

Ki-Cheol Yoon

Department of Biomedical Engineering,
College of Medicine, Gachon University,
38-13, Dokjom-ro 3, Namdong-gu,
Incheon 21565, South Korea;
Medical Devices R&D Center,
Gachon University Gil Medical Center,
21, 774 beon-gil, Namdong-daero Namdong-gu,
Incheon 21565, South Korea
e-mail: kcyoon98@gachon.ac.kr

Kwang Gi Kim¹

Department of Biomedical Engineering,
College of Medicine, Gachon University,
38-13, Dokjom-ro 3, Namdong-gu,
Incheon 21565, South Korea;
Medical Devices R&D Center,
Gachon University Gil Medical Center,
21, 774 beon-gil, Namdong-daero Namdong-gu,
Incheon 21565, South Korea;
Department of Biomedical Engineering,
College of Health Science, Gachon University,
191 Hambakmoero, Yeosu-gu,
Incheon 21936, South Korea;
Department of Health Sciences and Technology,
Gachon Advanced Institute for Health Sciences
and Technology (GAIHST), Gachon University,
38-13, 3 Dokjom-ro, Namdong-gu,
Incheon 21565, South Korea
e-mail: kimkg@gachon.ac.kr

Seung Hoon Lee

School of Medicine,
Eulji University,
77 Gyeryong-ro 771 Beon-gil, Jung-gu,
Daejeon 34824, South Korea;
Department of Neurosurgery,
Daejeon Eulji Medical Center, Eulji University,
95, Dunsanseo-ro, Seo-gu,
Daejeon 35233, South Korea
e-mail: nsish@eulji.ac.kr

Design of a Surgical Pen-Type Probe for Real-Time Indocyanine Green Fluorescence Emission Diagnosis

The advantage of handheld type surgical microscope is that the size of the probe is small and light, and that both the working distance (15–30 cm) and field of view (30 deg) can be adjusted. The shortness working distance will minimize the loss of light source energy. However, the currently developed handheld type surgical microscope is still large, heavy, and uses relatively high energy (600 mW/cm²). To address the aforementioned problems, this study aimed to develop a pen-type surgical fluorescence microscope that is compact, portable, and has an adjustable beam angle and working distance. These features enable real-time diagnosis. The pen-type probe consists of a laser diode, CMOS camera, light source brightness control device, filter, and power switch. The IR-cut filter inside the CMOS camera was removed to facilitate transmission of the fluorescence emission wavelength. In addition, a long-pass filter was attached to the camera so that the external light source was blocked and only the fluorescence emission wavelength was allowed to pass through. The performance of the pen-type probe was tested through a large animal experiment. Indocyanine green (2.5 mg/kg) was injected into a pig's vein. Fluorescence emission of 805–830 nm was achieved by irradiating an external light source (785 nm and 4 mW/cm²), and liver-uptake occurred after 2.4 min. The designed pen-type probe was capable of sufficiently fluorescence expression through low-energy irradiation, and the pen-type probe is small and light and easy to handle by hand because both the pen-based laser device and the camera device are integrated. In addition, it is easy to adjust the working distance and field of view. [DOI: 10.1115/1.4052587]

Introduction

Surgical diagnosis with indocyanine green (ICG) fluorescence dye is used to observe the flow conditions in blood vessels in the stomach, intestine, organ, liver, lymph node, and brain [1–5]. In particular, malignant tumors are complex and consist of tumors and blood vessels. Unfortunately, tumors and vasculature have the same color, making it difficult to identify the boundary between them with the naked eye. To observe the boundary between tumors and blood vessels, cancer surgery involves the use of surgical observation systems [2], such as surgical microscopes [6–11].

