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Lung Cancer in Northeastern Mexico: Epidemiology and Molecular Markers

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ABSTRACT

Background: Lung cancer is the leading cause of death among all cancers worldwide. The main risk factors are tobacco smoking as well as occupational risks, radiation, environmental pollutants, etc. According to the international literature, an incidence of 10-40% may be established for epidermal growth factor receptor gene mutation among patients with lung adenocarcinoma. **Material and methods:** This retrospective study was performed by reviewing all medical records available in the University Hospital "José Eleuterio González" Medical Oncology Service (December 2003 to December 2013). **Results:** A total of 560 patients diagnosed with pulmonary cancer were identified. Four hundred and twenty six had primary lung tumors. Geographical distribution of the cases was as follows: Nuevo León, 63.8%; Tamaulipas, 20.0%; San Luis Potosí, 12.9%; Zacatecas, 3.2%. Tobacco smoking was identified in 72.8% of cases; 75% of them had a history of more than 20 packs per year. Smoking mean time was 32.8 years. Less than 9% of patients had a history of pneumopathy; 78% had been diagnosed with COPD, 18.9% had a history of pulmonary tuberculosis, and 2.7% had nonspecific pulmonary fibrosis. Fourteen out of 16 cases (38.9%) resulted positive for epidermal growth factor receptor mutation, while only one case was anaplastic lymphoma kinase mutation positive. **Conclusion:** It is necessary to implement a Mexican cancer registry in order to determine the actual magnitude of and to fully characterize lung cancer in the Mexican population. This study is an effort to describe some features of the disease, but it is not yet enough to establish the prevalence of common mutations, so compilation of data will still be mandatory.
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INTRODUCTION

Considered as a 20th century pandemic in both developed and undeveloped countries, non-small cell lung cancer (NSCLC) poses an epidemiological challenge since there have been many efforts to elucidate the susceptibility to widely known risk factors. In Mexico, just as in the rest of Latin American countries, NSCLC has paramount importance because of its direct effects on patients, their families, and society.

Regardless of advances in early diagnosis and availability of treatment, unfortunately most of the patients are diagnosed at advanced stages of the disease, which implies a poor prognosis[3]. This fact, coupled with the lack of access to treatment (modern or conventional) makes NSCLC a disease with a real deleterious effect on society.

Within the economic aspect, many efforts have been made in order to measure the magnitude of this problem. The Arrieta, et al. trial showed a high institutional cost per patient, depending on the clinical stage at diagnosis (144,555 USD at stage IV vs. 13,456 USD at stage I)[4].

There are well-identified risk factors related to NSCLC, among them tobacco or snuff consumption (plus occupational carcinogens, radiation, environmental pollutants, etc.). Nevertheless, in developing countries some other factors have been identified, like chronic exposure to wood fire smoke and tuberculosis[5].

With the constant progress in understanding the molecular pathways that cause and promote cancer development, as well as the subsequent advent of so-called targeted therapies used in modern oncology, knowledge of the gene expression profile of NSCLC in our population has increased and it is essential these days.

The armamentarium for the management of lung cancer, includes:

- Epidermal growth factor receptor (EGFR) mutation tyrosine kinase inhibitors (TKI) like erlotinib, gefitinib, and afatinib.
- Targeted therapy rearrangements of the anaplastic lymphoma kinase (ALK) like crizotinib.
- Anti-angiogenesis drugs. For example, monoclonal antibodies against vascular endothelial growth factor (VEGF) (e.g. bevacizumab), or against EGFR (e.g. cetuximab).

In Europe, the European Medicine Agency (EMA) has approved five of these drugs for the treatment of advanced NSCLC: erlotinib, gefitinib, afatinib, and bevacizumab[6]. Recently, the group of indications for TKIs in NSCLC have been defined with more precision, and three types of tumors were included: (i) wild-type mutation for EGFR tumors; (ii) active mutations of EGFR tumors; and (iii) non-selected populations tumors[6].

The international literature has documented an EGFR mutation incidence of 10-40% for the adenocarcinoma population[3]. Latin American population studies evidence that EGFR mutation is 10-40% in adenocarcinoma populations[3].

