Role of Indocyanine Green in Fluorescence Imaging with Near-Infrared Light to Identify Sentinel Lymph Nodes, Lymphatic Vessels and Pathways Prior to Surgery – A Critical Evaluation of Options

Die Rolle von Indocyaningrün als Fluoreszenzfarbstoff in Kombination mit Nah-Infrarotlicht in der operativen Medizin zur Sentinellymphknoten-, Gefäß- und Lymphbahndarstellung – eine kritische Beurteilung der Möglichkeiten

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ABSTRACT

Modern surgical strategies aim to reduce trauma by using functional imaging to improve surgical outcomes. This reviews considers and evaluates the importance of the fluorescent dye indocyanine green (ICG) to visualize lymph nodes, lymphatic pathways and vessels and tissue borders in an interdisciplinary setting. The work is based on a selective search of the literature in PubMed, Scopus, and Google Scholar and the authors' own clinical experience. Because of its simple, radiation-free and uncomplicated application, ICG has become an important clinical indicator in recent years. In oncologic surgery ICG is used extensively to identify sentinel lymph nodes with promising results. In some studies, the detection rates with ICG have been better than the rates obtained with established procedures. When ICG is used for visualization and the quantification of tissue perfusion, it can lead to fewer cases of anastomotic insufficiency or transplant necrosis. The use of ICG for the imaging of organ borders, flap plasty borders and postoperative vascularization has also been scientifically evaluated. Combining the easily applied ICG dye with technical options for intraoperative and interventional visualization has the potential to create new functional imaging procedures which, in future, could expand or even replace existing established surgical techniques, particularly the techniques used for sentinel lymph node and anastomosis imaging.

ZUSAMMENFASSUNG

Moderne chirurgische Strategien zielen auf Reduktion von Trauma mit Nutzung funktioneller Darstellungsmethoden zur Verbesserung chirurgischer Ergebnisse. Die Relevanz von Indocyaningrün (ICG) als Fluoreszenzfarbstoff, zur Darstellung von Lymphknoten, Lymphbahnen, Gefäßen und Gewebegrenzen, wird in dieser Übersichtsarbeit interdisziplinär dargestellt und kritisch bewertet. Diese Arbeit basiert auf einer selektiven Literaturrecherche in PubMed, Scopus, Google Scholar und

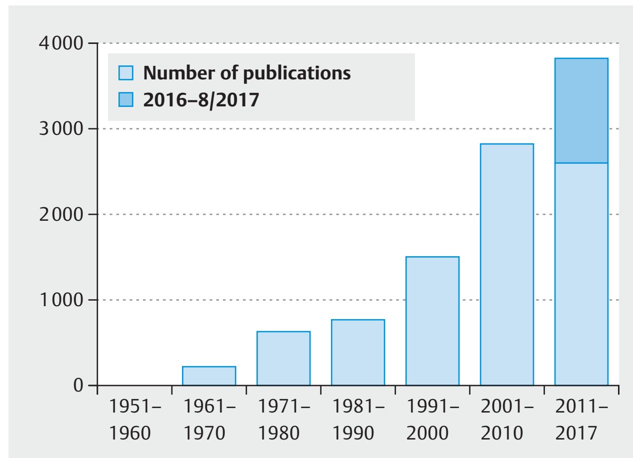
den klinischen Erfahrungen der Autoren. Aufgrund der einfachen, strahlungsfreien und komplikationsarmen Anwendung hat sich ICG in den letzten Jahren als eine wichtige klinische Indikatorsubstanz etabliert. In der onkologischen Chirurgie wird ICG zur Markierung von Sentinellymphknoten intensiv und mit vielversprechenden Ergebnissen genutzt und zeigt zum Teil verbesserte Detektionsraten im Vergleich mit den etablierten Verfahren. Durch Visualisierung und Quantifizierung von Gewebedurchblutungen kann ICG zu einer Verringerung von Anastomoseinsuffizienzen und Transplantatnekrosen führen. Die Darstellung von Organgrenzen, Grenzen von Lappenplastiken sowie deren postoperativer Vaskularisierung sind auch Gegenstand der wissenschaftlichen Evaluation. Die Kombination des leicht anwendbaren Farbstoffs ICG mit den technischen Möglichkeiten der intraoperativen und interventionellen Visualisierung hat das Potenzial, neue funktionelle Darstellungen zu ermöglichen und die bisher etablierten operativen Techniken, insbesondere die Sentineltechniken und Anastomosetechniken, zu erweitern und möglicherweise zukünftig abzulösen.

