Fluorescence real-time kinetics of Protoporphyrin IX after 5-ALA administration and factors predicting fluoresecence in low-grade glioma

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Background: Five-Aminolevulinic acid (5-ALA) has been established as a compound for inducing fluorescence and assisting resection in high-grade glioma. However, in low grade glioma (LGG) the clinical value of 5-ALA-induced fluorescence is unclear. Particularly, time-dependency and time kinetics have not been yet investigated. The purpose of this study was to investigate real-time kinetics of Protoporphyrin IX (PpIX) in LGG based on hyperspectral fluorescence-based measurements.

Methods: We evaluated patients harboring LGG surgically treated in our department. Patients received 5-ALA at a standard dose of 20 mg/kg b.w. 4 hours prior to surgery. Assessments were performed utilizing a hyperspectral camera. Fluorescence intensity (FI) and PpIX concentration (CPpIX) were measured in the tumor tissue. We furthermore evaluated apparent diffusion coefficient (ADC)-based tumor cell density, Ki-67/MIB-1 Index, chromosomal 1p/19q co-deletion and ^{18}F-fluoro-ethyl-tyrosine (^{18}F-FET)-PET values and their role for predicting fluorescence.

Results: 81 tissues from 25 LGG patients were included in this study. Tissues with fluorescence delivered a maximum of FI and CPpIX between 7-8 hours after 5-ALA administration. When visible fluorescence was available, peaks of FI and CPpIX were observed within a 7-8 hour time-frame regardless of MRI contrast-enhancement. GD-enhancement (p=0.008), Ki-67/MIB-1 Index (p<0.001), ^{18}F-FET-PET uptake ratio (p=0.038) and ADC-based tumor cellularity (p=0.017)

differed significantly between fluorescing- and non-fluorescing tissue. 1p/19q co-deletion was not reliable for predicting fluorescence. A logistic regression demonstrated ^{18}F-FET-PET uptake and Ki-67/MIB-1 Index as independent variables for predicting fluorescence.

Conclusion: We report in a fluorescence-based assessment of CPpIX in human LGG tissues. ^{18}F-FET-PET uptake and Ki-67/MIB-1 are independent strong factors for predicting fluorescence. Similar as previously reported in HGG, fluorescence peaked between 7-8 hours after 5-ALA application. In consequence, 5-ALA administration in patients with suspicious LGG should be 4-5 hours prior surgery, and always adapted to the clinic's own logistics environment.