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The impact of delayed diagnosis of lung cancer on the stage at the time of operation

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Abstract

Objective: The purpose of this investigation was to study the correlation between diagnostic delay and the stage of the lung cancer at the time of operation. A second objective was to study differences in symptoms between the patients grouped according to stage. **Methods:** A total of 172 patients consecutively admitted for surgery between 1 January 1994 and 1 June 1995 at the Department of Thoracic and Cardiovascular Surgery of Rigshospitalet National Hospital of Denmark were included in the retrospective study. Two groups of patients were compared, one group with good prognosis (patients in Stages I and II) and one group with poor prognosis (patients in Stages III and IV). The time-spans studied were: (1) interval from the patient's perception of the first symptom to operation; and (2) the time from first contact with the healthcare-system to operation. The median delay between the patient-groups was compared using the Mann–Whitney *U*-test. To compare the symptoms which brought the patients in contact with the healthcare-system, the χ^2-test was used. **Results:** In the time interval between appearance of the first symptom and operation, a significantly shorter median delay was found for patients with Stages I and II compared to Stages III and IV ($P = 0.037$). Concerning the interval from first contact with the healthcare system to operation a significantly shorter median delay was found for the group of patients in Stage I and II compared to the patients-group in Stage III and IV ($P = 0.017$). It was found that the cancer was an accidental finding, significantly more often in patients in Stages I or II compared to patients in Stages III or IV ($P = 0.0002$). **Conclusions:** A few months delay before final treatment of a non-small-cell lung cancer seems to have an impact on the perioperative stage of the cancer, and thereby on the patients prognosis. A screening of asymptomatic risk-group patients will result in recognition of early lung cancer. © 1997 Elsevier Science B.V.

Keywords: Lung cancer; Diagnostic delay; Stage; Surgery; Prognosis

1. Introduction

During the past 50 years the overall 5-year survival for patients with lung cancer has stayed constant at 5–10% [1]. This fact has been the main reason for the defeatism concerning treatment—surgical as well as medical [2]. The incidence of lung cancer (LC) in Denmark is approximately 3500 per year. Of this number, only 15–20% are operated. The 5-year survival after operation is approximately 30–35% [3]. Surgery is still the only treatment with potential for the cure of lung cancer; but good surgical results do not have much influence on the overall survival statistics.

When operated on in Stage I [4], expansive North American studies have clearly demonstrated a 5-year survival of 70–75% [5–7]. The corresponding 5-year survival concerning Stages II and III is about 35 and 9%, respectively. If recognized and operated on in Stages I or II, a considerable part of the LC-patients might thus be cured.

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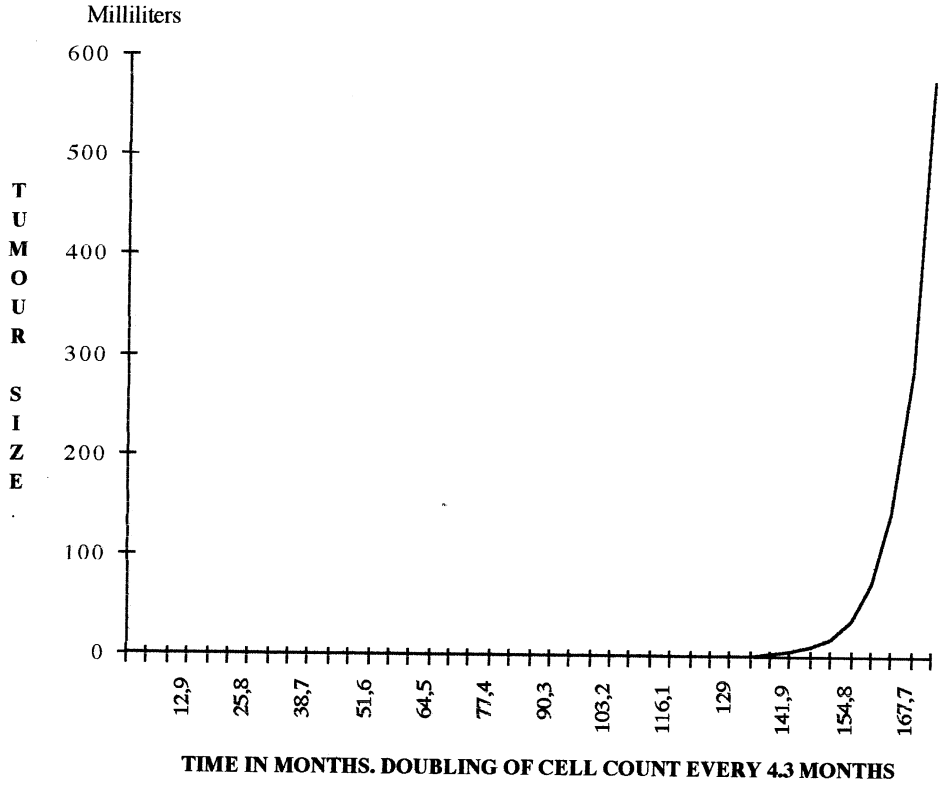

