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The impact of timeliness of care on survival in non-small cell lung cancer patients

Wpływ opóźnienia zależnego od chorego i od lekarza na przeżycie pacjentów z niedrobnokomórkowym rakiem płuca

Praca powstała w ramach projektu IGICHP PR 3.

Abstract

Introduction: It is uncertain whether timeliness improves clinical outcomes in lung cancer patients. The goal of the study was to analyse the influence of patient's and doctor's delays on survival of unselected population of NSCLC patients.

Material and methods: From 1995 to 1998, 8705 squamous cell lung cancer patient's and 1881 adenocarcinoma patient's were registered in Pulmonary Outpatients Clinics in all parts of Poland and subsequently in National Tuberculosis and Lung Diseases Research Institute Register (NTLDRIR).

Results: The median time from first symptom(s) to the beginning of a treatment was 92 days (mean —138.5 days). The median waiting time between first symptom(s) and first visit to a doctor's was 30 days (mean 57 days) and from first visit to a doctor's to referral to a chest physician — was 17 days (mean 41 days). Diagnosis of the NSCLC was established in a mean time of 71 days (median 40 days), but chest physician diagnosed patients in a mean time of 51 days (median 28 days).

The multivariate analysis revealed that ECOG performance status (PS) 2 (HR = 1.4) and 3+4 (HR = 2.23), clinical stage of the disease II (HR = 1.32), III (HR = 1.41), and IV (HR = 1.82) were independent negative predictors of survival. Non-surgically treated patients had worse prognosis than patients treated surgically (HR = 3.03). Lack of patient's delay had a significant positive impact on survival (HR = 0.88), particularly for patients in PS 0+1 (HR = 0.9) and 3+4 (HR = 0.9). Lack of doctor's delay was a negative predictive factor of survival (HR = 1.14). It was observed particularly in patients in performance status 2 (HR = 1.28).

Conclusions: The patient's delay and lack of doctor's delay had a negative impact on survival of NSCLC patients.

Key words: NSCLC, patient's delay, doctor's delay, survival, treatment delay, prognosis

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Streszczenie

Wstęp: Nie jest w pełni ustalonym, na ile opóźnienie diagnostyki i leczenia niedrobnokomórkowego raka płuca (NDRP) ma wpływ na przeżycie chorych. Celem badania było ustalenie wpływu opóźnienia zależnego od chorego i zależnego od lekarza na przeżycie chorych na NDRP w niewyselekcjonowanej populacji.

Materiał i metody: W okresie od 1995 do 1998 roku 8705 chorych na raka płaskonabłonkowego i 1881 chorych na raka gruczołowego płuca było zarejestrowanych w Rejestrze Instytutu Gruźlicy i Chorób Płuc.

Wyniki: Mediana czasu pomiędzy wystąpieniem pierwszych objawów a rozpoczęciem leczenia wynosiła 92 dni (śr. 138,5 dnia). Mediana czasu pomiędzy wystąpieniem pierwszych objawów a zgłoszeniem się do lekarza opieki podstawowej wynosiła 30 dni (śr. 57 dni), a mediana czasu pomiędzy zgłoszeniem się do lekarza a wizytą u specjalisty chorób płuc — 17 dni (śr. 41 dni). Rozpoznanie raka płuca ustalone było średnio w ciągu 71 dni (mediana 40 dni), Czas w jakim lekarze chorób płuc rozpoznawali raka płuca wynosił średnio 51 dni (mediana 28 dni). Analiza wieloczynnikowa wykazała, że stan sprawności 2 w skali ECOG (HR = 1,4), 3+4 (HR = 2,23), stopień zaawansowania klinicznego nowotworu II (HR = 1,32), III (HR = 1,41), IV (HR = 1,82) są niezależnymi czynnikami wpływającymi na przeżycie. Brak leczenia chirurgicznego był

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niezależnym negatywnym czynnikiem rokowniczym (HR = 3,03). Brak opóźnienia ze strony chorego wpływał pozytywnie na rokowanie (HR = 0,88), szczególnie u chorych w stanie sprawności 0+1 w skali ECOG (HR = 0,9) oraz 3+4 (HR = 0,9). Brak opóźnienia zależnego od lekarza znacząco negatywnie korelował z przeżyciem chorych (HR = 1,14). Szczególnie dotyczyło to chorych w stanie sprawności 2 (HR = 1,28).

Wnioski: Brak opóźnienia ze strony chorego wpływa pozytywnie na przeżywalność chorych na NDRP. Natomiast nie obserwowano tego typu zależności dla opóźnienia zawiązanego z procesem diagnostycznym, a wręcz przeciwnie chorzy dłużej diagnozowani charakteryzowali się lepszą przeżywalnością.

