Eur Respir J 2004; 24: 898–904
DOI: 10.1183/09031936.04.00113603
Printed in UK – all rights reserved

European Respiratory Journal
ISSN 0903-1936

CLINICAL FORUM

Lung cancer: clinical presentation and specialist referral time

G. Buccheri, D. Ferrigno

Lung cancer: clinical presentation and specialist referral time. G. Buccheri, D. Ferrigno. ©ERS Journals Ltd 2004.

ABSTRACT: Many textbooks describe symptoms and signs of lung cancer but refer to old series of patients.

To update knowledge about lung cancer presentation, a study was carried out on 1,277 consecutive lung cancer patients, who were seen in a single Institution from January 1989 to October 2002. A set of 33 anthropometric, clinical, physical, laboratory, radiological, pathological and follow-up variables was prospectively recorded for all patients. In addition, information was obtained concerning symptoms of alarm (*i.e.* potential concern), times to specialist referral and the mix of symptoms at presentation. Patients were carefully followed-up and their subsequent clinical course was recorded.

Casual discovery with absence of symptoms occurred more frequently towards the end of the study period and the prevalence of chest pain became less common. No other time-dependent changes were found in the presenting symptoms. Delay in specialist referral was longer when presentation was provoked by cough or by the occurrence of systemic symptoms, such as weight loss, anorexia and asthenia. Referral delay was longer towards the end of the study, perhaps related to an increase in the number of elderly patients with co-morbidities. Both alarm and prevalence symptoms were strong predictors of the clinical outcome, as found in both univariate analysis (favourable: casual discovery and chest infection; unfavourable: chest pain, dyspnoea, systemic symptoms and symptoms of local or systemic dissemination) and in multivariate analysis (favourable: chest infection).

Early presentation of lung cancer is characterised by a specific symptomatic pattern. Knowledge of this pattern may help to improve the rate of early diagnosis.

Eur Respir J 2004; 24: 898–904.

S.C. di Pneumologia, Azienda Ospedaliera "S. Croce e Carle", Cuneo, Italy.

Correspondence: G. Buccheri
S.C. di Pneumologia
Azienda Ospedaliera "S. Croce e Carle"
Cuneo
I-12100
Italy
Fax: 39 171616724
E-mail: buccheri@culcasg.org

Keywords: Diagnosis
diagnostic delay
lung cancer
prognosis
symptoms

Received: October 10 2003
Accepted after revision: August 4 2004

In lung cancer, the most important factor for survival is the stage of disease at diagnosis [1], which, in turn, depends on how early the tumour is discovered. When a tumour is diagnosed as an incidental finding in an asymptomatic patient, survival is better than when the diagnosis is based on symptoms [2]. It has been suggested that screening for lung cancer would cause a reduction in disease-specific mortality [3], increasing the rate of diagnoses made at an early stage. Low-dose spiral computerised tomography (CT) of the chest is clearly capable of detecting asymptomatic, intrapulmonary cancer nodules [4–6], but it remains to be ascertained whether mass screening really improves the overall survival of the screened population [7].

While awaiting the demonstration of a favourable cost-benefit ratio from mass intervention policies, the alarm threshold of patients and the discernment of the family doctors remains the most important factor determining how early lung cancer is diagnosed. The majority of patients present with symptoms either referable to the primary tumour or to the intrathoracic spread of lung cancer and/or the patterns of metastatic dissemination [8]. Textbooks of cancer medicine describe in detail symptoms and signs of lung cancer; however, many refer to data collected in 1960–1980 [9]. Over the last two decades, there has been a progressive shift of lung cancer demographics, with an increase in the number of elderly patients, females and adenocarcinomas [10]. It is possible that the symptomatic pattern might have changed. Yet, a timely diagnosis remains critical to improve curability [3] and a minimal delay to specialist referral is the most important pre-requisite for an early diagnosis.

This retrospective study aimed to: 1) provide a more recent profile of the clinical manifestations of lung cancer; 2) evaluate possible time-related changes in the occurrence of symptoms; and 3) explore the possible relationship between symptoms and time to specialist referral. In addition, the study investigated which symptoms, if any, were linked to prognosis and whether they had an independent impact on survival of patients with lung cancer.

Materials and methods

Patients

From January 1989 to October 2002, 1,277 consecutive unselected patients (1,096 males and 181 females, median age 66 yrs (range 32–90)), with a cytologically or histologically proven lung cancer, were referred to the Unit of Respiratory Medicine of the "S. Croce and Carle" Cuneo City Hospitals, a Third Referral Institution for a community of 500,000 people in north-west Italy. The accrual was uniformly distributed across the ~14 yrs of study, with the median accrual date

