Towards an Optical Biopsy during Visceral Surgical Interventions

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Keywords

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Abstract

Background: Cancer will replace cardiovascular diseases as the most frequent cause of death. Therefore, the goals of cancer treatment are prevention strategies and early detection by cancer screening and ideal stage therapy. From an oncological point of view, complete tumor resection is a significant prognostic factor. Optical coherence tomography (OCT) and confocal laser microscopy (CLM) are two techniques that have the potential to complement intraoperative frozen section analysis as in vivo and real-time optical biopsies. **Summary:** In this review we present both procedures and review the progress of evaluation for intraoperative application in visceral surgery. For visceral surgery, there are promising studies evaluating OCT and CLM; however, application during routine visceral surgical interventions is still lacking. **Key Message:** OCT and CLM are not competing but complementary approaches of tissue analysis to intraoperative frozen section analysis. Although intraoperative application of OCT and CLM is at an early stage, they are two promising techniques of intraoperative in vivo and real-time tissue examination. Additionally, deep learning strategies provide a significant supplement for automated tissue detection.

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Introduction

Cancer is the second leading cause of death globally [1] and will be the leading cause of death in a few decades due to the ageing world population and better treatment of cardiovascular disease [2]. In 2018, 18.1 million new cancer cases and 9.6 million cancer deaths occurred [2]. Lung cancer is already the sixth most frequent cause of death worldwide [3]. In comparison, lung cancer ranked ninth in the WHO Global Cause of Death Report some years ago [3]. In high-income countries there are even 3 malignancies among the top 10 most frequent causes of death [2, 3]. Even in low-income countries, the cumulative risk of cancer is already 1:8 for men and 1:10 for women [4]. The GLOBOCAN study showed that cancer ranks as the first or second cause of premature death in almost 100 countries worldwide [2]. The economic impact of cancer is considerable. The total annual cost of cancer was estimated at approximately USD 1.16 trillion in 2010, and treatment costs are expected to rise further [4, 5].

In women, breast cancer is the most frequently diagnosed malignancy (24.2%), followed by colorectal cancer (9.5%), and lung cancer (8.4%). Also, the highest mortality is found in women for these three entities (breast cancer, 15%; lung cancer, 13.8%; colorectal cancer, 9.5%).

David Benjamin Ellebrecht and Sarah Latus contributed equally to this work.

Fig. 1. Penetration depth and resolution of tissue examination devices.

Lung cancer is the most common malignant cancer diagnosis in men (14.5%), followed by prostate cancer (13.5%) and colorectal cancer (10.9%). Lung cancer also has the highest mortality rate (22%), followed by hepatocellular carcinoma (10.2%) and gastric carcinoma (9.5%) [2, 4, 5].

Despite existing efforts to reduce the risk of cancer and early cancer detection, diagnoses are often only made in advanced malignant stages. Consequently, in addition to prevention strategies, the goal of cancer treatment is early detection by cancer screening and ideal stage therapy. In this context, the gold standard of treatment of most solid tumors is complete surgical excision. Complete tumor removal determines a curative surgical intervention [6]. In this context, tumor-free resection margins are among the most prognostic factors [6–8].

Frozen sections play a potential role in intraoperative characterization of resection margins and are the key component of a surgeon's decision. However, operation procedures are often stalled for 20–60 min while histological results are awaited [9], which is costly [6]. In addition, only a limited number of sampling points are possible and repetitive examination can be difficult.

There is an increasing request for intraoperative navigation tools enabling individual cancer resection while protecting healthy tissue [6, 10]. The effort of introducing minimally invasive surgical techniques in oncological surgery entailed by reduced tactility and, in some cases, a limited intraoperative overview.