Słowa kluczowe: rak niedrobnokomórkowy płuca, opóźnienie zależne od chorego, opóźnienie zależne od lekarza, przeżycie, rokowanie

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Introduction

Lung cancer, at the end of XX millenium, is the most frequently diagnosed cancer in Poland and worldwide [1–3]. In the European Union about 200,000 new cases of lung cancer and 140,000 lung cancer deaths are recorded each year [1–5]. During the last few years about 24,000 cases of lung cancer were diagnosed in our country yearly [5]. In Poland lung cancer incidence has risen dramatically for several decades; however, from the beginning of the nineties stabilisation of the incidence in men was noticed, but there is a constant increase of lung cancer incidence in women [5]. The overall 5-year survival for patients with lung cancer is very low and varies between 15 % in the USA and Austria, through 6.2% in Poland, to 6% in Denmark [4–8]. It is well known that NSCLC patients with limited disease and in good performance status have better prognosis than those with extensive disease and bad performance status. NSCLC is a highly progressive disease, so it seems reasonable that fast diagnosis and administration of treatment ought to have an impact on survival [9–14]. Recently many studies providing documentation of the management process and outcome of NSCLC patients have been published [15–37]. Many of them presented series of hospital-based populations, particularly those treated by surgery, but very few presented patient's and doctor's delays in huge, unselected populations of lung cancer patients. The impact of patient's and doctor's delays on survival was the subject of selected papers [22, 30, 31, 33–37].

The British Thoracic Society and Joint Collegiate Council for Oncology, the UK National Health Service Cancer Plan, and the American College of Chest Physicians have made recommendations on the times for referrals and waiting in management pathways to improve care for lung cancer patients [38–40]. A 7-day period is recommended for referral to a chest physician and 2 weeks for establishing diagnosis.

The Polish health care system is generally public. It is based on primary care and a special network of Pulmonary Outpatients Departments and Pulmonary Hospitals. The primary care is accessible quite easily. A visit with a specialist requires referral by a general practitioner; however, there are some patients who are immediately hospitalized. The costs of healthcare are covered by the government.

The goal of this study was to assess prospectively the delay due to patients and doctors and its impact on survival of an unselected population of NSCLC patients registered in Pulmonary Outpatient Departments in all parts of Poland.

Material and methods

From 1995 to 1998 data on 8705 of squamous cell lung cancer patients and 1881 adenocarcinoma patients registered in Pulmonary Outpatient Departments from all parts of Poland were collected in the Register of the National Tuberculosis and Lung Diseases Research Institute (NTLDRI). The diagnosis of lung cancer was based on positive histological or cytological examinations (according to WHO criteria available at the time of the study). Data regarding gender, age, histological type of lung cancer, performance status according to ECOG scale, stage of the disease (TNM scale), treatment, survival, and delay due to patients and doctors were recorded by using a standardised questionnaire. From 1996 to 1998 the dates of first visit with a specialist and first bronchoscopy were noted as well. Every six months, follow-up information was obtained.

Survival was assessed as the time between diagnosis and date of death or last visit. Dates of death were confirmed in the Central Address Bureau at the end of 2003. The diagnosis of lung cancer was based on positive histological or cytological examination (according to WHO criteria available at the time of the study).

Patient's delay was defined as the time between first symptom(s) and the time of first visit to a doctor. Sufficient information for analysis of

patient's delay was available for 7358 patients. Doctor's delay was defined as the time between first visit to a doctor and treatment administration. This information was available from 6384 patient records. Therapy delay was defined as the time between diagnosis and start of treatment. Also, time between first visit to a doctor and first contact with a specialist, time between first visit with the specialist and bronchoscopy, diagnosis, and therapy were recorded.

Univariate and multivariate analysis by Cox proportional hazards ratio model and log-rank test were used to test the significance of prognostic factors including gender, age, stage, and performance status, and patient's and doctor's delays. A p value < 0.05 was considered as significant.

Results

The patients' characteristics are presented in Table 1. A total of 1064 (12%) women and 9322 (88%) men were included in this study. There were 1392 (13.2%) patients below 50 years old and 9194 (86.8%) patients were over 50 years old. Performance status 0+1 in ECOG scale was noticed in 5617 (58.1%) patients, 2 in 2989 (31%) patients, and 3+4 in 1048 (10.9%) NSCLC patients. The first clinical

stage of NSCLC was observed in 2464 (28.4%) patients, II in 1240 (14.3%), III in 3602 (41.5%), and IV in 1369 (15.8%). Regarding performance status and clinical stage of the disease, there was no difference between men and women. Surgical treatment was applied in 2472 (31.2%) patients, and 535 (6.8%) of them were treated by surgery with chemoradiotherapy. Radiotherapy or radiochemotherapy was administered to 1203 (15.4%) patients, chemotherapy to 1937 (24.7%) patients, 2369 (30.2%) patients were treated symptomatically, and 422 (5.4%) refused therapy.

