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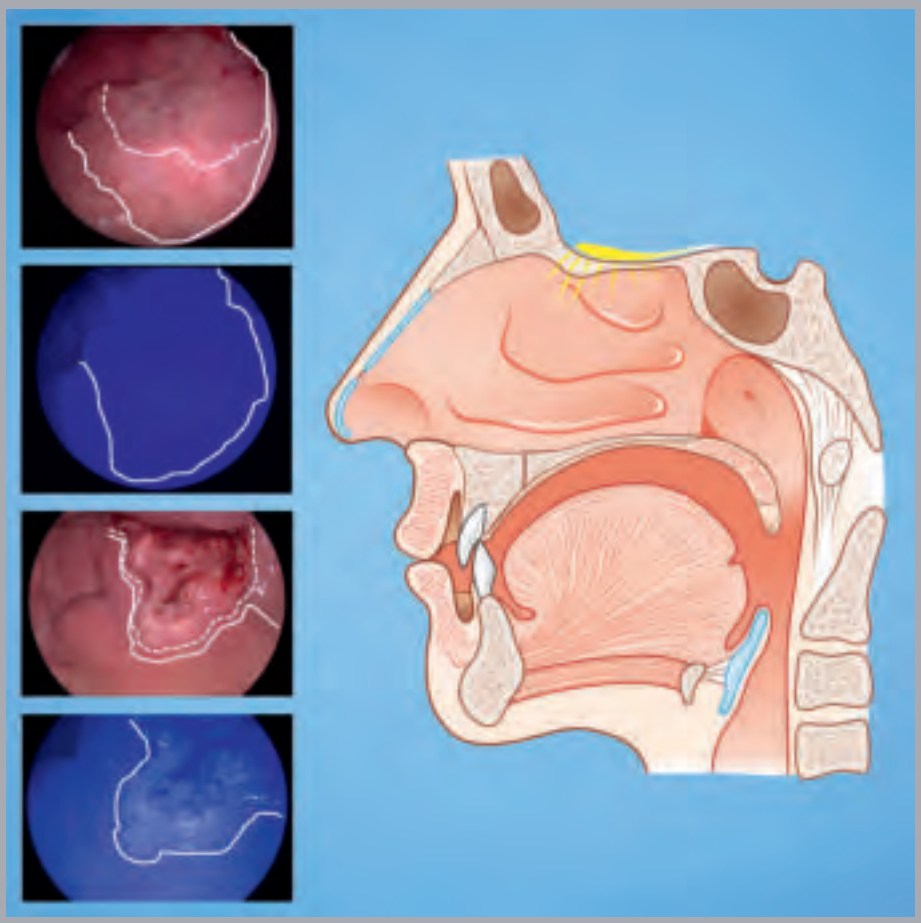
NEAR-INFRARED ENDOSCOPY WITH INDOCYANINE GREEN IN OTOLARYNGOLOGY



Florian SCHMIDT
Orlando GUNTINAS-LICHIUS

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Near-Infrared Endoscopy with Indocyanine Green in Otolaryngology

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1 Introduction

Despite excellent advances in the diagnosis and treatment of head and neck tumors in recent years, most tumors still go undiagnosed until they have reached an advanced stage. As a result, 30–50% of patients who have received curative therapy go on to develop a locoregional recurrence with a poor prognosis.[2] Besides a potentially long period of non-specific symptoms, difficult access to deep head and neck regions and field cancerization are among the reasons why it can be difficult to detect a head and neck tumor at an early stage. These same factors can also make it difficult to obtain clear margins (R0 resection) in the surgical removal of a tumor. Failure to obtain an R0 resection is a significant prognostic factor for local recurrence, which affects approximately 10–30% of patients with an advanced tumor in this setting. Because of field cancerization, the otolaryngologist who scrutinizes a suspicious lesion in the head and neck region may encounter a continuum of changes from inflammation to dysplasia and neoplasia with no clear dividing lines among them.[4] An early-stage tumor may be difficult to distinguish from chronic inflammation and dysplastic change, and the margins of an advanced tumor may be difficult to define. The current standard – and limiting factor – for evaluating these changes is inspection under white light, which forms the basis of physician decision-making and tissue sampling for histopathologic analysis.

The ideal solution would be a rapid, noninvasive optical imaging technique that could facilitate the detection of tumors at an early stage (early tumor detection) while also enhancing the identification of tumor margins (tumor margin detection) and the differentiation of benign and malignant processes (tumor discrimination). Due to the small dimensions of spaces in the head and neck region, especially in the larynx, it is also desirable to detect and define the extent of benign processes (e.g., papillomas) with greater accuracy so that their resection will sacrifice as little healthy mucosa as possible and preserve maximum function.

