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5-ALA-assisted stereotactic brain tumor biopsy improve diagnostic yield

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A B S T R A C T

Background: Abnormal tissue in stereotactic brain biopsies (SBB) is traditionally identified intraoperatively via pathological frozen section (FS), a time-consuming and error-prone process. The objective of this study was to assess the efficacy of 5-aminolevulinic acid (5-ALA) administration on SBB operation time, diagnostic yield, and the associated complication rate.

Methods: We retrospectively evaluated all consecutive patients undergoing SBB with preoperative 5-ALA administration and intraoperative assessment of fluorescence (5-ALA group) between 2010 and 2017 in a single center. They were compared to all consecutive patients who underwent traditional brain biopsy with FS (control group). Demographics, clinical data, diagnostic yield of biopsies, and complication rates were documented.

Results: In all, 376 patients underwent SBB for suspected oncological pathology during the study period. All 34 of the 5-ALA-assisted SBB were diagnostic compared to 96.8% of the control group. The mean operative time was the same for both groups, but it was significantly shorter for the 5-ALA patients with florescent samples compared to patients with negative fluorescence (61 ± 25 min vs. 136 ± 54 min, $P = 0.003$) and compared to the control group (74 ± 34 min vs. 61 ± 25 min, $P = 0.03$). Symptomatic bleed was absent in the 5-ALA group and present in 5.4% of the controls. No adverse events were associated with preoperative 5-ALA administration.

Conclusions: Preoperative administration of 5-ALA may improve the diagnostic yield of SBB and shortens operation time in cases of fluorescent pathological tissue. In addition, it may reduce the risk for associated postoperative symptomatic bleed. 5-ALA-assisted SBB is a viable alternative to traditional biopsies with FS.

Introduction

Stereotactic brain biopsies (SBB) are the gold standard procedure for the diagnosis of intracranial pathologies not amenable to surgical resection [1–8]. SBB have gained additional clinical importance with the introduction of molecular diagnostics and targeted therapies. Despite the rapid development of alternative, noninvasive methods for tumor characterization, such as magnetic resonance spectroscopy (MRS) [9] and radiomics [10,11], tissue diagnosis, and especially molecular phenotyping, are more important today than ever. It is now recognized that the genetic landscape of tumors is unstable, and that brain tumors tend to undergo genetic and epigenetic changes following treatment [12,13]. The progressive prolongation of survival of patients with primary and metastatic brain tumors, and the growing armamentarium of tailored treatment options have led to increasing demand for minimally invasive, consecutive tissue sampling techniques that are in constant need of optimization. Since the introduction of SBB in the 1940s, there have been ongoing technological and conceptual attempts at improving the diagnostic yield and reducing the complication rates [14–17]. Among these attempts is the development of computerized tomography (CT) and magnetic resonance imaging (MRI)-based frameless neuronavigation, and the introduction of real-time localization via navigated needle biopsy. Verification of a successful biopsy has traditionally been via intraoperative pathology in the form of frozen section (FS), followed by identification of the pathological tissue. Pathological verification

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via FS is considered a standard of care in tumor-related SBB in most centers. It is, however, a somewhat cumbersome procedure, since it prolongs the operation, necessitates a larger volume of tissue samples, and depends on the personal skills of the on-call pathologist.

The value of each of the technical methods, e.g., frame vs frameless, CT vs MRI studies, with and without fiducial markers, etc., has long been the subject of debate, and the effect of each method on the accuracy and safety of SBB has been investigated in a number of studies [1,4,6–8,17]. A novel technological improvement, "tumor photodiagnosis" has recently been introduced [18]. The method introduces a pathological tissue-specific marker, such as 5-aminolevulinic acid (5-ALA) or fluorescein that allows for the intraoperative detection of fluorescence if the obtained sample contains tumor, and thus providing rapid verification of the sample. This approach has several theoretical advantages, such as the reduction of operation time, since a positive fluorescence sample makes pathological verification via FS unnecessary. In addition, it may minimize the risk for intraoperative bleed since fewer samples are taken if the first one is positive.