Introduction

Modern surgical medicine aims to reduce trauma while maintaining the same outcomes or even improving them and is increasingly making use of functional imaging.

Indocyanine green (ICG) is used in innovative surgical techniques, for example to stain organs and tumor tissue, for the intraoperative imaging of flap plasty or bowel anastomosis vascularization and for the detection of sentinel lymph nodes [1 – 8].

The use of ICG in medicine has been described since the 1950s [9]. Particularly following recent developments in video endoscopy techniques, the use of ICG in medical practice has expanded to include many different specialties. Scientific and clinical interest in the medical application of indocyanine green (ICG) has greatly increased latterly; PubMed alone lists 1221 publications for the period from January 2016 to August 2017 (▶ **Fig. 1**). In view of the range of medical areas where ICG is used and the promising results, this review aims to describe and critically evaluate the current state-of-the-art in different surgical specialties.



▶ **Fig. 1** Number of “Indocyanine Green” publications in PubMed over various periods.

Characterization, metabolization

ICG is a tricarbocyanine dye which fluoresces, i.e. emits light, after excitation under near-infrared light at 806 nm light. ICG is highly soluble in water and binds to β-lipoproteins, particularly to albumin. Because of the high protein content of lymph, ICG accumulates in the lymphatic pathways and lymph nodes. ICG-dyed lymph nodes become visible 5 minutes after light excitation and remain visible for around 60 minutes [10]. The intravascular half-life of ICG is 3–4 minutes; elimination occurs through the liver [11]. ICG has been approved for use in intravenous applications in the USA since 1956. Injection of ICG into tissue, for example in oncologic lymph node imaging, is an off-label use.

