AUTOFLUORESCENCE DIAGNOSIS OF CANCERS OF THE UPPER AERODIGESTIVE TRACT
Principles, Techniques and Results

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Autofluorescence Diagnosis of Cancers of the Upper Aerodigestive Tract – Principles, Techniques and Results

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1.0 Cancers of the Upper Aerodigestive Tract

Epidemiology

The estimated annual incidence rate of malignant neoplasms of the upper aerodigestive tract (oral cavity, pharynx and larynx) in the European Union is approximately 143,900 new cases per year, and approx. 46,600 people die from these tumors annually. Europewide, these tumors rank sixth in annual incidence rates and seventh in tumor-related mortality. The male-to-female ratio has remained a fairly constant 4:1 with regard to incidence and mortality. Excessive drinking and smoking are considered the main risk factors for the development of these tumors. The sites of predilection for cancers of the upper aerodigestive tract are distributed as follows: oral cavity (including the tongue) 37.4%, oropharynx 21.0%, nasopharynx 1.9%, hypopharynx 14.5%, larynx 25.3%. The respective 5-year survival rates for all tumor stages in these regions are 43%, 39%, 48%, 27%, and 57%.

On a worldwide scale, cancers of the upper aerodigestive tract rank fifth among malignant diseases in prevalence and sixth in tumor-related mortality. The estimated global incidence is approximately 640,000 new cases annually, resulting in more than 350,000 deaths per year.

Histologically, more than 90% of these tumors are squamous cell carcinomas. This category includes verrucous carcinoma, spindle-cell sarcoma, basaloid cell carcinoma, and lymphoepithelial carcinoma. Other malignancies are adenocarcinomas, malignant lymphomas, and malignant soft-tissue carcinomas and bone tumors.

Both the incidence rates and mortality rates from these cancers have shown a substantial rise during the past decades in most industrialized countries (Figs. 1, 2). In Germany, for example, the incidence rate of upper aerodigestive malignancies rose from 16.0% to 20.9% from 1980 to 2003 while the overall mortality rate rose from 4.5% to 6.5%.

New cases in Germany per 100,000 population

Deaths in Germany per 100,000 population

Fig. 1 Progression of the incidence rate of malignant tumors of the upper aerodigestive tract in Germany since 1980.

Fig. 2 Progression of the mortality rate from malignant tumors of the upper aerodigestive tract in Germany since 1980.
Drawbacks of Conventional Diagnostic Methods

The incidence and mortality statistics could be improved by expanding primary and secondary preventive measures and by establishing innovative treatment modalities. Special emphasis should be placed on early tumor detection especially in high-risk patients, and on clearly delineating the abnormal tissue from healthy surrounding tissue. This should, of course, be followed by prompt, complete surgical resection of the (pre)malignant mucosal areas. There are two main rationales for early detection and accurate delineation:

1. The cure rate for an oral, pharyngeal or laryngeal malignancy depends on the T stage of the tumor, so early diagnosis is imperative24, 28, 39.

2. Leaving residual tumor or premalignant tissue at the resection site predisposes to local recurrence11, 12.

It appears, that the simple precaution of scheduling regular screening examinations in high-risk patients, preferably by the same primary attending physician or even by specially trained assistant medical staff, can significantly improve the long-term prognosis34, 35. But asymptomatic carcinomas in situ as well as microinvasive and early invasive squamous cell carcinomas often present initially as small, harmless-looking areas of reddened mucosa. Therefore, even an experienced examiner may find it difficult to assess the macroscopic appearance of these early lesions. Classic diagnostic imaging procedures such as CT and MRI are not suited for early detection of carcinomas.

Moreover, it is often difficult for surgeons to accurately define tumor margins and detect possible tumor extensions to ensure that the tumor can be fully encompassed in one session. We are faced, then, with a gap in our ability to detect head and neck tumors at an early stage and distinguish them from normal tissue, and it is clear that we need to close this gap.

2.0 Basic Principles of Autofluorescence Diagnosis

2.1 Historical Background

Staining Methods

In response to these challenges, various screening methods have been investigated in an effort to improve the early detection and surface delineation of early or secondary malignant mucosal lesions in the upper aerodigestive tract. Initial staining experiments with Lugol's solution yielded controversial results22, 25, and so this method has not gained wide acceptance. More encouraging results were achieved with toluidine blue, a metachromatic dye of the thiazine group that binds to intracellular DNA and RNA. The special affinity of toluidine blue for neoplastic tissue is probably based on an increased number of nucleic acids in neoplastic cells as well as the presence of larger and more numerous intracellular channels, making it easier for the stain to penetrate the tissue14. There have been a number of experimental and clinical studies on toluidine blue since the 1960s and, at least for the present, its routine use is not recommended based on available data21.

Methods in Fluorescence Diagnosis

As early as 1924, Policard reported on the red fluorescence emitted by endogenous porphyrins on superficial human neoplasms31. Three decades passed before it was discovered that the red fluorescence seen on ulcerating tumor surfaces was the result of microbial porphyrin synthesis by superficial bacteria15. There have been controversial discussions in the literature on tumor-specific enzyme deficits and a relative iron deficiency causing an accumulation of red-fluorescent heme precursors in the neoplastic tissue itself15, 16, 27, 28. Since these reports were published, the evaluation of a standardized diagnostic protocol based on endogenous porphyrin accumulation has become the subject of extensive research in otolaryngology.

By contrast, the phenomenon of autofluorescence (AF), or intrinsic tissue fluorescence, is based on the interaction of various fluorescent tissue compounds called fluorophores, that occur naturally in the body. Alfano et al. were the first authors to describe differences in the autofluorescent properties of normal and malignant tissues, thus establishing a theoretical foundation for the autofluorescence-based detection of tumors1. In 1995, Kolli et al. confirmed these results for mucosal neoplasms of the upper aerodigestive tract20. The practical clinical application of these theoretical findings for implementing new, reliable diagnostic methods has become the subject of numerous investigations in otolaryngology and other specialties.
2.2 Biophysical Principles of Fluorescence Diagnosis

Physical Basis of Fluorescence

Fluorescence is a physical phenomenon based on the interaction of light and matter, as shown schematically in Fig. 3. When photons strike the valence electrons (the electrons in the outermost shell) of an atom, they undergo an absorption process in which the energy of the photons is transferred to the atom or to the molecule containing the atom. This raises the atom or molecule to an excited state, provided the energy of the photons exactly equals the energy difference between two electron states of the atom or molecule. For atoms, these energy differences are precisely defined in terms of absorption lines. With molecules, however, the absorption patterns are spread out into broader bands as a result of intramolecular rotational and vibrational processes.