Optical imaging with near-infrared (NIR) fluorescence is a relatively new technique for real-time visualization during surgical procedures. Additionally, indocyanine green (ICG) has been approved for use as a fluorescent dye. To date, ICG fluorescence imaging has been used in the head and neck region in the form of ICG angiography for evaluating the perfusion of free muscle flaps after ablative tumor surgery and for evaluating skull base tumors.[3, 7] Similarly, NIR fluorescence with ICG has been used to assess blood flow in paranasal sinus malignancies and direct the planning of intra-arterial chemotherapy.[12] While ICG has become an established marker for sentinel node biopsies in other specialties, it has also been used in recent studies to direct sentinel node biopsies in patients with head and neck tumors.[5, 9]

The technique has also been applied to other tumor entities including the bronchoscopic detection of pulmonary metastases, the endoscopic diagnosis of early gastric carcinoma, and the detection of hepatic metastasis at open surgery.[1, 8, 11]

Because even small, hypervascular neoplasms can generally be visualized with ICG,[8] the technique is also of interest for evaluating a number of benign changes such as laryngeal polyps and Reinke edema.

2 NIR Fluorescence Endoscopy with Indocyanine Green

In 1852, *George Gabriel Stokes* described the mineral 'fluorite', which emits blue light when exposed to electromagnetic radiation. He called this phenomenon 'fluorescence' and coined the term 'fluorophores' for compounds possessing that property. The ability to fluoresce is a common phenomenon in nature. It occurs when energy is absorbed by delocalized electrons in aromatic ring structures. The absorbed light energy raises the electron to a higher energy state. When the electron returns to its original state, it loses energy and emits a photon, which is perceived as fluorescent light. The emitted fluorescent light has less energy than the absorbed 'exciting' light, because some of the absorbed energy is converted to heat.

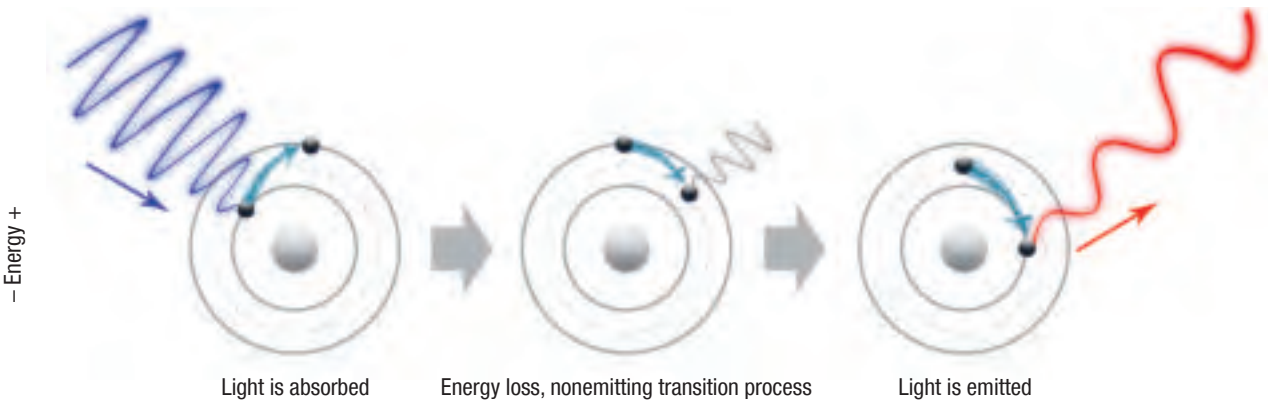


Fig. 1 Simplified diagram showing the principle of fluorescence.

Aromatic ring structures are a major component of many biological substances such as DNA, proteins, and sugar. Since the 1960s, their ability to fluoresce has been utilized for fluorescence imaging in the biosciences and medicine. The oldest known near-infrared (NIR) fluorescent dye in medicine is indocyanine green (ICG), which was approved by the FDA for angiography in 1959. Today it has a range of applications that include angiography in the eye and liver and the testing of liver and cardiac function.

ICG has an absorption peak of λ_{Ex} = 805 nm and an emission peak of λ_{Em} = 835 nm. The spectral properties of ICG in the NIR range of the spectrum preclude interference due to the autofluorescence of major blood constituents (hemoglobin and water). This results in a tissue detection depth of 0.5–1.5 cm for NIR fluorescence.[10] Following intravenous injection, ICG binds to plasma proteins in the vascular bed and can be visualized. Because NIR is outside the visible range of wavelengths, the NIR light does not alter the surgical field of view for the head and neck surgeon.

