıoğlu F, Erzen C, Kılıç T, Elmacı İ, et al. Early-postoperative magnetic resonance imaging in glial tumors: prediction of tumor regrowth and recurrence. Eur J Radiol. febrero de 2003;45(2):99-107.

9. Schucht P, Murek M, Jilch A, Seidel K, Hewer E, Wiest R, et al. Early Re-Do Surgery for Glioblastoma Is a Feasible and Safe Strategy to Achieve Complete Resection of Enhancing Tumor. Elder JB, editor. PLoS ONE. 13 de noviembre de 2013;8(11):e79846.

10. Louis DN, Perry A, Reifenberger G, von Deimling A, Figarella-Branger D, Cavenee WK, et al. The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. Acta Neuropathol (Berl). junio de 2016;131(6):803-20.

11. Lacroix M, Abi-Said D, Fourney DR, Gokaslan ZL, Shi W, DeMonte F, et al. A multivariate analysis of 416 patients with glioblastoma multiforme: prognosis, extent of resection, and survival. J Neurosurg. agosto de 2001;95(2):190-8.

12. Sawaya R, Hammoud M, Schoppa D, Hess KR, Wu SZ, Shi WM, et al. Neurosurgical outcomes in a modern series of 400 craniotomies for treatment of parenchymal tumors. Neurosurgery. mayo de 1998;42(5):1044-55; discussion 1055-1056.

13. Hirai T, Murakami R, Nakamura H, Kitajima M, Fukuoka H, Sasao A, et al. Prognostic value of perfusion MR imaging of high-grade astrocytomas: long-term follow-up study. AJNR Am J Neuroradiol. septiembre de 2008;29(8):1505-10.

14. Majós C, Cos M, Castañer S, Gil M, Plans G, Lucas A, et al. Early post-operative magnetic resonance imaging in glioblastoma: correlation among radiological findings and overall survival in 60 patients. Eur Radiol. abril de 2016;26(4):1048-55.

15. Wen PY, Macdonald DR, Reardon DA, Cloughesy TF, Sorensen AG, Galanis E, et al. Updated Response Assessment Criteria for High-Grade Gliomas: Response Assessment in Neuro-Oncology Working Group. J Clin Oncol. 10 de abril de 2010;28(11):1963-72.

16. Chaichana KL, Jusue-Torres I, Navarro-Ramirez R, Raza SM, Pascual-Gallego M, Ibrahim A, et al. Establishing percent resection and residual volume thresholds affecting survival and

recurrence for patients with newly diagnosed intracranial glioblastoma. Neuro-Oncol. enero de 2014;16(1):113-22.

17. Grabowski MM, Recinos PF, Nowacki AS, Schroeder JL, Angelov L, Barnett GH, et al. Residual tumor volume versus extent of resection: predictors of survival after surgery for glioblastoma: Clinical article. J Neurosurg. noviembre de 2014;121(5):1115-23.

18. Phillips HS, Kharbanda S, Chen R, Forrest WF, Soriano RH, Wu TD, et al. Molecular subclasses of high-grade glioma predict prognosis, delineate a pattern of disease progression, and resemble stages in neurogenesis. Cancer Cell. marzo de 2006;9(3):157-73.

19. Yoon S-J, Shim J-K, Chang JH, Moon JH, Roh T-H, Sung KS, et al. Tumor Mesenchymal Stem-Like Cell as a Prognostic Marker in Primary Glioblastoma. Stem Cells Int. 2016;2016:6756983.

20. Karsy M, Neil JA, Guan J, Mahan MA, Mark MA, Colman H, et al. A practical review of prognostic correlations of molecular biomarkers in glioblastoma. Neurosurg Focus. marzo de 2015;38(3):E4.

21. Siegal T. Clinical impact of molecular biomarkers in gliomas. J Clin Neurosci. marzo de 2015;22(3):437-44.

22. Ohno M, Narita Y, Miyakita Y, Matsushita Y, Arita H, Yonezawa M, et al. Glioblastomas with *IDH1/2* mutations have a short clinical history and have a favorable clinical outcome. Jpn J Clin Oncol. enero de 2016;46(1):31-9.

23. Beiko J, Suki D, Hess KR, Fox BD, Cheung V, Cabral M, et al. IDH1 mutant malignant astrocytomas are more amenable to surgical resection and have a survival benefit associated with maximal surgical resection. Neuro-Oncol. enero de 2014;16(1):81-91.

24. Weller M, Butowski N, Tran DD, Recht LD, Lim M, Hirte H, et al. Rindopepimut with temozolomide for patients with newly diagnosed, EGFRvIII-expressing glioblastoma (ACT IV): a randomised, double-blind, international phase 3 trial. Lancet Oncol. octubre de 2017;18(10):1373-85.

25. Lacroix M, Abi-Said D, Fourney DR, Gokaslan ZL, Shi W, DeMonte F, et al. A multivariate analysis of 416 patients with glioblastoma multiforme: prognosis, extent of resection, and survival. J Neurosurg. agosto de 2001;95(2):190-8.

