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Combined Use of 5-Aminolevulinic Acid and Intraoperative Low-Field Magnetic Resonance Imaging in High-Grade Glioma Surgery

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■ OBJECTIVE: **We sought to assess the impact of 5-aminolevulinic acid (5-ALA) and low-field intraoperative magnetic resonance imaging (iMRI) on the extent of resection of high-grade gliomas (HGGs). Results are compared with those obtained when using 5-ALA and iMRI separately.**

■ METHODS: **We retrospectively included patients with an HGG eligible for gross total resection (GTR) from January 2013 to January 2018. Patients were included according to 5-ALA surgical guidance (5A-group), iMRI (iMRI-group), or both (5A-iMRI-group). Surgical variables were registered, and presurgical and postsurgical radiologic and clinical variables were analyzed. Extent of resection ≥90%, complications, and new permanent neurologic deficit were compared using the chi-squared and analysis of variance tests. Other variables studied were mortality, average hospital stay, surgical time, and Karnofsky Performance Scale status before and after surgery.**

■ RESULTS: **Most of the 118 procedures carried out were in men (59.2%). The mean age was 58 years. Sixty patients (50.8%) were operated on using exclusively 5-ALA assistance (5A-group), 19 (16.1%) using iMRI (iMRI-group), and 39 (33%) combining both techniques (5A-IMRI-group). There were no statistically significant differences among 3 groups regarding extent of resection ≥90% (73% 5A, 73.7% iMRI, 71.8% 5A-iMRI, $P = 0.94$); complication rates (18.3% 5A, 5.3% iMRI, 7.7% 5A-iMRI, $P = 0.17$); new or worsening of preexisting neurologic deficit at 1-month follow-up (13.3% 5A, 10.5% iMRI, 15.4% 5A-iMRI, $P = 0.26$); average hospital stay in days (9.5 5A, 6.4 iMRI, 7.6 5A-iMRI, $P = 0.18$); Karnofsky Performance Scale; nor surgical time in minutes (212.4 5A, 187.9 iMRI, 201.4 5A-iMRI, $P = 0.13$).**

■ CONCLUSIONS: **In our experience, combined use of iMRI and 5-ALA does not improve the studied variables when compared with those technologies when used separately, even though a slight tendency of a superior effectiveness is observed when using iMRI individually.**

INTRODUCTION

Actual treatment for high-grade gliomas (HGG) is based on surgery—maximum safe resection (MSR)—followed by chemoradiotherapy.[1] Extent of resection (EoR) has been found to be a key prognostic factor for these patients.[2-7] Gross total resection (GTR) of the contrast-enhancing tumor benefits overall survival and progression-free survival rates.[2] However, due to the infiltrative growth of gliomas, GTR is difficult to achieve, even more so in tumors near eloquent areas, where the EoR is limited to preserve neurologic function.

Current technologic improvements in neurooncology include several intraoperative guidance systems that aim to guarantee MSR.[8,9] These mainly include 5-aminolevulinic acid (5-ALA)–induced fluorescence-guided surgery, intraoperative magnetic resonance imaging (iMRI), and intraoperative ultrasound.[10,11]

Key words
- 5-amino-levulinic acid
- Extent of resection
- Gross total resection
- High-grade glioma
- Intraoperative magnetic resonance

Abbreviations and Acronyms
5-ALA: 5-aminolevulinic acid
CR: Complete resection
EoR: Extent of resection
GTR: Gross total resection
HGG: High-grade glioma
iMRI: Intraoperative magnetic resonance imaging
MHS: Mean hospital stay
MRI: Magnetic resonance imaging
MSR: Maximum safe resection

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The introduction of iMRI helps the neurosurgeon perform more accurately the planned resection, with the only limitations of tumors near eloquent areas. Its usefulness and safety are well demonstrated and clearly outweigh its disadvantages, which are the costs and increase in surgical time.[12,13]

