

Intraoperative Imaging of the Microanatomy and Integration into the Clinical Workflow

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With current and future trends in surgery focusing more and more on minimally invasive procedures, intraoperative imaging technologies and approaches play an increasingly important role. At the moment, the research focus on the myriad of techniques outlined in the following article particularly centers around the improvement of intraoperative imaging as a diagnostic support tool for successful minimally invasive therapeutic measures.

One important convergence trend in minimally invasive surgery is the integration of diagnostic measures with therapeutic procedures. For example, the integration of patient examination and treatment has merged into modern practice within interventional radiology and intraoperative imaging. Intraoperative imaging has progressed tremendously in the area of technique development. Conventional imaging modules can be built into specially equipped operative theaters, and streamlined imaging systems can be applied for mobile intraoperative use to integrate imaging into a conventional OR.

Current medical research focuses on imaging of tissue clusters (microanatomy) and on visualization at the subcellular level (in vivo histology). One very important point to consider is the intraoperative differentiation of malignant or benign pathologies. Various research groups are working on the implementation of imaging modalities which allow an "optical biopsy" with sufficient sensitivity and specificity. The long-term goal is to shrink, diagnose and treat melanomas in a single surgical procedure.

High-resolution ultrasonography (HR-US) and endosonography are well-established imaging

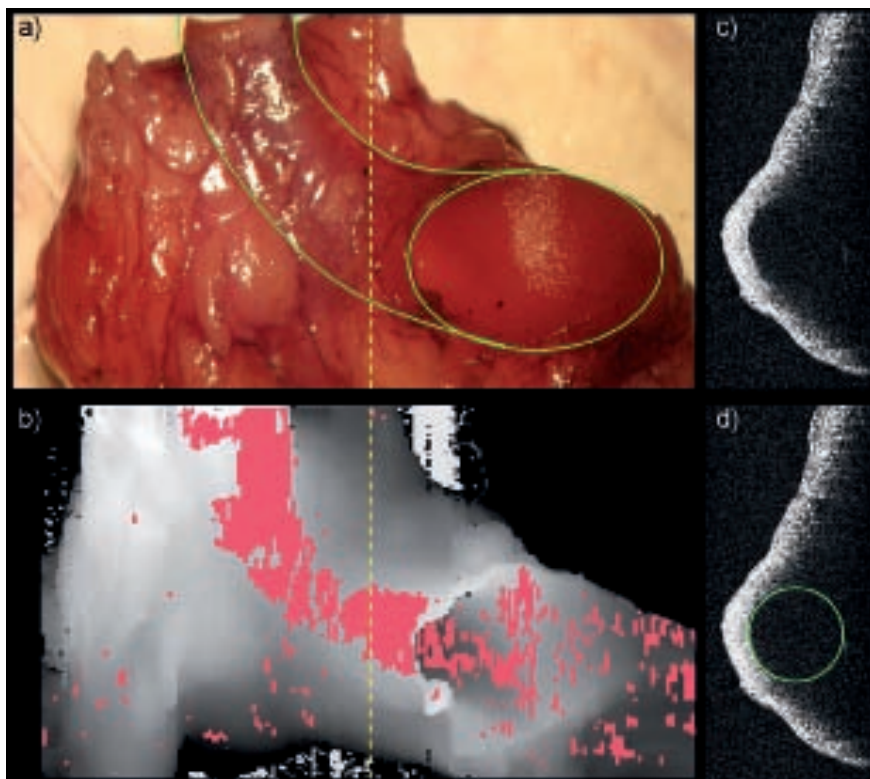


Fig. 1: Specimen with a vein embedded into fatty and connective tissue (a). The green lines indicate the course of the vessel. Picture b) shows a grey-scaled height map of the specimen extracted from a set of 184 consecutive 2D OCT images. The reddened areas have been generated by an automatic algorithm for detection of vessels within the 2D OCT images. Pictures c) and d) show the original OCT image corresponding to the position which is marked with the dashed yellow line in pictures a) and b). In picture d) the vessel is marked in green color.

techniques that can fulfill the demands for low-cost, non-ionizing and ease of use. HR-US is often referred to as ultrasound biomicroscopy (UBM), which has found clinical use primarily in ophthalmology for a number of procedures, including the diagnosis of squamous cell carcinomas.