26. Sanai N, Polley M-Y, McDermott MW, Parsa AT, Berger MS. An extent of resection threshold for newly diagnosed glioblastomas: Clinical article. J Neurosurg. julio de 2011;115(1):3-8.

27. Chaichana KL, Cabrera-Aldana EE, Jusue-Torres I, Wijesekera O, Olivi A, Rahman M, et al. When Gross Total Resection of a Glioblastoma Is Possible, How Much Resection Should Be Achieved? World Neurosurg. julio de 2014;82(1-2):e257-65.

28. Awad A-W, Karsy M, Sanai N, Spetzler R, Zhang Y, Xu Y, et al. Impact of removed tumor volume and location on patient outcome in glioblastoma. J Neurooncol. octubre de 2017;135(1):161-71.

29. Li X-Z, Li Y-B, Cao Y, Li P-L, Liang B, Sun J-D, et al. Prognostic implications of resection extent for patients with glioblastoma multiforme: a meta-analysis. J Neurosurg Sci. diciembre de 2017;61(6):631-9.

30. Almeida JP, Chaichana KL, Rincon-Torroella J, Quinones-Hinojosa A. The Value of Extent of Resection of Glioblastomas: Clinical Evidence and Current Approach. Curr Neurol Neurosci Rep [Internet]. febrero de 2015 [citado 28 de mayo de 2018];15(2). Disponible en: http://link.springer.com/10.1007/s11910-014-0517-x

31. Eyüpoglu IY, Hore N, Merkel A, Buslei R, Buchfelder M, Savaskan N. Supra-complete surgery *via* dual intraoperative visualization approach (DiVA) prolongs patient survival in glioblastoma. Oncotarget [Internet]. 3 de mayo de 2016 [citado 28 de mayo de 2018];7(18). Disponible en: http://www.oncotarget.com/fulltext/8367

32. Li YM, Suki D, Hess K, Sawaya R. The influence of maximum safe resection of glioblastoma on survival in 1229 patients: Can we do better than gross-total resection? J Neurosurg. abril de 2016;124(4):977-88.

33. Familiari P, Frati A, Pesce A, Miscusi M, Cimatti M, Raco A. The Real impact of Intraoperative MRI in newly diagnosed Glioblastoma Multiforme Resection: an Observational Analytic Cohort study from a Single Surgeon Experience. World Neurosurg [Internet]. enero de 2018 [citado 12 de junio de 2018]; Disponible en: http://linkinghub.elsevier.com/retrieve/pii/S1878875018300317

34. García-Baizán A, Tomás-Biosca A, Bartolomé Leal P, Domínguez PD, García de Eulate Ruiz R, Tejada S, et al. Resonancia magnética intraoperatoria de 3 teslas: Nuestra experiencia en patología tumoral. Radiología. marzo de 2018;60(2):136-42.

35. Napolitano M, Vaz G, Lawson TM, Docquier M-A, van Maanen A, Duprez T, et al. Glioblastoma surgery with and without intraoperative MRI at 3.0T. Neurochirurgie. agosto de 2014;60(4):143-50.

36. Pesudo Martínez JV, González-Darder JM, Felíu Tatay R, Gil Salú JL, Belloch Ugarte V, Vera Román J. Valoración del grado de resección de los gliomas supratentoriales de alto grado con resonancia magnética postoperatoria precoz. Neurocirugía. 2001;12(1):43-50.

37. Stupp R, Hegi ME, Mason WP, Fisher B, Belanger K, Hau P, et al. Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in

glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. 2009;10:8.

Table 1. Descriptive analysis, all the cases. Pre-operative variables.

| Variable | N (%) Mean / Mode |
|---|---|
| Age | 57.53 (23-81) / 51 years |
| Sex | |
| -Male | 32 (55.2%) |
| -Female | 26 (44.8%) |
| Presenting symptom | |
| -Headache | 18 (31%) |
| -Language alteration | 10 (17.2%) |
| -Crisis | 11 (19%) |
| -Behaviour alteration | 7 (12.1%) |
| -Hemiparesis | 3 (5.2%) |
| Site | |
| -Frontal | 14 (24.1%) |
| -Parietal | 12 (20.7%) |
| -Temporal | 25 (43.1%) |
| -Occipital | 7 (12.1%) |
| Hemisphere | |
| -Right | 27 (46.6%) |
| -Left | 31 (53.4%) |
| Eloquence | |
| -Grade I (noneloquent) | 25 (43.1%) |
| -Grade II (adjacent to eloquent area) | 29 (50%) |
| -Grade III (eloquent) | 4 (6.9%) |
| Mass effect | |
| 0 cm midline shift | 25 (43.1%) |
| <0.5 cm midline shift | 15 (25.9%) |
| 0.5-1 cm midline shift | 13 (22.4%) |
| >1 cm midline shift | 5 (8.6%) |
| Oedema | |
| - No oedema | 4 (7%) |
| - Oedema < contrast-enhancing tumour volume | 25 (43.9%) |
| - Oedema = contrast-enhancing tumour volume | 13 (22.8%) |
| - Oedema > contrast-enhancing tumour volume | 15 (26.3%) |
| Intensity of the tumour contrast | |
| -Low-intermediate uptake | 2 (3.4%) |
| -Intermediate-high uptake | 29 (50%) |
| -High uptake | 27 (46.6%) |
| Tumour perfusion values | 6.12 (2.25-15) / 5 |
| Mean pre-surgical tumour volume | 39.85 cc (1.2-182.5) |