Over the past decade, fluorescence-guided surgery has experienced a leading role in technology for HGG surgical assistance and most publications have been focused on the use of 5-ALA (Gliolán-Gebro Farma).[14] A randomized, controlled, phase III clinical trial confirmed an increased GTR and better progression-free survival after using it. Two main inconveniences are associated with 5-ALA: On the one hand, the surgeon can only visualize the tissue that is directly exposed to the light; hence there can be missing tissue under a clot or under cerebral parenchyma, resulting in false-negative findings. On the other hand, it is known that there is a wide range of light intensities attributable to the infiltrating nature of HGG, which entails a difficulty in distinguishing tumoral tissue and reactive peritumoral gliosis.[15]

In the present study, we describe a comparative retrospective study that evaluates the impact of combining low-field iMRI and 5-ALA–induced fluorescence in the resection of HGG. We compare resulting EoRs in groups using 5-ALA, iMRI, and 5-ALA and iMRI together.

MATERIAL AND METHODS

Data were obtained from the database of Oncological Neurosurgical section in the Neurosurgical Department of Hospital Clínic de Barcelona.

We retrospectively analyzed data from patients diagnosed with HGG, from January 2013 to January 2018, who underwent surgery with the objective to accomplish a complete resection (CR). We included primary and secondary surgical procedures. Exclusion criteria were 1) impossibility to obtain a postprocedural magnetic resonance imaging within the first 72 hours, 2) premature surgical ending for nonresection-related reasons (hemodynamic instability, pulmonary conditions…), and 3) final histologic diagnosis different from HGG (grades III and IV) according to the World Health Organization classification (2016).[16]

In case of 5-ALA–guided surgery, the indication and administration were performed as described previously[17] and the decision of assuming positive 5-ALA–induced fluorescence was done following the previously described criteria.[18]

Eligible patients for low-field iMRI surgical assistance were those with intraaxial brain tumors where GTR was intended. Standard safety MRI regulations were applied when low-field iMRI was used. The physiognomy of the patient and location of the surgical approach (i.e., posterior fossa) sometimes limited low-field iMRI use. The setting procedure and image acquisition were done following others authors' indications.[19] In our center, we have used the low-field iMRI (PoleStar N30, Medtronic, Minneapolis, Minnesota, USA) since March 2013.[20,21]

Assignment of patients to iMRI, 5-ALA, or conventional surgery was done independently of the present study design by choice of the attending neurosurgeon (according to the criteria described earlier). However, the real availability of the facilities changes over time. So, when low-field iMRI was out of order, resections were made with or without 5-ALA. Patients were classified attending to the real usage of these tools (per protocol analysis).

All patients included gave informed consent for brain tumor surgery and the Smart Operating Room Study conducted in our center. All patients underwent a standard microneurosurgical procedure. Tumor removal was performed using the operating microscope (Leica M720 OH5, Leica Microsystems, -Wetzlar, Germany- with FL400 oncologic fluorescence module) under neuronavigational guidance (StealthStation i7, Medtronic).

Intraoperative neuromonitorization and/or awake craniotomy were used in patients with tumors near eloquent areas. Lesions affecting the visual cortex or optic radiations were also considered eloquent areas.

Initial iMRI study included an axial 8 minutes T1 + gadolinium (Gadovist, 0.4 mL/kg [Gadobutrol, Bayer AG, Leverkusen, Germany]) sequence in cases of contrast-enhancing lesions. Second acquisition was performed after concluding the MSR (with or without 5-ALA–guided resection). If residual tumor was observed, the resection continued until MSR was achieved. Final iMRI control examination was done once tumor removal had concluded or until MSR was achieved without risk of causing neurologic deficits.

Patients were divided in 3 groups according to 5-ALA and iMRI use: 5-ALA exclusively (5A group), iMRI exclusively (iMRI group), and combined use (5A-iMRI group).

