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Effect of delays on prognosis in patients with non-small cell lung cancer

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Background: The effect of delay on survival in lung cancer remains uncertain. It is suggested that prompt management of non-small cell lung cancer (NSCLC) can influence prognosis. This study was undertaken to examine the relation between delay and prognosis in patients with NSCLC and to investigate the delay time from first symptom and from first hospital visit to start of treatment.

Methods: Two types of delay (symptom to treatment delay and hospital delay) were investigated in 466 patients treated for NSCLC at two institutions in central Sweden. Delays in relation to clinical characteristics were compared and the effects of delay times and other relevant factors on survival were assessed in multivariate analyses.

Results: Thirty five per cent of patients received treatment within 4 weeks of the first hospital visit and 52% within 6 weeks. Median symptom to treatment delay was 4.6 months and median hospital delay 1.6 months. Older age, advanced tumour stage, and non-surgical treatment were independently related to poor survival. Both prolonged hospital delay and symptom to treatment delay provided additional information when considered separately. In a final multivariate model only increased symptom to treatment delay gave significant information of a better prognosis. There was an association between a short delay and a poor prognosis which was most pronounced in patients with advanced disease.

Conclusion: When considering the whole study population and all stages of tumour together, shorter delay was associated with a poorer prognosis. This is likely to reflect the fact that patients with severe signs and symptoms receive prompt treatment. These findings indicate that the waiting time for treatment in patients with NSCLC is longer than recommended.

Waiting times for healthcare services are a constant problem. In cancer care, recommendations about maximum waiting times are sometimes made without knowledge of the possible influence of delay on survival. It is known that surgery in patients with early stage lung cancer can result in 5 year survival rates of 75–80%,[1] while there is no evidence that immediate treatment of patients with unresectable locally advanced non-small cell lung cancer (NSCLC) influences the prognosis.[2] However, the overall influence of the delay time in the diagnosis of NSCLC on survival remains poorly understood.[3–5] It appears that delay in the management of NSCLC is often longer than recommended in clinical practice.[6] Some studies have indicated that delay negatively affects the prognosis,[4 7] while others have not shown such an association.[3 5] In a recent Swedish study no association was found between prolonged delay time (by the patient or the doctor) and advanced tumour stage.[8]

The objective of this study was twofold: (1) to examine the relation between delay and survival in patients receiving treatment for NSCLC, and (2) to investigate the delay time from the first symptom and from the first hospital visit to the initial treatment.

METHODS

Swedish healthcare system

In Sweden a nationwide system of general practitioners most often represent the first line of care for patients presenting with non-acute symptoms or signs of disease. Patients with suspected lung malignancies are referred from this primary care to regional hospital based chest physicians for further assessment. Following diagnostic work up, treatment decisions are made after consultation with an oncologist or a thoracic surgeon.

Patients

Between 1 January 1995 and 31 December 1999, 750 patients were diagnosed with histologically confirmed NSCLC in the Uppsala and Västmanland healthcare regions in central Sweden. Patients in whom NSCLC was first diagnosed at necropsy (n = 94) and patients who received no cancer specific treatment (n = 190) were excluded from the study. The study population thus consisted of 466 patients who received treatment (curative or palliative) with surgery, chemotherapy, or radiation.

Data collection and follow up

Patients diagnosed with NSCLC during the study period were identified by an individually unique national registration number in the Regional Cancer Registry database in Uppsala (ROC).[9] Since the mid 1980s regional cancer registers have been operating within the confines of oncological centres in each administrative medical region of Sweden, where the registration, coding and major check up and correction work is performed. The regionalisation implies close contact between the registry and the reporting physician which simplifies the task of correcting and checking the material. Data on tumour stage, histopathological tumour type, and treatment were retrieved from the ROC register.[9]

Additional clinical information on individual patients was collected retrospectively from medical records kept at Uppsala University Hospital and the Västmanland County Hospital, where all diagnostic examinations and treatment had taken place. These records yielded information on (1) date of first symptom as stated by the patient, (2) date of initial visit to a chest physician, and (3) start date and type of treatment. Classification of the tumour stage was based on recorded information concerning findings at thoracotomy and med-

iastinoscopy, or on results of bronchoscopy, CT scan, bone scintigraphy, and clinical examination.

Two types of delay were studied: (1) symptom to treatment delay, defined as the length of time from the onset of symptoms until the start of treatment, and (2) hospital delay, defined as the length of time from the first hospital visit to the start of treatment. The date of onset of symptoms was available for 76% of the patients (n = 354) and the date of the first visit to a chest physician for 89% (n = 413). The date of the beginning of treatment was available for all patients (n = 466).