Latin American trial patients' evidence suggests that EGFR mutation incidence is located between the incidence reported in Asian population (40%) and that reported in Europe (15%)[7-10].

Regarding EML4-ALK mutation, internationally a 7% incidence has been reported in the mutation-positive population.

The aim of the trial was to find the NSCLC epidemiology in Northeastern Mexico (because there is no such data on that geographical area of the country), and design strategies that would allow an effective fight against this health problem.

MATERIAL AND METHODS

A retrospective trial was carried out with the approval of the University Hospital "José Eleuterio González" ethics committee. Clinical records, from December 2003 to December 2013, from the Medical Oncology Department, were reviewed. In addition to the review of clinical records (physical and electronic), we tried to get the maximum amount of information from the patients' relatives, contacted by telephone, to supplement the data obtained.

A database of NSCLC clinical cases was created, based on social and demographic characteristics, risk factors, clinical features, treatment, and clinical evolution. For statistical analysis, we used SPSS v15 software. With this software we could calculate the median and rank of discrete variables, as well as the mean and standard deviation for continuous variables and frequencies for nominal variables.

For the comparative analysis of qualitative variables, contingency tables were used, with the value of Chi-square to measure statistical significance. Regarding quantitative variables, the Kolmogorov-Smirnoff test was chosen, while for parametric variables, the Student *t* test was used, and for nonparametric variables we applied a Mann-Whitney U test.

RESULTS

A total of 560 patients diagnosed with a pulmonary tumor were identified, and 27 (4.9%) presented non-pulmonary primary tumor metastases, while some other non-pulmonary primary tumors were identified, such as mesothelioma (n = 3) and neuroendocrine tumors (n = 7). When studying only primary pulmonary tumor cases deserving analysis (n = 426), we found the following demographic and labor characteristics:

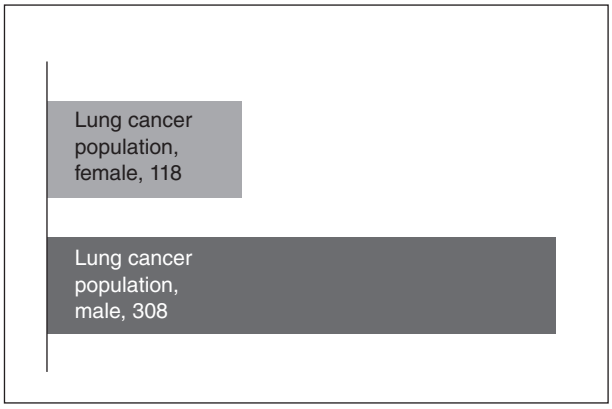

Figure 1. Gender distribution (n = 426).

– A total of 308 cases were men, and 118 were women (Fig. 1);

– Median age was 65.4 years;

– As for occupation, a larger number of cases from indoor workers were reported (58.9%) than outdoor workers (18.1%) or industrial workers (0.9%);

– 22.1% of the population was unemployed.

Regarding geographical distribution:

– 63.8% of the population was from the State of Nuevo León;

– 20% of patients were from the State of Tamaulipas;

– 12.9% were from the State of San Luis Potosí; and

– 3.22% were from the State of Zacatecas.

It was also recorded that 78% of the population had lived the last 10 years in Nuevo Leon, and 18% in Tamaulipas.

As for risk factors, it was found that 72.8% of the population was smoking as a positive background

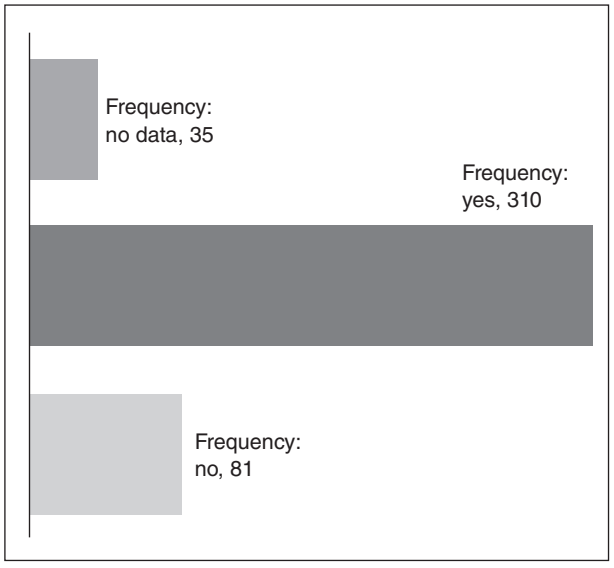

Figure 2. Smoking.

