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PHOTODYNAMIC DIAGNOSIS AND TREATMENT OF BRONCHIAL CANCER

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Abstract. Lung cancer is a leading cause of malignancy and its incidence increases worldwide. The disease develops deceitfully and only a small proportion of cancers is detected early enough to be treated radically. The main risk factor is cigarette smoking. Other risk groups consist of patients with various occupational hazards, with family history of lung cancer or those already treated for the disease. The risk is usually multiplied when smoking coexists with other risk factors. Considering terrifying epidemiologic data, methods of screening and early detection of the disease should be urgently elaborated and should cover well defined risk groups. Photodynamic bronchoscopy allows an early detection of pre-invasive lesions and carcinoma in situ, as well as of synchronous or metachronous lesions in patients with already detected disease. The use of photosensitizers permits to apply of laser therapy. In the present work, photodynamic diagnosis and treatment of bronchial cancer are reviewed. Although both sensitivity and specificity of photodynamic diagnosis is as yet not well established, the method may be suggested as a future screening tool in a population with present or past occupational hazard.

Key words:
Photodynamic diagnosis, Photodynamic treatment, Fluorescence bronchoscopy, Bronchial cancer, Screening

INTRODUCTION

Lung carcinoma is a leading cause of malignancy among men and the fifth cause among women [1]. As it usually originates from bronchial cells and grows in the lumen of a bronchus or peribronchially, the term bronchial cancer is used synonymously. The death rate is increasing worldwide. In 1990, the annual number of new cases in the world was estimated at 1.04 million, and their number is increasing at the rate of 3% per year [1]. In Poland, about 20 000 deaths due to lung cancer are registered per year [2]. Symptoms, such as a change of cough character, appearance of blood in sputum, weight loss, ostealgia and others show up very late, usually in an advanced stage of the disease. In the majority of cases the treatment of choice is surgery, but less than 10% of these patients are still available for radical treatment at the time of diagnosis. Only 30% of patients survive 5 years [2]. These data show that the diagnosis, commonly based on symptoms and patients' self-reporting, is usually made too late. The disease occurs predominantly in heavy smokers. Two pathological types are especially connected with smoking: small-cell lung cancer and squamous lung carcinoma. Many occupational hazards are also associated with a higher incidence of lung malignancy. In many cases the risk is multiplied by the coincidence of smoking habit. The increased risk has been proved in uranium [3] and radon-exposed miners [4], workers exposed to quartz [5], silicon carbide fibers [6], beryllium [7], nickel salts [8], silica [9] and in rubber workers [10]. Occupational exposure to diesel exhaust may also be connected with increased risk of lung cancer [11]. Best described is the relationship between lung cancer (usually adenocarcinoma) and exposure to asbestos fibers,

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the leading cause of occupation-related cancer death. Asbestos is the second after tobacco most fatal manufactured carcinogen. It has been acknowledged as a hazard for 60 years, but a legislation addressed to the control of lung cancer in workers exposed to asbestos had to wait till the 1970s [12]. Asbestos-associated lung cancers usually occur in patients showing signs of pulmonary asbestosis. According to some authors the cancer may be found in 12–55 % of patients with asbestosis [13]. Considering the epidemiological data on lung cancer and late final diagnosis, new methods of early detection and screening should be urgently elaborated.

Photodynamic diagnosis (PDD) is a new method of detecting neoplastic lesions. It is based on photochemical effect, an intracellular activation of photosensitizers by light of a specified wavelength. Naturally occurring substances or those applied from external sources may play a role of a photosensitizer. Sensitized lesions exposed to laser light undergo necrosis. This phenomenon has been used in the treatment of neoplastic lesions in various organs and is called photodynamic therapy (PDT). The photodynamic method has been successfully applied in the detection and treatment of skin malignancy [14], urinary bladder tumors [15], carcinoma of gastrointestinal tract [16], and cerebral tumors [17]. Recently, the usefulness of PDD and PDT in pulmonary medicine has been a subject of debate. The present review is dedicated to the validation of photodynamic method in the detection and treatment of bronchial carcinoma.

