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ORIGINAL ARTICLE

Diagnostic accuracy of intraoperative perfusion-weighted MRI and 5-aminolevulinic acid in relation to contrast-enhanced intraoperative MRI and ^{11}C-methionine positron emission tomography in resection of glioblastoma: a prospective study

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Abstract

The aim of our study was to compare depicted pre-, intra-, and postoperative tumor volume of met-PET, perfusion-weighed MRI (PWI), and Gd-DTPA MRI. Further, to assess their sensitivity and specificity in correlation with histopathological specimen. Inclusion criteria of the prospective study were histological confirmed glioblastoma (GB), age > 18, and eligible for gross total resection (GTR). Met-PET was performed before and after surgery. Gd-DTPA MRI and PWI were performed before, during, and after surgery. A combined 5-aminolevulinic acid (5-ALA) and iMRI-guided surgery was performed. Volumetric analysis was evaluated for all imaging modalities except for 5-ALA. A total of 59 navigated biopsies were taken. Sensitivity and specificity were calculated for Gd-DTPA MRI, PWI, met-PET, and 5-ALA according to the histology of specimen. Met-PET depicted significantly larger tumor volume before surgery ($p = 0.01$) compared to PWI and Gd-DTPI MRI. We found no significant difference in tumor volume between met-PET and PWI after surgery ($p = 0.059$). Both PWI and met-PET showed significantly larger tumor volume after surgery when compared to Gd-DTPA ($p = 0.018$ and $p = 0.003$, respectively). Intraoperative PWI reading was impaired in 33.3% due to artifacts. Met-PET showed the highest sensitivity for detection of GB with 95%. The lowest sensitivity was found with Gd-DTPA MRI (50%), while 5-ALA and intraoperative PWI showed similar results (69 and 67%). Met-Pet is the imaging modality with the highest sensitivity to detect a residual tumor in GB. Intraoperative PWI seems to have a synergistic effect to Gd-DTPA and 5-ALA. However, its value may be limited by artifacts. Both pre- and intraoperative PWI cannot substitute met-PET in tumor detection.

Keywords ^{11}C-methionine PET · PWI · Gd-DTPA MRI · 5-ALA · Glioblastoma

Introduction

High-grade gliomas (HGG) have a highly unfavorable prognosis [16, 19]. Gross total resection (GTR), if feasible, is a crucial step in the treatment path of these tumors [3, 20]. However, diffuse and infiltrative growth pattern mostly beyond gadolinium-enhanced borders in MRI hampers this goal [1]. Different imaging techniques such as intraoperative magnetic resonance imaging (iMRI), intraoperative ultrasonography (iUS), or 5-aminolevulinic acid (5-ALA)-assisted surgery help to achieve GTR in the combination with intraoperative neuromonitoring (IOM) and neuro-navigation [11, 24, 28]. Our group showed that the abovementioned intraoperative imaging methods are able to depict the infiltrative tumor tissue

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only to a certain extent, and only 5-ALA achieved significant correlation with histopathological findings [6]. At present, amino acid positron emission tomography is the only non-experimental technique that allows for a direct visualization of metabolically active glioblastoma (GB). Thus, it represents the diagnostic gold standard to detect an active tumor in GB [9, 12]. Stockammer et al. showed a strong correlation of amino acid PET and 5-ALA fluorescence in the detection of high-grade glioma implicating the advantage of the combined use of both techniques for planning and resection. [27] Nevertheless, the lack of intraoperative PET scanners, high costs, and limited availability hamper its routine use. Hence, most trials for GB rely on residual Gd-DTPA enhancement on postoperative MRI to assess the extent of resection. Perfusion-weighed MRI (PWI) is a well-established diagnostic sequence with a special value in differentiating radiation necrosis from active tumor. [10, 17] A first pilot study assessed its intraoperative use suggesting a potential benefit to improve the intraoperative detection of a residual tumor in order to achieve GTR. [24]

The aim of our study was to compare the diagnostic accuracy of PWI and Gd-DTPA in relation to ^{11}C-methionine PET (met-PET) in glioblastoma by a volumetric assessment of pre-, intra-, and postoperative imaging. Further, we aim to assess the sensitivity and specificity based on intraoperative specimens of intraoperative PWI and Gd-DTPA-enhanced iMRI and 5-ALA compared to preoperative met-PET.