Vital status was obtained through linkage to two national registers, the Swedish Cause of Death Register and a continuously updated national population register.

The study was approved by the ethics committee at the Uppsala University Hospital.

Statistical methods

Descriptive analyses were carried out for all 466 patients and included age, sex, histology, pathological stage, and treatment modalities. Median delay (with 25% and 75% interquartiles) was calculated for each of the characteristics. As delay times were not normally distributed, non-parametric tests were used. The Mann-Whitney test was used for pairway comparisons of delay and the Kruskal-Wallis test for analyses involving multiple groups. Differences in delay were considered significant if $p<0.05$.

The observed survival rate for all causes of death was calculated by the actuarial (life table) method. Univariate and multivariate analyses performed to identify factors related to death (from any cause) were based on the standard Cox proportional hazard model.[10] The time at risk was accumulated from the date of the start of treatment to death or, in those alive, to 1 April 2002. The relative hazard ($RH = \exp(b_1)$) was used as a measure of the risk of death in different categories, where b_1 is the basic parameter in the Cox model. All linear and categorised variables were first tested in their original continuous form, logarithmic and then with a set of dummy variables representing ranges, defined by commonly used or standard cut off points. Using age (in years) and delay times (in months) in a continuous logarithmic form provided the best discriminatory power—that is, the relation between the risk factors and the hazard function is logarithmic. This means that the relative hazards shown are associated with an increase by one unit of the logarithm of the risk factor.

In the multivariate models with all other variables considered, the types of delay were first included one by one in their continuous logarithmic form and then, in a final model, both types of delay were included. The possibility of an interaction between tumour stage and delay was tested by introducing an interaction variable.

A separate descriptive and survival (time from the date of decision not to treat to death or, in those alive, to 1 April 2002) analysis of delay was performed in patients with NSCLC who received no cancer specific treatment (n = 190).

All statistical calculations were performed with the SAS 6.12 statistical procedure (SAS Institute, Cary, NC).

RESULTS

Of the study population, 268 were men (mean age 65.8 years (range 43.6–86.2)) and 198 were women (mean age 63.9 years (range 39.3–89.3)). The two most common histopathological tumour types were adenocarcinoma (42%) and squamous cell carcinoma (33%). One hundred and fifty one patients underwent surgery (101 had surgery alone, 37 received adjuvant chemotherapy, eight had postoperative radiotherapy, and five had both additional chemotherapy and radiotherapy). Of the 315 patients who did not undergo surgery, 143 received chemotherapy, 99 had radiotherapy, and 73 had both chemotherapy and radiotherapy.

Clinical characteristics and delay

Symptom to treatment delay time

The median delay time between the first symptoms and treatment was 4.6 months. In patients with an advanced tumour stage (stage IV) the median delay was 3.4 months. This was significantly lower than the symptom to treatment

Table 1 Delays (in months) in relation to clinical characteristics in patients treated for non-small cell lung cancer between 1995 and 1999 (n = 466)

	Symptom to treatment delay*		Hospital delay†	
	Median	25–75% IQR	Median	25–75% IQR
All patients	4.6	3.0–7.1	1.6	0.9–2.4
Sex				
Female	4.6	3.2–6.8	1.5	1.0–2.6
Male	4.7	2.8–7.1	1.5	0.9–2.2
Age‡				
⩽70 years	4.7	2.5–6.9	1.5	0.9–2.1
>70 years	4.5	3.2–7.6	1.8	1.2–2.7
Stage§,¶				
I–II	5.5	3.8–8.0	1.9	1.4–2.9
IIIa	5.1	3.1–7.7	1.8	1.1–3.0
IIIb	4.6	3.0–7.4	1.5	0.9–2.3
IV	3.4	2.0–4.8	1.2	0.7–2.0
Histopathological type				
Squamous cell	5.1	3.2–7.6	1.7	1.0–2.5
Adenocarcinoma	4.3	2.8–6.6	1.5	0.9–2.2
Type of treatment**				
Surgery	5.3	3.7–6.9	1.8	1.3–2.7
Non-surgical	4.2	2.6–7.1	1.4	0.8–2.3

IQR = interquartile range.
*Time from onset of symptoms until start of treatment.
†Time from first visit to chest physician at the hospital until start of treatment (significant differences in delay if $p<0.05$).
‡Significant difference in hospital delay.
§Significant difference between patients with stage IV disease and those with stage I–II, IIIa and IIIb disease in a separate analysis for each group.
¶Significant difference in delay between patients with stage I–II and IIIB disease in both types of delay.
**Significant differences in both types of delay.

