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The Real impact of Intraoperative MRI in newly diagnosed Glioblastoma Multiforme Resection: an Observational Analytic Cohort study from a Single Surgeon Experience

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The Real impact of Intraoperative MRI in newly diagnosed Glioblastoma Multiforme Resection: an Observational Analytic Cohort study from a Single Surgeon Experience.

Running Title: Glioblastoma: A Single Surgeon's Experience with Intraoperative MRI.

Introduction

1. Background and Rationale

The target of glioma surgery is to improve overall survival (OS) maximizing the extent of tumor resection (EOR) while avoiding postoperative neurological morbidity¹⁻⁵. Preservation of the function predicts the final quality of life (QoL) as well as the eligibility to adjuvant therapies and at last Overall Survival^{2,5}. Intraoperative magnetic resonance (Io-MRI) has been shown to be useful in maximizing the extent of resection⁶⁻⁸.

The main reasons for performing a glioma resection with the aid of Io-MRI is the intraoperative resection assessment and brain shift control⁷⁻¹⁰: Io-MRI notably enhances Neuronavigation accuracy and provides precise and dynamic imaging^{7-9,11}. Additionally, we currently know that GBM is, in any case, an highly malignant brain tumor¹², but it is not a “single” entity: the role of MGMT methylation status on response on Temozolomide and subsequently on survival, has been investigated and demonstrated¹³, although the impact of IoMRI on the differential molecular pattern remains somewhat unexplored and deserves a specific mention.

1. Objectives

To the best of our knowledge a *single surgeon* study describing and quantifying the exquisite effect of Io-MRI on EOR, OS and PFS according to the weight of the MGMT methylation on such parameters, is still missing. Therefore, aim of this work is to retrospectively review and compare two subsets of patients suffering from Glioblastoma Multiforme (GBM) *operated on by the same surgeon, with or without* the aid of an Io-MRI system.

Materials and Methods

1. Study design and Setting

We report a retrospective analysis of surgical (EOR) and oncologic results (PFS and OS) of patients affected by GBM who underwent surgical resection by the senior author in the period ranging between March 2009 and January 2017. All the patients were operated on two different Neurosurgical Departments affiliated to the same University, one is equipped with an Io-MRI operative theatre and the other has a standard operative theatre: the use of Io-MRI was *not* randomized. The resulting design of the study is a retrospective observational cohort study in which the data analyzed were collected by two independent researchers, who were blinded to the objective and design of the study. This team, when reviewing the radiological data, was not blind to the “use/not-use” of Io-MRI, but was completely blind to the purpose of this investigation.

Patients data (age, sex, tumor location, Karnofsky Performance Status, neurological status pre- and post-surgery, pre- and post-operative tumor volume), MGMT methylation status were recorded.

2. Participants and Eligibility

To the initial GBM patients cohort, we applied the following inclusion criteria:

1. A preoperative KPS > 70%;
2. We included only patients presenting an American Society of Anesthesiologists score (ASA) between II and III.
3. All the patients suffered from GBM (according to WHO¹²),
4. The patients were included *only if* a successful *complete* Stupp Protocol¹³ was applied
5. All the patients received a standard conformational planning with a Linear Accelerator (LINAC), no stereotactic radiosurgical treatment was performed
6. Once the progression of the disease was noticed the patient and the relevant imaging were referred again to our attention, to evaluate the feasibility of a second surgery or to address the patient to a second line of adjuvant treatment.

7. The estimated target of the surgical procedure was the *total or subtotal resection of the lesions*: no biopsies were included;
8. All the patients included in the study were newly diagnosed GBM at their first surgery. Operating on recurrences makes a complete difference¹⁴.
9. Incomplete or wrong data on clinical, radiological and surgical records and/or lost to follow-up.

A total of 129 patients matched the inclusion and exclusion criteria and their clinical records were retrospectively re-evaluated for this study; 65 belonged to Group A (conventional microsurgical resection) while 64 belonged to Group B (Io-MRI aided microsurgical resection).

All the patients included underwent a preoperative brain MRI scan included an high field 1,5 Tesla volumetric study with the following sequences: T2w, FLAIR, isotropic volumetric T1-weighted magnetization-prepared rapid acquisition gradient echo (MPRAGE) before and after intravenous administration of paramagnetic contrast agent; diffusion tensor sequences (DTI) with 3D tractography and functional MRI (fMRI) completed our protocol for what concerns gliomas affecting eloquent locations^{7,8}.

