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Cătălin Aliuș
UNIVERSITARY EMERGENCY CLINICAL HOSPITAL, BUCHAREST, ROMANIA

Nicolae Bacalbașa
CAROL DAVILA UNIVERSITY OF MEDICINE AND PHARMACY, BUCHAREST, ROMANIA

Cristian Bălălău
CAROL DAVILA UNIVERSITY OF MEDICINE AND PHARMACY, BUCHAREST, ROMANIA

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Innovative Device for Indocianyne Green Navigational Surgery

Cătălin Aliuș[1], Nicolae Bacalbașa[2,3,4], Cristian Bălălău[2,5]

[1]Universitary Emergency Clinical Hospital, Bucharest, Romania
[2]Carol Davila University of Medicine and Pharmacy, Bucharest, Romania
[3]Ion Cantacuzino Clinical Hospital, Bucharest, Romania
[4]The Center of Excellence in Translational Medicine – Fundeni Clinical Institute, Bucharest, Romania
[5]Saint Pantelimon Emergency Clinical Hospital, Bucharest, Romania

ABSTRACT

Dynamic reality has been integrated into developing surgical techniques, with the goals of providing increased intraoperative accuracy, easier detection of critical anatomical landmarks, and better general results for the patient. Enhancement of the reality in surgical theaters using single or multi sensorial augmenters (haptic, thermic and visual) has been reported with various degrees of success. This paper presents a novel device for navigational surgery and ancillary clinical applications based on the fluorescent properties of Indocyanine Green (ICG), a safe, FDA-approved dye that emits fluorescence at higher wavelengths than endogenous proteins. The latest technological developments and the aforementioned convenient quantum behavior of ICG allow for its effective identification in tissues by means of a complementary metal-oxide semiconductor (CMOS) infrared camera. Following fundamental research on the fluorophor in different biological suspensions and at various concentrations, our team has built a device that casts a beam of excitation light at 780nm and collects emission light at 810-830nm, filtering ambient light and endogenous autofluorescence. The emission light is fluorescent and infrared, unlike visible light. It can penetrate tissues up to 1.6cm in depth, providing after digitization into conventional imaging anatomical and functional data of immense intra-operative value.

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***Corresponding author:**
Catalin Alius, Universitary Emergency Clinical Hospital, Bucharest, Romania,
E-mail: alius.catalin@gmail.com

Introduction

Although biomedical sciences have been using fluorescent imaging for decades mainly in microscopy, intra-operative fluorescence imaging for macroscopic structures is still an emerging technique and under constant development and improvement. The interest in navigational surgery using ICG is increasing rapidly, with authors reporting new applications and technique modifications almost constantly [1-3]. Augmented reality with near infrared fluorescence offers an enhanced surgical perspective within various specialties, providing supplementary intraoperative data such as delineation of biliary structures, evaluation of tissue perfusion when forming anastomoses or assessing flaps, lymph node dissection guidance, identification of vascular, and highly metabolic active structures, etc. [4-6]. All these advantages present an opportunity for surgeons to perform faster and more safely in a navigational environment which will undoubtedly become ubiquitous in the near future. ICG, a very safe fluorescent dye employed in clinical and surgical practice for more than 60 years, is currently approved by the FDA and used in the majority of the European States. Over the past decades, its unique near infrared fluorescent properties and excellent safety profile have led many surgeons to use it off label for different types of guided surgery [7-9]. Technology offered optical and electronic solutions for low yield photon emission systems only recently, rendering previous attempts to perfect the technique unsuccessful. Despite its enormous potential, the use of the method is limited for monetary reasons, hence our endeavor to develop an affordable device with good specifications and increased odds for market penetration. The prototype presented in the ensuing pages provides excellent image clarity in ambient light and a tissue penetration of up to 1.6cm. It consists of a CMOS camera,

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excitation and emission light, low and high pass filters, and a digitization software. The design of the device was based on spectrophotometric measurements on different matrices containing ICG, its parts being adapted to the unique behavior of the dye.

Discussions

Quantum behavior of ICG

The principle behind the method is based on the fluorescent properties of ICG. When illuminated with an excitation light from 750 to 800 nm, the molecule switches from fundamental state to a higher level of energy, absorbing it from the excitation light. Because the newly acquired excited state of the molecule is not stable, relaxation to ground state occurs almost instantaneously and the excess of energy is cast into photons with higher wavelengths (usually over 800nm), thus producing fluorescent light (Figure 1) [10]. The process has been synthesized in Figure 1, depicting a Jablonski diagram applicable to the molecule of ICG.

