Focus On Fluorescence

Focus on Fluorescence-Guided Surgery

A New Column

Welcome to the inaugural issue of *Focus on Fluorescence-Guided Surgery*. In this first issue, we have the privilege of interviewing Raul Rosenthal, MD, a co-editor of this column and a pioneering expert in fluorescence-guided surgery (FGS). Dr. Rosenthal is the regional chairman, Digestive Disease Institute; chairman, Department of General Surgery; director, the Bariatric and Metabolic Institute; and director, general surgery residency program at Cleveland Clinic Florida, in Weston. Dr. Rosenthal began using FGS more than 14 years ago and has been one of the pioneers in developing this type of technology in a variety of traditional open and minimally invasive surgical procedures.

We welcome feedback, comments and suggested topics for discussion.

Column Editors

Fernando Dip, MD **Raul Rosenthal, MD**

Figure 1. Indocyanine green (ICG).

DR. FERNANDO DIP: Can you explain what fluorescence-guided surgery (FGS) is?

DR. RAUL ROSENTHAL: FGS is a novel imaging technology used in real-time in the operating room. Using fluorescence, the surgeon can see more, and as a result, better understand the anatomy, analyze tissue or even detect tumors. This breakthrough technology is essential in some surgeries. FGS has different advantages in that it is safe, easy to use, has no learning curve and can be applied to almost all specialties.

DR. DIP: What is the history of the use of fluorescent imaging in medicine?

DR. ROSENTHAL: The use of fluorescence in medicine started many years ago. It was first used to analyze different types of microorganisms. Lividity was reported using fluorescent antibodies to recognize *Rickettsia prowazekii* in cell cultures.[1] Afterward, fluorescence allowed physicians to evaluate different types of cells.

The lack of high-quality imaging available on the market did not allow this technology to advance. In the last several years, technological advances that enabled significant improvement in the quality of imaging allowed researchers to fine-tune this technology in the OR safely.

In order to use fluorescence during a surgical procedure, a dye and an optical system with a specific light source and a camera capable of capturing the light images are required. Once the stain is administered, the surgical field is illuminated with a particular wavelength. The fluorescent dye is excited and releases light with a higher wavelength captured by filters and projected on a screen. In this way, the stained structures can be identified by the surgeon, and that is why it has been labeled "real-time surgery."

DR. DIP: Why do you consider this technology to be essential?

DR. ROSENTHAL: For many years, only white light was used in the OR to illuminate the surgical field. White light cannot penetrate blood and tissue more than a few microns, allowing only a superficial view of the tissues and structures.[2] Fluorescence, a near-infrared (NIR) technology, uses invisible light with a wavelength between 700 and 900 nm. In the NIR window absorption of the light, autofluorescence is minimal, allowing surgeons to see deeper structures than with white light.[3]

When surgeons operate, it is essential to understand the surgical anatomy to know exactly where the structures are located. Unfortunately, anatomic variations often make it difficult to recognize these structures. In addition, it is important to know if the tissues that will be sutured are well perfused. In some cases, tissues that look pink and well vascularized may not be well perfused. If a surgeon misidentifies and dissects a wrong structure or sutures non-vascularized tissue, this may result in an unexpected iatrogenic injury to the patient.

Despite many different technologies being developed to improve surgical outcomes, only a few have prevailed throughout the years and have been adopted as standard of care. A novel technology needs to meet at least three criteria to be accepted:

1. an actual clinical need exists;
2. the new technology solves a problem; and
3. the technology does not impede the workflow.[4]

In my opinion, FGS meets all three criteria. Unfortunately, the rate of intraoperative complications, such as bile duct injuries, anastomotic leaks and tumor recurrences, has not decreased over the years. Increasingly, more publications are now measuring surgical outcome improvements using FGS. Moreover, what is interesting about FGS is that it does not interrupt or impede the OR workflow. The entire FGS system is integrated. Light sources and filters can be activated simply by pushing a button without the need to stop or delay the procedure.

This technology is undoubtedly a new paradigm in the evolution of surgery. We have seen incredible advances that have changed the history of medicine and surgery in the past. Using analgesics and anesthetics allowed surgeons to perform more extensive operations. The use of antibiotics decreased the rate of infections and reduced the mortality rate after a variety of procedures. Minimally invasive surgery enabled quicker recovery when compared with open surgery. With the help of fluorescence, for the first time in the history of surgery, a surgeon can now see through the tissue.