However, the disadvantages of such cameras are that they are large and heavy (camera head: above 4 kg, whole: above 6 kg) with limited portability. In addition, they allow limited adjustments of the observed beam angles (maximum 30 deg) and working distances 15–30 cm [11–21]. Because a surgical camera uses a high-energy light source (50–160 mW/cm²) as the electromotive force of fluorescence emission, optical source beam energy loss

(above 58%) of the working distance (15–30 cm) and strong ambient light around the tissue (photobleaching) can occur [8,11]. In other words, the surgical microscope is difficult to apply in tissue observation because of the limited beam working distance control and adjustment of the left and right of the camera [12,15]. Moreover, surgical diagnostic systems are not portable because of their large size [8]. Several studies have been conducted on handheld surgical microscopes to overcome these problems [11].² The advantage of a handheld surgical microscope is that its size and working distance are less than those of a conventional surgical microscope. In addition, a handheld microscope offers a wide range of photography angles. In surgical microscopes, Novadaq SPY Elite and Iridium vision sense and Karl storz vitom ICG have a smaller and lighter camera part equipped with a light source [19]. Nevertheless, Hamamatsu, Novadaq SPY PHI, Fluoptics fluobeam, and Quest medical spectrum are also smaller and lighter in handheld form. Therefore, sufficient handling became possible during the surgical procedure [19]. However, the feature of these is that the camera part integrated with the light source is small and light, so it is possible to operate the surgery in a handheld form,

¹Corresponding author.

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²<https://www.amazon.co.uk/Smallest-Handheld-Fluorescence-Microscope-Professional/dp/B00DD8W28Q>

but the camera and the monitoring device are not integrated. That is, the camera and the monitoring device are separated from each other, and the monitoring device is quite large, which occupies a heavy and narrow surgical space for transport. Therefore, for this reason, the dimensions of handheld microscopes remain problematic. For example, although the device introduced in Ref. [20] is light-weight, it is excessively long. Meanwhile, although the working distance of the device reported in Ref. [17] (which uses image-guided Raman spectroscopy) is short, it requires an optical light source capable of producing high energy ($>600 \text{ mW/cm}^2$ @ 405 nm) for excitation. In particular, light source generators and monitoring devices are configured in a single system, with cameras and lasers exposed through wires. The camera and laser are not integrated and are independently configured. Moreover, the construction of the system is complex, which causes difficulties in using the camera and light source separately and necessitates substantial manpower for the surgery.

To solve the problems of the surgical fluorescence microscope, this study proposes a pen-type probe that is small and portable for real-time diagnosis. The performance of the proposed pen-type probe was evaluated through animal experiments using a light source of 785 nm and a fluorescence wavelength of 810 nm . During the animal experiment, the pig's brain was incised for the pen-type probe performance test, and an ICG fluorescence contrast agent was injected into the blood vessels of the brain, and an external light source was irradiated to the blood vessels to observe the blood circulation state. The reason is that numerous blood vessels are distributed in brain tumors. After extraction of the tumor, an ICG fluorescent contrast agent is used to observe the blood flow state of the blood vessels. At this time, the performance was evaluated as to whether the proposed pen-type probe could sufficiently observe the blood flow state of the blood vessels distributed in brain tumors.

The characteristics of ICG fluorescence contrast diagnosis have been approved by the United States Food and Drug Administration [12,13]. Therefore, it can be applied to observe the conditions of the heart, liver, blood flow, and blood vessels; and in angiography, cerebrovascular arteriovenous malformation, and vascular suture surgery [13,22–26].

Design of the Pen-Type Probe

A proposed pen-type probe consists of a laser diode (LD), drive module (for laser drive), small camera module (SE-8J200), switch (ON/OFF), laser brightness control performance, battery, long pass filter, and communication cable as shown in Fig. 1. From the figure, the cable connects between pen-type probe and external monitor. The fluorescence emission imaging captured by the camera can be seen in real-time on an external monitor through a cable.

The Thorlabs L785P090 laser diode was used, with excitation wavelength (λ_{ext}) and maximum optical source power (P_{ext}) of 785 nm and 19.1 mW , respectively, and operating voltage (V_{in}) of 2.0 V . Because the laser diode generates thermal energy, thermal energy control is essential. Thus, the laser diode was connected to a photodetector (PD) that can detect and control the heat generated by the laser diode. When heat is generated, the control unit of the drive module adjusts to the heat after its detection by the photodetector.

