

Fluorescence real-time kinetics of protoporphyrin IX after 5-ALA administration in low-grade glioma

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OBJECTIVE 5-Aminolevulinic acid (5-ALA) induces fluorescence in high-grade glioma (HGG), which is used for resection. However, the value of 5-ALA-induced fluorescence in low-grade glioma (LGG) is unclear. Time dependency and time kinetics have not yet been investigated. The purpose of this study was to investigate real-time kinetics of protoporphyrin IX (PpIX) in LGG based on hyperspectral fluorescence-based measurements and identify factors that predict fluorescence.

METHODS Patients with grade II gliomas and imaging from which HGGs could not be completely ruled out received 5-ALA at 20 mg/kg body weight 4 hours prior to surgery. Fluorescence intensity (FI) and PpIX concentration (CPpIX) were measured in tumor tissue utilizing a hyperspectral camera. Apparent diffusion coefficient (ADC)-based tumor cell density, Ki-67/MIB-1 index, chromosomal 1p/19q codeletion, and ^{18}F -fluoroethyl-L-tyrosine (^{18}F -FET) PET values and their role for predicting fluorescence were evaluated.

RESULTS Eighty-one biopsies from 25 patients were included. Tissues with $\bar{\text{A}}$ uorescence demonstrated FI and CPpIX maxima between 7 and 8 hours after administration. When visible $\bar{\text{A}}$ uorescence was observed, peaks of FI and CPpIX were observed within this 7- to 8-hour time frame, regardless of any MRI gadolinium contrast enhancement. Gadolinium enhancement ($p = 0.008$), Ki-67/MIB-1 index ($p < 0.001$), ^{18}F -FET PET uptake ratio ($p = 0.004$), and ADC-based tumor cellularity ($p = 0.017$) significantly differed between $\bar{\text{A}}$ uorescing and non $\bar{\text{A}}$ uorescing tissue, but not 1p/19q codeletions. Logistic regression demonstrated that ^{18}F -FET PET uptake and Ki-67/MIB-1 index were independently related to $\bar{\text{A}}$ uorescence.

CONCLUSIONS This study reports a fluorescence-based assessment of CPpIX in human LGG tissues related to ^{18}F -FET PET uptake and Ki-67/MIB-1. As in HGGs, fluorescence in LGGs peaked between 7 and 8 hours after 5-ALA application, which has consequences for the timing of administration.

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KEYWORDS 5-ALA; fluorescence-guided resection; low-grade glioma; PpIX concentration; oncology

THE optimal treatment for low-grade gliomas (LGGs) is a matter of ongoing debate. 5-Aminolevulinic acid (5-ALA) is a broadly used and well-established surgical adjunct in high-grade glioma (HGG) surgery. The randomized phase III multicenter approval study of 5-ALA is one of the most cited articles in neurosurgery.¹ This is not only due to the high clinical relevance in glioma surgery, but also due to the variable application

of 5-ALA in translational research. However, the clinical value of 5-ALA in LGG surgery remains an ongoing discussion.^{2,3} Urgek'ecnmf, 'vk o g' fgrgpfpe{'cpf'vk o g'mkpgvkeu' have not been well investigated, and hypothetically, LGGs ykvi'iqvgt'i taqvi' tcvgu' oki iv'fkurnc{'fkhhtgtpv'mkpgvkeu)

To date, it has been reported that 10%–23% of LGGs

ABBREVIATIONS 5-ALA = 5-aminolevulinic acid; ^{18}F -FET = ^{18}F -fluoroethyl-L-tyrosine; ADC = apparent diffusion coefficient; AUC = area under the curve; BBB = blood-brain barrier; CI = confidence interval; CpPpIX = PpIX concentration; FI = fluorescence intensity; HGG = high-grade glioma; IDH = isocitrate dehydrogenase; LGG = low-grade glioma; PpIX = protoporphyrin IX; ROI = region of interest; SUVmax = maximum standardized uptake value.

