



Clinical profile that facilitates the suspicion of lung cancer for a timely diagnosis

Perfil clínico que facilita la sospecha de cáncer de pulmón para un diagnóstico oportuno

Renata Báez-Saldaña,^{*,†} Alberto Vargas-Rojas,^{*,†} D. Yair Chavarría-Castro,^{*,†} Uriel Rumbo-Nava,^{*} Belinda Contreras-Garza,^{*,†} Paulina Guinto-Ramírez,^{*,†} Óscar Arrieta[§]

^{*}Instituto Nacional de Enfermedades Respiratorias Ismael Cosío Villegas. Mexico City, Mexico; [†]Facultad de Medicina, Universidad Nacional Autónoma de México. Mexico City, Mexico; [§]Instituto Nacional de Cancerología. Mexico City, Mexico.

ABSTRACT. Introduction: lung cancer (LC) is usually diagnosed late. Understanding how patients present at the time of their diagnosis it is useful for early identification of the disease. **Objective:** to identify the clinical profile of patients with lung cancer, allowing to suspect the diagnosis and to propose an algorithm for early referral. **Material and methods:** prospective case series of lung cancer. The general characteristics, smoking, exposure to wood smoke, time from symptom onset to diagnosis and the type and frequency of symptoms were studied and their association with pleural effusion was analyzed. **Results:** the median age was 65 years, 55% were men. History of smoking 50.2%, exposure to wood smoke 43.9%. The median time from symptom onset to diagnosis was 120 days and in 94% it was more than 3 weeks. The most frequent symptoms were cough 88%, cough for 3 weeks or more 94.6%, dyspnea 75.2%, chest pain 50%, weight loss 70%, and hemoptysis 22%. Malignant pleural effusion 44.9%. Dyspnea, chest pain and oxygen saturation < 88% simultaneously were associated with pleural effusion OR (95% CI) 7.54 (3.28-17.34). **Conclusions:** adult patients who report cough for 3 weeks or more and/or any of the following symptoms: dyspnea, chest pain, weight loss, hemoptysis, or fatigue that are not explained by established diagnosis, should be evaluated by chest x-ray for early referral to a specialized unit.

Keywords: lung cancer, symptoms, diagnosis, pleural effusion, early diagnosis lung cancer.

RESUMEN. Introducción: el cáncer de pulmón (CP) por lo general se diagnostica tardíamente. El entendimiento de cómo se presentan los pacientes al momento de su diagnóstico es útil para la identificación temprana de la enfermedad. **Objetivo:** identificar el perfil clínico de pacientes con cáncer de pulmón que permita sospechar el diagnóstico y proponer un algoritmo para su referencia temprana. **Material y métodos:** serie de casos prospectiva de cáncer de pulmón. Se estudiaron las características generales, tabaquismo, exposición a humo de leña, tiempo desde el inicio de síntomas al diagnóstico, y el tipo y frecuencia de los síntomas y se analizó su asociación con derrame pleural. **Resultados:** la mediana de la edad fue 65 años, 55% fueron hombres. Antecedente de tabaquismo 50.2%, exposición a humo de leña 43.9%. La mediana del tiempo desde el inicio de síntomas al diagnóstico fue de 120 días y en 94% éste fue de más de tres semanas. Los síntomas más frecuentes fueron tos 88%, tos por tres semanas o más 94.6%, disnea 75.2%, dolor torácico 50%, pérdida de peso 70%, hemoptisis 22%, derrame pleural neoplásico 44.9%. La presencia simultánea de disnea, dolor torácico y saturación de oxígeno < 88% se asociaron a derrame pleural OR (IC 95%) 7.54 (3.28-17.34). **Conclusiones:** en pacientes adultos que refieran tos por tres semanas o más y/o cualquiera de los siguientes síntomas: disnea, dolor torácico, pérdida de peso, hemoptisis o fatiga que no se expliquen con base en un diagnóstico deberán evaluarse mediante una radiografía de tórax para su referencia temprana a una unidad especializada.

