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Karolina P. Nalewaj, Paweł Krawczyk, Izabela Chmielewska, Janusz Milanowski

Department of Pneumonology, Oncology and Allergology, Medical University of Lublin, Lublin, Poland

Delays in the diagnosis of lung cancer patients in Poland

Address for correspondence:
Karolina P. Nalewaj, MD
Department of Pneumonology, Oncology and Allergology, Medical University of Lublin, Jaczewskiego 8, 20–954 Lublin, Poland
e-mail: kroz93@o2.pl

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ABSTRACT

Introduction. Lung cancer is the most common cause of death from malignant tumors in the world, with more than 2 million patients diagnosed every year. The most common symptoms of lung cancer are cough and shortness of breath. However, they appear late when the cancer is at an advanced stage. The standard measure of the correct diagnostic path in cancer patients is the time from the first symptoms of the disease to the final diagnosis. The aim of the study is to identify reasons for late diagnosis of patients with symptoms of lung cancer in Poland.

Material and methods. We performed an analysis of a survey conducted among 149 patients with lung cancer from the Department of Pneumonology, Oncology and Allergology at the Medical University of Lublin. The SPSS software was used to perform the analysis of these data. Males accounted for 56.4% of the patients, and the median age of the patients was 66.8 ± 7.2 years. The mean time from the first symptoms to the first appointment with a doctor was 5.3 weeks and from the first symptoms to diagnosis was 14.7 weeks.

Results. The time from the onset of symptoms and treatment initiation was significantly ($p = 0.04$) longer in patients living at a greater distance from cancer centers (24.1 weeks) than in patients living nearby (18.3 weeks). In patients who were treated with antibiotics before diagnosis, the time from the onset of the symptoms to the start of treatment was significantly longer ($p = 0.003$) than in patients who did not use antibiotics (26.8 weeks *vs.* 18.1 weeks).

Conclusions. The results of our study showed that Polish patients with suspected lung cancer are diagnosed too late, which has an impact on the stage at which the tumor is diagnosed.

Key words: delays, diagnosis, lung cancer, treatment, symptoms,

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Introduction

Lung cancer is the most common cause of death from malignant tumors in the world, with more than 2 million patients diagnosed every year. Annually, it is diagnosed in about 23000 Polish citizens while, according to the latest forecasts, in 10 years this number will rise to around 30000 per year. The incidence and mortality from lung cancer differ in individual countries, but the overall survival rate is low. According to the Surveillance, Epidemiology, and End Results (SEER) database, between 2012 and 2018, 5-year relative survival rates in non-small cell lung cancer (NSCLC), regardless of the disease stage, was 26%. However, the rate of small cell cancer (SCLC) was only 7%. For the whole population of lung cancer patients, 5-year relative survival was 22.9% [1, 2].

Unfortunately, the vast majority of patients are diagnosed at an advanced stage [3]. The low survival rate of lung cancer patients is due to long-term asymptomatic course of the disease and late initiation of diagnostic procedures. The incidence of lung cancer increases significantly among patients over the age of 65 years. Approximately 50% of all patients with lung cancer are at this age. This reflects the global increase in in life expectancy [4].

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The most common symptoms of lung cancer are cough (in over 90% of patients), shortness of breath, hemoptysis, chest pain, hoarseness, weakness, and weight loss [5]. As many as 80–90% of patients are former or current smokers [6]. Among men with lung cancer, 90% of the population were former or current smokers while 79% of women with this disease reported cigarette smoking. Nevertheless, the number of lung cancer patients who have never smoked is increasing [7].

Clinically, we distinguish SCLC (15% of lung cancer cases) and NSCLC (85% of lung cancer cases). Histologically, NSCLC is classified into adenocarcinoma (35–40%), squamous cell carcinoma (30%), large-cell carcinoma (2%), and other rare types of neoplasm. In the treatment of SCLC, chemoradiotherapy is used in limited disease (LD), whereas for patients with extensive disease (ED), either chemotherapy or chemoimmunotherapy is used. In the treatment of an early stage of NSCLC, surgery may be used seldom, which often is supplemented with preoperative chemotherapy or adjuvant chemotherapy. Chemoradiotherapy with the option of consolidating immunotherapy is used in the treatment of locally advanced NSCLC. These therapeutic methods can be used only in 20–25% of patients, depending on the stage of the disease, performance status of patients, and comorbidities. The therapeutic methods used in the treatment of advanced lung cancer include chemotherapy, molecularly targeted therapies, and immunotherapy, as well as a combination of these methods of treatment. [8].