Patients and methods

Study design

This was a single-center prospective and non-randomized study. Only patients with glioblastoma were enrolled in the study. An institutional ethics approval was obtained by the local ethical board (Ethikkommission Ulm No: 172/12). Inclusion criteria were patients above 18 years of age, eligible for GTR, and confirmed diagnosis of glioblastoma according to World Health Organization (WHO) Guidelines from 2007. Patients were recruited between March 2013 to June 2014 and September 2016 to May 2017. The study was conducted according to the international Declaration of Helsinki.

Imaging techniques and OR setup

^{11}C-methionine PET CT

Met-PET CT was performed within 1 week before and within 14 days after the surgery [2]. Three patients were not examined with met-PET after the surgery. Residual uptake was semi-quantitatively assessed by a specialist in nuclear medicine (AB).

Pre- and postoperative MRI

Gd-DTPA MRI and PWI were completed before surgery and within 48 h after surgical resection. Preoperative MRI images were performed no longer than 5 days preoperatively and included T1-weighted spin echo, T2-weighted turbo spin echo, fluid-attenuated inversion recovery (FLAIR), and diffusion-weighted imaging (DWI) sequences as well as PWI and T1 Gd-DTPA-enhanced MR images. Six patients did not have preoperative PWI, and three patients did not get postoperative PWI.

Assessment of residual Gd-DTPA uptake in postoperative MRI was categorically evaluated by a neuroradiologist. GTR was defined if no tumor rest in any sequences was found.

Intraoperative MRI

An intraoperative 1.5T MRI scanner is available (Espree, Siemens AG, Erlangen, Germany) at our department as a one-room solution since October 2008. During surgery, an intraoperative MRI scan was performed according to the surgeon's discretion. iMRI sequences included T1-weighted spin echo, T2-weighted turbo spin echo, FLAIR, PWI, and DWI sequences. Pre- and postoperative MRI images were performed either with the intraoperative scanner or with 1.5T MRI Symphony system (Siemens AG, Erlangen, Germany).

5-Aminolevulinic acid

5-ALA was administered orally, 4 hours before surgery in a common dose of 20 mg/kg body weight. Zeiss Pentero® 600 microscope was used intraoperatively with an integrated head-up display for neuro-navigation and Blue 400® filter to perform 405-nm fluorescence. Six patients did not receive 5-ALA preoperatively.

Study protocol

Surgeons were blinded for the results of the preoperative met-PET. In all patients, a typical white light resection under neuro-navigational guidance was performed, until the surgeon assumed GTR. After hemostasis was achieved, the surgeon scanned the resection cavity using 5-ALA, if this was applied before surgery. Conspicuous areas which could contain residual tumor were marked with neuro-navigation. After completion of the iMRI scan, areas with residual contrast enhancement or hyperperfusion in PWI were marked likewise. At all marked areas, 5-ALA, PWI, and iMRI were cross-referenced again and the results were recorded. As for PWI, regional cerebral blood volume (rCBV) was analyzed as the most relevant factor for detection of HGG [30, 31]. Then, navigated biopsies were harvested from these sites as previously published [4]. Histopathological assessment of all biopsies was

performed separately, and results were correlated with all image modalities including postoperative images.

The number of biopsies was individually based on the number of conspicuous findings in the imaging methods. For ethical reasons, harvesting of biopsies was at surgeon's discretion.

Imaging findings were classified by two neurosurgeons who rated the tissue depiction of 5-ALA, Gd-DTPA MRI, PWI, and preoperative met-PET as tumor-positive or negative. Intraoperative MRI findings were evaluated in close cooperation with the section of neuroradiology. These findings were correlated with the respective histopathological assessment of harvested biopsies.

Histopathological assessment

Harvested samples and main tumor tissue were examined in the local neuropathology. The neuropathologists were blinded for the categorization and the location of the biopsies. Two neuropathologists observed the samples separately. In case of disagreement, the neuropathologists agreed to a consensus diagnosis.

All samples were fixed in 4% buffered formalin and paraffin embedded. Human glioblastomas were classified according to the 2007 WHO classification of tumors of the central nervous system [20]. For this purpose, paraffin sections were stained with hematoxylin and eosin (H&E). Immunohistochemistry for glioblastomas was carried out with antibodies raised against glial fibrillary acidic protein (GFAP; polyclonal rabbit, 1/1000, DAKO, Glostrup, Denmark), microtubule-associated protein MAP2 (HM-2, 1/500, heat pretreatment, Sigma-Aldrich, St. Louis, MO, USA), and the ki67-epitope (MIB1, 1/100, heat pretreatment, DAKO, Glostrup, Denmark). "Most likely tumor-free tissue" was referred to samples, in which no tumor cells could be identified at the H&E level and no proliferation was detectable with anti-ki67. Hence, we explicitly categorized the infiltration zone beyond the solid part of the lesion as pathological tissue.