Palabras clave: cáncer de pulmón, síntomas, diagnóstico, derrame pleural, diagnóstico temprano del cáncer de pulmón.

Correspondence:

Renata Báez-Saldaña, MD

Instituto Nacional de Enfermedades Respiratorias Ismael Cosío Villegas.

Mexico City, Mexico.

E-mail: baezrd@unam.mx

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INTRODUCTION

Lung cancer in Mexico is one of the 10 leading causes of cancer incidence and mortality. Its age-standardized incidence and mortality rates are similar, 5.3 and 4.9 per 100,000 inhabitants.¹ This similarity is attributed to the fact that in the context of the natural history of lung cancer, it is usually diagnosed late, which is associated with a very low survival rate.² The low yield for early diagnosis is due on the one hand to the peculiarities of the lung anatomy such as the absence of nerve terminals for pain, thus, a malignant

lesion can grow and even metastasize outside the thorax before it causes symptoms. Another large part of the delay in diagnosis is attributed to both the patient and the physician. In the United Kingdom patients took a median of 12 months between the onset of symptoms and the first visit to the general practitioner.³ In another study of Swedish patients the average was 43 days with a maximum minimum interval of zero to 256 days⁴ and even when the patient presents to the general practitioner with symptoms suggestive of lung cancer, the latter may not consider the diagnosis because the symptoms are nonspecific and in general practice it is an infrequent pathology. Lung cancer can present with a wide range of symptoms, the most common being cough, dyspnea, chest pain, weight loss, dysphonia, anorexia and fatigue among others.^{5,6} And it has been termed a silent disease, as it lacks unique core symptoms or signs that can function as early indicators, hemoptysis can be considered an exception, as it is strongly associated with lung cancer, although it is quite rare as a silent first symptom.⁷

Chest X-ray is the first laboratory study that should be performed in patients with respiratory symptoms that could be due to lung cancer; ideally, it should be performed within 14 days to favor timely diagnosis;⁸ however, this was achieved in 35% of patients with suspected lung cancer according to the results of a recent study carried out in England, which also showed that the time between the first visit with the general practitioner and the performance of the chest X-ray was 49 days, with an interquartile range of five to 172 days.⁹ The delay in diagnosis could be reduced by screening asymptomatic subjects with risk factors and by better identification of the symptomatic patient who already has the disease. Although screening reduces the mortality incidence rate (IRR) between 0.85 [95% CI, 0.75-0.96] and 0.75 [95% CI, 0.61-0.90]¹⁰ in Mexico there is no active public screening program for lung cancer. In the present study we are going to refer to the clinical diagnosis of lung cancer in the symptomatic patient, because the information available to support the first contact physician in distinguishing between patients who may have lung cancer from those who have nonspecific symptoms associated with a benign respiratory disease is scarce. The relative importance of the clinical features of these cases has not been previously described in our population. Understanding how patients with lung cancer present at the time of diagnosis will be useful for early referral to a specialist, as well as for timely diagnosis of the disease. Our objective was to identify the symptom-based clinical profile of patients with lung cancer, which allows us to suspect the diagnosis and propose an algorithm for early referral.

MATERIAL AND METHODS

The study was approved by the institutional research and research ethics committees. The design is a prospective

case series that was developed from 2013 to 2019 in a referral hospital for respiratory diseases in Mexico City. Incident cases of any type of lung cancer confirmed by histopathological study were included. Incident cases of any type of lung cancer confirmed by histopathological study were included. Lung cancer was defined as primary cancer of any histological type derived from the lung, trachea or bronchi. In all cases, frontal chest X-ray, computed tomography of the chest and skull and bone scintigraphy were performed. Imaging studies such as PET-CT or cranial MRI were performed in selected cases according to the individual case. The biopsy procedures performed to reach the histopathologic diagnosis varied according to the most appropriate individual case. Among the most frequent procedures were fibrobronchoscopy, closed pleural biopsy and tomography-guided biopsy. Procedures such as thoracoscopy, thoracotomy or mediastinoscopy were performed when diagnosis was not obtained by the first mentioned methods. All patients received oncological and pneumological treatment according to the clinical stage and histological type.

