Near-Infrared Vascular Imaging and Near-Infrared Fluorescence Imaging

Number: 0846

POLICY

*Please see amendment for Pennsylvania Medicaid at the end of this CPB.

Aetna considers the use of near-infrared vascular imaging systems (e.g., AccuVein AV300 or VeinViewer) for assessment of cutaneous wound, and guiding vascular access experimental and investigational because their effectiveness has not been established.

Aetna considers near-infrared fluorescence (NIRF) imaging experimental and investigational for the following indications (not an all-inclusive list):

- Assessment of liver function
- Confirmation and identification of the position of gastro-epiploic vessels during minimally invasive esophagectomy
- Delineation of the ureters during laparoscopy
- Detection and resection of colorectal neoplasia
- Detection of ovarian cancer metastases
- Detection of tumor angiogenesis and monitoring of response to anti-tumor vasculature therapy
- Diagnosis of peripheral artery disease
- Diagnosis of rheumatoid arthritis
- Evaluation of coronary atherosclerosis

POLICY HISTORY

Last Review: 11/23/2021
Effective: 05/17/2013
Next Review: 09/22/2022

Review History

Definitions

Additional Information

Clinical Policy Bulletin

Notes
- Evaluation of soft tissue viability to guide debridement in trauma surgery
- Facilitation of selective arterial clamping during partial nephrectomy
- Guidance for sentinel lymph node mapping in gastric cancer
- Guidance in amputation surgery
- Guidance of surgery for intracranial meningioma
- Identification of vulnerable atherosclerotic plaques
- Imaging of matrix metalloproteinase 2 (MMP-2) as a biomarker of the vascular remodeling in arterio-venous fistulae
- Intra-operative anatomy navigation during minimally invasive surgery
- Intra-operative detection of hepatocellular cancer and needle tract implantation and peritoneal seeding after radiofrequency ablation
- Intra-operative detection of pancreatic cancer and metastases
- Intra-operative imaging of lung cancer/lung metastases/mesothelioma
- Localization of brain metastases
- Lymphatic imaging of Klippel-Trenaunay syndrome
- Lymphatic imaging in lymphangiomatosis
- Mapping of microvascular circulation in ischemic diseases
- Mapping of sentinel lymph nodes in endometrial cancer
- Navigation of laparoscopic anatomy during gastro-intestinal surgery.

Aetna considers the use of a hybrid NIRF-intravascular ultrasound (NIRF-IVUS) system for evaluation of coronary and peripheral artery diseases experimental and investigational because the effectiveness of this approach has not been established.

Aetna considers intra-operative near-infrared fluorescence imaging of extra-hepatic bile ducts (e.g., cystic duct, common bile duct and common hepatic duct) with intravenous administration of indocyanine green experimental and investigational for assessment of liver function because the effectiveness of this approach has not been established.

See also CPB 0111 - Indocyanine Green Angiography (../100_199/0111.html), CPB 0382 - Intravascular Ultrasound
BACKGROUND

Near-Infrared Vascular Imaging

Peripheral intravenous (PIV) catheter insertion is a common, painful, and sometimes difficult procedure for many infants and children in the pediatric emergency department (ED) because of the small caliber and impalpability of the veins. Changes in catheter design and adoption of new imaging techniques have been tried to facilitate line placement.

Near-infrared (NIR) imaging is a non-invasive and non-ionizing modality that has been employed to improve the success rate of PIV catheter placement in pediatric patients (e.g., reduce the number of attempts, the number of needle redirections, and the overall time to catheter placement). The VeinViewer® (Luminetx Corporation, Memphis, TN) is a NIR light device that delineates the running course of subcutaneous veins.

In an observational feasibility study, Cuper et al (2011) evaluated for the first time the value of visualizing veins by a prototype of a NIR vascular imaging system for venipuncture in children. Participants were children (0 to 6 years) attending the clinical laboratory of a pediatric university hospital during a 2-month period without (n = 80) and subsequently during a 1-month period with a prototype of an NIR vascular imaging system (n = 45). Failure rate (i.e., more than 1 puncture) and time of needle manipulation were determined. With the NIR vascular imaging system, failure rate decreased from 10/80 to 1/45 (p = 0.05) and time decreased from 2 seconds (1 to 10) to 1 second (1 to 4, p = 0.07). The authors concluded that the findings of this study showed promising results on the value of an NIR vascular imaging system in facilitating venipuncture.

Chapman et al (2011) examined the benefit of the VeinViewer, a device that delineates subcutaneous veins using NIR light and video technology, for PIV placement in children in the ED. A prospective, randomized
sample of children aged 0 to 17 years who required a non-emergent PIV in a tertiary care pediatric ED were enrolled in this study. Subjects were randomized to standard PIV cannulation (SC) or PIV cannulation with the VeinViewer (VV). The primary outcome measure was time to PIV placement. Secondary outcome measures included number of PIV attempts and pain scores as reported by the child, parent or guardian, and nurse using a 100-mm visual analog scale (VAS). A total of 323 patients completed the study: 174 boys and 149 girls. Age, sex, and body mass index (BMI) were not different between groups. There were no differences in time to PIV placement, number of PIV attempts, or pain scores for the overall study group. However, a planned subgroup analysis of children age 0 to 2 years (n = 107) did yield significant results for the geometric mean time to place the PIV (121 seconds [VV] versus 167 seconds [SC], p = 0.047) and for nurses' perception of pain (median VAS 34 [VV] versus 46 [SC], p = 0.01). The authors concluded that while no results were significant for the overall study group, subgroup analysis of children age 0 to 2 years suggested that the VeinViewer may decrease the time to PIV placement.

In a randomized controlled trial, Perry et al (2011) examined if the use of a NIR light venipuncture aid (VeinViewer) would improve the rate of successful first-attempt placement of IV catheters in a high-volume pediatric ED. Patients younger than 20 years with standard clinical indications for IV access were randomized to have IV placement by ED nurses (in 3 groups stratified by 5-year blocks of nursing experience) using traditional methods (standard group) or with the aid of the VeinViewer (device group). If a vein could not be cannulated after 3 attempts, patients crossed-over from one study arm to the other, and study nurses attempted placement with the alternative technique. The primary end point was first-attempt success rate for IV catheter placement. After completion of patient enrollment, a questionnaire was completed by study nurses as a qualitative assessment of the device. A total of 123 patients (median age of 3 years) were included in the study: 62 in the standard group and 61 in the device group. There was no significant difference in first-attempt success rate between the standard (79.0 %, 95 % confidence interval [CI]: 66.8 % to 88.3 %) and device (72.1 %, 95 % CI: 59.2 % to 82.9 %) groups. Of the 19 study nurses, 14 completed the questionnaire; 70 % expressed neutral or unfavorable assessments of the device in non-dehydrated patients without chronic
underlying medical conditions and 90% found the device a helpful tool for patients in whom IV access was difficult. The authors concluded that first-attempt success rate for IV placement was non-significantly higher without than with the assistance of the VeinViewer in a high-volume pediatric ED. They noted that nurses placing IVs did report several benefits to use of the device with specific patient groups, and future research should be carried out to demonstrate the role of the VeinViewer in these patients.

In a randomized controlled trial, Kim et al. (2012) examined if the use of the VeinViewer in infants and children facilitated peripheral venous access, especially in difficult cases. Pediatric patients between the ages of 1 month and 16 years who required peripheral venous access in the pediatric ward were included in this study. Prior to randomization, difficult intravenous access (DIVA) score, a 4-variable clinical prediction rule for first-attempt success, was estimated. These investigators compared the first-attempt success rates and procedural times between the VeinViewer group and a control group. They evaluated 111 patients: 54 in the VeinViewer group and 57 in the control group. Patient demographics and factors related to the success of vein access were similar for both groups. The overall first-attempt success rate was 69.4% (77/111) in the VeinViewer group and 66.7% (38/57) in the control group, a difference that was not statistically significant. However, the first-attempt success rate increased from (25%) 5/20 in the control group to (58%) 14/24 in the VeinViewer group for difficult veins with a DIVA score greater than 4 (p = 0.026). There were no significant differences in procedural time between the two groups. The authors concluded that the VeinViewer facilitated peripheral venous access for pediatric patients with difficult veins, which enhanced first-attempt success rates.

The AccuVein AV300 device was developed to assist venipuncture and IV cannulation by enhancing the visibility of superficial veins. It uses infrared light to highlight hemoglobin so that blood vessels are darkly delineated against a red background.

Sanchez-Morago et al. (2010) stated that despite major advances that have occurred in medicine and biotechnology in recent years, advances to locate veins have been very limited. The AccuVein AV300 is a portable manual instrument that enables nurses to locate certain peripheral veins.
This device does not substitute a nurse's traditional skill in locating veins by visual or feeling means, but rather this device supplements their skills and enhances them. This device is lightweight, intuitive, and does not require previous training for its use and hygiene since it never enters into contact with a patient's skin as it emits an infrared light on the skin, which reflects veins drawing them on the surface of the skin.

Kaddoum et al (2012) evaluated the effectiveness of the AccuVein AV300 in improving the first-time success rate of IV cannulation of anesthetized pediatric patients. Participants were randomized to cannulation with the AccuVein AV300 or standard insertion by experienced pediatric anesthesiologists. An observer recorded the number of skin punctures and cannulation attempts required, and the time between tourniquet application and successful cannulation or 4 skin punctures, whichever came first. There were 146 patients with a median age of 4.6 years (range of 0.18 to 17.1 years), 46.6 % were males, 80.8 % were light skin colored, and 15.7 % were younger than 2 years. The first-attempt success rates were 75 % (95 % CI: 63.8 to 84.2 %) using AV300 and 73 % (95 % CI: 61.9 to 81.9 %) using the standard method ($p = 0.85$). Patients with dark or medium skin color were 0.38 times less likely to have a successful first-attempt than patients with light skin color. The difference between the 2 treatment groups in number of skin punctures and the time to insertion was not significant. Although the AV300 was easy to use and improved visualization of the veins, the authors found no evidence that it was superior to the standard method of IV cannulation in unselected pediatric patients under anesthesia.

de Graaff et al (2014) evaluated the clinical utility of a NIR vascular imaging device (VascuLuminator®) in pediatric patients who were referred to the anesthesiologist because of difficult cannulation. There were 226 consecutive children referred to pediatric anesthesiologists by the treating pediatrician of the in- and out-patient clinic, because of difficulties with intravenous cannulation, were included in this cluster randomized clinical trial. The presence and use of the NIR vascular imaging device for peripheral intravenous cannulation (PIC) was randomized in clusters of 1 week. Success at first attempt (Fisher exact test) and time to successful cannulation (Log-rank test) were assessed to evaluate differences between groups. Success at first attempt in the group with the VascuLuminator® (59 %) was not significantly different from the control
group (54 %, p = 0.41), neither was the median time to successful cannulation: 246 s and 300 s, respectively (p = 0.54). The authors concluded that visualization of blood vessels with NIR light and with NIR vascular imaging device did not improve success of PIC in pediatric patients who are known difficult to cannulate.