Clinical application

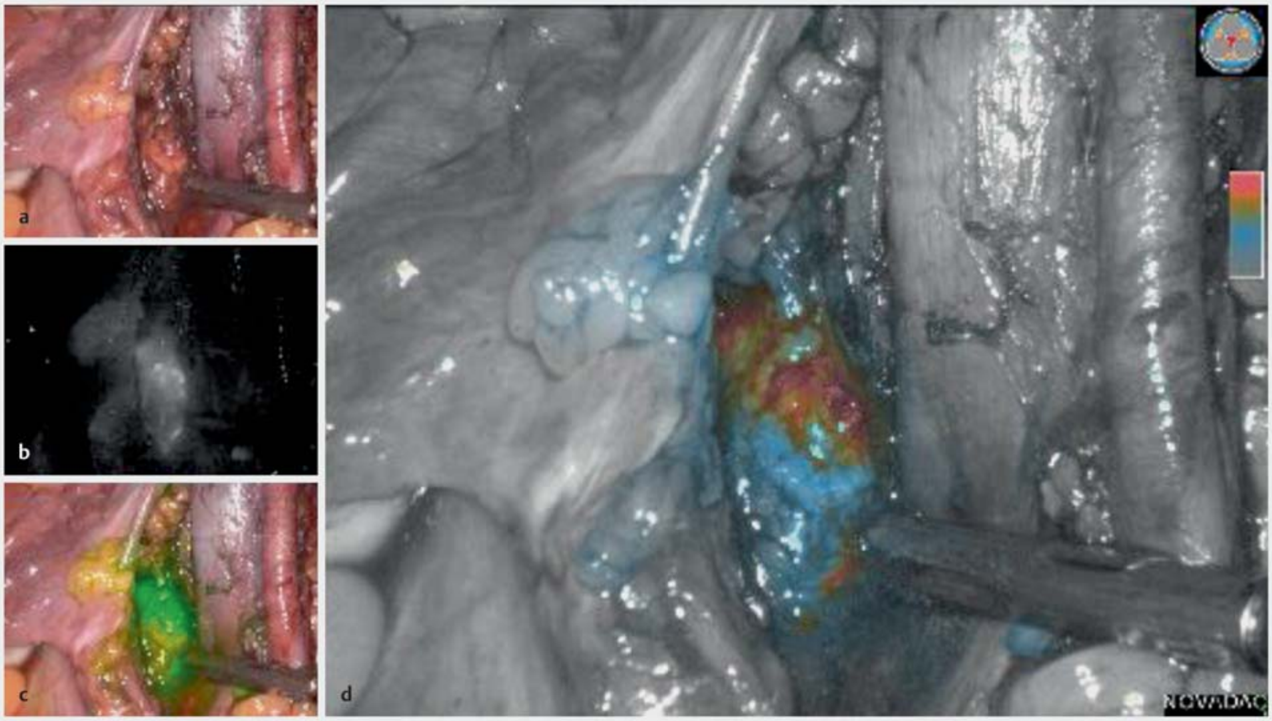
ICG is injected intraoperatively; it is easy to use logistically and does not increase surgical procedure times much [12]. In gynecological sentinel lymph node imaging ICG is injected into the uterine cervix, in rarer cases directly into the endometrium [13, 14]. Intravenous applications of ICG are required in fluorescence angiography, video angiography and the imaging of liver tissue [15 – 17]. The fluorescence of ICG is visualized using near-infrared light. A number of companies offer near-infrared cameras for open surgical, microscopic, laparoscopic and robot-assisted imaging of ICG, and a review article has compared the performance of these devices [18]. Modern imaging platforms are able to combine standard visible surgical images with fluorescence imaging under near-infrared light in real time (▶ **Figs. 2** and **3**). Color-coded quantified imaging of ICG makes it possible to differentiate between lymphatic pathways/lymph nodes and ICG fluorescence outside the lymphatic system (▶ **Fig. 2**).

Gynecology

In modern oncology radical surgery should not consist of the undifferentiated removal of a large amount of tissue with its associated trauma. As clinical and scientific knowledge has expanded in the last few decades, the extent of radical surgery to treat breast cancer has continually decreased without reducing oncological safety [19]. The standard surgical procedure is now based on the sentinel lymph node concept, which has been scientifically verified at the highest level of evidence [19 – 21]. The sentinel lymph node concept has also found its way into guidelines on vulvar and cervical cancer and endometrial carcinomas (USA) and is the preferred approach for certain constellations of findings [22 – 24].

The sentinel lymph node concept

The rationale behind the sentinel lymph node concept is based on the observation that after peritumoral or interstitial injection of a



► **Fig. 2** Intraoperative screen shot of fluorescence ICG sentinel lymph node biopsy in the right pelvis. **a** HD white light image of the site, **b** near-infrared image at the same site with pale-stained ICG-containing tissue. **c** Combined HD image with fluorescent green color. **d** Quantitative ICG image of fluorescence-containing tissue indicating the presence of a lymph node in the obturator fossa.

marker or tracer such as ICG or ^{99m}Tc, these substances are transported to the lymph nodes via the lymphatic pathways. The first lymph nodes to receive lymphatic drainage containing the tracer are referred to as the sentinel lymph nodes. Based on numerous studies, sentinel lymph nodes are considered to be representative for other lymph nodes in the same lymphatic drainage area; if the sentinel lymph node is tumor-free, radical lymphadenectomy is not required. This has led to a significant reduction in operating times and in the extent of surgical trauma and has reduced surgical and postoperative complications such as lymphedema or lymph cysts.