ICG has a very low risk potential, and the estimated allergy risk is just 1 in 42,000. The use of ICG is contraindicated in patients with liver failure or an allergy to iodine, a small amount of which is present in the tracer.[6]

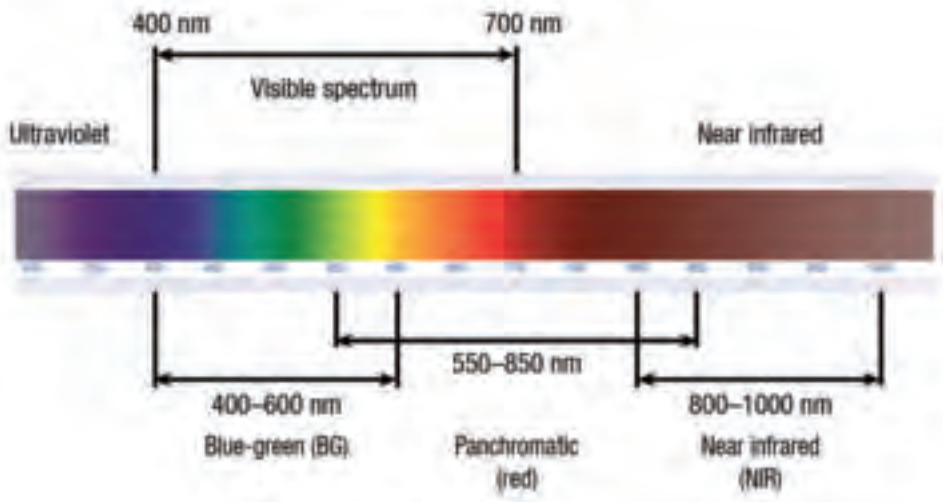


Fig. 2 Relationship between the near-infrared (NIR) range and visible light.

3 Clinical Application of NIR Endoscopy in Otolaryngology

The results presented below were all obtained with the KARL STORZ Near Infrared (NIR/ICG) system, which can be used for both standard white-light imaging and fluorescence imaging. Apart from the brilliant full-HD image quality in white-light mode, the system also provides background illumination with accurate color reproduction in NIR mode. Image quality can be optimized by activating the various IMAGE1 S modes (SPECTRA A*, SPECTRA B**, CLARA or CHROMA) via a software menu control.

The high user-friendliness of the system is appealing. The user can quickly switch between different operating modes by pressing a footswitch. Components are fully compatible with the current modular IMAGE1 S system, so the imaging station can easily be expanded for 3D imaging, flexible endoscopy, and open surgical procedures. Further details on the KARL STORZ NIR/ICG system and its components are given on pages 12 and 13 of this brochure.

The results presented here were documented in 52 patients treated at the Department of Otolaryngology, Head and Neck Surgery, at Jena University Hospital. All patients were examined under general anesthesia (indicated for the treatment of their disease, not for NIR endoscopy). The patients were informed about the off-label use of ICG. They underwent either panendoscopy or microlaryngoscopy, depending on the tumor location and whether the lesion was a suspected tumor or a malignancy. NIR endoscopy was performed as soon as the suspicious lesion was visualized and before it was biopsied; this was necessary to avoid loss of visualization due to bleeding from the biopsy site. The authors observed no complications. Two different sizes of 0° HOPKINS® endoscopes were used: diam. 5.8 mm, length 19 cm, and diam. 10 mm, length 20 cm, respectively.

Exclusion criteria from ICG NIR endoscopy were as follows:

- Autonomous thyroid adenoma.
- Severe impairment of renal, pulmonary or liver function.
- Age under 18 years.
- Refusal of informed consent to off-label use of ICG.

The established protocol for ICG NIR endoscopy was followed:

- The ICG powder (25 mg per bottle, e.g., ICG Pulsion® or a comparable brand) is dissolved in 15 mL of distilled water.
- The tumor or suspicious lesion is visualized.
- Five mL of the ICG solution is administered by i.v. bolus injection. The region of interest should show significant uptake within 1–2 minutes.
- The suspicious region is examined and video-documented with a 0° HOPKINS® endoscope in white-light mode and NIR mode. Additional documentation with other IMAGE1 S modes can be obtained as required.

* *SPECTRA A:* **Not for sale in the U.S.**
** *SPECTRA B:* **Not for sale in the U.S.**

