Advances in fluorescent-image guided surgery

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Abstract: Fluorescence imaging is increasingly gaining intraoperative applications. Here, we highlight a few recent advances in the surgical use of fluorescent probes.

Keywords: Fluorescent probes; lymphedema; robotic surgical procedures; staining and labeling; surgery; tumor imaging

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Introduction

The first use of fluorescent imaging in surgery dates to 1948 when surgeons noticed fluorescein concentration increased in malignant tissue and used this property to identify and localize intracranial neoplasms during neurosurgery (1). Since then, additional fluorescent agents have been used for a variety of surgical applications. Clinically, fluorescent agents can be used to establish positive margins with high resolution, map lymph nodes, detect residual disease, predict metastatic potential, and assist in drug delivery (2-8). Intraoperative fluorescence imaging offers the benefits of high contrast and sensitivity, low cost, ease of use, safety, and visualization of cells and tissues both *in vitro* and *in vivo* (9,10). Near-infrared contrast agents, such as the widely used indocyanine green (ICG), allow surgeons to visualize fluorescence wavelengths otherwise invisible to the naked eye while permitting deeper tissue penetration and enhanced contrast against autofluorescence (11,12). For the purpose of surgical oncology, an ideal probe provides the contrast required for resection of an entire tumor or affected lymph node while sparing healthy tissue (13). Therefore, a current challenge is to design probes with high selectivity for tumors, clear visualization, and minimal toxicity (14). Other applications of intraoperative fluorescent imaging, such as lymphatic imaging and angiography, also benefit from the development of new probes (10,12). An additional technical challenge remains in integrating new probes with surgical technology both existing and in development. We discuss three currently evolving uses of fluorescent probes in surgery: biochemically activatable "smart" probes, fluorescent imaging of the lymphatic system, and fluorescence-assisted robotic surgery. We also discuss new imaging modalities designed to improve detection of cancer.

Activatable fluorescent probes

Activatable fluorescent probes ("smart" probes) target tumor cells by taking advantage of the physiologic differences between cancerous and normal cells, thus enhancing tumor margin detection (15). These probes remain quenched until they are selectively activated into fluorescent molecules by tumor cells. Several strategies for this method of detection have been developed. One of the earliest examples of the use of these activatable fluorescent probes *in vivo* exploited the fact that proteolytic enzymes are of a higher concentration in tumors (16,17). The delivered agents, consisting of a fluorophore attached to a peptide, are cleaved by proteases to release a fluorescent molecule (16). This strategy has been applied to design activatable cell-penetrating peptides (ACPP) labeled with

a Cy5 fluorophore and conjugated to a macromolecular dendrimer carrier, which reduces nonspecific uptake by skin, cartilage, and kidney (18-21). Tumor surgery in mice guided by these conjugated ACPPs resulted in fewer residual cancer cells in a variety of cancer models (20,21). Owing to their selective uptake into cancer cells, ACPPs have also been employed to deliver anti-neoplastic agents such as monomethyl auristatin E specifically to tumors (22-24). Recently, ratiometric ACPPs have been adapted to identify quantifiably measure both primary tumors and metastases, providing detailed information about cancer invasion (18,25-27).

Probes have also been developed to simultaneously target matrix metalloproteinase (MMP) with an activatable fluorescent probe and human epidermal growth factor receptor 2 (HER2) with an "always-on" probe (15). Targeting these two important biomarkers, which are commonly overexpressed in breast cancer, has the potential to improve the detection of tumor margins and intraoperatively provide information regarding the molecular characteristics of the tumor (15,28). Another example of simultaneous targeting involves an activatable fluorescent peptide targeting MMP-2, a protease with increased activities in many cancers, and integrin $\alpha_v\beta_3$, involved in the activation of MMP-2 (29-31). This molecule improved the fluorescent signal over MMP targeting alone and revealed a potential new strategy for the delivery of chemotherapeutic agents (29).

Several protease-activated fluorescent probes for topical administration have been synthesized (32,33). These probes can be sprayed onto tissue surfaces that are suspected of harboring tumors and require a lower dose than systemic administration (32,34). Human clinical studies of these probes revealed that on-site topical administration of aspirated specimens provided rapid visualization and diagnosis of pancreatic tumors (35). Work with "always on" fluorescent molecules has demonstrated that probes can also be topically applied directly to esophageal neoplasia in patients (34). These probes, which bind specifically to high-grade dysplasia and esophageal adenocarcinoma in Barrett's esophageus, were safe and effective for localizing disease (34). These studies demonstrate another potential avenue for the delivery of smart probes.