being September 4, 1995. The pathological diagnosis of primary lung cancer was in accordance with the revised World Health Organization (WHO) classification of lung tumours [11] and included 496 squamous cell carcinomas, 293 adenocarcinomas, 144 small cell carcinomas, 82 large cell carcinomas and 262 unclassified anaplastic cancers (table 1). All patients were classified according to the 1997 staging system [12], either retrospectively [13] or prospectively. Pre-treatment clinical evaluation was based on clinical tests and examinations, and remained mostly unchanged during the study. It consisted of physical examination, assessment of present and past (6-months prior to diagnosis) body weight, and evaluation of performance status (Eastern Cooperative Oncology Group scale) [14]. Routine laboratory tests, including the measurement of two key tumour markers with prognostic significance, the carcinoembryonic antigen (CEA) [15] and the tissue polypeptide antigen (TPA) [16], were obtained in all patients. The diagnostic and staging evaluation comprised chest radiography, bronchoscopy and CT of the chest, upper abdomen and brain. In potentially resectable tumours, any radiological findings equivocal for mediastinal involvement were considered an indication for mediastinoscopy. Patients with dubious distant metastases were further investigated with other imaging studies or with targeted biopsies or needle aspiration. Based on these tests, surgery was appropriate for a minority of patients (18% of the cohort, 233 patients). In contrast, consistent with the early recognition of its potential benefits [17], chemotherapy was the most frequent treatment modality, either alone or in combination with thoracic irradiation (42% of the population, 541 patients). Radical radiotherapy was the only treatment in 5% (69 patients). The remaining patients received symptomatic or supportive care (34%, 434 patients). Details of the chemotherapy regimes used by the current group over the last two decades have been previously reported [13].

Survival was recorded from the time of the cyto-histological diagnosis to date of death or to the closure of the study (October 2002). The status of dead or alive at that date was verified by telephone contact with the patient, the family, the house doctor or the municipal office of the registry, and was available for all patients in the study. As per November 2002, 238 patients (19%) were still alive, after a median follow-up time (up to death or to the last follow-up contact) of 31 weeks (range 1–723).

Table 1. – Demographic and clinical characteristics of the study cohort

Characteristic	Subjects n	Median (range)	Frequency
Age yrs	1277	66 (32–90)	
Male sex y/n	1277		1096/181
Current smokers y/n	1277		993/284
Education E/ML/MH/H/U	1277		508/531/156/66/16
Previous lung diseases y/n	1277		517/760
Previous extra-pulmonary diseases y/n	1277		949/328
History of other cancers y/n	1277		137/1140
Referral delay[#]	1277	2 (0–48)	
Diagnostic period[¶]	1277		319/319/320/319
ECOG PS 0/1/2/3/4	1277		143/512/447/149/26
Weight loss[+]	1256	95 (59–125)	
Tumour cell type ES/S/A/L/U	1277		496/144/293/82/262
Serum blood tests			
Haemoglobin $g \cdot dL^{-1}$	1271	13.8 (6.6–20.0)	
White blood cells $n \cdot mm^{-3}$	1271	8550 (2890–36400)	
Platelets $n \cdot mm^{-3}$	1274	285000 (72000–982000)	
GOT $mg \cdot dL^{-1}$	1269	19 (5–550)	
GPT $mg \cdot dL^{-1}$	1267	19 (3–765)	
Lactate dehydrogenase $mg \cdot dL^{-1}$	1212	389 (81–10.120)	
Creatinine $mg \cdot dL^{-1}$	1269	0.9 (0.4–4.8)	
CEA $ng \cdot mL^{-1}$	1227	3 (0–7584)	
TPA $U \cdot L^{-1}$	1217	130 (10–5203)	
Stage of disease 0/1a/1b/2a/2b/3a/3b/4	1277		1/91/145/11/41/203/324/461
TNM staging factors			
T factor 0/1/2/3/4	1277		1/176/452/183/465
N factor 0/1/2/3	1277		480/120/446/231
M factor 0/1	1277		816/461
Lung metastases y/n	1277		184/1093
Brain metastases y/n	1277		140/1137
Liver metastases y/n	1277		118/1159
Renal/suprarenal gland metastases y/n	1277		100/1177
Bone metastases y/n	1277		120/1157
Primary treatment P/C/R/S	1277		434/541/69/233
Follow-up time weeks	1277	30.7 (1.3–722.6)	
Status alive/dead	1277		238/1039

y: yes; n: no; E: elementary; ML: middle-lower class; MH: middle-higher class; H: high school; U: university; ECOG PS: Eastern Cooperative Oncology Group performance status; ES: epidermoid or squamous cell cancer; S: small cell cancer; A: adenocarcinoma; L: large cell anaplastic cancer; U: unclassified or mixed cell type; GOT: glutamic oxalacetic transaminase; GPT: glutamic pyruvic transaminase; CEA: carcinoembryonic antigen; TPA: tissue polypeptide antigen; P: palliative and supportive care; C: chemotherapy; R: radio-chemotherapy; S: surgical resection. [#]: months from the first symptom of lung cancer (alarming symptom) to the specialist referral; [¶]: quartiles of the distribution of the dates of diagnosis (Period I: no. 319 (Jan. 1989–May 1992); Period II: no. 319 (Jun. 1992–Sep. 1995); Period III: no. 320 (Oct. 1995–May 1999); Period IV: no. 319 (Jun. 1999–Oct. 2002)); [+]: body weight at diagnosis in % of the usual weight.