Sampling was by convenience, and cases were included consecutively as they met the inclusion criteria.

Using a standardized format for the study, the general characteristics of the patients (age, sex, schooling, place of birth, place of residence), history of lung cancer in first-degree relatives, comorbidities, history of exposure to smoking, exposure to asbestos at work and in the home were collected. Smoking history included previous and current smoking and passive smoking. Symptoms, time of current illness, cough for more than three weeks, pleural effusion, number of physicians the patient visited before referral or arrival at the hospital, histological type of lung cancer, functional status according to the Eastern Cooperative Oncology Group (ECOG) and Karnofsky scale, clinical stage of disease according to the eighth TNM classification for lung cancer, and serum carcinoembryonic antigen levels in those cases where this variable was available were recorded.

Finally, a diagnostic and referral algorithm was proposed for patients with suspected lung cancer, based on symptoms and frontal chest X-ray findings.

Statistical analysis

Statistical analysis was performed using the STATA statistical package, version 17 (StataCorp LP, College Station, TX, USA).

Descriptive statistics were performed on the clinical characteristics of the sample studied, using median and interquartile range 25-75 (IQI) for the continuous scale variables, and nominal variables were summarized as frequency and percentage. Bivariate logistic regression

was used to analyze the association between the type of symptom by admission service (emergency versus outpatient) and by the presence or absence of pleural effusion. A significant p value < 0.05 was considered significant.

RESULTS

A total of 508 cases were studied, whose median (IIC) age was 65 (55-73) years, 280 (55.1%) were men, 179 (35.2%) cases reported a history of any type of cancer in a direct relative and 37 (7.28%) lung cancer.

The frequency of exposure history was as follows: active or past smoking 255 (50.2%) cases, with a median (IIC) smoking index of 20 (five to 47) pack-years; wood smoke 223 (43.9%) cases with a median (IIC) wood smoke exposure index of 99 (36-192) hours per year; exposure to asbestos in the home 129 (25.4%) cases.

Regarding comorbidities, 255 (50.2%) cases of the sample presented some comorbidity, of which the most frequent were arterial hypertension with 156 (30.7%) cases and diabetes with 94 (18.5%) cases (Table 1).

The median (interquartile range IQI) time from symptom onset to diagnosis was 120 (60-210) days, 30% of the cases reported a duration of current illness between 30 and 60 days and 459/488 (94.06%) cases reported a duration of

Table 1: Clinical characteristics of 508 patients with lung cancer.

Variables	n (%)
Age*	65 (55-73)
Male	280 (55.1)
Female	228 (44.9)
History of cancer in a family member	179 (35.2)
History of lung cancer in a relative	37 (7.28)
Smoking	255 (50.2)
Smoking rate†	20 (5-47)
Smoking rate > 30	108 (42.4)
Passive smoking	72 (14.2)
Wood smoke	223 (43.9)
Wood smoke index	99 (36-192)
Exposure to asbestos in the home	129 (25.4)
Any comorbidity	255 (50.2)
Arterial hypertension	156 (30.7)
Diabetes	94 (18.5)
Obesity	77 (15.2)
Overweight	117 (23.0)
COPD	42 (8.27)
Heart disease	35 (6.9)
Malnutrition	24 (4.7)
Other*	19 (3.74)

* Median (interquartile range 25-75).

Table 2: Signs and symptoms of lung cancer patients.

Symptoms and signs, n = 508	Total n (%)
Time from symptom onset to diagnosis (days)*	120 (60-210)
Time from symptom onset to diagnosis > 3 weeks	459/488 (94.06)
Number of physicians before diagnosis* (n = 339)	2 (1-3)
Cough	448 (88.2)
Cough > 3 weeks	406/429 (94.6)
Expectoration	323 (63.6)
Dyspnea	382 (75.2)
Hemoptysis	113 (22.2)
Chest pain	254 (50.0)
Fatigue	100 (19.7)
Weight loss	357 (70.3)
Kilograms of weight lost*	7 (5-11)
Anorexia	45 (8.9)
Fever	78 (15.4)
Chills	22 (4.3)
Dysphonia	27 (5.3)
Dysphagia	21 (4.1)
Nausea	13 (2.6)
SpO ₂ < 88%	168 (33.0)
Pleural effusion	228 (44.9)