The delays observed in each stage of the investigative process are detailed in Table 2. The mean total delay from first symptoms to treatment was 138 days (median 92 days). The mean patient's delay was 57 days (median 30 days). The mean waiting time between first visit to a doctor and diagnosis was 32 days (median 40 days). Fifty per cent of patients were treated during the first 6 days after diagnosis, but the mean time between diagnosis to start of therapy was 32 days. The mean time from first contact with a doctor until the date of first appointment to chest physician (specialist) was 41 days (median 17 days). Chest physicians diagnosed fifty per cent of patients during 28 days, but

Table 1. Characteristics of NSCLC patients

Tabela 1. Charakterystyka chorych na raka niedrobnokomórkowego płuca

	All	Men	Women
Age	10586 (100%)	9322	1264
Below 50 years	1392 (13.2%)	1099 (11.8%)	293 (23.2%)*
Over 50 years	9194 (86.8%)	8223 (88.2%)	971 (76.8%)
Performance status			
0+1	5617 (58.1%)	4923 (58.1%)	694 (59.6%)
2	2989 (31%)	2660 (31.1%)	329 (28.2%)
3+4	1048 (10.9%)	906 (10.7%)	142 (12.2%)
Clinical stage			
I	2464 (28.4%)	2149 (28.1%)	315 (30%)
II	1240 (14.3%)	1107 (14.45%)	133 (12.6%)
III	3602 (41.5%)	3187 (42%)	415 (39.4%)
IV	1369 (15.8%)	1179 (15.45%)	190 (18%)
Treatment			
Surgery	1937 (18.3%)	1641 (23.8%)	296 (31.9%)*
Surgery + combined	535 (6.8%)	445 (6.5%)	90 (9.7%)*
Chemoradiotherapy + radiotherapy	1203 (15.4%)	1076 (15.6%)	127 (13.8%)**
Chemotherapy	1365 (24.7%)	1213 (17.6%)	152 (16.3%)
Supportive care	2369 (30.2%)	2136 (30.9%)	233 (25%)*
Refused	422 (5.4%)	389 (5.6%)	33 (3.5%)*

* $p < 0.001$, ** $p < 0.05$

Table 2. The various delays (days) in NSCLC patients

Tabela 2. Opóźnienia zależne od chorego i od lekarza u pacjentów z rakiem niedrobnokomórkowym płuca

Delays	Number of patients	Mean ± SD (days)	Median (days)	Low quartile	High quartile
Patient's delay	7358	56.7 ± 117.3	30	9	61
First visit to the doctor — diagnosis	9274	32 ± 67.6	40	20	75
First visit to the doctor — first visit to the specialist	4824	40.6 ± 85.6	17	9	36
First visit to specialist — bronchoscopy	5279	29.1 ± 67.4	11	7	24
First visit to the specialist — diagnosis	5794	51.3 ± 91.5	28	16	47
Diagnosis — therapy	6944	32 ± 67.6	6	0	31
Symptom (s) — diagnosis	9537	116.2 ± 148.8	75	44	131
Symptom (s) — therapy	6289	138.5 ± 166.4	92	52	165

the mean specialist's delay was 51 days. Additionally, fifty per cent of patients had a bronchoscopy within 11 days (mean 30 days). It should be underlined that there were many cases diagnosed without any delays; however, there were some patients who had a very long period of symptomatic disease or who waited for proper diagnosis for several months.

Univariate analysis of prognostic factors that can influence survival revealed that male gender (hazard ratio — HR = 1.2), age over 50 years (HR = 1.22), performance status 2 (HR = 1.74), and 3+4 (HR = 2.83), clinical stage of the disease II (HR = 1.49), III (HR = 1.92), and IV (HR = 2.9) were significant adverse predictors of survival. Patients in whom surgery was applied had better prognosis than those receiving radiochemotherapy (HR = 2.34), chemotherapy (HR = 3.03), and those treated symptomatically (HR = 4.11) (Tab. 3). Lack of patient's delay had a positive (HR = 0.81) impact on survival, but lack of doctor's delay had a negative (HR = 1.18) impact on survival.