Study design

This was a retrospective analysis of a large, prospectively built database of patients with lung cancer. As recently described [18], the database was first designed in the early 1980s and then repeatedly renovated with the precise scope of investigating multiple, potentially important variables. For the purpose of this study, 33 variables that were available throughout the period in question were considered (table 1). In addition, the study analysed the variable of "no symptom" at presentation (incidental lung cancer discovery) and 14 other variables describing seven symptoms or groups of symptoms, classified as either symptoms of alarm (*i.e.* the first symptom for which the patient sought the advice of his family doctor) or co-incidental (prevalence) symptoms (*i.e.* any tumour-related symptom present at the time of diagnosis). Symptoms caused by intrapulmonary tumour or intrathoracic/extrathoracic dissemination were grouped in a single category called symptoms of local or distant dissemination. It included hoarseness, dysphagia, stridor and the manifestations of superior vena cava obstruction, along with the signs and symptoms of abdominal, neurological and skeletal metastasis. A third, distinct cluster of symptoms was systemic symptoms, such as weakness, anorexia and fatigue. Cough, bloody sputum, dyspnoea, chest pain and infection comprised the first group and were treated separately, each as a single variable. The symptoms of local or distant dissemination were treated together as another single variable. The same applied to systemic symptoms, which were treated as an additional single variable. In addition to symptoms, the following parameters were analysed: age, sex, smoking habit, education, co-morbidity, history of second cancer, referral delay and the diagnostic period, described by the quartiles of the distribution of the dates of diagnosis. Referral delay was defined as the time interval between the occurrence of the first symptom of alarm (as reported by the patients and confirmed by their relatives) and the date of the first specialist referral (normally made to the study group). Additional variables of the study were performance status, weight loss (defined as per cent of usual weight), tumour cell type, haemoglobin, total white cell and platelet counts, clinical stage, T, N and M factors, and the sites of metastasis. Finally, lactate dehydrogenase (LDH), pyruvic and oxalacetic transaminases, creatinine, CEA and TPA were measured. Follow-up programmes were the same for all patients and remained substantially unchanged during the study period. They consisted of clinical, laboratory and radiological reassessments performed at 3–4 week intervals during chemotherapy or every 3–6 weeks with palliative radiotherapy, or best supportive care. Patients treated by surgery were scheduled for clinical examination at longer intervals, ranging 3–6 months.

Statistical analysis

Nonparametric methods [19] were used for descriptive purposes and to assess statistical relationships between symptoms and the other variables (*i.e.* the Spearman rank test, the Mann-Whitney U-test or the corrected Chi-squared text, as appropriate).

Survival time (as described by the two variables follow-up time and status) was the dependent variable. Survival functions were obtained using the Kaplan-Meier method [20] and graphically plotted in weeks. Differences among survivals were tested statistically using the log-rank test [21].

To control for the effect of potential confounders, a few multivariate analyses, based on the Cox′s proportional hazards regression model [22], were performed. The proportional hazards assumption was tested graphically. The exponent of the coefficient estimated from the regression model can be assumed as hazard ratio (HR) of dying during the follow-up period for subjects in the exposed category of each variable, compared with the reference category, and after having allowed for the other factors entered in the model. The standard error of log (HR) was used to calculate the 95% confidence intervals (CI) of log (HR), with limits exponentiated to give then 95% CI for the HR.

A p-value <0.05 was regarded as statistically significant. All tests were two-sided.

Results

Symptoms

Table 1 reports the number of observations and either the frequency or the median (and range) for each of the 33 non-symptom-related variables. Table 2 summarises the frequency of the absence of symptoms (*i.e.* an incidental discovery of a lung cancer) and the overall mix of presenting symptoms. These latter are also split into the four quartiles of the study period (table 2). The diagnosis of lung cancer was incidental in ~12% of the sample, with a statistically significant increase in the last quartiles. At presentation, patients experienced two or three symptoms on average; the most common being cough

Table 2. – Overall and time-related symptomatic patterns

Symptomatic pattern	All series n (%)	Diagnostic period# n				p-value¶
		I	II	III	IV	
Non-symptomatic patients (incidental diagnosis)	158 (12.4)	20	51	39	48	<0.01
Symptomatic patients	1119 (87.6)	299	268	281	271	
Patients with						
Cough	639 (50.0)	184	153	160	142	<0.01
Systemic symptoms	630 (49.3)	174	153	157	146	NS
Dyspnoea	433 (33.9)	111	96	106	120	NS
Chest pain	402 (31.5)	142	105	87	68	<0.001
Bloody sputum	381 (29.8)	101	102	84	94	NS
Symptoms of local or distant dissemination	298 (23.3)	65	77	76	80	NS
Chest infection	252 (19.7)	67	60	72	53	NS
Mean number of symptoms per patient	2.38	2.82	2.78	2.64	2.59	

NS: nonsignificant. #: quartiles of the distribution of the dates of diagnosis (Period I: no. 319 (Jan. 1989–May 1992); Period II: no. 319 (Jun. 1992–Sep. 1995); Period III: no. 320 (Oct. 1995–May 1999); Period IV: no. 319 (Jun. 1999–Oct. 2002)); ¶: Yates corrected Chi-squared test.

