

## Delays in the Diagnosis and Treatment of Primary Lung Cancer: Are Longer Delays Associated with Advanced Pathological Stage?

Adnan Yilmaz<sup>1</sup>, Ebru Damadoglu<sup>1</sup>, Cuneyt Salturk<sup>1</sup>, Erdal Okur<sup>2</sup>, Leyla Yagci Tuncer<sup>1</sup>, Semih Halezeroglu<sup>2</sup>

*Sureyyapasa Thoracic and Cardiovascular Diseases Teaching and Investigation Hospital-Istanbul, <sup>1</sup>Department of Pulmonology, <sup>2</sup>Department of Thoracic Surgery*

### Abstract

We aimed to investigate the delays from the first symptom to thoracotomy and to examine whether the delays cause the stage advancement in lung cancer. This prospective study included 138 patients with non-small cell lung carcinoma who underwent thoracotomy. Clinical files of the patients were analyzed and a questionnaire was created to obtain information from the patients. The mean duration values were 81.3 days for the application interval, 61.3 days for the referral interval, 20.3 days for the diagnostic interval, and 21.9 days for the treatment interval. The application interval was longer than 30 days (patient delay) in 50 patients (37.9 %). The mean interval from the first visit to doctor to thoracotomy was 97.2 days. There was a doctor delay in 102 (73.9 %) patients; a referral delay in 83 patients (60.1 %), a diagnostic delay in 47 patients (36.4 %), and a treatment delay in 96 patients (69.6 %). The mean total duration was 176.2 days. Ninety-four patients (71.2 %) had a total delay. Mean total delay was 184.5 days in pathologic stage I, 187.3 days in stage II, 167.7 days in stage IIIA, 142.6 days in stage IIIB, and 150.3 days in stage IV ( $p>0.05$ ). Delays during the course between the first symptom and thoracotomy in lung cancer patients were a common problem among our patients. Prolonged durations in the application and referral of patients are the most significant cause of delays. Presence of delay or length of delay did not correlate with pathologic tumour stage in this study.

## Introduction

Lung cancer remains to be one of the most common and most lethal forms of cancer. Despite the advancements in modern diagnostic and therapeutic modalities, the prognosis of lung cancer is still very poor, with an overall 5-year survival rate of about 15 % worldwide (1). Only less than 20 % of patients with lung cancer can undergo pulmonary resection, which is the only curative treatment (2). Several factors such as age, sex, comorbidity, performance status, histology and stage of the disease affect the prognosis of patients (3). It has been documented that the survival and cure rates are higher in cancer patients diagnosed in the earlier stages (4, 5). However, diagnostic and treatment delays continue to remain very common problems among the patients with lung cancer (5–8). Some studies looking at the impact of delays on tumour stage and survival rate have shown that delays affected tumour stage and survival rate (9–11). On the other hand, others have reported that delays

---

Received 6 May 2008

Accepted 2 June 2008

were not associated with tumour stage and survival rate (5, 7, 8, 12). The aims of this study were to investigate the delays in patients with lung cancer from the first symptom to thoracotomy and to examine whether the delays affect the stage of lung cancer at the time of thoracotomy.

## Materials and methods

We investigated all the patients with primary lung cancer referred from the pneumology departments to first thoracic surgery department of Sureyyapasa Chest Diseases and Thoracic Surgery Training and Investigation Hospital between January 2005 and July 2006. Among the patients who underwent thoracotomy for lung cancer, those who had tumour pathology other than non-small cell lung carcinoma, patients who were referred to surgical department directly from other hospitals, the patients who did not accept responding the questionnaire, and those who did not remember some dates in their disease course were excluded from the study. There were 192 patients who underwent thoracotomy for lung cancer in this department during the period study was carried out. However, the study included 138 patients who had the inclusion criteria. Consent was obtained from each patient after full explanation of the purpose and nature of the study. Because patient medical records were used and a questionnaire was created to obtain data, ethics committee approval has not been obtained.

All patients had a preoperative bronchoscopy and computed tomography (CT) of the thorax and upper abdomen. Various techniques such as brain CT or MR, radionuclide bone scintigraphy, PET or PET/CT-were carried out in patients with symptoms or signs suggesting extrathoracic metastases. Twenty-three patients had PET/CT investigation preoperatively. Preoperative surgical mediastinal exploration was performed in those patients who presented with centrally located tumour, enlarged lymph nodes on CT or increased FDG uptake on PET/CT in mediastinal or hilar lymph nodes.