Fig. 1. Tumour growth as a function of time. Cell diameter = 10 μm, tumour volume = $\pi/(6 \times \text{diameter}^3 \times \text{cell count})$. Tumour volume is directly proportional to the number of cells.

Whether it is worth the money and the effort to try to detect and operate on the non-small lung cancers earlier, has already been questioned professionally [8]. It was stated, that since the lung cancers had been developing for more than 10 years before the detection, neither surgical nor medical treatment could be expected to have much effect in this late phase of the disease.

The development of a malignant lung tumour can, concerning cell-number, grossly be described mathematically by the exponential-function, $Y = 2^X$. The corresponding tumour-volume is easily computed using the appropriate formula (Fig. 1). The doubling-time (DT) of the tumour cells depends on the tumour type and varies between 1 month for small-cell LC and 6 months or more for adenocarcinomas [9].

In Fig. 1, the average DT corresponding to the material with its relatively high proportion of slow dividing adenocarcinomas is 3.8 months plus a correction of 0.5 months because there is a basis for the assumption that the tumour-growth decelerates somewhat with increasing tumour size [10]. The exponential model has its weaknesses, but is, nevertheless, the most useful tool [11] to describe tumour growth.

An LC which has passed 40 cell-doublings has reached a stage incompatible with survival [12,13]. Calculations of tumour-diameters using Fig. 1 show, that to reach a diameter of 1 cm (the lower limit to be X-ray detectable) it would take 130 months. After 130 months the tumour-volume expands rapidly. Hence, a small-size tumour cannot be considered benign [14].

Considering the ultimate steep rise of the tumour growth-curve in Fig. 1, it is reasonable to conclude that radical resection, while the LC is still of a small size, would prevent the expected explosive growth of the last months associated with high risk of local- and distant-spread of cancer-cells.

The purpose of this study has been:

1. to study the possible correlation between diagnostic delay preoperatively and the stage of the lung cancer at the time of operation;
2. to study the significant difference in symptoms between the patients grouped according to stage.

2. Materials and methods

All patients admitted for operation with primary lung cancer from January 1994 to April 1995 were studied retrospectively. The number of patients necessary for the study to be viable was calculated according to recommendations by Schoedt [15] on the pre-investigation assumptions that: $2\alpha = 0.05$ (α = error of first order); $\beta = 0.15$ (β = error of second order); standard

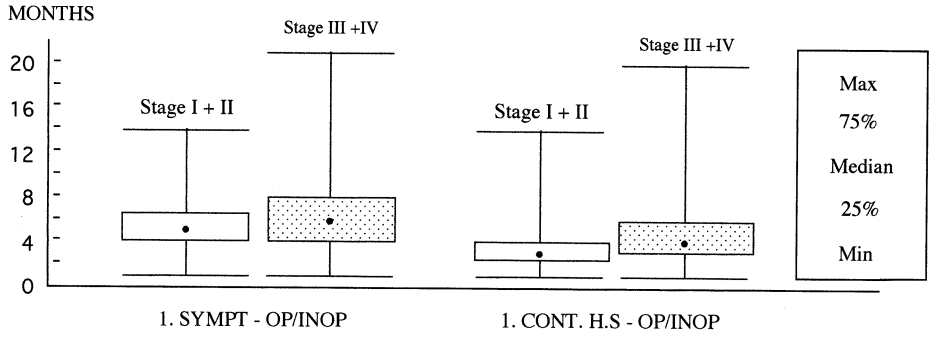

Fig. 2. Box plot for the median delay in relation to stage at surgery or at the time the patient is considered inoperable. Only the intervals, 1., symptom till end-point and 1., contact to the health system are shown. 1. SYMPT–OP/INOP, time-intervalspan from first symptom till the operation; 1. CNT.H.-S–OP/INOP, time-interval span from first contact to the health-system till the operation.

deviation (S.D.) = 4 months and the minimal relevant difference (M.R.D.) = 2 months. In total, it was calculated that at least 150 patients were to be included.