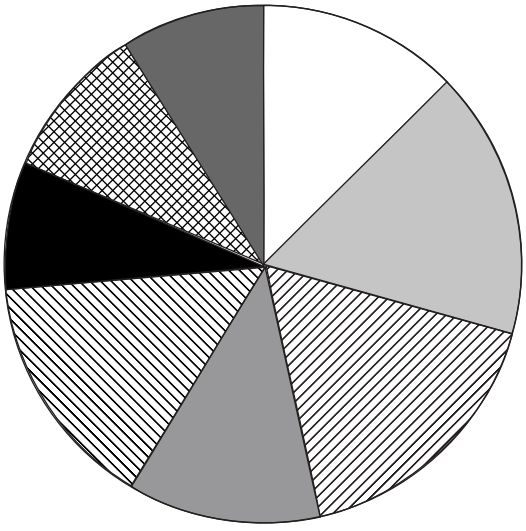

Fig. 1. – Frequency of no symptom (incidental discovery) and symptoms of alarm in 1,277 patients with lung cancer. □: no symptom (158/12%); ▫: cough (219/17%); ▨: bloody sputum (222/17%); ▪: dyspnoea (152/12%); ▧: chest pain (188/15%); ■: infection (102/8%); ■: systemic symptoms (122/10%); ■: metastatic symptoms (114/9%).

and systemic symptoms, followed by dyspnoea, chest pain and bloody sputum. Chest pain and cough were more common in the early years (table 2). Only chest pain changed in a consistent way, reducing in incidence during the study ($p<0.001$). Looking at the symptoms of alarm, bloody sputum and cough were the commonest (both present in ~17% of the sample), followed by chest pain and dyspnoea (respectively, in 15 and 12% of population). These data are shown graphically in figure 1.

Table 3 summarises the profile of the symptoms of alarm in the three main cell types, *i.e.* squamous, small cell and adenocarcinomas. The test of independence for a multi-way contingency table showed a statistically significant association between cell type and the symptomatic pattern ($p<0.001$). In particular, incidental diagnoses were more common in adenocarcinomas, while bloody sputum was more commonly reported with squamous cell lung cancers. Dyspnoea, chest pain and symptoms of mediastinal or distant dissemination were more frequent than expected in small cell carcinomas.

Table 3. – Alarming symptoms and tumour cell type[#]

Symptoms	Adenocarcinoma n (%)	Squamous cell n (%)	Small cell n (%)
No symptom (casual discovery)	57 (20.6)	40 (8.1)	14 (9.7)
Cough	51 (18.4)	95 (19.2)	19 (13.2)
Bloody sputum	37 (13.4)	119 (24.0)	15 (10.4)
Dyspnoea	32 (11.6)	52 (10.5)	28 (19.4)
Chest pain	38 (13.7)	53 (10.7)	28 (19.4)
Chest infection	14 (5.1)	55 (11.1)	9 (6.3)
Systemic symptoms	24 (8.7)	51 (10.3)	11 (7.6)
Symptoms of local or distant dissemination	24 (8.7)	31 (6.3)	20 (13.9)

[#]: test of independence for a multi-way contingency table: Chi-squared=89.862; p=0.000.

Referral delay

Multiple Spearman rank correlation tests and Mann-Whitney U-tests were performed, as appropriate, to explore the potential relationship between the delay in specialist referral and each of the other variables in the study. In summary, late referral was strongly associated with: presence of cough (Mann-Whitney U=147,955, $p<0.001$), systemic symptoms (Mann-Whitney U=133,294, $p<0.001$), poor performance status (Spearman Rho=0.116, $p<0.001$), increased weight loss (Spearman Rho=0.263, $p<0.001$), LDH (Spearman Rho=0.111, $p<0.001$), advanced stage of disease (Spearman Rho=0.119, $p<0.001$) and less effective therapy (*i.e.* palliative and chemotherapy treatments, Spearman Rho=0.110, $p<0.001$).

Disappointingly, a late referral became statistically more common in the later years of the study. The median delay in specialist referral was 1.47, 1.70, 1.91 and 2.39 months in 1st (the oldest), 2nd, 3rd and 4th quartiles of the dates of diagnosis (fig. 2). Figure 3 depicts the median referral delay of alarm symptoms. It shows that infections and bloody sputum were the only two symptoms capable of driving an earlier referral; however, systemic symptoms, cough and dyspnoea were the most neglected symptoms, being associated with a larger delay to referral.

