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Role of neurochemical navigation with 5-aminolevulinic acid during intraoperative MRI-guided resection of intracranial malignant gliomas

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ABSTRACT

Objective: To evaluate the role of the neurochemical navigation with 5-aminolevulinic acid (5-ALA) during intraoperative MRI (iMRI)-guided resection of the intracranial malignant gliomas.
Methods: The analysis included 99 consecutive surgical cases. Resection of the bulk of the neoplasm was mainly guided by the updated neuronavigation based on the low-field-strength (0.3 T) iMRI, whereas at the periphery of the lesion neurochemical navigation with 5-ALA was additionally used.
Results: In total, 286 tissue specimens were obtained during surgeries for histopathological examination. According to iMRI 98 samples with strong (91 cases), weak (6 cases), or absent (1 case) fluorescence corresponded to the bulk of the lesion and all of those ones contained tumor. Out of 188 tissue specimens obtained from the "peritumoral brain," the neoplastic elements were identified in 89%, 81% and 29% of samples with, respectively, strong (107 cases), weak (47 cases) and absent (34 cases) fluorescence. Positive predictive values of the tissue fluorescence for presence of neoplasm within and outside of its boundaries on iMRI were 100% and 86%, respectively.
Conclusion: Neurochemical navigation with 5-ALA is useful adjunct during iMRI-guided resection of intracranial malignant gliomas, which allows identification of the tumor extension beyond its radiological borders.

1. Introduction

Although according to strict criteria of evidence-based medicine, there is still insufficient prove that aggressive image-guided surgery of intracranial gliomas positively influences prognosis [1,2], multiple studies demonstrated significant association between resection rate and overall, progression-free, malignant transformation-free, neurological deterioration-free, and seizure-free survival [3–12]. Additionally, gross total tumor removal augments effectiveness of the adjuvant therapies [6,13]. Nowadays, the rate of radiologically total removal of the cerebral gliomas in selected groups of patients varies widely from 45% to 97% [4–7,9,10,12,14–23], and in our own experience constitutes 46% [24–27]. Use of intraoperative MRI (iMRI) seemingly has the strongest impact on such aggressive surgical practice [7,9,12,20,24–29]. Among other methods neurochemical navigation based on 5-aminolevulinic acid (5-ALA)-induced tissue fluorescence demonstrated particularly promising results and showed high effectiveness for intraoperative identification of the tumor borders [4,10,12,14,15,19,21–23,29–39]. In Tokyo Women's Medical University application of both techniques for guidance of brain tumor surgery was initiated more than decade ago [24–28,31,40,41]. The objective of the present study was evaluation of the role of the neurochemical navigation with 5-ALA during iMRI-guided resection of the intracranial malignant gliomas. Additionally, safety of 5-ALA administration was assessed.

2. Methods and materials

From May 2004 to June 2010, 97 consecutive patients with malignant gliomas underwent iMRI-guided tumor resection with

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additional neurochemical navigation using 5-ALA in the Intelligent Operating Theater of the Tokyo Women's Medical University. Two patients underwent such surgery twice at the time of initial diagnosis and at recurrence, which for the purpose of the data analysis were considered as separate cases.

2.1. General data

There were 64 men and 35 women. Their age varied from 17 to 83 years (median, 53 years). There were 80 newly diagnosed and 19 recurrent gliomas. Contrast enhancement of the tumor on T_1-weighted MRI was noted in 87 cases.

Tumor resection was performed using standard microneurosurgical technique according to the previously described concept of the information-guided surgery (Fig. 1) [25–27]. Removal of the bulk of the lesion was guided by the updated neuronavigation based on the low-field-strength (0.3 T) iMRI (AIRIS II^{TM}; Hitachi Medical Corporation, Tokyo, Japan). At the periphery of the tumor its removal was additionally guided by neurochemical navigation with 5-ALA and histopathological monitoring of the resected tissue [25–27,42].

2.2. Neurochemical navigation with 5-ALA

Clinical use of 5-ALA for neurochemical navigation during removal of the intracranial gliomas was approved by the Ethics Committee of the Tokyo Women's Medical University. Within 2 to 4 h before induction of anesthesia for craniotomy and tumor removal the patients were given perorally a single dose (20 mg/kg) of 5-ALA (Cosmo Bio Co., Ltd.; Tokyo, Japan) as a freshly prepared 50 mL of water solution. For observation of the tissue fluorescence and neurochemical navigation during resection of the neoplasm D-light (Karl Storz Co., Ltd., Tuttlingen, Germany) was used. The light source of the excited wave (375 to 440 nm) was applied to evoke a red fluorescence (635 nm) that was visible for the naked eye after passing through a low cut filter (Kenko Y2: cut under 480 nm; Kenko Tokina Co., Ltd., Tokyo, Japan). Additionally, a blue laser diode of a quartz laser source (VLD-Mi; M&M Co., Ltd., Tokyo, Japan) with a wavelength of approximately 405 nm was used for detection of the protoporphyrin IX fluorescence in the resected pathological tissue. Intensity of tissue fluorescence was assessed subjectively by 2 attending neurosurgeons (YM, TM) and graded as strong, weak, and absent (Fig. 2).