(Fig. 2), and among them, 75% smoked more than 20 packs/year, and the rest (25%) smoked less than 20 packs/year, with an average of 46.5 packs/year. An interesting fact is that the average total time smoking in the sample was 32.8 years**.** A total of 48 cases reported exposure to smoke from biomass (wood) and average exposure time of 12 hours between the population with such positive history (exposure to smoke from biomass), 27% (13 patients) had a greater than 50 hours exposure.

Regarding previous lung disease as a risk factor, most cases (91.3%, 389 patients) had no such history. In cases that did have previous lung disease, 78% had a diagnosis of COPD, 18.9% had pulmonary tuberculosis, and 2.7% had unspecified pulmonary fibrosis.

As for the symptoms at time of diagnosing pulmonary cancer, coughing was found in 34.5% of patients, thoracic pain in 13.6%, weight loss in 12.7%, and dyspnea in 12.2% of cases.

Regarding laterality, 60.6% of tumors were located at the right side, whereas 37.5% of tumors were located at the left side. In 1.9% of patients cancer was located at both sides.

As for the dominant lobe for tumor location, 50% of cases were located at the superior lobe; 26.4% were at hilar or perihilar regions, and 20.4% in the inferior lobe (Fig. 3).

Regarding tumor size, tumors were divided in < 5 and > 5 cm. A 32.9% of tumors measured < 5 cm, whereas the rest (67.1%) measured > 5 cm. A 65.7% of tumors were diagnosed at clinical stage IV; 27.4% at stage III; 4.2% at stage II; and only 1.4% was diagnosed at stage I. These data suggest that most of the tumors are diagnosed in advanced stages.

NSCLC accounts for 88.3% of cases, and small cell cancer accounted for 11.7%, which is similar to literature reports (Fig. 4).

Adenocarcinoma was the most frequent histological type (63.1% of all cases) followed by squamous cell carcinoma (32.2%). Other sub-types including neuroendocrine and large cells represented less than 5% (Fig. 5).

Most frequent complications at diagnosis of NSCLC were: pleural effusion (63%), neurological complications (14.2%), and superior vena cava (9%) syndrome. Thromboembolism and other complications (obstructive pneumonia, atelectasis) were uncommon (< 1% each).

Metastatic disease was documented from first consultation in 61% of patients. Most frequent sites for metastases were, in descending order: bone, CNS, contralateral lung, pleura, liver, adrenal gland, and other sites.

Notably, only 2.4% of patients underwent metastasectomy. As for the frequency of mutations of EGFR, most cases (390 patients, 91.5%) did not undergo the determining mutation test. Within the few (36 cases) patients who did undergo the test,