Table 2 Stage of lung cancer with respect to delay time, showing number of patients at each stage according to different delay

	Stage according to current TNM classification[19]			
	I–II	IIIA	IIIB	IV
Hospital delay*				
<1 month	17 (13)	8 (24)	41 (29)	46 (43)
1–2 months	50 (38)	13 (39)	57 (40)	35 (33)
2–3 months	36 (27)	4 (12)	22 (16)	17 (16)
>3 months	28 (21)	8 (24)	22 (15)	9 (8)
Symptom to treatment delay†				
<3 months	8 (9)	7 (25)	36 (27)	43 (43)
3–6 months	45 (49)	9 (32)	48 (36)	36 (36)
>6 months	39 (42)	12 (43)	50 (37)	20 (20)

Data are presented as n (%) within each disease stage.
*Missing (n = 53).
†Missing (n = 112).

delay in patients with less advanced disease. Patients with stage IIIB disease had a shorter delay than those with stage I–II disease. There were no significant differences in symptom to treatment delay in relation to sex, age, or histopathological type, but surgically treated patients had to wait longer than those receiving other types of treatment (table 1). Nine per cent of the patients with stage I–II disease were treated within 3 months from the onset of symptoms compared with 27% of patients with stage IIIB disease (table 2).

Hospital delay time

The median hospital delay was 1.6 months. The hospital delay time was longer in patients who subsequently underwent surgery than in those treated with chemotherapy and/or radiotherapy. Treatment started earlier in patients with stage IV or IIIB disease than in those with stage I–II (table 1).

Thirty five per cent of the patients received treatment within 4 weeks and 52% within 6 weeks following the first contact with a chest physician at the hospital. Of the patients who were candidates for surgery, 14% and 31% had been operated on within 4 and 6 weeks, respectively. Thirteen per cent of the patients with stage I–II disease were treated within 30 days of the first hospital visit compared with 29% of those with stage IIIB disease (table 2).

Survival

The mean follow up time from the start of treatment to death or 1 April 2002 was 20.4 months (range 0–85). The overall 3 year survival among patients treated for NSCLC was 31% (95% CI 27 to 36). In patients with symptom to treatment delay of less than 3 months the 3 year survival was 11%, while patients for whom there was a delay of more than 6 months had a survival of 35% (fig 1). Patients with the shortest hospital delay (<1 month) had the poorest prognosis (3 year survival of 19% compared with 43% in those with a hospital delay of more than 3 months, fig 2).

Risk factor analysis

The effects of all the variables on survival are shown in table 3. Older patients, those with an advanced tumour stage, and those who did not undergo surgical resection had worse survival. In the multivariate model, with all other variables in the model and types of delay time considered one by one, both prolonged hospital delay (RH 0.87, 95% CI 0.75 to 1.00) and symptom to treatment delay (RH 0.79, 95% CI 0.61 to 0.97) had a significant effect. However, in the final model which included both types of delay, only increased symptom to treatment delay was significantly related to better prognosis (table 3).

The introduction of an interaction variable showed a significant interaction between tumour stage and both symptom to treatment delay ($p = 0.003$) and hospital delay ($p = 0.005$). The association between short delay and poor prognosis was most pronounced in patients with an advanced tumour stage.

Patients with NSCLC who received no cancer specific treatment (excluded from the study population)

The mean age of the 190 patients who received no cancer specific treatment was 72.3 years (range 43.8–94.9); 34% were women and 66% men. Forty three per cent were

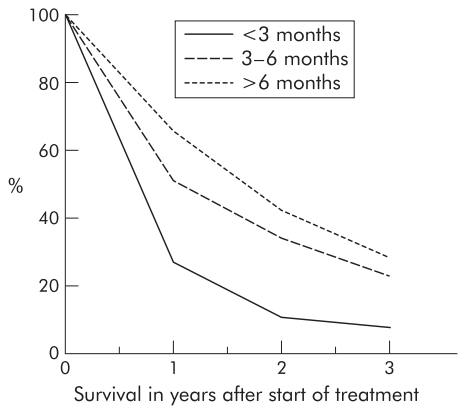

Figure 1 Overall survival in all patients treated for primary lung cancer during the study period (1995–9) in relation to symptom to treatment delay.