While axillary lymphatic drainage of breast cancer is almost always unilateral, matters are far more complicated with genital tumors, due to the possibility of unilateral, bilateral, superficial and deep dissemination [25].

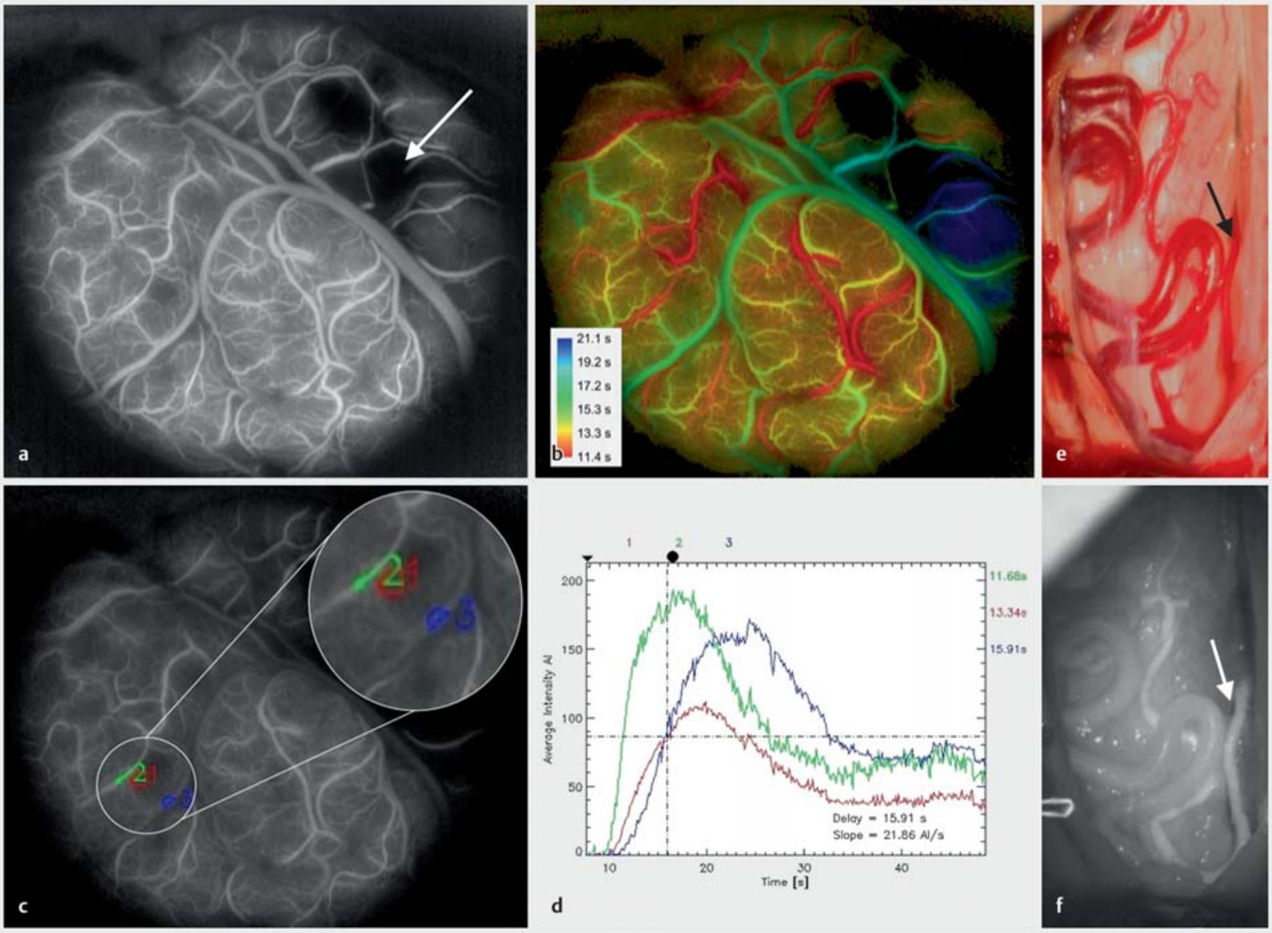
Detection rates of more than 90% and, as a correlate for oncologic safety, a false-negative rate of not more than 5% are considered the threshold values for sentinel lymph node biopsies in breast cancer [26]. The detection rates for cervical cancer are around 80%, with a bilateral detection rate for sentinel lymph nodes of between 50 and 61% [27].

