Fluorescence-guided resection of gliomas

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ABSTRACT

INTRODUCTION: Malignant gliomas remain associated with a poor prognosis despite both surgical treatment and radiochemotherapy.Previous studies have shown that complete resection of contrast-enhancing tumours is achieved in less than 20-30% of patients. 5-aminolevulinic acid (5-ALA) is a pro-drug that leads to accumulation of fluorescent protoporphyrins in malignant gliomas. The fluorescence can be visualized intraoperatively by use of a modified microscope. The Department of Neurosurgery at Aalborg Hospital has recently adopted this new technique as the first centre in Denmark. Our preliminary results are presented as a retrospective case series.

MATERIAL AND METHODS: All patients who had undergone 5-ALA fluorescence-guided surgery due to suspected malignant glioma were included. Patients received a standard preoperative dose of Gliolan. All patients had a postoperative cerebral magnetic resonance imaging scan done within 72 hours to determine their postoperative resection status.

RESULTS: To date, 13 patients have undergone fluorescence-guided surgery. Total resection was achieved in 54-70% of the patients depending on the inclusion criteria. Total or near total resection was achieved in 92% of patients.

CONCLUSION: The small numbers in our case series do not allow for direct comparison to be made, but show that our results on postoperative resection status fall within the range reported in other studies on the efficacy of 5-ALA. The literature offers mounting evidence in support of the role of aggressive cytoreductive surgery in patients with malignant gliomas.

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Intracerebral malignant gliomas remain associated with a poor prognosis despite both surgical treatment and radiochemotherapy.

Surgical treatment is complicated by the diffusely infiltrating nature of the malignant gliomas and the need to avoid damage to eloquent cortical areas during surgery. Furthermore, it is inherently difficult to define any marginal residual tumour during surgery. Previous studies have shown that complete resection of contrast-enhancing tumours is achieved in less than 20-30% of patients [1-3]. A recent report from the Danish Neuro-Oncology Registry (DNOR) has shown that this is also the case in all Danish centres [4].

The value of cytoreductive surgery has been the subject of much debate in the neurosurgical community for several years. However, recent studies have provided level II evidence substantiating the value of cytoreductive surgery in the management of malignant gliomas. Existing level II evidence also suggests a synergistic effect between aggressive cytoreductive surgery and radiochemotherapy [5-9].

5-aminolevulinic acid (5-ALA) is a pro-drug that causes fluorescent protoporphyrins in malignant gliomas to accumulate. The fluorescence can be visualized intra-operatively by the use of a modified microscope, which helps the surgeon define the tumour margins. The malignant tissue elicits red fluorescence under blue light illumination.

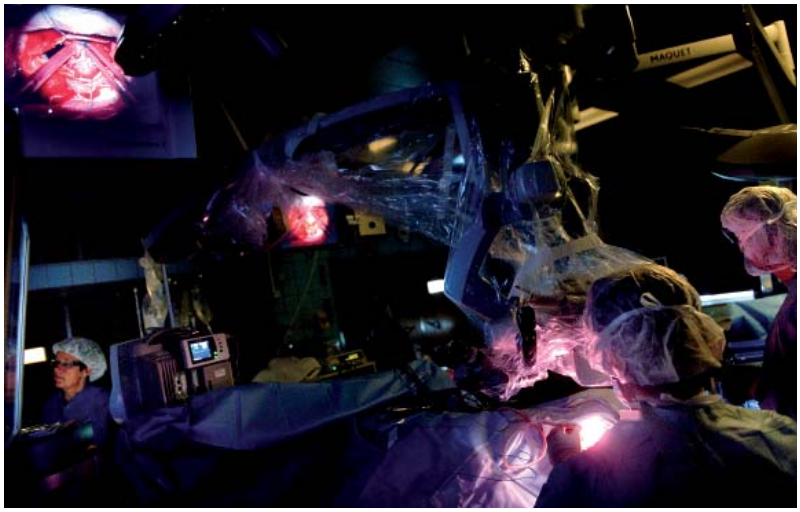
Stummer et al have recently provided level 1b evidence of markedly improved resection rates and improved six-month progression-free survival in 5-ALA fluorescence-guided surgery [10].

The Department of Neurosurgery at Aalborg Hospital has recently adopted this new technique as the first centre in Denmark.