Volumetric assessment

Tumor volume and metabolic volume (met-PET) depicted by all abovementioned imaging modalities except for 5-ALA were measured and calculated using iPlan 3.0 and Elements (Brainlab, München, Germany). The volumetric assessment was performed pre- and postoperatively for met-PET and pre-, intra-, and postoperatively for Gd-DTPA-enahanced MRI/iMRI and PWI MRI/iMRI. All image modalities were imported and fused to compare the localization of tumor or reference points. The met-PET tracer volume was defined according to the established tumor to normal brain ratio > 1.3 as published by Kracht et al. [13]

Statistical assessment

Statistical analysis was performed using SPSS 23.0 (IBM Corporation, Armonk New York, USA). Besides demographic data, sensitivity and specificity of pathological tissue were calculated after dichotomization of imaging results. The evaluation was performed using medcalc.org. General differences between the cohorts including different imaging modalities before and after surgery were analyzed. Direct comparison of Gd-DTPA MRI, met-PET, and PWI was performed with Wilcoxon test. Similarly, Wilcoxon test was used for direct comparison of residual tumor volume in intraoperative Gd-DTPA MRI and PWI. The signed test was used for evaluation of differences between imaging modalities.

Results

Patient characteristics and general assessment

A total number of 18 patients harboring a glioblastoma (GB) were assessed prospectively. All patients received pre-, intra-, and postoperative MRI with PWI and Gd-DTPA and pre- and postoperative MET-PET CT. Twelve patients received 5-ALA. The aim of surgery was GTR in all cases. This was defined as complete removal of a tumor suspected in postoperative MRI. The demographic data are summarized in Table 1. GTR evaluation in Table 1 is based on tumor remnant found in all postoperative sequences. Fifty-nine biopsies were harvested intraoperatively. One to 6 biopsies were taken per patient. Forty-two biopsies were performed after 5-ALA was given prior to surgery.

Volumetric assessment

The largest preoperative mean tumor volume was seen with met-PET (Table 2, Fig. 1). The difference was statistically

Table 1 Patients and tumor characteristics

N (biopsies)	59
N (patients)	18
Age (min-max, years)	32–67
Median (years)	53
Male ratio	66.7% (12)
Tumor location	
Frontal	66.7% (12)
Temporal	16.7% (3)
Parietal	5.6% (1)
Occipital	11.1% (2)
Recurrent tumor	22.2% (4)
Tumor side (left)	33.3% (6)
GTR	77.8% (14)

Table 2 Tumor volume according to different imaging modalities (Gd-DTPA MRI—gadolinium-weighted magnetic resonance imaging; Met-PET CT—methionine positron emission tomography; SE—standard error)

	Preoperative tumor volume in cm^3 (mean; SE)	Intraoperative tumor volume in cm^3 (mean, SE)	Postoperative tumor volume in cm^3 (mean, SE)
Met-PET CT	53.3; 17.4		3.6; 0.9
Gd-DTPA MRI	41.3; 13.4	2.1; 0.9	0.1; 0.1
Perfusion-weighted MRI	45.1; 15.9	6.6; 3.1	2.3; 1.1

significant when compared to PWI ($p = 0.01$, Wilcoxon test) and Gd-DTPA MRI ($p = 0.01$, Wilcoxon test). Mean tumor volumes and standard errors are summarized in Table 2 and depicted in Fig. 1. Perfusion and Gd-DTPA MRI showed no significant difference both between preoperative and between intraoperative tumor volumes ($p = 0.347$ and 0.131, respectively, Wilcoxon test), while PWI volume was slightly larger than Gd-DTPA volume (Table 2, Fig. 2). We found a significant difference between postoperative PWI and Gd-DTPA MRI tumor volume ($p = 0.018$, Wilcoxon test, Fig. 3). Simultaneously, the direct comparison between postoperative met-PET and PWI showed a trend to a significant difference ($p = 0.059$, Wilcoxon test). Postoperative met-PET volume of residual metabolic active zones was significantly larger than Gd-DTPA MRI ($p = 0.003$, Wilcoxon test, Fig. 3).

