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EFFICACY OF OPERATIVE ULTRASONOGRAPHY PLUS NEURONAVIGATION FOR BRAIN GLIOMA SURGERY: 2 – YEAR SINGLE CENTER EXPERIENCE IN A DEVELOPING COUNTRY

EFICACIA DE LA ECOGRAFÍA OPERATORIA MÁS NEURONAVEGACIÓN PARA LA CIRUGÍA DE GLIOMA CEREBRAL: EXPERIENCIA DE 2 AÑOS EN UN SOLO CENTRO EN UN PAÍS EN DESARROLLO

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Efficacy of Operative Ultrasonography Plus Neuronavigation for Brain Glioma Surgery: 2 – Year Single Center Experience in a Developing Country

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Efficacy of Operative Ultrasonography Plus Neuronavigation for Brain Glioma Surgery: 2 – Year Single Center Experience in a Developing Country

ABSTRACT

Background: preoperative MRI data has been the gold standard for the diagnosis and therapy of malignant gliomas for decades, and operative ultrasonography for the management of patients with neurological pathologies that require surgical treatment has been also used for many years as it provides additional image guidance for surgical procedure to neuronavigation techniques. The main objective of this study is to find out if the use of operative ultrasonography in glioma surgery could give greater benefit in the total resection of brain gliomas and how improvement influences the degree of neoplastic resection on the survival of patients. Methods: prospective case-control study that was performed at the ISSEMyM Licenciado Arturo Montiel Rojas Medical Center, of patients with a histopathological diagnosis of cerebral glioma treated by the neurosurgery service in the period between January 2018 and December 2020. Results: Thirty - two patients were included, with 13 patients (40.6%) with grade IV astrocytoma. Operative USG + NNV was used in 17 patients and a subtotal or total resection was achieved in 75% of the patients, with a significantly lower postoperative volumetry in patients operated on by NNV + USG (5.6mm3 $\pm$ 2.5), compared to NNV alone (8mm3 $\pm$ 2.8) However, these results did not affect tumor-free time, which was comparable between both groups. Conclusions: Surgical treatment of brain gliomas with USG + NNV has a good degree of tumor resection compared to those treated with NNV only, but the main factor affecting survival is the hystophatological grade of the tumor.

***Keywords**:* brain glioma, operative image, ultrasound

Eficacia de la Ecografía Operatoria más Neuronavegación para la Cirugía de Glioma Cerebral: Experiencia De 2 Años en un solo Centro en un País en Desarrollo

RESUMEN

Antecedentes: los datos preoperatorios de resonancia magnética han sido el patrón oro para el diagnóstico y tratamiento de los gliomas malignos durante décadas, y la ultrasonografía operatoria para el manejo de pacientes con patologías neurológicas que requieren tratamiento quirúrgico también se ha utilizado durante muchos años, ya que proporciona una guía de imagen para el procedimiento quirúrgico adicional a las técnicas de neuronavegación. El objetivo principal de este estudio es averiguar si el uso de la ultrasonografía operatoria en la cirugía del glioma puede aportar un mayor beneficio en la resección total de los gliomas cerebrales y cómo influye la mejora del grado de resección neoplásica en la supervivencia de los pacientes. Métodos: estudio prospectivo de casos y controles que se realizó en el Centro Médico ISSEMyM Licenciado Arturo Montiel Rojas, de pacientes con diagnóstico histopatológico de glioma cerebral tratados por el servicio de neurocirugía en el periodo comprendido entre enero de 2018 y diciembre de 2020. Resultados: Se incluyeron 32 pacientes, con 13 pacientes (40,6%) con astrocitoma grado IV. Se utilizó USG + NNV operatoria en 17 pacientes y se consiguió una resección subtotal o total en el 75% de los pacientes, con una volumetría postoperatoria significativamente menor en los pacientes intervenidos mediante NNV + USG (5,6mm3 + 2,5), en comparación con la NNV sola (8mm3 + 2,8) Sin embargo, estos resultados no afectaron al tiempo libre de tumor, que fue comparable entre ambos grupos. Conclusiones: El tratamiento quirúrgico de los gliomas cerebrales con USG + NNV tiene un buen grado de resección tumoral en comparación con los tratados sólo con NNV, pero el principal factor que afecta a la supervivencia es el grado histofatológico del tumor.