This article describes our preliminary experience presented as a retrospective case series.

MATERIALS AND METHODS

All patients who had undergone 5-ALA fluorescence-guided surgery due to suspected malignant glioma were included.



The photo shows that part of the operation is performed in a darkened operation theatre to allow the surgeon to more clearly see the fluorescent tissue. Source: Lars Horn, Baghuset Pressefoto.

ORIGINAL ARTICLE

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Preoperative imaging studies were available on all patients. All patients had either a cerebral computed tomography (CT) or a cerebral magnetic resonance imaging (MRI) scan done. Patients received a standard preoperative dose of 1,500 mg Gliolan (Medac, Germany) dissolved into 50 ml of sterile water 2-4 hours prior to surgery (one vial of Gliolan contains 1,500 mg; issues of cost-effectiveness were discussed when choosing the standard dose). The recommended dose is 20 mg/kg. No patients received a dose that was larger than recommended. A blue-filter modified microscope for fluorescence-guided surgery was used in all cases (Zeiss-Pentero microscope).

During all operations, tissue samples were obtained for histopathological examination.

All patients had a postoperative cerebral MRI scan done within 72 hours to determine their postoperative resection status.

All patient data were reviewed retrospectively by two experienced members of the neurosurgical staff.

Both pre- and postoperative images were evaluated by both staff members. The consensual assessment was noted in the patient database.

Preoperative images were assessed with respect to the anatomical location of the tumour and whether the tumour was located in or in near proximity to eloquent cortical areas. Areas of motor- and language functions were considered eloquent areas. The visual cortex was not considered an eloquent area in this context as this location would have no or little impact on the preoperative surgical planning.

TABLE 1

Patient data.

Patient ID	Tumour location	Accesible to total resection?	Eloquent/ non-eloquent cortex	Total/near total/ residual tumour	Newly developed postoperative neurological deficits	Tumour histology
1.	Frontal, left	Yes	Non-eloquent	Total	Yes	GBM
2.	Frontotemporal, left	Yes	Eloquent	Total	No	GBM
3.	Occipital, right, growth in ventricles	No	Non-eloquent	Near total	No	GBM
4.	Frontal, right	Yes	Non-eloquent	Total	No	GBM
5.	Occipital, right	Yes	Non-eloquent	Near Total	No	GBM
6.	Occipital, right	Yes	Non-eloquent	Total	No	GBM
7.	Frontal, right	Yes	Non-eloquent	Near total	No	GBM
8.	Parietooccipital, left	No	Eloquent	Residual	No	GBM
9.	Temporal, left	Yes	Non-eloquent	Total	No	GBM
10.	Parietal, left	Yes	Eloquent	Total	Yes	GBM
11.	Temporoparietal, left	Yes	Eloquent	Total	Yes	GBM
12.	Temporal, left	Yes	Non-eloquent	Near total	No	GBM
13.	Frontal, left, tumour with haemorrhage	Yes	Non-eloquent	Near total	No	PNET

GBM = glioblastoma multiforme
PNET = primitive neuroectodermal tumour

Preoperative images were also assessed as to whether the tumour was accessible to complete resection. To avoid biased opinions, the consensual assessment was noted before reviewing the postoperative images. Tumours crossing the midline and tumours with deep-seated locations involving the basal ganglia were considered inaccessible to complete resection. Tumours with ingrowth to the ventricles or multifocal locations were also considered inaccessible to complete resection.

The evaluation of the postoperative images was based on T1-weighted Fluid Attenuated Inversion Recovery (FLAIR) sequences before and after gadolinium contrast enhancement. If there was any doubt about the significance of a contrast-enhancing element, this was considered residual tumour. Three categories were applied: total resection, near-total resection (less than 5% residual tumour) and residual tumour.

All patient charts and results from histopathological examinations were reviewed. It was noted in the patient database if patients had any new persisting neurological deficits at the time of discharge.

RESULTS

To date, 13 patients have undergone fluorescence-guided surgery. These patients have all been included in this case series (see **Table 1**). Nine patients were male and four patients were female. Their median age was 63.5 years.

Judging from preoperative imaging, the tumour was located in non-eloquent areas in nine out of 13 patients and in close proximity to eloquent areas in the remaining four patients.

When reviewing all patient data, total resection had been achieved in seven out of 13 patients, which is equivalent to 54%.