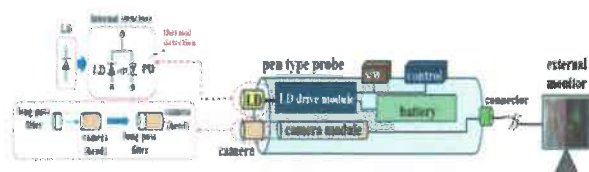


Fig. 1 Structure of a pen-type probe

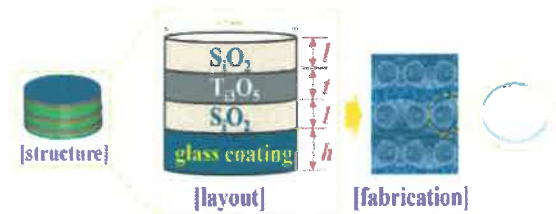


Fig. 2 Layout and structure of an optical long-pass filter

The Thorlabs MLD203P2 drive module was used, with an operating voltage and current of DC 5 V and 200 mA , respectively. A variable resistor (max. $10 \text{ k}\Omega$) was used for laser brightness control; therefore, the laser diode can adjust the optical source power. An endoscope camera was used in the complementary metal oxide semiconductor (CMOS) sensor. The camera has an operating voltage of 3 V . Its horizontal length and diameter are 4 mm and 1.5 mm .

The resolution, imaging frame, pixel size, field of view (FOV), and sensor type of the camera are 1600×1200 , 30 fps , $2.0 \mu\text{m}_{\text{pixel}}$, 60 deg , and CMOS sensor, respectively. The irradiation beam angle of the laser diode is free, i.e., 360 deg . The working distance is 10 mm . Then, the working distance was adjusted from 0 to 50 cm , and the realization environment was measured as 50 mm .

The infrared (IR)-cut filter of an internal camera structure is removed. Fluorescence dye (ICG) imaging could not be achieved because the emission wavelength (E_m) of ICG fluorescence dye imaging is in the IR band (above 800 nm) [4,12,13,27]. Thus, the IR band ($>800 \text{ nm}$) cannot transmit the IR-cut filter in the camera.

The camera lens (head) was connected to a long-pass filter with a cut-on wavelength of 800 nm . The long pass filter was fabricated using titanium oxide (Ti_2O_3), silicon oxide (SiO_2), and a glass-coated substrate, as shown in Fig. 2. The fabricated filter has a t , i , and h of 2 , 4 , and $0.4 \mu\text{m}$, respectively; its diameter is 1.5 mm .

The long pass filter only transmits the wavelengths emitted by the ICG fluorescence dye and produces a diagnostic image without any excitation wavelength. The measurement results of the fabricated long-pass filter are shown in Fig. 3. The cut-in wavelength, transmission (T), and reflection (OD : optical density) are 805 nm , 98% , and 0.2% , respectively.

The pen-type probe was equipped with a low-cost camera. Figure 4 shows the fabrication of the pen-type probe by three-dimensional printing.

The pen-type probe is lighter than the conventional surgical microscope, with an overall size and weight of $17 \times 2.5 \text{ mm}^2$ and 32 g ($\pm 2 \text{ g}$), respectively; the conventional surgical microscope weighs 6.0 kg [14].