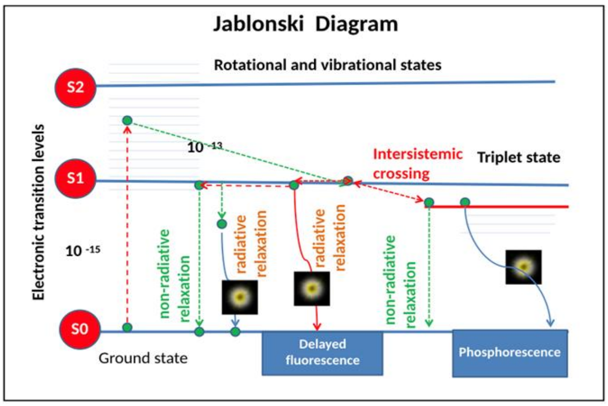

Figure 1. Jablonski Diagram for ICG

Although invisible to the naked eye, this light can be seen with infrared cameras and converted easily into conventional imaging. When tissues, blood, and secretions contain ICG they exhibit fluorescent properties as well, becoming visible in the near infrared spectrum. This happens by producing light captured by a CMOS camera and then digitizing it to a visible image that offers functional and anatomical details otherwise obscure to conventional imagery (Figure 2).

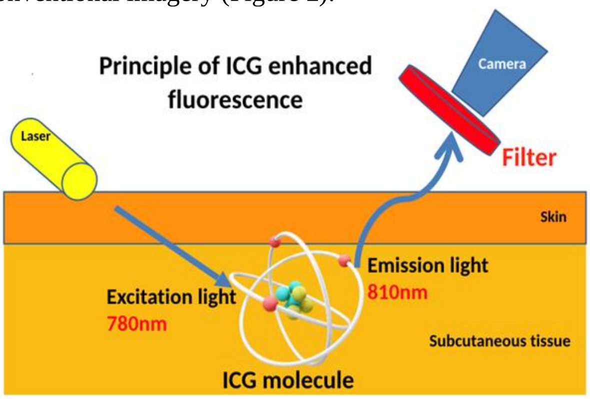

Figure 2. Principle of ICG enhanced fluorescence

Although simplified for didactic purposes, the process of ICG enhanced tissular fluorescence is not easily reproducible because of (i) endogenous fluorescence produced by various proteins in the human body, (ii) ambient light interferences on the camera sensor, (iii) the quantum yield of the fluorescent process, (iv) auto-quenching, (v) aggregation, (vi), dimerisation, (vii) fluorescence depolarization, (viii) molecular instability after reconstitution, and multiple other subtle processes [11,12]. Despite a plethora of clinical research involving ICG there have been few papers concerning the quantum behavior of this molecule, with the most comprehensive published over 40 years ago [12]. Like all polymethinic cyanides, ICG is amphiphilic and has a tendency to dimerisation at higher concentrations, leading to a decrease of the spectral interval between excitation and emission wavelengths (blue shift phenomenon) and to a reduction in the fluorescence intensity [13-15]. These have an enormous impact over the general performance of the optical system and any desired improvement of a device must take these observations into account. Following fundamental research using spectrofluorometry (Horiba Jobin Y von fluorolog) at different concentrations of ICG in water, water with albumin, bile, and blood, our team determined that the intensity of the generated fluorescence rises with the concentration of the dye up to a point from which the quantum yield drops. We determined this point at a dilution of 1/2500 from which H dimers started to appear in greater concentrations and affected the efficiency of the emission by a mechanism called auto-quenching. This observation has been suggested by Barros in 2010 on all polymethinic cyanide fluorophors [16-18]. When albumin was added to the solution, the fluorescence intensity spiked with 150% and generated a red shift phenomenon (Figure 3).