Technetium colloid (^{99m}Tc) with and without simultaneous blue staining to improve detection rates and intraoperative gamma probe detection are used in many medical specialties [20, 28–30]. All marking techniques have a learning curve for injection and detection [31, 32]. A learning curve of 50 negative sentinel lymph nodes has been reported for sentinel lymph node visualization in axillary staging [33].

Breast cancer

The sentinel lymph node procedure has been used for more than 20 years in the primary surgical treatment of clinically node-negative breast cancer. Currently, the standard approach is a radioisotope procedure with technetium colloid (^{99m}Tc). This requires the cooperation of gynecologists and nuclear medicine specialists. Marking the sentinel lymph node with Tc is usually done using a 2-day protocol and a dosage of 100–200 MBq and is checked preoperatively using lymph drainage scintigraphy. The use of scintigraphy is justified by existing regulations on radiation protection, although data is available which have shown that this verification is unnecessary for the surgical detection of lymph nodes [34]. The 2-day protocol and the logistics associated with nuclear medicine represent a hindrance in today's clinical care of breast cancer patients.

The use of ICG in axillary sentinel lymph node (SLN) biopsy was investigated quite early on [35]. Additional studies, the majority of which were done in Asia, have shown that a combination of ICG and blue dye is safe to use and highly sensitive. When both techniques were compared, ICG was found to have a higher rate of detection [1, 36–39]. Two recent publications in 2017 reported ICG detection rates of up to 100% in axillary SLN biopsy [40, 41]. The use of ICG in breast cancer biopsies has also been investigated



▸ **Fig. 3** Applications in neurosurgery. **a** shows reduced flow at the cortical surface with circulatory insufficiency (white arrow). At maximum flow this is particularly visible in the color-coded image (**b**, blue areas). **c** shows how ROIs (regions of interest) can be measured. Physicians can select an artery (green), vein (blue) or cortex (red). Areas of infarction or tumor areas can be highlighted. **d** shows the quantitative images for these regions. **e** Image of the spinal cord of a patient with a spinal arteriovenous fistula. Under white light illumination (black arrow), the suspicious vessel fills too quickly during ICG video angiography (**f**, white arrow), allowing it to be identified as a fistula vessel.

in Germany where it was found to be valid, feasible and with comparable results to those of methods using Tc; however, ICG was rated as more patient-friendly [42]. The administration of ICG prior to axillary surgery is simple: a periareolar intradermal injection is administered immediately before the start of surgery. Lymph nodes can already be detected a few minutes after the injection. The optimal concentration of ICG has been reported to be 3–6 µg/ml [43]. ICG administration is not associated with any cosmetically displeasing skin discoloration as occurs with the blue dye method. Elaborate logistics and expensive radiation protection measures as are required for Tc methods are unnecessary. The consumption costs of ICG are less than one quarter of those required for Tc technology, even excluding the additional time and personnel costs.

Two meta-analyses were published in 2016 and 2017 and evaluated 19 and 12 studies respectively, with around 2500 and 1700 patients. They reported that detection rates following ICG administration in the axilla were 93–100%, which is superior to some of the results obtained with technetium colloid techniques (± blue) [1, 44].

In summary, there is extensive data and evidence showing that the ICG technique is well suited for axillary staging in breast cancer patients. The savings in terms of resources compared to Tc techniques is a significant advantage which – given the foreseeable developments in the clinical care of breast cancer patients and the trend towards very short in-hospital stays and outpatient treatment – militates for this new method.