Experimental Results

A large animal (pig) experiment was performed to test the performance of the proposed pen-type probe. The animal was tested at the animal center of Osong Medical Innovation Foundation, KBIO (Osong Medical Innovation Foundation, KBIO). We

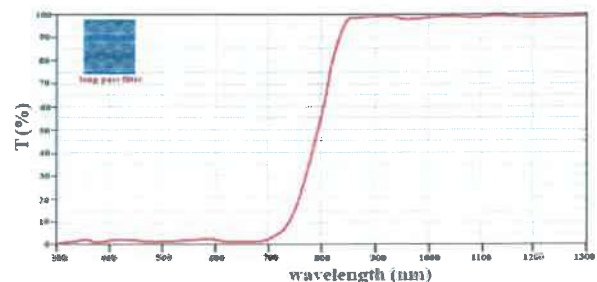


Fig. 3 Experimental result of fabricated a long-pass filter



Fig. 4 Fabrication of a pen-type probe using three-dimensional printing technique

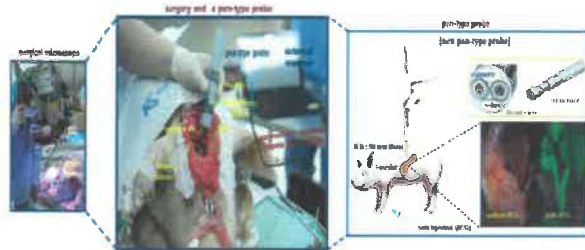


Fig. 5 Conventional pig (Farm) surgery and large animal test (a) test using conventional surgical microscope and NIR camera with laser (b) pen-type probe test

obtained permission from the Animal Institutional Review Board (IRB) of the Animal Ethics Commission. In the animal test, the conventional-type pig (Farm/male (1ea)/weight of 60 kg). An ICG fluorescent contrast agent was injected into the pig vein.

The fluorescence expression of the agent was determined according to the concentration. The fluorescent contrast agent was mixed with a 10 mL aqueous injection solution and 25 mg of ICG (Dongindang, Republic of Korea, one vial 25 mL/insurance code: 664100231). The mixture (0.2–0.4 mL) was injected into the pig vein by a syringe. The injected ICG fluorescent material binds to plasma protein [28].

Figure 5 shows the surgical environment for the animal test. As shown in the figure, the pen-type probe is connected to an external monitor by a cable.

The working distances were determined as 15 cm (conventional surgical microscope and NIR camera) and 50 mm (pen-type probe). However, the working distance of the pen-type probe is free between 50 mm and 50 cm.

For the animal test of ICG fluorescence emission, the optical source of the pen-type probe was irradiated to the vasculature of a pig. On the one hand, in order to prove the excellence of pen-type probe performance in animal experiments, we tested pen-type probe together with existing surgical microscopes. The conventional surgical microscope consists of an NIR camera and a laser (785 nm).

The excitation wavelength (λ_{ext}) and laser power with the conventional surgical microscope and NIR camera (Lt 225 NIR M/N, respectively) were 785 nm and 60 mW/cm², respectively. Then, the laser (785 nm) was used in the PerkinElmer Solaris optical imaging system and Thorlabs CPS780S (for NIR camera). The excitation wavelength (λ_{ext}) and LD power of the pen-type probe were 785 nm and 4.0 mW/cm², respectively.

The excitation wavelength (λ_{ext}) and laser diode power of the pen-type probe were 785 nm and 4.0 mW/cm², respectively. The laser diode (Thorlabs L785P90) power was adjusted from 0 mW/cm² to 19.0 mW/cm². The camera used was the SE-8J200 (endoscopy-type microscopy). When the laser diode of the pen-type probe was irradiated with a wavelength of 785 nm (4.0 mW/cm²) to a blood vessel, fluorescence was emitted from the blood vessel and the blood flow state could be observed. The fluorescence emission wavelength and power ranged from 805 to 830 nm [4,12,13,27].

Figure 6 shows the resulting fluorescence emissions in vascular flow experiments on large animals, including the state of blood flow through ICG fluorescence in blood vessels. Fluorescence emission images of blood flow were collected using an IR camera. The collected images could be observed through a cable.

Conventional surgical microscopes have poor clarity even though the light source irradiation power is 55–160 mW/cm² at a working distance of 15–30 cm. The reason is that when the working distance is 200 mm or more, the intensity of the light source decreases by 58% or more [23]. Therefore, fluorescence expression may be weak. In addition, it is filmed in black and white because of the characteristics of the NIR camera. However, the proposed pen-type probe minimizes the loss of light source intensity due to nearby working distance and allows color photographing on the camera, which can provide high resolution.

