Physica Medica 32 (2016) 218–225

Contents lists available at ScienceDirect

Physica Medica

journal homepage: http://www.physicamedica.com

Technical Notes

A palm-sized high-sensitivity near-infrared fluorescence imager for laparotomy surgery

Paul Dorval [a,b], Norman Mangeret [b], Stephanie Guillermet [b], Ihab Atallah [c], Christian Righini [c], Gabriele Barabino [d], Jean-Luc Coll [c], Philippe Rizo [b,e], Patrick Poulet [a,*]

[a] Laboratoire des sciences de l'ingénieur, de l'informatique et de l'imagerie, UMR 7357, Fédération de Médecine Translationnelle de Strasbourg, Université de Strasbourg/CNRS, 67412 Illkirch, France
[b] Fluoptics, 38040 Grenoble, France
[c] Institut Albert Bonniot, U-823, Université Joseph Fourier/INSERM, 38000 Grenoble, France
[d] Centre Hospilato-Universitaire de Saint-Etienne, 42000 Saint-Etienne, France
[e] CEA-LETI, Minatec, 38054 Grenoble, France

ARTICLE INFO

Article history:
Received 16 September 2015
Received in revised form 28 October 2015
Accepted 17 November 2015
Available online 2 December 2015

Keywords:
Fluorescence image-guided surgery
Near-infrared fluorescence
Molecular imaging
Indocyanine green

ABSTRACT

In laparotomy surgery guided by near-infrared fluorescence imaging, the access to the field of operation is limited by the illumination and/or the imaging field. The side of cavities or organs such as the liver or the heart cannot be examined with the systems available on the market, which are too large and too heavy. In this article, we describe and evaluate a palm sized probe, whose properties, weight, size and sensitivity are adapted for guiding laparotomy surgery.

Different experiments have been performed to determine its main characteristics, both on the illumination and imaging sides. The device has been tested for fluorescent molecular probe imaging in preclinical procedures, to prove its ability to be used in cancer nodule detection during surgery. This system is now CE certified for clinical procedures and Indocyanine Green imaging has been performed during clinical investigations: lymphedema and surgical resection of liver metastases of colorectal cancers.

Introduction

Current conventional surgical techniques use palpation and vision changes to determine the border between normal and cancerous tissues. These techniques led to positive tumor margin rate of only 15%–60% [1]. More specific imaging modalities have been developed and evaluated in preclinical and clinical tests to improve detection of cancerous tissues during surgery. Many medical imaging modalities have been adapted to the operating room, including fluoroscopy, ultrasound, computed tomography, and magnetic resonance imaging.

Wide field optical imaging techniques are well suited to the intra-operative environment and many contrast agents have been currently studied for guiding oncologic surgeons [2].

Among these optical techniques, fluorescence imaging appears very promising. The number of preclinical and clinical applications of Fluorescence Image Guided Surgery (FIGS) reported in the literature is increasing significantly, as exemplified by the following review articles on clinical FIGS [1,3,4]. Fluorescence imaging is now recognized to improve lymph node mapping, to guide Sentinel Lymph Node (SLN) surgery, to assess perfusion in vascular and reconstructive surgery, and to help on tumor resection. The technique is now widely used from neurosurgery, to head and neck, gynecology and urology, and is particularly well fitted to breast and digestive surgery [5].

The goal of FIGS systems is to image the distribution of fluorescent agents previously injected to the patient. The system should illuminate the region of interest with an excitation light and collect the subsequent fluorescence photons emitted. The basic research areas related to FIGS are mainly focused on the development of NIR fluorescent agents and of imaging devices.

Most of the FIGS systems are working in the Near-Infrared (NIR) range, between 650 and 850 nm. There are two main advantages of using the NIR part of the spectrum. (I) NIR photons penetrate deeper in the human organs, due to lower absorption even though the scattering remains the limiting factor, as compared to the visible range. (II) The auto-fluorescence of tissues in the NIR region is much lower than in the visible range.

The fluorescent agents can be divided in two classes: organic dyes or probes (when the dye molecule bears targeting capabilities) and nanoparticle-based probes. In the last years, great efforts have been made to develop new probes with low toxicity, strong NIR

* Corresponding author. Laboratoire des sciences de l'ingénieur, de l'informatique et de l'imagerie, UMR 7357, Université de Strasbourg/CNRS, 67412 Illkirch, France. Tel.: +33 368854051.
E-mail addresses: p.poulet@unistra.fr (P. Poulet), paul.dorval@live.fr (P. Dorval), gabriele.barabino@chu-st-etienne.fr (G. Barabino), jean-luc.coll@ujf-grenoble.fr (J.-L. Coll), philippe.rizo@fluoptics.fr (P. Rizo).

http://dx.doi.org/10.1016/j.ejmp.2015.11.006
1120-1797/

absorption and fluorescence quantum yield, fine photophysical properties: high stability, aqueous solubility and binding specificity when conjugated with cancer-targeting moieties [6]. Clinical applications request approved contrast agents. There are currently two NIR fluorescent dyes approved by the main regulation authorities: the US Food and Drug Agency (FDA) and the European Medicines Agency (EMA). Indocyanine green (ICG) and methylene blue (MB) are blood pooled and not targeted agents but clinical trials demonstrated that they are able to highlight tumors and SLN. ICG is the most widely used, either as free dye [7] or bounded on native serum albumin or on colloidal albumin [8]. Fluorescence imaging for guiding surgery is able to detect probes close from the surface of the surgical field. The 2D images of the sub surface contrast agent distribution are blurred by fluorescence photon scattering, especially for depth greater than 5 mm. Conventional camera sensors are able to detect the light up to 900 nm and to provide the required information to the surgeon. They are used in the large majority of published FIGS systems, and in all of the commercialized products.