In addition to macroscopic optical navigation techniques such as fluorescence angiography using indocyanine green [11–13], various methods of tissue identification are being tested. In this context, optical coherence tomography (OCT) and confocal laser microscopy (CLM) are two tools for intraoperative tissue navigation. Both techniques enable tissue examination with microscopic resolution (Fig. 1). While potentially providing more intraoperative information, enormous difficulties arise in

dealing with the surgical procedure and tissue identification. The solution could be the intraoperative support of the surgeon by computer-assisted image analysis using deep learning strategies [14]. In this review, we will explain OCT and CLM for intraoperative navigation and will give an overview of the current opportunities of optical biopsy during visceral surgical procedures, including approaches for automated tissue analysis.

Optical Coherence Tomography

Principle of OCT

OCT is an interferometric imaging modality that uses near infrared light for the acquisition of high-resolution 1D depth profiles (A-scans) of tissues. A laser beam is directed towards a tissue and the reflected light interferes with that of the reference arm of the OCT system (Fig. 2). Different reflective properties of subsurface tissue structures and boundaries lead to varying gray value intensities along the A-scan. Hence, morphological information and optical characteristics of tissues are observable. In general, OCT cross-sectional images or volumes are observed by deflecting the laser along one or two axes [15]. In addition to the gray values, the A-scan phase information can be used, for example, for Doppler OCT [16], needle-based elastography [17, 18], or OCT angiography [19] studies.

Two Fourier domain OCT systems have been proposed, namely swept-source OCT (SS-OCT) and spectral domain OCT (SD-OCT) [20]. Broadband light sources are used in SD-OCT systems. In contrast, SS-OCT systems are equipped with narrow-band swept laser sources [21]. The latter systems allow for A-scan rates of above 1 MHz. Depending on the light source, OCT provides an axial resolution of 2–10 μm and an imaging depth of about 1 mm in tissues.

Fig. 2. OCT system architecture. A light source emits infrared light which is split at a fiber optical coupler. Light reflected from a reference and a sample arm form an interference spectrum that is measured at a detector. A single scan results in a 1D depth profile (A-Scan). By taking multiple measurements at neighboring locations, several A-Scans can be combined to a 2D image (B-Scan) after signal processing (SP). Two optical setups for scanning small locations are sketched and their related cross-sectional B-scans are shown. **A** Optical scanning setup where mirrors redirect the light beam to form 2D and 3D scans. **B** Rotation and translation of a side-viewing needle probe which results in a cylinder-like 3D image volume.

There are various OCT devices deployed for intraoperative imaging. Portable handheld devices enable an ergonomic and flexible application of non-invasive cross-sectional OCT imaging in several intraoperative use cases [22]. Optical scanners (Fig. 2A) are embedded in these devices with a forward-imaging [23] or side-viewing [24] orientation. In addition, microscope-integrated OCT devices are commercially available and enable non-invasive 3D or even 4D visualization of subsurface tissues during surgical procedures [25–27].

Due to the limited penetration depth of OCT, customized optical probes are facilitated to enable image acquisitions from within the tissue. Again, optical scanners are integrated in needle probes for cross-sectional forward imaging [28]. In contrast, medical catheters [29] or needles [30] with embedded single-fibers allow for high-resolution 3D volume imaging of tissues while performing a rotation and translation of a side-viewing probe (Fig. 2B). Moreover, multifiber needle probes are facilitated for multimode imaging during punctures [31]. Multimodal tissue characterizations lead to an extensive intraoperative analysis. OCT and near infrared imaging complement each other in tumor studies [32]. Further studies proclaim the combination of high-speed OCT imaging and multispectral imaging in endoscopes [33].

OCT Application in Visceral Surgery

The most common applications of OCT are ophthalmology and ophthalmic surgery where conventional operating microscopes often provide a limited view [34]. Here, OCT has been shown to be beneficial by providing a cross-sectional view of the eye using optical scanning [35–37]. OCT has also been used for tissue characterization, for example for the detection of age-related macular degeneration [38] or glaucoma [39], which has also been studied with automatic deep learning methods [40, 41].

