Editorial

Colorful lighting in the operating room

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In recent trials, fluorescence image-guided surgery (FIGS) has proven useful in patients, resulting in superior outcomes compared to conventional procedures. To perform FIGS, a fluorescent dye or probe is injected intravenously or applied topically prior to the procedure. After a short waiting period, the areas of interest are illuminated with excitation light at specific wavelengths (colors). The energy from the excitation light is absorbed by the locally retained fluorochromes and discharged quickly, resulting in a pulse of emission light with longer wavelengths. Because of the wavelength difference between the excitation and emission light, high signal-to-background ratios are often obtained. The emitted light is either visualized directly or acquired through a charge-coupled device (CCD) camera and displayed on a monitor. Another advantage of FIGS is its real-time imaging capability. Surgeons can follow the fluorescent signal conveniently during the procedure without data acquisition delays.

The concept of FIGS is not completely new since visible contrast-enhanced diagnoses have been applied to guided procedures, such as acetic acid-assisted cervical cancer screening (1) or blue dye-guided sentinel lymph node (SLN) biopsy. However, the change from a visible signal to a fluorescence signal has significantly improved the sensitivity of the procedure. FIGS based on 5-aminolevulinic acid (5-ALA) and its derivative hexaminolevulinate (HAL) could be the first and most widely studied of these procedures (2,3). 5-ALA, an amino acid-like molecule, has no fluorophore, but it is the precursor of protoporphyrin IX (PpIX), which is fluorescent. In normal cells, 5-ALA is used to synthesize PpIX and converted almost instantly into the non-fluorescent hemoglobin after chelating an iron ion. The concentration of the intermediate PpIX is low in normal cells. Interestingly, the balance between PpIX and hemoglobin is altered in many cancer cells. PpIX accumulates intracellularly, becoming a natural fluorescent contrast agent with excitation at 405 nm and emission at 625 nm for cancer imaging. Under a blue illuminating light, a red fluorescent signal is observed in malignant tissues.

5-ALA has been applied to guide the resection of various tumors, such as bladder and brain cancers. Long-term follow-up studies of bladder cancer patients confirmed that 5-ALA- or HAL-assisted FIGS are significantly superior to conventional white light transurethral resection with respect to the residual tumor and recurrence-free survival rates. For example, in one study of 301 patients with superficial bladder cancer contrasted with intravesically instilled 5-ALA, the 8-year recurrence rate was decreased from 79% to 45% (4). In a recent US study of 551 patients with Ta or T1 urothelial bladder cancer, the median recurrence time was extended from 9.4 months in the conventional white light group to 16.4 months in the FIGS group with topically applied HAL (5). The significant clinical benefit of 5-ALA-based FIGS was also demonstrated in patients with glioma (6,7). In one randomized study, the FIGS aided by orally administrated 5-ALA via drinking water 2-4 h prior to procedure yielded a 6-month progression free survival of 41%, versus a rate of 21% in the control group using a conventional technique with white light (8). Based on these results, 5-ALA was approved to direct surgical procedures in adult patients with malignant glioma in Europe.

SLN biopsy is a critical procedure to determine the stage of certain cancers. Based on the status of the collected SLNs, physicians will develop an appropriate treatment plan. Conventional imaging techniques are insensitive for SLN assessment; thus, SLN biopsy is commonly required for staging, typically for breast cancer and melanoma. Clinically, ^{99m}Tc-nanocolloid and trypan blue are commonly

used as a radioactive tracer and color indicator, respectively, to locate SLNs. Although radiotracers have excellent sensitivity and are capable of penetrating thick tissues, radioactivity is always a concern for patients and medical staffs. In addition, the half-life of radiotracers also makes them less convenient for use. Conversely, nonradioactive blue dye is useful, but its low signal-to-background ratio and ability to only visualize superficial nodes are limiting factors. The addition of near infrared fluorescent (NIRF) imaging agents to conventional radioactive colloid or blue dyes could be valuable for the identification and assessment of SLNs.