Palabras clave: glioma cerebral, imagen operatoria, ecografía

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INTRODUCTION

Preoperative MRI data has been the gold standard for the diagnosis and therapy of malignant gliomas for decades, and intraoperative MRI-guided neurosurgery navigation is limited by its complex application and time cost[1]. In the other hand, operative ultrasonography (USG) for the management of patients with neurological pathologies that require surgical treatment has been also used for many years; however, its use is not as popular as in other surgical specialties due to its limitations that presents[2]. One of them is the bone covering that the brain has, formed by the cranial vault, so that this makes free access to brain exploration with ultrasound difficult. Another important point that limits ultrasound is the sensitivity of the brain to pressure; however, this sensitivity to pressure can be easily controlled by the neurosurgeon at the time of scanning with the ultrasound probe[3].

In the last decade, the advance in image processing and improvements in image quality have taken ultrasonography to another level; nowadays, it can be used for surgical navigation of deep brain lesions, define tumor borders and have satisfactory limits of the extension of the lesion; it even helps us to visualize tumor remains to a certain extent[3, 4]. Extra-axial lesions such as metastases and meningiomas; and, vascular lesions such as cavernous hemangiomas show well-defined images in terms of their tumor margins. On the other hand, borderlines in gliomas with high infiltration characteristics into surrounding brain tissue cannot be adequately distinguished. Furthermore, the edema generated by the glial neoplastic lesion alters the contrast between the tumor and healthy tissue, and intraoperative ultra-sonographic images obtained from infiltrated brain tissue are difficult to interpret because the borders are very poorly defined[5].

Neuronavigation (NNV) is an operative adjuvant that allows us to perform an exact surgical planning and obtain precise anatomical points to carry out the surgery in a safer way[6]. However, the “brain shift” phenomenon that occurs when exposing the brain through craniectomy in the first instance and dural opening afterwards, causes a deferral in the location of both deep and cortical lesions. This disadvantage observed with neuronavigation could be corrected by intraoperative ultrasound, since it offers us real live images of brain tissue[6]. The main objective of this study is to find out if the use of operative ultrasonography in glioma surgery could give greater benefit in the total resection of brain gliomas and how improvement influences the degree of neoplastic resection on the survival of patients.

METHODOLOGY

This is a prospective case-control study that was performed at the ISSEMyM Licenciado Arturo Montiel Rojas Medical Center, of patients with a histopathological diagnosis of cerebral glioma treated by the neurosurgery service in the period between January 2018 and December 2020. The present study was approved by the ethics and research committee of the institution (UEeIM 144/22) and to perform the procedure, informed consent specially designed for this study, was signed by the patients, or the relatives of the patients.

Patients

Surgical cases were selected from a series of patients with neoplastic lesions and a pathological diagnosis of gliomas. Radiological and operative clinical information was collected. As well as histopathological results, postoperative complications and follow-up data from the hospital information system. The inclusion criteria were the following: 1) patients > 18 years of age with a histopathological diagnosis of gliomas according to the WHO (World Health Organization) criteria published in 2021[7]; 2) patients who have received adjunctive treatment with radiotherapy and temozolamide[8]. Exclusion criteria: 1) patients who were lost to follow-up; 2) patients who did not wish to participate in the study; 3) patients without a complete postoperative protocol; 4) patients with a Karnofsky functional scale <50; 5) patients who received previous surgical treatment, radiotherapy or chemotherapy.

The clinical evaluation was performed with a complete neurological assessment, and the Karnofsky functional scale was used both pre and postoperatively (6 months). The pre and post-operative radiological evaluation was carried out with contrasted preoperative 1.5T MRI (Brand: General Electric Healthcare; Model: Sigma Creator 1.5 T; Manufacture; Tianjin - China), the day after surgery and at the end of the surgery. Management with radiotherapy and chemotherapy. For grade evaluation, the degree of resection, pre-operative and post-operative volumetry was performed with the ABC/2[9] formula; The degree of resection was evaluated as follows: 1) biopsy, resection of less than 50% of the volumetry; 2) partial from 51 – 75%; 3) subtotal 76 – 95% and 4) total > 95%, in a post-operative MRI study the day after surgery, evaluated by both the surgical team and the hospital imaging team.

Surgical technique

Surgery was performed with the patient with an anesthesia technique using balanced general anesthesia, with coordinated sequence induction for patient airway management. Neuronavigation (Brand: Medtronic; Model: Stealthstation S8; Manufacture: United States) and intraoperative ultrasound (Brand: Sonosite; Model: M – turbo; Manufacture: United States) were used for the procedure in a conventional manner. In the patients were transoperative USG was used, the transducer was placed epidurally centered on the lesion with the support of vascular USG Doppler, and the presence of "bright" hyperechogenic borders delimited by ultrasound in contrast to brain tissue was defined as a tumor. "healthy", defined as the "dark" halo, moderately hyperechogenic and hypoechogenic (Figures 1 and 2). In addition, the anatomical relationships observed in the preoperative imaging study, such as the ventricles, when they are hypoechoic in relation to the brain parenchyma or the tumor capsule, both showing greater echogenicity. The use of vascular USG Doppler was used to determine tumor and peritumor vascularity.