HOW DOES IT WORK?

The ability of a tissue to emit light when activated by a specified wavelength is called fluorescence. When external photosensitizers are not used, and a tissue emits light spontaneously, the term autofluorescence is frequently used. Here, the photosensitizer is a naturally occurring intracellular stain, such as: haemoglobin, porphyrin derivative, melanin, cytochrome, or some plasma proteins. The process may be intensified by application of such substances from external sources. Hematoporphyrin derivatives (HpD) are usually applied intravenously or orally, several hours before examination. First therapeutic application of HpD dates from the 1960s, when it was used to treat breast cancer. An active component of HpD, dihematoporphyrin ethers (DHE) is commonly used today. After intravenous injection, DHE is distributed to all tissues, but is eliminated from healthy cells within 6 h. It is retained longer in lungs (approximately 12 h), reticuloendothelial system (about 24 h) and skin (small amounts are detected 30 to 80 days after application). After 48 h it is hardly found in a healthy tissue but is detected at high concentrations in a tumor. At that time a ratio of DHE concentration in malignant and healthy tissue is 2–3:1 [18].

A recently introduced marker with tumor-localizing properties is 5-aminolevulinic acid (5-ALA). Administration of 5-ALA, a precursor of protoporphyrin IX (PpIX) in the biosynthetic pathway of heme, results in a selective accumulation of PpIX in neoplastic tissue. Both the ability of neoplastic tissue to accumulate porphyrin derivatives and the phenomenon of autofluorescence can be explained by altered activity of the heme biosynthetic pathway enzymes within transformed cells. Navone et al. [19] showed *in vitro* in human breast carcinoma cells, a 20-fold increase in porphyrin synthesis and the increased activities of three porphyrin biosynthesis enzymes: ALA-dehydratase, porphobilinogenase and uroporphyrinogen decarboxylase. Hypoxia of neoplastic cells may slow-down a porphyrin metabolism. Low cellular pH and changed pK values, influencing ionization and intracellular distribution of a photosensitizer in transformed cells, should also be considered as mechanisms promoting its selective accumulation in malignant tissue [20,21].

A typical equipment for photodynamic diagnosis consists of: a fiberscope, a violet light source (xenon short-arc lamp or Kr ion laser), PDD camera, and usually a video-recorder. Exposure of a cancer to violet light (405 nm) induces fluorescence of a photosensitizer, which is detected as red light (two peaks at 630 and 690 nm). Due to application of filters, and depending on the type of equipment, the final picture appears in green, blue or violet (healthy tissue) and red or purple (malignant or premalignant lesions) (Figs. 1–3). Such "sensibilized" lesions can be further exposed to red light of 630 nm from argon-pumped dye