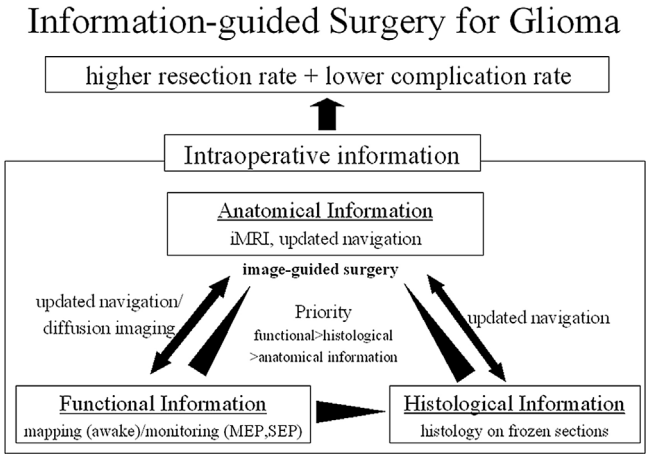

Fig. 1. Main principles of the information-guided surgery for glioma. To maximize resection rate and minimize the risk of postoperative neurological morbidity anatomical data obtained with intraoperative MRI (iMRI) are integrated with functional and histological information. MEP, motor evoked potentials; SEP, somatosensory evoked potentials. From Muragaki et al. [26].

Safety of 5-ALA administration was assessed according to the Common Terminology Criteria for Adverse Events version 3.0 [43]. Eyes and skin of patients were protected from the strong light sources during 24 h after administration of the drug [14,29,30,37].

2.3. Histopathological investigation

In total, during resection of 99 tumors, 286 separate biopsy specimens were obtained (mean number per case, 3 ± 2; median, 2; range, 1–10). Final histopathological diagnosis of the tumor was established according to the current WHO criteria [44] on the paraffin-embedded tissue sections stained with hematoxylin and eosin and appropriate antibodies for immunohistochemistry.

2.4. Postoperative evaluation of the tumor resection rate

Evaluation of the tumor resection rate was done by comparison of the preoperative and postoperative MRI obtained within 3 days after surgery, using 1.5 T clinical scanner (ExcellArt; Toshiba Medical Systems, Tokyo, Japan). In contrast-enhanced tumors (87 cases) any contrast-enhanced area on postoperative T_1-weighted images, beside evident vessels, was considered as residual neoplasm. In non-enhancing gliomas (12 cases) any hyperintense area on T_2-weighted images was considered as residual neoplasm.

2.5. Statistics

Chi-square test was used for statistical comparisons of the groups. The level of significance was determined at $P < 0.05$.

3. Results

Mean tumor resection rate was $95\% \pm 8\%$ (range, 60–100%). In 51 cases (52%) no residual tumor was identified on postoperative MRI. There was no perioperative mortality. Early complications were noted in 66 patients (67%) and are characterized in Table 1. At 3 months after surgery the neurological status of 9 patients (9%) still was worse than before intervention. Histopathological investigation revealed 32 WHO grade III gliomas and 67 WHO grade IV gliomas (Table 2).

During surgery 5-ALA-induced tissue fluorescence was revealed in all 99 cases and its maximum intensity was characterized as strong (93 cases; 94%) or weak (6 cases; 6%). In total, 251 tissue samples from the fluorescent areas were obtained for histopathological examination and tumor was identified in 230 cases (92%). Neoplastic elements were revealed in 186 out of 198 (94%) and in 44 out of 53 (83%) specimens obtained from the areas of strong and weak fluorescence, respectively ($P = 0.0108$).

Table 1
Early postoperative complications in the present series.

Complications	Number of cases
Motor deficit	24 (24%)
Seizures	12 (12%)
Aphasia	11 (11%)
Disturbances of consciousness	7 (7%)
Dysarthria	5 (5%)
Deep venous thrombosis	5 (5%)
Fever	5 (5%)
Visual disturbances	4 (4%)
Sensory deficit	2 (2%)
Hemianopsia	2 (2%)
Impairment of hearing	2 (2%)
Dysphagia	2 (2%)