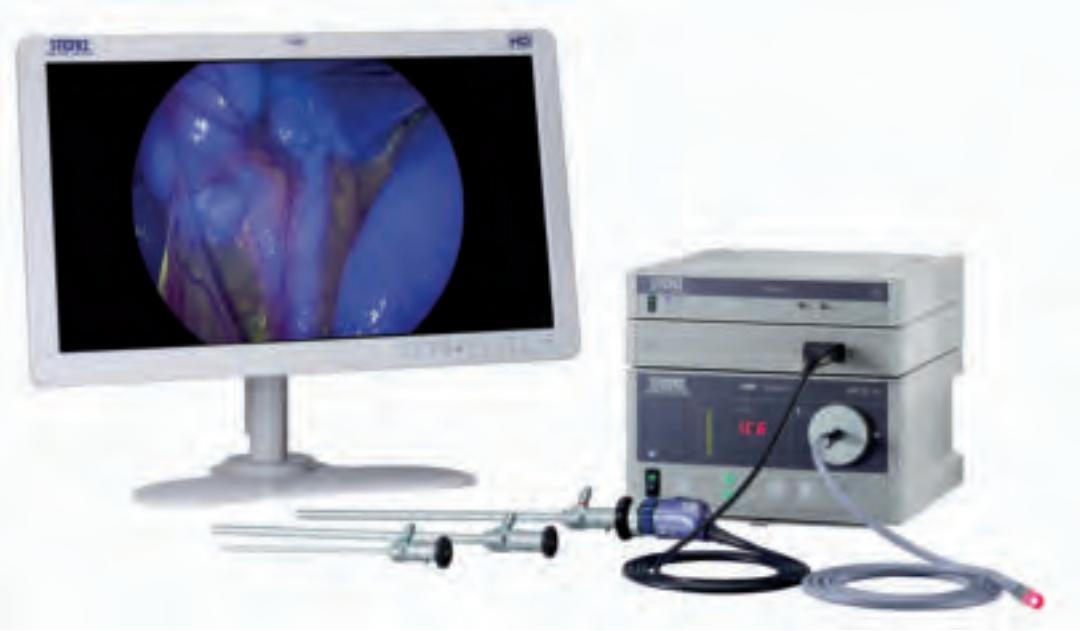


Fig. 3 The NIR/ICG system from KARL STORZ is capable of white-light imaging in addition to ICG fluorescence imaging in near-infrared light.

4 Illustrative Clinical Cases

Several typical illustrative cases are presented and described below.

4.1 Laryngeal Carcinoma (Glottic)

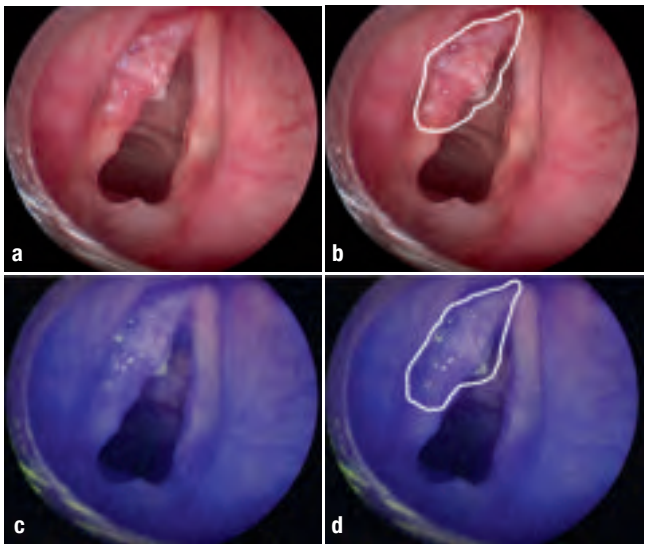


Fig. 4 Left-sided glottic carcinoma (**a**). The leukoplakic and hyperkeratotic areas typically do not show intravascular ICG fluorescence. Normally (see also **Fig. 9**) the ICG image shows fine submucous vascularity on the vocal cord. While the tumor margins are poorly visualized in the white-light image, especially anteriorly and anterolaterally (**a, b**), the tumor is clearly demarcated from surrounding healthy tissue in the NIR/ICG image (**c, d**).

4.2. Oropharyngeal Carcinoma (Uvula and Soft Palate)

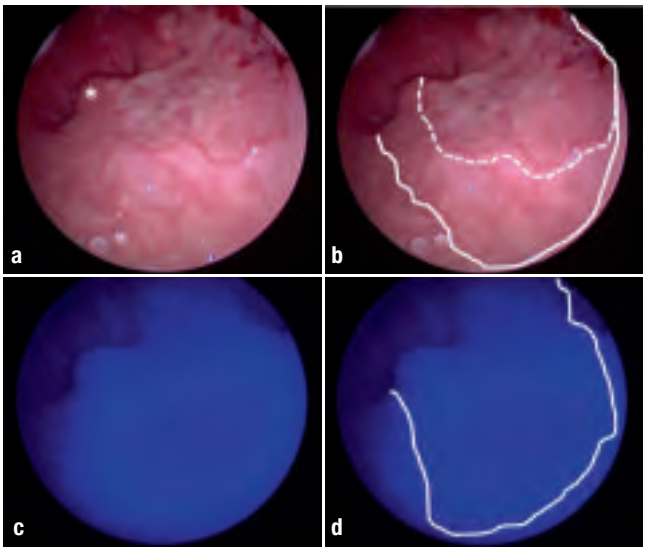


Fig. 5 The tumor margins may be deceptive (**broken line**) when viewed under white light (**a, b**). The tumor margins actually run farther medially and superiorly in the soft palate on the right side (**solid line**), consistent with the homogeneous fluorescence in the NIR/ICG image (**c, d**). ✱ = uvula.