Statistic analysis

The SPSS v.21.0 program (IBM, Inc, Anmonk New York, United States) was used; a value of $p<0.05$ was considered statistically significant. For numerical variables, the T-student test was performed for independent samples. For the analysis of dichotomous nominal variables and for ordinal qualitative variables, we used X2, Kruskall-Wallis, and survival analysis was performed with Kaplan-Meyer curves and the Log-Rank test.

RESULTS

During the study period, 32 patients who met the inclusion criteria were included, with a mean age of 52.5 years, with 53.1% female patients. The main clinical manifestation that occurred in patients was headache in 46.9%. The laterality of the lesions was 50% left and right. The main location of the lesions was in the frontal and temporal region in 34.4% of the patients (11 cases). The histological grade of the operated patients was: 3 patients (9.4%) with grade I astrocytoma; 11 patients (34.4%) with grade II astrocytoma; 5 patients (15.6%) with grade III astrocytoma and 13 patients (40.6%) with grade IV astrocytoma. The clinical / functional status of the patients evaluated with the pre-operative Karnofsky scale was 85.3 (+ 11), with 46.9% of the patients with a Karnofsky > 90 (Table 1).

Operative USG + NNV was used in 17 patients with a percentage of 53.1%; and only neuronavigation was used in 15 patients with 46.9%; a subtotal or total resection was achieved in 75% of the patients, with a preoperative volumetry of 32.7cm3 (+ 9.2) vs. postoperative volumetry of 6.7cm3 (+ 2.8) respectively, with a statistically significant difference (p= <0.0001). All patients received Fractionated Stereotactic Radiosurgery (FSRT) with linear accelerator (LINAC, Brand: Elekta; Model: Sinergy; Manufactured: United States), with an average dose of 43.8Gy (+ 14.7) and Temozolamide as postoperative chemotherapy treatment (Table 1).

Post-operative complications occurred in 12.5% of the patients: 2 with neurological deficit, 1 hemorrhage, 1 with CSF (cerebrospinal fluid) fistula. There was a surgical mortality of 3.1% (1 patient).

Functional status and survival

The post-operative Karnofsky was 79.3, with 28.2% of the patients with a value >90, with a statistically significant difference with respect to the preoperative state (p=0.003, (table 1). According to the WHO classification, there was no statistically significant difference in the preoperative functional status according to the Karnofsky classification, however, in the postoperative period, at 6 months of postoperative follow-up, patients with grade I and II tumors they had a statistically significant better Karnofsky compared to patients with grade III and IV lesions (Figure 3A).

The average volumetry in the postoperative period was 6.7mm3, with no statistically significant difference according to the degree of the lesions (Figure 3B). The degree of resection was statistically higher in higher-grade lesions (III and IV) than in lower-grade ones (Figure 3C). Mean tumor-free time was 17.1 months (1–48 months, Table 1), with tumor-free time not significantly significant compared to lesion grade (Figure 3D).

During follow-up, an average survival of 19.9 months (+ 15.4, Table 1) was recorded, with 19 patients dying at the end of the study. Survival was higher in patients with lower grade lesions with statistical significance compared to higher-grade lesions (Figure 3E), with mortality at the end of the study statistically higher in grade IV lesions (Figure 3F).

Intraoperative ultrasound + NNV vs NNV alone

Both groups were analyzed and paired, finding that they are statistically comparable both in demographic aspects and in histological grade. We found that the functional status at 6 months was

similar in both surgical groups (NNV + USG = 78.2 vs NNV alone = 80.6), without finding statistical significance (Figure 4A). On the other hand, we recorded a significantly lower postoperative volumetry in patients operated on by NNV + USG (5.6mm3 ± 2.5), compared to NNV alone (8mm3 ± 2.8) (Figure 4B). This result went hand by hand with a statistically significant higher degree of resection in patients operated with NNV + USG as an auxiliary compared to patients operated with NNV alone (Figure 4C). However, these results did not affect tumor-free time, which was comparable between both groups (USG + NNV = 27.2 months vs. NNV alone = 22.4 months, p= 0.8) (Figure 4D). It also did not influence final survival (USG = 23.5 months vs. 32.3 months, p= 0.22) (Figure 4E). Final mortality was also not influenced by the surgical results with both auxiliaries (USG + NNV = 70.5% vs. NNV alone = 50%, p= 0.1) (Figure 4F), the main factor influencing final survival and mortality being the degree of the resected lesion.