Clinical files of the patients were analyzed by 2 authors of this study, and a questionnaire was created to obtain data by the interview with the patients. For each patient, the following information was gathered based on these data: (1) sex, (2) age, (3) symptoms, (4) tumour histology, (5) pathological TNM stage, (6) date of initial symptoms, (7) date of first doctor visit, (8) date of admission to pneumology department of our hospital, (9) date of diagnosis, and (10) date of thoracotomy. Pathological TNM stage was based on thoracotomy and pathological reports.

The following time intervals and delays were determined for each patient: *patient's application interval* was defined as the time passed between the onset of symptoms and the first doctor visit. It was calculated in 132 patients who had symptoms. The application interval that exceeded 30 days was considered indicative of a *patient's delay* (13). *The referral interval* was defined as the time from the first doctor visit to admission to one of the pneumology departments of our hospital for the further investigation, and the interval that exceeded 14 days was consid-

ered indicative of a *referral delay*. The *diagnosis interval* was regarded as the time passed between the admission to our hospital and the pathological diagnosis was made. Because 9 patients admitted to pneumology departments with a pathological diagnosis, this interval was calculated in 129 patients in whom the diagnosis was established in our hospital. The diagnosis interval that exceeded 14 days was considered as indicative of a *delayed diagnosis*. The *treatment interval* was the time passed from the diagnosis to thoracotomy, and the interval that exceeded 14 days was considered as indicative of a *delayed treatment*. *Doctor's interval* was defined as the time from the first doctor visit to thoracotomy and the interval that exceeding 6 weeks was considered as indicative of a *doctor's delay*. The *total interval* was the time between the onset of symptoms and thoracotomy, and if exceeding 72 days it was considered indicative of a *total delay* (14, 15). Figure 1 demonstrates the time intervals and delays used in this study.

### Statistical analysis

The data were analyzed using the SPSS statistical program. Time intervals were compared among stages using Kruskal-Wallis test. Proportions were analysed with exact test. A p-value of less than 0.05 was considered significant.

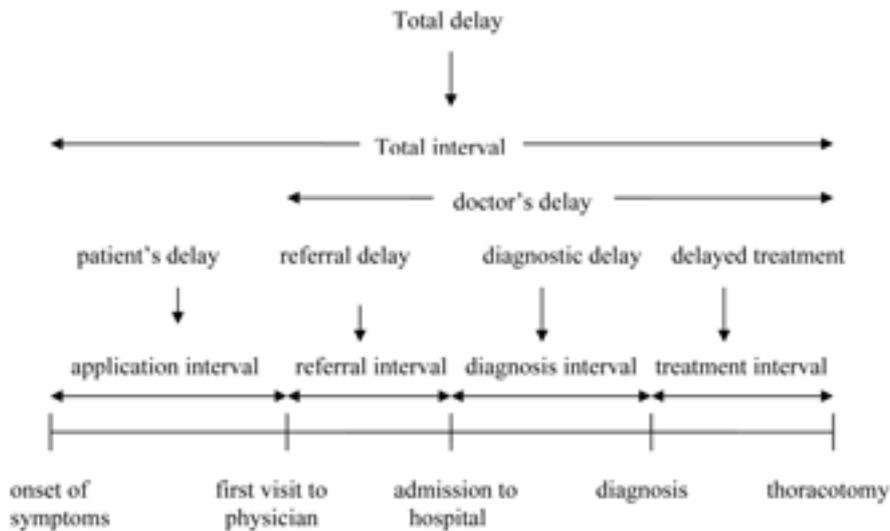


Figure 1. Components of the time from onset of symptoms to thoracotomy and delays.

## Results

The study included 138 patients with non-small cell lung carcinoma consisting of 133 (96.4 %) men and 3 (3.6 %) women with a mean age of 58.1 years (range 28–78). Demographic characteristics of the study population are presented in Table 1.

The mean duration between the first existence of symptom and thoracotomy was 176.2 days; 81.3 days for application, 61.3 days for referral, 20.3 days for diagnosis and, 21.9 days for treatment ( Table 2).

