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State of the art of fluorescence guided techniques in neurosurgery

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Abstract

Achieving a safe and extensive neoplasm resection can be considered the main goal of brain tumor surgery. This paper is first aimed at providing an overview of the evolution of those tools serving the purpose. From the dawn of neurosurgery to the present days, major innovations have followed one another. However, those techniques may frequently lack of an instant biological feedback on the true extension and the infiltration of the tumor. Intraoperative fluorescence modalities could indeed fill this gap. Fluorescence guided surgery will be therefore introduced and discussed in this context. Our focus will be on the most commonly fluorescence techniques used in neurosurgery, namely 5-aminolevulinic acid, sodium fluorescein and in indocyanine green. Mode of action, strengths and weaknesses and level of evidence of each modality will be discussed.

Introduction

High grade gliomas (HGGs) are the most frequent primary malignant brain tumours in adults. Giant strides have been recently made in their treatment, currently combining surgery, chemotherapy, and radiotherapy in a multimodal context. Despite these huge advancements, there is still a long way from a definitive cure. In the present day, surgery remains a first, crucial step. The pursuit of extensive but safe resection might drive the surgeon: **gross total resection** (GTR) is indeed of utmost importance in extending overall survival (OS) and progression free survival (PFS). [1-3]. Nonetheless, **prognosis** improvement is at odds with incomplete identification of tumour margins, which turns out to be a major problem during surgery. Intraoperative fluorescence, together with ultrasounds and other visualization tools had provided a fertile ground for experimentation in this area: after being extensively investigated for appropriate applications in neurosurgery, they are now considered some of the hottest topic in brain tumour surgery [4-12]. Three are the most commonly used compounds: 5-**aminolevulinic acid (5-ALA), sodium fluorescein (SF) and indocyanine green video-angiography (IG-VA).** Bearing in mind those as the milestones in the fluorescence-guided surgery field, it is important to take into account also other dyes currently used for a rapid tumour detection and pathological tissue examination in other settings such as cancer-selective alkylphosphocholine analogues, tetracyclines, cresyl violet, acridine orange, and acriflavine. In addition, activity-based and targeted molecular probes are emerging tools with the potential of providing biomolecular specificity and a better surgical visualization: this is why they are currently becoming more popular [13]. To tackle the complexity of the issue of fluorescence with a view of achieving GTR, a good first step is to approach it as a whole. We will first analyze intraoperative tools history, then the role of fluorescence: our attempt is to proper address biological mechanism, strengths and weaknesses, finally giving an overview about the related level of evidence.

Neurosurgical tools and innovations: a brief history

A comprehensive timeline (Figure 1) of neurosurgical advancements covers almost one century and a half of breakthroughs and innovations. Some of them, namely fluorescence, were swept under the scientific rug: their application to the field is now experiencing a new dawn. It is worth noticing how the need for a safe but extensive resection has always played a large role in the search for tools and techniques to achieve these goals.

First traces of this ongoing process can be found looking back at the **beginning of the neurosurgical era**. Indeed, our pioneer leaders considered this compromise between safety and extent of resection as something to strive for: at the dawn of neurosurgery diagnosis and surgery

planning were their main priorities. Accordingly, all their efforts were aimed to develop **preoperative** imaging techniques fit for the purpose.

The starting point is 1896: Krause and Cushing began to use intraoperative X-rays in neurosurgery [14]. The innovations continued throughout the twentieth century: Dandy employed pneumoencephalography in 1919 [15, 16]. Of note, a flourishing period had just begun: in 1927 Moniz introduced cerebral angiography for brain tumours [17, 18]; simultaneously, Penfield was starting to use intraoperative brain stimulation to map the cortex and guide resection [19]. If asked to quickly summarize whether the core of this first portion of our timeline is, we would answer with a simple statement: **a clear pre-operative recognition of pathological structures.**

However, decades passed before this goal was achieved: CT was introduced to clinical use only in 1973 [20-22]; several years later and after the spreading of contrast-enhanced CT the introduction gadolinium-enhanced MRI represented a further advancement: since 1987 it guarantees a more precise and safe surgery by means of a better tumour definition before surgery [23].