Table 2. Descriptive analysis, all the cases. Post-operative variables.

| Variable | N (%) or Mean / Mode |
|---|---|
| Biopsy | |
| -IDH wild type | 41 (70.7%) |
| -IDH mutant | 1 (1.7%) |
| -IDH NOS | 16 (27.6%) |
| Early complications | 12 (23%) |
| -Transient hemiparesis | 5 (9.6%) |
| -Language alteration | 4 (7.7%) |
| -Infection | 1 (1.9%) |
| -Hemianopia | 1 (1.9%) |
| -Medical complication | 1 (1.9%) |
| Late complications | 7 (13.4%) |
| -Infection | 3 (5.8) |
| -Hydrocephalus | 2 (3.8%) |
| -Medical complication | 2 (3.8%) |
| Adjuvant treatment | |
| -STUPP | 52 (91.2%) |
| -Nothing | 5 (8.8%) |
| Start of adjuvant treatment | 8.19 (3-20) weeks / 6 weeks |
| Functional status | |
| -KPS on diagnosis | 92.12 (70-100) /100 |
| -KPS on discharge | 93.4 (60-100) /100 |
| -KPS on recurrence | 86.43 (30-100) /100 |
| Time to dependence | |
| -Partial | 12.41 (0-39) months |
| -Total | 14.5 (0-44) months |
| Outcome | |
| -Overall survival | 20.92 (2-69) months |
| -Progression free survival | 13.49 (0.5-69) months |

Table 3. Residual tumour volume pre and post early re-operation.

| | Variable | N (%) Mean / Mode |
|---|---|---|
| Results of first operation | Complete resection | 24 (41.4%) |
| | Partial resection | 34 (58.6%) |
| | Mean residual volume | 2 cc (0-16.2 cc) / 0 cc |
| Management of tumour remnants | Early re-operation | 11 (32.35%) |
| | No early re-operation | 23 (67.64%) |
| Final result on discharge (includes patients with and without re-operation) | Complete resection | 34 (58.62%) |
| | Partial resection: discharge with remnants | 24 (41.37%) |
| | Mean residual volume on discharge | 1.65 cc (0-16.2 cc) / 0 cc |
| | Residual volume on discharge | |
| | 0 cc | 34 (57.7%) |
| | 0.1-2 cc | 14 (25%) |
| | >2 cc | 10 (17.3%) |

Table 4. Outcome comparison between re-operation and no re-operation.

| | | Mean (St. Error) | Median (St. Error) | P |
|---|---|---|---|---|
| Overall survival | Early re-operation | 30.3 months (7.16) | 21 months (1.45) | 0.013 |
| | No early re-operation | 12.7 months (1.92) | 10 months (1.49) | |
| | Not necessary | 23.21 months (3.44) | 14 months (7.3) | |
| PFS | Early re-operation | 16.6 months (5.7) | 12 months (4.7) | 0.012 |
| | No early re-operation | 6.75 months (1.9) | 4 months (0.36) | |
| | Not necessary | 15.84 months (2.94) | 10 months (4.54) | |

PFS: progression free survival.Re-op: re-operation. Not necessary:complete resection at first surgery

Table 5. Overall survival and progression free survival related to complete or partial resection, all the cases.

| | | Mean (St. Error) | 95% CI | Median (St. Error) | 95% CI | p |
|---|---|---|---|---|---|---|
| Overall survival | Complete resection | 26.4 months (3.62) | 19.3- 33.5 | 21 months (2.057) | 16.95-25 | 0.002 |
| | Partial resection | 12.64 months (1.84) | 9.02-16.26 | 10 months (1.25) | 7.6-12.4 | |
| PFS | Complete resection | 17.59 months (3.49) | 10.75-24.4 | 12 months (3.82) | 4.05-19.4 | 0.001 |
| | Partial resection | 6.708 months (1.79) | 3.18-10.23 | 4 months (0.38) | 3.25-4.74 | |

PFS: progression free survival.