DR. DIP: What does a surgeon need to start using this technology?

DR. ROSENTHAL: The technology is straightforward. We create fluorescence light using near-infrared light and a specific dye that will glow when illuminated. The equipment is very similar to what we already have in the OR. The only difference is that we can activate different light modes. We can use standard white light or activate the NIR mode to see the tissues with fluorescence. With this new equipment, we can operate using fluorescence and white light simultaneously. With this overlay image, the procedure is safer because we have more information while operating.

Before the procedure starts, a fluorescent dye must be administered. One of the most commonly used dyes is indocyanine green (ICG). ICG can be injected intravenously, subcutaneously or intratumorally, depending on the structures that need to be identified.

ICG is used because it is safe and was approved by the FDA in 1959 (Figure 1). Many surgeons have already been using ICG to evaluate liver function tests. ICG has several advantages. It is selectively filtered and secreted by the liver. Since it is not metabolized in the liver, ICG can be used in other procedures, such as hepatobiliopancreatic surgery.[5] The adverse effects are very minimal to none and it remains in the body for at least 24 hours. As soon as it is injected, ICG binds to proteins. Although it is not specific to most organs or tumors, it can identify and differentiate various tissues.

DR. DIP: What are the main surgical arenas in which this technology has a place?

DR. ROSENTHAL: This technology has been adopted in almost all surgical procedures. For example, ENT [ear, nose and throat] surgeons use NIR-guided surgery to evaluate the location and perfusion of the parathyroid glands during thyroidectomies to avoid postoperative hypocalcemia. The use of autofluorescence can help to detect the location of the parathyroid glands.[6] Once the thyroid is dissected, ICG can be intravenously administered and the perfusion of the parathyroid glands can be determined. This is crucial in deciding if the parathyroid gland needs to be removed, reimplanted or left in the surgical field.[7-9]

In gastrointestinal surgery, leaks due to unperfused tissues may occur. With the use of ICG and NIR light, we can evaluate the vitality of the tissue and, in some cases, change the site of anastomoses. This problem can be seen in esophageal, foregut and colorectal surgery. We know that a leak can be caused by issues such as tension of the stumps, a patient's lack of adequate

Figure 2. Perfusion assessment in colorectal surgery.

nutrition and lack of perfusion. We are trying to eliminate at least one crucial variable with this technology.

In colorectal surgery, more and more reports support the use of this technology. Years ago, Jafari et al reported a multi-institutional study evaluating perfusion assessment in laparoscopic left-sided/anterior resection (PILLAR II) using fluorescence.[10] After analyzing 139 patients, they concluded that NIR angiography is a safe and feasible tool for intraoperative assessment of tissue perfusion during colorectal resection (Figure 2).

Lastly, Neddermeyer and his group published similar results when analyzing 132 colorectal resections (70 sigmoid resections and 62 total mesorectal excisions [TMEs]), of which 70 (53%) were performed with ICG near-infrared fluoroangiography (NIFA) and 62 (47%) without it. Following ICG/NIFA, the transection line was changed in nine cases (12.9%). Overall, 10 patients (7.6%) developed an anastomotic leak—one patient (1.4%) in the ICG/NIFA group and nine (14.5%) in the non-ICG/NIFA group (P=0.006).[11]

Plastic surgery is another field in which FGS is extensively used. When performing a free flap, surgeons need to evaluate, in real time, the small vessels to avoid tissue necrosis and failure of a flap. In the past, flap dissection was guided only by the surgeon's experience and universal zonal classification based on the perforator distribution. Now, ICG angiography allows the objectification and visualization of the perfused areas directly after the flap harvest.[12]

Another important use of this technology is sentinel lymph node identification in some tumors. Cancer staging is crucial to selecting the best treatment for a patient. For many years, the use of Tc-99m [radiosotope technetium-99m] was the standard of care for sentinel lymph node identification in different types of tumors. Since NIR-guided surgery was developed, many studies have compared the use of Tc-99m and ICG for sentinel lymph node identification. FGS has been demonstrated to be as accurate as Tc-99m to identify the sentinel lymph nodes. Moreover, FGS does not use radiation; it is a real-time procedure, and the surgeon can follow the lymph vessels through the skin and, most importantly, the node can be dissected, protecting surrounding tissues.[12]