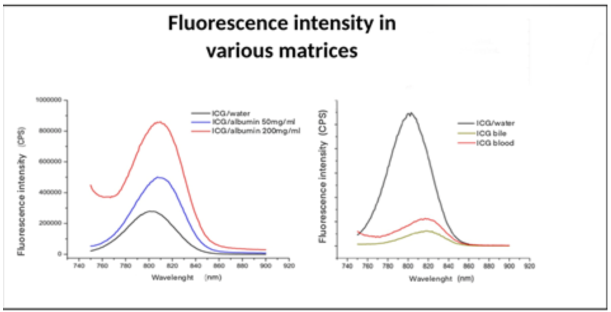

Figure 3. Fluorescence intensity in different matrices at spectrofluorometry

The intricacies of these phenomena have not been elucidated up to this date, but apparently the binding between albumin and ICG reduces formation of oligomeric complexes. This is one of the reasons we support using albumin as a solvent when performing sentinel lymph node biopsy with ICG. When using integral blood and bile, the fluorescent intensity is reduced drastically mainly because of endogenous pigment interferences, autofluorescence, and binding to various molecules contained in the solvent. Furthermore, an increase in the concentration did not improve the readings, but addition of albumin did (Figure 4).

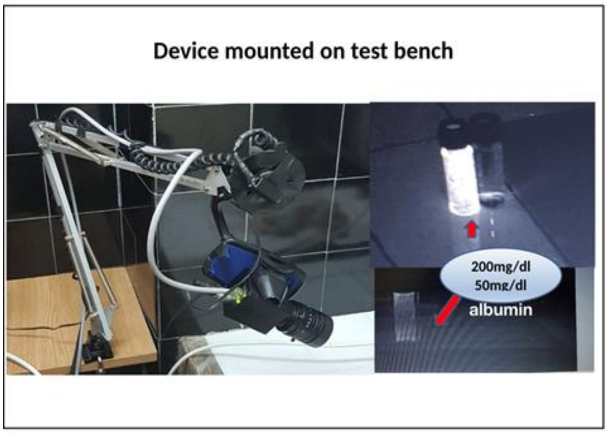

Figure 4. Increased intensity of fluorescence after addition of albumin

Clinical translation and technical specifications of the device

Fluorescent systems using ICG would not have sparked such a vibrant interest in the surgical community if human biology had not had been exhibiting a convenient particularity: hemoglobin absorbs electromagnetic radiation with wavelengths under 650nm, and water higher than 900nm. Since two thirds of the body is water, this window of opportunity between 650 and 900 nm is suitably filled by ICG, which absorbs at around 750-780nm and emits between 810-840nm depending on the solvent (water, bile, blood). ICG has been in use for over 60 years in ophthalmology with fewer complications than any other imaging dyes, is FDA approved, and its fluorescence can now be harnessed efficiently with modern cameras and newer generation optical systems. Nevertheless, for a successful clinical translation of any sort of surgical device using fluorescence, there are minimal mandatory requirements and performance conditions: (i) a source of excitation light, (ii) an optical system for harnessing emission light (iii) a camera with visible and infrared spectra,(iv) optical filters, (v) a digital image processor, (vi) a display, and (vii) a storage device.

Fluorescent systems use three main types of excitation light sources: halogen lamps, light emitting diodes (LED), and laser diodes. Broadband lamps offer a large illumination filed, but have the lowest efficacy and very poor spatial confinement. LED's have better power and a much-reduced broadband but are not indicated for dyes with small Stokes shifts, in this case requiring complex filtering systems to prevent interferences of the excitation light with the emission light. Laser diodes have the advantage of monochromatic light, hence a fixed wavelength requiring no spectral confinement of the excitation light, and they come in various output powers [19,20]. The choice of the emission light source is dependent on the cost, mounting method, the desired field of view, and the sensitivity of the camera sensor. Based on spectrophotometric measurements Indoviewer was equipped with a 780nm laser diode of 50mW of power with continuous light. The laser diode was fixed on a detachable magnetic small plate to allow for an adjustable angle and area of illumination.

The introduction of complementary metal-oxide semiconductor (CMOS) cameras was revolutionary for low yield fluorescent light systems, allowing good quality images for low intensity fluorescent light. We used a Nocturn GV camera with a DO-2595 lens with manual focus and a f-stop of 0,95. This provided a working distance starting from 0,5m, which is ideal for fixed devices such as our own. The lens had 2 filters attached: an IR 850nm and an RG 780. These high and low pass filters are used to narrow the spectral window of the light impressing the sensor and to shield off the ambient light interferences and the excitation light (Figure 5).