Clinical trials have recently begun using LUM015, a protease-activated fluorescent molecule, constituting the first in-human phase 1 clinical trial of this type of imaging probe (36). The activation of LUM015 relies on cathepsin proteases, enzymes commonly overexpressed by tumors (37). LUM015 is optically inactive under normal conditions, but upon proteolytic cleavage by specific cathepsins, a covalently attached quencher molecule is released and fluorescence signal greatly intensifies (36). LUM015 was injected intravenously into 15 patients with either invasive ductal carcinoma or soft tissue sarcoma and was well tolerated with no adverse pharmacological activity (36). Tumors were surgically removed and examined *ex vivo* by fluorescent imaging (36,38). Six hours after injection, fluorescence signal in tumors was significantly higher than in adipose tissue or muscle, demonstrating the tumor-selective biodistribution and activation of LUM015 (36). These findings helped validate the use of LUM015 for intraoperative imaging as a means to intraoperatively define tumor margins, detect residual cancer cells, and reduce the rates of reexcision. Pharmacokinetics were similar between humans and mice, an encouraging finding that could increase the likelihood of additional activatable probes being translated to use in humans (36,39).

An additional strategy that does not rely on protease catalysis for activation instead uses a self-assembling polymer micelle conjugated to anti-HER2 antibodies with fluorescent probes encapsulated inside (40). These fluorescent probes become activated upon degradation of the micelle after its uptake into HER2-positive tumors, validating their potential use in visualizing and classifying tumors (40). Another probe design that relies on the unique surface environment of cancer cells takes advantage of the cell surface glycoprotein fibroblast activation protein-alpha to activate a fluorescence signal (41). Novel activatable probes targeting additional physiologic characteristics of cancer cells, such as thiol concentration, decreased pH, surface lectins, and antibody binding, are also currently in development (8,42-46). Translating these activatable probes into clinical studies could significantly increase the number and quality of intraoperative imaging tools available during cancer excision.

Endogenously synthesized fluorescent porphyrins have been used in the clinic to guide malignant glioma resection (47-50). Their use has allowed physicians to achieve a significantly higher rate of complete resections compared to surgeries done without the use of fluorescent visualization (47-51). Though not considered an activatable probe in the traditional sense, fluorescent porphyrin synthesis is stimulated in cancerous tissue by 5-aminolevulinic acid, a natural biochemical precursor of hemoglobin that is orally administered prior to surgery (49). This biological pathway further exemplifies the potential to exploit differences in

cancer metabolism in designing selective probes with higher diagnostic accuracy and increased signal, two important challenges that remain in the implementation of fluorescent agents in surgery (52).

As new cancer targets are identified, fluorescent probes can be designed to bind them selectively. If these biomarkers are sufficiently specific for tumor cells, low systemic concentrations of fluorescent probes can achieve high concentrations within tumors and define tumor edges without the need for enzymatic activation. Such is the case for recently developed "always-on" probes that bind cancer biomarkers including urokinase plasminogen activator, folate receptor-α, carbonic anhydrase IX, and albumin degradation (53-57). However, combining the discovery of novel biomarkers with activatable fluorescent molecules has the potential to further increase selectivity and improve intraoperative tumor imaging.

Fluorescent imaging of the lymphatics

Fluorescent ICG has frequently been used as an alternative to dyes or radioactive gamma probes to guide sentinel lymph node biopsy (58-60). Fluorescent molecules offer the advantages of ease of use ease of use and low invasiveness compared to methods requiring exposure to radiation (58). ICG was effectively used as a surgical guide to accurately detect and remove axillary sentinel lymph nodes (58). Sentinel nodes were more likely to be identified by the fluorescence method than the blue dye method (60). Improved accuracy of sentinel lymph node biopsy allows the sparing of healthy nodes and potentially of the healthy portions of nodes partially invaded by metastasis, reducing the risk of post-surgical lymphedema. (59) The ability to precisely track lymphatic flow could also aid the design lymphatic-delivered therapies (59).

A recent study highlighted the use of a novel macrophage-specific fluorescent probe for intraoperative lymph node staging (61). Discovered via a high-throughput screen, this probe selectively binds monocytes and macrophages, the latter of which are a main component of lymph nodes (61). A deficient fluorescent signal caused by the replacement of macrophages by disseminated tumor cells could therefore diagnose the precise location of a nodal metastasis (61). Because of its unique binding property, this probe could be used not only to detect metastases *in vivo* but also to track local inflammation and adenopathy (61). Such studies lay the foundation for *in vivo* imaging technology that could eliminate unnecessary lymph node biopsies or dissections, reducing the postoperative complications of cancer therapies.

