Fluorescence-guided resections of malignant gliomas using 5-ALA

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Abstract:
It is generally accepted that the completeness of resection in malignant gliomas should be as complete as possible. Maximal cytoreductive surgery is generally performed aiming at removing at least that part of the tumor that accumulates a contrast agent for magnetic resonance imaging (contrast-enhanced MRI) (1;2). Complete resection of contrast enhancing tumor regions as judged by post-operative MRI is only achieved in a minority of patients (3-6), one of the reasons for this being the difficulty in detecting contrast-enhancing tumor margins intraoperatively (3).

Much effort has been put into the development of methods to improve intraoperative tumor detection, such as neuronavigation (7), ultrasound (8), interventional CT (9) or nuclear magnetic resonance imaging (MRI) (10). A direct optical identification of glioma tissue is suggested to be possible by fluorescence imaging of ALA-induced PpIX (11;12). Five-aminolevulinic acid (ALA) is a natural biochemical precursor of hemoglobin. Exogenous administration of ALA elicits the synthesis and accumulation of fluorescent porphyrins in various epithelia and cancerous tissues (13;14). Malignant glioma tissue has also been demonstrated to specifically synthesize and accumulate porphyrins, mainly PpIX in response to ALA administration. PpIX shows red fluorescence when excited with violet-blue light and can be visualized after appropriate modifications to a standard neurosurgical microscope (15). The resulting fluorescence has been under investigation as an intra-operative marker for residual malignant glioma tissue with the aim of improving the surgical treatment of these tumors (11;15).

In order to obtain approval for marketing a prospectively randomized multicentre study was performed. This study featured two primary efficacy variables, firstly, the percentage of patients with histologically confirmed malignant gliomas without residual contrast-enhancing tumor on early, postoperative MRI and secondly, progression-free survival at six months, defined strictly by the presence of contrast-enhancing tumor on MRI. Two groups were compared, one group with fluorescence-guided resection (FL-group) and one group with conventional microsurgery (WL-group).

In the FL-group the tumor was resected using fluorescence-guidance after ALA (20 mg/kg) had been administered orally 3 hours prior to induction of anesthesia. In the WL-group the tumor was resected as thoroughly as possible using the same microscope and conventional white, xenon illumination. Patients received dexamethasone pre- and postoperatively until post-operative MRI had been obtained. Surgical treatment was followed by radiotherapy.
Patients were enrolled and randomized by 32 investigators at 18 study centers throughout Germany. For a list of participating centers see acknowledgements. Results of 270 patients (FL-group: n = 139; WL-group: n = 131) were analyzed (16).

Patients in the FL- and WL-groups were comparable at baseline regarding tumor histology and demography data, KPS, NIH Stroke Score. Glioblastoma multiforme Grade IV had been diagnosed in 88% of cases in the FL-group and in 89% of cases in the WL-group, at least 97% were grade IV-tumors in both groups.

**Primary efficacy variables:** In the FL-group 64.7% of patients did not show residual, contrast-enhancing tumor on early post-operative MRI, compared to 35.9% in the WL-group (p < 0.0001). With respect to the second primary efficacy variable, Kaplan-Meier estimates for progression-free survival at 6 months were 41% for patients in the FL-group and 21.1% for patients in the WL-group (logrank test, p = 0.0003).

**Secondary efficacy variables:** Volume of residual tumor was small in both treatment arms. However, patients in the FL-group had less residual tumor on early postoperative MRI than patients in the white light group, with median volumes of 0.0 cm³ vs. 0.7 cm³ (p < 0.0001).

**Safety:** No significant pattern of change was detected between the FL- and the WL-group regarding laboratory parameters, except at 24 hours after surgery, when Gamma-GT, ALT/GPT and AST/GOT values were higher in the FL-Group (p = 0.047, p = 0.003 and p < 0.001, respectively), but no longer after 7 days or 6 weeks. Median KPS six weeks after surgery was 90% for both treatment groups, and this remained unchanged three and six months after surgery. No significant differences were noted in the distributions of NIH Stroke Scores, although the median of patients in the WL-group had improved at 48 hours after surgery compared to baseline, whereas patients in the FL-group remained unchanged at this time. No evident differences in the NIH Stroke Score were noted at 7 days or thereafter.

Taken together, the phase III randomized study demonstrated efficacy and safety of fluorescence-guided resections using 5-ALA and thus 5-ALA was approved by EMEA for marketing within Europe.

Since the original study, the standard of therapy of malignant gliomas was changed from adjuvant radiotherapy to adjuvant concomitant radiochemotherapy. Thus, the concept of cytoreductive surgery has to be rechallenged. Recent data, however, confirm that cytoreductive therapy of malignant gliomas plays an important role in increasing the efficacy of adjuvant therapies which is also the case for concomitant radiochemotherapy.

**References**