In this study, we aimed at validating the usefulness of 5-ALA as an intraoperative marker for tumor-positive samples for SBB. Specifically, we examined the effect of the preoperative administration of 5-ALA on operation time and the risk of intraoperative bleed.

Methods

We conducted a historical cohort study in which all adult patients who underwent SBB in our institution between 2010 and 2017 were identified in the hospital database and their medical records were reviewed. Excluded were 27 patients who underwent frame-based SBB and those who underwent SBB for a non-oncologic etiology, such as suspected vasculitis or diffuse demyelinating disease. Three additional patients were excluded due to an unexpected prolongation of the surgery time (equipment malfunction in 2 cases and anesthetic instability in one case). The use of preoperative 5-ALA, operation time, positive fluorescence, diagnostic yield, and postoperative biopsy-related morbidity and mortality were documented. The final pathology result was extracted from the formal pathological report. A biopsy was determined as being non-diagnostic after a senior neuropathologist reviewed the sample, and following discussion by members of the neuropathological board.

This study was approved by the local institutional review board (0756–17). 5-ALA is routinely administered preoperatively to all tumor patients in our center, thus patient informed consent was not required for participation in the current study.

SBB procedure

All SBB were performed by a senior neurosurgeon who was assisted by a resident. All the patients received 1.5 gr of oral 5-ALA hydrochloride (Biosynth AG, Switzerland) 4 h before surgery. All SBB were performed according to the departmental standard of care, which includes patient registration to a fusion of CT and MRI scanning on which the trajectory and target planning was made. In the case of an enhancing lesion, the enhancing region was chosen as the target. A frameless SBB using the Brainlab VarioGuide (BrainLab AG, Feldkirchen, Germany) system was performed. Briefly: following the registration and assembly of the VarioGuide system, a twist drill was used for trephination, and the navigated biopsy needle was introduced into the target. Multiple samples were taken in 4 quarters of the lesion and sent for FS and permanent pathology. Fluorescence was assessed under a 440-nm blue light source by means of a standard neurosurgical microscope (Zeiss OPMI Pentero) in a darkened room. The diagnostic yield was reported as the calculated ratio of diagnostic biopsies and overall biopsies for each study group.

Statistical analysis

The SPSS 24.0 (IBM Corp.) was used for all analyses. The Chi-square test and Student's t-test were used for comparison of proportions and means. A P value of < 0.05 was considered statistically significant in all cases.

Results

A total of 376 biopsies were performed for suspected neoplasms and they were included in this study. Demographics and pathologies for the patients in each group are detailed in Table 1. The majority of the patients in both the 5-ALA ($n = 34$) and control ($n = 342$) groups had high-grade gliomas, followed by low-grade gliomas, and CNS lymphomas. The area of contrast enhancement as seen on T1-weighted MRI studies after the injection of gadolinium was chosen as the preferred target in all cases. Twenty-eight of these cases (82.4%) had positive fluorescence (5-ALA+) intraoperatively (Fig. 1, see Fig. 2 to for example of positive fluorescence). Of those 5-ALA + samples, 10 had a positive FS, and 18 had negative FS, all with a positive final pathology, Table 2. Of the 6 non-fluorescent samples (5ALA-), 4 had a negative FS but a positive final pathology, indicating a possible deviation from the enhancing target, but nevertheless consisting of a tumor-representative sample. Two 5-ALA- biopsies had a positive FS and a positive final pathology, indicating false negative and false positive rates for photodiagnosis of 5.8% and 0%, respectively, in our cohortFig. 2.

Mean operative time

The overall mean operative time was the same for the 2 study groups. The mean ± SD operative time was 74 ± 34 min for the patients in the control group and 70 ± 37 min for the patients in the 5ALA group. However, focusing on the patients from the 5-ALA group who had positive fluorescence ($n = 28$) revealed that their mean operative time was significantly shorter than that of the control group (61 ± 25 min, $P = 0.03$). Moreover, the mean operative time for the 5-ALA patients who did not have positive fluorescence was significantly longer compared to that of the control group (136 ± 54 min, $P = 0.003$) as possible resampling and trajectory adjustments were made.