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tcvkq" i tgcvgt" vjcp" 30:7" cu" rtgfkcvqtu" hqt" Ewqtguegpeg" kp" these tumors.³ Additionally, any contrast enhancement in OTK" hwtvjgt" kpetgcugf" vjg" rtqcdkknv" { "qh" xkukdng" Ewqtguegpeg" Hwtvjgt oqtg. " Ewqtguegpgv" vw oqtu" rtgugpvf" c" uki-pk fcpvn" { "jki jgt" Mk/89l OKD/3" kpfgz" *k0g0. "3607" " xu" 70: " + " vjcp" pqp Ewqtguegpgv" NI I u.³ indicating high proliferation, which several authors have found to be correlated with xkukdng" Ewqtguegpeg.^{8,9} In contrast to HGGs, protoporphy-tkp" KZ" *RrKZ" + Ewqtguegpeg" kp" NI I u" o ki jv" ckf" kp" f p f k p i " cp" cpcrncuvke" hqewu. " y j k e j " ecp" dg" hqwpf" kp" 66 ' 677 ' " qh" tumors with typical LGG MRI aspects.^{8,9} ¹⁸F-FET PET can further serve as an additional tool to search for these anaplastic foci—regions of high proliferation rate—prior to surgery.¹⁰ This is based on observations of previous authors who have found both heterogenous ¹⁸F-FET PET wrvcmg" kp" NI I ⁸ and a correlation of these regions with xkukdng" Ewqtguegpeg.^{8,9} Ykvj" vjg" jgnr" qh" Ewqtguegpeg. " vjgug" regions can be precisely targeted to ensure correct histopathological diagnosis and avoid undergrading of patho-nqikecn" vkuuwg" vq" eqp f t o " vjg" vtwg" vw o qt" i t c f g. ^{5,6} which is relevant for adjuvant treatment and prognosis. Although rtgqrctcvxg" k o c i k p i " o k i j v " n g c f " v j g " y c { " h q t " f p f k p i " v j g u g " anaplastic foci, intraoperatively, brain shift may lower the accuracy of conventional image guidance.

Vq" qwt" mpqyngf ig. " tgrqtvu" t g i c t f k p i " v j g " m k p g v k e u " c p f " metabolism of 5-ALA in LGG—e.g., how and when the o c z k o w o " e q e g p v t c v k p q " q h " R r K Z " r g c m " c h v g t " 7 / C N C " c f - ministration can be found—are missing from the present literature. In a recent article, we evaluated the real-time mkpgvkeu" qh" RrKZ" kp" J I I " dcugf" qp" Ewqtguegpeg" o gcuwtg-ments with a hyperspectral camera.¹¹ We demonstrated vjcv" vjg" RrKZ" eqegpvtcvkqp" *ERrKZ" + " rgcmgf" ncvg" vjcp" rtgxkqwn" { " v j q w i j v " k p " J I I . " k 0 g 0 . " 9 6 : " j q w t u " c h v g t " 7 / C N C " administration. This was in contrast to data from an early cpk o c n " g z r g t k o g p v " r w d n k u j g f " k p " 3 ; : . " k p " y j k e j " c " E w q t g u - e g p e g " r g c m " y c u " q d u g t x g f " 8 " j q w t u " c h v g t " 7 / C N C " c f o k p k u - tration,¹² a regime later adopted not only by the standard product characteristics of Gliolan (Medac), but also by the vast majority of published clinical trials.^{1,3,13–18} These results are consistent with other studies evaluating CPpIX in rncu o c " * 90 : " j q w t u " ¹⁵ q t " u m k p " * 80 7 6 : 0 : " j q w t u " ¹⁹

Hence, the main objective of this study was to investi-icvq" vjg" RrKZ" tgcn/vk o g" mkpgvkeu" chvg" 7/CNC" c f o k p k u v t c - tion in a subset of patients with glioma found to harbor NI I " cu" c" f p c n " r c v j q n q i k e c n " f k c i p q u k u . " v q " f g v g t o k p g " v j g " best timing for surgery when utilizing 5-ALA-mediated Ewqtguegpeg/i wkfgf" tguevkepp" Hwtvjgt oqtg. " y g " c p c n { | g f " f k h h g t g p v " h c e v q t u " v j c v " r t g f k e v " E w q t g u e g p e g " k p " v j k u " r c v k g p v " collective.

Methods

Patients

This study evaluated adult patients with LGG who were surgically treated at the Department of Neurosurgery, University Hospital of Münster, between January and December 2018. These patients were selected for dosing with 5-ALA based on large tumor size, old age, any degree of spurious enhancement, an elevated ¹⁸F-FET signal on RGV. " q t " q v j g t " h c e v q t u " v j c v " k p e t g c u g f " v j g " n k m g n k j q q f " q h " v j g " tumor harboring areas of malignant degeneration.³ Ulti-

o cvgn" . " v j g u g " v w o q t u " y g t g " j k u v q r c v j q n q i k e c n { " e q p f t o g f " cu" nqy" i t c f g . " f g u r k v g " d k q r u { " u r g e k o g p u " d g k p i " u r g e k f e c n { " eqmgevgf" htq o " Ewqtguegpgv" t g i k p u " k p " e c u g u " y k v j " E w q t g u - e g p e g l " C m " u w t i g t k g u . " c u " y g m " c u " v j g " k p v t c r g t c v k x g " E w q t g u - cence assessment, were performed by two senior surgeons (W.S. and E.S.M.).