Fluorescent contrast agents are injected into the veins to observe blood circulation. In the figure, purple is the tissue around the blood vessel and white is showing the blood circulation state. When a fluorescent contrast agent is injected into the blood vessel and monitored externally through camera photography, it appears white in the blood vessel.

The reason why surrounding tissues look purple is because of the influence of the CMOS sensor of the camera. The first picture on the left in the experimental method is the step before injection

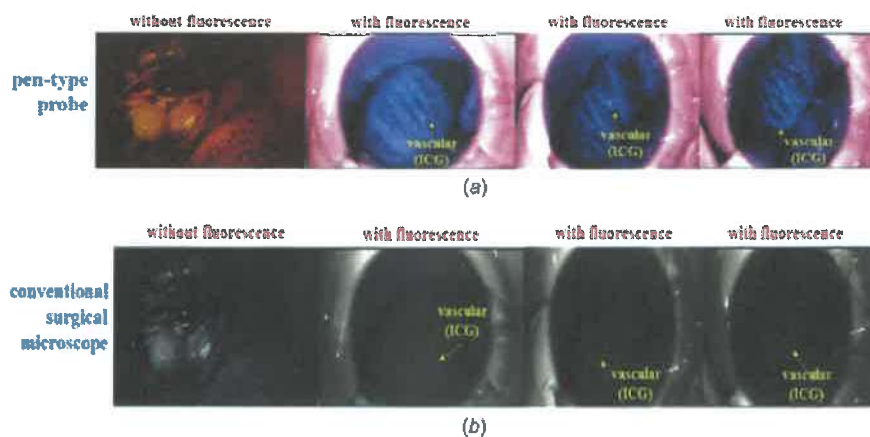


Fig. 6 Experimental results of large animal (a) conventional surgical microscope (b) pen-type probe camera

Table 1 Comparison for performance of hand-held-type surgical microscope

	Present work	Raman spectroscopy probe [17]	Fluobeam [18,31]	Spy PHI [18,31,32]
Optical source power [mW/cm ²]	4.0	600	382	800
Working distance [mm]	50.0	0.50	260	30
Resolution [pixels]	1600 × 1200	640 × 480	720 × 576	1920 × 1080 (1080 P)
Frame rate [fps]	30	30	25	60
FOV [mm ²]	76 × 42	1.07 × 1.07	20.0 × 14.0	19.0 × 13.0
Sensor	CMOS	CCD	CCD	CCD

of the fluorescent contrast agent. The experimental sequence turns off the lighting in the operating room when irradiating an external light source after injecting a fluorescent contrast agent. Therefore, darken the operating room to minimize external light noise. And after injecting a fluorescent contrast agent while irradiating an external light source, the blood circulation state of the blood vessels is observed on an external monitor.

The fluorescent contrast agent has a liver uptake phenomenon owing to its half-life of 3.4 min. Then, the Refs. [4,27,29,30] of ICG fluorescence has average 2.4 min (0.01 mg/kg) liver uptake phenomenon.

Discussion

A pen-type probe consists of a battery. The pen-type probe is connected via a camera, monitor, and USB cable. The camera will operate at a voltage of 3 V but will receive a 5 V supply from the monitor. Meanwhile, the drive module of the laser diode operates at 5 V. At this point, the power to the drive module of the laser diode is connected to the power of the camera module and operates at 5 V supplied by the monitor. However, the pen-type probe is equipped with a separate battery. The reason is that batteries can be used when installing a wireless camera in a pen-type probe and can be used as a spare power source when the power supply is unstable in the operating room.

Pen-type probes need to consider the importance of batteries because they need to test their performance using wireless cameras in the future to increase portability. The pen-type probe's camera appears to be better than the others, as shown in Table 1.