* Median (interquartile range 25-75).

current illness > 3 weeks. The most frequent symptom was cough with 448 (88%) cases, with a median (IIC) cough duration of 120 (60-216) days, followed by dyspnea 382 (75.2%) cases and weight loss 357 (70.3%). Pleural effusion was observed in 228 (44.9%) cases (Table 2).

Regarding clinical laboratory findings, the frequency of leukocytosis, lymphopenia, neutrophilia, anemia and hypoalbuminemia were variable, ranging from 16.8 to 18.8% for thrombocytosis and lymphopenia, respectively, to 37% for hypoalbuminemia. Carcinoembryonic antigen was elevated in 176/190 (60.7%) cases.

Adenocarcinoma represented 76% of the total histological types of lung cancer, followed by squamous cell carcinoma with 11% and small cell carcinoma in 9.7% of the cases. The most frequent stages at diagnosis were III and IV, with 494 (97.2%) cases. The most frequent extrathoracic metastases were to bone with 117 (23%) cases and to the central nervous system with 55 (10.8%) cases. The functional

status measured by the Eastern Cooperative Oncology Group (ECOG) scale, 153/360 (42.5%) cases were in the 0 and 1 classification, and with the Karnofsky scale the score between 70 and 80 was the most frequent with 168 (47%) cases. Median (IIC) survival was 117 (28-299) days.

The symptoms and signs that were associated with a patient's arrival to the emergency department were: dyspnea, fever, pleural effusion and an oxygen saturation < 88%. The remaining symptoms both respiratory and constitutional showed no association [Table 3](#).

Dyspnea, chest pain and oxygen saturation < 88% were analyzed together, because they were the symptoms that presented the strongest association with pleural effusion when performing the bivariate analysis, and a positive trend was demonstrated when having one to three symptoms, for the latter the association was OR (95% CI) 7.54 (3.28-17.34) ([Table 4](#)).

The algorithm proposed for the diagnosis and referral of patients with suspected lung cancer was based on symptoms and frontal chest X-ray findings ([Figure 1](#)).

DISCUSSION

The present study demonstrated the clinical profile of patients who arrived at the hospital with lung cancer at the time of diagnosis. Of these, 96% showed respiratory symptoms for more than three weeks without an explanatory diagnosis. Half of the cases had exposure to smoking and 43.9% to wood smoke. The main symptoms with a frequency greater than or equal to 50% in decreasing order were cough, dyspnea, weight loss and chest pain,

similar to what has been reported in other studies;^{5,6} 60% had elevated carcinoembryonic antigen biomarker. Of the patients, 57.3% were admitted to the emergency department for dyspnea and fever associated with oxygen saturation < 88% and pleural effusion, the latter present at a high frequency in 44.9% of cases. Therefore, we evaluated the symptoms associated with pleural effusion, which were dyspnea, chest pain and oxygen saturation < 88%. When the three variables were presented simultaneously, a positive association OR (95% CI) 7.54 (3.28-17.34) was observed. Cough is the most frequent symptom of lung cancer and the results of the present study confirm this. According to a meta-analysis on the value of symptoms for the diagnosis of lung cancer, those with the highest value measured by diagnostic odds ratio (OR) were hemoptysis 6.39 (3.32-12.28), followed by dyspnea 2.73 (1.54-4.85), cough 2.64 (1.24-5.64) and chest pain 2.02 (0.88-4.60).¹¹ Hemoptysis is the only symptom that has demonstrated association with lung cancer and the one with the highest predictive value compared to other respiratory symptoms.¹² However, this occurs in only 21.6% of cases,¹³ whose frequency was similar in our study 22.2% and which compared to cough, dyspnea and chest pain is quite minor, so its absence does not rule out at all the possibility of lung cancer in the patient with other respiratory symptoms.