In the case of atoms and most molecules, the inevitable return from the unstable excited state to the ground state occurs by „non-radiative“ reversal with the release of heat (Fig. 3 1). A small percentage of molecules, however, return to their ground state by the indirect route of „intersystem crossing“ (Fig. 3 2) or by the „radiative“ process of fluorescent light emission (Fig. 3 3). Because a portion of the excitation energy always undergoes non-radiative relaxation before fluorescent light is emitted, the energy of the fluorescent photon is always less than that of the excitation photon. As a result, the emitted fluorescent light is shifted toward longer wavelengths. Because the efficiency of the fluorescent emission (fluorescence quantum efficiency) is very low, the emitted fluorescent light is much weaker than the excitation light, and the measurement of this light requires a very sensitive detection method.

If the concentration distribution of tissue-inherent fluorescent compounds (fluorophores) displays tumor-specific differences, it should be possible to selectively visualize the tumor tissue by means of suitable instrumentation. Two main types of instrumentation may be used for this purpose: (1) spectral (e.g., wavelength-resolving) systems and (2) one- and two-dimensional imaging systems. The fluorescence excitation of the information-bearing fluorochrome in the tissue can be optimized by applying a suitable excitation wavelength. At the same time, a suitable observation filter set can be used to suppress the visualization of reflected excitation light and other non-specific fluorescent compounds. When these measures are taken, a satisfactory image quality can be obtained despite the low quantum yield of the emitted fluorescent light.

Fig. 3
Schematic representation of the theoretical principles of fluorescence. Atoms or molecules that are excited by photons normally return to their ground state by giving off heat 1. A select group of molecules may also return to their ground state by undergoing „intersystem crossing“ 2 or by emitting fluorescence 3.
Basic Principles of Tissue Optics

Apart from fluorophore distribution in the tissue and applied excitation wavelengths, the optical tissue properties act as a third key factor in determining the total tissue fluorescence. The various interactions that may occur between light and tissue (which is an optically „turbid“ medium) are shown schematically in Fig. 4. Typically, a small percentage of the overall incident light that impacts a tissue surface (approximately 2%) is directly reflected while the rest enters the tissue. As a result of refraction and scattering effects, a large percentage of the incident photons either reemerge from the tissue surface by diffuse reflection or are transmitted all the way through the tissue layer. The degree of transmission depends on the tissue thickness. Another portion of the incident light energy is absorbed by various tissue components, most notably melanin, hemoglobin, and especially in the infrared range also water (Fig. 5). Endogenous tissue fluorophores make only a small contribution to overall tissue absorption. As a result of all these factors, the penetration depth of light in tissue increases with the wavelength of the light (Fig. 5).

It is clear, that tissue autofluorescence not only depends on differences in the concentration of fluorophores but is critically influenced by the distribution of fluorophores in different tissue layers.

Fig. 4
Diagram showing the basic types of light-tissue interaction. The light incident upon the tissue is subject to various factors that collectively determine the propagation of the light.

Fig. 5
The upper graph shows the wavelength-dependent efficiency of various tissue absorbers and of the tissue itself. The penetration depth of light in tissue, shown in the lower graph, is inversely proportional to tissue absorption. The range of wavelengths used in the D-LIGHT C/AF System (KARL STORZ, Tuttingen, Germany) is shown in gray.
## Basic Principles of Autofluorescence Diagnosis

The endogenous fluorophores that chiefly determine the autofluorescent properties of tissues are listed in Tab. 1. They consist of respiratory chain enzymes (NADH [nicotinamide adenine dinucleotide], FAD [flavin adenine dinucleotide]) and structural proteins (collagen, elastin, keratin). When excited by an appropriate light stimulus, these compounds emit visible fluorescent light in the violet to green region of the spectrum. Additionally, there are intermediate products of heme biosynthesis (porphyrins) that produce a red fluorescent emission. The aromatic amino acid tryptophan has an excitation band in the ultraviolet range; so it is not useful for the present method of autofluorescence diagnosis and is not listed in the table. We also disregard intra- and extracellular keratin at this point, which is excitable over a broad range of wavelengths but does not appear to be tumor-specific in its occurrence or its fluorescence intensity. It is considered more of an undesired factor that can impede tissue delineation.

While the porphyrins display a very narrow range of excitation and emission properties (Fig. 6), FAD and NADH (Figs. 7, 8) as well as the fluorescent structural proteins collagen, elastin, and keratin have relatively broad excitation and emission bands. Thus, all of these molecules (except tryptophan) are excitable to some degree by exposure to short-wave visible light.

---

**Fig. 6**
Excitation-emission matrix of pure protoporphyrin IX.

**Fig. 7**
Excitation-emission matrix of FAD (flavin adenine dinucleotide).

**Fig. 8**
Excitation-emission matrix of NADH (nicotinamide adenine dinucleotide) in an ex vivo tissue sample.
**Figure 9** shows a greatly simplified schematic diagram of the complex principles that underlie the autofluorescence diagnosis of malignant tumors. With suitable instrumentation, we can detect and measure the tumor-specific differences in fluorescence intensities and wavelengths, which have two main causes:

1. Neoplastic tissue in the upper aerodigestive tract contains smaller concentrations of the intracellular fluorophore enzymes NADH and FAD than normal tissue (in a ratio of usually 100:1). This could account for the lower intensity of cellular autofluorescence found in tumor tissue compared with normal tissue. Additionally, tumor tissue (at least in the upper aerodigestive tract) appears to have greater mitochondrial activity, and thus greater aerobic metabolic activity, than normal tissue. This shifts the balance from fluorescing NADH and FAD to the non-fluorescent compounds NAD and FADH (Fig. 10).