DISCUSSION

When we talk about ultrasound imaging we refer to the use of sound waves of a frequency above that audible to human hearing (>20kHz), to create an image with pulsed ultrasound waves, and as they travel through different tissues of varying acoustic impedance they are reflected back to the transducer that processes to generate an image[10]. Operative ultrasonography has been used for navigation and control of neoplastic resection for decades[6]. Initially, doubts were raised describing advantages and disadvantages of each of these operative adjuvants, but despite this, both intraoperative ultrasound and neuronavigation contribute to the planning, control, and resection of gliomas. Advances in technology in recent years have helped the neurosurgeon to obtain better results in terms of the degree of resection obtained in these patients, by improving contrast-enhanced MRI or CT images for NNV or the use of high-frequency USG[11, 12]. The main objective of this study was to evaluate how operative USG could improve surgical results in glioma surgery. As is well known, the extent of tumor resection of gliomas influences the survival of patients, having an impact on their survival and improving the survival of those who suffer from it.

The Norwegian Group published a retrospective study of 192 patients reported that the use of USG + NNV improved survival in glioma surgery[13]. Serra et al.[14] demostrated gross total resection un 95.5% in 22 patients with high – grade tumors. Aliasgar V. Moiyadi, et al.[4] evaluated whether USG improved

glioma resections and performed surgical management of 50 patients, with total tumor resection achieved in 51% of cases, and predicted tumor residual status in 78% of the patients. V.M. Tronnier, et al.[12] compared 3D neuronavigation using MRI with the use of USG in 136 patients, 101 with brain gliomas and 35 with other types of neoplastic pathologies (metastases and meningiomas). USG was used in 70% of patients reporting good observation of preoperative tumor margins; however, this delimitation compared to that observed in the MRI after tumor resection was observed to be deficient with difficult interpretation of the resection margins, and they concluded that NNV by intraoperative MRI had better results than USG for resection of brain gliomas[12, 15]. Woydt et al., Chacko et al. and Rygh et al. concluded that intraoperative USG can detect residual tumor with high sensitivity and improved gross total resection[16-18].

In glioma surgery it is still doubtful that the amount of tumor resection is associated with prolonged patient survival, and has been a long-term debate[15, 19]. To date, there has been a change in the literature in terms of tumor resection concepts, from gross total resection to supramaximal tumor resection[19, 20]. The degree of tumor resection directly influences the survival of tumor-free patients, and it has been documented in previous works that the higher the degree of tumor resection, the greater the survival[21, 22]. Molecular mechanisms are predictors of tumor-free and disease-free survival[23-25]; however, in our center, since we did not have molecular markers in the pathology service, the molecular classification of the operated tumors could not be performed. In addition, it is known that gliomas, whether high or low grade, despite receiving surgical treatment with total tumor resection, they all require complementary management with concomitant chemotherapy and radiotherapy, thus supporting the survival benefit of the patients under this management protocol[26].

Brain lesions have been classified according to their operative echogenecities as: 1) Hyperechogenic, such as metastasis, cavernous lesions, craniopharyngioma, hemangioma, some gliomas and acute blood; 2) Moderately hyperechogenic, as most glial tumors and edema; and 3) hypoechogenic, for example cystic lesions, necrotic part of high – grade gliomas, abscesses, bone and cronic blood[2]. USG allows the update of preoperative imaging and enables the use of functional imaging to guide surgery[10]. Based now on the use of operative USG and as seen on the viewing screen, normal brain tissue has relatively low echogenicity (hypoechoic), the opposite of easily seen hyperechogenic tumors[10]; this can be

affected by perilesional edema, by tumor infiltration into underlying brain tissue, or by the histological grade of the lesion being treated. Even, patients with tumor recurrence and those who have received cerebral radiotherapy tend to make changes in the cerebral echogenicity seen by USG, taking into consideration that radiation increases the echogenicity of the irradiated tissue[3, 11].

USG remains controversial as a tool for assesing tumor resection during operation, and it is important to define the margins of the tumor on the image; Wu DF et al.[1] found that the use of intraoperative real - time USG imaging with preoperative MRI is valuable for image - guided high grade glioma resection as it could improve tumor detection and resection control, mainly in solid component brain tumors than mainly cystic component tumors with thin walls[1]. As an intraoperative imaging modality, USG offers a versatile, cost – effective, and efficient method of imaging when compared with operative MRI[10].