All the procedures of Group B (Io-MRI aided), were performed in BrainSUITE. Patients heads were placed in MR head-coil-frame, with integrated fiducials that were preoperatively recognized by a frame-based Neuroavigation system (VectorVision, BrainLAB AG, Feldkirchen, Germany) (Figure 1). A dedicated pointer equipped with fiducials was recognized by the Neuronavigator and used to identify the lesion and localize the proper skin incision.

After dural opening, we acquired an intraoperative volumetric MRI for neuronavigation to correct the potential brain shift in about 15' of total acquisition and processing average time^{1,8}. BrainSUITE has an integrated operative microscope (Zeiss NC4 multivision, Germany). At the end of the procedure, the last MRI was performed in all cases in order to verify the complete resection or the presence of residual tumor that needed further resection.

All the procedures of Group A (conventional resection), were performed with an infrared-based Neuronavigator (Stealth III, Medtronic, USA), in a standard neurosurgical theatre, with a standard operative microscope (Zeiss OPMI, NC4, Germany). In the first postoperative day, the patients underwent volumetric Brain MRI scan to evaluate the EOR.

Since surgery in BrainSUITE is performed *outside the 5-gauss line*, for both subgroups all the ordinary surgical and microsurgical instruments were used.

For both subgroups, a standard total intravenous anesthesia protocol with Propofol (1mg/kg) and Remifentanyl (0,5 µg/kg/min) has been used. If intraoperative neuromonitoring of the motor pathway was performed, no muscle relaxants were administered. For patients operated on in BrainSUITE an MRI-compatible respirator and an anesthesia care monitor were provided. Intraoperative monitoring methodology and Io-MRI compatible devices were previously reported elsewhere⁹.

We employed a functional neuronavigation approach combined with intraoperative neuromonitoring.

The necessity of further resections after a first intraoperative MRI was recorded.

In general, both with or without Io-MRI, it was intraoperatively judged necessary to stop tumor excision when:

1. white matter appeared free of disease in any aspect of the surgical cavity,
2. despite a directly visualized or Io-MRI proven remnant, neuromonitoring outlined a risk for postoperative motor morbidity,
3. intraoperative MRI (for patients treated with the aid of Io-MRI) showed GTR of the contrast enhancing lesion.

3.Data sources and Quantitative variables

The extent of resection (EOR) was determined by a team of independent researchers, blind to the objective of the study, through a comparison between the MR images obtained before surgery and the last postsurgical intraoperative MRI (Group B) or the first MRI after surgery (Group A). EOR was calculated on the ground of a manual segmentation of the tumor outline in the planning software. Gross Total Resection (GTR), was defined as a confirmed reduction of the preoperative volume of the tumor of at least 95%.

In case of GTR, “tumor progression” was defined as the first MRI scan demonstrating the presence of pathologically enhancing tissue characterized by an MRI pattern (relying mostly on Perfusion

Weighted Imaging) inconsistent with a cerebral radiation injury (which is in fact a “pseudoprogression”¹⁵). In case of incomplete resections (<95% volume reduction) a volumetric increase of the residual disease detected at the first postoperative MRI scan was considered as disease progression.

A close range dedicated neuro-imaging follow-up program was routinely performed in both Institutions. This program included:

1. A standard early (maximum 24 hours after surgery) postoperative volumetric brain MRI (for Group A) or the last intraoperative volumetric MRI (for group B).
2. At approximately one month from surgery (25-35 days) a volumetric brain MRI scan was repeated for a first step follow-up control and to provide information for the radiation treatment planning.
3. After the end of irradiation, a volumetric brain MRI scan was performed every three months.

Generally the treatment was considered to be stopped when disease showed volumetric progression despite the second line of adjuvant treatment. Both subgroups received a surgical and adjuvant treatment with:

1. *The same operative microscope,*
2. *Similar infrared-based Neuronavigation system,*
3. *Similar microsurgical instruments,*
4. *The same microsurgical technique performed by the same surgeon, the senior author.*
5. *The same adjuvant treatment and follow-up program.*

Progression Free Survival (PFS) was defined as the interval between the last intraoperative or the first postoperative day MRI scan and the first MRI scan demonstrating tumor regrowth and was coded as a continuous variable. For statistical purposes, to compare the two subgroups, PFS was also considered at twelve months (PFS-6m) and coded as a “dichotomic” variable (1/0 - Yes/No). Since the present cohort is extremely biologically homogeneous, we found useful to add Overall Survival (OS) data. OS data were retrospectively retrieved by phone calls.