In the original 5-ALA study by Stummer et al, 61% of patients received a total resection [10]. In that study, inclusion criteria dictated that distinct tumour characteristics were present on preoperative imaging, that the tumour was accessible to complete resection and that histopathology was diagnostic of malignant glioma.

If the same inclusion and exclusion criteria are applied to our patient data, patients number three and eight would be excluded as the tumour was not accessible to complete resection judging from the preoperative imaging. Patient number 13 would be excluded due to histological criteria and due to a somewhat unclear preoperative imaging suggestive of haemorrhage in a not clearly defined tumour.

If these criteria are applied, total resection would have been achieved in seven out of ten patients, which is equivalent to 70%.

As in the original 5-ALA study, the volume of the residual tumour was generally low in our series. Reviewing

the complete dataset, total or near-total resection was achieved in 12 out of 13 patients, which is equivalent to 92%.

As mentioned above, the tumour was located in close relation to eloquent cortical areas in four out of 13 patients and in non-eloquent areas in the remaining nine patients.

In a single patient whose tumour was located in a non-eloquent area, new neurological deficits were observed postoperatively. This patient had developed a paresis of the right lower extremity. On postoperative imaging, signs of fresh ischaemia were noted in the distribution area of the pericallosal artery. The newly developed neurological deficits were attributed to accidental closure of this artery. This is seen as a complication of a general nature and should not be attributed to an extended fluorescence-guided resection per se.

Postoperative neurological worsening was observed in two patients whose tumours were located in eloquent areas. One patient experienced a worsening of pre-existing aphasia and a newly developed slight right-sided hemiparesis. The second patient experienced worsening of a pre-existing aphasia.

Histopathological examinations resulted in a definitive diagnosis of glioblastoma multiforme (GBM) in 12 out of 13 patients. The last patient was diagnosed with a primitive neuroectodermal tumour (PNET), which was described as a ganglio-neuroblastoma grade IV with some differentiation approximating a glioblastoma.

In all patients, the tumour exhibited usable fluorescence during surgery.

No toxic side-effects were observed among the patients in this case-series.

DISCUSSION

In conclusion, total resection was achieved in 54-70% of patients depending on the inclusion and exclusion criteria deployed. The patient numbers are too small to make any direct comparison with the original 5-ALA study by Stummer et al [10], but their results on postoperative resection status are in the same range as the results reported in the present study.

Total or near-total resection was achieved in 92% of patients.

As previously mentioned, recent studies have provided level II evidence substantiating the value of maximal cytoreductive surgery (total resections) in the management of newly diagnosed glioblastomas [5, 9, 10].

Only few studies provide conclusions about the benefit of different degrees of resection. Specifically, it has remained unclear which proportion of contrast-enhancing tumour must be resected to achieve a meaningful survival advantage.

A recent study published in July 2011 in Journal of Neurosurgery [11] provided new important insights on this topic. The authors included 500 consecutive, newly diagnosed patients with glioblastomas in a well-designed retrospective study. All patients had a postoperative MRI scan done within 48 hours. Utilizing multivariate analysis, the authors found that a significant survival advantage was seen in subtotal resections with an extent of resection of only 78% of the tumour and that stepwise improvement in survival was evident even in the 95%-100% range.

The original 5-ALA study by Stummer et al and a subsequent analysis of the same dataset [10, 12] showed that fluorescence-guided resections are generally safe, but carry a slightly higher risk of temporary neurological impairment – especially among patients with pre-existing neurological deficits who have not responded to steroids.

Again, the numbers in our dataset are too small to make any direct comparisons, but they do suggest an increased risk of postoperative neurological worsening among patients with pre-existing deficits.

CONCLUSION

Total resection was achieved in 54-70% of patients depending on the inclusion criteria used. Total or near-total resection was achieved in 92% of patients.

The small numbers in our case-series do not allow direct comparisons to be made, but show that our results fall in the same range as reported in the original 5-ALA study by Stummer et al [14] with regard to postoperative resection status.

The literature offers mounting evidence in support of the role of aggressive cytoreductive surgery in patients with newly diagnosed malignant gliomas.

Several studies also suggest a synergistic effect between aggressive cytoreductive surgery and radiochemotherapy.

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CONFLICTS OF INTEREST: none

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