Fluorescence Behavior and Dural Infiltration of Meningioma Analyzed by 5-Aminolevulinic Acid–Based Fluorescence: Operating Microscope Versus Mini-Spectrometer

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■ OBJECTIVE: **To compare fluorescence intensity of tumor specimens, as measured by a fluorescence-guided surgery microscope and a spectrometer, to evaluate tumor infiltration of dura mater around meningiomas with help of these 2 different 5-aminolevulinic acid (5-ALA)-based fluorescence tools, and to correlate fluorescence intensity with histopathologic data.**

■ MATERIAL AND METHODS: **In a clinical series, meningiomas were resected by 5-ALA fluorescence-guided surgery. Fluorescence intensity was semiquantitatively rated by the surgeon at predefined points. Biopsies were harvested and fluorescence intensity measured by a spectrometer and histopathologically analyzed. Sampling was realized at the level of the dura in a centrifugal direction.**

■ RESULTS: **A total of 104 biopsies ($n = 13$ tumors) were analyzed. Specificity and sensitivity of the microscope were 0.96 and 0.53 and of the spectrometer 0.95 and 0.93, respectively. Fluorescence intensity as measured by the spectrometer was correlated to histologically confirmed tumor burden. In a centrifugal direction, tumor burden and fluorescence intensity continuously decreased (along the dural tail). Below a threshold value of 639 arbitrary units no tumor was histologically detectable.**

■ CONCLUSIONS: **At the level of the dura the spectrometer was highly sensitive for detection of meningioma cells. The surgical microscope showed false negative results and missed residual tumor cells in more than one half of the cases. The complementary use of both fluorescence tools may improve resection quality.**

INTRODUCTION

Approximately 30% of all tumors of the central nervous system are meningiomas, and more than 90% of them are classified as benign.[1,2] Standard therapy is neurosurgical resection.[3] Overall recurrence rate is approximately 20% at long-term follow-up.[4] This recurrence rate largely depends on degree of resection, as defined by the Simpson grading system.[5] It is hypothesized that recurrent tumor most often develops from residual tumor cells at the resection margins.[6] Although in some instances residual tumor has to be left for the sake of neurologic integrity, most recurrences develop from intraoperatively overlooked tumor.

Hence, a refinement of intraoperative tumor detection methods, especially at the end of surgery, is needed. This would improve quality of resection and reduce risk of recurrence.

5-aminolevulinic acid (5-ALA)-based fluorescence-guided surgery (FGS) has been established as standard in glioma surgery.[7,8] Clinical evidence is accumulating that FGS also may be promising for meningioma resection.[9–13] Although a FGS microscope is easy to use, many confounding factors may affect the quality of detection and resection, e.g., subjective assessments, distance

Key words
- 5-ALA
- Fluorescence-guided surgery
- Meningioma
- Microscope
- Spectrometer

Abbreviations and Acronyms
5-ALA: 5-Aminolevulinic acid
AU: Arbitrary units
FGS: Fluorescence-guided surgery
H&E: Hematoxylin and eosin
PpIX: Protoporphyrin IX disodium salt
ROC: Receiver operating curve
WHO: World Health Organization

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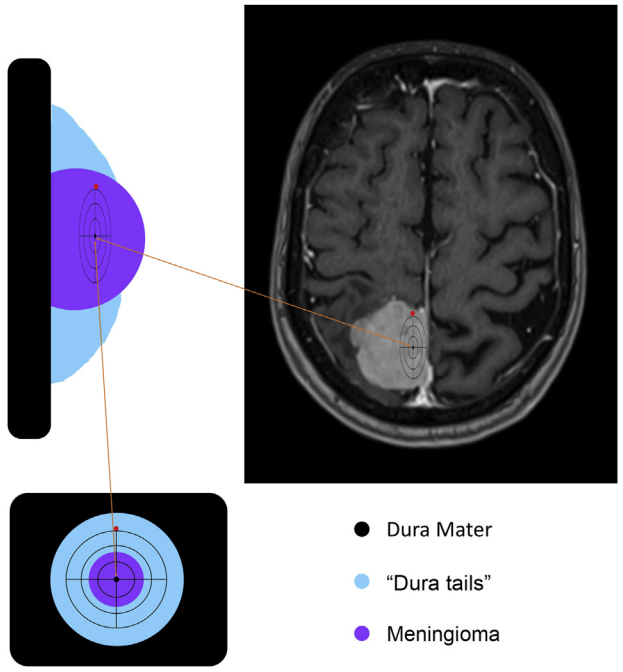