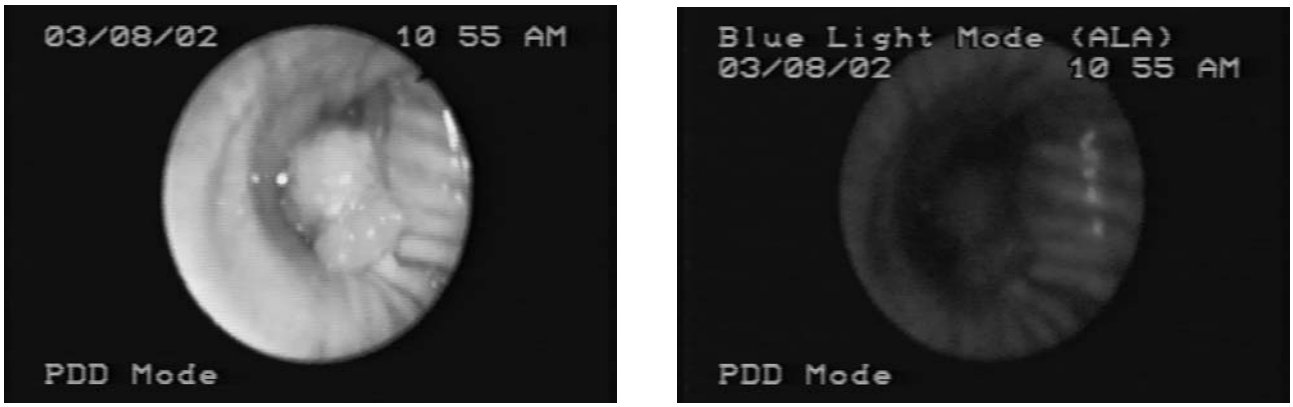

Fig. 1A. Infiltration of right upper bronchus in white-light conventional bronchoscopy.
Fig. 1B. The same lesion in violet light after nebulized 5-ALA. The examination was performed with STORZ Endovision TELECAM SL with TELECAM PDD camera. Squamous cell carcinoma in histopathologic examination. All examples of conventional bronchoscopy and PDD examinations shown in this paper come from a collection of the Department of Pneumology and Allergology, Medical University of Łódź.

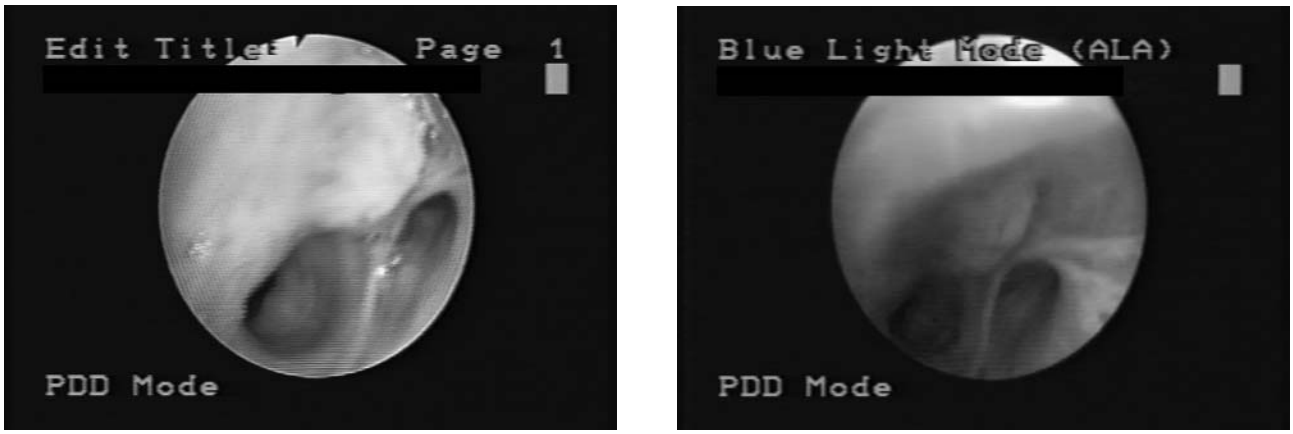

Fig. 2A. Squamous-cell carcinoma occluding main lower bronchus.
Fig. 2B. No clear staining in violet light after nebulized 5-ALA. Such big tumors do not stain easily, probably due to necrosis of superficial layers. If not qualified for surgical treatment, they should be treated with palliative intent by PDT, Nd-YAG laser resection or other methods. The examination was performed with STORZ Endovision TELECAM SL with TELECAM PDD camera.