Indocyanine green (ICG) is a clinically approved fluorescent dye for liver function analysis and ophthalmic angiography. It has broad fluorescent excitation and emission spectra, the maxima of which are approximately 780 and 830 nm, respectively, which vary depending on the environment. Because the ICG signal is beyond the visible range, the fluorescent images are collected through CCD cameras. In a recent trial of patients with clinically node-negative breast cancer, ICG was added to the conventional blue dye and ^{99m}Tc-nanocolloid contrast protocols (9). ICG was injected adjacently to the blue dye injection site but immediately before the blue dye injection. SLNs were collected in 104 procedures based on the various information collected using three detection strategies. The SLNs were pathologically analyzed to validate the sensitivity and specificity of each detection method. Among the 201 nodes collected that were blue and/or radioactive, all were ICG-positive, indicating that ICG is highly sensitive for detecting SLNs. All 25 cancer-positive nodes were fluorescent, blue, and radioactive. The combination of blue dye and ICG is the most sensitive (95%) for detecting SLNs. Similar encouraging results using ICG were reported in other studies of breast cancer (10). Another advantage of using ICG is that the deeper tissue penetrating property of NIRF makes transcutaneous lymphatic vessel tracking possible, allowing for more precise, targeted dissection (9).

The same FIGS concept with ICG has also been tested in patients with prostate cancer (11). Unlike SLNs in the breast, the pelvic nodes are buried deep in the tissue, and blue dye has little utility in guiding SLN biopsy. The greater sensitivity of ICG has been exploited in this setting via injection into the prostate in addition to currently used ^{99m}Tc-nanocolloid. In a small-scale study of 26 intermediate- to high-risk patients, a strong correlation was observed between radioactive and fluorescent nodes (12). In fact, the fluorescent navigation proved more sensitive than conventional radiotracer guidance, as it facilitated the identification of approximately 20% more sentinel nodes. In addition, the real-time fluorescence mapping of lymphatic vessels is extremely useful in directing SLN dissection, allowing surgeons to identify primary and secondary nodes precisely. A recent approach of formulating ICG with ^{99m}Tc-nanocolloid could significantly simplify the procedure (13). Importantly, the *in vivo* biodistribution of this dual fluorescent-radioactive tracer was the same as that of the unmodified parent ^{99m}Tc-nanocolloid.

Fluorescent molecular imaging agents, such as fluorescein-labeled folate or heptapeptides, displayed utility in guiding procedures in ovarian and colon cancers. The folate probe was injected intravenously a few hours before the procedure (14). Using a home-built intraoperative multispectral imaging system, small malignant tumors (<1 mm) could be visualized clearly under the fluorescent channel. As confirmed by the histological results, the fluorescent signal was only observed in the folate-positive tumors. In another trial, FIGS in colon cancer was guided using a fluorescent heptapeptide selected from a phage library (15). Instead of intravenous injection, the peptide probe was administered topically using a standard endoscopic spray catheter 5 min prior to imaging. Using an approved gastrointestinal confocal fluorescent imaging system, the cancerous tissue and cells were identified with 81% sensitivity and 82% specificity.

Although various fluorescent probes and imaging systems, optimized for different cancer types and locations, remain to be developed and approved, the encouraging results from these recent clinical trials suggest that the era of FIGS is emerging. Fluorescent probes in the visible range are convenient because surgeons can directly view the enriched areas without additional equipment. However, tissue autofluorescence may significantly reduce the signal-to-background ratio. Furthermore, visible light can only penetrate short distances. Although light in the near-infrared range is more ideal in this regard, its invisibility to the naked eye does complicate detection. As observed in the aforementioned examples, various imaging devices, such as fluorescent laparoscopes or endoscopes, have been developed to monitor the fluorescent signal. A projection of the fluorescent image and/or an overlay with the white light image is required during the procedure. To mitigate this limitation of indirect visualization, prototypes of fluorescent imaging goggles have been reported (16,17). These goggles allow real-time visualization for physicians to direct the procedure without a time cost. Given the promise of these

pilot studies, it can be foreseen that in the near future, in addition to standard theater lights, multiple-color lighting will become a standard feature of the modern operating room.

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