5-aminolevulinic-acid guided resection

Fluorescence-guided surgery (FGS) with 5-aminolevulinic acid (5-ALA) has proven to assist neurosurgeons to achieve a more complete brain tumor resection. However, 5-ALA-guided surgery is limited since it is often difficult to distinguish the color difference between the resected areas of malignant brain tumors from their background.

In addition to stereotactic localization as well as intraoperative brain mapping, techniques to enhance visual identification of tumor intraoperatively may be used and include 5-aminolevulinic-acid (5-ALA). 5-ALA is metabolized into fluorescent porphyrins, which accumulate in malignant glioma cells. These property permits use of ultraviolet illumination during surgery as an adjunct to map out the tumor. This has been proven with RCT where the use of 5-ALA leads to more complete resection (65% vs. 36%, p < 0.0001), which translates into a higher 6-month progression-free survival (41% vs. 21.1%, p = 0.0003) but no effect on OS 1).

Fluorescein can be used as a viable alternative to 5-ALA for intraoperative fluorescent guidance in brain tumor surgery. Comparative, prospective, and randomized studies are much needed 2).

Indications

5-Aminolevulinic-acid Guided Resection Indications.

Doses

The highest visible and measurable fluorescence was yielded by 20 mg/kg. No fluorescence was elicited at 0.2 mg/kg. Increasing 5-ALA doses did not result in proportional increases in tissue fluorescence or PPIX accumulation in plasma, indicating that doses higher than 20 mg/kg will not elicit useful increases in fluorescence 3).

Application of 5mg/kg ALA was evaluated as equally reliable as the higher dose regarding the diagnostic performance when guidance was performed using a spectroscopic system. Moreover, no PpIX was detected in the skin of the patients 4).

Over time, several other tumour entities have been identified to metabolize 5-ALA and show a similar fluorescence pattern during surgical resection.

Further research is warranted to determine the role of 5-ALA accumulation in post-ischaemic and inflammatory brain tissue 5).

The positive predictive values (PPVs), of utilizing the most robust ALA fluorescence intensity (lava-like orange) as a predictor of tumor presence is high. However, the negative predictive values (NPVs), of utilizing the absence of fluorescence as an indicator of no tumor is poor. ALA intensity is a strong predictor for degree of tumor cellularity for the most fluorescent areas but less so for lower ALA intensities. Even in the absence of tumor cells, reactive changes may lead to ALA fluorescence 6).
Reviews

Senders et al., systematically review all clinically tested fluorescent agents for application in fluorescence guided surgery (FGS) for glioma and all preclinically tested agents with the potential for FGS for glioma.

They searched the PubMed and Embase databases for all potentially relevant studies through March 2016.

They assessed fluorescent agents by the following outcomes: rate of gross total resection (GTR), overall and progression free survival, sensitivity and specificity in discriminating tumor and healthy brain tissue, tumor-to-normal ratio of fluorescent signal, and incidence of adverse events.

The search strategy resulted in 2155 articles that were screened by titles and abstracts. After full-text screening, 105 articles fulfilled the inclusion criteria evaluating the following fluorescent agents: 5 aminolevulinic acid (5-ALA) (44 studies, including three randomized control trials), fluorescein (11), indocyanine green (five), hypericin (two), 5-aminofluorescein-human serum albumin (one), endogenous fluorophores (nine) and fluorescent agents in a pre-clinical testing phase (30). Three meta-analyses were also identified.

5-ALA is the only fluorescent agent that has been tested in a randomized controlled trial and results in an improvement of GTR and progression-free survival in high-grade gliomas. Observational cohort studies and case series suggest similar outcomes for FGS using fluorescein. Molecular targeting agents (e.g., fluorophore/nanoparticle labeled with anti-EGFR antibodies) are still in the pre-clinical phase, but offer promising results and may be valuable future alternatives. 7)

Shortcomings

5-ALA, methylene blue, and fluorescein suffer from short wavelength emissions in the visible spectrum, and for 5-ALA rapid bleaching 8) These shortcomings limit signal intensity, tissue penetration, resolution, and tumor-to-background ratio (TBR) due to nonspecific uptake in healthy tissue, autofluorescence, tissue absorbance, scattering, and photobleaching 9) 10)

Complications

Findings suggest that the administration of 5-ALA or the combined effect of 5-ALA, anaesthesia and tumour resection can cause a mild and reversible elevation in liver enzymes. It therefore appears safe to change the regime of monitoring. Routine blood samples are thus abolished, though caution remains necessary in patients with known liver impairment 11).

For near infrared imaging, additional investigators have explored fluorescein as well as novel near-infrared (NIR) agents 12) 13) 14)

Stummer et al. showed that 5-ALA guided resections carry a higher risk of post-operative neurological deterioration than conventional resections (26% vs 15%, respectively), even though the difference vanished within weeks 15).

Just as tumour tissue is often indiscernible from normal brain tissue, functionally critical tissues are indistinguishable from tissues with less clinically relevant functions.
Thus, knowing when to stop a resection due to proximity to areas of crucial neurological functions is of obvious and utmost importance. Detailed knowledge of the normal brain anatomy and distribution of function is not sufficient during glioma resection. Interindividual variability and functional relocation (i.e., plasticity) induced by the presence of an infiltrating tumour requires an exact functional brain map at the site of surgery in order to spare areas involved in crucial (so-called eloquent) functions. Preoperative localisation of function, either with functional MRI (fMRI) or navigated transcranial magnetic stimulation (nTMS), provides an approximate map.

Furthermore, intra-operative direct cortical and subcortical Electrostimulation (DCS) for functional analysis of the tissue in the tumour’s infiltration zone is required for accurate identification of areas that need to be spared in order to retain the patient’s functional integrity. Motor evoked potentials (MEP) provide real-time information on the integrity of the primary motor cortex and the corticospinal tract. Direct cortical mapping and phase reversal identify the primary motor and sensory cortices. Subcortical mapping can estimate the distance to the pyramidal tract, acting as guidance close to functionally critical areas. When integrated into the existing surgical tools, continuous and dynamic mapping enables more extensive resection while simultaneously protecting motor function. Using these techniques and a detailed electrophysiological “Bern-concept”, a group achieved complete motor function protection in 96% of patients with high-risk motor eloquent tumours. Furthermore, localisation of cortical and subcortical regions relevant to language function is essential for speech preservation during resection of gliomas in proximity to presumed speech areas and requires the patient to be awake during the brain mapping part of surgery. Similarly, intra-operative mapping of visual functions may contribute to increased resections while avoiding tissue essential for vision within the temporal and occipital lobes.

References