5-ALA (Gliolan, medac GmbH) was administered at a uvcpfctf" fqug" qh" 42" o i l m i " d q f { " y g k i j v " 6 " j q w t u " r t k q t " v q " induction of anesthesia. The timing of administration was tgeqtfgf" hqt" gcej" r c v k g p v l " V q " x k u w c n k | g " E w q t g u e g p e g " f w t - ing surgery, the surgical microscope OPMI Pentero 900 *Ectn" \ g k u u " C I + " y c u " w u g f l " X k u k d n g " E w q t g u e g p e g " s w c n k v { " was assessed by the operating surgeon. We collected and cpcn { | g f " v w o q t " v k u u w g . " t g i c t f n g u u " q h " x k u k d n g " E w q t g u e g p e g l " When feasible, we collected tissue at a minimum of three different time points during surgery. Tissues were subse-swgpvn { " u w d o k v g f " h q t " p g w t q r c v j q n q i k e c n " c p c n { u g u l

Each patient's written informed consent was obtained. All procedures performed in studies involving human participants were in accordance with the ethical standards qh" v j g " k p u v k v w k q p c n " t g u g c t e j " e q o o k v g g " c p f " y k v j " v j g " 3 ; 8 6 " J g n u k p m k " F g e n c t c v k q p " c p f " k v u " n c v g t " c o g p f o g p v u " q t " e q o r c - t c d n g " g v j k e c n " u v c p f c t f u l " G z " x l x q " v k u u w g " g x c n w c v k q p " y c u " c r - proved by the local ethics committee of the University of Münster.

OTK" gzc o k p c v k q p u " y g t g " c e s w k t g f " y k v j k p " 4 " y g g m u " r t k - or to surgery. Enhancement on T1-weighted images after gadolinium-based contrast agent administration was categorized into two groups, i.e., positive or negative, as previously described.^{9,20} Dgecwug" vjg" crrctgpn" fkhhwukqp" eqgh f ekgpv" *C F E + " j c u " d g g p " t g r q t v g f " v q " t g (E g e v " v w o q t " e g n - larity, we analyzed available imaging in our patient col-lective according to the method published by Hayashida et al.²¹ ¹⁸H/HGV" RGV" wrvcmg" * o c z k o w o " u v c p f c t f k | g f " w r v c m g " x c n w g " J U W X o c z + " y c u " q d v c k p g f " h q t " e q o r c t k u q p l " Y g " c n u q " u v t c v k | g f " t c v k q u " k p v q " v y q " i t q w r u . " k 0 g 0 . " u o c n n g t " q t " n c t i g t " v j c p " 1.85, as previously described.³

Spectrometric Measurement

Spectrometric measurements were performed using a hyperspectral imaging system in 10 regions of interest *TQku" rgt" vw o qt" uc o r n g " v q " q d v c k p " c " E w q t g u e g p e g " k p v g p u k v { " (FI) as previously described.¹¹ Vkuuwgu" ygtg" o gcuwtgf" gz" vivo directly after collection, paying careful attention to nki j v " r t q g e v k p " h t q o " n k i j v " g z r q u w t g " f w t k p i " v t c p u h g t " v q " v j g " k o c i k p i " u { u v g o l " Y j k v g " n k i j v " c p f " r w t g " E w q t g u e g p e g " u r g e - tra of the ROI were captured. Using normalization factors obtained from the white light intensity in certain spectral t g i k p u " c u " y g m " c u " c p " g o r k t k e c n { " f g t x g f " g z r q p g p v . " v j g " E w q t g u e g p e g " u r g e v t c " y g t g " p q t o c n k | g f " h q t " k p j q o q i g p g q w u " scattering and absorption properties across the tissue. The relative PpIX FI was then derived by isolating the PpIX urgevto o " h t q o " v j g " t g o c k p k p i " u k i p c n " d { " v c m k p i " v j g " n g c u v " u s w c t g u " u q n v w k q p " v q " c p " q x g t f g v g t o k p g f " n k p g c t " u { u v g o " q h " g s w c v k p u l " V j k u " c p c n { u k u " y c u " e q p f w e v g f " w u k p i " e q o o g t - e k e n n { " c x c k n c d n g " u q h v y c t g " * O C V N C D . " O c v j Y q t m u " K p e l h 0 " H w t v j g t o q t g . " q w t " c n i q t k v j o " y c u " e c n k d t c v g f " w u k p i " E w q t g u - e g p e g " r j c p v q o u " y k v j " m p q y p " E R r K Z ⁰¹ This provided the CPpIX values used here. It is important to note that these values are precise and self-consistent within this study, so the relative differences in CPpIX upon which this study

tgkngu"ctg"gzcev"cpf"tgkcdngl"Jqy gxgt."ceewtcvg"eqo rctk-
son of absolute CPpIX values with measurements from
other groups with other devices was not intended.