The primary endpoint was EoR. It was evaluated by 2 blinded independent neurorradiologists in a postoperative high field MRI performed in less than 72 h postoperatively. Complete resection was achieved when no gadolinium-enhanced area was found, near total resection when resection was $\geq$90% of the gadolinium-enhanced area, and partial resection when EoR was <90%.

Secondary variables analyzed were new onset or worsening of a previous neurological deficit (postoperatively and at 1 month) and surgery related complications within the first month. Data regarding functional status before and after the surgery, using the Karnofsky Performance Status scale, mortality rate, surgical time, and average hospital stay.

Chi-squared test was used to perform the statistical analysis for qualitative variables, ANOVA test was used for quantitative analysis. Significance was set at $P < 0.05$ bilateral and analysis was performed with SPSS 20.0 (SPSS, Inc., Chicago, Illinois, USA).

RESULTS

A total of 115 patients met the inclusion criteria, and 118 surgeries were performed according to the study protocol: 60 (50.8%) in the 5A group, 19 (16.1%) in the iMRI group, and 39 (33%) in the 5A-iMRI combined group. No patients were lost during the follow-up for the first month. Three patients initially intended to be operated on with 5-ALA and iMRI couldn't have a correct intraoperative imaging done (unacceptable iMRI signal-to-noise ratio) and were considered as an exclusively 5A-group. There were no additional crossovers. No adverse events regarding the use of iMRI or 5-ALA were registered. All patients underwent a 72-hour postoperative magnetic resonance imaging (MRI) to assess resection rate, therefore no patients

Table 1. Basal Features of Groups

	5A	iMRI	5A-iMRI	*P*
Number	60	19	39	
Mean age (range)	62.3 (35–82)	55.9 (35–81)	55.8 (21–82)	$P = 0.02307$
Sex male-to-female (% male)	36:24 (60%)	12:7 (63.2%)	23:16 (59%)	$P = 0.97$
Tumor location				$P = 0.69$
Frontal	8	9	18	
Parietal	20	4	9	
Temporal	26	4	9	
Occipital	5	2	3	
Insular	1	0	0	
Right (%)	27 (45%)	9 (47.4%)	21 (53.9%)	
Left	33	10	18	
Eloquent area (%)	16 (26.7%)	8 (42.1%)	14 (35.9%)	$P = 0.20$
Intraoperative monitorization	17	8	13	$P = 0.525276$
MEP + SSEP	15	8	12	
Awake + MEP + SSEP	2	0	1	
Reintervention (%)	4 (6.7%)	8 (42.1%)	11 (28.2%)	$P = 0.000142$
Preoperative Karnofsky Performance Scale	87.8	91.6	89.7	$P = 0.30$
Histopathologic diagnosis				
Glioblastoma	55 (91.67%)	9 (47.4%)	31 (79.5%)	
Gliosarcoma	2 (3.3%)	0	5 (12.8%)	
Anaplastic oligodendroglioma	2 (3.3%)	4 (21%)	3 (7.7%)	
Anaplastic astrocytoma	0	6 (31.6%)	0	
Anaplastic gangliocytoma	1 (1.7%)	0	0	

iMRI, intraoperative magnetic resonance imaging; MEP, motor evoked potential; SSEP, somatosensory evoked potentials.

were excluded from the analysis for this reason. There were 3 cases in which final histopathologic diagnosis was *metastasis*, so they were excluded from analysis.

Basal features of the groups are shown in **Table 1**. The 5A group reported a higher mean age (62.3 years old) than the other 2 groups, though this difference was not statistically significant ($P = 0.023$). The iMRI group cohort included more patients with reoperations, up to 47.6% of the patients (28.2% in 5A-iMRI group and 6.7% in 5A group). This difference was not statistically significant ($P < 0.05$).

Histopathologic examination showed mainly glioblastoma ($n = 95$, 80.5%), followed by anaplastic oligodendroglioma ($n = 9$, 7.6%), gliosarcoma ($n = 7$, 5.9%), anaplastic astrocytoma ($n = 6$, 5.1%), and anaplastic ganglyocytoma ($n = 1$, 0.9%).

