Photodiagnosis and Photodynamic Therapy (2014) 11, 481—490

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/pdpdt

Impact of 5-aminolevulinic acid fluorescence-guided surgery on the extent of resection of meningiomas — With special regard to high-grade tumors

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Available online 10 August 2014

KEYWORDS
5-ALA;
Aminolevulinic acid;
Fluorescence guided surgery;
High grade;
Meningioma;
Skull base

Summary
Background and objectives: In high-grade meningiomas and a subgroup of clinically aggressive benign meningiomas tumor control is still insufficient. Recently 5-ALA fluorescence in meningiomas was reported. The impact of 5-ALA fluorescence-guided surgery (FGS) on surgical decision-making and extent of resection has not yet been systematically analyzed, especially not in high-grade meningiomas. The present study deals with three main questions regarding 5-ALA FGS in meningiomas: to assess the potential for discriminating different WHO grades intra-operatively, to analyze the influence on surgical strategy and to evaluate the impact on extent of resection.
Methods: Data from 31 meningiomas operated with 5-ALA FGS were retrospectively analyzed. Intraoperative fluorescence was graded by the surgeon as ''*no*'', ''*low*'' or ''*high*''. Correlations between semi-quantitative fluorescence and histological features (WHO grade) were analyzed. The influence of 5-ALA fluorescence on surgical strategy and the impact of 5-ALA FGS on degree of resection (Simpson grade and post-operative imaging) were studied. In tumors showing infiltrative growth the extent of resection of fluorescence positive tissue was evaluated.
Results: The population comprised 19 WHO grade I, 8 grade II and 4 grade III tumors (61% benign and 39% high-grade meningiomas). 94% of the tumors showed positive fluorescence. Different fluorescence intensities were observed: ''*no*'' in two, ''*high*'' in 12 and ''*low*'' in 17 tumors, respectively. A significant correlation between fluorescence intensity and WHO grade was found ($\rho = 0.557$, $p = 0.001$). 5-ALA improved the extent of resection in 3/16 (19%) of grade I and in 6/8 (75%) of grade II/III meningiomas. This improvement was not measurable by the Simpson grading as rated by the surgeon and controlled on post-operative imaging.

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http://dx.doi.org/10.1016/j.pdpdt.2014.07.008

Conclusions: In the present population a strong correlation between fluorescence intensity and WHO grade was observed. 5-ALA FGS improved the extent of resection in meningiomas. Especially in high-grade tumors additional information on brain and neurovascular infiltration was provided. The improved resection was not measurable by Simpson's grading necessitating an additional item, which rates residual fluorescence. Long-term studies are necessary to evaluate a possible impact of FGS on recurrence and overall survival.

Introduction

Meningiomas are the most common non-glial primary brain tumors accounting for about one third of all cerebral neoplasms [6,41]. Current standard of care for symptomatic or growing meningioma is surgical resection [18,37]. Radiotherapy is an option for residual or recurrent tumor [10,29]. Histological features (WHO grade, Ki-67 and progesterone receptor status) and extent of surgical resection (Simpson grade) are generally accepted prognostic factors for PFS in meningioma management [2,10,21,30]. Despite complete surgical excision, recurrence rates of up to 20% at 10 years are reported for benign WHO grade I tumors [23]. High-grade meningiomas (WHO grade II/III) are characterized by much higher recurrence rates despite adjuvant radiotherapy [6,11,12,22]. Tumor recurrence or progression is most likely due to microscopic infiltration undetected during resection [27].

For malignant gliomas fluorescence-guided surgery (FGS) based on 5-ALA has been shown to improve outcome. In a clinical phase 3 trial FGS resulted in a higher rate of complete resections and increased progression-free survival [31]. Stimulated by these results 5-ALA induced fluorescence in meningiomas has increasingly been investigated [3,7,9,19,25,32]. In benign, circumscribed meningiomas FGS was described to be helpful to detect tiny remnants easily missed with conventional intraoperative white-light microscopy [25]. In high-grade meningiomas commonly featuring infiltrating growth 5-ALA FGS might improve extent of resection as in malignant gliomas. At present, the number of reported high-grade meningiomas in the literature is very small [3,19,25]. So far no differences in fluorescence behavior between different WHO grades were reported in contrast to gliomas. Moreover, the impact of 5-ALA FGS on surgical strategy and extent of resection has not yet been systematically analyzed.

Based on the current knowledge, we conducted an observational study about 5-ALA FGS in our institution with special regard to high-grade meningiomas. The study had three objectives concerning 5-ALA FGS: (1) to assess the potential of discriminating different WHO grades intra-operatively, (2) to analyze the influence on intraoperative decision-making and (3) to evaluate the impact on extent of resection.

Patients and methods

General remarks

Over the past 6 years 5-ALA FGS was offered as part of the neurosurgical clinic's braintumor protocol in gliomas, unclear brain tumors, in case of known high-grade meningioma as well as in meningioma showing unusual features. Contraindications to 5-ALA administration were age under 18 years, pregnancy, hypersensibility to 5-ALA, porphyria, and disturbance of hepatic enzymes or non-adherence to protocol. Informed consent concerning off-label use of 5-ALA was obtained as needed. All patients treated by 5-ALA FGS in which final histological examination resulted in meningioma were included in this analysis. The study was approved by the institutional review board.

Fluorescence-guided surgery

Surgery was planned by means of pre-operative CT and/or MR imaging. 5-ALA was orally administered 3—4 h prior to surgery (20 mg/kg) according to the established glioma protocol [31]. Surgery was performed with neuronavigation (Brainlab, Feldkirchen, Germany) in all patients. Fluorescence was visualized using a specially equipped operating microscope (Carl Zeiss OPMI® Pentero® 800 with option Blue 400, Jena, Germany). Following surgical exposure, fluorescence intensity was immediately assessed by the surgeon to rule out photo-bleaching. Intensity was observed before and after opening of the tumor capsule. Intratumoral fluorescence intensity was rated by the surgeon in a semi-quantitative manner as ''*no*'', ''*low*'' or ''*high*'' intensity (Fig. 1a—f) [28,39]. Special attention was paid to keep the field of view clear of any possible disturbances of fluorescence (e.g. blood). Tumor dissection and resection was routinely carried out in the white-light mode. Periodically, the operating field was checked in fluorescence mode (blue-light mode, 440 nm). Finally, the resection cavity was inspected with blue light in order to detect any residual and/or infiltrating tumor tissue. The surgeon at the end of surgery scored extent of resection with Simpson's grading system. Simpson grade 1 and 2 were considered ''complete'' and grade 3—5 ''incomplete''. Resection grade was verified on post-operative MR imaging. The patients were protected from bright light during the first 24 h after surgery. Final histological assessment was obtained from an experienced neuropathologist, the 2007 WHO classification was applied [22]. Each patient was followed clinically and with radiological imaging in an outpatient setting.

Data analysis

SPSS Statistics 22.0 (IBM Corporation, Somers, USA) was used to calculate Spearman's rank correlation coefficient. $p < 0.05$ and $p < 0.01$ were considered significant and highly