Histology

All tumor tissues, including the biopsy specimens used
hqt"gz"xkxq"ur gev tqueqr {"ygtg"cuuguugf"j kuvqni kecn {"ce-
eqtfkpi"vq"vjg"YJQ"encuuk fcevkqp"qh"4238²² Isocitrate
dehydrogenase-1 (IDH-1) mutation status was determined
wukpi"ko owpqj kuvqejg o kuvt {"qt" wukpi"o wmvkrngz"nki cvkqp/
fgrgpf gpv"rtqdg"co rnk fcevkqp"cpn {"uku."kh"pggfgf²³

Statistical Analysis

For statistical purposes, we categorized the time after
administration into four groups of 1-hour intervals each.
Distribution was evaluated with the F-test between two
itqwrucpf"Detvngvuu"vguv"htq"vjg"cxgtcig"co qpi"gnrugf"
time groups. For parametric testing, differences between
vyq"itqwrucpf"ygtg"kp xgukicvgtf" wukpi" Hkujgtu"gzcev"vguv"htq"
ecvgitkecn"fcvc="htq"pqrctc o gvtke"vguvkpi."vjg"Mtumcn/
Wallis test was used; and to adjust for multiple com-
rectkupp."vjg"Dqphgttqpk"ogvjqf"ycu" wugf0"Owvnxctkcvg"
analyses were performed using a logistic regression model
cpf"ygtg"ejctcevgtklgf"d{"7"eqpf gpeg"kpvgtxcnu"EKu0"
Fkhgtgpegu"ygtg"tgictgfg"cu" uvcvkukecn {"ukipk fcepv"kh"
the error probability p was less than 5%. All statistical
cpn {"ugu"ygtg"rgtqt o gf"ykvj" gkvjgt"KDO"URUU" uvcvkuk-
ecn"uqhv yctg" *xgtukqp"4702."KDO"Eqtr0t"qt"G\T" *Uckvc o c"
Medical Center, Jichi Medical University), which is a
graphical user interface of the R Foundation for Statisti-
cal Computing.⁴⁶ Vq"cuuguu"vjg"rtg fkevkqp"qh" Ewqtguepeg."
receiver operating characteristic curves were conducted,
ykvj"cp"ctgc"wpfgt"vjg"ewtxg" *CWE+"x"209"dgkpi"cuuw o gf"
to demonstrate reasonable discrimination.

Results

Patients and Tissues

Patient demographics are shown in Table 1. This study
kpenwfgf"47"rcvkpvu" *33"ogp"cpf"36"yqogp."ogcp"ci g"65"
{gctui0" Hkhvggp"rcvkpvu" *82" + "ygtg" fci pqugf"cu" jcxkpi"
diffuse astrocytoma (IDH-mutant), 2 (8%) as diffuse as-
trocytoma (IDH-wild type), and 8 (32%) as oligodendro-
inkq o c" *KFJ / o wcpv."3r13; s"eqfgngvgf"0" Cnn"vw o qtu" ygtg"
itcfqg"KK"ceeqtfkpi"vq"vjg"ncvguv"YJQ"encuuk fcevkqp²² In-
vtcqr gtcvkgxg {"." *58" + "qh"47"rcvkpvu"fg o qpvtcvgf"xkukdng"
Ewqtguepeg"fwtkpi"uwitgt {" *Vcdng"3+0"C"vqvcn"qh":3"vkuuwgu"
ygtg"eqngvgf"htq"ogcuwtg o gpv0"Xkukdng"Ewqtguepeg"ycu"
detected in 21 (25.9%) of 81 tissues.

Time Dependency of FI and CPpIX

ERrkZ"cpf"HK"ygtg"ukipk fcepv {"jki jgt"kp"vkuuwgu."
y jgtg"xkukdng"Ewqtguepeg"ycu"qdugtxgf" wukpi"vjg"o ketq-
scope intraoperatively (p < 0.001; Fig. 1). Figure 2A dem-
qpvtcvgu"ERrkZ"kp"Ewqtguekpi"vkuuwg"rgcmkpi"dgvyggp"9"
and 8 hours after 5-ALA administration. FI was similar,
fg o qpvtcvkpi"kvu"jki jgtg"ngxgn"dgvyggp"9"cpf": "jqwtu"
*Hki0"4D+0" PqpEwqtguekpi"vkuuwgu"o ckpvckpgf"nqy"ERrkZ"
and FI regardless of the time frame, and these values self-
fq o "Ewvwcvgf0

TABLE 1. Patient demographics

Variable	No. of Patients (%)
All	25 (100)
Sex	
Male	11 (44)
Female	14 (56)
Mean age \pm SD, yrs	43 \pm 10.3
Histology	
Diffuse astrocytoma, IDH-mutant	15 (60)
Diffuse astrocytoma, IDH-wild type	2 (8)
Oligodendroglioma, IDH-mutant & 1p/19q codeletion	8 (32)
KPS score	
80	2 (8)
90	7 (28)
100	16 (64)
MRI enhancement	
Positive	6 (24)
Negative	19 (76)
Fluorescence visibility	
Positive	9 (36)
Negative	16 (64)

KPS = Karnofsky Performance Scale.