Table 2 shows results regarding the main variables studied. In relation to the primary objective, EoR ≥90% was highest in group 5A (75%), followed by the iMRI group (73.7%), and finally the 5A-iMRI group (71.8%). These differences are not statistically significant ($P = 0.94$).

The occurrence of new neurologic deficit or worsening of the preexisting ones in the immediate postoperative period was 21.7%, 20.5%, and 15.8% in 5A, 5A-iMRI, and iMRI, respectively ($P = 0.86$). The rates of deficits remaining 1 month postoperatively were 13.3%, 15.4%, and 10.5% in 5A, 5A-iMRI, and iMRI, respectively ($P = 0.87$).

In relation to the *complications rate*, an incidence of 12.7% was recorded. The group with more complications was 5A (18.3%): 3 superficial infections of the surgical wound (*S. aureus*), 1 encephalitis (*Escherichia coli*), 2 patients with postoperative seizures, 1 infarction of the right anterior choroidal artery, 1 epidural hematoma, and 3 surgical bed hematomas. In the group 5A-iMRI, the complications rate recorded was 7.7%: 1 superficial infection of the surgical wound, 1 meningitis (*Listeria*), and 1 epidural hematoma. In the iMRI group the complications rate was 5.3%: 1 cerebrospinal fluid leak.

Related to the mortality 1 month after the surgery, 1 of the patients in the iMRI died 4 weeks after the intervention because of severe pneumonia. One patient in the 5A group

Table 2. Results of Main Variables Studied

	5A	iMRI	5A-iMRI	*P*
Number	60	19	39	
Resection ≥90% (%)	45 (75%)	14 (73.7%)	28 (71.8%)	$P = 0.93923$
Complete resection (%)	20 (33.3%)	10 (52.6%)	19 (48.7%)	$P = 0.177787$
Partial resection (%)	15 (25%)	5 (26.3%)	11 (28.2%)	$P = 0.93923$
New postoperative neurologic deficit (%)	13 (21.7%)	3 (15.8%)	8 (20.5%)	$P = 0.85691$
Neurologic deficit at 1 month (%)	8 (13.3%)	2 (10.5%)	6 (15.4%)	$P = 0.876956$
Complications (%)	11 (18.3%)	1 (5.3%)	3 (7.7%)	$P = 0.169956$
Mortality (%)	1 (1.7%)	1 (5.3%)	0	
Mean KPS (%)	82.6	86.8	85.4	$P = 0.412523$
MHS (days)	9.5 +- 7.2	6.4 +- 2.9	7.6 +- 7.9	$P = 0.17585$
Surgical time (minutes)	212.4 ± 51	187.9 ± 41	201.4 ± 44	$P = 0.129251$

iMRI, intraoperative magnetic resonance imaging; KPS, Karnofsky Performance Scale; MHS, mean hospital stay.

died 4 weeks after the surgery due to encephalitis caused by *E. coli* and status epilepticus. No deaths were registered in the 5A-iMRI group.

In relation to the Karnofsky Performance Status scale 1 month after the surgery, there were no statistically significant differences between the groups (P = 0.41).

Regarding average hospital stay, no statistically significant differences were observed between groups, although there is a tendency to be lower in the iMRI group (6.4 days).

When analyzing the *surgical time* associated with the procedures, no statistically significant differences were found among the 3 groups, being the shortest time in the iMRI group (187.9 minutes) than in the other groups (5A 212.4 minutes, 5A-IMR 201.4 minutes).

In 17 surgeries, the resection had to end prematurely due to conflict with eloquent areas during intraoperative monitoring. In these cases, the MSR limited the EoR. These patients were excluded from the subgroup analysis of the procedures without intraoperative neurophysiologic limitations. The results are presented on **Table 3**.