Table 5. Comparison between early surgery and non-early surgery.

| Variable | Early re-intervetion | No early re-intervention | p |
|---|---|---|---|
| Sex | | | |
| -Male | 6 (31.6) | 13 (68.4%) | 0.914 |
| -Female | 5 (33.3%) | 15 (66.7%) | |
| Age | | | |
| ≤45 | 2 (50%) | 2 (50%) | |
| 46-64 | 7 (35%) | 13 (65%) | 0.54 |
| ≥65 | 2 (20%) | 8 (80%) | |
| Hemiphere | | | |
| -Right | 6 (37.5%) | 10 (62.5%) | 0.545 |
| -Left | 5 (27.8%) | 13 (72.2%) | |
| Eloquence | | | |
| -Grade I (noneloquent) | 6 (54.5%) | 5 (45.5%) | |
| -Grade II (near eloquent) | 4 (21.1%) | 15 (78.9%) | 0.159 |
| -Grade III (eloquent) | 1 (25%) | 3 (75%) | |
| Early complication | | | |
| -Yes | 1 (11%) | 8 (89%) | 0.253 |
| -No | 10 (40%) | 15 (60%) | |
| Late complication | | | |
| -Yes | 1 (25%) | 3 (75%) | 0.316 |
| -No | 10 (33%) | 20 (67%) | |
| KPS post 1º surgery | | | |
| 80 | 0 (0%) | 4 (100%) | |
| 90 | 1 (7.7%) | 12 (92.3%) | 0.004 |
| 100 | 10 (58.8%) | 7 (41.2%) | |
| IDH | | | |
| Wild type | 8 (32%) | 17 (68%) | 0.942 |
| NOS | 3 (33.3%) | 6 (66.6%) | |
| RTV post 1º surgery | 3.65cc | 3.85cc | 0.920 |

Figure 1. Pre and postsurgical measurement (A, C), pre and postsurgical volume (B, D) obtained with Brainlab iPlan Stereotaxy 3.0.5. Initial MRI (E), control MRI with residual volume (F). This patient underwent re-operation a few days later. Control MRI with complete resection (G).

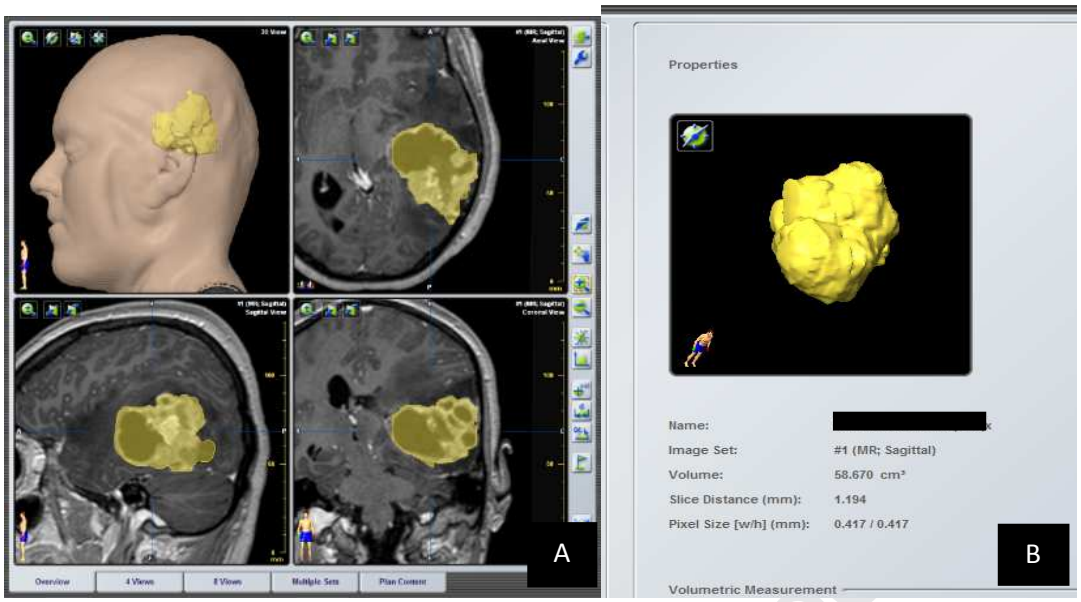
Figure 2. Survival Funtions shows higher total survival at the end of follow up in the re-operation group (blue) compared to the no re-operation group (green).

Figure 3. Survival funtions shows higher progression free survival in the re-operation group (blue) compared to the no re-operation group (green).

Figure 4. Survival funtions shows higher survival in patients with complete resection (blue) compared to patients with partial resection (green).

Figure 5. Survival functions shows higher progression free survival in patients with complete ressection compared to patients with partial resection. PEndofFollowup: Progression end of follow up.