Most of these patients first consult a general practitioner or an internist for one or more of these symptoms. In the first level of care or in a general practice, cough is very frequent, and given the unspecificity of this symptom, on most occasions the diagnosis of lung cancer, or at least suspecting it, is a challenge for the physician, since

Table 3: Association between selected clinical variables and the clinical department through which the cases initially arrived at the institution.

Symptoms	Emergencies N = 291 n (%)	Outpatient consultation N = 217 n (%)	OR (95% CI)	p
Cough	254 (87.3)	194 (89.4)	0.81 (0.47-1.41)	0.465
Dyspnea	233 (80.1)	149 (68.7)	1.83 (1.22-2.75)	0.003
Hemoptysis	67 (23.0)	46 (21.2)	1.11 (0.73-1.70)	0.625
Chest pain	150 (51.6)	104 (47.9)	1.11 (0.73-1.70)	0.420
Fever	54 (18.6)	24 (11.0)	1.83 (1.1-3.00)	0.022
Fatigue	56 (19.2)	44 (20.3)	0.94 (0.6-1.46)	0.772
Weight loss	197 (67.7)	160 (73.7)	0.75 (0.50-1.1)	0.142
Dysphonia	14 (4.8)	13 (6.0)	0.79 (0.36-1.72)	0.558
Dysphagia	13 (4.5)	8 (3.7)	1.22 (0.50-3)	0.662
Vena cava syndrome	3 (1.03)	1 (0.46)	2.25 (0.23-21.78)	0.484
Pleural effusion	163 (56.0)	65 (30.0)	2.98 (2.05-4.32)	0.000
Oxygen saturation < 88%	115 (39.5)	53 (24.4)	2.02 (1.37-2.98)	0.000

Table 4: Symptoms associated with pleural effusion in patients with lung cancer.

Symptoms	With pleural effusion N = 228 n (%)	Without pleural effusion N= 280 n (%)	OR (95% CI)	p
Cough	200 (87.7)	248 (88.6)	0.92 (0.54-1.58)	0.767
Dyspnea	192 (84.2)	190 (67.9)	2.53 (1.63-3.90)	0.000
Hemoptysis	37 (16.2)	76 (27.1)	0.52 (0.33-0.81)	0.004
Chest pain	135 (59.2)	119 (42.5)	1.96 (1.38-2.80)	0.000
Fever	37 (16.2)	41 (14.6)	1.13 (0.70-1.83)	0.622
Fatigue	54 (23.7)	46 (16.4)	1.58 (1.01-2.4)	0.042
Weight loss	162 (71)	195 (69.6)	1.07 (0.73-1.57)	0.730
Dysphonia	15 (6.6)	12 (4.3)	1.57 (0.72-3.43)	0.255
Dysphagia	8 (3.51)	13 (4.6)	0.75 (0.30-1.83)	0.524
Oxygen saturation < 88%	88 (38.6)	80 (28.6)	1.57 (1.08-2.28)	0.017
Dyspnea, chest pain and oxygen saturation < 88% combined				
None of the 3	13 (5.7)	36 (12.9)	Referencia	
At least 1 of the 3	64 (28.1)	117 (41.8)	1.5 (0.75-3.06)	0.247
At least 2 of the 3	102 (47.7)	109 (38.9)	2.59 (1.30-5.16)	0.007
3 of the 3	49 (21.5)	18 (6.4)	7.54 (3.28-17.34)	0.000

in general practice only 0.2% of patients presenting with cough for more than three weeks have lung cancer.¹⁴ In the United Kingdom the time between first consultation and referral for lung cancer is a median of 14 days, with longer intervals of between 60 and 90 days documented in 17.9% of cases.¹⁵ In our study, the median time between the onset of symptoms and referral to our institution was 120 days, which we consider to be a very long time, which could partly explain why 97% of the cases arrived at an advanced stage of the disease, again highlighting the priority of recognizing symptoms for faster referral, as there is evidence to suggest that when patients have faster access to the study, their survival is better.¹⁶ Also, there is evidence that several consultations prior to diagnosis occur during this time interval.¹⁷ Specifically, one-third of patients diagnosed with lung cancer have received medical attention by a general practitioner for symptoms attributable to cancer three or more times prior to diagnosis.¹⁸ We did not measure the number of times they consulted a physician, but the number of physicians the patient consulted prior to referral to the institute, the median was two physicians with a minimum-maximum range of zero to 10 physicians.