Resection rates ≥90% were observed in the 78.8% of the 5A group (+3.8%), 80% of the iMRI group (+6.3%), and 79.4% of the 5A-iMRI group (+7.6%). The differences between groups are not statistically significant (P = 0.99). No statistically significant differences were observed in terms of appearance/worsening of previous neurologic deficit or postoperative complications.

DISCUSSION

In this study, we have analyzed retrospectively the differences in the EoR when the surgery is assisted by 5-ALA and/or iMRI in 3 cohort of patients. Our results suggest that the 3 techniques (5-ALA alone, iMRI alone, and the combination of both) are comparable in terms of resection rates, complications, and neurologic deficits.

The EoR is 1 of the main prognostic factors in patients with HGG.[2-7,20] The estimated benefits of CR include increased survival, improvement of the progression-free survival, and better quality of life.[22-24] Achieving CR can be substantially difficult due

Table 3. Results of Main Variables in Group Not Limited by Intraoperative Neuromonitoring

	5A	iMRI	5A-iMRI	Significance Level
Number	52	15	34	
Resection ≥90% (%)	41 (78.8%)	12 (80%)	27 (79.4%)	$P = 0.99466$
Partial resection (%)	11 (21.2%)	3 (20%)	7 (20.6%)	
New postoperative neurologic deficit (%)	11 (21.2%)	2 (13.3%)	7 (20.6%)	
Neurologic deficit at 1 month (%)	8 (15.4%)	2 (13.3%)	5 (14.7%)	
Complications (%)	10 (19.2%)	1 (6.6%)	3 (8.8%)	

iMRI, intraoperative magnetic resonance imaging.

to the proximity of eloquent areas and the diffuse glial area between healthy and affected tissue. The role of surgery is to achieve MSR.[25-27] To accomplish CR, all the intraoperative assistant systems evaluated in the present study can be used.

The gold standard for the evaluation of the EoR is the degree of contrast-enhancing tumor removal assessed in the postoperative MRI (before first 72 hours postsurgical procedure), according to the RANO criteria.[28] There has been much controversy about the minimal resection from which the survival improves in these patients.[2,8,9] In our daily clinical practice and for scientific purposes, we consider GTR when the extent of resection is ≥90%.

Using 5-ALA, Stummer et al[7] reported a CR rate (considered as EoR of 100%) of 65% compared with conventional surgery (36%). In the Spanish study VISIONA (2013), a CR rate of 67% was recorded.[29] The last 2 published meta-analyses regarding the use of 5-ALA, place the CR rate for the 5-ALA group in 61.9%[28] and 65%,[11] respectively. In the present study, the CR rate (≥90%) in the 5A group is 73% (78.8% excluding those cases in which the resection was limited by eloquent areas). The presented data agree with the most recent and relevant publications.

Analyzing the use of the iMRI, the prospective randomized study realized by Senft et al[13] demonstrated that low-field iMRI improves the EoR, obtaining a CR of 96% in the iMRI group versus a 68% in the control group ($P = 0.023$). This study excluded the tumors involving eloquent areas.[13] Recent meta-analyses place the CR rate among 70%[28] and 96%.[11] In 2015, in our hospital, the CR rate was 70%,[20] whereas in the present study, the CR rate is 73.3%. If we consider the same conditions as in the Senft group, an 80% of CR would have been accomplished. Our results are similar than those published. In our experience we have observed that the EoR could improve thanks to the experience of use. Both Senft's work and the present study refer to the use of a low-field iMRI. Several references have been made to describe similar results assisted with high-field MRI. In the available literature, there is no definite association between the use of high-field MRI and better outcomes when compared with low-field MRI and its association to 5-ALA, until today, and therefore could be a potential study to be developed in the near future.

