Commentary on:
In Vivo Real-Time Discrimination Among Glioma, Infiltration Zone, and Normal Brain Tissue via Autofluorescence Technology
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The Border Zone of Tumor. Where is the Border? What is a Surgical Border for Patients?

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The border zone of different tissues is often the object of discussion, considering that the definition of the border is always ambiguous, especially in cases of tumor. The population of different cells in this area largely depends on the character of those cells in terms of the ability of cell motility and the status of tissue barrier, such as extracellular matrices. Gliomas, especially malignant gliomas, are known to possess a highly invasive nature. The surgical extent of resection is determined by the intraoperative macroscopic appearance, sometimes assisted by the information of a navigation system based on the preoperative images, that is easily influenced by the intraoperative brain shift in many cases. Therefore, the surgery often results in an incomplete resection.

To overcome these demerits, 5-aminolevulinic acid (5-ALA) photodiagnosis has been developed and widely used in the surgery of malignant gliomas. This technique is very helpful to find tumor tissue, however, the expression level of protoporphyrin IX, the derivative of 5-ALA, varies in each case depending on the activities of enzymes in the porphyrin biosynthesis pathway. Also, the fluorescence is weakened by the photobleaching phenomenon of protoporphyrin IX by prolonged exposure to strong light.[1] This phenomenon induces false-negative detection, however, false-positive fluorescence is seen in many recurrent cases with infiltrated inflammatory cells, such as neutrophils, in the peritumoral edematous zone.[2] Essentially, 5-ALA-induced visible fluorescence in malignant gliomas is limited in regions with low-density tumor cell infiltration. Therefore, it is still difficult to identify the border of the tumor even with 5-ALA photodiagnosis.

Recent technologies have enabled us to analyze tumor cell biology. Those include the direct detection of isocitrate dehydrogenase- (IDH) 1 mutation by real-time polymerase chain reaction,[3] and the measurement of 2-hydroxyglutarate, indirect detection of IDH gene mutation, by liquid chromatography/electrospray ionization tandem mass spectrometry.[4] These methods are quite useful for detecting low-grade gliomas with IDH-1 mutation in surgical specimens. However, both methods are not real-time, although they can analyze the biological characteristics. Also 3-dimentional distribution of tumor cells is hardly recognized even in multiple samplings.

Precise identification of the border zone at the microscopic level also remains an outstanding challenge of glioma neuropathology and neuro-oncological surgery. As a gold standard, intraoperative pathological diagnosis is the direct solution for the determination of the resective limit. However, the repeated examinations of all parts of the surgical plane is impractical with respect to time.

In an article recently published in **WORLD NEUROSURGERY**, Chang et al.[5] reported their technical development of "In Vivo Real-Time Discrimination Among Glioma, Infiltration Zone, and Normal Brain Tissue via Autofluorescence Technology." The mechanism of this method is based on autofluorescence change because of the nicotinamide adenine dinucleotide phosphate depletion in tumor cells by the Warburg effect, and the decreased level of lipofuscin probably owing to less intracellular accumulation by quick cell division. The advantage over the 5-ALA photodiagnosis is the use of endogenous substances that do not change in the expression level during surgery. This technology will contribute to the real-time recognition of the glioma distribution in the brain.

There were some reports on the autofluorescence measurement of ex vivo tumor samples[6] and in vivo tumor surface,[7] but these 2 methods are not in situ and no real-time method. On the

Key words
- Auto-fluorescence
- Glioblastoma
- Infiltration
- Optical-fiber

Abbreviations and Acronyms
5-ALA: 5-Aminolevulinic acid
IDH: Isocitrate dehydrogenase

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contrary, the Chang et al.[5] technique is a real-time autofluorescence detection method, that is ideal for the detection of tumor cell distribution. Examining the experimental results, the threshold of tissue discrimination is somewhat difficult to determine. The lowest fluorescence intensity of normal tissue is nearly same with the intensity range of tumor tissue. This intermediate level of intensity will cause confusion for the surgeons regarding the decision of the extent of resection. The factors that cause this ambiguity consist of sensitivity and specificity. Even with this autofluorescence method, its detection sensitivity will be affected by the population of target cells and its selectivity may be affected by the other components such as red blood cells and the other cell types.

