A review of indocyanine green contrast agent in surgery

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Introduction

Fluorescence Imaging (FI) is one of the most popular imaging modes in biosciences. Its benefits include:

- High contrast: only the target is visible, not background
- High sensitivity: a very small concentration can be made visible
- Gives molecular information: makes (bio)chemistry visible
- Great tools for research: several possible imaging modes
- Cheap: optical instrumentation quite simple
- Easy to use: resembles classical staining

Fluorescent imaging is a relatively new imaging mode so that it is still developing. Also indocyanine green seems to have an excellent application and development potential meaning that a lot of engineering development is still needed.

Indocyanine green

ICG was developed for NIR photography by Kodak Research Laboratories in 1955 and it was approved for clinical use already in 1956.[1] It fluoresces at about 800 nm. The excitation and fluorescence maximums depend somewhat on the molecular environment and the concentration of ICG. It has clinically excellent properties:

- non-toxic and non-ionising
- short lifetime in blood circulation
- binds to blood albumin (does not leak from circulation)
- operates in tissue optical window (NIR)
- simple and cheap imaging devices
- not much background NIR autofluorescence in tissue.

It has been used in clinical applications since late 50s. So what is so new in ICG angiography? Recently new medical applications, mainly in surgery, has been introduced. Some of the ICG's subexcellent properties provide challenge to research and engineering development:

- need some NIR imaging device to be visible (fluorescein does not)
- very recent in many applications like cancer and reconstructive surgery
- need some illumination control etc auxiliary devices
- not many chemical derivatives for more specific physicochemical imaging
- injection solution contains some sodium iodide (allergic reaction possible)
- unstable in solution (10 h) and non-linear fluorescence vs concentration.

Development of even better NIR contrast agents is going on. Some of the proposed new molecules are based on ICG while there are also totally different approaches like quantum dot based contrast agents.[2,3]

ICG Angiography (ICGA)

ICG has been used for decades in ophthalmology for imaging retinal blood vessels i.e. in retinal angiography. However, fluorescein operating in visual wavelengths has been much more popular in retinal angiography (visible without any cameras).

The principle of fluorescence imaging is simple: illuminate with excitation wavelength (blue rays, Figure 1) and image at emission wavelength (red rays, Figure 1). Only a couple of filters are needed in addition to proper camera and light source. Every CCD-camera is in principle able to record NIR. Most cameras are not allowed to do so by a filter that cuts NIR wavelengths, which would spoil visual image.

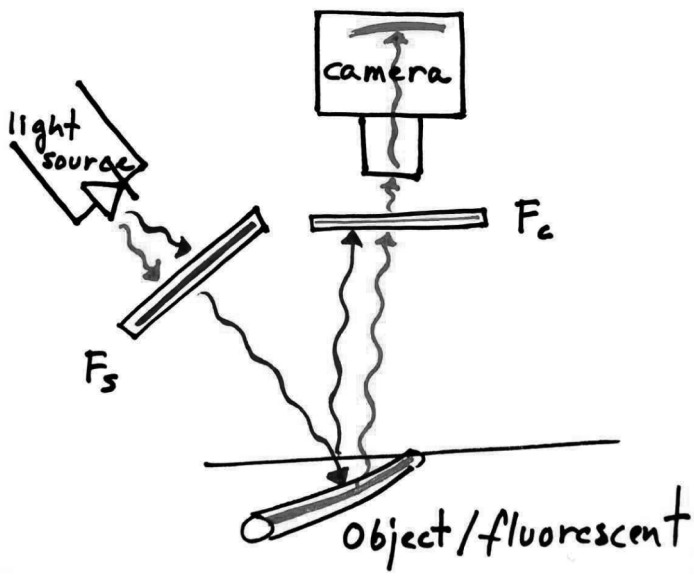

Figure 1. Fluorescence imaging (F_s = high pass filter for source; F_c = low pass filter for camera).

Surgical applications

Traditional medical applications of ICG are retinal angiography (and laser surgery thereon), liver monitoring and blood flow, and cardiac output monitoring. ICG is fast removed from circulation by liver to bile juice which fact is used to liver monitoring. It also gives the option to inject ICG several times during operation if needed. Recent interest on ICG is based on new applications in surgery and especially in angiography related to intraoperative monitoring of blood circulation in vital organs.

Intraoperational angiography

As compared to other angiography methods (X-ray, CT, MRI, PET) ICGA can be easily and economically used intraoperationally, when blood vessels are exposed allowing direct or nearly direct visual observation. Thus e.g. in neurosurgery, bypass coronary surgery, flap operations in reconstructive surgery, wound and trauma surgery, and laparoscopic surgery, where it is important to check that blood circulation is recovered, ICGA has most potential. The imaging protocol is simple, which is really a benefit in intraoperational applications. ICG is given as an injection (bolus) to systemic blood circulation and imaging is done during a period of few minutes after injection. A new bolus can be given after about 15 minutes if needed.

Neurosurgery

Neurosurgery is ideal for ICGA because operations are done under a microscope (and camera) and because the blood veins are mainly located on brain and thus can be seen visually. Milestones in neurosurgery include:

- introduction of ICGA for neurosurgery [4]
- ICGA with surgical microscope [5]
- Leica 2006, FDA approval of ICGA surgical microscope
- Zeiss 2007, commercial surgical microscope with ICGA
- Zeiss 2009, ICGA dynamics display software.

Coronary bypass surgery

Coronary arteries are also ideal for ICGA because they are, like brain arteries, on the organ they supply blood to. Milestones in coronary bypass surgery include:

- Pig model of coronary bypass angiography with ICG [6]
- FDA approval for ICGA device SPY for coronary angiography (2005)
- Comparison of ICGA and ultrasound flow metering at University of Toronto: Feb 2004–March 2005
- GRIIP clinical trial (phase III) at Sunnybrook Health Sciences Centre: July 2005 - June 2009

Lymph node harvesting

Lymph nodes are the initial site for metastases for most cancers. A real problem in cancer surgery is that the lymph nodes are difficult to harvest during operation. Currently radioactive Technetium-99 isotope labeling is used to detect lymph nodes. This may be replaced by ICG NIR imaging. Here ICG is injected under skin from where it flows via lymph circulation to lymph nodes revealing them when lit with excitation light.[7–9]

Photodynamic and photothermal therapy

When an ICG molecule is excited it can further transfer energy to other molecules. When exiting oxygen ICG turns out to be a photodynamic therapy agent. In principle, e.g. after having been used to reveal lymph nodes a strong illumination with NIR light could be used to destroy metastatic nodes. This gives a potential route to cancer surgery automation resembling eye laser operations. NIR absorption can be used also with high intensities for thermal effects. Combined with e.g. albumin ICG based tissue welding is possible, which further gives potential for automation in microsurgery.

Research challenges

New clinical applications of ICGA are just emerging, thus much research is needed in order to fully benefit all potentials of this technology. Here are some obvious fields of further research:

- Image processing of ICGA information, also in real-time
- combining ICG and other imaging modalities like visual, CT, MRI and PET
- imaging deeper (tomography)
- imaging device development (laparoscopy)
- new derivatives of ICG for more specific imaging modes
- nano-encapsulation of ICG for non-angiography applications
- capillary circulation monitoring
- processing of spectral information and chemometry.

New and extremely interesting ICG imaging and image processing works start emerging.[10]

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