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Experimental optical imaging during pancreatic cancer interventions

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Citation

Manen, L. van. (2023, December 13). *Experimental optical imaging during pancreatic cancer interventions*. Retrieved from <https://hdl.handle.net/1887/3672215>

Version: Publisher's Version

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Note: To cite this publication please use the final published version (if applicable).

Chapter 8

The clinical usefulness of optical coherence tomography during cancer interventions

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Journal of Cancer Research and Clinical Oncology. 2018 Oct;144(10):1967-1990.

Abstract

Introduction

Tumor detection and visualization plays a key role in the clinical workflow of a patient with suspected cancer, both in the diagnosis and treatment. Several optical imaging techniques have been evaluated for guidance during oncological interventions. Optical coherence tomography (OCT) is a technique which has been widely evaluated during the past decades. This review aims to determine the clinical usefulness of OCT during cancer interventions focussing on qualitative features, quantitative features and the diagnostic value of OCT.

Methods

A systematic literature search was performed for articles published before May 2018 using OCT in the field of surgical oncology. Based on these articles an overview of the clinical usefulness of OCT was provided per tumor type.

Results

A total of 785 articles were revealed by our search, of which a total of 136 original articles were available for analysis, which formed the basis of this review. OCT is currently utilised for both preoperative diagnosis and intraoperative detection of skin, oral, lung, breast, hepatobiliary, gastrointestinal, urological and gynaecological malignancies. It showed promising results in tumor detection on a microscopic level, especially by using higher resolution imaging techniques, such as high definition OCT and full-field OCT.

Conclusion

In the nearby future, OCT could be used as an additional tool during bronchoscopic or endoscopic interventions and could also be implemented in margin assessment during (laparoscopic) cancer surgery if a laparoscopic or handheld OCT device will be further developed to make routine clinical use possible.

Introduction

Tumor detection and visualization plays a key role in the clinical workflow of a patient with suspected cancer, both in the diagnosis and treatment. During the last decades, numerous imaging modalities, such as ultrasound (US), computed tomography (CT), magnetic resonance imaging (MRI), have proven additional value in establishing the diagnosis of an oncologic patient. Nevertheless, pathologic analysis of representative tumor biopsies is often necessary for establishing the correct diagnosis.

Furthermore, intraoperative detection of the tumor margins is difficult, as surgeons currently mainly rely on visualization and palpation. Pathological techniques to examine the margins intraoperatively, such as frozen section analysis and imprint cytology have been extensively researched for the purpose of reducing the percentage of positive margins in breast cancer surgery for instance. However, all these methods have drawbacks, such as time-consuming and resource-intensive nature, difficulty in visualizing high-grade carcinomas, and imprecision, due to sampling errors and poor resolution.[1-3] With their ability to image molecular and physiological changes that are associated with cancer sensitively and non-invasively, optical imaging devices, such as optical coherence tomography (OCT), have the potential to improve intraoperative tumor detection.[4,5]

OCT is a technique that uses the interference of light to generate 2-dimensional cross-sectional images. It was first described in 1991 and is often denoted as the optical analog of ultrasound; it detects back-reflected light, instead of sound, from tissues.[6] In the field of cardiology and ophthalmology it is already used as part of standard clinical care.[7] OCT is, in contrast to other optical image modalities, able to image non-invasively and without the need for tissue preparation. The technique produces images, which are comparable to low-resolution histology. The resolution in comparison to US is 10-50 times better, and usually lies in the range of 1-20 μm in axial and transverse direction, depending on the modality used. This technique could be applied both for *ex vivo* and *in vivo* use. Moreover, in the last years OCT was used during endoscopy or bronchoscopy, by incorporating OCT into flexible fiberoptic probes, which could be inserted in the accessory channel of the majority of standard of care scopes. [8,9] For imaging with higher resolution and more cellular detail, high definition OCT (HD-OCT) and full-field OCT (FF-OCT) have been developed. HD-OCT is a commercially available system dedicated to skin imaging (Skintell®, Agfa Healthcare Mortsel, Belgium and München, Germany) providing axial and transversal resolution of 3 μm over 1.8 x 1.5 mm field of view, however with penetration depth limited to 570 μm . The penetration depth is also limited to first few hundred microns in FF-OCT that directly acquires 2D en face images (without beam scanning) by illuminating the full field of view with a white-light source, such as a halogen lamp.[10,11] In FF-OCT three-dimensional imaging can be performed, by stepping the reference mirror and recording successive en face images resulting in a stack of images.[12] With a speed limitation, which is caused by the long acquisition times, higher resolution OCT imaging can be only applied for *ex vivo* imaging.

The aim of this review is to determine the clinical usefulness of OCT and its variants during cancer interventions for both preoperative diagnosis and intraoperative tumor detection, with a focus on qualitative features, quantitative features and the diagnostic value of OCT, which are described per tumor type.

Methods

A literature search in PubMed was performed for articles using OCT in the field of surgical oncology, published before May 2018. The search consisted of different keywords: "optical coherence tomography" or "OCT" combined with general terms ("oncology", "oncologic", "tumor", "tumors", "malignancy", "malignancies", "cancer") and more tumor-specific MeSH terms ("skin neoplasms", "oral neoplasms", "lung neoplasms", "breast neoplasms", "pancreatic neoplasms", "liver neoplasms", "bile duct neoplasms", "esophageal neoplasms", "stomach neoplasms", "colorectal neoplasms", "prostate neoplasms", "kidney neoplasms", "urinary bladder neoplasms", and "ovarian neoplasms"). Case reports, (systematic) reviews, non-human studies and articles not written in English were excluded from the analysis.

Results

A total of 785 articles were revealed by our search, of which two were found by manual search on the SPIE digital library. After exclusion of 649 articles, that did not meet our eligibility criteria, a total of 136 original articles remained, of which an overview is given in Figure 1. The included articles, which form the basis of this review, are discussed separately per cancer type. An overview of the diagnostic value of OCT for tumor detection, including relevant study characteristics, is provided in Table 1.

Skin cancer

Skin tumors are usually divided into melanoma and non-melanoma cancer. Because of its aggressive character, the only curative treatment for local melanomas is surgical resection in combination with sentinel lymph node mapping. However, in the last years novel target therapies were developed which showed great potential in patients with unresectable or metastatic melanoma.[13] For basal cell carcinoma (BCC), which is a non-melanoma cancer and the most common type of cancer in caucasians worldwide, many treatment options are available and applied, dependent on the tumor characteristics and patient's preference.[14] Mohs micrographic surgery is currently performed in many clinics, to obtain free resection margins. Nevertheless, it would be preferable for both the patient and surgeon to obtain real-time feedback of the margin involvement during surgery. Many studies have determined the capacity of OCT for visualization of different types of skin cancer.

MALIGNANT MELANOMA

OCT images of a malignant melanoma showed irregular structures in the lower epidermis, which corresponded to histology. The basement membrane zone was also not visible, which made these characteristics specific for malignant melanoma.[15] Moreover, other characteristics have been investigated. In general, two characteristics were often visible: 1) the presence of horizontal highly reflective cords in the epidermis and dermis, which probably correspond to dense collagen cords of encapsulated tumor lobules; 2) the presence of large vertical icicle-shaped structures reaching the reticular dermis with the peak aspect, which corresponded to tumor cells and lymphocytes infiltration on histology (Figure 2).[16-18]

BASAL CELL CARCINOMA

Several specific features for BCC were suggested, of which disruption of layering, hyporeflective rounded areas surrounded by a hyperreflective halo (honeycomb structure), peripheral palisading and dilated vessels, well circumscribed black/signal poor areas were the most common and characteristic.[10,16,17,19-34] Two studies evaluated the diagnostic accuracy of OCT in detecting basal cell carcinomas *in vivo*, showing good results with sensitivity and specificity ranging from 79-94% and 85-96%, respectively.[19,23] Ulrich et al. evaluated the diagnostic value of OCT combined with clinical and dermoscopic assessment with sensitivity and specificity of 96% and 75%, respectively, which resulted in a higher diagnostic accuracy compared to clinical and dermoscopic information.[35] However, even for experienced observers it was difficult to distinguish BCC from actinic keratosis, which was illustrated by the 50% error rate.[19] Differentiation between the several BCC subtypes was difficult, however variants of OCT like HD-OCT and multi-beam swept source OCT (MSS-OCT) showed potential for clinical use.[10,16,34] Moreover, many studies were performed to assess the surgical margins during Mohs surgery.[27,32,36-42] Conventional OCT yielded to a sensitivity of 19% and specificity of 56%, whereas HD-OCT showed an improved sensitivity of 75% and a specificity of 64%.[36,37]

CONCLUSION

Diverse specific tumor characteristics for both melanoma and BCC were composed. In case of melanoma, no diagnostic studies were performed with OCT. OCT showed good results in BCC detection, however margin assessment, which is clinically most relevant, was much more difficult even with higher resolution OCT.

Oral cancer

Oral cancer, of which squamous cell carcinoma accounts for 90% of the cases, is often treated by a combination of surgery and radiotherapy.[43] Due to the difficult location and the surrounding vital structures, it is of outmost important to achieve complete tumor removal. OCT was utilised in 10 studies to evaluate its potential use.

ORAL (PRE-)CANCEROUS LESIONS

Several parameters were important to distinguish between benign and (pre)malignant oral lesions, such as disorganization of epithelial stratification (irregular collagen vessels), epithelial and/or keratin thickening, micro-structure invasion, heterogeneous cell distribution, and disorganization of the basement membrane.[44-46] Four studies in 19 to 125 patients showed that dysplasia detection was possible both after training of independent reviewers and using quantitative analysis.[47-50] Computer analysis, using a 70% standard deviation of the epithelial thickness, yielded a sensitivity of 82% and a 90% specificity, which indicated that epithelial thickness is one of the most characterizing features of oral dysplasia.[50,51] Squamous cell carcinoma was very well identified, resulting in a sensitivity of 82% and 93% and a specificity of 87% and 93%, as demonstrated by Wilder-Smith et al. and Hamdoon et al.[44,45] De Leeuw et al. evaluated 57 FF-OCT images for presence of cancerous lesions, yielding a 85% accuracy for reviewer 1 and a 89% accuracy for reviewer 2.[46] In both studies image assessment was performed by two independent reviewers, who used the main features of malignancy on OCT images. Using a variant of OCT, Swept Source

OCT (SS-OCT), Tsai et al. performed quantitative analysis and showed that in premalignant tissue, the epithelium became significantly thicker and the standard deviation became larger, due to epithelial disorganization.[52,53]

CONCLUSION

Several characteristics for (pre)malignant oral tissue were proposed, all showing good diagnostic accuracies. These morphological characteristics were confirmed by quantitative analysis, nevertheless no intraoperative studies were yet performed for real-time evaluation of the surgical resection margins.

Lung cancer

The diagnosis of lung cancer, which is the most common cancer in men worldwide, is often made by CT and flexible bronchoscopy. However, bronchoscopy lacks sensitivity, especially for early stage malignancies.[54] Five studies utilized OCT as an additional imaging tool for visualization of lung cancer both during bronchoscopy and after surgery on resected specimens.

OCT DURING BRONCHOSCOPY

Bronchial malignancies were generally characterized on OCT images by a thickened epithelium wall and loss of subepithelial identifiable microstructures. Tumor invasion was visible as a disappearance and/or disturbed architecture of the basement membrane.[55-57] In normal lung tissue, the basement membrane and the lamina propria were visualized as highly reflective layers, due to the presence of collagen vessels. Deeper layers containing seromucinous glands, connective tissue and cartilage, were characterized by polymorphic light and dark areas.[55,56] Hariri et al. composed specific OCT criteria for the different tumor types: adenocarcinoma, squamous cell carcinoma and poorly differentiated carcinoma.[58] Adenocarcinomas were characterized by round or angulated signal-poor to signal void structures, which were typically small and secondly by lack of signal-intense (bright) nests. Squamous cell carcinoma could be recognized by the presence of signal intense nest (brighter than surrounding tissue), which were round or irregularly shaped. These nests may have variably sizes and sometimes also areas of necrosis were visible as signal-poor areas. Lack of round/angulated signal-poor structures and lack of signal-intense nests were specific for poorly differentiated carcinomas.

These criteria were applied by Hariri et al. in a prospective validation cohort, in which three readers evaluated 153 OCT images acquired from five patients, divided over two assessments (separated by 7 months) preceded by a training session.[58] The overall accuracy improved from 81.8% to 83.3% after the second assessment.

SURGICAL RESECTED SPECIMENS

FF-OCT provided high resolution images of both normal and malignant resected lung specimens up to a depth of 5-15 μm . Normal lung tissue was recognized by the typical leace-like pattern, which was formed by the alveoli and their septal walls, visible as signal-void dark areas and bright areas respectively. Other lung components could also be identified, such as the pleura (bright signal), blood vessels and bronchi (dull grey signal). Adenocarcinomas, characterized by their

predominant lepidic growth pattern, could be really well identified. Tumor cells were also larger than normal cells, although they appeared to have a similar signal (dull grey) as normal cells.[59]

CONCLUSION

Although, the diagnostic accuracy was fairly high and OCT during bronchoscopy seems feasible in above mentioned studies, OCT is yet not adequate as a complete replacement for tissue biopsy. However, it has the potential to be implemented in bronchoscopy procedures for diagnosis of lung tumors. Intraoperative use for margin assessment of tumor detection is yet not evaluated.

Breast cancer

Breast cancer, which is the most common type of cancer in women, is responsible for 14% of the cancer-related deaths annually.[60] In breast cancer surgery, it is extremely important that borders of the excised specimen do not contain any tumor cells, since these positive margins are associated with a higher risk of local recurrence of the primary tumor.[61] Not only margin assessment, but also intraoperative staging by sentinel lymph node mapping is often performed in breast cancer patients.[62] Eight studies evaluated the use of OCT in resected surgical specimens and five studies evaluated the use of OCT for lymph node analysis.

TUMOR DETECTION SURGICAL SPECIMENS

Diverse tumor-specific criteria were developed based on histological features. Invasive ductal adenocarcinomas, which showed infiltrating tumor cells in surrounding tissue and surrounding fibrous tumor stroma were clearly visible.[63-65] Mucinous carcinomas could be recognized by mucin with floating tumor cells, which were reflected in the OCT image. Assayag et al. proposed three FF-OCT specific criteria for malignancy in addition to macroscopic characteristics, such as absence of normal breast tissue structures and presence of stellate lesions: 1) Presence of adipocytes with irregular size (fat infiltration); 2) Highly scattering trabecula aspect of fibrous tissue; 3) Presence of dark grey areas surrounded by white fibrous structures; 3).[63] Especially white fibrous structures were suspect for tumor stroma, whereas grey fibrous structures were associated with scar fibrous tissue in benign breast lobules. Furthermore, *ex vivo* analysis of resection margins was performed by Nguyen et al.[66] Thirty-seven breast cancer specimens were used for analysis, divided into a training set and a study data set. Of each specimen, 5 to 10 images were taken, resulting in 210 images used for the study data set and pathologic analysis by one researcher. Analysis showed a sensitivity and specificity of 100% and 82%, respectively, in tumor detection compared to histology, which is the current golden standard. Feasibility of multimodal imaging, by combining OCT with ultrasound and dye-enhanced wide-field polarization imaging, was demonstrated by Patel et al. and Curatolo. et al.[67,68]

Recently, a handheld OCT camera has been developed, which has been used in two studies, that evaluated the diagnostic accuracy of the camera after obtaining the *ex vivo* final margins in 46 and 35 patients, respectively.[69,70] *In vivo* imaging was feasible, although *ex vivo* images of the margins could be directly correlated to the histology slices, which consequently were used in both cohorts (Figure 3). After comparison of histology with readers interpretation, they showed a diagnostic accuracy in tumor detection at the surgical margins varying between 58% and 88%. The

authors stated that this variability could be explained by the minimal training preceded by image evaluation and by the experience in studying OCT images of the reader.

LYMPH NODES DETECTION

Normal lymph nodes were characterized by a distinct capsule that was highly scattering, in comparison to the lower scattering cortex. The lymphoid follicles, which were visible as a circular texture on the OCT image, could also be clearly observed in the cortex.[71,72] Lymph node invasion was characterized by loss of normal tissue architecture, presence of highly heterogeneous tendril-like structures and the presence of areas with highly backscattering areas, possibly due to changes in size and texture of the cell nuclei. One study compared the diagnostic accuracy of OCT to histology, after training of three reviewers, which resulted in an overall sensitivity and specificity of 58.8% and 81.4%, respectively.[73]

In order to improve the capability to distinguish benign and malignant invasion of lymph nodes, parametric imaging of the local attenuation coefficient was applied in OCT images and showed promising results in two feasibility studies.[72,74] FF-OCT showed a more detailed view of the lymph nodes, of which the strong stromal reaction, caused by tumor invasion, was one of the most characterizing morphological features for lymph node invasion on FF-OCT images. FF-OCT showed an improved sensitivity of 89% and specificity of 87% compared to regular OCT after training of two independent reviewers.[75]

CONCLUSION

OCT was used for both tumor detection and sentinel lymph node detection in breast cancer patients. Diverse specific criteria were applied and showed high diagnostic accuracy in margin assessment compared to histology. A handheld OCT camera, which could be used intraoperatively, was also applied for margin assessment and showed promising results. This indicates that with more training and further development, OCT could be used as an additional tool for intraoperatively tumor detection. For lymph node detection, especially FF-OCT was able to distinguish malignant invasion of lymph nodes from benign lymph nodes with high sensitivity and specificity.

Hepatopancreaticobiliary (HPB) tumors

The diagnosis of pancreaticobiliary cancers is often made by taking biopsies during endoscopic intervention. However, the current diagnostic accuracy for both pancreatic and biliary malignancies lacks sensitivity.[76,77] Moreover, in liver and pancreatic surgery, tumor positive resection margins defined as ≤ 1 mm tumor-to-margin distance, are found up to 24% and 75%, respectively.[78,79] Consequently, some progress in diagnostic accuracy of HPB tumors could be made. Nine studies evaluated the use of OCT both during endoscopy and in resected specimen.

OCT DURING ENDOSCOPY

OCT was used to distinguish malignant and benign pancreatic duct strictures both *in vivo* and *ex vivo* during routine endoscopic retrograde cholangiopancreatography (ERCP) procedures.[80-83] By using disturbance of normal three-layer architecture with heterogenous backscattering as marker for presence of tumor, *ex vivo* analysis of 100 OCT images of 10 patients showed an overall

sensitivity and specificity for tumor detection of 78.6% and 88.9%, respectively.[80] Moreover, a concordance between OCT and histology for detection of a pancreatic adenocarcinoma was seen in 97.6% of the 126 images.[80]

In vivo analysis resulted in a 100% accuracy for detection of neoplastic pancreatic ductal strictures. [82] Two criteria for malignant strictures were used: 1) unrecognizable layer architecture; 2) heterogeneous backscattering of signal.

Biliary duct imaging using OCT was performed in 2009 by Arvanitakis et al.[84] They used the above mentioned criteria for detecting of malignant biliary strictures, which was accurate in 84% of the included 37 patients. OCT seemed favorable in preoperative detection of unknown biliary strictures compared to randomly taken biopsies, which resulted in a 67% accuracy in the same cohort.

Besides ERCP, endoscopic ultrasound- fine needle aspiration (EUS-FNA) is often used for taking biopsies for establishing the diagnosis of pancreatic masses. Grieve et al. evaluated the feasibility of FF-OCT in evaluation of FNA specimens acquired during EUS.[85] Three images of pancreatic ductal adenocarcinomas (PDAC), two images of neuroendocrine pancreatic tumors and two images of pancreatic metastases from renal cell carcinomas were included in the analyses and compared to the histology. PDAC was recognized by intense dark malignant cell clusters with irregular borders and high nuclear density. Glandular differentiation was indicated by atypical tall columnar epithelium and the presence of luminal spaces. Neuroendocrine pancreatic tumors were also easily identified by areas with neoplastic endocrine tumor cells, which appeared darker than normal pancreatic tissue. Pancreatic renal cell metastases showed a fair matching with histology. One of the two images showed good correspondence and was recognised by sheets of large cells, which compressed the vessels.

SURGICAL RESECTED SPECIMEN

Iftimia et al. used OCT for detection of several types of pancreatic cystic tumors: mucinous cystic neoplasm (MCN), intrapapillary mucinous neoplasm (IPMN) and serous cystadenoma (SCA).[86] After developing OCT criteria for differentiating between MCNs, SCAs and IPMNs, the investigators (a gastroenterologist, a radiologist and a pathologist) underwent training based on 20 OCT images of fresh resected pancreatic specimens. After that, they were independently asked to evaluate 46 OCT images, resulting in a high sensitivity in distinguishing mucinous vs non mucinous cystic lesions (95.6% for the gastroenterologist and 100% for the radiologist and pathologist).

Van Manen et al. evaluated the accuracy of FF-OCT in detecting pancreatic tumors in resected surgical specimens.[87] Two pathologists were asked to evaluate 100 FF-OCT images after a training set, which resulted in a combined sensitivity and specificity of 72% and 74%, respectively, compared to histologic diagnosis. Moreover, they developed specific criteria for different types of pancreatic tumors. Especially, in case of pancreatic ductal adenocarcinoma, disorganization of glands and presence of tumor stroma were really well visible (Figure 4). However, due to low endogenous contrast, cell nuclei could not be visualized, whereas sometimes the collagen dominated the field of view due too much backscattering, which was mistaken for tumor stroma.

Zhu et al. evaluated the feasibility of FF-OCT in resected liver specimens.[88] Normal liver structures, such as blood vessels, bile ducts and sinusoidal spaces, could be really well identified. Hepatocellular carcinoma was recognized by the presence of nuclear atypia and large tumor nodules separated by thick fibrous bands.

CONCLUSION

The role of OCT was evaluated both during endoscopy and on resected specimens of both cystic and solid tumors. OCT during ERCP showed high accuracy in detection of pancreatic or biliary strictures. Mucinous cystic lesions could be really well identified and distinguished from non-mucinous lesions. FF-OCT was feasible in *ex vivo* EUS-FNA biopsies, pancreatic and liver specimens. Especially, in liver and pancreatic specimens, diverse tumor characteristics were found.

Oesophageal cancer

Oesophageal cancer, one of the most lethal cancers in the western world, is usually divided in adenocarcinoma and squamous cell carcinoma (SCC).[89] One of the independent risk factors for an oesophageal adenocarcinoma is a Barrett's oesophagus (BE), which is a transition of normal squamous mucosa into columnar (gastric) epithelium (=metaplasia), which could be considered as a pre-malignant stadium. Currently, most patients with BE undergo endoscopic surveillance, which is controversial. Moreover, development into dysplastic or neoplastic tissue could only be detected by taking biopsies, frequently accompanied with a sampling error.[90] Thirteen studies evaluated the role of OCT during endoscopy in patients with suspected oesophageal lesions.

BARRETT'S OESOPHAGUS AND ADENOCARCINOMA

Bouma et al. performed the first *in vivo* study in 32 patients, who underwent routine endoscopy, and developed some characteristics of BE on OCT images.[91] Due to high scattering of the metaplastic epithelium, there was a loss of normal layered architecture. In normal oesophageal tissue, the five oesophageal wall layers (squamous epithelium, lamina propria, muscularis mucosae, submucosa and muscularis propria) could easily be recognised by their relative difference in reflection.[91-94] Together with the presence of inhomogeneous tissue contrast and abnormal and disorganised glands below the epithelial surface, visible as pockets of low reflectance, it is called BE. Especially, patients with BE without dysplasia or low grade dysplasia, the muscularis mucosae and submucosal layers often could be preserved.[95,96] Poneros et al. applied these criteria in a validation cohort in patients, who underwent routine upper endoscopy, which resulted in a sensitivity and specificity of 100% and 93% for BE detection, respectively.[97] OCT was also used for detection of BE before and after radiofrequency ablation treatment. Unfortunately, in the minority of the patients (7.7%), OCT was capable to distinguish normal glands from buried Barrett's glands.[98] Another study showed a 81% sensitivity and 66% specificity in detection of BE, indicating that OCT is currently not accurate enough compared to histology.[99] One study evaluated the capacity of OCT for detection of oesophagus dysplasia.[100] Normally, dysplasia is divided in low-grade and high grade dysplasia, which consequently results in different clinical approach, i.e. resulting in oesophageal resection or not. Dysplasia was detected on OCT by reduced light scattering and loss of tissue architecture, which are currently the only known criteria. Evaluation of 314 OCT images of 33 patients by four endoscopists resulted in a sensitivity and

specificity (compared to histology of the biopsies) of 68% and 82%, respectively.[100] However, the authors did not make any difference between low-grade dysplasia, high-grade dysplasia or neoplasia. Chen et al. more specifically described high grade dysplasia as presence of irregular and distorted glandular architecture and closely packed glands.[95]

Adenocarcinomas were characterized on OCT images by a neoplastic epithelium, which contains large pockets of mucin surrounded by fibrotic and hypervascular tumor stroma.[91] Sometimes infiltration of heterogeneous structures into the muscular layers could be seen as a feature of tumor invasion. Irregular shape and crowd of submucosal glands also advocated the presence of adenocarcinoma (Figure 5).[95,101] Detection of adenocarcinoma in patients who underwent upper endoscopy for several reasons showed potential, with a detection rate of 95%.[102]

SQUAMOUS CELL CARCINOMA

Hatta et al. compared the capability of OCT for SCC invasion detection in the different layers of the oesophagus to histology.[93] Superficial invasion into the epithelium layer was difficult to distinguish from normal oesophagus tissue. However, the researchers were able to detect the tumor invasion level with a high overall accuracy: 92.7%. Furthermore, they compared the diagnostic accuracy of OCT with high-frequency EUS in a larger cohort of 123 patients.[103] OCT showed a significantly higher accuracy than high-frequency EUS (90.1% vs 77.1%; $P=0.0046$).

CONCLUSION

OCT has been evaluated for establishing the diagnosis of oesophageal SCC, BE and adenocarcinoma. Diverse characteristics of BE, dysplasia, adenocarcinoma, and SCC were applied, which showed promising results. However, differentiating between normal glands and Barrett's and tumor glands was really difficult.

Colon cancer

Screening for colon cancer is currently mainly performed by using fecal occult blood testing, in suspected cases followed by endoscopy.[104] Adenomatous polyps, which carry risk of cancer development are often found during colonoscopy. They can macroscopically be divided based on their growth pattern into tubular and villous polyps and microscopically they are generally classified as low-grade or high-grade dysplasia. Currently no studies have described the use of OCT for cancer detection, however six studies assessed the use of endoscopic OCT as a screening tool for premalignant polyp detection.

DETECTION OF (PRE)MALIGNANT TISSUE

Tearney et al. first described the feasibility of OCT during colonoscopy for premalignant tissue detection.[105] Normal colonic wall features were described by Westphal et al.[106] The mucosa was visible as a reflective layer, including an underlying thin hyperreflective line, whereas the submucosa appeared highly variable probably caused by compression related to the colonoscopy procedure. Pfau et al. described the different features visible on OCT concerning the most common forms of polyps and showed that adenomatous polyps were significantly more disorganized and more hypo-reflective than hyperplastic polyps.[107] Colorectal neoplasms were described as polyps

with an uneven surface. On OCT, areas of malignant cells appeared bright, whereas non-cellular regions were less reflecting.[92] Quantitative analysis was performed for colorectal cancer in two studies, which showed that malignant tissue has lower scattering properties and less variation of signal intensity from the surface yielding a 78% sensitivity and 74% specificity.[108,109]

CONCLUSION

The use of OCT during colonoscopy for tumor detection has not been frequently analysed. Currently, presumably quantitative analysis could be performed for both tumor and polyp detection, however the diagnostic accuracy lacks sensitivity.

Urological cancer

Most of the time surgery is not the first choice of treatment for urological cancers.. Establishing the correct diagnosis before chemoradiotherapy is of outmost important. Therefore, OCT has been mainly used as an additional tool during biopsy taking in both five studies for prostate, six studies for renal and seven studies for bladder cancer detection, respectively.

PROSTATE CANCER

D'Amico et al. first described the feasibility of OCT for detection of tumor in prostate biopsies. [110] The first large cohort study, performed by Dangle et al. included 100 samples of which 10 had positive surgical margins.[111] Using homogeneity of the prostate epithelium and presence of prostatic stroma as assessment criteria, OCT yielded a sensitivity of 70% and specificity of 84%. More detailed information about malignant features were visualized using FF-OCT, such as presence of irregular gland contours, infiltration of variably sized glands between benign glands, and the presence of cribriform patterns.[112] These characteristics were used during analysis by three independent pathologists, resulting in a 63% sensitivity and 74% specificity. However, a learning curve was observed, leading to a diagnostic accuracy of 82% at the end of the assessment. More recently, quantitative analysis of prostate biopsies showed significant differences in attenuation coefficient between normal and malign prostate tissue.[113,114]

RENAL CANCER

Linehan et al. performed the first *ex vivo* study on 20 resected renal specimens.[115] Generally, in malignant tissue there was a lack of normal structures, however in some cases tumor samples had heterogeneous areas, which mimicked normal kidney tissue. Furthermore, high sensitivities and specificities (up to 100%) for renal tumor detection were achieved in another study by Lee et al.[116] Three pathologists evaluated 35 OCT images of both normal and tumor resected specimens. Renal tumors were characterised by increased scattering tumor nests, which were separated by hyposcattering stroma.[116] More specific, distinguishing renal cell carcinoma and renal oncocytoma (benign renal tumor) was possible by both morphological characteristics and after quantitative analysis of the attenuation coefficient.[116-118] Computer analysis also showed the attenuation coefficient of normal renal parenchyma to be significantly differed from malignant tumors.[117,119] Moreover, several signatures of different kidney tumors could be recognized as described by Jain et al.[120] After training, the uropathologist was able to distinguish benign and malignant tumors (67 FF-OCT images) with a 100% accuracy and achieved a 80% accuracy for correct subtyping of these tumors.

BLADDER CANCER

Seven studies evaluated the diagnostic value of OCT for the detection of cancer in bladder biopsies or resected specimens in populations varying between 21 and 116 patients.[121-127] Disorganized tissue layers and sub-epithelial nests of tumor cells were often found in tumorous biopsies. By using these criteria, sensitivities between 84% and 100%, and specificities between 65% and 89% for tumor detection could be achieved. By using FF-OCT, more details of tumor cells, such as presence of large nuclei and newly formed blood vessels, appearing as small bright spots, could be visualized. After training of the reviewers, a diagnostic accuracy up to 96% could be obtained, as demonstrated by Montagne et al.[121]

CONCLUSION

OCT was capable to distinguish urological tumors from benign tissue with varying accuracies. For quantitative analysis, the attenuation coefficient seems the most informative parameter.

Ovarian cancer

Ovarian cancer is a disease with a dreadful prognosis, making it the most lethal gynaecological malignancy.[60] Treatment mainly consists of surgery, especially in early-stage disease. Eight studies, evaluated the use of OCT for detection of ovarian cancer, of which two during surgery.

RESECTED SPECIMEN

Two studies evaluated the tumor characteristics based on qualitative analysis using OCT and FF-OCT, respectively.[128,129] Ovarian malignancies were characterized by presence of hyperintense regions with irregular patterns, which turned out to be disorganised collagen fibers. Ovarian metastases could also be detected as shown by Stegehuis et al.[129] Metastatic tumor cells appeared light grey in a web-like organisation, resulting in a distorted ovarian cortex architecture. Furthermore, other studies analysed tumor images quantitatively, focussing on optical coefficients, which were derived from normalized histograms.[130-133] After building a logistic classifier model, Nandy et al. were able to achieve a 91.6% sensitivity and a 87.7% specificity for tumor detection based on FF-OCT images.[133]

LAPAROSCOPIC SURGERY

Boppart et al. first described the use of OCT, integrated in a laparoscopic system, in one resected ovary specimen, containing a serous papillary cystadenocarcinoma.[134] Presence of cysts, which are surrounding by papillary structures, were characterizing for this tumor type. *In vivo* application of laparoscopic OCT was performed by Hariri et al. in 30 ovaries of 17 patients, who underwent surgical resection.[135] They described different features of ovarian tumors, such as papillary serous cystadenoma or adenocarcinoma. An adenoma was characterized by large, simple cystic structure with a sharp, regular, well-demarcated cyst lining. Complex, multicystic signal void structures surrounding by tumor stroma, which have a more heterogeneous signal intensity than normal stroma, were suspect for adenocarcinomas.

CONCLUSION

Several subtypes of ovarian tumors could be recognized by using OCT both *ex vivo* and during laparoscopic surgery. However, until today no large patient cohort studies have been reported.

General conclusion and future perspectives

The introduction of OCT shows new opportunities during oncologic interventions. In this review, the role of OCT was evaluated for different tumor types. We have shown that several characteristics for both normal tissues and the different tumor types were established. In case of Barrett's oesophagus, even metaplasia could be detected. OCT could be integrated during bronchoscopic and endoscopic procedures. However, the diagnostic value of OCT was evaluated in limited studies, of which an overview is provided in Table 1. In general, it can be concluded, based on this overview, that use of OCT for guiding of biopsy location during bronchoscopy, intraoperative margin assessment in case of breast cancer surgery and for visualization of pancreatobiliary strictures during ERCP might be useful. Especially, in case of breast cancer, a developed handheld device showed promising diagnostic accuracy, which could be valuable during surgical intervention.

The great advantage of OCT is its non-invasive, reproducible and well-tolerated characteristics for human use. However, some drawbacks could be mentioned. First of all, OCT is a relatively new modality, which needs extensive training and setting-up new clinically relevant features by building extensive atlases for instance, before adopting into clinical practice. That also states the need for automatic feature extraction and even automatic tumor detection, which was recently performed by Marvdashti et al. who integrated an automatic classifier based on known characteristics and new features, resulting in a high diagnostic accuracy of 95.4%.[136] However, due to the availability of several OCT systems classification is difficult, although matching of optical properties is possible. [137] Standardization for signal intensities for each device, which has been done after the introduction of CT devices by using Hounsfield units, would make analysis easier.[138] Secondly, the imaging depth is restricted up to maximum 1-2 mm in OCT and to less than 1 mm in its high resolution variants (HD-OCT, FF-OCT). Conventional OCT with resolution between 7-10 μm showed less microscopic details compared to the current gold standard, histology. Nevertheless, further developing of new variants of conventional OCT with increased resolution, such as FF-OCT, could improve the quality of the images, which make tumor detection feasible into the clinical practice. However, even with FF-OCT, which provides images with resolution comparable to histology, the endogenous contrast of for instance cell nuclei is not good enough for visualization. Techniques to improve the subcellular contrast, such as dynamic FF-OCT, are being developed, enhancing both structural and functional information through the detection of the intracellular activity.[139] Recently, also a handheld FF-OCT rigid endoscope has been developed, with a faster and more sensitive camera integrated than current FF-OCT systems, which paves the way for intraoperative use.[140] Finally, sometimes signal of highly backscattering tissues, such as collagen vessels or tumor stroma, disturbed the OCT images and made distinguishing benign and malignant tissue from each other complicated. On the other hand, it was shown that stroma alignment is significantly different between benign and malignant tissue for pancreatic cancer [141] and breast cancer[142], and could therefore contribute to better detection of tumors on OCT images. Such information can be possibly obtained using polarization-sensitive OCT, which in addition to tissue microarchitecture can provide images of tissue birefringence.[136] Hariri et al. showed that Polarization Sensitive OCT (PS-OCT) has a potential to help in differentiation between lung tumor and fibrosis and Kiseleva et al. used PS-OCT to diagnose mucosal pathologies in *in vivo* human bladders.[143,144] Also, other functional OCT variants, such as Doppler-OCT that visualizes tissue vasculature and spectroscopic OCT that

differentiates tissue types based on signal attenuation, as well as multimodality approaches are currently a topic of research.[117,119,145,146]

In conclusion, OCT showed promising results in tumor detection and with the development of novel probes allowing integration in bronchoscopy, flexible or rigid endoscopy, needles [147], handheld cameras and tethered capsules [148,149] could add important value during both preoperative diagnosis as well for intraoperative use in obtaining tumor free resection margins in the nearby future.

Figure 1. Flow diagram of study inclusion.

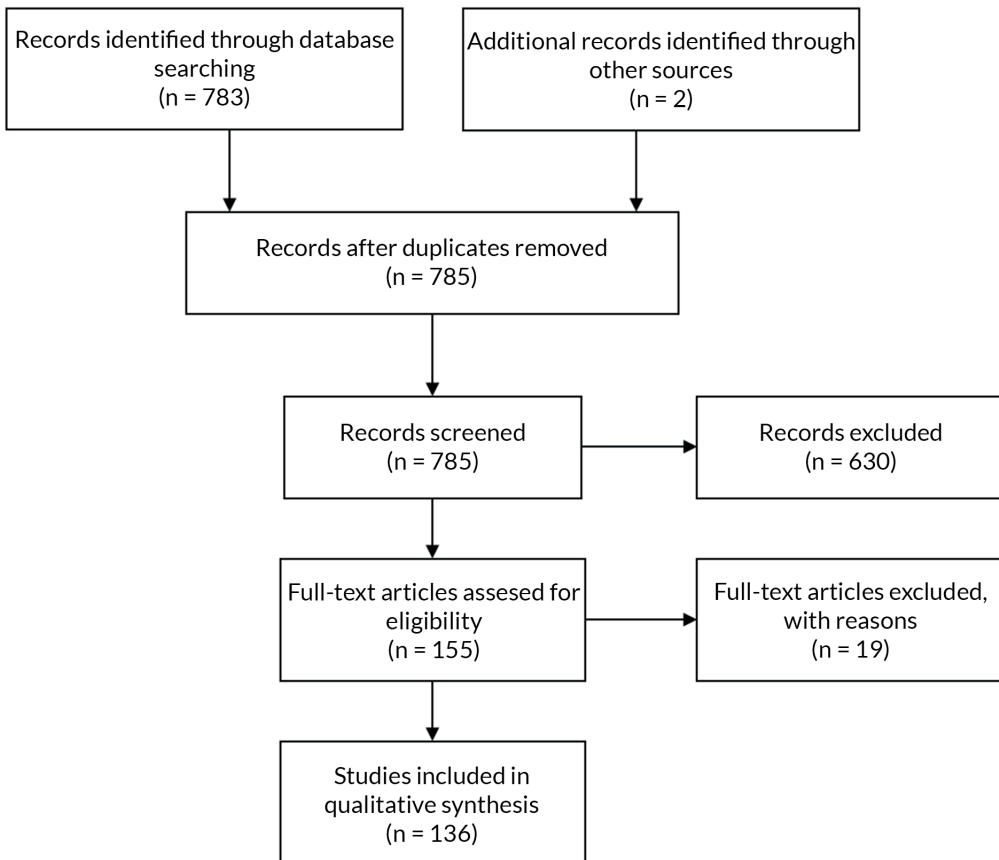


Table 1. Overview of clinical studies evaluating the diagnostic value of optical coherence tomography for tumor detection.

Tumor type	Reference	Technique, Manufacturer	Technical specifications	Study design	Analysis	Sensitivity (%)	Specificity (%)	Detection rate (%)			
		Resolution: axial x lateral (µm)	Penetration depth (mm)	Acquisition time/image (seconds)	N (images)	Implementation	Samples				
Basal cell carcinoma	Mogensen et al. 2009	(Polarization-sensitive) OCT, Technical University of Denmark	8 x 24	N.S.	3	Ex vivo	Suspected lesions	6 reviewers of which 2 reviewed all images.	79, 94	85, 96	-
	Jorgensen et al. 2008	OCT, Riso National Laboratory, Roskilde, Denmark	10 x 20	1.3	4	Ex vivo	Suspected lesions	Machine based learning	-	-	81
Oral cancer	Ulrich et al. 2015	OCT, Vivosight Scanner, Michelson Diagnostics Ltd (Orpington, Kent, UK)	5 x 7.5	1.2-2	N.S.	In vivo	Suspected lesions	Clinicians of participating centres	96	75	-
	Cunha et al. 2011	OCT, EX1301, Michelson Diagnostics Ltd (Orpington, Kent, UK)	10 x 7.5	1.5	N.S.	Ex vivo	Resection margin	2 Mohs surgeons	19	56	-
Oral cancer	Maier et al. 2014	HD-OCT, Skintell, Agfa HealthCare, Belgium	3 x 3	0.45-0.75	120	Ex vivo	Resection margin	1 experienced investigator	74	64	-
	Wilder-Smith et al. 2009	OCT, Niris™ system, Imalux (Cleveland, OH)	5-10 (not exactly specified)	1-2	1.5	Ex vivo	Biopsies	2 reviewers	93	93	-
Lung cancer	Hamdoon et al. 2016	OCT, EX1301, Michelson Diagnostics Ltd (Orpington, Kent, UK)	<10 x <10	1.5	<0.1	Ex vivo	Resected SCC specimens	2 reviewers	82	87	-
	De Leeuw et al. 2015	FF-OCT, Light CT scanner, LL-Tech SAS (Paris, France)	1.5 x 1.0	N.S.	N.S.	Ex vivo	Resected head and neck specimens	2 pathologists	88, 90	81, 87	-
Breast cancer	Hariri et al. 2015	OCT, Harvard Medical School (Boston, USA)	6 x 30	2-3	N.S.	Ex vivo	Resection specimens	1 pathologist 1 OCT expert 1 surgeon	80 (AC) 83 (SCC) 86 (PDC)	89 (AC) 87 (SCC) 98 (PDC)	-
	Nguyen et al. 2009	OCT, University of Illinois, Urbana-Champaign (Illinois, USA)	6 x 35	1-2	5	Ex vivo	Resection margin	1 trained researcher	100	82	-
Breast cancer	Zysk et al. 2015	Handheld OCT, University of Illinois, Urbana-Champaign (Illinois, USA)	<15 x <15	N.S.	N.S.	In vivo and ex vivo	Resection margin	1 pathologist 1 surgeon 1 radiologist	55-65	68-70	-
	Erickson-Bhatt et al. 2015	Handheld OCT, University of Illinois, Urbana-Champaign (Illinois, USA)	9 x 9	N.S.	N.S.	Ex vivo	Resection margin	5 trained OCT readers	92	92	-
Breast cancer	Nolan et al. 2016	OCT, Biopitigen Inc. (Morrisville, USA)	11 x 11	N.S.	300-600	Ex vivo	Lymph nodes	3 analysts	59	81	-
	Grieve et al. 2016	FF-OCT, LL-Tech SAS (Paris, France)	1 x 1.6	0.20-0.30	600	Ex vivo	Lymph nodes	1 pathologist 1 non-medical OCT expert	92 / 85	83 / 90	-

Tumor type	Reference	Technique, Manufacturer	Technical specifications	Acquisition time/image (seconds)	N (images)	Study design	Samples	Analysis	Sensitivity (%)	Specificity (%)	Detection rate (%)
Pancreaticobiliary cancer	Testoni et al. 2005	OCT, Pentax, Lightlab Imaging (Westford, MA, USA)	Resolution: axial x lateral (μm) 5-10 x 5-10	1 radial mm /s	100	Ex vivo	Resection specimens	3 observers	79	89	-
	Testoni et al. 2007	OCT, Pentax, Lightlab Imaging (Westford, MA, USA)	5-10 x 5-10	1 radial mm /s	11	In vivo (during ERCP)	Pancreatic duct strictures	N.S.	100	100	-
	Arvanitakis et al. 2009	OCT, PENTAX Corporation (Tokyo, Japan) / Lightlab Imaging Ltd. (Boston, USA)	10 (not exactly described)	N.S.	35	In vivo (during ERCP)	Biliary duct strictures	2 endoscopists	53	100	-
	Iftimia et al. 2011	OCT, Physical Sciences, Inc. (Andover, USA)	9.5 x 25	N.S.	46	Ex vivo	Resected cysts	1 pathologist 1 gastroenterologist 1 radiologist	95	95	-
	Van Manen et al. 2017	FF-OCT, Light CT scanner, LL-Tech SAS (Paris, France)	1.5 x 1.0	>1	100	Ex vivo	Resected specimens	2 pathologists	72	74	-
Oesophageal cancer	Zuccaro et al. 2001	OCT, manufacturer not specified	12 x 20	1	138	In vivo (endoscopic)	AC	23 individuals	-	-	95
	Hatta et al. 2010	OCT, Light Lab Imaging (Boston, Mass) and HOYA (Tokyo, Japan)	11 x 30	N.S.	144	In vivo (endoscopic)	SCC	1 gastroenterologist	-	-	93
	Hatta et al. 2012	OCT, Light Lab Imaging (Boston, Mass) and HOYA (Tokyo, Japan)	11 x 30	N.S.	131	In vivo (endoscopic)	SCC	1 gastroenterologist	-	-	95
Colorectal cancer	Ashok et al. 2013	(Fourier Domain) OCT, University of Edinburgh (Edinburgh, UK)	6.2 x 17	1.2	62	Ex vivo	Resected specimens	Computer	78	74	-
	Dangle et al. 2009	OCT, Nirx™ System, Imalux Corporation (Cleveland, OH, USA)	10-20 x 10-20	1.5	100	Ex vivo	Resection margin	N.S.	70	84	-
Prostate cancer	Lopater et al. 2016	FF-OCT, Light CT scanner, LL-Tech SAS (Paris, France)	1.5 x 1.5	>1	119	Ex vivo	Biopsies	3 pathologists	63	74	-
	Lee et al. 2012	OCT, manufacturer not specified	4 x 14	N.S.	35	Ex vivo	Resected specimens	Three observers	96	96	-
Renal cancer	Jain et al. 2015	FF-OCT, Light CT scanner, LL-Tech SAS (Paris, France)	1.5 x 0.8	N.S.	67	Ex vivo	Resected specimens	1 uropathologist	100	100	-
	Wagstaff et al. 2016	OCT, Illumien™ Optis™, St. Jude Medical (Saint Paul, MN, USA)	15 x 20	N.S.	40	Ex vivo	Renal biopsies	Computer	86	75	-

Tumor type	Reference	Technical specifications				Study design			Analysis		Diagnostic value	
		Technique, Manufacturer	Resolution: axial x lateral (µm)	Penetration depth (mm)	Acquisition time/image (seconds)	N (images)	Implementation	Samples	Analysis	Sensitivity (%)	Specificity (%)	Detection rate (%)
Bladder cancer	Manyak et al. 2005	OCT, manufacturer not specified	10 x 15	1	1.5	87	Ex vivo	Biopsies	1 reviewer	100	89	-
	Hermes et al. 2008	OCT, Aachen University (based on Sirius 713, Heidelberg Engineering GmbH, Lubeck, Germany)	3 x 10	N.S.	4-16	142	Ex vivo	Resected specimens	1 reviewer	84	78	-
	Goh et al. 2008	OCT, Niris Imaging System (Imalux, Cleveland, OH)	10 x 20	1-2	1.5	94	In vivo	Biopsies and resected specimens	1 surgeon	100	90	-
	Ren et al. 2009	OCT, Stony Brook University, (New York, USA)	10 x 10	2.1	8 frames / s	110	In vivo	Biopsies	urologists/OCT researchers	94	81	-
	Karl et al. 2010	OCT, Niris Imaging System (Imalux, Cleveland, OH)	10 x 20	1-2	1.5	102	In vivo	biopsies	N.S.	100	65	-
	Gladkova et al. 2011	Cross-polarization OCT, Institute of Applied Physics of the Russian Academy of Sciences (Nizhny Novgorod, Russia)	15 x 25	N.S.	N.S.	2	Ex vivo	Biopsies	7 reviewers	94	84	-
Ovarian cancer	Montagne et al. 2017	FF-OCT, Light CT scanner, IL-Tech SAS (Paris, France)	1.5 x 1.0	>1	N.S.	24	Ex vivo	Resected specimens	2 unexperienced reviewers; 1 FF-OCT expert	Unexperienced: 93 Expert: 100	Unexperienced: 78 Expert: 89	-
	Nandy et al. 2016	FF-OCT, manufacturer not specified	1.6 x 3.9	N.S.	N.S.	56	Ex vivo	Resected specimens	Computer: logistic classifier model	92	88	-

Abbreviations:

OCT: optical coherence tomography

N.S.: not specified

HD-OCT: high definition optical coherence tomography

SCC: squamous cell carcinoma

ACC: adenocarcinoma

PDC: poorly differentiated carcinoma

FF-OCT: full field optical coherence tomography

Figure 2. Example of corresponding OCT and histology images of two melanomas.

Upper panel (A and C): Hematoxylin and eosin (H&E) images of a superficial spreading melanoma. Lower panel (B and D): OCT images of distorted skin architecture, including large vertically arranged icicle-shaped structures (*). Prominent hyperreflective structures are corresponding to dense collagen cords of encapsulated tumor lobules. Reprinted by permission from Elsevier: *Journal of the American Academy of Dermatology*. [16] © 2007.

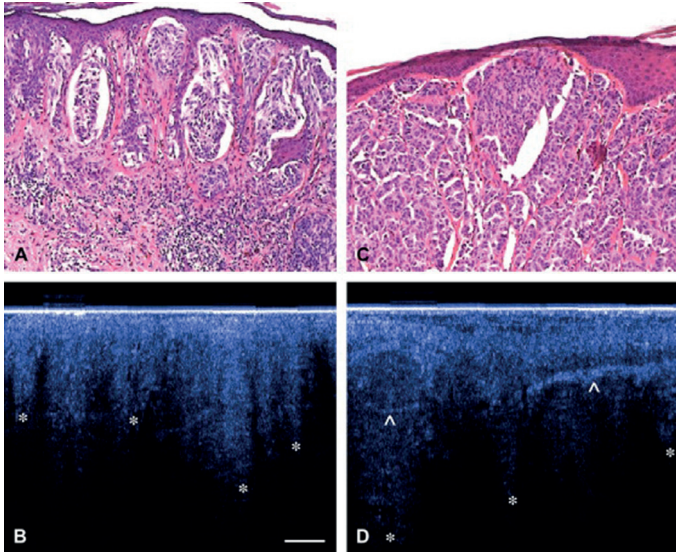


Figure 3. Handheld OCT during breast cancer surgery.

Upper panel: Normal breast tissue with well-defined boundaries, linear structures, and regular texture. Middle panel: Arrow shows an example of a ductal carcinoma in situ, characterized by irregular texture and significant shadowing. Lower panel: An example of an invasive ductal carcinoma (arrows) showing regions with disturbed tissue architecture. Reprinted by permission from Springer Nature: *Annals of Surgical Oncology*. [69] © 2015.

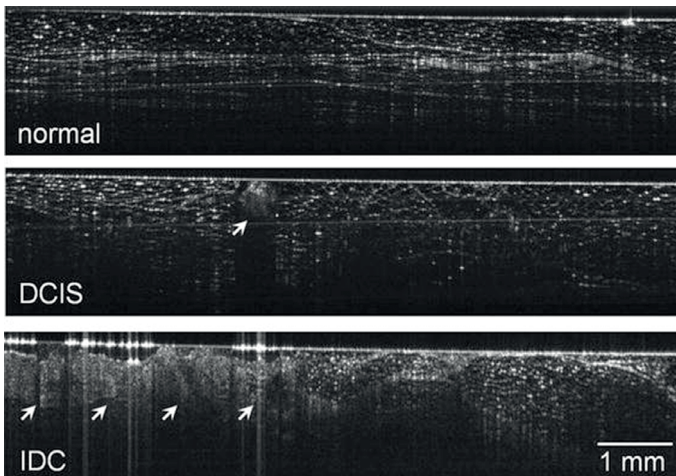


Figure 4. FF-OCT images of the pancreas.

Upper panel: FF-OCT image and corresponding Hematoxylin and eosin(H&E) image of normal pancreatic tissue.
 Lower panel: An example of a FF-OCT image of a moderately differentiated pancreatic adenocarcinoma with corresponding H&E image, showing tumor cells infiltrating into fat tissue (Bar= 250 μ m).

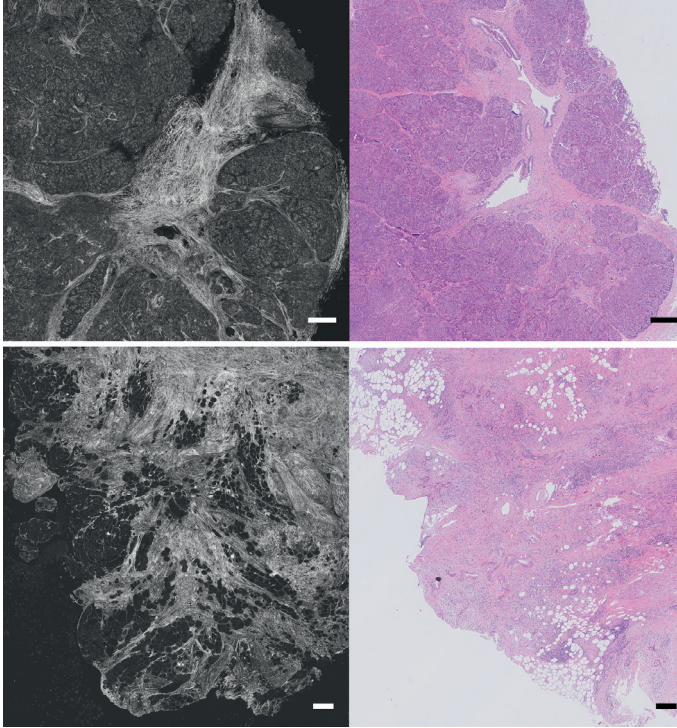
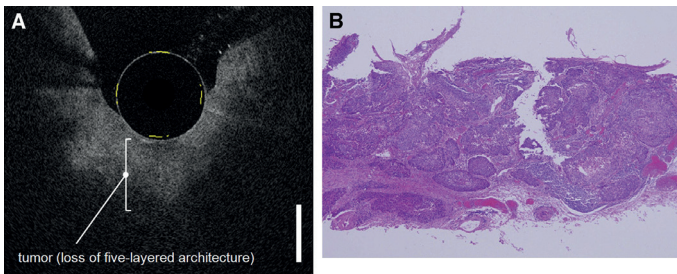


Figure 5. Example of endoscopic OCT of an esophageal squamous cell carcinoma.

Corresponding OCT (A) and histology (B) image of tumor invasion in the submucosal layer, resulting in a loss of the five-layered architecture (Bar= 1000 μ m). Reprinted by permission from Elsevier: *Gastrointestinal Endoscopy*,[93] © 2010.



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