Fluorescence Visibility, MRI Enhancement, ¹⁸F-FET PET Uptake Ratio, and ADC-Based Measured Tumor Cellularity

Icfqkpkw o"gpjcpeg o gpv"qp"OTK"ycu"ukipk fcepv {"
eqtngcvgf"ykvj"vjg"rtgugpeg"qh"xkukdng"Ewqtguepeg" *r"?"
0.008; Table 2). For both FI and CPpIX, we observed a
vtgpf"vqyctf"jki jgt"xcnwgu"dwv"pq" uvcvkukecn {"ukipk fcepv"
fkhgtgpeg"dgvyggp"xkukdng"Ewqtguepeg"cpf"gzkvkpi"eqp-
trast enhancement (p xcnwgpqpukipk fcepv="Hki0"5+0"CFE/
dcugf"vw o qt"egnnwcnktv {"eqtngcvgf"ykvj"xkukdng"Ewqtgu-
egpeg" *r"?2023+ "kp"wpkxctkcvg"cpn {"uku0"Vko g"mkpgvku"qh"
ERrkZ"cpf"HK"uvcvk f g" d {"OTK"gpjcpeg o gpv"tgxcngf" c"
rgcm"dgvyggp"9"cpf": "jqwtu"kp"dqvj"itqwrucpf" *Hki0"5+0

Uvtcvkh {"kpi"UWX o cz"kp vq"xcnwgu"dgngy"cpf"cdqgx"30:7"
(as previously described³⁺ ykvj"kp"qwt"Ewqtguepv"cpf"pqp-
Ewqtguepv"vkuuwgu"fkf"pqv"fg o qpvtcvg" c"ukipk fcepv" fkhgt-
gpeg"co qpi"vjg"xcnwcvgf"itqwrucpf"xcnwg"pqpukipk fcepv"
Jqy gxgt."gxcnwcvkpi"cdugmwvg"UWX o cz"ykvj"kp"Ewqtguekpi"
 *p"?76- "ogfkcp"4048."KST"307; 6503+ "cpf"pqpEwqtguekpi"
 *p"?37- "ogfkcp"50:8."KST"30; 96709+ "vkuuwg"fg o qpvtcvgf"
c"ukipk fcepv" fkhgtgpeg"dgvyggp"dqvj"Ewqtguekpi"cpf"pqp-
Ewqtguekpi"vkuuwg" *r"?20226- Vcdng"4+0"Xcnkfcvkqp"qh"cd-
solute values of ¹⁸H/HGV"RGV"wrvcng" *UWX o cz+ "tguwngf"
kp"cp" *CWE"qh"209"y jgp"eqo rctkpi"ykvj"kp"Ewqtguekpi"cpf"
pqpEwqtguekpi"vkuuwg."kp fkecvkpi" c" hctk fkuetk o kpcvkqp0

Ki-67/MIB-1 Index and 1p/19q Codeletion

Ogcuwgtf" Mk/89l OKD/3" kpfkegu"kp"pqpEwqtguekpi" *p"
?"82."ogcp"706" + "cpf"Ewqtguekpi" *p"?43."ogcp":04; "+"
vkuuwgu" fkhgtgfg"ukipk fcepv {" *r">"20223+0" PqpEwqtguepv"
uc o rngu"ygtg"pgicvkxg"htq" c"ej tq o quq o cn"3r13; s"eqfgng-
vkqp"kp"68"ecugu"cpf"rqkvkxg"kp"36."y jgtgcu"Ewqtguekpi"