To simplify the analysis of our work and find out which adjuvant was more effective in terms of tumor resection, the pre- and postoperative tumor volume measurement system was used[9]. In addition, the use of 3 degrees of resection, either this total, subtotal, partial resection and biopsy, already described in the results section, let us know that operative USG + NNV had a better percentage of efficacy for total or subtotal tumor excision compared to NNV alone. A neurosurgeon, who faces with the special situation of a glioma, whether it is primary or recurrent, may consider their use for its surgical management as it has been shown that using both in combination (NNV + USG), or intraoperative magnetic resonance in the absence of the above, would help to obtain a degree of total tumor excision[12, 27]. The special value of the use of intraoperative USG is mainly based on the fact that the images obtained are in real time and has lower costs, and is considerable appeal as an intraoperative imaging modality principally because of its availability, affordability, limited additional constraints, and ease of use. It provides additional image guidance for surgical procedure to Neuronavigation techniques[28].

There were limitations in the present work, such as the lack of adequate histopathological diagnosis, with review of slides by neuropathology to corroborate the diagnosis; also, since we did not have molecular markers in our institution, it could not be classified according to the new WHO review. The lack of access to materials such as fluorocein or 5-ALA that would have helped us to perform a supramaximal excision in the operated patients, and there was also no intraoperative magnetic resonance imaging as an adjuvant to corroborate a total excision. That is why ultrasound and

neuronavigation were the instruments that helped us with tumor resection, since they are part of the equipment that we have at our institution.

CONCLUSION

Surgical treatment of brain gliomas with USG + NNV has a good degree of tumor resection compared to those treated with NNV only, but the main factor affecting survival is the hystophatological grade of the tumor.