Cervical and endometrial carcinoma

In their meta-analysis, Rusicto et al. reported that the results after using ICG for sentinel lymph node imaging in early cervical and endometrial carcinoma were equal to those obtained using the current standard of ^{99m}Tc and blue dye [45]. Several recent publications found significantly better overall detection rates and bilat-

▶ **Table 1** Results of the current studies on sentinel lymph node imaging with blue dye, technetium + blue dye and indocyanine green in cervical and endometrial carcinoma, which were published after the meta-analysis by Ruscito et al. in 2016 [45]. Data from the meta-analysis by Lin and colleagues [3] on endometrial carcinoma are also included.

Publication	Entity	Parameter	Blue dye	Technetium + Blue dye	Indocyanine green
Eriksson et al. 2017 [46] n = 472	Cervical cancer and endometrial carcinoma	Rate of detection	81%	–	95%
		Bilateral rate of detection	54%	–	85%
Beavis et al. 2016 [47] n = 30	Cervical cancer	Rate of detection	–	–	100%
		Bilateral rate of detection	–	–	87%
Buda et al. 2016 [2] n = 144		Rate of detection	–	95%	100%
		Bilateral rate of detection	–	76.3%	98.5%
Lin et al. 2017 [3] n = 2236	Endometrial carcinoma	Rate of detection	76% (71–81%)	86% (82–90%)	93% (89–96%)
		Sensitivity	90% (79–96%)	92% (84–96%)	87% (76–93%)

eral rates of detection when ICG was used compared to conventional procedures (▶ **Table 1**) [2, 46, 47].

The most recent data from a prospective, multicenter cohort study which compared the outcomes after removal of sentinel lymph nodes and complete lymphadenectomy in endometrial carcinoma (FIRES trial) showed a high sensitivity of 97.2% and a negative predictive value of 99.6% for the accurate detection of lymph node metastases in endometrial carcinoma [48]. In their highly regarded Lancet Oncology article, Rossi et al. concluded that sentinel lymph node biopsy can be used safely to replace diagnostic (staging) lymphadenectomy procedures [48].

Visceral Surgery

ICG is used in visceral surgery for the objective measurement of blood flow in colorectal anastomosis. Other areas of application are based on the elimination of ICG through the liver and biliary ducts. ICG is used in cholangiography and for the detection of subcapsular liver tumors. In biliary excretion disorders, ICG accumulates in hepatocellular carcinomas and around metastases of adenocarcinomas in non-cancerous liver tissue.

A new area of application which is still in its experimental stages is the use of ICG to detect peritoneal tumor foci of colorectal cancers. Recent studies have shown that detection during cytoreductive procedures is possible, and in almost one third of cases, this led to a change in the planned procedure [49, 50].

ICG fluorescence angiography for colorectal anastomosis

Insufficient perfusion of an anastomosis after colorectal resection, also known as anastomotic insufficiency (AI), is a serious complication with significant rates of morbidity and mortality. The incidence of anastomotic insufficiency is between 3 and 19%. Deep anterior rectal resections are particularly associated with high rates of anastomotic insufficiency [51, 52]. Although risk factors for AI are multifactorial, impaired perfusion plays a central role [52, 53].