Theoretically, it is not easy to determine the surgical border, considering that a marginal zone consists of tumor cells and normal cells in 1 place in the case of infiltrating tumors. Clinically, the ideal resection of malignant glioma is the supramaximal resection without any damage to the brain functions. Li et al.[8] reported that the complete resection of the T1 contrast-enhancing region and additional resection of the T2-weighted-fluid-attenuated inversion recovery abnormality region may present a significant added survival advantage. In terms of the therapeutic extirpation of invading tumors, a resection border can be defined as a margin by which the number of residual tumor cells is less than what can be destroyed by the other therapeutic options such as radiotherapy, chemotherapy, molecular targeting therapy, or patient's tumor immunity.

Clearly, the functional deterioration by excessive resection of intensified T2-weighted-fluid-attenuated inversion recovery region induce the decreased activity of daily living and instrumental activity of daily living, sometimes followed by the mental depression that is known to shorten overall survival.[9] Consistently, maximal safe resection without functional deterioration is the fundamental surgical strategy. Given that a small number of tumor cells in the border zone could be hardly detected by any technology, the surgical limits can be determined by brain mapping technique as functional limits. Naturally, there are brain functions that cannot be identified by asleep intraoperative brain mapping, and, in that case, awake surgery may be a solution. Additionally, the setting of safety margin is important considering possible postoperative ischemic change by surgery.[10-12] A realistic surgical border will be determined by these points-of-view considering patients' quality of life.

REFERENCES

1. Stummer W, Stocker S, Wagner S, et al. Intraoperative detection of malignant gliomas by 5-aminolevulinic acid-induced porphyrin fluorescence. *Neurosurgery*. 1998;42:518-525.
2. Utsuki S, Oka H, Sato S, et al. Histological examination of false positive tissue resection using 5-aminolevulinic acid-induced fluorescence guidance. *Neurol Med Chir (Tokyo)*. 2007;47:210-213.
3. Adachi JI. Rapid IDH1 gene mutation analysis for intraoperative pathological diagnosis. *JSM Neurosurg Spine*. 2014;2:1028.
4. Kanamori M, Maekawa M, Shibahara I, et al. Rapid detection of mutation in isocitrate dehydrogenase 1 and 2 genes using mass spectrometry. *Brain Tumor Pathol*. 2018;35:90-96.
5. Chang KT, Lin YY, Lin YY, et al. In vivo real-time discrimination among glioma, infiltration zone, and normal brain tissue via autofluorescence technology. *World Neurosurg*. 2019;122:e773-e782.
6. Poulon F, Jamme F, Ibrahim A, et al. Endogenous fluorescence analysis under deep UV excitation to discriminate human brain tumor tissue: difference between glioblastoma and healthy control tissue. In: Raposo M, Andrews D, Ribeiro PA, eds. *Proceedings of the 5th International Conference on Photonics, Optics and Laser Technology (PHOTOPTICS 2017)*. Setúbal, Portugal: Science and Technology Publications; 2017:152-157.
7. Butte PV, Fang Q, Jo JA, et al. Intraoperative delineation of primary brain tumors using time-resolved fluorescence spectroscopy. *J Biomed Opt*. 2010;15:027008.
8. Li YM, Suki D, Hess K, Sawaya R. The influence of maximum safe resection of glioblastoma on survival in 1229 patients: can we do better than gross-total resection? *J Neurosurg*. 2016;124:977-988.
9. Gathinji M, McGirt MJ, Attenello FJ, et al. Association of preoperative depression and survival after resection of malignant brain astrocytoma. *Surg Neurol*. 2009;71:299-303.
10. Smith JS, Cha S, Mayo MC, et al. Serial diffusion-weighted magnetic resonance imaging in cases of glioma: distinguishing tumor recurrence from postresection injury. *J Neurosurg*. 2005;103:428-438.
11. Ulmer S, Braga TA, Barker FG 2nd, Lev MH, Gonzalez RG, Henson JW. Clinical and radiographic features of peritumoral infarction following resection of glioblastoma. *Neurology*. 2006;67:1668-1670.
12. Yamaguchi F, Ten H, Higuchi T, et al. An intraoperative motor tract positioning method in brain tumor surgery. *J Neurosurg*. 2018;129:576-582.

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