4.3 Oropharyngeal Carcinoma (Soft Palate and Tonsil)

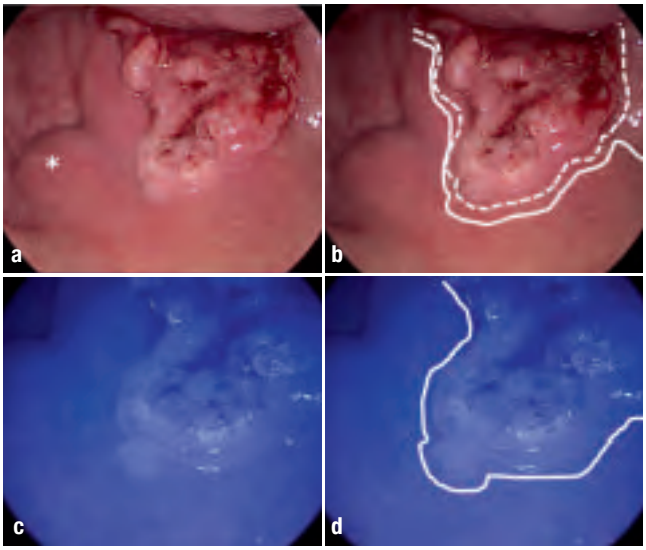


Fig. 6 The tumor has a small leukoplakic rim (**broken line**) in the white-light image, with some pooling of ICG in the tumor ulcerations. Actually the tumor has a broad rim, indicated most clearly by the fingerlike extension in the NIR/ICG image. ✱ = uvula.

4.4 Laryngeal Carcinoma (Supraglottic)

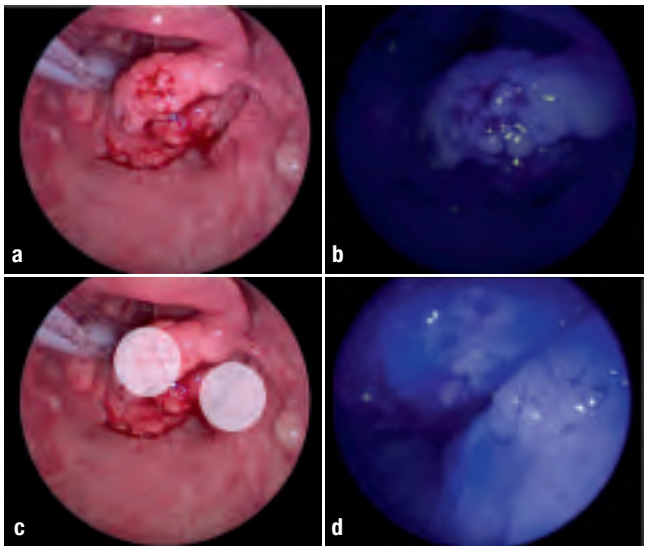


Fig. 7 Example of a head and neck tumor. The circled areas (**c**) are magnified on the right, displaying regions of both homogeneous and very inhomogeneous signal with some pooling of ICG. Superficial vessels show ICG signal only in normal mucosa. Hyperkeratotic and leukoplakic areas may be completely ICG-negative. ✱ = epiglottis.

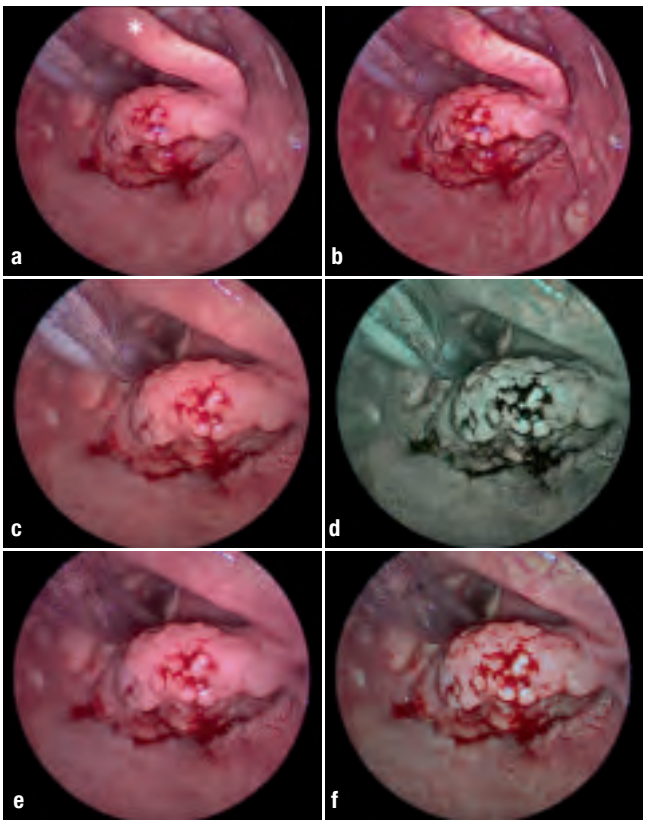


Fig. 8 The same tumor as in **Fig. 7**, viewed under white light (**a, c, e**). The images were acquired in different IMAGE 1 S modes: CHROMA (**b**), SPECTRA A* (**d**) and SPECTRA B** (**f**).