Duration between the first symptom and thoracotomy was longer than 72 days in 94 patients (71.2 %). Of the patients, 50 (37.9 %) had patient's delay and 102

*Table 1.* Demographic characteristics of the study population

|                           | n   | %    |
|---------------------------|-----|------|
| Sex                       |     |      |
| Men                       | 133 | 96.4 |
| Women                     | 5   | 3.6  |
| <b>Presenting Symptom</b> |     |      |
| No symptom                | 6   | 4.3  |
| Cough                     | 77  | 58.3 |
| Chest pain                | 50  | 37.9 |
| Dyspnea                   | 29  | 22   |
| Hemoptysis                | 46  | 34.8 |
| Sputum                    | 3   | 2.3  |
| Others                    | 40  | 30.3 |
| <b>Tumour Histology</b>   |     |      |
| Squamous                  | 83  | 60.1 |
| Adenocarcinoma            | 48  | 34.8 |
| Adenosquamous             | 1   | 0.7  |
| Non-small cell            | 6   | 4.4  |
| Location of tumour        |     |      |
| Right lung                | 64  | 46.4 |
| Left lung                 | 74  | 53.6 |
| <b>Pathological Stage</b> |     |      |
| I                         | 67  | 48.6 |
| II                        | 32  | 23.2 |
| III A                     | 17  | 12.3 |
| III B                     | 19  | 13.8 |
| IV                        | 3   | 2.1  |

Table 2. Values in the intervals

| Interval              | n   | Mean (days) | SD (days) | Median (days) | 95 % CI (days) |
|-----------------------|-----|-------------|-----------|---------------|----------------|
| <b>Application</b>    | 132 | 81.3        | 176.8     | 18            | 51.1-111.5     |
| <b>Doctor's Delay</b> | 138 | 97.2        | 108.1     | 56            | 81.8-118.8     |
| Referral              | 138 | 61.3        | 110.2     | 20.5          | 42.9-79.7      |
| Diagnosis             | 129 | 20.3        | 28.9      | 11            | 15.3-25.3      |
| Treatment             | 138 | 21.9        | 19.4      | 19            | 18.7-25.2      |
| <b>Total Delay</b>    | 132 | 176.2       | 210.5     | 98            | 140.3-212.1    |

(73.9 %) had doctor's delay. Referral interval was longer than 14 days in 83 patients (60.1 %), diagnostic work ups took more than 14 days in 47 patients (36.4 %) and waiting time for thoracotomy more than 14 days in 96 patients (69.6 %). There were 276 delays occurring in 138 patients in 4 different steps (application, referral, diagnosis, and treatment) during the disease course between the first symptom and thoracotomy. Delays were due to a late admission to a doctor after the first symptoms in 50 patients (18.1 %), and a prolonged referral time in 83 patients (30.1 %), a diagnostic interval in 47 patients (17 %) and a waiting time for thoracotomy in 96 patients (34.8 %) (Table 3).

Distribution of intervals with respect to pathological stage is shown in Table 4, and patients with delay with respect to pathological stage in Table 5. There was no significant difference among stages.

## Discussion

This study shows that there are several delays in different steps from the onset of symptoms to thoracotomy among our patients with lung cancer. These delays are due to either patients themselves, as they admitted to a doctor lately (*patient's delay*) or prolonged durations in referral of patients by the doctor, diagnostic work-ups and waiting time for thoracotomy (*doctor's delay*). The mean and median application intervals of patient to a doctor after their first symptoms were 81.3 and 18 days, respectively. Our median application interval compares favourably with 21 days of Koyi and co-workers' (6) and 30 days in Özlu and co-workers' studies (16) while mean interval compares less favourably with 30.3 days in Gonzalez and co-workers' (17) and, 41 days in Salomaa and co-workers' studies (5). Mean total duration of 176 days between the first symptom and thoracotomy in our study is shorter than Koyi and co-workers' series (203 days) and longer than Billings and Wells' series (109 days) (6, 7).

We found that the rate of doctor's delay was higher than that of patient's delay.