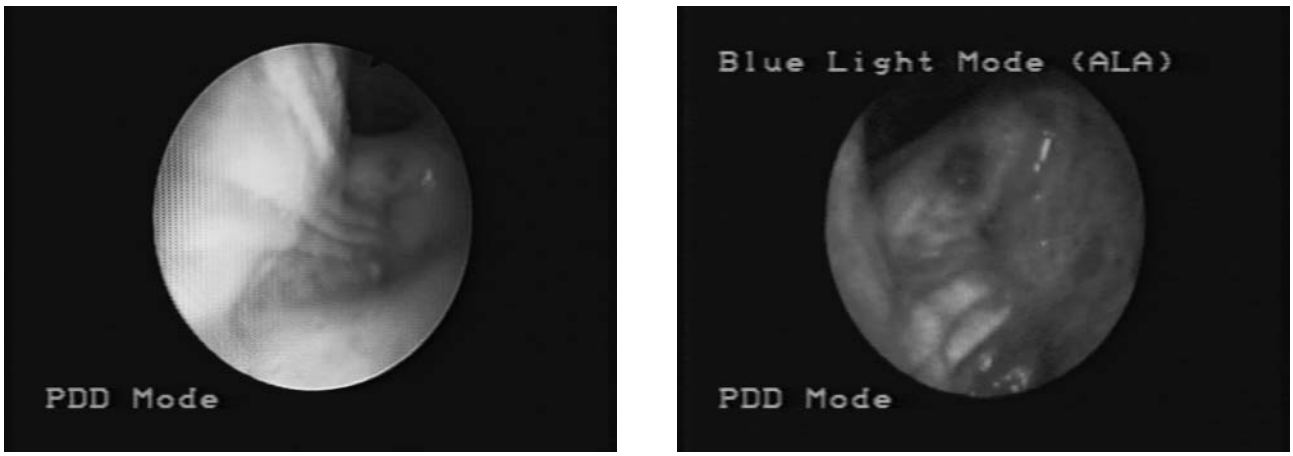

Fig. 3A. A bronchial stump of a patient operated due to squamous carcinoma of a right upper bronchus. No clear evidence of recurrence visible in white light conventional bronchoscopy.
Fig. 3B. The same case in violet light after nebulized 5-ALA. The examination was performed with STORZ Endovision TELECAM SL with TELECAM PDD camera. Weak staining in PDD. Recurrence of squamous cell carcinoma observed in histopathologic examination.

laser or other types of laser of similar characteristics (low energy, no thermal and coagulating effects). This leads to curative necrosis of sensibilized and laser exposed tissue (PDT). The cytotoxicity may be caused by generation of free radicals and singlet oxygen. The ischemic necrosis of a tumor may be mediated by tromboxan A_2.

WHAT DO WE DETECT?

Gregorie et al. [22] in their early work presented the results of the use of porphyrin derivatives in 226 patients suffering from a variety of neoplastic diseases. Fluorescence was shown in 76% of patients. In 10%, fluorescence was not present despite evident neoplastic tumors. Benign tumors showed fluorescence in about 20%. The authors concluded that the method is neither sensitive nor specific enough to be promoted as clinically valuable. However, further studies provided more optimistic results. Soon it was shown that not all types of tumors are available for PDD. The method was proved excellent for detecting superficial cancers of urinary bladder [15] and skin [23]. Tumors that form submucosal infiltrates and differ from squamous carcinomas are difficult to visualize. This is also true for bronchial cancers. In addition, the sole bronchoscopy has its natural limitations in the detection of peripheral lesions. In everyday practice the major problem, however, is the detection of preneoplastic or early neoplastic changes in conventional white-light bronchoscopy. These lesions are small and composed of few cell layers. They are either invisible in conventional bronchoscopy or present only as a subtle change in light reflex, and of color of mucosa or as other minimal changes that are difficult to detect even by an experienced bronchoscopist. The median greatest dimension of carcinoma in situ (CIS) is 8 mm and half of dysplastic lesion is ≤1.5 mm [24]. Recently, Pierard et al. [25] have presented data of 177 endobronchial biopsies from sites determined by fluorescence bronchoscopy (autofluorescence). Among these biopsies, 28% were normal, 24% showed non-preneoplastic changes, 32% metaplasias, 5% dysplasias and 2% CIS (9% of biopsies were non-diagnostic). These data confirm that the method is oversensitive, however, as in everyday life all diagnoses have to be proved by biopsy, it does not lower its value in detecting lesions not yet visible in white light. The histologic type detected by fluorescence bronchoscopy was squamous carcinoma in 60% and adenocarcinoma in 40% of cases. A summary of results from various studies comparing conventional white-light bronchoscopy and a specific autofluorescence bronchoscopy (lung imaging fluorescence endoscope, (LIFE – Lung device, Xillix Technologies Corp.) enabled to gather a large number of data [24]. A British Columbia Cancer Agency Lung Health Study [26], a major component of this meta-analysis, included 511 patients (54% of men, aged 58 ± 10 years and 46% of women, aged 56 ± 8 years), current or ex-smokers, with cigarette consumption over 30 pack-years. In fluorescence-positive histopathologic samples, 5% were normal, 30% evaluated hyperplasia and metaplasia, 44% mild dysplasia, 13% moderate dysplasia, 6% severe dysplasia, 1.6% CIS and 0.4% invasive carcinoma. The meta-analysis which included about 1500 patients showed the detection rate ranging from 71 to 88%, specificity from 57 to 71%, positive predictive value (PPV) from 25 to 47% and negative predictive value (NPV) from 92 to 95%. Comparison with corresponding values achieved by white-light bronchoscopy showed 2-3 times lower detection rate (27 to 51%) and lower NPV (about 85%). These results indicate a supremacy of fluorescence over white-light bronchoscopy in detecting early lesions.