Some studies have demonstrated the potential use of multicolor quantum dots, each with a sharply defined emission spectrum, to simultaneously map lymphatic flow from multiple lymphatic basins (62-64). Fluorescent mapping of lymph flow from different regions can provide insight into drainage mechanisms and help surgical planning, reducing the incidence of postoperative lymphedema. Additionally, quantum dots offer the advantages of selective localization to and accumulation in axillary lymph nodes (65).

Beyond identifying sentinel lymph nodes intraoperatively, fluorescent molecules have also been used to examine secondary lymphedema as a complication following lymph node dissection. Preoperatively, ICG fluorescence can be used to assess the functional severity of lymphedema of the extremities and can help stage and select patients for surgical treatment (66-73). Compared to lymphoscintigraphy (the alternative method of imaging lymphedema), ICG fluorescence lymphography is more accurate, less invasive, and of a lower cost, making it more suitable for routine evaluations (74-76). Fluorescence visualization can also be utilized in evaluating other causes of lymphedema, such as lipedema, Fabry's disease, congenital Milroy lymphedema, lymphatic malformations, or lymphedema praecox (71,77,78). Fluorescence lymphography is an important tool for lymphedema evaluation partially due to the fact that, unlike lymphoscintigraphy, fluorescent imaging can discriminate the lymphatic vessel contractility responsible for lymph flow (78-80).

Fluorescence lymphography is useful in early stages and mild cases of lymphedema, which is important when considering that lymphedema progresses slowly and may appear long after cancer treatment (81,82). Visualizing a "splash pattern" of fluorescence after ICG injection indicates a very early stage of lymphedema, even if the limb is otherwise asymptomatic (83). This allows physicians to detect lymphedema even in a subclinical stage, allowing for a timelier diagnosis and treatment of lymphedema (83). Fluorescent visualization provides better insight into lymphatic function when assessing lymphatic function prior to, during, or after surgery (79). It also helps determine the suitability of a lymphaticovenular shunt operation, one of the surgical treatments for lymphedema (74). ICG fluorescence is used intraoperatively to identify active lymphatic channels during lymphaticovenular shunt operations (79,84-88). Fluorescence imaging allows for the

prompt identification of the functional lymphatic vessels and helps predict postsurgical outcomes (66).

Recent cases have demonstrated the versatility of ICG fluorescent visualization in potentially guiding the treatment of a multitude lymphatic disorders. Fluorescent imaging of lymphatic flow has been used outside of the realm of cancer and lymphedema as a means of aiding therapy for chylothorax (89,90). Chylothorax results from leakage of lymph from the thoracic duct or its tributaries, causing chyle to accumulate within the pleural cavity (89,91). It is a rare but serious complication following heart surgery in children (89). In one case involving a pediatric patient with chylothorax, ICG fluorescence helped physicians visualize obstructed lymphatic drainage and guide the choice of surgical intervention (89). ICG fluorescence lymphography was also used intraoperatively in two adult patients with lymphatic injury following an esophagectomy (90,92). In one case of chylothorax, ICG fluorescent imaging was used to identify the precise site of a chyle fistula, allowing surgeons to suture it and prevent chyle leakage (90). In a case of chylorrhea, intraoperative fluorescence navigation aided in thoracic duct ligation, successfully stopping the chylorrhea (92). These studies demonstrate that fluorescent probes could feasibly be employed to increase the efficiency of chylothorax and chylorrhea treatment and to reveal the pathogenesis of these poorly understood conditions (89,90,92-94). As a whole, fluorescent visualization has the potential to significantly increase our understanding of the lymphatic system, guide surgical intervention, and manage therapies (95).

Fluorescence-assisted robotic surgery

Fluorescent imaging has been used in a wide variety of applications to help guide robotic-assisted surgeries. Robotic surgeries are ideal for several procedures because they are precise, minimally invasive, and capable of reducing blood loss and shortening postoperative stay (96). Fluorescence has been used intraoperatively in these surgeries to visualize vascular and lymphatic anatomy, evaluate tissue perfusion, map biliary anatomy, identify lesions, and image metabolic activity (96-103). Combining the minimally-invasive approach of robotic surgery with the accuracy and precision of fluorescence has the potential to improve safety and outcomes in a wide range of treatments, with several studies already highlighting the benefits.