In summary, there is currently insufficient evidence on the effectiveness of near-infrared vascular imaging for guiding vascular access. Well-designed studies are needed to validate these preliminary findings.

Assessment of Cutaneous Wound

Paul and colleagues (2015) stated that the ability to phenotype wounds for the purposes of assessing severity, healing potential and treatment is an important function of evidence-based medicine. A variety of optical technologies are currently in development for non-invasive wound assessment. To varying extents, these optical technologies have the potential to supplement traditional clinical wound evaluation and research, by providing detailed information regarding skin components imperceptible to visual inspection. These assessments are achieved through quantitative optical analysis of tissue characteristics including blood flow, collagen re-modeling, hemoglobin content, inflammation, temperature, vascular structure, and water content. Technologies that have, to this date, been applied to wound assessment include: NIR imaging, thermal imaging, optical coherence tomography (OCT), orthogonal polarization spectral imaging, fluorescence imaging, laser Doppler imaging, microscopy, spatial frequency domain imaging, photoacoustic detection, and spectral/hyper-spectral imaging. The authors presented a review of the technologies in use or development for these purposes with 3 aims: (i) providing basic explanations of imaging technology concepts, (ii) reviewing the wound imaging literature, and (iii) providing insight into areas for further application and exploration. They stated that non-invasive imaging is a promising advancement in wound assessment and all technologies require further validation.

Near-Infrared Fluorescence Imaging
Schols et al (2013) provided an overview of current developments in surgical optical imaging for improved anatomic identification and physiologic tissue characterization during laparoscopic gastro-intestinal surgery. A systematic literature search in the PubMed database was conducted. Eligible studies reported on any kind of novel optical imaging technique applied for anatomic identification or physiologic tissue characterization in laparoscopic gastro-intestinal surgery. Gynecologic and urologic procedures also were included whenever vascular, nerve, ureter, or lymph node imaging was concerned. Various surgical imaging techniques for enhanced intra-operative visualization of essential tissue types (i.e., blood vessel, bile duct, ureter, nerve, lymph node) and for tissue characterization purposes such as assessment of blood perfusion were identified. An overview of pre-clinical and clinical experiences was given as well as the potential added value for intra-operative anatomic localization and characterization during laparoscopy. The authors concluded that implementation of new optical imaging methods during laparoscopic gastro-intestinal surgery can improve intra-operative anatomy navigation. This may lead to increased patient safety (preventing iatrogenic functional tissue injury) and procedural efficiency (shorter operating time). They stated that near-infrared fluorescence imaging seems to possess the greatest potential for implementation in clinical practice in the near future.

Harke et al (2014) presented a single-surgeon, matched-pair analysis to show the feasibility of combining the technique of selective clamping with usage of NIR fluorescence (NIRF) imaging in robot-assisted partial nephrectomy and to investigate short-term renal function outcomes. A total of 22 patients underwent selective clamping partial nephrectomy with the application of indocyanine green (ICG). Out of this cohort, a matched-pair analysis for R.E.N.A.L. nephrometry parameter was employed for 15 exactly matching partners. Demographic, surgical, pathological and kidney function data were collected for the initial cohort, and matched-pair comparison was made between the subgroups retrospectively. Robot-assisted partial nephrectomy without clamping of the hilum was possible in 21 patients; in 1 patient, main artery clamping was necessary due to bleeding. Mean clinical tumor size was 37.7 mm. Mean selective clamping ischemia time was 11.6 mins with an estimated blood loss of 347 ml. No intra-operative complications occurred, and post-operative complications (n = 4), including 2 major urological
(urinoma, late-onset acute hemorrhage) complications, were found. There were no side effects of ICG administration. Matched-pair analysis for 15 patients showed similar demographic and surgical data without any significant differences in tumor characteristics. Comparing short-term renal function outcomes, significantly decreased estimated glomerular filtration rate reduction in the selective clamping group with an absolute loss of 5.1 versus 16.1 ml/min in the global ischemia cohort (p = 0.045) could be observed. The authors concluded that robot-assisted partial nephrectomy with selective clamping of the tumor feeding vascular branches is a promising technique for reduced ischemic renal trauma. This may lead to improved kidney function preservation.

Press and Jaffer (2014) noted that coronary artery disease (CAD) is an inflammatory process that results in buildup of atherosclerosis, typically lipid-rich plaque in the arterial wall. Progressive narrowing of the vessel wall and subsequent plaque rupture can lead to myocardial infarction and death. Recent advances in intra-vascular fluorescence imaging techniques have provided exciting coronary artery-targeted platforms to further characterize the molecular changes that occur within the vascular wall as a result of atherosclerosis and following coronary stent-induced vascular injury. These investigators summarized recent developments in catheter-based imaging of coronary arterial-sized vessels; focusing on 2-dimensional NIRF molecular imaging technology as an approach to identify inflammation and fibrin directly within coronary artery-sized vessels. The authors concluded that intravascular NIRF is anticipated to provide new insights into the in-vivo biology underlying high-risk plaques, as well as high-risks stents prone to stent re-stenosis or stent thrombosis.

Sarkaria et al (2014) stated that during esophagectomy, identification and preservation of the right gastro-epiploic vascular arcade are critical and may be challenging with minimally invasive approaches. These researchers assessed the use of near-infrared fluorescence imaging fluorescence angiography (NIFI-FA) during robotic-assisted minimally invasive esophagectomy (RAMIE) as an aid to visualize the gastric vasculature with mobilization. After intravenous administration of 10 mg of ICG, a robotic platform with NIR optical fluorescence capability was used to examine the gastric vasculature in patients undergoing RAMIE. A total of 30 (71 %) of 42 patients undergoing RAMIE were assessed using NIFI-FA during mobilization of the greater gastric curve and fundus; 11
were excluded because the system was not available, and 1 was excluded because of documented allergy to iodinated contrast. The median time from ICG administration to detectable fluorescence was 37.5 seconds (range of 20 to 105 seconds). Near-infrared fluorescence imaging FA identified or confirmed termination of the vascular arcade in all 30 cases. Subjectively, NIFI-FA often identified otherwise unvisualized small transverse vessels between the termination of the vascular arcade and the first short gastric artery, as well as between the short gastric arteries. Identification and/or confirmation of the vascular arcade position during mobilization of the greater curve/omentum were also aided by NIFI-FA. The authors concluded that although there are limitations to the current technology, NIFI-FA may be a useful adjunct to confirm and identify the position of gastro-epiploic vessels, allow for safer and more confident dissections during gastric mobilization, as well as potentially decrease serious intra-operative vascular misadventures.

Ma et al (2014) stated that pathological angiogenesis is crucial in tumor growth, invasion and metastasis. Previous studies demonstrated that the vascular endothelial growth inhibitor (VEGI), a member of the tumor necrosis factor super-family, can be used as a potent endogenous inhibitor of tumor angiogenesis. Molecular probes containing the asparagine-glycine-arginine (NGR) sequence can specifically bind to CD13 receptor, which is over-expressed on neovasculature and several tumor cells. Near-infrared fluorescence optical imaging for targeting tumor vasculature offers a non-invasive method for early detection of tumor angiogenesis and efficient monitoring of response to anti-tumor vasculature therapy. These researchers developed a new NIRF imaging probe on the basis of an NGR-VEGI protein for the visualization of tumor vasculature. The NGR-VEGI fusion protein was prepared from prokaryotic expression, and its function was characterized in-vitro. The NGR-VEGI protein was then labeled with a Cy5.5 fluorophore to afford Cy5.5-NGR-VEGI probe. Using the NIRF imaging technique, these investigators visualized and quantified the specific delivery of Cy5.5-NGR-VEGI protein to subcutaneous HT-1080 fibrosarcoma tumors in mouse xenografts. The Cy5.5-NGR-VEGI probe exhibited rapid HT-1080 tumor targeting, and highest tumor-to-background contrast at 8 hours post-injection (pi). Tumor specificity of Cy5.5-NGR-VEGI was confirmed by effective blocking of tumor uptake in the presence of unlabeled NGR-VEGI (20 mg/kg). Ex-vivo NIRF imaging further confirmed in-vivo
imaging findings, demonstrating that Cy5.5-NGR-VEGI displayed an excellent tumor-to-muscle ratio (18.93 ± 2.88) at 8 hours pi for the non-blocking group and significantly reduced ratio (4.92 ± 0.75) for the blocking group. The authors concluded that Cy5.5-NGR-VEGI provided highly sensitive, target-specific, and longitudinal imaging of HT-1080 tumors. They stated that as a novel theranostic protein, Cy5.5-NGR-VEGI has the potential to improve cancer treatment by targeting tumor vasculature.

Cornelissen and colleagues (2018) stated that NIRF imaging technique, after administration of contrast agents with fluorescent characteristics in the near-infrared (700 to 900 nm) range, is considered to possess great potential for the future of plastic surgery, given its capacity for peri-operative, real-time anatomical guidance and identification. These investigators provided a comprehensive literature review concerning current and potential future applications of NIRF imaging in plastic surgery, thereby guiding future research. A systematic literature search was performed in databases of Cochrane Library CENTRAL, Medline, and Embase (last search October 2017) regarding NIRF imaging in plastic surgery. Identified articles were screened and checked for eligibility by 2 authors independently. A total of 48 selected studies included 1,166 animal/human subjects in total; NIRF imaging was described for a variety of (pre)clinical applications in plastic surgery; 32 articles used NIRF angiography, i.e., vascular imaging after intravenous dye administration; 10 articles reported on NIRF lymphography after subcutaneous dye administration. Although currently most applied, general protocols for dosage and timing of dye administration for NIRF angiography and lymphography are still lacking; 3 articles applied NIRF to detect nerve injury, and another 3 studies described other novel applications in plastic surgery. The authors concluded that future standard implementation of novel intra-operative optical techniques, such as NIRF imaging, could significantly contribute to peri-operative anatomy guidance and facilitate critical decision-making in plastic surgical procedures. They stated that further investigation (i.e., large multi-center randomized controlled trials [RCTs]) is needed to establish the true value of this innovative surgical imaging technique in standard clinical practice and to aid in forming consensus on protocols for general use.
Esposito and colleagues (2020) stated that NIRF imaging with ICG has been recently adopted in pediatric minimally invasive surgery (MIS) in order to improve intra-operative visualization of anatomic structures and facilitate surgery. These researchers reported their preliminary experience using ICG technology in pediatric urology using laparoscopy and robotics. ICG technology was adopted in 57 laparoscopic or robotic urological procedures performed in the authors' unit over a 24-month period: 41 (38 laparoscopic; and 3 robotic) left varicocele repairs with intra-operative lymphography and 16 renal procedures (12 laparoscopic; and 4 robotic) including 9 partial nephrectomies, 3 nephrectomies and 4 renal cyst deroofings. The ICG solution was injected intravenously in renal procedures or into the testis body in case of varicocele repair. Regarding the timing of the administration, the ICG injection was performed intra-operatively in all cases and allowed the visualization of the anatomic structures in a matter of 30 to 60 s. The dosage of ICG was 0.3 mg/ml/kg in all indications. All procedures were completed laparoscopically or robotically without conversions. No adverse and allergic reactions to ICG and other complications occurred post-operatively. This study described for the 1st time in pediatric urology that ICG-guided NIRF imaging may be helpful in laparoscopic and robotic procedures. In case of varicocele repair, ICG-enhanced fluorescence allowed to perform a lymphatic-sparing procedure and avoided the risk of post-operative hydrocele. In case of partial nephrectomy, ICG-guided NIRF was helpful to visualize the vascularization of the non-functioning moiety, identify the dissection plane between the 2 moieties and check the perfusion of the residual parenchyma after resection of the non-functioning pole. In case of renal cyst deroofing, ICG-guided NIRF aided to identify the avascular cyst dome and to guide its resection. No real benefits of using ICG-enhanced fluorescence were observed during nephrectomy. The authors concluded that their preliminary experience confirmed the safety and efficacy of ICG technology in pediatric urology and highlighted its potential advantages as adjunctive surgical technology in patients undergoing laparoscopic or robotic urological procedures. These researchers noted that the use of NIRF was also cost-effective as no added costs were required except for the ICG dye (cost 40 Euro per bottle). The most common and useful applications in pediatric urology included varicocele repair, partial nephrectomy and renal cyst deroofing. The main limitation was the specific equipment needed in laparoscopy, that is not available in all centers whereas the robot is equipped with the Firefly software for NIRF.
Detection of Ovarian Cancer Metastases