Another major OCT application is percutaneous coronary intervention with intravascular OCT (IVOCT), in which the artery is scanned with a rotating needle probe. The images can be used for identifying plaque deposits [42] and imaging microstructures such as high-risk thin-capped fibroatheroma in the arterial wall [43, 44]. Automated tissue characterization for decision support during interventions has also been studied using deep learning methods [45, 46].

So far, OCT has not been extensively used in visceral surgery. However, there have been numerous studies exploring the use of OCT in this context. For example, healthy and malignant tissue extracted from the gastrointestinal tract has been analyzed with OCT and correlated with histological findings in ex vivo analyses [47, 48]. Also, in vivo experiments in the gastrointestinal tract have been performed with a flexible OCT probe [49]. The authors concluded that an “optical biopsy” might be feasible with OCT. Similarly, Pfau et al. [50] found that in vivo OCT scans of colon adenomas, hyperplastic polyps, and normal colon tissue can be distinguished by medical experts. More recently, 3D OCT systems have been employed where imaging is performed with pullbacks, similar to IVOCT [51]. Intraperitoneal OCT imaging has also been explored, although Cahill et al. [52] concluded that confident diagnosis based on the obtained OCT signal was not feasible.

Similar to other applications, automatic tissue analysis with OCT could improve diagnostic performance and benefit the physician during interventions. For typical endoscopic videos, automated in vivo polyp detection and classification has been studied using deep learning methods [53]. For OCT, in vivo studies for automated assessment are still rare [54]. However, ex vivo studies have shown that there are measurable features that could help colon cancer classification [55].

Fig. 3. Principle of confocal microscopy. **A** Transmitted light approach patented by M. Minsky in 1957. Light from a photon source is focused onto a pinhole (A). The condenser lens focuses the light to a spot (B) within the specimen. Light, which passes the specimen, is focused by an objective lens at a second pinhole (C). Points A, B, and C are in conjugate (confocal) focus. The path of out-of-focus light is represented by the red lines and is rejected and not transmitted to the detector. **B** Epi-illumination setup of modern confocal laser scanning microscope. AOTF, acousto-optic tunable filters; PMT, photomultiplier tube detectors.

Furthermore, OCT has been explored in the context of prostate cancer. Needle-based OCT volume imaging has been used for ex vivo tissue analysis [56]. The signal attenuation allowed for the distinction of benign and malignant colon tissue, suggesting that an optical biopsy might be feasible. Similar results have been obtained using full-field OCT instead of a needle-based approach [57]. While results appear to be promising, fully automated diagnosis, for example using deep learning, has not been studied so far.

Moreover, bladder cancer has been studied using endoscopic OCT systems [58]. Recently, automated tissue layer segmentation using deep learning has been presented, suggesting that in vivo decision support might be feasible [59].

OCT has also been employed with other organs for tissue characterization and the possibility of performing an optical biopsy. Typical examples include interventions for

breast cancer [30, 60], lung cancer [61, 62], brain tumors [63, 64], and lesions in the upper aerodigestive tract [65, 66]. For most applications, automatic tissue characterization has been studied, for example using deep learning for classifying A-scans from a needle probe in the context of breast [67], lung [68], and brain [69] tissue. Also, B-scans were automatically classified for lesion characterization in the upper aerodigestive tract [70]. A comprehensive overview of more applications is given by van Manen et al. [71].

To summarize, the application of OCT for tissue analysis has been studied for multiple organs. There have been promising studies for visceral surgery; however, application during interventions is still lacking. Recently, automated tissue characterization with OCT and deep learning has demonstrated initial success, suggesting that an optical biopsy during interventions might be feasible for some applications.