4. Statistical methods

The sample was analyzed with SPSS version 18. Comparison between nominal variables have been made with χ^2 test. EOR and PFS means were compared with One Way and Multivariate ANOVA analysis along with Contrast analysis and Post-Hoc Tests. Kaplan-Meier survival analysis assessed survival. Continuous variables correlations have been investigated with Pearson's Bivariate correlation. Threshold of statistical significance was considered $p < .05$.

5. Potential source of Bias and Study size

We addressed no missing data since incomplete records were an exclusion criteria. A potential source of bias is expected from exiguity of the sample, which nevertheless, in regards to the endpoints selected, presents an excellent post-hoc statistical estimated power ($1 - \beta = 0.96$ for $\alpha 0.05$ and effect size 0.6).

The informed consent were approved by the Institutional Review Board of our Institution. Before surgical procedure, all the patients gave informed written explicit consent after appropriate information. Data reported in the study have been completely anonymized. No treatment randomization has been performed. This study is perfectly consistent with Helsinki declaration of Human Rights.

Results

1. Participants

In the period between March 2009 and June 2016, 129 patients, matching the exclusion and inclusion criteria, suffering from GBM underwent surgery in our departments and were retrospectively evaluated for this study. The senior author performed all the resections.

2. Descriptive data

The final cohort consisted of 68 males and 61 females, and the average age was 57.04 ± 11.87 years (Range 36-78); 56 tumors (43.4%) were located in frontal lobe, 32(24.8%) in temporal, 17(13.1%) in parietal lobe, 16(12.4%) in occipital lobe and the remaining 8(6.2%) were insular or deep-seated. All the relevant details are included in Table 1. The two groups appeared to be adequately matched (Table 1).

The average EOR was $86.23\% \pm 10.51$ for Group A and $94.01\% \pm 7.42$ for Group B. This difference was statistically significant ($p.005$). GTR ($>95\%$ tumor volume reduction) was 28/65 patients (43.1%-Group A) versus 43/64 patients (67.2%-Group B), realizing a GTR rate increase of 24.1% (Figure 2A). Group B patients underwent an Io-MRI after a first resection, to assess the EOR. During the surgical procedure, in a total of 38/64 patients (59.37%), the Io-MRI disclosed a remnant that deserved a further resection which was safe and feasible according to intraoperative neuromonitoring findings, anatomical and functional imaging eloquent area landmarks. Direct experience with Io-MRI, brought the first operator, senior author of the present paper, to adopt a strategy of a “first cautious resection”, before completing a more aggressive debulking after intraoperative control. Thus, whenever available, the use of Io-MRI definitely modifies the resection strategy.

3. Outcome data and Main Results

The median PFS was 5.38 ± 2.32 months for Group A versus 7.89 ± 2.75 for Group B; mean OS was 13.38 ± 4.06 months for Group A versus 16.43 ± 3.41 for Group B. These differences were statistically significant ($p.001$ and $p.001$). Progression Free Survival at six months (PFS-6m) accounted for 49.23% (32/65) of Group A and 78.12% (50/64) of Group B; the PFS increase was as high as 28.89% ($p.001$ –Figure 2B).

PFS, OS and EOR showed a strong statistical correlation, coherently with was expected for an homogeneous cohort of GBM (OS-PFS $r.454$; EOR-OS $r.718$; EOR-PFS $r.416$, p . between .001 and .002).

4. Other analyses

In regards to Kaplan-Meier survival curves, Io-MRI demonstrated a strong positive effect on all the investigated outcome variables: PFS, OS and EOR ($p.>.001$; $p.>.001$ and $p.002$ respectively, Figure 3A and B).