The major current uses of fluorescence-assisted robotic surgeries are in gastroenterologic, urologic, and gynecologic surgeries. During robotic-assisted esophagectomy, ICG allowed surgeons to examine and preserve the right gastroepiploic vascular arcade (97). It often identified small vessels that would not have otherwise been visualized (97). In robot-assisted laparoscopic gastrectomy, fluorescence imaging was used to identify lymph nodes from different lymphatic basins, helping surgeons sample the lymph nodes and stage gastric cancer patients (104). Because ICG is metabolized mainly by hepatic parenchymal cells and secreted into the bile, it has been used to visualize the biliary tree during robotic cholecystectomy for gallstone disease (101,105,106). This application of fluorescent imaging is safe, effective, and particularly helpful with obese patients or in cases of acute cholecystitis, two cases that make the surgery more challenging (101,106). In one case, fluorescent imaging during robotic cholecystectomy helped avoid surgical injury by identifying an aberrant canaliculus, a structure that is otherwise difficult to detect (100).

When applied to robotic-assisted colorectal surgery intended to spare the sphincter of rectal cancer patients, fluorescent imaging was used to simultaneously map local lymph nodes and assess perfusion status (4). This served the dual benefit of demarcating lymph node edges and preventing anastomotic leak, the most significant complication following this surgery (4,107). To this point, causes of anastomotic leakage after rectal surgery is considered unpredictable, but the ability to precisely visualize complex and possibly abnormal vasculature has the potential to reduce rates of ischemic injury (107). Additional studies have confirmed the benefit of fluorescent imaging in robotic-assisted surgeries for colorectal cancer, guiding surgeons and allowing them to adjust their planned incisions (98,99,108). One group employed a novel combination of fluorescence visualization and augmented-reality three-dimensional imaging to guide robotic duodenopancreatectomy in a patient with an intraductal papillary mucinous neoplasm (109). This research emphasizes the role of technological breakthroughs in surgery, robotics, and computer science in improving patient care.

Fluorescence-guided robotic surgery has found a wide range of applications in urologic procedures (110). The first use of this technology in this field helped to both identify renal vasculature and differentiate tumors from normal parenchyma in laparoscopic nephrectomy for renal cortical tumors (102). Interestingly, later studies showed that malignant kidney tumors tended to be hypofluorescent while benign tumors ranged from isofluorescent to

hyperfluorescent, validating that ICG can also help differentiate between different tumor types (103). In robotic nephrectomies where warm ischemia is induced by renal artery clamping, using fluorescent visualization as a visual aid helped reduce the overall time the kidney was ischemic (111). As seen with other surgeries, ICG alerted surgeons to abnormal vascular anatomy, helping them avoid unintended injuries that would be otherwise difficult to predict (112,113). This technology could help surgeons spare larger portions of the kidney in partial nephrectomy and reduce postoperative complications, blood loss, and metastasis (113,114). Similarly, ICG was used in robotic partial adrenalectomy to differentiate between adrenal mass and normal parenchyma, helping to spare as much of the adrenal gland as possible while completely excising the tumor (115,116). This was also performed on the basis that several types of neoplasms are hypofluorescent on ICG imaging compared to normal tissue (115,116). Preclinical studies are currently underway to validate the use of fluorescence in anatrophic nephrolithotomy to identify avascular renal planes, assisting the removal of staghorn calculi (117). Intraureteric injection of ICG was used to identify the ureter and locate ureteral strictures in robotic-assisted ureteral construction (118,119). One group used a novel technique of imaging near-infrared fluorescence without an injectable contrast agent during robotic-assisted laporoscopic surgery of the urinary tract (120). Instead, they imaged the near-infrared emission of white light from endoscopic instruments (120). They were able to precisely identify the extent of a ureteric stricture, bladder diverticula, and tumor locations (120).

In robotic radical prostatectomy, ICG was injected into the prostate to mark prostatic tissue and map potential sentinel lymph nodes (121). Because ICG is not prostate specific, new fluorescent tracers that achieve targeting via prostate-specific membrane antigen are being developed to enhance tissue contrast (122). Bladder cancer patients underwent an experimental technique in which ICG was injected both directly into the tumor and intravenously (123). This permitted tumor marking, sentinel lymph node detection, and mesenteric vasculature identification to be accomplished simultaneously (123).

In a recent study, Paley *et al.* combined fluorescent lymph node mapping with robotic hysterectomy in patients with endometrial cancer (124). They found that this technology can help accurately and safely avoid full lymphadenectomies in women with high grade metastatic tumors, thus preventing secondary complications such as lymphedema (124). Previous research has confirmed that combining robotic-assisted hysterectomies with fluorescent sentinel lymph node mapping outperformed colorimetric dyes (125-128). These studies and their successors have the potential to change the standard of care for endometrial cancer therapy, which as of yet does not have a consensus regarding the utility of sentinel lymph node mapping (124).