Early detection programs that include social marketing interventions may increase the likelihood that patients will see a primary care physician when they first present with symptoms, who in turn increases the level of suspicion that leads to a chest x-ray and an increase in diagnosis rates by referral of these cases.¹⁹ However, there is concern about overburdening the health system due to the evaluation of patients with symptoms not due to lung cancer.²⁰ Therefore, it is suggested that programs could preferentially target those at high risk of lung cancer such as people with a

history of smoking, and in the case of Mexico also those with a history of exposure to wood smoke and occupational exposure. It is important to note that in the cases included in this study, smoking was reported in 50.2% of the cases, so that in Mexico the possibility of lung cancer must be considered whether or not this risk factor is present. In general, one out of every seven cases of lung cancer occurs in people who have never smoked.²¹ In our population this proportion was higher, almost one to one, 49.8% are non-smokers; however, the population has other types of exposures that are risk factors for lung cancer and that must be considered, such as exposure to wood smoke, which was present in 43.9%, and although it is considered a probable carcinogen,²² it is associated with high rates of lung cancer.²³

The route of entry of patients to the referral center, whether by scheduled consultation or emergency department, suggests the severity of the disease and the difficulty patients have in being referred from the onset of their symptoms. One third of lung cancer cases are diagnosed in the emergency room;²⁴ in the setting of our cases, 57.28% of them presented to the emergency department where the approach was initiated, this constitutes a much higher frequency than that referred elsewhere and reflects once again the delay in diagnosis, which contributes to cases arriving at such advanced stages of the disease. Of the cases admitted to the emergency department, 56% had pleural effusion, which in a patient with lung cancer classifies it as an advanced stage.

Unlike tissue biomarkers in lung cancer, serum biomarkers are not widely used; in fact, diagnostic and treatment guidelines for lung cancer do not recommend them, giving priority to respiratory and constitutional

symptoms and signs as the initial criteria for requesting a chest X-ray and referral within a period of no more than two weeks.^{8,25}

Of the multiple biomarkers for lung cancer, one of the most studied and the one we have available at our institution is carcinoembryonic antigen (CEA), which we use as a diagnostic support to evaluate response to treatment and prognosis. In our population, we documented that 60% had elevated this biomarker, so it could be useful to guide the diagnosis and referral for suspected lung cancer when a patient presents with respiratory symptoms without a diagnosis that explains it.

Strengths and limitations

The results are valid, as they were derived from a prospective design with a large n. The clinical profile we describe includes symptoms that occurred with a frequency of 50% or more, except for hemoptysis, which had a frequency of 22.2%, a respiratory symptom that has the highest predictive value and diagnostic value. The group of symptoms that we describe independently of exposure to risk factors, are the same that have demonstrated the highest diagnostic value associated with lung cancer and,

taking into account previous evidence on the subject, offer a possible benefit for the diagnosis of lung cancer based on symptoms in the patient seeking medical attention at a first level of care. The proposed algorithm pathway is based partly on patient symptom findings and mainly on the experience of the investigators (Figure 1).

The results of this study are derived from hospital-based research at one center, so they may not be generalizable. Also, due to its purely descriptive design and the fact that only lung cancer cases were included, it is not possible to obtain estimators of the diagnostic value of the symptoms or of the clinical profile described. In addition, although we described the time between the onset of symptoms and the time it took for referral to the tertiary care unit, we did not investigate the period between the onset of symptoms and the first visit to the physician, which of course affects the time from the actual condition to the time of diagnosis.