Table 3. Distribution of patients in the intervals in respect to delay criteria

| Intervals                   | n   | %    |
|-----------------------------|-----|------|
| <b>Application Interval</b> | 132 | 100  |
| ≤ 30 days                   | 82  | 62.1 |
| > 30 days                   | 50  | 37.9 |
| <b>Doctor's Delay</b>       | 138 | 100  |
| ≤ 6 weeks                   | 36  | 26.1 |
| > 6 weeks                   | 102 | 73.9 |
| <b>Referral Interval</b>    | 138 | 100  |
| ≤ 2 weeks                   | 55  | 39.9 |
| > 2 weeks                   | 83  | 60.1 |
| <b>Diagnosis Interval</b>   | 129 | 100  |
| ≤ 2 weeks                   | 82  | 63.6 |
| > 2 weeks                   | 47  | 36.4 |
| <b>Treatment Interval</b>   | 138 | 100  |
| ≤ 2 weeks                   | 42  | 30.4 |
| > 2 weeks                   | 96  | 69.6 |
| <b>Total Delay</b>          | 132 | 100  |
| ≤ 72 days                   | 38  | 28.8 |
| > 72 days                   | 94  | 71.2 |

The mean and median durations after the first doctor visit to thoracotomy were 97.2 and 56 days, respectively, while a previous study reported these durations being 56 and 33 days after the first doctor's visit and 33 and 9 days after the second doctor's visit (6). Analysis of the total number of delays in our study revealed that therapeutic delays were the most common part of doctor's delay as the mean duration between the diagnosis and thoracotomy was 21.9 days. However, when the total extent of delays is considered, the application and the referral intervals appeared as the main parameters prolonging the duration. The delays in diagnostic work-ups (mean of total diagnostic time: 20.3 days) occurred in relatively lesser extent among our patients.

Several study groups have made recommendations for referral and waiting times in the diagnosis and treatment pathways of lung cancer (13–15, 18). According to one Brazilian study, an application interval exceeding 30 days is considered as a patient's delay (13). The British Thoracic Society (BTS) recommends that all patients should be seen for an initial evaluation by a pulmonary physician within 1 week of referral from their primary care physician and, diagnostic testing should be performed within 2 weeks of the decision (14). The Swedish Lung Cancer Study Group (18) recommends that in 80 % of all patients, diagnostic tests should be completed

Table 4. Distribution of intervals in respect to pathological stage

|                      | PATHOLOGICAL STAGE |             |            |            |              |
|----------------------|--------------------|-------------|------------|------------|--------------|
|                      | I                  | II          | III A      | III B      | IV           |
| <b>Interval</b>      | (days)             | (days)      | (days)     | (days)     | (days)       |
| <b>Application †</b> |                    |             |            |            | † p>0.05     |
| Mean                 | 86.9               | 85.6        | 102.3      | 43.8       | 40.7         |
| SD                   | 170.9              | 168.4       | 282.9      | 87.8       | 34.4         |
| Median               | 15.0               | 23.0        | 25.0       | 16.0       | 60.0         |
| CI, 95 %             | 43.8-129.9         | 22.7-148.4  | 43.1-247.7 | 1.5-86.1   | -44.7-126.0  |
| <b>Doctor ‡</b>      |                    |             |            |            | ‡ p>0.05     |
| Mean                 | 104.3              | 97.5        | 65.4       | 98.6       | 103.0        |
| SD                   | 118.6              | 120.0       | 64.4       | 82.6       | 87.5         |
| Median               | 68                 | 55.0        | 50.0       | 75.0       | 56.0         |
| CI, 95 %             | 75.4-133.2         | 54.2-140.9  | 32.3-98.5  | 58.8-138.5 | -114.5-320.5 |
| <b>Total †</b>       |                    |             |            |            | † p>0.05     |
| Mean                 | 184.5              | 187.3       | 167.7      | 142.6      | 150.3        |
| SD                   | 202.9              | 195.3       | 344.5      | 103.1      | 108.2        |
| Median               | 105.0              | 108.0       | 81.0       | 101.0      | 136.0        |
| CI, 95 %             | 133.4-235.6        | 114.4-260.2 | -9.4-344.8 | 92.9-192.3 | 118.5-419.2  |

Table 5. Distribution of the patients having delay in respect to pathological stage

|                          | PATHOLOGICAL STAGE |           |           |           |          |
|--------------------------|--------------------|-----------|-----------|-----------|----------|
|                          | I                  | II        | III A     | III B     | IV       |
| <b>Presence of delay</b> | n (%)              | n (%)     | n (%)     | n (%)     | n (%)    |
| <b>Patient's delay †</b> |                    |           |           |           | † p>0.05 |
| Yes                      | 40 (63.5)          | 18 (60.0) | 10 (58.8) | 13 (68.4) | 1 (33.3) |
| No                       | 23 (36.5)          | 12 (40.0) | 7 (41.2)  | 6 (31.6)  | 2 (66.7) |
| <b>Doctor's delay ‡</b>  |                    |           |           |           | ‡ p>0.05 |
| Yes                      | 17 (25.4)          | 9 (28.1)  | 7 (41.2)  | 3 (15.8)  | --       |
| No                       | 50 (74.6)          | 23 (71.9) | 10 (58.8) | 16 (84.2) | 3 (100)  |
| <b>Total delay †</b>     |                    |           |           |           | † p>0.05 |
| Yes                      | 19 (30.2)          | 7 (23.3)  | 7 (41.2)  | 4 (21.1)  | 1 (33.3) |
| No                       | 44 (69.8)          | 23 (76.7) | 10 (58.8) | 15 (78.9) | 2 (66.7) |