In this study, we present the preliminary results on reasons for delays in the diagnosis of patients with lung cancer.

Material and methods

An analysis was performed of patients with lung cancer diagnosed and treated in the Department of Pneumonology, Oncology and Allergology at the Medical University of Lublin. Patients were enrolled in the study in 2021 and 2022 and asked to complete a survey designed by the authors and composed of 29 questions. So far, 149 adult patients have been included in the study, regardless of the histological type of cancer and treatment modality applied.

Quantitative variables are represented by mean ± standard deviation (SD). The consistency of the distribution of continuous variables with the normal distribution was confirmed using the Kolmogorov-Smirnov test. The statistical significance of the differences between the mean values of independent continuous variables with a normal distribution was assessed with Student's t-test and the independent variables with the distribution inconsistent with the normal distribution using the Mann-Whitney U test. Categorical variables were compared using Pearson's chi-square test. $P < 0.05$ was adopted as statistically significant. All calculations were performed with the SPSS software.

All patients were informed about the purpose of the study and gave their written consent to participate in it. The study was approved by the local Bioethics Committee at the Medical University of Lublin (approval number — KE-0254/14/2021).

Results

In total, 149 patients were included in the study. The majority were males (56.4%), and the median age was 66.8 ± 7.2 years (range from 39 to 85 years). The mean BMI (body mass index) of the patients was 26.3 ± 4.7, and 19% of the patients were obese (BMI over 25). The vast majority of patients (89.9%) were in very good or good general condition [performance status (PS) according to World Health Organization (WHO) classification: 0 or 1].

The majority of patients (73%) inhabited rural areas. Over 50% of the respondents lived in distant areas (> 5 km) from primary health care (Tab. 1).

Cigarette smokers were the majority (116 respondents, 77.9%) of the total population, and 73.3% of this group were current cigarette smokers. Former smokers were defined as those who had not smoked for at least 5 years. Small-cell carcinoma was diagnosed in 15.4% of patients, and NSCLC in 76.5% of patients. At diagnosis, 80.5% of patients had distant metastases.

Table 1. Epidemiological characteristics of patients in relation to the distance from the general practice (GP)

	Home close to a general practice n = 71 (48%)	Home far from a general practice n = 78 (52%)	p
Age (years)	67.5 ± 7.3	66.2 ± 7.0	0.273
BMI (kg/m^2)	26.2 ± 4.6	26.3 ± 4.9	0.834
Time from the first symptoms to the first GP appointment (weeks)	6.7 ± 14.9	4.1 ± 7.9	0.8
Time from the first symptoms to diagnosis (weeks)	16.9 ± 16.5	12.7 ± 12.2	0.082
Time from symptoms to start treatment (weeks)	18.3 ± 13.0	24.1 ± 17.1	0.041

In 15.4% of patients with non-squamous NSCLC, mutations in the *EGFR* gene were found while rearrangements of the *ALK* or *ROS1* genes were seen in 4.6% of patients. PD-L1 expression on tumor cells was found in 86% of patients with NSCLC, and in 27.2% of patients, high expression of PD-L1 was diagnosed (≥ 50% of tumor cells with PD-L1 expression).

Surgery was performed in 24 patients (16.1%). Radiotherapy was used in 34.9% of patients while 83.1% of patients received chemotherapy, including 77.2% of patients who were treated with platinum-based regimens. In 16% of patients, molecularly targeted therapies were used. In patients treated with these therapies, osimertinib (25%), erlotinib (18.8%), and crizotinib (18.8%) were most often used. In 44.3% of patients, immunotherapy was administered (monotherapy or in combination with chemotherapy). Pembrolizumab was most commonly used (23% of patients). Immunotherapy in the first-line treatment was used in 15.6% of patients and in the second-line therapy — in 24.5% of patients. Thirty-one point five percent of patients had been treated with at least one antibiotic up to six months before diagnosis.

Symptoms of lung cancer were found in 71.8% (Tab. 2). The most common was cough (31.8%). Twelve point five percent had general symptoms at the time of diagnosis.

The mean time from the symptom onset to the first medical appointment was 5.3 ± 11.8 weeks. More than half (55.7%) of patients reported to their general practitioner (GP) with the first, disturbing symptoms. The time from the development of the first symptoms to diagnosis was 14.7 ± 14.6 weeks. The mean time from the first symptoms to the first chest X-ray examination was 6.8 ± 12.1 weeks. Mean time from the onset of symptoms to the chest computed tomography (CT) exam was 10.8 ± 13.8 weeks (Tab. 3).