Figure 6. COX regression residual volumen and survival. The graphic show a clear relation between residual volumen and survival. The lower the residual volumen the greater the survival.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Name:
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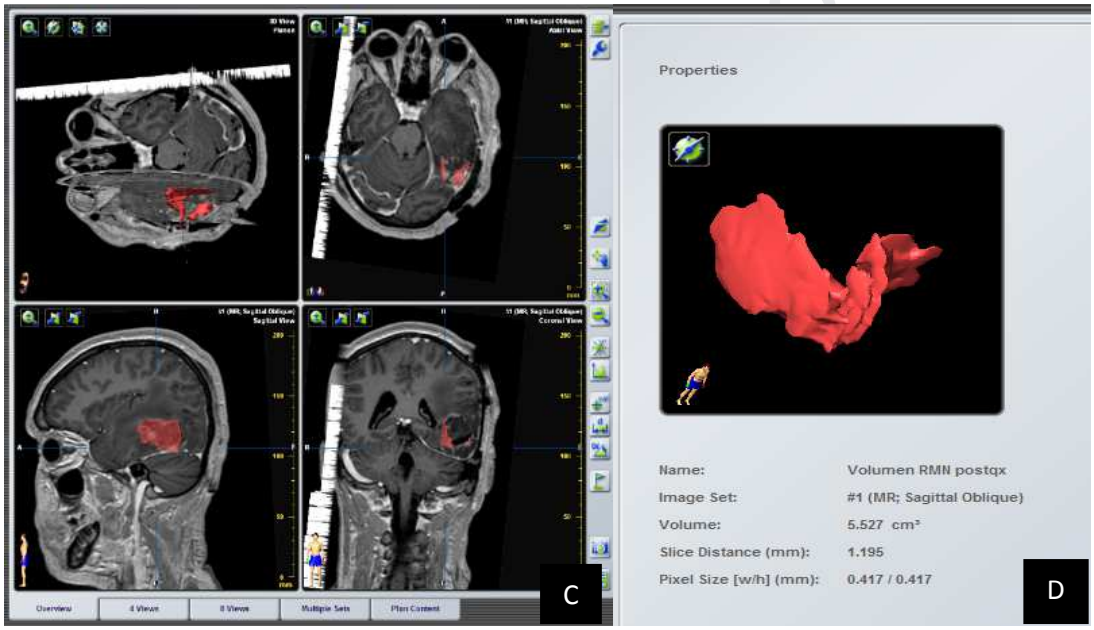
Pixel Size [w/h] (mm): 0.417 / 0.417
Volumetric Measurement
B