When it comes to the **intraoperative setting**, different considerations have to be made. Indeed, it took a great deal of time before intraoperative techniques reached a significant impact. It was not until 1948 that Moore introduced SF as a tool to **differentiate between the pathological and healthy tissue**. [24]. In 1957 the first intra-operative microscope was pioneered by Kurze [25]; at the time Feindel improved the SF technique [23]. Since the end of 1980s neuronavigation gained a crucial role and it became extensively adopted in neurosurgery operating rooms [26-28]; in addition intraoperative ultrasound [29-33] and intraoperative MRI [34] have recently joined those advancements.

It is easy to note how innovations in the intraoperative setting overlapped with the diffusion of the aforementioned pre-operative visualization tools: the majority of them are now of common use in neurosurgical patients' treatment.

Fluorescence and brain tumors: where are we

When talking about brain tumour surgery it is always worth emphasising that we must make every effort to find a tool which helps us in maximizing resection without compromising safety. Again, an increasing number of papers stated a relation between the extent of resection (EOR) and the survival in neuro-oncological patients. EOR is directly related to a **detailed intraoperative tumour identification**. A specific tool is needed to achieve this objective [35-37].

This should hold **four main features**:

1) use in an intraoperative setting

2) easy real-time performance

3) analogue resolution compared to cell

4) high tumour specificity

In addition to this, cost effectiveness and easy administration should be taken into account.

Currently available **fluorescent dyes** match the majority of those criteria: several of them have been considered, but only three are the ones with a widespread use. A different mode of action is what stands out when first considering them: **5-ALA** is metabolic tracer; **SF** is a fluorochrome which accumulates in Blood Brain Barrier (BBB) impaired areas; **IG** a pure vascular tracer. In this context our purpose is to offer a concise but in-depth look at the three of them. In agreement with that, we will focus on proper explanation of their functioning, brief summary of pros and cons and a final recap of the level of evidence in a GTR framework (Figure 2).

5-aminolevulinic acid (5-ALA)

5-ALA is a **non-fluorescent prodrug**. Precursor of heme synthesis pathway, it is first absorbed by tumoral cells and then converted into a fluorescent protoporphyrin IX (PpIX). When placed under blue-violet light, the latter is able to return red light in the visible spectrum frequencies; by doing so, tumour tissue is easily differentiated from non-pathological one [38, 39]. By translating it into a mere neurosurgical context, the potential of this tool can be fully explored.

After its administration, HGG cells are able to produce or collect 5-ALA-derived porphyrins. At this point, PpIX need to be excited. A surgical microscope with a xenon light source able to change between white bright and the violet-blue light (370–440 nm) is imperative in 5ALA-fluorescence guided surgery [40]. Once excited, the fluorescent mass has an emission peak between 635 and 704nm: to see the lesion as a red fluorescent mass a second filter is added to the microscope lens [38].

The main challenge of this technique relies on its **specificity** and **sensitivity** when it comes to tumoral tissue: respectively, 100% and 85%. However, this important advantage is not without some limitations:

1) Elevated **costs** (almost 1000 euros for each vial)
2) **Oral administrations** hours before anaesthesia in order to reach the blood peak concentration, and allow a proper visualization of fluorescent tissue
3) Requirement of a **dark surgical field**, not suitable for all surgeons
4) Risk of **skin sensitization** within 24h after the operation, with the need to avoid patient's exposure to sunlight [41]

A **randomized, multicenter, phase III trial** was conducted on newly diagnosed HGG cases in Europe. The aim was to assess safety and benefits of 5-ALA in achieving GTR. First, they demonstrated 5-ALA in induced intraoperative fluorescence was a crucial step forward in

increasing resection margins. Second, they showed the amount by which, improving GTR, 5-ALA correlates with OS and PFS. As a matter of fact, they increased respectively from 11.8 months in the control group to 16.7 months in the ALA group ($p<0.0001$) and from 21% at 6 months in the control group to 41% in the ALA group ($p<0.0003$) [18].

As a side note, the aforementioned promising data are specifically related to HGG glioma surgery. Indeed, this drug has also been studied in **other intracranial tumors** like low grade glioms, metastases, lymphomas, meningiomas and ependymomas. However, various degrees of sensibility and specificity were reported in such cases [42, 43].

Sodium Fluorescein (SF)

SF is an **easily available, biosafe and cheap fluorescein dye**. It is visible by the naked eye at high doses (20 mg/kg body weight); under the yellow 560 nm surgical microscope filter SF is observable even at lower dosages, all resulting in an improved tissue detection. Before bringing it into neurosurgical field, it has been extensively used for many years especially by ophthalmologists [44]. With a peak excitation of 465-490 nm and a 540-690 nm emission spectrum, it was first introduced by Moore et al. in 1948 [24].