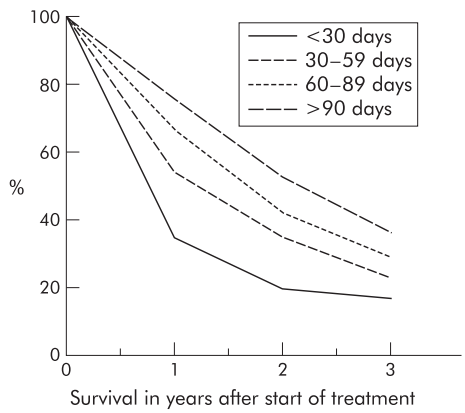

Figure 2 Overall survival in all patients treated for primary lung cancer during the study period (1995–9) in relation to hospital delay.

diagnosed with adenocarcinoma and 21% had squamous cell carcinoma; 42% had stage IV disease, 42% had stage IIIB, 5% stage IIIA, and 11% stage I–II.

The median delay from the start of symptoms to the date of decision not to treat was 3.6 months. The median hospital delay time (from the first visit to a chest physician at the hospital to the date of decision not to treat) was 0.8 months. Compared with the study population, patients who received no cancer specific treatment had a shorter hospital delay (median hospital delay 0.8 and 1.6 months, respectively). Three year survival was 5% in patients who did not receive any cancer specific treatment.

DISCUSSION

The results of this study indicate that neither longer symptom to treatment delay time nor longer hospital delay time are associated with a poorer prognosis, corroborating findings in earlier studies.[3 5] On the contrary, the prognosis was poorer in patients with a shorter delay. A similar pattern has been observed in studies of the influence of referral delay on breast cancer survival.[11] Moreover, our results show that patients with limited disease have to wait significantly longer for treatment than those with advanced disease.

There was an interaction between tumour stage and delay—that is, the association between short delay and poor outcome was most pronounced in patients with advanced disease. This probably indicates that the severity of signs and symptoms at presentation influences the speed of the medical decision process and also correlates with prognosis. The effect of delay on prognosis was less pronounced in patients with stage I–II disease. This should be interpreted with care as the population sample with early stage disease was insufficient to permit a separate analysis. The present study cannot therefore categorically state in which patients it is important to ensure minimal delay based on prognosis.

This study is one of the few that have assessed the influence of delay time in relation to survival. The date of the start of treatment was available for all patients. For 89% of all cases we were able to retrieve information on the date of the first visit to a chest physician. One weakness is that the data were obtained retrospectively from patients' records. Information on the date of onset of the first symptoms was retrieved for 76% of patients. This date may have been difficult for the patients to recall exactly, but we have no reason to believe that any misclassification in this respect would vary systematically by outcome (survival).

The specific date of the decision to treat or not to treat is not easily retrievable. Delay times from decision not to treat and from start of treatment are not comparable since patients who receive cancer specific treatment have to wait longer for treatment. The current study population was therefore defined as those who received cancer specific treatment. About 40% of all patients received no such treatment. These patients were somewhat older and had more advanced disease, but were identical in histopathological distribution to those receiving treatment.

The Swedish Lung Cancer Study group recommends that in 80% of all patients diagnostic tests should be completed within 4 weeks from consultation with a chest physician and that treatment should be started within 2 weeks thereafter.

Table 3 Relative hazards (RH) (risk for death) and 3 year survival in patients treated for NSCLC between 1995 and 1999 (n = 466)