Survival analyses

The absolute and relative impact on prognosis of referral delay and symptoms of alarm are summarised in tables 4 and 5 and in figure 4. Univariate analyses of survival (table 4) showed that a short time to referral (fig. 4), an incidental diagnosis, a diagnosis not prompted by dyspnoea, by chest pain and, above all, by systemic or metastatic symptoms were all associated with a better clinical outcome. Patients with lung cancer diagnosed because of the onset of a chest infection also had a favourable prognosis.

Tables 5 summarise the best multivariate models of survival obtained with the incorporation of the symptoms of alarm. In the first model, only alarm symptoms were considered: the model was significantly predictive of the

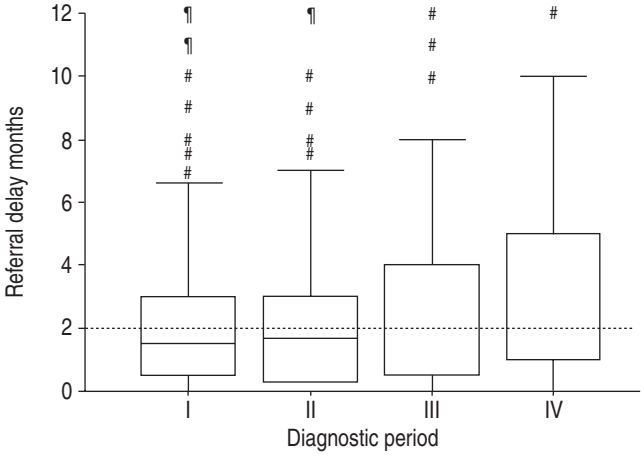

Fig. 2. – Box and whisker plot of the distribution of the referral delay (time between the first symptom and the first specialist evaluation), by diagnostic period (Period I: Jan. 1989–May 1992; Period II: Jun. 1992–Sep. 1995; Period III: Oct. 1995–May 1999; Period IV: Jun. 1999–Oct. 2002). -----: median referral delay for the whole group of patients; [#]: anomalous outliers; [¶]: extreme outliers.

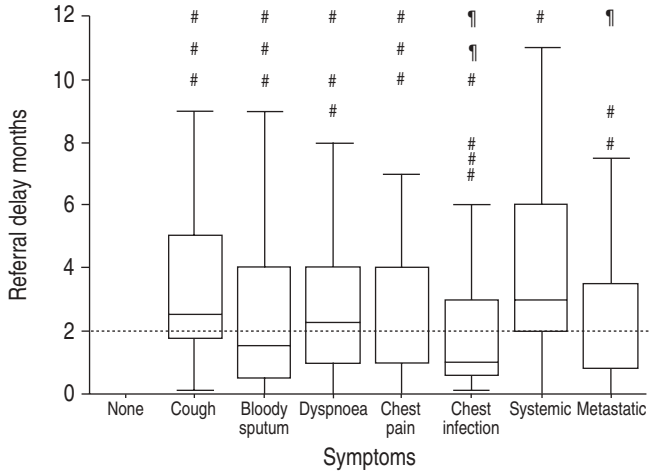

Fig. 3. – Box and whisker plot of the distribution of the referral delay (time between the first symptom and the first specialist evaluation), by alarm symptom (Period I: Jan 1989–May 1992; Period II: Jun 1992–Sep 1995; Period III: Oct 1995–May 1999; Period IV: Jun 1999–Oct 2002). -----: median referral delay for the whole group of patients; #: anomalous outliers; ¶: extreme outliers.

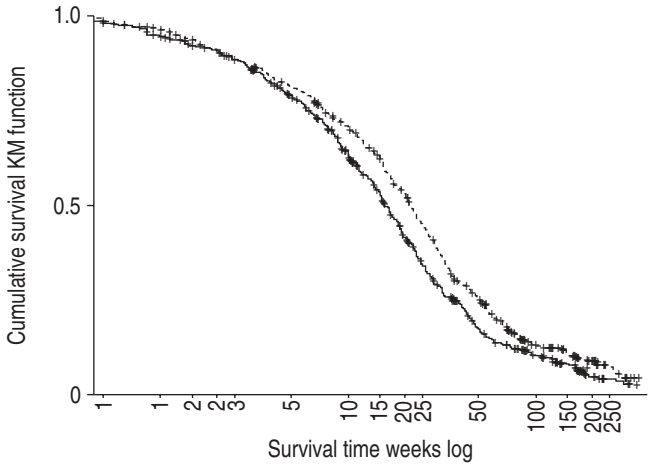

Fig. 4. – Kaplan-Meier (KM) estimate of survivals by referral delay (-----: ⩽2 months from the first symptom to the pathological diagnosis; ——: >2 months from the first symptom to the pathological diagnosis). The difference was statistically significant ($p<0.001$, log rank test; more statistics are available in table 4).

outcome (global Chi-squared=96.6, $p<0.001$) and included, in order of entry, the variable no symptom (HR=0.76, 95% CI 0.62–0.93) and the variables metastatic/systemic symptoms, chest pain and dyspnoea (all with HR between 2 and 1.5). In a second model, the variables performance status, weight loss and stage of disease were added to those already included in the first model and, still, three alarm symptoms (*i.e.* infection, cough and bloody sputum) emerged as significant co-factors. It is noteworthy that, in the first model, the variables systemic and metastatic symptoms acted as a surrogate of performance status and stage of disease. They were, in fact, excluded in the second model, in which the surrogated factors were made available.