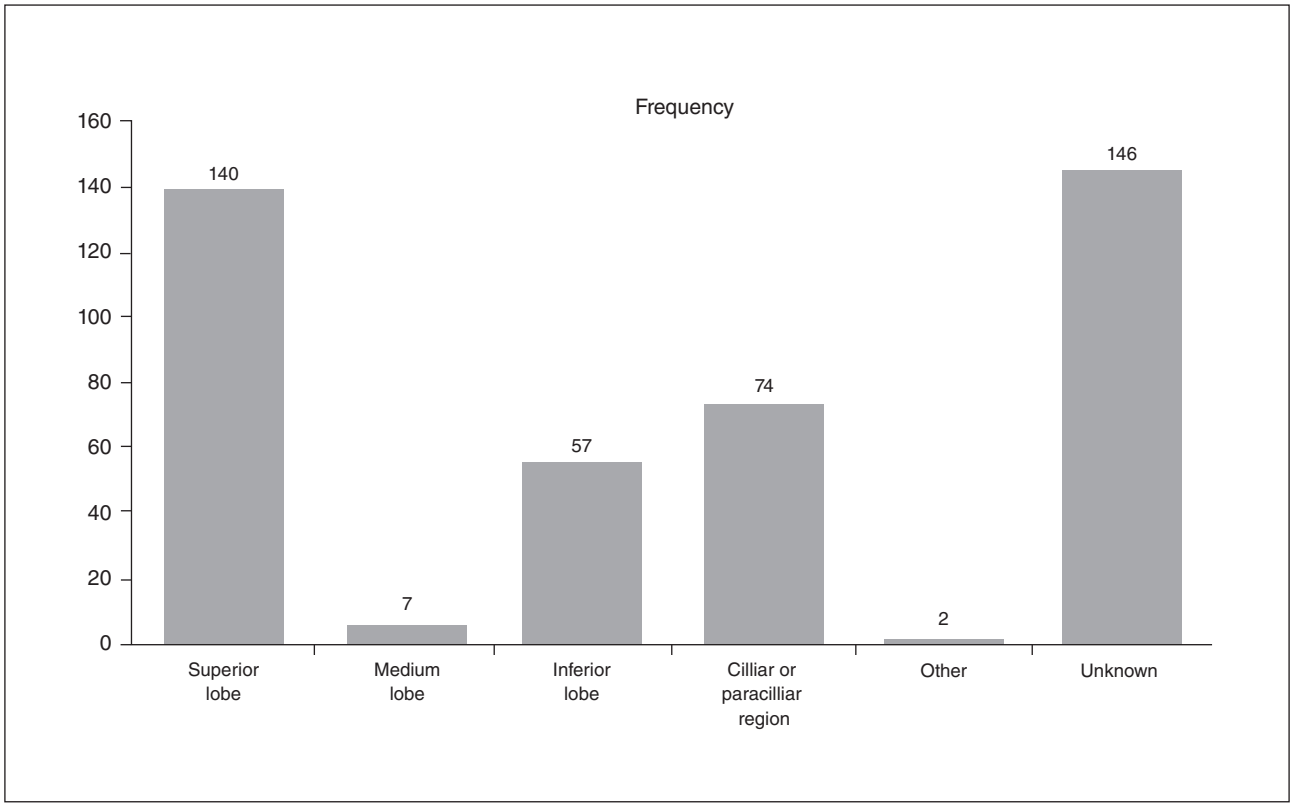

Figure 3. Tumor localization.

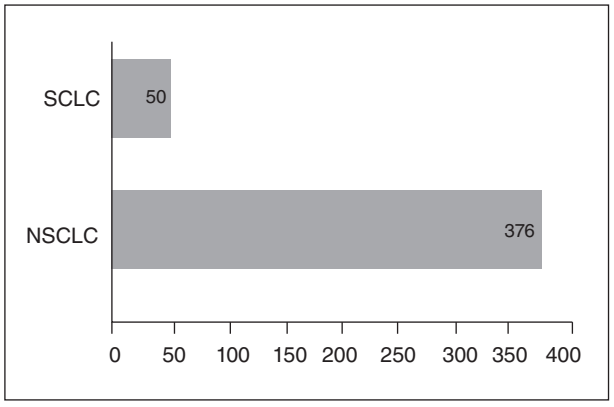

Figure 4. Small cell lung cancer versus non-small cell lung cancer. NSCLC: non-small cell lung cancer; SCLC: small cell lung cancer.

the result was positive in 14 patients (38.9%), and negative in 22 patients (61.1%). Within the 14 positive cases for EGFR mutation, eight patients were identified by immunohistochemistry, and four by fluorescence in situ hybridization (FISH), and in two cases the method performed was not reported. The ALK gene mutation was tested solely in 13 patients (3.1%). It was negative in 12 patients, and positive in one (immunohistochemistry).

Regarding treatment, in the field of first-line chemotherapy, 226 cases were identified; 67 patients had to receive a second line of treatment, and only 20 patients had access to a third line. The most used scheme was carboplatin/paclitaxel combination, which was used in 34.5% of patients, but targeted therapies were also prescribed in < 1% of patients. As for the number of cycles administered, higher frequencies were between 4-6 cycles. Response to the most frequent first-line treatment was progression in 42% of cases, but it must be said that the global benefit found (adding partial response, complete response, and stable disease) was 58% among the clinical cases that could be quantified (Fig. 6).