* *SPECTRA A:* **Not for sale in the U.S.**
** *SPECTRA B:* **Not for sale in the U.S.**

4.5. Vocal Cord Polyp

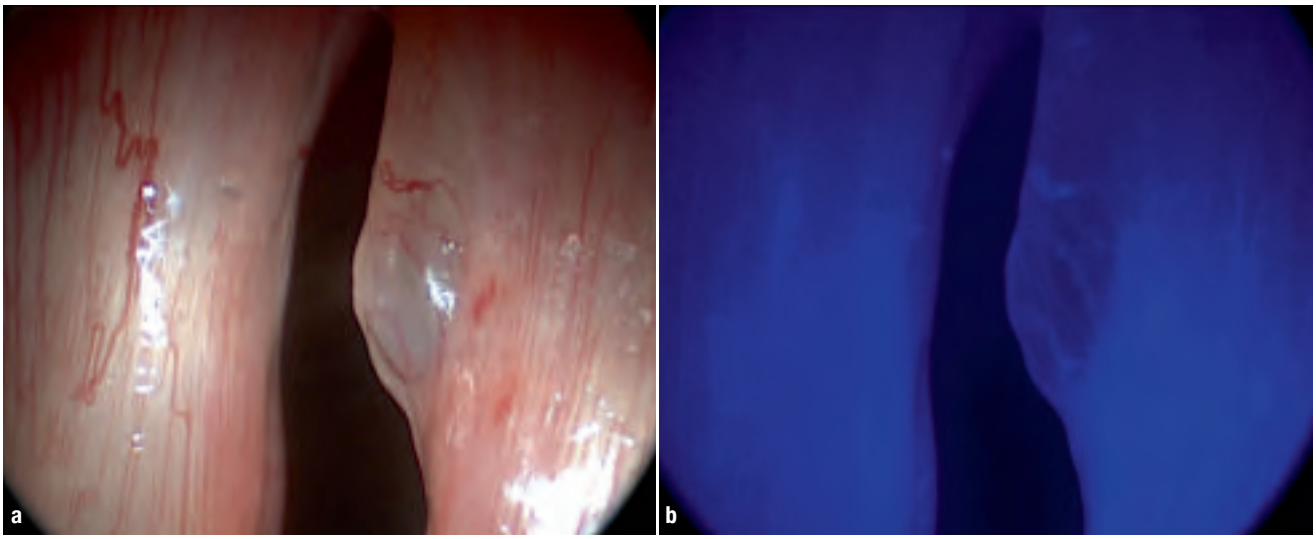


Fig. 9 The sharp division between the right vocal cord polyps and the edge of the vocal cord itself is defined more clearly in the NIR/ICG image due to the (probably subepithelial) vascular pattern (**b**) than in the white-light image (**a**). The vascular pattern throughout the NIR/ICG image is unlike that seen on the surface of a malignant tumor.

5 Conclusions and Outlook

NIR/ICG endoscopy is easy to perform with the devices presented herein, and is safe for patients. A few minutes after injection of the dye, a stable fluorescent image is produced that remains discernible for up to 15 minutes during endoscopy (longer persistence was not investigated). Switching between white-light and ICG images and comparing the images (by choosing other IMAGE1 S modes, if necessary; this needs to be investigated by further study) is particularly helpful for improved differentiation between tumor, perifocal inflammation, and normal mucosa. The next step should be to validate these findings in a clinical study with targeted tissue sampling based on ICG images. Further study is also needed to determine whether NIR/ICG endoscopy is not only useful diagnostically but could also provide intraoperative guidance for tumor resections.

6 References

1. ANAYAMA T, QIU J, CHAN H, NAKAJIMA T, WEERSINK R, DALY M et al. Localization of pulmonary nodules using avigation bronchoscope and a near-infrared fluorescence thoracoscope. Ann Thorac Surg 2015;99(1):224–30. doi:10.1016/j.athoracsur.2014.07.050.

2. ARGIRIS A, KARAMOUZIS MV, RABEN D, FERRIS RL. Head and neck cancer. Lancet 2008;371(9625): 1695–709. doi:10.1016/S0140-6736(08)60728-X.