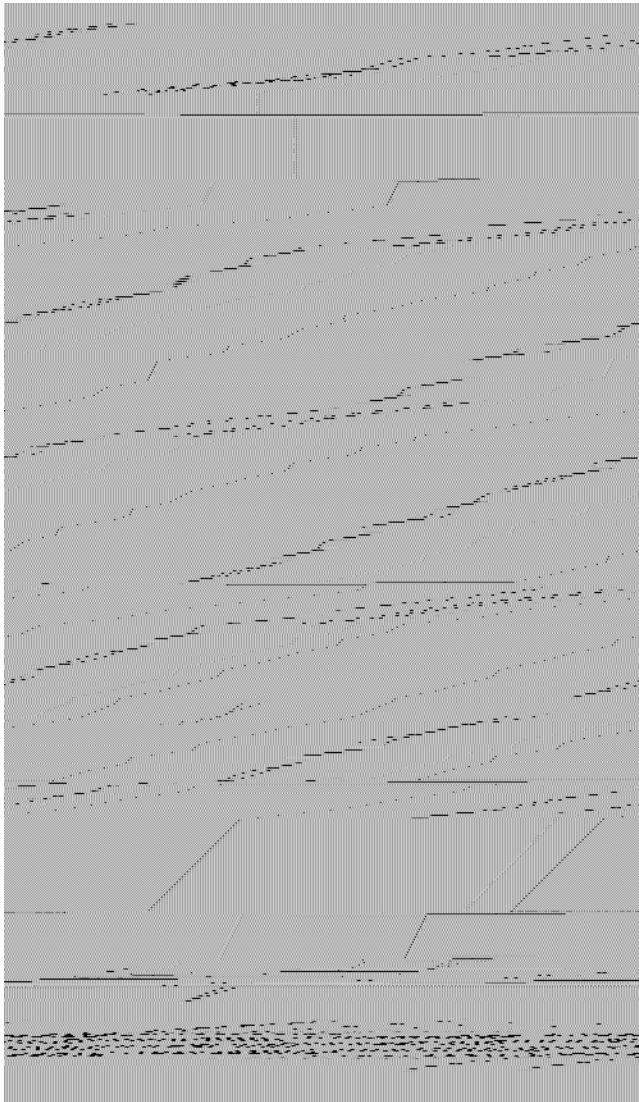


FIG. 1. Box-and-whisker plots demonstrating the relationship between visible fluorescence and CPpIX (A) or FI (B). Visible fluorescence was significantly correlated with CPpIX and FI (** $p < 0.001$). The mean is represented by "X." a.u. = arbitrary units.

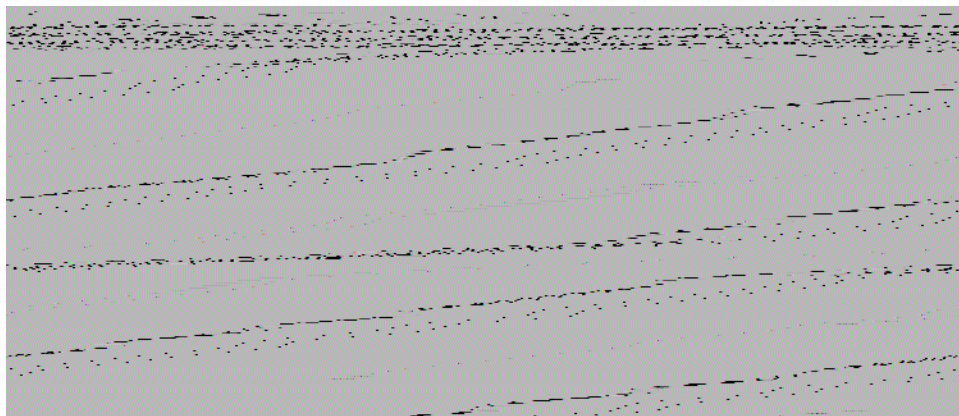


FIG. 2. Time dependency of CPpIX and FI categorized by intraoperative visible fluorescence. In fluorescent tissue, the maximum average of both CPpIX (A) and FI (B) was observed 718 hours after 5-ALA administration. Non-fluorescent tissue (not displayed) did not demonstrate a relevant time kinetic. The error bar represents the standard error of the mean. Figure is available in color online only.

tissue did not demonstrate a codeletion in 12 cases and was present in 9. Stratifying between positive and negative $e_j t q o q u q o c n^3 r l 3; s^e q f g n g v k q p^c o q p i^d q v j^E w q t g u e k p i^i t q w r u^f k f^p q v^f g o q p u v t c v g^c p\{u k i p k f e c p v^f k h h g t g p e g\}$

Multivariate Analysis

From all analyzed variables, a logistic regression model $g n^f g o q p u v t c v g^f v j g^M k/891 O K D/3^k p f g z^* r^?^20233^Q T^50885^; 7^' ^E K^305776; 0; 26^+ c p f^{18 F-F E T P E T a b s o l u t e U W X o c z^* r^?^2025; ^Q T^70; 7^.; 7^' ^E K^302; 46540736^+ v q^d g^k p f g r g p f g p v^h c e v q t u^h q t^r t g f k e v k p i^E w q t g u e g p e g\} I c f q-l i n i u m e n h a n c e m e n t o n M R I, A D C-b a s e d c e l l u l a r i t y, a n d 3 r l 3; s^e q f g n g v k q p^f k f^p q v^t g c e j^u v c v k u v k e c n^u k i p k f e c p e g^k p^m u l t i v a r i a t e a n a l y s i s (T a b l e 2).$