Table 1. eCLM used in visceral surgery studies [121, 122] in comparison to an interoperative OCT system [22]

	Optiscan/Pentax	Cellvizio (Mauna Kea Technologies)	iOCT (Haag-Streit)
Type	Endoscope based	Probe based	Probe based (SD-OCT)
Wavelength, nm	488 and 790	488 and 660	830
Frame rate	0.8 fps (1,024 × 1,024 pixels) 1.6 fps (1,024 × 512 pixels)	9–12 fps (up to 40 fps)	35,000 A-scans/s
Lateral resolution, μm	0.7	1.4–3.5 ^a	Dependent on NA A-scan depth: 3.8 mm ^b
Axial resolution, μm	7	10–70 ^a	5 ^b
FOV, μm	475 × 475	240 × 240 to 600 × 500 ^a	5,000 × 5,000 to 30,000 × 30,000
Working distance, μm	250	0–10 ^a	175,000
Distal tip diameter, mm	5	0.3–4.2 ^a	

FOV, field of view; fps, frames per second; NA, numerical aperture of the lens.

^a Depending on confocal microprobe. ^b Specified in air.

Confocal Laser Microscopy

Historical Perspective and Principle of CLM

After the establishment of microscopy as an important part of biological and medical research, microscopists soon noticed that scattered light from unfocussed areas of a specimen decreased the image quality. Especially for an increasing thickness of specimen, scattered out-of-focus light has a negative effect on image contrast. Therefore, the need to examine tissue without interference from out-of-focus light, and additionally in vivo, was the driving force behind the development of confocal microscopy [72].

The first confocal microscope is generally credited to Marvin Minsky from 1955. In 1957, he filed the first confocal microscope patent [73, 74]. Twelve years later, Davidovits and Egger [75] published the first application of a confocal laser microscope. However, it took until the mid-1980s for CLM to achieve its breakthrough, benefited by several major technological advances, such as bright and stable laser light sources or software for analyzing the images [74]. White, Amos, and Fordham [76] built the first confocal laser scanning microscope. Offering some advantages compared to the conventional fluorescence microscopy, CLM became a cornerstone of biomedical research [77, 78]. Due to its excellent lateral resolution and increased contrast, CLM made it possible to examine single cells or specific molecules within a cell ex vivo as well as in vivo [76, 79].

Scanning a point source of light across the specimen and using a pinhole, elimination of out-of-focus light is the key to the confocal approach [74]. Minsky [73] described a transmitted light approach of CLM in his patent: emitted light from a light source is bundled by the pinhole and focused by a condenser lens into the specimen. The light, which passes through the specimen, is focused by

the objective lens onto another pinhole. Points A, B, and C are in conjugate (confocal) focus. Out-of-focus light does not reach the detector (Fig. 3A) [73, 74, 80]. Figure 3B shows the setup of a modern confocal laser scanning microscope using acousto-optic tunable filters, a dichroic mirror, and photomultiplier tube detectors.

Most visceral surgery studies dealing with CLM are based on two commercially available confocal endomicroscopy systems (Table 1). A general handicap of eCLM is the application of intravenous or topical fluorescent agents to achieve contrast. We evaluated a CLM device developed for a minimal-invasive surgical approach and intraoperative diagnostics that does not need any fluorescent contrast dye. The endoscope CLM system consists of a modified Rostock Cornea module of the Heidelberg Engineering Retina Tomograph II HRT II (Heidelberg Engineering GmbH, Heidelberg, Germany) and a specially developed rigid endoscope (Karls Storz SE & Co. KG, Tuttlingen, Germany; Fig. 4). The light source is a 670-nm diode laser. The circular scan field is 300 × 300 μm with a maximum lateral and axial resolution of 1–2 μm . The penetration depth (*z*-axis) is between 100 and 450 μm depending on the tissue. The scan rate is 40 frames/s [9, 81, 82]. The special feature of this CLM device is that it does not require any fluorescent dye. Induced fluorescence of the tissue alone is sufficient for imaging. Introduced through a laparoscopic or thoracoscopic port, surgeons can use the CLM camera device like any other surgical instrument [9, 83].