There are few publications related to the combined use of 5-ALA and iMRI. Tsugu et al[30] compared the use of 5-ALA and the combined use of 5-ALA-iMRI in 33 patients, obtaining an EoR of 68.7% in the 5-ALA group versus 91% in the combined group. They recommended the use of iMRI in all cases and concluded that iMRI is helpful in those tumors that did not present positivity for 5-ALA. Coburger et al[8] compared a group of 33 patients operated on with 5-ALA-iMRI and a group of 33 patients operated on with iMRI only, showing a higher rate of CR in the combined group (100% vs. 82%, $P < 0.01$), without showing any increase of complications or new neurologic deficits. In our institution, the CR rate obtained when combining the 2 technologies is 71.8%. When we compare this rate with the other 2 groups, we do not appreciate statistically significant differences. The previous statement remains invariable when excluding tumors involving eloquent areas (which represented 22% of the sample). With these data, we cannot state that the combined use of 5-ALA and iMRI increases the CR rate more than they do separately. We suspect that the combination of intraoperative MRI and 5-ALA has a synergistic effect in glioma surgery.

In 8 patients (6.7% of the total), there was an increase in the tumoral volume in the initial preoperative iMRI compared with the diagnostic MRI, which led to a limitation of the resection due to the infiltration of essential eloquent areas (left hippocampus, $n = 2$, basal ganglia, $n = 3$, and internal capsule, $n = 3$). In five (62.5%) of those patients, a partial resection was achieved. This fact highlights the need to operate on oncologic cases as soon as possible to avoid this situation. It also gives added value regarding the use of iMRI.

It has been postulated that the use of 5-ALA could imply an increase of postoperative neurologic deficits because of extending the resection beyond the contrast enhancement area in the MRI.[31] In this series, a higher rate of new-onset or worsening neurologic deficits was observed in the immediate postoperative period (21.7% 5A, 15.8% iMRI, and 20.5% 5A-iMRI) and at 1 month (13.3% 5A, 10.5% iMRI, and 15.4% 5A-iMRI) in the groups assisted with 5-ALA. These differences did not turn out to be statistically significant. However, there is a trend toward superior postoperative deficits when operating with 5-ALA assistance, so we advise using extreme caution when operating under 5-ALA assistance without neurophysiologic monitoring. In all cases in which the postoperative neurologic deficit improved at 1 month of follow-up ($n = 8$), intraoperative neurophysiologic assistance was performed, indicating that those patients had some eloquent area involved.

As for the surgical time, we did not find significant differences between the 3 groups. This fact may be due to the experience accumulated in the use of the iMRI.[18] This supports the idea of using both systems when available.

Finally, the combined use of 5-ALA and iMRI has not reported having an impact on the mean hospital stay (MHS) of the patients. The only factor with impact on MHS is the complication rate, lower in our study within the iMRI group.

Our study limitation is that it is a retrospective analysis with a long inclusion period (5 years) in which the learning curve for both techniques could have a relevant role in the results. We could also discuss whether the resection of the enhancing area is the best way to measure the EOR, as some authors have postulated.[32] The homogeneity of the groups could also be discussed because in the iMRI group there was a higher number of reoperated patients (42.1%) and a higher incidence of non glioblastoma multiforme in the histologic examination (52.6%). In 5 patients from this group the choice to use iMRI without 5-ALA was taken by the fact that the previous histologic diagnosis was of low-grade glioma. Despite differences between the group composition, we decided to continue with the study considering that the different histopathologic diagnosis (within the high-grade gliomas) does not influence the EoR, although it does in the survival of the patient[3] (variable not evaluated in the present study).

CONCLUSIONS

The results of the series presented do not demonstrate scientific evidence of the superiority of the iMRI and 5-ALA tools used in combination versus their separate use, nevertheless we present some results that highlight the superiority of the iMRI compared with the fluorescence in terms of variables such as postoperative morbidity, EoR and MHS that could significantly impact on a cost-benefit ratio and efficiency improvement. Other studies should be conducted to evaluate other clinically relevant variables such as survival and quality of life.

Studies with a higher number of patients or multicentric studies of centers with availability of these technologies should be conducted to demonstrate scientifically their authentic usefulness. However, standardizing the surgical technique when using 5-ALA and iMRI might be a critical point when designing comparable populations.

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