Pairwise comparison of tumor depiction

When comparing all imaging modalities pair-wise, met-PET is associated with significantly higher numbers of positive findings (Table 3). Postoperative residual tumor detected by PWI and met-PET is depicted in Fig. 4.

Comparison of tumor detection based on histopathological assessment

Considering all positive tumor probes, we have evaluated mitotic index (ki-67), percent of necrosis found in the biopsies, and the percent of solid tumor, tumor infiltration zone, and normal brain tissue (all in % of the respective specimen). All data are summarized in Fig. 5.

Sensitivity and specificity

After the histopathological assessment, in 58 (98.3%) of all samples, tumor cells were confirmed in harvested tissue, while only in 1 (1.7%) biopsy only tumor-free tissue was confirmed. We calculated sensitivity and specificity of imaging results after dichotomization of data. The sensitivity of preoperative met-PET to detect pathological tissue was 95% (85–99%, confidence interval (CI) 95%, Table 4). The sensitivity of PWI was 67% (53–79%, CI 95%, Table 4). Using 5-ALA, the sensitivity was 69% (53–82%, CI 95%, Table 4), and using Gd-DTPA MRI, the sensitivity was 50% (43–70%, CI 95%, Table 4). No valid specificity could have been calculated

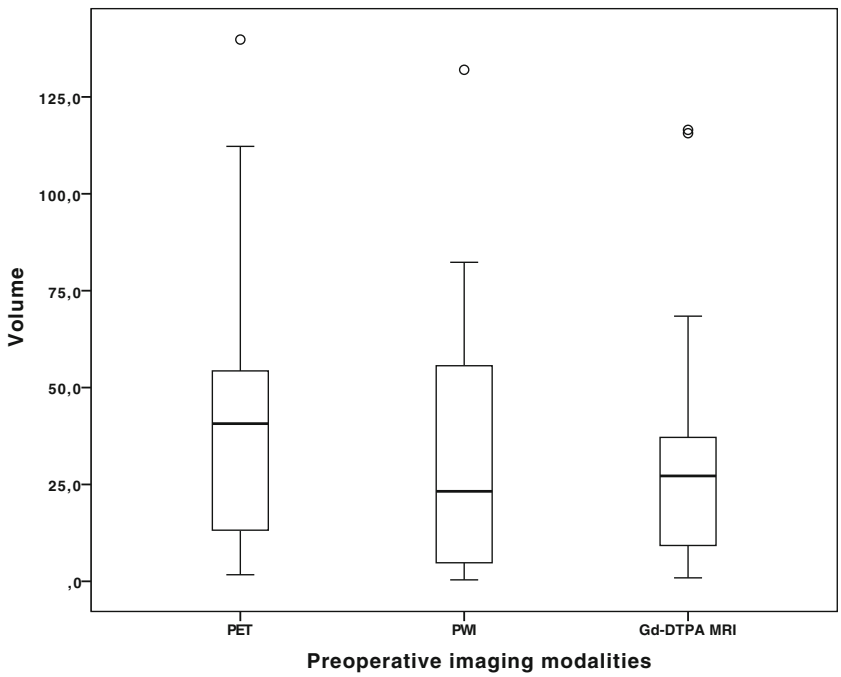

Fig. 1 Initial tumor volume according to different imaging modalities (Gd-DTPA MRI—gadolinium-enhanced magnetic resonance imaging; PET—positron emission tomography; PWI—perfusion-weighted magnetic resonance imaging)