The mean time from CT examination to bronchoscopy was 24.1 ± 26.2 days, and from bronchoscopy to pathological diagnosis was 20.3 ± 29.5 days. The time from receiving the pathomorphological results to the examination of predictive factors (*EGFR* mutations, *ALK,* and *ROS1* rearrangements, as well as PD-L1 expression testing in non-squamous NSCLC or only PD-L1 expression testing in squamous NSCLC) was 13.8 ± 25.4 days. The duration of the examination of predictive factors was on average 7.6 ± 7.4 days. The time from bronchos-

Table 2. Presence of symptoms of lung cancer in analyzed patients

	Men	Women	p, χ^2
Presence of symptoms	63 (75%)	44 (68%)	p = 0.325 χ^2 = 0.967
Cough	17 (20%)	17 (26%)	p = 0.395 χ^2 = 0.728
General symptoms	15 (18%)	4 (6%)	p = 0.03 χ^2 = 4.511
Respiratory symptoms	45 (54%)	40 (62%)	p = 0.329 χ^2 = 0.949
More than one symptom	11 (13%)	14 (22%)	p = 0.171 χ^2 = 1.871
Infection treated < 6 months before diagnosis	29 (35%)	18 (28%)	p = 0.373 χ^2= 0.792

Table 3. Numbers and percentages of patients with and without delay in lung cancer diagnosis

	Average (weeks)	Without delay (n, %)	< 1 month (n, %)	1–6 months (n, %)	> 6 months (n, %)
Time from first symptoms to diagnosis	14.7	42 (28.2%)	11 (7.4%)	65 (43.6%)	31 (20.8%)
Time from first symptoms to first medical appointment	5.3	54 (36.2%)	49 (32.9%)	34 (22.8%)	12 (8.1%)
Time from first symptoms to first X-ray	6.8	42 (28.2%)	30 (20.1%)	45 (30.2%)	32 (21.5)
Time from first symptoms to first CT	10.8	39 (26.2%)	22 (14.8%)	67 (45%)	21 (14.1%)
Time from first symptoms to visit a consultant	7.3	72 (48.3%)	23 (15.4%)	40 (26.8%)	14 (9.4%)

copy to final diagnosis and therapeutic decision was 34.3 ± 36.8 days. The mean time from the onset of symptoms to the start of treatment was 21.0 ± 15.3 weeks. The time from bronchoscopy to the start of treatment was 41.1 ± 17.6 days, and from histopathological results to the start of treatment was 38 days (Fig. 1).

The time from the onset of treatment was significantly ($p = 0.04$) longer in patients living in areas further from cancer centers (24.1 weeks) than in patients living nearby (18.3 weeks). Another statistically significant difference ($p < 0.001$) concerned the time from the first symptoms to diagnosis, which was longer in patients receiving antibiotics (20.3 weeks) compared to patients without this treatment (12 weeks). Furthermore, in patients who had been treated with antibiotics before diagnosis, the time from the onset of first symptoms to the start of the treatment was statistically significantly longer ($p = 0.003$) than in patients who did not use antibiotics (26.8 weeks *vs.* 18.1 weeks). Patients treated with antibiotics had a significantly ($p < 0.03$) longer time from the first symptoms to the first visit to a consultant (10.5 weeks *vs.* 5.7 weeks) and to the first CT examination (15.5 weeks *vs.* 8.5 weeks) compared to patients who had not been treated with antibiotics (Tab. 4).

Discussion

Although diagnostic and therapeutic strategies have improved in recent years, lung cancer remains the leading cause of cancer death worldwide. Patients often report to their GP late, which may partly result in a higher mortality rate. Mitchell et. al. [9] demonstrated that delays in diagnosis of lung cancer are mainly due to the failure to recognize abnormalities visible on chest X-ray and failure to perform key diagnostic procedures at the right time. Schabath et. al. [10] indicated that quick diagnosis and access to effective modern methods of treatment are important determinants of cancer patient outcomes. Higher indicators of