Multivariate analysis of survival revealed that performance status 2 (HR = 1.47), 3+4 (HR = 2.23), clinical stage of the disease II (HR = 1.32), III (1.41) and IV (HR = 1.82), nonsurgical treatment (HR = 2.65), and lack of doctor's delay (HR = 1.14) were negative prognostic factors, but lack of patient's delay (HR = 0.88) was a positive prognostic factor (Tab. 4).

Performance status of patients was one of the most powerful prognostic variables identified in our study and was tightly connected with therapy. Therefore, multivariate analysis of previously presented factors on groups of patients divided according to performance status was performed (Tab. 5). Type of treatment and clinical stage of the disease were significant predictors of survival. However, female gender and younger age were not

Table 3. Hazard ratio for death in NSCLC patients — univariate analysis

Tabela 3. Analiza jednoczynnikowa ryzyka zgonu pacjentów z rakiem niedrobnokomórkowym płuca

	HR	P value
Gender		
Women	1.0	
Men	1.2	0.001
Age		
Below 50 years	1.0	
Over 50 years	1.22	0.001
Treatment		
Surgical	1.0	
Chemoradiotherapy	2.34	0.001
Chemotherapy	3.03	0.001
Symptomatically	4.11	0.001
Refused	2.81	0.001
Performance status		
0+1	1.0	
2	1.74	< 0.001
3+4	2.83	< 0.001
Clinical stage		
1	1.0	
2	1.49	0.001
3	1.92	0.001
4	2.9	0.001
Patient's delay		
Over 30 days	1.0	
Below 30 days	0.81	0.001
Doctor's delay		
Over 52 days	1.0	
Below 52 days	1.18	0.001

Table 4. Multivariate analysis of hazard ratio for death of NSCLC patients**Tabela 4. Analiza wieloczynnikowa ryzyka zgonu pacjentów z rakiem niedrobnokomórkowym płuca**

	HR	P value
Gender		
Women	1.0	
Men	1.08	0.115
Age		
Below 50 years old	1.0	
Over 50 years old	1.02	0.244
Treatment		
Surgical	1.0	
Non-surgical	3.03	0.001
Performance status		
0+1	1.0	
2	1.47	0.001
3+4	2.23	0.001
Clinical stage		
1	1.0	
2	1.32	0.001
3	1.41	0.001
4	1.82	0.001
Patient's delay		
Over 30 days	1.0	0.001
Below 30 days	0.88	
Doctor's delay		
Over 42 days	1.0	0.001
Below 42 days	1.14	

found as factors influencing survival. Lack of patient's delay had significant positive impact on survival in NSCLC patients in good PS (0+1) (HR = 0.9) and bad PS (3+4) (HR = 0.9). Negative impact on survival was observed in the group of patients in medium performance status with a lack of doctor's delay (HR = 1.28).

Discussion

The delays: due to patients, in diagnosis, and treatment, may result in worse clinical outcome. On the other hand, these delays can influence the psychosocial morbidity of patients with lung cancer. The overall survival of lung cancer patients is very low, i.e. less than 40 % survived one year and 6–15% of them survived 5 years [2–5, 7]. Surgery is still the only treatment with the potential of cure for lung cancer, but only 15–30% of patients are operated on [6–8, 10, 11, 14]. The survival benefit

depends on the performance status and clinical stage of the disease. It has been demonstrated that 70–75% of patients in clinical stage I of lung cancer survived 5 years. The corresponding percentages of patients in clinical stages II and III surviving 5 years were 35% and 5%, respectively [6, 7, 14].

In Poland during the last 10 years the percentage of patients undergoing surgical treatment has been constantly increasing. In 1990–1995 about 17% of patients received surgical treatment [7, 8]; however, in the examined group of patients registered in NTLDRIR (1995–1998) — 25% of patients were treated by surgery. This was probably due to better medical service of Pulmonary Departments. Additionally, there was better cooperation with thoracic surgery departments, which were in many cases closely connected with pulmonary departments.

Calculations of curves of tumour growth revealed that in the late phase the tumour volume expanded rapidly. The detection period of a tumour less than 2 cm is very tight. Therefore, many patients are observed in advance disease stage. It seems that delays in diagnosis and therapy may influence survival.

In our study, patients' delays varied widely, but the median delay was comparable with that observed in many European countries and the USA [26, 28, 30, 33–37].