Table 1
Demographics, tumor location and final pathology of 376 patients who underwent a frameless stereotactic brain biopsy with or without preoperative oral administration of 5-ALA.

	5-ALA group (n = 34)	Control group (n = 342)
Age, y, mean (± SD)	63 ± 13	62 ± 14
Supratentorial	97%	95.6%
Location		
Cortical	17%	10%
Subcortical	35%	27%
Deep	47%	63%
Pathology		
HGG	27 (79%)	188 (55%)
LGG	3 (8.5%)	49 (15%)
Lymphoma	3 (8.5%)	59 (17%)
Metastasis	1 (3)	25 (7%)
Other	0	10 (3)
Non-diagnostic	0	11 (3)

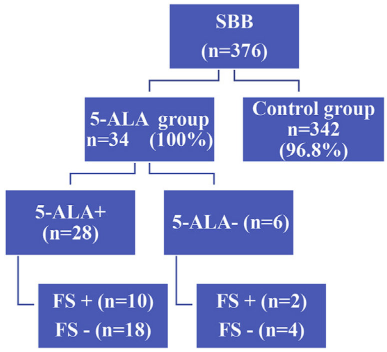

Fig. 1. Stereotactic brain biopsies cohort distribution showing the number of cases in each group. Percentage represents diagnostic accuracy. 5-ALA+, positive fluorescence. 5-ALA-, negative fluorescence. FS, frozen section.

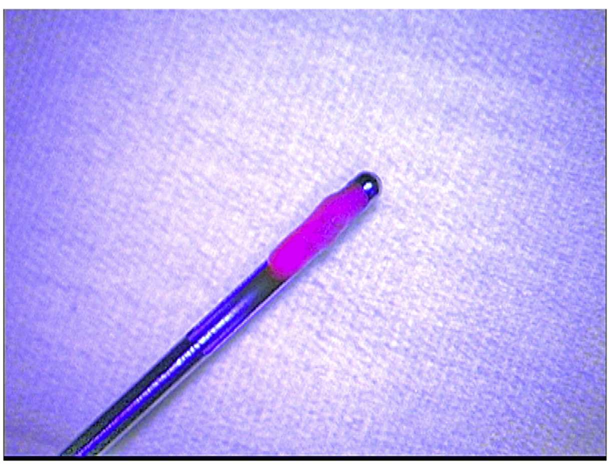

Fig. 2. Stereotactic needle biopsy of glioblastoma with fluorescence after the switch to violet-blue excitation light.

Table 2
Positive intraoperative fluorescence according to final pathological result.

Pathology	5-ALA+/All patients who received 5ALA
HGG	23/27 (85%)
LGG	2/3 (66%)
Lymphoma	2/3 (66%)
Metastasis	1/1 (100%

Diagnostic yield

The diagnostic yield of the 5-ALA group was higher compared to that of the control group (100% vs. 96.8%, respectively, $p = 0.28$). Specifically, 11 SBB (3.2%) from the control group were non-diagnostic on final pathology. Interestingly, the FS was positive for pathological tissue in 5 of the 11 SBB despite a non-diagnostic final pathology. From these data, it emerged that the positive predictive value (PPV) of FS was 97.5%, and the negative predictive value (NPV) was 20%, with a sensitivity and specificity of 97.8% and 18.1%, respectively. These results further emphasize the need for additional markers of pathological tissue. Since there were no cases of non-diagnostic biopsy in the 5-ALA group, the PPV for 5-ALA was 100% and the NPV was not applicable.

Postoperative complications

There was a higher rate of postoperative bleed among the patients in the control group, as recorded on a routine postoperative CT. The postoperative CT of 22 patients from the control group (6.4%) demonstrated a bleed, of which 7 had a symptomatic bleed, yielding a total symptomatic bleed complication rate of 2%. None of the 5-ALA patients sustained any postoperative bleed ($p = 0.12$).