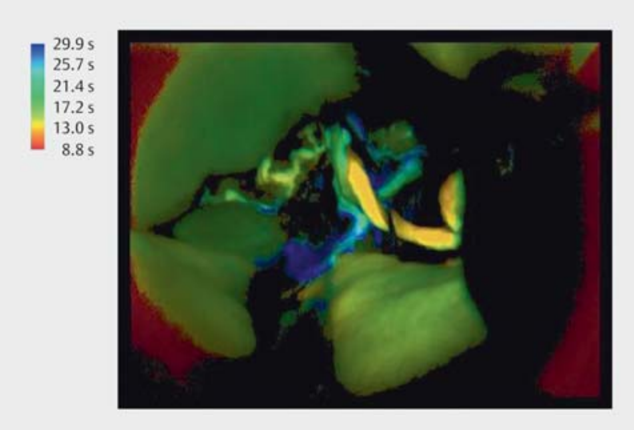
Often only subjective clinical tests are available for the intraoperative evaluation of perfusion. The color of the intestinal wall, the extent of peristalsis, the pulse of the arterial arcades supplying the area, and mucosal bleeding are used to estimate perfusion [54]. ICG fluorescence angiography has emerged as the most promising technology for the objective measurement of perfusion. In several case series, the use of ICG led to a change in the planned point of transection in the intestine in up to 19% of cases, reducing the subsequent rate of anastomotic insufficiency [55–57]. A prospective, multicenter study (PILLAR II) found that the use of fluorescence imaging led to a revision of the planned resection site in 8% of cases; the final insufficiency rate was 1.4% [58]. In a review of published clinical studies which looked at a total of 916 patients, the AI risk in the fluorescence group was 3.3% compared to a rate of 8.5% in the group without ICG fluorescence measurement [59]. Another review article found that the use of ICG fluorescence resulted in a change of surgical procedures in 11 of 16 studies. In two of the studies, the rate of anastomotic leakage was reduced by 4 and 11%, respectively. Only one of the studies reported no improvement in the AI rate in the fluorescence group [60].

In summary, the use of ICG fluorescence angiography in colorectal surgery is feasible and useful, although controlled randomized studies are still lacking.

ICG in hepatobiliary surgery

ICG has been used in hepatic function examinations for more than 20 years. Imaging tissue structures has only become relevant in recent years. The first fluorescent cholangiography was described in 2009 [61]. Other studies have reported an accumulation of ICG in hepatocellular carcinoma and multifocal adenocarcinoma [62, 63]. Improvements in imaging have led to the visualization of hepatic segment borders, allowing anatomical resections to become more precise [16, 64, 65]. ICG fluorescence angiography has been used after split liver transplantations to evaluate vascular reconstruction [66].

As the number of robot-assisted, minimally invasive surgical procedures in hepatobiliary surgery increases, the first series on laparoscopic robotic cholecystectomies with ICG fluorescent cholangiography have been published [67, 68]. One study showed a



▶ **Fig. 4** Color-coded imaging (FLOW® 800) of the afferent (yellow-orange) artery and the efferent vein (green) of a microvascular, latissimus dorsi tissue flap after successful anastomosis.

reduction in complication and conversion rates compared to laparoscopic resection [68].

The accumulation of ICG in hepatic focal lesions could be useful in minimally invasive liver resection where palpation of the finding is not possible. The detection depth is only 5–10 mm and a number of false positive and negative findings have been reported, so that a final assessment of the benefit of ICG fluorescence imaging cannot yet be made here [16, 66].

Plastic Surgery

Intraoperative ICG angiography

There are numerous procedures in plastic reconstructive surgery which can be used to monitor the tissue transplants, and each method has its own limitations and advantages [69, 70]. Apart from the purely clinical examination, there is no established standard yet. Two different aspects can be investigated with ICG angiography. ICG angiography can be used to make a valid assessment of the vascular anastomosis and its patency [71, 72], and it can also be used to make predictions about the perfusion of the transplanted tissue [73, 74]. While this technology was described quite early on [63], it was initially not introduced into standard clinical practice for the perioperative evaluation of the perfusion of tissue transplants. The use of ICG for objective evaluations of perfusion requires surgical microscopes and special software [74 – 76]. The use of ICG to interpret findings is based on direct, quantitative, real-time flow measurements which show perfusion as visual images which can be used to evaluate both anastomoses and tissue transplants in the immediate and vulnerable postoperative phase.