A well established way of lung cancer screening is sputum cytology examination. For instance in Japan, sputum of heavy smokers, over 45 years old, is examined routinely. Although four large and randomized trials conducted at the Mayo Clinic, John Hopkins Oncology Center, Memorial Sloan-Kettering Cancer Center and in Czechoslovakia in the 1970s and 1980s did not demonstrate cancer-specific benefit from screening, the shift toward earlier diagnosis and increased rates of resectability were observed [27–29]. When fluorescence bronchosopy is added to sputum cytology, the detection rate of premalignant lesions and CIS is significantly increased [26,29]. Due to the cited investigators, the relative sensitivity may increase by approximately 6 times, when compared to conventional bronchoscopy. One of the most important disadvantages of fluorescent method is its high cost, thereby it cannot be used as a common screening method in countries with limited health service funds. How-

ever, limiting risk groups, for instance to heavy smokers (i.e., 30 pack-years), aged 40 years and older, with occupational risk, family history of lung cancer, or bronchial obstruction and pre-selected on the basis of the presence of moderate to severe dysplasia or neoplastic cells in sputum, could be a reasonable solution. One should keep in mind that 56% of non-invasive carcinomas become invasive [30]. Studies on sputum cytology revealed that 11% of moderate dysplasia and up to 46% of severe dysplasia will progress to invasive cancer [31,32]. These data show how important it is to select these patients as early as possible.

Another group of patients that can benefit from fluorescence examination of bronchial tree are those who have already been treated due to lung cancer. It provides an opportunity to detect early signs of recurrence in bronchial stump. Moreover, synchronous or metachronous lesions may be detected. For instance, eight neoplastic lesions were found in four of the nine patients consisting a high risk group selected by Venmans et al. [30]. The Japanese authors [33] provide the incidence rate of multiple lung carcinomas in patients with roentgenographically occult squamous cell carcinoma as 22%. Pierard et al. [25] found synchronous cancers in over 9% of patients with resectable primary lung cancer, and the incidence of synchronous preneoplastic lesions was much higher. These authors suggest that fluorescence bronchoscopy may be a useful adjunct in the preoperative evaluation of lung cancer. It seems reasonable to perform fluorescence bronchoscopy periodically (for instance once a year) in patients already treated for lung cancer.