A FIGS system mostly consists of an imaging head linked to one or several control boxes including hardware and software to acquire and display images. The imaging head provides, at least, the excitation light for detection of the fluorescent probes and the camera to record their distribution. It can also deliver white light for illumination of the operative field and a simultaneous acquisition of its image, either in color or in black and white.

FIGS devices dedicated to laparotomy can be classified into two categories. Some of them use a mechanical arm holding a bulky and heavy imaging head. This is the case for experimental systems, for the FLARE and mini-FLARE systems available from the Frangioni Laboratory's [9], but also for commercial systems like the Novadaq SPY®. The second category corresponds to hand-held heads, as found in the Hamamatsu PDE®, Mizuho HyperEye® [10], Quest Artemis® [10], and Fluoptics Fluobeam® devices [11].

The FIGS systems use an imaging channel, which collects the light in the wavelength range of the fluorescence emitted by the excited probes. It also collects the ambient light of the theater, as well as the shadow-less surgical light. Therefore, performing sensitive fluorescence acquisitions requires the surgical light to be turned off, or the use of pulsed irradiation and gated acquisition with an expensive intensified CCD. Some FIGS systems, such as the Fluobeam® or the Flare and mini-FLARE, provide additional filtered white light illumination without adding any bias on the fluorescence image. Due to their size, most of these devices are only able to image the surgical field from the top and are not well-suited for visualizing sides of cavities or organs. Head and neck cancer is one of the fields where decreasing the footprint of fluorescence imaging devices is essential [12].

The miniaturization of fluorescence technologies has already been addressed in some studies using eye vision [12], single detectors [13], and cameras [14]. Hand free, wireless goggles FIGS instrumentation was also developed and evaluated. According to the recent development of minimally invasive surgery, some flexible endoscopic and laparoscopic fluorescence imaging systems were developed [15]. Commercial laparoscopic systems are available such as Karl Storz GmbH's D-Light P, Novadaq's Firefly® or VisionSense's VSiii Iridium. Some of these systems are used into robot-guided surgery [16]. Their practical use in open surgery is limited by their reduced sensitivity, due to transmission loss in the laparoscope, as compared to devices dedicated for hand-held use [15].

The objective of this work is to evaluate a palm-sized FIGS system overcoming the limitations of available instrumentation for laparotomy surgery, having in mind that the new device should provide a white light illumination of the surgical field and should have detection sensitivity comparable to the one of existing larger devices. Even though a poor sensitivity could be compatible with usual ICG imaging, the issue of the detection limit should be addressed in order to reduce the ICG injected dose, for multiple injection indications, and for molecular probes imaging, to detect very low concentration of new markers. A former instrument called FluoSTIC was designed and validated in pre-clinical studies [17].

The experiences acquired during the development of the Fluobeam® and the FluoSTIC systems were merged to develop a new FIGS system called Fluostick™ [18]. Its weight, approximately 200 g, is about 3 times lower than those of other hand-held systems available on the market or described in the literature. Likewise, its diameter is 2 times lower than those of other systems. It can then be held like a pen, between fingers, and not in the hand. It is already approved by regulatory authorities for clinical use.

In order to fit the operational constraints of the surgery possibly extended to the use of fluorescent molecular imaging probes, we considered that the following characteristics are essential:

- The sensitivity of the device should allow performing acquisitions at 25 frames per seconds (fps) on classical ICG procedures, but also when using imaging probes.
- The lag between acquisition and display should be shorter than 100 ms. The speed of imaging together with the lag must be controlled because as soon as the spatial resolution of the system increases there is a high sensitivity of the operator to the lag between what happen on the field and what is displayed on the screen.
- The fluorescence excitation should stay in Class1 Laser (safe under all conditions of normal use) and the white light illumination in RG0 or RG1 (no risk in terms of maximum exposure limits under normal conditions of use). The goal is to ensure that the device can be used safely in any indication without protection spectacles that might reduce the visual perception of the surgeon.
- The white light illumination should have a Color Rendering Index (CRI) greater than 90 in order to comply with the standard IEC 60601-1-41.
- The head of the device should be small enough to be able to image lateral structures inside the surgical field, whose dimensions should be roughly 10 cm in diameter and 10 cm in depth, i.e. for maxilo-facial surgery.

The present article aims to evaluate the Fluostick™ device, in terms of technical characteristics and in terms of operational use on preclinical and clinical indications.

Materials and methods

Developed instrument

The system is composed of a control box linked to the miniaturized optical head through a custom cable. In the operating room, the camera head and the cable are slipped in a sterile drape cover with an optical windowed tip. The control box is set on a table at 1.5 meters from the surgical field, in the non-sterile zone of the theater. The control box is linked to a computer, thanks to a RJ45 cable. Specific software drives the system, displays the images in real time and saves them when requested. This device is based on an excitation fibered laser. The illumination is provided by only one white LED, whose band-pass is filtered between 405 and 700 nm.

The oblong format allows fitting the sensor, the laser excitation and the white light illumination one next to the other as independent parts. The oblong section fits a rectangle of 34×24 mm. Figure 1 displays schematics of the inside of the optical head and the disposition of its components.

A curved shape has been given to the optical head with the purpose of making it easier to handle. Moreover, the profiles of the