2. The varying distribution of endogenous fluorophores in different tissue layers (Tab. 1) has an important bearing on fluorescence. This is because (pre)malignant thickening of the epithelial layer (Tab. 2) can make it more difficult for the excitation light to enter (and fluorescent signals to leave) the submucous tissue layers. This minimizes the contribution of the structural proteins collagen and elastin to the total fluorescent emission.

### Excitation and emission peaks of the principal endogenous fluorophores

<table>
<thead>
<tr>
<th>Fluorophore</th>
<th>Occurrence</th>
<th>Excitation peaks (nm)</th>
<th>Emission peaks (nm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NADH</td>
<td>ic / ubiquitous</td>
<td>260, 350</td>
<td>440, 450</td>
</tr>
<tr>
<td>FAD</td>
<td>ic / ubiquitous</td>
<td>450</td>
<td>515</td>
</tr>
<tr>
<td>Collagen</td>
<td>ec / submucosal</td>
<td>330</td>
<td>390</td>
</tr>
<tr>
<td>Elastin</td>
<td>ec / submucosal</td>
<td>350</td>
<td>420</td>
</tr>
<tr>
<td>Keratin</td>
<td>ic+ec / epithelial</td>
<td>340</td>
<td>430</td>
</tr>
<tr>
<td>Protoporphyrin</td>
<td>ic / superficial</td>
<td>405</td>
<td>635</td>
</tr>
</tbody>
</table>

Tab. 1

**Tab. 2**

Average epithelial thickness of normal mucosa and (pre)malignant lesions of the upper aerodigestive tract determined microscopically in tissue sections stained with hematoxylin and eosin (adapted from Arens 2005 b).

<table>
<thead>
<tr>
<th>Normal epithelium</th>
<th>145 µm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade III dysplasia, carcinoma in situ</td>
<td>490 µm</td>
</tr>
<tr>
<td>Microinvasive carcinoma</td>
<td>915 µm</td>
</tr>
</tbody>
</table>

**Fig. 10**

Dependence of tissue autofluorescence on the energy metabolism of different cells. As aerobic glycolysis increases (right), the balance is shifted away from fluorescent NADH and FAD, and the intensity of the fluorescence declines.
Thus, with autofluorescence excitation in the near-UV and visible short-wave spectral range, both of these phenomena tend to weaken the green fluorescent emissions that are measured in tumor tissue as compared with normal tissue. The structural protein keratin emits a pale green to whitish fluorescence in response to photoexcitation. Unfortunately, this protein cannot contribute to autofluorescence diagnosis because it does not seem to have a distinct tumor specificity.\(^4\)

Porphyrians emit a red fluorescence, but they are of questionable value in the diagnosis of upper aerodigestive neoplasms.

2.3 Equipment for Fluorescence Diagnosis

Excitation Light Source

The D-LIGHT C/AF System (Fig. 11) is a high-performance system manufactured by KARL STORZ, Germany. Light is generated by the electrical discharge of xenon gas, which becomes ionized and emits a bright light. The power output is in the range of approximately 50 – 500 W and is proportional to the gas pressure.

The white light from the unfiltered xenon short-arc lamp can first be used in the white-light mode for normal illumination of the oral cavity, pharynx, and endolarynx. When desired, an optical band-pass filter can be placed in the observation path to narrow the white-light spectrum to a range of approximately 375–440 nm, producing a violet-blue light. The operator can switch between the white-light and blue-light mode by pushing a button or activating a foot-switch, or this can be done automatically by switching the endo-video camera to the blue-light mode (when both devices are interconnected). Switching to blue-light mode excites endogenous structural proteins (collagens, elastins), nicotinic acid derivatives (NADH), and flavins (FAD) to emit fluorescence in the green spectral range while endogenous porphyrins emit a red fluorescence.

The xenon short-arc lamp in the D-LIGHT C/AF system requires periodic maintenance to ensure a constant and reliable high light output. The lamp has an average life span of approximately 500 hours, after which the light output, and thus the fluorescence intensity of the tissue, show a noticeable decline. When the lamp has been operating for a total of 500 hours, a red warning light is illuminated on the front cover of the D-LIGHT C/AF, indicating that the lamp should be replaced to ensure optimum excitation intensity.

Light Guide

The optimum device for transmitting light to the endoscope is a fluid light cable (e.g., from KARL STORZ, Germany). The blue-light transmission of this light cable exceeds that of conventional fiberoptic cables by a factor of approximately\(^10\). This device has the added advantage of blocking out undesired residual infrared light.
Endoscopes

In order to observe the faint autofluorescence, specular and diffuse reflections of the excitation light must be effectively filtered out of the optical path of the endoscope. Otherwise these reflections, which are many times brighter than the fluorescent signal, would mask the tumor-specific autofluorescence. This problem is solved by using special straight-ahead and forward-oblique telescopes equipped with observation filters near the eyepiece that can be conveniently engaged for fluorescence endoscopy. A large selection of commercially available endoscopes (Fig. 12) are offered with diameters and viewing angles that are optimally suited for the particular geometry of the area to be examined.

Camera System

For videoendoscopic autofluorescence imaging a high-resolution video camera with electronic gain is required. The image captured by the endoscope and transmitted by the light cable is processed further with a CCD (charge-coupled device) camera system (Endovision TRICAM® SL-PDD and Endovision TELECAM® SL-PDD, KARL STORZ, Fig. 13), that converts the light signal into an electrical signal. The heart of the camera system is the CCD sensor chip, which consists of a matrix (PAL version 752 x 582) of photosensitive cells called pixels. When photons strike a camera detector unit (pixel), energy is transferred to the semiconductor electrons of the sensor chip. This induces a so-called „internal photoelectric effect“ by which free electrons (negative) along with positively charged “holes” are generated simultaneously. The strings of liberated electrons are sequentially transferred by applied voltages to an electrode layer on the semiconductor. There, a readout amplifier generates an electrical voltage for each pixel that is proportional to the charge and thus to the quantity of light that the camera has detected. The voltages are electronically processed to yield two-dimensional gray-scale images.