PHOTODYNAMIC TREATMENT OF BRONCHIAL CANCER

The possibility to use laser for the treatment of previously sensitized neoplasm is very promising. Lesions radiated with non-thermal laser undergo necrosis. This process that involves generation of oxidants may be enhanced when hyperbaric conditions are applied [34]. So far in pulmonary medicine PDT has been used for two main purposes: radical management of early bronchial carcinoma and palliative treatment of bronchial obstruction caused by advanced endobronchial tumors. The application of laser is most promising in the treatment of early carcinoma. As PDT can destroy tumor cells within the layer of mucosa, tumors that exceed bronchial cartilage may not be treated. The present experience allows to formulate the following optimal conditions for achieving a radical effect: the tumor should not exceed bronchial cartilage, should be visible in its full length, and measure less than 10 mm in their longitudinal extension, local lymph node should not be involved and no signs of peripheral tumor should be detected on computed tomography. Fujimura et al. [33] examined 2 273 000 patients in a mass screening program and found 1422 patients with lung carcinoma. Among them 255 had roentgenographically occult disease determined by sputum cytology. Finally, of all these patients only 13 fulfilled the above mentioned criteria and could have been treated with curative intent. Only one patient experienced recurrence of the disease and had to be treated surgically. These data show that if a candidate for PDT is selected according to these strict criteria, the results may be excellent. This method can be especially recommended to patients with chronic obstructive pulmonary disease, a frequent coexisting pathology, to avoid surgical excision of lung parenchyma. Besides, the procedure does not require general anesthesia and only prolonged bronchofiberoscopy is necessary. Thus patients with high operative risk, and other coexisting health problems can be safely treated. Another example is a central localization of a lesion, which makes impossible the surgical treatment.

In the whole spectrum of methods, PDT may be one to be used for palliative treatment of bronchial obstruction. One can choose between: Nd-YAG laser therapy (causing thermal excision of a tumor), brachytherapy (intrabronchial irradiation), electrocautery, cryotherapy, balloon dilatation or stent insertion. As no golden mean has as yet been elaborated, a combination of some of these methods is sometimes needed. In many centers, Nd-YAG laser therapy is used most frequently. The comparison of PDT and laser ablation with Nd-YAG laser showed that both methods have similar morbidity and mortality rates. Some authors suggest that PDT is a better choice because it is technically easier, potentially safer and does not require

general anesthesia [35]. Combined Nd-YAG and subsequent PDT may also be an effective palliative treatment in patients with inoperable endobronchial cancer [36]. PDT has also been used for palliative treatment of non-pulmonary metastatic endobronchial tumors [37], bronchial carcinoid [38], and recurrent bronchial cancer [39].

COMMON PROBLEMS

The side effect most commonly associated with application of photosensitizer is photosensitivity, which is manifested as sunburn or periorbital edema. Various forms of protection against sun beams must be used when a photosensitizer is applied generally. New generations of photosensitizers with reduced skin toxicity have been developed [40]. Improvement of autofluorescence equipment would allow to avoid the use of photosensitizers. Another way to surmount this problem is to apply a photosensitizer locally. For instance, for diagnostic purposes 5-ALA may be administered via inhalation (nebulization) with promising results [41]. Neither skin nor respiratory toxicity has been reported. This form of application of a photosensitizer is also cost-saving. The present authors have gained their own experience with nebulized 5-ALA for PDD. However, its usefulness for photodynamic therapy has not as yet been assessed.

Photodynamic palliative therapy of patients with advanced bronchial carcinoma brings about the risk of serious bronchial hemorrhage, which may occur within few days after the procedure and may be fatal. This complication applies to treatment of tumors invading bronchial wall and big vessels. Considering the high risk of fatal hemorrhage in these patients regardless of the treatment, and potential advantages of opening of occluded central airways, this method should be recommended for a selected group of patients. Other complications include: cough, dyspnoea, bronchitis and pneumonia.

CONCLUSIONS

Photodynamic bronchoscopy is a very promising method, especially useful for detecting preneoplastic lesions and carcinoma in situ. Other potential diagnostic applications include: detection of early synchronous neoplastic lesions in patients subjected to surgical treatment or metachronous lesions in patients operated due to bronchial carcinoma in the past. A bronchial stump may be more precisely searched for recurrence. Subsequently, all these lesions can be radically and safely treated by non-thermal laser or alternatively, treated surgically at an early stage. Unfortunately, the equipment and the procedure itself is expensive, and thus cannot be used as a common screening method in the general population. The studies should concentrate on the selection of well defined risk groups, including heavy smokers, genetically predisposed, and finally those with occupational risk. The serious disadvantage of fluorescence bronchoscopy is its subjectivity, responsible for significant inter-observer variability. The risk of under-diagnosis lowers with a growing number of performed examinations. New technologies should be developed to increase sensitivity and specificity, as well as safety of photodynamic diagnosis and treatment of bronchial carcinoma.

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