There are a range external programs for the analysis of images, including the IC-VIEW, the IC-CALC (Pulsion Medical Systems AG, Munich, Germany), the SPY 2001 Imaging System (Novadaq, Bonita Springs, FL, USA) and the SPY Elite® System (LifeCell Corp., Branchburg, NJ, USA). The FLOW® 800 tool (FLOW 800; Carl Zeiss AG, Oberkochen, Germany) is a special case as it is integrated in the surgical microscope which is useful for intraoperative use and analysis. It can be used for flow analysis as it calculates emitted fluorescence signals and can create color coding based on fluorescence intensity (▶ **Fig. 4**) [74 – 78]. This ability to evaluate microanastomoses and tissue transplants intraoperatively has made the intraoperative assessment of flap plasties significantly easier and has improved success rates [79 – 81]. Perfusion can be validly evaluated by using the analyzed data to detect anastomotic complications or inadequate tissue perfusion in border areas during the postoperative period [74, 75, 80, 82 – 84].

Neurosurgery

Video angiography was introduced at the start of the millennium. In its current form where fluorescence video angiography is integrated in the surgical microscope, it is indispensable in modern neurosurgical operating rooms [85, 86].

Vascular neurosurgery

In vascular neurosurgery, ICG is primarily used to visualize vascular pathologies (angiomas, aneurysms) and their origins, to differentiate these lesions from adjacent vessels which are not part of the pathology, to show transfers from venous to arterial circulation (fistulas) and, above all, to monitor treatment success intraoperatively after eliminating fistulas or aneurysms.

ICG video angiography is used in cerebral cavernoma surgery and the surgery of arteriovenous malformations (AVM), dural arteriovenous fistulas (dAVF) [87] and aneurysms [88], and to treat spinal vascular pathologies ([89], ▶ **Fig. 3 e** and **f**). In more than 90% of cases, the results of ICG video angiography corresponded to those obtained by digital subtraction angiography, currently the gold standard for the imaging of vascular anomalies [88]. Hybrid surgery with angiography or intraoperative cross-sectional imaging is currently needed to carry out subtraction angiography intraoperatively. The use of these additional techniques significantly increases operating times, which is why they have been largely abandoned in favor of ICG.

Further improvements in video angiography include color-coded and (semi-)quantitative video angiography (▶ **Fig. 3 c** and **d**), which provides even more information about regional perfusion.

Cerebral tumor surgery

As evaluating vascular conditions around malignancies is also very important in cerebral tumor surgery, ICG video angiography can offer certain advantages. Intraoperative vascular imaging is particularly useful to evaluate transit feeders and draining veins during the resection of malignancies [90].

Evaluation of cerebral trauma

A very recently published article reported on the use of quantitative ICG video angiography to determine blood flow parameters in the cerebral vessels during decompressive craniectomy for traumatic brain injury. A clear correlation between cranial pressure and clinical outcome was recorded after 3 months. It is probable that ICG video angiography will be useful to assess prognosis in future [91].

Conclusion

Using ICG in medicine is simple, radiation-free and safe, and ICG has been shown to be an excellent marker after both interstitial and intravascular administration. The detection rates of ICG-dyed sentinel lymph nodes are at least as good as those reported for established techniques and sometimes even superior. Moreover, using ICG to detect sentinel lymph nodes is less expensive and logistically simpler than protocols which use technetium colloid (^{99m}Tc) the day before surgery, when it is administered by nuclear medicine specialists in accordance with radiation protection regulations [19, 20].

ICG has been used in medicine for more than fifty years, and side effects are very rare. After a total of 240 000 ICG administrations, Garski et al. reported only four intolerance reactions [92].

Although intravascular ICG injection has been approved since the 1950s and is used in standard clinical practice, interstitial injection of ICG is still off-label.

The limitations of ICG video angiography are its low penetration depth, which means that only superficial processes can be evaluated, and the fact that an interval of several minutes is necessary between two video angiographies to allow the initially injected ICG to flow out of the venous and arterial system again. The scientific data on the use of ICG are excellent. However, further prospective randomized studies will be necessary to establish this method in routine clinical practice.

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Conflict of Interest

AH: Perform live surgery and participation in expert meetings for Olympus.

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