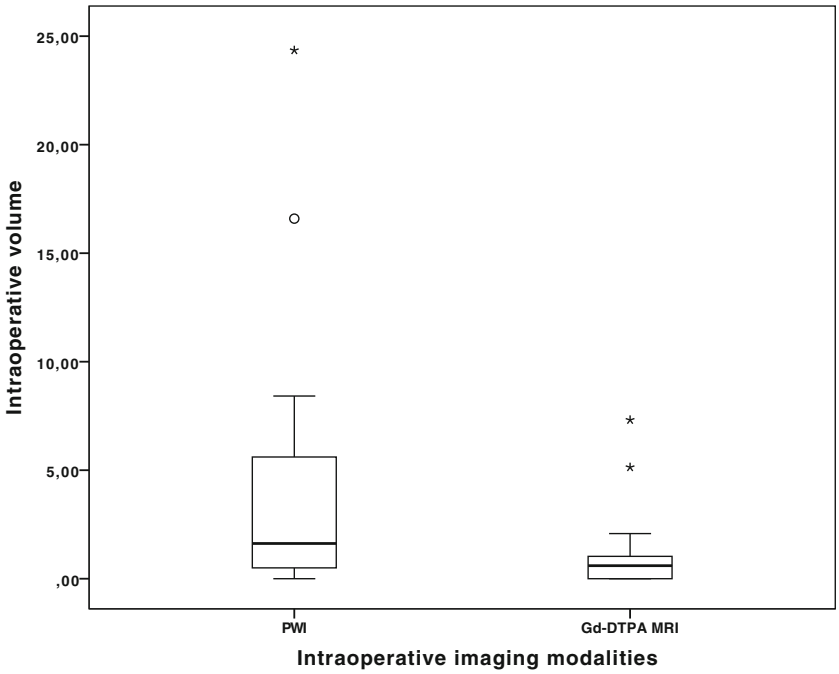

Fig. 2 Intraoperative residual tumor volume according to Gd-DTPA MRI and PWI (Gd-DTPA MRI—gadolinium-enhanced magnetic resonance imaging; PWI—perfusion-weighted magnetic resonance imaging)

based on the fact that only one true negative sample was harvested.

Discussion

GB are infiltrative neoplasms that recur inevitably and result in shorter life expectancy [15, 16]. Nevertheless, GTR is related to longer OS and better tumor control in gliomas [3, 7, 14, 21, 26]. The infiltrative growth pattern in regard to achieving GTR is challenging, and various intraoperative imaging techniques try to increase the extent of resection (EoR) [22–24]. HGGs have been shown to spread beyond Gd-DTPA-enhanced MRI borders and to invade surrounding brain parenchyma without visible limits [1]. In this concern, Li et al. showed that safe supramaximal resection beyond Gd-DTPA MRI depiction is associated with prolonged survival in GB patients [18]. Amino acid PET seems to characterize the

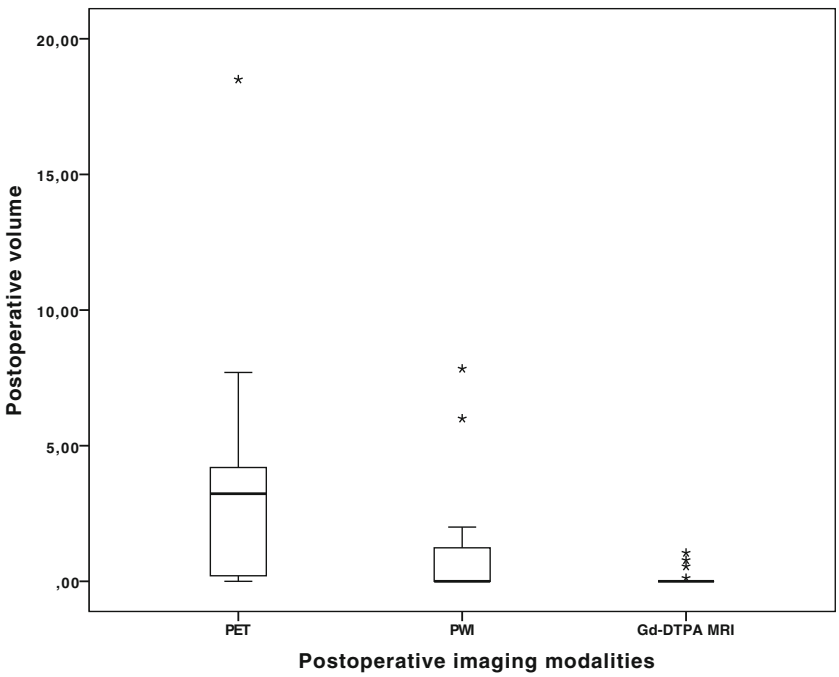

Fig. 3 Postoperative tumor volume according to Gd-DTPA MRI, met-PET CT, and PWI (Gd-DTPA MRI—gadolinium-enhanced magnetic resonance imaging; met-PET CT—methionine positron emission tomography; PWI—perfusion-weighted magnetic resonance imaging)

Table 3 Pairwise comparison of positive tumor lesions according to different imaging modalities