Color images are produced by means of three-chip CCD technology. Three-chip CCD cameras (Endovision TRICAM® SL-PDD) are equipped with a prism block that diverts red and green light to the sides while allowing blue light to pass through. A CCD chip is mounted on the block at each of the sites where the three colors emerge, and the data from the three chips is combined to generate a color image. This type of system provides optimum color and spatial resolution.
A special camera system is needed due to the relatively low intensity of the fluorescence emitted from the tissue. The camera model described above is therefore equipped with a “blue-light mode” (fluorescence mode), which when activated also automatically switches the light source from white light to blue-violet fluorescence excitation light. Whilst in this mode, the camera embodies three modifications that distinguish it from conventional endoscopic cameras:

1. The transmission characteristics have been modified to significantly increase the sensitivity of the camera in the green and red channels over the blue channel, so that endogenous tissue fluorophores are better represented in terms of their wavelength characteristics. This differs from the ordinary white-light mode, in which the various color channels are “white-balanced” as they are in standard cameras to obtain an image with maximum color fidelity.

2. Unlike other commercially available endoscopic cameras, the fluorescence-compatible camera system described above offers maximum image integration times of up to 2 seconds/frame in the blue-light mode so that adequate image brightness can be achieved even at extremely low light intensities. It should be noted, however, that when the integration time is longer than 1/15 of a second, significant “jiggle” artifacts will occur even when the examiner tries to hold the endoscope absolutely still.

3. The gain describes the relationship between the electrons measured in the CCD chip and the output signal of the camera. Increasing the gain setting makes the image brighter but also increases noise, and so a tradeoff must be made between image brightness and image quality. When the system is switched to the blue-light mode, the camera control unit automatically adjusts the gain setting to “High”, increasing it from the “Medium” setting used in the ordinary white-light mode.

Imaging and Documentation
The light source-camera system of KARL STORZ is used most effectively in conjunction with high-quality accessories for image display (TFT flat-screen monitor) and documentation equipment (KARL STORZ AIDA® DVD or KARL STORZ AIDA® Compact II). A color video printer permits the direct, on-site printout of images that can be placed in the patient’s record.
3.0 Clinical Application and Results

Technique of Autofluorescence Diagnosis

In practical terms, autofluorescence diagnosis in the upper aerodigestive tract is similar in many respects to a traditional endoscopic examination using a camera and video documentation unit. The procedure can be performed in the conscious patient or under general anesthesia.

First the white balance is adjusted (with the endoscope filter control set in the middle “W” position and the cold light source and camera in the white-light mode). When the region of interest is localized, standard endoscopy is performed. Before switching to the blue-light mode, the operator should make sure that the room lights have been dimmed and that additional light sources (especially the internal illumination of suspension laryngoscopes) have been switched off; otherwise the stray light could distort the image information in the blue-light mode and prevent an accurate evaluation (Fig. 14). In patients under general anesthesia, meticulous care should be taken to avoid causing small hemorrhages during intubation or laryngoscope insertion, since strong light absorption by the heme molecule in blood pigment can make it very difficult to assess the autofluorescent findings. If hemorrhage occurs, meticulous hemostasis should be obtained and the site cleansed of blood residues prior to activation of the blue-light mode.

After turning the endoscope filter control clockwise to the “AF” position, the operator can simultaneously switch the camera and light source to the blue-light mode by push-button control on the camera head or by pressing a foot pedal switch (if connected). The successful, synchronous switching of both devices can be tested as follows:

- The message “Blue Light Mode” should be displayed in the upper left corner of the screen
- The color of the light emerging from the endoscope should be blue-violet. Failure of the light source to switch to the blue-light mode is usually due to a faulty connection between the two devices.

The autofluorescence examination can now be carried out. By holding the endoscope steady, using a scope with a relatively large cross section, and utilizing the “blue light auto-exposure mode” (standard camera settings), the operator should be able to obtain image sequences of satisfactory brightness with little or no noise or jiggle. Problems in this area can often be resolved by modifying the integration time and adjusting the gain using the push-buttons on the camera head and via the control panel connected to the camera control unit (further details can be found in the operating manual supplied by the manufacturer). Even with a poor light yield and a restless patient, it should be possible to achieve a reasonable tradeoff between image brightness and image quality. Optimum image sharpness is maintained after switching back to the white-light mode by adjusting the distance of the endoscope tip from the tissue or by turning the gold focusing ring on the camera head.

Fig. 14
The internal light of the laryngoscope has been left on, causing distortion of the autofluorescence image.
Figs. 15
Normal appearance of the endolarynx at the level of the vocal folds by indirect laryngoscopy in the white-light mode and blue-light mode.

Figs. 16
Normal appearance of the floor of the mouth in the white-light and blue-light modes.
The autofluorescence sequences displayed on the screen are subjectively classified into three groups:

1. **Normal autofluorescence**: Normally stratified, non-keratinized squamous epithelium with a normal submucosa shows a typical homogeneous, pale green fluorescence (Figs. 15, 16). Transitional areas with different fluorescent properties between the healthy squamous epithelium of the vocal cords and the respiratory epithelium of the supraglottic region usually cannot be identified. Areas of edematous swelling (e.g., Reinke edema, Fig. 17) display normal fluorescence intensities. Superficial capillary blood vessels show greater contrast with surrounding green fluorescence due to light absorption by the hemoglobin.

2. **Increased autofluorescence**: As the superficial cell layers become more keratinized (e.g., in hyperkeratosis), the strong fluorescence of keratin becomes increasingly apparent. These areas show an intense pale green to whitish fluorescence when examined by autofluorescence endoscopy (Fig. 18). A similar appearance is found in superficially heavily keratinizing (pre)malignant mucosal lesions, so that sites that show increased autofluorescence should be biopsied to exclude malignancy.
Figs. 19
Direct laryngoscopic appearance of a pT1b glottic carcinoma of the anterior commissure in the white-light and blue-light modes.