3. BETZ CS, ZHORZEL S, SCHACHENMAYR H, STEPP H, MATTHIAS C, HOPPER C et al. Endoscopic assessment of free flap perfusion in the upper aerodigestive tract using indocyanine green: a pilot study. J Plast Reconstr Aesthet Surg 2013;66(5): 667–74. doi:10.1016/j.bjps.2012.12.034.

4. BRAAKHUIS BJ, BRAKENHOFF RH, LEEMANS CR. Second field tumors: a new opportunity for cancer prevention? Oncologist 2005;10(7):493–500. doi:10.1634/theoncologist.10-7-493.

5. CHRISTENSEN A, JUHL K, CHARABI B, MORTENSEN J, KISS K, KJAER A et al. Feasibility of Real-Time Near-Infrared Fluorescence Tracer Imaging in Sentinel Node Biopsy for Oral Cavity Cancer Patients. Ann Surg Oncol 2015. doi:10.1245/s10434-015-4883-7.

6. HOPE-ROSS M, LA YANNUZZI, GRAGOUDAS ES, GUYER, SLAKTER JS, SORENSON JA et al. Adverse reactions due to indocyanine green. Ophthalmology 1994;101(3):529–33.

7. INOUE A, OHNISHI T, KOHNO S, NISHIDA N, NAKAMURA Y, OHTSUKA Y et al. Usefulness of an Image Fusion Model Using Three-Dimensional CT and MRI with Indocyanine Green Fluorescence Endoscopy as a Multimodal Assistant System in Endoscopic Transsphenoidal Surgery. Int J Endocrinol 2015;2015:694273. doi:10.1155/2015/694273.

8. ISHIHARA R. Infrared endoscopy in the diagnosis and treatment of early gastric cancer. Endoscopy 2010;42(8):672–6. doi:10.1055/s-0029-1244205.

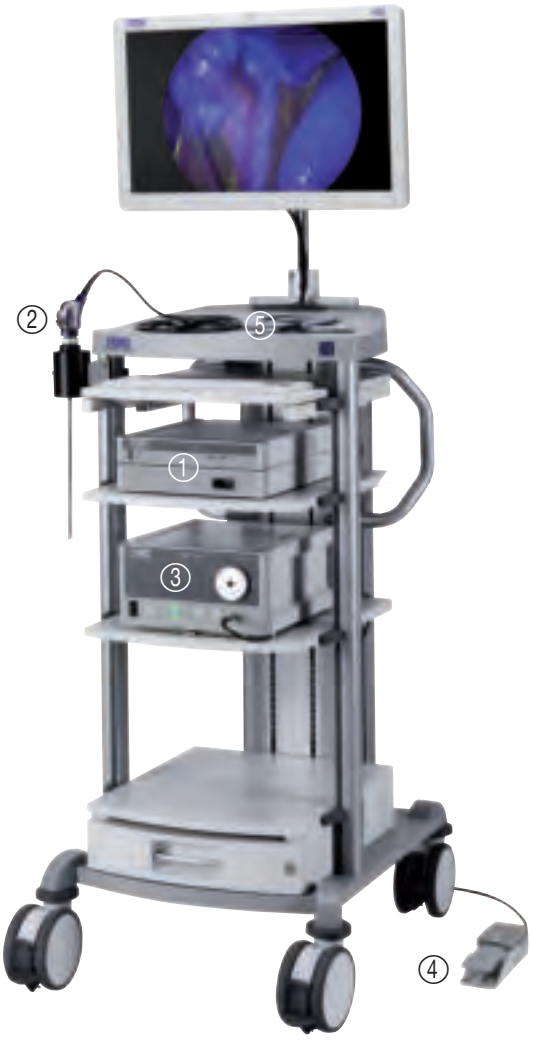
9. NAKAMURA T, KOGASHIWA Y, NAGAFUJI H, YAMAUCHI K, KOHNO N. Validity of sentinel lymph node biopsy by ICG fluorescence for early head and neck cancer. Anticancer Res 2015;35(3):1669–74.

10. SCHAAFSMA BE, MIEOG JS, HUTTEMAN M, VAN DER VORST JR, KUPPEN PJ, LOWIK CW et al. The clinical use of indocyanine green as a near-infrared fluorescent contrast agent for image-guided oncologic surgery. J Surg Oncol 2011;104(3):323–32. doi:10.1002/jso.21943.

11. VAN DER VORST JR, SCHAAFSMA BE, HUTTEMAN M, VERBEEK FP, LIEFERS GJ, HARTGRINK HH et al. Near-infrared fluorescence-guided resection of colorectal liver metastases. Cancer 2013;119(18): 3411–8. doi:10.1002/cncr.28203.