In order to assess the impact of Io-MRI on the differential MGMT methylation status, we furthermore classified our patients in a 4 steps nominal variable as follows:

1. 50 patients operated on without Io-MRI presenting a *not* methylated MGMT
2. 48 patients operated on with Io-MRI presenting a *not* methylated MGMT

3. 15 patients operated on without Io-MRI presenting a methylated MGMT
4. 16 patients operated on with Io-MRI presenting a methylated MGMT

Interestingly, Kaplan-Meier analysis (Figure 4A), along with a Univariate ANOVA analysis (Figure 4A) disclosed that MGMT methylated *plus* Io-MRI conveys a progressive survival advantage among the four different subgroups, being the most effective advantage the one obtained by treating with the aid of Io-MRI the MGMT methylated patients. Precisely, the survival difference between the MGMT methylated and unmethylated patients, in regards to the use of Io-MRI is a statistically significant amount of approximately 2.7 months for both the eloquently and non-eloquently located lesions.

5. *Complications*

In the entire cohort we recorded the following surgical complications: 3 patients (2 belonging to Group A and 1 Group B) presented an hemorrhagic complication (surgical cavity hematoma/venous infarction – 2,32% of patients); two of those patients required surgical revision and one of them suffered from a postoperative neurological vegetative state and died at 20th postoperative day. A total of 4 patients (2 belonging to Group A and 2 to Group B) presented a CSF flow disturbance and 1 patient developed a surgical cavity infection (belonging to Group A) for an overall surgical complication rate of 6.2% in the entire cohort. Three of the CSF disturbances were managed surgically, the remaining, a mild temporal horn entrapment was stable in serial follow-up MRI scans and was deemed to be managed conservatively. The surgical cavity infection required a surgical revision. Surgical complication did not show significant differences between the two subgroups.

We also recorded a total of 4 medical complication: 3 pneumonia, 1 myocardial infarction, 1 kidney failure. One of the patients suffering from pneumonia and the patients affected by myocardial infarction died. Thus, the resulting overall mortality rate was 3/129 (2.32%).

We furthermore recorded a total of 20 neurological postoperative deficits: 11 patients presented a new or worsening of a preexisting motor deficit (6 belonging to Group A and 5 Group B), 9 of such patients presented a minor transient impairment and resolved within 30 postoperative days in 2 cases the deficit was permanent (1.55% of 129). We recorded a total of 6 new or worsening of a preexisting speech disturbances, (1 improved at 30 days, 3 were stable at follow-up and 2 completely resolved within 30 days) and 2 new visual field deficits (permanent, at follow-up), plus the vegetative state patient. There

was no statistically significant difference among the two subgroups in regards to the incidence of surgical or neurological complications, a fine analysis of the complications incidence, however, did not in the main endpoints of the present work.

Discussion

In the present study, we investigate the impact of a 1.5 Tesla intraoperative MRI on extent of resection and therefore on the PFS in a uniform cohort of patients affected either by MGMT methylated and unmethylated GBMs. The target of glioma surgery, is not only improve survival but also increase the time of acceptable QoL¹⁻⁵.

GTR as measured by absence of contrast enhancing tumor or T2w/FLAIR hyperintensity after surgery has being widely accepted to be associated with extended overall survival and PFS in High-grade gliomas, low-grade gliomas and even recurrent gliomas^{4,16-18}.

There is a growing evidence in the current Literature supporting the role of extensive resections to improve survival in GBM patients. Lacroix et al. reported a large series of GBM, with a longer survival (13 months) in patients with 98% resection of the tumor versus resection less than 98% (8.8 months)¹⁷. Sanai and Berger analyzed in a review all the relevant Literature reporting that the higher is the EOR the longer the OS and PFS will be, both for low- and high-grade gliomas¹⁸.

Intraoperative MRI systems were developed as surgical tools to improve visualization of tumor remnants that would otherwise remain unresected^{7-9,19-21}; nevertheless, the true impact of intraoperative MRI in GBM surgery has not been completely investigated and, surprisingly, when analyzing Literature, some of the experience reported do not support its use in high grade glioma surgery²².

Kubben et al, in a systematic review regarding the use of Io-MRI, analyzing a limited number of highly comparable short series of patients, could report a class II of evidence supporting the use of Io-MRI in increasing EOR, enhancing quality of life, prolonging survival after resection of gliomas in respect to conventional microsurgical resection¹⁹.