C
Properties
Name: Volumen RMN postqx
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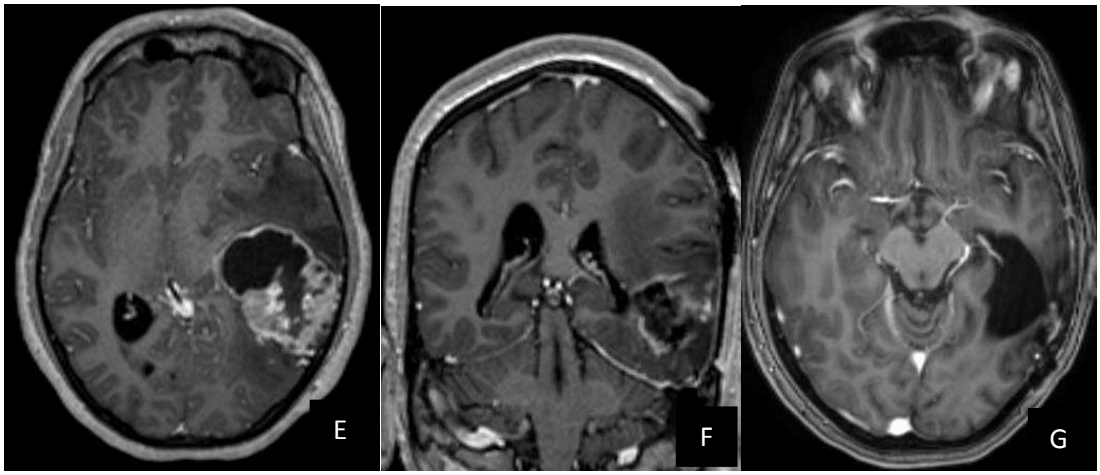
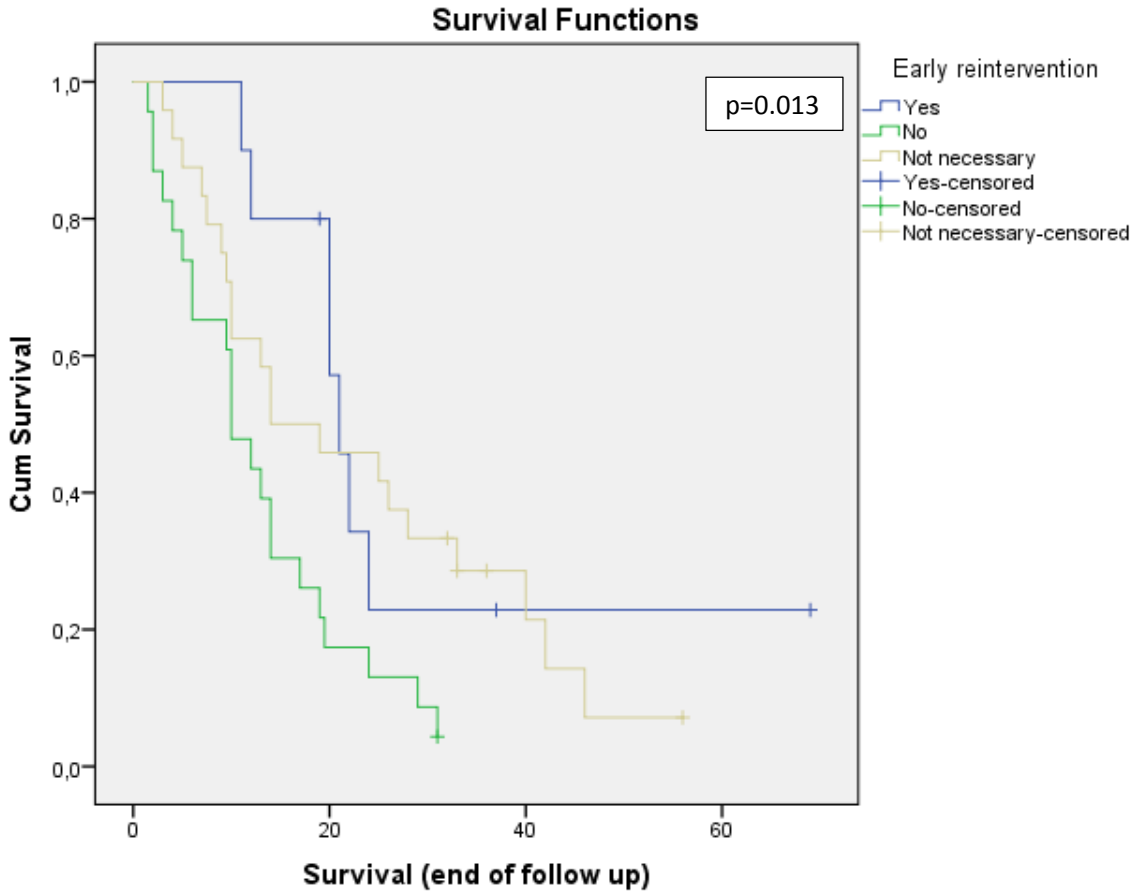
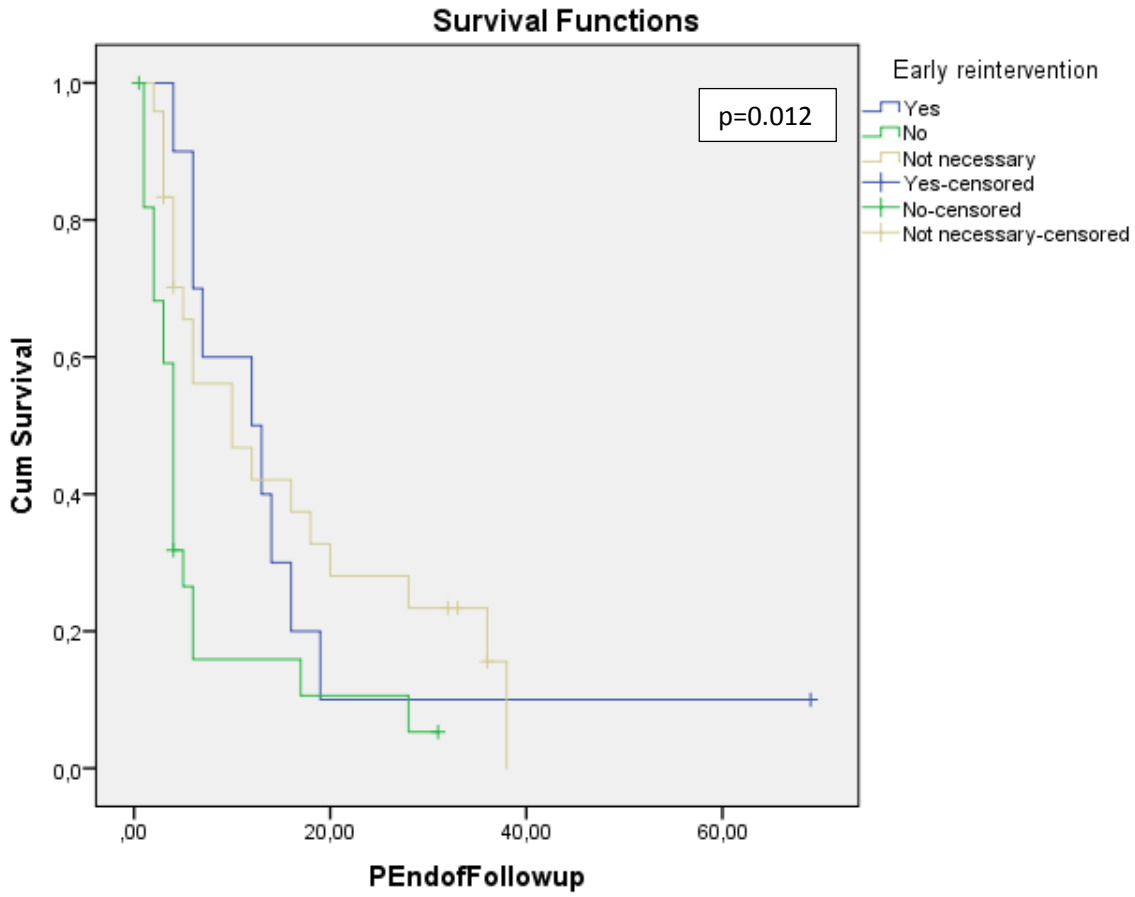
Volume: 5.527 cm³
Slice Distance (mm): 1.195
Pixel Size [w/h] (mm): 0.417 / 0.417
D