12. YOKOYAMA J, OHBA S, FUJIMAKI M, KOJIMA M, SUZUKI M, IKEDA K. Significant improvement in superselective intra-arterial chemotherapy for advanced paranasal sinus cancer by using indocyanine green fluorescence. Eur Arch Otorhinolaryngol 2014; 271(10):2795–801. doi:10.1007/s00405-013-2846-9.

The KARL STORZ NIR/ICG System



① **IMAGE1 S**
- brilliant FULL HD image quality
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- telescopes for optimal fluorescence excitation and detection; can be used for white light and fluorescence modes
- telescopes with various lengths and diameters

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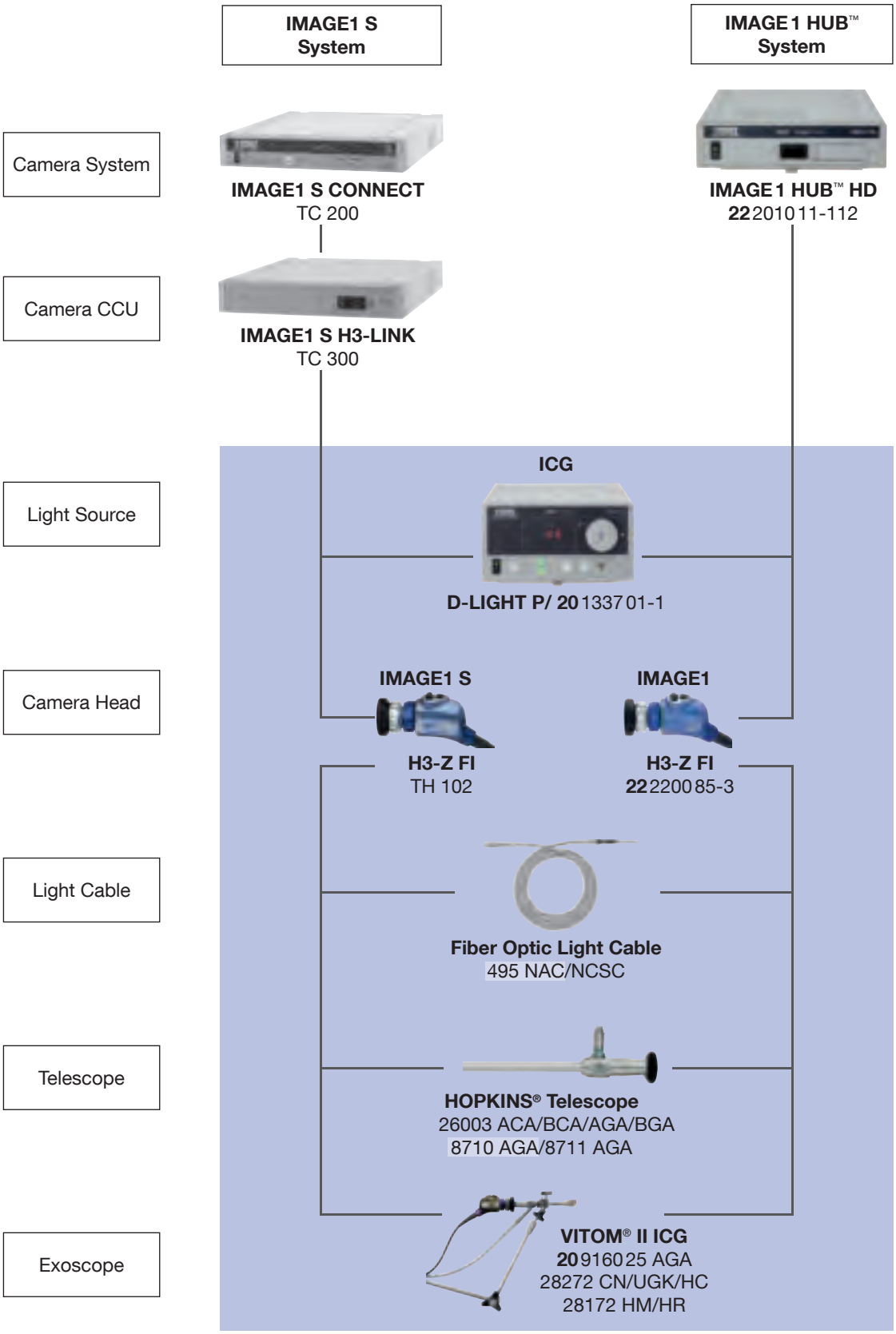
- best daylight spectrum; white light and fluorescence modes
- with enhanced background display

④ **Footswitch**
- fast switch between white light and fluorescence mode

⑤ **Autoclavable fiber optic light cable**
- optimal light transmission in the white light and NIR spectral range

* *SPECTRA A:* **Not for sale in the U.S.**

It is recommended to check the suitability of the product for the intended procedure prior to use.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