Contact endoscopy (CE) is a further development of conventional rigid endoscopes, routinely used in otolaryngology. At magnifications up to factor 150, the most superficial cell layers of mucosal processes can be examined. While CE does not allow for cross-sectional imaging, it does provide visualization of the mucosal vessel structures (e.g. teleangiectasias) in unstained mucosa. Cell membranes and nuclei can be visualized after being stained with non-toxic agents such as methylene blue.

Optical coherence tomography (OCT) is a cross-sectional imaging method based on back-scattering of photons emitted by a broadband light source (e.g. superluminescence diodes). This imaging method is essentially comparable to the principle of sonography. The level of depth is displayed when

the signal beam is replaced with a set split reference beam. One- or two-dimensional scans of the probe beam provide 2D or 3D visualizations of the specimen at a resolution of approximately 10 μm . Ex vivo experimental devices achieve up to 3 microns of axial resolution. The depth of penetration is approximately 0.5 to 2 mm, depending on tissue type.

OCT is now established in ophthalmology as a diagnostic tool for the ocular fundus. Research groups are currently exploring the potential of this technique for in vivo examination of cutaneous or mucosal processes. Intraoperative OCT allows the identification of tissue borders. This could be an enormous future advantage for radical tumor resection combined with maximum preservation of function, or for identification of submucosal tumor growth, as it is sometimes seen in adenoidcystic carcinomas. Among others, new light sources such as femtosecond-lasers are investigated as a basis of an integrated device for optical biopsy and therapeutic laser therapy. These approaches also require a (semi-)automatic interpretation of the OCT imaging data (Fig. 1).

Laser scanning confocal microscopy (LSM) is known as fluorescence imaging in experimental settings. Some manufacturers provide endoscopic LSMs for examination of colorectal neoplasms or pathologies predominantly of the urinary bladder. A refinement of LSM is Multiphoton Microscopy (MM) with even better axial resolution, allowing imaging of subcellular structures as nuclei and filaments. Increase of laser fluence enables the investigator to selectively cut or excise parts of these structures. An adaptation of these systems to in vivo conditions and the evaluation of a potential medical benefit have to be resolved in the future (Fig. 2).

In contrast to the techniques explained above, autofluorescence and induced fluorescence do not represent the histologic structure of tissues or cells, but rather depend on alterations of the cell metabolism. Autofluorescence (AF) is mainly used in bronchoscopies for detection of altered mucosa. Its principle is based on the ability of flavin mononucleotide (FMN) in normal cells, to emit green fluorescence when they are exposed to blue light. Due to a lack of FMN in malignant cells they do not emit green fluorescence, and one obtains a negative image of the tumors. AF has also been validated by some authors for inspection of the upper airways, especially the larynx. In contrast, induced fluorescence (IF) is based on selective accumulation of protoporphyrine IX (PP IX) in neoplastic tissue that can be detected as a violet fluorescence. Induction of tumor tissue to fluorescence is achieved via administration of 5-aminolevulinic acid (5-ALA, a precursor of PP IX) that can be applied via inhalation, i.v. injection and peri- or intra-tumoral infiltration. It accumulates more or less selectively in tissues with a high regeneration rate. Especially in the mouth cavity and the oropharynx, it is well known that even normal cells contain physiologically relevant quantum of PP IX, so that false-positive results have to be expected in these areas.

Integration of the diverse imaging methods into the clinical environment is a demanding issue due to several reasons:

- High-resolution implies large datasets. Pre-interpretation of raw data could be an adequate solu-

tion, but who will be responsible for any iatrogenic impairment caused by misleading filtering and presentation of imaging data?