The first symptoms of lung cancer are often recognised as an infection or are connected with age or other coexisting disease(s) [29, 41]. NSCLC is a highly progressive disease and when the symptoms appear the disease is already advanced. In our study it was shown that the lack of delay from first symptoms to first visit to the doctor had a positive impact on survival of NSCLC patients, both for patients with good and bad performance status. Christensen et al. revealed that delay before final treatment of NSCLC patients had an impact on preoperative stage of the cancer, but Billing et al. did not observe such a correlation [17, 18].

A systematic review of the data presented in the literature showed that median time from first visit to a doctor to referral to a specialist vary from 13 days to 33 days, which is longer than recommended [22, 23, 30, 33–37]. In our unselected population the median referral time was 17 days. Nevertheless, in some patients the time between first visit to a doctor and the visit to a specialist was rather long, influencing the mean delay reported in this study. It may be due to technical difficulties, additional diseases, problems with cooperation, low suspicion of cancer - particularly in younger patients (more than 13 % were below 50

Table 5. Multivariate analysis of hazard ratio for death in NSCLC patients according to performance status**Tabela 5. Analiza wieloczynnikowa ryzyka zgonu pacjentów z rakiem niedrobnokomórkowym płuca zależna od stanu sprawności**

	Performance status 0+1		Performance status 2		Performance status 3+4	
	HR	P value	HR	P value	HR	P value
Gender						
Women	1.0		1.0		1.0	
Men	1.12	0.086	1.01	0.933	1.08	0.557
Age						
Below 50 years old	1.0		1.0		1.0	
Over 50 years old	1.02	0.694	1.02	0.838	0.96	0.765
Treatment						
Surgical	1.0		1.0		1.0	
Non-surgical	2.63	0.001	2.66	0.001	3.52	0.001
Clinical stage						
1	1.0		1.0		1.0	
2	1.38	0.001	1.2	0.05	1.29	0.2
3	1.42	0.001	1.40	0.001	1.39	0.047
4	1.79	0.001	1.7	0.001	2.31	0.001
Patient's delay						
Over 30 days	1.0	0.037	1.0	0.156	1.0	0.037
Below 30 days	0.9		0.92		0.9	
Doctor's delay						
Over 42 days	1.0	0.132	1.0	0.001	1.0	0.132
Below 42 days	1.07		1.28		1.07	

years of age), and errors in interpretation of chest X-rays [29, 41]. In Poland the incidence of tuberculosis was rather high at the time of investigation (about 34.4/100,000), and in many patients over 60 years of age post-tuberculous lesions might be observed in chest radiological examinations causing misdiagnosis and diagnostic delay [42].

It was revealed in our data, as in others, that well-known predictors such as clinical stage of the disease, performance status, and type of therapy had an impact on survival of NSCLC patients [6, 8–10, 33–37]. Gender and age were found to be significant factors influencing survival in univariate analysis but not in multivariate analysis when variables such as patient's and doctor's delays were added to the model. When multivariate analysis was performed on separate groups of patients divided according to performance status, a longer period with symptoms had a negative impact on survival, but only for patients in good and bad performance status. Unexpectedly, we revealed that doctor's delay had no impact on survival in patients in good and bad performance status. Therefore,

NSCLC patients in medium performance status with prolonged diagnosis and/or longer period to treatment onset had a better prognosis. It is possible that in the group of patients in medium performance status diagnostic procedures were applied quickly to severely ill patients in whom even a very fast diagnosis would not change the very bad prognosis. On the other hand, in this group of patients the performance status, relatively not good, might be connected with cancer or with concomitant diseases.

Olsson et al. in the review mentioned above, identified 15 studies analysing the correlation between patient's and doctor's delay and survival [30]. Eight of them showed no association between timeliness and outcome. Others, among them data from screening programmes, demonstrated worse survival in patients with delayed diagnosis [33–36]. Recently, Salomaa et al., Gould et al., and Skaugh et al. also proved that timeliness of diagnosis had a negative impact on survival in unselected populations of non-small cell lung cancer patients [22, 27, 37].

The results of this study indicated that patient's and doctor's delays were not as short as we would like them to be. NSCLC is a very progressive disease. When the disease is symptomatic it is often locally or generally advanced, so prolonged periods of symptoms or diagnostic procedures only slightly influence survival.

Analysis pointed out that to improve the outcome of lung cancer patients we have to change diagnostic procedures to reveal the disease at an early stage [43–45].

Taking into consideration the doubling time of lung cancer cells observed, delays seem unacceptable. Among patients who were diagnosed for a longer period of time there were some who were potentially operable at the time of first symptoms or visit, but not at the time of diagnosis. Also, the diagnostic process, which lasts for several months, has a negative influence on patients and their families.

Conflict of interest

The authors declare no conflict of interest.

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