1. Key results and Interpretation

In our experience the key-advantages of Io-MRI are:

1. *To restore neuronavigation accuracy during surgery*
2. *To solve the problem of brain shift,*
3. *To intraoperatively identify residual tumor⁷⁻⁹.*

A prospective, randomized, controlled trial by Senft et al. report a significant improvement in PFS at 6 months in Io-MRI group versus “conventional surgery” group without any difference in postoperative neurological deficits²³. However the impact of this prospective trial is in our opinion slightly limited by the small number of patients recruited. This trial provides a preliminary *strong evidence* that supports the use of Io-MRI in resection of newly diagnosed GBM. But in our opinion, apart from the study size, there are several limitations:

1. The patients included suffered from different WHO grading of gliomas
2. Different neuronavigators were employed,
3. Most of all, 1,5 Tesla and 3 Tesla Intraoperative MRI are, according to our opinion and our experience, completely different instruments which results are not completely superimposable for such a fine analysis since 1.5 Tesla MRI presents of course an lower spatial resolution and may underestimate residuals in respect to 3 Tesla, which, by the way, presents more artifacts than conventional 1.5 Tesla imaging^{24,25}: in other words, according to our opinion, to draw definitive conclusion on EOR, all the patients should be investigated with a similar MRI and of course with the same radiological protocol.

Our results and our experience is consistent with the results of Senft et al., and we definitely agree with their finding. The aim of our study was to empower this evidence and drive it “one step-beyond”, through a retrospectively analyzed, strongly comparable and strictly matched cohort of patients in which the weight of multiple potential source of bias is excluded.

Further notable prospective trials²⁶, outlined the role of Io-MRI in increasing the EOR. Similarly to the work of Senft et al. the trial of Hatiboglu et al. is focused on the exquisite impact of Io-MRI on the EOR, providing the evidence (on 44 patients) that such tool increased significantly the EOR from 84%

to 99% with additional tumor removal after the intraoperative scan for enhancing gliomas and from 63% to 80% for what nonenhancing gliomas are concerned. In these author's experience, importantly, in 15 (52%), this was achieved with the contribution of iMRI.

In specific regards to our experience with Io-MRI aided GBM surgery, at the beginning of the resection it is usually simple to differentiate, under operative microscope, between normal and pathological tissue, but when dealing with smaller remnants, after the most of the resection has been carried out, the transition between normal and pathological tissue becomes generally more difficult and in such condition, we noticed the real utility of the Io-MRI.

Furthermore, notable is the cumulative progressive impact of the Io-MRI in the surgical treatment of GBM patients according to their MGMT methylation status, it conveys an additional progressive survival advantage in respect to the simple effect on survival of the sole MGMT which positive impact on OS has been extensively investigated and recognized¹³.

Naturally, Io-MRI is more time consuming than conventional surgery and the costs are usually higher; however immediate intervention for incomplete procedures (such as residual tumor) or possible complications can prevent re-operation and decrease hospitalization length and treatments cost²⁷.

Indeed, EOR, according to Literature¹⁷ is the main prognostic factor determining the final OS. Therefore, whenever possible, a second surgery, after a first partial resection, should always be planned, determining an increase in the overall hospitalization and treatment related cost.

Not to mention the importance "brain shift" correction, critical to approach eloquent areas gliomas⁷⁻⁸. Eloquent structures such as corticospinal tract or arcuate fasciculus may "move" averagely up to 4 mm. In other cases, the displacement of the eloquent structures is caused by the resection itself⁷⁻¹⁰. An intraoperative correction is therefore critical for a satisfactory safety of the resection.

Since its introduction, Io-MRI underwent important comparison trials with intraoperative ultrasonography, a more accessible and less time consuming intraoperative imaging: these reports outlined the superiority of Io-MRI in improving EOR and detecting residual disease²⁸⁻²⁹, outlining a

role limited to an accurate pre-debulking tumor delineation performed with intraoperative ultrasonography.

It is our opinion that strong, prospective controlled trials are necessary to validate and to describe the role and the real impact of intraoperative CT and ultrasound imaging as compared to the result of the Io-MRI aided glioma surgery.

Therefore, to date, Io-MRI remains, according to Literature and to our experience, the most accurate instrument to visualize tumor remnant after resection.