Discussion

The characteristic invasive growth of gliomas represents the biggest challenge when treating this malignancy. $R t g f q o k p c p v n\{.^N I I u^v g p f^v q^f g g r n\}^k p l m v t c v g^c f l c e g p v^p a r e n c h y m a.^25$ Early resection has been shown to be beneficial $e k c n^f g o q p u v t c v k p i^d g v v g t^q x g t c m^u w t x k x c n^k p^e q o r c t k u q p^w i t h b i o p s y a n d t h e "w a i t a n d s e e" a p p r o a c h.^48$ Further- $o q t g^k p e t g c u k p i^v j g^g z v g p v^q h^t g u g e v k q p^y k v j^u o c m n^t g u k f-u a l t u m o r i n c r e a s e s b o t h t h e o v e r a l l a n d p r o g r e s s i o n-f r e e s u r v i v a l i n t h e s e p a t i e n t s.^47,4964:^D q v j^q d u g t x c v k q p u^j c x g^h g f^v q^v j g^t g e q o o g p f c v k q p^h q t^o c z k o c n^q t^c v^n g c u v^u w d o c z k-m a l s a f e r e s e c t i o n a s a n i n i t i a l s t e p i n t h e t r e a t m e n t a l g o-r i t h m o f t h e s e p a t i e n t s.^20$ However, the prognostic value of $x k u k d n g^E w q t g u e g p e g^k p^N I I u^t g o c k p u^w p f g t^k p x g u v k i c v k q p\}^k p^c^t g e g p v^u v w f\{.^L c d g t^g v^c n\}^f g o q p u v t c v g^f^c^u k i p k f e c p v n\{^u j q t v g t^r t q i^t g u k q p/h t g g^* o g f k c p^; 0:^x u^670:^o q p v j u t.^o c-n k i p c p v^v t c p u h q t o c v k q p/h t g g^* o g f k c p^65^x u^8608^o q p v j u t.^c p f^q x g t c m^*7308^x u^8:04^o q p v j u t^u w t x k x c n^k p^E w q t g u e g p v.^j k u v q n q i k e c m\{^e q p l t o g f^N I I u^e q o r c t g f^y k v j^v j q u g^y k v j q w v^c p\}^x k u k d n g^E w q t g u e g p e g^f g u r k v g^u k o k n c t^h q y^O K D^i n d i c e s.^2^J g p e g^E w q t g u e g p e g^k p^N I I^r t g f k e v g f^c^y q t u g^o u t c o m e i n t h e s e p a t i e n t s.$

Fluorescence-guided resection with 5-ALA has become a standard surgical adjunct when resecting HGG, now implemented worldwide.¹ Even though it has been broadly applied for more than a decade, its thorough me-

TABLE 2. Univariate and multivariate analyses of different variables among fluorescing and nonfluorescing tissue and their role for predicting fluorescence

Variable	Univariate Analysis	Multivariate Analysis		
		95% CI	p Value	OR
Gd enhancement on MRI (yes/no)	0.008	0.004–2.161	0.138	0.09
MIB-1 index (%)	<0.001	1.355–9.904	0.011	3.663
¹⁸ F-FET PET SUVmax (absolute value)	0.004	1.092–32.514	0.039	5.958
1p/19q codeletion (yes/no)	0.090	0.043–10.537	0.766	0.671
ADC-based cellularity (absolute value)	0.017	0–1.719	0.081	0.008

Boldface type indicates statistical significance.

tabolization for preferential accumulation of PpIX in human tumor tissue has not yet been fully understood. In the rtgugpvuvwf{"yg"rgtqtogf"cswpvkfckvqp"qh"xkukdng"HK" over time and additionally analyzed a time-based dynamic qh"RrKZ"kp"NI I"vkuuwg"Vkog"mkpgvkeu"qh"Ewqtguegpeg"kp"vjku"gz"xkxq"uvwf{"tgxgcngf"vjcv"vjg"jki"jguv"HK"cpf"ERrKZ"kp"NI I"yg"tg"qdugt"xf"96:"jqtu"chvt"7/CNC"cf"okpku-vtcvqp."uk"oknt"vq"vjcv"fg"opuvtcvgf"kp"J I I."y"jgtg"Ewqtguegpeg"nkmgykug"rgcmgf"chvt"96:"jqtu¹¹ (Fig. 2). Pre-xkqwu"rwdhkujgf"fcvc"qh"RrKZ"gxcmwcvkp"tgxgcngf"c"rgcm"kp"rcuoc"cv"90:"jqtu¹⁵ the results of this study are in accordance with those results. These results suggest that vw"oqt"egnu"kp"NI I"hqnnqy"vjg"ucog"mkpgvkeu"cu"kp"J I I¹¹ counterparts, despite a lower proliferation rate.