Tummers et al (2015) noted that in ovarian cancer, 2 of the most important prognostic factors for survival are completeness of staging and completeness of cytoreductive surgery (CRS). Therefore, intra-operative visualization of tumor lesions is of great importance. Pre-clinical data already demonstrated tumor visualization in a mouse-model using NIRF imaging and ICG as a result of enhanced permeability and retention (EPR). These researchers determined the feasibility of intra-operative ovarian cancer metastases imaging using NIRF imaging and ICG in a clinical setting. A total of 10 patients suspected of ovarian cancer scheduled for staging or CRS were included. Patients received 20 mg ICG intravenously after opening the abdominal cavity. The mini-FLARE NIR fluorescence imaging system was used to detect NIRF lesions. These investigators reported that 6 out of 10 patients had malignant disease of the ovary or fallopian tube, of which 2 had metastatic disease outside the pelvis; 8 metastatic lesions were detected in these 2 patients, which were all NIR fluorescent. However, 13 non-malignant lesions were also NIR fluorescent, resulting in a false-positive rate of 62 %. There was no significant difference in tumor-to-background ratio between malignant and benign lesions (2.0 versus 2.0; \( p = 0.99 \)). The authors concluded that this was the first clinical trial demonstrating intra-operative detection of ovarian cancer metastases using NIRF imaging and ICG. Despite detection of all malignant lesions, a high false-positive rate was observed. Therefore, they stated that NIRF imaging using ICG based on the EPR effect is not satisfactory for the detection of ovarian cancer metastases.

Intra-Operative Anatomy Navigation during Minimally Invasive Surgery

Schols et al (2015) stated that NIRF imaging, using contrast agents with fluorescent characteristics in the near-infrared (NIR: 700 to 900 nm) window, is considered to possess great potential for clinical practice in the future of minimally invasive surgery (MIS), given its capacity for intra-operative, real-time anatomical navigation, and identification. These researchers provided an overview of the literature concerning the current and potential future applications of fluorescence imaging in supporting anatomical guidance during MIS, and thereby guiding future research. A systematic literature search was performed in the PubMed and Embase.
databases. All identified articles were screened and checked for eligibility by 2 authors. In addition, literature was sought by screening references of eligible articles. After administration of a fluorescent dye (e.g., ICG), NIRF imaging can be helpful to improve the visualization of vital anatomical structures during MIS. Extra-hepatic bile ducts, arteries, ureters, sentinel lymph nodes, and lymph vessels have successfully been identified using NIRF imaging. A uniform approach regarding timing and route of dye administration has not yet been established. Optimization of both imaging systems and fluorescent dyes is needed to improve current shortcomings. New pre-clinical dyes are considered for optimization of NIRF imaging. The authors concluded that future implementation of new intra-operative optical methods, such as NIRF, could significantly contribute to intra-operative anatomy navigation and facilitate critical decision-making in MIS. Moreover, they stated that further research (i.e., large multi-center randomized controlled trials) is needed to establish the true value of this innovative optical imaging technique in standard clinical practice.

Lymphatic Imaging in Lymphangiomatosis/Klippel-Trenaunay Syndrome

Rasmussen et al (2015) stated that lymphangiomatosis is a rare disorder of the lymphatic system that can impact the dermis, soft tissue, bone, and viscera and can be characterized by lymphangiomas, swelling, and chylous discharge. Whether disordered lymphangiogenesis in lymphangiomatosis affects the function and anatomy of the entire systemic lymphatic circulation or is localized to specific sites is not fully known. These researchers reported the case of a 35-year old Caucasian female diagnosed with whole-body lymphangiomatosis at 2 months of age and who continued to present with progressive disease was imaged with NIRF lymphatic imaging. While the peripheral lymphatics in the extremities appeared largely normal compared to prior studies, these investigators observed tortuous lymphatic vessels, fluorescence drainage from the peripheral lymphatics into lymphangiomas, and extensive dermal lymphatics in the left thigh and inguinal regions where the subject had previously had surgical assaults, potentially indicating defective systemic lymphangiogenesis. The authors concluded that further research into anatomical and functional lymphatic changes associated with the progression and treatment of lymphangiomatosis could aid in understanding the pathophysiology of the disease as well as point to
Rasmussen and colleagues (2017) noted that the relationship between lymphatic and venous malformations in Klippel-Trenaunay syndrome is difficult to assess. These investigators described NIRF lymphatic imaging to assess the lymphatics of a subject with a large port-wine stain and right leg edema. Although lymphatic vessels in the medial, affected knee appeared dilated and perhaps tortuous, no definitive abnormal lymphatic pooling or propulsion was observed. The lymphatics in the affected limb were well defined but less numerous than in the contralateral limb, and active, contractile function was observed in all vessels. The authors concluded that NIRF lymphatic imaging enabled the clinical assessment of lymphatics in lympho-venous malformations. These preliminary findings need to be validated by well-designed studies.

Furthermore, an UpToDate review on "Klippel-Trenaunay syndrome: Clinical manifestations, diagnosis, and management" (Frieden and Chu, 2017) does not mention NIRF imaging as a management tool.

Mapping of Microvascular Circulation in Ischemic Diseases

Namikawa and colleagues (2015) noted that NIRF imaging has better tissue penetration, allowing for the effective rejection of excitation light and detection deep inside organs. Indocyanine green generates NIRF after illumination by an NIR ray, enabling real-time intra-operative visualization of superficial lymphatic channels and vessels transcutaneously. The HyperEye Medical System (HEMS) can simultaneously detect NIR rays under room light to provide color imaging, which enables visualization under bright light. Thus, NIRF imaging using ICG can provide for excellent diagnostic accuracy in detecting SLNs in cancer and microvascular circulation in various ischemic diseases, to assist surgeons with intra-operative decision-making. Including HEMS in this system could further improve the SLN mapping and intra-operative identification of blood supply in reconstructive organs and ischemic diseases, making it more attractive than conventional imaging. Moreover, the development of new laparoscopic imaging systems equipped with NIR will allow fluorescence-guided surgery in a minimally invasive setting. The
authors concluded that future directions, including the conjugation of NIR fluorophores to target specific cancer markers might be realistic technology with diagnostic and therapeutic benefits.

Mapping of Sentinel Lymph Nodes in Endometrial Cancer

In a pilot study, Plante and associates (2015) reported their initial experience with ICG for sentinel lymph node (SLN) mapping in cervical and endometrial cancer using a new endoscopic fluorescence imaging system. These researchers reviewed all patients who underwent primary surgery for early-stage endometrial and cervical carcinoma with SLN mapping using fluorescence imaging followed by pelvic lymphadenectomy from February to July 2014. Intra-cervical injection of ICG at 3 and 9 o'clock was performed in all cases; SLNs were ultra-staged on final pathology. Sensitivity and specificity values were calculated. A total of 50 patients were included in the study (42 endometrial and 8 cervical cancers). The median age was 62 (24 to 88) years and median BMI was 29 (19 to 56). The median SLN count was 3.1 (0 to 7) and median lymph node count was 15 (2 to 37). The overall and bilateral detection rate was 96 % (48/50) and 88 % (44/50). Positive SLNs were identified in 22 % of patients (11/50), including 8 isolated tumor cells (ITC), 2 micro-metastasis and 1 macro-metastasis. There was 1 side-specific false negative case. Sensitivity, specificity and NPV were 93.3 %, 100 % and 98.7 %, per side, respectively. Para-aortic node dissection was performed in 22 % of cases. Two had para-aortic node metastasis both in patients with positive pelvic SLN. There were no allergic reactions to the ICG. The authors concluded that based on their experience in this pilot study, NIRF imaging with ICG is an excellent and safe tracer modality for SLN mapping with a very high overall (96 %) and bilateral (88 %) detection rate. The findings of this pilot study need to be validated by well-deigned studies.

An UpToDate review on "Endometrial carcinoma: Pretreatment evaluation, staging, and surgical treatment" (Plaxe, 2015) states that "One of the most important prognostic factors for endometrial carcinoma is the presence of extrauterine disease, particularly pelvic and paraaortic lymph node metastases. The approach to lymph node assessment is controversial, particularly in women presumed to have early stage disease .... Sentinel lymph node biopsy for endometrial carcinoma is still
investigational. A meta-analysis of 26 studies including 1,101 sentinel node procedures found a sensitivity of 93% for the detection of lymph node metastases in women with endometrial carcinoma. According to the sentinel lymph node hypothesis, tumor cells migrate from a primary tumor and colonize one or a few lymph nodes (i.e., the sentinel lymph node) before involving other lymph nodes. Peritumoral injection of a dye or tracer permits identification of a sentinel lymph node in most patients, and its status accurately predicts the status of the remaining regional nodes. The site of injection of the tracer for endometrial carcinoma is controversial. Studies have evaluated cervical, subserosal, and hysteroscopically-guided endometrial injection. The meta-analysis of 26 studies described above found that pericervical injection was associated with a significantly increased rate of detecting any sentinel node and that hysteroscopic injection was associated with a significantly decreased detection rate”. This review does not mention near-infrared fluorescence imaging as a management tool.