2. Limitations and Generalisability

The main limitation of the study lies in its retrospective nature. Furthermore the patients were not randomly allocated to the subgroups. In respect to other retrospective trials²⁰, we had the same adjuvant treatments protocol, similar MRI scanners, similar instruments, same neuronavigator, same operative microscope, and most of all same surgeon, in the context of two ultra-selected and completely superimposable cohorts of patients.

Conclusions

In the present study, we present the experience of a single surgeon in performing surgery for GBM with the aid of a 1.5T Io-MRI: once the follow up and adjuvant therapies are completely homogenized for all the patients included in the cohort, it appears surprisingly clear that Io-MRI, similarly to what previously demonstrated in another similar retrospective investigation³⁰, is a safe and effective tool that optimizes significantly both the EOR and the OS of the patients.

Disclosure

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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Abbreviations:

MRI: Magnetic Resonance Imaging, **Io-MRI:** Intraoperative Magnetic Resonance Imaging, **fMRI:** Functional Magnetic Resonance Imaging, **DTI:** Diffusion Tensor Imaging, **MPRAGE:** Magnetization-Prepared Rapid Gradient-Echo; **QoL:** Quality of Life, **KPS:** Karnofsky Performance Status; **EOR:** Extent of Resection.

Table and Figure Captions

Table 1 – Patient's Demographics

Figure 1 – An Intraoperative neuronavigation image.

Figure 2 – **A.** Gross Total Resection and **B.** Progression Free Survival at 6 months comparison between the two groups on the ground of the use of Intraoperative MRI.

Figure 3 – Kaplan-Meier survival curve that describes the impact of Io-MRI on **A.** PFS and **B.** Overall survival

Figure 4 – **A.** Kaplan-Meier survival curve that describes the impact of Io-MRI *plus* MGMT methylation status on Overall survival **B.** ANOVA analysis chart disclosing the relevant trend of survival for the aforementioned 4 subgroups of patients

Table 1. Patient's demographics

	N=129 patients		P value
Subgroup	B (Io-MRI)= 64		A (Non Io-MRI) =65
Sex	Male N=35 – 54.7% Female N=29 – 45.3%		Male N=33- 50,8% Female N=32; 49.2%
Age	56.61±10.49		57.56±13.52
KPS at admission	86.4 (70-100)		87.1 (70-100)
Volume in cm³	26.8±11.3		27.4±10.9
MGMT methylated	16/64 patients (25.0%)		15/65 patients (23.1%)
EOR	94.01%±7.42		86.23%±10.51
GTR (>95% reduction)	43/64 patients (67.2%)– Further resection after a first procedure for 38/64 patients (59.37%)		28/65 patients (43.1%)
PFS at 6 months	78.12% (50/64)		49.23% (32/65)
PFS	7.89±2.75 months		5.38±2.32 months
OS	16.43±3.41 months		13.38±4.06 months
Location	Frontal 27 (42.2%) Temporal 15 (23.4%) Occipital 9 (14.1%) Parietal 8 (12.5%) Insular 5 (7.8%)	Frontal 29 (44.6%) Temporal 17 (26.1%) Occipital 7 (10.8%) Parietal 9 (13.8%) Insular 3 (4.6%)	
Eloquence of Location, according to function	Non eloquent location 32 (50.0%) Motor (CST) 17 (26.6%) Visual (OR) 4 (6.3%) Speech (AF/UNC/IFOF) 11 (17.2%)	Non eloquent location 33 (50.7%) Motor (CST) 15 (23.1%) Visual (OR) 5 (7.7%) Speech (AF/UNC/IFOF) 12 (18.5%)	

Io-MRI: Intraoperative MRI; **NS:** Not significant, **PFS:** Progression Free Survival; **OS:** Overall Survival; **CST:** Corticospinal tract, **OR:** Optic Radiation, **AF:** Arcuate Fasciculus, **UNC:** Uncinate Fasciculus, **IFOF:** Inferior Fronto-Occipital Fasciculus, **KPS:** Karnofsky performance status.

Highlights

1. This is the first “single surgeon” personal series about Io-MRI in glioma surgery
2. In glioma surgery the aims are to preserve quality of life and prolong survival
3. Io-MRI significantly increased EOR in this cohort of patients
4. Io-MRI significantly prolonged survival in this cohort of patients
5. Io-MRI plus methylated MGMT convey a progressive survival advantage