The LC staging is according to the international system for staging lung cancer [16].

A total of 61 women and 111 men were included. The median age for the women was 61 years (minimum to maximum: 41–82 years). The median age for the males was 66 years (minimum to maximum: 35–82 years). Out of the total number of 172 patients, 37 were considered inoperable based on the results of the preoperative examination. Concerning the distribution of inoperable patients, there were 9 out of a total of 14 in Stage IV, 20 out of a total of 50 in Stage IIIB, 5 out of a total of 39 in Stage IIIA, 1 out of a total of 18 in Stage II and 2 out of a total of 51 in Stage I. The preoperative investigation included chest X-ray, CAT-scan, respiratory function, fine-needle biopsy and broncho-mediastinoscopy. The patients operated on in the study were, in addition, staged by histologic examination of the resected material.

The data were recovered from the patients hospital files.

The end-point for each case and the time for the final staging was the date when the patient was either operated on or considered inoperable.

The time-spans studied were: (1) the interval between the patient's perception of the symptom, which made him contact the health-system, till the end-point, i.e. day of operation or the day where the patient was judged as inoperable (1. SYMPT-OP/INOP); (2) the time interval from 1., contact with the health-system till the end-point (1. CNT H.S-OP/INOP); (3) the time interval from first referral to hospital till the end-point (REF.-OP/INOP); and (4) the time interval from first admission to hospital to the end-point (1. ADM-OP/INOP).

The 20 asymptomatic patients in the group with good prognosis and the 6 asymptomatic patients in the group with poor prognosis, were included in the interval: 1., contact with the health-system till the end-point.

In addition, the patient's primary symptoms in relation to the stage of the disease at the time of end-point, were investigated.

2.1. Statistics

The Mann–Whitney U-test was used to compare the patients in Stages I and II, as one group, with the patients in Stages III and IV, as the other group. The patients were grouped as such because of the fact that resected patients in Stages I and II, has a good prognosis compared to the patients in higher stages [5–7].

The χ^2-test was used to compare the group, Stages I and II, with the group, Stages III and IV, concerning accidentally found LCs.

Significance was determined at $P < 0.05$. Statistical software used was StatisticaMac version 4.0.

3. Results

The median delays concerning the intervals, 1. symptom till end-point and 1. contact to the health system till end-point are shown in the box-plots in Fig. 2. The median delays concerning the interval, 1. referral to hospital till the end-point, are 3 months for Stages I and II and 2 months for Stages III and IV.

In the interval, 1., admission till the end-point, the median delays for Stages I and II and Stages III and IV were 2 months in both groups.

It is remarkable that the median waiting time is as long as 2 months from 1., admission to hospital till operation.

The relation between first symptom and stage at the end-point is shown in Table 1. Coughing as the first symptom is most common in all stages apart from Stage IV. Hemoptysis, an alarming symptom, is far more common in Stage IV, than in the other stages ($P = 0.033$, χ^2).

Table 1
First symptoms in relation to the stage at the time of surgery or at the time the patient is considered inoperable

Symptom	LC stage[a]			
	I (%)	II (%)	III (%)	IV (%)
Persistent cough	29 (15)	33 (6)	30 (29)	9 (3)
Dyspnoe	13 (7)	11 (2)	33 (32)	13 (2)
Hemoptysis	12 (6)	0 (0)	10 (10)	31 (5)
Pneumonia	12 (6)	28 (5)	13 (12)	13 (2)
Miscellaneous[b]	9 (5)	17 (3)	17 (17)	37 (6)
Asymptomatic	33 (17)	22 (4)	7 (7)	0 (0)
	108 (56)	111 (20)	110 (107)	113 (18)

[a] The results are given as percentage of the total per group and the numbers are given in parens.
[b] Headache, loss of weight, shoulder-pain, fewer, fatique and transitory ischemic attacks.

Symptoms such as headache, loss of weight, shoulder pain, fever, fatigue and transitory cerebral ischemic attacks are relatively more common in Stage IV; but play a modest role in the other stages ($P = 0.006$, χ^2). Dyspnoea is also more common in Stages III and IV compared to Stages I and II ($P = 0.034$, χ^2).

Accidentally found LCs make up a remarkably large proportion of Stages I and II compared to the other stages and the difference is significant ($P < 0.0002$).