Figs. 20
Appearance of a moderately differentiated squamous cell carcinoma of the right tonsil that has spread to the tongue base and crossed the midline.

3. Decreased autofluorescence: Sharply circumscribed areas of decreased autofluorescence, sometimes containing reddish spots, are suspicious for (pre)malignant change (Figs. 19, 20) and should definitely be investigated by tissue biopsy. Tumor precursors (e.g., severe grades of epithelial dysplasia) cannot be positively distinguished from invasive cancers based on their autofluorescent properties. The intensity of autofluorescence is decreased for two reasons: (1) the concentration of fluorescent molecules is decreased in mucosa that has undergone malignant transformation, and (2) thickening of the epithelial layer obscures the connective-tissue autofluorescence coming from the submucosa (see “Biophysical Principles of Fluorescence Diagnosis”). Inflammatory thickening of the mucosa (Fig. 21) and other changes such as submucous hemorrhages (Fig. 22) and fibrotic changes due to previous surgery (Fig. 23) may also cause decreased autofluorescence for the same reasons. However, inflammatory and other non-neoplastic thickening usually cause less well-defined areas of decreased autofluorescence than neoplastic changes, so that a differentiation is often possible for the experienced investigator. Nevertheless, any lingering doubts should be resolved by tissue biopsy.
Figs. 21
Chronic laryngitis in the anterior glottic region visualized by direct laryngoscopy. The blue-light image shows a patchy, ill-defined area of decreased autofluorescence intensity.

Figs. 22
Reinke edema with hemorrhagic areas visualized by direct laryngoscopy. The light-absorbing subepithelial blood residues lead to patchy, ill-defined areas of decreased autofluorescence intensity.

Figs. 23
Incipient fibrotic scar formation and local inflammatory reaction seven days after the resection of a pT1 G3 squamous cell carcinoma of the anterior floor of the mouth.
Extensive infiltration of the tongue base by a T4 G2 tonsillar carcinoma. The difficulty of visualizing the affected region limits our ability to delineate tumor extent and to define the benign or malignant nature in both the white-light and blue-light modes.

Normal red fluorescence on the dorsum of the tongue caused by porphyrin-forming bacteria.

Well-exposed anatomical areas that are normally lined with smooth mucosa such as the oral cavity, oropharynx, and endolarynx are the easiest areas to evaluate in the autofluorescence mode. Exceptions are the body and base of the tongue and the hypopharynx, which do not seem especially suitable for autofluorescence diagnosis. This is because it is often difficult to sufficiently inspect the hypopharynx and tongue base (Fig. 24) endoscopically, while at the same time naturally occurring porphyrin-forming bacteria on the dorsum of the tongue cause a physiological red fluorescence that adversely affects the assessment of autofluorescence intensities. (Fig. 25).

Despite all of these practical tips, the acquisition of autofluorescent sequences and their accurate clinical evaluation require a high degree of expertise, that can be gained only through a learning process based on the conduct of numerous examinations.
Results

The two groups of authors who contributed to this brochure have documented the successful use of the AF system in the early diagnosis and differentiation of oral, pharyngeal, and laryngeal squamous cell carcinomas based on experience in several hundred patients examined within the framework of experimental clinical studies. The results of this research have already appeared in several publications² ⁵ ⁹ ²³.

In one prospective study in 111 patients with laryngeal lesions of suspected malignancy, squamous cell carcinomas were detected with a sensitivity of 97% and a specificity of 84% by direct autofluorescence laryngoscopy using the system described above²³. In a subsequent study of 116 patients evaluated by indirect autofluorescence laryngoscopy, cancerous lesions were diagnosed with a sensitivity of 90% and a specificity of 87%² (Tab. 3). In a smaller study of 56 patients with suspected or histologically confirmed oral or oropharyngeal carcinomas, the lesions were diagnosed with a sensitivity of 88% but a specificity of only 56%⁶ (Tab. 3). The examiners in these studies applied the same subjective criteria for classifying „suspicous“ and „normal“ findings that are described under “Technique of Autofluorescence Diagnosis” in this brochure. The above studies also included spectral analyses, that showed a marked difference in the autofluorescence intensities of tumor tissue and normal tissue (Fig. 26). These spectral findings provide the main theoretical basis for the subjectively evaluated image data and (along with histopathological correlations) establish a solid scientific foundation for autofluorescence diagnosis.

Additionally, all of the studies showed that the combination of white-light and autofluorescence endoscopy could significantly increase both the sensitivity and specificity of the diagnosis of (pre)malignant mucosal lesions in the upper aerodigestive tract. The authors also emphasized the improved visual delineation of neoplastic areas with respect to healthy mucosa, making it easier to perform a complete surgical resection. For example, there were a number of cases in which dysplastic margins of invasive tumors could be visualized (and removed in one sitting) only by autofluorescence imaging owing to the elevated contrast between affected and normal mucosa. The authors also reported on the lack of invasiveness and practical convenience of the procedure as additional advantages.

False-positive findings (decreased autofluorescence with a nonmalignant histopathology) were relatively common and resulted mainly from scar tissue or pronounced local inflammatory reactions in the mucosa (e.g., postirradiation mucositis). False-negative findings (negative autofluorescence despite (pre)malignant histopathology) were generally rare and resulted mostly from pronounced hyperkeratosis of the examined areas that caused optical „masking“ of clinically significant lesions.

<table>
<thead>
<tr>
<th>Histopathological findings</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Pre) malignant (D III/OC, PEC)</td>
<td>97.3%</td>
<td>83.8%</td>
</tr>
<tr>
<td>Non-malignant (normal tissue, D I/II)</td>
<td>90.5%</td>
<td>86.8%</td>
</tr>
<tr>
<td>Direct AF laryngoscopy (n=111 biopsies)</td>
<td>Suspicious: 72 / Not suspicious: 6</td>
<td></td>
</tr>
<tr>
<td>Indirect AF laryngoscopy (n=116 biopsies)</td>
<td>Suspicious: 53 / Not suspicious: 16</td>
<td></td>
</tr>
<tr>
<td>AF diagnosis (OC/OP) (n=137 biopsies)</td>
<td>Suspicious: 72 / Not suspicious: 24</td>
<td></td>
</tr>
</tbody>
</table>

AF: autofluorescence; OC: oral cavity; OP: oropharynx

Tab. 3 Summary of the results of the contributing authors on the sensitivity and specificity of autofluorescence diagnosis (adapted from Malzahn 2002, Betz 2002, and Arens 2004).