	No (%) of patients	Percentage 3 year survival (95% CI)	Univariate		Multivariate	
			RH	(95% CI)	RH	(95% CI)
Sex						
Male	268 (58)	32 (26 to 39)	1.0	Reference	1.0	Reference
Female	198 (42)	31 (25 to 36)	1.0	(0.8 to 1.2)	1.1	(0.9 to 1.3)
Age						
<70 years	307 (66)	31 (26 to 37)	1.0	Reference	1.0	Reference
⩾70 years	159 (34)	31 (24 to 39)	1.0	(0.8 to 1.2)	1.3	(1.1 to 1.5)
Logarithmic (per year)*	–	–	1.3	(0.6 to 2.1)	2.6	(1.9 to 3.3)
Squamous cell cancer						
No	314 (67)	27 (22 to 32)	1.0	Reference	1.0	Reference
Yes	152 (24)	39 (32 to 48)	0.7	(0.4 to 0.9)	0.8	(0.6 to 1.1)
Stage						
I–II	143 (31)	69 (61 to 76)	1.0	Reference	1.0	Reference
IIIA	37 (8)	41 (25 to 56)	3.0	(0.8 to 5.1)	1.9	(1.4 to 2.4)
IIIB	157 (34)	16 (10 to 22)	5.4	(2.1 to 8.7)	2.7	(2.3 to 3.1)
IV	129 (28)	6 (2 to 10)	9.6	(5.2 to 14.1)	4.5	(4.1 to 4.9)
Surgical treatment						
No	315 (68)	14 (10 to 17)	1.0	Reference	1.0	Reference
Yes†	151 (33)	69 (61 to 76)	0.2	(0.02 to 0.5)	0.5	(0.1 to 0.8)
Hospital delay‡						
<1 month	112 (27)	19 (12 to 28)	1.0	Reference	1.0	Reference
1–2 months	155 (38)	34 (26 to 41)	0.8	(0.5 to 1.0)	1.0	(0.8 to 1.3)
2–3 months	78 (19)	36 (25 to 46)	0.7	(0.4 to 0.9)	0.9	(0.6 to 1.3)
>3 months	68 (16)	43 (31 to 55)	0.6	(0.3 to 0.9)	0.8	(0.6 to 1.2)
Logarithmic (per month)§	–	–	0.75	(0.6 to 0.8)	0.98	(0.8 to 1.1)
Symptom to treatment delay¶						
<3 months	93 (26)	11 (5 to 17)	1.0	Reference	1.0	Reference
3–6 months	139 (39)	31 (23 to 39)	1.0	(0.7 to 1.2)	0.9	(0.7 to 1.2)
>6 months	122 (35)	35 (26 to 43)	0.9	(0.6 to 1.1)	0.8	(0.6 to 1.1)
Logarithmic (per month)	–	–	0.65	(0.4 to 0.8)	0.80	(0.6 to 1.0)

*Associated with an increase by one unit in the logarithm of age in years.
†With or without other treatment.
‡Missing (n = 53).
§Associated with an increase by one unit in the logarithm of delay per month.
¶Missing (n = 112).

In our study only 51% of the patients received treatment within 6 weeks from the first consultation with a chest physician. Only 31% of the surgically treated patients had undergone operation within 6 weeks.

The median delay of 4.6 months (mean 5.8 months) from the first symptom to the commencement of treatment was lower than was found in a recent Swedish study (mean 6.7 months)[8] and somewhat higher than has been reported by UK investigators (median 3.6 months).[12] Generally, patients with malignancy tend to seek help late, failing to recognise that their symptoms are sufficiently severe to warrant consulting a doctor.

In the present study the observed hospital delay time was comparable to the estimate of 1.1 months reported by Jones and Dudgeon.[13] A range of recommendations has been made in different countries. In the UK it is advocated that radical radiotherapy should start within 2 weeks after it is requested.[6] In Canada a maximum of 4 weeks is recommended from the first visit to a family physician to diagnosis and it is considered that the waiting time from completion of diagnostic tests to surgery should not exceed 2 weeks.[14]

Surgically treated patients had a longer hospital delay time than those treated non-surgically, a difference that is likely to reflect the extra time needed to refer patients to thoracic surgery units where additional treatment considerations are made. This delay may be minimised by involving both surgeons and oncologists earlier in the chain of management.[15] A multidisciplinary team approach with rapid access to investigations has been found to reduce the median time to 5 weeks from the initial physician's consultation at a peripheral clinic to treatment.[15 16] A reduction in delay time will probably not only increase the number of patients who are candidates for surgery,[15] but will also have psychological benefits for the patients.[16]

The poor prognosis in patients treated for NSCLC is confirmed in the present study with only about one third surviving 3 years.[1 17] More than two thirds (69%) of the patients presented with advanced disease (stage III–IV), which is the main reason for the poor results.

At present the biological behaviour of lung cancer cannot be assessed accurately as there is no reliable method for identifying tumours with aggressive phenotypes. Patients with such tumours may benefit from prompt treatment. Potentially curable lung cancers initially grow slowly; it is estimated that it takes about 130 months for a tumour to reach a diameter of 1 cm.[4 18] The tumour volume expands exponentially, going from being potentially curable to incurable over a period of 1 month.[6] It may be assumed that the patients with the best prognosis are those with the slowest growing tumours (who can be observed over a period of months without passing the limits of being curable).

Two main conclusions can be drawn from this study. Firstly, our results indicate that longer delay before treatment of lung cancer patients is not associated with a poorer prognosis. This finding probably indicates that patients with more advanced disease receive treatment more promptly because of the severity of their signs and symptoms. Those who still have a chance of cure generally have to wait longer, which implies a risk for progression of the disease and additional psychological stress. Secondly, the delay time for treatment of lung cancer is currently longer than is recommended.

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