		5-ALA	Gd-DTPA MRI	PWI
Met-PET	Positive	12	27	18
	Same	28	29	37
	Negative	2	3	2
	p	0.013	< 0.001	< 0.001
Gd-DTPA MRI	Positive	6		11
	Same	17		29
	Negative	19		17
	p	0.015		0.345
PWI	Positive	10		
	Same	21		
	Negative	10		
	p	1.000		

biological activity of gliomas more precisely and can depict metabolic active regions that are described as hot spots [15]. We have conducted a prospective assessment of patients harboring a glioblastoma eligible for GTR. The main aim of our study was to assess the additional value of met-PET and intraoperative as well as postoperative PWI after combined 5-ALA and iMRI-assisted resection of GB. Furthermore, histopathological results of navigated biopsies were correlated with met-PET, 5-ALA, PWI, and Gd-DTPA findings to determine sensitivity and specificity of all imaging methods. Finally, we have evaluated and compared the volumetric analyses of all imaging techniques except for 5-ALA before surgery, intraoperatively, and after surgery. According to our knowledge, this is the first report comparing the histopathological correlation of preoperative met-PET as well as preoperative, intraoperative, and postoperative Gd-DPTA MRI, PWI, and 5-ALA.

PWI has been shown to detect the tumor progress and to distinguish between real recurrence and pseudoprogression [10, 17]. Roder et al. suggested PWI as a relevant intraoperative imaging technique in glioma surgery [24]. This method could depict metabolic activity of GB more accurately than Gd-DTPA. The sensitivity of PWI was higher than the sensitivity of Gd-DTPA MRI in our study. Nevertheless, we found no significant difference in intraoperative tumor volume between PWI and Gd-DTPA-enhanced MRI even if intraoperative PWI volume was larger. Our impression was that intraoperative artifacts resulting from water/air interface compromise the PWI reading. Based on that, interpretation of intraoperative PWI findings is partially limited. On the other hand, PWI seems to have a synergistic effect with intraoperative Gd-DTPA and even with 5-ALA. Hence, it provides additional information regarding tumor remnants and might be beneficial in order to increase EoR in glioma surgery.

According to our results, met-PET is the imaging modality with the highest sensitivity to detect glioblastoma. Tumor detected by met-PET in preoperative settings showed the largest tumor volume compared to preoperative Gd-DTPA MRI or PWI. Pirotte et al. showed that in patients with anaplastic astrocytoma and glioblastoma total amino-acid-PET-tracer-uptake based resection lead to significant longer survival [23]. Congruent with our results, amino acids PET seems to depict malignant gliomas more precisely and might be a more suitable tool to define the target for surgical planning with the aim to increase the extent of resection beyond contrast enhancement, resulting in better tumor control and longer survival. However, postoperative Gd-DTPA MRI is still the standard imaging modality in the postoperative detection of tumor remnants with significant influence on decision-making for further adjuvant therapy. Amino acids PET seems to be more appropriate for the definition of postoperative target volume for radiotherapy and should be the basis of decision-making for both surgical planning and adjuvant treatment.

Interestingly, even if met-PET volume after the surgery was larger than in PWI, the difference was not statistically significant, implicating the important role of PWI in GB patients. Simultaneously, according to our data, in PWI, postoperative tumor volume was significantly larger in direct comparison with postoperative Gd-DTPA MRI. This fact underlines the importance of PWI to characterize residual active tumor regions potentially comparable with the results detected by met-PET. However, Filss et al. showed that amino acid PET imaging depicts more precisely the residual tumor borders when compared to PWI [8]. Nevertheless, even if the sensitivity of PET is

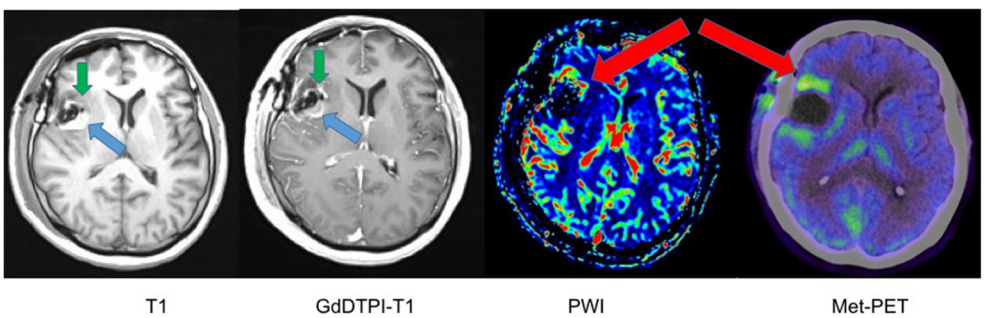

Fig. 4 Pairwise comparison of positive tumor lesions according to different imaging modalities

