

HotTopic

Laser endomicroscopy for the intraoperative diagnostic**Laser-Endomikroskopie für die intraoperative Diagnostik**

It is not always easy to detect malignant tumor tissue in the digestive organs. “For example, it is often necessary to take several biopsies in the bile duct before diagnostic clarity is achieved” says Prof. Schirra, Senior Physician at the Medical Clinic II at Ludwig-Maximilians-University (LMU) Munich. It is not possible with currently available diagnostic methods to visually assess whether the site harboring the malignant transformation has been “caught” in the biopsy process. However, the introduction of new methods might improve the success rate considerably in the not too distant future. Using probe-based confocal laser endomicroscopy (pCLE), it is possible, during the endoscopic examination of the bile duct, to identify the pattern of a suspicious area (Figure 1). According to a preliminary study by Meining et al. [1], “the biopsy success rate increased from 75% to 90% when pCLE was applied” explained Prof. Schirra. For gastroenterologists, this is a “considerable step forward”.

The new device (Cellvizio®; Mauna Kea Technologies, Paris, France) was bought with financial support from the German Research Foundation (DFG), by T.E.A.M., a network of twelve clinics and institutes, most of them being associated with the University Hospital of Munich. T.E.A.M. stands for “Transluminale und Endoskopische Arbeitsgemeinschaft München” and according to their spokesperson, Physicist Dr. Herbert Stepp, “its aim is to conduct pioneering scientific research in intraoperative diagnostics”.

The development of the intraoperative diagnostics has a tradition at the University Hospital of Munich. In the early 1990s, the laser research laboratory, at that time a part of the urological clinic, developed a fluorescence method that depicted cancer tissue as a brilliant red color (Figure 2).

This has been used routinely since 2005, providing a reliable method for the diagnosis of bladder cancer and brain tumors. It visualizes cancer cells within the bladder epithelium that previously could not be seen or detected with other devices. Using image-processing technology the T.E.A.M. group hopes to further improve this method to enable the mapping of the entire bladder wall in a single high-resolution image.

Prospects of the combined techniques

However, the fluorescence method does not yield information about the exact type of tissue alteration – a red fluorescent area can also be a benign inflammation. “To clarify, this requires the level of microscopic resolution that is now possible with the pCLE”, says Dr. Stepp. Here, the physician pushes a very thin probe into the working channel of an endoscope until it reaches the tissue in order to position the probe onto the area of interest. It is then possible to depict cells that are approximately up to 150 μm under the tissue surface. The device can be used in organs with a cavity, such as the bladder, the throat or the digestive tract.

However, the pCLE cannot determine the invasion of a tumor into the underlying connective tissue. This can be determined with an ultrasonic probe or – with even better resolution – by using another new method, the optical coherence tomography (OCT). This method is currently being tested at the University Hospital of Munich using two loaned devices (Figure 3). PD Dr. med. C. S. Betz from the Department of Otorhinolaryngology, Head & Neck Surgery is aiming to improve the reliability of tissue biopsy by using OCT to detect signs of microinvasion in

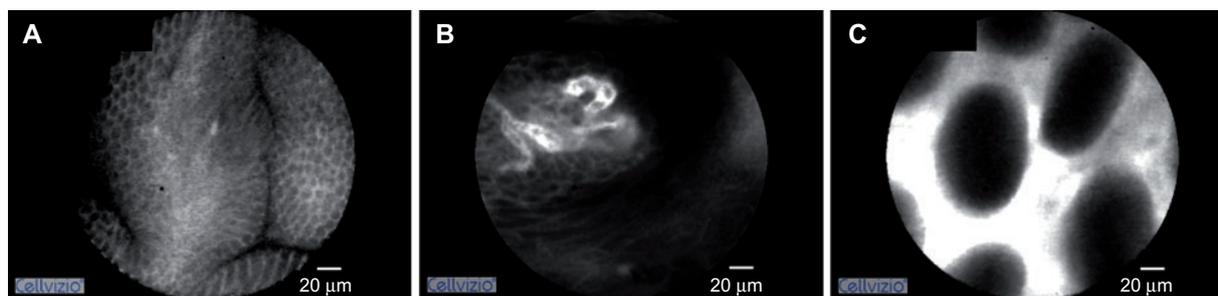


Figure 1 Different structures in the mucous membrane of the esophagus (A,B) and in the stomach (C), as shown in microscopic resolution with the new confocal endoscopy device Cellvizio® (Mauna Kea Technologies, Paris, France). The resolution is so high that single erythrocytes can be seen in the blood capillaries (B). The images are captured parallel to the tissue surface.

