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# Delayed Detection of a 5-Aminolevulinic Acid *In Vivo*: A Case of Metastatic Breast Cancer

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A 44-year-old female patient who had been diagnosed with breast cancer visited our oncology department. She had developed right-side weakness and mild dysarthria, and MRI revealed a 4-cm cystic-enhancing lesion in her left frontal lobe. Her surgery was postponed 48 hours after receiving 5-aminolevulinic acid (5-ALA), because a problem with thyroid function that had not been noticed before was discovered. The main lesion was enhanced on navigation and appeared to be a gross tumor; its 5-ALA uptake was very high. Specimens obtained from this location were histologically confirmed to contain tumor cells. The operation was completed, and removal of all enhancing lesions was confirmed by MRI within 24 hours postoperatively. The pathology report confirmed metastatic ductal carcinoma. The clinical efficacy of 5-ALA was confirmed even 48 hours after administration into a metastatic brain tumor from breast cancer.

**Keywords** Aminolevulinic acid; Brain Neoplasms; Carcinoma, ductal; Breast.

## INTRODUCTION

The use of 5-aminolevulinic acid (5-ALA) was first introduced in human malignant glioma patients in 1998 [1,2]. A randomized, controlled phase III study confirmed more complete resection of malignant gliomas and better progression-free survival after 5-ALA administration than without 5-ALA [3-5]. 5-ALA has been approved for human use in Europe, Asia, and the United States of America. With oral administration, 5-ALA is a safe compound with minimal side effects [6-8]. It is currently one of the standard adjuvant treatment tools for malignant glioma [6]. In addition, it is well tolerated in metastatic or benign tumors, such as meningiomas [9-11].

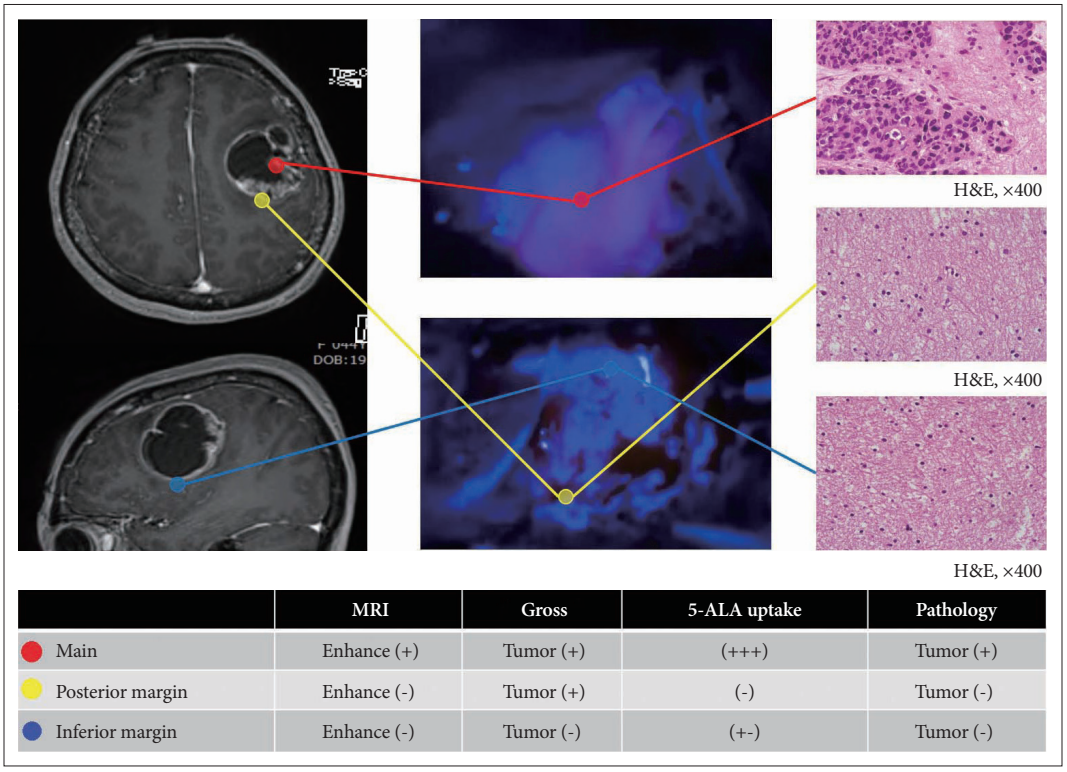
Occasionally, surgery cannot be performed immediately after drug administration. In our patient, although surgery was delayed for 48 hours, the authors were still able to detect 5-ALA. Therefore, we would like to report the case and share it.



