Fluorescence Imaging/ Agents in Tumor Resection

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KEYWORDS

• Fluorescence-guided resections • 5-Aminolevulnic acid • Fluorescein • Gliomas • Glioblastoma

KEY POINTS

- Intraoperative fluorescence imaging enables real-time intraoperative identification of diseased brain tissue, which can be exploited for resection. As a tool, it expands the existing armamentarium but does not obviate immaculate surgical technique, a profound understanding of surgical anatomy, and the copious use of mapping and monitoring techniques.
- 5-Aminolevulinic acid is approved for intraoperative fluorescence imaging in many countries of the world.
- This compound is nonfluorescent and is converted to the fluorescent moiety PPIX within the tumor cell. A large body of literature supports its use in gliomas but also in other neurosurgically relevant tumors, for example, meningiomas.
- Fluorescein sodium, an older compound, has recently been receiving new attention. Fluorescein is extravasated at the breached blood-brain barrier, thus marking areas of blood-brain barrier breakdown, which are associated with brain tumors. The potential and pitfalls of this approach are subject to ongoing investigations. The regulatory status is unresolved.
- Novel, targeted fluorochromes are in preclinical and early clinical development and may provide high selectivity and high fluorescence yields in the future.

Video content accompanies this article at http://www.neurosurgery.theclinics.com.

INTRODUCTION

It is commonly acknowledged that even experienced neurosurgeons, using the optical information provided by the surgical microscope, their tactile sense, and a profound knowledge of anatomy, will not always be able to discriminate normal brain from brain infiltrated by tumor. This is of importance in malignant gliomas for which it is now well accepted that safe maximal resections are of benefit for both the rates of recurrence and the life expectancy of the patients.[1–6] It was many years ago that Albert and colleagues,[7] 1994, first demonstrated conclusively how strongly neurosurgeons tend to overestimate the degree of resection in malignant gliomas when relying on optical and tactile senses alone by correlating the surgeon's impression of radicality with early postoperative MRI. Neuronavigation, introduced during the early 1990s, was certainly helpful in overcoming this problem but suffers from the limitation of brain shift and frequent

Disclosures: The author has provided consultant and speakers services to Medac (Wedel), Carl Zeiss (Oberkochen), Leica (Heerburg).

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Neurosurg Clin N Am 28 (2017) 569–583
http://dx.doi.org/10.1016/j.nec.2017.05.009

interruptions of surgery for orientation.[8,9] Intraoperative imaging using the MRI was the next game changer (see Ganesh Rao article,"Intraoperative MRI and Maximizing Extent of Resection", in this issue). Even though the value of intraoperative MRI is undisputed, the high price of dedicated systems and the additional effort required for obtaining images still limits the distribution of such systems into many neurosurgical wards. The ideal technique for intraoperative identification of tissue would provide real-time tissue information during the actual process of resection, without the worries related to brain shift, and still be affordable. Intraoperative tissue fluorescence has the power to fulfill these requirements. With diseased tissue showing fluorescence in contradistinction to nondiseased tissue, and fluorescence being made visible to the surgeon, the surgeon can potentially operate directly on the tissue. It must be remembered, however, that any form of tissue staining in the brain does not diminish the responsibility of the surgeon to carefully reflect on whether to resect and to minimize risks to patients, optimally using state-of-the-art mapping and monitoring technology.[10] Fluorescence also does not obviate an intimate knowledge of surgical anatomy while respecting microsurgical principles of resection or wise selection of patients. See **Box 1** for advantages and disadvantages of fluorescence imaging.

Box 1
Potential advantages and disadvantages of fluorescence imaging

Advantages

- Real-time information
- Information provided through the surgical microscope with accustomed magnification
- Information provided from tissue and not from image
- No concern for brain shift
- Can be repeated as often as necessary
- Depending on type of fluorescence extended parts of the surgery can be performed using fluorescence only

Drawbacks

- Only 2-dimensional information
- Fluorescence can be obscured by overhanging tissue, blood, hemostatic agents
- Fluorophores can be bleached or destroyed by coagulation
- Requires additional drugs in many cases; regulatory issues

Fluorescence is a tool and not a therapy. The information from tissue fluorescence needs to be used wisely, while respecting principles of case selection, microsurgery, and mapping and monitoring of neurologic function.

FLUORESCENCE: THEORETIC BACKGROUND

In general, fluorescence is a characteristic of many dyes that, when illuminated by light with a short wave-length, emit light of a longer wavelength. By using appropriate filters, the emission light can be excluded from the observer, allowing only the emitted fluorescence light to become visible. Thus, the observer can perceive the distribution of the dye selectively. If the dye is associated with tumor tissue, the distribution of otherwise not clearly visible tumor can be perceived based on tissue fluorescence.

In general, 4 types of approaches to intraoperative fluorescence can be distinguished (**Table 1**). Tissue fluorescence based on passive permeability, for example, indocyanine green (ICG) or fluorescein; tissue fluorescence induced by specific metabolic characteristics (eg, 5-aminolevulinic acid [ALA]); autofluorescence; and, finally, fluorescence derived by fluorescent probes targeting or being retained by brain tumor tissue. These methods differ much in their background, selectivity, stage of clinical development, and versatility. In general, when evaluating these methods and to allow a comparison, several aspects need to be kept in mind:

- The selectivity of accumulation
- Time dependency of signal and signal strength
- Visibility of the fluorochrome to the surgeon

SELECTIVITY OF ACCUMULATION

Selectivity of tumor delineation, of course, is a crucial issue when considering an agent or technique for intraoperative fluorescence imaging. The surgeon needs to be able to rely on fluorescence to truly highlight tumor and not normal, functionally intact, or edematous brain. However, defining or measuring selectivity of an agent for delineating tumor is difficult and wrought with numerous biases and error sources.[58] For the sake of this article, it should be understood that measures of diagnostic accuracy (sensitivity, specificity) are not defined for intraoperative fluorescence imaging, depend very strongly on where