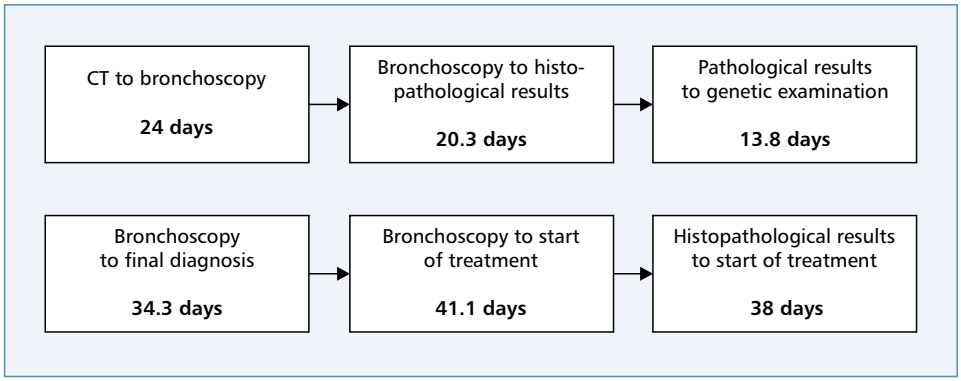

Figure 1. Duration of the diagnostic process from the first computed tomography (CT) examination in lung cancer patients

Table 4. Duration of individual diagnostic stages in patients who had received and had not received antibiotics before cancer diagnosis

	Patients treated with antibiotics 6 months before cancer diagnosis	Patients not treated with antibiotics 6 months before cancer diagnosis	p
Time from the first symptoms to the first medical appointment (weeks)	7.5	4.3	0.005
Time from the first symptoms to diagnosis (weeks)	20.3	12	< 0.001
Time from symptoms to the start of treatment (weeks)	26.8	18.1	0.003
Time from the first symptoms to the first visit to a visit a consultant (weeks)	10.5	5.7	0.003
Time from the first symptoms to the first X-ray examination (weeks)	9.9	5.3	0.004
Time from the first symptoms to first computed tomography (weeks)	15.5	8.5	< 0.001

survival for patients with lung cancer are observed in high-efficiency healthcare systems. Patients in Japan or Israel have much higher five-year survival rates (33% and 27%, respectively) than patients from Bulgaria, Poland, or Brazil (10%). Early diagnosis contributes to reducing mortality due to early initiation of treatment [10]. Early diagnosis also limits financial outlays. Total direct healthcare expenditure related to lung cancer is significant. In the United States, the total estimated medical cost of lung cancer diagnosis and treatment was $12.1 billion in 2010 and was expected to increase to $15.2 billion in 2020 [11]. Additionally, prompt cancer diagnosis to improve therapeutic outcomes is a priority for many European governments. For example, the UK government policy focuses on increasing the proportion of cancers diagnosed early (i.e. in stage 1 or 2) from half to three-quarters by 2028 [12].

According to the National Institute for Health and Care Excellence (NICE) guidelines, the time from the manifestation of disturbing symptoms observed by a physician to performing a chest X-ray or referral to a specialist doctor with suspicion of lung cancer should be 2 weeks or less [13]. Meanwhile, our study showed that in Poland the average waiting time for an appointment with the specialist was 7.3 weeks, and the time to the first X-ray was 6.8 weeks. The time from the onset of symptoms to the first GP visit was 5.3 weeks. This may be due to the fact that the symptoms are ignored by patients and by physicians (e.g. due to similarity in symptoms of lung cancer and chronic diseases, such as chronic obstructive pulmonary disease, as well as insufficient access to GPs in Poland). A study at Turku University Hospital in Finland showed that the time from first symptoms to diagnosis was 98 days, between the first visit to a GP and diagnosis — 52 days, and 15 days from the specialist visit to diagnosis [14].

The Cancer Care Ontario guidelines state that patients with suspicion of lung cancer on X-ray or with a high clinical probability of cancer should be referred for a chest CT scan within two weeks. They should wait no longer than 2 weeks for an appointment with a specialist [15]. According to the British Thoracic Society, the results of the histopathological examination should be completed within 2 weeks from the time of sample collection. The presence of predictive factors should be determined within 2 weeks. In patients in the early stage of NSCLC, surgery should be performed within a maximum of 8 weeks from qualification. If necessary, adjuvant chemotherapy should be given within 120 days after surgery. Chemotherapy should be given within 7 days from the treatment decision [16]. On the other hand, a study from Canada showed that the average total waiting time from the appearance of the first symptoms to the start of treatment was 4.5 months [17]. These results are comparable to those obtained in our study.