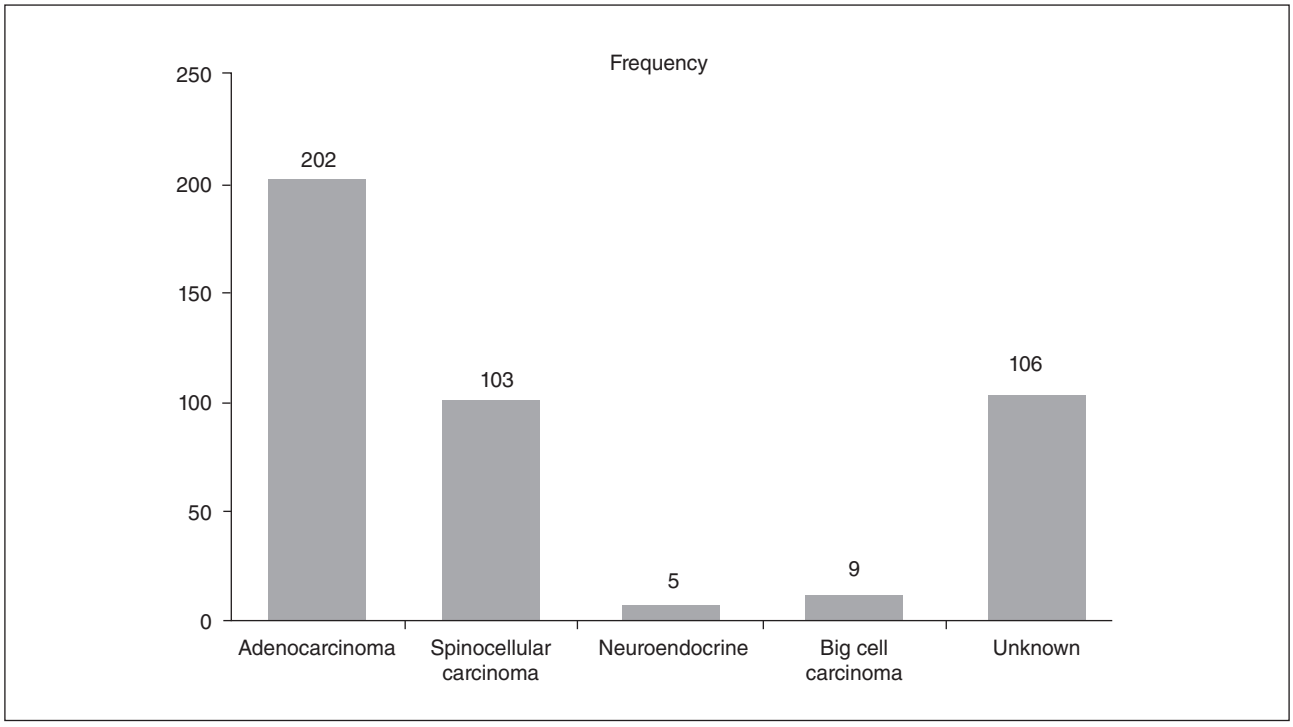

Figure 5. Histological subtype of non-small cell lung cancer.