Fig. 26 Examples of fluorescence spectra recorded from tumor tissue and normal tissue in response to excitation with the D-LIGHT C/AF System. Note that the intensities in normal tissue are substantially higher than in tumor tissue.
It may be possible to further optimize the method (especially for detecting oral and oropharyngeal tumors) by additionally administering 5-aminolevulinic acid via inhalation for pharyngo-laryngeal and, via oral rinse, for intraoral cancers. This compound induces a tumor-selective accumulation of red fluoresenting protoporphyrin IX (see survey article).

Another study was conducted to determine how the value of autofluorescence diagnosis might relate to the clinical experience of the examiner. There were a total of 12 participants: 6 with < 2 years clinical experience in otolaryngology, 3 with < 5 years experience, and 3 with > 7 years experience. Following a brief introduction to the method, each participant was shown 30 pairs of slides with microscoposcopic findings. In each pair of images, the first image was acquired in the white-light mode and the next image in the autofluorescence mode. For each image, the participant was asked to make a clinical assessment of the mucosal lesion that was displayed. The participants were also asked to rate the subjective information gained from the AF image with regard to lesion’s extent and therapeutic decision making.

Of the 30 cases presented, the least experienced colleagues (< 2 years) changed their initial impression of the white-light image after seeing the AF image in an average of 9 cases (30%). The more experienced colleagues (< 5 years and > 7 years) changed their assessment in only 5 cases (16%) and 4 cases (13%), respectively. In 78% of the cases where the least experienced colleagues revised their initial impression after being shown the autofluorescence images, their clinical assessment was improved. Moreover, the younger colleagues reported an information gain on lesion extent in 16 cases (53%) and in 12 cases (40%), respectively. The experienced specialists, on the other hand, revised their assessment of lesion extent in only 7 cases (23%) (Fig. 27). There were 7 cases (23%) in which the least experienced participants changed their therapeutic decision based on the AF findings, compared with 4 cases (13%) in the more experienced group and 2 cases (7%) in the highly experienced group (Fig. 27).

These results indicate that especially colleagues with less oncological experience can improve their assessment of suspicious mucosal lesions by means of autofluorescence diagnosis. The more experienced the laryngologist, however, the less likely he or she is to benefit from the additional information provided by this technique. Thus, autofluorescence diagnosis would appear to be most helpful in the clinical training of young physicians in continuing education and also for ENT physicians in private practice who see far fewer suspicious lesions than their colleagues who practice at centers specializing in oncology.

**Conclusion**

The main advantage of autofluorescence diagnosis using the system described is that it provides a consistently improved contrast between tumor tissue and normal tissue, which can facilitate early diagnosis and surface demarcation. This is the basis for the high sensitivity of the method, which approaches 100%. Tissue altered by chronic inflammation is particularly likely to cause false-positive findings, resulting in a relatively low specificity. The procedure is free of side effects and can be performed on an outpatient basis or intraoperatively under general anesthesia. Also, the equipment is user-friendly and easy to handle. In summary, we may conclude that autofluorescence diagnosis provides an efficient adjunctive option to traditional methods of tumor diagnosis in the upper aerodigestive tract.
Figs. 28
Glottic laryngeal carcinoma (pT1b) visualized by direct laryngoscopy.

Figs. 29
Glottic laryngeal carcinoma (pT1a) visualized by indirect laryngoscopy.

Figs. 30
Glottic laryngeal carcinoma (pT1b) visualized by indirect laryngoscopy.
Figs. 31
HPV-associated papillomatosis of the larynx visualized by direct laryngoscopy.

Figs. 32
Intraoperative direct laryngoscopy as a means of control following the resection of a pT1b glottic laryngeal carcinoma.

Figs. 33
Inflammatory myofibroblastic tumor of the anterior commissure visualized by direct laryngoscopy.
Figs. 34
Poorly differentiated squamous cell carcinoma of the anterior floor of the mouth (pT2).

Figs. 35
Moderately differentiated squamous cell carcinoma of the uvula and right anterior pillar (pT2).
References


10. CHANG SK: Understanding the variations in fluorescence spectra of gynecologic tissue. Doctoral thesis at the University of Texas, Austin TX, USA (2004)


HOPKINS® Telescopes
for Autofluorescence/Photodynamic Diagnosis (PDD) during rigid direct laryngoscopy

8712 AP – CP

8712 AP  HOPKINS® Straight Forward Telescope 0°, enlarged view, for autofluorescence/photodynamic diagnosis (PDD), diameter 5 mm, length 24 cm, autoclavable, fiber optic light transmission and filter exchanger incorporated, color code: green

8712 BP  HOPKINS® Forward-Oblique Telescope 30°, enlarged view, for autofluorescence/photodynamic diagnosis (PDD), diameter 5 mm, length 24 cm, autoclavable, fiber optic light transmission and filter exchanger incorporated, color code: red

8712 CP  HOPKINS® Lateral Telescope 70°, enlarged view, for autofluorescence/photodynamic diagnosis (PDD), diameter 5 mm, length 24 cm, autoclavable, fiber optic light transmission and filter exchanger incorporated, color code: yellow

495 FP  Fluid Light Cable, diameter 3 mm, length 250 cm

8711 AP

8711 AP  HOPKINS® Straight Forward Telescope 0°, for autofluorescence/photodynamic diagnosis (PDD), diameter 10 mm, length 20 cm, autoclavable, fiber optic light transmission and filter exchanger incorporated, color code: green