CONCLUSIONS

Adult patients of any age, with or without risk factors for lung cancer, who report cough for three weeks or more without an explanatory diagnosis and/or any of the following symptoms: dyspnea, chest pain, weight loss, hemoptysis or

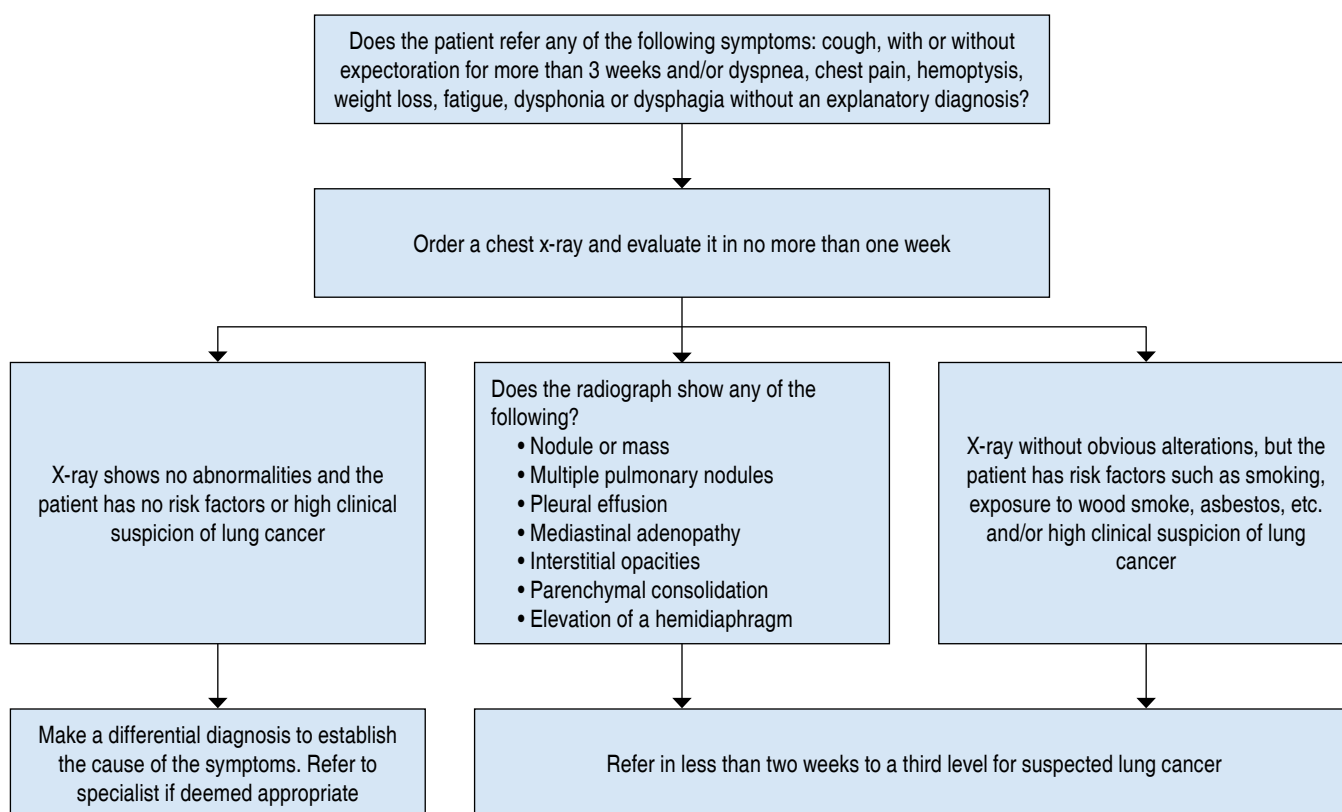


Figure 1: Proposed algorithm for diagnosis and referral of patients with clinical suspicion of lung cancer.

fatigue, should be evaluated clinically and at least with a chest X-ray, and referred to a specialized unit for suspicion of lung cancer. In cases with these characteristics we suggest performing CEA measurement.

Cases with simultaneous dyspnea, chest pain and oxygen saturation < 88% are 7.5 times more likely to have pleural effusion associated with lung cancer.

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