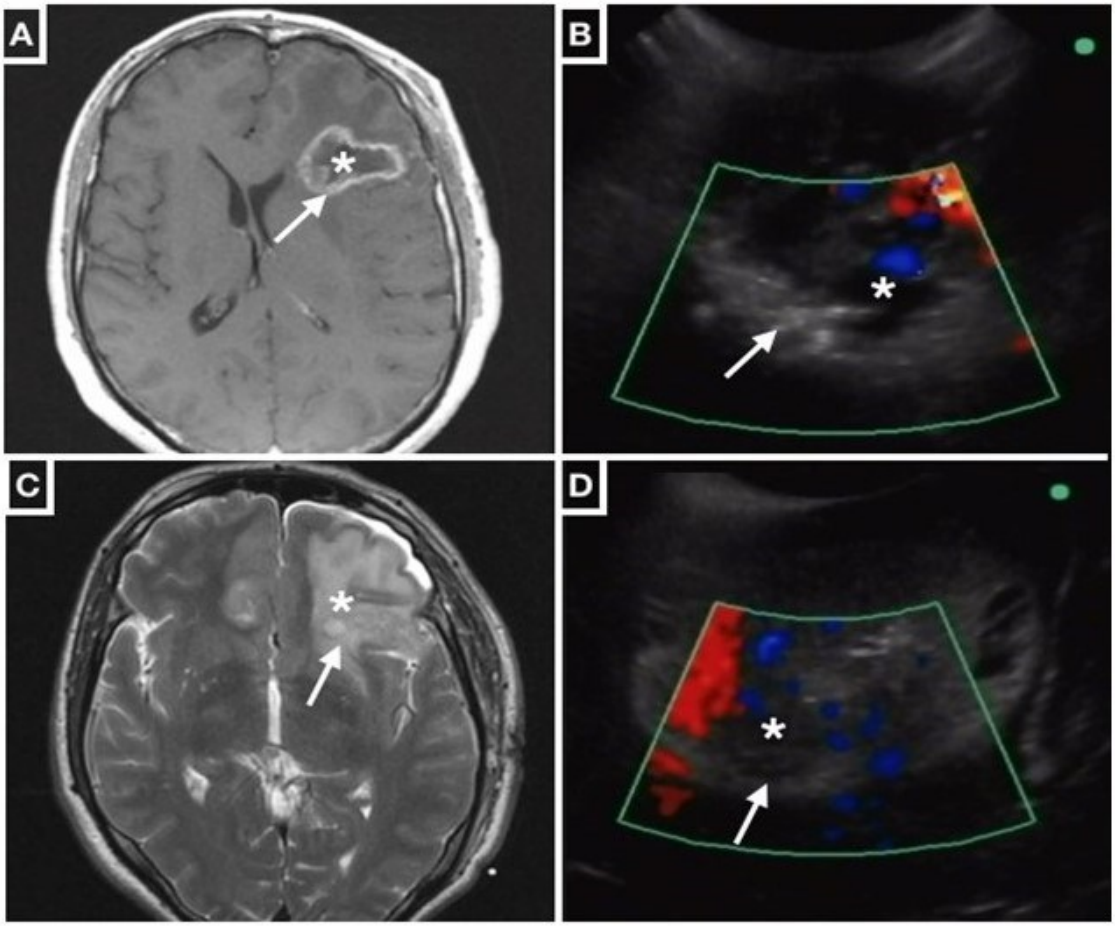

Figure 1. A) Pre - operative T1 contrast enhanced MRI of a patient with a high grade left frontal glioma with a necrotic center (white asterisc) and a ring enhancing periphery (white arrow) **B)** Operative USG at the begining of the surgical procedure with hypoechoich center (white asterisc) and hyperechoic periphery of the tumor (white arrow) **C)** Post - operative T2 MRI with residual tumor (white arrow) and edema (white asterisc) **D)** Operative USG at the end of the surgical procedure with an area of higher echogenity than the initial operative USG (white asterisc) corresponding to probable edema, and an area of hyperechogecity (white arrow) of probable residual tumor.