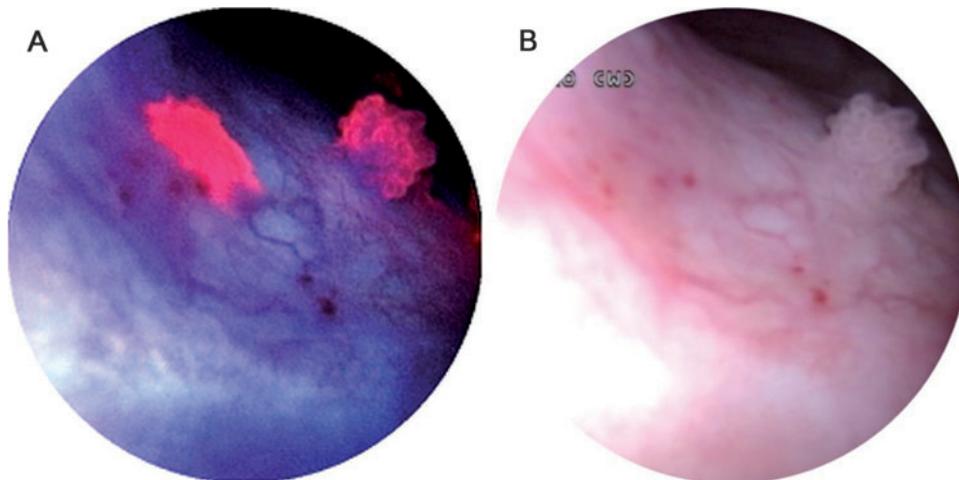


Figure 2 Using fluorescence diagnostics (A) it is often possible to detect flat malignant tumors that would otherwise remain undetected if regarded from the normal endoscopic perspective (B). (From: Pottier R, Krammer B, Baumgartner R, Stepp H, editors. Photodynamic therapy with ALA: A clinical handbook. Cambridge: RSC Publishing; 2006; courtesy of PD Dr. med. D. Zaak, Department of Urology, LMU Munich.)

flat lesions in the oral cavity and taking the tissue sample from these “hot spots”. The same is true for the diagnosis of neoplasia on the cervix, where OCT proved to be a useful adjunct to normal colposcopy in research carried out by Dr. med. J. Gallwas and PD Dr. med. Ch. Dannecker of the Department of Gynecology.

“Just how OCT and pCLE will make progress in the future it is not clear”, commented Dr. Stepp. Several clinical studies have been carried out at the University Clinic of Mainz with the aim of diagnosing intraepithelial neoplasia and colorectal cancer *in vivo*, and at the same time examining the potential of pCLE in the colon. After about 10 years, patients with chronic inflammatory colonic disease have a high cancer risk. The first results using pCLE for detection of early neoplasia in these patients are encouraging. The pCLE is so new that the clinical importance has to be investigated in further prospective studies especially in diseases with a high risk of cancer or in small organs which are not easy accessible to forceps biopsies, something that has encouraged

Prof. Schirra’s team to prepare a study using the pCLE in the bile duct. In the esophagus, studies are concerned with the detection of precancerous lesions in patients with “Barrett’s syndrome”, a chronic inflammatory disease. A first clinical study by Sharma et al. [2] showed that additional use of pCLE significantly improved the ability to detect neoplasia in Barrett’s esophagus patients compared with high definition endoscopy alone.

Outlook

It is possible that intraoperative diagnosis will in the future proceed as follows: fluorescence diagnostics will be used to localize suspicious tissue areas, followed by microscopic differentiation of the suspicious cells using pCLE *in situ*, and finally detection of the microinvasion of tumor cells into the connective tissue using OCT. However, until this procedure becomes reality, it will have to remain a vision.

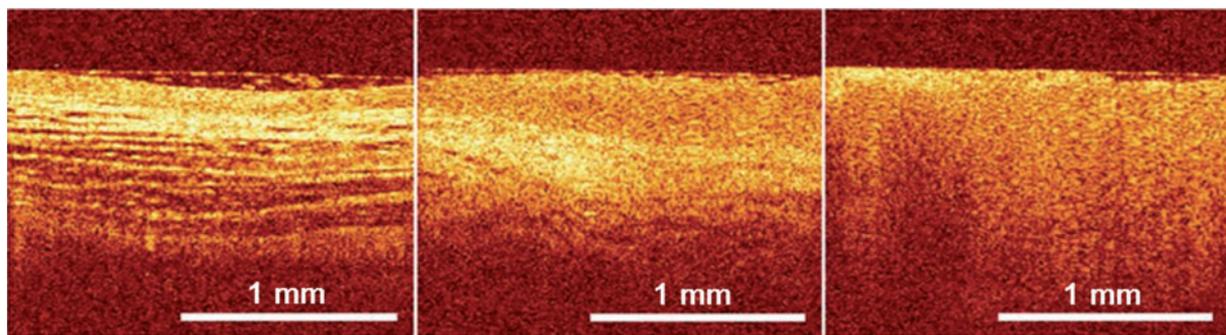


Figure 3 OCT images from the oral cavity. This technique generates images perpendicular to the surface, with a depth of approximately 1.5 mm. The images from left to right show the transition from a normal tissue layer structure to micro invasive carcinoma. (Courtesy of PD Dr. med. C.S. Betz, Department of Otorhinolaryngology, Head & Neck Surgery, LMU Munich.)

“Until we decide further”, says Prof. Schirra, “we will continue to take tissue samples and the final decision, as always, will be taken by the pathologist.” Thanks to pCLE, the samples that the pathologist receives are already often better than they were before. Moreover, quite “incidentally”, the value of all new optical methods will be tested for their scientific value (Adapted from: “Laserendomikroskopie für die intraoperative Diagnostik”, www.medizin-edv.de).

References

- [1] Meining A, Chen YK, Pleskow D, Stevens P, Shah RJ, Chuttani R, Michalek J, Slivka A. Direct visualization of indeterminate pancreaticobiliary strictures with probe-based confocal laser endomicroscopy: a multicenter experience. *Gastroint Endosc* 2011;74(5):961–8.
- [2] Sharma P, Meining AR, Coron E, Lightdale CJ, Wolfsen HC, Bansal A, Bajbouj M, Galmiche JP, Abrams JA, Rastogi A, Gupta N, Michalek JE, Lauwers GY, Wallace MB. Real-time increased detection of neoplastic tissue in Barrett’s esophagus with probe-based confocal laser endomicroscopy: final results of an international multicenter, prospective, randomized, controlled trial. *Gastroint Endosc* 2011;74(3):465–72.

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