E
F
G


Survival Functions
p=0.013
Early reintervention
Yes
No
Not necessary
Yes-censored
No-censored
Not necessary-censored
Cum Survival
1,0
0,8
0,6
0,4
0,2
0,0
0
20
40
60
Survival (end of follow up)


Survival Functions
p=0.012
Early reintervention
Yes
No
Not necessary
Yes-censored
No-censored
Not necessary-censored
Cum Survival
1,0
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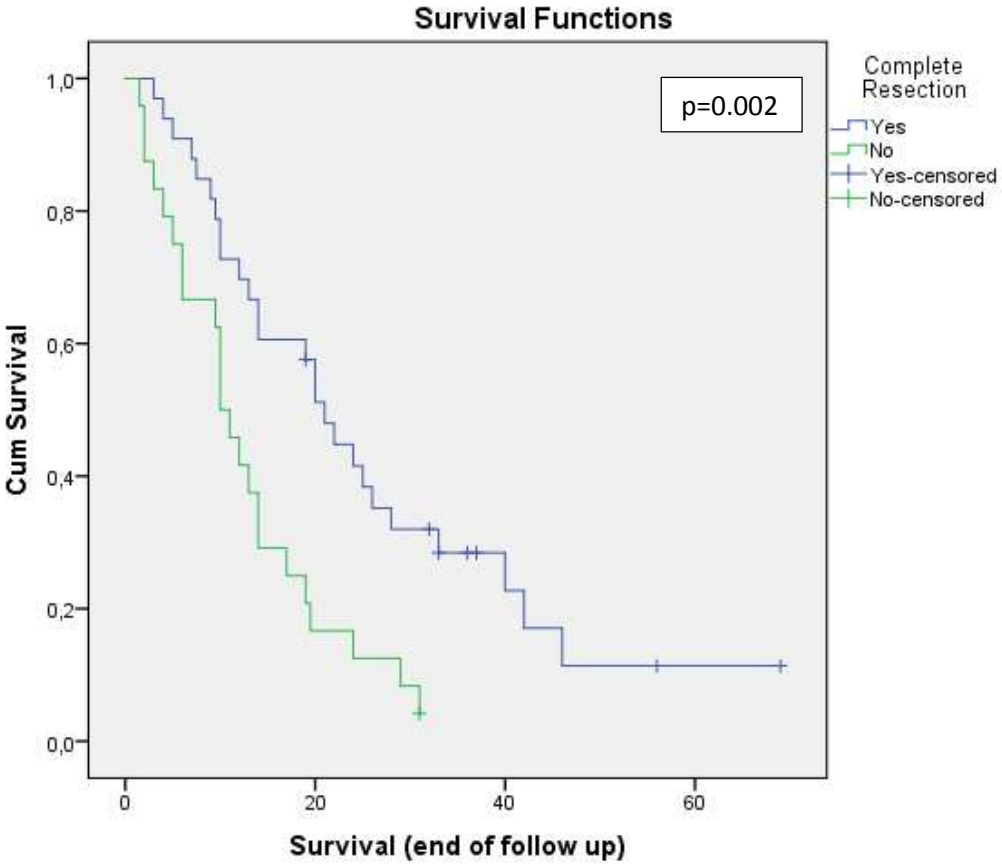
0,6
0,4
0,2
0,0
,00
20,00
40,00
60,00
PEndofFollowup