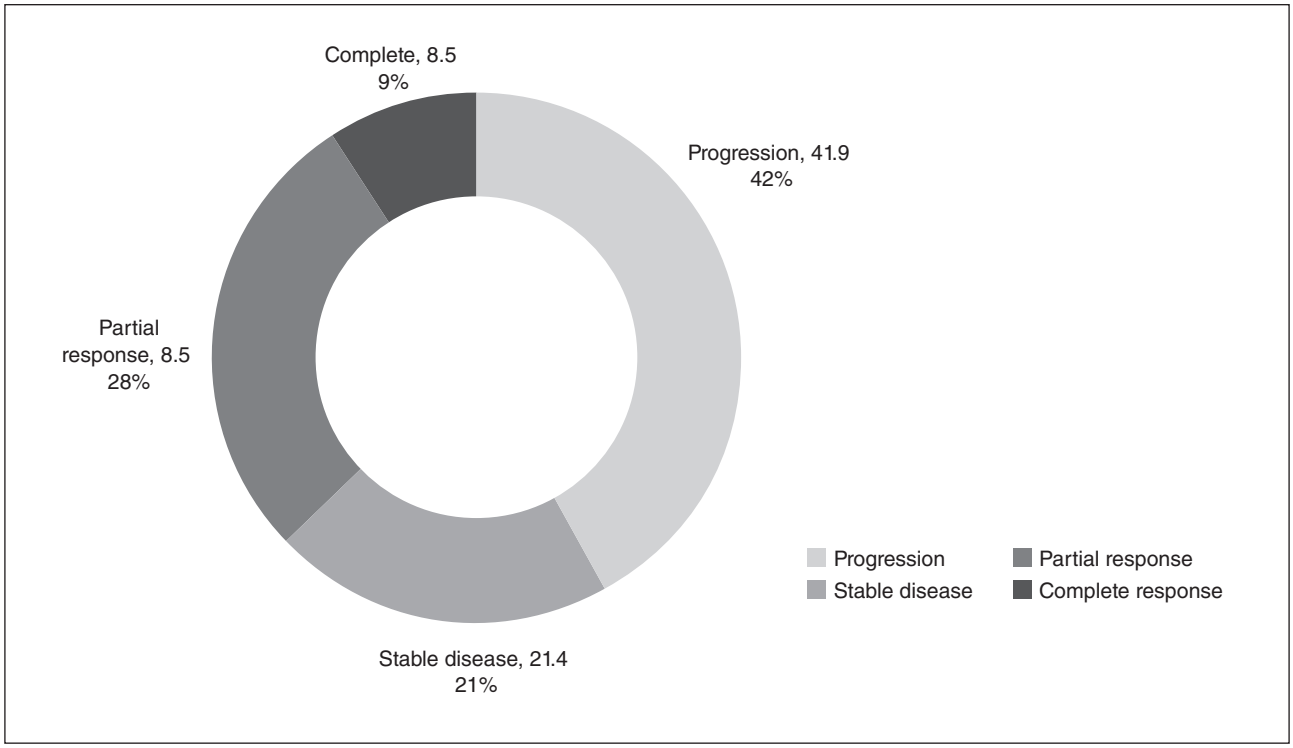

Figure 6. First-line chemotherapy response.

DISCUSSION

Initial analysis of identified NSCLC cases in a 10-year period reveals some heterogeneity of the lung cancer origin, since a very important number was identified as metastatic tumors of non-pulmonary primary sites, and primary tumors of the mesothelioma kind. After removing cases of non-primary lung tumors, the total sample to analyze was 426 patients: 308 men (72.3%) and 118 women (27.6%). Such gender distribution differs from current trends estimated in other populations, which could suggest the high prevalence of tobacco consumption among the male population in northeastern Mexico, in contrast with Central Mexico, where it has been reported that only 50% of cases are men, while women have a smoking background in only 30% of cases[11].

Data from SEER in the United States (2004-2008) recorded an average age of 71 years at diagnosis for NSCLC and bronchi, and did not identify clinical cases under 20 years[12]. Median age reported by this trial was 65.4 years, after discarding cases of patients younger than 20 (n = 1). This average is a little less than the one reported by the literature, which can be explained by the fact of beginning to smoke earlier in Mexican populations, or by other causes not totally identified. In the National Institute of Cancer, the average presentation age is 59 years. These data, along with the reports in this series, suggest an earlier presentation age.

Regarding the geographical distribution of NSCLC, most (63.8%) patients were born in the State of Nuevo León, or had been resident there for the last 10 years (78%), followed by the State of Tamaulipas (origin 20%, and residence for the last 10 years 18%). In this respect, previous studies have shown a higher prevalence of NSCLC among northern states compared with southern ones[13].

It is noteworthy that 72.8% of the population had a positive history of smoking, with an average of total years of smoking of 32.8. In a descriptive study, the National Cancer Institute reported a positive history of smoking in 57.8% of 914 patients with lung cancer studied[14].

Data from exposure to smoke from biomass (wood): we obtained an average exposure of 12 hours/smoke and a percentage of 8.7% with greater exposure of 50 hours/smoke, indicating that it is an underrated exposure due to the loss of data, since it is well known that women in rural areas have a high rate of exposure.