within 4 weeks from consultation by a specialist, and treatment should be started within 2 weeks thereafter. In the Canadian recommendations (15), a maximum of 4 weeks' elapse could be accepted between the first visit to a general practitioner and diagnosis, and the waiting time for surgery should not exceed 2 weeks. Salomaa et al (5) reported that about half of their patients fulfilled the criteria of the BTS recommendations. Sixty-six percent of their patients fulfilled the diagnostic delay criteria, and 49 % the treatment delay criteria of the Swedish Lung Cancer Study Group. Only 26 % could keep the Canadian recommendation of 4-week limit. According to the Brazilian study criteria, there was a patient delay in 37.9 % of our patients. Our criteria for doctor's, institutional, diagnosis, treatment and total delays were based on the BTS and Canadian recommendations. The rates of delay were 73.9 % for doctor's delay, 60.1 % for institutional delay, 36.4 % for diagnosis, 69.6 % for treatment, and 71.2 % for total delay in our series.

Delays may be due to several factors depending on the characteristics of the region and the population and status of the institution where the data were collected as well as the healthcare system applied. A British study noted that pre-hospital delays varied depending on the severity of symptoms, level of patient education and complex socioeconomic factors, and the main cause of delays was the multiplicity of pre-treatment investigations for histological verification, tumour staging, and assessment of co-morbidity in different institutions while scarcity of thoracic surgeons and limited theatre time were additional contributory factors in the delay in surgical patients (19). A study in Turkey associated the delays with prolonged durations in the appointments for imaging procedures as a part of an organisational problem in the health care system (16). Multiple appointments for patients requiring frequent hospital visits and long durations between appointments were the explanations of most of the multifactorial delays in a Canadian study (8). Less than 40% of our patients applied to a doctor later than 30 days after their first symptoms appeared. Indeed, this is not completely the result of healthcare system since the primary healthcare is free for all the people but relatively rare behaviour of applying a doctor for mild symptoms among undereducated people. Longer referral time seemed as another main problem in delays. This might be due to partly the duration passed between the distance of patient's lodgement and one of the main referral hospitals for lung cancer in Turkey or the long durations spent in the second or even the third opinions taken by the patients and or family after they have learned the suspicious diagnosis of cancer. However, an organisation remains to be established to take at least the chest X-ray at the first doctor visit in symptomatic patients in risk group for this very common disease, and then refer them to the closest centre where the treatment could be achieved.

Whether the delay advances the tumour stage is an important debate. Some studies indicated the delays as affecting the prognosis negatively (9, 10, 20), while others could not show such an association (5, 7, 12, 18). In the report of Christensen et al (9), a few months delay had an impact on the perioperative stage of the cancer, and thereby on the prognosis. O'Rourke and Edwards analyzed 29 lung cancer patients who were awaiting radical (potentially curative) radiotherapy, and found

that 21 % of potentially curable patients became incurable on the waiting list (10). On the other hand, it was shown in some studies that presence of delay (5) or the length of delay (5, 7) did not correlate with the tumour stage. Among the patients in advanced stages in our series, there was neither higher incidence of delay nor the longer delays when compared to earlier stages. Similarly, absence of delay or shorter delays were not associated entirely with only earlier stages; all the stages included similar distribution in this regard.

To sum up, delays in all the steps along the period between the first symptoms to thoracotomy appear to be a common problem among our patients with lung cancer. Socio-medical efforts should be spent to lower the durations in the periods between “the symptoms and application to a doctor” and “referral by the doctor to an institution where the diagnostic and therapeutic measures take place”. Presence of delay or length of delay does not correlate with tumour stage in patients who underwent thoracotomy; however, the final conclusion on this subject can only be given with the additional results of the studies that compare parameters among the patients in operable and inoperable stages.