## CASE REPORT

A 44-year-old female patient who had been diagnosed with breast cancer visited the oncology department at our facility. She had developed right-side weakness and mild dysarthria, and MRI revealed a 4-cm cystic-enhancing lesion in her left frontal lobe. The patient was scheduled for surgery; on the morning of surgery, she was given 5-ALA prior to induction of anesthesia. However, after an additional thyroid function test at an endocrinologist's recommendation, the surgery was postponed due to complications of Grave's disease. As a result, this patient underwent surgery 48 hours after administration of 5-ALA. She underwent simple craniotomy in the supine position; after estimating the location of the tumor with a neuro-navigation system, the surgeon performed cortisectomy to locate and remove the lesion.

While removing the tumor, its blue fluorescence was assessed frequently via microscopy. The main lesion was enhanced on navigation and appeared to be a gross tumor; its 5-ALA uptake was very high. Specimens obtained from this location were histologically confirmed to contain tumor cells (Fig. 1, red dot). After removal of the tumor, the posterior margin was grossly inspected, but there was no 5-ALA uptake. In the specimen obtained from this location, tumor cells could not be confirmed




| | MRI | Gross | 5-ALA uptake | Pathology |
|---|---|---|---|---|
| Main | Enhance (+) | Tumor (+) | (+++) | Tumor (+) |
| Posterior margin | Enhance (-) | Tumor (+) | (-) | Tumor (-) |
| Inferior margin | Enhance (-) | Tumor (-) | (+-) | Tumor (-) |

**Fig. 1.** A 44-year-old female patient underwent tumor resection 48 hours after oral administration of 5-aminolevulinic acid (5-ALA). During the procedure, the main lesion was enhanced on navigation and appeared to be a gross tumor; its 5-ALA uptake was also very high. Specimens obtained from this location were histologically confirmed to contain tumor cells (red dot). At the posterior margin, a tumor was grossly suspected, but there was no 5-ALA uptake. In the specimen obtained from this position, tumor cells could not be confirmed histologically (yellow dot). At the inferior margin, there was almost no 5-ALA uptake, and tumor cells could not be confirmed histologically (blue dot) in this area.

histologically (Fig. 1, yellow dot). Additionally, in the inferior margin, there was almost no 5-ALA uptake, and tumor cells could not be confirmed histologically (Fig. 1, blue dot). The surgical procedure was completed, and all previously enhancing lesions were confirmed to have been removed on MRI within 24 hours after the operation. The pathology report confirmed metastatic ductal carcinoma.

The patient recovered and was discharged without further neurologic deterioration.

## DISCUSSION

The use of 5-ALA has opened many opportunities for brain tumor surgeons. The tumor fluorescence derived from 5-ALA enables more complete resection of contrast-enhancing tumors, leading to improved progression-free survival in patients with malignant brain tumors [3,12,13].

It is known that 5-ALA is a non-fluorescent prodrug that leads to intracellular accumulation of fluorescent porphyrins in highly proliferative cells [14]. It elicits synthesis and accumulation of fluorescent porphyrins in tissues, which results in accumulation of porphyrins within malignant tumor cells that can be visualized with a microscope [3]. Using *in situ* spectrography, solid fluorescing tissue is distinguished by its strong protoporphyrin IX signal with peaks that range from 635 nm to 704 nm [11].

Although there are slight differences among users, the recommended dosage of 5-ALA is 20 mg per kilogram of body weight; it should be administered 2 to 4 hours before the patient is anaesthetized. A prospective study found that maximal fluorescence intensity was observed 7–8 hours following drug administration, and weak fluorescence peaked later than strong fluorescence, at 8–9 hours [15]. The authors recommended that 5-ALA be administered 4–5 hours prior to surgery, which is a longer time than in the existing protocol. However, in the present study, fluorescence was detected even later than previously expected.

Surgery may be delayed due to unpredictable situations. However, as shown in the present case, the uptake of 5-ALA may persist long enough to identify pathologic findings without additional doses. The present case was metastatic breast cancer, although the finding may be patient-specific. Therefore, more case results with various pathologies and basic research into this subject should be supported in the future to

confirm our findings.

In conclusion, although it is difficult to generalize the results of this one case, the clinical efficacy of 5-ALA was confirmed 48 hours after 5-ALA was administered to a patient with a metastatic brain tumor from breast cancer. It is hoped that further laboratory studies and clinical evidence will reinforce this result.

## Ethics Statement

The study protocol was reviewed and approved by the Institutional Review Board (IRB) of The Catholic University of Korea, Uijeongbu St. Mary's Hospital (No. UC22RISI0008), and adhered to the recommendations of the Declaration of Helsinki for biomedical research involving human subjects (2013). For this type of study, formal consent is not required, and informed consent was waived by IRB.

## Availability of Data and Material

Data sharing not applicable to this article as no datasets were generated or analyzed during the study.

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Conceptualization: Min Ho Lee, Tae-Kyu Lee. Data curation: Hyung Min Kim. Formal analysis: Min Ho Lee. Visualization: Min Ho Lee. Writing—original draft: Hyung Min Kim. Writing—review & editing: Min Ho Lee, Tae-Kyu Lee.

## Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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None

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