- Subcellular imaging provides information on single cells, but the surgeon has to treat the entire tumor. Surgery by hand is accurate to a tenth of a millimeter maximally, visual control via surgical microscopes and micromanipulators for laser surgery are mandatory. But there is not only the problem of alignment of different scales, one also has to relocalize the additional imaging information within the patient's anatomy. Intraoperative edematous swelling or tissue shift due to partial tumor removal can alter the spatial configuration completely.

- Apart from costs and spatial restriction, communication problems do often hinder the parallel use of intraoperative assistance devices. Most manufacturers protect their hardware interfaces, conceal software communication protocols and open them only for research purposes. Truly integrated surgery

Fig. 2: Femtosecondlaser cut of a single actin fiber in a living endothelial cell. The fiber retracts after cutting due to tension. Specimen: bovine capillary endothelial cells, fixed, stained with green fluorescence protein.

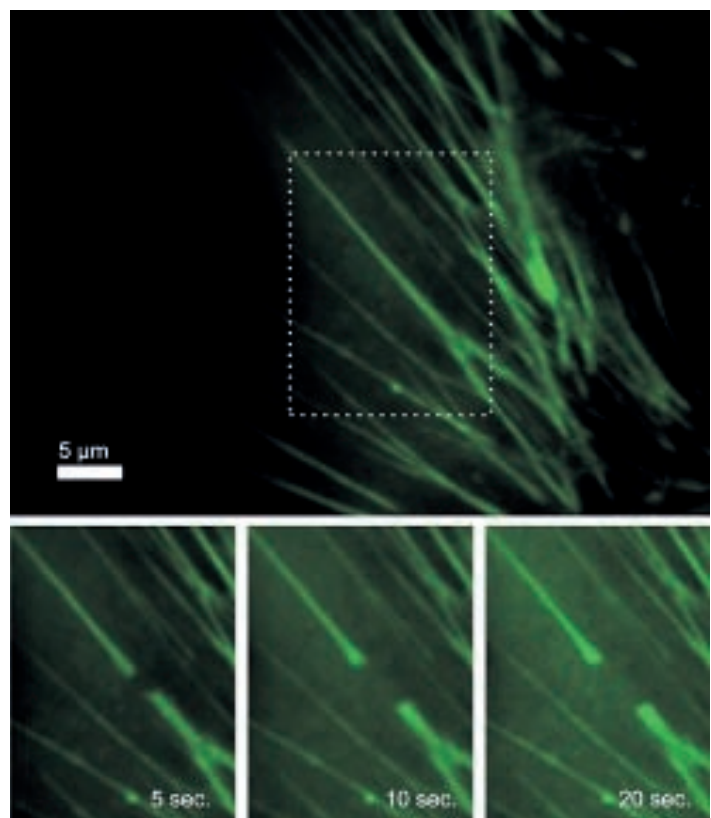




Fig. 3: MultiVision enables the surgeon to superimpose color contours and data into both eyepieces of the surgical microscope. Moreover, video data, pre-operative data, endoscope images as well as the entire touchscreen interface can be injected into the MultiVision display.

environments can only be implemented by (cooperation of) market leaders of diverse areas of medical engineering. Good examples for all-embracing multimodal surgical equipment are the OR1 from Storz or the BrainSuite of BrainLAB with an integrated ZEISS surgical microscope. The ZEISS surgical microscopes offer an intuitive open interface for almost any kind of visual additional information via MultiVision™ technology (Fig. 3). Furthermore, Carl Zeiss provides hardware and software interfaces for navigation systems; OPMI® Pentero® is even equipped with features for video documentation and networking capabilities via DICOM.

Highly-specific solutions and custom-made designs without open-source base will not promote any true integration. Only a fruitful collaboration of research, clinic and industry will compass further amelioration of high-standard medicine which meets ergonomic aspects, soaring financial limitations and the expectations of today's patients.

Image courtesy:

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