Furthermore, National Comprehensive Cancer Network’s clinical practice guideline on “Endometrial carcinoma” (Version 2.2015) states that “The role of SLN mapping is currently being evaluated. No prospective randomized trials have been reported that evaluated this technique in endometrial cancer”.

Diagnosis of Rheumatoid Arthritis

Krohn and colleagues (2015) stated that near-infrared fluorescence optical imaging (FOI) is a novel imaging technology in the detection and evaluation of different arthritides. Fluorescence optical imaging was validated in comparison to magnetic resonance imaging (MRI), grey-scale ultrasonography (GSUS), and power Doppler ultrasonography (PDUS) in patients with early rheumatoid arthritis (RA). Hands of 31 patients with early RA were examined by FOI, MRI, and US. In each modality, synovitis of the wrist, metacarpophalangeal joints (MCP) 2-5, and proximal interphalangeal joints (PIP) 2-5 were scored on a 4-point scale (0 to 3). Sensitivity and specificity of FOI were analyzed in comparison to MRI and US as reference methods, differentiating between 3 phases of FOI enhancement (P1-P3). Intraclass correlation coefficients (ICC) were calculated to evaluate the agreement of FOI with MRI and US. A total of 279 joints (31 wrists, 124 MCP and 124 PIP joints) were evaluated. With
As the reference method, overall sensitivity/specificity of FOI was 0.81/0.00, 0.49/0.84, and 0.86/0.38 for wrist, MCP, and PIP joints, respectively. Under application of PDUS as reference, sensitivity was even higher, while specificity turned out to be low, except for MCP joints (0.88/0.15, 0.81/0.76, and 1.00/0.27, respectively). P2 appeared to be the most sensitive FOI phase, while P1 showed the highest specificity. The best agreement of FOI was shown for PDUS, especially with regard to MCP and PIP joints (ICC of 0.57 and 0.53, respectively), while correlation with MRI was slightly lower. The authors concluded that FOI remains an interesting diagnostic tool for patients with early RA, although this study revealed limitations concerning the detection of synovitis. They stated that further research is needed to evaluate its full diagnostic potential in rheumatic diseases.

Evaluation of Coronary Atherosclerosis

Verjans and associates (2016) examined if ICG-enhanced NIRF imaging can illuminate high-risk histologic plaque features of human carotid atherosclerosis, and in coronary atheroma of living swine, using intravascular NIRF-OCT imaging. A total of 8 patients were enrolled in the BRIGHT-CEA (Indocyanine Green Fluorescence Uptake in Human Carotid Artery Plaque) trial; 5 patients were injected intravenously with ICG 99 ± 25 mins before clinically indicated carotid endarterectomy; 3 saline-injected endarterectomy patients served as control subjects. Excised plaques underwent analysis by intravascular NIRF-OCT, reflectance imaging, microscopy, and histopathology. Next, following ICG intravenous injection, in-vivo intracoronary NIRF-OCT and intravascular ultrasound imaged 3 atheroma-bearing coronary arteries of a diabetic, cholesterol-fed swine. Indocyanine green was well-tolerated; no adverse clinical events occurred up to 30 days post-injection. Multi-modal NIRF imaging including intravascular NIRF-OCT revealed that ICG accumulated in all endarterectomy specimens. Plaques from saline-injected control patients exhibited minimal NIRF signal. In the swine experiment, intracoronary NIRF-OCT identified ICG uptake in all intravascular ultrasound-identified plaques in-vivo. On detailed microscopic evaluation, ICG localized to plaque areas exhibiting impaired endothelial integrity, including disrupted fibrous caps, and within areas of neovascularization. Within human plaque areas of endothelial abnormality, ICG was spatially related to localized zones of plaque
macrophages and lipid, and, notably, intra-plaque hemorrhage. The authors concluded that the findings of this study demonstrated that ICG targets human plaques exhibiting endothelial abnormalities and provided new insights into its targeting mechanisms in clinical and experimental atheroma. They stated that intra-coronary NIRF-OCT of ICG may offer a novel, clinically translatable approach to image pathobiological aspects of coronary atherosclerosis.

Osborn and colleagues (2017) stated that metabolic and molecular imaging continues to advance the understanding of vascular disease pathophysiology. At present, 18F-FDG PET imaging is the most widely used clinical tool for metabolic and molecular imaging of atherosclerosis. However, novel nuclear tracers and intravascular optical NIRF imaging catheters are emerging to assess new biologic targets in-vivo and in coronary arteries. This review highlighted current metabolic and molecular imaging clinical and near-clinical applications within atherosclerosis and venous thrombo-embolism (VTE), and examined the potential for metabolic and molecular imaging to affect patient-level risk prediction and disease treatment. The authors stated that intravascular NIRF molecular imaging showed promise for high-resolution molecular imaging and can be integrated with intravascular US or OCT, strengthening the ability to provide comprehensive molecular-structural imaging of atherosclerosis and stent biology. However, NIRF imaging is in its infancy for clinical translation and will require clinical outcome studies to determine its value. Given its invasive requirement, NIRF imaging will likely be used to further stratify patients already undergoing percutaneous coronary intervention (PCI) for acute coronary syndrome (ACS) or stable angina.

Assessment of Liver Function

Narasaki and colleagues (2017) stated that post-operative liver failure is a serious complication after major hepatectomy, and peri-operative prediction of its incidence using current technology is still very difficult. Near-infrared fluorescence imaging allows quantitative assessment of the fluorescent signal from ICG in regions of interest on the liver surface. This method might offer a new promising modality for evaluating regional liver reserve. However, data are lacking regarding the relationship between liver function and fluorescent signals on the liver surface after
intravenous ICG injection. This study was conducted to obtain the data necessary to apply NIR fluorescence imaging as a modality for measuring liver function. This study included 16 patients who underwent open hepato-pancreatobiliary surgery between March 2011 and March 2012. After laparotomy, ICG was injected intravenously at 2.5 mg/L of liver volume, then the fluorescence intensity (FI) and signal-to-background ratio (SBR) in the lateral segment of the liver were assessed for 15 minutes. Intra-operative blood samples were also obtained to measure the plasma clearance rate of ICG (ICGK). Correlations between ICGK, liver volume, and SBR, as well as between ICGK, liver volume, and rate of change of FI were analyzed. The experimental procedure was performed in all 16 patients. The FI of the liver increased rapidly after ICG injection, then became more gradual, reaching a near-plateau after 15 minutes. A significant correlation was seen between ICGK and the rate of change of FI up to 15 minutes ($|rS| = 0.5725$, $p < 0.05$). The authors concluded that this was the first report to show a relationship between liver function and fluorescent signals on the liver surface after intravenous ICG injection. They stated that intra-operative NIR fluorescence imaging with ICG may be useful as a new method for assessing liver function.

Guidance of Surgery for Intracranial Meningioma

Lee and colleagues (2018) stated that meningiomas are the most common primary tumor of the central nervous system. Complete resection can be curative, but intra-operative identification of dural tails and tumor remnants poses a clinical challenge. Given data from pre-clinical studies and previous clinical trials, the authors proposed a novel method of localizing tumor tissue and identifying residual disease at the margins via pre-operative systemic injection of a NIR fluorescent contrast dye. This technique, what the authors call "second-window ICG (SWIG)", relies on the visualization of ICG approximately 24 hours after intravenous injection. A total of 18 patients were prospectively identified and received 5 mg/kg of SWIG the day prior to surgery. An NIR camera was used to localize the tumor prior to resection and to inspect the margins following standard resection. The SBR of the tumor to the normal brain parenchyma was measured in triplicate. Gross tumor and margin specimens were qualitatively reported with respect to fluorescence. Neuropathological diagnosis served as the reference gold
standard to calculate the sensitivity and specificity of the imaging technique; 18 patients harbored 15 World Health Organization (WHO) Grade I and 3 WHO Grade II meningiomas. Near-infrared visualization during surgery ranged from 18 to 28 hours (mean of 23 hours) following SWIG infusion; 14 of the 18 tumors demonstrated a markedly elevated SBR of $5.6 \pm 1.7$ as compared with adjacent brain parenchyma; 4 of the 18 patients showed an inverse pattern of NIR signal (i.e., stronger in the adjacent normal brain than in the tumor ($SBR 0.31 \pm 0.1$)). The best predictor of inversion was time from injection, as the patients who were imaged earlier were more likely to demonstrate an appropriate SBR. The SWIG technique demonstrated a sensitivity of 96.4 %, specificity of 38.9 %, positive predictive value (PPV) of 71.1 %, and a negative predictive value (NPV) of 87.5 % for tumor. The authors concluded that systemic injection of NIR SWIG the day before surgery can be used to visualize meningiomas intra-operatively. They noted that intra-operative NIR imaging provided higher sensitivity in identifying meningiomas than the unassisted eye. In this study, 14 of the 18 patients with meningioma demonstrated a strong SBR compared with adjacent brain. These researchers stated that in the future, reducing the time interval from dye injection to intra-operative imaging may improve fluorescence at the margins, although this approach requires further investigation.

Intra-Operative Imaging of Lung Cancer / Lung Metastases/Mesothelioma

Keating and associates (2017a) stated that complete tumor resection is the most important predictor of patient survival with non-small cell lung cancer (NSCLC). Methods for intra-operative margin assessment after lung cancer excision are lacking. These researchers evaluated NIR intra-operative imaging with a folate-targeted molecular contrast agent (OTL0038) for the localization of primary lung adenocarcinomas, lymph node sampling, and margin assessment. A total of 10 dogs with lung cancer underwent either video-assisted thoracoscopic surgery or open thoracotomy and tumor excision after an intravenous injection of OTL0038. Lungs were imaged with an NIR imaging device both in-vivo and ex-vivo. The wound bed was re-imaged for retained fluorescence suspicious for positive tumor margins. The tumor SBR was measured in all cases. Next, 3 human patients were enrolled in a proof-of-principle study. Tumor fluorescence was measured both in-situ and ex-vivo. All
canine tumors fluoresced in-situ (mean Fluoptics SBR, 5.2 [range of 2.7 to 8.1]; mean Karl Storz SBR 1.9 [range of 1.4 to 2.6]). In addition, the fluorescence was consistent with tumor margins on pathology; 3 positive lymph nodes were discovered with NIR imaging. Also, a positive retained tumor margin was discovered upon NIR imaging of the wound bed.

Human pulmonary adenocarcinomas were also fluorescent both in situ and ex-vivo (mean SBR, greater than 2.0). The authors concluded that NIR imaging can identify lung cancer in a large-animal model. In addition, NIR imaging can discriminate lymph nodes harboring cancer cells and also bring attention to a positive tumor margin. In humans, pulmonary adenocarcinomas fluoresce after the injection of the targeted contrast agent.