This is relevant, because exposure to biomass smoke for more than 50 years is associated with pulmonary cancer in nonsmoking Mexican women (OR: 1.9; 95% CI: 1.1-3.5), especially the adenocarcinoma type[15]. The finding of a low percentage of working in air-polluting industries does not rule out at all its contributions, and encourages further analysis seeking this information.

Regarding diseases that have been related to NSCLC, we reported that the vast majority was COPD (78%) and pulmonary tuberculosis (18.9%), both linked to lung cancer. It is important to note that the presence of pulmonary tuberculosis may increase the risk of prostate cancer up to 11 times (particularly adenocarcinoma in Asian populations)[16].

The clinical presentation of NSCLC in the study population is within the range described in the literature: cough (8-75%), weight loss (0-68%), dyspnea (3-60%), chest pain (20-49%), and hemoptysis (6-35%)[17].

Regarding the histology, 376 cases were classified as NSCLC (88%) and 50 cases as small-cell carcinoma (12%), which again is similar to that reported in most studies[3].

Several studies have documented the frequency of the main diseases and the results have shown that adenocarcinoma represents 38.5% of all cases of NSCLC[3,12].

When comparing our findings with the international literature, histological subtypes of adenocarcinoma and squamous cell tumor are slightly elevated over reported data. It was not like that in the large-cell group, which is similar to documented data. More than 65% of the tumors were diagnosed in clinical stage IV; 27.4% in clinical stage III; 4.2% in stage II; and only 1.4% were diagnosed with stage I, indicating the failure in preventing and occurrence of very late diagnosis, since advanced stage still dominates the incidence (85%).

If we compare these figures with those reported by the National Cancer Institute, we observe a higher percentage of locally advanced tumors in this institution: 82% of metastatic disease, 16% of locally advanced disease, and 1.2% in early stages[18]. Most frequently found complications in our study were (in descending order): pleural effusion (63%), neurological complications (14.2%), and superior vena cava (9%) syndrome.

We found that 4.8% of patients underwent surgery, a fact that is certainly related to the very low percentage of patients diagnosed in the early stages of the disease. The most common sites of distant metastases were central contralateral lung, pleura, liver, and nervous system for the whole group of patients with NSCLC.

With respect to the frequency of EGFR mutations, a determination of this mutation was not performed in 390 patients (91.5%) so we only have information from a small sample of patients. In the subgroup with the mutation test (36 cases) the result was positive in 14 patients (38.9%) and negative in 22 (61.1%). Of the 14 that tested positive for EGFR mutation, eight underwent immunohistochemistry, four had FISH, and the method was not reported in two patients.

Identification of ALK mutation was performed in only 13 patients (3.1%), and it was negative in 12 and positive in one patient by immunohistochemistry. It is evident that there is a long way to go and, although emerging, efforts are underway to get to know the molecular typing of NSCLC in northeastern Mexico. As a reference we have the University Cancer Center, which has already carried out systematic research on mutations of EGFR and ALK genes.

CONCLUSIONS

The absence of a Mexican cancer registry, outside the center of the country, represents an undeniable constraint to assessing the real magnitude and characteristics of lung cancer in our population and thus achieving better planning strategies to fight this disease. The findings of this study are not sufficient to determine the prevalence of the most common genetic mutations associated with NSCLC, so it is necessary to implement these tests in a standardized way and continue with the collection of this information. As we know in depth the great problems of NSCLC and the effect and real burden of this disease is recognized, more and better resources must be allocated to treat the disease.

This report, with the characteristics of pulmonary cancer in the northeast of the country, shows the urgency of improving patient genotyping efforts more efficiently in order to give and receive better treatment. It is most important to improve early diagnosis of NSCLC and to establish screening programs in high-risk patients, improve the system of referring patients diagnosed or suspected of such disease to tertiary centers, and improve education of the population on recognizing symptoms that may be suspected as NSCLC.

DISCLOSURE OF INTEREST

The authors of this study declare that information has been calculated based on approved

methodologies and without any mediated conflict of interest with respect to the procedures and objectives of the trial. The information was obtained based on the professional experience of the authors, as well as technical criteria and methodology approved by the appropriate academic institutions.

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