Discussion

The results of this study suggest that the use of 5-ALA in SBB for neurooncological patients provides advantages in accuracy of diagnosis, shortens operative time, and improves the safety profile compared to traditional FS. These data support the approach that tumors with positive fluorescent samples observed intraoperatively during SBB preclude the need for FS, thereby obviating the waiting time for the pathology report. With SBB becoming increasingly more important in the setting of molecular-derived targeted therapies for both primary and secondary brain tumors, improving its efficiency and safety profile is now crucial.

SBB are considered safe and accurate neurosurgical procedures that are usually indicated for inoperable brain lesions when tissue diagnosis is required. Many attempts have been made to improve the diagnostic yield of these procedures [2]. Frame-based stereotaxis, which had been considered the gold standard for SBB, has gradually been replaced in many centers by frameless systems, such as the VarioGuide (BrainLab AG, Feldkirchen, Germany) system, which is routinely used in our center as well. Frameless SBB was proven to be equal to frame-based SBB in terms of accuracy and diagnostic yield, and superior in terms of patient satisfaction regardless of the specific system that had been used [1,4,6,8]. Diagnostic accuracy of SBB ranges between 89 and 98% in various published series [3–6]. The reason for this variation is unknown, since there are no available data on the multiple confounders, such as surgeon experience, target size, or target location. Diagnostic yield is associated with the number of samples taken, as well as with a positive FS [7]. Our results of increased diagnostic yield with the use of 5ALA photodiagnosis are in line with several publications [16,17]. In a series published by Jain et al. the diagnostic yield was 76.5% when one sample had been obtained, and 100% for biopsies in which more than 5 samples were taken [7]. A positive FS is considered the gold standard for the intraoperative diagnosis of pathological tissue, despite its two main limitations of being time consuming and error prone. In their work in 700 centers and more than 32000 FS, Novis and Zarbo et al. [19] estimated the time the pathologists receive the FS sample to the time they return FS diagnoses to the surgeons as being 20 min [19]. In our present study, not waiting for the FS results saved approximately 15 min of operation time. Agreement of FS with final pathology for brain tumors was found to be 77.8% in a recent study in which the majority of cases were not SBB [20]. Those authors, however, did not provide information on false-positive FS, since most of the tissue was obtained in open surgery. In our study, there were 4 cases in which the FS finding was positive, and the final pathology was negative, raising the possibility that another confirmation via photodiagnosis might have prevented those false-positive biopsies.

Avoiding complications is crucial in SBB, in which the approach is minimally invasive to allow for prompt initiation of oncological treatments. While clinically silent, postoperative bleeds may be more common than expected [21], with clinically significant hemorrhages having been reported in 3–4%, and mortality usually around 1–2% [4,22]. Routine postoperative CTs are performed for every SBB in our center, and the rate of symptomatic bleed was 5.8% for the control group. Interestingly, the FS was negative in 13/20 patients who sustained a clinically significant bleed. The mean operation time for those patients was 90 ± 37 min suggesting that either more samples had been obtained, or that there had been a change in the target, both of which could have possibly increased the risk for significant bleed. There were no significant post-operative bleeds and operative time was much shorter in the 5-ALA group. One possible explanation for those results is that fewer samples were required for certainty of diagnosis, thus minimizing the potential risk of complications.

Limitations

The main limitation of the current study lies in its retrospective design. In a prospective study, Kiesel et al. [23] demonstrated a PPV of 100% for fluorescent samples, which led to the latter's recommendation that there is no need for intraoperative histopathology in cases with positive fluorescence [23]. Our study is the first to compare brain tumor samples with and without the administration of 5-ALA, and, although it is retrospective, our results support that recommendation. Our findings also suggest that 5-ALA assisted SBB may have lower complication rates and shorter operation time, but the many possible confounders of a retrospective study may have affected our results, such as selection bias for the 5-ALA group and surgeon bias. Despite these possible confounders, the procedures were performed in a single neurosurgical center with consistent methodology and by multiple surgeons.

Conclusions

A 5-ALA-assisted SBB is a viable alternative that reduces operation time and complication rates. It improves the diagnostic yield and may spare the need for performing traditional biopsies with FS.

Conflict of interest

None.

Disclosure of funding

None.

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