Keating and colleagues (2017b) noted that pulmonary metastasectomy is widely accepted for many tumor types because it may prolong survival and potentially cure some patients. However, intra-operative localization of pulmonary metastases can be technically challenging. These researchers proposed that intra-operative NIR molecular imaging can be used as an adjunct during disease localization. They inoculated 50 C57BL/6 mice with Lewis lung carcinoma (LLC) flank tumors. After flank tumor growth, mice were injected through the tail vein with ICG before operation, and intra-operative imaging was used to detect pulmonary metastases. On the basis of these experiments, these investigators enrolled 8 patients undergoing pulmonary metastasectomy into a pilot and feasibility clinical trial. Each patient received intravenous ICG 1 day before operation, followed by wedge or segmental resection. Samples were imaged on the back table with an NIR camera to confirm disease presence and margins. All murine and human tumors and margins were confirmed by pathologic examination. Mice had an average of 4 ± 2 metastatic tumors on both lungs, with an average size of 5.1 mm (interquartile range [IQR] 2.2 mm to 7.6 mm). Overall, 200 of 211 (95 %) metastatic deposits were markedly fluorescent, with a mean tumor-to-background ratio (TBR) of 3.4 (IQR 3.1 to 4.1). The remaining tumors had a TBR below 1.5. In the human study, intra-operative NIR imaging identified 6 of the 8 pre-operatively localized lesions. Intra-operative back table NIR imaging identified all metastatic lesions, which were confirmed by pathologic examination. The average tumor size was 1.75 ± 1.4 cm, and the mean ex-vivo TBR was 3.3 (IQR 3.1 to 3.7). Pathologic examination demonstrated melanoma (n = 4), osteogenic sarcoma (n =
2), renal cell carcinoma (n = 2), chondrosarcoma (n = 1), leiomyosarcoma (n = 1), and colorectal carcinoma (n = 1). The authors concluded that systemic ICG identified subcentimeter tumor metastases to the lung in murine models, and this work provided proof of principle in humans. They stated that future research is focused on improving depth of penetration into the lung parenchyma.


Kennedy and colleagues (2017) noted that although difficult to achieve, complete resection of malignant pleural mesothelioma is paramount to improving patient survival. Surgeons have traditionally been limited to using visual inspection and manual palpation to locate and remove cancerous tissue. However, intra-operative molecular imaging (IMI) is a promising new technology in surgery. Molecular imaging utilizes a fluorescent tracer that selectively accumulates in cancer cells. An imaging device is then used to detect and augment the fluorescent signal emitted from the fluorescent cancer cells. Investigators had demonstrated that molecular imaging with either ICG or a folate receptor alpha (FRα) targeted fluorophore can accurately identify a number of intra-thoracic malignancies. Early studies of intra-operative imaging have suggested its efficacy for malignant pleural mesothelioma. In a murine model of mesothelioma, intra-operative imaging was found to have sensitivity of 87% and specificity of 83%. In a pilot human study, 8 patients with biopsy-proven epithelial malignant pleural mesothelioma were administered 5 mg/kg of intravenous ICG injection 24 hours prior to resection. The following day, a NIR imaging device was used to detect tumor fluorescence intra-operatively. After what was believed to be complete tumor excision, the wound bed was re-imaged for residual fluorescence indicative of retained tumor. When residual fluorescence was detected, additional tissue was resected, if feasible, and specimens were sent for pathologic correlation. In all cases, intra-operative fluorescence localized to mesothelioma deposits which were confirmed on final pathology. Following resection, fluorescence was confirmed ex-vivo with a mean TBR of 3.2 (IQR: 2.9 to 3.4). The authors concluded
that it is hoped that this technology will improve outcomes for mesothelioma patients by allowing for a more complete oncologic resection.

Localization of Brain Metastases

Lee and colleagues (2017) noted that approximately 100,000 brain metastases are diagnosed annually in the United States. These researchers have pioneered a novel technique, ”SWIG”, which allows for real-time intra-operative visualization of brain metastasis through normal brain parenchyma and intact dura. A total of 13 patients with intra-parenchymal brain metastases were administered ICG at 5mg/kg the day prior to surgery. A NIR capable camera was used intra-operatively to identify the tumor and to inspect surgical margins. Neuropathology was used to assess the accuracy and precision of the fluorescent dye for identifying tumor. ICG was infused at 24.7 ± 3.45 hours before visualization. All 13 metastases fluoresced with an average SBR of 6.62. The SBR with the dura intact was 67.2 % of the mean SBR once the dura was removed. The NIR signal could be visualized through normal brain parenchyma up to 7 mm. For the 39 total specimens, the mean SBR for tumor specimens (n = 28) was 6.9 whereas the SBR for non-tumor specimens (n = 11) was 3.7. The sensitivity, specificity, PPV and NPV of NIR imaging for tumor was 96.4 %, 27.3 %, 77.1 %, and 75.0 %, respectively. The authors concluded that SWIG relied on the passive accumulation of dye in abnormal tumor tissue via the enhanced permeability and retention (EPR) effect. It provided strong NIR SBR, which can be utilized to localize tumors prior to dural opening. They stated that the use of SWIG for margin assessment remains limited by its lack of specificity (high false-positive rate); however, ongoing improvements in imaging parameters show great potential to reduce false-positives.

Delineation of the Ureters during Laparoscopy

Al-Taher and colleagues (2018) stated that iatrogenic ureteric injury remains a risk in laparoscopic pelvic procedures; NIRF imaging is a promising new technique for enhanced intra-operative visualization of anatomical structures that could improve the safety of laparoscopic surgery. A new dye, IRDye 800-BK, has been developed for intra-
operative visualization of the ureters using NIRF. The present study was a first evaluation of the performance of IRDye 800-BK for ureteric imaging during NIRF laparoscopy. This study consisted of 3 parts: real-time in-vivo NIRF imaging using IRDye 800-BK in pigs during laparoscopic surgery, ex-vivo NIRF imaging of freshly explanted pig ureters and ex-vivo NIRF imaging of explanted human ureters. In all animals, both left and right ureters were visualized throughout the laparoscopic procedure for 120 mins, with the best results at a dose of 0.15 mg dye per kg bodyweight; NIRF imaging was successful in all human and porcine ureters studied, with a range of dye concentrations. The authors concluded that this novel dye enabled visualization of the ureters; NIRF imaging with this dye appeared a valuable addition to conventional white light laparoscopy. Moreover, they stated that further studies are needed to determine if it can become a worthwhile addition to improve clinical practice.

The authors stated that a drawback of the ex-vivo experiments is that 2 influences were studied at the same time: dye concentration and wall thickness. Ideally, different concentrations of dye should be tested in the same ureters, and the same concentration in different ureters. The first of these types of experiment was not feasible, because the fluorescent signal was retained in the ureter wall. Such an experiment could therefore be performed only using artificial material. The second experiment has not yet been undertaken. These researchers noted that despite the promising results, the present findings must be interpreted with caution. Owing to the limited availability of pigs and ureters, it was not possible to study enough ureters for solid statistical conclusions to be drawn. Another drawback was that concentrations of dye in the urine were not measured. This required availability of the structural formula of the dye and a method for such measurement. These were not available to the authors in this early phase of development and application of the dye. These investigators also stated that it was disappointing in the ex-vivo study that even the smallest layer of fat covering the ureter prevented a decent signal from being obtained. It is known that penetration of the NIRF signal is limited to approximately 10 mm; NIRF imaging with a stronger dye or with optimized equipment was hoped to enhance such penetration. The present experiment showed that the signal may be improved with use of a better dye, but that this did not affect depth penetration per se. In the in-vivo study, nevertheless, the
porcine ureters could be identified clearly without any manipulation or dissection of the overlying tissues. This suggested that IRDye 800-BK has the potential to detect the ureter in spite of the overlying peritoneum. They stated that future studies should evaluate the maximum depth of penetration of the NIRF signal and the clinical value of this dye in human subjects.

Detection and Resection of Colorectal Neoplasia

Jones and colleagues (2018) used a tumor-targeting, NIRF peptide to evaluate early detection and to guide surgical removal of polyps in a genetically engineered rat model of spontaneous colorectal cancer (CRC). This peptide, LS301, was conjugated to Cy7.5 and applied topically to the colon of adenoma-bearing Pirc rats; 10 minutes after administration, rats underwent targeted NIR laser colonoscopy. Rats were also evaluated by white light colonoscopy and narrow-band imaging, for comparison to the NIR technique. Unlike white light and narrow-band colonoscopy, NIR imaging detected unexpected flat lesions in young Pirc rats; NIR imaging was also used to assess resection margins after electro-cauterization of polyps. Tumor margins remained negative at 5 weeks post-surgery, demonstrating successful polypectomy. The authors concluded that the findings of this study showed that NIR-targeted colonoscopy is an attractive strategy to improve screening for and resection of colorectal neoplasia. These researchers stated that a drawback of this study was that they employed topical application of Cy7.5-LS301 in the rat model. They chose this route of administration to be consistent with the technique Charanya et al used for NIR colonoscopy of tumor-bearing mice. However, topical application of an NIR peptide is not clinically practical, due to the large quantity of the imaging agent that would be needed. These investigators have now established an optimal intravenous injected dose in Pirc rats and will use this method of administration for future studies. Moreover, these researchers stated that they have not yet tested their ability to detect recurrent disease in the rat model; and they plan to evaluate the ability of the peptide to do so in longer term longitudinal studies.

Evaluation of Soft Tissue Viability to Guide Debridement in Trauma Surgery
In a case-report, Pruimboom and co-workers (2018) presented the use of NIRF imaging using ICG and its potential for the evaluation of soft tissue viability in a traumatic case. The authors stated that standard implementation of this novel imaging modality might decrease the number of surgical debridement procedures in complex traumatic wounds. Moreover, they stated that further clinical studies are needed to assess the appropriate timing of performing NIRF imaging and to obtain generalized quantification methods of NIRF images, hence determining a precise cut-off point. Consequently, the possible advantages of NIRF imaging in terms of cost-effectiveness in trauma surgery need to be determined.