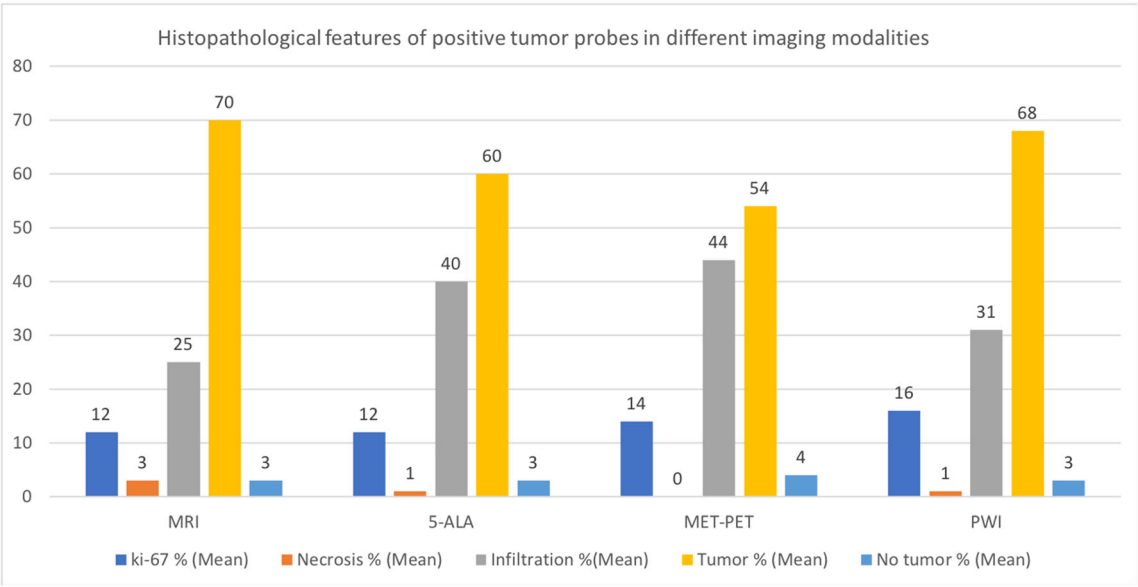

Fig. 5 Postoperative Gd-DTPI, PWI, and met-PET CT images showing suspected tumor remnant in PWI and met-PET CT (red arrow—tumor remnant; blue arrow—residual blood clot; green arrow—vessels)

higher, the costs and availability of PET are surely the limiting factors, so PWI might be an alternative with justifiable results and with the advantage of intraoperative use that might increase EoR beyond Gd-DTPA enhancement in iMRI-assisted surgery.

5-ALA has been used for many years to delineate tumor from unaffected brain parenchyma resulting in higher rates of GTR and better survival [29]. Despite this fact, it has been shown that even 5-ALA has some limitations. There are hints in the literature that blood-brain barrier disruption as depicted by Gd-DTPA may not be related to 5-ALA accumulation [9]. Additionally, Floeth et al. demonstrated that 5-ALA fluorescence cannot be considered as a reliable surrogate for amino acid uptake and that ^{18}F-FET had higher sensitivity in the detection of gliomas [9]. Similarly, our data confirmed lower sensitivity for tumor detection of 5-ALA when compared to met-PET. Additionally, we found a sensitivity of PWI similar to 5-ALA.

Evaluating the malignancy of samples and correlating them with positive findings in different imaging modalities, all of them seem to depict true malignant regions of GB. Therefore, the increased tumor volume in met-PET and PWI represents solid tumor and not "only" infiltration zone. Hence, increasing EoR beyond contrast enhancement leads to a further resection of solid tumor and not only infiltration zone. 5-ALA, PWI, and preoperative met-PET according to our data help to achieve this goal. Gd-DTPA-positive lesions are only the peak of an iceberg as reflected by other imaging modalities. The resection of the Gd-DTPA-positive MRI areas as the most malignant parts of the tumor results in better survival according to the actual data [3]. Further prospective studies must evaluate if resection of areas beyond Gd-DTPA uptake in not-eloquent localized GB leads to prolonged survival.