Table 4. – Kaplan-Meier survival estimates for diagnostic delay and type of presentation

Variable	Categorisation	Survival# median (95% CI)	p-value¶
Referral delay+	⩾2	43.43 (37.83–49.02)	<0.01
	>2	31.86 (28.07–35.65)	
Alarm symptoms			
No symptom (casual discovery)	Yes	66.43 (51.96–80.90)	<0.001
	No	33.14 (30.03–36.25)	
Cough	Yes	38.86 (30.79–46.92)	<0.05
	No	35.86 (32.19–39.53)	
Bloody sputum	Yes	46.43 (34.47–58.39)	NS
	No	34.86 (31.58–38.14)	
Dyspnoea	Yes	26.71 (14.06–39.37)	<0.01
	No	37.57 (33.76–41.39)	
Chest pain	Yes	27.86 (21.43–34.28)	<0.01
	No	39.29 (35.48–43.09)	
Chest infection	Yes	49.71 (42.65–56.78)	<0.01
	No	35.14 (31.89–38.40)	
Systemic symptoms	Yes	17.86 (10.82–24.90)	<0.001
	No	38.86 (35.40–42.31)	
Symptoms of local or distant dissemination	Yes	24.14 (19.59–28.69)	<0.001
	No	38.86 (35.29–42.43)	

CI: confidence interval; NS: nonsignificant. #: weeks; ¶: log rank test; +: months from the first symptom of lung cancer (alarming symptom) to the specialist referral (fig. 4).

Finally, in the largest model containing both alarm symptoms and all the variables listed in table 1, two symptoms (*i.e.* chest infection and cough) retained an independent prognostic predictability.

Discussion

In 1989, the Interdisciplinary Group for Cancer Care Evaluation (GIVIO) described the clinical presentation, the referral pattern and the diagnostic delay of patients with primary lung cancer from 20 Italian hospitals [23]. It was reported that most patients (78%) had one or more symptom related to the tumour and in an additional 9% of the cases symptoms were related to the presence of distant metastases. The median diagnostic time from the first symptom to the final diagnosis was 50 days, with a significantly longer delay in patients first seen by their general practitioner compared with those who sought first care in hospital outpatient clinics [23]. After more than a decade, we are now reporting the results of a continuation study, started from, roughly, the same epoch and prolonged to the present time. An obvious difference is the multi-centre nature of the previous study, which pictured the average Italian situation, as compared to the single institution character of the current investigation, representing a specific region of the country (Piedmont, in the north-west of Italy).

There are a number of sources of delay in the referral process for a patient with lung cancer, and clinical guidelines have been developed to improve medical practice [24]. Sources of delay include the patient, the family doctor and the referral specialist [25–28]. In a recent Swedish study [25], 134 lung cancer patients were investigated prospectively. The median delay for the patients, *i.e.* from the first symptom(s) until the family doctor was contacted, was 21 days. From the first contact with the doctor until referral to the specialist the median time was 33 days. From the first visit to the specialist to diagnosis the median time was 9 days. The median time from first symptom(s) until treatment or the decision not to treat (the sum of all delays) was 189 days, *i.e.* ~6 months [25]. A large epidemiological survey from Poland [26], conducted on 20,561 lung cancer patients registered from 1995 to 1998, reported that the median delay caused by patients was ~46 days. The median delay caused by doctors (time between first

Table 5. – Cox's regression analysis[#]: summary of results

Variables explored	Valid subjects n	Overall Chi-squared	p-value	HR (95% CI)
Alarm symptoms only[¶]	1277	96.593	<0.001	
No symptom				0.763 (0.621–0.937)
Symptoms of local or distant dissemination				1.955 (1.573–2.431)
Systemic symptoms				1.787 (1.446–2.208)
Chest pain				1.532 (1.278–1.838)
Dyspnoea				1.539 (1.263–1.877)
Alarm symptoms and the main PF[+]	1256	436.137	<0.001	
ECOG PS				1.504 (1.390–1.628)
Stage of disease				1.309 (1.259–1.359)
Chest infection				0.586 (0.454–0.753)
Cough				0.718 (0.603–0.855)
WL				0.985 (0.975–0.995)
Bloody sputum				0.800 (0.673–0.950)
Alarm symptoms and any other potential PF[ƒ]				
All the alarm symptoms and 31 other pretreatment variables	1147	672.609	<0.001	