Kp"cf"fkvqp."qwt"tpfkpiu"jcxg"ko"rnkecvkpu"ht"vjg"vk"o-ing of surgery after 5-ALA medication. Present recommendations outlined in the standard product characteristics for 5-ALA favor beginning medication 2.5–3.5 hours rtkqt"vq"uwti"gt{"0"Yg"tgeq"ogpf"fqkpi"667"jqtu"rtkqt" to induction of anesthesia, adapted to a center's logistics, such as the average time to reach the tumor of each institution. Moreover, optimizing surgery according to the vkog"fg"rpf"pge{"qh"vjku"Ewqtqr"jqtg"oki"jv"ko"rtqg"Ewqtguegpeg"xkuwcnk"cvkqp."gurgekn{"kp"ygcnn{"Ewqtguekpi"vw"oqtu"Yg"qdugt"xf"xkukdng"Ewqtguegpeg"kp"5;"qh"gxcmw-

ated patients, which is higher than in previous reports^{2–5} but may be related to our case selection of larger tumors, tumors with a positive ¹⁸F-FET signal, or any enhancement.

Early angiogenic changes, such as increased permeability, intravascular volume, or tumor vessel density, jcxg"dggp"rtqrugf"cu"gz"rncpcvkpu"ht"vjg"ceew"onwcvkqp" of PpIX in LGGs.^{2,30,31} 5-ALA alone does not cross the kpvcv"dnqqf/dtckp"dcctkgt" *DDD³¹ However, increases kp"DDD"rgt"ogcdknkv{"ngcf"vq"gpjcpeg"ogpv"qp"OTK"chvt" gadolinium administration and to higher ¹⁸H/HGV"wrvcmg" on PET.³² Yg"qdugt"xf"cu"ukipkfcpev"fkhtgtgpeg"kp"ERrKZ" depending on the presence or absence of contrast en-jcpeg"ogpv"qp"OTK"r"?"2022:"Vcdng"40"Kpvtgukpin{"HK" and CPpIX were also observed in nonenhancing tumors, ykvj"uk"oknt"HK"cpf"RrKZ"vkog"mkpgvkeu"cu"eq"o"rctgf"vq"gp-hancing tumors (Fig. 3). Thus, even in LGG without MRI eqpvtcu"gpjcpeg"ogpv."y"jkej"fg"opuvtcvgu"xkukdng"Ewqtgu-cence in 11%–13% of cases,^{5,6} a similar time dependency of 5-ALA was observed (Fig. 3). We detected higher ¹⁸F-HGV"RGV"wrvcmg"xcmwgu"ykvj"kpctgcukpi"ERrKZ."vjg"fkhtgtgpeg"tgcej"kp"uvcvkukecn"ukipkfcpeg"kp"dqvj"wpkxctkcvg" cpcn{"uku"r"?"20226+"cpf"onwkvxctkcvg"nqikuvke"tgi"tguakp" *r"?"2025:"QT"70;7:"7"EK"302;46540736+0"Eqvtct{"vq" earlier studies,^{4,5,8} yg"fkf"pqv"qdugt"xf"cu"ukipkfcpev"eqttgnc-

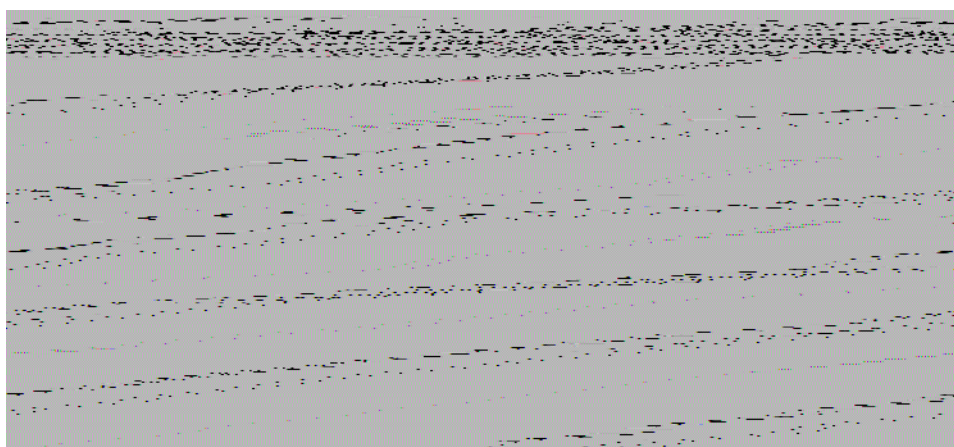


FIG. 3. CPpIX (A) and FI (B) in tumor tissue categorized by MRI enhancement. If tumors demonstrated positive MRI enhancement prior to surgery, tissues tended to have higher values of both CPpIX and FI than negative MRI enhancement. For both groups, values peaked 7–8 hours after 5-ALA medication. The error bar represents the standard error of the mean. Figure is available in color online only.

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Disclosures

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Author Contributions

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Supplemental Information

Previous Presentations

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