The difference in median-delay from the patient's perception of the first symptom till the end-point, is significant (Table 2) concerning Stages I and II compared to Stages III and IV ($P = 0.037$).

The difference in median-delay from first contact with the health-system to the end-point is according to Table 2, significantly concerning Stages I and II compared to Stages III and IV ($P = 0.017$). Fig. 2 illustrates the difference between the two groups.

Regarding the time intervals, referral to hospital till end-point or/and first admission to hospital to end-point, no significance can be shown.

4. Discussion

The aim of this study was not to examine the results of LC-treatment, but to study the possibility of improving the results of surgical treatment of lung cancers by earlier recognition and treatment.

Our study has shown, that even a few months delay in diagnosis and treatment has a significant influence on the stage of the lung cancer and therefore for the prognosis of the disease. This is in agreement with the exponential growth-model for the lung cancer discussed earlier (Fig. 1).

The patient himself is responsible for the longest delay, but also the doctor's delay must be shortened to improve the patient's prognosis (Fig. 2).

It is not possible to show any significance concerning median delay in the two time-intervals, referral to hospital till end-point and admission to hospital till end-point. The M.R.D. in these intervals is so small that it would take a very large number of patients to demonstrate a significant difference. On the other hand, this non-significance indicates the fact, that in the hospital, management functions reasonably well once the LC-patient is referred to surgical treatment. The 20 symptomless patients in Stages I and II and the 6 in Stages III and IV had to be considered in the time-interval and first contact to the health-system till end-point, as their LC's were found while they had contact with the health-system for other reasons.

It is obvious that the group of symptomless patients which often presents with small tumours would be expected to end-up in a group with a good prognosis. The concept of this investigation was to start with the stage at operation or the time where the patient was considered inoperable and look back on the time-intervals of the patient's illness. One might claim, that a small tumour could tolerate a longer delay than a more advanced tumour and in spite of this end up in a favourable stage. It might be possible, but a long delay combined with a favourable stage, would compromise the statistical significance shown here. The median delay from 1., contact to the health system till the end-point, for the 20 symptomless patients in Stage I and II is 2 months with a minimum of 1 month and a maximum of 5 months. The median delay from 1., contact to the health system till the end-point for the corresponding 6 patients in Stages III and IV is 4 months with a minimum of 2 months and a maximum of 6 months. In the material, it looks as if patients with the

Table 2
Difference between the patients in Stages I and II and Stages III and IV according to time-intervals

Interval	P-value: Stages I and II vs. III and IV	Statistical method
From 1., symptom till operation or inoperability	0.037	Mann–Whitney U-test
From 1., contact with the health-system till operation or inoperability	0.017	Mann–Whitney U-test
1., symptom: occasionally found	0.0002	χ^2-test

combination of a favourable stage at operation and a long delay only exist in very small numbers. A probable reason could be, that at the time the tumour can be seen on chest X-ray, it is somewhere at the beginning of the steep slope of the growth-curve in Fig. 1. At that time, a delay of even 3–4 months might be fatal and send the patient into a stage with a poor prognosis.

Patients with lung cancer at Stage IV often present with unspecific symptoms different from the other symptoms suspicious of lung cancer because of metastases to other organ-systems. The symptoms may, therefore, be more alarming and result in a more aggressive attitude from the healthcare system and shorter diagnostics. This could explain why the median delay in the interval, 1. REF.-OP/INOP is shorter for the patients in Stages III and IV than for patients in Stages I and II.

In Section 1 it was mentioned that, surgical treatment of non-small cell lung cancers in Stages I and II has a good prognosis [6] and why early detection and surgical treatment of these cancers should be given a high priority.

A general education of the population concerning early symptoms of lung cancer, i.e. long-standing coughing, dyspnoe, pneumonia and hemoptysis, may increase the patient's awareness of the symptoms and the urgency with regard to medical attention, thereby leading to earlier definitive treatment.

The defeatist attitude, widespread in the community and among doctors is, according to this study, not justified, but is self-sustaining since it delays the diagnosis and the surgical treatment.

The part of this investigation concerning the significant differences in the proportion of accidentally found lung cancers confirms Stage I and II LCs as often asymptomatic. The only possibility as regards finding asymptomatic lung cancers is by screening risk-groups. In the light of the recent revision of the often cited three great North American studies, The Memorial-Sloan Kettering Study, The Mayo Study and The John Hopkins Study, screening of risk groups should be re-considered [2,5–7]. The discussion and the conclusions in the paper by Strauss should be considered [17].

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