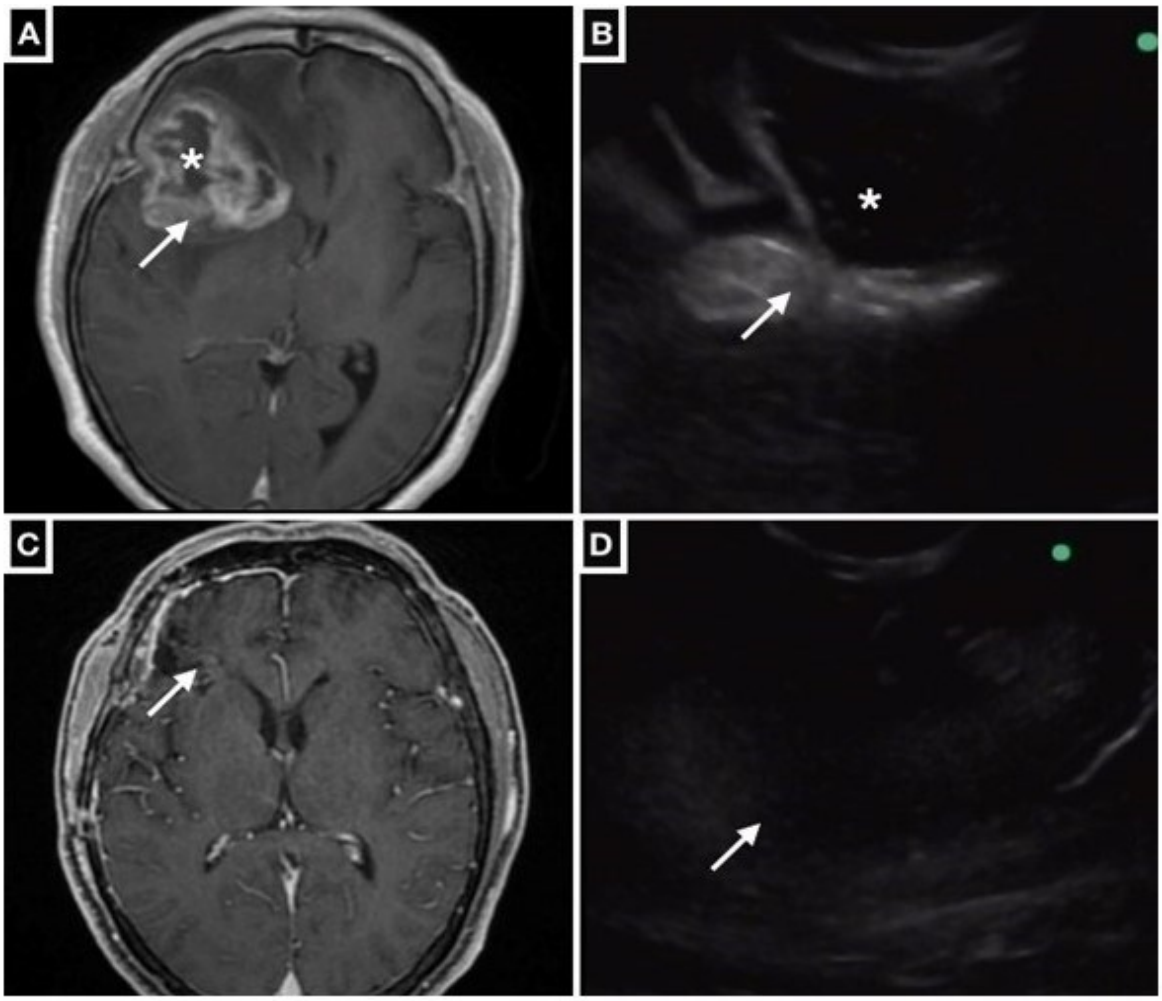

Figure 2. A) Pre - operative T1 contrast enhanced MRI of a patient with a high grade right anterior insular glioma with a necrotic center (white asterisc) and a ring enhancing periphery (white arrow) **B)** Operative USG at the begining of the surgical procedure with hypoechoich center (white asterisc) and hyperechoic periphery of the tumor (white arrow) **C)** Post - operative T2 MRI with grtoss total resection (white arrow) **D)** Operative USG at the end of the surgical procedure with an area of isoechogenity with no image of posible residual tumor (white arrow).

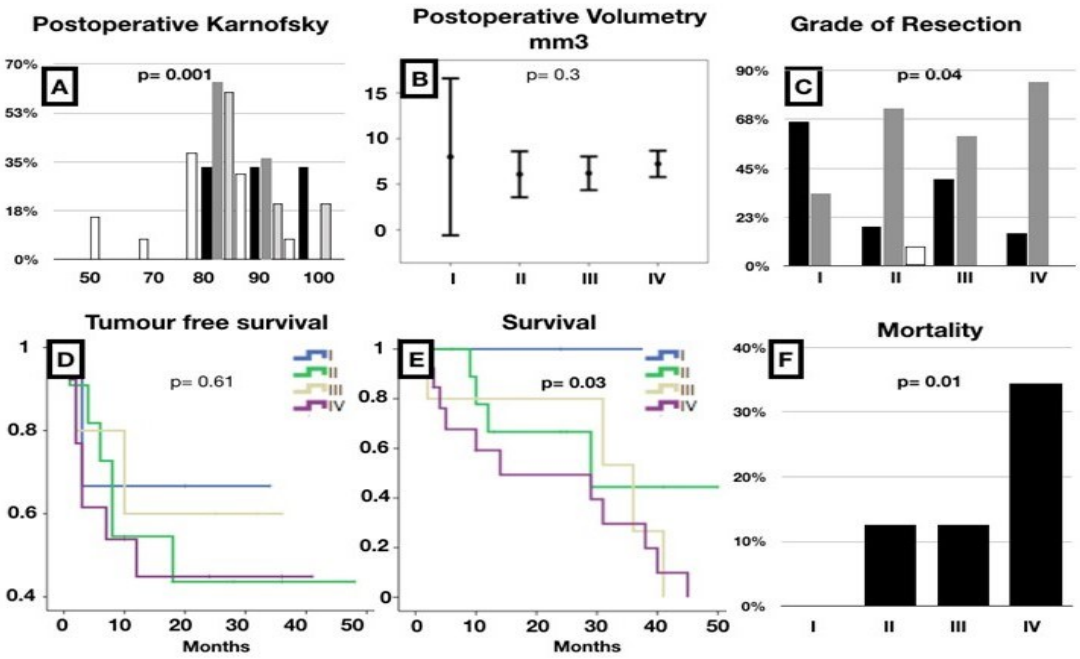

Figure 3. A) Barr chart of postoperative Karnofsky scale by hystological grade of tumour (I black, II gray, III light gray and IV white); **B)** Barr - error chart of postoperative volumetry compared by grade of tumour; **C)** Barr charts of grade of resection of tumours (partial = black, subtotal = gray, total = white); **D)** Survival chart of tumour free survival by hystological grade during follow - up. **E)** Survival chart of final survival by tumour hystoligical grade during follow - up. **F)** Barr chart of final mortality by hustological grade of tumours at the end of the study.