Survival Functions
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Complete Resection
Yes
No
Yes-censored
No-censored
Cum Survival
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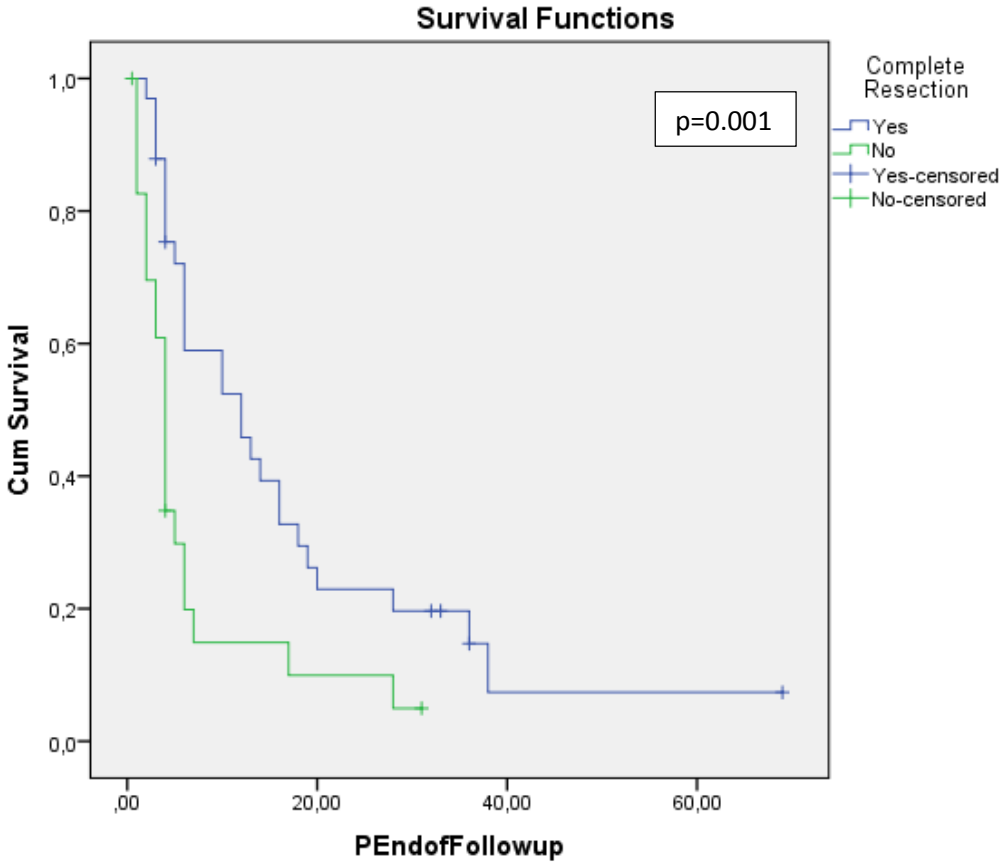
0,6
0,4
0,2
0,0
0
20
40
60
Survival (end of follow up)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Complete Resection
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Yes-censored
No-censored
Cum Survival
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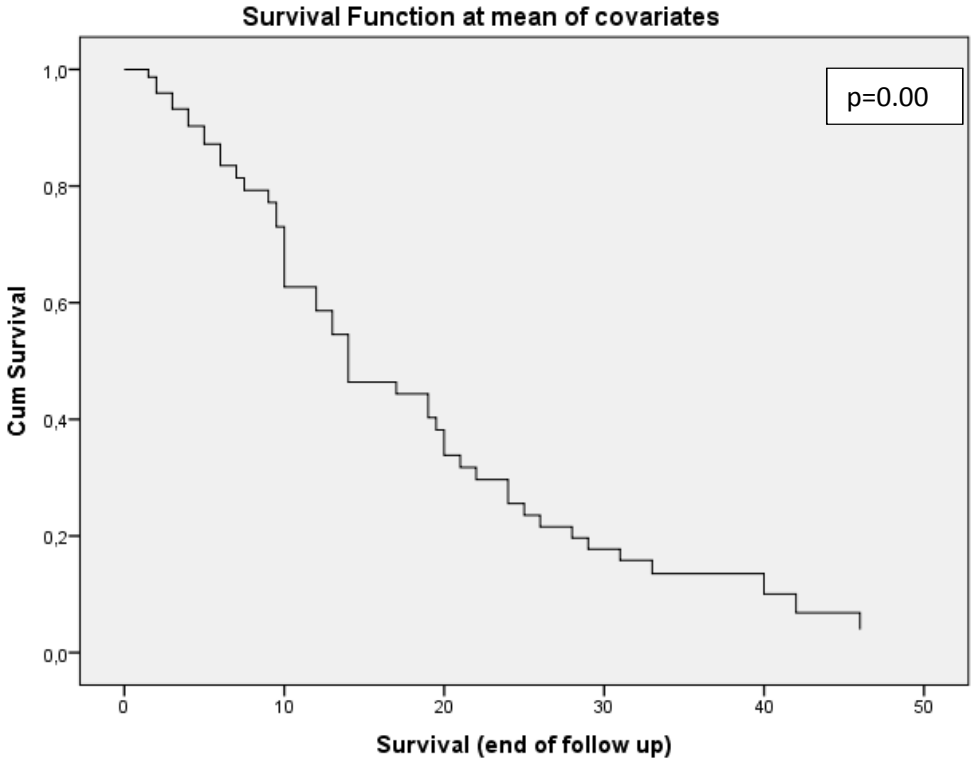
,00
20,00
40,00
60,00
PEndofFollowup



## Highlights

Complete resection in glioblastoma improve the prognosis of patients.

Some patients have residual tumour volumen after first surgery.

Early control MRI can shows the residual tumour.

Patients with residual tumour can be re-operated as soon as posible.

When there is residual tumour, early-reoperation improve prognosis compared with patients without re-operation.

## Abbreviation list

iMRI: intraoperative magnetic resonance imaging.

KPS: Karnofsky scale

MRI: magnetic resonance imaging.

OS: overall survival.

PFS: progression-free survival.

rCBV: relative cerebral blood volume.

Re-op: re-operation

Credit Author Statement.

Dra. Troya-Castilla: Conceptualization, data curation, investigation, methodology, data analysys, writing, visualization.

Dr. Kaen: Conceptualization, methodology, review.

Dr. Márquez-Rivas: Conceptualization, methodology, review.

Dr. Infante Cossio: review and supervisión

Professor Ruis: data analysis.

Dr. Narros: methodology and review.

Dra. Pombo: data curation, visualization.

Dra. Cancela: review.

Dr. Segura: visualization and review

Dr. Arráez: review

**Declaration of interests**

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: