EDITORIAL ARTICLE

METHODS OF SPECTRAL DIAGNOSTICS IN MODERN PREVENTION OF ONCOLOGICAL DISEASES

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ABSTRACT

This paper contains structured information on photodynamic diagnostics. Photodynamic diagnostics is a young diagnostic modality used in the detection of pre-neoplastic and very early neoplastic lesions. A characteristic feature of the presented method is its completely non-invasive nature and thus the possibility of multiple repetitions at the same patient. This is very important in modern health care and in preventive measures.

Aim of the paper: The article aims to present technical and diagnostic possibilities of a photodynamic method as one of the possible modalities of screening diagnostics in patients with ambiguous clinical picture of early neoplastic lesions.

KEY WORDS: early cancerous changes, spectral analysis, spectrum, lasers, LED diodes, photodynamic diagnostics

In the 20th century we witnessed a rapid civilization development based mainly on the development of new technologies. The 21st century will be based on the development of interdisciplinary discoveries from the border of broadly defined physics, chemistry and biology. Undoubtedly, we will see most discoveries in space technologies and medicine. An example in the field of medicine is photodynamic diagnostics intensively developed in recent years. This is an excellent example of using knowledge in the field of physics, biology and biochemistry to develop a modern technique of medical imaging diagnostics used in visualizing early cancerous lesions. This method may be an important diagnostic branch with high screening utility because it allows to quickly and in a non-invasive way determine the nature of the examined lesion in patients with suspected neoplastic lesions. This is important in the current health care system where low-cost, non-invasive methods for mass diagnostics of patients are sought.

The first works related to photodynamic diagnostics were done already at the turn of the 19th and 20th centuries. At the time, interest was given to the fact that the lighting of the slipper animalcule (*Paramaecium Caudatum*) caused a lethal effect at low acridine levels. In comparative tests using a similar concentration of the dye in the solvent, but without access to light, this effect did not occur [1].

The first use of the photodynamic method took place in 1903. Eosin was then used as a photosensitizer. In 1911 hematoporphyrin was used as a photosensitizer. In 1924, tumor fluorescence was demonstrated in mice based on the action of endogenous porphyrins. Also, that year, the accumulation of exogenous hematoporphyrin in cancer cells was more than 4 times higher than in healthy cells. The first commercial photosensitizer was created in the 1960s under the name HpD and was a mixture of various porphyrin derivatives. At the same time, a number of studies were carried out on the optical properties of tissues and cells, as well as light itself, which is subject to complex physical phenomena in the cell. Light as an electromagnetic wave in a cell is subject to transmission and absorption. There is also reflection, Raman dispersion and elastic dispersion. Energy is transferred by fluorescence or phosphorescence [2].

In the course of experiments, the usefulness of this method has been demonstrated for the diagnosis of early neoplastic lesions based on fluorescence by differentiating neoplastic tissues from normal (Fig. 1).

Photodynamic diagnostics is a non-invasive diagnostic method. It allows one to analyze the observed lesion in real time in the visible light range. This means that it allows one to perform an analysis on the patient's skin at any place and time. It also means the ability to analyze patient's internal structures that can be diagnosed using speculum and endoscopes. Thus, in addition to dermatology, this method is constantly being developed within gastroenterology,
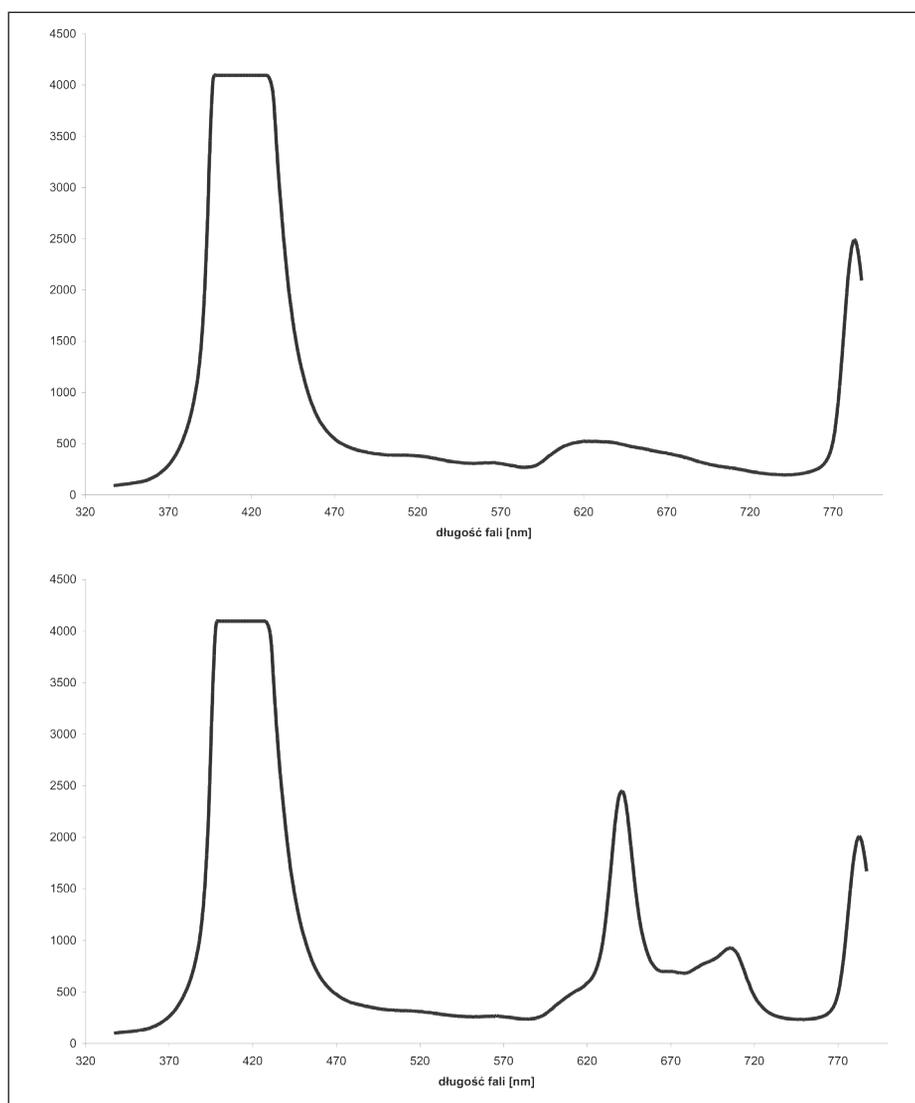
Fig. 1. Spectrum of healthy tissue and neoplastic tissue (own material).

gynecology, urology and pulmonology. A characteristic feature of this method, due to the use of visible light, is the possibility of repeated analyzes of the same area. This enables not only very accurate identification of the dysplastic area but also monitoring of the treatment process.

The method is based on the phenomenon of light emission by tissues. The affected tissue contains protoporphyrin, which emits light of a different, defined wavelength as a result of the light brought into it. For this phenomenon to occur, the observed tissue is illuminated with blue light. The whole process must take place in the so-called optical skin window. It is the range of visible light that penetrates deepest into the tissue. The maximum transmittance used for photodynamic therapy is in the range of 800-1200 nm. Dynamic diagnostics use a shorter length ensuring light penetration to a depth of 0.5-2 mm. This range was specified in the 400 – 500 nm range. For precise selection of the wavelength of light and at the same time ensuring adequate energy, the light generated by lasers is used. Laser light provides strictly defined and repeatable physical parameters. Most often blue light with a wavelength of 405 nm is used to induce autofluorescence. A certain difficulty, however, is still the high cost of devices generating the laser beam. The solution to this problem was the use of xenon or mercury light sources equipped with appropriate barrier filters. This solution, much cheaper than a laser, however, generated large amounts of heat, difficult to eliminate in treatment room conditions. In addition, strictly defined and short life span of this type of light sources generated high operating costs. The applied optical filters allowed for obtaining a heterogeneous wavelength. In the case of lasers, the wavelength was strictly defined, while in the case of optical filters, the wavelength was in the range of 20-80 nm next to the required peak. Digital cameras are the indispensable equipment for autofluorescent diagnostic systems. Modern cameras are miniature and light with high resolution transducers. In addition, dedicated software allows the use of proprietary measurement methods to obtain specific numerical values in the area of the observed and analyzed area. This makes it possible to compare the obtained images and thus creates broad analytical possibilities and monitoring of the treatment process itself [3].

The fastest development of photodynamic diagnostics took place in pulmonology. Bronchial tree imaging during standard bronchoscopic examination has been perfectly developed. Dedicated diagnostic systems have been created to enable standard bronchoscopy and subsequent testing using the possibility of tissue autofluorescence. Endoscopic examinations carried out so far in white light did not always give a full diagnostic response specifying the nature of the observed lesion. The result of image analysis was often not clear-cut. In addition, the observed area suspected of dysplastic lesions at a very early stage of development in white light is almost imperceptible. A reliable diagnosis requires a biopsy specimen for histopathological analysis and the final diagnosis is made on the basis of this examination. Often in the case of a white light test, the collection of a specimen from the affected area is unsuccessful. Autofluorescence diagnostics fully solves this problem. The doctor conducting tests in blue light, through the appropriate software of the whole device, sees healthy tissues as green areas. All irregularities are shown in shades of red. The intensity of the red color depends largely on the stage of the tumor formation process. This fact undoubtedly constitutes the superiority of the proposed solution over classic endoscopic techniques performed in white light. In the absence of certainty as to the observed area after switching to blue light, the examining physician can clearly see where from which the histopathological examination should be taken. Thus, using this method results in less burden on the patient himself. No further endoscopic tests are needed to burden the health care system, but also to cause a great feeling of patient discomfort. In the field of pulmonology, clinical tests and diagnostic devices available on the market have been used in the diagnosis of early neoplastic lesions such as bronchopulmonary cancer. Autofluorescence diagnostics is especially useful in patients whose cancer cells were found in sputum, but imaging tests such as chest X-ray or classic bronchoscopy did not give a definitive diagnostic result. In pulmonology, autofluorescent diagnostics are used in patients qualified for surgery, after the surgery to monitor the extent and possible recurrence as well as to assess the pathomorphological assessment of the upper respiratory tract mucosa [4].

In addition to pulmonology, the second application of autofluorescence diagnostics is its use in assessing colorectal lesions. During the colonoscopy, the image of the mucosa is assessed. This allows one to unambiguously assess changes in ulcerative colitis and colitis that often last for several years. High diagnostic utility has been demonstrated in the assessment of colorectal polyps with diagnosis such as adenoma villosum and tubulovillosum. In the field of preventive medicine, the presented method is extremely useful in periodic assessment in patients after previous resection and anastomosis of the lower gastrointestinal tract as a result of colorectal cancer or surgery as a result of complications after long-term inflammation of the intestinal walls. This is especially true for patients with suspected recurrent tumorigenesis revealed in clinical history or biochemical tests. Prophylactic treatment also applies to genetically burdened patients, who naturally have a significantly higher risk of developing cancer [5].

Also, the upper gastrointestinal tract can be diagnosed using autofluorescent methods. It is a method widely used in assessing lesions within the esophagus and the stomach. It allows you to search for dysplastic lesions within the Barret's esophagus, significantly facilitating the accurate collection of specimens for histopathological examination. It also allows the assessment of benign ectopic or papillary lesions within the mouth and esophagus [6].

Available research results show the great potential of photodynamic therapy in urology. This applies in particular to bladder disorders that require very high precision when collecting specimens for histopathological examination. Very high usefulness in imaging urinary tract lesions has been demonstrated. This method can be used as a screening test with very high sensitivity while maintaining minimal invasiveness in the field of imaging of the bladder and ureters. Indication for cystoscopy using fluorescence imaging is the suspicion of intraepithelial bladder cancer (in situ) in patients with a history of hematuria and inflammation of the urinary tract resistant to anti-inflammatory drugs for over 3 months. Patients after transurethral resection or neoplastic foci within the bladder wall may also be referred for the purpose of assessing the radicality of the procedure and for assessing new or recurrent neoplastic foci [7].

Photodynamic diagnostics is also used in gynecology in the early stages of vulvar and cervical lesions. An indication for carrying out the test using this technique is to obtain an abnormal cytological test result of a swab taken from the cervix showing endothelial features of a high-grade lesion. A vulva analysis is also performed after radical treatment as a result of a neoplastic lesion and in patients with suspected relapse. Scleroderma and lichen sclerosis with confirmed dysplasia are assessed. The effectiveness of autofluorescence studies in imaging of lesions in gynecology in women with confirmed human papillomavirus infection has also been demonstrated, which did not show clinical lesions but had confirmed dysplasia in cytological examination [8].

The importance of photodynamic diagnostics has been demonstrated in dermatology. It is conditioned by its completely non-invasive character and practically unlimited repetition. Subassemblies for the construction of autofluorescent diagnostics systems for dermatology are characterized by simplicity and do not require engineering studies necessary in the case of endoscopy to obtain the possibility of integrating cameras of different manufacturers, with many models and endoscope mounting systems, which must also be combined with appropriate light sources. The use of the LIF method in the diagnosis of skin cancers is conditioned by a high concentration of nicotinamide adenine nucleotide redox. A number of lesions such as melanoma, other skin cancers, birthmarks, seborrheic warts and psoriasis have similar fluorescence. Only melanoma has much weaker fluorescence compared to healthy skin. The location of skin cancer, especially basal and squamous cell carcinoma, is greatly facilitated by the topical use of a photosensitizer. Neoplastic skin lesions can occur in every

layer. Basal cell carcinoma accounts for about 70-80% of all skin cancers. In second place is squamous cell carcinoma, the incidence of which is 20-25%. Unlike squamous cell carcinoma, basal cell carcinoma does not usually lead to metastasis, but it can infiltrate deeper tissues. An important condition for curing any cancerous lesion is its quick and reliable diagnosis. The detection of basal cell carcinoma, despite being easily histopathologically diagnosed, is often delayed for many years, usually due to the patient. Usually, the lesion is neglected, and its variability of the image diminishes the alertness of the doctor and the patient [9].

Nowadays, new diagnostic systems for localization and often identifying early cancerous lesions are raising the expectations of medicine. Interest in these methods depends on their high sensitivity and resolution compared to traditional diagnostic imaging methods such as computed tomography, magnetic resonance imaging or ultrasound. The most modern optical diagnostic methods, unlike histopathological tests, do not require the collection of biological material. Exciting radiation, often from the visible light range, is led to the examined lesion by optical fibers and emission spectra are received and analyzed in real time. An additional advantage is the fact that the studied areas can be analyzed many times. In recent years there has been an increase in interest in tissue autofluorescence. Only in few diagnostic centers in the world this method is generally available, because it requires very expensive optical diagnostic equipment and highly qualified interdisciplinary staff.

Therefore, spectral analysis is a support for treatment planning, often informing about the biochemical structure of the observed lesion. Specialized algorithms and models developed for tri-modal laser spectroscopy are helpful here.

Tri-modal laser spectroscopy is currently the most developed technique for tissue spectral analysis. The Massachusetts Institute of Technology is constantly at the forefront of ongoing work. This method provides information on the cellular and tissue structure and characterizes the biochemical structure of the examined tissue. It is based on the phenomena of dispersion, fluorescence and backscatter. Although this method is still in the testing and analysis phase, it already gives information characterizing and identifying the examined lesion [10].

Spectral studies contribute to faster and more accurate analysis of the observed lesion suspected of developing cancer. It seems reasonable to say that this diagnosis should be in addition to commonly available diagnostic tests.

The paper presents examples of disease entities for which the photodynamic method is applicable. According to the current standard, the definitive test is a histopathological test. However, in early neoplastic lesions, the area of the lesion is often unnoticeable when examined in white light. The optimal situation would be the possibility of conducting a fluorescent examination in all suspected patients, thus guaranteeing a single procedure and removal of a section from the pathologically changed area.

Efficacy in the treatment, for example, squamous cell carcinoma in situ is high and oscillates in the range of 75-92%

[11, 12]. The same is true for basal cell carcinoma. In the case of detection of endothelial cervical neoplasia, the sensitivity of the method was 60% and the specificity 90% [13].

Photodynamic diagnostics enables quick and correct formulation of an unambiguous diagnosis, which significantly shortens the treatment process. Thanks to this method, it is possible to collect a slice from very early neoplastic lesions or ambiguous lesions in the clinical picture of recurrence processes. This applies to any changes that can be seen on the skin or with the help of endoscopic instrumentation [14].

The correct image of skin or mucosa may mask pathological changes in some cases. The diagnostic process of these changes is completed very quickly if it is possible to verify them. This is of great importance not only for the doctor, but also for the patient. The current economization of health care forces to look for increasingly cheaper and faster diagnostic methods that allow one to start therapeutic procedures faster or a faster, negative verification favorable for the patient.

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Conflict of interest

Authors declare no conflict of interest.

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