495 FR  Fluid Light Cable, diameter 5 mm, length 250 cm

8710 AP

8710 AP  HOPKINS® Straight Forward Telescope 0°, for autofluorescence/photodynamic diagnosis (PDD), diameter 5.8 mm, length 20 cm, autoclavable, fiber optic light transmission and filter exchanger incorporated, color code: green

495 FP  Fluid Light Cable, diameter 3 mm, length 250 cm
**HOPKINS® Telescopes**

for Autofluorescence/Photodynamic Diagnosis (PDD) during indirect laryngo-pharyngoscopy


**Tele-Laryngoscope**, with integrated HOPKINS® lateral telescope 70°, for autofluorescence/photodynamic diagnosis (PDD), angle of view 50°, diameter 5.8 mm, length 20 cm, **autoclavable**, fiber optic light transmission and filter exchanger incorporated, color code: yellow

**Tele-Laryngo-Pharyngoscope** with integrated HOPKINS® Lateral Telescope 90°, for autofluorescence/photodynamic diagnosis (PDD), 4x magnification, focusing device, **autoclavable**, diameter 10 mm, working length 15 cm, fiber optic light transmission and filter exchanger incorporated, color code: blue

**Fluid Light Cable**, diameter 3 mm, length 250 cm

*It is recommended to check the suitability of the product for the intended procedure prior to use.*
**HOPKINS® Telescopes**

for Autofluorescence/Photodynamic Diagnosis (PDD) of Nose and Paranasal Sinuses, diameter 4 mm, length 18 cm

for Diagnosis and Detection of Carcinomas

7230 AP – FP

- **HOPKINS® Straight Forward Telescope 0°**, enlarged view, for autofluorescence/photodynamic diagnosis (PDD), diameter 4 mm, length 18 cm, **autoclavable**, fiber optic light transmission and filter exchanger incorporated, color code: green

7230 BP

- **HOPKINS® Forward-Oblique Telescope 30°**, enlarged view, for autofluorescence/photodynamic diagnosis (PDD), diameter 4 mm, length 18 cm, **autoclavable**, fiber optic light transmission and filter exchanger incorporated, color code: red

7230 FP

- **HOPKINS® Forward-Oblique Telescope 45°**, enlarged view, for autofluorescence/photodynamic diagnosis (PDD), diameter 4 mm, length 18 cm, **autoclavable**, fiber optic light transmission and filter exchanger incorporated, color code: black

495 FS

- **Fluid Light Cable**, diameter 2 mm, length 220 cm
D-Light C/AF-System

Special features:
- For photodynamic early diagnosis in the upper airways
- Facility for switching between reduced white light, autofluorescence mode and Protoporphyrin IX fluorescence mode (optional)
- With integrated KARL STORZ Communication Bus (KARL STORZ-SCB®)

Specifications:

<table>
<thead>
<tr>
<th>Lamp Type</th>
<th>XENON 15 V, 300 Watt</th>
</tr>
</thead>
<tbody>
<tr>
<td>Color Temperature</td>
<td>6000 K</td>
</tr>
<tr>
<td>Light Outlets</td>
<td>1</td>
</tr>
<tr>
<td>Light Intensity Adjustment</td>
<td>continuously adjustable, either via a membrane keyboard or KARL STORZ Communication Bus Signal</td>
</tr>
<tr>
<td>Dimensions w x h x d</td>
<td>305 x 165 x 335 mm</td>
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<tr>
<td>Weight</td>
<td>11 kg</td>
</tr>
<tr>
<td>Certified to</td>
<td>IEC 601-1 and UL 544, protection class 1/CF</td>
</tr>
</tbody>
</table>

Cold Light Fountain D-LIGHT C/AF SCB

including:
Cold Light Fountain D-LIGHT C/AF, with KARL STORZ-SCB®, power supply: 100 – 125/220 – 240 VAC, 50/60 Hz
Mains Cord
SCB Connecting Cable, length 100 cm
One-Pedal Footswitch, one-stage, for switch function
**TRICAM® SL II**

Camera Control Unit

---

![TRICAM® SL II Camera Control Unit SCB](image)

202230 11U1  **TRICAM® SL II Camera Control Unit SCB**

color systems **PAL/NTSC**, with **KARL STORZ-SCB®** and integrated digital Image Processing Module including:

**TRICAM® SL II Camera Control Unit SCB**

- **Mains Cord**
- **Keyboard**, with US English character set
- 2x **Connecting Cable**, for controlling peripheral units, length 180 cm
- **BNC/BNC Video Cable**, length 180 cm
- **S-Video (Y/C) Connecting Cable**, length 180 cm
- **Special RGBS Connecting Cable**, length 180 cm
- **SCB Connecting Cable**, length 100 cm
- **DV Connecting Cable**, 6 pin to 4 pin, length 450 cm

---

**Specifications:**

<table>
<thead>
<tr>
<th>Video Output</th>
<th>Input</th>
<th>Control Out/Input</th>
<th>Camera Control Unit (CCU)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Composite signal at BNC socket</td>
<td>Keyboard input for character generator and control functions, 6-pin Mini-DIN socket</td>
<td>KARL STORZ-SCB® to 6 pin Mini-DIN socket (2x), 3.5 mm stereo jack plug (ACC 1, ACC 2)</td>
<td>Dimensions: 305 x 88 x 254 mm (w x h x d)</td>
</tr>
<tr>
<td>- S-Video signal to 4 pin Mini-DIN socket (2x)</td>
<td>- RGBS signal to 4x BNC sockets</td>
<td>- Composite signal at BNC socket</td>
<td>Weight: 2.7 kg</td>
</tr>
<tr>
<td>- RGBS signal to 4x BNC sockets</td>
<td>- DV signal to 6 pin DV socket</td>
<td>- Power Supply: 100-240 VAC, 50/60 Hz</td>
<td></td>
</tr>
</tbody>
</table>

Certified to IEC 601-1, 601-2-18, CSA 22.2 No. 601, UL 2601, and CE acc. to MDD, protection class 1/BF.
TRICAM® SL II
Camera Heads