One of the areas in which FGS is frequently used is hepatobiliary surgery. Laparoscopic cholecystectomy is one of the most common procedures performed worldwide. Unfortunately, bile duct injuries still occur, ranging between 0.4% and 1% (Figures 3A and 3B). The majority occur because the cystic duct and main bile duct are misidentified.[13,14] It has been shown recently that FGS can increase visualization of the extrahepatic bile ducts threefold compared with white light. To perform a fluorescent incisionless cholangiography, ICG is administered intravenously 45 minutes before the procedure. Then ICG is eliminated by the liver and remains in the extrahepatic bile ducts for at least 24 hours. When the fluorescent system is activated, the cystic ducts and main bile duct glow and can be visualized easily by the surgeon, making the procedure safer. Retrospective studies are demonstrating improvement in outcomes, such as decreased conversion rates. More recently, a cost-effectiveness evaluation came out in favor of the routine use of fluorescent cholangiography during laparoscopic cholecystectomy as a cost-effective surgical strategy.[15]

DR. DIP: Is there a role for cancer identification with FGS?

DR. ROSENTHAL: The use of this technology for cancer tissue detection is still under evaluation. Unfortunately, cancer is an unresolved problem associated with high morbidity and mortality rates. Early-stage detection and tumor resection seem to be the most powerful tools for treatment. Nevertheless, sometimes complete resection is very difficult. Cancer tissue, on some occasions, may look like normal tissue, thus residual cancer cells might remain in the surgical

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field. With fluorescence, the surgeon can detect tumor cells that otherwise cannot be seen with white light.[16] Newer wavelengths and dyes are areas under evaluation. Researchers are studying different electromagnetic spectrum ranges to visualize cancer cells. The first part of the electromagnetic spectrum is between 650 and 900 nm and the second area is between 1,000 and 1,700 nm. Longer wavelengths allow more penetration, minimal tissue absorption and low autofluorescence.[17]

In terms of new dyes, several publications have reported the delineation of tumors using different probes. Steinkamp et al developed a probe (ONM-100) that could assist the surgeon during tumor resection. These authors studied 13 patients with squamous cell carcinoma of the neck who received the probe before the procedure.[18] During the procedure, fluorescence of the tumor and background allowed for better analysis by the surgeon. Fluorescent lesions on the resection margins showed occult carcinomas and severe dysplasia. Some investigators are working with antibody dye conjugates, such as SMG-101, that can identify adenocarcinoma of the colon with predictive positive values ranging from 99.04% to 90.24%.[19]

Probes required rigorous trials to evaluate efficacy and adverse effects prior to approval for human use and are currently not available.

DR. DIP: Do you recommend the use of this technology routinely or selectively?

DR. ROSENTHAL: In some cases, it would probably be essential to adopt FGS routinely, especially in centers with residents and in some procedures when the anatomy may frequently vary. This is the case for laparoscopic cholecystectomy, where we may find a variation in the anatomy of the bile ducts in 21% of cases.[20] If a bile duct is misidentified, this may create an injury. These complications increase morbidity and mortality rates and have a negative impact on a patient's quality of life, as well as increasing the cost of health services. We now have the technology to perform a safer procedure using fluorescence.

Our group started using FGS for laparoscopic cholecystectomies. We performed a fluorescent incisionless cholangiography to visualize Calot's triangle during the procedure. The results were so impressive that we decided to publish the main reasons to support its routine use.

The use of this technology is feasible. The majority of manufacturers have included the capability for FGS in their equipment, making the use of technology more accessible. The contraindications for its implementation are few. Thus, we can administer ICG to almost all patients. The technology is beneficial because it provides additional information to the surgeon that might simplify some procedures. The learning curve is minimal. FGS is safe because the wavelength used is in the NIR spectrum and does not harm any tissue.[21]

DR. DIP: This technology seems to be very useful. What are the main barriers to adoption of this technology?

DR. ROSENTHAL: All new technology must overcome the process of adoption. Innovators will accept the technology almost immediately, whereas skeptics might never adopt it no matter how useful it is. Time will determine the real need for this technology in the OR for different applications.

Recently, using the Delphi method, the International

Figure 3A. Calot's triangle using white light.

Figure 3B. Calot's triangle under fluorescence view.

Society for Fluorescence Guided Surgery (ISFGS) surveyed to determine the main barriers to adopting the use of FGS. A total of 94 surgeons responded. They reported that, in their institutions, the use of FGS represents 20% of the procedures performed. The majority (69%) work in academic centers. Interestingly, the cost of the equipment was reported by 25% of the surgeons as being the main barrier, followed by training at 30%, and lack of access to the equipment at 44%.

As physicians, our responsibility is to follow the evidence published in peer-reviewed, high-impact journals. What we do know is there are more and more reports that support the use of FGS in various procedures.[22,23] The adoption of FGS varies around the world. The most common adoption seems to be for gastrointestinal and transplant surgery, especially in Asian Pacific countries, whereas in Western countries, FGS is used more commonly for colorectal and plastic surgery procedures.[24]

DR. DIP: What is the future of fluorescence-guided surgery?

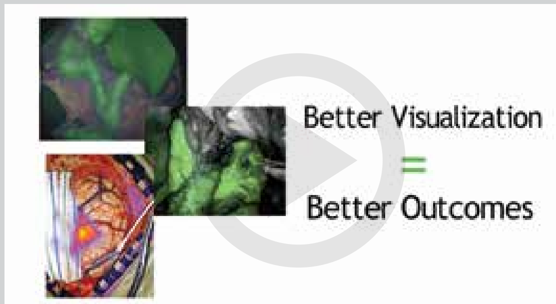
DR. ROSENTHAL: For the majority of procedures, this technology will evolve and likely become the standard of care, or at least a readily available tool in the surgeon's armamentarium. Considerable improvements in the specificity of the technology will occur over time, and a greater number of structures will be seen in real time. This technology is certainly here to stay, and its adoption will increase.

There are some aspects of this technology that are being evaluated:

- **Quantification of the intensity of the fluorescent signals is essential.** Unfortunately, absolute fluorescence intensity depends on patient conditions and may differ when different types of lights or cameras are used. To decrease that variability, normalization of the measurement of time–intensity curves may be used.[25] Some manufacturers are developing software that can analyze the images in real time. To date, the interpretation of images has been subjective. Surgeons can see images that glow or not and make decisions according to their experience. Understanding of the images depends on the interpretation by the surgeon.
- **Time–intensity curves.** Some groups recently analyzed the fluorescence behavior of tissue vascularization in 13 patients in whom 17 flaps were performed. After administration of 7.5 mg of ICG intravenously, the behavior of tissue fluorescence was described for three minutes. Software created a time-intensity curve of the measured intensity in arbitrary units. The researchers showed when tissue is critically poorly perfused, the areas in the perfusion curve are lower than the curves obtained in well-perfused flaps. This fact is significant because objectivity in the interpretation of the images is guaranteed.[25]
- **Dynamics of perfusion.**
  1. Leak prevention. Fluorescent intensity might be essential to evaluate the quality of the tissue. What some surgeons are currently evaluating is that the time it takes for ICG to reach the anastomotic site may be an essential factor to consider.[26] This is referred to as the "dynamics of perfusion."
  2. Tumor evaluation. Undoubtedly, evaluating the dynamics of ICG in tissues is a hot topic. It is known that benign and malignant lesions have different vasculatures. Cancer cells are characterized by a chaotic and leaky vasculature that might be recognized with fluorescence imaging. Although understanding the images for some tumors is complex in the OR, unique software that creates algorithms is used to learn different fluorescent patterns.[27]
- **New structures.** Some groups are evaluating the use of different wavelengths, filters and dyes to visualize other structures, such as nerves. Some researchers are using the autofluorescence properties of nerves to visualize them. Others are trying to tag nerves with different fluorescent probes to differentiate them from other structures.
- **New dyes.** It is likely that, in the future, a surgeon will be able to select a dye to visualize a specific tissue or cell. Specifically, patients with colorectal tumors will be given a specific stain marked with an antibody that identifies that tumor and not another tissue. To visualize ureters during colorectal surgery, a specific dye will be administered for ureters and that does not mark any other adjacent structure.

For a full list of references, visit generalsurgerynews.com

The ISFGS wishes to acknowledge its Corporate Council—Arthex, Diagnostic Green, Karl Storz, Medtronic, Olympus, Optimedic, OnLume and Richard Wolf—for their continued generous support.



VIDEO Introduction to the International Society for Fluorescence Guided Surgery (ISFGS)
youtube.com/watch?v=6jptxzks0dE

ISFGS

The International Society for Fluorescence Guided Surgery (ISFGS) is dedicated to the global advancement of FGS, connecting surgeons, nurses, other allied professionals, and patients, and growing the overall awareness and implementation of FGS worldwide. Visit ISFGS at www.isfgs.org and visit the ISFGS patient portal at ISFGSpatientportal.