To sum up, 5-ALA, iMRI, and intraoperative PWI might have a positive synergistic effect giving different information about infiltrating tumor cells which could result in simpler and larger EoR. In this concern, the combination between met-PET before the surgery as a tool for surgical planning and intraoperative 5-ALA and PWI with Gd-DTPA MRI could result in an improved tumor detection to increase EoR in non-eloquent locations and might lead to longer survival.

Table 4 Sensitivity of different imaging modalities to detect tumor tissue (Gd-DTPA MRI—gadolinium-weighted magnetic resonance imaging; Met-PET CT—methionine positron emission tomography; 5-ALA—5-aminolevulinic acid)

Met-PET CT	95%
5-ALA	69%
Perfusion-weighted MRI	67%
Gd-DTPA MRI	50%

Limitations

In our study, almost all samples which were harvested intraoperatively confirmed tumor tissue, so no relevant specificity could have been calculated. Even if met-PET achieved the highest sensitivity, it was not able to detect a tumor in all samples. Glioblastoma should be considered as a systemic disease, and surgical resection is only the first step in the treatment path that cannot lead to complete healing of the disease. Gd-DTPA MRI enhancements are obviously the only tip of the iceberg and the tumor infiltration spread beyond Gd-DTPA MRI and even beyond met-PET boundaries. Our study encompasses several systematic biases. The small number of

patients and monocentric study design might have influenced the data negatively. The subjective assessment of images could have biased the study as well. Furthermore, the surgeon was not blinded for the intraoperative imaging evaluation because it would not have been possible otherwise to assess intraoperative 5-ALA and Gd-DTPA MRI depiction. Met-PET is not available in intraoperative settings. Hence, during surgery, brain shift and small aberrations in neuro-navigation could have biased the data and histopathological correlation of met-PET with navigated biopsies. Furthermore, postoperative met-PET was typically performed 7–14 days after surgery. Even if Buchman et al. reported that there is no relevant difference in regard to surgical-induced morphological changes in PET CT after 72 h, these artifacts could have led to potentially false-positive postoperative findings in met-PET [2]. Met-PET depicts metabolic activity of GB, while MRI imaging is related to blood-brain barrier disruption so the comparison of both imaging methods is relative. Nevertheless, the precise definition of the therapeutic target might finally improve PFS and OS of GB patients. 5-ALA was not administered to all patient in our study. Thus, slightly fewer biopsy data (42 vs. 59) exists for this modality. Finally, GTR was lower in our study compared to the previously published data on the combined approach of 5-ALA and iMRI which is most likely due to a selection issue of patients not amenable to GTR [5, 25]. However, the aim of our study was to compare tumor depiction and assessment of malignancy by an imaging method and not the surgical outcome. Thus, the results should most likely not be affected by this bias.

Future perspectives

As for MRI and infiltrative growth of GB, different sequences as FLAIR need to be evaluated and compared to other imaging methods in further studies in order to define the limits of MRI. Ultra-early postoperative MRI as defined in our previous publication could be relevant in this concern to minimize surgically induced changes in FLAIR and evaluate the infiltrative growth of HGG more precisely and closely to met-PET [21]. Further, we aim to evaluate and compare the predictive value of residual met-PET or PWI MRI changes in postoperative imaging to predict tumor recurrence. Finally, PWI might be an additional planning tool which is not related to high costs and might help to define resection target in the absence of amino acid PET. Large prospective studies must evaluate this role of PWI for further outcome.

Conclusion

Intraoperative PWI showed similar sensitivity for detection of glioblastoma as 5-ALA. Although, it is prone to artifacts limiting its evaluation. Yet, PWI provides relevant pre-, intra-, and postoperative information on the extent of tumor invasion. Met-PET has the highest sensitivity to identify residual GB. It provides a more realistic image of the infiltrative spread of GB in preoperative and postoperative images compared to contrast enhancement alone and could be the most appropriate method to define the therapeutic target and hereby the ideal method for surgical planning. Gd-DTPA MRI has the lowest sensitivity to detect the "real" GB infiltration and shows only the tip of the iceberg of this disease.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval An institutional ethics approval was obtained by the local ethical board (Ethikkommission Ulm No: 172/12). The study was conducted according to the international Declaration of Helsinki.

Statement of informed consent Informed consent was obtained.

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