CLM Applications in Visceral Surgery

Already a few years after the first commercially available CLM devices were introduced, CLM was applied in clinical settings. CLM was used to examine the cornea and retina by ophthalmologists [84–87], and dermatolo-

Fig. 4. Prototype of an endoscopic CLM device.

gists implemented CLM in their skin cancer and auto-inflammation diagnostics [88, 89]. The clinical application of CLM as confocal laser endomicroscopy (eCLM) started in 2004 with the *in vivo* diagnosis of intraepithelial neoplasia and colorectal cancer [90]. Since then, eCLM has established itself as an integral part of endoluminal diagnostics in gastroenterology [91–99]. The eCLM was also evaluated in urology and pneumology [100, 101].

Examining resection margins, CLM devices were used for intraoperative optical biopsy in breast surgery [102] and in brain tumor surgery [103–105]. The first steps for the intraoperative application of CLM were performed in pilot studies, *in vivo* in animal models or *ex vivo* on human tissue in visceral surgery. Several animal studies showed that *in vivo* tissue examination is safe and feasible [106–110]. Schneider et al. [110] showed that CLM enables the user to distinguish between normal and metastatic liver tissue in an orthotopic murine model of colorectal cancer liver metastasis. Mennone and Nathanson [108] demonstrated that it is feasible to distinguish normal from cirrhotic liver tissue. In 2008, Goetz et al. [111] performed the first *in vivo* intraoperative liver tissue examination during laparoscopy. Twenty-five patients with liver disease were examined during routine minilaparoscopy. The authors found that confocal diagnosis of moderate-to-severe steatosis and pericellular fibrosis correlated well with histopathologic analysis of subsequent biopsies. Fuks et al. [112] published their results in 2019, showing that the sensitivity and specificity of *in vivo* intraoperative tissue examination were 67 and 100% for peritoneal and 38 and 100% for hepatic carcinogenesis, respectively. Using CLM *ex vivo* during renal cancer surgery, a further study showed that it is possible to distinguish normal from cancer tissue [113]. The Needle-Based, *In Vivo* Feasibility Study is going to evaluate CLM for prostatic cancer diagnosis [114]. Risi et al. [115] and Chene et al. [116] showed that optical biopsy by CLM enables the differentiation between normal and malignant tissue in tubal lesions and

ovarian surface epithelium. In a recent study, we were able to show that the CLM system described above not only enables tissue examination [9], but also differentiates between benign and malignant colon and peritoneal tissue, respectively [83]. A correlation between primary cancer lesions and metastasis was also achieved [83].

A general limitation of CLM is the low tissue penetration depth (100–450 μm). As a result, the abdominal organs can only be examined superficially. In addition, the different CLM patterns of the various tumor entities might confront the surgeon with enormous intraoperative difficulties in dealing with the surgical procedure and tissue identification. The solution could be the intraoperative support of the surgeon by a computer-assisted image analysis using deep learning strategies. Several studies have shown the application of deep learning strategies in CLM tumor identification of brain tumors, melanoma, and oral cavity cancer [14, 117–119]. In a recent study, we were able to show that deep learning can differentiate between cancer and healthy tissue [120]. However, deep learning is still in its incipient stages in visceral surgery tissue classification.

Conclusion

OCT and CLM do not yet represent a standard for intraoperative tissue analysis. Recent study results show that these are two promising methods of intraoperative *in vivo* and real-time tissue examination. However, further studies are needed to further develop OCT and CLM for the application in visceral surgery. In this context, it should be considered that these procedures are not competing but complementary approaches of tissue analysis to intraoperative frozen section analysis.

While still lacking intraoperative application, automated tissue analysis, in particular using deep learning methods, has gained popularity both for OCT and CLM.

Providing immediate visualization of tissue boundaries and properties could greatly benefit surgeons during interventions.

Statement of Ethics

Ethical considerations were not applicable to this review.

Disclosure Statement

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Author Contributions

D.B.E., S.L., and N.G. contributed to the conception and design, and drafting and revision of the article. A.S. and T.K. contributed to drafting and revision of the article. All authors provided final approval of the version submitted.

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