## References

1. American Cancer Society. Cancer facts and figures 2006. Atlanta (GA): American Cancer Society; 2006.
2. Scagliotti GV (2001). Symptoms and signs and staging of lung cancer. *Eur Respir Mon* 17: 86–119.
3. Birim Ö, Kappetein AP, van Klaveren RJ, Bogers AJC (2006). Prognostic factors in non-small cell lung cancer surgery. *EJSO* 32: 12–23.
4. Robinson E, Mohilever J, Zidan J, Sapir D (1984). Delay in diagnosis of cancer. Possible effects on the stage of diseases and survival. *Cancer* 54: 1454–60.
5. Salomaa ER, Sallinen S, Hiekkanen H, Liippo K (2005). Delays in the diagnosis and treatment of lung cancer. *Chest* 128: 2282–8.
6. Koyi H, Hillerdal G, Branden E (2002). Patient's and doctor's delays in the diagnosis of chest tumours. *Lung Cancer* 35: 53–7.
7. Billings JS, Wells FC (1996). Delays in the diagnosis and surgical treatment of lung cancer. *Thorax* 51: 903–6.
8. Liberman M, Liberman D, Sampalis JS, Mulder DS (2006). Delays to surgery in non-small-cell lung cancer. *Can J Surg* 49: 31–6.
9. Christensen ED, Harvald T, Jendresen M, Aggestrup S, Petterson G (1997). The impact of delayed diagnosis of lung cancer on the stage at the time of operation. *Eur J Cardiothorac Surg* 12: 880–4.
10. O'Rourke N, Edwards R. Lung cancer treatment waiting times and tumour growth (2000). *Clin Oncol* 12: 141–4.
11. Korsgaard M, Pedersen L, Sorensen HT, Laurberg S (2006). Delay of treatment is associated with advanced stage of rectal cancer but not of colon cancer. *Cancer Detect Prev* 30: 341–6.
12. Aragonese FG, Moreno N, Leon P, Fontan EG, Folque E (2002), The Bronchogenic Carcinoma Cooperative Group of the Spanish Society of Pneumology and Thoracic Surgery (GCCB-S). Influence of delays on survival in the surgical treatment of bronchogenic carcinoma. *Lung Cancer* 36: 59–63
13. Silva PPA, Pereira JR, Ikari FK, Minamoto H (1992). Cancer de pulmao e retardo diagnostico: analise de 300 cases. *Rev Ass Med Brasil* 38: 145–9.
14. British Thoracic Society (1998). BTS recommendations to respiratory physicians for organising the care of patients with lung cancer: The Lung Cancer Working Party of the British Thoracic Society Standards of Care Committee. *Thorax* 53 (suppl 53): 1–8.

15. Simunovic M, Gagliardi A, McCready D, Coates A, Levine M, DePetrillo D (2001). A snapshot of waiting times for cancer surgery provided by surgeons affiliated with regional cancer centers in Ontario. *Can Med Assoc J* 165: 421–5.
16. Özlü T, Bülbül Y, Öztuna F, Çan G (2004). Time course from first symptom to the treatment of lung cancer in the Eastern Black Sea Region of Turkey. *Med Princ Pract* 13: 211–4.
17. Gonzalez JM, de Castro FJ, Barrueco M, Cordovilla R, Fernandez JL, Gómez FP, Moreno de Vega B, Ramos J, Serrano AR (2003). Delays in the diagnosis of lung cancer. *Arch Bronconeumol* 39: 437–41.
18. Myrdal G, Lambe M, Hillerdal G, Lamberg K, Agustsson TH, Stahle E (2004). Effect of delays on prognosis in patients with non-small cell lung cancer. *Thorax* 59:45–9.
19. Devbhandari MP, Bittar MN, Quennell P, Barber P, Krysiak P, Shah R, Jones MT (2007). Are we achieving the current waiting time targets in lung cancer treatment? Result of a prospective study from a large United Kingdom Teaching Hospital. *J Thorac Oncol* 2: 590–2.
20. Jensen AR, Mainz J, Overgaard J (2002). Impact of delay on diagnosis and treatment of primary lung cancer. *Acta Oncol* 41: 147–52.

*Corresponding author:*

Associate Professor Adnan Yilmaz  
Maltepe Zumrutevler Atatürk Cad.  
Abant Apt. No: 30 İstanbul/Turkey  
Phone: + 90 216 3058324  
Email: adnandr\_63@yahoo.co.uk