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ORIGINAL ARTICLE

5-Aminolevulinic acid fluorescence guided resection of malignant glioma: Hong Kong experience

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Summary *Background:* 5-Aminolevulinic Acid (5-ALA) induced fluorescence is useful in guiding glioma resection. The extent of 5-ALA accumulation is beyond gadolinium contrast enhancement.[1,2] Supratotal resection may be achieved, potentially granting patients with better survival.

We present our experience on 5-ALA guided glioma resection in Chinese ethnics.

Method: Sixteen Patients ingested 5-ALA (Gliolan, Medas Germany) 20 mg/kg·m^2 4 h before surgery. The tumor resection was guided by fluorescence with neurosurgical microscope. Patient was monitored for general condition, especially for new neurological deficits. Postoperative MRI served as the assessment for extent of resection (EOR).

Result: High grade glioma was confirmed in 12 cases, low grade glioma in three and one inflammation. 5-ALA was used in ten patients with known malignant glioma, and in six patients with presumed diagnosis of malignant glioma. Fifteen cases had positive fluorescence. The intensity was strong in eight and moderate in seven cases. MRI suggested total resection was achieved in 9 patients, near total resection in two and five had subtotal resection. EOR was associated with duration between ingestion of 5-ALA and timing when microscope was brought in for visualization of fluorescence ($p = 0.038$). Two patients suffered from temporary visual field defects. One patient developed hemiparesis after surgery.

Conclusion: 5-ALA is a useful intra-operative guidance for resection. It increases the percentage of total removal of the tumor. It should be used within the window period of the action (4–12 h).

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1. Introduction

Glioblastoma remains the most malignant and most common brain tumor. A modest survival benefit was proven in the adjuvant treatment by radiotherapy[3] and temozolomide.[4] The philosophy of resecting malignant gliomas has also changed dramatically. Surgery was considered primarily diagnostic in the past. A biopsy or a conservative debulking surgery was the former practice, knowing the ultimate dismal outcome of glioblastoma. However, in recent decades ample evidences have emerged that surgical resection plays an important role in the disease outcome. In the study presented by Sinai et al, a stepwise improvement in overall survival was described once EOR was over 78%. The benefit was even more prominent within 90%—100% of the EOR range.[5] Since then, surgical resection became one of the mainstays of treating malignant glioma.

Macroscopically, it is difficult to differentiate malignant tissue from adjacent normal brain tissue. Besides, the brain shift due to craniotomy is attributive to difficulty in locating the tumor during surgery. Conventionally, the tumor bulk to be excised is considered as contrast enhancement on MRI T1 sequence. Yet glioma is notorious for its infiltrative pattern of growth, the infiltrative tumor tissue is not always in association with disrupted blood barrier. Current radiological techniques are insufficient to determine tumor boundaries. In most of the cases, the tumor tissue may extend far beyond the property of contrast enhancement.[1,2]

5-aminolevulinic acid (5-ALA) is a natural precursor of heme which can also be found endogenously. The exogenous source of 5-ALA leads to superfluous accumulation of fluorescent protoporphyrin IX in malignant glioma tissue. Its take-up in WHO grade III and IV glioma is almost 6 times more than normal brain tissue.[6] The metabolite, protoporphyrin IX can be elicited by blue light with a specific wavelength (400—410 nm) and further emits red-violet fluorescence. With a properly adjusted microscope, the luminescence can be seen clearly by neurosurgeons, serving as an excellent real-time tumor marker guiding tumor resection intraoperatively.

In the presented study, we report our experience in using 5-ALA as a surgical adjunct in resecting malignant glioma.

2. Method

2.1. Design and patients

The study was conducted in a retrospective manner. The data of those patients who had 5-Aminolevulinic Acid (Gliolan, Medas Germany) assisted glioma resection were collected and reviewed.

Patient selection criteria of using 5-ALA were as follow: known history of malignant glioma (recurrence or second resection of newly diagnosed malignant glioma); specific MRI features suggesting malignant glioma (heterogenous gadolinium contrast enhancement with or without central necrosis). Only in cases where total resection of tumor were feasible and aimed for would 5-ALA be prescribed.

5-ALA was contraindicated in patient with any one of these conditions: 1. existing fixed neurological deficit; 2. tumor infiltrating functional areas of the brain unless guided by intraoperative brain mapping; 3. only tumor debulking is opted; 4. tumor extended to ventricular system; 5. multiple, bihemispheric lesions; 6. allergy to 5-aminolevulinic acid; 7. history of porphyria; 8. pregnant patients.

All patients were sent for a pre-operative MRI scan to confirm the location of the tumor before surgery. The MRI images would be registered in neuronavigation system to enhance the accuracy of exposure during surgery. For patients with presumed diagnosis of malignant glioma, using 5ALA as an adjunct for resection was a joint decision among patients, neuroradiologists and neurosurgeons.

2.2. Surgical procedure and grading of the fluorescence intensity

5-ALA (Gliolan, Medas Germany) was prescribed to patient at a dosage of 20 mg/kg·m^2 three to 4 h before anesthesia. Craniotomy was done under traditional white light. Ultrasound and neuronavigation system were used to localize the tumor before opening dura. Surgical microscope was then brought in for excision of the tumor. Exciting blue light with an optical filter for the red light was switched on whenever the surgeon needed, especially when they encountered vague boundaries between glioma tissue and normal brain tissue. Due to the blue light's inability in penetrating tissues and also to avoid photo-bleaching, white light and blue light were used alternately during resection. Excision of the tumor was then guided by integration of all techniques including ultrasound, neuronavigation as well as 5-ALA fluorescence. After a presumed total removal of the tumor, the blue light and the filter were switched on again, ensuring that the whole cavity where the tumor had seated, was clean without any residual fluorescence. Intensity of the fluorescence was described by the in-charge surgeon as "solid", "red", "vague", "pinkish" or "no fluorescence".

2.3. Post-operative monitoring

Patients were all protected from photosensitivity in intensive care unit for at least 24 h after surgery. Neurological functions were followed-up after surgery, monthly after discharge and six months after surgery. All patients were sent for post-operative MRI within 24 h (Day 1 MRI) after surgery to determine the extent of resection (EOR). An experienced neuro-radiologist would determine the EOR by studying the pre-operative MRI and Day 1 MRI. No residual of contrast enhancement on T1 post-contrast and subtraction scans equaled to total resection. For those cases in which more than 95% of enhancement was removed, the cases would be labeled as "near total resection". More than 5% of residual enhancing signal on the Day 1 MRI was suggestive of a subtotal resection in the case.

2.4. Primary and secondary objectives

The primary outcome of the study was the percentage of patients who had brain tumors totally excised under the

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