HR: hazard ratio; CI: confidence interval; PF: prognostic factors; ECOG PS: Eastern Cooperative Oncology Group performance status; WL: weight loss (% of usual body weight). [#]: stepwise forward regression (likelihood ratio); [¶]: No symptom, local invasion symptoms, systemic symptoms, chest pain, dyspnoea; [+]: ECOG PS, stage, chest infection, cough, WL, bloody sputum; [ƒ]: ECOG PS, stage, tissue polypeptide antigen, primary treatment, white blood cell count, lactate dehydrogenase, WL, chest infection, smoking habit, liver metastasis, N factor, cough, age, T factor, brain metastasis, small cell type, glutamic oxalacetic transaminase.

visit to the doctor and the date of diagnosis) was 65 days and the median time between diagnosis and therapy was an additional period of 30 days. Delays were significantly different from region to region [26]. A retrospective audit of the time involved in the management of patients with lung cancer referred for consideration of surgery at the Royal Brompton Hospital in London has been previously carried out on 194 patients [27]. The median interval between the onset of symptoms and their first chest radiograph was 39 days, and between the onset of symptoms and referral to a surgeon by a chest physician was 112 days. In conclusion, the 2-month delay between the onset of the first symptom and the first referral to a lung cancer specialist (a time course that includes both patient and family doctor delay) is somewhat longer than the average national delay [23] (whose figure of 50 days also included the specialist delay) and roughly on line [25] or somewhat better [26] than reported internationally.

The recently observed increase in the time from the first symptom to the first specialist visit is a truly harmful signal, if one considers the global efforts that are directed to its reduction and the critical importance of early diagnoses [4–6]. Various reasons may be suggested to explain this phenomenon, the main being the changing demographics of lung cancer, which is now increasingly more common in elderly patients, who are prone to significant co-morbidity [29]. Early symptoms of lung cancer are never specific, even in otherwise healthy individuals, but they may be incredibly difficult to identify in the present of concomitant illness. Another possible explanation is more technical and related to issues of the health system organisation in Italy. Recently, our family doctors have been given the option of asking directly for a CT scan in cases with doubtful shadows on plain chest radiography. The additional time for the preliminary CT passage was previously absent and might explain the observed increase in the referral times. Indeed, waiting lists are significantly longer for clinical investigations requested by general practitioners than by specialists, at least in our country. For this reason, we sincerely believe that our family doctors would help their patients more by referring them directly to the respiratory physician if lung cancer is a possibility.

There are other findings of interest in the current investigation. An incidental diagnosis of lung cancer was made in some 10% of the patients and was associated with a significantly better survival. This percentage seems to increase progressively over the 14-yrs of the study, while the general Italian population continued the trend of aging. The elderly boost the number of contacts with the health service, making the discovery of asymptomatic illnesses more likely. Such a phenomenon might have occurred in our geographic area, explaining the observed increase of incidental diagnosis. Unsurprisingly, a casual diagnosis of lung cancer led to a non-symptomatic disease, in an early stage of development, and was followed by a longer survival. This occurs in any disease and in any screening programme, as lead time is increased when a person is diagnosed by chance [7]. The commonest symptoms alerting the patients and/or the doctors were bloody sputum and cough, found as the first symptom of disease in >30% of the patients. This percentage did not change across the period of study. However, while bloody sputum was associated to a prompt referral to the specialist, cough was neglected for a long while. Nevertheless, both symptoms, when the diagnostic process was provoked by their onset, were linked to a better prognosis. Unfortunately, another 20% of patients will present with systemic or metastatic symptoms, and for them the disease is already advanced at the time of its first manifestation. Finally, the prognostic significance of clinical manifestations of lung cancer are worthy of a mention. Symptoms are important predictors of survival and remain such, even when other more robust prognostic factors are considered in multivariate analysis. In our study, seeking medical advice for an unexplained cough or for a respiratory infection was sign of a better ultimate outcome, independent of all the other prognostic factors [30].

In conclusion, lung cancer mortality has not changed significantly in decades [31]. In spite of the scepticism [7], early detection might improve such a dismal record [32]. A simple and cost-effective way to improve the current low early detection rate is to alert the public and the front-line doctors of the multiple clinical manifestations of the disease.

Acknowledgements. The authors would like to thank the Cuneo Lung Cancer Study Group (CuLCaSG) for technical and financial support.