Imaging of Matrix Metalloproteinase 2 Activity as a Biomarker of Vascular Remodeling in Arterio-Venous Fistulae

Nadolski and colleagues (2018) attempted to establish the capability of NIRF imaging for the detection of matrix metalloproteinase 2 (MMP-2) activity as a biomarker of vascular remodeling (VR) in arterio-venous fistulae (AVFs) in-vivo; AVFs were created in the right groins of Wistar rats (n = 10), and sham procedures were performed in the contralateral groins. Fistulography via a left common carotid artery approach confirmed stenosis (greater than 50 %) in a subset of animals (n = 5) 4 weeks after AVF creation. After administration of MMP-2-activated NIRF probe, NIR imaging was performed in-vivo and ex-vivo of both the AVF and the sham-treated vessels to measure radiant efficiency of MMP-2-activated NIRF signal over background. Histologic analyses of AVF and sham-treated vessels were performed to measure VR defined as inward growth of the vessel caused by intimal thickening. AVFs demonstrated a significantly higher percentage increase in radiant efficiency over background compared with sham vessels (45.5 ± 56 % versus 16.1 ± 17.8 %; p = 0.008). VR in AVFs was associated with increased thickness of neointima staining positively for MMP-2 (161.8 ± 45.5 μm versus 73.2 ± 36.7 μm; p = 0.01). A significant correlation was observed between MMP-2 activity as measured by relative increase in radiant efficiency for AVFs and thickness of neointima staining positively for MMP-2 (p = 0.039). The authors concluded that NIRF imaging could detect increased MMP activity in remodeled AVFs compared with contralateral sham vessels; MMP-2-activated NIRF signal correlated with the severity of
intimal thickening. They stated that these findings suggested NIRF imaging of MMP-2 may be used as a biomarker of the vascular remodeling underlying stenosis.

Intra-Operative Detection of Hepatocellular Carcinoma and Needle Tract Implantation and Peritoneal Seeding after Radiofrequency Ablation

Nakamura and associates (2018) noted that radio-frequency ablation (RFA) for hepatocellular carcinoma (HCC) is already fully established worldwide. Needle tract implantation and peritoneal seeding occasionally occur by RFA, and the prognosis of these cases is thought to be poor. In a single-case study, intra-operative real-time NIRF system by (ICG incidentally detected both needle tract implantation and peritoneal seeding. As the utility of this system for identification of implanted and disseminated lesions after RFA for HCC has not been widely reported, the investigators reported a case of successful detection by real-time ICG-NIRF imaging and subsequent resection. A 76-year old man originally underwent medial sectionectomy for HCC in 2009. When repeated intra-hepatic recurrence occurred, he underwent RFA and transcatheter arterial chemo-embolization (TACE) for recurrent HCC twice at segment III and once at segment IV. In 2013, the second hepatectomy for recurrent HCC at segment VIII was performed. In 2016, he had recurrent HCC at segment III around a previous RFA and TACE scar; therefore, left lateral sectionectomy was planned. ICG-NIRF system was used to observe a main intra-hepatic metastasis at segment III and to search for other tumors in the remnant liver. Although there was no signal on the surface of the remnant liver, tiny signals were observed in the abdominal wall and greater omentum. These tumors were on the needle tract of the previous RFA; both lesions, therefore, were resected. These tumors were pathologically proven to be HCC metastases. The patient has had no recurrence 14 months after the last hepatectomy. The authors concluded that ICG-NIRF system might be helpful in the detection of not only intra-hepatic lesions but also needle tract implantations or peritoneal seeding. Moreover, they stated that RFA should be avoided in patients with high risk of needle tract implantation and peritoneal seeding. These preliminary findings need to be validated by well-designed studies.
The authors stated that ICG-NIRF system has some drawbacks. The system is restricted to detection of fluorescence for tumors 5 to 10 mm from the liver surface. There were also false-positive results for liver cysts and dysplastic tumors in severe liver cirrhosis. They stated that this system might be helpful in the detection of needle tract implantations or peritoneal seeding.

Intra-Operative Detection of Pancreatic Cancer and Metastases

Hoogstins and colleagues (2018) stated that NIRF is a promising novel imaging technique that can aid in intra-operative demarcation of pancreatic cancer (PDAC) and thus increase radical resection rates. In a phase-I clinical trial, these investigators evaluated the effectiveness SGM-101, a novel, fluorescent-labeled anti-carcinoembryonic antigen (CEA) antibody. The trial examined the tolerability and feasibility of intra-operative fluorescence tumor imaging using SGM-101 in patients undergoing a surgical exploration for PDAC. At least 48 hours before undergoing surgery for PDAC, 12 patients were injected intravenously with 5, 7.5, or 10 mg of SGM-101. Tolerability assessments were performed at regular intervals after dosing. The surgical field was imaged using the Quest NIR imaging system. Concordance between fluorescence and tumor presence on histopathology was studied. In this study, SGM-101 specifically accumulated in CEA-expressing primary tumors and peritoneal and liver metastases, allowing real-time intra-operative fluorescence imaging. The mean TBR was 1.6 for primary tumors and 1.7 for metastatic lesions. One false-positive lesion was detected (CEA-expressing intra-ductal papillary mucinous neoplasm); false-negativity was observed twice as a consequence of overlying blood or tissue that blocked the fluorescent signal. The authors concluded that the use of a fluorescent-labeled anti-CEA antibody was safe and feasible for the intra-operative detection of both primary PDAC and metastases. They stated that more prospective research is needed to determine the impact of this technique on clinical decision making and overall survival (OS).

Hybrid Near Infrared Fluorescence-Intravascular Ultrasound (NIRF-IVUS) System
Bozhko and colleagues (2017) (i) assessed a novel hybrid NIRF-intravascular ultrasound (NIRF-IVUS) system in coronary and peripheral swine arteries in-vivo; (ii) evaluated simultaneous quantitative biological and morphological aspects of arterial disease. Two 9-F/15-MHz peripheral and 4.5-F/40-MHz coronary NIRF-IVUS catheters were engineered to enable accurate co-registration of biological and morphological readings simultaneously in-vivo. A correction algorithm utilizing IVUS information was developed to account for the distance-related fluorescence attenuation due to through-blood imaging. Corrected NIRF (cNIRF)-IVUS was applied for in-vivo imaging of angioplasty-induced vascular injury in swine peripheral arteries and experimental fibrin deposition on coronary artery stents, and of atheroma in a rabbit aorta, revealing feasibility to intravascularly assay plaque structure and inflammation. The addition of ICG-enhanced NIRF assessment improved the detection of angioplasty-induced endothelial damage compared to stand-alone IVUS. In addition, NIRF detection of coronary stent fibrin by in-vivo cNIRF-IVUS imaging illuminated stent pathobiology that was concealed on stand-alone IVUS. Fluorescence reflectance imaging and microscopy of resected tissues corroborated with the in-vivo findings. The authors concluded that integrated cNIRF-IVUS enabled simultaneous co-registered through-blood imaging of disease related morphological and biological alterations in coronary and peripheral arteries in-vivo. Clinical translation of cNIRF-IVUS may significantly enhance knowledge of arterial pathobiology, leading to improvements in clinical diagnosis and prognosis, and aid to guide the development of new therapeutic approaches for arterial diseases.

Diagnosis of Peripheral Artery Disease

van den Hoven and colleagues (2019) noted that in the diagnosis of peripheral artery disease (PAD), the ankle-brachial index (ABI) plays an important role. However, results of the ABI are unreliable in patients with severe media sclerosis. Near-infrared (NIR) fluorescence imaging using ICG can provide information regarding tissue perfusion and has already been studied in oncologic, reconstructive, and cardiac surgery. For patients with PAD, this technique might give insight into skin perfusion and thereby guide treatment. These researchers carried out a systematic review of the literature on the use of NIR fluorescence imaging in patients with PAD. PubMed, Medline, Embase, and Cochrane were searched for
articles and abstracts on the application of NIR fluorescence imaging using ICG as fluorescent dye in patients with PAD. The search strategy combined the terms "fluorescence", "ICG", or synonyms and "peripheral artery disease" or synonyms. The extracted data included fluorescence parameters and test characteristics for diagnosis of PAD. A total of 23 articles were found eligible for this review using 18 different parameters for evaluation of the fluorescence signal intensity. NIR fluorescence imaging was used for 4 main indications: diagnosis, quality control in revascularization, guidance in amputation surgery, and visualization of vascular structures. For the diagnosis of PAD, NIR fluorescence imaging yielded a sensitivity ranging from 67% to 100% and a specificity varying between 72% and 100%. Significant increases in multiple fluorescence parameters were found in comparing patients before and after revascularization. The authors concluded that NIR fluorescence imaging could be used for several indications in patients with PAD; NIR fluorescence imaging appeared promising in diagnosis of PAD and guidance of surgeons in treatment, especially in patients in whom current diagnostic methods are not applicable. These researchers stated that further standardization is needed to reliably use this modality in patients with PAD.

Guidance for Sentinel Lymph Node Mapping in Gastric Cancer

Skubleny and associates (2018) noted that sentinel node navigation surgery (SNNS) for gastric cancer (GC) using infrared visualization of ICG is intriguing because it may limit operative morbidity. These investigators performed a meta-analysis on the diagnostic utility of ICG and infrared electronic endoscopy (IREE) or NIR fluorescent imaging (NIFI) for SNNS exclusively in GC. They carried out a search of electronic databases Medline, Embase, SCOPUS, Web of Science, and the Cochrane Library using search terms "gastric/stomach" and "tumor/carcinoma/cancer/neoplasm/adenocarcinoma/malignancy" and "indocyanine green"; search was completed in May 2017. Articles were selected by 2 independent reviewers based on the following major inclusion criteria: diagnostic accuracy study design; ICG was injected at tumor site; IREE or NIFI was used for intra-operative visualization. A total of 327 titles or abstracts were screened. The quality of included studies was assessed using the Quality Assessment of Diagnostic Accuracy Studies-2; 10 full text studies were selected. A total of 643 patients were
identified with the majority of patients possessing T1 tumors (79.8%). Pooled identification rate, diagnostic odds ratio (DOR), sensitivity (Sen), and specificity (Spe) were 0.99 (0.97 to 1.0), 380.0 (68.71 to 2101), 0.87 (0.80 to 0.93), and 1.00 (0.99 to 1.00), respectively. The summary receiver operator characteristic (ROC) for ICG + IREE/NIFI demonstrated a test accuracy of 98.3%. Subgroup analysis found improved test performance for studies with low-risk QUADAS-2 scores, studies published after 2010 and submucosal ICG injection. IREE had improved DOR, Sen, and identification rate compared to NIFI. Heterogeneity among studies ranged from low (I² less than 25%) to high (I² greater than 75%). The authors concluded that they found encouraging results regarding the accuracy, DOR, and Spe of the test. The Sen was not optimal but may be improved by a strict protocol to augment the technique. These researchers stated that given the number and heterogeneity of studies, these findings must be viewed with caution.