An interesting application of fluorescence in robotic surgery involved its use in identifying nervous tissue in patients undergoing a robotic thymectomy (129). After injecting ICG, physicians were able to identify the periocardiophrenic neurovascular bundle with an 80% success rate (129). This technology could reduce surgery time and the risk of accidental nerve injury. During robotic anatomic segmentectomy, a procedure used to treat early-stage lung cancer, ICG was used to demarcate boundaries of lung segments for surgical resection (130). ICG could also identify the parathyroid glands in a canine model, suggesting yet another potential use in visualizing specialized tissue (131). Although additional studies are needed to fully validate the utility of fluorescent imaging in robotic-assisted surgeries, a growing body of evidence indicates that coupling these technologies has the potential to further increase the efficacy and safety of these procedures.

In vivo microscopy and nanotechnology

For many years now, several groups have focused on using live microscopy for better detection of certain cancer types, including notably oral cancer (132). Autofluorescence microscopy helps to better delineate cancerous tissues from normal tissues and assists in oral mucosa, where that differentiation may be very difficult. At Rice University, one collaboration between bioengineering laboratories and surgical oncologist has helped to develop an FDA approved device which harnesses a multispectral digital microscope, or one capable of several different imaging modalities to help better define cancerous lesions. Richards-Kortum and colleagues ran clinical trials and demonstrated this type of imaging may help better direct surgical biopsy and definitive therapy (133). This is one example of how advanced microscopy and multimodal imaging has led to an intraoperative guidance of resection.

Other labs have focused on the use of quantum dots or gold nanoshells to help label tumors and to provide for cellular imaging with near infrared microscopy that can penetrate human tissues (134,135). These very small

materials can be fine-tuned in order to fluoresce or to generate heat when excited in order to serve as fluorescent markers of cells and tissues or to target tissues for ablation. Groups have shown this technology to be useful even in *in vivo* single molecular imaging for sentinel node navigation; they specifically developed it for molecular targeting drug-delivery systems (136). These advances represent a paradigm shift in the way we think about operations and intraoperative imaging. Imagine a situation where the surgeons can see only affected nodes and lymphatic channels, where they can have cellular resolution for their surgical resections or for image guidance. In the future these technologies could be combined and cells could be labelled and then utilized as therapeutic and they could be monitored *in vivo*.

Conclusions

Fluorescence imaging technology is gaining several new surgical applications. At the same time, the technology itself is frequently being updated, with many new fluorescent probes and imaging strategies in development. However, several obstacles and limitations still exist that must be overcome for fluorescent imaging to gain even wider use than its current applications. One question that remains is whether the potential benefits of fluorescent imaging warrant the cost of adding it to a surgical field. For example, one study estimated the cost adding near-infrared fluorescence imaging to robotic partial nephrectomy to be approximately $100,000 and the cost of ICG per vial to be approximately $100 (137). Additionally, imaging agents must undergo the same FDA approval process as other pharmaceutical drugs, making it take approximately a decade and $150 million for a fluorescent probe to become available on the market (3). These probes, however, seem much less lucrative to develop as they are only administered around the time of surgery rather than prescribed to be taken frequently. More evidence confirming the reduction of postoperative complications could help validate the initial time and expense required.

Iodine is rapidly excreted by the body and has a low penetrative ability (3,96). This means that to achieve sufficient contrast it must be administered very close to the time of surgery or the dose must be increased (36). The presence of inflammation, fibrosis, or excess fat also makes visualizing ICG more difficult (96,138). Another limitation to the implementation of these fluorescent probes is their contraindications. For example, approximately 1% of the population is hypersensitive to iodine and cannot be given ICG (139). Another contraindication is elevated liver function tests (113). Alternative imaging molecules must be sought for these patients. Additionally, newer detection methods could improve imaging by quantitatively assessing and mapping fluorescence intensity instead of relying on qualitative evaluation.

Studies are underway to identify molecules capable of selectively targeting specific tissues, many of which could have a significant clinical impact. Recently developed fluorescently labeled peptides can specifically label degenerated nerve branches, which in the future could aid patients undergoing surgical nerve repair (140). Another fluorescent probe was capable of quantitatively evaluating traumatic brain injury (141). Though these probes have not yet been used in humans, combining them with existing imagining and surgical technology has the potential to increase the efficacy of future surgeries. A great deal of current research and clinical trials are examining the potential use of quantum dots as an alternative fluorescent marker (65,142-145). These molecules would overcome the obstacle of iodine allergy and can be easily modified to alter their biodistribution and fluorescence emission. They also allow quantitative detection, have a high fluorescence intensity, and have a long emission lifetime. As fluorescence imaging becomes more sophisticated and targeted, additional surgical applications will follow, benefiting both patients and physicians.

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Footnote

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