For use with TRICAM® SL II Camera Control Unit 202230 11U1

TRICAM® PDD Three-Chip Camera Head

<table>
<thead>
<tr>
<th>Image Sensor</th>
<th>Pixels</th>
<th>Resolution</th>
<th>Signal-to-Noise Ratio</th>
<th>AGC</th>
</tr>
</thead>
<tbody>
<tr>
<td>- 3x 1/3&quot; CCD chip</td>
<td>- 752 (H) x 582 (V) pixels per chip (PAL)</td>
<td>min. 750 lines (horizontal)</td>
<td>&gt; 60 dB</td>
<td>Microprocessor-controlled</td>
</tr>
<tr>
<td></td>
<td>- 768 (H) x 494 (V) pixels per chip (NTSC)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Min. Sensitivity | Exposure Control | Lens

- Parfocal Zoom
- PDD Camera Head:
  - < 0.05 Lux in integration mode ¼ sec.,
  - 3 Lux (f = 1.4 mm) in standard mode
- 1/4 sec.-1/sec. (PAL)
- 1/4 sec.-1/sec. (NTSC)
- PDD: integrated Parfocal Zoom Lens, f = 25-50 mm

Specifications:

TFT-Flat Screen Monitor
Multinorm Liquid Crystal Display, PAL and NTSC with automatic switch-over

19" HD Monitor, color systems PAL/NTSC, max. screen resolution 1280 x 1024, image format 4:3, power supply 100 – 240 VAC, 50/60 Hz, wall-mounted with VESA 100 adaption, including:
External 24 VDC Power Supply
Mains Cord

Monitor Stand, with integrated cable channel, for use with 26" HD Monitor 9826 NB and 19" HD Monitor 9619 NB
Data Management and Documentation

KARL STORZ AIDA® – Exceptional documentation

The name AIDA stands for the comprehensive implementation of all documentation requirements arising in surgical procedures: A tailored solution that flexibly adapts to the needs of every specialty and thereby allows for the greatest degree of customization.

This customization is achieved in accordance with existing clinical standards to guarantee a reliable and safe solution. Proven functionalities merge with the latest trends and developments in medicine to create a fully new documentation experience – AIDA.

AIDA seamlessly integrates into existing infrastructures and exchanges data with other systems using common standard interfaces.

WD 200-XX® AIDA Documentation System, for recording still images and videos, dual channel up to FULL HD, 2D/3D, power supply 100–240 V AC, 50/60 Hz including:

- USB Silicone Keyboard, with touchpad
- ACC Connecting Cable
- DVI Connecting Cable, length 200 cm
- HDMI-DVI Cable, length 200 cm
- Mains Cord, length 300 cm

WD 250-XX® AIDA Documentation System, for recording still images and videos, dual channel up to FULL HD, 2D/3D, including SmartScreen® (touch screen), power supply 100–240 V AC, 50/60 Hz including:

- USB Silicone Keyboard, with touchpad
- ACC Connecting Cable
- DVI Connecting Cable, length 200 cm
- HDMI-DVI Cable, length 200 cm
- Mains Cord, length 300 cm

*XX Please indicate the relevant country code (DE, EN, ES, FR, IT, PT, RU) when placing your order.
Workflow-oriented use

**Patient**
Entering patient data has never been this easy. AIDA seamlessly integrates into the existing infrastructure such as HIS and PACS. Data can be entered manually or via a DICOM worklist. All important patient information is just a click away.

**Checklist**
Central administration and documentation of time-out. The checklist simplifies the documentation of all critical steps in accordance with clinical standards. All checklists can be adapted to individual needs for sustainably increasing patient safety.

**Record**
High-quality documentation, with still images and videos being recorded in FULL HD and 3D. The Dual Capture function allows for the parallel (synchronous or independent) recording of two sources. All recorded media can be marked for further processing with just one click.

**Edit**
With the Edit module, simple adjustments to recorded still images and videos can be very rapidly completed. Recordings can be quickly optimized and then directly placed in the report. In addition, freeze frames can be cut out of videos and edited and saved. Existing markings from the Record module can be used for quick selection.

**Complete**
Completing a procedure has never been easier. AIDA offers a large selection of storage locations. The data exported to each storage location can be defined. The Intelligent Export Manager (IEM) then carries out the export in the background. To prevent data loss, the system keeps the data until they have been successfully exported.

**Reference**
All important patient information is always available and easy to access. Completed procedures including all information, still images, videos, and the checklist report can be easily retrieved from the Reference module.
Equipment Cart

Equipment Cart
wide, high, rides on 4 antistatic dual wheels equipped with locking brakes 3 shelves, mains switch on top cover, central beam with integrated electrical subdistributors with 12 sockets, holder for power supplies, potential earth connectors and cable winding on the outside,

Dimensions:
Equipment cart: 830 x 1474 x 730 mm (w x h x d),
shelf: 630 x 510 mm (w x d),
caster diameter: 150 mm

including:
Base module equipment cart, wide
Cover equipment, equipment cart wide
Beam package equipment, equipment cart high
3x Shelf, wide
Drawer unit with lock, wide
2x Equipment rail, long
Camera holder

Monitor Swifel Arm,
height and side adjustable, can be turned to the left or the right side, swivel range 180°, overhang 780 mm, overhang from centre 1170 mm, load capacity max. 15 kg, with monitor fixation VESA 5/100, for usage with equipment carts UG xxx
Recommended Accessories for Equipment Cart

**UG 310**

**Isolation Transformer,**
200 V–240 V; 2000 VA with 3 special mains socket, expulsion fuses, 3 grounding plugs, dimensions: 330 x 90 x 495 mm (w x h x d), for usage with equipment carts UG xxx

**UG 410**

**Earth Leakage Monitor,**
200 V–240 V, for mounting at equipment cart, control panel dimensions: 44 x 80 x 29 mm (w x h x d), for usage with isolation transformer UG 310

**UG 510**

**Monitor Holding Arm,**
height adjustable, inclinable, mountable on left or right, turning radius approx. 320°, overhang 530 mm, load capacity max. 15 kg, monitor fixation VESA 75/100, for usage with equipment carts UG xxx
Notes: