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# The benefits of targeted endoscopic biopsy performed using the autofluorescence based diagnostic technique in 67 cases of diagnostically difficult gastrointestinal tumors

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ABSTRACT

*Introduction:* The search for new diagnostic and therapeutic procedures is an essential task in contemporary oncology. The purpose of our study was the evaluation of the practical usefulness of autofluorescence endoscopy (AFE) using the Onco-LIFE system, compared with the use of white light endoscopy (WLE), and the estimation of the correlation between the histopathological evaluation with the degree of lesions' Numerical Color Value (NCV index) and the method's sensitivity and specificity valuation.

*Material:* 67 patients were analyzed at the Center for Laser Diagnostics and Therapy. All patients previously had a gastrointestinal tract tumor, which appeared malignant, but without histopathological confirmation. We measured NCV, estimated the correlation of the clinical diagnosis based on histopathological evaluation with the degree of NCV index from gastrointestinal lesions, and calculated the sensitivity and specificity of this method.

*Results:* In the group of 67 patients, we found 44 cases of primary or secondary cancers and 7 cases of non-epithelial malignancies. In this group (51 patients) we identified 13 colorectal cancers and 38 upper gastrointestinal cancers. Based on the NCV index at NCV > 1.0, we revealed, that the sensitivity for malignant neoplastic lesions was 100% and the specificity was 73%, while for NCV > 1.5, the sensitivity for malignant neoplastic lesions was 86% and the specificity 100%.

*Conclusion:* AFE using the Onco-LIFE system is a helpful tool to perform targeted biopsies at the outset. A significant correlation was found between lesions' NCV index and the grade of dysplasia or tumor malignancy. AFE sensitivity and specificity is higher than WLE. Further studies are needed, especially performed by expert endoscopists.

## 1. Introduction

The search for new diagnostic and therapeutic procedures is an essential task in contemporary oncology [1–3]. The prevention of the development of gastrointestinal cancer, in particular the detection and resection of polyps, is the reason why screening endoscopy is conducted. Endoscopic methods are, and will continue to be, the gold standard diagnostic tool in the diagnosis of organic gastrointestinal diseases as, apart from the actual imaging of available sections of the gastrointestinal tract, they also allow for targeted biopsy of pathological changes. The problem is, that a lot of lesions, especially small, flat or depressed-type colorectal tumors, are missed during conventional white light colonoscopy endoscopy (WLE). Therefore, new and advanced endoscopic imaging technologies are used to improve sensitivity and specificity of endoscopic procedures. These new methods include autofluorescence endoscopy (AFE), narrow-band imaging (NBI), high-resolution endoscopy (HRE), trimodal imaging (ETMI) and chromoendoscopy (CE). There have been a lot studies that compare the diagnostic efficacy of AFI, NBI, and AFI combined with NBI and WLE in detecting gastrointestinal lesions [4–7]. At our Center for Laser Diagnostic and Therapy at the Medical University of Silesia in Bytom, we performed endoscopic examination enriched with AFI and NBI.

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We usually use Onco-LIFE (Light-Induced Fluorescence Endoscopy) (Xillix, Richmond, Canada) to assess abnormal, potentially-cancerous tissue. Onco-LIFE operates in two imaging modes: conventional white light imaging mode (also referred to as color imaging mode) and fluorescence imaging mode. The system's immediate, simultaneous and repeatable ability to change the light source simply by pressing one button, allows us to evaluate the tissues' fluorescence when excited by monochromatic light [8]. This system consists of an endoscopic light source and video camera for use with conventional endoscopes. Using the Onco-LIFE system the relative differences in intensity between the blue light-induced green autofluorescence and the red autofluorescence can be displayed numerically, offering some quantification of the fluorescence changes (NCV, numerical color value) [9,10].

Based on more than 20 years' experience, observations and research using pathological evaluation of fluorescence we have introduced standards of diagnostic procedures based on the use of AFI methods for early and advanced oncological diagnosis [11,12].

In medicine, the term "tumor" is a collective word describing an abnormal pathological structure, that show evidence of growth (in a benign or malignant pattern), fills a specific space and can be detected on palpation or seen in imaging or endoscopic studies. The unstoppable progression of atypical and dysplastic cells is furthered by angiogenic cytokines. Newly formed and growing vessels and developing supporting tissues are the basis for further autonomous continuous growth and tumor evolution. A rapidly growing tumor undergoes focal necrosis, which, with the help of stimulated macrophages and the process of initiated healing, undertakes pseudo-repair processes [13]. In the course of tumor development, new cell lines appear, resulting from successive cells mutations, which begin to win the battle for cancer development, because they are more easily distinguishable and more easily shared by replacing the less varied. It is also easier to contaminate healthy tissues, including the distal ones, which are the root of tumor metastasis. Multiplicity and diversity of tumor cells and the involvement of many cell clones in its structure causes unequal and non-homogenous tumor structure, and thus makes it difficult to make a proper diagnosis on the basis of random tumor biopsy, which is in fact a very small piece. Knowledge of the histopathological structure of the tumor is essential for the diagnosis of the disease, which in turn determines the implementation of appropriate therapeutic treatment [14,15]. In the case of tumors, the primary treatment is removal of the tumor. The lack of histopathological confirmation of cancer disease may raise legal controversy or lead to questions regarding the appropriacy of the treatment. The definitive diagnosis of the type and nature of the tumor, the stage of its progression and infiltration, the degree of malignancy, and the spread of the tumor process, give the basis for radical therapy, or for dropping aggressive antineoplastic treatment, qualifying a patient with advanced cancer for palliative symptomatic treatment [16,17,18].

The purpose of our study was the evaluation of the practical usefulness of autofluorescence endoscopy using the Onco-LIFE system, compared to white light endoscopy, and the estimation of correlation the histopathological evaluation with the degree of lesions' NCV index. The method's sensitivity and specificity valuation was also performed.

## 2. Material and method

### 2.1. Patients

Between 2011 and 2016, 67 patients who had previously had a tumor of the gastrointestinal tract which appeared malignant but which had not been confirmed by histopathological examination, were examined further using AFE at the Center for Laser Diagnostics and Therapy. Endoscopic and clinical images clearly pointed to the malignant nature of the changes, but the lack of histopathological confirmation of the malignant nature of the tumor inhibited the proper treatment of these patients. Within this group, 48 patients had been diagnosed with probable cancerous upper gastrointestinal tumors, and 19 patients with a suspected malignant tumor of the lower gastrointestinal tract. Prior to referral to the Diagnostic and Laser Therapy Center, the majority of the patients (78%; 53/67) had been subjected more than once to classic endoscopic examinations with the biopsy of tumor tissue. Lack of compliance with the clinical and histopathological image, resulted in the referral of patients for further fluorescence diagnostics for targeted biopsy.

### 2.2. Autofluorescence diagnostic based technique

The Onco-LIFE light source provides both white light illumination and fluorescence excitation. The light source features include dual-mode operation for white light and fluorescence endoscopy with 150 W super-high-pressure mercury (Hg) arc main lamp with halogen backup lamp. The red and green wavelengths of the autofluorescence image are filtered and amplified by image-intensifying cameras. Their relative intensities are measured and this information is used to display a computer-enhanced image delineating abnormal areas of fluorescence. We use the Onco-LIFE camera in conjunction with the Onco-LIFE camera controller, that transduces endoscopic images. The camera features include dual-mode operation for white light and fluorescence endoscopy and a high-sensitivity, high-dynamic-range, color image sensor for the acquisition of color images. The images are analysed and are presented as a single real-time image on a monitor.

AFE of the gastrointestinal tract shows the non-homogenous structure of the pathological tissue. The tumor surface exhibits heterogeneous fluorescence, which directly shows the irregular distribution of fluorophores accumulated in various tumor-building tumors. High fluorescence fields are interlaced with low fluorescence areas that are close to normal or clearly lower, and correlated with NCV index. Thus, by performing targeted biopsies under the control of an image of induced autofluorescence and NCV index, we can say with confidence that the tumor site is representative for a targeted biopsy (performed during endoscopic examination for actual histopathological assessment).

In the study summary, comparing the result of histopathological examination with the NCV index, the sensitivity and specificity of our method were estimated. In some cases, we also used endoscopic ultrasonography (EUS).

## 3. Results

67 endoscopic diagnostic tests were performed on suspected gastrointestinal tumors using AFE. With the exception of one case of suspected duodenoid hemangioma (confirmed using endoscopic ultrasound (EUS; UMQ 130 by Olympus), 66 targeted biopsies were consequently performed from the control of the intensity of fluorescence induced by monochromatic light. At the same time, the results of objective fluorescence (NCV) measurements from different areas of the assessed tumors were recorded, and samples were taken from the places with the highest NCV. AFE revealed malignant neoplasms in 51 cases, whilst allowing us to exclude malignant neoplasm in 15 cases. We have found 44 cases of primary or secondary cancers and 7 cases of non-epithelial malignancies. In this group of 51 patients 13 colorectal cancers and 38 upper gastrointestinal cancers were detected (Tables 1,2). All diagnosed primary colon cancer were exophytic lesions. In this group with cancer (44 patients) we found only one patient (2,5%) with primary cancer with NCV ranging from 1.0-1.5. In another 11 cases NCV was between 1.5 – 1,99, and in other 70% (32 patients) NCV exceeded 2.0. In 23 cases (55%), NCV exceeded 2.5 (Table 1). NCV values for other cancer lesions are presented in Table 1. The types of primary oesophageal and gastric cancer are presented in Table 1. GI carcinoid tumors and gastric lymphomas have a plural form, and NCV values ranged from 1.0 to 1.5 NCV (Tables 1,2). The transfer of clear-celled kidney cancer to the stomach took the form of finger protruding polyp