Narrowing its field of use to the brain surgery, the main point is that this drug accumulates in the intracellular space via an altered BBB. It is important to highlight how this mode of action brings along a main limitation: **SF-based resection allows an improved visualization and removal in damaged BBB areas**. What said has 2 major implications:

1) Compared to 5-ALA, SF **has no specificity for tumoral cells.** Not showing the extent of infiltration decreases the accuracy of both tumour identification and surgical removal.
2) The fluorescent area corresponds to **enhancing nodule** seen at pre-operative MRI T1 after gadolinium administration; by some papers, this enhancing nodule is addressed as the target of the GTR.

Whilst the use of SF may be a very effective, safe, and cheap way to achieve the goal of a GTR, it is well known recurrences occur around surgical cavity. [41, 45]. is at present still a matter of debate Whether the enhancing nodule resection is enough to guarantee the best chance of cure in HGG patients [46-48]. The level of evidence is related to a series of observational cohort studies: all of them confirmed an increased rate of GTR and a good effect on PFS [49-52].

Main advantages of SF employment are:

1) **Reasonable cost** (7 euros/patient) compared to 5ALA (800 euros/patient) [53]

2) **Fast administration**, which is intravenous and just before tumour resection [54]

3) **Few** reported **side effects**, namely skin reactions, syncope, respiratory or cardiac adverse effects, and seizures .[54]

One final remark has to be made regarding tumors other than HGG. As distinct from what previously reported about 5-ALA, the efficacy of this dye is also demonstrated in other tumors like **metastases** [55].

Indocyanine-green video angiography (IG-VA)

ICG is a **near infrared diagnostic dye** with an absorption and emission peaks of 805 and 835nm, respectively. Microscope-integrated IG-VA has been introduced with the aim to visualize cerebral vessels during vascular neurosurgery [56-60].

IG-VA with FLOW 800 pioneered a broadening of its uses, now including also brain tumor surgery.

The idea behind this novel application is that IG-VA use brings it with significant benefits:

1) Useful information about **tumor-related brain perfusion changes**, aiding in the identificaion of helpful landmarks for the surgical approach
2) Direct monitoring of blood flow in the exposed vessels and brain parenchyma **during microsurgical resection**
3) Visualization of real time changes in brain vascularization, **preventing potential complications associated with the resection** such as local hypoperfusion or venous infarction [61].

Later, **Second Window-IG (SWIG)** was developed. [47] This novel technique takes advantages of the BBB permeability in peritumoral areas. It uses the same SF principle to guarantee IG accumulation in the abnormal tissues, allowing its intraoperative visualization.

SWIG has a main benefit: **high sensitivity for tumoral tissue detection**. Apart from gliomas, SWIG has demonstrated its efficacy in a variety of intracranial diseases, namely **meningiomas, metastases, pituitary adenomas, chordomas, and craniopharyngiomas**. [62].

Nonetheless, SWIG fail to recognize areas of altered signal in FLAIR sequence on preoperative MRI. A **main limitation** of its use is thus related to low sensitivity for these neoplastic "non-enhancing" lesion. Further considerations are limited by the paucity of additional data.

Conclusion

Fluorescent agents' employment provides substantial benefits for brain tumour surgery. Broadly speaking, they increase GTR. This correlates with a better prognosis, as claimed by the pertaining literature. 5 ALA, SF and ICG-VA are the ones with a greater use in this neurosurgical setting. Taken individually, each of them has its own mode of action, strength and weakness and a different level of evidence. Indeed, 5-ALA only was tested in multi-center randomized controlled trial [38, 63]; SF use relies instead on several observational cohort studies showing positive correlation with PFS [49-52]; ICG-VA is still at first stage in neuro-oncology. Since it would require precisely designed studies, direct comparison between 5-ALA and SF is not possible to the present day. **As a part of a larger group of neurosurgical innovation, fluorescence finds a crucial role in the EOR improvement**. Improving PFS and OS, it should be considered among the most **promising tools towards the direction of an extensive and safe resection.**

Figure 1 *From its beginning to the present day: a timeline of brain surgery*

Figure 2 *Fluorescence: brief summary of pros and cons*

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