In a meta-analysis, He and colleagues (2018) examined the diagnostic value of NIR or fluorescent ICG guided sentinel lymph node (SLN) mapping in GC. Clinical studies were retrieved from the electronic database PubMed, Embase, Medline, Web of science, and the Cochrane Library. Quality assessment was conducted by an adapted checklist of QUADAS-2. A bivariate mixed-effects model was used to pool the data. Evaluation of articles quality, analysis for publication bias, summary ROC (SROC) curves, and meta-regression were also performed. Subgroup analysis was used to explain the heterogeneities. A total of 13 clinical studies (971 patients) were included. The NIR or FI involved IREE, infrared ray laparoscopic system (IRLS), and FI system. Significant evidence of heterogeneity was found for Sen and Spe: I² = 91.1% and I² = 98.2%, respectively. The pooled SLN Sen, Spe, positive likelihood ratio (PLR), negative likelihood ratio (NLR), and DOR were 0.94 (95% CI: 0.80 to 0.99), 1.00 (95% CI: 0.60 to 1.00), 34.0 (95% CI: 9.25 to 125.29), 0.06 (95% CI: 0.02 to 0.22), and 252.50 (95% CI: 94.93 to 671.61), respectively. Area under curve (AUC) of SROC curve was 1.00 (95% CI: 0.99 to 1.00), and the summary operating point (cut-off value) was SENS = 0.94 (95% CI: 0.80 to 0.99) and SPEC = 1.00 (95% CI: 0.60 to 1.00). Subgroup analysis showed that NIR imaging, imaging performed 20 mins after intra-operative injection, pre-operative injection (especially for FI imaging), stained with immunohistochemistry (IHC) (+hematoxylin-eosin [HE]), cT1 stage, submucosa injection (especially for cT1), mean number
of SLN greater than or equal to 5, study size greater than 26 were associated with higher SLN sensitivity. In terms of ICG concentration, diluted ICG concentration that 0.5 mg/ml (compared with 5 mg/ml) in NIR imaging and 0.05 mg/ml (compared with 0.5 mg/ml) in FI system showed higher sensitivities. However, the differences in tumor diameter (less than or equal to 30 mm versus greater than 30 mm), gastrectomy methods (opening versus laparoscopy), lymphadenectomy methods (LBD versus pick-up), and publication year (in or after 2010 versus before 2010) did not achieve statistical significance. The authors concluded that ICG combined with NIR or FI guided SLN mapping was technically feasible for GC. Based on the small sample size evidence, the IREE and IRLS devices may have higher sensitivity than FI in current clinical studies; and there may be an excessive ICG concentration used for current SLN mapping in GC. Moreover, these researchers stated that well-designed further studies with large sample size are needed to confirm the best procedure and suitable criteria.

Fluorescence Sentinel Lymph Node Mapping for Colorectal Cancer

Picchetto and associates (2020) noted that sentinel lymph node (SLN) mapping using NIRF imaging is a recent technique to improve nodal staging in several tumors. The presence of colo-rectal cancer (CRC) micro-metastases has recently been defined as N1 disease and no longer as N1mi, determining the need for adjuvant chemotherapy. In CRC, the reported rate of SLN micro-metastases detected by ultra-staging techniques is as high as 30 %. In a prospective study, these researchers presented the preliminary results of the sensitivity analysis of NIRF imaging for ex-vivo SLN mapping and the research of micro-metastases in CRC, in patients with node-negative disease (NND). On the specimen of 22 CRC patients, 1-ml of ICG (5 mg/ml) was injected submucosally around the tumor to identify SLNs. NND SLNs were further investigated with ultra-staging techniques. A total of 363 lymph nodes were retrieved (59 SLNs; mean per case: 2.7). The detection, sensitivity and false-negative rate were 100 %, 100 % and 0 % respectively. Ultra-staging investigations showed no micro-metastases in the NND SLNs. The authors concluded that ex-vivo SLN fluorescence-based detection in CRC was confirmed to be easy to perform and reliable. In this preliminary report of an ongoing study, the SLN assay was congruent with the nodal status, as confirmed by histological investigations.
Intra-Operative Near-Infrared Fluorescence Imaging of Extra-Hepatic Bile Ducts for Assessment of Liver Function

Yanagi and co-workers (2019) noted that ICG fluorescence imaging is a promising tool for intra-operative decision-making. These researchers examined the use of near-infrared fluorescence cholangiography (NIRF-C) with ICG in primary surgery for biliary atresia (BA). They carried out NIRF-C with ICG in 10 BA patients and observed the fluorescence of their hilar micro-bile ducts and hilar exudate in order to evaluate the appropriate level at which to dissect the hilar fibrous corn. These investigators compared the jaundice outcome of 10 patients using NIRF-C (Group A) to that of 35 historical patients in whom NIRF-C had not been used (Group B). The mean age of patients was 74.8 days. The classification of BA was type I in 2 cases and type-III in 8 cases; NIR-FC visualized the hilar micro-bile ducts, and the incidence of positive fluorescence was 80%. The ratio of post-operative normalization of hyperbilirubinemia in Group A was significantly higher than that in Group B (1.0 versus 0.65, p < 0.05). The authors concluded that NIRF-C provided important objectifiable information regarding the biliary structures in surgery of BA. These researchers stated that although the number of cases was small (n = 10), these findings suggested that NIRF-C may be useful for improving the outcome of primary surgery for BA.

Wu and associates (2020) stated that biliary tract injury remains the most dreaded complication during laparoscopic cholecystectomy. New intraoperative guidance technologies, including NIRF cholangiography with ICG, are under rigorous evaluation. Previous studies had revealed the limitations of traditional NIR light (NIR-I, 700 to 900 nm) in visualizing the biliary tract structures in specific clinical situations. These researchers examined the feasibility of performing the extra-hepatic cholangiography in the second NIR window (NIR-II, 900 to 1,700 nm) and compared it to the conventional NIR-I imaging. The absorption and emission spectra, as well as fluorescence intensity and photostability of ICG-bile solution in the NIR-II window were recorded and measured. In-vitro intralipid phantom imaging was carried out to examine tissue
penetrating depth in NIR-I and NIR-II window. Different clinical scenarios were modeled by broadening the penetration distance or generating bile duct injuries, and bile duct visualization and lesion site diagnosis in the NIR-II window were evaluated and compared with NIR-I imaging. The fluorescence spectrum of ICG-bile solution extended well into the NIR-II region, exhibiting intense emission value and excellent photo-stability sufficient for NIR-II biliary tract imaging. Extra-hepatic cholangiography using ICG in the NIR-II window reduced background signal and enhanced penetration depth, providing more structural information and improved visualization of the bile duct or lesion location in simulated clinical scenarios, out-performing the NIR-I window imaging. The authors concluded that the commercially available and clinically approved agent ICG exhibited remarkable NIR-II emission when excreted into bile and could be an excellent fluorophore for real-time NIR-II bile duct imaging.

Fluorescence cholangiography in the NIR-II window allowed adequate visualization of biliary tract structures with increased penetration depth and high resolution, and might be considered as a valid option for safe cholecystectomy in case of inflammation or obesity, surpassing the performance of the NIR-I window. By switching the detection of traditional silicon-based cameras to emerging indium gallium arsenide-based cameras could promisingly improve the fluorescence surgical navigation system and ensure safe biliary operation, accelerating the clinical translation of NIR-II imaging technology.

In a retrospective study, Wang et al (2020) examined the effect of NIRF cholangiography (NIRF-C) in laparoscopic cholecystectomy. Consecutive patients who underwent NIRF-C-assisted laparoscopic cholecystectomy (n = 34) or conventional laparoscopic cholecystectomy (n = 36) were enrolled in this trial. Identification of biliary structures, the operation time, intra-operative blood loss, and post-operative complications were analyzed. Laparoscopic cholecystectomy was completed in all patients without conversion to laparotomy. The median operation time and intra-operative blood loss were not significantly different between the 2 groups. No intra-operative injuries or post-operative complications occurred in either group. In the NIRF-C group, the visualization rate of the cystic duct (CD), common bile duct (CBD), and common hepatic duct (CHD) before dissection was 91 %, 79 %, and 53 %, respectively. The success rate of cholangiography was 100 % in the NIRF-C group. NIRF-C was more effective for visualizing biliary structures in patients with a BMI of less
than 25 than greater than 25 kg/m2. The authors concluded that NIRF-C was a safe and effective technique that allowed real-time identification of the biliary anatomy during laparoscopic cholecystectomy; NIRF-C aided in improving the efficiency of dissection.

These researchers stated that a disadvantage of NIRF-C was that its tissue penetration ability was limited to 5 to 10 mm. In obese patients, Calot’s triangle is often covered with a thick layer of fat, limiting the effectiveness of NIRF-C. In this study, these investigators examined the relationship between visualization of the extra-hepatic bile duct and the BMI and found that visualization of biliary structures by NIRF-C was better in patients with a BMI of less than 25 than greater than 25 kg/m2, especially for visualization of the CHD. More importantly, repeated images of the bile duct structure during dissection of Calot’s triangle could be obtained during NIRF-C-assisted procedures; thus, NIRF-C is a highly suitable technique for obese patients. The association between the timing and dose of ICG and optimal visualization of the bile ducts when performing NIRF-C remains unknown. In most recent studies, the timing of ICG injection varied from 30 to 60 mins before the commencement of surgery. Longer times of 2.5 to 24 hours have also been reported.

Finally, adequate images of the extra-hepatic bile duct were able to be obtained in all studies. In patients with normal liver function, 95 % of the ICG was captured by hepatocytes and excreted into the bile within 15 mins after injection. For patients with impaired liver clearance, however, how long this process would take is unclear; thus, exactly when ICG should be injected to obtain the best image of the bile ducts remains unknown. Another problem is the uncertainty regarding the dose of ICG injection. These researchers employed a dose of 2.5 mg in this trial. This dose was based on the current literature; however, the dose that can provide the best bile duct image is unclear. Therefore, future studies should focus on the relationship between the optimal dose and timing of ICG administration and bile duct visualization. Furthermore, this study had several drawbacks inherent to retrospective studies, and the number of patients was limited.

Shibata and co-workers (2021) noted that bile duct injury is one of the most serious complications of laparoscopic cholecystectomy; and intra-operative ICG cholangiography is expected to be a routine method for helping avoid bile duct injuries. In a retrospective study, these
researchers examined 25 patients who underwent intra-operative cholangiography using ICG fluorescence. Two methods of ICG injection were used: intra-biliary injection (percutaneous trans-hepatic gallbladder drainage [PTGBD], gallbladder [GB] puncture and endoscopic nasobiliary drainage [ENBD]) at a dosage of 0.025 mg during the operation or intravenous injection with 2.5 mg ICG pre-operatively. There were 24 patients who underwent laparoscopic cholecystectomy and 1 patient who underwent hepatectomy. For laparoscopic cholecystectomy, the average operation time was 127 (50 to 197) mins, and estimated blood loss (EBL) was 43.2 (0 to 400) g. The ICG administration route was intravenous (IV) injections in 12 cases and intra-biliary injection in 12 cases (GB injection: 3 cases, PTGBD: 8 cases, ENBD: 1 case). The course of the biliary tree was able to be confirmed in all cases that received direct injection into the biliary tract, whereas bile structures were recognizable in only 10 cases (83.3 %) with IV injection. The post-operative hospital stay was 4.6 (3 to 9) days, and no post-operative complications (Clavien-Dindo greater than or equal to IIIa) were observed. For hepatectomy, a tumor located near the left Glissonian pedicle was resected using a fluorescence image guide. Biliary structures were fluorescent without injury after resecting the tumor. No adverse events (AEs) due to ICG administration were observed, and the procedure was able to be carried out safely. The authors concluded that ICG fluorescence imaging allowed surgeons to visualize the course of the biliary tree in real time during cholecystectomy and hepatectomy. This is considered essential for hepatobiliary surgery to prevent biliary tree injury and ensure safe surgery.