References

1. Vansteenkiste J, Buccheri G, Carney DN, *et al.* Prognostic factors in nonsmall cell lung cancer. *Eur Resp J* 2002; 12: 156–171.
2. American Thoracic Society and European Respiratory Society. Pretreatment evaluation of non-small-cell lung cancer. *Am J Respir Crit Care Med* 1998; 156: 320–332.
3. Strauss GM, Gleason RE, Sugarbaker DJ. Screening for lung cancer - another look; a different view. *Chest* 1997; 111: 754–768.
4. Sone S, Takashima S, Li F, *et al.* Mass screening for lung cancer with mobile spiral computed tomography scanner. *Lancet* 1998; 351: 1242–1245.
5. Henschke CI, McCauley DI, Yankelevitz DF, *et al.* Early Lung Cancer Action Project: overall design and findings from baseline screening. *Lancet* 1999; 354: 99–105.
6. Kaneko M, Kusumoto M, Kobayashi T, *et al.* Computed tomography screening for lung carcinoma in Japan. *Cancer* 2000; 89: 2485–2488.
7. Patz EF Jr, Goodman PC, Bepler G. Screening for lung cancer. *N Engl J Med* 2000; 343: 1627–1633.
8. Beckles MA, Spiro SG, Colice GL, Rudd RM. Initial evaluation of the patient with lung cancer: symptoms, signs, laboratory tests, and paraneoplastic syndromes. *Chest* 2003; 123: 97S–104S.
9. Minna JD, Higgins GA, Glatstein EJ. Cancer of the lung. *In*: De Vita Jr VT, Hellman S, Rosemberg SA, eds. Cancer. Principles and Practice of Oncology, 2nd Ed. Philadelphia, J.B. Lippincott Co., 1985; pp. 507–597.
10. Franceschi S, Bidoli E. The epidemiology of lung cancer. *Ann Oncol* 1999; 10: Suppl. 5, S3–S6.
11. World Health Organization. International histological classification of tumours. Berlin, Springer-Verlag, 1991.
12. Mountain CF. Revisions in the International System for Staging Lung Cancer. *Chest* 1997; 111: 1710–1717.
13. Buccheri G, Ferrigno D. Prognostic value of stage grouping and TNM descriptors in lung cancer. *Chest* 2000; 117: 1247–1255.
14. Zubrod CG, Scheiderman MA, Frei E, *et al.* Appraisal of methods for the study of chemotherapy in man: comparative therapeutic trial of nitrogen mustard and triethylene thiophosphoramide. *J Chron Dis* 1960; 11: 7–33.
15. Buccheri GF, Violante B, Sartoris AM, Ferrigno D, Curcio A, Vola F. Clinical value of a multiple biomarker assay in patients with bronchogenic carcinoma. *Cancer* 1986; 57: 2389–2396.
16. Buccheri GF, Ferrigno D, Sartoris AM, Violante B, Vola F, Curcio A. Tumour markers in bronchogenic carcinoma. Superiority of tissue polypeptide antigen to carcinoembryonic antigen and carbohydrate antigenic determinant 19–9. *Cancer* 1987; 60: 42–50.
17. Buccheri G. Chemotherapy and survival in non-small cell lung cancer. The old "vexata question". *Chest* 1991; 99: 1328–1329.
18. Buccheri G, Ferrigno D. Lung tumour markers in oncology practice: a study of TPA and CA125. *Br J Cancer* 2002; 87: 1112–1118.
19. Siegel S. Nonparametric statistics for the behavioural sciences. New York, MacGraw Hill, 1956.
20. Kaplan EL, Meier F. Non-parametric estimation from incomplete observations. *J Am Stat Assoc* 1958; 58: 457–481.
21. Peto R, Pike MC, Armitage P. Design and analysis of randomized clinical trials requiring prolonged observation of each patient: II analysis and examples. *Br J Cancer* 1977; 35: 1–39.
22. Cox DR. Regression models and life tables. *J R Stat Soc* 1972; 34: 187–220.
23. Diagnosis and first-line treatment of patients with lung cancer in Italian general hospitals. G.I.V.I.O. (Interdisciplinary Group for Cancer Evaluation). *Tumori* 1989; 75: 163–167.
24. BTS recommendations to respiratory physicians for organising the care of patients with lung cancer - introduction. *Thorax* 1998; 53: Suppl. 1, S1–S8.
25. Koyi H, Hillerdal G, Branden E. Patient′s and doctors′ delays in the diagnosis of chest tumours. *Lung Cancer* 2002; 35: 53–57.
26. Radzikowska E, Roszkowski K, Glaz P. Rak pluca. Opoznienia w procesie diagnostyczno-leczniczym [Lung cancer-diagnosis and therapy delay]. *Pneumonol Alergol Pol* 2001; 69: 600–610.
27. Lee J, Marchbank A, Goldstraw P. Implementation of the British Thoracic Society recommendations for organising the care of patients with lung cancer: the surgeon′s perspective. *Ann R Coll Surg Engl* 2002; 84: 304–308.
28. Aragoneses FG, Moreno N, Leon P, Fontan EG, Folque E. Influence of delays on survival in the surgical treatment of bronchogenic carcinoma. *Lung Cancer* 2002; 36: 59–63.
29. Jemal A, Chu KC, Tarone RE. Recent trends in lung cancer mortality in the United States. *J Natl Cancer Inst* 2001; 93: 277–283.
30. Buccheri G, Ferrigno D. Prognostic factors in lung cancer: tables and comments. *Eur Respir J* 1994; 7: 1350–1364.
31. Janssen-Heijnen ML, Coebergh JW. Trends in incidence and prognosis of the histological subtypes of lung cancer in North America, Australia, New Zealand and Europe. *Lung Cancer* 2001; 31: 123–137.
32. McCarthy PM, Jelsing NC. An advocacy perspective on screening and early diagnosis of lung cancer. *Cancer* 2000; 89: 2510–2514.