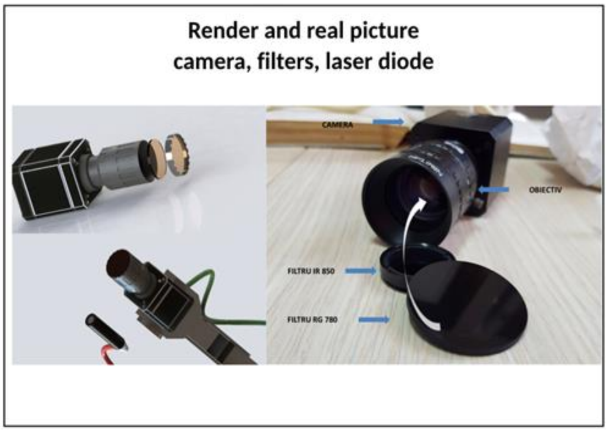

Figure 5. Rendered images with the detachable laser diode and a real picture with the camera, the lens and the optical filters

The whole system was mounted on an articulated mechanical arm fixed in position by a clamp at the base as shown in Figure 6. For future research a handheld miniaturized version was proposed for ease of handling and instant mobility of the area of illumination.

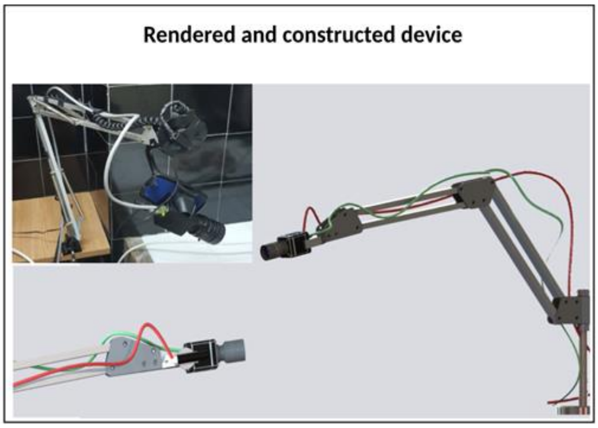

Figure 6. Rendered and constructed device

Clinical applications of the device and testing

ICG-enhanced surgery remains an emergent method, although it was first used for breast sentinel lymph node biopsy in 2000 and in colorectal surgery after 2007. Over the past years a significant surge in interest led to a rise in the number of reports worldwide. The main clinical applications compatible with our device cover a large array of specialties encompassing breast cancer and melanoma-related sentinel lymph node surgery, assessment of vascular pedicles, pancreatic stumps, liver resections, surgery for lymphedema, wound evaluation, bowel surgery including anastomoses and colonic sentinel lymph nodes, tumor marking, metastatic deposits identification, dissection of biliary tree and parathyroids, assessment of drug delivery devices (Porta-A-Cath), etc. (Figure 7) [21-23].

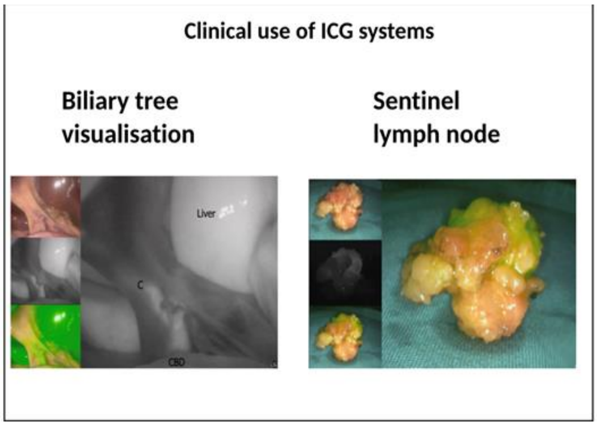

Figure 7. Personal images with ICG enhanced surgery using NOVADAQ technology

ICG is used in general surgery for identification of the biliary tree to facilitate faster and safer dissection of the pedicles. In a personal study we demonstrated that the use of ICG assisted cholecystectomy reduced the duration of this operation by 10 minutes and increased the rates of identification of anatomical landmarks at the beginning of the surgery in high BMI patients [24, 25].

Although some authors suggest that with adequate training there should not be any differences in iatrogenic biliary injuries in laparoscopic versus open cholecystectomies, we believe that the use of ICG enhanced surgery promotes cheaper, safer, and faster procedures.