Figure 1. Schematic drawing of the preoperative tumor mapping: on the axial image (T1 with gadolinium, 3-mm slice thickness) with maximum tumor diameter a virtual crosshair was placed in a tangential plane to the tumor at the level of dura mater (*upper right*). The crosshair defined 4 sectors, with 12 o'clock being the most rostral tumor extension (*upper left*). Each tumor was divided in 4 directions (3, 6, 9, and 12 o'clock) (*lower left*). Intraoperative sampling was defined according to this reference frame.

between tumor and light source, light absorption, and scattering properties of biological tissue.[14] To overcome these shortcomings and to improve fluorescence detection, dedicated spectrometers have been developed.[11,14,15] In a preliminary study, we recently examined the usefulness of a "mini-spectrometer" for clinical use.[11] We think that a combination of an FGS microscope and such a mini-spectrometer may be additive tools in meningioma surgery.

The objectives of the present study were as follows: 1) to compare fluorescence intensity of tumor specimens as measured by a FGS microscope and a spectrometer, 2) to evaluate tumor infiltration of dura mater around meningiomas (along the so-called dural-tail) with help of these 2 different 5-ALA–based fluorescence tools, and 3) to correlate fluorescence intensity with histopathologic data.

MATERIAL AND METHODS

Tumor specimens were harvested from patients with meningioma who were operated in the Department of Neurosurgery of Heinrich Heine University Duesseldorf in the period from March 2015 to March 2017. As part of the department's tumor program, every patient with a primary or secondary brain tumor routinely is offered 5-ALA–based FGS. The resected tumor material was divided in specimens for routine histopathologic diagnosis and specimens for fluorescence intensity quantification.

The study was approved by the local ethics committee (number of registration: 4266). Only fully informed patients who wished to participate in the study and who had signed an informed consent preoperatively were included. Exclusion criteria were as follows: Patients who were taking phototoxic drugs such as sulfonamides, tetracyclines, or fluoroquinolones; patients who had liver damage and/or elevated liver enzymes (glutamic oxaloacetic transaminase, glutamate-pyruvate transaminase, gamma-GT, alkaline phosphatase, cholinesterase or bilirubin); and patients with cardiovascular diseases such as coronary heart disease, previous myocardial infarction, heart failure or active myocarditis, or cardiomyopathy.

Preoperative Tumor Mapping and Coordinates of Biopsies

Planning was performed for each patient on a preoperative magnetic resonance imaging study. On the axial image (T1 with gadolinium, 3-mm slice thickness) with maximum tumor diameter, a virtual crosshair was placed in a tangential plane to the tumor at the level of dura mater. The crosshair defined 4 sectors, with 12 o'clock being the most rostral tumor extension. Each tumor was divided in 4 directions (3, 6, 9, and 12 o'clock). Concentric circles with increasing radius (5-mm intervals) were centered on the tumor center. The location of each intraoperative tumor biopsy was defined according to this coordinate system (Figure 1). Planning was performed on an IBM PC with special imaging software (Sectra Workstation IDS7, version: 18.1, Sectra AB; Linköping, Sweden).

Patient Preparation

Before the operation, all patients received 5-ALA according to a standardized clinical protocol.[8] In brief, patients received 5-ALA

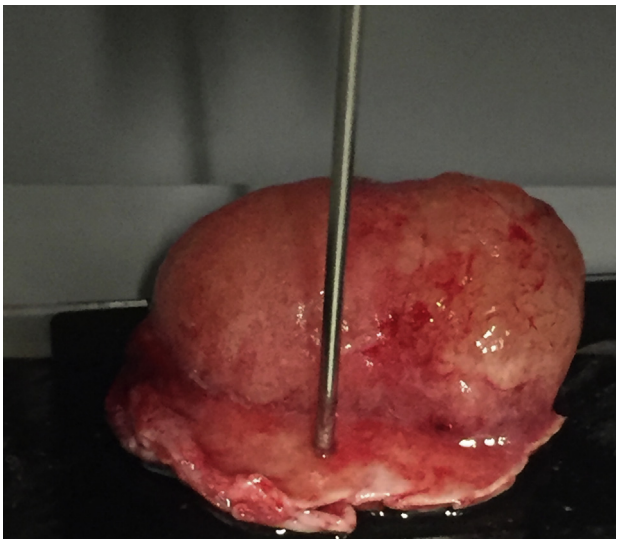

Figure 2. Hand-held fiber optic placed on the dura tail of an en bloc–resected tumor.