Lung cancer screening can reduce the relative risk of dying from lung cancer by 20%, but when combined with smoking cessation, this benefit has been estimated to be as high as 38%. Smoking cessation reduces the risk of dying from lung cancer, but it is known that the risk of lung cancer in ex-smokers is still higher compared to non-smokers. The relative risk of developing lung cancer is low if smoking was stopped at a young age [18]. Intensive anti-smoking campaigns are needed, as well as encouragement from primary healthcare workers. Each patient presenting with respiratory symptoms should undergo the Fagerström test, and they should be informed about the harmful effects of smoking. In some cases, anti-nicotine therapy should also be administered. As the number of smokers decreased, there was an overall decrease in the incidence of lung cancer. However, despite the overall reduction in the incidence of this cancer, a significant increase in the incidence of lung cancer among non-smokers was noted [19]. Several studies have suggested that lung cancer in non-smokers differs from smoking-induced lung cancer in both biological and epidemiological terms, and it should therefore be considered as an entirely separate entity. The term "non-smoker" classically refers to people who have smoked less than 100 cigarettes in their lifetime. Regarding the type of cancer, NSCLC (mainly adenocarcinoma) is more common in non-smokers. Studies have shown that lung cancers in non-smokers are much more common in women. Worldwide, 15–20% of men and up to 50% of women diagnosed with lung cancer have never smoked. This demographic group has significant geographic variations, as 60–80% of Asian women with lung cancer have never smoked. In a US study, approximately 19% of women and only 9% of men with lung cancer were non-smokers [20].

In our study, as many as 31.5% of patients had been treated with antibiotics due to respiratory tract infections prior to cancer diagnosis. Most patients had been treated with at least one antibiotic; in one case, before the lung cancer diagnosis, the patient had been prescribed 7 antibiotics (from different groups). These patients had no evidence of inflammation, (e.g. fever), and the symptoms they reported to their GPs were cough, shortness of breath, and hemoptysis. General practices ordered laboratory and imaging tests and referred them to a pulmonologist after the antibiotic treatment failure. This situation prolonged the diagnostic and therapeutic process by several weeks. According to the literature, symptoms of a respiratory tract infection may mask the developing neoplasm [21]. As shown in a study conducted in Sweden in 2009–2016, pneumonia may be an early symptom of lung cancer, and it is often the subject of differential diagnosis of this disease. Compared to healthy subjects, significantly more patients received at least one antibiotic treatment

in the three years prior to diagnosis of cancer. Patients diagnosed with lung cancer were twice as likely to take at least one antibiotic compared to healthy controls. Importantly, 7% of lung cancer patients had used at least four courses of antibiotic therapy in the three years prior to cancer diagnosis, which may suggest inappropriate and too frequent prescribing of these drugs [22, 23].

Respiratory tract infections often precede the diagnosis of lung cancer. In addition, chronic pulmonary obstructive disease and infections are more common in smokers, who have a higher risk of lung cancer, and take antibiotics more often due to an exacerbation [24]. Particular oncological vigilance should be undertaken when no improvement is observed after the use of an antibiotic in a patient with cough or dyspnea, or the improvement is temporary and slight. The occurrence of hemoptysis should always result in referring the patient to a specialist. After the failure of the first-line antibiotic therapy, diagnostics methods should be extended to imaging examinations or the patients should be referred to a pulmonologist.

Conclusions

The results of our study showed that patients with suspicion of lung cancer are diagnosed with considerable delay in Poland, which has an impact on the disease stage and patient' performance status at the final diagnosis. The vast majority of delays in the Polish healthcare system occur before and during a visit to the general practitioner. This study found that most patients experienced long delays between the first examinations carried out in connection with suspected lung cancer and the final diagnosis. Therefore, most of the patients were diagnosed at advanced stages of the disease. Treatment costs of lung cancer increase significantly with the higher stages at which the cancer is diagnosed. Procedures that diagnose lung cancer at an earlier stage can allow for lower resource consumption and costs of treatment. Algorithms for managing a patient with symptoms of lung cancer should be directed to physicians.

Systemic changes are necessary for patients to be diagnosed quickly and efficiently. Patients in Poland have access to most of the latest therapeutic methods used in the world. Thanks to this, we can classify lung cancer as a chronic disease. In the future, we plan to conduct a survey among another 200–250 people and also extend the results to aspects such as overall survival or progression-free survival, depending on the time of diagnosis and treatment methods.

Conflict of interest

Authors declare no conflict of interest.

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