These researchers stated that one disadvantage of this method is the difficulty in identifying biliary trees, especially in cases with severe inflammation or thick tissue. In this study, the course of the bile tree was able to be confirmed in all cases by direct injection into the biliary tract, whereas bile structures were recognizable in 10 cases (83.3 %) with IV injection. Near-infrared light was reported to only be able to penetrate tissue to a depth of about 5 to 10 mm. The biliary structure in liver parenchyma or in cases covered by thick tissue is difficult to visualize, so peeling back the surrounding tissue is needed to detect the fluorescence. Of note, the BMI in the case where biliary structures could be detected was 30.4. While some previous reports have suggested no relationship between the BMI and the identification of biliary structures under fluorescent cholangiography, others have noted that all patients in whose
structures were not able to visualize were obese. Another issue with this method is that when IV injection is chosen, there are no established standards concerning the timing or concentration of ICG. In the most reported cases of IV injection, 2.5 mg/body of ICG was administered 30 to 60 mins before surgery. In the present cases, 2.5 mg/body of ICG was administered about 1 hour prior to surgery. In this retrospective study, the interval from IV administration of ICG to the detection of each biliary structure was examined in detail, and the fluorescence signal from CD could be confirmed at 48.59 mins, that from CBD at 42.03 mins and that from CHD at 48.02 mins after the administration of ICG. The CD could be detected in only 33.3 % before ICG injection. However, the CD, CBD and CHD were observed in 75 % of cases by ICG injection and NIFS imaging. After dissection of the Calot triangle, the detection rate of the biliary structures was 83.3 %. One reason for the failed detection after dissection may have been because the IV-administered ICG had not yet been excreted into the biliary system. Furthermore, the high degree of fluorescence noise from the liver may have hampered the identification of the biliary structure in these cases. Masaru et al (2021) reported that the identification of the biliary tract could be improved by performing ICG administration on the day before the operation rather than just before surgery. The ICG concentration and fluorescence intensity did not always match. These investigators stated that while there have been several reports on ICG fluorescent cholangiography, standards have yet to be established; a detailed examination of the optimal dose and administration time should be carried out in a future study.

Lai et al (2021) stated that NIRF-C using ICG is increasingly used to help in identifying extra-hepatic biliary anatomy. The use of ICG cholangiography for laparoscopic cholecystectomy is suggested to be safe and feasible. These investigators reviewed the dosage and timing of IV administration of ICG, its efficacy and potential usage. Medline and PubMed searches were carried out using the key words "fluorescent cholangiography", "ICG cholangiography", "near-infrared fluorescent cholangiography" and "laparoscopic cholecystectomy" to identify relevant articles published in English between 2010 to 2020. Reference lists from the articles were reviewed to identify additional pertinent articles. Several factors could influence the quality of the fluorescence imaging, including the dose and timing of ICG injection, liver function, the thickness of fatty tissue and the presence of inflamed tissues due to acute pathology.
Various devices tested also have a different sensitivity to the fluorescence signal; RCTs showed fluorescence cholangiography were comparable to traditional intra-operative cholangiography in visualizing the extra-hepatic biliary anatomy. However, there is still no consensus in the dosing of ICG and the time interval between ICG injection and detection of biliary fluorescence. Fluorescence cholangiography's ability to enhance such visualization could potentially reduce bile duct injury risks and shorten the operative time; however, no valuable data for bile duct injury prevention or detection could be retrieved. The authors concluded that NIRF-C is a safe, non-irradiating technique to identify and aid in the visualization of extra-hepatic biliary anatomy. Laparoscopic cholecystectomy with real-time NIRFC allowed a better visualization and identification of biliary anatomy; thus, it has potential as a means of increasing the safety of laparoscopic cholecystectomy. Whether this would translate into reducing complication rates must still be determined. The dosage and timing of IV administration of ICG relative to the operative procedure still requires optimization to ensure reliable images.

**CPT Codes/ HCPCS Codes/ICD-10 Codes**

Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by “+”

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Near-infrared vascular imaging systems (e.g., AccuVein AV300 or VeinViewer) for guiding vascular access:</td>
<td></td>
</tr>
<tr>
<td>CPT codes not covered for indications listed in the CPB:</td>
<td></td>
</tr>
<tr>
<td>0287T</td>
<td>Near-infrared guidance for vascular access requiring real-time digital visualization of subcutaneous vasculature for evaluation of potential access sites and vessel patency</td>
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</table>

*Evaluation of soft tissue viability to guide debridement in trauma surgery, imaging of matrix metalloproteinase 2 (MMP-2) as a biomarker of the vascular remodeling in arterio-venous fistulae - no specific code:*

Other CPT codes related to the CPB:

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
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<tbody>
<tr>
<td>47380</td>
<td>Ablation, open, of 1 or more liver tumor(s); radiofrequency</td>
</tr>
<tr>
<td>47382</td>
<td>Ablation, 1 or more liver tumor(s), percutaneous, radiofrequency</td>
</tr>
<tr>
<td>Code</td>
<td>Code Description</td>
</tr>
<tr>
<td>----------</td>
<td>----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>50545</td>
<td>Laparoscopy, surgical; radical nephrectomy (includes removal of Gerota's fascia and surrounding fatty tissue, removal of regional lymph nodes, and adrenalectomy)</td>
</tr>
<tr>
<td>50546</td>
<td>Laparoscopy, surgical; nephrectomy, including partial ureterectomy</td>
</tr>
<tr>
<td>50548</td>
<td>Laparoscopy, surgical; nephrectomy with total ureterectomy</td>
</tr>
<tr>
<td>50947</td>
<td>Laparoscopy, surgical; ureteroneocystostomy with cystoscopy and ureteral stent placement</td>
</tr>
<tr>
<td>50948</td>
<td>Laparoscopy, surgical; ureteroneocystostomy without cystoscopy and ureteral stent placement</td>
</tr>
<tr>
<td>50949</td>
<td>Unlisted laparoscopy procedure, ureter</td>
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</table>

ICD-10 codes not covered for indications listed in the CPB:

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>S01.00xA</td>
<td>Open wound of head</td>
</tr>
<tr>
<td>S01.95xS</td>
<td></td>
</tr>
<tr>
<td>S11.011A</td>
<td>Open wound of neck</td>
</tr>
<tr>
<td>S11.95xS</td>
<td></td>
</tr>
<tr>
<td>S21.001A</td>
<td>Open wound of thorax</td>
</tr>
<tr>
<td>S21.95xS</td>
<td></td>
</tr>
<tr>
<td>S31.000A</td>
<td>Open wound of abdomen, lower back, pelvis and external genitals</td>
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<tr>
<td>S31.839S</td>
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<tr>
<td>S41.001A</td>
<td>Open wound of shoulder and upper arm</td>
</tr>
<tr>
<td>S41.159S</td>
<td></td>
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<tr>
<td>S51.001A</td>
<td>Open wound of elbow and forearm</td>
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<tr>
<td>S51.859S</td>
<td></td>
</tr>
<tr>
<td>S61.001A</td>
<td>Open wound of wrist, hand and fingers</td>
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<tr>
<td>S61.559S</td>
<td></td>
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<tr>
<td>S71.001A</td>
<td>Open wound of hip and thigh</td>
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<tr>
<td>S71.159S</td>
<td></td>
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<tr>
<td>S81.001A</td>
<td>Open wound of knee and lower leg</td>
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<tr>
<td>S81.859S</td>
<td></td>
</tr>
<tr>
<td>S91.001A</td>
<td>Open wound of ankle, foot and toes</td>
</tr>
<tr>
<td>S91.359S</td>
<td></td>
</tr>
</tbody>
</table>

*Near-infrared fluorescence imaging:*
<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
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</thead>
<tbody>
<tr>
<td>HCPCS codes not covered for indications listed in the CPB:</td>
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</tr>
<tr>
<td>C9756</td>
<td>Intraoperative near-infrared fluorescence lymphatic mapping of lymph node(s) (sentinel or tumor draining) with administration of indocyanine green (ICG) (List separately in addition to code for primary procedure)</td>
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<tr>
<td>ICD-10 codes not covered for indications listed in the CPB (not all-inclusive):</td>
<td></td>
</tr>
<tr>
<td>C00.0 - D49.9</td>
<td>Neoplasms [detection of tumor angiogenesis and monitoring of response to anti-tumor vasculature therapy]</td>
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<tr>
<td>I25.1 - I25.9</td>
<td>Chronic ischemic heart disease</td>
</tr>
<tr>
<td>I70.0 - I70.92</td>
<td>Atherosclerosis [identification of vulnerable atherosclerotic plaques]</td>
</tr>
<tr>
<td>I73.00 - I73.9</td>
<td>Other peripheral vascular diseases [peripheral artery disease]</td>
</tr>
<tr>
<td>M05.00 - M05.9</td>
<td>Rheumatoid arthritis with rheumatoid factor</td>
</tr>
<tr>
<td>M06.00 - M06.9</td>
<td>Other rheumatoid arthritis</td>
</tr>
<tr>
<td>M08.00 - M08.99</td>
<td>Juvenile arthritis</td>
</tr>
<tr>
<td>Q87.2</td>
<td>Congenital malformation syndromes predominantly involving limbs [Klippel-Trenaunay syndrome]</td>
</tr>
</tbody>
</table>

The above policy is based on the following references:

Near-Infrared Vascular Imaging

4. Kaddoum RN, Anghelescu DL, Parish ME, et al. A randomized controlled trial comparing the AccuVein AV300 device to standard insertion technique for intravenous cannulation of
Near-Infrared Vascular Imaging and Near-Infrared Fluorescence Imaging


Near-Infrared Fluorescence Imaging


18. Matsumura M, Kawaguchi Y, Kobayashi Y, et al. Indocyanine green administration a day before surgery may increase bile duct


29. Plaxe SC. Endometrial carcinoma: Pretreatment evaluation, staging, and surgical treatment. UpToDate [online serial].
Waltham, MA: UpToDate; reviewed August 2015.


AETNA BETTER HEALTH® OF PENNSYLVANIA

Amendment to
Aetna Clinical Policy Bulletin Number: 0846 Near-Infrared Vascular Imaging and Near-Infrared Fluorescence Imaging

There are no amendments for Medicaid.

Revised 11/23/2021