Boni reports no anastomotic leaks in a series of patients on whom assessment with ICG was performed before formation of anastomoses [24-26]. Similarly, a multi-center study on 146 patients undergoing left sided colectomies demonstrated a 1.4% rate of anastomotic leaks and 11 anastomotic re-dos after intraoperative ICG evaluation. None of the 11 patients had any complications [25,27]. Upper gastrointestinal surgery benefited from ICG enhanced surgery in gastric resections and eso-jejuno anastomoses with reductions in anastomotic leaks from 18% to 3% in a report published by Karampinis [26, 28].

In emergency surgery, ICG is used for evaluation of bowel perfusion in strangulated hernias and non-occlusive mesenteric ischemia [27-29]. In endocrine surgery, Kahramangi reports a rate of parathyroid identification of 93% using ICG on a cohort of 33 patients [30, 31]. In plastic surgery, the method is useful in identification and assessment of vascular pedicles, flap viability, and lymphatico-venular anastomoses [32,33]. Apart from these applications some authors reported preliminary data on experimental ICG tagged monoclonal antibodies against tumor antigens and nanoparticulated ICG for cancer therapy [34, 35].

Indoviewer was bench-tested on animal tissues and produced very good quality images at optimum concentrations of ICG and a maximal depth penetration of fluorescent light of up to 1.6cm. Studies in operating theaters will follow after safety certification and ethical committee approval (Figure 8).

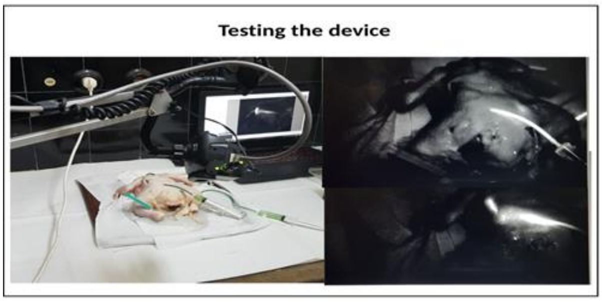

Figure 8. Functional device during tests

Future research directions

Although Indoviewer is a functional prototype awaiting patenting, at the moment our team is committed to continuong improvement in terms technical specifications and ergonomics. In this regard, a handheld miniaturized version using battery power and wireless imaging transmission has been contemplated. Preliminary schematics show viability of the idea, but an increase in production costs will be inevitable. This might hinder our efforts to offer an affordable device that can be used ubiquitously (Figure 9).

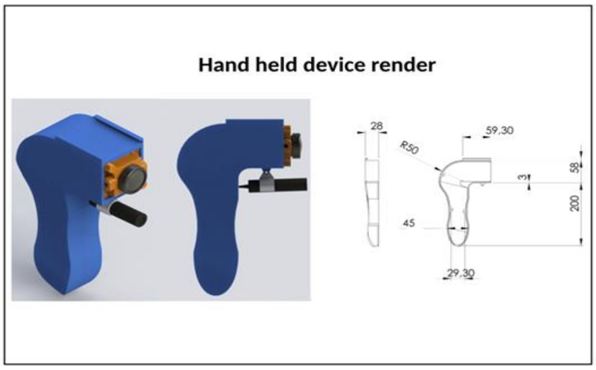

Figure 9. Future research proposal for a hand held ICG device

Pulsating laser light could employ higher power specifications with less thermal effect, but would impact cost containment strategies, as it requires a complementary module for pulsating light.

Technical alternatives with goggles-projected augmented reality are viable, but will restrict surgeon`s mobility, will affect the ergonomics, and might distract the surgeons from their immediate environment. Apart from significant cost escalation, this is another reason virtual reality (complete separation of the surgeon from his environment) is not a recommended option for use with ICG at the moment.

Conclusions

The unprecedented technological progress of the last decades has opened research perspectives into bio-imaging with applications in all surgical specialties. ICG-enhanced surgery is a new emerging method based on old principles, unmet technologically for more than half a century. Our device is a functional prototype with very good light penetration and clear image that might be used ubiquitously due to its affordability and versatility. We believe that improved versions of the Indoviewer could integrate more sophisticated augmented reality modules that will increase its performances and expand its range of clinical applications.

Conflict of interest disclosure

There are no known conflicts of interest in the publication of this article. The manuscript was read and approved by all authors.

Compliance with ethical standards

Any aspect of the work covered in this manuscript has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

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