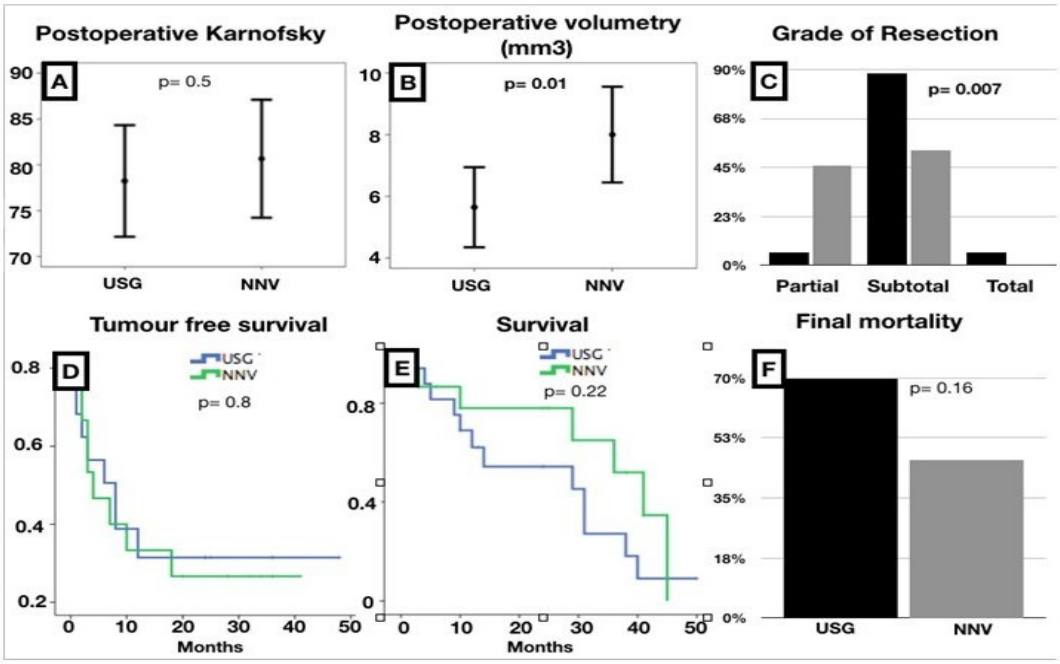

Figure 4. A) Barr - error chart of postoperative volumetry of tumours surgically treated, comparing both surgical techniques. **B)** Barr - error charts of postoperative Karnofsky of patients surgically treated comparing both techniques. **C)** Barr charts with percentage of patients that died by the end of follow - up of the study. **D)** Barr chart of grade of resection of tumours comparing both surgical techniques, USG in Black / NNV in Gray. **E)** Survival charts of the percetage of patients free of tumour during follow - up. **F)** Survival charts of the percetage of patients alive during follow - up.

Table 1.Baseline characteristics of patients and surgical outcomes

Baseline characteristics of patients				
Mean (IQ) age (years)		52.5 (21 – 81)		
Gender		Female	17 (53.1%)	
		Male	15 (46.9%)	
Symptoms		Headache	15 (46.9%)	
		Seizures	5 (15.5%)	
		Motor symptoms	6 (18.8%)	
		Cognitive symptoms	5 (15.56%)	
		Cranial hypertension	1 (3.1%)	
Side of the lesion		Right	16 (50%)	
		Left	16 (50%)	
Site of the lesion		Frontal lobe	11 (34.4%)	
		Temporal lobe	11 (34.4%)	
		Parietal lobe	8 (25%)	
		Insular lobe	1 (3.1%)	
		Basal nuclei	1 (3.1%)	
Preoperative Kamofsky (SD)	85.3 (11.06)			
		50	1 (3.1%)	
		70	2 (6.3%)	
		80	14 (43.8%)	
		90	8 (25%)	
		100	7 (21.9%)	**p= 0.003**
Postoperative Kamofsky	79.3 (11.6)			
		50	2 (6.3%)	
		60	1 (3.1%)	
		70	5 (15.6%)	
		80	15 (46.9%)	
		90	7 (21.9%)	
		100	2 (6.3%)	
WHO grade classification		I	3 (9.4%)	
		II	11 (34.4%)	
		III	5 (15.6%)	
		IV	13 (40.6%)	
Surgical technique		USG	17 (53.1%)	
		NNV	15 (46.9%)	
Preoperative volumetry in mm^3 (SD)		32.7 (9.2)		
Postoperative volumetry in mm^3 (SD)		6.7 (2.8)		**p < 0.0001**
Grade of resection		Partial resection	8 (25%)	
		Subtotal resection	(23 (71.9%)	
		Total resection	1 (3.1%)	
Surgical complications	12.5% (4)			
		Haemorrhage	1 (3.1%)	
		New neurological deficit	2 (6.3%)	
		LCR fistula	1 (3.1%)	
Surgical mortality		3.1% (1)		
Tumour free survival (IQ) (months)		17.1 (1 – 48)		
Survival (IQ) (months)		19.9 (1 – 50)		
Patients alive at 5 years period		13 (40.6%)		

Statistically significant differences are shown in bold. SD=Standard Deviation. IQR=Interquartile range. *USG*= operative ultrasonography; *NNV* = Neuronavigation; *WHO* = world health organization

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