The resolution, frame, and pixel size of a pen-type probe camera is excellent (more than two times) and better than that obtained in previous studies [11,17,18]. However, Spy PHI has resolution and frame rate of 1080 P and 60 fps, respectively.³ Of course, the Spy PHI image imaging performance will be much better than the pen-type probe. However, the SPY PHI has a high unit price because the main body system equipped with monitoring is and depends on imports. Also, the maintenance cost is high as well as the unit price. In addition, Spy PHI has to be moved from the storage area to be used in the operating room, and it is difficult to move it in a narrow operating room because of its heavy. In addition, the system takes up a lot of volume in a narrow operating. The external irradiation optical source power (laser module) of a conventional surgical microscope was 600–800 mW/cm², and the working distance was 0.5 mm and 200–260 mm [11,17,18,31–33]. However, the external irradiation optical intensity will have losses of approximately 58% when the working distance is above the minimum of 200 mm [23].

To generate ICG fluorescence emission, it is necessary to increase the optical source intensity or decrease the working distance. If the optical intensity of the laser diode (Thorlabs, L785PO) is increased, then the laser diode will cause thermal breakage because of its vulnerability to heat, as proven by the experiment. If the working distance of a conventional surgical microscope is decreased, then the field of view of the surgical lesion narrows [34].

The pen-type probe's laser diode enables the adjustment of the laser diode power and working distance. The pen-type probe's

laser diode and working distance were adjusted to 4 mW/cm² and 50 mm, respectively, while the FOV was obtained as 60 deg. Thus, the vascular flow condition can be monitored according to ICG fluorescence emission. The maximum photographing angle of a conventional surgical microscope is 30–60 deg [35], while that of the pen-type probe is free (360 deg) [36–39]. Therefore, the pen-type probe does not have a blind spot, and the field of view of the surgical lesion is broader than that of the conventional surgical microscope. The camera of a pen-type probe is integrated the fundamentally CMOS sensor. The we have selected the CMOS sensor camera. The reason is as follows.

The size of a CMOS camera is smaller than the CCD camera due to simple structure of a module. The power consume of a CMOS sensor is lower than CCD camera, and the response time is significantly faster more than CCD camera. The FOV and dynamic range of a CMOS camera are wideness.⁴

Laser irradiation should be conducted within a safe range of tissues, and in accordance with international medical standards (IEC 60601-2-41). The maximum irradiation power of a laser diode is 19 mW; the actual laser diode power used is within 4 mW; and is reduced by approximately 2.89 to 40 times. For this reason, it can be reduced to a small size, making it portable and suitable for a narrow operating room.

Conclusion

In this paper, the design and fabrication for a pen-type probe is presented which has small size and it is possible to portable. The suggested pen-type probe is composed of a laser diode, an endoscope camera, a brightness control device of a light source, a power supply, a communication cable, and external monitor.

A pen-type probe can be observed the shape of tumor and blood vessel flow by difference of colors, and it can be observed the boundary between tumor and blood vessel through the difference of colors. In addition, a pen-type probe can observe the remanent state of a tumor by using fluorescence dye at an external monitor. In a pen-type probe, the detected image transfer to external monitor through the communication cable. A proposed pen-type probe has not an optical density loss nor a blind spot.

The pen-type probe is judged to be suitable for observing blood circulation after blood vessel or tumor extraction in the field of surgery or internal medicine in the future, and its application value is expected to be high.

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³<https://www.stryker.com/se/en/endoscopy/products/spy-phi/index-eu.html>

⁴<https://www.techbriefs.com/component/content/article/tb/supplements/ptb/features/articles/20063>

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Nomenclature

CMOS = complementary metal oxide semiconductor

E_m = emission wavelength

FOV = field of view

ICG = indocyanine green

IR = infrared

IRB = Animal Institutional Review Board

LD = laser diode

OD = reflection, optical density

PD = photodetector

P_{ext} = optical source power

SiO_2 = silicon oxide

T = transmission

Ti_2O_5 = titanium oxide

V_{in} = operating voltage

λ_{ext} = excitation wavelength

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